

# Functional coupling of human cortical sensorimotor areas during bimanual skill acquisition

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## Summary

Bimanual co-ordination of skilled finger movements is a high-level capability of the human motor system and virtually always requires training. Little is known about the physiological processes underlying successful bimanual performance and skill acquisition. In the present study, we used task-related coherence (TRCoh) and task-related power (TRPow) analysis of multichannel surface EEG to investigate the functional coupling and regional activation of human sensorimotor regions during bimanual skill acquisition. We focused on changes in interhemispheric coupling associated with bimanual learning. TRCoh and TRPow were estimated during the fusion of two overlearned unimanual finger-tapping sequences into one novel bimanual sequence, before and after a 30-min training period in 18 normal volunteers. Control experiments included learning and repetition of complex and simple unimanual finger sequences. The

main finding was a significant increase in interhemispheric TRCoh selectively in the early learning stage ( $P < 0.0001$ ). Interhemispheric TRCoh was also present during the unimanual control tasks, but with lower magnitude, even if learning was involved. Training improved bimanual sequence performance (from  $58.3 \pm 24.1$  to  $83.7 \pm 15.3\%$  correct sequences). After training, interhemispheric (bimanual) TRCoh decreased again, thereby approaching levels similar to those in the unimanual controls. We propose that the initial increase in TRCoh reflects changes in interhemispheric communication that are specifically related to bimanual learning and may be relayed through the corpus callosum. The present data might also offer a neurophysiological explanation for the clinical observation that patients with lesions of the corpus callosum may show deficits in the acquisition of novel bimanual tasks but not necessarily in the execution of previously learned bimanual activities.

**Keywords:** bimanual movement; motor learning; EEG; coherence; mapping

**Abbreviations:** ANOVA = analysis of variance; SMA = supplementary motor area; TRCoh = task-related coherence; TRPow = task-related power

## Introduction

Bimanual co-ordination of skilled finger movements is an outstanding capability of the human motor system, and bimanual performance at a high level of skill, such as playing the piano, almost always requires training. Little is known about the neurophysiological processes and the neuroanatomical correlates of bimanual skill acquisition. It is likely that not only the activation of particular regions such as the supplementary motor area (SMA) and the lateral premotor cortex (Sadato *et al.*, 1997) but also the functional coupling between the premotor and sensorimotor areas of the two hemispheres is important for the precise timing and execution of bimanual movements. Lesion studies strongly suggest that interhemispheric exchange of premotor and

sensorimotor commands plays a major role in bimanual activities (Sperry, 1968; Leonard *et al.*, 1988; Geffen *et al.*, 1994). However, how interhemispheric interactions in the sensorimotor system may change as a function of bimanual skill acquisition is still completely enigmatic and has not been addressed in neurophysiological experiments in humans or non-human primates. The present study was designed to assess the functional coupling between brain regions during bimanual skill acquisition in humans, and focuses on learning-related changes of interhemispheric coupling in the sensorimotor system.

Inter-regional functional coupling can be assessed non-invasively with task-related coherence (TRCoh) analysis of

oscillatory activities in different brain regions. Changes in inter-regional correlated oscillations in animals can reflect behavioural measures (Engel *et al.*, 1991; Murthy and Fetz, 1992; Sanes and Donoghue, 1993; Singer, 1993, 1994; Bressler, 1995, 1996; deCharms and Merzenich, 1996; Laurent *et al.*, 1996; Roelfsema *et al.*, 1997). This technique has also proved to be useful when applied to surface EEG data (Rappelsberger *et al.*, 1994; Andrew and Pfurtscheller, 1995, 1996b; Thatcher, 1995; Brazdil *et al.*, 1997; Classen *et al.*, 1998; Gerloff *et al.*, 1998; Manganotti *et al.*, 1998; Rappelsberger and Petsche, 1988), and is thus available as an instrument for non-invasive studies in humans. Classen *et al.* (1998) demonstrated significant TRCoh between the visual and motor cortex in a visuomotor tracking task; Gerloff *et al.* (1998) identified different amounts of network-like activation of human cortical motor areas during internal and external pacing of movement. In both studies, changes in the beta band (13–30 Hz) were most sensitive to motor task-related modulation.

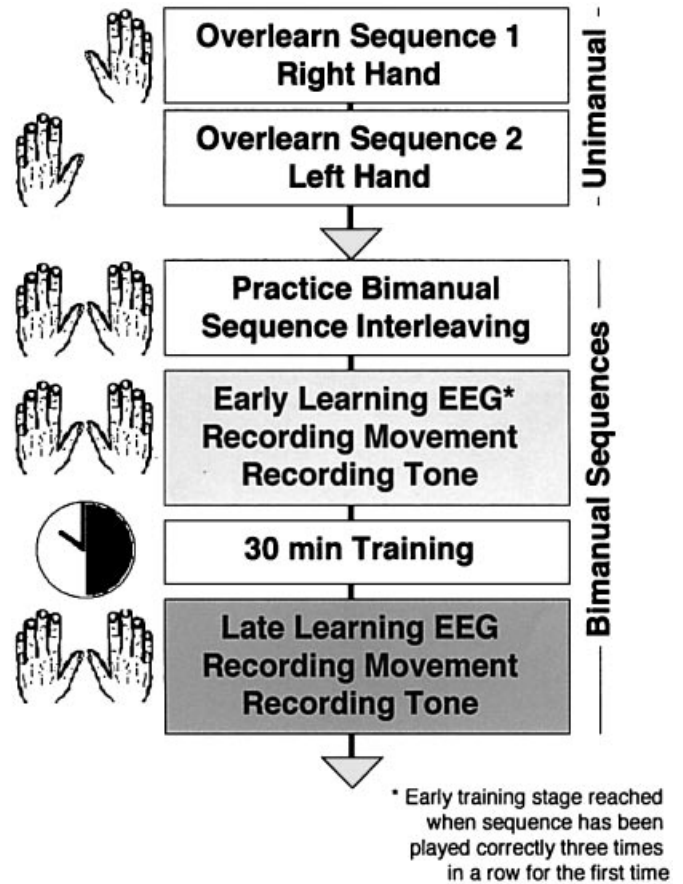
EEG coherence analysis is complemented by the analysis of regional changes in oscillatory brain activity known as event-related desynchronization (Salmelin and Hari, 1994; Toro *et al.*, 1994a, b; Stancak and Pfurtscheller, 1995, 1996; Zhuang *et al.*, 1997; Manganotti *et al.*, 1998; Pfurtscheller, 1988). We now believe it is best to refer to this phenomenon as negative ‘task-related power change’ (TRPow) since the term ‘desynchronization’ has been used with different meanings in reference to regional spectral power changes and inter-regional coherence (Steriade and Amzica, 1996; Steriade *et al.*, 1996a, b).

The present study focused on the main question of whether specific changes of interhemispheric functional coupling could be a basis of bimanual skill acquisition. To address this question, TRCoh and TRPow were estimated during the fusion of two overlearned unimanual finger-tapping sequences into one novel bimanual sequence, and the results before and after a 30-min training period were compared in 18 normal subjects. Control experiments included learning and repetition of complex and simple unimanual finger sequences.

## Method

### Subjects

We studied 18 normal subjects (10 men and 8 women) whose mean age was  $40.2 \pm 5.8$  (SD) years. All subjects were right-handed according to the Edinburgh handedness inventory (Oldfield, 1971). The protocol was approved by the National Institutes of Health, NINDS Review Board, and all subjects gave their written informed consent for the study. In the bimanual paradigm and the simple unimanual repetition task, 13 subjects were tested. Four subjects had to be excluded because of artefacts in the EEG recordings or insufficient task performance. Eight subjects participated in the unimanual sequence learning control paradigm. Three of these had previously participated in the bimanual experiment.



