Aus der Klinik für Neurologie und Klinische Neurophysiologie

Campus Benjamin Franklin der Medizinischen Fakultät

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DISSERTATION

„ *Event-related desynchronization (ERD) of sensorimotor EEG rhythms in hemiparetic patients with acute hemispheric stroke*“

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von

Magdalena Stępień

aus Szczecin, Polen

Gutachter:

1. Prof. Dr. G. Curio
2. Prof. Dr. med. T. Platz
3. Priv.-Doz. Dr. med. A. Hartmann

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Part I

Introduction

Stroke results in damage to brain tissue. If the motor system of the brain is affected, it may lead to hemiparesis or hemiplegia - a weakness on one side of the body. The daily life quality of stroke patients is significantly reduced due to high dependency and communication problems.

Worldwide, stroke belongs to the leading causes of disability. The rehabilitation of stroke patients still remains a challenge because the available treatments are not sufficient.

Fast technical progress and growth of knowledge in neuroscience has led to development of new devices. They potentially introduce new rehabilitation methods and enable patients more independent communication with the outer world. Brain computer interface (BCI) belongs to the results of this extended research. BCI allows for direct communication between brain and computer without involvement of the muscles. In this approach, the brain signals can be recorded with different methods. One of them is the electroencephalography (EEG). The activity patterns visible in the EEG are decoded and translated into computer commands.

Shortly before and during movement certain patterns are observed in the EEG. They are necessary for BCI to decode the user´s intent. These patterns have been exhaustively studied in healthy subjects. Imaging studies suggest that stroke changes brain functioning in the process of planning and execution of movements. Therefore, it can be assumed that after stroke the EEG patterns are altered. In this case, BCI might be unable to decode the patient commands. The EEG studies on stroke in the context of BCI are few and they are not conclusive. It is even more difficult to find data concerning patients in acute phase of stroke.

A short time after brain damage, neuronal cells show high plasticity for reorganization of the injured interconnections. In order to re-establish correct motor activation patterns, this period is crucial for rehabilitation

Our present knowledge is insufficient to apply EEG-based BCI systems in stroke patients . For further advance in this technique, a better understanding of stroke-related changes of the EEG-patterns is needed.

This thesis focuses on the relationship between lesion location and movement-related activation patterns in patients after acute stroke. The goal of this thesis was to gain a deeper insight into changes of the neuronal network after stroke with a view to a possible future implementation of an EEG-based BCI.

Part II

Basic knowledge

1 Organization of the motor system

The motor system consists of a central and a peripheral part. Within the central motor system, the impulses for a voluntary movement are generated in the motor cortices of the cerebral cortex (neocortex) by the upper motor neuron (first order neuron). Several areas of the cerebral cortex are designated as motor areas: the primary motor cortex and secondary motor cortices i.e. premotor, supplementary and posterior parietal cortex. The signal is modified by other structures of the central motor system such as basal ganglia and cerebellum. Descending through the brainstem, the upper motor neuron projects on the lower motor neuron (second order neuron) within the ventral horn of the spinal cord. The lower motor neuron, together with sensory neuron and the muscles, comprises the peripheral motor system (Roland, 1984).

1.1 Motor areas of the cerebral cortex

The primary motor cortex (Brodmann Area 4) has its location in the precentral gyrus and is characterized by topographic representation of different parts of the body. This type of somatotopic neuronal organization can be depicted as homunculus - a distorted human figure being a projection of the body parts on the cortical surface. The medial part of the gyrus contains the representation of the leg and foot, followed laterally by arm and hand, eventually terminating with the representation of the face, tongue and mouth. (See figure 1). Recent findings show however, that the cortical organization is even more complex: the muscle representations repeat and additionally overlap broadly (Sanes and Donoghue, 2000). The primary motor cortex has an essential role in the movements of the distal muscles of the extremities, especially in the fine finger movement.

The premotor cortex occupies lateral Brodmann areas 6 and 8 and is localized rostrally to the primary motor cortex. The lateral surface of the area 6 innervates proximal and trunk musculature. It is involved as well in motor guidance of movements i.e. body orientation toward a target. The supplementary motor cortex located on the medial aspect of area 6 contributes to planning and coordinating of complex bilateral movements (Goldberg, 1985; Shima and Tanji, 1998). Both premotor and supplementary motor cortex project somatotopically to the primary motor cortex (Strick, 1988).

Studies examining the interconnectivity between cortical areas showed that the motor cortex has projections from the posterior parietal cortex (Areas 5 and 7) as well as from the somatosensory cortex (Area 3) (Jones et al., 1978).

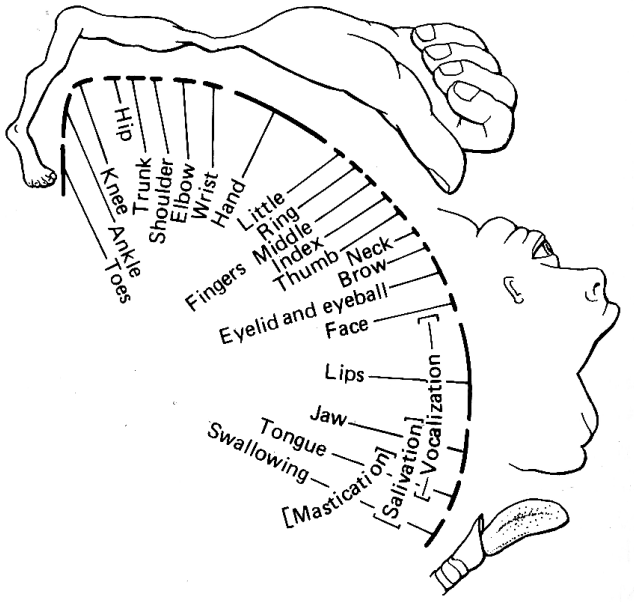


Figure 1: Motor homunculus is a distorted representation of body map overlaid upon primary motor cortex. Each body part is placed over the areas of the motor cortex that innervates it. The distortion is caused by the fact that the size of each body part is proportional to its corresponding cortical region as well as to the grade of movements precision.
(Modified after Penfield and Rasmussen (1990))

The posterior parietal lobe receives and integrates sensory information of different modalities i.e. tactile, visual, somatosensory, auditory, vestibular into motor commands. It verifies the body's spatial location and therefore allows for a precise navigation of the movement in space.

The connections between the area 3 and motor cortex provide information feedback after the movement (Noback et al., 2005b). (See figure 2).

1.2 Motor pathways

The movement commands reach the muscles via two nerve pathways originating from the motor cortical areas: pyramidal and extrapyramidal tract. The pyramidal tract is responsible for the voluntary innervation of the musculature and can be further subdivided. The first part, the corticospinal tract (CST), originates in the motor cortex, descends through the internal capsule and projects directly onto motor neurons in the spinal cord. 10% of the nerve fibers descend without crossing (anterior CST) and 90% of the fibers cross over into the medulla (lateral CST). Due to this fact, the electrical stimulation of a motor hemisphere leads to a contralateral limb movement (Gilbert, 2001; Rizzolatti et al., 1998). The pyramidal tract is essential for fine motor manipulations and independent movements of the distal extremities. The extrapyramidal tract contains motor pathways lying outside the pyramidal tract. This part of the motor system is involved in gross rather than fine movements. It influences the muscle

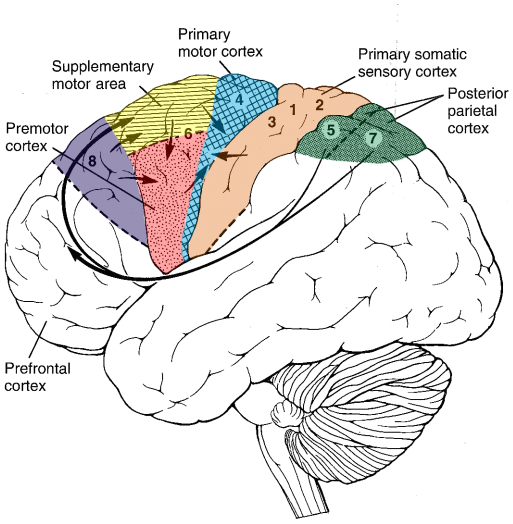


Figure 2: According to the classification of Brodmann, the primary motor cortex corresponds with Area 4 within the precentral gyrus. This part of the neocortex is responsible for controlling and executing voluntary movements. The secondary motor cortices include supplementary motor cortex (Area 6), the premotor cortex (Areas 6 and 8) and the posterior parietal cortex (Areas 5 and 7). The supplementary motor cortex, which is localized rostrally to the primary motor cortex, is responsible for planning and coordination of bilateral movements. The premotor cortex has an influence on the regulation of posture. Area 5 of the posterior parietal cortex receives signals from somatosensory cortex (Areas 1, 2 and 3), whereas area 7 contributes to the integration of the somatosensory, visual and proprioceptive input. Based on this information, it determines the position of the body in space and can produce a movement plan before the involvement of the other motor cortices.

(Source: `http://predator.pnb.uconn.edu/~wwwpnb/virtualtemp/nervous/Motor_and_Sensory_Cortexes.htm`)

tone and the postural control. These different pathways are modulated by higher instances of the motor system such as basal ganglia, cerebellum and sensory areas of the cerebral cortex (Noback et al., 2005c).

1.3 Other major components of the motor system

1.3.1 Basal ganglia

The basal ganglia are a group of subcortical nuclei in the brain interconnected with the motor cortices, the thalamus and the brainstem. One of their functions lies in the initiation and selection of voluntary movements.

The basal ganglia are composed of striatum, pallidum, substantia nigra and subthalamic nucleus. The cerebral cortex is directly connected with the striatum which transmits the received signal further to other basal ganglia. One of them is pallidum - subdivided into pars interna and pars externa - which output serves as an inhibitory pathway to the motor cortices. The main input for the subthalamic nucleus comes from the motor cortices and the striatum. Its output neurons project on the pallidum. The substantia nigra can be subdivided in two parts: pars compacta - providing excitatory dopaminergic input to the striatum and pars reticulata - resembling the function of the pallidum (Noback et al., 2005a). (See figure 3).

When the basal ganglia are damaged as in patients with Parkinson's disease, their role becomes apparent. These patients have difficulties in initiating the movements. The further primary symptoms concern the tremor, rigidity and slowness of movements.

1.3.2 Cerebellum

The cerebellum is linked in many loops within the motor system. It integrates the input coming from the motor cortex and the sensory, proprioceptive feedback provided by the spinal cord. Having the information about the position of the body in space, the cerebellum can update and fine-tune the movement plan leading to its coordination (Pellionisz and Llinás, 1980). Afterwards, the feedback information is sent back through the thalamus to the cortical motor areas.

1.4 Voluntary movement

Voluntary movement, for example reaching out a hand in order to greet another person, requires the involvement of several levels of the motor system in its hierarchical order. The information about the spatial coordinates of the movement is propagated by the posterior parietal lobe to the primary motor cortex, the premotor and supplementary motor cortex. The primary motor cortex generates the neural signals for the execution of movement. The premotor cortex regulates the proximal and the axial

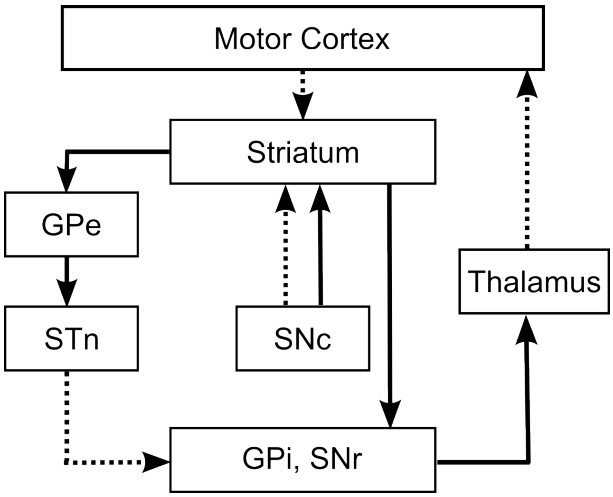


Figure 3: Basal ganglia scheme. The dotted line signifies excitatory neuronal pathways and the regular line represents inhibitory connections. On the direct pathway, the motor cortex and substantia nigra pars compacta (SNc) send stimulatory impulses to the striatum. With its neuronal connections, the striatum inhibits the pallidum pars interna (GPi), which further inhibits the thalamus. The thalamical excitatory neurons project on the motor cortex closing the direct loop. The effect of this sequence is excitatory: the cortex excites itself via the direct pathway. The indirect pathway passes through the striatum inhibiting the pallidum pars externa (GPe) which sends inhibitory impulses to the subthalamic nucleus (STn). As a result the pallidum pars interna (GPi) and the substantia nigra pars reticulata (SNr) are activated by the STn. GPi projects with its inhibitory neurons on thalamus, which activates the motor cortex. The net effect of this pathway is inhibitory.

(Modified after Nestler et al. (2001))

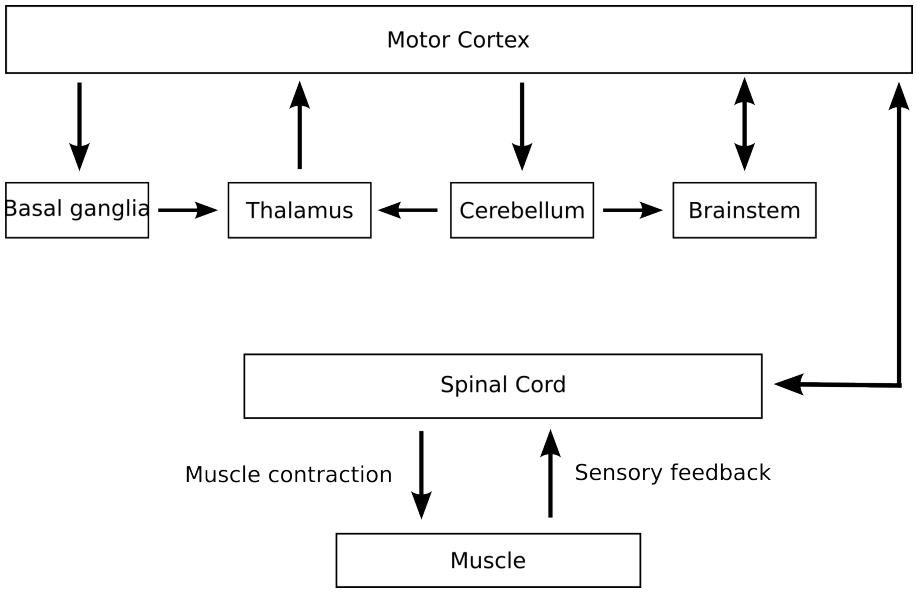


Figure 4: The motor system is characterized by hierarchical organization. A voluntary movement is planned and prepared by the motor cortices. The basal ganglia receiving the input from the motor cortex are involved in the process of selection and initiation of movement. The thalamus is also interconnected within this loop. Together with the frontally localized secondary motor cortices, the cerebellum plays its role in precise coordination of the movement. When the exact plan of the movement is created, the primary motor cortex sends the information via motor neurons to the muscles to contract. Afterwards, a sensory feedback is given indirectly to the motor cortex through the somatosensory motor regions.

musculature, the supplementary motor cortex controls the simultaneous and complex movements. The information gathered about distal limb movements is sent directly through the pyramidal tract to the spinal cord. The signals contributing to the proximal limb movements and posture control are conveyed by the extrapyramidal pathway. The plan of the movement is corrected within neural pathways including the input from other motor instances. Within the feedback loop, the neurons of the basal ganglia analyze and initiate the movement and the cerebellum allows for motor coordination. At the end, the plan of the movement is sent to the spinal cord and conveyed by motor neurons to the muscles. A person reaches out a hand and the sensory feedback information is sent to the somatosensory cortex (Hülshoff, 2000). (See figure 4).

