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To Barbara, Chiara, Cinzia, Claudia,
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With affection

Consciousness of our powers augments them.

Vauvenargues

The highest possible stage in moral culture is when we recognize that we ought to control our thoughts.

Charles Darwin

A human being is part of the whole, called by us "universe," a part limited in time and space. He experiences himself, has thoughts and feelings, as something separate from the rest- a kind of optical delusion of consciousness. This delusion is a kind of prison for us, restricting us to our personal desires and to affection for a few persons nearest to us. Our task must be to free ourselves from this prison by widening our circles of compassion to embrace all living creatures and the whole of nature in its beauty.

Einstein

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ABSTRACT

The first part of my thesis presents an overview of the different approaches used in the past two decades in the attempt to forecast epileptic seizure on the basis of intracranial and scalp EEG. Past research could reveal some value of linear and nonlinear algorithms to detect EEG features changing over different phases of the epileptic cycle. However, their exact value for seizure prediction, in terms of sensitivity and specificity, is still discussed and has to be evaluated. In particular, the monitored EEG features may fluctuate with the vigilance state and lead to false alarms. Recently, such a dependency on vigilance states has been reported for some seizure prediction methods, suggesting a reduced reliability. An additional factor limiting application and validation of most seizure-prediction techniques is their computational load. For the first time, the reliability of permutation entropy [PE] was verified in seizure prediction on scalp EEG data, contemporarily controlling for its dependency on different vigilance states. PE was recently introduced as an extremely fast and robust complexity measure for chaotic time series and thus suitable for *online* application even in portable systems. The capability of PE to distinguish between preictal and interictal state has been demonstrated using Receiver Operating Characteristics (ROC) analysis. Correlation analysis was used to assess dependency of PE on vigilance states. Scalp EEG-Data from two right temporal epileptic lobe (RTLE) patients and from one patient with right frontal lobe epilepsy were analysed. The last patient was included only in the correlation analysis, since no datasets including seizures have been available for him. The ROC analysis showed a good separability of interictal and preictal phases for both RTLE patients, suggesting that PE could be sensitive to EEG modifications, not visible on visual inspection, that might occur well in advance respect to the EEG and clinical onset of seizures. However, the simultaneous assessment of the changes in vigilance showed that: *a*) all seizures occurred in association with the transition of vigilance states; *b*) PE was sensitive in detecting different vigilance states, independently of seizure occurrences. Due to the limitations of the datasets, these results cannot rule out the capability of PE to detect preictal states. However, the good separability between pre- and interictal phases might depend exclusively on the coincidence of epileptic seizure onset with a transition from a state of low vigilance to a state of increased vigilance. The finding of a dependency of PE on vigilance state is an original finding, not reported in literature, and suggesting the possibility to classify vigilance states by means of PE in an authomatic and objectic way.

The second part of my thesis provides the description of a novel behavioral task based on motor imagery skills, firstly introduced (Bruzzo *et al.* 2007), in order to study mental simulation of biological and non-biological movement in paranoid schizophrenics (PS). Immediately after the presentation of a real movement, participants had to imagine or re-enact the very same movement. By key release and key press respectively, participants had to indicate when they started and ended the mental simulation or the re-enactment, making it feasible to measure the duration of the simulated or re-enacted movements. The proportional error between duration of the re-enacted/simulated movement and the template movement were compared between different conditions, as well as between PS and healthy subjects. Results revealed a double dissociation between the mechanisms of mental simulation involved in biological and non-biologial movement simulation. While for PS were found large errors for simulation of biological movements, while being more acurate than healthy subjects during simulation of non-biological movements. Healthy subjects showed the opposite relationship, making errors during simulation of non-biological movements, but being most accurate during simulation of non-biological movements. However, the good timing precision during re-enactment of the movements in all conditions and in both groups of participants suggests that perception, memory and attention, as well as motor control processes were not affected. Based upon a long history of literature reporting the existence of psychotic episodes in epileptic patients, a longitudinal study, using a slightly modified behavioral paradigm, was carried out with two RTLE patients, one patient with idiopathic generalized epilepsy and one patient with extratemporal lobe epilepsy. Results provide strong evidence for a possibility to predict upcoming seizures in RTLE patients behaviorally. In the last part of the thesis it has been validated a behavioural strategy based on neurobiofeedback training, to voluntarily control seizures and to reduce there frequency. Three epileptic patients were included in this study. The biofeedback was based on monitoring of slow cortical potentials (SCPs) extracted online from scalp EEG. Patients were trained to produce positive shifts of SCPs. After a training phase patients were monitored for 6 months in order to validate the ability of the learned strategy to reduce seizure frequency. Two of the three refractory epileptic patients recruited for this study showed improvements in self-management and reduction of ictal episodes, even six months after the last training session.

KEYWORDS

Epilepsy; Temporal Lobe Epilepsy; Online Seizure Prediction; Permutation Entropy; Receiver Operating Characteristics (ROC) analysis; Control; Paranoid Schizophrenia; Mental Simulation task; Biological and non-biological motion; Slow cortical potentials (SCPs); Neurofeedback (NF).

LIST OF ABBREVIATIONS IN ALPHABETIC ORDER

AC: Alternate Current
AUC: Area Under Curve
AED: Antiepileptic Drug
BOi: Biological Other Imagery
BOr: Bilogical Other Re-Enactment
BSi: Biological Self Imagery
BSr: Biological Self Re-Enactment
BDI: Beck Depression Inventory
BOLD: Blood Oxygen-Level Dependent
BORB: Birmingham Object Recognition Battery
BPRS: Brief Psychiatric Rating Scale
CT: Computed Tomography
Cz: Vertex
CVN:Contingent Negative Variation
EEG: Electroencephalogram
Ep: Epileptic Patients
GAF: Global Assessment Of Function
Hls: Healthy Subjects
H1: First hypothesis
H2: Opposite hypothesis
IQ: Intelligent Quotient
Interict: Interictal Phase
LGS: Lennox-Gastaut Syndrome
Ls: Lyapunov Exponents
L_{max}: Largest Lyapunov Exponent
LFPs: Local Field Potentials
LKS: Landau-Kleffner Syndrome
MPE: Mean Proportional Error
MMPI: Minnesota Multiphasic Personality Inventory
MRI: Magnetic Resonance Imaging
MST: Multiple Subpial Transections
MUA: Multi-Unit Activity
NBi: Non-Biological Imagery
NBr: Non-Biological Re-Enactment
NF: Neurofeedback
NREM: Non-Rapid Eye Movement
PE: Permutation Entropy
PDS: Paroxysmal Depolarization Shift
POMS: Profile Of Mood States
Post 1: Postictal Phase 1
Post 2: Postictal Phase 2
Preict: Preictal Phase
PS: Paranoid Schizophrenia
REM: Rapid Eye Movement
ROC: Receiver Operating Characteristics
RTLE: Right Temporal Lobe Epilepsy
SANS: Scale For Assessment Of Negative Symptoms
SAPS: Scale For Assessment Of Positive Symptoms
Schiz: Schizophrenics
SCPs: Slow Cortical Potentials
SD: Standard Deviation
SMR: Sensorimotor Rhythm
SOP: Seizure Occurrence Period
SPH: Seizure Prediction Horizon
TLE: Temporal Lobe Epilepsy
VNS: Vagus Nerve Stimulation
WAIS: Wechsler Adult Intelligence Scale

INTRODUCTION

1. Historical background.

Epilepsy is characterized by sudden recurrent and transient disturbances of perception or behaviour resulting from excessive synchronization of cortical neuronal networks; it is a neurological condition in which an individual experiences chronic abnormal bursts of electrical discharge in the brain. It is a disease known from ancient times, and it was believed to be "given by the Gods". In fact, the term "epilepsy" was first mentioned more than 3,000 years ago, in ancient Babylon as "*miqtu*". It was thought to be an attack by demons or gods. Stone tablets found in Babylon, contain detailed observations of epilepsy, the types of seizure, provoking factors, symptoms after seizures and so on. Out of a collection of fourty stone tablets which describe all the then known illnesses, four or five deal exclusively with epilepsy. The ancient Greeks saw epilepsy as a supernatural phenomenon, the "*holy sickness*". To their way of thinking, only a god could throw a person to the ground, deprive him of his senses, cause convulsions, and afterwards bring him back to life, apparently quite unaffected. The great Greek physician Hippocrates was the first one to realize that it was a disease of the brain and tried to treat it as such. Religious beliefs avoided systematic, scientific investigations in epilepsy until the 1800s (Temkin, 1994). Epilepsy is now considered a window to the brain's anatomy and function and is, therefore, an increasingly active, interdisciplinary field of research.

The "sacred" or "divine" disease is among the most common disorders of the nervous system, second only to stroke, and affects approximately 1% of the world's population (Annegers, 1996; Forsgren *et al.*, 2005). Estimates of incidence rates (number of new cases per year) range from 24 to 53 per 100 000. The high incidence of epilepsy stems from the fact that it occurs as a result of a large number of causes, including genetic abnormalities, developmental anomalies, febrile convulsions, as well as brain insults such as craniofacial trauma, central nervous system infections, hypoxia, ischemia, and tumors.