**Fig. 1** Procedure flow chart showing unimanual and bimanual practise and training blocks.

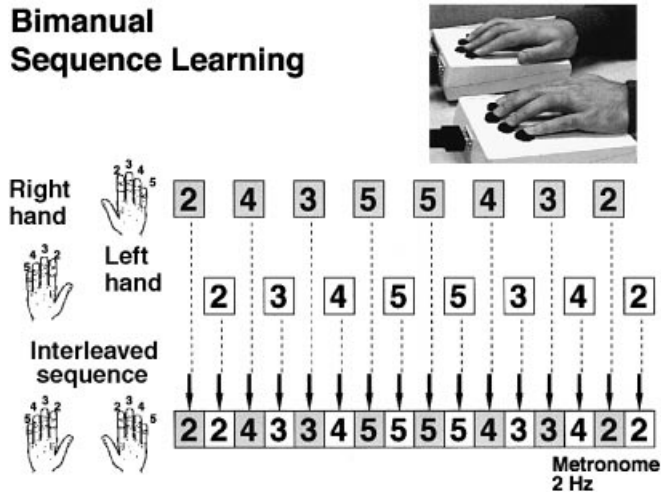
### Experimental design

Subjects were seated comfortably in a chair with both elbows and both wrists resting on a table with supportive cushions. The hands were positioned palm-down on a keyboard so that all fingers except the thumb could be moved freely to press one specific key each. Subjects performed repetitive, brisk flexions of fingers II–V followed by brief elevations. The moving hands were concealed under a small adjustable board in order to prevent visual feedback.

In preparation for the main task, subjects had to overlearn one simple short keypress sequence with each hand (Fig. 1). A sequence was considered overlearned when it could be performed 10 times in a row without errors. The right hand-sequence and the left hand-sequence each consisted of eight keypresses and they were executed following the 1-Hz beat of a metronome.

In the main task, subjects had to combine the two overlearned unimanual motor sequences into a single bimanual sequence by interleaving right and left finger movements in an alternating fashion (asynchronous bimanual movements). The resulting sequence consisted of 16 keypresses, played at a frequency of 2 Hz (Fig. 2). The start of each sequence was self-initiated by the subjects.

Similarly to playing the piano, the necessary motor skill of pressing a key was simple. The task difficulty resulted from



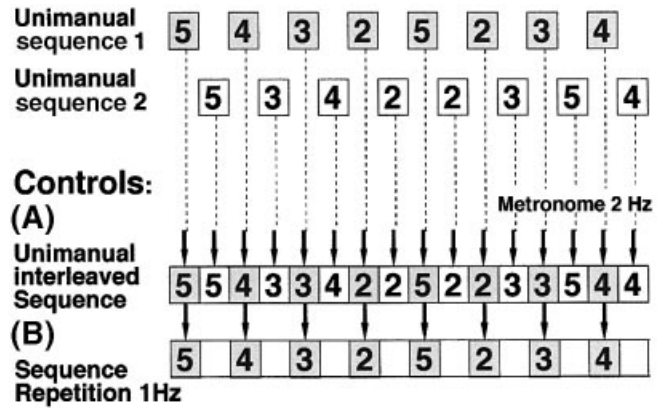
**Fig. 2** Bimanual sequence learning. The experimental setup is shown in the photograph. The two unimanual sequences and their fusion into the interleaved bimanual sequence are shown. Numbers indicate fingers (2 = index, 3 = middle, 4 = ring, 5 = 5th finger). Arrows indicate metronome beats.

the required bimanual co-ordination and memory retrieval at a required speed. Subjects were corrected on-line by the investigator during the initial phase of interlacing the activity of both hands until they were able to play the sequence correctly at least once three times in a row. We classified the learning stage at this point as ‘early learning’ and recorded keypresses, EEG and EMG during a series of complete sequences (average  $13 \pm 3$  sequences, corresponding to  $208 \pm 48$  keypresses) (movement). Each ‘movement’ session was followed by a rest condition during which the subjects listened to the metronome without moving (tone). A second movement session was recorded after a 30-min training period, during which subjects practised in order to improve the accuracy of the sequence and the precision of the timing. This stage was termed ‘late learning’. For all conditions, subjects sat comfortably in a dimly lit room, looked at a stationary fixation point to prevent eye movements and were instructed to avoid eye-blinks, swallowing or any movement other than the required finger movements.

## Control experiments

### Control experiment 1

For each subject, one of the original, short, unimanual, overlearned sequences was randomly selected, and TRCoh and TRPow were determined before and after the (bimanual) training period of 30 min. The purpose of this control was to detect potential non-specific effects of repeated sequence execution within an experimental session on the performance of any given sequence, irrespective of being unimanual or bimanual. It was called the ‘unimanual sequence repetition’ paradigm.



**Fig. 3** Unimanual sequence learning controls. (A) Unimanual interleaved sequence. Other than during the bimanual task, both the original and the interleaved sequence are played with the same hand. (B) Pure sequence repetition of an original unimanual sequence does not involve any kind of new co-ordination task during the recording.

### Control experiment 2

This was the main control experiment. Subjects were asked to interleave two overlearned unimanual sequences (8 keypresses, 1 Hz movement rate) into one longer (16 keypresses) and faster (2 Hz) but nevertheless unimanual sequence (Fig.3). This paradigm corresponded to the bimanual learning experiment in all details, except that the combined (‘interleaved’) sequence had to be performed with one hand only. In this control experiment, right and left hands were tested separately, with novel sequences of similar difficulty. Mirror-like symmetrical key presses were avoided, and the order of testing the right and left hand was randomized. This was called the ‘unimanual sequence learning’ paradigm. Comparing the results of the unimanual sequence learning and the bimanual experiment would reveal effects that were exclusively due to bimanuality.

### Finger sequences

In the bimanual experiment, the sequence for the right hand was R2–R4–R3–R5–R5–R4–R3–R2 and that for the left hand was L2–L3–L4–L5–L5–L3–L4–L2. The original finger sequences were learned by heart following visual instruction by numbers representing key-presses (2 = index finger, 3 = middle finger, 4 = ring finger, 5 = fifth finger). The bimanual target sequence, which had to be generated through interleaving, was R2–L2–R4–L3–R3–L4–R5–L5–R5–L5–R4–L3–R3–L4–R2–L2.

The unimanual learning sequences were selected to be difficult enough to require a similar amount of training as the bimanual sequences. After random selection of the starting hand, those starting with the right hand combined the two original sequences into R5–R5–R4–R3–R3–R4–R2–R2–R5–R2–R2–R3–R3–R5–R4–R4, followed by the left-hand experiment with the task sequence L2–L5–L4–L4–L3–L3–L5–L2–L5–L3–L4–L4–L2–L2–L3–L5. All other subjects

started with the left hand playing the mirror sequence L2–L2–L3–L4–L4–L3–L5–L5–L2–L5–L5–L4–L4–L2–L3–L3 to perform equally difficult tasks. The target sequence for the second (right) hand in the experiment was R5–R2–R3–R3–R4–R4–R2–R5–R2–R4–R3–R3–R5–R5–R4–R2.

In all paradigms, mirror-like symmetrical key sequences were avoided because there is evidence that asymmetrical or parallel bimanual movements are more challenging (Brinkman, 1984; Chan and Ross, 1988; Sadato *et al.*, 1997).

In all experiments we evaluated the brain activation in a time window of 256 ms before and after the keypresses. The unimanual control paradigms were tested for both sides, and all further processing and comparison with bimanual data was done on pooled data from both hands.

### Data acquisition

Continuous EEG was recorded from 28 (silver–silver chloride) surface electrodes, mounted in a cap (Electro-Cap International, Eaton, Ohio, USA). Impedances were kept below 5 k $\Omega$ . Data were sampled at 250 Hz, the upper cutoff was 50 Hz and the time constant was set to direct current (DC amplifiers and software by NeuroScan, Herndon, Va., USA). Linked earlobe electrodes served as the reference. There have been contradictory suggestions as to which reference is ideal for coherence measurements (Fein *et al.*, 1988; Rappelsberger *et al.*, 1989; Andrew *et al.*, 1996a; Nunez *et al.*, 1997). Linked earlobe and common-average references may introduce a common signal to all other channels, which is problematic if the reference signal is contaminated by task-related activity. None of our areas of interest was located closer than  $\sim 7$  cm to the reference electrodes. Therefore, in our paradigm the linked earlobe reference was extremely unlikely to pick up task-related activity. The influence of a common reference could be eliminated by computing reference-free derivations (Hjorth, 1975; Andrew *et al.*, 1996a). However, these derivations tend to underestimate distributed cortical sources with largely radial generators, which can be a disadvantage for detecting activation of mesial and lateral premotor areas. Furthermore, and most importantly, we minimized signals common to activation and rest conditions by using a subtractive approach to determine task-related coherence and power changes (see below for a detailed description).

