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Synchronised oscillations of the human sensorimotor cortex

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Review

Abstract. Oscillations are a prominent feature of macroscopic human sensorimotor cortical activity as recorded non-invasively with electroencephalography (EEG) and magnetoencephalography (MEG). The advent of whole-scalp MEG systems allowing rapid non-invasive recording from the entire cortex and accurate localisation of neural sources, and the development of refined signal analysis methods are important factors that led to an increasing interest in studies of sensorimotor oscillations during the last 10 years. Investigations on healthy subjects revealed frequency-specific localisation and modality-specific reactivity of 10 Hz and 20 Hz sensorimotor oscillations. Task-specific coherence between motor cortical and electromyographic oscillations, reflecting cortico-motoneuronal coupling, point towards a functional role of precentral oscillations in the cortical control of voluntary movements. Furthermore, abnormal cortico-motoneuronal coupling may underlie clinical symptoms of motor disorders, such as tremor. Thus, investigation of oscillatory sensorimotor activity proceeds from phenomenology to function and provides an interesting approach to address questions in human motor physiology and pathophysiology.

Key words: sensorimotor oscillations, cortical rhythms, coherence, MEG, EEG, motor binding, cortical drive

INTRODUCTION

Oscillations, typically in the 8-40 Hz frequency range, are a prominent feature of intrinsic human brain activity. The best known rhythms are the 8-13 Hz occipital alpha rhythm which gave rise to the discovery of the human electroencephalogram (EEG) by Berger (1929), and the centro-parietal μ-rhythm, first described by Gastaut (1952).

Over decades, analysis of cortical rhythms has mainly been applied in clinical neurology and psychiatry to correlate, by visual inspection, signal phenomenology with behavioural states and brain disorders. Although clinically useful on a descriptive level, this approach was of limited value in contributing to our knowledge about the origin and the functional significance of cortical rhythms.

Oscillations may be the result of an oscillatory firing pattern of single neurones due to intrinsic biophysical characteristics or may result from the properties of the network architecture comprising inhibitory interneurones and feedback connections. At least for thalamic oscillations a combination of both mechanisms has been demonstrated (for a review, see Steriade and Llinas 1988). The cellular bases and the network characteristics underlying cortical rhythms are still largely unknown although it is likely that both intrinsic cell properties and operations in synaptic cortico-thalamocortical networks conjointly underlie spontaneous cortical oscillations (Steriade 1997).

During the last 10 to 15 years, considerable progress has been made from qualitative description of rhythmic oscillations towards quantitative analysis of their temporospatial and spectral characteristics, reactivity and interactions. Fast and non-invasive recordings have become feasible with whole-scalp MEG systems (Ahonen et al. 1993), refined analysis tools allow a quantitative assessment of oscillatory components in measured data, and the notion that synchronisation of oscillatory neuronal firing represents a physiological coding mechanism to bind together spatially separated populations of neurones provided a stimulating conceptual background (Eckhorn et al. 1988, Gray et al. 1989; for a review, see Singer 1993).

The findings prompted by these recent advances point towards a functional role of cortical oscillations in the control of movements rather than reflecting a functionally non-significant epiphenomenon.

The increasing interest in the function of human sensorimotor oscillations is substantiated by a number of recent reviews covering different facets of this topic (Hari and Salmelin 1997, Farmer 1998, Hari and Salenius 1999, Mima and Hallett 1999, Pfurtscheller and Lopes da Silva 1999, Brown 2000).

In this review, we focus on recording and analysis of macroscopic sensorimotor oscillations, their relation to local field potentials and neural firing, their spectral and temporospatial characteristics, and on the recently discovered frequency coupling between motor cortex oscillations and electromyographic activity of contracting muscles.

MEASUREMENT OF SENSORIMOTOR OSCILLATIONS AND THEIR RELATION TO NEURAL FIRING

Since the discovery of electroencephalography (EEG) by Hans Berger in 1929, this technique has been the classical method and is still widely used for the assessment of sensorimotor oscillations (Berger 1929). However, due to the blurring effects of the extracerebral tissues EEG scalp recordings have been of limited value for localisation of the underlying generators of rolandic oscillations. This drawback has been overcome by magnetoencephalography (MEG) which measures basically the same underlying neurophysiological process as EEG. MEG makes use of the fact that intracellular neuronal currents associated with postsynaptic potentials give rise to an orthogonal magnetic field that unlike the electric field is barely distorted by surrounding tissues. This and the development of devices consisting of large arrays of extremely sensitive SQUID (superconducting quantum interference device) detectors covering the whole scalp (Ahonen et al. 1993) has made it possible to accurately localise generators of sensorimotor oscillations in individual brains and to quantitatively study their reactivity and dynamics (for a review, see Hari and Salmelin 1997).

The relation between macroscopic oscillations recorded with MEG or EEG and the firing of cortical neurones can to some extent be inferred from simultaneous recordings of local field potential (LFP) oscillations and single unit activity in the sensorimotor cortex because MEG/EEG signals can be regarded as spatially integrated LFPs. In the sensorimotor cortex of awake monkeys discharges of two third of the recorded units were entrained with LFP oscillations (Murthy and Fetz 1992, 1996a,b). Even pyramidal tract neurones that show no periodic firing in their autocorrelograms can exhibit significant phase locking with LFP oscillations (Baker et al.

1997). Generally the majority of single neurones tend to fire just before (Murthy and Fetz 1996b) or at the negative deflection of the LFP oscillations in the cortex (Baker et al. 1997, 1999, Donoghue et al. 1998). Nevertheless the relationship between LFP oscillations and single- or multi-unit discharge has been found to be diverse and complex during different phases of a sensorimotor task (Donoghue et al. 1998). This is not surprising since a LFP reflects the average of the synaptic input to a large number of neurones close to the recording electrode whereas an extracellular single unit recording only measures action potentials as a result of suprathreshold excitatory postsynaptic potentials. When LFPs produce suprathreshold activation this would result in a correspondence of LFP and neural discharge and oscillatory spiking. In other instances, LFP oscillations may be subthreshold with no associated cell firing at the recording site (Murthy et al. 1994).

The polarity of LFP oscillations in the monkey motor cortex reverses completely between the cortical surface and a depth of 1 mm indicating that the source of the LFP signals is in the superficial cortical layers (Murthy and Fetz 1996a). Since these layers are particularly involved in cortico-cortical transmission (e.g. Jones 1986, Felleman and Van Essen 1991) this would suggest that cortico-cortical connections may participate in the generation of oscillations. However, the exact sites of origin of LFP oscillations as well as the relative contributions of intrinsic oscillatory properties of neurones and circuit interaction to the generation of oscillations in the sensorimotor cortex are still unresolved.

ANALYSIS OF OSCILLATORY ACTIVITY

Different signal analysis methods have been applied to recordings of rhythmic oscillations. Although somewhat trivial it is important to keep in mind that the choice of the analysis tool will likely affect the results. For example, as pointed out below, the prevalence of the rolandic mu rhythm has been reported to be around 10% on visual inspection of the EEG but up to 100% if quantitative spectral analysis was used. In the following paragraph, methods will be briefly introduced that can be applied to analyse oscillatory activity.