1.1 Epileptic seizures.

The hallmark of epilepsy is *recurrent* seizures[1]. The seizures are due to sudden development of synchronous neuronal firing in the cerebral cortex and are recorded by electrodes on or inside the brain. Electroencephalography, the recording of the electrical field of the "encephalos" (the Greek word for the brain; it means "what is inside the head"), was first demonstrated in 1875 by the British neurophysiologist Richard Caton (Caton, 1875), who recorded the electrical activity from brain tissues of rabbits and monkeys. Other scientists followed his lead. However, it was not until the late 1920s, that the practical and diagnostic value of electroencephalography was demonstrated in humans using scalp electrodes. This is due to the work of the German psychiatrist Hans Berger, who also coined the term EEG (Berger, 1929). Electroencephalographic (EEG) recordings from the epileptic brain show that these discharges may begin locally in portions of the cerebral hemispheres (partial/focal seizures, with a single or multiple foci) or begin simultaneously in both cerebral hemispheres (generalized seizures).

Epileptic seizures are caused by parts of the brain eliciting abnormal electrical activity. The region of seizure generating tissue, or the epileptogenic focus, can be due to structural abnormalities that disrupt normal neural circuitry. As already said above, these abnormalities may be genetic, caused by head injury, infection, stroke or tumor. In such cases when the cause is known, it is termed *symptomatic epilepsy*. Other classifications include *idiopathic epilepsy*, when there is no identifiable cause but a genetic basis is presumed, and *cryptogenic epilepsy*, when neither classification fits and the cause in unknown.

Just as there can be multiple causes, individuals can be affected by one or more types of seizures. *Partial seizures* begin in a localized area, while *generalized seizures* develop over a widespread area on the cortex of the brain. Partial seizures can be further subdivided into simple and complex, where only *complex seizures* can cause loss of consciousness. *Generalized* seizures are grouped into six major categories. *Absence* seizures (also known as *petit mal*) are characterized by a partial loss of consciousness when the individual briefly appears vacant and unresponsive. Involuntary muscle twitches, particularly in the face, are often seen. *Myoclonic* seizures consist of very brief and sporadic arrhythmic movements. *Tonic* seizures consist of sudden stiffening movements involving the head, body, or extremities that often occur during sleep. *Clonic* seizures

[1] It is also important to dispel a common myth that epilepsy and seizures are the same thing. Although seizures are the primary symptom of epilepsy, they can have other causes, such as high fever, malignant hypertension, or drug abuse. In these cases, the seizures stop when the condition improves, whereas seizures in epilepsy are a chronic long-term condition.

are characterized by repeated, rhythmic motor movements, often involving a large portion of the body as well as causing unconsciousness. *Tonic-clonic* seizures (also called *grand mal*) begin with the tonic phase of sudden stiffening movements when the individual may experience symptoms such as loss of orofacial motor control resulting in tongue biting or clenched teeth and/or urinary incontinence. This is followed by the clonic phase of rhythmic body movements. After the seizure, the individual may be emotionally distraught, feeling confused or sleepy. *Atonic* seizures consist of a sudden loss of muscle tone. A brief atonic seizure may elicit mild symptoms such as drooping of the head, but often the seizure is prolonged and the individual falls down from loss of postural tone. *Status epilepticus* is the term given to describe the life-threatening condition when an individual experiences prolonged or successive seizures with no recovery time. Depending on the medical professional, seizure activity can be considered status epilepticus if it lasts a minimum of five minutes up to a more conservative 30 minutes.

Seizures come and go, in a seemingly unpredictable way. In some patients, seizures can occur hundreds of times per day; in rare instances, they occur only once every few years.

If seizures cannot be controlled, the patient experiences major limitations in family, social, educational, and vocational activities. These limitations have profound effects on the patient's quality of life, as well as on his or her family (Elger, 2001). In addition, frequent and long, uncontrollable seizures may produce irreversible damage to the brain (Tatum *et al*, 2001). However, it still is not clear if seizures are the *cause* or the *result* of such a damage, that worsens over time if left untreated (Berg & Shinnar, 1997). For example, it is a widely held view that seizures from mesial temporal structures arise because of damage to hippocampal circuitry. The characteristic circuit abnormalities include drop out of neurons, simplification of the dendritic tree (reduced synaptic input), sprouting of dentate granule cell axons (increasing the number of excitatory-excitatory feedback connections), and increase in glial cell elements (sclerosis). There is a concomitant loss in neurotransmitter receptors in the hippocampus (Dudek & Spitz, 1997).

Hence, dozens of epileptic syndromes exist, classified based on the symptoms and brain regions affected. One of the more common forms of epilepsy is temporal lobe epilepsy (TLE). The most striking symptoms are often not the typical motor behavior seen in partial seizures. Individuals may perceive sounds or smells that are not present, or visual disturbances, such as objects appearing larger or smaller than they are. Psychological symptoms can often be the most striking, when derealization or strong spiritual sensations may be experienced. One of the most common epileptic syndromes in childhood is benign childhood epilepsy with centrotemporal spikes. It is considered benign as seizures are infrequent, often responsive to treatment, and typically subside in adolescence. Despite the optimistic prognosis, neuropsychiatric testing shows that cognitive

difficulties can exist in areas such as language and memory (Croona *et al.*,1999; Monjauze *et al.*, 2005). Another common syndrome is childhood absence epilepsy. As the name implies, it consists of absence seizures usually starting around or slightly after the pre-school years, and has a similar prognosis to benign childhood epilepsy. Less frequent and more severe is Lennox-Gastaut Syndrome (LGS), which can consist of multiple types of seizures, developmental delay, and a high prevalence of status epilepticus. Prognosis is often poor, especially those with earlier onset (Chevrie & Aicardi, 1972; Roger *et al.*, 1987), although some can have near complete remission of symptoms. Another more rare form of epilepsy, with only around 200 reported cases since 1957, is Landau-Kleffner Syndrome (LKS). Initial symptoms consist of the abrupt onset of seizures and regression of language skills. Partial seizures may be further subdivided into both simple and complex seizures. This refers to the effect of such a seizure on consciousness; simple seizures cause no interruption to consciousness (although they may cause sensory distortions or other sensations), whereas complex seizures interrupt consciousness to varying degrees. This does not necessarily mean that the person experiencing this sort of seizure will fall unconscious (like fainting). For example, a complex partial seizure may involve the unconscious repetition of simple actions, gestures or verbal utterances, or simply a blank stare and apparent unawareness of the occurrence of the seizure, followed by no memory of the seizure. Other patients may report a feeling of tunnel vision or dissociation, which represents a diminishment of awareness without full loss of consciousness. Still other patients can perform complicated actions, such as travel or shopping, while in the midst of a complex partial seizure. The effects of partial seizures can be quite dependent on the area of the brain in which they are active. For example, a partial seizure in areas involved in perception may cause a particular sensory experience (for example, the perception of a scent, music or flashes of light) whereas, when centred in the motor cortex, a partial seizure might cause movement in particular groups of muscles. This type of seizure may also produce particular thoughts or internal visual images or even experiences which may be distinct but not easily described. Seizures centred on the temporal lobes are known to produce mystical or ecstatic experiences in some people. These may result in a misdiagnosis of psychosis or even schizophrenia, if other symptoms of seizure are disregarded and other tests are not performed. Unfortunately for those with epilepsy, anti-psychotic medications prescribed without anticonvulsants in this case can actually lower the seizure threshold further and worsen the symptoms. When the effects of a partial seizure appear as a 'warning sign' before a larger seizure, they are known as an *aura*: it is frequently the case that a partial seizure will spread to other parts of the brain and eventually become generalized, resulting in a tonic-clonic convulsion. The subjective experience of an aura, like other partial seizures, will tend to reflect the function of the affected part of the brain.

2. Epilepsy and electroencephalography.

Epileptic neurons exhibit a distinct shift of the resting membrane potential (the so-called *paroxysmal depolarization shift*, PDS (Goldensohn & Purpura, 1963; Matsumoto & Ajmone-Marsan, 1964a, 1964b) that is accompanied by an increase of intracellular calcium and a massive burst of action potentials (500-800 per sec). PDSs originating from a larger cortical region are associated with steep field potentials (known as *spikes*) recorded in the scalp EEG. Focal seizures are assumed to be initiated by abnormally discharging neurons (so-called *bursters*) that recruit and entrain neighboring neurons into a critical mass (Traub & Wong, 1982; Sanabria, *et al*., 2001). This process manifests itself as an increasing synchronization of neuronal activity accompanied by a loss of inhibition. The build-up of such a critical mass might be mediated by facilitating processes in the sense of nonspecific predisposing factors that permit seizure emergence by lowering the threshold (Engel, 1989). In this context the term "*critical mass*" should not be interpreted in the sense of a highly localized mass phenomenon that would be easily accessible for conventional EEG analyses that, however, fail to detect it. Instead, the interactions between neurons that play a crucial role in seizure generation, probably take place on different spatial and temporal scales and are known to be *nonlinear* in nature (Bruzzo *et al*., 2006a, Bruzzo, 2007; Bruzzo *et al.*, 2007; Bruzzo & Vimal, 2007). In recent years, technical advantages such as digital video-EEG monitoring systems as well as an increased computational power led to a highly sophisticated clinical epilepsy monitoring allowing one to process huge amounts of data in real time. In addition, chronically implanted intracranial electrodes allow continuous recording of brain electrical activity from the surface of the brain and/or from within specific brain structures at a high signal-to-noise ratio with a high spatial resolution. Due to its high temporal resolution and its close relationship to physiological and pathological functions of the brain, electroencephalography is regarded as indispensable for clinical practice despite the rapid development of imaging technologies like magnetic resonance tomography or positron emission tomography. The electrical activity recorded using electroencephalography is generated by postsynaptic sum potentials of cortical neurons and results from a superposition of a very large number of individual processes. The human brain consists of approximately 1011 individual neurons with a total of 1014 to 1015 synaptic connections. Depending on the nature of these synapses, neurons can have an either excitatory or inhibitory effect on other neurons resulting in a complex interaction of neurons and synapses, which in effect ensures the functionality of the brain (Zschocke, 2002).