Two monopolar EMG channels were recorded from surface electrodes positioned over the right and left forearm flexors (flexor digitorum superficialis and profundus), with each pair of electrodes located  $\sim 15$  cm apart (distal tendon reference). The high-pass filter for EMG was set to 30 Hz. The EMG was recorded from corresponding positions of both forearms to control for mirror movements. Metronome beats (1 kHz, 130 dB at speaker level, 33.33 ms duration) at a constant rate of 2 Hz externally paced the subjects' keypresses.

### Digitization and MRI

In one subject, we digitized the positions of the cap-mounted electrodes with respect to the anatomical landmarks of the

head and coregistered them with the individual MRI, in order to obtain additional information on the approximate positions of the 28 electrodes relative to the underlying cerebral cortex. For digitization of the electrode positions and anatomical landmarks (nasion, left and right preauricular points), a magnetic field digitizer (Polhemus, Colchester, Vt., USA) was used. The 3D-MRI data were obtained from a 1.5 T magnetic resonance imager (General Electric, Milwaukee, Wis., USA; UNIX software 5.5). A fast spoiler gradient echo pulse sequence was applied, and 124 contiguous slices with a thickness of 1.5 mm and a pixel size of 0.974 mm were obtained (repetition time, 300 ms; echo time, 2.1 ms; flip angle, 20 $^{\circ}$ ; field of view, 24 cm; matrix, 256  $\times$  256; resolution, 16 bits). The MRI was read into the Curry software (Philips, Hamburg, Germany) for coregistration with the electrode positions.

Analysis of the anterior and posterior commissure and their orthogonal (vertical) projections to the cortex revealed that electrode FCz was located over the mesial frontocentral cortex including the region of the SMA, Cz slightly anterior to the mesial end of the central sulcus, and C3/4 over the lateral precentral and postcentral gyri. This was consistent with previous analyses of the relationship between electrodes in the 10/20 system and the underlying cortical anatomy (Steinmetz *et al.*, 1989).

### Data analysis

The EEG data were analysed with two approaches in the frequency domain: (i) task-related coherence (TRCoh) and (ii) task-related power (TRPow).

For both analysis techniques, EEG signals were digitally filtered off-line (1–50 Hz; slope 24 dB/octave). Each sequence period was segmented into non-overlapping epochs of 512 ms (allowing a frequency resolution of  $\sim 2.0$  Hz). After removal of slow drifts by linear trend correction ('linear detrend' module of the Neuroscan Software, NeuroScan, Herndon, Va., USA) and baseline correction of the single sweeps, a threshold rejection algorithm was applied to the EEG channels (entire sweep length) to eliminate all trials contaminated by gross eye movements, head movements or electrode artefacts. The remaining sweeps were inspected visually to control for minor artefacts that might have escaped the thresholds used. This method has been fully described in an earlier publication (Gerloff *et al.*, 1998). Approximately 160 artefact-free epochs of tone and 160 artefact-free epochs of movement per subject were obtained for each task. Each data segment of 512 ms was Hamming-windowed to reduce spectral leakage.

For the analysis of TRCoh and TRPow, a discrete Fourier transform was computed for each 512-ms epoch and all electrodes. Spectral power and coherence were calculated in two frequency bands: alpha (8–12.9 Hz) and low beta (13–20.9 Hz). Both frequency ranges have proved valuable in recent studies on coherence during finger movements (Classen *et al.*, 1998; Gerloff *et al.*, 1998, Manganotti *et al.*, 1998).

The TRPow values were also calculated for each frequency bin  $f_j$  (bin width 1.96 Hz).

### Task-related coherence

TRCoh was calculated according to the following equation, implemented in commercial software (NeuroScan):

$$\text{Coh}_{xy}(\lambda) = |R_{xy}(\lambda)|^2 = \frac{|f_{xy}(\lambda)|^2}{f_{xx}(\lambda)f_{yy}(\lambda)} \quad (1)$$

Equation 1 is the extension of Pearson's correlation coefficient to complex number pairs (Papoulis, 1984; Bronstein and Semendjajew, 1987). In this equation,  $f$  denotes the spectral estimate of two EEG signals  $x$  and  $y$  for a given frequency bin ( $\lambda$ ). The numerator contains the cross-spectrum for  $x$  and  $y$  ( $f_{xy}$ ), the denominator the respective autospectra for  $x$  ( $f_{xx}$ ) and  $y$  ( $f_{yy}$ ). For each frequency the coherence value ( $\text{Coh}_{xy}$ ) is obtained by squaring the magnitude of the complex correlation coefficient  $R$ , and is a real number between 0 and 1. Instead of modelling raw coherence estimates in the statistical analysis, we used transformed estimates,  $\text{atanh}(\text{Coh}_{xy})$ , where  $\text{atanh}$  is the inverse hyperbolic tangent. The reason for the transformation was that raw coherence estimates have non-constant variance (Brockwell and Davis, 1991; Halliday *et al.*, 1995), since coherence is restricted to be  $\leq 1$ . The transformed coherences have approximately constant variance. Although the transformed coherence is slightly less easily interpretable than raw coherence, it is more suitable for the analyses of variances that we use below. The transformation is nearly linear when coherence is less than  $\sim 0.6$ , so it has little effect on the interpretation or statistical analysis in this range.

In order to separate the task-related coherence ( $\text{TRCoh}_{xy}$ ) from background coherence levels in each subject and electrode pair, we subtracted the transformed coherence in the resting state ( $\text{Coh}_{xy,\text{tone}}$ ) from transformed coherence in the active state ( $\text{Coh}_{xy,\text{move}}$ ):

$$\text{TR}[\text{atanh Coh}_{xy}] = \text{atanh Coh}_{xy,\text{move}} - \text{atanh Coh}_{xy,\text{tone}} \quad (2)$$

TRCoh magnitude increments were expressed as positive values, and decrements were expressed as negative values. Coherence increments or decrements between baseline and movement conditions for each pair of electrodes were displayed as colour-coded 'link' plots, which permitted the inspection of the magnitude and spatial patterns of TRCoh. Link plots were processed for the original TRCoh before normalization for statistical accuracy. The subtractive approach also eliminates the bias in the absolute coherence inflation introduced by the reference electrodes. To average the frequency bins we used the concept of pooled coherence as described by Amjad *et al.* (1997). For all subjects, electrode pairs and conditions, the number of frequency bins pooled was equal.

### Task-related power

For TRPow analysis, EEG signals were filtered, segmented, trend- and baseline-corrected, inspected for artefacts, Hamming-windowed and Fourier-transformed as described for TRCoh. As with TRCoh, we chose to model a transformed version of power, in this case  $\log(\text{Pow}_x)$ . The reason for the transformation was that raw power estimates are more variable at higher power levels, while  $\log(\text{Pow}_x)$  has approximately constant variance at all power levels (Brockwell and Davis, 1991; Fuller, 1996). These claims are theoretically true, and we also observed them to be true in our power estimates.

For statistical evaluation, task-related relative power at electrode  $x$  ( $\text{TRPow}_x$ ) was obtained by subtracting the transformed ( $\log$ ) power at rest ( $\text{Pow}_{x,\text{tone}}$ ) from transformed power in the active state ( $\text{Pow}_{x,\text{move}}$ ):

$$\text{TR}[\log \text{Pow}_x] = \log(\text{Pow}_{x,\text{move}}) - \log(\text{Pow}_{x,\text{tone}}) \quad (3)$$

In general, TRPow decreases (activation) were expressed as negative values, and TRPow increases were expressed as positive values. Use of a subtractive approach on log-transformed power values corresponds to the division of untransformed data. Thus, equation 3 preserves the relative approach of contrasting activation and rest conditions, but shifts the strictly subtractive technique towards a proportional one. Since other algorithms that include division of untransformed power data have previously yielded valid results (Pfurtscheller and Berghold, 1989; Leocani *et al.*, 1997), this effect of the log transformation was considered acceptable. The band-averaged power was calculated as the average of the transformed power for the discrete frequencies within one frequency band. Topographical power maps were constructed using a linear four-nearest neighbours interpolation (NeuroScan). For mapping, the untransformed TRPow values were used.