Such complicated activity as a voluntary movement is only possible due to communication between neuronal cells. For better understanding of the EEG, as a method of investigation in this study, an insight into communication of the neuronal networks is given in the following chapters.

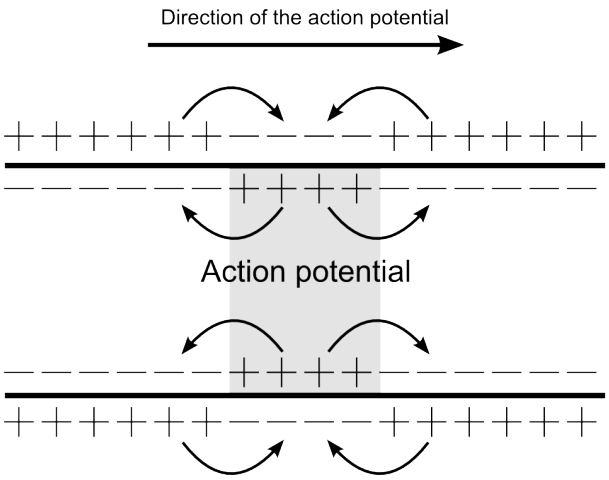


Figure 5: A membrane of a neuronal cell is polarized. Within the neuron a negative potential with respect to exterior can be measured. A stimulus can influence and change this potential difference causing sodium channels to open. The influx of the sodium ions reduces the voltage across the membrane leading to a wave of depolarization spreading along the cell - action potential. At its peak, the sodium channels close and potassium gates open allowing for potassium ions efflux and thus, restoring the normal potential of the membrane.

2 Insight into neuronal communication

2.1 Action potential

Neuronal cells communicate with each other by generating action potentials that propagate changes in the membrane potential. The resting membrane of a neuron is polarized, i.e., there is a potential difference between its sides. It results from different intra- and extracellular ion concentrations. Within the membrane special channels adapted for ion transport can be found. When the membrane, is at rest, they remain mostly closed. If the cell is activated for a brief period of time, the membrane potential becomes positive (depolarization) and afterwards rapidly returns back to its original negative level (repolarization). This process is defined as an action potential. The depolarization is accompanied by the influx of positive ions (sodium-ions) into the cell, whereas during the repolarization there is an efflux of positive ions (potassium-ions) out of the cell (Duffy et al., 1989). (See figure 5).

2.2 Synaptic potential

Only fluctuations of the membrane potential that are slow enough and that are accompanied by a sufficient electric current are detectable by scalp electrodes. Due to the very brief duration of the action potential (about 1 ms), it cannot be recorded by EEG. However, the synaptic membrane potential fulfills both of these criteria. It results from the process of synaptic transmission between the brain cells. An activated neuron releases chemical transmitters into the synapse, a junction between two

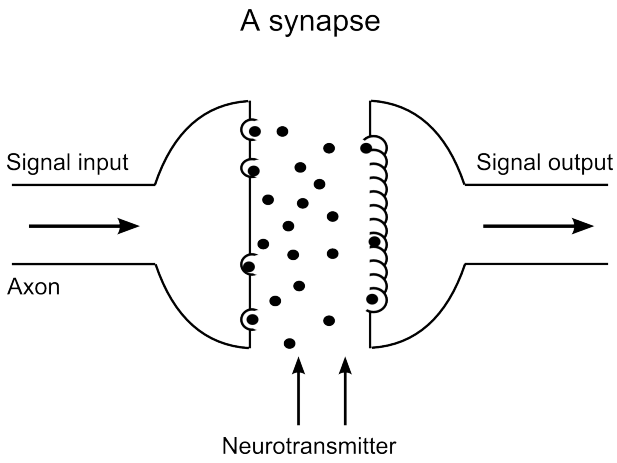


Figure 6: The figure shows on its left side an axon of a neuronal cell relaying nerve impulses to the other neuronal cell at a site called a synapse. When a signal reaches the synapse there is a release of neurotransmitters. These chemical messengers travel across the synaptical cleft to reach the next neuronal cell. The neurotransmitters enter the cell binding to the receptors located on the membrane of the signal receiving neuron. As a result, biochemical reactions take place causing or preventing a new signal to be send along the axon, depending on the type of neurotransmitter involved into this process.

neurons. These transmitters bind to the receptors in a post-synaptic neuronal cell. (See figure 6).

Depending on the transmitter type, ion channels start to open or close and evoke electrical changes within the membrane of the second neuron. When the transmitter evokes depolarization, an electrical change in the postsynaptic membrane is called excitatory postsynaptic potential (EPSP). When a neurotransmitter causes hyperpolarization, the electrical potential is called inhibitory postsynaptic potential (IPSP). A single synaptic potential is not sufficient to trigger an action potential. Each neuronal cell is interconnected with many other neurons. The action potential can be achieved either by the simultaneous firing of many neuronal cells on the postsynaptic membrane or by successive potential changes summating at a single site. These are examples of spatial and temporal summation, respectively (Duffy et al., 1989).

2.3 Field potentials

Secondary to the changes of the membrane potential, there are voltage changes in the extracellular space known as field potentials. When the cell is depolarized, the opening of the channels causes a cascade of positive ion influx, so the immediate vicinity becomes more negative and the further surrounding extracellular fluid remains positive. In order to balance this local negativity, there is a flow of cations from the neighboring extracellular space. In case of hyperpolarization, the anions flow into the neuronal cell leading to an excess of cations within the extracellular space near to the synapse. As a result, a flow of the cations away from the positive region of the synapse in the direction of the

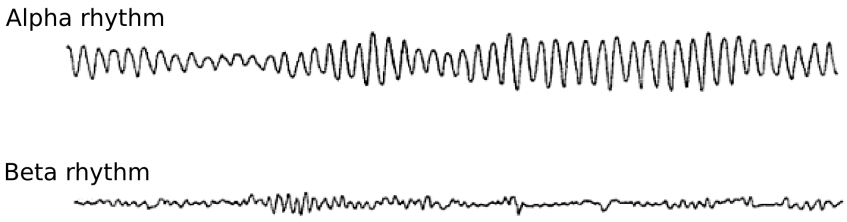


Figure 7: Spontaneous brain oscillations reflect a state of the brain that is not caused by any outer stimulus. In this drawing only two of them, alpha and beta, are depicted. The frequency of alpha rhythm ranges from 8-12Hz. It can be observed in the posterior brain regions in adults who are relaxed and awake. Eyes opening induces its attenuation. Beta oscillations are characterized by the frequency from 12 to 35Hz. This rhythm has a broader distribution: from frontal to posterior brain regions.
(Modified after Zschocke (1995))

negativity at a distance can be observed (Duffy et al., 1989).

3 Electroencephalography

The field potentials and therewith the electrical activity of the brain can be measured extracellulary with electroencephalography (EEG). This technique was introduced by Berger (1929). The signals are measured with electrodes positioned on the surface of the scalp. Afterwards they are amplified and digitized for further data analysis.

3.1 Oscillatory activity of EEG

The recorded brain signals are due to rhythmic variations in voltage. This oscillatory activity of various frequencies and spatial distributions is associated with different states of the brain. There is a variety of rhythms that can be observed in EEG related to increased or decreased mental activity as in sleep. The frequency of the oscillations are named sequentially according to the Greek alphabet i.e. alpha, beta, gamma, mu etc. (See figure 7).

3.1.1 Alpha rhythm

The alpha rhythm within the 8-12Hz band can be best obtained in a relaxed state of wakefulness with eyes closed and is most prominent over the posterior regions of the brain - symmetrically in occipital,

parietal and posterior temporal lobe. Opening of the eyes results in an attenuation of this rhythm (Berger, 1930; Jasper and Penfield, 1949; Chatrian et al., 1959). These oscillations are characterized by sinusoidal wave forms. Although not all details concerning the genesis of the alpha rhythm are clearly identified yet, thalamocortical loops seem to play a major role in its generation. Animal models have shown that the appearance of the alpha rhythm is in synchrony with the activity of the thalamus. Hughes et al. (2004) proposed that the metabotopic glutamate receptor present in the lateral geniculate nucleus of the thalamus induces alpha oscillations (Steriade et al., 1990).

3.1.2 Mu rhythm

The mu rhythm bears a close resemblance to the occipital alpha rhythm in terms of frequency and amplitude. However, it differs in its topography and function. It is composed of an alphoid frequency and its wave is arch-shaped Gastaut (1952). Mu rhythm is detectable over the central cortical regions, also spreading into parietal lobes and is associated with beta activity placed more anterior to it within the precentral region of the sensorimotor cortex (Jasper and Andrews, 1938; Maddocks et al., 1951; Schütz and Müller, 1951). The beta signal arises from the motor cortex and the alphoid oscillations from the sensory cortex (Nashmi et al., 1994; Salmelin and Hari, 1994). It can be blocked not only by active, passive or reflexive movements but also by imagined movement (Gastaut, 1952; Chatrian et al., 1959), whereas it shows a poor or no responsiveness to eyes-opening (Chatrian et al., 1974). Although the attenuation is bilateral, it is more pronounced at the contralateral hemisphere in respect to the site of movement (Klass and Bickford, 1957; Chatrian et al., 1959). There are different hypotheses trying to explain the origin of the mu rhythm: neuronal hyperexcitability restricted to the central sulcus (Van der Drift and Magnus, 1961), superficial cortical inhibition (cortical idling) (Bostem et al., 1965) and cortical idling turning mu rhythm into an afference-dependent phenomenon (Kuhlman, 1978).

3.1.3 Beta rhythm

In EEG recordings, a rhythmical activity within a frequency band of 12Hz –35Hz is regarded to be the beta rhythm. This type of oscillations is found in normal subjects (Fortuin and Künkel, 1983; Kozelak and Pedley, 1990). It is physiologically distributed mainly over the frontal, central and posterior brain regions. The frontal beta rhythm can be quite often found in normal subjects that are allowed to fall asleep. The frontocentral beta activity is intertwined in its function with the mu rhythm and can also be blocked by motor activity. The beta rhythm that can be recorded in the posterior brain areas is thought to be an alpha equivalent associated with alpha-like reactivity to eye opening and eye closure. Apart from this spatially confined beta oscillation, diffusely distributed beta activity is present in normal subjects and cannot be linked with any characteristic physiological rhythm .

Since other oscillatory rhythms are not within the focus of this thesis, they will not be discussed

further.

3.2 Event-related desynchronization (ERD)

Apart from the oscillatory activity, in EEG recordings other distinct processes can be observed. The main interest of this work lies in recognition of one of the EEG movement correlates - event-related desynchronization (ERD). This phenomenon is directly correlated with movement preparation and its execution.

Event-related desynchronization (ERD) is defined as a relative power decrease of the EEG signal in a particular frequency band. The desynchronization of cortical oscillations during information processing was first described by Berger. He observed that eye opening leads to attenuation of the occipital alpha rhythm. Some years later, further studies revealed that the ERD of central mu-rhythms strongly correlates with the processing of movement preparation and its execution (Jasper and Penfield, 1949; Pfurtscheller and Aranibar, 1979; Pfurtscheller et al., 1980).

About 2 seconds prior to voluntary movement onset, ERD of the mu and central beta rhythm over the contralateral sensorimotor cortex can be observed. (See figure 8). It continues during the performance of unilateral movement and spreads bilaterally over the central region in a symmetric way (Pfurtscheller and Lopes, 1999). The contralateral dominance of early ERD is thought to be a representation of an unconscious initiation of a voluntary movement. The lateral bilateralization of ERD is caused by the recruitment of both sensorimotor cortices (Pfurtscheller and Berghold, 1989).

Pfurtscheller (1981) demonstrated the existence of two kinds of ERD correlating with a movement, i.e., beta- and mu-ERD within the sensorimotor cortex. Whereas the central beta rhythm can be found in the primary somatomotor cortex, the central mu rhythm occurs more in the posterior area, within the primary sensorimotor cortex (Pfurtscheller and Neuper, 1994; Salmelin et al., 1995). Compared to mu-ERD, beta-ERD is of shorter duration and shows a faster recovery after motor activation.

The ERD can be interpreted as a change in local interactions between pyramidal neurons and interneurons influencing the frequency components of the EEG, i.e., increased cellular excitability in neuronal pathways connecting thalamus with cortex while information processing (Steriade and Llinás, 1988). So ERD is a correlate of activation within the cortical areas processing a movement (Pfurtscheller and Neuper, 1992). The observed increase or spreading of ERD is assumed to result from a contribution of different neuronal assemblies into the processing. Enhancement of ERD can be observed in more complex tasks, more efficient performance (Klimesch, 1996; Sterman et al., 1996) or if more attention is needed (Derambure et al., 1993). The ERD can be applied as an assessment measure of cortical functioning.

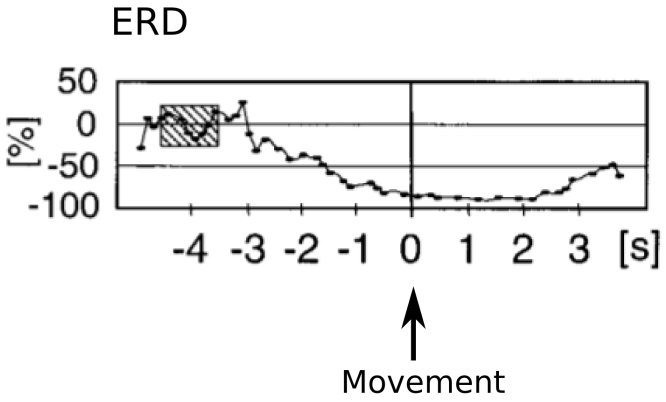


Figure 8: Relative power attenuation of the brain oscillations in a certain frequency band is called event-related desynchronization (ERD). The drawing represents ERD evoked by a hand movement (arrow). The gray square depicts a time window taken for the baseline power measurement.
(Modified afterPfurtscheller and Lopes (1999))

4 Stroke

4.1 Definition and epidemiology

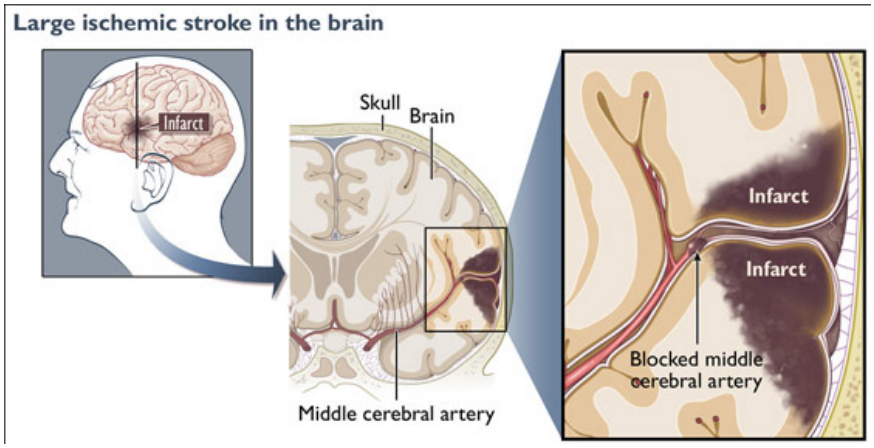
Stroke is defined by the World Health Organization (WHO) as a syndrome characterized by "rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 hours or longer or leading to death, with no apparent cause other than of vascular origin" (Who, 1989). The clinical symptoms are caused by an acute loss of neuronal cell function due to impaired blood flow resulting from a vessel blockage (ischemia) or its rupture within the brain (hemorrhage).

