

Contributions of descending and ascending pathways to corticomuscular coherence in humans

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Non-technical summary Neural activity in parts of the cerebral cortex related to movement oscillates at frequencies around 20 Hz. These oscillations are correlated with similar rhythms in contracting muscles on the opposite side of the body. In this work, we used an analysis method called directed coherence to investigate the direction of oscillatory coupling. We find that oscillations travel not only from cortex to muscle (as expected for a motor command), but also back from muscle to cortex (reflecting sensory input). This oscillatory loop may allow the cortex to measure features of the limb state, integrating sensory inflow with the motor command.

Abstract Corticomuscular coherence in the beta frequency band (15–30 Hz) has been demonstrated in both humans and monkeys, but its origin and functional role are still unclear. Phase–frequency plots produced by traditional coherence analysis are often complex. Some subjects show a clear linear phase–frequency relationship (indicative of a fixed delay) but give shorter delays than expected; others show a constant phase across frequencies. Recent evidence suggests that oscillations may be travelling around a peripheral sensorimotor loop. We recorded sensorimotor EEGs and EMGs from three intrinsic hand muscles in human subjects performing a precision grip task, and applied directed coherence (Granger causality) analysis to explore this system. Directed coherence was significant in both descending (EEG→EMG) and ascending (EMG→EEG) directions at beta frequencies. Average phase delays of 26.4 ms for the EEG→EMG direction and 29.5 ms for the EMG→EEG direction were closer to the expected conduction times for these pathways than the average delays estimated from coherence phase (7.9 ms). Subjects were sub-divided into different groups, based on the sign of the slope of the linear relation between corticomuscular coherence phase and frequency (positive, negative or zero). Analysis separated by these groups suggested that different relative magnitudes of EEG→EMG and EMG→EEG directed coherence might underlie the observed inter-individual differences in coherence phase. These results confirm the complex nature of corticomuscular coherence with contributions from both descending and ascending pathways.

(Resubmitted 21 April 2011; accepted after revision 27 May 2011; first published online 30 May 2011)

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Abbreviations 1DI, first dorsal interosseus; AbDM, abductor digiti minimi; AbPB, abductor pollicis brevis; EEG, electroencephalogram; EMG, electromyogram; LFP, local field potential.

Introduction

Oscillations in the 15–30 Hz range have been widely documented in the motor systems of both humans and monkeys (Tiihonen *et al.* 1989; Murthy & Fetz, 1992; Salmelin & Hari, 1994). These oscillations are present in the sensorimotor cortex during sustained contraction and are coherent with contralateral muscle activity (Conway *et al.* 1995; Baker *et al.* 1997; Salenius *et al.* 1997; Halliday *et al.* 1998). However, many details of the generation, propagation and function of these oscillations are still unclear.

The most obvious pathway to mediate corticomuscular coherence is the corticospinal tract, and there is good evidence that this must be involved: corticospinal cell activity does encode motor cortical oscillations (Baker *et al.* 2003*b*). However, this is unlikely to be the sole pathway. In a feedforward linear system with fixed delay, coherence phase should vary linearly with frequency, with a slope equal to the delay between the two signals (Rosenberg *et al.* 1989). Cassidy & Brown (2003) showed that such delay estimation is subject to errors unless the coupling is unidirectional. Some authors have found such a linear relationship (with cortex leading muscle), although the estimated delays are generally lower than those expected from corticospinal conduction times (Mima *et al.* 2000). Computational modelling suggests that delay estimates from corticomuscular coherence generated purely by corticospinal pathways should be longer than measures of conduction time produced using stimulation (Williams *et al.* 2009), meaning that the low values found experimentally are even more discrepant. Others find that the coherence phase is constant over a range of frequencies (Halliday *et al.* 1998). In a previous paper, we found subjects conforming to either pattern (Riddle & Baker, 2005). We interpreted these varied phase–frequency relationships as suggesting that corticomuscular coherence may involve other pathways, as well as the corticospinal tract. In addition, administration of different drugs can alter the power of cortical oscillations and coherence selectively, a result inconsistent with purely efferent conduction of oscillations from motor cortex to the periphery (Baker & Baker, 2003; Riddle *et al.* 2004).

Several pieces of evidence suggest the corticomuscular coherence is generated by a loop between cortex and the periphery, involving not just descending (motor) propagation, but also transmission in an ascending (sensory) direction. Grosse *et al.* (2003) showed that in some circumstances, muscle could lead cortex. If the arm is cooled, the conduction time is slowed in both sensory and motor pathways. The increase in the phase delay estimated from corticomuscular coherence delay is around twice the increase in motor conduction times (Riddle & Baker, 2005), and therefore more closely matches the

increase in total conduction time around a sensorimotor loop. Direct recordings from putative muscle spindle afferents in monkeys show that their discharge encodes oscillations in EMG activity (Baker *et al.* 2006). Finally, oscillations are present in both somatosensory and motor cortex (Witham & Baker, 2007; Witham *et al.* 2007), and corticomuscular coherence is present in recordings from both sides of the central sulcus (Tsujimoto *et al.* 2009; Witham *et al.* 2010). The exact contributions of descending and ascending pathways remain unknown, but the existence of bi-directional coherence would be important in determining the function of these oscillations (Baker, 2007).

Coherence is a measure of correlation, and does not therefore allow assignment of the direction of interaction between two signals. By contrast, Granger causality (directed coherence) can provide information about possible causal relationships. These methods have been previously applied to corticomuscular coherence in monkey, using invasive recordings of local field potentials from different sensorimotor areas (Tsujimoto *et al.* 2009; Witham *et al.* 2010). In this paper we apply directed coherence methods to a large database of sensorimotor EEG and EMG recordings previously gathered from human subjects performing a precision grip task. Application of these methods provides clear evidence for bidirectional corticomuscular coherence in man. Delay estimates produced by directed coherence agree better with those expected based on computational modelling and known conduction times in the human nervous system than those generated from standard coherence analysis.