For time-course analysis of the TRPow changes seen in the main experiment (bimanual task), artefact-free EEG epochs were bandpass-filtered for alpha (8–12.9 Hz) and beta (13–20.9 Hz) bands (filter slope, 24 dB/octave), rectified and time-averaged (Leocani *et al.*, 1997). For baseline correction, a constant baseline power value was obtained for each electrode from the corresponding tone condition and subtracted. The time course was evaluated in 32 ms time windows, from 256 ms before to 256 ms after keypress onset.

### Statistical analysis

We used a factorial analysis of variance (ANOVA) design to assess the significance of TRPow and TRCoh differences between the different conditions and learning stages. TRCoh and TRPow were analysed separately in the alpha (8–12.9 Hz) and low beta (13–20.9 Hz) bands.

We defined electrodes of interest and the resulting electrode pairs of interest, similarly to the region-of-interest approach that has been used in neuroimaging techniques such as PET, MRI and SPECT (single photon emission tomography)

(Rascoll *et al.*, 1993, 1994; Shibasaki *et al.*, 1993). The electrodes of interest were chosen on the basis of prior anatomical and physiological knowledge. Included were electrodes known to overlie approximately the lateral premotor cortex and primary sensorimotor cortex of the left and right hemispheres (left: FC3, C3, CP3; right: FC4, C4, CP4) and the mesial frontocentral cortex, which includes the SMA (Fz, FCz, Cz) (Homan *et al.*, 1987; Steinmetz *et al.*, 1989; Gerloff *et al.*, 1996a). The electrode pairs of interest consisted of all possible pairwise combinations between the electrodes of interest.

Additionally, to test in a hypothesis-free fashion which electrodes of interest and electrode pairs of interest samples contributed substantially to the variance introduced by our experimental design, we performed a principal component analysis. We entered the coherence values for all conditions (movement 1, tone 1, movement 2, tone 2; 1 = before training, 2 = after training) and determined eigenvalues for each main component (three components for four conditions) and loading factors for each electrode pair. The loading factors were ranked and plotted as a function of electrode pair, and the cutoff point was defined and visually determined as the first prominent change in slope when starting from the maximum value. This procedure reduced the number of electrode pairs under consideration from 378 to 22 (alpha) and 28 (low beta).

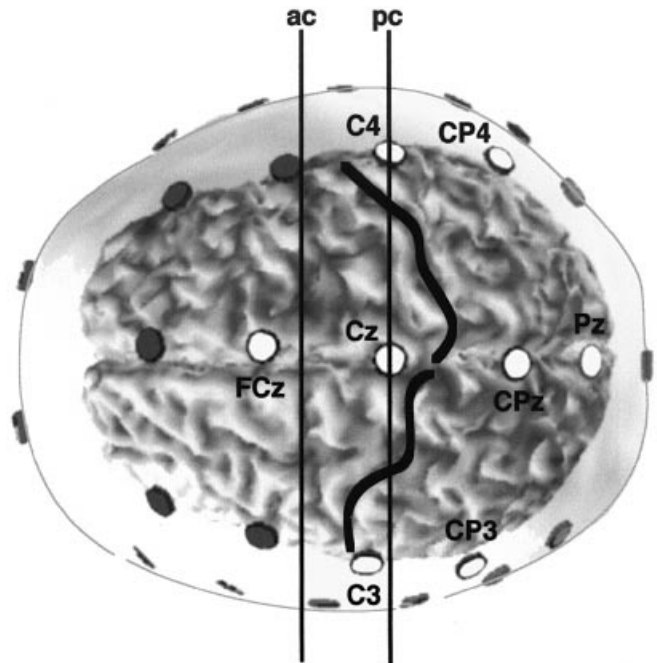
In the present series of experiments, we had no *a priori* hypothesis for task-related decoupling of different brain regions (cf. Classen *et al.*, 1998). Therefore, pairs with negative TRCoh values were not considered. To further reduce the risk of false positives, only electrodes with at least two links to other electrodes were considered potential nodes of the coherence network that might be differentially active during the various conditions tested (Fig. 4).

## Results

### *Regions of interest and electrode pairs of interest*

The principal component analysis identified electrodes and electrode pairs that were part of but not completely identical with our *a priori* regions of interest. Therefore, the electrodes of interest and electrode pairs of interest were adjusted for further analysis according to the principal component analysis results.

The principal component analysis pointed to a significant contribution of C3 and CP3, C4 and CP4, but not FC3 and FC4 in the present paradigm. Thus, the electrodes of interest overlying approximately the primary sensorimotor cortex of the left and right hemispheres were redefined as left central (C3, CP3) and right central (C4, CP4), with only two electrodes each. Accordingly, the electrodes of interest in the anterior midline overlying the region of the SMA were redefined as mesial frontocentral, with the electrodes FCz and Cz. An additional region of interest was determined on



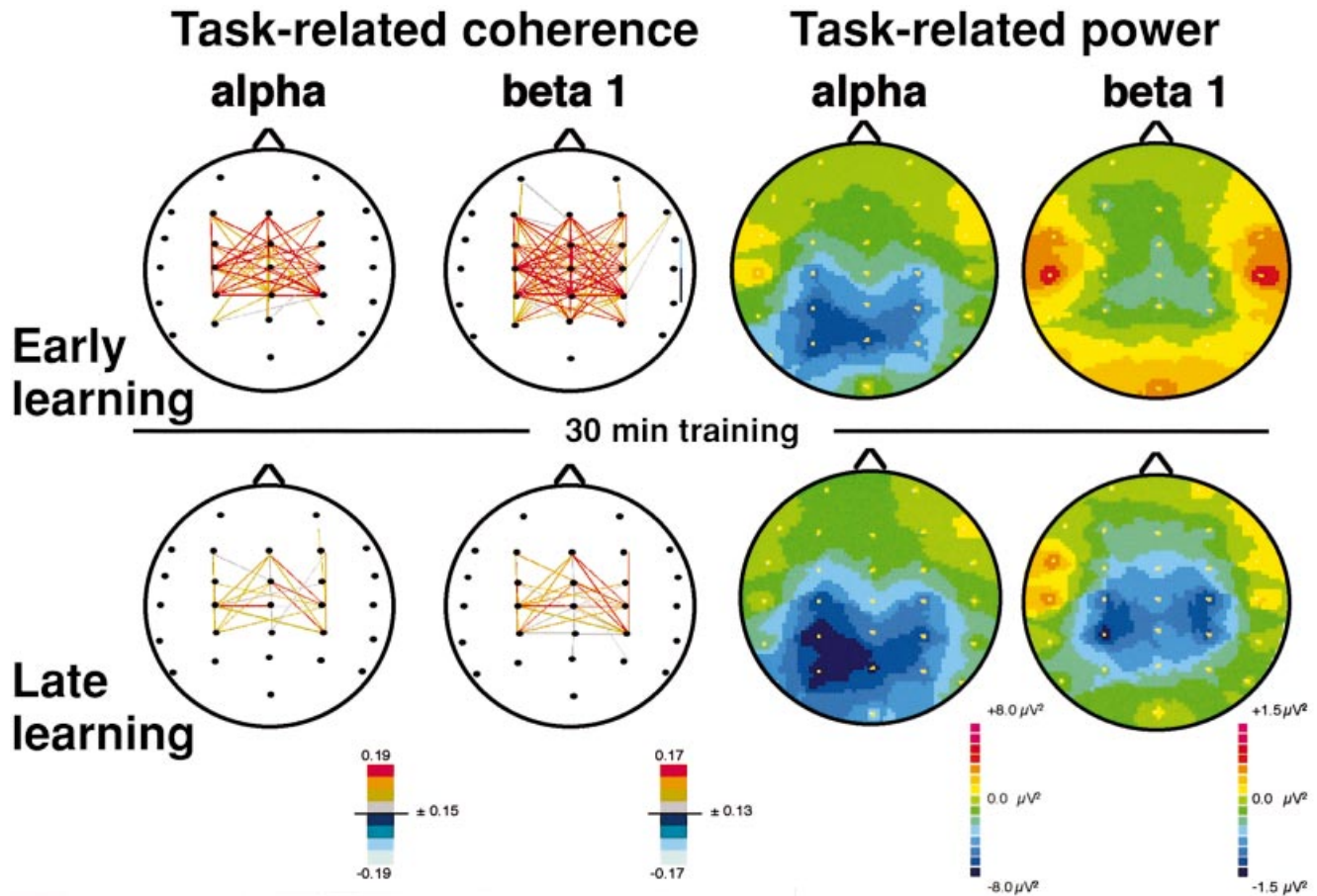
**Fig. 4** Position of electrodes of interest in one subject in relation to the cortex as seen in MRI. The anterior and posterior commissure and their orthogonal (vertical) projections (ac, pc) to the cortex revealed that electrode FCz was located over the mesial frontocentral cortex, including the region of the SMA and Cz slightly anterior to the central sulcus (marked).

the basis of the principal component analysis in the posterior midline and was termed mesial parieto-occipital (CPz, Pz). This part of the cortex conceivably includes the area of the precuneus (Homan *et al.*, 1987; Steinmetz *et al.*, 1989; Hoffman and Strick, 1995).

