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Magnetoencephalographic and electroencephalographic studies of spontaneous activity and evoked responses in the sensorimotor system

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Academic Dissertation

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Abbreviations

ACF	Autocorrelation function
DFA	Detrended fluctuation analysis
EEG	Electroencephalography
EPSP	Excitatory postsynaptic potential
ER	Evoked response
ERD	Event-related desynchronization
IPSP	Inhibitory postsynaptic potential
ISI	Interstimulus interval
MEG	Magnetoencephalography
MI	Primary motor cortex
MNS	Median nerve stimulation
PET	Positron emission tomography
PPC	Posterior parietal cortex
SI	Primary somatosensory area
SII	Secondary somatosensory area
SEF	Somatosensory evoked field
SEM	Standard error of mean
SEP	Somatosensory evoked potential
SQUID	Superconducting quantum interference device
TMS	Transcranial magnetic stimulation
VPL	Ventroposterolateral nucleus of the thalamus
VPM	Ventroposteromedial nucleus of the thalamus

List of original publications

This thesis is based on five publications, which are referred to by their Roman numerals.

I. Nikouline VV, Linkenkaer-Hansen K, Wikström H, Kesäniemi M, Antonova EV, Ilmoniemi RJ, and Huttunen J. Dynamics of mu-rhythm suppression caused by median nerve stimulation: a magnetoencephalographic study. Neurosci Lett 2001, 294: 163–166.

II. Nikouline VV, Wikström H, Linkenkaer-Hansen K, Kesäniemi M, Ilmoniemi RJ, and Huttunen J. Somatosensory evoked magnetic fields: relation to pre-stimulus mu rhythm. Clin Neurophysiol 2000, 111: 1227–1233.

III. Schürmann M, Nikouline VV, Soljanlahti S, Ollikainen M, Başar E, and Ilmoniemi RJ. EEG responses to combined somatosensory and transcranial magnetic stimulation. Clin Neurophysiol 2001, 112: 19–24.

IV. Linkenkaer-Hansen K, Nikouline VV, Palva JM, and Ilmoniemi RJ. Long range temporal correlations and scaling behavior in human brain oscillations. J Neurosci 2001, 21: 1370–1377.

V. Nikouline VV, Linkenkaer-Hansen K, Huttunen J, and Ilmoniemi RJ. Interhemispheric phase synchrony and amplitude correlation of spontaneous beta oscillations in human subjects: a magnetoencephalographic study. NeuroReport 2001, 12: 2487–2491.

Abstract

Recent findings indicate that spontaneous cortical neuronal activity may have an impact on different brain functions, including changes in the integrative properties of neurons, information transmission, and detection of stimuli. The character and biological significance of spontaneous activity remains poorly understood, particularly in humans. The studies of the thesis aimed at characterization of spontaneous 10- and 20-Hz activity with magnetoencephalography (MEG) and electroencephalography (EEG) in human subjects, with emphasis on the activity originating in the sensorimotor areas of the cortex.

A relationship between the spontaneous mu rhythm (rolandic 10-Hz oscillations) and somatosensory processing was demonstrated. The results indicate that there is a slight positive correlation between the amplitude of the P35m component of somatosensory evoked fields and the amplitude of pre-stimulus mu rhythm. Albeit weak, this dependency can be interpreted as evidence for regulation of somatosensory processing via changes in spontaneous activity. An enhancement of the P25 component of the somatosensory evoked potential was consistently observed for transcranial magnetic stimulation (TMS) concurrent with somatosensory stimulus. This enhancement can be interpreted (1) as an indication of local interaction between the somatosensory evoked cortical activity and TMS-evoked activity or (2) as supporting a relationship between the background EEG and the evoked potential, this relationship being disrupted by TMS. In turn, somatosensory stimuli have strong influence on spontaneous activity. Median nerve stimulation suppressed mu rhythm at both contra- and ipsilateral somatosensory cortices, but the attenuation was clearly lateralized, being at least 20% stronger contra- than ipsilaterally. Moreover, in the course of the experiment repeated stimulation significantly reduced suppression of mu rhythm in the ipsilateral but not in the contralateral hemisphere. The strong ipsilateral suppression of mu rhythm in the beginning of the experiment may reflect the presence of nonspecific arousal-like activation. Amplitude fluctuations of 10- and 20-Hz oscillations were found to be correlated over thousands of oscillation cycles and to obey power-law scaling behaviour. A hypothesis is formulated that the long-range correlations, and the power-law scaling behavior of spontaneous oscillations find a unifying explanation within the theory of self-organized criticality. Spontaneous rolandic 20-Hz activity (beta oscillations) demonstrated also long-range interhemispheric phase synchrony. Functionally, the phase synchrony can be interpreted on the basis of bilaterality of movement organization. A positive interhemispheric correlation was also found for the amplitude of spontaneous beta oscillations over long time intervals (> 1 s). The low-frequency correlation of spontaneous rhythmic activity may be the source of the low-frequency correlations of the hemodynamic responses in homologous areas, that have been reported previously and have been interpreted to reflect functional connectivity between these areas. Thus, taken together these results indicate that the spontaneous oscillatory activity of the brain can be highly organized in terms of both long-range temporal and spatial correlations.

Introduction

All movements, thoughts and perceptions are accompanied by specific brain activity. In fact, under normal circumstances, the brain is always active, generating enormously complex patterns of neuronal firing. We understand fairly well the cellular mechanisms responsible for the generation of action potentials and postsynaptic potentials, we know micro- and macro-anatomy of the nervous system, but we are far away from the understanding of how thousands of neurons are working as a whole, being involved in the organization of a particular event. It is generally believed that reliable functioning of the nervous system is dependent on the cooperative activity of many neurons in the network. The present thesis is about the neuronal oscillations in the human brain, particularly in the sensorimotor system, measured by magnetoencephalography (MEG) and electroencephalography (EEG). These two methods give no information about single-unit activity but are suitable for the description of the oscillations, created by synchronous performance of a large number of neurons. The main emphasis in the thesis is on studying neuronal activity that is not directly related to any clearly defined cognitive, motor or perceptional tasks. In the literature, this type of neuronal oscillations is often called spontaneous activity. I regard spontaneous activity as neuronal oscillations, which are present both within and outside the time-window of neuronal processing of sensory information. It is also important to note here, that spontaneous activity can be modified by the sensory stimuli. This activity is surprisingly pronounced and may be orders of magnitude larger than the responses evoked by sensory stimuli, thus indicating a very high degree of correlation between the neurons.

Although brain research using EEG and MEG techniques has over many years been mainly focused on evoked responses, recent years have witnessed a renaissance of research on spontaneous cerebral oscillations. This has been facilitated by the development of brain imaging techniques. For example, multi-channel MEG allows to differentiate parieto-occipital and rolandic 10-Hz rhythms, whereas these are not easy to separate in EEG recordings. Transcranial magnetic stimulation (TMS) might also prove to be useful as a tool to modify spontaneous activity or to emulate synchronous synaptic bombardment of a target network, similar to the bombardment created by a large number of neuronal action potentials coinciding in time.

Several recent experiments in cats show that the continuous spontaneous activity is a general basis for the proper functioning of the network, where a simple factor — the number of synaptic events — is a critical requirement (Paré et al., 1998; Destexhe and Paré, 1999). Spontaneous activity might even be beneficial for the robust detection of sensory information (Nuñez et al., 2000). Taken together, these facts suggest that spontaneous oscillations are important for proper brain functioning. At the same time, it is not rare to encounter in the literature statements questioning the significance of spontaneous oscillations. Clearly, our understanding of the spontaneous cerebral oscillations is still largely incomplete.

The present studies aimed at improving our understanding of cortical oscillations, especially in the sensorimotor system. Rolandic and occipital oscillations as well as somatosensory evoked responses were studied with whole-scalp EEG and MEG techniques and with TMS.

Review of literature

Oscillatory brain activity

As a reaction to an external event, the brain generates evoked responses. However, a prominent oscillatory brain activity is evident even in the absence of any external stimuli. Although being spontaneously generated, this oscillatory activity may change as a result of experimental manipulations. Experiments in cats revealed a high degree of correlation between the activity of a single neocortical neuron (measured extracellularly) and the spontaneous/evoked (measured with optical imaging) dynamics of the whole network in which this neuron was embedded (Tsodyks et al., 1999). This correlation is a demonstration of synchronous activation of separate functional domains with similar properties over the extended cortical areas. Recent data have revealed an increase of membrane conductance during epochs of intense synaptic bombardment compared to the periods that were free of extensive synaptic events (Paré et al., 1998; Destexhe and Paré, 1999). It is also known that dendritic attenuation of synaptic potentials and currents depends on the membrane conductance. Therefore the change in the conductance imposes strict conditions on the convergence or coincidence of many synaptic inputs required for the cell discharge. As a net effect, different levels of spontaneous activity might be a powerful mechanism affecting the susceptibility of the network to incoming stimuli (Hô and Destexhe, 2000).

One should also take into account that background activity can be decomposed into two components: a) tonically active conductance of the neuronal membrane and b) voltage fluctuations of the neuronal membrane. It is exactly the tonically active membrane conductance that is related to the aforementioned changes in cell responsiveness as a function of spontaneous synaptic events. Furthermore, the responsiveness of neurons can be enhanced in the presence of voltage fluctuations as was shown in the experiments with modeling of the neuronal activity (Hô and Destexhe, 2000). A remarkable feature of this enhancement is that it was found for a level of background activity similar to the background activity recorded *in vivo*. This suggests that spontaneous oscillations might represent conditions close to optimal for enhancing the responsiveness of the neurons, thus facilitating information transmission. Similar results were obtained for the somatosensory system of rats (dorsal column nuclei), where the effectiveness of signal transmission was demonstrated to be dependent on pre-stimulus oscillatory activity (Nuñez et al., 2000). Taken together, these recent studies imply a functional importance of spontaneous oscillations. The issue of pre-stimulus oscillatory activity and the characteristics of the sensory processing in human cortical activity were addressed in study II of the present thesis.

Brain oscillations in humans are often defined in terms of the frequency content and reactivity. The rhythms relevant for the present study are: occipital alpha and central mu rhythm (8–13 Hz) and central beta rhythm (~ 20 Hz). Terminologically speaking, one may refer to mu and beta rhythms as 10-Hz and 20-Hz oscillations, respectively. In some cases both frequencies are regarded as the two components of mu rhythm (Hari and Salmelin, 1997). Unless mentioned otherwise, mu rhythm refers to 10-Hz oscillations in the present thesis.

All studies were performed with subjects being wakeful. However, the aforementioned brain rhythms may also be present during some sleep stages (Yamada and Kooi, 1975; Duntley et al., 2001).

Alpha rhythm

Alpha rhythm is a prominent 8–13 Hz activity, which is visible in MEG and EEG recordings above parietal and occipital regions of the head. This rhythm shows strong amplitude modulation in the eyes open *vs.* eyes closed condition, being stronger in the latter. We used this

feature of the alpha oscillations in study IV as an approach allowing us to study dynamics of alpha activity with quantitatively different levels of its mean amplitude.

The sources of alpha rhythm have been reported to be located in the calcarine fissure, the parieto-occipital sulcus and the surrounding occipital and parieto-occipital areas (Chapman et al., 1984; Williamson and Kaufman, 1989; Salmelin and Hari, 1994a). Lopes da Silva et al. (1973) showed in animal experiments a high coherence between the cortical alpha rhythm and alpha rhythm in the lateral geniculate body, thus suggesting the importance of the thalamo-cortical connections for the generation of this activity. Alpha oscillations are known also to propagate across the cortex (Lopes da Silva et al., 1980).

Alpha oscillations are most clearly affected by changes in the visual environment. Vanni et al. (1997) demonstrated with MEG that the amplitude of alpha rhythm is inversely related to saliency or familiarity of the presented visually objects. An increase of alpha rhythm amplitude was shown in the occipital areas, which are related to the ignoring of visual information (Worden et al., 2000).

Although alpha rhythm is most directly related to visual processing, its reactivity with respect to different cognitive tasks is well recognized (Ray and Cole, 1985). Klimesch et al. (1999) in EEG experiments demonstrated an increase in the amplitude of alpha rhythm only for its upper frequency range (10–12 Hz) during mental activity, but not for the 8–10 Hz oscillations. An interesting positive correlation was reported in combined positron emission tomography (PET) and EEG measurements between the power of alpha activity and the regional cerebral blood flow in amygdala and hypothalamus, thus possibly reflecting a link between emotional states and alpha oscillations (Sadato et al., 1998).

The dynamic of alpha rhythm is also affected by sleep-wakefulness cycles. It was suggested that the enhancement of theta/low-frequency alpha activity in the waking electroencephalogram in the short sleepers may be the result of long-term adaptation to chronically short sleep (Aeschbach et al., 2001).