Methods

Experiments were performed on 39 young, healthy volunteer subjects (15 female; age range 18–45). Subjects gave informed written consent in accordance with the *Declaration of Helsinki* and all procedures were approved by the Human Biology Research Ethics Committee of the University of Cambridge, where experiments were carried out. Standard coherence results from most of these experiments ($n = 35$ subjects) have been reported in our previous publications (Baker & Baker, 2003; Riddle *et al.* 2004, 2005, 2006).

Recording

Bipolar EMGs were recorded from three intrinsic muscles in the right hand (first dorsal interosseus, IDI; abductor pollicis brevis, AbPB; abductor digiti minimi, AbDM) using adhesive surface electrodes (Biotrace 0713 C, MSB Ltd, Marlborough, UK). Two adhesive scalp electrodes (Neuroline 720 00-5, Medicotest, St Ives, UK) were

positioned at 30 mm lateral to the midline and 20 mm anterior and posterior to the interaural line to record bipolar left sensorimotor EEG. The anterior electrode was connected to the non-inverting input of the amplifier. Signals were amplified (gain 100–5000, EMG; 20000–50000, EEG) and filtered (bandpass 30 Hz–2 kHz, EMG; 3 Hz–2 kHz, EEG) prior to being digitised (~ 5 kHz sampling rate) using a Power1401 interface (Cambridge Electronic Design Ltd, Cambridge, UK) connected to a computer running Spike2 software (Cambridge Electronic Design Ltd).

Task

Subjects were asked to perform a precision grip task using two levers held between the index finger and thumb of the right hand. The levers were connected to torque motors and optical encoders, allowing measurement of displacement and generation of force under computer control. The forces exerted by the motors simulated the action of a spring (initial force of 1 N required to move from end-stop, followed by linear increase of force with increasing displacement, spring constant 0.025 N mm^{-1}). Visual feedback of lever and target position was provided via cursors on a computer screen. The task required a hold–ramp–hold pattern of lever movement, as shown in the top trace of Fig. 1A. The target initially shifted to a displacement of 12 mm, which was held for 3 s. This was followed by a 2-s-long linear ramp to 24 mm displacement. Finally, the target remained fixed at 24 mm for a further 3 s. At the end of the second hold period the targets returned to zero displacement, and subjects released the levers. This task has been previously shown to lead to large corticomuscular coherence during the two hold periods (equivalent to the COMP1 condition of Kilner *et al.* 2000). Since coherence phase estimates have lower noise if coherence is larger (Rosenberg *et al.* 1989), optimisation of the task is also likely to improve the reliability of phase estimates.

Cooling

Thirteen of the subjects underwent the cooling protocol previously reported in Riddle & Baker (2005). The above task was performed before and after cooling the arm with water thermostatically maintained at 10°C . Electrical stimulation of the median nerve at the wrist allowed measurement of F- and M-wave latencies in the AbPB muscle, from which the peripheral motor conduction time was calculated (for further details see Riddle & Baker, 2005).

Analysis

Figure 1B shows a time-resolved coherence analysis between EEG and 1DI in a single subject (this plot was produced by the wavelet coherence analysis method described in Baker & Baker, 2003). As previously reported, coherence around 20 Hz was greatest during the two hold periods of the task. Accordingly, the directed coherence analysis which is the focus of this paper used only data from these two sections of the task.

All signals were first re-sampled to a standard rate of 5 kHz, as the precise acquisition rates had varied across experiments. EMG signals were rectified before analysis. For standard coherence analysis, three non-overlapping 4096 point long sections were taken from each hold period and used for the Fourier analysis (a total of six sections per trial). This gave a frequency resolution of 1.22 Hz. Coherence was calculated using formulae given in detail

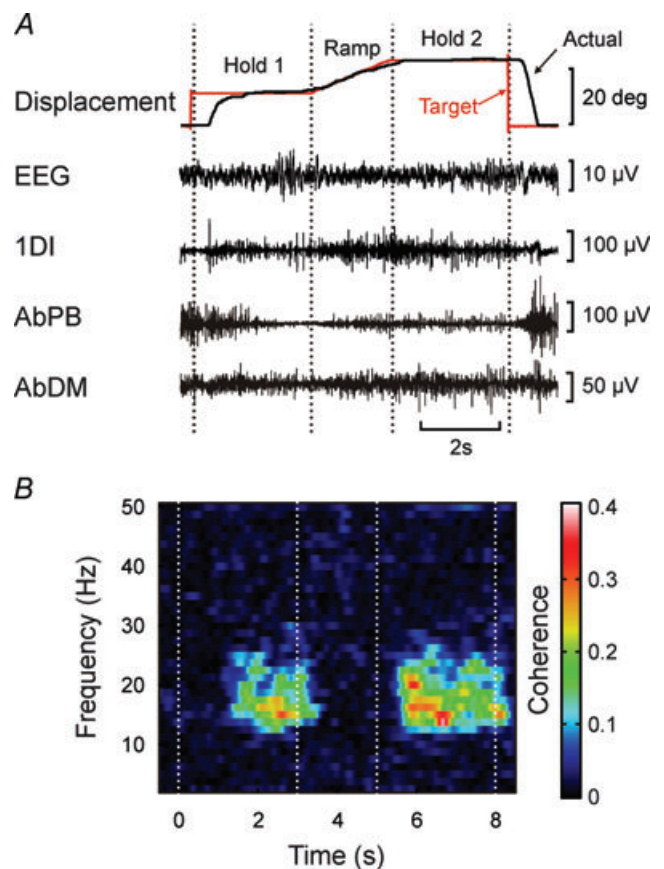


Figure 1. Example of single trial and average time-resolved corticomuscular coherence

A, raw traces from one subject (2rd) for one trial. Top trace shows both the target position (red) and the actual lever position (black). Other traces show EEG and the EMG signals from three intrinsic hand muscles. All signals have been down-sampled to 200 Hz. Dotted lines indicate the two hold periods. B, time-resolved corticomuscular coherence plot for subject in A. Dotted lines indicate the two hold periods.

in our previous publications (Baker *et al.* 1997) and was considered significant ($P < 0.05$) if it was greater than Z where

$$Z = 1 - 0.05^{(1/L-1)} \quad (1)$$

and L is the total number of non-overlapping sections, equal to the available number of trials multiplied by six (Rosenberg *et al.* 1989). Average coherence spectra were computed across subjects; significance limits for these average spectra were determined as described in Evans & Baker (2003).