For TRPow analysis, these four regions (each consisting of two electrodes of interest) were entered separately into the ANOVA (factor region). For TRCoh analysis, the total number of links between the electrodes of interest was 16 (16 electrode pairs of interest), which were grouped into six major connections: left central to right central, left central to mesial frontocentral, right central to mesial frontocentral, left central to mesial parietal, right central to mesial parietal and mesial frontocentral to midparietal. The six connections were entered separately into the ANOVA (factor connection).

### *Movement-related time course of regional activation*

The pattern of cortical activation associated with bimanual movements (TRPow<sub>α</sub> and TRPow<sub>β1</sub>) largely resembled a steady state for the period from 256 ms before to 256 ms after keypress onset, both before and after training. The absence of phasic changes in the millisecond range is probably related to the relatively long time constants of spectral power changes in the alpha and beta bands compared with time-averaged evoked potentials (Pfurtscheller and Berghold, 1989; Leocani *et al.*, 1997).



**Fig. 5** Bimanual sequence learning. Execution- and training-related changes in TRCoh link-plots (left) and TRPow maps (right) during bimanual sequence playing before (upper panel) and after (lower panel) training. Interhemispheric TRCoh decreased significantly during training in both the alpha and the lower beta band (beta 1). TRPow decreased further during training.

### Execution of bimanual sequences

#### TRPow

The execution of bimanual finger sequences was associated with bilateral TRPow decreases in the central region (electrodes C3/4, CP3/4, P3/4, CPz, Pz) in the alpha and low beta bands, and, more pronounced in the low beta band, over the mesial frontocentral cortex (electrodes FCz, Cz) (Fig. 5). Inspection of 2-Hz frequency bins indicated that, as a rule, TRPow changes were broad-band changes. To account for this, all statistical analyses refer to relatively wide frequency ranges (alpha, 8–12.9 Hz; low beta, 13–20.9 Hz). The movement-related TRPow decreases in the regions of interest were significantly different from the tone controls (ANOVA plus contrast,  $F_{\alpha} = 24.91$ ,  $P = 0.0001$ ;  $F_{\beta} = 8.12$ ,  $P = 0.0005$ ).

#### TRCoh

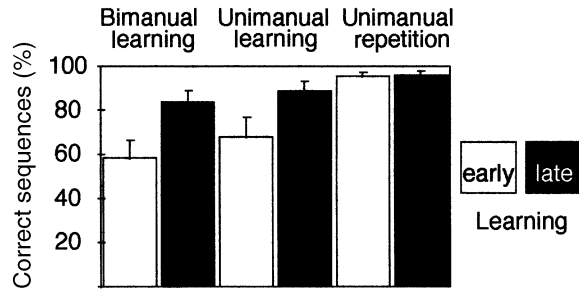
The execution of bimanual finger sequences was associated with TRCoh increases in the alpha and low beta bands. In the alpha band, the electrode pairs with the largest TRCoh increases were confined to the central region, approximately

spanning a quadrangle from F3 to F4 to CP3 and CP4 (Fig. 5). The peak TRCoh values occurred between the right and the left lateral central regions interhemispherically and from there to the mesial frontocentral area. In general, the TRCoh patterns were symmetrically distributed. Within each hemisphere, functional links between CP3/4, C3/4, FC3/4 and F3/4 were most prominent. Links between the central sensorimotor areas and the mesial and posterior parietal cortex were sparse (Fig. 5). In the low beta band, the highest TRCoh values occurred in similar electrode pairs as in the alpha band, again linking both lateral central areas with each other and the mesial frontocentral cortex.

### Learning of bimanual sequences

#### Task performance

As a result of training, bimanual sequence performance improved from a mean of correctness of  $58.3 \pm 24.1\%$  (SD) to  $83.7 \pm 15.3\%$ . This improvement occurred only in the sequences which were specifically practised during the training period and not in the (unimanual control) sequences,



**Fig. 6** Behavioural data showing the training-related increase in the percentage of correct sequences in both of the learning paradigms but not in the repetition paradigm. Error bars indicate 1 standard error.

which were simply repeated in the beginning and at the end of the experimental session (control experiment 1).

### TRPow

TRPow after training showed greater decreases in the lower beta band in all regions of interest (ANOVA,  $F = 9.02$ ,  $P = 0.003$ ). In the alpha band there was a similar trend (ANOVA,  $F = 3.27$ ,  $P = 0.07$ ) (Fig. 5).

### TRCoh

TRCoh (all electrode pairs of interest pooled) was maximal during the early bimanual learning phase and decreased significantly after the 30-min training period in both frequency bands ( $F_{\alpha} = 19.33$ ,  $P = 0.0001$ ;  $F_{\beta} = 31.6$ ,  $P = 0.0001$ ) (Fig. 5). Contrast analyses indicated that this was true for the coupling of left central and right central cortex, left central to mesial frontocentral cortex, right central to mesial frontocentral cortex, left central to mesial parietal and right central to mesial parietal, but not for the connection from mesial frontocentral to midparietal cortex.

## Repeated execution of overlearned unimanual sequences

### Task performance

Repeating simple overlearned sequences did not result in significant changes in error rates [mean of correctness of  $95.5 \pm 5.9\%$  (SD) before and  $95.9 \pm 5.7\%$  after training] (Fig. 6).

### TRPow

The decreases in movement-related TRPow in the regions of interest were significant (ANOVA plus contrast,  $F_{\alpha} = 28.8$ ,  $P = 0.0001$ ;  $F_{\beta} = 28.3$ ,  $P = 0.0001$ ). In the alpha band, the decreases in TRPow during execution of overlearned unimanual finger sequences (maximum over C3/4, CP3/4, P3/4) tended to be lower than during early bimanual sequence

learning (Fig. 5 versus Fig. 7). In the low beta band, TRPow decreases were less focused during unimanual than during bimanual sequence performance. Similarly to the changes that occurred in TRPow before versus after training in the bimanual learning experiment, there was some reduction in the TRPow decreases over the central region following the training period in association with the simple unimanual movement sequences (Fig. 7). However, this effect was smaller for the repeatedly executed, previously overlearned unimanual sequences than for the specifically practised, novel bimanual sequences and was significant only in the alpha band ( $F_{\alpha} = 11.7$ ,  $P = 0.0007$ ;  $F_{\beta} = 1.32$ ,  $P = 0.25$ ).

### TRCoh

The bimanual training period had no influence on the TRCoh patterns related to the performance of overlearned unimanual finger sequences.

During repeated execution of overlearned unimanual sequences, TRCoh increases in the alpha band were maximal in pairs of electrodes linking C3, C4 and the mesial frontocentral region. In the low beta band, the highest TRCoh was seen in electrode pairs linking both central areas with each other and the mesial frontocentral cortex in a quadrangle limited by F3, F4, CP3 and CP4. The most prominent links occurred between the right and the left central sensorimotor areas and from there to electrodes overlying the mesial frontocentral cortex. Links of both central sensorimotor areas to the parietal mesial and the posterior parietal cortex were sparse. When compared directly, TRCoh values were lower in association with simple repetitive unimanual performance than with early bimanual sequence learning in the alpha and low beta bands (alpha:  $F_{\alpha} = 26.3$ ,  $P = 0.0001$ ; beta:  $F_{\beta} = 68.7$ ,  $P = 0.0001$ ).

## Learning of unimanual sequences

### Task performance

As in the bimanual learning task, subjects improved in unimanual sequence performance after the (unimanual) training period of 30 min, from a mean of correctness of  $67.8 \pm 25.7$  (SD) to  $88.6 \pm 13.1\%$  (Fig. 6).