Mu and beta rhythms

The features of EEG mu rhythm were originally described by Gastaut (1952). It is composed of 10- and 20- Hz components that are frequently phase-locked, creating the well-known "comb-like" pattern. In EEG recordings, mu and beta rhythms have maximum amplitude above the central head regions, corresponding approximately to C3 and C4 locations according to the international 10–20 system (Pfurtscheller, 1986). MEG studies show that the mu rhythm is generated near the primary somatosensory cortex in the vicinity of N20m sources and the beta rhythm is generated more anteriorly, presumably in the motor cortex (Tiihonen et al., 1989; Salmelin and Hari, 1994b). Electrocorticographic recordings have revealed sources of mu and beta rhythms in both pre- and postcentral gyrus (Arroyo et al., 1993; Crone et al., 1998).

Electroencephalographic experiments in humans revealed lack of mu-rhythm coherence between the right and left hemispheres, thus probably indicating at least partially independent sources (Leeuwen et al., 1978). The phase synchrony between the beta rhythms in the two hemispheres is addressed in study V. The issue of interhemispheric phase-locking may be important for the understanding of the mechanisms responsible for the organization of bilaterally distributed brain functions.

The mu rhythm is a prominent feature of both the wake and sleep human electroencephalogram. However, during the sleep it occurs only during the rapid eye movement stage (Duntley et al., 2001).

The reactivity of mu and beta rhythms is for the most part related to sensorimotor tasks. The mu rhythm has been shown to be suppressed after somatosensory stimulation, the attenuation being

stronger in the contralateral than in the ipsilateral hemisphere (Gastaut, 1952; Pfurtscheller, 1989). More recent MEG experiments (Salenius et al., 1997b) have revealed stronger contralateral attenuation of the 20-Hz rhythm after the median nerve stimulation, but bilaterally equal attenuation of the 10-Hz rhythm. The reactivity of mu rhythm to somatosensory stimulation is investigated in study I. An initial decrease in the amplitude of mu and beta rhythms after somatosensory stimulation is followed by their increase, which occurs 100–300 ms earlier for beta than for mu rhythm (Salenius et al., 1997b). An attenuation of mu and beta rhythms during the preparation and execution of movement (e.g. thumb twitch, index finger abduction) has been shown in both EEG and MEG studies (Derambure et al., 1993; Salmelin and Hari, 1994b; Leocani et al., 1997; Crone et al., 1998). The post-movement period is characterized by an increase in amplitude of both mu and beta rhythms (Salmelin and Hari, 1994b; Pfurtscheller et al., 1998; Taniguchi et al., 2000). Both rhythms are also modulated by visual perception (Vanni et al., 1999).

A coherence was observed recently between the electroencephalographic beta rhythm and muscle activity during maintained voluntary contractions (Conway et al., 1995; Salenius et al., 1997a; Mima and Hallett, 1999), suggesting involvement of cortical neurons in the generation of motor-unit synchronization.

Self-Organized Criticality

The traditional way to model the complexity of EEG and MEG activity is to treat these oscillations on the basis of low-dimensional chaotic systems (Babloyantz and Destexhe, 1986). Using this framework, the EEG complexity is usually indexed by the correlation dimensions (Grassberger and Procaccia, 1983). The results of this approach in general indicate that EEG does not represent low-dimensional chaos (Pritchard and Duke, 1995; Paluš, 1996; Cerf et al., 1997; Stam et al., 1999), except in rare and very transient segments of the signals (~ 1–10 s).

An alternative framework for conceptualizing apparently complex systems and for analyzing their dynamics is the theory of self-organized criticality (SOC; Bak et al., 1987, 1988), which we applied in study IV for the analysis of spontaneous oscillations in 10- and 20-Hz frequency ranges. In physics, a critical point is reached when a set of parameter values is chosen so that a system balances at the state of a phase transition. Self-organized critical phenomena, in contrast, emerge naturally in nonlinear multi-unit systems, which reach a critical state unavoidably because of their intrinsic dynamics, i.e., without external tuning. Once a complex system has evolved to the critical state, several parameters that characterize the system's spatio-temporal behaviour obey a power-law distribution. This indicates that there is no characteristic scale for the underlying process. Systems evolve by themselves and the interactions between local elements of a given system keep the dynamics in the critical state. This intrinsic dynamic is the basis for the manifestation of long-range correlations, which can be revealed using scaling analysis (Peng et al., 1994; Bak, 1997).

A sand-pile model is considered to be the archetype of a self-organized critical system (Bak, 1997). Sand is slowly dropped onto a surface, forming a pile. As the pile grows, avalanches of different sizes occur. The frequency-area distribution of this system was found to satisfy a power-law distribution, showing no typical size of the avalanches. Power-law scaling behaviour has been revealed for complex systems such as forest fires (Malamud et al., 1998), earthquakes (Bak 1997), financial markets (Mantegna and Stanley, 1995), and heartbeats (Peng et al., 1995).

Some authors have hypothesized that the principle of SOC would be beneficial for the brain mechanisms to process information optimally (Stassinopoulos and Bak, 1995). They argue that the system at a critical state has a very high susceptibility, allowing even very small inputs (e.g., sensory stimuli) to propagate through the entire system, changing its behaviour radically.

Synchrony in the brain

Activity in the brain is characterized by the synchronous activation of many neurons. This is true both for the neurons belonging to a local network and for those located in areas remote from each other (long-range synchrony). The use of MEG and EEG techniques allows one to study only the long-range synchrony, because of the spatial resolution of these methods. Long-range synchrony on the level of the cortex can be created by subcortical structures, e.g., mesencephalic reticular formation (Munk et al., 1996) or mediated by cortico-cortical connections (Engel et al., 1991; Singer 1999). Recently, the idea of synchronized activity was advocated as being important for the facilitation of information transmission between the neuronal networks (Hô and Destexhe, 2000). In a model, these authors demonstrated that coinciding (synchronized) activity of many neurons is needed for reliable detectability of the events in a target cell on the basis of spatial averaging, which is an alternative to the averaging of events in time.

Originally, the synchronization of neuronal activity was proposed as a way to solve the binding problem, i.e., the integration of many simultaneous processes (Singer, 1999). Synchronized activity is linked to the required operation and only those activities evoked by common tasks are bound together in a dynamically formed ensemble. Spontaneous synchrony in turn is thought to represent a relatedness or preparation of a given coupled neuronal population for a further joint involvement in a particular task (Singer, 1999; Fries et al., 2001). Although the binding hypothesis is popular among neuroscientists, some data appear to be controversial to this point of view. The main argument of these researchers was a demonstration of the cortical oscillations which were not related to the stimulus parameters and psychophysical measures of the animals' performance (Young et al., 1992; Bair et al., 1994).

Proposed originally for sensory processing, the importance of synchrony has been also demonstrated for sensorimotor coordination (Roelfsema et al., 1997). In this study, the authors have shown an increase of synchrony between the neuronal action potentials in sensory and motor areas of cat brain during the preparation and execution of a task. Another example of synchrony in the motor system is a demonstration of coupling between electroencephalographic 20-Hz oscillations in the human motor cortices and the muscle activity (Conway et al., 1995; Mima and Hallett, 1999).

Human EEG and MEG studies demonstrated recently a variety of findings related to long-range synchrony (Varela et al., 2001). In EEG experiments related to face perception, Rodriguez et al. (1999) showed synchronization between occipital, parietal and frontal areas when subjects were able to identify a face pattern in ambiguous visual stimuli. Another study demonstrated an increased inter- and intrahemispheric coherence of EEG signals in the case of conscious perception of a visual stimulus in a binocular rivalry task (Srinivasan et al., 1999). Using EEG technique, Miltner et al. (1999) have shown an increased coherence between the visual and parietal cortical areas in a paradigm based on visuotactile association. One should mention, however, that studies related to the synchronization issue are for the most part based on correlative approaches. An important part here would be a demonstration of brain mechanisms that are not only correlated with synchronization patterns but are critically dependent on them.

Somatosensory system and primary motor cortex

Receptors and spinal cord

The processing of stimuli in the somatosensory system starts from the receptor level. The parceling of the information begins already on this level, where different modalities are represented by different receptors. Basically, four modalities constitute the whole spectrum of sensations in the somatosensory system: mechanoreception (sense of touch), thermoception, nociception, and

proprioception (Gardner et al., 2000). Mechanoreception is based on the slowly adapting Merkel disks and Ruffini corpuscles, and the rapidly adapting Meissner and Pacianin corpuscles. Thermoception and nociception are represented by bare nerve endings. Proprioception is represented by the ruffini-like and pacianiform-like endings, bare nerve endings, and Golgi endings. Each of these receptor types belongs to a dendrite of a neuron, whose soma is located either in the dorsal root ganglion or in the trigeminal ganglion. Medium and large diameter axons that carry tactile and proprioceptive information enter the dorsal column and either terminate in layers IIb and III or turn to ascend in the gracial and cuneate fasciculi to the medulla. This ascending pathway is located in the dorsal column. The dorsal-column part of the somatosensory system conveys tactile and proprioceptive information. Small-diameter fibers that carry information about temperature and pain terminate in layers I, IIa, V, VI, and X of the spinal cord. Axons from these layers give rise to the anterolateral pathway, which conveys information about thermal and nociceptive stimuli.

Brain stem and thalamus

The dorsal column pathway consists of axons that terminate in the gracile (information from the lower parts of the body) and cuneate (information from the upper parts of the body) nuclei in the caudal medulla. These nuclei give rise to axons that decussate and go to the ventroposterolateral nucleus (VPL) of the dorsal thalamus. VPL contains modality-specific neurons with small receptive fields (Somjen, 1972). Neurons of the anterolateral system project to reticular formation, superior colliculus, periaqueductal gray region, and to the dorsal thalamus (Somjen, 1972). Neurons of these structures have wide receptive fields and can respond to stimulation of the different modalities (Whitlock and Perl, 1959).

Somatosensory afferentation from head largely belongs to the trigeminal nerve system and reaches ventroposterormedial nucleus (VPM) of the thalamus. The representation of somatosensory features in the trigeminal system may arise from the interactions of neurons within and between the primary somatosensory cortex and VPM nucleus, so that multiple coding strategies may be used simultaneously to represent the location of tactile stimuli (Ghazanfar et al., 2000).

Primary somatosensory cortex (SI)

SI includes Brodman areas 3a, 3b, 1 and 2 and has a clear somatotopic organization, representing contralateral parts of the body (Kaas, 1991).

The majority of projections to SI arise from the ipsilateral VPL and VPM nuclei of the thalamus. Thalamic projections have higher density in areas 3a and 3b than in the areas 1 and 2 (Jones and Powell, 1970; Jones, 1975). The thalamocortical fibers terminate mainly on the neurons of layers IIIb and IV (Jones, 1975; Shanks and Powell, 1981). Groups of thalamo-cortical fibers with similar properties of place and modality terminate in patches of 400–500 μm (Mountcastle, 1998). Each fiber divides to form a bundle of terminal axon segments and synaptic buttons that distribute throughout its particular patch (Jones, 1995). Divergence and convergence occur in SI for coding of place but not of modality (Alloway and Burton, 1991; Mountcastle 1998).

Neurons in areas 3b and 1 mainly respond to cutaneous stimulation; areas 3a and 2 predominantly respond to deep stimuli, both cutaneous and proprioceptive (Somjen, 1972). It seems that area 1 is the only one primarily responsible for the analysis of moving stimuli (Bodegard et al., 2000). Area 3b has the largest cortical surface related to digit representation (Sur et al., 1980) and cells with the smallest receptive fields (Paul et al., 1972).

Areas 1, 2, and 3 are tightly interconnected. Area 3b sends fibers to area 1 and to a smaller extent to area 2 (Vogt and Pandya, 1978; Shanks et al., 1985). An ablation of area 3b abolishes the

cutaneous response in area 1, suggesting that information is processed in sequence from area 3b to area 1 (Garraghty et al., 1990). Area 1 in turn sends fibers to area 2. Area 3a projects to areas 1 and 2 (Jones et al., 1978). Interconnections between these areas suggest an increase in the number of neuronal networks involved in the processing of somatosensory information as time goes by after the stimulus presentation. This in turn implies that the later stages of somatosensory processing might be in statistical sense more susceptible to the changes in the internal state of these networks.

The area SI is primarily responsible for the sensory coding of somatosensory stimuli. Almost any damage within this area produces severe deficits that are related to the discrimination of topical, amplitude and texture-like features of the somatosensory stimuli (Gardner and Kandel, 2000). Stimulation of this area evokes sensations similar to numbness and tingling (Penfield and Jasper, 1954). These sensations were dependent on the site of the stimulation, revealing somatotopic organization of the somatosensory cortex. Being somatotopically organized, SI area can undergo significant plastic changes, e.g., in case of amputation (Ramachandran, 1998). Surprisingly, however, these changes do not have an effect on the conscious perception of stimulation of neighboring undamaged nerves (Moore and Schady, 2000). Recently it was shown also that not only the somatotopical organization of SI matters when deciding about the spatial location of the stimuli, but also the temporal structure of the neuronal response is of a great importance (Panzeri et al., 2001).