Stroke arouses a major public health concern, being responsible for 10% of deaths worldwide and almost 90% of deaths in industrialized countries among people aged over 65 years (Bonita, 1992; Who, 2004). In the western world, stroke is ranked as the second biggest cause of death and the leading cause of serious, long-term disability (Donnan et al., 2008).

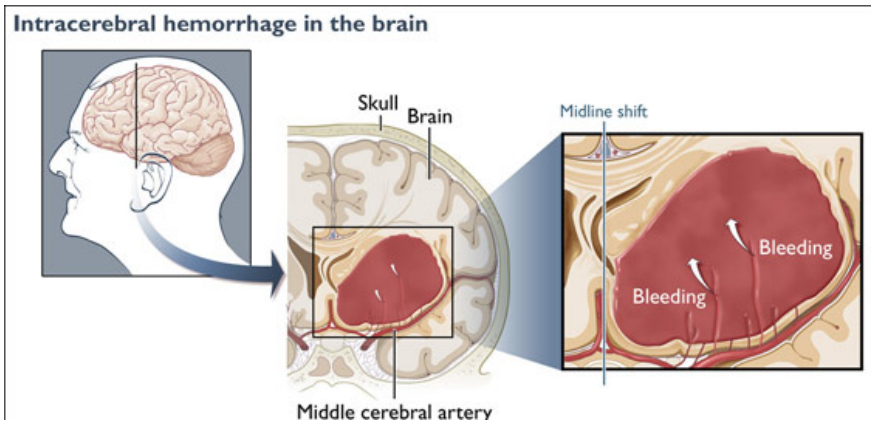
4.2 Neuropathology of stroke

Ischemic stroke accounts for 80% of all brain infarctions originating from a decreased or absent blood flow depriving neurons of energy substrates. Intracerebral hemorrhage occurs in 10-15% of all stroke patients leading to brain tissue injury by increased localized pressure and disrupted blood circulation (Bamford et al., 1988). (See figure 9). Eventually, in both cases, the release of destructive biochemical substances influences the tissue damage.

The neuronal death is caused by a cascade of interrelated mechanisms. Primarily, the depletion of glucose and oxygen results in a disturbed production of high energy compounds such as adeno-



(a) Brain infarction



(b) Brain hemorrhage

Figure 9: A cerebrovascular attack - stroke - occurs when brain is rapidly losing its functions due to disturbed blood supply accompanied by a lack of oxygen and glucose. As shown in figure it can be caused by a) ischemia or b) hemorrhage. Ischaemic strokes may have different origins: thrombosis of a local brain vessel, embolism due to atherosclerosis of a large vessel or of cardiac origin, venous thrombosis and systemic hypoperfusion of the brain as in case the of shock. A bleeding leading to a stroke is mainly caused by chronic high blood pressure, which weakens the walls of blood vessels making them burst. Less common causes are malformations of brain blood vessels, tumors, head injuries, bleeding disorders or vasculitis.

(Source: `http://uwmedicine.washington.edu/Facilities/Harborview/CentersOfEmphasis/Neuro/StrokeCenter/terms.htm`)

sine triphosphate (ATP). Consequently, energy dependent processes such as transport of excitatory neurotransmitter glutamate by the uptake carriers are impaired and thought to be the major cause of neuronal death. The increased extracellular concentration of glutamate causes an influx of calcium into the neuronal cells. Intracellular calcium activates destructive enzymes such as proteases, lipases or endonucleases digesting the cell and eventually triggering its death (Siesjö, 1981; Rothman and Olney, 1987; Hademenos and Massoud, 1997). Simultaneously, the production of oxygen radicals is induced, damaging both the cellular and extracellular elements and activating programmed cellular death known as apoptosis (Siesjö et al., 1989; Kroemer et al., 1995).

4.3 Reorganization

4.3.1 Definition of reorganization

Reorganization, also known as well as brain plasticity, is a process of restructuring neuronal network following its damage. Lesion-induced changes can be of different origins. Pathways that have homologous function can take over the activities of the damaged areas, new interconnections within the neuronal assemblies may be formed (synaptogenesis) or functionally silent brain regions can be recruited (Wall and Egger, 1971; Wall, 1980).

4.3.2 Reorganization in patients after stroke

Reviewing the studies on neuronal reorganization caused by stroke, one encounters several problems. Firstly, in comparison with an abundance of brain mapping studies, there are only few implementing the EEG-technique in order to analyze ERD in stroke patients. Secondly, most of them focus on chronic stroke patients and thus, the acute changes within the brain are still not well investigated. Moreover, the lesion's location is seldom taken as a separate criterion for analysis of stroke-related changes of the sensorimotor brain oscillations. Hence, most of the conclusions derived from studies refer to changes observed in mixed groups of patients with cortical and subcortical stroke. Although these obstacles make it difficult to compare the studies, some main reorganization patterns can be defined.

4.3.3 Topographical changes after stroke

Main reorganization patterns Stroke leads to reorganization of the motor system resulting in activation patterns that are not found in healthy subjects. These changes are probably needed to maximize control of remaining motor output (Jones and Schallert, 1994; Nudo and Milliken, 1996). There is still little known about this process, but from the brain mapping and encephalographic studies with hemiparetic patients after monohemispheric stroke, five main pathological motor system activation patterns

during movement of the paretic limb emerge: i) ipsilateral activation of the sensorimotor cortex (unaffected hemisphere) (Green et al., 1999; Wiese et al., 2005) ii) recruitment of the adjacent neuronal networks to the lesion (Luft et al., 2004) iii) activation of secondary motor cortices or somatosensory cortex in the affected hemisphere (Platz et al., 2000; Luft et al., 2004) iv) enlarged activation in the contralateral primary motor cortex (Rossini et al., 1998) v) bilateral activation of the motor cortex (Chollet et al., 1991; Verleger et al., 2003). The observed remapping of the hand representation and new activation patterns of the motor system may be a reflection of changed connections between the primary and secondary motor cortex which can enable further access to motor neuronal pathways. The observed diversity of the activation patterns is associated with the variability of the groups of patients studied: lesion location (Chen et al., 2000; Shelton and Reding, 2001; Luft et al., 2004), time interval since stroke (Feydy et al., 2002) or degree of recovery (Ward et al., 2003).

Reorganization in subcortical stroke In hemiparetic patients suffering from subcortical lesion coactivation of ipsilateral motor pathways can be found. Several theories were proposed to explain this observation. This pattern may be thought of as a brain's attempt to activate the unaffected uncrossed anterior corticospinal tract fibers (Shelton and Reding, 2001), interhemispheric reorganization in corpus callosum (Boroojerdi et al., 1996; Liepert et al., 2000; Luft et al., 2004), a "reflex-like activation of the unaffected motor system to compensate for possible failure of the affected hand" (Verleger et al., 2003), reorganization of the intact hemisphere due to overuse of the intact hand or as an involvement of the ipsilateral cortex in higher-order motor processing, i.e., temporospatial organization and selection of the movement rather than recruitment of the uncrossed corticospinal pathways (Feydy et al., 2002; Gerloff et al., 2006). In some patients, additional recruitment of sensory and secondary motor structures, e.g., premotor cortex was recorded (Platz et al., 2000; Feydy et al., 2002; Luft et al., 2004; Gerloff et al., 2006). This can be due either to higher excitation level of pyramidal cells being a part of motor and premotor regions or revealing brain's ability to activate projections from these areas to brainstem motor systems during movement preparation (Platz et al., 2000). Other studies report an extended activation of primary sensorimotor cortex towards the face area (Weiller et al., 1992, 1993; Dettmers et al., 1997; Calautti et al., 2001) or a posterior shift of the activation peak (Rossini et al., 1998; Luft et al., 2004) in subcortical stroke survivals .

Reorganization in cortical stroke Chronic patients with cortical lesions showed an activation of areas at the rim of the infarct, and similar to subcortical group, ipsilateral overactivation for paretic hand movement (Cramer et al., 1997; Green et al., 1999; Luft et al., 2004). The posterior shift and inferior extension of primary motor cortex activation is seen both in cortical and in subcortical strokes and might be due to unmasking within the corticospinal tract, which means that the existing but beforehand functionally silent synapses are activated (Pineiro et al., 2001; Rossini et al., 2003). Apart

from these brain activation patterns, further findings were reported in studies with cortical stroke patients. For paretic hand movements, an overactivation in the intact hemisphere was observed (Cramer et al., 1997; Green et al., 1999) and for healthy hand movements either normal (Green et al., 1999) or decreased activation in the lesioned hemisphere was demonstrated (Cramer et al., 1997).

4.3.4 Changes of brain oscillations

In one of the first mu-ERD studies on acute stroke patients, Pfurtscheller et al. (1980) measured five subjects with mild hemiparesis after stroke. In two of patients with right hemispheric stroke, a reduction of alpha-ERD amplitude in the affected hemisphere for intact and paretic hand movements in comparison with healthy hemisphere was observed. Unfortunately, the authors did not report if the patients suffered from cortical or subcortical stroke. Interestingly, such results were obtained although on visual inspection of the clinical EEG no abnormalities were seen.

These findings were confirmed by the next study of Pfurtscheller et al. (1980). Two patients suffering from mild hemiparesis after cortical stroke in its acute phase presented with decrease of alpha-ERD in the damaged hemisphere: one of them for paretic and the other one for healthy hand movement. A third patient with subcortical lesion of basal ganglia also exhibited reduced amplitude of alpha-ERD over the affected hemisphere for intact hand performance.

In the course of subsequent research, Pfurtscheller et al. (1981) reported some significant differences in alpha-ERD between patients after acute cortical and subcortical stroke. One of the aims of this study was the investigation of the alpha-ERD symmetry defined as significant increase or decrease of ERD compared to healthy hemisphere. For paretic hand movements, patients with deep subcortical lesions presented either with symmetric or asymmetric ERD, in contrast to subjects with cortical stroke displaying mostly ERD asymmetry, which was defined either as increase or decrease of ERD in comparison with the unaffected hemisphere. Moreover, if subcortical and cortical structures were both affected, either symmetrical or extinguished ERD was present. The authors report also that the increased power attenuation was rarely found in either group of patients.

Platz et al. (2000) reported that the beta-ERD during movement in subacute and chronic subcortical stroke patients did not significantly differ from that of the controls. Further, an increase of alpha-ERD was observed in left frontolateral brain areas independently on the lesions side during movement execution (Platz et al., 2000). As some of the authors suggest this type of activation is directly correlated with a heightened attention and effort needed to perform the task (Weiller et al., 1992; Jueptner et al., 1997; Platz et al., 2000).

In the groups of patients in chronic stage after stroke, further changes in brain organization were noticed. Recently, Gerloff et al. (2006) showed that the task-related power in mu- and beta frequency recorded for paretic hand movements in subcortical stroke patients had reduced amplitudes over the affected hemisphere and enhanced amplitudes over the intact hemisphere. The enhanced activity

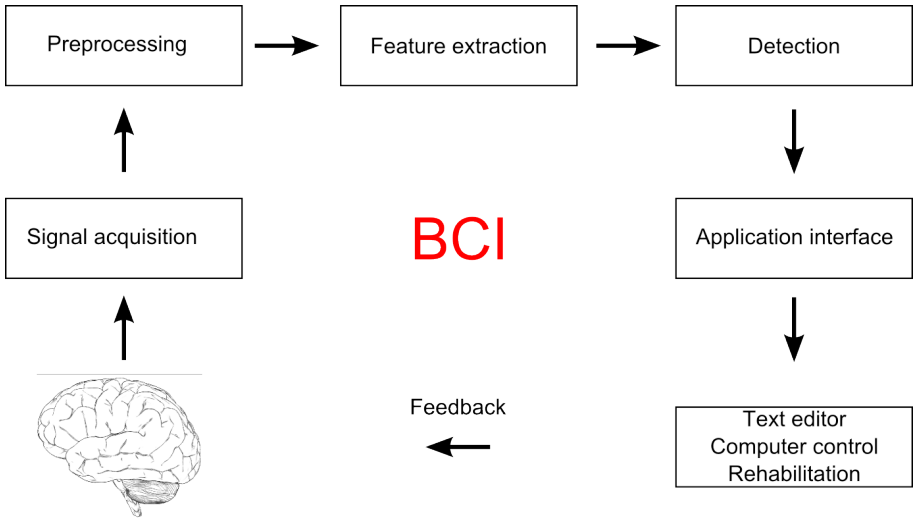


Figure 10: Brain-computer interface (BCI) can make it possible to decode brain signals and to translate them into computer commands. EEG-based BCI records brain signals. i.g., oscillations with the help of electroencephalography. Further, they are processed by an algorithm, the desired features are extracted and detected. The brain signal can be utilized for example, by a text editor or rehabilitation devices.

(Modified after Wolpaw and McFarland (2004))

occurred both in the movement's preparation and its execution.

5 Brain-computer interface (BCI)

Brain-Computer interfaces (BCIs) are devices utilizing voluntarily generated or induced changes in brain activity for direct communication between human brain and computer without requiring any muscular involvement. The cerebral electric activity correlating with an intention of a hand or foot movement can be recorded with electroencephalography (EEG) or electrocorticography (ECoG) from electrodes outside (non-invasive BCI) or inside (invasive BCI) the brain, respectively. Apart from EEG-BCI there is a variety of other methods used for recording the brain activity such as magnetoencephalography (MEG), positron emission tomography (PET) or functional magnetic resonance imaging (fMRI). However, the EEG-based BCI due to its simplicity and inexpensive equipment offers at present the best system for the potential users - patients with severe neuromuscular disorders.