The analysis of synchronization phenomena in the epileptic brain using different measures of synchronization therefore seems to be a promising approach to investigate both the spatial and the temporal dynamics of the epileptic brain. Led by a growing interest in the possibility of seizure prediction (Litt & Lehnertz, 2002), a question of particular interest is whether bivariate time series analysis can contribute to this field.

The aim of the present thesis is to investigate and compare the suitability of measures for different forms of synchronization for the detection of interaction between dynamical systems using both model data from coupled systems and time series of the neuronal electrical activity recorded simultaneously in different regions of the brain. Consequently I would test if a univariate measure is sensible enough for seizure prediction.

2.1 Spatial-temporal dynamics in epilepsy.

As it has previosuly been pointed out, one of the most disabling aspects in epilepsy is the sudden, unforeseen way in which epileptic seizures strike “like a bolt from the blue” (Mormann, *et al.*, 2005). It is undisputed that a method capable of predicting the occurrence of seizures would significantly improve the therapeutic possibilities (Elger, 2001) and thereby the quality of life for epilepsy patients. A question of particular interest is whether apart from clinical prodromi (which are found only in some of the patients (Rajna, *et al.*, 1997) characteristic and objective features can be extracted from the continuous EEG that are predictive of an impending seizure. Much research has been carried out on this topic, and recent studies have reported certain measures derived from the theory of dynamical systems to be to some extent capable of extracting information from the EEG that allow the detection of a preictal state.

PREDICTION

3. Detection and prediction of seizures in scalp-EEG data.

The literature on seizure prediction is too voluminous to be listed in completeness. A comprehensive overview of this topic can be found in Litt & Echauz (2002), Litt & Lehnertz (2002), or Lehnertz *et al*. (2007) and Mormann, *et al.* (2007). After some early works on the predictability of seizures dating back to the 1970's (Viglione & Walsh, 1975), attempts to extract seizure precursors from the EEG were carried out by different groups using mostly linear approaches such as spectral analysis (Duckrow & Spencer, 1992; Rogowski *et al.,* 1981) or pattern detection by analyzing spike occurrence (Gotman *et al.,* 1982; Lange *et al.,* 1983).

In 1998, Osorio and colleagues proposed that both seizure detection and prediction methods should be evaluated with respect to *sensitivity* (the fraction of correct predictions to all seizures) and false prediction rate (the number of false predictions in a given time interval, or *specificity*). In the estreme case of a very low threshold every seizure will be predicted, increasing sensitivity up to 100%. This is achieved at the expense of a large number of false alarms during interictal phases. Because of this interdependency, sensitivity always has to be evaluated together with the false prediction rate.

Recently, Winterhalder *et al.* (2003) have extended this approach, suggesting the ''*seizure prediction characteristic*'' to evaluate and compare the performance of seizure prediction methods. Namely, a seizure prediction method has to forecast an upcoming epileptic seizure by raising an alarm in advance of seizure onset. A perfect seizure prediction method would indicate the exact point in time when a seizure occurs. This ideal behavior is not expected of current prediction methods analyzing EEG data. These authors indicate this uncertainty as the *seizure occurrence period* (SOP), the period during which the seizure is to be expected.

In addition, to render a therapeutic intervention or a behavioral adjustment possible, a minimum window of time between the alarm raised by the prediction method and the beginning of SOP is essential. This window of time is denoted as the *seizure prediction horizon* (SPH).

These two periods have to be taken into account to judge a correct prediction. For a correct prediction, a seizure must not occur during the seizure prediction horizon, but during the seizure occurrence period. The exact time of seizure onset may vary within SOP, thereby reflecting the uncertainty of the prediction. It is preceded by the seizure prediction horizon SPH, which mirrors the capability of the method to give an alarm early enough for a proper reaction.

If the seizure prediction horizon were long enough, a simple warning would enable a patient to prepare himself for an arising seizure. The patient could avoid a dangerous situation. Instead of warning the patient, an intervention by an implanted ‘‘brain pacemaker’’ is also imaginable. This device could activate a minipump to deliver anticonvulsive drugs into the epileptic focus or trigger electrical stimulations, controlling the seizure (Sterman, 2000). Anyway, interventions like the administration of anticonvulsive drugs and triggering an electrical stimulation are accompanied by possible side effects which may add up to relevant neuropsychological impairment, if too many interventions based on false predictions are carried out.

Even if all seizures can be predicted correctly, at least 50% of all alarms would be false alarms for patients during monitoring. This percentage increases to 97% in the case of epileptic patients under normal conditions. In conclusion, as a minimum requirement, a seizure prediction method should be superior to unspecific seizure prediction methods, such as the random or periodical prediction methods, by achieving a significantly higher seizure prediction characteristic.

3.1 Linear and non linear measures to predicting of seizures

One of the simplest linear statistics that can be used for investigating the dynamics underlying the EEG is the *variance* of the signal calculated in consecutive non-overlapping windows. Let s_i denote the EEG signal at time *i.* The variance of this EEG signal is given by

$$\sigma^2 = [s_i - \mu]^2$$

where the mean is $\mu = [s_i]$, and $[\cdot]$ is the average taken over the time interval being considered. Esteller *et al.* (2005) suggested measuring the energy of the signal in consecutive windows of the EEG signal. The *F-test* (Press *et al.,* 1992) provides a statistical test of the hypothesis that two given data sets have different variances. The F statistic is the ratio of one variance to the other, so that F>1 and F<1 both indicate significant differences. The probability that F would be as large as it is if the first data set’s underlying distribution actually has smaller variance than the second is given by $p = Q(F|\nu 1,\nu 2)$ where $\nu 1$ and $\nu 2$ are the number of degrees of freedom in the first and second data sets, respectively. A popular approach for investigating the EEG signal is to utilise its *power spectrum* (Blanco *et al.,* 1995). There are a number of different statistics that aim to summarise the information contained in the power spectrum. These include calculation of the total integral of the power spectrum over all non-zero frequencies (note that this equals the variance of the signal) and the median frequency, which estimates the ‘typical’ frequency present in the signal (Widman *et al.,*

2000). It has also been postulated that rhythmic behaviour, characterised by a peak in the power spectrum at a specific frequency, can be used to identify epileptic seizures (Murro, 1991).

The *auto-correlation function* ρ_K of a process s_i is given by (Chatfield, 1989)

$$\rho_K = [s_i - \mu][s_{i+K} - \mu]$$

where k is the time lag, ρ_K quantifies the amount of linear correlation between the signal and itself shifted by a time lag k. This function satisfies ρ_0=1; values of ρ_K ~ 1 reflect strong linear correlations; ρ_K ~ - 1 implies strong linear anticorrelations; and ρ_K ~ 0 indicates that no linear correlations exist. Because neuronal functioning is essentially non linear, analyses of brain electrical activity can provide new information about the complex dynamics of the underlying networks when methods derived from the theory of non linear dynamics are employed (Iasemidis *et al.,* 1990; Lopes da Silva, 1987; Pijn *et al.,* 1991). In epilepsy, it has been shown that the spatio temporal dynamics of the area of the brain giving rise to epileptic seizures (epileptogenic focus) is characterized by temporary transitions from high to low dimensional system states (dimension reductions). These dimension reductions allow the lateralization and possibly localization of the epileptogenic focus even without the necessity to record seizures or spikes (Lehnertz & Elger, 1998). Furthermore, they represent a sensitive measure to investigate the influence of antiepileptic drugs on the dynamics of the epileptogenic focus.

The aim of my project was therefore to test whether prolonged and pronounced transitions from high to low dimensional system states characterize a pre seizure phase. The identification of this phase having a sufficient length would enable new diagnostic and therapeutic possibilities in the field of epileptology.The non-linear analysis of data recorded from an experimental system usually begins with a state space reconstruction. An advantage of obtaining a multi-dimensional state space is that it may reveal the underlying dynamics. First attempts to use nonlinear time series analysis on EEG data, were started in the 1990's (Iasemidis *et al.,* 1999) using the *largest Lyapunov exponent* [2] to describe changes in brain dynamics.

[2] The Lyapunov exponents (Ls) measure the average rate of expansion and folding that occurs along different local directions within an attractor in the phase space. If the phase space is of *p* dimensions, we can estimate theoretically up to *p* Lyapunov exponents. Methods for calculating these dynamical measures from experimental data have been published (Iasemidis *et al*., 1990; Wolf *et al*., 1985). The estimation of the largest Lyapunov exponent (L_{max}) in a chaotic system has been shown to be more reliable and reproducible than the estimation of the remaining exponents (Grassberger Procaccia, 1983; Vastano & Kostelich, 1986).

The first studies to describe characteristic changes shortly before an impending seizure in a larger group of patients used the *correlation dimension* [3] as a measure for neuronal complexity in the EEG (Lehnertz & Elger, 1998) or the *correlation density* (Martinerie *et al*., 1998). These studies were followed by others employing measures such as *dynamical similarity* (Le Van Quyen *et al.*, 2001; Navarro *et al.*, 2002). In a recent study, certain signal patterns ("*bursts*") and changes in signal energy were reported to be of predictive value (Litt & Lehnertz, 2002).