SI areas of the two hemispheres are interconnected via the corpus callosum showing both matched and mismatched projections for similar body parts (Zhang and Deschenes, 1997; Krubitzer et al., 1998). It was reported also that a complete callosotomy might abolish any responses to tactile stimulation in the ipsilateral somatosensory cortex (Fabri et al., 1999). These results are important for the interpretation of the results related to bilateral activation of both hemispheres after the unilateral somatosensory stimulation (study I).

As a trend in the current neurophysiological studies of sensory systems, evidence has accumulated about the unimodal sensory areas being involved in the processing of more than one modality. The somatosensory system is not an exception. Results indicate that SI neurons can be involved in the retaining of visual information that has been associated with the touch of an object (Zhou and Fuster, 2000). The presence of such cells suggests that nontactile stimuli, associated with touch, have access to cortical neuronal networks engaged in the haptic sense.

Secondary somatosensory cortex (SII)

SII is located within and along the upper bank of the Sylvian fissure. Animal experiments have shown that neurons in SII have large, often bilateral, poorly demarcated and extensively overlapping receptive fields (Whitsel et al., 1969).

Thalamic inputs to SII originate mostly from VPL projections (Jones and Powel, 1970). SII also has reciprocal intra-hemispheric connections with areas 1, 2 and 3b of SI (Jones et al., 1979). In addition to the fibers from SI cortex, the neurons of SII cortex receive input from the contralateral SII cortex (Burton and Robinson, 1987). Serial processing after the somatosensory stimulation in humans was suggested in electro- and magnetoencephalographic experiments showing initial activation of SI, with the following activation of SII (Allison et al., 1989b; Forss et al., 1994a; Wikström et al., 1996).

Recent MEG experiments showed that there could be parallel processing of somatosensory information in the human contralateral SI and ipsilateral SII cortices (Forss et al., 1999). These results are at variance with the data showing that ipsilateral SII activation is rather mediated via the corpus callosum (Fabri et al., 1999).

SII area is generally believed to be responsible for the processing of somatosensory information that is more complex than just a mere coding of stimuli. It was shown that lesions of SII seriously affect learning of manual skills (Ridley and Ettlinger, 1976).

Magnetoencephalographic study of SII area revealed an important role of this area in the integration of sensory information into motor programs (Huttunen et al., 1996) and for processes where attention is required (Steinmetz et al., 2000). SII area is also a strong candidate for the processing of nociceptive information (Valeriani et al., 2000).

Posterior Parietal Cortex (PPC)

PPC also receives quite a substantial amount of somatosensory information. The most extensively studied parts of the PPC are Brodmann's areas 5 and 7. Area 7 receives somatosensory projections mainly from the areas SI and SII. An important finding is that the neurons in this area can be activated both by cutaneous, kinaesthetic and visual stimuli (Hyvärinen and Poranen, 1974), thus revealing truly multimodal nature of this area. A visuotactile interaction was shown also in a study where tactile stimulation enhanced activity in the visual cortex, most likely via the back-projections from multimodal parietal areas (Macaluso et al., 2000). Neurons in PPC often require very complex pattern of stimulation. Sakata et al. (1973) showed that neurons in area 5 might respond only when there is an activation of several joints and sometimes even bilateral stimulation is required. Activation of posterior parietal cortex in humans in response to simple somatosensory stimulation was suggested in MEG studies (Forss et al., 1994a).

Others areas related to somatosensory processing

Richer et al. (1993) found that stimulation of the posterior cingulate gyrus in humans leads to contralateral tactile sensations, whereas ipsilateral sensations were evoked by stimulation in the vicinity of the cingulate sulcus. PET experiments demonstrated that temperature sensations activated the insular cortex (Craig et al., 2000). Hemodynamic studies (PET and functional magnetic resonance imaging experiments in humans) revealed also activation of the supplementary motor area by somatosensory stimuli (Fox et al., 1987; Korvenoja et al., 1999). Cerebellar cortex was proposed to have an inhibitory effect on the SI responses in cats (Kolodziejak et al., 2000).

Primary motor cortex (MI)

MI corresponds to Brodmann's area 4, being located in the precentral gyrus. This area contains large efferent pyramidal neurons (Betz cells) from which the corticospinal projections originate. Similar to primary somatosensory cortex, MI is topographically organized with specific regions representing each part of the body on the contralateral side. However, myotopy in MI holds only for the large body divisions, such as the leg, face, and arm. When assembled into a comprehensive map, sites for any particular body part appear widely distributed, multiple, and overlapping (Donoghue et al., 1992; Nudo et al., 1992). In humans area 4 was subdivided into areas '4 anterior' and '4 posterior' on the basis of cytoarchitecture and quantitative distributions of transmitter-binding sites (Geyer et al., 1996). Moreover, the topography may be changed, demonstrating remarkable plasticity. Transection of a given motor nerve can lead to a substitution of a corresponding area in MI by the representation of adjacent body parts (Donoghue et al., 1990). Although MI is characterized by the predominant representation of the contralateral parts of the body, imaging studies often reveal a bilateral activation of MI cortices during the preparation and execution of unilateral movements (Cramer et al., 1999; Kinoshita et al., 2000). Simultaneous activation of the two MI areas might reflect tight functional coupling of these areas. This coupling in turn was shown to be beneficial for the organization of highly skilled bilateral movements (Andres et al., 1999). The probable consequences of this bilateral activation are also discussed in study V.

There is also a tight relationship between somatosensory processing and movement organization. Rosén and Asanuma (1972) discovered in monkeys that information generated in sensory receptors (in muscles, skin, and joints) during movement are sent back to the same neurons in the motor cortex that generated the movement.

Neurons in the area MI are primarily responsible for controlling movement kinematics and dynamics. Evarts (1968) demonstrated that MI pyramidal tract neurons change their discharge frequency according to the force exerted. Activity of MI neurons is also correlated with the direction and the velocity of the movement, and also with the position of the joints (Thach, 1978; Ashe et al., 1994).

Somatosensory evoked responses

Different types of electric and mechanical somatosensory stimuli can be used to evoke cerebral responses in human subjects. Electric stimuli are most commonly used for the stimulation of the major nerve trunks (e.g., median, tibial, peroneal nerves). Electric stimulation directly activates nerve fibers evoking a synchronous afferent volley, which produces well-defined and easily recordable responses in the cortex. The disadvantage of electrical stimulation is unspecific stimulation of afferent fibers that are related to different somatosensory modalities. Alternatives to electric stimulation include air-puffs or mechanical vibrations (Forss et al., 1994b; Jousmäki and Hari, 1999).

When applying electric stimulation, it is preferable to have current-output stimulators, since the strength of the current will not be affected by changes in the impedance.

Somatosensory evoked potentials (SEP)

The sensitivity of EEG recordings to both tangential and radial sources as well as relatively low spatial resolution can make interpretations of the SEP components difficult and ambiguous. However, matching of EEG responses with intracortical and MEG recordings allows one to clarify SEP component genesis.

Because of the complex anatomy of the somatosensory cortical networks, it is quite clear that somatosensory stimuli should evoke multiple sources in the cortex. In recent years, the generation of the cortical short-latency responses (< 40 ms) have been clarified. The current generator of N20/P20 (parietal/frontal) to upper extremity stimulation most likely arises at the postcentral bank of the central sulcus, corresponding to area 3b (Broughton et al., 1981; Allison et al., 1989a). There is also evidence suggesting that the P22 component is generated in the crown of the postcentral gyrus in area 1 (Allison et al., 1991). However, location of N30 generators remains unclear. Some authors have suggested that the potential distribution of this component implies the presence of radially oriented components in the precentral gyrus (Papakostopoulus and Crow, 1980; Desmedt and Cheron, 1981). Another explanation for the N30 component is related to the existence of a tangential source in area 3b (Broughton et al., 1981; Allison et al., 1989a). A recent source modeling study provides evidence for a pre-central N30 generator, predominantly tangentially oriented and located within the motor cortex (Waberski et al., 1999).

P27 has a maximum of its potential distribution above the contralateral parietal area (Desmedt and Cheron, 1980; Yamada et al., 1984; Deiber et al., 1986). In fact, some authors refer to this peak as P25 because of its latency being often around 25 ms (Abbruzzese et al., 1990; Gandevia and Ammon, 1992; Ugawa et al., 1996). This peak is most likely generated in the postcentral cortex, possibly in area 1 (Allison et al., 1991). Area 1 is largely situated on the surface of the postcentral gyrus. Superficial location makes neurons in this area especially susceptible to

transcranial magnetic stimulation. This observation is especially relevant for the interpretation of the modulation of P27(P25) amplitude by TMS pulses (study III).

The interpretation of the generation of the long-latency (>40 ms) components is somewhat problematic, as 1) the potentials of these components show considerable interindividual variation (Goff et al., 1977; Desmedt and Tomberg, 1989; Srisa-an et al., 1996) and 2) the amplitude and latency of these components are very susceptible to experimental conditions. EEG dipole fitting suggests that N60 is located in the posterior bank of the central sulcus contralateral to the stimulated hand (Srisa-an et al., 1996). However, a somatotopic organization for N60 has not been revealed (Karhu et al., 1992; Srisa-an et al., 1996).

Proprioceptive stimulation of human upper limb evokes a double positive peak at contralateral central locations (P70, P190) and a single negative frontal N70 component (Arnfred et al., 2000). Very late SEP components with latencies of about 300 ms (P300) are most likely related to the conscious detection of stimuli (Hashimoto et al., 2000).

Fast EEG oscillations (~ 600 Hz) were found as being superimposed on the N20 component (Curio, 2000). Sources of these oscillations were located both in the thalamus and primary somatosensory cortex (Gobbelé et al., 1998).

SEPs are widely used in the clinic. SEP abnormalities, reflecting pathology in the brain or spinal cord, are present in up to 90% of patients with definite multiple sclerosis (Chiappa, 1990). SEPs are useful in classifying the type of origin of myoclonus (Hallet et al., 1979). Intraoperative SEPs are recorded routinely using electrode strips or grids of electrodes applied directly to the exposed cortex during neurosurgical procedures in and around the somatosensory cortex (Kraft et al., 1998). The N20 response is used to identify the primary somatosensory cortex in the postcentral gyrus. By inference, the motor cortex in the precentral gyrus can be localized as well, and this information is used to guide the surgical procedure.

Somatosensory evoked fields (SEF)

The study of somatosensory evoked fields began with the work of Brenner et al. (1978) on the steady-state somatosensory responses. This work was followed by many other SEF studies (Hari et al., 1984, Huttunen et al., 1987; Ishibashi et al., 2000). The SEF response after upper limb stimulation starts with deflection peaking at 20 ms (N20m). The N20m deflection has a dipolar field pattern and the N20m dipole points anteriorly, being situated in SI cortex. This dipole orientation corresponds to a tangential model with the source in area 3b (Allison et al., 1989a). Fast (600 Hz) MEG oscillations were shown to be superimposed on the N20m component (Curio et al., 1997). A corresponding source for these oscillations was located at the primary somatosensory cortex near the hand area.

The next deflection peaks at about 30–35 ms (P35m). The dipole of P35m also appeared to be located in SI area and points posteriorly (Tiihonen et al., 1989).

P35m is followed by N45m and P60m components, also generated in area SI (Huttunen et al., 1987; Wikström et al., 1996). In the latter study, the authors suggested a scheme where P35m is generated by an early inhibitory response, N45m is produced by secondary EPSPs and P60m component reflects late IPSPs in pyramidal neurons of area 3b. Though SEFs vary across subjects in the 100-ms post-stimulus interval, there is remarkable similarity of SEFs within an individual between left and right hemispheres as well as across successive experimental sessions (Tecchio et al., 2000). SEFs are known to be somatotopically organized (Nakamura et al., 1998). Ishibashi et al. (2000) suggested also that somatotopic organization is more pronounced for N20m and P60m than for P35m.

Since both the mu rhythm and the aforementioned SEF components are generated in the area SI, it is reasonable to assume that the mu rhythm and the processing of somatosensory information may be interrelated. Therefore, we examined the relationship between the amplitude

and latency of the SEF components and the amplitude of the pre-stimulus mu rhythm (study II). We also investigated the influence of somatosensory stimulation on the dynamics of the spontaneous mu rhythm (study I).

Initial activation in SI area is followed by activity in SII and PPC. It has been shown that area SII is bilaterally activated after unilateral stimulation, with pronounced activity around 100 ms (Hari et al., 1984; 1993; Simões and Hari, 1999). However, an early activation of area SII (20–30 ms) was also proposed recently on the basis of a MEG study, which used the signal-space projection method (Karhu and Tesche, 1999).

