Exp Brain Res
DOI 10.1007/s00221-013-3545-x

RESEARCH ARTICLE

Quantifying connectivity via efferent and afferent pathways in motor control using coherence measures and joint position perturbations

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Received: 22 February 2013 / Accepted: 23 April 2013

Abstract The applicability of corticomuscular coherence (CMC) as a connectivity measure is limited since only 40–50 % of the healthy population presents significant CMC. In this study, we applied continuous joint position perturbations to obtain a more reliable measure of connectivity in motor control. We evaluated the coherence between joint position perturbations and EEG (position-cortical coherence, PCC) and CMC. Healthy subjects performed two isotonic force tasks against the handle of a wrist manipulator. The baseline task was isometric; in the perturbed task, the handle moved continuously with small amplitude. The position perturbation signal covered frequencies between 5 and 29 Hz. In the perturbed task, all subjects had significant PCC and 86 % of the subjects had significant CMC, on both stimulus and non-stimulus frequencies. In the baseline task, CMC was present in only 45 % of the subjects, mostly on beta-band frequencies. The position perturbations during an isotonic force task elicited PCC in all subjects and elicited CMC in most subjects on both stimulus and non-stimulus frequencies. Perturbed CMC possibly arises by two separate processes: an intrinsic process, similar to the process in an unperturbed task, involving both efferent and afferent pathways; and a process related to the excitation of the afferent and efferent pathways by the perturbation. These processes cannot be separated. PCC, however, reflects connectivity via the afferent pathways only. As PCC was present in all healthy subjects, we propose this coherence as a reliable measure for connectivity in motor control via the afferent pathways.

Keywords Coherence · EEG · EMG · Proprioception · Motor control · Perturbations · Afferent pathways · Efferent pathways

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Introduction

The control of movement involves numerous interactions between various parts of the central nervous system (CNS), including multiple cortical areas, the basal ganglia, cerebellum, brainstem and the spinal cord. Interactions between these areas are quantified by various measures of correlation between recorded activity from the different structures. Widely applied measures of correlation are coherence and phase synchronization between pairs of EEG or MEG channels to quantify cortico-cortical connectivity (Varela et al. 2001) and study the formation of functional networks within the brain (Stam and van Straaten 2012).

A frequently applied measure of connectivity in motor control is the coherence between cortical activity and muscle activity: corticomuscular coherence (CMC) (Conway et al. 1995; Mima et al. 2000; Baker 2007; Halliday et al. 1998). Due to the large distance between the recording sites, there is no effect of volume conduction which may impede the

Published online: 12 May 2013

detection of connectivity between neural populations close together (Fries 2005). CMC is generally found in the beta band (15–30 Hz) and indicates synchronization between neural oscillations in the cortex and the spinal cord, although the physiological processes generating CMC are not fully understood. Since muscle activity, as well as cortical activity, is measured inside a closed-loop system, ordinary CMC arises via both efferent and afferent pathways. This bi-directional nature of CMC is widely accepted, and the descending motor contribution as well as the ascending sensory contribution to CMC has been studied (Witham et al. 2011; Mima et al. 2001a; Riddle and Baker 2005; Pohja and Salenius 2003). In addition, a recent study using invasive recordings in monkey showed that it is likely that coherent oscillation in the motor control system arises within the closed loop and is not the result of a single oscillatory motor drive (Williams et al. 2009). Although the contribution of both pathways can be shown using directed coherence or similar techniques (Gourévitch et al. 2006; Kaminski and Blinowska 1991), separate properties of the pathways cannot be determined (Schouten and Campfens 2012).

Corticomuscular coherence is not an epiphenomenon and has been shown to have a functional role in motor control. CMC varies with different aspects of motor control such as attention (Kristeva-Feige et al. 2002; Johnson et al. 2011), performance (Kristeva et al. 2007), exerted force (Witte et al. 2007; Mima et al. 1999), fatigue (Yang et al. 2009, 2010), type of the task (Masakado and Nielsen 2008; Baker et al. 1997), experience with the task (Perez et al. 2006; Mendez-Balbuena et al. 2011) and activity preceding the task (Riddle and Baker 2006; Omlor et al. 2011).

Corticomuscular coherence has also been measured in a clinical setting to study movement disorders such as various types of tremor (van der Meer et al. 2010; Grosse et al. 2003; van Rootselaar et al. 2006), including the tremor present in Parkinson's disease (Florin et al. 2010; Amtage et al. 2009). In addition, CMC has been proposed as an attractive measure of connectivity in motor control after stroke (Braun et al. 2007; Fang et al. 2009; Meng et al. 2009; Yao and Dewald 2006). In stroke patients, some studies reported reduced CMC magnitude in the affected hemisphere when compared to the unaffected hemisphere (Mima et al. 2001b) or compared to healthy controls (Fang et al. 2009). However, Braun et al. (2007) found no difference in CMC magnitudes but instead reported increased dispersion of CMC in the affected hemisphere compared to the unaffected hemisphere in well-recovered stroke patients. Although the experimental evidence is limited, Braun et al. (2007) hypothesized a relation between CMC magnitude and motor function in well-recovered stroke patients, where high CMC indicates better motor function. If such relation exists, CMC may be used to monitor the cortical contribution to the recovery of patients after stroke.

A potential limitation for the clinical applicability of CMC as a measure for connectivity in motor control is the large inter-individual variation in CMC that is normally obtained from a static, isometric force task. Only 40–50 % of healthy subjects express significant CMC during such a static task, and the strength and bandwidth of CMC vary between individuals (Mima et al. 2000; Mendez-Balbuena et al. 2011; Ushiyama et al. 2011). With such large inter-individual differences within a healthy population, the absence of CMC does not necessarily indicate abnormal connectivity. This results in a limited general applicability of CMC during a static task to derive conclusions about the presence or strength of the efferent and afferent pathways in individual subjects or patients.

To serve as an individual measure for connectivity in motor control, interventions that could reduce inter-individual difference in CMC or additional measures are needed. Recently, it was demonstrated that transient electrical or mechanical peripheral perturbations during a static task increase and even elicit CMC in healthy subjects (McClelland et al. 2012). Subjects without pre-stimulus CMC did show CMC 400 ms after the stimulus. The authors concluded that relevant sensory input could play a crucial role in modulating and revealing CMC.