Common to all of these analyses is the fact that they employ *univariate* measures. It is only recently that *bivariate* measures, namely, the difference of the largest Lyapunov exponents of two channels (Iasemidis *et al.*, 2001) and non-linear interdependence measures (Elger *et al*., 2000), as well as a multivariate approach based on simulated neuronal cell models (Schindler *et al.*, 2002) have been applied to the EEG of epilepsy patients.

In earlier studies (Mormann *et al.*, 2000), the degree of *phase synchronization* between EEG signals from different recording sites has been analyzed, and the phenomenon of a distinct drop in synchronization before seizures that was usually not found during the interictal period has been demonstrated. This decrease in synchronization was found to occur well in advance, sometimes hours, before a seizure, leading to the conclusion that a seizure may be seen as the mere "tip of the iceberg" (Mormann *et al.*, 2000) in the sense of it being the climax of successive changes in brain dynamics that start long before the actual seizure. These findings have since then been confirmed by another study (Le Van Quyen *et al.*, 2001) qualitatively describing *preictal drops* in phase synchronization in patients with focal epilepsies of neocortical origin.

Despite of the many publications reporting evidence for the existence of a pre-seizure state, to date no report of a prospective or quasi-prospective prediction of seizures has been published.
A major problem with most of the studies presented to date is that they do not sufficiently (or not at all) investigate the specificity of the described precursors using interictal EEG as control. In addition, many of these studies rely on the use of *a posteriori* knowledge, e.g., by selecting the best channel out of a large number of channels, or bear the risk of an in-sample over-training of parameters used to calculate measures for the extraction of predictive information. Another problem is that up to now no comparison of the performance of different approaches for seizure prediction has been published. Furthermore, there is little experience with continuous long-term-recordings

[3] The Lyspunov exponents (Ls) measure the average rate of expansion and folding that occurs along different local directions within an attractor in the phase space. If the phase space is of *p* dimensions, we can estimate theoretically up to *p* Lyapunov exponents. Methods for calculating these dynamical measures from experimental data have been published (Iasemidis *et al*., 1990; Wolf *et al*., 1985). The estimation of the largest Lyapunov exponent (L_{max}) in a chaotic system has been shown to be more reliable and reproducible than the estimation of the remaining exponents (Grassberger Procaccia, 1983; Vastano & Kostelich, 1986).

over days, and no study has been published that comprises different patients from different centers using different presurgical evaluation protocols and acquisition systems.

However, as recently suggested by Mormann *et al.,* (2007), the improvement of algorithms relies on a better comprehension of the confounding variables that may influence the measures used in the algorithms, decreasing their sensitivity and specificity.

In this regard, investigations on data sets of long lasting recordings have revealed fluctuations of EEG features that may be influenced by different vigilance states. In fact, it has recently been reported a dependency of false predictions on the state of vigilance, suggesting a reduced reliability of some seizure-prediction methods (Schelter *et al.,* 2006).

An additional factor limiting application and validation of most of seizure-prediction techniques is their computational load (Bruzzo *et al.,* 2006; Bruzzo, 2007; Bruzzo *et al.,* 2007). During the last two decades, in fact, a number of interesting methods have been proposed to detect dynamical changes. They include, among others, recurrence plots (Eckmann & Procaccia, 1986) and recurrence quantification analysis (Trulla *et al.,* 1996) recurrence time statistics based approaches (Gao, 2001; Rieke *et al.,* 2002), space-time separation plots (Provenzale *et al.,* 1992) and their associated probability distributions (Yu *et al.,* 1998), metadynamical recurrence plot (Manuca & Savit, 1996), statistical tests using discretized invariant distributions in the reconstructed phase space (Hively & Protopopescu, 2003), cross-correlation sum analysis (Kantz, 1994), and nonlinear cross prediction analysis (Schreiber, 1997). Most of these methods are based on quantifying certain aspects of the nearest neighbors in phase space, and, as a result, are computationally expensive. The proposed conceptually simple and easily calculable measure of *Permutation entropy* (PE) (Bandt & Pompe, 2002) can be effectively used to detect qualitative and quantitative dynamical changes. It was also suggested as useful screening algorithm for epileptic events in EEG data (Cao *et al.,* 2004; Bruzzo *et al.,* 2006, Bruzzo, 2007; Bruzzo *et al.,* 2007; Li *et al*., 2007). PE is an extremely fast and robust complexity measure for chaotic time series (Bandt & Pompe, 2002; Cao *et al.,* 2004; Li *et al.,* 2007) and thus suitable for online application even in portable systems. The use of PE is further encouraged by its similarity to Lyapunov exponent suggested for seizure prediction. At the present, PE has been applied only to intracranial EEG data in order to predict epileptic seizures (Cao *et al.,* 2004; Li *et al.,* 2007). PE is a measure of complexity in a system and can distinguish between random and regular (i.e. periodic) behavior (Bandt & Pompe, 2002). Hence, PE could be sensitive to regularities present during seizure and even in the preictal phase. However, also distinct vigilance states are typically characterized by different degrees in regularity of EEG.

In my study, I would like to prove the reliability of PE in the detection of fluctuation of vigilance levels and in seizure prediction from scalp EEG. The succeeding aim of my project was to test the capability of PE to distinguish between preictal and interictal state on the basis of scalp EEG, using Receiver Operating Characteristics (ROC) analysis, with particolar attention also to the role of changes in vigilance states. In fact, ROC analysis provides a good indication for the overall separability in terms of sensitivity and specificity of a characterizing measure. Moreover with ROC, a threshold for amplitude values of a measure is continuously varied, and the sensitivity (ratio of true positive classifications to total number of positive classifications) of the discrimination based on this threshold is plotted against 1 minus the corresponding specificity (ratio of true negative classifications to total number of negative classifications). The resulting curve is termed ROC curve. The definitions of sensitivity and specificity can either be based on the hypothesis that values from the second (i.e., the preictal) amplitude distribution are generally lower than those from the first (i.e., the interictal) distribution (H1) or on the opposite hypothesis (H2). In the case of H1, the terms “positive” and “negative” relate to whether an amplitude value is below or above the threshold, respectively, while the characterization “true” or “false” indicates whether values below the threshold belong to the second distribution (i.e., values from the preictal period) and values above the threshold belong to the first distribution (i.e., values from the interictal period) or not. If H2 is chosen as the ROC hypothesis, definitions must be adjusted accordingly. The area under the ROC-curve can be used to quantify the degree to which the two distributions can be distinguished. For identical distributions this area is 0.5, while for distributions that are completely non-overlapping, values of 0 or 1 are attained, depending on which ROC hypothesis was used for the definition of sensitivity and specificity. The capability of a measure to distinguish between the interictal and preictal period, i.e., its potential predictive performance, can thus be quantified by the area under the ROC curve where in case of H1 an area greater than 0.5 corresponds to preictally decreased values as compared to the interictal values and vice versa. For a better comparability of the different measures, ROC values were always determined for both hypotheses H1 and H2, and the larger one was selected thus achieving a performance value that is always ≥ 0.5 by construction. Furthermore, all analysis parameters were chosen to yield maximum performance values.

CONTROL

4. Seizures Control.

Antiepileptic drugs (AED) are the main form of treatment for epilepsy. Although many AED's have been developed, approximately one-third of epilepsy patients are not responsive to pharmaceutical treatments (Engel, *et al.,* 1993). If non-responsive to medication, surgical options can be considered. One common method is the removal or resection of epileptogenic tissue. Before resection, the patient undergoes extensive electrophysiological, neuroimaging and neuropsychiatric testing to strictly localize the epileptogenic tissue. Brain tissue can also be lesioned such as in a corpus callosotomy, where the main tract of fibers connecting the two hemispheres of the brain is severed to disrupt the pathways responsible for propagating generalized seizures.

A newer surgical method is *multiple subpial transections* (MST), where multiple parallel incisions are made in a restricted region of cortex in order to disrupt synchronous neural activity responsible for seizure generation. MST can be a viable alternative to resection when the epileptogenic tissue transcends critical areas in the brain, and removal of the tissue may result in serious cognitive impairment. MST is sometimes combined with resection to improve seizure activity slightly more effectively than MST alone (Spencer, *et al.,* 2002; Zhao, *et al.* 2003). A less invasive surgical treatment is *vagus nerve stimulation* (VNS), where an electrical stimulator implanted in the neck directs intermittent pulses to the vagus nerve. The patient can also activate the stimulator magnetically if they feel a seizure about to begin in order to prevent the seizure or reduce its severity. Common side effects of this treatment, such as voice alterations and tingling sensations, tend to be mild to moderate, and subside with time (Ben-Menachem, 2002). One increasingly used noninvasive treatment for children is the *ketogenic diet*. It consists of low carbohydrate, high protein, and high fat consumption, similar to the popularized Atkins diet but more strict. Although it can be an effective alternative (Kossoff, *et al.,* 2003; Sinha & Kossoff, 2005), the child's growth should be closely monitored as it may be negatively affected by the restrictive diet (Peterson, *et al*., 2005; Santoro & O'Flaherty, 2005). *Neurofeedback* (NF) is a method in which a patient attempts to regulate the abnormal brain activity responsible for seizures. Scalp electrodes relay the brain's electrical activity usually in visual form on a screen, providing feedback for the patient's progress. Neurofeedback can be a low-cost noninvasive solution with long term benefits, shown in repeated studies to have consistent positive results (Sterman, 2000; Uhlmann & Froscher, 2001; Walker & Kozlowski, 2005).