When a train of stimuli is used, area SII produces a sustained field, while SI activation follows stimuli with sharp transient responses up to 12 Hz, thus possibly suggesting weaker inhibitory processes in SII than in SI (Forss et al., 2001).

Activity in the posterior parietal cortex peaks at around 70–110 ms (Forss et al., 1994a). Hoshiyama et al. (1997) showed that PPC has some somatotopic organization in parallel with the 'homunculus' in SI, with the hand area being much wider than the foot area.

Experimental techniques

Magneto- and Electroencephalography (MEG, EEG)

When a neuron is active, small currents flow in the intra- and extracellular space. Synchronous activation of many neurons can be measured as a difference of potentials between two points on the scalp (EEG). Alternatively, the magnetic field produced by the cellular currents can be measured with SQUID sensors (Superconducting Quantum Interference Device; Hämäläinen et al., 1993). MEG and EEG detect mostly currents associated with dendritic excitatory and inhibitory postsynaptic potentials (EPSP and IPSP, respectively; Lewine and Orrison, 1995). Postsynaptic activity from different types of neurons, however, has a very distinct impact on MEG and EEG. Stellate neurons have symmetric dendritic organization. When symmetrically activated, these neurons would produce no potential variation or magnetic field at a distance. Pyramidal cells, however, have a very strong asymmetric dendritic tree, which consists of an apical dendrite and a number of basilar dendrites. Activation of these neurons can cause a strong measurable EEG and MEG signal at a distance (Lewine and Orrison, 1995).

The unique feature of the MEG technique is the transparency of the skull, scalp and brain tissue to the magnetic fields. An EEG signal, however, is strongly influenced by the head properties (like cerebrospinal fluid, skull and fontanelles, Hämäläinen et al., 1993).

Another difference between EEG and MEG is that the latter measures mostly primary currents oriented tangentially with respect to the surface of the head (e.g., sulcus dipoles) (Hämäläinen et al., 1993). EEG is sensitive both to radial and tangential sources.

Transcranial Magnetic Stimulation (TMS)

TMS can be used to activate neurons in different cortical regions. Magnetic pulses induce in the brain electric currents, which lead to changes in the membrane potential (Barker et al., 1985). Both brain and peripheral nerves can be stimulated using rapidly changing magnetic fields of about 2–3 Tesla. Two types of coils are used in TMS: circular and figure-of-eight coils. In circular coils, the current flow in the brain will be strongest under the circumference of the coil, being virtually absent near the center of the coil. Figure-of-eight coils produce the maximal current at the intersection of the two wings, thus producing a more focal stimulation.

TMS induces currents in the brain, thus in principle evoking both depolarization and hyperpolarization of the neuronal membrane. The electric field in the brain should be about 100

mV/mm in order to produce a neuronal activation (Ilmoniemi et al., 1999). Both longitudinal and transverse electric field components cause the activation of axons (Ruohonen et al., 1996). An excitation at bends of axons or at synaptic terminals are the most probable when stimulating the brain (Roth, 1994). It was shown also that the corticospinal axons can be directly activated at deep locations using anodal transcranial electrical stimulation (Suihko, 1998).

TMS is most widely used in studies of the motor cortex, especially the hand representation area. Stimulation of distinct parts of motor cortex produces a response in a particular hand muscle with a latency of about 20 ms. Lateral-to-medial currents in the brain activate corticospinal neurons both directly and transsynaptically, while anterior-to-posterior currents activate these neurons predominantly transsynaptically (Di Lazzaro et al., 1998).

Another interesting application of TMS is the possibility to produce so-called reversible "functional lesions" in the brain. For example, one may produce a transient scotoma while stimulating the visual cortex (Amassian et al., 1989; Corthout et al., 1999; Kamitani and Shimojo, 1999) or disrupt memory processes, especially when stimulating prefrontal and parietal cortices (Jahanshahi et al., 1998; Pascual-Leone et al., 1999; Kessels et al., 2000).

A promising application of TMS is its combination with different imaging techniques. TMS has been used simultaneously with EEG (Ilmoniemi et al., 1997), positron-emission tomography (Paus et al., 1997) and functional magnetic resonance imaging (Josephs et al., 1999), providing information on the reactivity and connectivity of the stimulated cortical areas.

TMS is also used in clinical practice. Single pulse TMS can be used to assess the excitability thresholds of the motor cortex and the central conduction time of the corticospinal impulses, in combination with the surface electromyography measurement. E.g., in amyotrophic lateral sclerosis central conduction time may be mildly delayed or desynchronized, which was demonstrated with TMS (Martínez and Trejo, 1999). Rapid-rate TMS was found to be useful in treatment of psychiatric disorders. Stimulation of dorsolateral prefrontal cortex has been shown to have an antidepressant effect (George et al., 1995). Stimulation of left temporoparietal cortex leads to a reduction of auditory hallucinations in schizophrenia patients (Hoffman et al., 2000). Stimulation of motor cortex has been reported to improve motor performance in Parkinson’s disease (Pascual-Leone et al., 1994).

Aims of Study

The main emphasis in the present thesis is put on the understanding of spontaneous activity, particularly in the sensorimotor system. The goal was to explore these oscillations in a context of peripheral stimulation, evoked responses and internal dynamics. Figure 1 shows schematically essential links related to the studied issues. The particular aims of the studies were:

To study the reactivity of spontaneous sensorimotor oscillations to the somatosensory stimulation; and to find a basis for high susceptibility of these oscillations to the stimuli (study I and IV).

To analyze the influence of the spontaneous activity on the processing of somatosensory information (study II and III).

To characterize the temporal and spatial (interhemispheric) structure of spontaneous activity in the sensorimotor system (study IV and V).

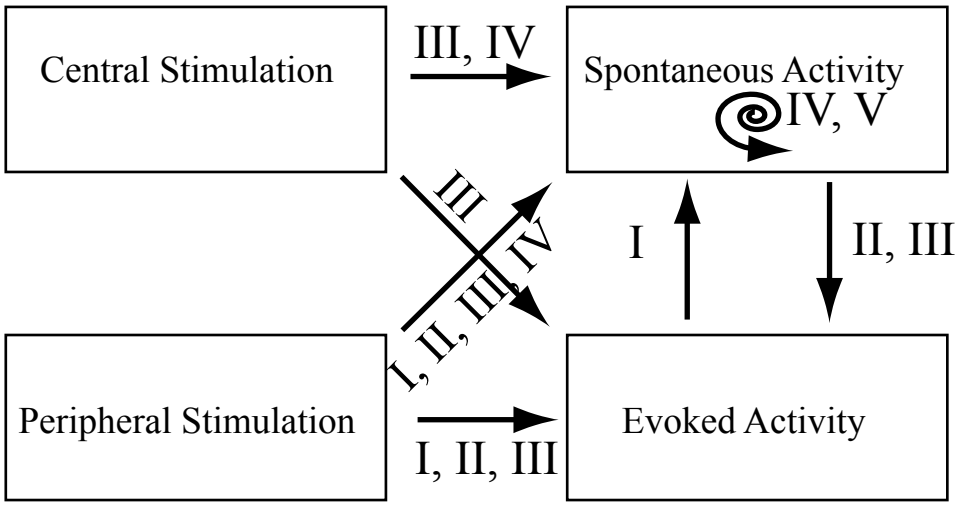

Figure 1. Conceptual scheme showing studied issues in the present thesis. The arrows indicate a link between the elements of the scheme. The Roman numerals on the arrows correspond to a particular study. Central stimulation is defined as an event, which leads to the changes in the neuronal activity, but this event is not related to the peripheral stimulation. Examples of the central stimulation might be TMS or mental operations. The reactivity of spontaneous oscillations was explored in studies I and IV; the relationship between spontaneous activity and evoked responses was addressed in studies II and III; temporal and spatial dynamics of spontaneous oscillations were examined in study IV and V.

Materials and Methods

A summary of the experimental setups is given in Table 1. All subjects were right-handed (20–45 years age range). In the MEG studies, subjects sat comfortably in a chair in a magnetically shielded room (Euroshield Ltd.) and were either watching a video film (studies I and II) or sitting relaxed with eyes closed (studies IV–V). In study III, subjects sat still while fixating their gaze on a marker.

Study	Subjects M F	Age	Hardware	Type of data	Band-pass, Sampling frequency	Stimulation, ISI
I	5 1	23–35	MEG, 122 channels	ER, SA	0.03–100 Hz, 300 Hz	Bilateral, 4.4 s
II	7 4	21–45	MEG, 122 channels	ER, SA	0.03–330 Hz, 1000 Hz	Unilateral, 2–2.5 s
III	5 2	22–37	EEG, 60 channels & TMS	ER	0.5–450 Hz, 1450 Hz	Unilateral, 1.5–2.5 s
IV	9 1	20–30	MEG, 122 channels EEG, 64 channels	SA	0.3–90 Hz, 300 Hz	None
V	5 2	23–32	MEG, 306 channels	SA	0.03–100 Hz, 300 Hz	None

Table 1. Summary of the methods.
M – males, F – females, ER – Evoked responses, SA – Spontaneous activity. ISI – interstimulus interval.

Stimulation

Median nerve stimulation (MNS) was used for the stimulation of the right hand in studies II and III; alternating bilateral MNS was used in study I. Stimuli were 0.2 ms rectangular current pulses with the strength being adjusted above the motor threshold for the abductor pollicis brevis. The interstimulus interval was 2–2.5 s in study II, 1.5–2.5 s in study III and 4.4 s per each hand in study I.

Recordings

MEG recordings were performed with the 122-channel planar-gradiometer system (Neuromag Ltd.) and with the 204-planar-gradiometer + 102-magnetometer system (Vectorview TM, 4D-Neuroimaging Ltd.). The position of the head was determined by detecting the weak currents passed through coils attached to the surface of the head. Data were stored on a hard disk for subsequent off-line analysis. EEG recordings were performed with a MEG-compatible setup, which included 64 electrodes mounted on a cap (Virtanen et al., 1996). A special 60-channel amplifier with an option to be gated during the TMS pulse was used for the simultaneous TMS–EEG recordings (Virtanen et al., 1997). Off-line averaging of the evoked responses was performed in studies I and III. Epochs were rejected from the following analysis if they were contaminated by artifacts (eye blinks, head movement or muscle activity). The peak latency and amplitudes of SEPs or (SEFs) were used for the analysis of evoked responses. The base-line for the averaging was 50 ms preceding the stimulus.

Data analysis

The outlines of data analysis are presented below:

Study I. Event-related desynchronization was induced by the alternating stimulation of the left and right median nerves. Single-trial display and consecutive sub-averaging were utilized in order to reveal the dynamics of mu-rhythm suppression.

Study II. The amplitude of the pre-stimulus mu rhythm was evaluated in three pre-stimulus time intervals (380, 480, and 980 ms). The pre-stimulus amplitudes of mu rhythm were sorted according to magnitude with 20-percentile steps, producing 5 groups of epochs in each subject. Somatosensory evoked fields were then averaged selectively according to these groups. These are referred to as groups 1 (weak mu rhythm) to 5 (strong mu rhythm) in the following text.

Study III. TMS was applied to centro-parietal region either simultaneously with the MNS or 10 ms after it. Block-design was used in order to present MNS, TMS or MNS+TMS conditions. An important issue here was to differentiate between the responses which are obtained by concurrent TMS+MNS stimulation and the responses obtained via the arithmetical summation of TMS responses and MNS responses (synthTMS+MNS). Special shamTMS condition was also introduced as an additional control for the acoustical stimulation, which is produced by the TMS coil discharge.

Study IV. Spectra, autocorrelation function, and DFA were used in order to reveal long-range correlations. As reference data we used broadband environmental noise of the empty magnetically-shielded room and surrogate signals. The latter were obtained by first calculating the Fourier transform of the original EEG recording, randomizing the Fourier phases, and then performing the inverse Fourier transform.

Study V. We calculated synchronization index for intra- and interhemispheric pairs of signals. This index was evaluated for different levels of beta rhythm amplitude. The interhemispheric correlation of the oscillation amplitudes was calculated using the Pearson's coefficient.

A substantial part of the analysis was based on the application of wavelet transformation to the raw data. Wavelet analysis decomposes a time series into time-frequency space (Torrence and Compo, 1998). One of the most common wavelets is the Morlet wavelet, which consists of a plane wave modulated by a Gaussian. The modulus of the complex-output $W(t,f)$ represents the amplitude of the signal at time t and at frequency f. This approach therefore allows one to study amplitude dynamics of a particular rhythmic brain activity (e.g., alpha, mu, and beta rhythms).