In this study, we aim to obtain a reliable measure for connectivity in motor control that is present in all healthy subjects by applying continuous mechanical joint position perturbations during an isotonic force task. We investigated two measures: coherence between the position perturbation signal and EEG (position-cortical coherence, PCC) and CMC. Since the perturbation signal is measured outside the physiological feedback loop, PCC represents uni-directional causality: cortical activity is evoked by the applied perturbation, and cortical activity does not influence the perturbation. PCC is therefore a measure for the response evoked by the perturbation and reflects activity of the ascending sensory pathways only. Oscillatory input has been applied in the visual and auditory system to evoke a cortical response: a steady-state evoked potential (Herrmann 2001). We expect that the position perturbation will elicit PCC and CMC at the stimulus frequencies via the same afferent pathways. Possibly the position perturbation affects CMC on the non-stimulus frequencies as well due to an interaction between responses to the perturbation and the intrinsic process leading to CMC in a baseline task. Part of this work was presented in abstract form (Campfens et al. 2011).

Methods

Twenty-two healthy volunteers participated in this study (nine women, mean age 27 years, age range 23–35, four

subjects were left-hand dominant). The dominant hand was determined using the "Dutch handedness questionnaire" (van Strien 1992). All measurements were conducted in accordance with the *Declaration of Helsinki* and were approved by the Medical Ethics Review Committee of the Medisch Spectrum Twente (Enschede, the Netherlands). All subjects gave signed informed consent before participating.

Experimental setup

Subjects were seated next to a wrist manipulator (Moog Inc., Nieuw-Vennep, the Netherlands), see Fig. 1. The wrist manipulator (WM) is an actuated rotating device with a single degree of freedom that can exert flexion and extension perturbations to the wrist joint. The lower arm of the subject's dominant hand was strapped in an arm rest while the subject held the handle of the WM. The axis of rotation of the WM was aligned with the axis of rotation of the wrist. The neutral angle is defined as when the handle keeps the thumb in line with the lower arm, resulting in a slight extension of the wrist. The lever of the WM is equipped with a force transducer to measure the torques exerted by the subject. Due to the high stiffness of the WM, the subject has no influence on the angular position of the handle.

EEG was measured from 64 electrodes on the scalp, placed according to the 5 % electrode system (Oostenveld and Praamstra 2001) using a standard EEG cap with Ag/AgCl electrodes (WaveGuard cap by ANT, Enschede, the Netherlands). Electrode impedances were below 5 kOhm. EMG was measured from the m.flexor carpi radialis (EMG_{FCR}) and the m.extensor carpi radialis (EMG_{ECR}) using bipolar Ag/AgCl electrode pairs placed on the muscle belly (diameter: 1 cm, inter-electrode distance: 2 cm). To monitor eye blinks, the vertical electrooculogram (EOG) was measured from the left eye. All physiological signals were sampled at 2,048 Hz (refa system by TMSi, Oldenzaal, the Netherlands). The angle of the WM and torque on the lever were synchronously recorded on a separate system (porti system by TMSi, Oldenzaal, the Netherlands) at 2,048 Hz.

Protocol

Subjects exerted a constant wrist flexion torque to the handle of the WM, while the WM either kept the neutral angle or imposed a continuous position perturbation. Subjects received visual feedback of the exerted and target torque via a display. Subjects were instructed to keep the exerted torque within a block of 1.8 ± 0.27 Nm. For the

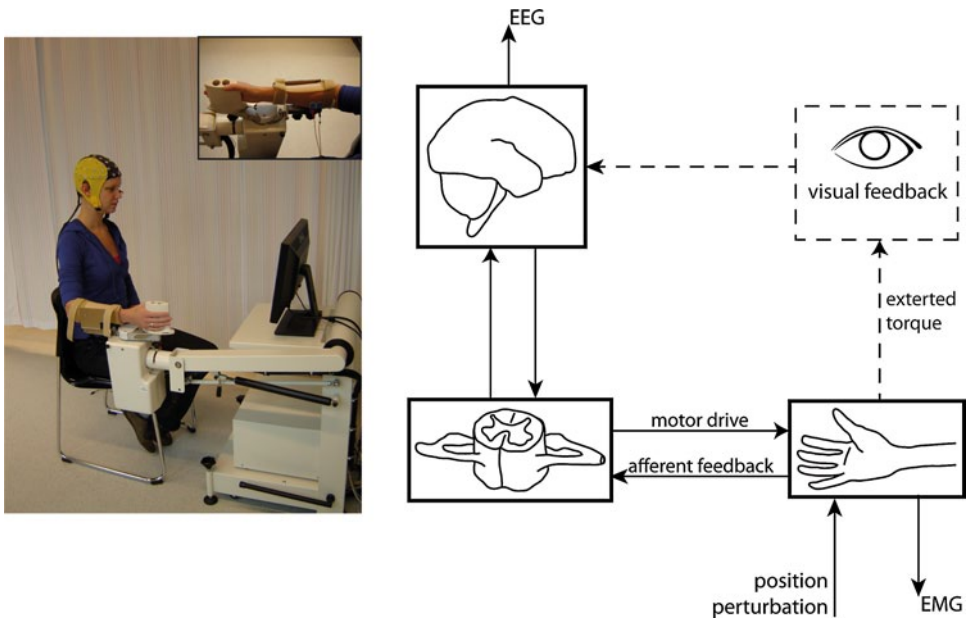

Fig. 1 Overview of the experimental setup (*left*) and scheme of all signals (*right*). The subject holds the lever of the WM, and the lower arm is strapped in an arm rest using Velcro straps. To support the subject, visual feedback of the target torque and the exerted torque (2 Hz low-pass filtered with third-order Butterworth filter) are provided on the display in front of the subject. EEG is measured using a head cap (64 channels), EOG is measured to monitor eye blinks and bipolar EMG is measured from the flexor carpi radialis (FCR) and extensor carpi radialis (ECR). During the position perturbations, the handle of the WM continuously moves around the neutral position with a small amplitude. As the subject has no influence on the position of the handle, coherence between position perturbation and EEG represents a uni-directional relation via the afferent sensory pathways while CMC represents connectivity involving activity via both the efferent and the afferent pathways

visualization, the exerted torque was filtered online (third-order low-pass Butterworth, 2 Hz) to remove the stimulus frequencies. The target torque of 1.8 Nm is comparable with 15 % of maximum voluntary contraction torque for an average subject. The constant neutral angle served as a baseline task, similar to the standard procedure to measure CMC. During the position perturbations, the handle moved continuously with small amplitude around the neutral angle. For each of the two tasks—baseline and perturbed—five trials of 55 s were recorded. The baseline trials were performed first. Ten subjects performed a second set of five baseline trials to assess a possible carryover effect of the perturbation on baseline CMC. Between trials, subjects were given sufficient rest time to prevent fatigue.