In particolar, learned self regulation of specific AC frequency components and of slow cortical potentials (SCPs) of the electroencephalograph (EEG) has been shown to be of considerable clinical value (Kotchoubey *et al.*, 2001). In this thesis, I attempt to describe the first Italian NF study, carried out on three epiletic patients; it has represented a demanding SCPs self-training, both for trainer and patients (including also a 6 months-follow-up phase) recruited from the Operative Unit of Monitoring Epilepsy at the Department of Neurological Sciences of Bologna (Italy).

4.1 Slow cortical potentials (SCPs).

Slow cortical potentials (SCPs) are direct current potential shifts of large neuronal assemblies of the cortex, lasting between several hundred milliseconds and several seconds. They are presumed to reflect the extent to which apical dendrites of the cortical pyramidal cells are depolarized. SCP amplitudes are regulated within tight limits by a negative feedback-loop consisting of a cortical-basal ganglia threshold regulation system that maintains cortical activation within acceptable medium limits (Birbaumer *et al.*, 1990). The reduction of the excitation threshold of cortical assemblies leads to glutamatergic stimulation of mainly inhibitory GABAergic structures within the basal ganglia, such as the putamen and pallidum (Braitenberg & Schütz, 1991) compensating cortical hyperexcitation via the basal ganglia and thalamus. Individuals can learn to voluntarily control SCPs through feedback and operant learning procedures. Combined recordings from the cortical surface and from single cortical cells at different depths and from different cortical layers (Caspers, 1974; Mitzdorf, 1985; Rebert, 1973; Requin *et al.*, 1984; Stamm *et al.*, 1975) revealed a strong relationship between local field potentials (LFPs) near the tip of the electrode at the apical dendrites (layer I and II) and SCPs at nearby cortical surface locations (Birbaumer *et al.*, 1990; Speckmann & Elger, 1999 for reviews). The correlation between single and multi-unit activity (MUA) and SCPs is less pronounced because MUA is mainly present during the output-mode of the pyramidal layers in deeper cortical structures distant from the cortical surface. The interpretation of the neurophysiological basis of slow cortical positivities from scalp recordings is less clear cut (Birbaumer, 1999; Mitzdorf, 1985). A decrease of cortical positivity below baseline values may result from active inhibition of apical dendritic neural activity or simply from a reduction of firing of afferent inflow and subsequent reduced postsynaptic activity. In any case, slow cortical positivities do indicate decreased brain activity in the area under the electrode. Increased firing and depolarization of the cortical input structures and apical dendrites as reflected in surface negative SCPs appears mainly in experimental situations employing anticipatory attention and

preparation (Rockstroh *et al.*, 1989) or delayed response tasks (Stamm & Rosen 1972) and tasks using continuous stimulation of several seconds. In humans, a reliable methodology to induce stable SCPs recordings in both directions, positive and negative, consists of extensive training of self-regulation and voluntary control of SCPs (Birbaumer *et al.*, 1990; Birbaumer, 1999).

5. Neurofeedback for seizures control

The most spectacular and popularized results in the emergine field of biofeedback (or ‘‘physiological regulation’’ as it is presently called) were the self-regulation of brain waves. Increase and decrease of alpha frequency of the EEG were supposed to create ‘‘meditative’’ states with many beneficial effects in the periphery and on behavior.

Theta wave augmentation and reduction had profound effects on vigilance and attention (Birbaumer, 1977). Slow cortical potentials (SCP) control allowed anatomically specific voluntary regulation of different brain areas with area specific effects on behavior and cognition (for an overview, Rockstroh *et al*, 1989). Warning voices such as experiments by Mulholland and his group (Mullholland & Evans, 1966) demonstrating perfect control of alphawaves throughmanipulation of the oculomotor systemand decoupling of eye fixation went largely unheard. Sterman (Sterman & Friar, 1972; Sterman, 1981) was the first to propose self-control of epileptic seizures (Elbert *et al.*, 1984) by an augmentation of sensorimotor rhythm (SMR).

SMR in human subjects is recorded exclusively over sensorimotor areas with frequencies of 10 to 20 Hz and variable amplitudes. Pfurtscheller *et al.* (2005) localized the source of human SMR in the sensorimotor regions following the homuncular organization of the motor and somatosensory cortical strip. Imagery of hand movement abolishes SMR over the hand region; imagery or actual movement of the legs blocks SMR in the interhemispheric sulcus. Pfurtscheller called this phenomenon event-related desynchronization and synchronization (Pfurtscheller *et al*., 2005). On the basis of careful animal experiments (Sterman & Clemente, 1962a, 1962b), Sterman demonstrated incompatibility of seizures in motor and premotor areas in the presence of SMR. Cats exhibited maximum SMR during motor inhibition and various sleep stages.

Presence of spindles during different sleep stages, particularly during rapid eye movement (REM) sleep indicated recruitment of inhibitory thalamo-cortical circuits and blocked experimentally induced seizures. Sleep spindles and SMR share identical physiological mechanisms. Epileptic cats and humans were trained to increase SMR, and, after estensive training ranging from 20 to more than 100 sessions, Sterman (1977) was able to demonstrate seizure reduction and complete remission in some patients with drug-resistant epilepsy. It is important to

note that SMR is often called mu-rhythm following a suggestion of Gastaut (Gastaut, 1952; Gastaut *et al.,* 1952) who noted its abolition in some types of seizures. As illustrated in Figure 1, successful voluntary brain control depends on activity in premotor areas and the anterior parts of the basal ganglia.

Fig. 1 Self-regulation of slow cortical potentials on regional metabolic changes measured with fMRI

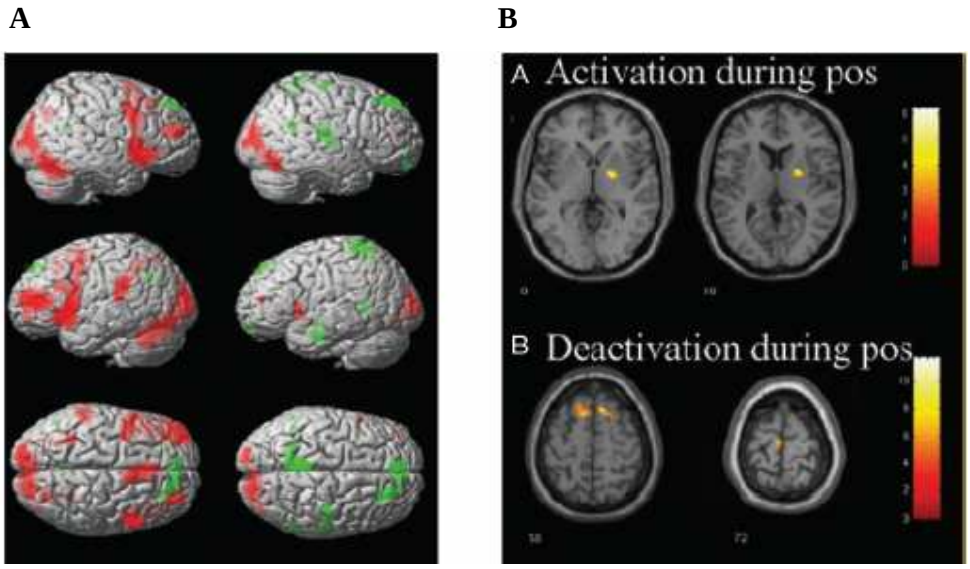


Fig. 1 Effects of self-regulation of slow cortical potentials (SCPs) on regional metabolic changes measured with fMRI. Left: BOLD responses during self-produced cortical negativity (left column) and positivity (right column). Red colored brain areas indicate activation, green color deactivation. Right: **A**: Activation of anterior basal ganglia during self-induced cortical positivity. **B**: Related deactivation of premotor areas during cortical positivity (from Hinterberger *et al.*, 2003).

Birbaumer *et al*. (1990) had proposed earlier that physiological regulation of SCP and attention depends critically on *anterior basal ganglia* activity regulating local cortical activation thresholds and SCPs in selective attention and motor preparation. Braitenberg (Braitenberg & Schuez, 1991) created the term ‘‘thought pump’’ (‘‘*Gedankenpumpe*’’ in German) for this basal ganglia–thalamus–cortical loop. Taken together, the extensive literature on the SCPs also suggests that operant-voluntary control of local cortical excitation thresholds underlying goal-directed thinking and preparation depends on an intact motor or/and premotor cortical and subcortical system.

Encouraged by the reliable and lasting effects of brain self regulation on various behavioral variables and by Sterman’s case demonstrations, Birbaumer and colleagues conducted several

controlled clinical studies on the effect of SCP regulation on intractable epilepsy (Kotchoubey *et al.,* 2001; Rockstroh *et al.,* 1989, 1993). Based on their neurophysiological model of SCP regulation, patients with focal epileptic seizures were trained to down-regulate cortical excitation by rewarding them for cortical positive potentials and perception of SCP changes. After extremely long training periods, some of these patients gained close to 100% control of their SCPs and seizure suppression. Namely, epileptic patients suffering from a dysregulation of cortical excitation and inhibition and consequent brain lesions can learn to control their brain responses both within the laboratory and in daily life. Given that the cerebral loop involved in this type of operant learning, encompasses basal ganglia, jointly with cerebellum, the functional structure to work out timing of motor actions are modulated by the NF.