Phase was calculated by taking the argument of the cross-spectrum. Confidence limits on the phase were calculated as (Rosenberg *et al.* 1989):

$$\Delta\theta(f) = 1.96\sqrt{\frac{1}{2L} \left(\frac{1}{\text{Coherence}(f)} - 1 \right)} \quad (2)$$

Directed coherence was calculated using the methods outlined in our previous work (Baker *et al.* 2006; Williams *et al.* 2009, 2010), using data only from the hold phases of the task. Rectified EMG and EEG recordings were down-sampled to a 200 Hz sampling rate. An autoregressive (AR) model of order 100 was fitted to the 400 points available from each task hold period, using a publicly available program (ArFit, Schneider & Neumaier, 2001). A detailed discussion of the choice of AR model order is provided in Witham *et al.* (2010, end p. 3 onwards). Briefly, rather than determine statistically what model order is justified by the data, we use an arbitrarily high order, and then subsequently test individual values of directed coherence in each bin for statistical significance. Use of a large order allows examination of the directed coherence phase spectrum with high frequency resolution, providing more confidence in delay estimates. AR model coefficients were then averaged, and used to calculate directed coherence and phase. As in Witham *et al.* (2010), we used the normalization of directed coherence suggested by Geweke (1982):

$$\begin{aligned} \text{Directed coherence}_{i \leftarrow j}(f) \\ = \frac{|H_{ij}(f)H_{ij}^*(f)C_{jj}|}{|H_{ij}(f)H_{ij}^*(f)C_{jj} + H_{ii}(f)H_{ii}^*(f)C_{ii}|} \end{aligned} \quad (3)$$

where H_{ij} is the directional transfer function representing the causal influence of signal j on signal i , H_{ji} is the directional transfer function representing the causal influence of signal i on itself, C_{kk} is the covariance of the noise innovations of signal k in the AR model, and complex conjugation is denoted by $*$. Using this normalisation, the directed coherence can be interpreted as the proportion of the variance in signal i which is explained by the past history of signal j (a coefficient of determination, Pierce, 1982). Significance limits for directed coherence

were estimated by numerical Monte Carlo simulation as in Witham *et al.* (2010).

For both coherence and directed coherence, phase delays were calculated by fitting a line to the phase–frequency plot using linear regression with a model as follows:

$$\theta(f) = 2\pi T f + \theta_0 \quad (4)$$

where $\theta(f)$ is the phase at frequency f , T is the delay, and θ_0 is the phase offset at $f = 0$ Hz. Mima *et al.* (2000) previously showed that incorporation of a constant phase offset was required to model the phase–frequency relationship adequately. This offset is likely to arise because peak neural activity shows a non-zero phase relation with peak local field potential (Baker *et al.* 2003b); in addition, the projection of local field potentials onto the scalp, and their recording by a bipolar EEG montage, may add further phase offsets. For this analysis, phases from all three intrinsic hand muscles were superimposed (since the conduction times for these muscles should be similar) and only frequencies with significant coherence/directed coherence were used. These procedures are the same as we have used in previous publications (e.g. Riddle & Baker, 2005). The frequency range over which to calculate the phase–frequency regression was selected on an individual basis to be where the coherence/directed coherence was consistently above the significance level in at least one muscle, in the range 10–40 Hz. Delays are presented as the maximum likelihood value returned by the regression fit and the 95% confidence interval. All analysis routines were implemented in the MATLAB package (The MathWorks Inc., Natick, MA, USA).

Results

Single subject data

In a previous paper, Riddle & Baker (2005) reported that subjects could be divided into two groups based on the observed coherence phase–frequency relationship. Their Group A had a linear relationship between phase and frequency, with a negative slope (indicating cortex led muscle). Their Group B had no significant relationship between coherence phase and frequency. One subject appeared to demonstrate both patterns over different frequency ranges. In this paper, where we examined data from a greater pool of subjects, we found a third group (denoted here as Group C) where coherence phase was linearly related to frequency, but with a positive slope (muscle leading cortex). Out of 39 subjects, 11 were classified as Group A, 18 as Group B and 10 as Group C.

Figure 2 shows examples of the coherence and directed coherence spectra for a single subject from each of these groups. The coherence spectra (averaged across all three

intrinsic hand muscles recorded, Fig. 2A) had clear peaks in the 15–30 Hz range for all subjects, despite their very different coherence phase–frequency relationships (Fig. 2B). Subject 2rd had a significant regression, with a negative slope implying a delay of 7.5 ± 1.9 ms (cortex leading muscle). Subject 8cnr had a regression slope not significantly different from zero (2.9 ± 4.0 ms) and subject 10jmk had a positive regression slope implying a delay of 5.3 ± 3.6 ms (muscle leading cortex).

Figure 2C shows the directed coherence spectra for all three subjects. Subject 2rd had significant directed coherence in both the EEG→EMG and EMG→EEG directions between 10 and 30 Hz. Both directed coherences

were smaller in magnitude than the coherence; we previously showed with simulated data that this could occur when causal connections are present in both directions (Witham *et al.* 2010). Linear regression of the directed coherence phase–frequency relationships (Fig. 2D) yielded implied delays of 24.6 ± 2.5 ms for the EEG→EMG direction and 23.6 ± 3.6 ms for the EMG→EEG direction. Note that for directed coherence, the sign of the slope of the phase–frequency relationship is always the same, and unlike the situation with coherence phase does not yield any information about the direction of an interaction. For the other subjects, directed coherence was smaller, although it did rise