The position perturbation signal (Fig. 2) consisted of a sum of sine waves (5, 9, 13, 17, 21, 25 and 29 Hz), and the phases of the sine waves were optimized such that the perturbation contained maximal power (Pintelon and Schoukens 2001). The perturbation signal had a period of 1 s, and peak-to-peak amplitude was 0.03 rad (1.7°). The power of the sine waves decreased with frequency, giving the perturbation a flat velocity spectrum. Since we expect the neuromuscular system to have nonlinear responses, the perturbation signal was designed to reveal nonlinear responses (Pintelon and Schoukens 2001): possible responses at even and odd higher harmonics of the stimulus frequencies appear at non-stimulus frequencies. Since the perturbation signal contains multiple frequencies, nonlinearity could also result in power at higher harmonics of combinations of stimulus frequencies, including both positive and negative frequency components. These higher harmonics at frequency combinations also do not coincide with the stimulus frequencies. The beta band was included in the position perturbation signal because this frequency band is involved in oscillatory coupling in an unperturbed task; we expected that including beta-band frequencies increases the chance of eliciting PCC and CMC by a perturbation.

Data analysis

Recorded signals were visually inspected and processed off-line using MATLAB 7.11 (the MathWorks, Inc., Natick, MA, USA). Raw EEG and EOG signals were band-pass filtered (2–70 Hz), and the EEG was transformed to a nearest neighbor Laplacian derivation. EMG was band-pass filtered (2–500 Hz). The filters were fourth-order Butterworth filters applied with zero lag. All signals were inspected visually.

Power spectral density

All signals were segmented in 1 s segments (2,048 samples)—the period of the perturbation—with 75 % overlap between segments; the use of overlapping segments decreases the bias and variance of the coherence estimates (Bortel and Sovka 2007; Carter 1987). The EOG was used to remove segments containing eye blinks. Segments where the average exerted torque deviated more than 10 % from the target force were removed as well. The 50-Hz component (power line artifact) was removed from each segment using the discrete Fourier transform (Oostenveld et al. 2011). To exclude the possibility of movement artifacts in the EMG signal, frequency components below 75 Hz were filtered from the EMG using an ideal high-pass filter: EMG was transformed to the frequency domain using the fast Fourier transform (FFT), frequencies below 75 Hz are set to zero, and the resulting signal is transformed back to the time domain using the inverse FFT. After this high-pass filtering, the EMG was rectified. The use of high-pass filtering prior to rectifying EMG is shown to be suitable for coherence analysis by Boonstra and Breakspear (2012).

All segments were transformed to the frequency domain using the FFT. The power spectral density (PSD, Φ_{xx}) and cross-spectral density (CSD, Φ_{xy}) were estimated per task for every individual subject using

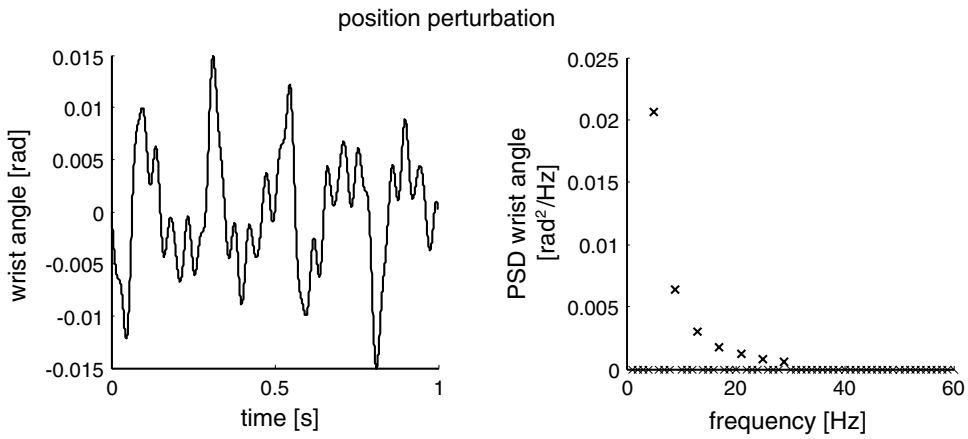

Fig. 2 Time series (*left*) and PSD (*right*) of the position perturbation

$$\Phi_{xx}(f) = \frac{1}{N}\sum_{i=1}^{N} X_i^*(f) \cdot X_i(f) \quad (1)$$

and

$$\Phi_{xy}(f) = \frac{1}{N}\sum_{i=1}^{N} X_i^*(f) \cdot Y_i(f) \quad (2)$$

respectively, where $X_i(f)$ and $Y_i(f)$ are the Fourier coefficients at frequency f estimated from the ith data segment. The asterisk indicates the complex conjugate, and N is the total number of segments.

The power spectra of the EEG and EMG signals in the baseline and the perturbed task were compared, considering stimulus and non-stimulus frequencies separately. The non-stimulus power of the EEG (NSP_{EEG}) was defined as the integral of the log-transformed PSD over non-stimulus frequencies between 1 and 60 Hz. The non-stimulus power of the rectified EMG signals ($NSP_{EMG\text{-}FCR}$ and $NSP_{EMG\text{-}ECR}$) included the power on non-stimulus frequencies between 1 and 200 Hz. The stimulus power of EEG and rectified EMG (SP_{EEG}, $SP_{EMG\text{-}FCR}$ and $SP_{EMG\text{-}ECR}$) was the log-transformed power summed over the stimulus frequencies. All power measures were compared between the baseline and perturbed task; statistical significance was evaluated using paired Student's t tests with $\alpha = 0.05$.

Coherence

The (magnitude squared) coherence ($C_{xy}(f)$) was calculated between signals according to

$$C_{xy}(f) = \frac{|\Phi_{xy}(f)|^2}{\Phi_{xx}(f)\,\Phi_{yy}(f)}. \quad (3)$$

The CMC was expressed as coherence between EEG channels and EMG_{FCR} and was calculated per task for every subject. Coherences between the position perturbation and EEG/EMG_{FCR} (PCC and position-musculo coherence, PMC) were only evaluated at stimulus frequencies.