On the basis of $W(t,f)$, long-range correlations in MEG and EEG signal were calculated in study IV using detrended fluctuation analysis (DFA, Peng et al., 1994, 1995). In DFA, the modulus of the wavelet-transformed signal at a center frequency f is first integrated over time to produce a vector y of the cumulative sum of the signal amplitude around its average value, where N is the number of samples in the signal. The integrated signal is then divided into time windows of size τ. For each window, the least-squares fitted line (the local trend) is computed; the y-coordinate of this line is denoted $y_\tau(t)$. The integrated signal, $y(t)$, is detrended by subtracting the local trend, $y_\tau(t)$, in each window. The average root-mean-square fluctuation, $<F(\tau)>$, of this integrated and detrended time series is computed as:

$$< F(\tau) >= \sqrt{\frac{1}{N}\sum_{t=1}^{N}\left[y(t) - y_\tau(t)\right]^2}$$

This procedure is repeated for all time window sizes. The scaling is often of a power-law form:

$$< F(\tau) > \propto \tau^{\alpha}$$

The scaling exponent α is extracted with linear regression in double-logarithmic coordinates using a least-squares algorithm. A self-similarity parameter of $\alpha = 0.5$ characterizes the ideal case of an uncorrelated signal, whereas $0.5 < \alpha < 1.0$ indicates power-law scaling behaviour and the presence of temporal correlations over the range of τ.

In study V, phase information from the wavelet-transformed data was used in order to calculate phase synchronization within one hemisphere and between the two hemispheres. Given two time series X and Y, with the corresponding wavelet transforms $W_X(t,f)$ and $W_Y(t,f)$, the cross-wavelet spectrum is defined as $W_{XY}(t,f) = W_X(t,f)\ W_Y^*(t,f)$, where $W_Y^*(t,f)$ is the complex conjugate of $W_Y(t,f)$. The phase θ between the two signals is defined then as the four-quadrant inverse tangent of $Im(W_{XY}(t,f))/Re(W_{XY}(t,f))$, where *Im* and *Re* are the imaginary and real parts of $W_{XY}(t,f)$, respectively.

The synchronization index (S) is a measure of the strength of the synchrony between the two signals and is defined as:

$$S = \frac{1}{N}\left|\sum_{t=1}^{N} \exp(j\theta(t))\right|$$

where N is the total number of time samples and j is the imaginary unit. S varies between 0 and 1 (Lachaux et al., 1999).

Statistical analysis was performed with Fisher's test, ANOVA, non-parametric Friedman's ANOVA, and Wilcoxon matched-pairs test.

Results and Discussion

Study I. Suppression of mu rhythm by somatosensory stimulation

Results

It can be seen that the mu-rhythm event-related desynchronization (ERD) is clearly lateralized to the contralateral side (Fig. 2). Averaged across the subjects, ERD in the contra- and ipsilateral hemispheres was (mean ± SEM) 53 ± 7 and 33 ± 5%, respectively, for the stimulation of left median nerve (Wilcoxon Matched Pairs Test, $P < 0.05$) and 56 ± 7 and 31 ± 6% for the stimulation of the right median nerve (Wilcoxon Matched Pairs Test, $P < 0.05$). The maximum of ERD occurred at 333 ± 20 and 382 ± 35 ms in the contra- and ipsilateral hemispheres, respectively, for left median nerve stimulation; and at 343 ± 7 and 380 ± 43 ms, respectively, for right median nerve stimulation. The ERD latencies did not differ significantly between the contra- and ipsilateral hemispheres (Wilcoxon Matched Pairs Test, $P > 0.05$). The ERD in the ipsilateral hemisphere became less prominent in the course of the experiment and the Friedman's ANOVA showed significant differences for the ERD belonging to the four different consecutive subaverages ($P < 0.001$ for left and $P < 0.001$ for right median nerve stimulation; Fig. 3). However, ERD remained stable in the course of the experiment in the contralateral hemisphere.

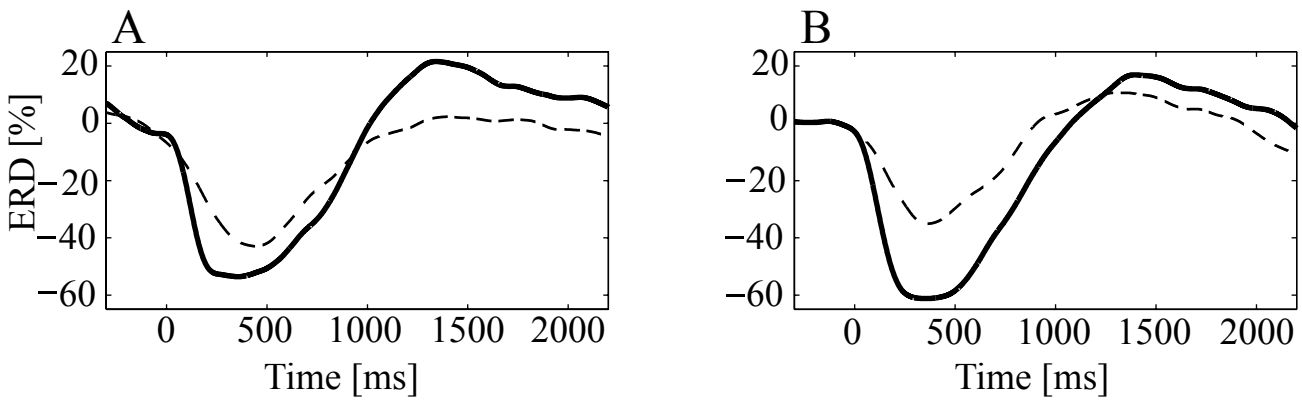

Figure 2. ERD in the contra- and ipsilateral hemisphere of a representative subject. A. Left median nerve stimulation, B. Right median nerve stimulation. Solid and dashed lines show ERD for the contra- and for the ipsilateral hemisphere, respectively.

Discussion

As it was pointed out by Pfurtscheller and Lopes da Silva (1999), calculation of ERD requires presence of a strong spontaneous rhythm (in our case 10-Hz activity). Moreover, the importance of a masking effect of evoked responses on the ERD was also recognized (Kalcher and Pfurtscheller, 1995). In the present study both aforementioned issues were carefully taken into account; we selected subjects with strong mu rhythm and used wavelet-based filters that only pick up signals down to 9 Hz. Therefore, the strength of the ERD was not considerably contaminated by the leakage of energy from SEFs, where the largest components lie in the 4–6 Hz frequency range.

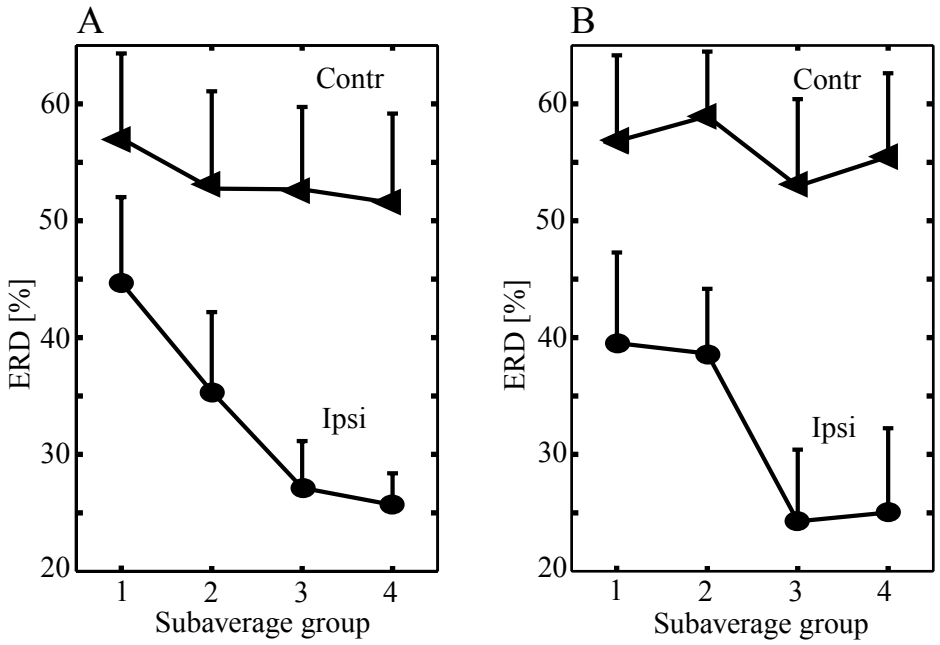

Figure 3. ERD values of four consecutive subaverage groups in the course of the experiment. A. Stimulation of the left median nerve. B. Stimulation of the right median nerve. Ellipsoids and triangles denote ipsi- and contralateral hemispheres, respectively. Bars represent the standard errors of the mean.

The contralateral predominance of mu-rhythm ERD to somatosensory stimulation agrees with previous EEG study (Pfurtscheller, 1989), but differs from a recent MEG study, where no inter-hemispheric asymmetry in the level of 7–15 Hz rhythm suppression was shown (Salenius et al., 1997b). The differences between the results of the latter and the present study may be related to the different parameters for band-pass filtering (7- and 9-Hz lower cut-off frequencies, respectively), which is critical in order to avoid the masking effect from SEFs.

ERD in the contra- and ipsilateral hemisphere behaved differently in the course of the experiment. It was significantly attenuated towards the end of the experiment in the ipsi-, but not in the contralateral hemisphere. It is interesting to note here that contralateral P35m and P60m SEF components show an attenuation and N20m remains stable in the course of the experiment (see study II). This fact and the stability of the contralateral ERD suggest that ERD in the contralateral hemisphere is rather triggered by the initial thalamic afferent volley than by the subsequent somatosensory processing.

Different behaviour of ERD in the two hemispheres may reflect a combination of specific and nonspecific activation during somatosensory stimulation. Nonspecific ERD can be related to the so-called arousal activation, known to be most pronounced for the first repetitions of the stimuli (Graham, 1997; Siddle and Lipp, 1997). The specific ERD is more directly related to the arrival of the somatosensory afferent volley and therefore would be stronger in the contra- than in the ipsilateral hemisphere. Therefore, both the strength and dynamics of the non-specific ERD should be more visible in the ipsilateral hemisphere, where it is not masked largely by the specific ERD.

Study II. Pre-stimulus mu rhythm and somatosensory evoked fields

Results

The mean pre-stimulus amplitude of mu rhythm varied between the groups 1 (small mu amplitude) and 5 (large mu amplitude) by a factor of 2.3–5 across the subjects. The latencies of all three SEF components did not change with respect to the amplitude of the pre-stimulus mu rhythm. Table 2 contains the information about the changes in the amplitude of N20m, P35m, and P60m, when comparing the sub-averages belonging to the weakest (group 1) and strongest (group 5) pre-stimulus mu rhythm. As it follows from the table 2, the amplitude of P35m was the most sensitive to the changes in the mu-rhythm amplitude. Figure 4 shows also individual data for the SEFs averaged with respect to different amount of pre-stimulus mu rhythm during the 480-ms pre-stimulus interval.

	Pre-stimulus Interval		
Component	380-ms	480-ms	980-ms
N20m	n.s.	n.s.	n.s.
P35m	+ 12 %	+ 13%	+ 12%
P60m	n.s.	n.s.	n.s.

Table 2. Modifications of SEF component amplitudes as a function of pre-stimulus mu-rhytm strength. n.s. not significant; + indicates significant ($P < 0.05$, Wilcoxon matched pairs test) increase of the component amplitude in the fifth group compared to the first one.

P35m and P60m attenuated progressively toward the end of the 25–30 min experimental session in three and six subjects, respectively. In these subjects, P35m decreased by 22–51% and P60m by 15–44% from the first averaged $n/5$ epochs to the last averaged $n/5$ epochs, where n is the

total number of epochs. However, mu-rhythm amplitude did not show any systematic changes in the course of the experiment.

Discussion

The results of this study indicate a remarkable stability of the amplitude and the latency of the SEF components with respect to the pre-stimulus mu rhythm. The amplitude of P35m was most clearly affected for all three pre-stimulus intervals, being positively correlated with the amplitude of mu rhythm. P35m changed on average by 8–21% and mu-rhythm amplitude varied by 130–400%, indicating that the slight enhancement of P35m, albeit significant, was at least one order of magnitude smaller than the changes in the level of mu rhythm. Previously, Arieli et al. (1996) demonstrated independence of visually evoked responses and the spontaneous activity. This study implies that when non-phase locked activity is eliminated (i.e., by averaging) one should get the same response in different subaverages. This is in agreement with our study, which shows relative stability of SEFs with respect to variable mu rhythm. Another study shows, however, that pre-stimulus membrane potential is positively correlated with the magnitude of the visually evoked responses (Azouz and Gray, 1999). Predictability of the responses is certainly easier for the single unit activity than for the summated electrical activity of a large population of neurons. However, a recent study in cats demonstrated that summated neuronal corticographic activity might be better as a response predictor, when spontaneous synchronization between different brain areas is evaluated (Fries et al., 2001).