6. Mental simulation: a possible link between epilepsy and schizophrenia.

Starting points: some considerations from the neuroscience literature

To undertake a novel setup/method for seizures prediction based completely on behavioral aspects, the following evidences have well been thoughted-out:

1. Since the nineteenth century, psychotic episodes have been described in epilepsy especially during postictal/interictal phases. (Nopoulos *et al.,* 1999 Nopoulos *et al.,* 2001; Sachdev, 1998).
2. Accumulating evidence indicates that individuals both with epilepsy and with schizophrenia manifest abnormalities into the structures cerebellum and basal ganglia (Jahanshahi *et al.*, 2006; deputized to secrete dopamine (see Chen, 2006, for dopamine hypotheses in epilepsy) and Lovestone *et al.*, 2007; Trimble, 1977, for dopamine hypotheses in schizophrenia).
3. Basal ganglia are involved in interval timing of long intervals (seconds-range).
4. Morover, in schizophrenia is well known a disfunction in forward models (Frith *et al.,* 2000) for biological motion (and, it has not been yet demonstrated for non biological) that could explain the disfunction in self-agency. Is it also true for epilepsy over all phases of their epileptic cycle?

First step: A mental task including simultaion of non-biological motion

Research on motor imagery could show many similarities to motor execution. Motor imagery is accompanied by changes of heart rate; increase in CO_2-pressure and in respiration frequency (Decety *et al.,* 1993; Wuyam *et al.,* 1995). Hence physiological parameters change as if the body would execute real movements. Further, executed and imagined movements (e.g. writing a letter or walking a certain distance) show the same durations (Decety & Michel, 1989).Primary motor cortex seems to be involved in motor imagery (Fadiga *et al.,* 1999; Lotze *et al.,* 1999; Schnitzler *et al*, 1997). Finally, training with motor imagery improves the dynamics of motor performance (Yàguez *et al.,* 1998). These findings leave behind the impression that motor imagery is nothing else than motor execution with inhibition of the final motor pathways. Nevertheless, experiments in patients with parietal lesions (Sirigu *et al.,* 1996) and in schizophrenic patients (Danckert *et al.,* 2002) revealed also dissociation between these two motor functions. In healthy subjects, temporal aspects of both imagined and actual pointing movements conform to spatial constraints (e.g.: target width,

movement amplitude), whereas in schizophrenic and parietal patients this dependency is lost in motor imagery, despite being preserved in execution. These findings raise the question whether the similarity between motor imagery and motor execution is just superficial and whether motor imagery is rather a mental simulation of perceptual events and as such, relatively independent from motor execution. Further it is unclear, whether mental simulation of non-biological movements (i.e. motion that is not generated by living beings, by contrast to biological motion) depends on the same mechanisms as motor imagery.

Lesion studies demonstrated dissociation between the ability to perceive both types of motion. Patients being completely 'motion blind' still could discriminate biological motion (McLeod *et al.,* 1990). The opposite pattern has also been reported (Schenk & Zihl, 1997). This dissociation raises the question, whether mental simulation of the two movement types relies on different mechanisms as well. Motor imagery has been suggested to depend on forward models (Jeannerod, 1995), mapping the motor representation of the to be imagined movement on the representation of its sensory effects. The simulation of a non-biological movement could rely on forward models for biological movements with similar dynamics. Alternatively, distinct models specific for the dynamics of non-biological movements could be involved. In order to investigate these issues, I designed a paradigm including simulation of both movement types (see section "*Materials and methods*" subtitled *prediction*).

Psychotic episodes in epilepsy have been described already since the nineteenth century (Sachdev, 1998). Demanding cohort and epidemiological investigations have been done to correlate this neurological disease to psychosis (Flor-Henry, 1969; Flugel *et al., 2006;* Ishii *et al*, 2006; Mace, 1993; Matsuura *et al.,* 2004; Mendez *et al.,* 1993; Quin *et al.,* 2005; Sachdev, 1998; Taylor, 2003; Trimble, 1977). Additionally, there are neuroimaging and neuropathological data linking epilepsy with schizophrenia-like psychosis (Bruton *et al.,* 1994; Nopoulos *et al.,* 1999; Nopoulos *et al.,* 2001; Roberts *et al.,* (1990).

However, many aspects of this linkage still remain controversial. For example, psychotic episodes are traditionally classified according to their temporal relationship to seizure occurrence, as ictal, postictal (or peri-ictal) and interictal. However, it has not been shown whether this classification reflects distinct pathophysiologies (Sachdev, 1998; Taylor, 2003). Also the linkage of psychotic episodes to a certain type of epilepsy, in particular the temporal lobe epilepsy (TLE), remains unclear (Sachdev, 1998). In particular, it has been noted that the similarity between epilepsy and schizophrenia does not automatically mean a common origin of the psychotic symptoms (Cummings 1993). In literature there are no reports on behavioral procedures used to investigate the relationship between these two disorders.

The aim of the present study was to investigate whether the behavioral performance of epileptic patients would be similar to that of schizophrenic patients, previously assessed by the same task by Bruzzo *et al.,* 2007 (see also above). Briefly, the previous study in schizophrenia investigated the mechanisms underlying mental simulation of biological and non-biological movements. Subjects had to either simulate mentally or to overtly reproduce previously executed or observed movements of both types. Duration of the respectively real movement was compared to the duration of the either simulated or re-enacted movement. Healthy controls showed a very high timing precision when simulating biological and a strong distortion when simulating non-biological movements. Schizophrenic subjects, however, showed the opposite.

Given this double dissociation, authors concluded that processes underlying mental simulation of biological and non-biological movements are separate from each other. Performance of both subject groups was almost perfect for both movement types, when movements had to be re-enacted. This second finding confirmed that perception, attention and memory for movements were not the reason for the distorted timing performance during mental simulation. The simulation of biological motion in schizophrenic patients could be impaired as a consequence of a dysfunction of forward models (Frith *et al.,* 2000). Forward models are crucial for predicting the sensory effects of actions (Wolpert *et al.,* 1995) and allow healthy subjects to precisely imagine biological movements (Jeannerod, 1995).

A dysfunction of forward models has also been suggested to be responsible for one main positive symptom in paranoid schizophrenia, the delusion of agency, namely, the belief that self-produced movements are caused by external forces or other persons (Frith & Done, 1989; Blakemore *et al.,* 2002).This erroneous attribution of agency could be explained by the inability to match the perceived sensory effects of the own movement to the predicted effects.

Given this possible implication of disturbed forward models in the explanation of one main psychotic symptom in schizophrenia, I hypothesized that that forward models are also malfunctioning in epilepsy. This should result in similar performance of epileptic patients in the described behavioral task, previously performed with schizophrenic patients. However, we expected a variation of patients' performance over the epileptic cycle, as psychotic episodes are reported to be more frequent in the post-ictal and interictal phases of this cycle (Adachi, 2000; Perrine & Kiolbasa, 1995; Umbricht *et al.,* 1995). Considering this possibility I conducted the behavioral task daily during a longitudinal study, hence including all different phases of the epileptic cycle.

MATERIALS AND METHODS

PREDICTION

7. Implementation of Permutation Entropy (PE) on scalp-EEG data.

Patients

Three patients (2 males and 1 female) suffering from drug-resistant focal epilepsy undergoing longterm computerized video-EEG recording for presurgical evaluation were studied. All patients underwent awake and sleep EEG recording for characterization of interictal epileptiform abnormalities, and 1,5/3 T brain Magnetic resonance imaging (MRI) or Computed tomography (CT). Clinical features and interictal/ictal EEG data of the patients are illustrated in Table 1. Identification of the epileptogenic zone was based on the clinical and EEG features of the seizures, and on evaluation of MRI data. Informed consent was obtained from all patients after the purpose of the study was explained.

Table 1. Clinical features of the patients

	Patient 1(17/M)	Patient 2 (47/F)	Patient 3(36/M)
Age [years] at the epilepsy onset	9	14	20
Seizure frequency	Daily	3-4/Month	Weekly
Interictal scalp-EEG	Left temporal spikes associated with slow waves	Right anterior temporal spikes associated with theta activity	Right frontal spikes associated with theta activity
Ictal semiology	Psychomotor arrest, loss of consciousness, right upper limb dystonia, left upper limb gestural automatism	Epigastric sensation or fear, spitting, loss of consciousness, eye and head deviation on the right, secondary generalization	Mild head deviation on the right, loss of consciousness, left upper limb automatisms
Ictal EEG pattern	Diffuse desynchronization followed by diffuse or predominant on the left hemisphere high amplitude slow rhythmic activity	EEG flattening followed by rhythmic spike activity in the right temporal leads, then bilateral spread	Diffuse EEG flattening followed by irregular diffuse spike-wave activity
Brain MRI/CT	MRI: dysplasia of the left mesio-temporal lobe extended to the ipsilateral insular cortex	MRI: dysplasia of the right amygdale and right hippocampus hypertrophied CT: anterior hippocampus and temporal pole lesion	MRI not performed because of metal clips in the liver level CT: right frontal post-traumatic malacic lesion
Results of seizure video-EEG recording	Left mesio-temporal seizures with possible spread to frontal regions	Right antero-mesial temporal lobe seizures	No seizure recorded
Neurological examination	Unremarkable	Unremarkable	Unremarkable

EEG data

A standard bipolar montage with 18 Ag/AgCl electrodes was used. Signals were amplified, band-pass filtered (0.1K-70 Hz), sampled at 200 Hz, and stored on a video-EEG system (Telefactor Corporation, West Conshohocken, Pennsylvania, USA). Video-EEG recording was performed only during daytime, from about 8 a.m. until 7 p.m. in the evening. Patient P1 was recorded over 8 days (total of 61 h and 4 seizures), P2 over 2 days (total of 14 h and 2 seizures), and P3 over 5 days (total of 40 h, without seizures). Video EEG data were reviewed by two epileptologists to detect epileptic seizures. Staging of the different vigilance states was performed over the whole recording according to the criteria reported by Drury *et al.,* 2003 illustrated in Table 2. Data of patient P3 were included only to study dependency of PE on vigilance state, as no seizures were present in the dataset.