Significance of coherence values was determined using the approximation of the confidence limit (CL) by Bortel and Sovka (2007). They provided an approximation for the number of degrees of freedom for the probability density function and CL formula of the magnitude squared coherence for overlapping segments. The confidence level was set to 0.95 ($\alpha = 0.05$). To limit false positives, a subject was considered to have CMC for a task if CMC was largest at electrodes over the contralateral motor cortex.

Subjects were divided in two groups based on the presence of CMC in the baseline task. The "baseline CMC+" group had significant CMC in the baseline task, and the "baseline CMC−"group did not have significant CMC in the baseline task. For subjects in the baseline CMC+ group, the electrode at the contralateral side with the highest CMC was used for single channel analysis. In the baseline CMC− group, C3 (right-handed subject) or C4 (left-handed subject) was used for single channel analysis. An exception was made if the signal quality at C3 (C4 for left-handed subjects) was poor; in such cases, C1 (C2 for left-handed subjects) was used. For single channel analysis of CMC in the perturbed task, the same electrode was used as in the baseline task. Mean significant CMC amplitude between 1 and 60 Hz was calculated by taking the averaged CMC over the bins where the CMC exceeded CL. In the baseline tasks, this typically only includes frequencies in the beta band. In addition, topoplots of the total significant CMC and PCC visualized the spatial distribution of coherence over the scalp.

Results

Power spectral density

Examples of time series recorded in the perturbed task of a representative subject are presented in Fig. 3. The PSDs of the EEG were similar in the baseline and perturbed task (Fig. 4). No significant difference of EEG power was detected between the baseline and perturbed task both on stimulus and on non-stimulus frequencies (SP_{EEG}: $p = 0.28$; NSP_{EEG}: $p = 0.46$). In the perturbed task, the PSD of the EMG_{FCR} showed maxima at the stimulus frequencies. A significant difference in EMG_{FCR} power was present both on stimulus and on non-stimulus frequencies ($SP_{EMG\text{-}FCR}$: $p < 0.001$; $NSP_{EMG\text{-}FCR}$: $p < 0.01$). The power of the EMG_{FCR} on the stimulus and non-stimulus frequencies increased by 12 and 4 %, respectively. A significant difference was also present in the power of the EMG_{ECR} on both stimulus and non-stimulus frequencies ($SP_{EMG\text{-}ECR}$: $p < 0.001$; $NSP_{EMG\text{-}ECR}$: $p < 0.01$). The power of the EMG_{ECR} on the stimulus and non-stimulus frequencies increased by 32 and 28 %, respectively.

Coherence at contralateral motor cortex

Typical PCC and CMC spectra for the baseline and the perturbed task are presented in Fig. 5; these examples show the significant PCC and the increased CMC in the perturbed task. The CMC spectra in the perturbed task have more sharp peaks compared to the baseline CMC spectra. The peaks in the CMC spectra mostly coincide with higher PCC, although CMC peaks are also found at non-stimulus frequencies. Figures 6 and 7 summarize for all individual subjects the presence (Fig. 6) and amplitude (Fig. 7) of significant CMC and PCC. In the perturbed task, all subjects had significant PCC and more subjects had CMC compared

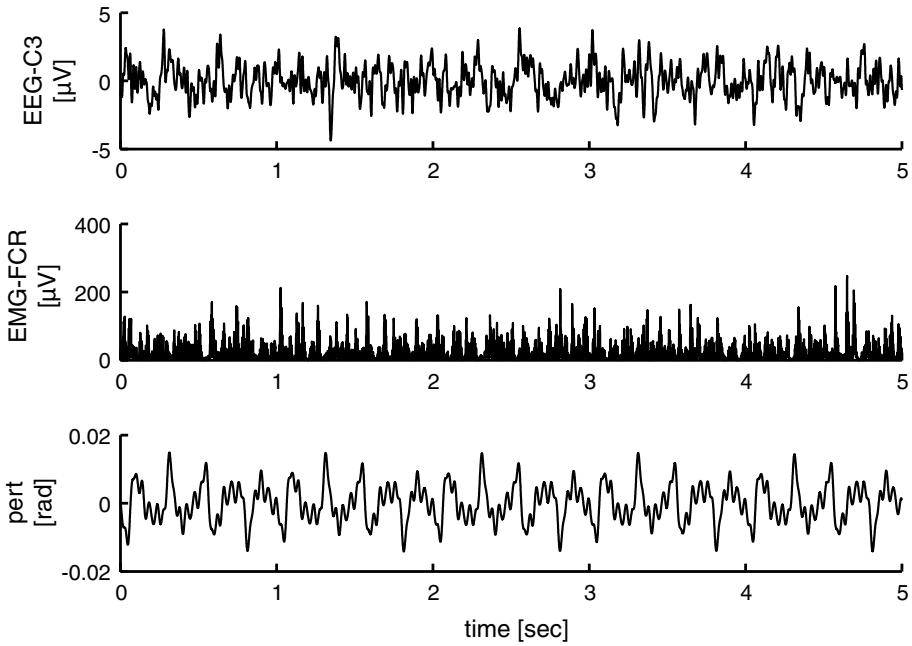

Fig. 3 Example of time series in the perturbed task of a representative subject (S08). *Upper row* EEG at electrode C3. *Middle row* high-pass filtered (cutoff: 75 Hz) and rectified EMG_{FCR}. *Bottom row* position perturbation signal

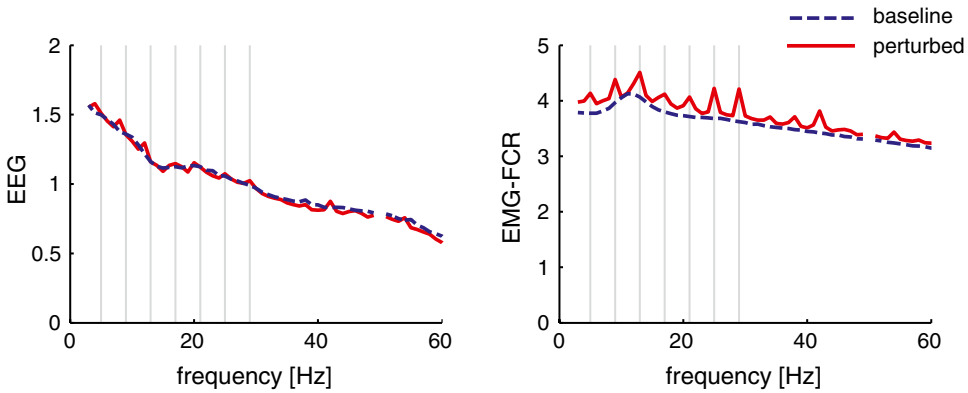

Fig. 4 Grand average log-transformed PSD of EEG (*left*) and EMG_{FCR} (*right*) in both tasks. *Gray vertical lines* indicate stimulus frequencies. No statistical difference was detected in EEG power, and EMG power changed significantly at stimulus and at non-stimulus frequencies

to the baseline task. In general, the perturbation resulted in PCC and CMC in the baseline CMC− group and even increased CMC in the baseline CMC+ group.