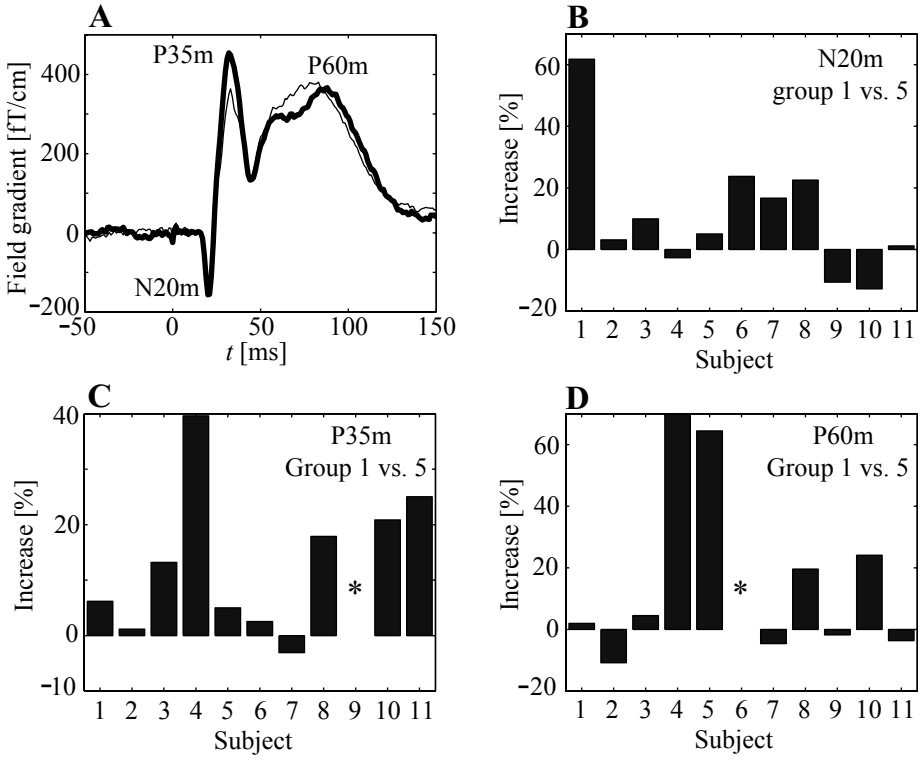

Figure 4. Examples of changes in amplitudes of SEFs belonging to different levels of pre-stimulus mu rhythm (interval 480-ms). A. SEFs averaged with respect to the smallest (group 1, thin line) and the largest (group 5, thick line) mu rhythm for a representative subject. B. Differences in the amplitude of N20m between SEFs belonging to groups 5 and 1 for 11 subjects. C. As in B, but for P35m deflection and 10 subjects. D. As in C, but for P60m deflection. Star indicates missing component in a particular subject.

There was no systematic trend across the subjects for the amplitude of pre-stimulus mu rhythm to be changed during the experiment. This fact suggests an absence of unspecific factors related to the duration of the experiment, which would affect in a similar way spontaneous activity and the evoked responses. It was reported that the high level of vigilance might increase electroencephalographic 10-Hz activity in central area, where mu rhythm is generated (Higuchi et al., 2001). These results would indicate that the amplitude of SEF components can be higher in case of increased vigilance.

Changes in SEFs with respect to pre-stimulus activity are surprisingly small compared to those reported for the visual and auditory modalities. Rahn et al. (1993) reported a 40% increase of the N1-P2 auditory complex when stimuli were applied during weak alpha activity compared with averaging performed without any evaluation of pre-stimulus activity. Romani et al. (1988) reported a two-fold decrease of the auditory N1-P2 when the stimulus was preceded by strong *vs.* weak delta and theta activity. Increased amplitude of delta activity in EEG is known to be associated with the drowsiness (Chapotot et al., 2000), thus suggesting that decrease in vigilance is associated with the decrease in N1-P2 complex. Brandt et al. (1991) showed a five-fold increase in the N1-P2 visual complex from weak to strong levels of pre-stimulus alpha activity. Pronounced modulation of auditory and visual responses with respect to pre-stimulus oscillatory activity can be explained by high susceptibility of these components to the functional state of the underlying them network.

Mu rhythm is known to be attenuated during the preparation to movement (Pfurtscheller, 1989) and by somatosensory stimulation (Salenius et al., 1997b). An attenuation of short- and middle-latency SEPs was also reported in tasks related to planning and execution of movement (Cohen and Starr, 1985; Huttunen and Homberg, 1991). The aforementioned studies indicate that during movement and tactile stimulation, somatosensory evoked responses and mu rhythm are positively correlated. This correlation suggests an existence of mechanisms which may equally affect both spontaneous activity and somatosensory responses. These same mechanisms may probably also explain our findings concerning the weak enhancements of P35m and P60m in the case of large amplitude mu rhythm.

Study III. Somatosensory evoked potentials modulated by TMS

Results

In this study, TMS was applied to the left sensorimotor cortex, and the right median nerve was stimulated to elicit SEP. An example of the evoked responses for all experimental conditions is shown in Figure 5. The most robust result was an increase of somatosensory parietal P25 component for realTMS+MNS condition compared to synthTMS+MNS condition. The following detailed analysis was performed for this component in the left hemisphere. For comparison, the amplitude differences between conditions were analyzed also in the right hemisphere in the 25–30 ms latency range. The results are presented as the difference between 1) realTMS+MNS and synthTMS+MNS, and 2) shamTMS+MNS and synth_shamTMS+MNS, in order to distinguish them from simple arithmetic summation of the responses to different types of stimulation.

The amplitude of the P25 enhancement in the left hemisphere was higher for real TMS than for sham TMS. An increase of P25 component was stronger for 0-ms delay TMS than when TMS followed MNS by 10-ms. This was observed consistently for all the 6 subjects with data for both conditions (ANOVA for shamTMS *vs.* realTMS, 0ms *vs.* realTMS, 10 ms: $P < 0.01$; post-hoc quadratic test $P < 0.01$; Fig. 6).

There were no significant changes in the right SEPs belonging to the different conditions (ANOVA $P > 0.05$).

The P25 enhancement measured as the difference between "TMS+SEP" and "synthTMS+SEP" had a spatial distribution with the maximum in close proximity to the stimulated point.

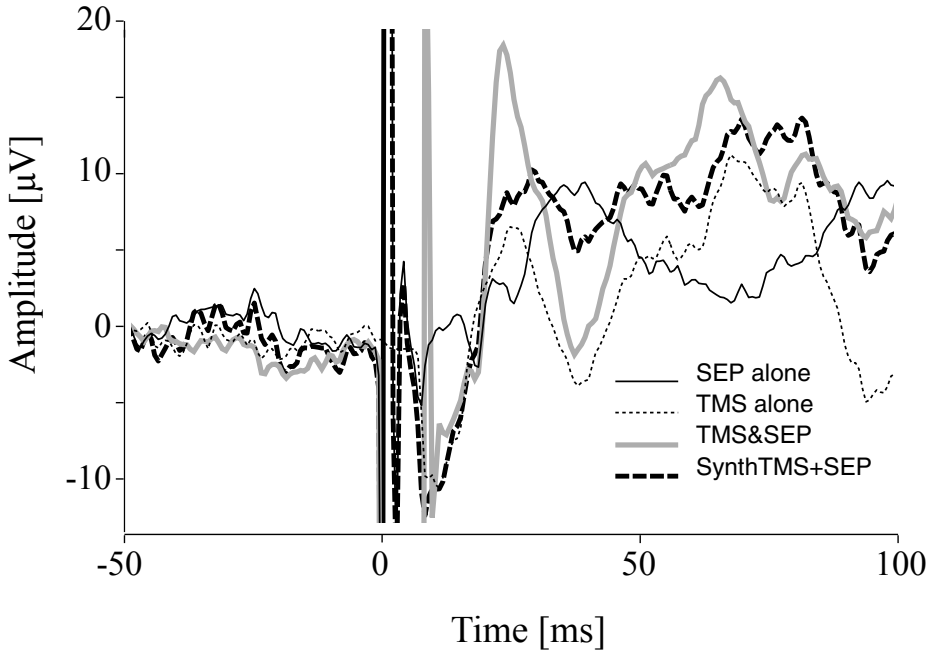

Figure 5. "TMS", "SEP", and "TMS&SEP" waveforms (for P25 component) recorded in typical subject; positivity upwards. The shaded area shows the P25 enhancement. The stimuli were delivered at 0 ms. Somatosensory stimuli caused an artifact in the recordings (0–2 ms in condition SEP). In condition SEP&TMS, the artifact was prolonged (0–10 ms). This was due to the sample-and-hold circuitry underlying the amplifier's gating feature, which served to exclude TMS-related artifacts.

Discussion

The results of the present study show that TMS modulates SEP when being applied simultaneously with the median nerve stimulation. The increase of P25 was topographically organized with the maximum above the centro-parietal area of the contralateral hemisphere. These results are congruent with the earlier studies by Kujirai et al. (1993a) and Seyal et al. (1993) revealing similar enhancement of P25 induced by TMS. While these studies dealt with the TMS before (10–150 ms) and simultaneously with the MNS, our experimental setup permitted a comparison between TMS applied simultaneously with and 10 ms after the somatosensory stimulus. When delayed by 10 ms, TMS did not have any significant effect on the amplitude of P25 component. Additional control experiments with "sham TMS" showed that the acoustical click associated with the TMS is not the reason for the changes in SEP.

The data analysis was not performed on the responses later than P25 because of their possible contamination by a re-afferent response from the muscular twitches caused by TMS.

The authors of both previous studies (Kujirai et al., 1993a; Seyal et al., 1993) argued that most likely the increase of P25 is caused by the inhibitory process, which takes place few millisecond after the stimulation of the cortex. The main point of Seyal et al. (1993) was to explain P25 (as part of N1-P1 complex) enhancement as a result of synchrony, which follows hyperpolarization. Synchronization of neuronal activity through the preceding hyperpolarization

was confirmed in the other studies (Mainen and Sejnovski, 1995; Nowak et al., 1997). Kujirai et al. (1993a) explained the same P25 increase by the decrease in membrane resistance during the hyperpolarization. An idea about the effect of hyperpolarization comes from the experiments in animals, where it was shown that an electric pulse applied to the exposed cortex produced a long-lasting (~ 100 ms) IPSP in the cortical neurons (Krnjevic et al., 1966; Rosenthal et al., 1967).

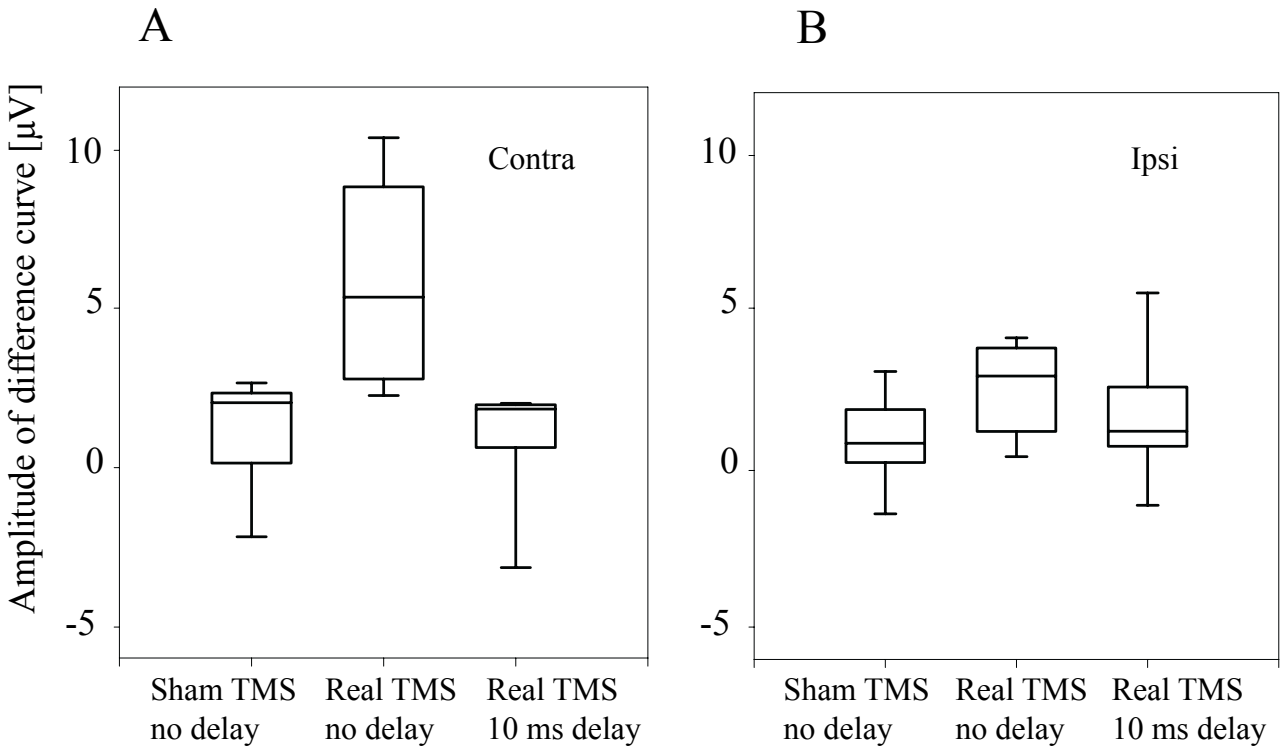

Figure 6. Amplitudes of the difference curves "TMS&SEP" minus "synthTMS+SEP" in three conditions ("sham TMS", "real TMS no delay", and "real TMS 10-ms delay"). Box-and-whisker plots (showing the 5th percentile, 10th percentile, median, 90th percentile and 95th percentile) illustrate the differences between conditions and the distribution within the group of subjects. A. Contralateral hemisphere; B. Ipsilateral hemisphere.