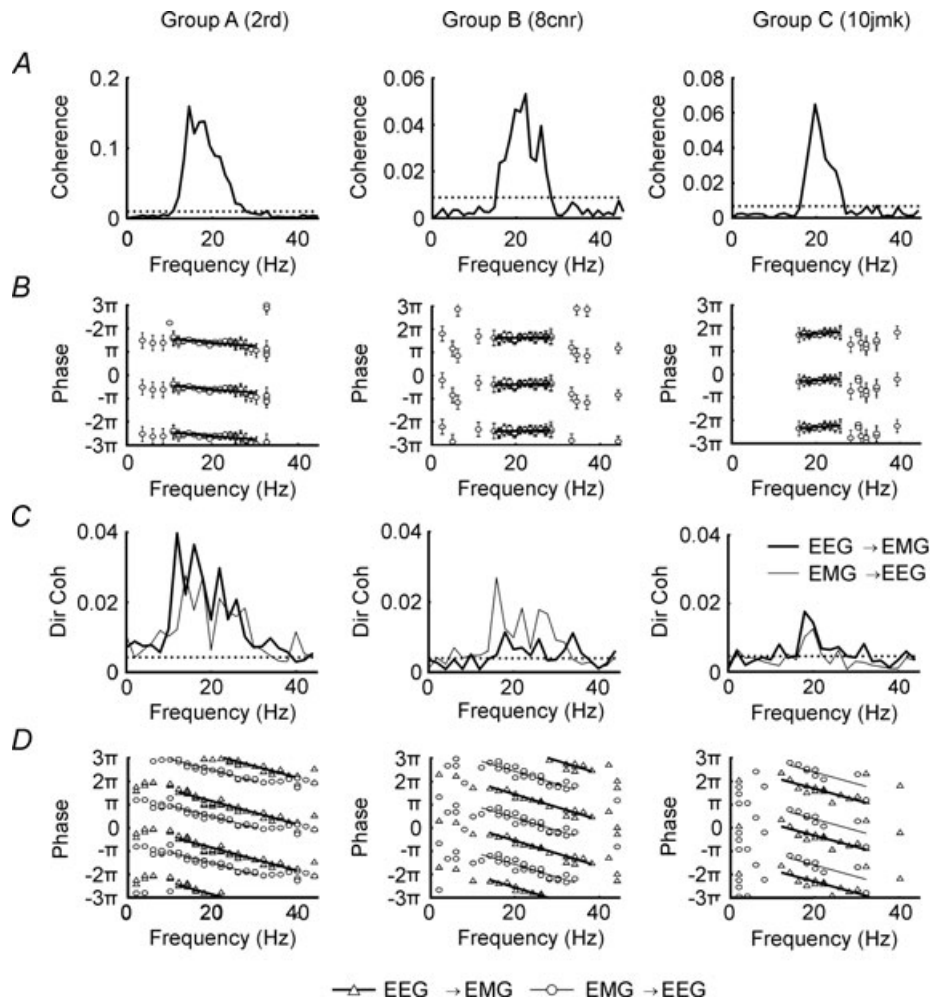


Figure 2. Coherence and directed coherence results for three subjects

A, coherence spectra for the three subjects. Spectra have been averaged across all three EEG–EMG combinations. Dotted line represents 95% significance level. B, phase spectra for subjects in A. Phase has been plotted three times to avoid wrap-around effects. Results from the three EEG–EMG combinations have been overlaid. Lines represent best-fit result from regression analysis over frequency range of interest. C, directed coherence (Dir Coh) spectra for three subjects in A. Results for EEG→EMG (thick line) and EMG→EEG (thin line) directed coherence, averaged across all three EEG–EMG combinations, have been overlaid. Dotted line represents 95% significance level. D, phase spectra from directed coherence analysis for subjects in A. Results for EEG→EMG (triangles) and EMG→EEG (circles) directions and for the three EEG–EMG combinations have been overlaid. Phase has been plotted three times to avoid wrap-around effects. Lines represent best-fit result from regression analysis over frequency range of interest.

consistently above the significance level (Fig. 2C). Despite this, significant linear phase–frequency relationships were found for both directions (Fig. 2D), with implied delays in the EEG→EMG direction of 26.6 ± 2.5 ms for 8cnr and 18.4 ± 1.9 ms for 10jmk. The corresponding EMG→EEG phase delays were similar, at 19.8 ± 4.5 ms and 31.0 ± 8.0 ms, respectively.

Population results

Figure 3 shows results averaged across all subjects after separating into the three groups described above. As previously reported (Riddle & Baker, 2005), coherence was larger for Group A than Group B. Coherence for

the novel Group C was larger than Group B but smaller than Group A in amplitude (Fig. 3A). Figure 3B presents the distribution of coherence phase delays. Average delays were -11.0 ± 1.8 ms for Group A (mean \pm SEM), and 15.9 ± 2.8 ms for Group C. Average Group B delays were -1.9 ± 2.5 ms, which was not significantly different from zero ($P > 0.05$, t test).

The average directed coherence spectra are shown in Fig. 3C. Group A had clear peaks around 20 Hz in both directions, whereas for Groups B and C directed coherence was greater in the EMG→EEG direction. For Group B, directed coherence lacked defined peaks, but was significantly different from zero over a range of frequencies. Despite the variability in the EEG→EMG directed coherence between the different groups, the