In the baseline task, ten out of twenty-two subjects (45 %) had significant CMC between EEG at the contralateral motor cortex and EMG_{FCR}, mostly in the beta band. In seven subjects, the maximal CMC was at electrode C3, in two subjects (S11 and S14) at electrode C2 and in one subject (S20) at electrode FC3. Subjects in the baseline CMC+ group had significant CMC on frequencies ranging from 11 to 41 Hz. The number of frequencies on which a subject in the CMC+ group had significant CMC always exceeded the number which would be expected from a false positive (expected from a false positive is 2–3 significant frequencies in the range of 1–60 Hz and with $\alpha = 0.05$). Twelve subjects did not have CMC in the baseline task.

In the perturbed task, all subjects had significant PCC and nineteen of twenty-two subjects (86 %) had significant CMC. From the three subjects without CMC in the perturbed task, two subjects came from the baseline CMC− group. The three subjects without significant CMC in the perturbed task did have PCC. One subject had significant CMC in the baseline task, and not in the perturbed task. In all nine subjects with significant CMC in both tasks, CMC amplitude was higher in the perturbed task (Fig. 7).

The presence of PCC was very similar to the CMC at the stimulus frequencies: if significant CMC was found at a stimulus frequency, the PCC was also significant at that frequency in nearly all subjects. Only three subjects had significant CMC but no significant PCC at that frequency (S09 at 13 Hz, S11 at 29 Hz and S22 at 5 Hz). Seventeen subjects had significant PCC at frequencies where the CMC did not exceed the CL.

The PMC was significant at almost all stimulus frequencies in all subjects. The PMC was high compared to CMC and PCC and could be as high as 0.8 in some subjects.

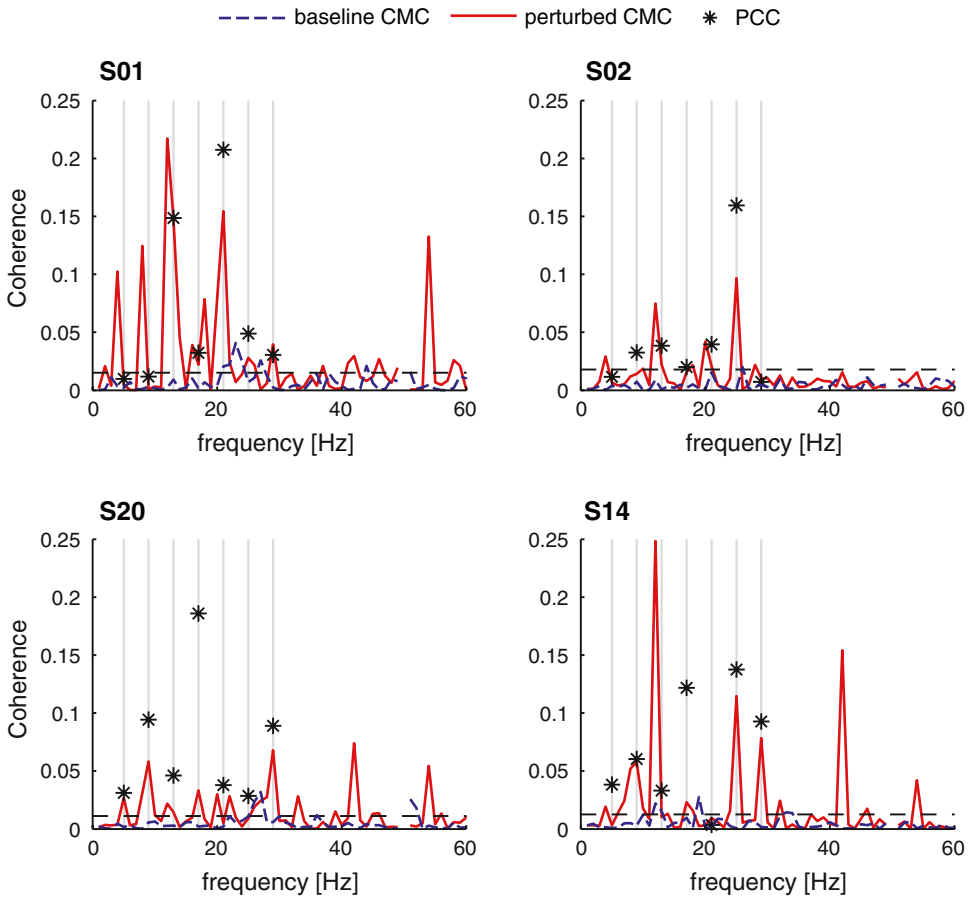

Fig. 5 Individual CMC and PCC spectra of four representative subjects from the group baseline CMC+ (S01, S14 and S20) and baseline CMC− (S02). *Dashed horizontal lines* indicate the CL. *Gray vertical lines* indicate the stimulus frequencies

Four of the ten subjects that performed the second baseline task after the perturbed task had significant CMC in the first baseline task. Two of these subjects had significant CMC in the second baseline task as well and in the same frequency band. One subject had no significant CMC in the first baseline task but did show significant CMC in the second baseline task.

There was a large variability in the frequencies at which individual subjects had significant CMC in the perturbed task. Almost all subjects with significant CMC in the perturbed task had significant CMC on at least one stimulus frequency. Only one subject (S16) had no significant CMC on the stimulus frequencies, although this subject had significant PCC on four stimulus frequencies. Of the stimulus frequencies, significant PCC or CMC was found at 5 Hz in the fewest number of subjects. Significant CMC at 29 Hz was present in the highest number of subjects. Significant PCC was found most often on 21 Hz.

Significant CMC was found on non-stimulus frequencies in all subjects with CMC in the perturbed task; especially, the number of subjects with significant CMC at 12 and 42 Hz is noticeably higher than on other non-stimulus frequencies.