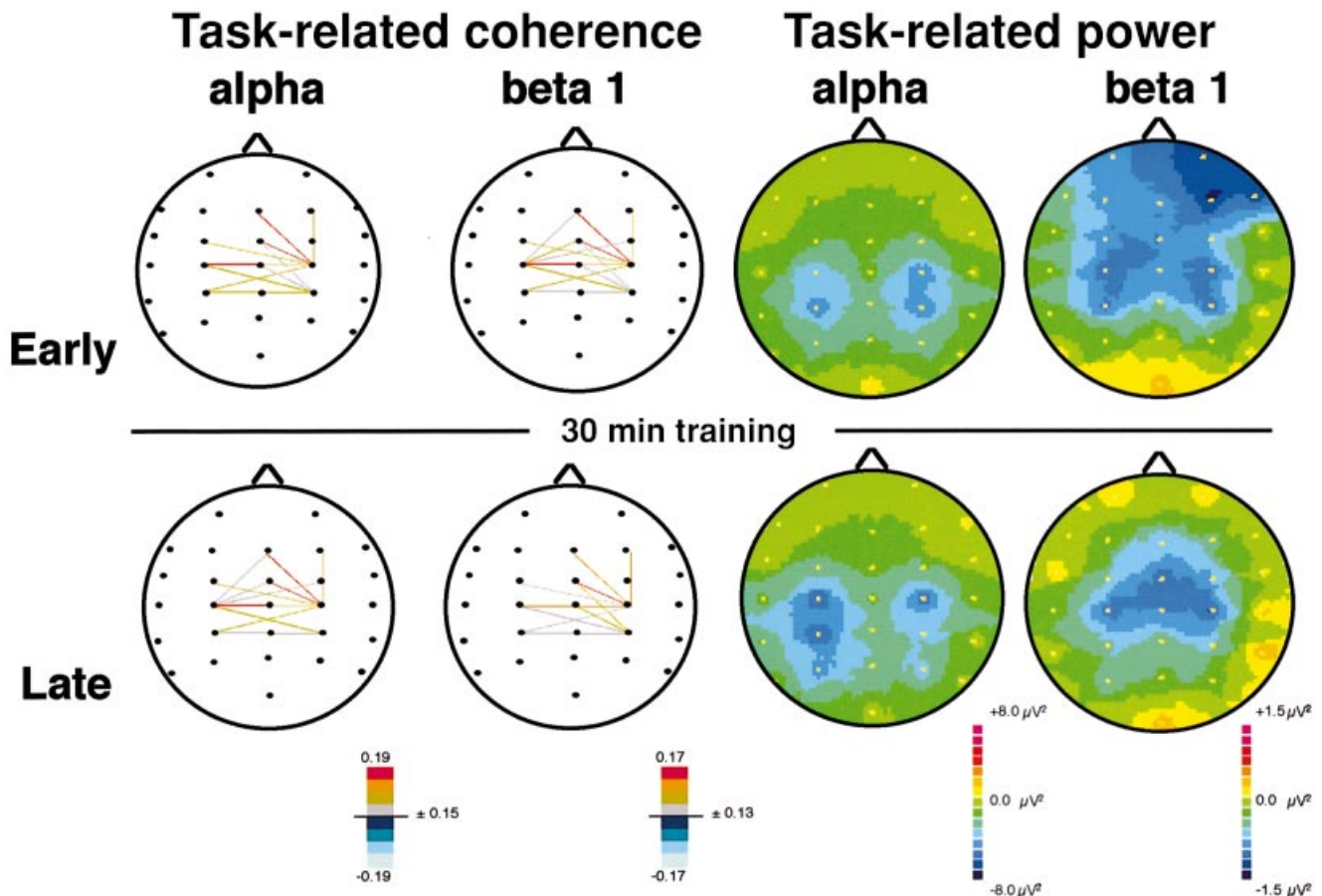
### TRPow

The TRPow patterns were similar before and after training. The execution of unimanual complex sequences was associated with TRPow decreases over the bilateral centroparietal and right parietal cortex in the alpha band, and the decrease was slightly higher over the mesial frontocentral cortex in the low beta band (Fig. 8).

### TRCoh

In contrast to the bimanual sequence learning paradigm, unimanual training had no significant effect on the TRCoh





**Fig. 7** Unimanual sequence repetition. Execution- and training-related changes in TRCoh link-plots (left) and TRPow maps (right) during unimanual sequence repetition before (upper panel) and after (lower panel) training. Interhemispheric TRCoh and TRPow did not change after training.

(Fig. 8) despite the clear behavioural learning effect as reflected by the increase in the percentage of correct sequences (Fig. 6). During both the early and late stages of learning unimanual sequences, the highest TRCoh values occurred between the bilateral central and the frontomesial cortex, being more pronounced over the right hemisphere and largely confined to a quadrangle defined by F3, F4, CP3, CP4; this was similar to the topography seen with bimanual movement sequences. On direct comparison, TRCoh increases (all electrode pairs of interest pooled) during early unimanual sequence learning were lower than during early bimanual sequence learning in the low beta band ( $F_{\beta} = 31.3$ ,  $P = 0.0001$ ). In the alpha band, there was a similar trend ( $F_{\alpha} = 3.24$ ,  $P = 0.072$ ).

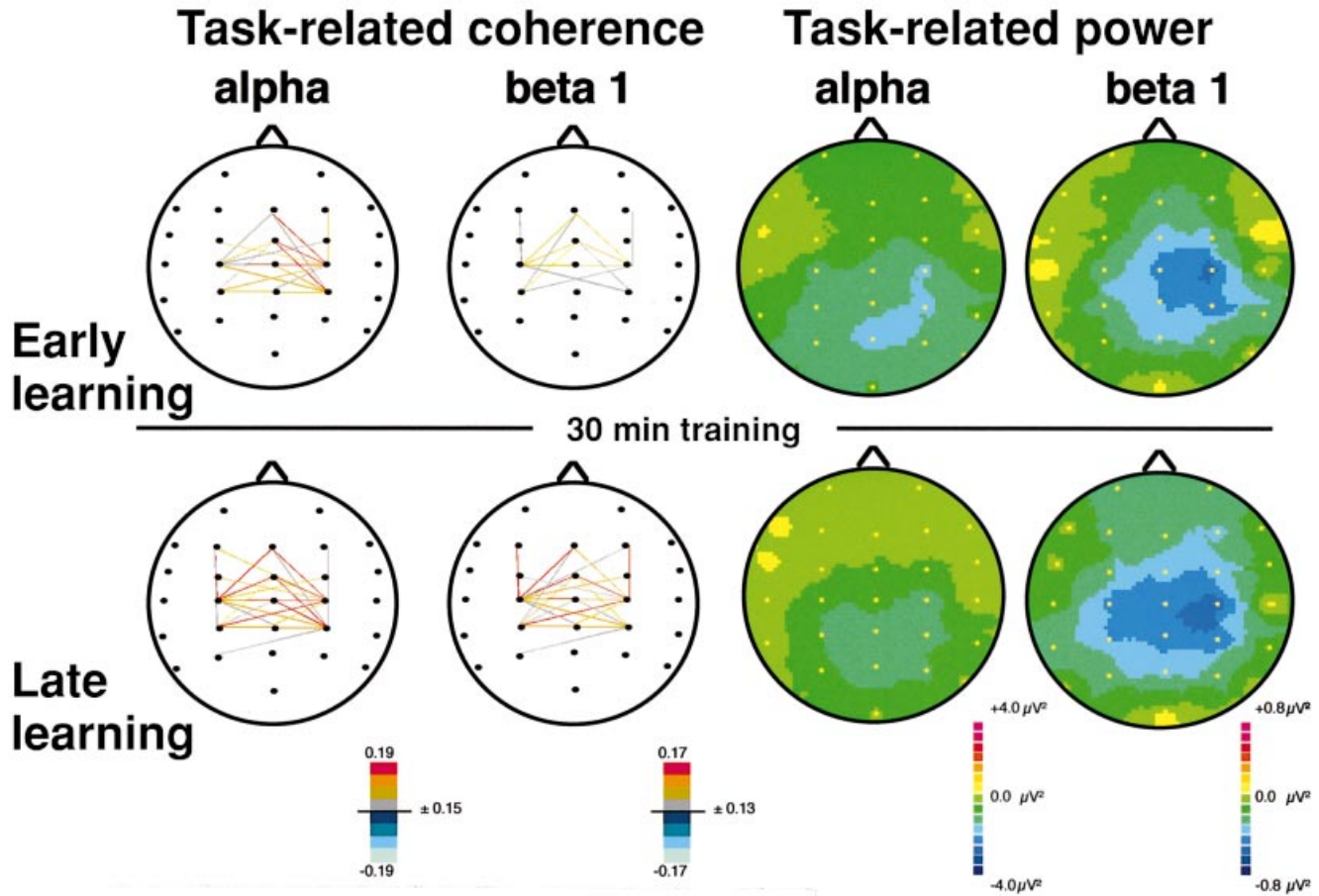
#### ***Interhemispheric TRCoh during bimanual learning, unimanual repetition and unimanual learning***