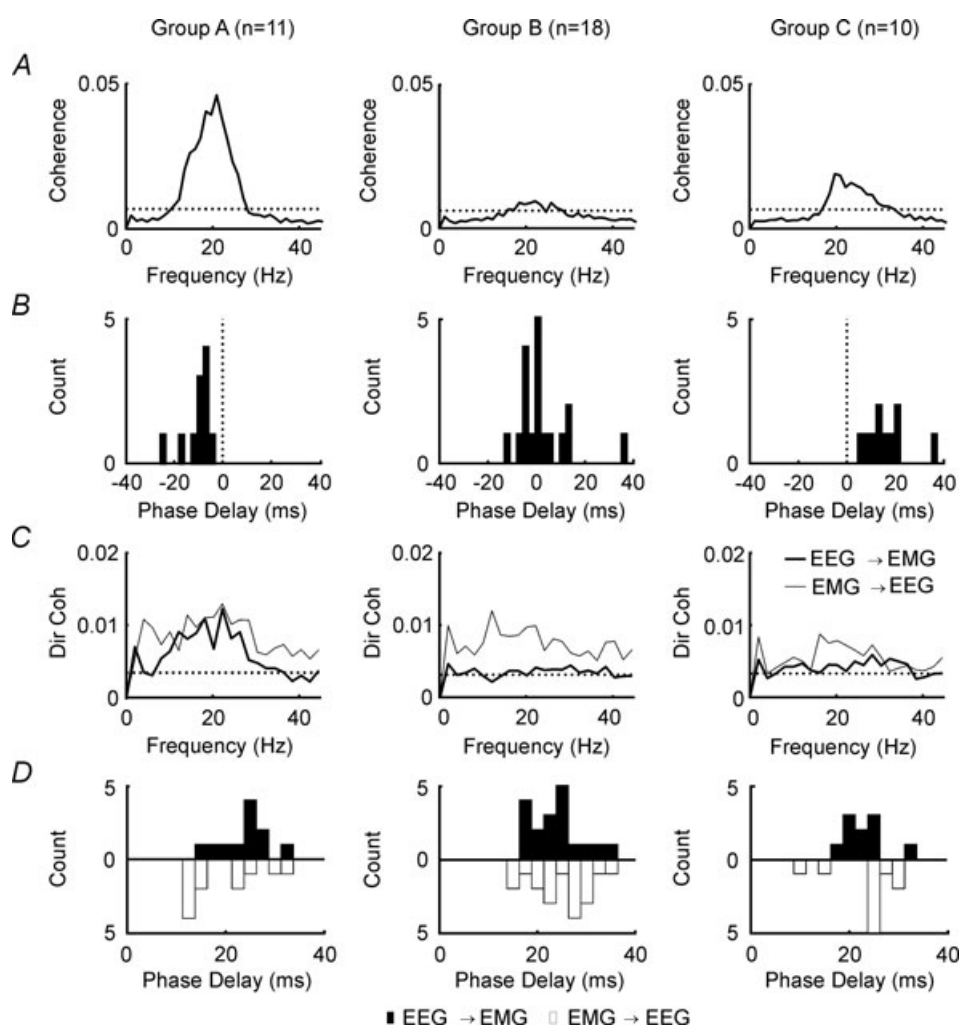


Figure 3. Average coherence and directed coherence results

A, coherence spectra for three groups, averaged over all subjects in that group and all three muscles. Dotted line represents 95% significance level. B, histograms of phase delays for each group. Dotted line shows zero phase delay. C, directed coherence (Dir Coh) spectra for each group, averaged across subjects and muscles. Results for EEG→EMG (thick line) and EMG→EEG (thin line) have been overlaid. Dotted line represents 95% significance level. D, histograms of phase delays from directed coherence analysis. EEG→EMG results shown on top (filled bars) with EMG→EEG results below (open bars).

phase delays for this direction seemed to follow the same distribution (Fig. 3D). In fact, the mean EEG→EMG phase delays were remarkably similar across groups: Group A, 23.4 ± 1.5 ms; Group B, 23.7 ± 1.3 ms; Group C, 22.5 ± 1.4 ms (mean \pm SEM). Although directed coherence was often higher in the EMG→EEG direction (Fig. 3C), the phase–frequency relationships were slightly more variable with a wider range of phase delays (Fig. 3D). The mean phase delays for the three groups were: Group A, 19.4 ± 2.2 ms; Group B, 24.7 ± 1.4 ms; Group C, 23.7 ± 2.1 ms.

Overall the mean phase delays were 23.3 ± 0.8 ms for the EEG→EMG direction and 23.0 ± 1.1 ms for the EMG→EEG direction. On average, men have larger bodies and hence greater motor conduction delays than women; this is accentuated because conduction velocities are slightly faster in women (Robinson *et al.* 1993). However, although there was a small difference between delays calculated from the EEG→EMG directed coherence phase according to the sex of the subject, this was not significant (22.8 ± 1.2 ms for female subjects *versus* 23.6 ± 1.1 ms for male subjects; Mann–Whitney *U* test, $P > 0.05$). The delays for the EMG→EEG directed coherence phase showed a small difference in the other direction (23.6 ± 1.5 ms for female subjects *versus* 22.9 ± 1.5 ms for male subjects; Mann–Whitney *U* test, $P > 0.05$).

It is possible that the different phase–frequency relationships were due to differences in task performance. We investigated this possibility by looking at the lever displacement traces from the task. Variability in displacement was assessed within a trial by taking the standard deviation of displacement during the hold period and then averaging across trials, and between trials by taking the average displacement during the hold period and then calculating the standard deviation across trials. No significant differences on either measure were seen between the three groups (Kruskal–Wallis test, $P > 0.05$). Reaction time was measured as the time it took for subjects to reach the target for the first hold period after the go cue (calculated separately for each trial and then averaged across trials). This also showed no significant differences between the three groups (Kruskal–Wallis test, $P > 0.05$).

Longitudinal study

Since we have used the same behavioural task in our laboratory over a number of years in different studies, we were fortunate in having some recordings from the same subject separated by long intervals. Results from one such subject who showed especially high corticomuscular coherence are illustrated in Fig. 4 from three recording sessions over a 2 year period. Over this time, the slope of the phase–frequency relationship varied from negative (-5.5 ± 4.2 ms; cortex leading muscle) to positive

(8.9 ± 5.9 ms; muscle leading cortex) and then to not significantly different from zero (-1.5 ± 8.1 ms), such that this subject would have been classified first in Group A, then Group C and finally Group B. As found across the population of subjects, coherence was larger when there was a negative phase–frequency regression slope (cortex leading muscle) than when the slope was positive or zero (Fig. 4A).