The intent of the user can be determined within the BCI technique from different electrophysiological signals, e.g. event-related potentials (ERPs) (Farwell and Donchin, 1988), EEG oscillations (Wolpaw and McFarland, 2004) or slow cortical potentials (SCPs) (Birbaumer et al., 1999). Further, the recorded brain signals are amplified and transmitted to the computer. Subsequently, an adaptive BCI algorithm decodes and translates the signals into commands within a computer application. The BCI changes the input such as a voluntary intention of a subject to move a hand into device com-

mands e.g. cursor control in real time (Tecchio et al., 2007). In this way the neuromuscular system is bypassed on the pathway to perform an action. (See figure 10).

In the case of stroke, BCI could be potentially applied for communication programs, computer or wheelchair control improving significantly the independence and life quality of the affected patients (Pfurtscheller and Neuper, 2006). This technique could also be implemented in the field of rehabilitation. Despite the present rehabilitative treatment, one third of the stroke patients regain only poor or no motor control over the affected hand (Lai et al., 2002). From the recent studies it is known that not only active and passive movement of the affected limb are crucial for the process of rehabilitation, but even its imagination or stimulation (Stevens and Stoykov, 2003). These practices induce recruitment of the silent synapses and pathways in the affected hemisphere leading to reorganization within sensorimotor areas (Papathanasiou et al., 2003; Birbaumer and Niels, 2006). The process observed is correlated with an increase of motor control over the hemiparetic limb in some patients (Murase et al., 2004). The next step of intergrating the BCI system into the rehabilitation process could be the use of a visual feedback, e.g. as virtual hand movement combined with virtual reality. This possibility could potentially not only enhance the subject's motivation but also result in the patients rehabilitation(Holden, 2005).

6 Goals of our study

The reorganization processes of the brain after stroke can be analyzed with different methods and in various types of lesions.

The knowledge about the reorganization processes of the motor system after stroke is mainly derived from a multitude of imaging studies (fMRI, PET etc.). These imaging techniques focus especially on spatial distribution of the activation patterns. However, when using these methods the time course of an event cannot be as precisely described as with electroencephalography. EEG as a technique of research allows for observing the oscillatory and event-related brain activity due to its high time resolution. If the interest is focused on the oscillatory activity within the neural network, the event-related desynchronization (ERD) may be chosen as a parameter. In control subjects the ERD reflects the neural activation before and during performance of a movement.

The present understanding of the probable stroke-related oscillatory changes is not satisfactory due to the small number of studies that analyzed this phenomenon. The existing ones concentrate on changes in chronic stroke patients although most of the reorganization processes take place during the acute phase of stroke. From the research on acute stroke in patients with deep and superficial brain lesions, emerges only a partial picture of stroke - induced brain activation changes. Precise investigations of the dynamic changes within the neuronal networks during the acute phase of stroke could therefore lead to a better understanding of their interconnectivity and their functions.

The reorganizational ERD patterns in acute stroke are not well understood. Further, it is not clear, if cortical lesions influence the neural oscillations differently than subcortical lesions.

The aim of this study was to investigate the relationship between the lesion location and the dynamics of the neural oscillations in acute phase of stroke and to answer following questions:

1. What kind of oscillation changes can be observed in acute stroke within the motor system ?
2. Does the lesion's location influence the brain oscillations?
3. Is there any correlation between the grade of paresis and the severity of ERD changes?

The investigations of the possible stroke-related ERD changes could probably also have a practical aspect. The reorganizational oscillatory patterns seen in stroke patients could be applied for ERD-based brain-computer interface (BCI). With this knowledge probably the movement-related ERD patterns could be better recognized by the BCI in stroke patients, enabling them to use this novel communication and rehabilitation system.

Part III

Methods

7 Paradigm

7.1 Participants

7.1.1 Control group

As a control group, ten healthy, age-matched individuals (mean age 53 years, range 43-68, 7 males and 3 females) were chosen. They had no history of any neurological or mental disorders and were not taking any medication at the time of the experiment that could have had an influence on EEG.

7.1.2 Patients

For this study, 17 patients (mean age: 57 years, range 41-68, 10 males and 7 females) were recruited as inpatients of the Department of Neurology of the Charite Klinikum Benjamin Franklin, Berlin.

Admission criteria were:

1. First unilateral, cortical or subcortical stroke in area of the motor system. If multifocal lesions were present, patients with clear unilateral neurological signs were accepted.

2. Acute phase of stroke: 2-14 days after the event.

3. Presence of hemiparesis, hemiplegia or decreased level of fine motor skills.

4. Evidence of the lesion was based either on the image produced in computer tomography (CT) or Magnetic Resonance Imaging (MRI) technique.

Patients with present or previous brain or psychiatric disorders were excluded from this study. None of the patients received central acting analgetics, anticonvulsants, neuroleptics or antidepressants at the time of EEG examination.

Patients were divided accordingly to the lesion level into two groups: either with cortical lesions (n=7) or with subcortical lesions (n=10). They participated at this study on average 7 days after stroke (range: 2-13 days). Three patients had hemiplegia and 14 hemiparesis (n=5 left hemiparesis, n= 9 right hemiparesis, n=3 right hemiplegia). According to the standard neurological examination, the mean motor strength was 3.6 and ranged between 0 and 5, however patients with the upper limb strength of 5 showed decreased fine finger movement. (See table 1).

Each participant of this study received a standard neurological examination and motor strength evaluation using Copenhagen Stroke Scale by Olesen et al. (1988). Informed consent was obtained from all participants. The study was approved by the local ethics committee of Charité - Universitätsmedizin Berlin.

8 Evaluation of the motor deficit

At the time of the EEG experiments, patients were evaluated with two motor stroke scales: Copenhagen Stroke Scale and Motor Grading Scale.

The 10-item Copenhagen Stroke Scale (CSS) was invented by Olesen et al. (1988). It is designed to estimate initial severity of neurological deficit in stroke patients. The patients are assessed with the help of 10-40 score, where 10 points relate to a normal function. The mean score for patients was 13.2 and ranged between 10 and 24 points. (See table 5).

The strength of the upper limb was evaluated according to the standard British Medical Research Council Motor Grading Scale (Hmso, 1976). The patient was instructed to move the upper limb against the resistance of the examiner. Within this scale the motor strength can be graded between 0 (no muscle movement) and 5 (normal muscle movement). For practical reasons, grade 4 may be differentiated into 4-, 4 and 4+ in order to discriminate between severe, moderate and mild weakness, respectively. (See table 4). For further detailed information see the attached Copenhagen Stroke Scale and the standard British Medical Research Council Motor Grading Scale in the appendix to this work.

Patient no.	Age (years)	Gender	Time after stroke (days)	Brain lesion	Lesions side	CSS	Upper limb strength
Subcortical group							
1	49	F	6	Internal capsule, Thalamus	L	10	4+
2	62	M	9	Basal ganglia	L	11	5
3	68	M	7	Basal ganglia	R	17	2
4	62	M	5	Thalamus	R	11	4+
5	59	M	7	Internal capsule	L	11	4+
6	67	F	8	Basal ganglia	L	24	0
7	46	M	2	Thalamus	L	10	5
8	65	M	11	Basal ganglia	L	10	5
9	64	M	4	Basal ganglia	R	12	4+
10	60	F	8	Basal ganglia	L	13	4
Cortical group							
11	45	M	7	Lower frontal, temporal, precentral, postcentral, parietal gyrus	L	18	0
12	48	F	13	precentral, postcentral, parietal gyrus	R	13	4
13	52	F	4	Higher frontal, precentral, postcentral gyrus	R	10	4+
14	51	M	10	Frontal, temporal, precentral gyrus	L	11	4+
15	41	M	10	Lower frontal, precentral, postcentral gyrus	L	10	4+
16	63	F	4	Frontal, precentral gyrus	L	11	4+
17	67	F	6	Frontal, precentral gyrus	L	22	0

CSS = Copenhagen Stroke Scale, F = female, M = male, L = left, R = right

Table 1: Characteristics of stroke patients

9 CT and MRI image evaluation

Each of the patients had at least one CT or MRI brain scan either with . The lesion location was analyzed with help of the neuroanatomical atlas by Mai et al. (1997).

10 Behavioral task

The subjects were in semi-supine position in front of a computer screen with their arms resting at their bedsides. Each hand was in contact with a special ergonomic mouse (E-Quill-Airo2bic-mouse made by Dr. Elisabeth Seveke), which allowed a comfortable semi-pronated position of the hand. Subjects performed two different tasks described here as 'active' and 'rest' condition. Two types of visual stimuli were presented to the subjects: arrows pointing the the left or to the right side, referred to further as 'left arrow' and 'right arrow'. The stimulus sequences consisted of alternating presentation of two stimuli for each side: after two left arrows, two right arrows followed (LLRRLL..). The duration of each stimulus and inter-stimulus interval was 1.5 second. (See figure 11).

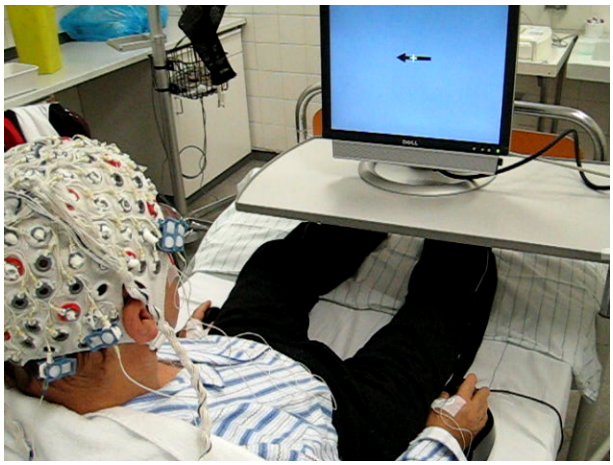
In the active condition task subjects were asked to press a mouse button with an index finger as required by the direction of the presented arrow. If the execution of the movement was not possible due to hemiplegia, the patients were instructed to keep on trying pressing a mouse button. They were taught to perform the response as close in time as possible to the presentation of the visual stimuli - "staying on beat". During the rest condition task, subjects were asked to observe passively arrow stimuli on the computer screen. Subjects were asked to relax and to reduce the number of blinking, swallowing and moving during the recordings.

The rest condition task consisted of two sessions and the active condition of four sessions. During the experiment the order of the recorded session was as follows: the rest condition task, two active sessions, afterwards second rest condition task and final two active sessions. Each session lasted approximately 8 minutes including 4 breaks each 15 seconds long. In each session, 50 left arrows and 50 right arrows were presented .

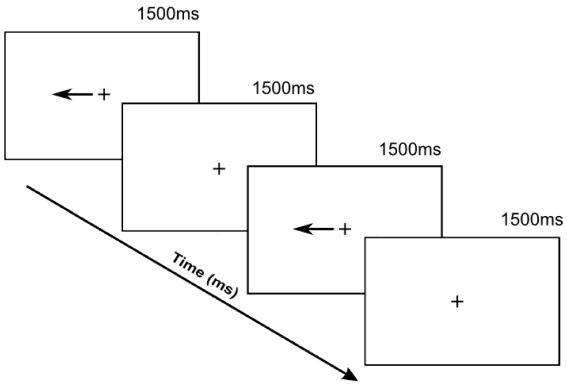
Finally, an EEG at rest with eyes closed for one minute was recorded.

11 Data acquisition

A 65-channel EEG including vertical and horizontal electrooculogram (EOG) and surface electromyogram (EMG) of the left and right index fingers (M. interosseus I) were recorded using Ag/AgCl electrodes, BrainAmp amplifiers and BrainVision Recorder software (Brain Products GmbH, Munich, Germany). During the data acquisition, EEG and EMG signals were band-pass filtered between 0.1-250Hz and digitized at a rate of 1000Hz. In order to reduce the number of data and facilitate the



(a) Each patient and control subject was seated comfortably in front of the computer screen with his/her hands resting on ergonomic computer mice as shown in this photograph.



(b) All participants were shown a sequence of two left followed by two right pointing arrows according to the scheme LLRRLL. Each stimulus was presented for 1.5 seconds with an inter-stimulus interval of the same duration.

Figure 11: Paradigm scheme

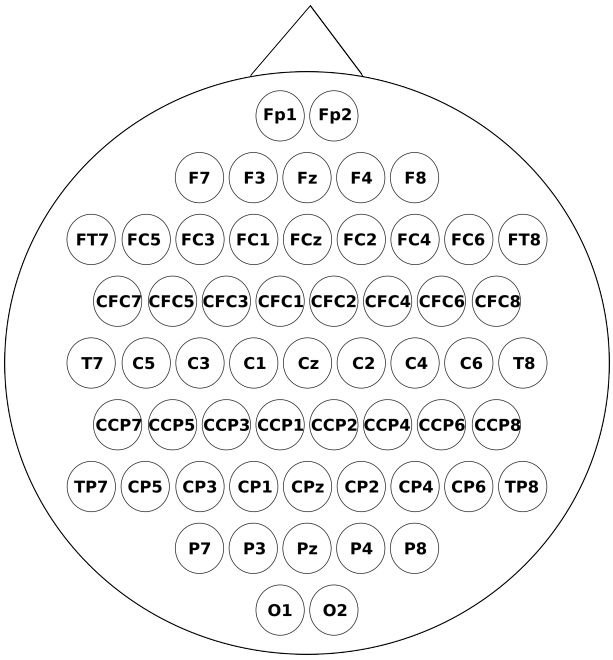


Figure 12: This figure represents the chosen electrodes montage. The electrodes were placed according to 10-20 system with a nose-reference.

post-processing, the data were down-sampled with frequency of 200 Hz. EEG electrodes were placed according to the extended International 10-20 system (Jasper, 1958) with the reference electrode on the nose. (See figure 12).

12 Data analysis

For EEG Analysis MatLab (Mathworks, Natick, MA) software was used. EEG data was segmented into epochs and those with artifacts were rejected. Such rejection was performed on the basis of sorting epochs amplitude in an ascending order epochs which amplitude showed considerable discontinuities in its distribution were removed. In addition to the nose referenced data, for the following analysis, Laplacian derivations was used as well. In this procedure, an averaged activity of four surrounding electrodes is subtracted from the activity of the channel of interest (Graimann and Pfurtscheller, 2006; Hjorth, 1975). In this procedure a final set of electrodes was used for the analysis: FC3, FCz, FC4, C5, C3, C1, Cz, C2, C4, C6, CP3, CPz, CP4. (See figure 13).

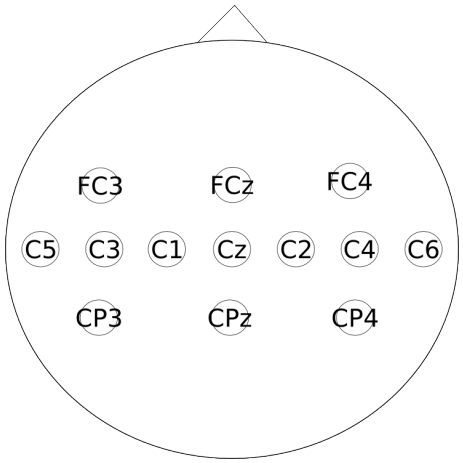


Figure 13: The electrodes montage shown after Laplacian transformation.