Across all conditions, the highest interhemispheric TRCoh values (coupling of left central and right central cortex) occurred in the early bimanual learning phase, and were

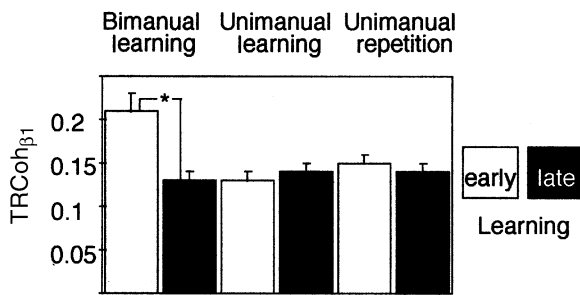
significantly higher than in all unimanual controls (unimanual repetition:  $F_{\alpha} = 12.3$ ,  $P = 0.005$ ;  $F_{\beta} = 54.0$ ,  $P = 0.0001$ ; unimanual sequence learning:  $F_{\alpha} = 17.9$ ,  $P = 0.001$ ;  $F_{\beta} = 40.3$ ,  $P = 0.0001$ ). The main effect of bimanual training was a decrease in this initially elevated interhemispheric TRCoh ( $F_{\alpha} = 12.6$ ,  $P = 0.004$ ;  $F_{\beta} = 40.3$ ,  $P = 0.0001$ ) to levels comparable with the unimanual control tasks. Thus, as soon as a certain degree of overlearning was reached in the bimanual sequences, interhemispheric TRCoh no longer differed between bimanual and unimanual motor sequences (Fig. 9).

#### **Discussion**

The present results indicate that inter-regional and, in particular, interhemispheric functional coupling between human premotor and sensorimotor areas is enhanced during acquisition of a novel bimanual skill and returns to a baseline level once intensive training has stabilized bimanual performance at a high level of accuracy. We propose that the modulation of interhemispheric coupling during bimanual skill acquisition is a specific correlate of bimanual learning,



**Fig. 8** Unimanual sequence learning. Execution- and training-related changes in TRCoh link-plots (left) and TRPow maps (right) during unimanual sequence playing before (upper panel) and after (lower panel) training. Interhemispheric TRCoh did not decrease significantly after training either in the alpha band or in the lower beta band. There were no significant training-related TRPow changes.



**Fig. 9** Training-related interhemispheric TRCoh $_{\beta 1}$  in all three paradigms. In the early bimanual learning phase TRCoh values were significantly higher than in the unimanual controls (\*).

possibly relayed through the corpus callosum. With respect to information processing, one might speculate that the greater initial coupling corresponds to a greater need of command integration when bimanual processes are not yet safely established as motor routines, and that the system becomes more efficient after training.

### *Learning-related increase and decrease in interhemispheric functional coupling between premotor and sensorimotor areas*

Enhanced interhemispheric functional coupling occurred during the early stage of bimanual co-ordination learning, but not during the repetition of sequences or during the learning of unimanual sequences. Therefore, it is likely that this phenomenon reflects physiological processes specifically related to bimanual skill acquisition. Although it has never been demonstrated directly with physiological techniques, an important role of interhemispheric communication for bimanual co-ordination is intuitive and in line with the specific deficits that occur in acallosal patients, who often show a lack of bimanual precision, bimanual tapping errors (Leonard *et al.*, 1988) and mirror movements (Hanakita and Nishi, 1991). However, the situation appears to be more complex than this.

After a performance level of nearly 100% had been reached in the bimanual sequencing task, interhemispheric coupling decreased again. TRCoh levels after the 30-min training

period were comparable with those associated with unimanual sequence execution and the learning of unimanual sequences. This observation adds further support to our interpretation that the initially enhanced interhemispheric coupling is a specific neurophysiological substrate of active bimanual integration. One could predict from these findings that patients with lesions of the corpus callosum have greater difficulties in acquiring new bimanual tasks than in executing bimanual tasks that they had learned prior to the disease. In fact, Sperry (1968) has already reported on patients after total commissurotomy who had deficits in novel asynchronous bimanual movements but not in skills that were well practised before surgery. The corpus callosum appears to have a role in bimanual movements with significant degrees of conscious control, but a lesser role in overlearned bimanual actions. Whether this is related to the control of well trained motor programmes at subcortical levels, to the use of ipsilateral pathways or to control of activity from a single hemisphere (Geffen *et al.*, 1994) remains speculative.

In the present paradigm, the reported dynamics of interhemispheric coupling were specific for bimanual co-ordination. Similar coherence modulation was not exhibited in the control experiment on unimanual sequence learning. The degree of difficulty, necessary motor skill, memory retrieval and attention and the type of learning were very similar in the two tasks. Imbalances due to lateralization were accounted for by testing and pooling both hands in all unimanual experiments. The behavioural results (sequence correctness and interstimulus intervals) showed similar improvement and error rates. The only difference between the two learning paradigms was the use of two hands or only one hand. Thus, it seems plausible to attribute the different neurophysiological results to the factor of bimanuality.

Lower TRCoh after training was not exclusively observed in interhemispheric pairs of interest but was also seen in the links between parietal and frontomesial areas overlying the SMA and in other intrahemispheric links, suggesting that interhemispheric interactions do not play an exclusive role during the acquisition of bimanual skills. Since bimanual skill acquisition has not yet been addressed in similar paradigms with other neurophysiological and neuroimaging techniques, direct comparisons with previous human or non-human primate studies cannot be made.

Neuroimaging studies on the roles of different human cortical areas during motor sequence learning have yielded somewhat contradictory results, in particular regarding the SMA (Jenkins *et al.*, 1994; Sakai *et al.*, 1998). Jenkins reported SMA activation during performance of overlearned sequences and Sakai found activation in the pre-SMA during early and intermediate learning stages. Increases in motor cortical activation related to early learning have been reported previously with unimanual tasks in PET (Grafton *et al.*, 1992) and EEG (Zhuang *et al.*, 1997) studies. In both these studies, however, subjects acquired novel unimanual sequences (e.g. in a serial reaction time task), while in the present experiments they had to integrate previously

memorized and practised sequences into novel ones. Thus, it is likely that our experiment reflects a later learning stage than described by Zhuang *et al.* (1997). Further, in our paradigm learning was fully explicit. The lack of significant changes in regional activation with unimanual sequence learning may, therefore, be related to this difference in the experimental design.

### ***Cortical regions involved in bimanual sequence learning***

The highest TRCoh and TRPow values in all paradigms were found in the central part of the electrode array, overlying primary sensorimotor areas, the premotor cortex and sensory association areas. The pairs with the highest TRCoh in all three paradigms were connections within those regions of known relevance for motor control. There was no substantial change in TRCoh between central and temporal or occipital regions.

Similar to the concept of event-related desynchronization (Pfurtscheller, 1988; Salmelin and Hari, 1994; Toro *et al.*, 1994a, b; Stancak and Pfurtscheller, 1995, 1996), TRPow decreases are likely to represent regional cortical activation (Zhuang *et al.*, 1997; Classen *et al.*, 1998; Gerloff *et al.*, 1998; Manganotti *et al.*, 1998). Two patterns of regional activation were evident in all paradigms. In the alpha band, this pattern included electrodes overlying the primary somatosensory cortex and bilateral parietal association areas, and in the low beta band the maximum activation extended more towards the frontomesial electrodes Cz and FCz, overlying the region of the SMA. The slightly different topographies of TRPow in the alpha and beta frequency ranges are consistent with previous findings (Gerloff *et al.*, 1998; Manganotti *et al.*, 1998). It has lately been suggested that alpha and beta rhythms reflect different systems (Salmelin and Hari, 1994; Pfurtscheller *et al.*, 1996). Beta power seems to be more sensitive for evaluating motor aspects of co-ordination; alpha may be more specifically related to somatosensory processing. In the present experiment, learning-related changes had similar characteristics in the alpha and lower beta bands, with a preponderance in the beta band. One might, therefore, speculate that the learning-related changes occurred in both the motor and somatosensory cortical circuits with relative emphasis on the processing of motor commands.