As with the standard coherence, directed coherence was higher in the first available recording, where there were clear peaks in both ascending (Fig. 4B) and descending directions (Fig. 4C). In later recordings the directed coherence was smaller and peaks less evident, although directed coherence remained above significance in both directions. Despite these variations, the delays calculated from the directed coherence phase frequency regression lines were fairly consistent in both directions (28.3 ms, 30.1 ms and 32.3 ms for the EEG→EMG direction and 33.3 ms, 30.7 ms and 32.9 ms for the EMG→EEG

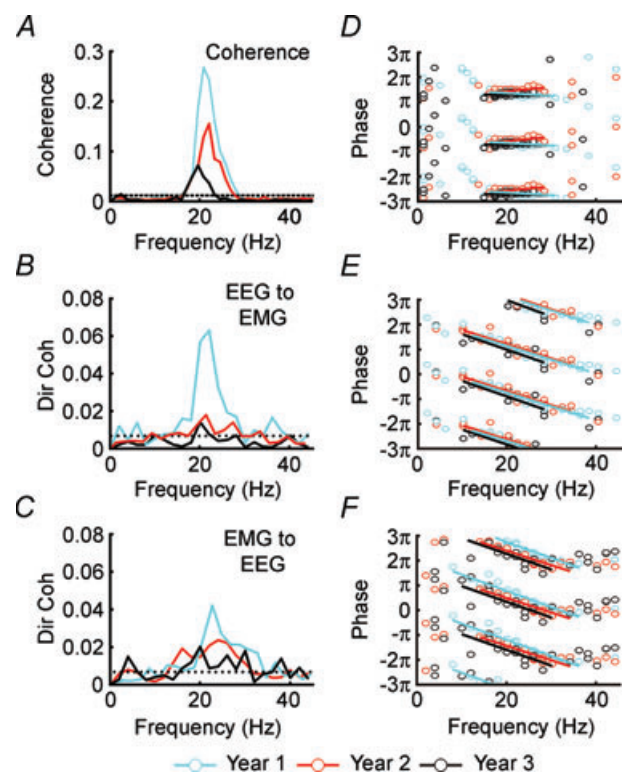


Figure 4. Longitudinal study of coherence and directed coherence in a single subject (snb)

A, coherence spectra for each experiment overlaid, averaged across the three muscles. Dotted line represents the largest significance level. B and C, as A for EEG→EMG directed coherence spectra and EMG→EEG directed coherence spectra, respectively. D, coherence phase spectra for each experiment overlaid. Phases from the three muscles have been overlaid and plotted three times to avoid wrap-around effects. E and F, as D for EEG→EMG directed coherence phase and EMG→EEG directed coherence phase, respectively.

direction). The phase values for the descending direction overlaid well (Fig. 4E) and had lower variation than the phase values for the ascending direction (Fig. 4F).

Effects of cooling the arm

Four Group A subjects, six Group B and three Group C subjects took part in the cooling study. The effects of cooling the arm and thereby slowing the peripheral nerve conduction times on coherence and directed coherence are shown in Fig. 5. The effect of cooling on coherence has been reported previously (Riddle & Baker, 2005). The averaged coherence and directed coherence plots are shown in Fig. 5A–C. The coherence spectra showed a small increase post-cooling across all frequencies (more noticeable either side of the 20 Hz peak). The EEG→EMG directed coherence showed a larger increase around the

20 Hz frequency range with cooling and the EMG→EEG directed coherence spectra showed little difference with cooling.

The phase spectra pre- and post-cooling are shown for a single representative individual (subject 2rd, Fig. 5D–F). For both directions in this subject the phase delays increased with cooling (from 24.6 ± 2.6 ms to 37.3 ± 2.8 ms for EEG→EMG and from 23.6 ± 3.6 ms to 40.7 ± 7.9 ms for EMG→EEG). Across all subjects, we compared the increase in phase delays for the EEG→EMG direction with the increase in peripheral motor conduction delays, measured from the F-wave evoked by electrical stimulation of the median nerve at the wrist. In our previous paper (Riddle & Baker, 2005), the increase in coherence phase delays was approximately double the increase in peripheral motor conduction times. If we consider only the descending direction, then we would expect that the increase in phase delays should be approximately equal to the increase in peripheral motor conduction times. The mean increase in conduction time was $4.9 \text{ ms} \pm 0.7 \text{ ms}$ compared to a mean increase in EEG→EMG phase delay of $6.5 \text{ ms} \pm 1.3 \text{ ms}$. The mean increase in EMG→EEG phase delay was slightly longer at $7.6 \pm 1.5 \text{ ms}$. A regression analysis (constrained to pass through the origin) between change in peripheral motor conduction time and change in phase delay produced a slope of 1.2 ± 0.5 for the EEG→EMG direction (Fig. 6A) and 1.3 ± 0.6 for the EMG→EEG direction (Fig. 6B).