Localization of coherence

Both in the baseline and in the perturbed task, no significant coherence was found at the ipsilateral motor cortex. Topoplots indicated that significant PCC and CMC were generally present on multiple electrodes in the perturbed task (Fig. 8), including the electrode(s) where CMC was present in the baseline task (baseline CMC+ group). The electrode where maximal coherence occurred in the perturbed task was not necessarily the electrode where maximal CMC was present in the baseline task.

Discussion

In this study, we investigated the use of angular joint position perturbations and coherence measures as a novel tool to reliably quantify connectivity in motor control. CMC is a correlation measure that reflects activity via both descending and ascending pathways. Contrary, coherence between position perturbation and EEG (PCC) is introduced as a uni-directional correlation measure reflecting activity via the ascending afferent pathways. Small wrist

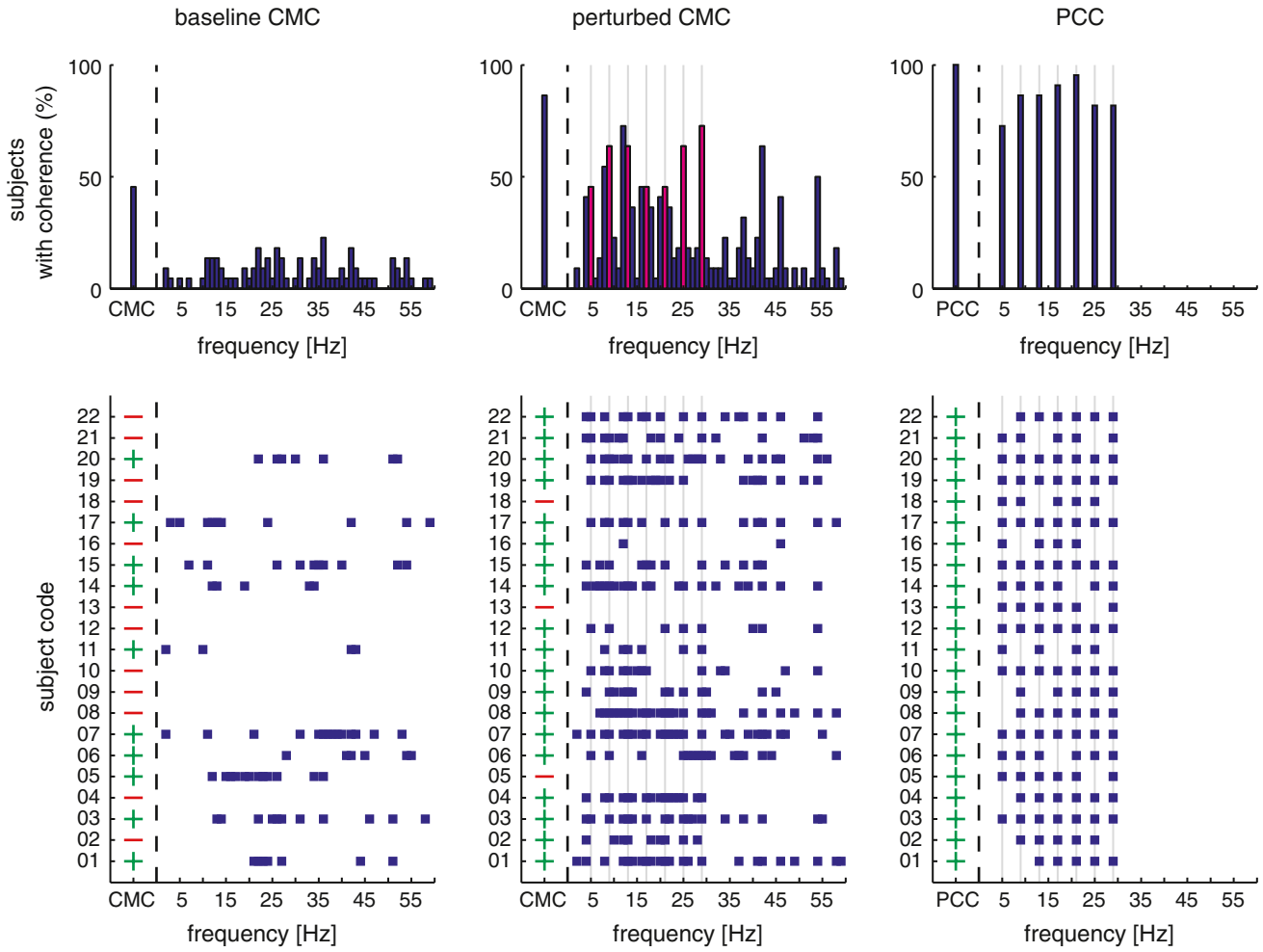

Fig. 6 Overview of CMC and PCC in the baseline and perturbed task in all subjects. *Upper row* percentage of subjects with CMC per frequency. *From left to right* baseline task CMC, perturbed task CMC and PCC. *Lower row* CMC presence in the individual subjects. On the vertical axis, the subject code, a '+' in the first column indicates CMC, a '−' indicates no CMC. The frequencies with CMC in the individual subjects are indicated by the dots. *From left to right* baseline task CMC, perturbed task CMC and PCC. *Gray vertical lines* indicate the stimulus frequencies

perturbations induced PCC in all subjects. These perturbations increased the number of subjects presenting CMC and the amplitude of CMC, on both stimulus and non-stimulus frequencies, but did not evoke significant CMC in all subjects.

In the isometric, isotonic motor task without perturbations, ten out of twenty-two subjects (45 %) had significant CMC, mostly on beta-band frequencies. This is in line with other studies, reporting significant CMC during isotonic, isometric motor tasks in 40–50 % of healthy subjects (Ushiyama et al. 2011; Mima et al. 2000; Mendez-Balbuena et al. 2011). The second baseline task performed by ten subjects showed that even within a subject, the presence of CMC is variable; in one subject, CMC appeared in the second baseline task and in two subjects significant CMC disappeared. The low number of healthy subjects presenting significant CMC in a static motor tasks and the within-subject variation limits the clinical applicability of CMC as a measure of connectivity in motor control.

Mechanical perturbations elicit coherence

The addition of small continuous position perturbations during an isotonic force task had a large effect on CMC. In the perturbed task, all subjects had significant PCC and nineteen of twenty-two subjects (86 %) had significant CMC. In subjects with significant CMC in both tasks, the CMC was higher in the perturbed task with an average increase of 109 % of the mean significant CMC amplitude.