Table 2. EEG features of behavioral states

BEHAVIORAL STATE DESIGNATION	**CRITERIA**
Awake with eyes open	Attenuation of alpha-theta increased EMG and other movement artefacts
Awake with eyes closed	Posterior alpha or theta rhythm
Drowsiness	Diffuse alpha-theta, slow eye movements, loss of alpha-theta, V-waves
Stage 2 NREM	Spindles, K-complexes, <20% 2 Hz delta
Stage 3 or 4NREM	>20% 2Hz delta of 75µV
REM	Low voltage mixed frequency fast, sawtooth waves

Data Analysis

Original sample frequency was reduced from 200 to 66.67 Hz by maintaining every third sample in order to limite the mutual information. PE was calculated over time using a moving window technique (window size 15 sec). The signal of each time window and each separate EEG channel was analyzed as one scalar time series {xt}t=1,...,T, with T=1000.

These time series were embedded to a *m*-dimensional space: $X_t=[x_{t,}\ x_{t+L},...,x_{t+(m-1)L}]$, with *m* being the embedding dimension and *L* being the time lag. For all values of *t* the real values of $X_t=[x_{t,}\ x_{t+L},...,x_{t+(m-1)L}]$ were arranged in an increasing order: $X_t=[x_{t+(j1-1)L} \leq x_{t+(j2-1)L} \leq ... \ x_{t+(jm-1)L}]$. Hence, each vector X_t is uniquely mapped onto $\pi=[j1\ ,\ j2\ ,\ .\ .\ .\ ,\ jm]$, where π is one of *m*! possible permutations of the vector [1,2,…,*m*]. If each of the *m*! permutation is considered as a symbol, then this procedure allows the mapping of the original continuous time series onto a symbolic sequence (Bandt & Pompe, 2002). The frequency of each possible permutation π, as obtained during the sorting process of all vectors X_t, was calculated as $p(\pi)$. Permutation entropy was calculated as

$$H(m)=-\ \Sigma\ p(\pi)\ \ln\ p(\pi),$$

where the sum runs over all *m*! permutations π of order *m*. As H(*m*) can maximally reach ln(*m*!), the permutation entropy was normalized as H(*m*)/ln(*m*!).

Hence, possible values are: $0 \leq H(m)/\ln(m!) \leq 1$. Permutation Entropy is a measure of regularity in the time series (Bandt &Pompe, 2002). The upper bound (i.e. H(*m*)=ln(*m*!)) is attained, when all *m*! possible permutations appear with the same probability. Instead, with increasing regularity (i.e. probabilities for different permutations π becoming more different from each other) H(*m*) decreases. The embedding dimension *m* was chosen of order 4, and the time lag *L*=1. Small values of *m* may not be able to reflect regularities of higher order. For practical purposes, Bandt & Pompe recommended *m* = 3, .., 7. Increasing *m* may lead to memory restrictions due to the large number of *m*! possible permutations. Here, *m*=4 was chosen empirically. Larger values (*m*=5, 6, 7) didn't reveal significant differences on visual investigation of the resulting PE profiles.

Subsequently, it was tested the possibility to classify instances of the resulting PE values as belonging to the preictal phase (positive class) or to the interictal phase (negative class), by comparing PE values to a certain threshold.

The quality of a decision model based on a threshold discrimination can be evaluated by the percentage of PE values resulting from a preictal phase and being attributed correctly to this phase (*sensitivity*) and the percentage of PE values resulting actually from an interictal phase, but being misattributed to the preictal phase (*1-specificity*). However, the threshold for such a binary classifier system can be chosen arbitrarily at any level in the range of amplitudes, which the PE measure can assume. A Receiver Operating Characteristic (ROC) curve is a graphical plot of the sensitivity *vs.* (*1 – specificity*) for a binary classifier system as its discrimination threshold is varied (cf., paragh. 3.1, Fig. 2 a, b).

ROC curves were calculated for both hypotheses, i.e. PE amplitudes either decrease or increase in the preictal phases compared to the interictal phases.

Under the hypothesis of preictal decrease, for each possible threshold (steps of 0.01) in the range from 0 to 1, the percentage of preictal time windows with PE amplitudes below threshold , indicating sensitivity, and the percentage of interictal time windows with PE amplitudes below threshold, indicating 1-specificity, were calculated. By plotting for each tested threshold the sensitivity *vs.* 1-specificity, a series of points resulted, determining the profile of the ROC curve (Fig. 2b). Sensitivity and specificity for the opposite hypothesis (i.e., preictal increase) and the corresponding ROC curve were calculated in a similar fashion by reverting threshold dependencies. The area under the ROC curve (AUC) as a measure of separability of pre- and interictal amplitude distributions was determined.

The more different the AUC value from 0.5 and the closer to 0 or 1 (depending on the tested hypothesis), the better the separability of the two distributions. However, only AUC values larger than 0.5 indicate validity of the chosen hypothesis (i.e. measures in preictal phase being either larger or smaller than threshold), while values below 0.5 would support the opposite hypothesis. The duration of the delay between the first changes in the brain state and the onset of a seizure are still under discussion. However, the separation between preictal and interictal phases is one necessary precondition to perform ROC analysis. In order to define the duration for the preictal phase leading to the best results, ROC analysis was performed for a range of durations lasting from 5 minutes before seizure onset to the maximum, allowed by the minimal distance of two subsequent seizures.

The duration was varied in steps of 2.5 minutes within this range. Periods, lasting 40 min from onset of seizures, were excluded from analysis, as the postictal EEG signal may be consistently different either from interictal and preictal signals. Reassuming, for each EEG channel, each hypothesis (i.e. preictal increase or decrease of PE values), and each of the hypothesized preictal phase durations, the AUC value was calculated. Furthermore, for each EEG channel, that

hypothesis and that duration of preictal phase were determined, which lead to the maximal AUC value. In addition, it was controlled for a possible dependency of PE on vigilance state. The mean PE amplitude over all channels was calculated for each time window. Then, the linear correlation between PE amplitude and vigilance state, determined as reported above according to Drury *et al.*, 2003 was calculated.

Fig. 2 Amplitude distribution of PE for interictal and preictal phases

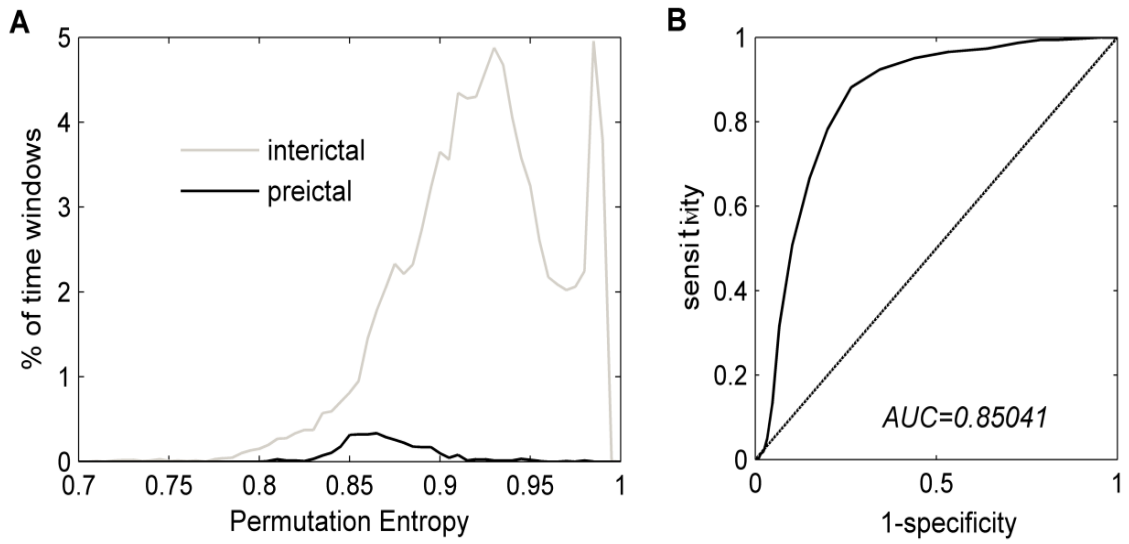


Fig 2 (**a**) Amplitude distribution of PE for interictal (gray line) and preictal (black line) phase as resulting for one channel of patient P1**.** (**b**) ROC curve, indicating separability of amplitude distributions shown in panel a. The hypothesis, used for calculation, was preictal decrease. A ROC curve equal to the diagonal (gray line) would indicate for all possible thresholds the same probability for true and false alarms (i.e. detection of preictal state). Thus, as the ROC curve becomes different from the diagonal, the separability becomes better. The AUC value can be taken as a measure for this difference. The more different the AUC value from 0.5 and the more close to 0 or 1 (depending on the tested hypothesis), the better the separability.

6.1 Statistical evaluation of PE for predictability of seizures.

Fig. 2 shows the distribution of PE amplitude in pre- and postictal phase (panel a) as well as the AUC curve (panel b) for one selected channel of Patient 1.

AUC values were calculated for both hypotheses: a preictal increase or decrease of PE values. The maximal AUC values were yielded for all seizures and for all EEG channels under the assumption of a preictal decrease in PE (Fig. 3a). This was equally true for both patients with recorded seizures (Patients 1 and 2).