Since EEG, MEG and LFP data represent continuous time series, the same analysis methods are applicable to these data. In general, we want to infer from the measured time series on processes in specific cortical areas or neuronal populations. We may distinguish three categories of methods according to their objectives: (1) optimisation of source representation, (2) characterisation of the time series, (3) characterisation of interdependencies between time series. Methods in the first category may be used to obtain more appropriate estimates of the activity of a region of interest whereas methods from the second category are beneficial for a quantitative assessment of distinct features in the signal. Cortico-muscular and cortico-cortical interactions may be evaluated by utilising techniques from the third category.

Optimisation of source representation

The signal measured outside the head by a MEG sensor or a scalp EEG electrode is often taken as an approximation of the cortical activity below the sensor. However, depending on the sensor characteristics this approximation can be rather unsatisfactory. Especially signals recorded by scalp EEG are distorted by the inhomogeneous conductivity profile in the head and depend on the position of the reference electrode. Surface laplacian or cortical imaging methods may be used to obtain reference-independent representations of higher spatial resolution (Perrin et al. 1987, Nunez 1988, Lagerlund et al. 1995). In many cases it is reasonable to explain the measured data by a dipole model (Scherg 1992, Hämäläinen et al. 1993, Scherg and Ebersole 1993). A dipole model approximates the real current density distribution with a point-like current source. Other methods are available to estimate extended current density distributions (Ioannides et al. 1990, Hämäläinen et al. 1993, Pascual-Marqui et al. 1994). Linear transformations can be used to maximise desired properties of the data (Robinson and Vrba 1997, Gross and Ioannides 1999). This approach does not make any assumption about the number or the spatial characteristics of the sources. The transformations can be designed to enhance the signal-to-noise ratio from a region of interest (ROI) or to minimise interferences from sources outside the ROI. The latter technique is useful for estimating the activity of a ROI, thereby optimising the source representation.

Characterisation of oscillatory signals based on frequency domain and time-frequency domain representations

Once a satisfactory source representation has been obtained different measures may be used to describe its time course of activation and to quantify distinct features in the time series. Together with their confidence limits they can be used to assess the relation between features in the signal and specific brain states, functions or dysfunctions.

For the analysis of oscillatory activity measures based on frequency domain representations are of particular interest. The Fourier Transform (FT) is a linear transformation of the data which leads to a complex frequency domain representation X(f) of the time series x(t) (Brillinger 1983). In continuous data without trigger events, measures derived from the FT can be averaged over time (Welch 1967). However, sometimes it is desirable to obtain time-dependent measures which necessitates time-dependent frequency domain representations. This can be achieved by calculating the FT in a moving window (Short-Time Fourier Transform - STFT). A limitation of the STFT is the constant analysis window that is used for all frequencies. This leads to a suboptimal time-frequency resolution. The trade-off between time- and frequency resolution is described by the uncertainty principle $\Delta t\ \Delta f \geq 1/4\pi$. The time-bandwidth product on the left-hand side of the equation is minimised with a complex valued Gabor function G (Gabor 1946, Sinkkonen et al. 1995)

$$G(f,t)= \exp(-t^2/2\sigma+i2\pi ft)$$

where σ affects the time-frequency resolution. For a specific frequency f, G is a function of time and can be convoluted with the time series x(t) to obtain a complex valued representation $X(t,f)=x(t)*G(f,t)$ of the temporal evolution of f. Other time-frequency representations may be obtained using wavelets or Wigner-Ville distributions (see, Cohen 1989).

Different measures can be derived from the complex valued time-frequency representation (TFR) X(t,f) of the time series x(t):

The power spectrum $P_{xx}(t)=X(t,f)X^*(t,f)$ (X^* denotes the complex conjugate of X) shows the distribution of power across frequency. The power spectrum allows an identification of frequency bands which contain most of the power or which exhibit task-dependency. If based on a time-frequency representation the temporal evolution of power in the frequency band can be observed.

The use of TFRs is particularly beneficial for epoch data. The conventional approach of averaging the data time-locked to the external events yields a representation of the neuronal activity that is phase-locked to the stimulus (evoked response). TFRs allow a discrimination of additional features thus providing a better characterisation of the time series. Whereas the average of the real part $1/N\ \Sigma \mathrm{Re}(X_i(t,f))$ (i is the index for the N epochs) corresponds to the traditional average, the average of the squared absolute values $1/N\ \Sigma|X_i(t,f)|^2$ allows the identification of induced activity, i.e. frequency-specific activity that is time-locked (but not necessarily phase-locked) to the event (Sinkkonen et al. 1995, Tallon-Baudry et al. 1998, Rodriguez et al. 1999, Tallon-Baudry and Bertrand 1999).

Other methods for the detection of time-locked power changes (increases or decreases) in a specific frequency band calculate the smoothed average of the squared or rectified bandpass filtered signal (Salmelin et al. 1995, Pfurtscheller and Lopes da Silva 1999). These methods have been frequently applied in EEG and MEG studies to characterise frequency- and modality-specific reactivity of sensorimotor oscillations (for reviews, see Hari and Salmelin 1997, Pfurtscheller and Lopes da Silva 1999). Nevertheless, when applying these analysis techniques phase information is lost.

Phase relationships between signals, e.g. between motor cortex and EMG oscillations, may contain important physiological information. The phase can be calculated from the TFRs by computing the arctangent of the ratio of the imaginary and the real part of X(t,f). Another possibility is to use the Hilbert transform of the bandpass filtered signal for the computation of the complex valued analytic function $A(t)e^{i\Phi(t)}$ (Gabor 1946). From this function the instantaneous phase (t) and amplitude A(t) can be computed (Rosenblum and Kurths 1998). This allows the separate investigation of phase and amplitude dynamics (Fig. 1).

Characterisation of interdependencies between signals

Several measures for the characterisation of interdependencies between two signals x(t), y(t) rely on their cross spectrum $P_{xy}(f)=X(f)Y(f)$ which can be seen as a complex valued covariance measure in the frequency domain.