Our results may appear different from the results in van der Meer et al. (2010) who used a similar approach applying position perturbations to the wrist to investigate

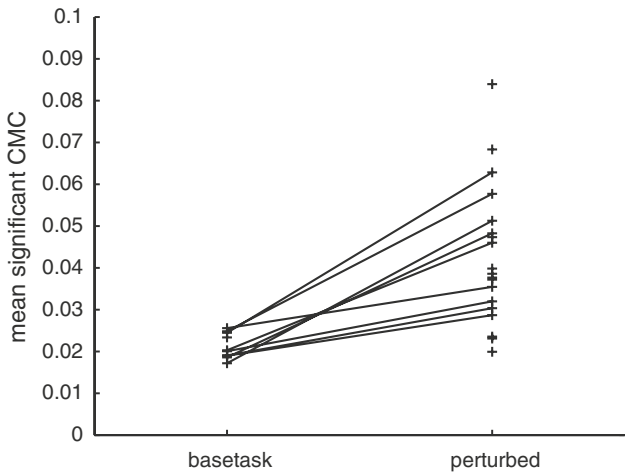

Fig. 7 Mean significant CMC amplitude over all frequencies under 60 Hz, for all subjects with CMC in the baseline or perturbed task. Each subject is represented as a *cross*, *lines* indicate the subjects presenting CMC in both tasks

intermuscular drive in dystonia patients and healthy controls during an isotonic force task. In this study, no CMC was elicited in the healthy controls when position perturbations were applied. However, van der Meer et al. applied perturbations up to 12 Hz while we applied a perturbation also including frequencies in the beta band. Williams and Baker (2009) showed that Renshaw cell recurrent inhibition reduces oscillatory coupling at frequencies under approximately 10 Hz which may explain why van der Meer et al. found no CMC. We argue, therefore, that to elicit CMC using a continuous perturbation, the perturbation signal should contain frequencies in the beta band.

Possible confounding factors

Significant PCC or CMC in the perturbed task could have resulted from artifacts caused by the WM. However, in the EMG signal, possible (movement) artifacts were removed by high-pass filtering and rectification. In the EEG, such artifacts would be distributed over the whole scalp and be accompanied by an increase in EEG power. Significant PCC and CMC were predominantly localized over the contralateral motor cortex, as expected (Conway et al. 1995), and the EEG power was not significantly different between baseline and perturbed task. Therefore, we rule out the possibility of artifacts as a cause for the significant PCC and CMC in the perturbed task.

In comparison with the baseline task, the power of the EMG signals increased on stimulus and on non-stimulus frequencies, with clear maxima at stimulus frequencies and some higher harmonics. By itself, an increase in power is not sufficient to explain the increased presence of CMC in the perturbed task as coherence is normalized by signal power. Coherence is primarily a measure for phase synchronization between two signals as phase synchronization is a necessary condition for significant coherence (Bruns 2004). Only if the increased signal power reduces the relative amount of measurement noise, the increased signal power could improve SNR and increase coherence. The PCC is independent from changes in EMG power. The absence of changes in EEG power at the stimulus

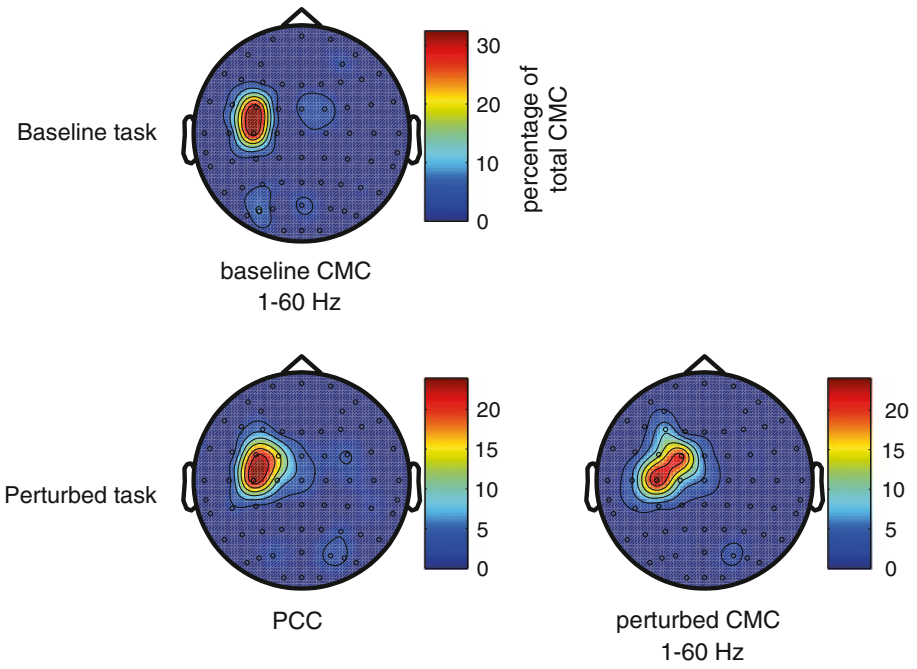

Fig. 8 Topoplots of the CMC and PCC expressed as percentage of the total coherence over all electrodes of a representative subject (S07). *Top row* baseline task. Significant CMC summed over all frequencies between 1 and 60 Hz. *Bottom row* perturbed task. *Left plot* shows significant PCC over all stimulus frequencies. *Right plot* shows the significant CMC over all frequencies between 1 and 60 Hz

frequencies indicates that PCC indeed arose from phase locking of ongoing cortical oscillations to the perturbation.

Origin of coherence at stimulus and non-stimulus frequencies

Corticomuscular coherence indicates significant phase synchronization between EEG and EMG but does not show how this synchronization arises. In general, coherence can arise due to multiple processes: a uni-directional relation between two signals (open loop system), a bi-directional relation (closed-loop system) or a common drive to two signals. Although the coherence between EEG and EMG has been studied for over 15 years, the process generating CMC during an isometric, isotonic remains poorly understood. Currently, it is widely accepted that in an unperturbed task, this CMC involves activity via both the descending efferent and the ascending afferent pathways connecting cortical and spinal neurons forming a closed-loop system with unknown inputs.