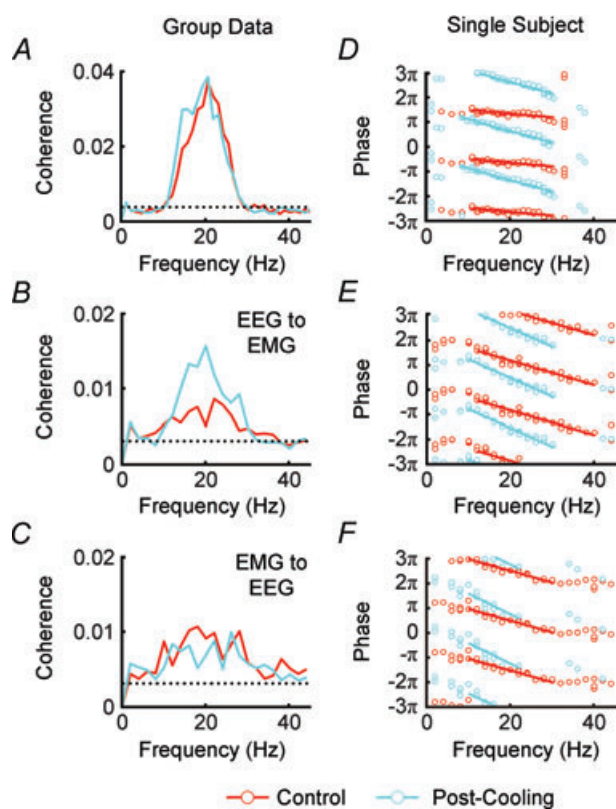


Figure 5. Effect of cooling on coherence and directed coherence

A, pre- and post-cooling coherence spectra averaged across 13 subjects. Dotted line shows 95% significance level. B, average pre- and post-cooling EEG→EMG directed coherence spectra. C, average pre- and post-cooling EMG→EEG directed coherence spectra. D, coherence phase spectra for single subject (2rd) pre- and post-cooling. Phase has been plotted three times to avoid wrap-around effects. Continuous lines represent best fit. E, pre- and post-cooling EEG→EMG directed coherence phase spectra for subject in D. F, pre- and post-cooling EMG→EEG directed coherence phase spectra subject in D.

Discussion

Bidirectional corticomuscular coherence

This study provides evidence that corticomuscular coherence in humans measures contributions from both ascending and descending pathways. This was originally suggested on the basis of the effects of drugs (Baker & Baker, 2003; Riddle *et al.* 2004) and also the changes in coherence phase seen following cooling the arm, which lengthens peripheral conduction times (Riddle & Baker, 2005). Grosse *et al.* (2003) also suggested a mixture of ascending and descending pathways based on finding phase delays that indicated muscle led cortex.

Corticomuscular coherence, and especially its phase, was previously shown to vary markedly between subjects (Riddle & Baker, 2005). Previous studies reported that phase was either linearly related to frequency with negative slope (indicating cortex leads muscle with a constant delay), or constant with frequency (Halliday *et al.* 1998; Mima *et al.* 2000). Here we found a third group of recordings, where phase was linearly related to frequency with positive slope suggesting that the muscle led the cortical recordings. This has also been seen previously for coherence between cortex and proximal upper limb muscles in patients with myoclonus (Grosse

et al. 2003). This inter-subject variability led us previously to suggest that in all cases coherence was probably measuring bidirectional influences (Riddle & Baker, 2005), with the relative strength of ascending and descending connections changing between different subjects.

The present findings appear to support this conclusion. All subject groups showed evidence of both EEG→EMG and EMG→EEG directed coherence above chance levels (Fig. 3). However, subjects with negative coherence phase–frequency regression slopes had approximately equal directed coherence in each direction, whereas subjects with either constant coherence phase or positive phase–frequency slopes had dominant directed coherence in the EMG→EEG direction.

It remains unclear why coherence should vary so much between subjects, all of whom efficiently performed this simple task. One possibility is that minor differences in structural anatomy cause a different projection of activity from pre- and post-central cortices onto the scalp surface, so that our single channel EEG emphasised sensory or motor elements of the brain's activity to different extents. However, we showed that the same subject could yield data consistent with each of the three Groups on different recording days (Fig. 4). Electrodes were placed accurately on the scalp relative to bony landmarks, so it is likely that the relationship of the recording sites to brain structure remained unchanged, even over the 2 year period examined. In addition, corticomuscular coherence is of similar amplitude from both pre- and post-central cortex using focal invasive recordings in monkeys (Witham *et al.* 2010); the directed coherence measures are likewise similar. Differences in the relative mixing of somatosensory and motor activity in surface EEG is thus unlikely to explain the inter-subject differences.

An alternative explanation is that subjects performed the task in subtly different ways, with a variable reliance on oscillatory feedback from muscles. It is known that sensory feedback from the hand is under descending control, which can effectively gate incoming information – for example, during voluntary movement (Chapman *et al.* 1987). Changes in sensory gating could lead to the observed differences in directed coherence between subjects. Additionally, it seems reasonable that even the same subject, approaching the task afresh after an interval of a year, might adopt a different strategy for motor performance with corresponding changes in the coherence pattern seen. Although there were no measureable differences in task performance (based on lever displacement traces), this does not rule out subtle differences in the strategy used.

The present findings in man differ markedly from those using invasive local field potential (LFP) recordings in monkey (Tsujimoto *et al.* 2009; Witham *et al.* 2010). Both of the previous monkey studies report that directed

coherence is dominant in the descending (cortex to muscle) direction, irrespective of whether recordings come from somatosensory or motor areas. By contrast, we found that in Group A subjects, directed coherence was similar in both directions; in Groups B and C, the ascending direction dominated. Again, this discrepancy may be explained by differences in the reliance on sensory feedback between monkeys and human subjects. In experiments on awake behaving animals the task is necessarily highly overtrained. In our laboratory, animals are often trained for a year, and will have performed many tens of thousands of trials of the task before data are ever recorded. By contrast, our human subjects typically familiarise themselves with the task for just a few trials before we commence recordings. This may promote a greater use of oscillatory sensory feedback compared to the situation in monkey.

Delay estimates

One advantage of the methods which we used for calculation of directed coherence is that it provides an

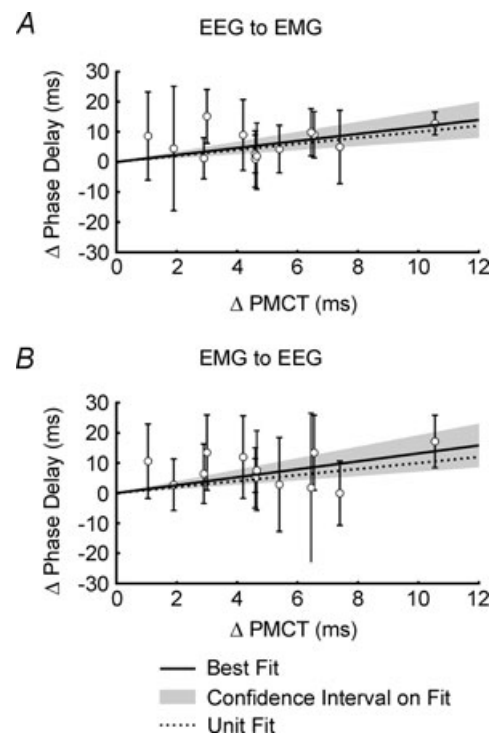


Figure 6. Comparison of change in phase delay and change in PMCT with cooling

A, comparison of change in PMCT and change in EEG→EMG phase delay for the 13 subjects shown in Fig. 5. Error bars show confidence limits on individual phase delay differences. Continuous line represents best fit, shaded area represents slope \pm confidence limits and dotted line shows unity slope. B, as A but for EMG→EEG phase delay.