Krnjevic et al. (1966) reported that often neurons discharge for 10–20 ms after electrical stimulation of the cortex. The authors hypothesized that this discharge may belong to the inhibitory neurons, which are responsible for the following hyperpolarization in the target cells. This means that these inhibitory neurons would continue bombardment of their targets as long as 20 ms after the stimulation. It might explain why TMS did not have a strong effect on P25 when being applied 10 ms after the median nerve stimulation, when the hyperpolarization is probably not yet fully developed.

TMS can be used to "change the state of electrical brain activity" immediately before a peripheral stimulus reaches the brain. It has been proposed that the ERs partially result from a reorganisation of spontaneous EEG activity in terms of amplitude enhancement (Başar 1980, 1999 "resonance hypothesis") and phase re-ordering (Sayers et al. 1974). TMS may induce a global yet uniform change of brain activity, which would lead to a change in evoked responses, e.g., P25 component.

Study IV. Long-range temporal correlations in spontaneous brain oscillations

Results

An example of alpha activity is presented in Fig. 7. The main results are shown in Table 3. Power spectrum of wavelet-transformed data at 10-Hz frequency (occipito-parietal and central areas) and at 20-Hz (central areas) revealed no characteristic peaks. Moreover, we found a linear decay of power spectral density with increasing frequencies in double-logarithmic coordinates in the range of 0.005–0.5 Hz; i.e., a $1/f^{\beta}$ type of a power spectrum: $P(f) \approx f^{-\beta}$. This type of $1/f^{\beta}$ spectrum was observed for both MEG and EEG data.

The autocorrelation analysis of the wavelet transformed data revealed significant correlation with the time lag of > 100 s. The decay of this function for both MEG and EEG data was characterized by a power law: $ACF(t) \approx t^{-\gamma}$ (see Table 3).

Neither reference recordings (MEG) nor surrogate data (EEG) demonstrated a $1/f^{\beta}$ type of a power spectrum or gradually decaying autocorrelation function.

As a next step we calculated the self-similarity parameter α of the DFA. Uncorrelated signals yield $\alpha = 0.5$, which was demonstrated for both wavelet transformed reference recordings and surrogate data. For all data sets (10-Hz and 20-Hz oscillations) we found α significantly larger than 0.5 (see details in Table 3, Fig. 8), indicating the presence of long-range correlations in brain oscillations. We did not find significant differences for the parameter α between the eyes-closed and eyes-open condition for alpha oscillations. The only significant differences were found for the parameter α being larger for central 10-Hz than 20-Hz activity ($P < 0.005$).

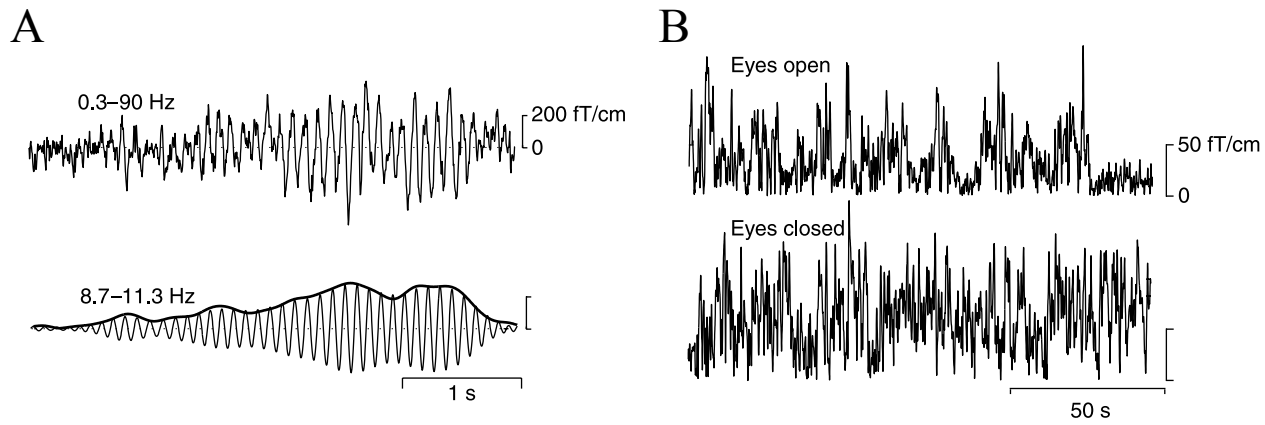

Figure 7. Alpha oscillations, dominating the spontaneous activity, fluctuate in amplitude on a wide range of time scales. A. MEG signal from the occipital region and the eyes-open condition. The 4-s epoch of broadband MEG (0.3–90 Hz, upper curve) displays a typical transition from low alpha activity to large-amplitude 10-Hz oscillations (lower curve). The thick line of the lower curve indicates the amplitude envelope of the bandpass-filtered signal (8.7–11.3 Hz) obtained with the wavelet filter. B. Continuous and pronounced fluctuations in the alpha-oscillation amplitude are seen in 150-s epochs from conditions eyes-open (upper curve) and eyes-closed (lower curve).

	Alpha				Ref.Rec.	Surr.Data	Mu	Beta
	MEG		EEG		MEG	EEG	Closed	Closed
	Closed	Open	Closed	Open			MEG	MEG
β	0.44	0.52	0.36	0.51	0.03	0.05	n.c.	n.c.
DFA, α	0.71	0.71	0.68	0.70	0.51	0.50	0.73	0.68
ACF, γ	0.58	0.73	0.52	0.81	*	*	0.46	0.70

Table 3. Summary of the results for three methods in study IV: quantification of $1/f^{\beta}$ type of a power spectrum (β exponent), Detrended fluctuation analysis (DFA, α), Decay of autocorrelation (ACF, γ). * power-law fitting was not possible, n.c. – not calculated. Ref. Rec. – reference recordings, Surr. Data – surrogate data.

Discussion

The results of this study indicate that the spontaneous neuronal oscillations in 10- and 20-Hz frequency range are correlated over periods of hundreds of seconds. These long-range temporal correlations were demonstrated by means of three complementary methods, thus indicating robustness of the findings. It was reported previously that it is impossible to distinguish the dynamic of spontaneous EEG from that of the filtered white noise if the segments are longer than 2–15 s, when using approaches relevant to low-dimensional systems (Cerf et al., 1997; Stam et al., 1999). The present study opens up a new way for exploring the complexity of oscillations, with the methods based on scaling analysis.

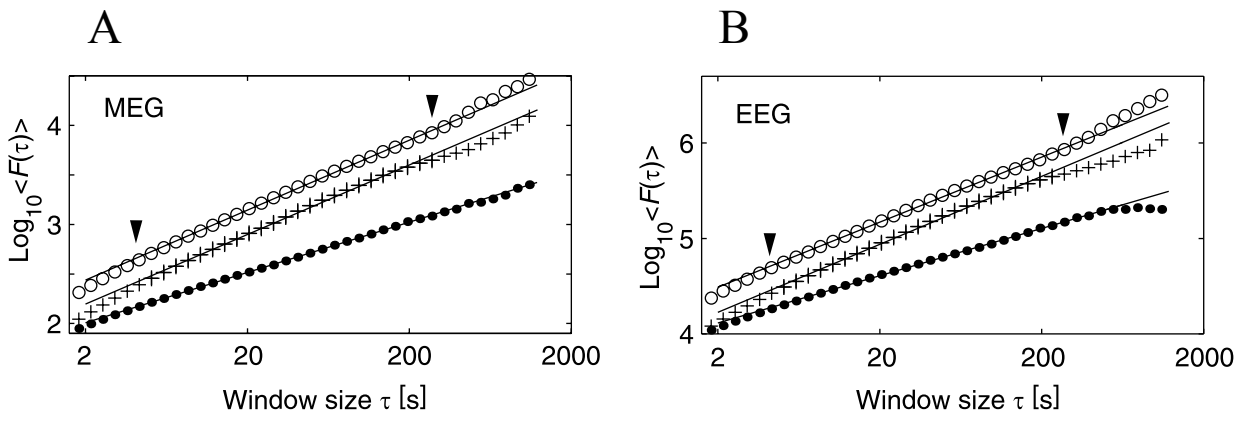

Figure 8. Alpha oscillations exhibit robust power-law scaling behaviour and long-range temporal correlations. Double-logarithmic plots of the DFA fluctuation measure, $F(\tau)$, show power-law scaling in the time-window range of 5–300 s for both MEG (A) and EEG data (B). Circles, eyes-closed condition; Crosses, eyes-open. The dots represent reference recording and surrogate data for the MEG and EEG, respectively.

The data presented here suggest that the neuronal network underlying 10- and 20-Hz oscillations may operate at a "critical" state, which is achieved through local interactions between the neurons. It is important to note here that there is no special parameter to tune in order to arrive to a "critical" state, which is characterized by the scale-free dynamics (Bak, 1997). This would imply that the local rules of interactions between the neurons are the basis for the development of spatio-temporal long-range correlations. EEG and MEG are the measures of a population of neurons, therefore, precise understanding of the aforementioned local rules may require studies on the single cell level. It is important to note here that global factors such as the level of vigilance may contribute to the dynamics of EEG oscillations, however in SOC framework any influences (local or global) are treated as potentially being able to contribute to the creation of long-range correlations.

As it was demonstrated in theoretical studies, networks operating at the critical state are able to swiftly reorganize their activity upon changing demands (Chialvo and Bak, 1999). If our assumption is right, and a fractal structure of neural oscillations arises from self-organized neural network being at the critical state, then one would expect the spontaneous activity to be effectively disrupted by externally imposed perturbations. It is in line with the experimental data showing that spontaneous brain activity both at 10- and 20-Hz is changed dramatically as a reaction to both external and internal perturbations (Hari and Salmelin, 1997; Crone et al., 1998).

One might think of the self-organized criticality in the nervous system as a dynamic state, which is not possible to avoid, but which is beneficial for the processing demands.

Study V. Phase synchronization and amplitude correlation of beta oscillations

Results

The maximum of beta activity was detected above the central and frontal areas of the head. Phase-lag distributions revealed a highly non-uniform pattern, usually being characterized by one prominent peak (Fig. 9) for both intra- and inter-hemispheric pairs of signals. Even the smallest (most flat) peaks were significantly larger than those obtained from shuffled data sets. Peaks in phase-lag distributions were larger for intra- than for inter-hemispheric pairs of signals, which was congruent also with the synchronization index obtained for the intra-hemispheric and inter-hemispheric pairs of signals, $S = 0.20$ and $S = 0.1$, respectively.

An important point for the evaluation of phase synchrony is the amplitude of beta oscillations in each signal for a given pair of sensors. We noticed that the prominent beta oscillations in one hemisphere could coincide with practically no beta activity in the other hemisphere. Therefore phase values for these "no-beta" segments can not be used for the evaluation of synchronization. Synchronization index was thus calculated on the basis of an amplitude threshold. The 50-percentile and 75-percentile amplitude thresholds were used for each of two signals in a given pair. The summary of the results is presented in Table 4.

We quantified also the amplitude correlation of the beta oscillations between the two hemispheres. A remarkable feature of these oscillations was their growing similarity between the hemispheres with the increase of time window (Fig. 10). The coefficient of correlation for the amplitude correlation of the beta oscillations (obtained with the wavelet transform) was 0.16 ± 0.03. We calculated also coefficient of correlation for low-pass filtered amplitude envelope of beta oscillations. This filtering was needed in order to reveal low-frequency interhemispheric amplitude correlation of beta rhythm. The coefficient of correlation was increasing with the decrease of cut-off frequency, reaching the value of 0.58 at 0.1 Hz.