### ***Primary sensorimotor cortex***

TRPow decreases in electrodes overlying the primary sensorimotor cortex were seen in all paradigms. Modulation of primary sensorimotor cortex activity has previously been shown in various studies, in the performance of bimanual sequences (Sadato *et al.*, 1997) and in the performance and learning of unimanual sequences in PET (Seitz *et al.*, 1990; Grafton *et al.*, 1992; Jenkins *et al.*, 1994; Schlaug *et al.*,

1994; Hikosaka *et al.*, 1995, 1996; Jueptner *et al.*, 1997a, b; Sadato *et al.*, 1997), functional MRI (Rao *et al.*, 1993; Karni *et al.*, 1995) and EEG (Zhuang *et al.*, 1997; Manganotti *et al.*, 1998) studies.

### *Parietal cortex*

In our paradigm the parietal cortex was constantly activated (TRPow) during bimanual and unimanual sequence performance, before and after bimanual and unimanual training. Parietal activation (TRPow<sub>β</sub>) was increased during bimanual sequence performance after training. An important role of the parietal cortex in the processing of finger movements with defined spatial characteristics (e.g. complex keypress sequences) has been postulated by Catalan *et al.* (1998), who showed an increase in regional cerebral blood flow in bilateral posterior parietal areas and the precuneus related to the length of more or less complex finger sequences. The increase in parietal activation after training suggests involvement of these regions in the storage of motor programmes. This interpretation gains support from Sakai *et al.* (1998), who observed a transition of brain activation from frontal to parietal areas in visuomotor sequence learning.

In addition, the functional coupling of the left and right lateral centroparietal cortex and between left and right central regions and the mesial parieto-occipital cortex showed dynamic modulation due to training. TRCoh between these regions was highest in the early phase of bimanual learning and decreased after training. The different behaviours of TRPow and TRCoh during learning emphasize that these two aspects of information processing can operate to some extent independently from each other. It seems that, during the early phase of bimanual co-ordination learning, interhemispheric communication is most important, while after systematic training the storage of the acquired new motor routine might rather be reflected in increased and parietally pronounced regional activation.

### *Frontomesial premotor cortex (SMA)*

The SMA participates in planning (Tanji and Shima, 1994; Gerloff *et al.*, 1997a) and execution of sequential unimanual and bimanual movements (Shibasaki *et al.*, 1993; Jenkins *et al.*, 1994; Sadato *et al.*, 1997). It is thus physiologically plausible, and further supported by our and previous coregistration results, that mesial frontocentral TRPow changes (particularly in the low beta band) reflect neuronal activity in the SMA. However, in contrast to Sadato *et al.* (1997), we did not find significant differences in regional activation between unimanual and bimanual sequence performance in the present paradigm. This may be related to the different sequences used in our and Sadato's PET study, but it could also be related to lower sensitivity of the surface EEG in detecting regional activity changes in deeper brain regions such as the SMA.

While systematic studies on the role of the SMA in

bimanual learning are not available, SMA activation during unimanual learning has been the target of several experiments. Using PET methods, Jenkins *et al.* (1994) came to the conclusion that the SMA proper is important for the execution of sequential movements, but that the lateral premotor and prefrontal areas are more crucial for the learning of novel sequences. This finding was supported by data on monkeys obtained by Hikosaka *et al.* (1996) and recent data on humans obtained by Jueptner *et al.* (1997a). For Lang *et al.* (1990), the SMA has the function of controlling the initiations of movements in a difficult bimanual sequence so as to fit them into a very precise timing plan. Other studies have pointed to a more relevant function of the SMA for motor learning (Sakai *et al.*, 1998).

In our study, all paradigms showed similar TRPow after the training period. However, the TRCoh between the frontocentral mesial cortex and other regions changed as a function of bimanual learning, suggesting perhaps a pacemaker role of the SMA during the early stages of bimanual learning.

### ***Task-related coherence as a measure of inter-regional functional coupling***

We propose that the learning-related increase and decrease in interhemispheric coherence during bimanual skill acquisition reflect modulation of interhemispheric communication in the motor system. The interpretation of TRCoh as an indicator of interhemispheric communication is supported by development-related changes (Knyazeva *et al.*, 1994; Koyama *et al.*, 1997), lesion data after callosal and hemispheric lesions (Rusinov *et al.*, 1981; Sazonova, 1993; Harmony *et al.*, 1994) and by results of studies in non-human primates (Singer, 1969; Engel *et al.*, 1991; Munk *et al.*, 1995; Nowak *et al.*, 1995; Salerno and Georgesco, 1996).

There is evidence for a direct relationship between inter-regional coupling measured with TRCoh and information exchange. Koeda showed a notable interhemispheric coherence decrease for all frequency bands corresponding with the completeness of commissural agenesis in seven patients (Koeda *et al.*, 1995). Similar results were found in acallosal patients (Kuks *et al.*, 1987; Nielsen *et al.*, 1993; Nagase *et al.*, 1994). Anterior callosotomy in three patients with intractable epilepsy led to a decrease in interhemispheric coherence (Brazdil *et al.*, 1997). The decrease occurred in several frequency bands with maximum reduction in the region corresponding to the section. It seems, therefore, most likely that interhemispheric TRCoh during bimanual sequence performance as seen in the present experiment depends highly on intact callosal connections and reflects communication between hemispheres. The data of Classen *et al.* (1998), which showed that the inter-regional coherence between the motor and visual cortex during a visuomotor task was specific for integrative sensorimotor behaviour, lend further support to this view.

The physiological significance of the observed interhemispheric coupling is also supported by the results of van Leeuwen (1978) and Schoppenhorst *et al.* (1980), who concluded that the mu-rhythms over the right and left hand sensorimotor areas are probably generated by relatively independent neural systems and are not generally coherent in simple motor tasks. Our results show that the mu-rhythms of the two hemispheres can be coupled during bimanual skill acquisition and that the amount of interhemispheric coupling depends on the stage of learning.

Correlated oscillatory activity can evolve as a property of corticocortical networks (Traub *et al.*, 1996) and can be the basis of the binding of several features into a single perceptual entity. However, coherence can also be caused by a third 'pacemaking' structure. Candidate pacemakers involve a variety of cortical and subcortical regions. Both the SMA and the dorsal lateral premotor cortex have been shown to be important for bimanual performance (Sadato *et al.*, 1997), but subcortical structures like the basal ganglia and the cerebellum (Seitz *et al.*, 1990; Grafton *et al.*, 1992; Jueptner *et al.*, 1997b; Shadmehr and Holcomb, 1997) were also significantly activated in PET and functional MRI in similar experiments. It is likely that both corticocortical communication (through the corpus callosum) and pacemaker influence play a role in co-ordinating the oscillatory activities in the two hemispheres during early bimanual skill acquisition.

TRCoh increases do not *per se* differentiate between inhibitory and excitatory connectivity (Manganotti *et al.*, 1998). Increased coherence between homologous sensorimotor areas of the hand could as well be a correlate of inhibition of the non-target hand, in order to gain bimanual control. Transcallosal projections of GABAergic neurons to relevant areas could be the substrate of interhemispheric inhibitory coherence (Jones, 1993) in order to suppress mirror movements. Hence, our present results would also be consistent with the general notion that learning new bimanual co-ordination tasks involves the suppression of pre-existing, preferred co-ordination tendencies as a prerequisite for building new co-ordination modes (Swinnen *et al.*, 1993). The post-training reduction in the initial interhemispheric (bimanual) TRCoh to levels comparable with unimanual controls would be consistent with a lesser need to suppress contralateral influences without losing co-ordination accuracy once the bimanual sequence has been extensively practised.

Significant changes in TRCoh were not necessarily accompanied by significant changes in TRPow. In general, TRPow appeared to be less affected by the training procedures. The dissociation of TRCoh and TRPow lends further support to a differential physiological meaning of the two measures.

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