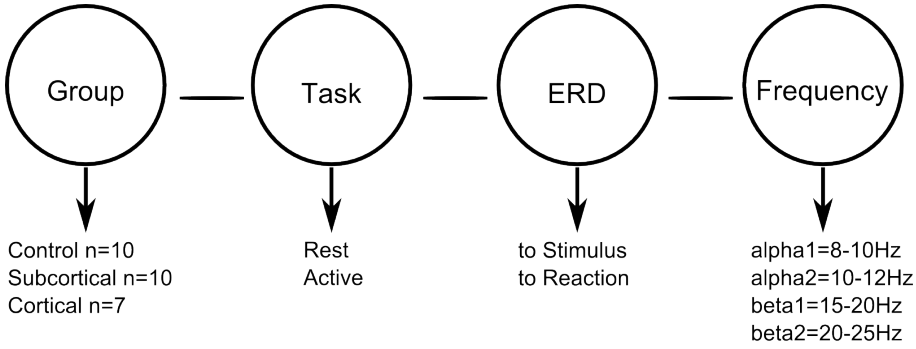


Figure 14: The ERD amplitude was measured in three groups: controls and patients with cortical and subcortical lesions. For all of them the analysis was conducted for both "rest" and "active" tasks in relation to the presented stimulus or subjects' reaction in four frequency bands as shown in this picture.

12.1 ERD analysis

12.1.1 ERD amplitude

The amplitude of neuronal oscillations in the motor task was analyzed in each group separately: controls, patients with cortical and subcortical stroke. The amplitude of oscillations was evaluated in four frequency bands: 8-10, 10-12, 15-20, 20-25Hz. Increase of oscillations was referred to as event-related desynchronization (ERD). ERD was calculated with respect to the appearance of the visual stimuli or the onset of the motor response and it is referred to as "ERD to stimulus" and "ERD to reaction", respectively. (See figure 14). For means of enveloping the amplitude of the oscillations, Hilbert transform was applied (Rosenblum et al., 2002; Graimann and Pfurtscheller, 2006). An epoch window -1000 ms to 1100 ms was chosen around each event. For ERD to reaction, the mouse button presses prior to visual cues, incorrect with the stimulus side or exceeding the the maximal time of 1.5 seconds after stimulus presentation, were excluded from the analysis. Importantly, all the participants

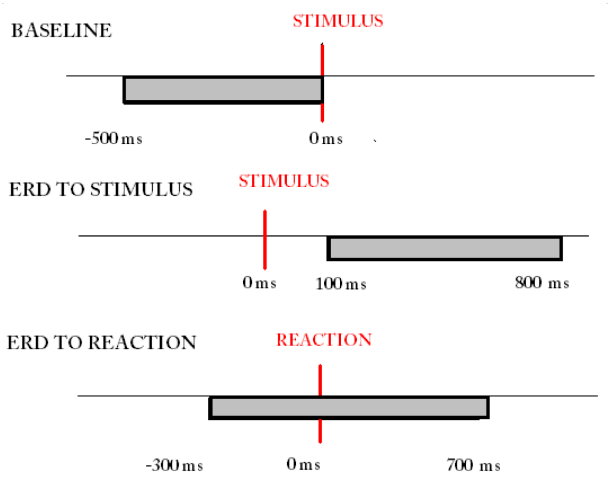


Figure 15: For ERD analysis certain time windows were chosen. The baseline was measured in an interval from 500 ms before the stimulus till its presentation defined as 0 ms. In "rest" task the the deepest amplitude decrease was calculated in post-stimulus interval from 100 ms to 800 ms and in "active" task 300ms before to 700 ms after reaction.

mostly reacted after the presented arrows. After averaging of the epochs, ERD was obtained according to the following equation:

$$ERD\% = \frac{(POST - PRE)}{PRE} * 100$$

and depicted as a percentage value. PRE means averaged activity, defined as baseline in pre-stimulus interval (-500ms to 0 ms). POST is measured as the deepest amplitude decrease in post-stimulus interval (100ms to 800 ms) for ERD to stimulus and (-300ms to 700 ms) for ERD to reaction. (See figure 15). An electrode with strongest ERD in left and right sensorimotor areas was chosen for each condition. Though the averaging of epochs with respect to visual cues does not allow exact appreciation of amplitude dynamics locked to the movement, it gives an insight into stimulus-related motor activity. This procedure allowed including of hemiplegic patients into the study.

12.2 Assessment of ERD localization source

In order to estimate a possible topographical change in the presence of ERD, two separate analysis of anterior/posterior and medial/lateral shift were conveyed. As zero points the C3 (0,0) was used for electrode left hemisphere and the C4 (0,0) electrode for the right hemisphere. In estimation of anterior/posterior shift the electrode anterior to C3/C4 was ascribed a value of -1 (0, -1) and for the posterior shift, the value 1 (0,1). (See figure 16). For the analysis of medial/lateral localization change lateral electrodes to C3/C4 was given the value -1 (-1,0) and the medial electrodes received the value

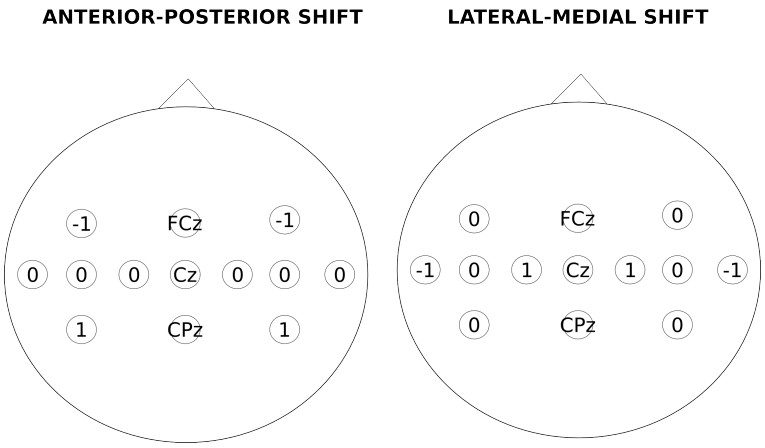


Figure 16: These figures present the method of ERD localization assessment. On both pictures the electrodes within the left and the right hemisphere were assigned values -1, 0 or 1. The electrodes C3 and C4 were ascribed values (0,0) as reference points. The figure on the left side shows the method for estimation of the anterior-posterior shift and the figure on right side presents for assessment of the the latera-medial ERD localization.

1 (1,0). (See figure 16). The electrodes showing the deepest decrease of ERD amplitude were found and ascribed the aforementioned mentioned values. In statistical evaluation of the data, the three-way ANOVA testing was chosen.

13 Statistical evaluation with analysis of variance (ANOVA)

13.1 General description of ANOVA

ANOVA (analysis of variance) is a statistical method that focuses on comparing the variances of the means of several groups to the variances within the samples (Hoel, 1976).

The variance is a measure of variability indicating how spread out the samples within a group are. It is computed as the average squared deviation of each number from its mean. The variance (σ^2) of samples in a population can be denoted with the following formula:

$$\sigma^2 = \frac{\Sigma(X-\mu)^2}{N}$$

where X is a single variable, μ is the population mean and N the number of scores (Hoel, 1976).

The significance of the ANOVA results depends on the sample size and the level of certainty applied for testing, i.e., p-value. Further assumptions within ANOVA are that the samples are independent and drawn from a normal distribution.

ANOVA, as any other statistical method, uses the hypothesis called the null hypothesis - a general assumption concerning the samples in the observed population. The ANOVA's null hypothesis (H_o)

is true, when there is no difference between the means (m) of the variables. It can be depicted in the following way:

$$H_o = m_1 = m_2 = m_3 = ... = m_n$$

When the data contradicts the null hypothesis, then a result can be called significant.

A rejection of the ANOVA's null hypothesis indicates that there are significant differences between the means of the groups. In the present study the significance level was 0.05 (p-value). To decide which of the variables are significantly different from each other, one should perform post-hoc tests, e.g. Tukey's test. It compares the means of every group to the means of every other group. Further, it identifies whether the difference between two group means is greater than allowed by the standard error (Hoel, 1976).

The comparisons allowed by ANOVA can be simple or compound. In the simple type of test, the mean of one group is compared with mean of one other group. e.g.,. *m1* with *m2*. Compound testing allows for comparing two sets of groups means, where each set may have two or more groups. e.g., *m1*, *m2* with *m3*, *m4.*

13.1.1 Application of ANOVA method to the study

Three-way ANOVA for repeated measures was used for statistical analysis of ERD strength. The populations of interest were three groups of subjects: i) control, ii) with cortical lesions and iii) with subcortical lesions. Following independent variables were used for within-group comparisons: *Hemisphere, Laterality* and *Frequency.* The factor *Hemisphere* describes the hemisphere in which the ERD was measured. The *Laterality* refers to the hand performing the movement in relation to the hemisphere in which the ERD was analyzed. *Frequency* indicates the frequency band in which the ERD was computed. These three main independent variables were further subdivided into variables as shown in the tables 4 and 5. ANOVA compared the means variance of the subpopulations in a simple and compound testing procedure as explained above. The ANOVA test was separately computed for the "rest task" and for the "active task". Following statistical comparisons for both tasks were tested with ANOVA: i) within each group, ii) each patient group separately compared to control group, iii) between cortical and subcortical group. When the main effect of ANOVA was significant, the null hypothesis was rejected and Tukey's test was applied. It was used for both simple and compound statistical comparisons.

13.1.2 Within-group ANOVA testing

Altogether three separate within-group ANOVA tests were computed for: control group and for two patient groups. For this type of statistical comparisons the independent variables were subdivided in a following way:

Hemisphere	Healthy				Affected			
Laterality	Contralateral		Ipsilateral		Contralateral		Ipsilateral	
Frequency	8-10Hz	10-12Hz	8-10Hz	10-12Hz	8-10Hz	10-12Hz	8-10Hz	10-12Hz
Subject 1	*X1*	*X21*	*X31*	*X41*	*X51*	*X61*	*X71*	*X81*
Subject 2	*X2*	*X22*	*X32*	*X42*	*X52*	*X62*	*X72*	*X82*
Subject 3	*X3*	*X23*	*X33*	*X43*	*X53*	*X63*	*X73*	*X83*
Subject n	*Xn*	*X2n*	*X3n*	*X4n*	*X5n*	*X6n*	*X7n*	*X8n*
Subject ⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮
Mean	*m1*	*m2*	*m3*	*m4*	*m5*	*m6*	*m7*	*m8*

Table 2: ANOVA table for statistical analysis of ERD values (*X*) in alpha frequency for patients group. In the case of controls, the factor "*Hemisphere*" was subdivided into "*Left*" and "*Right*" hemisphere.

a) *"Hemisphere"*: "*Left*" and *"Right"* for the control group and "*Healthy*" and "*Affected*" for the groups of patients;

b) "*Laterality*": "*Contralateral*" and *"Ipsilateral"*. For example: If a patient was moving the paretic hand and the ERD was measured in the affected hemisphere, its amplitude value was coded in the table within the main column "*Affected Hemisphere*"and specified as "*Contralateral*";

c) "*Frequency*": two bands of alpha frequencies: "*8-10Hz*" and "*10-12Hz*" or two bands of beta frequencies: "*15-20Hz*" and "*20-25Hz*".

Since ANOVA allows for both simple and compound comparisons, both types of this test were applied for this study. An example of a simple comparison is the analysis of variance between the means of the columns described as follows: "*Unaffected hemisphere*Contralateral*8-10Hz*" vs. "*Affected Hemisphere*Contralateral*8-10Hz*". In a compound test, two sets of means can be compared with each other, where each set contains two or more groups of means ex. "*Unaffected hemisphere*" (mean from set of means: *m1, m2, m3, m4*) vs. "*Affected Hemisphere*" (mean from set of means: *m5, m6, m7, m8*). (See table 2).

13.1.3 ANOVA testing between the control group and patient groups

In order to compare statistically the control group with each of the patient groups, a new independent variable "*Averaged hemisphere*" was introduced. It refers to the averaged ERD amplitude values of the left and right hemispheres for each subject of the control group. It can be formulated as follows:

$$AvH = \frac{LH+RH}{2}$$

where *AvH* is the averaged ERD value, *LH* is the ERD value measured in the left hemisphere and the *RH* is the ERD value measured in the right hemisphere. As a result of this computation the ERD values of the averaged control hemisphere were compared with the ERDs from the healthy and affected hemisphere of patient groups, separately. (See table 3).

Hemisphere	Averaged hemisphere Control group				Patients Group - Unaffected hemisphere			
Laterality	Contralateral		Ipsilateral		Contralateral		Ipsilateral	
Frequency	8-10Hz	10-12Hz	8-10Hz	10-12Hz	8-10Hz	10-12Hz	8-10Hz	10-12Hz
Subject 1	*X1*	*X21*	*X31*	*X41*	*X51*	*X61*	*X71*	*X81*
Subject 2	*X2*	*X22*	*X32*	*X42*	*X52*	*X62*	*X72*	*X82*
Subject 3	*X3*	*X23*	*X33*	*X43*	*X53*	*X63*	*X73*	*X83*
Subject n	*Xn*	*X2n*	*X3n*	*X4n*	*X5n*	*X6n*	*X7n*	*X8n*
Subject ⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮
Mean	*m1*	*m2*	*m3*	*m4*	*m5*	*m6*	*m7*	*m8*

Table 3: ANOVA table for statistical analysis for between-group comparison. In this example the averaged ERD values of the control group are compared with the ERD values derived from the unaffected hemisphere of a patient group for alpha frequency.

For statistical analysis between the control group and each of the patient groups four separate tests were conveyed: "*Averaged control group hemisphere*" vs. "*Unaffected hemisphere*" of patients and "*Averaged control group hemisphere*" vs. "*Affected hemisphere*" of patients both for alpha and beta frequency.

13.1.4 ANOVA testing between the cortical group and the subcortical group

The third type of analysis resulted in statistical comparison between the cortical and the subcortical group of patients. The independent variable "*Hemisphere*" was in this testing replaced by the factor "*Group"*. It refers either to the "*Cortical group*" or "*Subcortical group*". In this type of analysis also four separate tests were conveyed: "*Unaffected hemisphere*" vs. "*Unaffected hemisphere*" and "*Affected hemisphere*" vs. "*Affected hemisphere*" for alpha and beta frequency.

13.1.5 Comparisons conducted in statistical analysis

For "rest" and "active" task a statistical evaluation with ANOVA and if needed, with Tukey's test was conveyed separately for alpha and beta frequency for ERD mean values of sample groups. The exact description can be found in the appendix.

Part IV

Results

14 ERD analysis

14.1 "Rest" task

In this task, subjects were asked to observe stimuli presented on the computer screen. The time window for the analyzed ERD was set around the visual cues -100 ms to 800 ms.

14.1.1 Control group

A presentation of stimuli in all frequency bands did not elicit any differences of ERD amplitudes between left and right hemispheres of the control group for any comparisons described in 15.1.