The most common measure which describes the relationship between two time series is the coherence, that is the magnitude squared cross spectrum divided by the power spectra of both time series. $C_{xy}(f) = |P_{xy}(f)|^2/(P_{xx}(f)P_{yy}(f))$. The value of coherence is bounded between 0 and 1 whereby $C_{xy}(f_1)=1$ indicates a

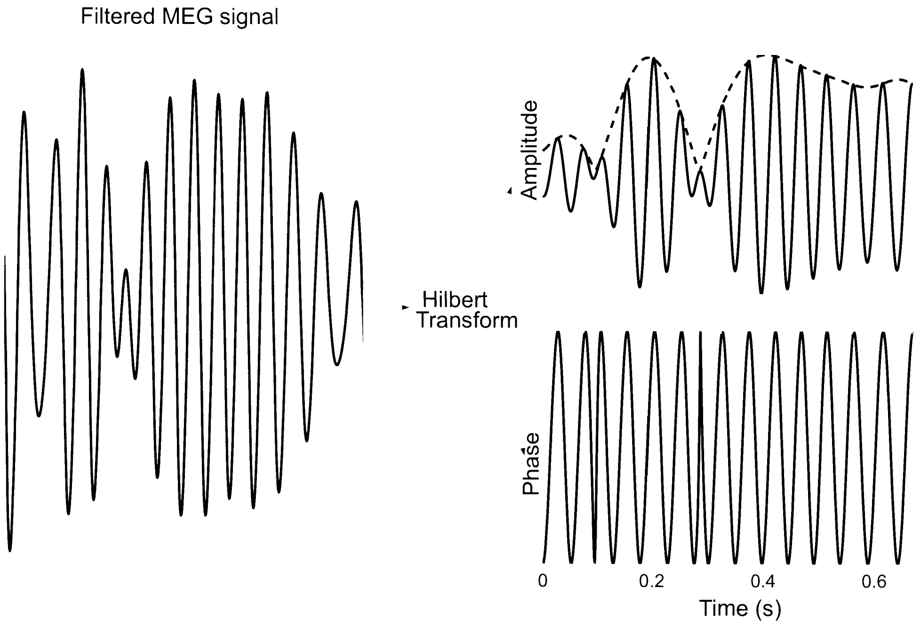

Fig. 1. Separation of amplitude and phase information. The upper left panel shows the filtered MEG signal. Applying the Hilbert transform yields the instantaneous amplitude (plotted as dashed line in the upper right panel together with the filtered signal) and the instantaneous phase (plotted as cosine of the phase in the lower right panel).

perfect linear relation at frequency f_1. Timing information between both time series may be obtained from the phase spectrum $\phi_{xy}(f)=\arctan(\mathrm{Im}(P_{xy}(f))/\mathrm{Re}(P_{xy}(f)))$. A delay between two stationary time series x, y would appear in the phase spectrum as a line in the frequency band of significant coherence. However, it should be noted that FFT based methods rely on the assumption of stationarity of the time series which is usually not the case for human MEG/EEG data (Kowalik and Elbert 1994). Other methods have been suggested which are based e.g. on autoregressive models (Schack et al. 1999a,b).

The classical coherence measure depends on dynamic changes of both phase and amplitude. However, it is important to separately characterise phase and amplitude dynamics and their contributions to interactions of time series since it has been shown that especially the phase dynamics may play an important role for the interaction of neuronal processes (Tass et al. 1998, Rodriguez et al. 1999).

In principle, phase and amplitude estimates can be computed *via* the Hilbert transform or by using wavelets. These methods take into account the non-stationarity of the data. Having extracted the phase from the signal, the phase difference between two time series can be estimated. A synchronisation index that is a measure for the deviation of the phase difference distribution in comparison to a random distribution can be calculated and tested for significance against surrogate data (Tass et al. 1998, Lachaux et al. 1999).

This approach is illustrated in Fig. 2 with simulated signals. Two coupled, non-identical, noisy Rössler oscillators were simulated with three different degrees of coupling strength. Phase differences obtained from the Hilbert transform are plotted there together with the respective histograms of phase differences (after calculating the modulo 2π). The diagonal line shows the phase difference from the weakly coupled oscillators. The histogram is almost uniform. In case of the medium and strong coupling (middle and lower line respectively) histograms deviate more and more from the uniform dis-

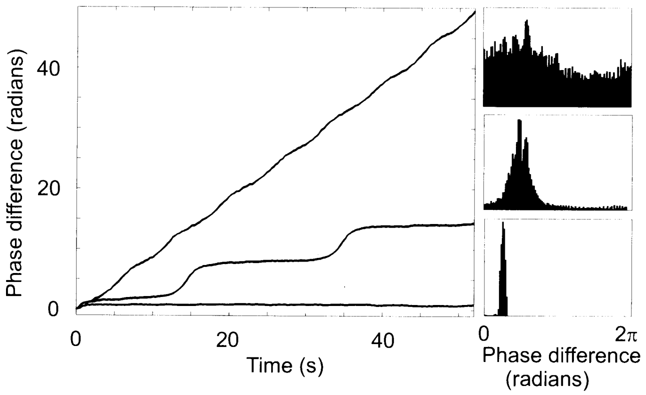

Fig. 2. Phase differences between two noisy Rössler oscillators. The left figure shows the phase differences of coupled Rössler oscillators for the three different degrees of coupling strength. The right figure shows the histograms of phase differences (modulo 2π) plotted next to the corresponding phase difference line. The top line and histogram show the case of strong coupling, the middle line and histogram the case of intermediate coupling and the lower line and histogram the case of weak coupling.

tribution indicating a higher degree of phase locking. Although still further work is needed in order to identify relevant measures for the characterisation of interactions between neuronal populations the available techniques have already been successfully applied to MEG and EEG recordings and appear to be of particular importance to unravel the functional significance of sensorimotor oscillations.

FUNCTIONAL PROPERTIES OF SENSORIMOTOR OSCILLATIONS

Sensorimotor oscillations were first described by Gastaut (1952) in the human EEG and denoted as μ-rhythm (Fig. 3). On visual inspection of the routine EEG μ-rhythm has been reported to occur in 3-14 % (Klaas and Bickford 1957, Niedermeyer and Koshino 1975). However, when spectral analysis techniques and multiple electrode arrays are used the prevalence of μ-rhythm increases up to 100 % (Kuhlman 1978, Pfurtscheller 1986).

Sensorimotor oscillations typically consist of frequency components around 10 Hz and 20 Hz (Niedermeyer 1993) with the 10 Hz usually slightly faster than the occipital alpha rhythm (van Leeuwen et al. 1978). The typical arch-like shape of the μ-rhythm emerges when these two components are transiently phase-locked.

The magnetic counterpart of the electric μ-rhythm has been shown to originate close to the primary somatosensory hand area (Tiihonen et al. 1989, Salmelin and Hari 1994a). Salmelin et al. (1995) investigated in detail the differential localisation of 10 Hz and 20 Hz oscillations in eight healthy subjects by identifying source locations during the rebounds after movements. 20 Hz oscillations of the hand area clustered, on average, anterior to 10 Hz oscillations which extended to the postcentral gyrus. However, there was a substantial spatial overlap of 10 Hz and 20 Hz sources. This finding is in good agreement with earlier electrocorticographic studies in humans (Jasper and Penfield 1949, Gastaut 1952, Papakostopoulos et al. 1980), cats and monkeys (Buser 1987) indicating that the 20 Hz component mainly originates in the anterior bank of the central sulcus while the 10 Hz component concentrates mainly in the postcentral gyrus. Interestingly, for 10 Hz oscillations the sources clustered close to the hand region, regardless of the body part moved. In contrast, the sources of the 20 Hz oscillations followed the somatotopic organisation of the body parts along the precentral gyrus, shifting from the most medial position for foot movements *via* the hand area to the most lateral location for mouth movements. These results in-