In the perturbed task, a position perturbation was added to the closed-loop neuromuscular system which elicited significant CMC on both stimulus and non-stimulus frequencies. The perturbation acts as an external excitation of the neuromuscular system, primarily exciting muscle spindles and Golgi tendon organs. Via the spinal reflex loop, the perturbation elicits a response in the EMG. In addition, an EEG response to the perturbation is elicited via afferent sensory pathways, this is quantified by PCC and represents a process similar to how steady-state evoked potentials are evoked in the visual or auditory system (Herrmann 2001). A transcortical reflex loop provides a second pathway that can elicit an EMG response. With the perturbation as a common input signal driving the EEG and EMG, CMC is also induced. If significant CMC at a stimulus frequency was observed, this was almost always accompanied by significant PCC. This suggests that the common drive of the position perturbation is indeed the main contributor to CMC at the stimulus frequencies. PCC and CMC at the stimulus frequencies both represent activity of the same ascending afferent pathways; in addition, CMC at the stimulus frequencies can contain contributions from the descending efferent pathways due to transcortical reflexes. Note that the coherence due to a common drive to EEG and EMG represents a different process than the process due to which CMC arises in the unperturbed task, but still involves both the efferent and the afferent pathways.

In our study, EEG activity was evoked by sensory input by an external perturbation. Evidence exists that also in non-perturbed conditions EEG activity has a large sensory component. Recently, Jain et al. (2012) found similar averaged EEG waveforms in active and passive pedalling tasks. This suggests that afferent sensory input is a large contributor to the EEG during an active task. Witham et al. (2011) applied directed coherence (Granger causality) analysis and showed that both efferent and afferent pathways contribute to unperturbed CMC. It was also found that the contribution of both pathways varies considerably between subjects.

Recently, McClelland et al. (2012) showed that CMC during a isometric task can even be modulated by sensory input. After a sudden mechanical perturbation, the CMC was initially decreased for 400 ms and reappeared with a larger amplitude after the initial reflexive activation. Even subjects without significant CMC in the pre-stimulus period showed significant CMC in the post-stimulus rebound period, resulting in 100 % of the subjects showing significant CMC post-stimulus. Possibly the rebound response found by McClelland et al. contributes to the response to the continuous perturbation although we were not able to elicit significant CMC in all subjects.

In the perturbed task, significant CMC was found on several non-stimulus frequencies as well; the likelihood of finding significant CMC at some harmonics of the stimulus frequencies (8, 12 and 42 Hz) was even comparable to the likelihood of finding CMC at the stimulus frequencies: more than 50 % of the subjects had CMC on at least one of these frequencies. The CMC at non-stimulus frequencies may represent CMC generated by the same intrinsic mechanisms as in an unperturbed task. However, as the neuromuscular system is highly nonlinear, CMC at these frequencies may also be a sign of nonlinear responses to the perturbation. In a recent study, Langdon et al. (2011) presented such nonlinear responses of the somatosensory system. Neural oscillations, recorded using EEG, phase locked to a single frequency vibrotactile stimulation, not only on the frequency of the stimulation but also on higher harmonics: *n*:*m* phase locking. The phase locking was not accompanied by power changes at stimulated frequencies. The responses we found at specific non-stimulus frequencies suggest that the phase locked oscillations described by Langdon et al. (2011) may also occur in an active motor task. Using a linear analysis technique, such as coherence, it is not possible to separate these nonlinear responses to the perturbation from the intrinsic mechanisms generating unperturbed beta-band CMC. Possibly, these processes can be separated using granger causality (Florin et al. 2011), multi-frequency phase locking measures, or by using multiple position perturbations with different frequency contents. However, such analysis is outside the scope of the current study. Our aim was to obtain a reliable measure of connectivity in motor control with less variability between healthy subjects. We present PCC as an attractive measure connectivity via the afferent pathways present in all healthy subjects. Significant CMC is also induced by the position perturbation in most subjects and represents connectivity

involving both the efferent and the afferent pathways arising by two simultaneous processes.

Corticomuscular coherence in an unperturbed task is modulated by various factors, which may also influence CMC in the perturbed task. Attention toward the task is known to influence CMC amplitude (Kristeva-Feige et al. 2002; Johnson et al. 2011). The experiment was set up to limit the necessity of behavioral changes in the perturbed task: subjects perceived the tasks as easy, the tasks did not require a high level of precision, and for the visual feedback, the exerted torque was low-pass filtered. However, the sensation of the position perturbation may have had an alerting effect, increasing attention toward the task and contributing to the found increase in CMC.

Another possible contributing factor to the CMC amplitude in the perturbed task is the increased co-contraction, indicated by the increased EMG power in that task. Co-contraction may lead to increased CMC levels when the co-contraction results from an increased cortical motor drive, thus raising the signal-to-noise ratio in the EMG. However, Mima et al. (1999) found no change in CMC magnitude with weak to moderate (up to 60 % MVC) contraction levels such as the contraction levels in our baseline and perturbed task. Furthermore, the peaks at the stimulus frequencies in the EMG power spectral densities suggest that the co-contraction originates at least partly from the spinal reflex loops (Matthews 1993) and not from an increased cortical motor drive.

As a final note, the use of an external excitation to quantify connectivity via afferent sensory pathways is not uncommon in research and clinical practice. The response to electrical stimulation of the median nerve at the wrist is widely used in clinical practice. Also, the response evoked by muscle stretch has been studied (Abbruzzese et al. 1985; MacKinnon et al. 2000; Seiss et al. 2002). MacKinnon et al. (2000) and Seiss et al. (2002) compared the location of sources generating the evoked potentials elicited electrically and by muscle stretch. Both studies reported that the response evoked by muscle stretch originated from sources in the motor cortex, while the electrically elicited evoked potentials originated from the sensory cortex. The muscle stretch evoked potential may therefore provide additional information about sensorimotor function compared to the electrically evoked potential which only represents sensory function. PCC may be viewed as a frequency domain equivalent of the muscle stretch evoked potential.

Conclusion

A limitation of CMC as a measure for connectivity during an isometric motor task is the absence of significant CMC in over 50 % of the healthy population. The aim of this study was to develop a reliable measure of connectivity in motor control. Using an isotonic motor task with an added position perturbation, that excites the beta band, we elicited significant PCC in all subjects, while significant CMC was elicited in 86 % of the subjects. PCC is a reliable measure for connectivity via the afferent pathways that was present in all healthy subjects.

Conflict of interest The authors declare that they have no conflict of interest.

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