14.1.2 Patient groups

For both patient groups in four frequency bands the ANOVA revealed no significant differences of ERD amplitude between healthy and affected hemisphere for all comparisons in 15.2.

14.1.3 Control vs. cortical group and control vs. subcortical group

The null hypothesis for the comparisons between control group and each of the patient groups in all frequency bands listed in 15.3 could not be rejected.

14.1.4 Cortical vs. subcortical group

Comparisons listed in 15.4. showed no difference of ERD amplitude in any frequencies between cortical and subcortical group of patients applying

14.2 "Active" task

In "active" task, ERD was measured in a time window around the moment -300 ms to 700 ms when subjects were pressing the mouse button as prompted by the visual stimuli. In order to include the hemiplegic patients in the analysis, ERD amplitude was also calculated in respect to stimulus in a time window 100 ms to 800 ms.

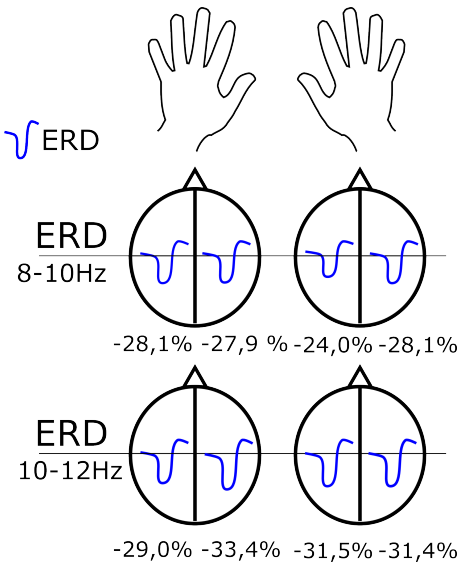


Figure 17: Maps showing the results for the control group in active task for alpha frequency. The numbers indicate the mean ERD amplitude for each condition. On the left side of this figure, the ERD mean amplitude values are presented for left and on the right side for right hand movements.

14.2.1 Control group

For control group, just as in "rest" task, ANOVA did not detect any differences of ERD amplitude between left and right hemispheres in four frequency bands for any of the given comparison types as in 15.1. (See figure 17).

14.2.2 Cortical group

ERD amplitude in respect to movement In compound comparisons no difference between the healthy and affected hemisphere was detected. ANOVA showed a significant interaction between *Hemisphere*Laterality*Alpha frequency* in patients with cortical strokes $F=21.95$, $p<0.01$. For simple comparisons following results were found:

1. Within the cortical stroke group, the affected hemisphere showed a smaller 8-10Hz-ERD and 10-12Hz-ERD (alpha1-ERD=-7,4%/ alpha2-ERD=-8,7%) compared to the unaffected hemisphere (alpha1-ERD=-16%/ alpha2-ERD=-14,8%) when each was contralateral to the acting hand.
   (Comparison: *"Unaffected hemisphere*Contralateral*8-10Hz"* vs. *"Affected hemisphere*Contralateral*8-10Hz"*).
   (See (A) in figure 19).

2. When cortical stroke patients moved their paretic hand, the ipsilateral (i.e., contralesional) alpha-ERD was stronger (alpha1-ERD=-11,8%/ alpha2-ERD=-14,7%) than the contralateral (ipsilesional) ERD (alpha1-ERD=-7,4%/ alpha2-ERD=-8,7%), which was true for both of the

alpha frequencies.
(Comparison: *"Unaffected hemisphere*Ipsilateral*8-10Hz"* vs. *"Affected hemisphere*Contralateral*8-10Hz"*).
(See (B) in figure 19).

3. Only in the 8-10Hz band in hemispheres with a cortical stroke, was the ERD stronger for ipsilateral (non-paretic) (alpha1-ERD=-12,0%) than for contralateral (paretic) (alpha1-ERD=-7,4%) hand movements.
(Comparison: *"Affected hemisphere*Contralateral*8-10Hz"* vs. *"Affected hemisphere*Ipsilateral*8-10Hz"*).
(See (C) in figure 19 and figure 20).

4. For non-paretic hand movements, the ERD amplitude was stronger in unaffected hemisphere (contralateral) (alpha1-ERD=-16%/ alpha2-ERD=-14,8%) than in the affected hemisphere (ipsilateral) (alpha1-ERD=-12,0%/ alpha2-ERD=-9,9%) for 10-12Hz and marginally significant for 8-10Hz.
(Comparison: "*Unaffected hemisphere*Contralateral*Band*" vs. "*Affected hemisphere*Ipsilateral*Band*").
(See figure 18).

5. The unaffected hemisphere had a stronger ERD (alpha2-ERD=-14,7%) than the affected hemisphere for ipsilateral hand movements in 10-12Hz (alpha2-ERD=-9,9%). No such differences were detected for 8-10Hz.
(Comparison: *"Unaffected hemisphere*Ipsilateral*10-12Hz"* vs. *"Affected hemisphere*Ipsilateral*10-12Hz"*).
(See figure 18).

6. In unaffected hemispheres, the 8-10Hz-ERD was stronger for contralateral (non-paretic) hand (alpha1-ERD=-16,0%) than for ipsilateral (paretic) hand movements (alpha1-ERD=-12,0%).
(Comparison: *"Unaffected hemisphere*Contralateral*8-10Hz"* vs. *"Unaffected hemisphere*Ipsilateral*8-10Hz"*).
(See figure 18).

ANOVA showed no significant differences for both of the compound and single comparisons for the cortical stroke group in either beta frequency band. (See figure 18).

ERD amplitude in respect to visual cue

An interaction *Hemisphere*Laterality* was found to be significant ($F=12.69$, $p<0.05$). In simple comparisons Tukey's test showed that the alpha-ERD is stronger over unaffected hemisphere (alpha-ERD=-14,9%) than over the affected hemisphere (alpha-ERD=-9,2%) for contralateral hand move-

ments (Comparison: *"Unaffected hemisphere*Contralateral*8-12Hz"* vs. *"Affected hemisphere* Contralateral*8-12Hz").*

14.2.3 Subcortical group

ERD amplitude in respect to movement and to visual cue In the subcortical group, no significant difference between the healthy and the affected hemisphere was found both in alpha and beta frequency bands for simple and compound comparisons mentioned in 15.2 in respect to movement and to visual cue.

14.2.4 Control vs. cortical group

ERD amplitude in respect to movement Compared to the control group (alpha-ERD=-29,2%), in patients with cortical strokes, the amplitude of alpha-ERD was decreased for both, affected (F=7.53, p<0,05) (alpha-ERD=-9,5%) and, marginally significant (F=4.04, p<0,06), also for the unaffected hemispheres (alpha-ERD=-14,3%) (Comparisons: "*Averaged hemisphere*" vs. "*Affected hemisphere*" and "*Averaged hemisphere*" vs. "*Unaffected hemisphere*"). The main effect of *Laterality* and *Frequency, Laterality vs. Frequency*, *Laterality vs.Group*, *Frequency vs. Group*, *Laterality vs. Frequency vs. Group* were not significant.

ERD amplitude in respect to visual cue These results were supported by the analysis of ERD amplitude in respect to visual stimulus. A significant decrease of alpha-ERD amplitude was measured for affected (F=8.64, p<0.01) (alpha-ERD=-10,7%) and for unaffected hemisphere (F=5.98, p<0.05) (alpha-ERD=-13,8%) in comparison to control group (alpha-ERD=-28,9%) .

14.2.5 Control vs. subcortical group

ERD amplitude in respect to movement and to visual cue The analysis revealed also that there were no differences in the strength of ERD between averaged control hemispheres (alpha-ERD=-29,2%) and unaffected (alpha-ERD=-23,8%) or affected (alpha-ERD=-26,6%) hemispheres of subcortical group. The amplitude of beta-ERD in the healthy and affected hemisphere did not differ significantly from the ERD in the control group in any of the listed simple and compound comparisons 15.3.

14.2.6 Cortical vs. subcortical group

ERD amplitude in respect to movement The comparison of ERD for unaffected hemispheres between the patient groups did not show any significant differences (Comparison: "*Unaffected hemisphere*" vs. "*Unaffected hemisphere*"). However, an alpha-ERD in the affected hemisphere was signif-

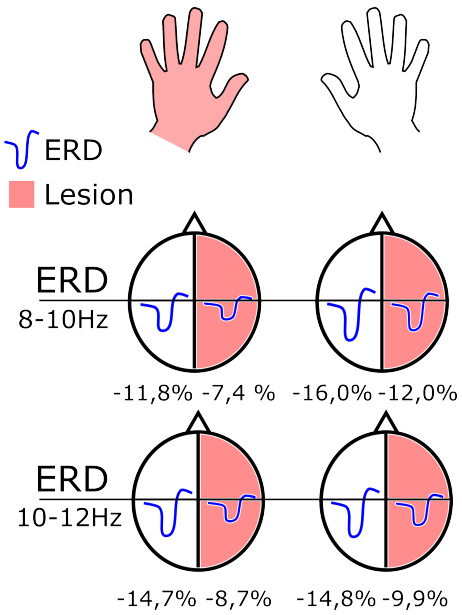


Figure 18: Maps showing the results for the cortical group in active task for alpha frequency. The numbers indicate the mean ERD amplitude for each condition. The red colour indicates lesioned hemisphere and paretic hand. On the left side of this figure, the ERD mean amplitude values are shown for paretic and on the right side for non-paretic hand movements.

icantly stronger in patients with subcortical lesions (alpha-ERD=-26,6%) than in patients with cortical strokes (alpha-ERD=-9,5%) (F=14.0, p<0.01) (See (D) in figure 19). (Comparison: "*Affected hemisphere*" vs. "*Affected hemisphere*"). In beta bands, the simple and compound testing did not reveal any significant differences between the groups.

ERD amplitude in respect to visual cue The analysis in respect to visual stimuli confirmed the results mentioned above. Also for this comparison no difference in ERD amplitude in alpha frequency could be detected between the unaffected hemispheres of both patient groups. Whereas, over the hemispheres with subcortical lesions (alpha-ERD=-24,0%) in comparison to the ones with cortical strokes (alpha-ERD=-12,2%) significantly stronger ERD was measured (F=9.72, p<0.01). Beta band showed no significant differences between the two patient groups in simple and compound testing.

14.3 ERD amplitude vs. degree of paresis

Individual ERD amplitude values as ERD to stimulus in "active task" were verified against the degree of hand paresis in patients. According to the standard British Medical Research Council Motor Grading Scale patients showed grades of paresis (Hmso, 1976) between 0 (hemiplegia) and 5 (normal force). Patients with hemiplegia were included in both groups. The amplitude of ERD was measured in the affected hemisphere for paretic hand movements. Patients with hemiplegia were asked

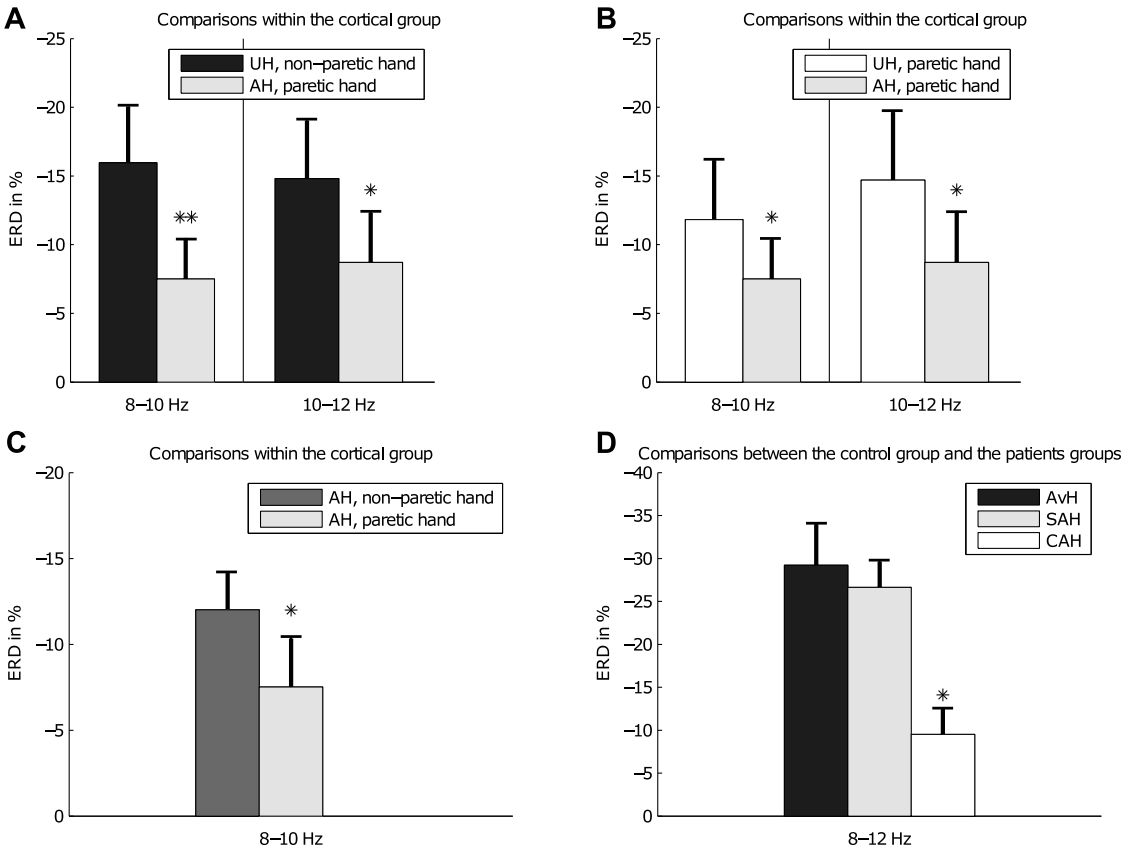


Figure 19: The bars depict the ERD means in percentage values. The whiskers indicate the standard error of the mean. UH - unaffected hemisphere, AH - affected hemisphere. Asterisk (*) denotes $p < 0,05$, (**) $p<0,01$.

Fig.18(A) Comparison of the mean alpha-ERD values between unaffected and cortically affected hemispheres for contralateral hand movements.

Fig.18(B) Comparison of the mean alpha-ERD values between unaffected and cortically affected hemisphere for paretic hand movements.

Fig.18(C) Comparison of the mean alpha-ERD values between ipsilateral and contralateral hand in cortically affected hemispheres.

Fig.18(D) Comparison of the mean alpha-ERD values between averaged control hemisphere (AvH) and subcortically (SAH) and cortically affected hemisphere (CAH) of patients for alpha frequency.