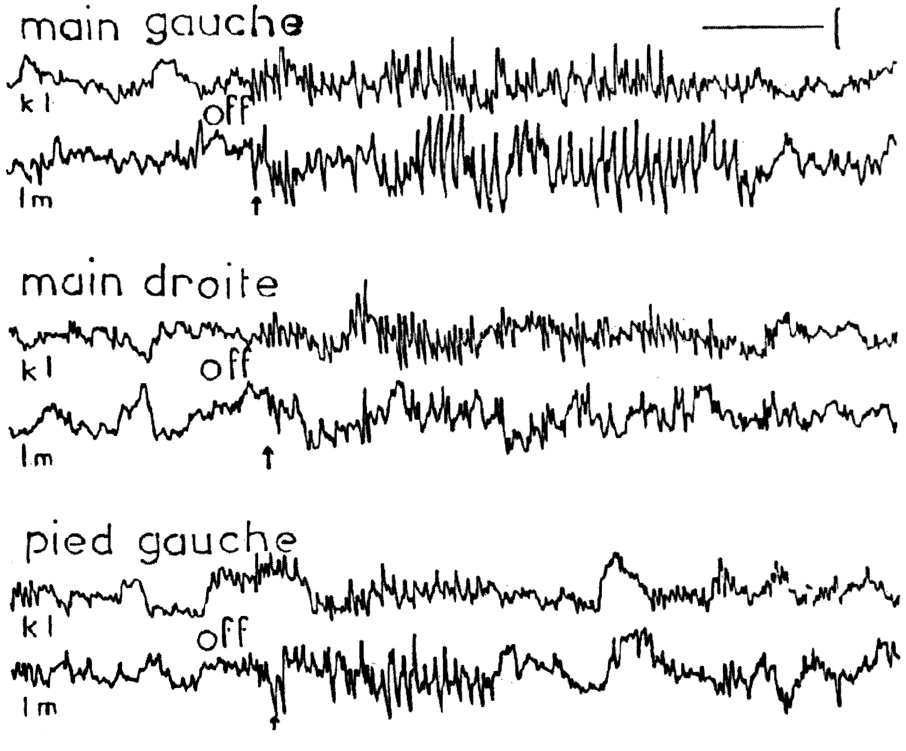

Fig. 3. Original electrocorticographic recordings from the right sensorimotor cortex taken from Gastaut (1952) illustrating rolandic μ-rhythm and its attenuation by movements. The traces show two bipolar recordings from precentral (k-l) and premotor (l-m) sites. During movements (prior to "off") of the left hand (*main gauche*), the right hand (*main droite*) and the left foot (*pied gauche*) the μ-rhythm is suppressed. Following termination ("off") of movement the μ-rhythm becomes clearly visible. The effect is stronger for movements of contralateral than ipsilateral hand or contralateral leg. Calibration bars: vertical 100 μV, horizontal 1 s. Reproduced from (Gastaut 1952), with permission © Masson Editeur.

dicate that 10 Hz and 20 Hz oscillations are related to separate functional networks. That is further supported by studies demonstrating differences in the temporal behaviour of task-related modulation. Already visual inspection of EEG traces revealed that rolandic oscillations display a stimulus- and task-specific reactivity. Unlike the occipital alpha activity, the µ-rhythm is not substantially affected by closing or opening the eyes, but is suppressed by tactile stimulation, motor preparation, and movements (Jasper and Penfield 1949, Gastaut 1952, Chatrian et al. 1959). In more recent studies, frequency-specific and task-related reactivity has been accurately described by applying quantitative analysis to whole-head MEG and multi-channel EEG recordings of healthy human subjects (for reviews, see Hari and Salmelin 1997, Pfurtscheller and Lopes da Silva 1999). It has been shown that voluntary movements result in a transient decrease of the amplitude of both frequency components of the µ-rhythm 1-2 s before movement, followed by a brief increase above premovement baseline 1-2 s after relaxation (Pfurtscheller 1992, Salmelin and Hari 1994b, Toro et al. 1994, Nagamine et al. 1996). The rebound to the offset of a movement is about 300 ms faster and much stronger for the 20 Hz than for the 10 Hz band (Pfurtscheller 1981, Salmelin and Hari 1994b). Similarly, Salenius et al. (1997c) reported that the rebound occurring after median nerve stimuli starts 0.1-0.3 s earlier in the 20 Hz than 10 Hz band.

As illustrated in Fig. 4, rebounds of sensorimotor oscillations associated with median nerve stimuli resemble

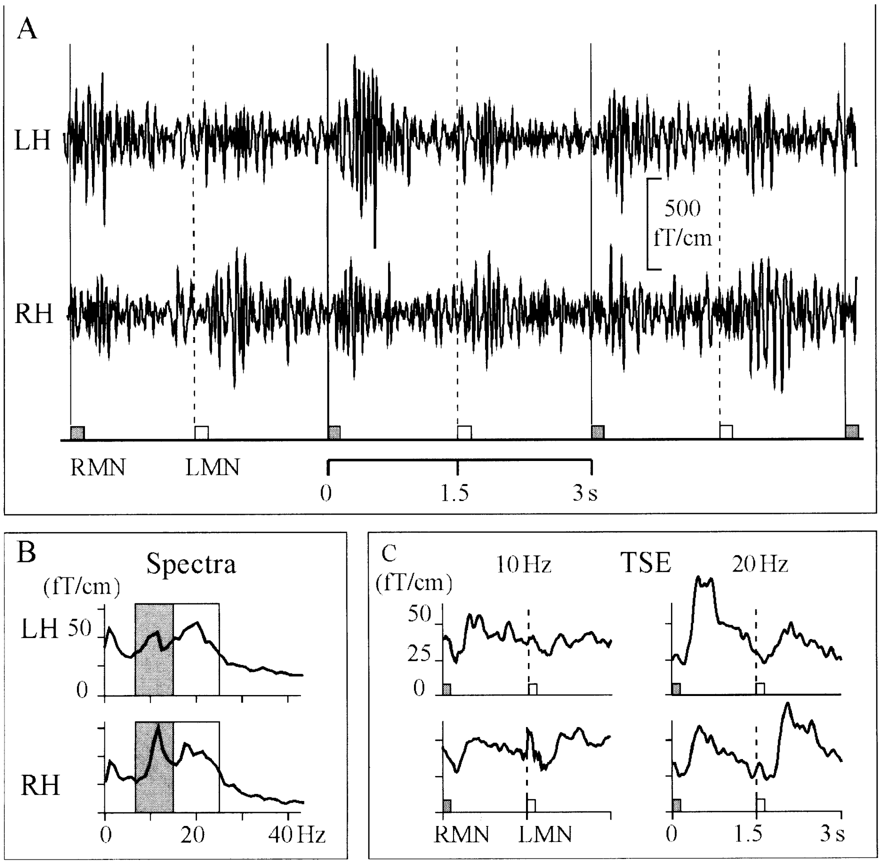

Fig. 4. A, spontaneous MEG activity (passband 5-40 Hz) recorded from sensors over the left (LH) and right (RH) sensorimotor hand area during electric stimulation delivered alternately to right (solid vertical lines, RMN) and left median nerves (dashed vertical lines, LMN) in a single subject. Note that each median nerve stimulus is followed by a burst of oscillatory activity predominantly in the contralateral hemisphere. B, amplitude spectra corresponding to the signals shown in A. Note the frequency peaks around 10 Hz and 20 Hz. C, event-related average amplitudes of oscillations around 10 Hz and 20 Hz. TSE (temporal spectral evolution; Salmelin and Hari 1994b) gives the average amplitudes (50 epochs to median nerve stimuli) of passband-filtered and rectified cortical signals shown in A as a function of time, thus quantifying the effects of the stimuli on 10 Hz and 20 Hz oscillations. Note that the transient increase (rebound) of oscillatory activity after median nerve stimulation occurs predominantly in the 20 Hz range, and more in the contralateral than ipsilateral hemisphere. Adapted from Salenius et al. (1997c).