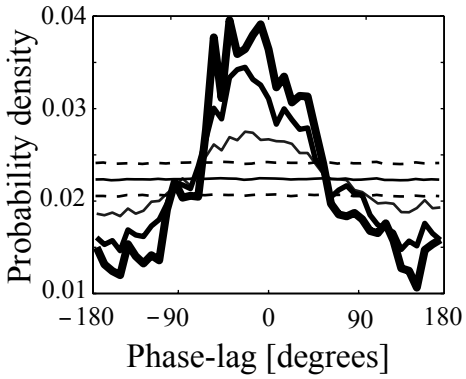

Figure 9. Phase synchrony between beta oscillations in the two hemispheres (for one subject). Phase-lag distribution for: no amplitude-threshold (thin line) calculations, 50 percentile amplitude threshold (middle thick line) and 75 percentile amplitude threshold (thick line) calculations. The solid horizontal line and the dashed lines represent mean and three standard deviations of 1000 simulations, respectively.

Discussion

This study clearly shows that beta oscillations in the left and right motor cortices are phase-locked and correlated in amplitude. We used a new approach in order to quantify phase-relationship of the two processes. This approach is quite different from the coherence function, which is traditionally used in neuroscience. The coherence function is not a unique measure of phase-synchrony, it measures also amplitude correlation, being therefore a biased measure (Tass, 1999). The phase-lag distributions presented in our study show that one can always find a preferential lag value. The typical phase-lag in our study was around 0 degrees, however lags of 10–90 degrees were observed.

The inter- and intrahemispheric synchronization increased with the increase of beta oscillation amplitude. The S-index was 170% larger for 75-percentile threshold approach then for no-threshold calculations.

	Left hemisphere	Right hemisphere	Inter-hemispheric
S (no threshold)	0.21 ± 0.05	0.20 ± 0.02	0.10 ± 0.01
S (50 percentile)	0.41 ± 0.07	0.40 ± 0.04	0.19 ± 0.01
S (75 percentile)	0.55 ± 0.07	0.55 ± 0.04	0.27 ± 0.20

Table 4. Synchronization index for different amplitude of beta oscillations.
The values are given as mean ± SEM.

It was proposed that spontaneous (internal) synchronization serves as a mechanism for binding of anatomically separate but functionally related areas (Singer, 1999; Fries et al., 2001). Beta oscillations seen in MEG under physiological conditions are known to be generated in the motor cortex (Salmelin and Hari, 1994b) and they are tightly related to the preparation and execution of a movement (Pfurtscheller and Lopes da Silva, 1999; Crone et al., 1998; Conway et al., 1995). The synchronization of beta oscillations between the two hemispheres may thus be regarded as being beneficial for the organization of bilateral movements (Andres et al., 1999). The synchronization also implies that structures, when being synchronized, should behave as a whole and this can be not desirable when only a given area is involved in a particular activity. For the motor system an example of such a problem can be the organization of unilateral movements. So, it

has been noticed but poorly understood that both contra- and ipsilateral hemispheres are active during the preparation of unilateral movements (Cheyne and Weinberg, 1989; Cramer et al., 1999). One reasonable explanation for the origin of the ipsilateral activity is the development of inhibitory processes in the ipsilateral hemisphere, which is related to the suppression of a "mirror" movement by the other hand (Kristeva et al., 1991). The need for this suppression may arise because of the concerted action of the synchronized neurons in the two motor cortices, as revealed in the present study.

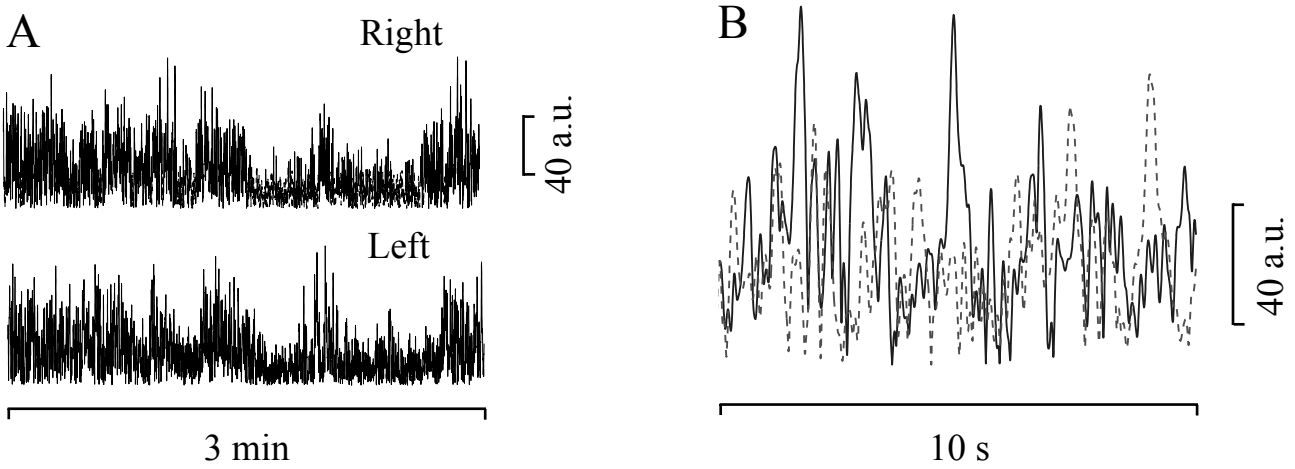

Figure 10. Interhemispheric amplitude correlation of beta oscillations.
A. Fluctuation of beta oscillation amplitude in the right (upper panel) and left (lower panel) hemispheres for three minutes (one subject). Note the similarity in the amplitude dynamic of the two signals. The amplitude is given in the arbitrary units (a.u.). B. Enlarged version of the last 10 seconds presented in A. The dashed and solid line represent left- and right-hemisphere beta oscillations, respectively. Note the different behaviour of these two curves on this time scale.

Another finding of our study is the demonstration of strong amplitude correlation of beta oscillations in the two hemispheres, when taking into account beta activity smoothed in time. We believe that this low-frequency correlation may give rise to the observed correlation between the hemodynamic signals belonging to homologous areas in the two motor cortices (Biswal et al., 1995; Lowe et al., 2000).

Methodological remarks

The results of the present thesis were obtained with MEG and EEG techniques. Three major factors should be considered when using these methods. The first factor is related to the fact that MEG and EEG are the measures of activity of many neurons. In the classical theory, neuronal oscillations are thought to reflect the quasi-synchronous local postsynaptic responses of a set of geometrically ordered cells distributed in a layer array. The main elements in this array are pyramidal cells in the cortex. Relations of post-synaptic potentials and EEG oscillations may show tight correlation for evoked responses but not for spontaneous EEG potentials (Creutzfeld, 1995). The second factor is related to the inverse problem, meaning that there are infinite number of source configurations that produce exactly the same measured data. The third factor is about the true nature of spontaneous oscillations. Leaving aside their obvious usefulness for the clinic, it remains uncertain whether these oscillations are more than epiphenomenal signs of the activity of many neurons, or are active agents, or function as signal carriers, or serve as a mechanism for binding together actions of different neuronal populations (Mountcastle, 1998).

Another critical issue is related to the proper representation of the signals and particularly neuronal oscillations in time-frequency domain. This problem was formulated by Shannon (1948) as the uncertainty principle, implying that it is not possible precisely to represent signal in both frequency and time space. Two extremes of the signal representation are 1) the signal itself, when it is fully defined in time domain, but frequency information might be not easy to extract and 2) the Fourier transform of the signal, when the frequency spectrum is defined, but the temporal information is lost. The wavelet transform, used in the present study, is a way to represent signal simultaneously in both frequency and time domain. However, a compromise between the two domains unavoidably implies that accuracy in frequency and in time will be smeared to a certain extent.

An important issue is also the averaging procedure, which is normally applied in order to achieve a better signal-to-noise ratio of the analyzed processes. The main assumption for the averaging is the stability of the response from one epoch to another. Unfortunately this assumption is not always met, which produces errors in the interpretation of the obtained results. The most typical example is the habituation of the responses in the course of the experiment. Therefore, habituation would lead to quantitatively different responses in the beginning and the end of the experiment. Another reason for trial-to-trial variability in the evoked responses was recently shown in studies of synchronous activity (Fries et al., 2001). The authors demonstrated that the neuronal response depends critically on the synchronization of given areas in the gamma frequency range before the presentation of the stimulus.

Summary

An understanding of the spontaneous neuronal activity is one of the intriguing topics in neuroscience. The present results are related for the most part to the 10- and 20-Hz sensorimotor rhythms. The traditional way to study cortical oscillations is to correlate their dynamics with different tasks. The emphasis of the present thesis was on characterizing sensorimotor activity when there is no particular cognitive or motor task.

The relationship between the characteristics of SEF and spontaneous mu rhythm was explored. Stability of N20m was shown with respect to the highly variable amplitude of 10-Hz oscillations. P35m and to a much lesser extent P60m exhibited small positive correlation with the amplitude of the pre-stimulus mu rhythm. The variability in the amplitude of SEF components was very small (not more than 21%) compared to the changes in the amplitude of mu rhythm. The latencies of N20m, P35m, and P60m were unchanged with respect to the pre-stimulus 10-Hz oscillations. We conclude that the characteristics of SEF components are relatively stable compared to the large variations in mu rhythm amplitude. SEFs demonstrate much weaker variability than the long-latency components of auditory and visual responses, which are heavily dependent on the pre-stimulus spontaneous activity.

Suppression of mu rhythm was investigated both in contra- and ipsilateral hemispheres following unilateral somatosensory stimulation. The strength of this suppression was more pronounced in the contra- than in the ipsilateral hemisphere, thus demonstrating clear lateralization of the mu-rhythm reactivity to median nerve stimulation. The difference between the suppression in the contra- and ipsilateral hemisphere depended on whether it was measured in the beginning or in the end of the experiment. This is because the repeated stimulation significantly reduced mu-rhythm suppression in the ipsilateral, but not in the contralateral hemisphere in the course of the experiment. We believe that the reactivity of mu rhythm is in part based on a nonspecific, arousal-like component, which is attenuated toward the end of the experiment, being most clearly evident in the ipsilateral hemisphere.

In agreement with previous studies, we show that TMS, when being applied simultaneously with the median nerve stimulation, leads to an enhancement of the P25 SEP component. No such increase was found for TMS delayed by 10 ms with respect to median nerve stimulation. Control experiments show that the obtained increase of P25 can not be explained by the side effects of TMS, such as acoustical click and vibration sensations. The increase was topographically organized, being maximally pronounced in the vicinity of center of stimulation. We believe that the observed effect most likely can be explained by the hyperpolarization of the cortical neurons caused by the TMS pulse. An alternative explanation may be related to the uniform resetting of the spontaneous pre-stimulus activity in terms of the resonance hypothesis of the evoked response generation.

Using detrended fluctuation analysis, power spectrum and autocorrelation function we showed that the amplitude of spontaneous oscillations exhibit long-range temporal correlations of a power-law form. This correlation may extend up to more than hundred seconds. The scaling exponents of neuronal oscillations were invariant across subjects, thus suggesting similar generation mechanisms. No difference was found for the scaling exponents between eyes-open and eyes-closed conditions. However, we found different scaling exponents for the 10- and 20-Hz rolandic components, indicating that distinct neuronal populations and/or mechanisms may underlie these oscillations. The power-law scaling behaviour in neuronal oscillations may be explained in terms of the theory of self-organized criticality, which offers a general mechanism for the emergence of correlations in a stochastic multiunit system. In line with the theoretical studies, we proposed that the neuronal system in a critical state is able to adapt swiftly to new situations.

Synchronization in the nervous system is important for our understanding of how the brain operates as a whole. This issue was addressed in the study where spatial long-range phase

synchrony of the beta oscillations was investigated. We demonstrated intra- and interhemispheric phase coupling, especially for the high-amplitude beta rhythm. We believe that this spontaneous synchrony between two hemispheres may be utilized for the organization of bilateral movements. However, operating as a whole, simultaneous activity of this distributed network may be undesirable for the unilateral movements. We show also a positive correlation for the amplitude of spontaneous beta oscillations between the two hemispheres. Remarkably, this correlation was strongest for the low-frequency components of amplitude modulation. This beta-amplitude correlation may give rise to the correlation of hemodynamic signals (< 0.8 Hz), that was reported for the homologous areas of motor cortices.

Conclusions

Slight positive correlation was demonstrated for the amplitude of somatosensory evoked fields and the amplitude of pre-stimulus mu rhythm, thus suggesting relative independence of evoked and spontaneous activity.

Somatosensory stimulation suppresses mu-rhythm amplitude predominantly in the contralateral hemisphere. In the ipsilateral hemisphere this suppression is attenuating in the course of experiment, which most likely reflects the presence of non-specific activation.

An enhancement of the P25 component of the somatosensory evoked potentials was consistently observed for TMS concurrent with somatosensory stimulation. This enhancement can be explained through inhibitory processes caused by TMS.

Amplitude fluctuations of 10- and 20-Hz oscillations are correlated over hundreds of seconds. Observed power-law scaling behavior of spontaneous oscillations may find unifying explanation within the theory of self-organized criticality.

Interhemispheric phase synchrony and amplitude correlation are revealed for beta oscillations. Functionally, these findings can be related to the organizations of bilateral movements.

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