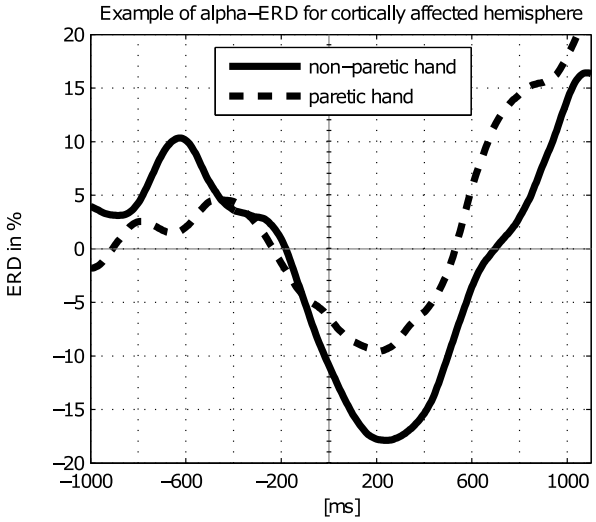


Figure 20: Alpha-ERD during non-paretic (continuous line) and paretic (dotted line) hand movements in the cortically affected hemisphere of one of the patients. „0 ms“ signifies the time of the movement. The alpha-ERD amplitude decrease for non-paretic hand movement exceeds the alpha-ERD amplitude for mouse button presses with use of paretic hand.

to attempt to make a hand movement with their index finger. The results of the analysis show that the affected hemispheres of the hemiplegic patients produced ERD amplitude values comparable with those of patients with mild hemiparesis. No significant correlation between the degree of hemiparesis and the ERD amplitude value was detected for either the subcortical or the cortical group in 8-10Hz and 10-12Hz frequency bands. (See figure 21).

14.4 ERD localization analysis

The analysis of ERD localization (anterior/posterior and lateral/medial) showed that there was no shift between the left and right hemispheres in the control group or between non-affected and affected hemisphere in the patient groups. In comparison between the control group and each of the patient groups, no significant differences were detected. Nor did the ERD localization differ between the two patient groups. In hemiplegic patients, who presented either with subcortical or with cortical lesions, no clear localization change of the signal was observed.

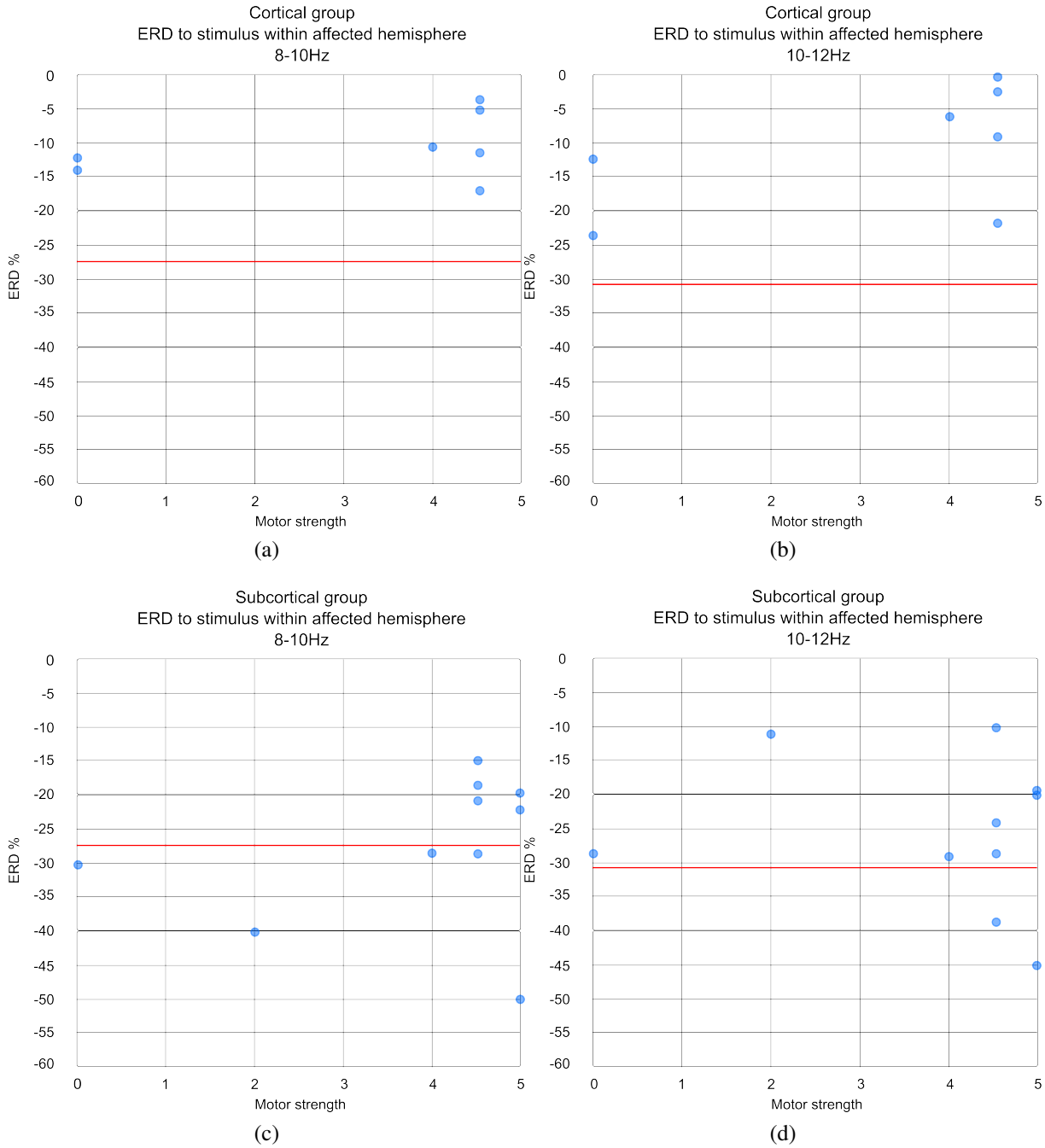


Figure 21: The plots show the relationship between the grade of paralysis (from 0-no force to 5-full force) and the ERD to stimulus amplitude for alpha frequency during "active" task. While the hemiparetic patients were pushing the mouse button, hemiplegic ones were asked to try to move their index finger. The figure shows the relationship between the amplitude values of ERD to stimulus in the cortical group for frequency of 8-10Hz and 10-12Hz (figures (a) and (b) respectively) and in the subcortical group for frequencies of 8-10Hz and 10-12Hz (figures (c) and (d) respectively).

Part V

Discussion

14.5 General considerations

From recent studies it is known that the lesion's location influences spatial and qualitative properties of the brain motor activation patterns (Chollet et al., 1991; Green et al., 1999; Luft et al., 2004; Rossini et al., 1998). The remapping of the hand motor representation might be an indication of changed neural network connections within the motor cortices. The interpretation of the results is problematic due to their heterogeneity which is probably related to the variability between the patients examined - the lesion location (Chen et al., 2000; Shelton and Reding, 2001; Luft et al., 2004), time interval since stroke (Feydy et al., 2002) or degree of recovery (Ward et al., 2003).

In order to gain knowledge about changes within the brain motor system, EEG patterns such as neuronal oscillations can be examined. A reliable parameter is the event-related desynchronization (ERD) during movement preparation and execution (Pfurtscheller and Aranibar, 1979; Pfurtscheller and Neuper, 1992; Leocani, 1997; Pfurtscheller, 1997, 1998). However, there are only few studies conducted on event-related desynchronization in hemiparetic patients after stroke. Moreover, most of the studies on reorganizational processes focus on the chronic stage of stroke. Chronic stroke patients with subcortical lesions displayed a reduced amplitude of alpha- and beta-ERD over the affected hemisphere and its enhancement over the intact hemisphere for paretic hand movements (Gerloff et al., 2006). A study with subacute and chronically ill stroke patients by Platz et al. (2002) showed no differences in the amplitude of movement-related beta-ERD between patients and normal subjects. In acute stroke patients, changes of alpha-ERD were found by Pfurtscheller et al. (1980). Two hemiparetic subjects presented with a reduction of alpha-ERD over the affected hemisphere compared to the unaffected hemisphere for paretic and non-paretic hand movements. The lesion's location was not given. In a subsequent study on ERD in acute stroke patients, Pfurtscheller et al. (1980) observed a reduction of alpha-ERD over the hemisphere with acute cortical stroke in two patients. The decrease over the damaged hemisphere was measured in one patient for non-paretic hand movements and in the other one for paretic hand movements. Also, an attenuation of ERD over the affected hemisphere was noticed in a patient with subcortical stroke during non-paretic hand movements. In a subsequent study, the influence of lesion location on alpha-ERD during acute stage of stroke was presented (Pfurtscheller et al., 1981). Patients with acute subcortical stroke showed both symmetric or asymmetric alpha-ERD for paretic hand movements. For the same conditions, subjects with cortical lesions displayed mostly asymmetries between damaged and intact hemisphere. In the case of patients with both cortical and subcortical lesions, symmetrical or extinguished ERD was reported.

The main finding of this study is that the lesion's location has an influence on the neuronal rhythmic activity in the sensorimotor brain regions. Secondly, it was demonstrated that the hemispheric cortical stroke affects brain oscillations in both affected and unaffected hemisphere. Interestingly, relative preservation of the alpha-ERD amplitude in a hemisphere with a cortical stroke for non-paretic hand movements could exhibit a potential for rehabilitation through training of the remaining cortical network with enforced use of the paretic hand. Further, it was shown that deep lesions as in the case of patients with subcortical stroke, do not influence the oscillatory dynamics. Finally, though the groups of patients studied showed only slight clinical deficits in arm strength, the results have shown changes in the event-related desynchronization in cortically affected subjects. Thus, it can be concluded that event-related desynchronization is a very sensitive parameter that provides an insight into minor changes of neuronal networks.

14.6 "Active" task

14.6.1 Control group

Contrary to the findings described byPfurtscheller and Aranibar (1977, 1979); Pfurtscheller et al. (1980); Pfurtscheller and Neuper (1992), the control group showed a lack of contralateral enhancement of ERD amplitudes for right-hand and left-hand movements. The ERD magnitude in both hemispheres was similar. This inconsistency could be probably related to differences between the task paradigms. In our study subjects were confronted with an externally paced task. The contralateral enhancement of ERD amplitudes found by Pfurtscheller et al. (1980) in his study were based on an internally paced task which is a voluntary movement. Our finding of non-lateralized ERDs after externally paced movements is consistent with the results of Alegre et al. (2003). They showed, in a predictable rhythmic stimulus-induced paradigm, that alpha-ERDs had a bilateral distribution and no lateralization was found. From this point of view, symmetrical alpha-ERD over left and right hemispheres for control group with no clear lateralization has to be concerned as normal.

Relatively low alpha-ERD amplitude in our control group in comparison to other studies (Pfurtscheller and Aranibar, 1979; Pfurtscheller and Arnibar, 1980; Pfurtscheller, 1981) might be as well due to different paradigm design. As observed by Gerloff et al. (1998) in internally paced performances the task-related power decrease is stronger than during externally paced movements.

14.6.2 Patients with cortical stroke

For paretic and non-paretic hand movements, alpha-ERD attenuation was recorded within the hemispheres with cortical lesions in comparison with the intact hemisphere as in previous studies (Pfurtscheller et al., 1980,?). Though the contralesional alpha-ERD was stronger than the ipsilesional one for performance with the paretic hand, this result cannot be interpreted as an ipsilateral overactivation within

the unaffected hemisphere. It is due to the fact that the alpha-ERD over the unaffected hemisphere in patients with cortical lesions was to a minor extent decreased and not increased in comparison with the control group as reported by Cramer et al. (1997); Green et al. (1999). This incongruency in results might be caused by the differences in time intervals between the day of stroke and the the day of the EEG measurement. It could be hypothesized that also during the acute stage of stroke the amplitude dynamics of brain oscillations might develop changes in time, as it was shown during recovery after stroke (Nelles et al., 1999; Calautti et al., 2001; Feydy et al., 2002). This study examines the changes of neural oscillations much earlier after the stroke event (mean time 8 days) than previous reports (Platz et al., 2000; Gerloff et al., 2006; Pfurtscheller et al., 1980, 1981) (mean time 18 days). This has to be taken into account especially when considering the findings of Jones and Schallert (1994) who observed that the neural arborization in the unaffected hemisphere has its peak around the 18th day after lesion. The continuous process of reorganization as well of the intact hemisphere could possibly explain the marginally reduced alpha-ERD over the unaffected hemisphere in patients after cortical stroke.

It was observed that cortical stroke influences neural reorganization in both affected and unaffected hemispheres. It was shown that the the amplitude of the oscillations is proportional to the number of synchronously active neuronal cells (Elul, 1971; Nunez and Srinivasan, 2006). The brain oscillations are generated by local and remote neural networks (Jones et al., 2000; Kang et al., 2000).Therefore, when such network is disrupted e.g. due to stroke, its reactivity could be as well changed. This might cause a decrease of ERD as seen in the present study.

14.6.3 Patients with subcortical stroke

Subcortical stroke did not influence alpha-ERD amplitude in the affected or the unaffected hemisphere compared to the alpha-ERD amplitude values in the control group. Furthermore, no interhemispherical differences were detected. This finding is in line with interhemispherical ERD symmetries found in patients with subcortical stroke lesions previously described by Pfurtscheller et al. (1981).

An important difference between both groups of patients was observed. Hemispheres after subcortical stroke showed stronger alpha-ERD amplitude than the ones after the cortical lesions. These two types of lesions seem to have a different influence on neural oscillations reactivity, though both of them lead to a cortical dysfunction (Corbett et al., 1994; Kang et al., 2000).

Likewise, as for patients with cortical strokes, the group with subcortical lesions showed no considerable changes in beta-ERD for the paretic and intact hand performance was found.

14.6.4 ERD localization

Though many authors have described topographical changes of the motor activation patterns due to reorganizational processes after stroke (Green et al., 1999; Luft et al., 2004; Wiese et al., 2005), in this study no relevant shifts of ERD source could be found in any of the groups. This result can be interpreted at least in three ways. Importantly, EEG, as the method of research applied in this study, unlike the fMRI and other techniques chosen in the aforementioned works does not allow for a high topographical resolution. The other factor that might have influenced these results was the mild degree of hand paresis. A slight affection of the motor system presumably does not cause a shift of the motor activation source. The time factor should be considered as well, since the cited studies present results of patients in a chronic stage of stroke. The findings in hemiplegic patients are inconsistent and therefore no particular pathological pattern of motor activation can be distinguished.

14.6.5 Correlation between the ERD amplitude and the degree of hemiparesis

This study did not show any significant relationship between the ERD amplitude and the degree of paresis. By this qualitative analysis it was demonstrated though that ERD seems to be a very sensitive measure in respect to grade of clinical affection for assessment of changes within the neuronal network. This finding is true for cortically lesioned subjects. Since the subcortical lesions do not influence to the same degree the oscillatory dynamics, ERD phenomenon seems to be more dependent on cortical neuronal networks. This result is in line with the works of Pfurtscheller and Neuper (1992), describing ERD as a reliable measure in estimation of cortical functioning.

14.7 "Rest" task

When subjects were passively observing the visual stimuli presented within the "rest" task, no interhemispherical ERD differences over the sensorimotor cortex were measured in any of the three groups. This result is in line with findings showing that the central mu and beta rhythms and their desynchronization are closely related to the processing of movements and not the visual cues (Gastaut, 1952; Chatrian et al., 1959, 1974; Pfurtscheller and Lopes, 1999).