those after voluntary hand movements (Salmelin and Hari 1994b): they are bilateral but significantly stronger in the contralateral hemisphere. The rebound to median nerve stimuli was significantly stronger in the left than in the right hemisphere (Salenius et al. 1997c). Since all subjects of this study were right-handed, this asymmetry has been suggested to reflect a larger cortical area devoted to the hand in the dominant than non-dominant hemisphere.

Considering that the rebound after median nerve stimuli is best evoked in relaxed subjects and occurs about 0.5 s after stimulation, it seems unlikely that this enhancement of sensorimotor oscillations is directly related to motor or sensory processing. A more plausible explanation is that the afferent volley caused by median nerve stimuli synchronises cortical oscillators, resulting in macroscopic, rhythmic oscillatory bursts which slowly decay to reach the base level. The time course of oscillatory activity supports such a view: it starts to rise sharply 0.2-0.3 s after median nerve stimuli, peaks at 0.4-1 s and then slowly decays over seconds (Salenius et al. 1997c).

Because the rebound to median nerve stimuli is a very reproducible phenomenon and is less variable than spontaneously occurring bursts of oscillatory activity, it is a useful measure to quantify task-related changes of rolandic oscillations. Suppressions of the rebound were observed during different sensorimotor tasks. The suppression during exploratory finger movements is stronger than during repetitive non-exploratory finger movements, or during passive tactile stimulation of the hand (Salenius et al. 1997c). Interestingly, also mental imagination of exploratory finger movements suppresses rolandic 20 Hz activity (Schnitzler et al. 1997).

The latter finding is in agreement with earlier observations that mere thinking about a movement can block the rolandic μ-rhythm in the EEG (Gastaut 1952, Chatrian et al. 1959). The 20 Hz suppression during motor imagery appears to be weaker than during actual exploratory movements but stronger than during static finger stretch (Schnitzler et al. 1997). Assuming that the suppression of the rebound is a sensitive indicator of cortical activation, and that 20 Hz oscillations are predominantly generated in the primary motor cortex, these results suggest that the primary motor cortex is involved in motor imagery.

Taken together, the available data indicate that 10 Hz and 20 Hz rolandic oscillations arise at least in part from different neuronal populations with 20 Hz oscillations being more related to the motor system than 10 Hz oscillations.

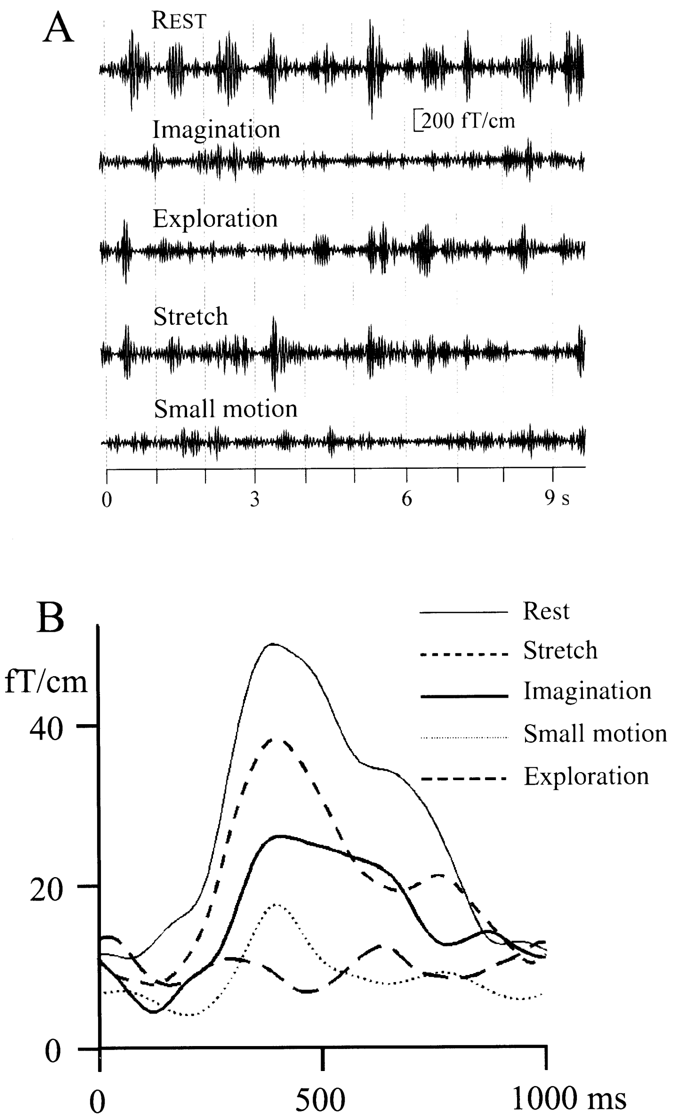

Fig. 5. Effect of sensorimotor tasks and motor imagery on the median nerve evoked rebound of 20 Hz oscillations. A, 10 s intervals of 20 Hz MEG oscillations (bandpass filter 18-25 Hz) recorded over the left sensorimotor hand area of a single subject during right median nerve stimulation (dashed lines) and performance of various sensorimotor tasks with the right hand. Note the bursts following each stimulus and the attenuation of these bursts during the tasks. B, quantification of task-related changes of 20 Hz oscillations shown in A using the TSE (temporal spectral evolution) method. Note that movement (Exploration, Small motion) supresses oscillations most strongly. Simple static finger stretch (Stretch) led to slight and motor imagery to a 50 % reduction of the 20 Hz rebound. Adapted from Schnitzler et al. (1997).

In several studies quantification of sensorimotor oscillatory activity has been applied to characterise pathophysiological changes in movement disorders such as Parkinsons disease (PD). Mäkelä et al. (1993) reported that the resting tremor observed in hemiparkinsonian patients was associated with uni- or bilateral dampening of the 10 Hz oscillations occurring during tremorless periods, thus resembling the suppression observed during voluntary movements, and suggesting that the sensorimotor cortex participates in the generation of PD tremor.