accurate representation of how the directed coherence phase varies with frequency. This allows the slope of any linear relationship to be assessed, and the corresponding delay to be determined. In agreement with our previous work (Riddle & Baker, 2005), the delays which we measured from the standard coherence phase–frequency relationship were often smaller than the known conduction delays from cortex to muscle assessed by stimulation (Fig. 3B). By contrast, delays measured using directed coherence were often larger. Following arm cooling, the increases in delays estimated from directed coherence agreed well with the increases measured by nerve stimulation. By comparison, delays measured from coherence phase increased approximately twice as much as expected from the nerve stimulation results.

The modelling study of Williams & Baker (2009) described multiple features which can influence the delays estimated using corticomuscular coherence in a purely feedforward system (i.e. including only descending connections). These included extra delays caused by the motor unit action potential, the duration of the cortico-motoneuronal EPSP, and a phase advance (apparent negative delay) produced by motoneuron properties. Directed coherence should be similarly affected, except that it will yield correct directional estimates even in a circuit where both feedforward and feedback pathways exist (see Fig. 1; Witham *et al.* 2010). Williams & Baker (2009) estimated that the measured delay should be around 32 ms for human hand muscles, when forces are sufficiently high that motoneuron firing rates are dispersed across the pool. Most of the measurements of phase delay for the EEG→EMG direction in Fig. 3D lie between 20 and 40 ms, in reasonable agreement with the computational modelling.

In the EMG→EEG direction, accurate estimates of the conduction time from the periphery to somatosensory cortex are provided by the somatosensory evoked potential. This is recorded following electrical stimulation of a peripheral nerve, and comprises multiple peaks at different latencies. The earliest inflection, at ~20 ms (N20 component), probably reflects the initial somatosensory cortical processing associated with the stimulus (Allison *et al.* 1991; Baker *et al.* 2003a); later peaks may reflect activity in other areas (Gardner *et al.* 1984). Coherence phase measures should not be expected to relate to the earliest (onset) latencies measured with stimulation, but rather to something approximating the ‘mean’ latency, averaged over all components of the response – it is for this reason that for descending coherence the width of the motor unit action potential must be taken into account (Williams & Baker, 2009). The present estimates of phase delay in the ascending direction were often greater than 20 ms (Fig. 3D), presumably corresponding to an averaging over all components of the cortical response, rather than just the N20.

In LFP recordings from monkey (Witham *et al.* 2010), delays from the motor cortex to hand muscles estimated from directed coherence are around 62 ms; delays from somatosensory cortex are somewhat lower, at around 36 ms. Both figures are substantially longer than expected from the known corticospinal conduction delays in monkey, even given the factors which can prolong coherence delay measurements described above. It is not clear why measurements from small local neural populations should be longer than expected, whereas the present measurements from EEG agree broadly with the predictions of modelling. It may be that the higher spatial resolution of LFP accesses fluctuations in oscillations which are spatially heterogeneous, and which influence motoneurons via indirect pathways with longer conduction times. Examples of such pathways are slow corticospinal axons (Philips & Porter, 1977), the reticular formation and reticulospinal tract (Davidson & Buford, 2006; Davidson *et al.* 2007; Riddle *et al.* 2009), C3–C4 propriospinal interneurons (Alstermark *et al.* 1999; Isa *et al.* 2006) and segmental spinal interneurons (Yanai *et al.* 2007; Riddle & Baker, 2010). In that case, directed coherence delay estimates from LFP would represent delays averaged over all pathways. By contrast, the greater spatial averaging inherent in EEG might cause heterogeneous oscillations to cancel, leaving only globally coherent components. Different cortical sites might exert either excitatory or inhibitory actions via indirect pathways, such that no net effect of these routes to the motoneuron would be visible in the directed coherence. In that case, EEG→EMG coherence could relate mainly to direct cortico-motoneuron conduction over fast corticospinal fibres (as assumed in the computational modelling), whereas LFP→EMG coherence would additionally include contributions from indirect and slower pathways.

Functional considerations

This paper adds to the increasing body of evidence that corticomuscular coherence is not purely a motor phenomenon, but also has contributions from sensory systems. This may provide a clue to the function of beta band oscillations in the primate motor system. One suggestion is that oscillations act as a ‘test pulse’: by sending a known signal to muscle and measuring the resulting sensory reafference, the sensorimotor system may learn something of the state of the periphery (MacKay, 1997; Riddle & Baker, 2006; Baker, 2007). An alternative idea is that oscillations act to promote a stable motor state (Gilbertson *et al.* 2005). Reflex responses to peripheral feedback indicating a perturbation are enhanced during oscillatory epochs (Gilbertson *et al.* 2005), as is the N20 component of the somatosensory

evoked potential (Lalo *et al.* 2007). These changes in the response to externally generated input may reflect a different mode of sensory processing which integrates sensory reafference into the motor command to ensure maintenance of a stable output. Whilst these two hypotheses differently emphasise a sensory or motor function for oscillatory activity in motor control, both envisage a central role for sensory feedback. Our finding of a substantial feedback contribution to corticomuscular coherence in human subjects thus provides additional support to these concepts of the functional role of oscillatory activity in motor control.

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Author contributions

C.N.R., M.R.B. and S.N.B. contributed to all aspects of the study. C.L.W. analysed data and drafted the paper. Experiments were carried out in the Anatomy Department, Cambridge University. All authors approved the final version of the manuscript.

Acknowledgements

The authors would like to thank all the subjects who gave their time to this study. Funded by the Wellcome Trust.