14.8 Methodological issues and limitations

The differences between our findings and the reported previously by other groups may be due to various reasons. Firstly, the limited number of subjects within each group and interindividual variations may lead to insignificant results. Patients were divided only into two groups, since the number of subjects in each group did not allow for further subclassification.

Secondly, due to the occurrence of neural network adaptation after stroke, the time interval between the measurement and the event is of importance. Therefore, varying time intervals of measurement may lead to divergent results.

One should also consider the movement paradigm chosen for this study. In other studies investigating ERD changes after stroke, the motor task is based on a voluntary movement. In this study, subjects accomplished movements externally paced in order to enable inclusion of hemiplegic patients. This difference in our and previously conducted studies may explain the inconsistent results in our control group concerning the lack of lateralization of event-related desynchronizations.

14.9 Outlook

In future studies with acute stroke patients, sample sizes should be increased. Thus, patients with deep subcortical lesions at the brainstem level, patients with cortical and subcortical lesions as in our study as well as additional patients with transient ischemic attacks (TIAs) could be examined in such a study in order to look for further differences in brain reorganization patterns as related to the level of the lesion. Likewise, further stratification not only according to the level of lesion but also according to the lesion side, the lesion volume and the grade of hemiparesis is of interest.

In view of EEG-based brain-computer interface further investigations on acute stroke patients are needed. The subcortical stroke patients displayed no significant difference in ERD patterns in comparison with controls. It could be therefore assumed that for the BCI algorithm, ERDs both in healthy as in subcortically affected hemisphere can be distinguished as in healthy subjects. To verify this hypothesis, an online BCI-experiment with acute stroke patients would be necessary.

Part VI

Summary

In this study we investigated event-related desynchronizations in 17 hemiparetic patients after acute stroke (2-13 days) subcortical (n=10) and cortical (n=7) lesions and age-matched healthy subjects (n=10) during performance of a simple motor task. Subjects pressed a mouse button either with their left or right index finger as required by a visual stimulus. Secondly, in a "rest" condition, data were recorded in a similar setting where subjects were only observing visual cues. In the second "active" task, subjects pressed a mouse button either with their left or right index finger as required by a visual stimulus. A 65-channel EEG, including EOG and EMG, was recorded. Event-related desynchronization (ERD) was measured for both tasks in four frequency bands: 8-10Hz, 10-12Hz, 15-20Hz and 20-25Hz. For interhemispherical comparisons, an electrode with the strongest ERD over

the motor cortex was chosen. The data were statistically analyzed with analysis of variance (ANOVA) and, if needed, with post-hoc Tukey's test.

The analysis of the "rest" task did not reveal any differences of ERDs between the two hemispheres of the two groups, nor did in-between group comparisons. In the "active" task for paretic hand movements the cortical stroke patients showed with a stronger ipsilateral (contralesional) than contralateral (ipsilesional) alpha-ERD. The hemisphere with cortical lesions exhibited stronger 8-10Hz - ERD for ipsilateral (healthy) than for contralateral (paretic) hand movements. Within the cortical group, for contralateral hand movements, the alpha-ERD found in the affected hemisphere was smaller than in the unaffected hemisphere. In comparison with the control group, in patients with cortical stroke the amplitude of the alpha-ERD was decreased for both the affected and the unaffected hemispheres. No interhemispherical difference of the alpha-ERD amplitude was found in patients with subcortical stroke. Likewise, the alpha-ERD measured in the unaffected and affected hemisphere did not differ from the control group, but was significantly stronger in the affected hemisphere than in patients with cortical stroke. No significant differences were detected for either of the beta frequency bands.

The aim of this study was to gain insight into the kinds of changes in the dynamics of the neuronal oscillations in the acute phase of stroke. The other goal was to prove if the lesion location has a significant influence on the brain oscillations. Moreover, this work was intended to investigate possible correlations between the grade of the paresis and the severity of ERD changes.

This research resulted in finding the relationship between the lesion location and changes of the neuronal rhythmic activity in the sensorimotor brain regions. It was shown that the deep lesions, as in case of patients with subcortical stroke, do not influence the oscillatory dynamics. Further, it was demonstrated that the cortical stroke affects brain oscillations both in the affected and the unaffected hemispheres. A significant decrease of alpha-ERD amplitude within the affected hemisphere was found in comparison with controls and with patients after subcortical stroke. When comparing the unaffected hemisphere of the cortical group with that of the control group, marginally decreased values for the alpha-ERD were observed.

Interestingly, relative preservation of the alpha-ERD amplitude in a hemisphere with a cortical stroke for non-paretic hand movements could exhibit a potential for rehabilitation through training of the remaining cortical network with enforced use of the paretic hand.

Finally, though the groups of patients studied showed only slight clinical deficits in arm strength, the results showed changes in the amplitude of the event-related desynchronization in cortically affected subjects. However, no correlation between the grade of paresis and the severity of ERD changes was detected. Nevertheless, it can be concluded that event-related desynchronization is a very sensitive parameter giving an insight into minor changes of neuronal networks.

For further studies of brain plasticity, more patients after stroke should be investigated in order to allow for a more detailed stratification according to precise lesion location, lesion size and grade of

hemiparesis.

From the perspective of future EEG-based brain-computer interfaces for stroke patients, these findings are relevant. Firstly, since the ERD patterns in subcortical patients did not significantly differ from the ERD patterns of the control group, it could be assumed that BCI algorithms could probably discriminate the power attenuation both in the healthy and in the affected hemispheres of these stroke survivors. If so, BCI could be potentially applied already in the early rehabilitative phase after subcortical stroke. Secondly, in view of the results concerning patients after cortical stroke, the recognition of the ERD patterns by the BCI algorithms might be a greater challenge, seeing that the power attenuation in this group differed significantly from the one observed in controls. Considering the findings of this study, an online BCI-experiment with acute stroke patients would be an interesting perspective for further investigations to verify both assumptions.

Part VII

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Part VIII

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Part IX

Appendix

15 Scales applied for estimating the paralysis grade

The shown scales were used in assessment of motor strength for all subjects included in this study.

15.1 Standard British Medical Research Council Grading Scale

This is presented in Table 4.

Grading Motor Strength	
Grade	Description
0/5	No muscle movement
1/5	Visible muscle movement, but no movement at the joint
2/5	Movement at the joint, but not against gravity
3/5	Movement against gravity, but not against resistance
4/5	Movement against resistance, but less than normal
5/5	Normal strength

Table 4: Grading Motor Strength according to the British Medical Research Council

15.2 Copenhagen Stroke Scale

This is presented in Table 5.

1. Level of consciousness
a. Completely lucid
b. Somnolent, can be verbally aroused and then cooperated satisfactorily
c. Difficult to awake, cooperated somewhat poorly
d. Worse

2. Speech difficulty
a. Normal speech
b. Slightly abnormal speech
c. Speaks poorly and/or comprehends poorly
d. Mutism or unintelligible speech or severe comprehension difficulty

3. Neglect
a. None
b. Mild, i.e. the patient does not spontaneously mentions his deficits, is sloppy and unworried
c. Severe, often with denial

4. Conjugate gaze deviation
a. None
b. Mild
c. Marked, perhaps with forced head turning

5. Facial palsy
a. None
b. Mild
c. Median
d. Complete

6. Hemianopsia
a. None
b. Likely
c. Definite and total

7. Straight arm raising
a. Normal power
b. Against resistance
c. Against gravity but not against resistance
d. Not possible

8. Function of the hand
a. Normal
b. Decreased fine finger movement (buttoning, taking a cup)
e. Paralysis

9. Straight leg raising
a. Normal
b. Against resistance
c. Against gravity but not resistance
d. Not possible

10. Gait
a. Normal
b. Possible without devices (cane, delta-walker, or similar)
c. Possible with devices
d. With support of one person
e. With support of two persons
f. Worse

Table 5: Copenhagen Stroke Scale. The CSS score is between 10 and 40 point, however 10 points related to a normal function in each of the given categories. Scoring: a = 1, b = 2, c = 3, d = 4, e = 5, f = 6

16 ANOVA statistical analysis

This chapter presents the exact statistical comparisons conveyed with ANOVA in this study.

1. Control group
    (a) Compound comparison:
        i. "*Left hemisphere"* vs. *"Right hemisphere*"
        ii. "*Left hemisphere*Contralateral*" vs. "*Right hemisphere*Ipsilateral*"
        iii. "*Left hemisphere*Ipsilateral*" vs. "*Right hemisphere*Contralateral*"
        iv. "*Left hemisphere*Contralateral*" vs. "*Right hemisphere*Contralateral*"
        v. "*Left hemisphere*Ipsilateral*" vs. "*Right hemisphere*Ipsilateral*"
    (b) Simple comparisons: for each of four frequency bands separately, ex. for 8-10Hz:
        i. "*Left hemisphere*Contralateral*8-10Hz*" vs. "*Right hemisphere*Ipsilateral*8-10Hz*"
        ii. "*Left hemisphere*Ipsilateral*8-10Hz*" vs. "*Right hemisphere*Contralateral*8-10Hz*"
        iii. "*Left hemisphere*Contralateral*8-10Hz*" vs. "*Right hemisphere*Contralateral*8-10Hz*"
        iv. "*Left hemisphere*Ipsilateral*8-10Hz*" vs. "*Right hemisphere*Ipsilateral*8-10Hz*"
        v. "*Left hemisphere*Contralateral*8-10Hz*" vs. "*Left hemisphere*Ipsilateral*8-10Hz*"
        vi. "*Right hemisphere*Contralateral*8-10Hz*" vs. "*Right hemisphere*Ipsilateral*8-10Hz*"
2. Patient groups
    (a) Compound comparisons:
        i. "*Unaffected hemisphere*" vs. "*Affected hemisphere*"
        ii. "*Unaffected hemisphere*Contralateral*" vs. "*Affected hemisphere*Ipsilateral*"

iii. "*Unaffected hemisphere*Ipsilateral*" vs.
"*Affected hemisphere*Contralateral*"

iv. "*Unaffected hemisphere*Contralateral*" vs.
"*Affected hemisphere*Contralateral*"

v. "*Unaffected hemisphere*Ipsilateral*" vs.
"*Affected hemisphere*Ipsilateral*"

(b) Simple comparisons: for each of four frequency bands separately, ex. for 8-10Hz:

i. "*Unaffected hemisphere*Contralateral*8-10Hz*" vs.
"*Affected hemisphere*Ipsilateral*8-10Hz*"

ii. "*Unaffected hemisphere*Ipsilateral*8-10Hz*" vs.
"*Affected hemisphere*Contralateral*8-10Hz*"

iii. "*Unaffected hemisphere*Contralateral*8-10Hz*" vs.
"*Affected hemisphere*Contralateral*8-10Hz*"

iv. "*Unaffected hemisphere*Ipsilateral*8-10Hz*" vs.
"*Affected hemisphere*Ipsilateral*8-10Hz*"

v. "*Unaffected hemisphere*Contralateral*8-10Hz*" vs.
"*Unaffected hemisphere*Ipsilateral*8-10Hz*"

vi. "*Affected hemisphere*Contralateral*8-10Hz*" vs.
"*Affected hemisphere*Ipsilateral*8-10Hz*"

3. Control group vs. each of the patient groups separately

(a) Compound comparisons:

i. "*Averaged hemisphere*" vs. "*Unaffected hemisphere*"

ii. "*Averaged hemisphere*" vs. "*Affected hemisphere*"

iii. "*Averaged hemisphere*Contralateral*" vs.
"*Unaffected hemisphere*Contralateral*"

iv. "*Averaged hemisphere*Ipsilateral*" vs.
"*Unaffected hemisphere*Ipsilateral*"

v. "*Averaged hemisphere*Contralateral*" vs.
"*Affected hemisphere*Contralateral*"

vi. "*Averaged hemisphere*Ipsilateral*" vs.
"*Affected hemisphere*Ipsilateral*"

(b) Simple comparisons: for each of four frequency bands separately, ex. for 8-10Hz:

i. "*Averaged hemisphere*Contralateral*8-10Hz*" vs.
"*Unaffected hemisphere*Contralateral*8-10Hz*"

ii. "*Averaged hemisphere*Ipsilateral*8-10Hz*" vs.
"*Unaffected hemisphere*Ipsilateral*8-10Hz*"

iii. "*Averaged hemisphere*Contralateral8-10Hz*" vs.
"*Affected hemisphere*Contralateral8-10Hz*"

iv. "*Averaged hemisphere*Ipsilateral8-10Hz*" vs.
"*Affected hemisphere*Ipsilateral8-10Hz*"

4. Cortical groups vs. subcortical group

   (a) Compound comparisons:

      i. "*Unaffected hemisphere*" vs. "*Unaffected hemisphere*"

      ii. "*Affected hemisphere*" vs. "*Affected hemisphere*"

      iii. *Cortical group "Unaffected hemisphere*Contralateral*" vs.
      *Subcortical group "Unaffected hemisphere*Contralateral*"

      iv. *Cortical group "Unaffected hemisphere*Ipsilateral*" vs.
      *Subcortical group "Unaffected hemisphere*Ipsilateral*"

      v. *Cortical group "Affected hemisphere*Contralateral*" vs.
      *Subcortical group "Affected hemisphere*Contralateral*"

      vi. *Cortical group "Affected hemisphere*Ipsilateral*" vs.
      *Subcortical group "Affected hemisphere*Ipsilateral*"

   (b) Simple comparisons: for each of four frequency bands separately, ex. for 8-10Hz:

      i. *Cortical group "Unaffected hemisphere*Contralateral*8-10Hz*" vs.
      *Subcortical group "Unaffected hemisphere*Contralateral*8-10Hz*"

      ii. *Cortical group "Unaffected hemisphere*Ipsilateral*8-10Hz*" vs.
      *Subcortical group "Unaffected hemisphere*Ipsilateral*8-10Hz*"

      iii. *Cortical group "Affected hemisphere*Contralateral*8-10Hz*" vs.
      *Subcortical group "Affected hemisphere*Contralateral*8-10Hz*"

      iv. *Cortical group "Affected hemisphere*Ipsilateral*8-10Hz*" vs.
      *Subcortical group "Affected hemisphere*Ipsilateral*8-10Hz*"

Curriculum vitae

Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht.

Publikationsliste

1. M. Stępień, J. Conradi, G. Waterstraat, F. U. Hohlefeld, G. Curio, V. V. Nikulin, Event-related desynchronization of sensorimotor EEG rhythms in hemiparetic patients with acute stroke, Neuroscience Letters 2010 (*in press*)

Erklärung

Ich, Magdalena Stępień, erkläre, dass ich die vorgelegte Dissertationsschrift mit dem Thema: „ Event-related desynchronization (ERD) of sensorimotor EEG rhythms in hemiparetic patients with acute hemispheric stroke“ selbst verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel benutzt, ohne die (unzulässige) Hilfe Dritter verfasst und auch in Teilen keine Kopien anderer Arbeiten dargestellt habe.

Berlin, den 15.08.2010

Magdalena Stępień