Furthermore, PD patients exhibit alterations in the attenuation of sensorimotor oscillations shortly before and during voluntary movements. When hemiparkinsonian patients perform a movement with their akinetic hand, the premovement attenuation of contralateral 10 Hz oscillatory activity is significantly delayed (Defebvre et al. 1996). This finding has been taken as evidence for the impairment of movement programming in PD. Chronic administration of L-Dopa can partially restore this effect (Defebvre et al. 1999). Similarly, the degree of premovement 10 Hz attenuation was found to be stronger 1 h after L-Dopa intake than after overnight withdrawal of medication in a group of PD patients (Brown and Marsden 1999, Wang et al. 1999). Moreover, the medication-related increase of 10 Hz attenuation was significantly correlated with a reduction in bradykinesia as demonstrated by an improvement in size and speed of movement (Brown and Marsden 1999, Wang et al. 1999). These results have been interpreted to support the hypothesis that basal ganglia control the release of cortical areas from oscillatory 10 Hz idling activity during preparation and execution of voluntary movement (Brown and Marsden 1998).

CORTICO-MOTONEURONAL COUPLING

Recent data suggest that oscillations around 20 Hz may have a role in the coordination of motor cortex activity with the spinal motor neurone pool. Conway et al. (1995) using a single channel magnetometer found a significant coherence in the 13-35 Hz range between oscillatory MEG signals from the motor cortex and the rectified electromyogram from the interosseus muscle during weak isometric contraction. They related the finding to the previously observed synchronisation of hand muscle motor units at frequencies of 16-32 Hz (Farmer et al. 1993) and proposed involvement of cortical neurones in the generation of motor unit synchronisation. The findings of Conway et al. (1995) were confirmed by Salenius et al. (1997b) who employed a whole-scalp sensor array to demonstrate somatotopic arrangement of MEG-EMG coherences. The maxima of coherent MEG signals occurred close to the brain midline during lower limb muscle contractions and laterally along the central sulcus during upper limb muscle contractions. These results suggest that the coherent cortical oscillations in the 20 Hz range originate in the primary motor cortex, in agreement with findings in the monkey (Murthy and Fetz 1992, Sanes and Donoghue 1993, Baker et al. 1997). It is likely that there is a close relationship between the coherent 20 Hz oscillations and the μ-rhythm recorded from the motor cortex. Although μ-rhythm, in general, decreases shortly before and during voluntary movement or during isometric contraction, it has been shown that MEG-EMG coherence increases during the μ-rebound which occurs after median nerve stimuli (Salenius et al. 1997a).

While MEG-EMG coherence in the 20 Hz range is typically observed during weak isometric contractions it is largely abolished during stronger contractions and during ongoing movements. However, recent investigations demonstrated MEG-EMG coherence at 30-60 Hz during maximal contractions and during the last 20-30° of a phasic wrist extension movement (Brown et al. 1998). In these conditions the EMG shows rhythmic oscillations around 40 Hz which give rise to a detectable muscle sound known as Piper rhythm (Piper 1907). Occasionally, MEG-EMG coherence in the 40 Hz range seems to occur during preparation and execution of slow finger movements (Salenius et al. 1996). Functionally, the Piper coherence has been proposed to be related to the attentional demands of tonic and phasic contractions (Brown 2000). Whereas cortico-muscular coherence was initially shown in MEG recordings it has recently also been demonstrated between EEG activity recorded from the scalp over the sensorimotor cortex and 20 Hz oscillations in contralateral upper limb muscles (Halliday et al. 1998, Mima et al. 2000). However, so far there have been no reports in humans of coherence between EEG and 40 Hz Piper oscillations in the EMG. This has been attributed to the low pass filtering effects of the skull and other interposed tissues (Brown 2000).

The temporal relationship between cortical and muscular signals has remained controversial among different investigators. A direct cortical drive to muscle should be associated with time lags comparable to cortico-muscular conduction time through fastest pyramidal tract fibres

(Rothwell et al. 1991). However, Conway et al. (1995) found zero phase shift between MEG and EMG oscillations. Similar findings were reported with scalp recorded EEG (Halliday et al. 1998). On the other hand, other authors (Salenius et al. 1997b, Brown et al. 1998, Mima et al. 1998, 2000) reported that the cortical signal precedes the EMG signal. But only the difference in the delay between muscles and not the absolute lag between cortex and muscle was consistent with conduction *via* fast pyramidal pathways. The absolute latencies determined from cross-correlograms were shorter than one would expect from cortico-muscular conduction times. As discussed by Brown et al. (1998) this discrepancy may be attributed to a physiologically inappropriate choice of the MEG reference signal for the latency measurement. Time lags agree in general with conduction times if they are measured from the major down-going instead of the strongest up-going cross-correlogram peak. There is some evidence from monkey data (Murthy and Fetz 1996a, Baker et al. 1997) and EEG and MEG recordings in patients with cortical myoclonus (Kugelberg and Widen 1954, Mima et al. 1998) that cortical motor output discharge occurs just at the time of this peak. Thus, it likely represents the physiologically appropriate and meaningful MEG signal for time lag measurements. Apart from this issue several other points may contribute to the inconsistent findings regarding phase lags between MEG and EMG signals. For example, in most studies, FFT-based analysis methods were used that assume stationarity of the signal.

However, this requirement is not fulfilled for MEG and EMG signals. Furthermore, the assumption of a broad region with a linear dependence of phase difference on frequency is not always valid. Moreover, the width of the frequency band chosen for the linear fit and the degree of linearity in that band can substantially affect the results. To overcome these problems Gross et al. (unpublished) used instantaneous phases from the Hilbert transform to calculate delays between MEG and EMG during weak isometric muscle contractions. The delays determined both from phase differences between MEG and EMG, and those from signals averaged with respect to zero phase of the EMG nicely agreed with absolute cortico-muscular conduction times to arm and leg muscles. Thus, the available evidence strongly suggests that a phase lag exists between 20 Hz motor cortical and muscle oscillations and that the motor cortex signals precede EMG activity by an interval consistent with known cortico-muscular conduction times. Functionally, this implies a hierarchical organisation of the 20 Hz cortico-muscular interaction supporting the notion that motor cortex drives the spinal motoneurone pool (Hari and Salenius 1999). It has been suggested that oscillatory cortical output may subserve effective driving of motor units while maintaining the cortico-spinal firing rate as low as possible. Although the idea of motor unit driving by oscillatory activity seems to be a plausible physiological explanation for cortex-muscle coherence it is still conceivable that both occurrence of oscillations and cortex-muscle coherence are functionally non-significant epiphenomena. Future studies will have to proof that variation of cortex-muscle coherence is associated with a change in behavioural functions.

Although the physiological significance of cortico--muscular coherence is far from clear there is already evidence that abnormal cortico-muscular coupling phenomena may play a role in the pathophysiology of movement disorders. In patients with Parkinsons disease, Volkmann et al. (1996) found significant cortico-muscular coherence at the 3 Hz to 6 Hz resting tremor frequency which may reflect the activity of a central tremor generator. Tremor-evoked activity was reported to arise from sources in contralateral premotor, motor, and somatosensory cortices, and thalamus. Thus, parkinsonian resting tremor seems to involve the same cortical structures as voluntary movements.

Application of recently developed analysis tools appropriate for non-stationary time series revealed 1:2 phase-coupling between tremor EMG and MEG signals recorded above the contralateral sensorimotor and premotor cortex in a PD patient (Tass et al. 1998). The temporal variation of the phase synchronisation index, reflecting the coupling strength between MEG and EMG mirrored the time behaviour of the synchronisation between agonist and antagonist muscle. Interestingly, in addition to cortico-muscular 1:2 synchronisation, a significant 1:1 phase-locking between sensors of sensorimotor and premotor cortex was evident during tremor periods suggesting that abnormal cortico-cortical synchronisation may reflect abnormal agonist-antagonist muscle coordination which produces the resting tremor.

Whereas an abnormal cortico-muscular coupling occurs in the tremor frequency range the physiological cortico-muscular coherence during isometric contraction in the 20 Hz and 40 Hz range seems to be reduced in PD (Salenius et al. 1999). Instead, at least in some patients, low-frequency (5-12 Hz) coherence emerges. L-Dopa seems to reduce or abolish low frequency coherence and enhances the physiological cortico-muscular coherence (Salenius et al. 1999). These findings fit the above-mentioned hypothesis of basal ganglia and L-Dopa inhibiting synchronisation at low (idling) frequencies, and at the same time facilitating higher frequency sensorimotor oscillations and synchronisation of motor elements (Brown and Marsden 1998).

These reports provide promising perspectives on how investigation of coupling phenomena of sensorimotor cortical oscillations may enhance our understanding of pathophysiological mechanisms in movement disorders.

FUNCTIONAL SIGNIFICANCE

The possible functional significance of sensorimotor oscillatory activity is a matter of continuous debate with no definite conclusion up to now. Beyond the still conceivable interpretation of sensorimotor oscillations reflecting epiphenomena with no functional significance several hypotheses exist about their specific functional roles including: (1) idling state keeping the system in a flexible condition, (2) mechanism to drive the spinal motoneurone pool, (3) increase of attention, and (4) motor binding.

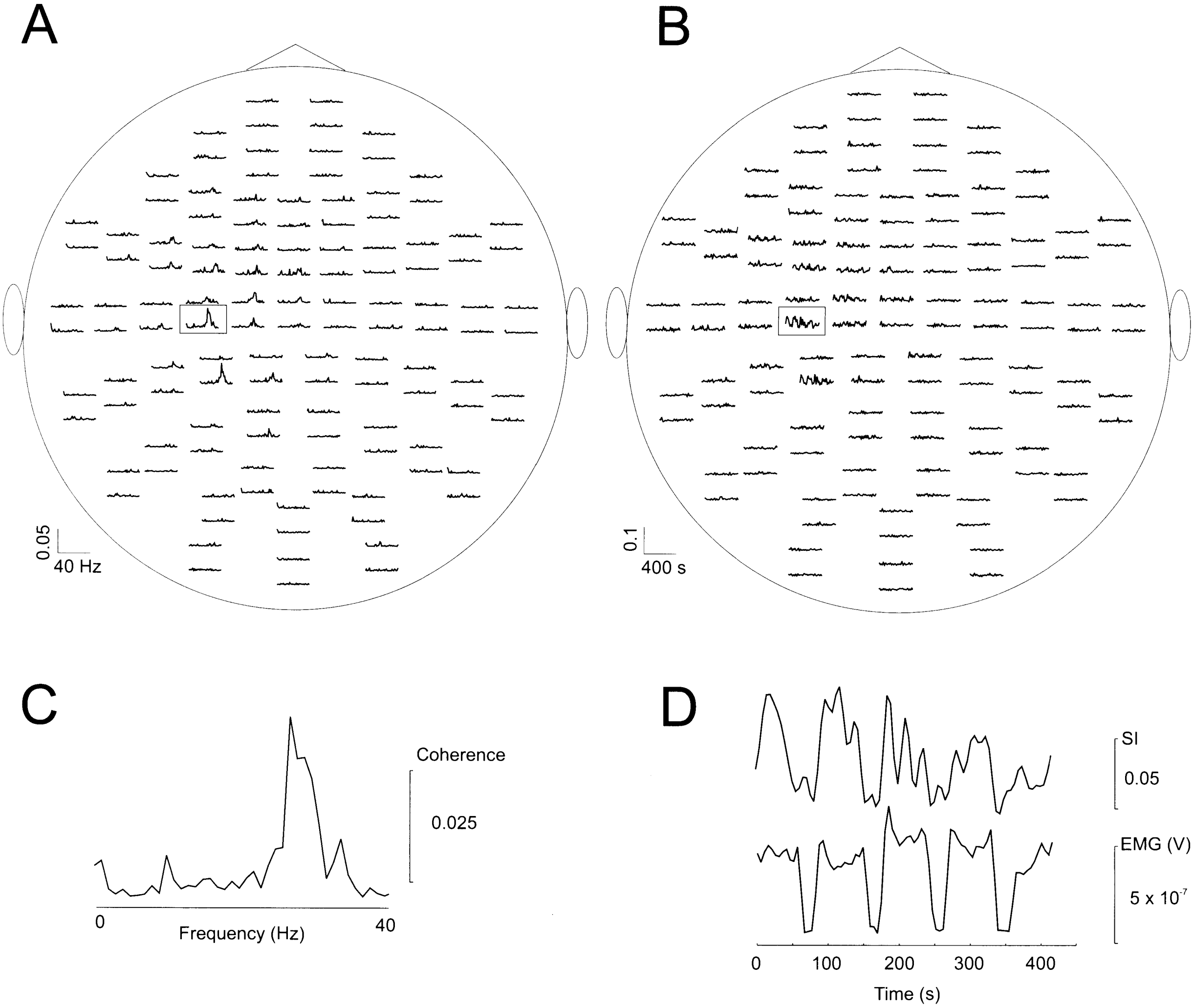

Fig. 6. A, coherence as function of frequency and B, the synchronisation index as function of time between rectified EMG recorded from the right extensor indicis muscle and all MEG signals. The sensor array is viewed from above. Traces are plotted in pairs corresponding to the two orthogonal planar gradiometers at each sensor location. 60 s long periods of isometric contraction were alternatingly followed by 30 s periods of rest. The channel above the left sensorimotor cortex showing the strongest coherence and synchronisation index is marked by a rectangle and depicted in C and D. The synchronisation index (SI) allows a quantification of phase locking over time. The index in D, which was computed in the 25-29 Hz frequency band in a 10 s window moving in 5 s steps across the data, is shown together with the mean EMG amplitude in the same windows.

Idling

In particular, the appearance of 10 Hz oscillations in a sensory cortical area has been proposed to reflect an idling state that could be a manifestation of increased gain in the network (Lopes da Silva et al. 1974). According to this view the oscillatory state may allow to regulate the mean membrane potential level within a neuronal population and thereby control the input-output transfer of information (Lopes da Silva 1991). By such a mechanism the somatosensory cortex may increase its sensitivity to facilitate discrimination between signals and noise when peripheral input remains constant, and thus actively gate sensory input to the cortex. In agreement with this interpretation sensorimotor oscillations are strongest when the modality-specific sensory input is minimal or monotonous, or immediately after suppression caused by a sensory stimulus or a voluntary movement. Furthermore, the predominantly postcentral generator sites of 10 Hz oscillations are compatible with this view.

Attention

Oscillations in sensorimotor cortex have been suggested previously to play a role in attention in cats (Bouyer et al. 1981, Montaron et al. 1982, Bouyer et al. 1987), dogs (Lopes da Silva and Storm van Leeuwen 1977) and monkeys (Rougeul et al. 1979, Rougeul-Buser 1994) where they may facilitate the responsiveness of neurones. The findings of several more recent studies are compatible with the attention hypothesis. Sensorimotor oscillations were less prominent during a highly overtrained motor task which required minimal attention to peripheral stimuli, but occurred more often during an attentionally demanding retrieving task when the monkey had to use sensory feedback continuously to execute appropriate movements (Murthy and Fetz 1996a). Furthermore, the variability of sensorimotor oscillations with respect to different phases of motor behaviour seems to favour the notion that they reflect a global process, such as attention, active in conjunction with motor planning or preparation rather than details of motor action (Donoghue et al. 1998). The observation that oscillations increased dramatically when monkeys were shown a leather glove that had been used to capture them also suggests a relation to increased attention or arousal (Murthy and Fetz 1996a). In an EEG study on normal human subjects, Nashmi et al. (1994) investigated what motor behaviours were associated with increased sensorimotor oscillations. Repetitive hand movements did not result in increased fast oscillations compared to the relaxed state. However, both motor preparations and focused attention, whether movements were performed or not, were associated with an increase of fast oscillatory activity in the sensorimotor region. Thus, these results also suggest a facilitatory effect of attention and motor preparation on the occurrence of sensorimotor oscillations.

During attentive periods before execution of a movement synchronous oscillations could serve to bring functionally related neurones closer to firing threshold and facilitate their interactions. Such a widespread increase in excitability could help in recruiting diverse groups of neurones for an intended sensorimotor behaviour (Murthy and Fetz 1996a). However, this view seems difficult to reconcile with a decreased cortical excitability, demonstrated by transcranial magnetic stimulation, during the μ-rhythm rebound elicited by median nerve stimuli (Chen et al. 1999). However, in this context it is important to keep in mind that LFP oscillations represent cortical activity on a much smaller spatial scale than macroscopic EEG and MEG oscillations. The spatial integration of LFPs to macroscopic signals recorded outside the head will naturally lead to a loss of detailed spatial information. Thus, it may well be that several functionally heterogeneous oscillations exist in the sensorimotor cortex. In scalp recordings quantitatively dominating oscillations will be detected preferentially.

To further test the validity of the attention hypothesis animal experiments are needed where only the attentional demand of a sensorimotor task is varied.

Cortico-motoneuronal drive

The presence of coherence between motor cortex and EMG oscillations during isometric muscle contraction suggests that the oscillations may act as a component of the descending motor cortical command, in addition to changes in the neuronal firing rates, to recruit spinal motoneurones. Simulation studies indeed demonstrate that synchronous oscillations would act as a stronger input to recruit spinal motoneurones than an asynchronous command having the same overall firing rate (Murthy et al. 1994, Baker et al. 1997). It has therefore been suggested that oscillations might represent an efficient means of maintaining a tonic drive to motoneurones with as slow firing rates as possible (Baker et al. 1997, Hari and Salenius 1999). According to this view, oscillations may reflect a stable dynamic state with relatively low computational effort which might be advantageous for the maintenance of steady isometric contraction. During such a task, the motor cortex could be operating in a mode of increased oscillatory activity with efficient motoneurone recruitment. However, it has been suggested that the highly predictable nature of oscillatory firing may limit cortical processing capacity, and therefore a different mode may be required for skilled movements (Kilner et al. 1999). This would agree with findings of monkey experiments showing that LFP oscillations recorded in primary motor cortex during a precision grip task are clearly less during the movement than the hold phase (Baker et al. 1997). Similarly, cortico-muscular coherence in the 20 Hz range is observed during the hold phase and disappears during movement (Kilner et al. 1999). Whether recruiting of motoneurones during movement does not involve synchronous oscillatory activity but asynchronous cell firing at high rates (Maier et al. 1993, Bennett and Lemon 1996) or whether efficient drive of motoneurones may be achieved by synchronous high frequency oscillations in the 30-100 Hz range (Brown et al. 1998, Marsden et al. 2000) remains controversial. In any case, the available data are consistent with a possible role of sensorimotor oscillations in the efficient recruitment of motor units during isometric contractions.

Motor binding

In the visual areas coherent oscillations at around 40 Hz have been proposed as a mechanism to bind together spatially distributed but functionally related neurone pools (Singer 1993). Applied to the motor system, the binding hypothesis would predict that different cortical sites exhibit independent oscillations that become synchronised preferentially during movements or behaviours involving the coordination of neural responses at these sites. Whereas several studies have now confirmed the presence of oscillations which may transiently synchronise over spatially separate areas of the sensorimotor cortex (Murthy and Fetz 1996a,b, Baker et al. 1997, Donoghue et al. 1998), no precise relation between synchronisation of LFPs and different components of movement or EMG activity has been found (Murthy and Fetz 1996a). Furthermore, synchronisation between two cortical sites did not occur more often when the sensorimotor task involved the two recording sites. This led the authors to conclude that synchronisation of LFP oscillations appears too non-specific to be directly involved in mediating the control or execution of movements but may rather have a more general role in higher-order and attention-related aspects of motor behaviour (Murthy and Fetz 1996a).

Further experiments revealed that synchronised discharges in spatially segregated but functionally conjugated neurones could encode complex aspects of behaviour like movement direction. By using cross--correlation techniques from single- and multi-neuron recordings in monkey motor cortex it was demonstrated that interactions caused by correlated activity carry additional information about movement direction beyond that based on the firing rates of independently acting neurones (Hatsopoulos et al. 1998, Grammont and Riehle 1999, Maynard et al. 1999). These results suggest that synchronisation at the level of unit activity could potentially provide an additional coding dimension for movement direction beyond that based on the firing rates of independently acting neurones.

In a recent electrocorticographic study on patients with intractable seizures significant coherence between recording sites of sensorimotor cortex and EMG of muscles involved in a phasic and tonic motor task was reported to occur at discrete frequencies within a broad range of 7-100 Hz (Marsden et al. 2000). Importantly, these distributed sites were in turn coherent with each other at the same frequency, and the occurrence of coherence was to some extent task- dependent. Thus, so far, these results provide the strongest evidence that synchronisation of LFP oscillations may act as a binding mechanism in the human motor system in order to bring together selected cortical elements into a given task.

Taken together, thorough analysis of sensorimotor oscillatory brain activity and cortico-motoneuronal coupling has lead to new insights into their functional role. Recording techniques, analysis methods, and the conceptual framework have reached a highly sophisticated level and offer exciting prospects for the investigation of physiological and pathophysiological mechanisms of the human sensorimotor system.

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