The calculation of AUC values was repeated for each channel, varying the duration of the assumed preictal phase. In this way the duration leading to the best AUC value was determined.

In both patients (Patient 1 and Patient 2) these durations were similar between the different EEG channels (Patient 1: minimum=30 min, median=32.5 min, maximum=45 min, Patient 2: median=15 min, minimum=15 min, maximum=20 min]. By comparing the maximum AUC values obtained for the different channels of each patient, the median, maximum and minimum AUC values were respectively 0.771, 0.861, 0.574 for Patient 2 and 0.815, 0.85, 0.654 for Patient 1.

7.2 Mental imagery task.

Participants

Schizophrenics and healthy controls

It has been investigated mental simulation in a broader context, recruiting 10 right-handed (according to the Edinburgh Inventory, Oldfield, 1971) paranoid schizophrenic patients (diagnosis according to the DSM-IV TR criteria, APA, 2000), from the Department of Neurological Sciences, (University of Bologna, Italy) and 10 matched healthy volunteers (5 women and 5 men, mean age (±SD) 28.7±2.63, range 26-32; mean education level (±SD) 16.3±4.06), with normal or corrected-to-normal visual acuity in both eyes. None of the healthy participants had neurological, psychiatric, or other medical problems. All subjects were naive to the purposes of the experiment. Information about the experimental hypothesis was provided only after the experiment was completed. Participants gave their written informed consent for their participation in the study.

Before the beginning of the study, schizophrenic patients underwent a clinical assessment using a battery of neuropsychological tests: WAIS, (Wechsler, 1955); Scale for Assessment of Negative Symptoms (SANS) (Andreasen, 1983); Scale for Assessment of Positive Symptoms (SAPS) (Andreasen, 1984), Wisconsin Card Sorting Test, (Heaton, Chelune, Talley, Kay, & Curtiss, 1993); Beck Depression Inventory (BDI) (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961); Profile of Mood States (POMS) (McNair, Lorr, & Droppleman, 1971), Brief Psychiatric Rating Scale (BPRS) (Overall & Gorham,1962); Global Assessment of Function (GAF) (APA, DSM IV-TR, 2000); Birmingham Object Recognition Battery (BORB) (Riddoch & Humphreys, 1993). A summary of patients' data is given in Table 3.

Table 3. Descriptive variables of paranoid schizophrenic patients

Age (SD)	31.4 ± 4.11, range (27–41)
Sex	Males n = 5
	Females n = 5
Handedness	Right n = 10
	Left n = 0
	Ambidexstral n = 0
Education (yr)	10.6 ± 2.55
Age at onset (±SD)	<18 yr n = 2, 17
	>18 yr n = 8, 23.88 ± 1.73
Duration of illness (±SD)	8.9 ± 4.28, range (3–15)
Dose (mg/day) of atypical antipsychotics	Risperidone n = 3 (1.5–6.0)
	Olanzapine n = 1 (7.5–30)
	Clozapine n = 3 (40–160)
	Quetiapine n = 3 (200–800)
Intelligence measures (WAIS-R)	Verbal IQ 99.6 ± 6.60
	Performance IQ 100.4 ± 1.58
	Full-scale IQ 100 ± 4.69
Wisconsin Card Sorting Test (perseverative errors)	3.2 ± 0.92
Beck Depression Inventory (BDI)	11.6 ± 0.52
Negative Symptoms (SANS total scores)	53.5 ± 6.07, range (45–60)
Positive Symptoms (SAPS total scores)	17.5 ± 6.29, range (10–28)
POMS	19.1 ± 1.97
BPRS (Brief Psychiatric Rating Scale)	25 ± 2
Global Assessment of Function (DSM-IV TR)	74.6 ± 2.17
Birmingham Object Recognition Battery	24.9 ± 2.28

The main demographic and clinical details of patients (n = 10) involved in the experiment are reported with mean ± standard deviation values.
Note: There is no information in the literature on possible effects of medications on tasks similar to those used in the present work.

The pilot study with epileptic patients

Five patients were recruited affect by different form of epilepsy at the Unity of Monitoring Epilepsy (Dep.of Neurologial Sciences, University of Bologna, Italy).

The local ethics committee at University of Bologna, Italy approved the procedures in accordance with the ethical standards of the 1983 Declaration of Helsinki. All patients were entered into the study after providing informed consent approved by local Institutional Review Board (University of Bologna, Italy).

Performance of all patients was assessed in four different phases: *i*) preictal phase (within 24 hours before seizure onset, *ii*) two postictal phases, respectively 24 hours (postictal 1) and 72 hours after seizure onset (postictal 2), and *iii*) interictal phase, period between postictal phase of foregoing and preictal phase of next following seizure.

All patients were in good physical health, determined by a physical examination and laboratory evaluation including a complete blood count, glucose and hepatic enzymes, renal and thyroid analyses.

Medication level of anticonvulsive drugs was constant over all four phases, in which the experiment was conducted. There is no information on possible effects of medications on our experiment. No subjects showed psychogenic seizures.

7.3 The longitudinal study: predicting epileptic seizures by a mental imagery task.

Epileptic Patients

Due to the promising results (see section Results 8.1) obtained in the pilot study with epileptic patients, I decide to performe a longitudinal study. Four patients from the Department of Neurological Sciences - Bellaria Hospital University of Bologna (Italy) were recruited by a cluster sampling technique. All were females and right-handed, according to the assessments made with the Edimburgh Inventory (Oldfield, 1971), with onset and duration of illness respectively before 18 yr, (11±1.41), (15±8.49) and education, 9.5±2.12).

- Patient s1 (32ys): Right temporal lobe with cortical dysplasia, (polytherapy: Carbamazepine+Topiramate: 400; 100 mg)
- Patient s2 (29yr): Right temporal lobe with cortical dysplasia. (polytherapy: Topiramate Phenytoin+Levetiracetam: 100mg + 900+ 200 mg).

- Patient s3 (31ys): Extratemporal lobe Epilepsy, Generalized, with focus on the left lobe, (politherapy: Gabapentin+Lamotrigine: 900mg+200mg).
- Patient s4 (38 ys) idiopathic secondary generalized, seizures focus on the right; (middling cared, in monotherapy: Carbamazepine).

Medication level of anticonvulsive drugs was constant over all four phases, in which the experiment was conducted. There is no information on possible effects of medications on our experiment. Before the beginning of the study, all epileptics underwent a clinical assessment and a neuropsychological assessment reported in Table 3 in order to ascertain that all patients were able to understand the task. No subjects showed psychogenic seizures.

The local ethics committee at University of Bologna, Italy approved the procedures in accordance with the ethical standards of the 1983 Declaration of Helsinki.

All patients were entered into the study after providing informed consent approved by local Institutional Review Board (University of Bologna, Italy). All patients were in good physical health, determined by a physical examination and laboratory evaluation including a complete blood count, glucose and hepatic enzymes, renal and thyroid analyses. Each subject was observed over a period of 29 days. The experimental task was undertaken every day at the same time (s1 16:00; s2: 19:00; s3: 14:00; s4.13:00), excluding weekends and holidays. This period included 17 recording days and 6 seizures for s2; 18 recording days and 11 seizures for s1; 18 recording days and 8 seizures for s3, and 17 recording days and 7 seizures for s4.

Table 3. Neuropsychological assessment

TEST	PATIENTS
INTELLIGENCE MEASURES (WAIS-R)	
Verbal IQ	100.6 (±4.60)
Performance IQ	102.6 (±3.58)
Full-scale IQ	102 (±4)
WISCONSIN CARD SORTING TEST, perseverative errors	3.29 (±0.76)
BECK DEPRESSION INVENTORY	9.86 (±1.07)
POMS	17.43 (±1.51)
BPRS (brief psychiatric rating scale)	23.86 (±1.07)
Global Assessment of Function (DSM-IV-TR)	77.29 (±4.60)
Birmingham Object Recognition battery	25.14 (±2.27)

It has been reported scoring and standard deviation (±SD) of all patients underwent by neuropsychological assessment.

Procedure

Subjects were required to mark on a calendar accurately day, hour and behavioral situation in which seizures occurred. Hence, subjects could not be kept totally naïve about the aim of the study. They were just told that the aim was to investigate time estimation across epileptic phases. However, nothing was told about the working hypothesis (i.e.: the expected difference among the experimental conditions and phases of epileptic cycle).

The procedure was approved by the local ethics committee at the University of Bologna, Italy, and was in accordance with the ethical standards of the 1983 Declaration of Helsinki.

Subjects were seated in front of a laptop. The experimenter was sitting on the right side of the subject for the whole duration of the experiment (Fig 3).

Task

At the beginning of each experimental trial, subjects were either shown a parabolic movement of a disk on a computer screen (non-biological movement; NB), or they had to execute a comparable parabolic movement with their own arm and index finger (biological movement self, BS), or to look at the experimenter performing such a movement (biological movement other, BO).
In case of the non-biological movement, the disk (diameter 1.8 cm) started at the lower margin of the screen and moved up and down following a parabolic trajectory. The horizontal and vertical coordinates (*x* and *y*; units in cm) of the centre of the disk on the screen (screen size: 33cm x 21cm) were calculated as a function of time (*t*):

$$x = 16.5 + 6.6\sin[z(t)]$$

and

$$y = 16.8 - 15.8\sin[z(t)]^2$$

with $z(t) = (2t\text{-}d)\pi / 2d$; and *d* being the movement duration. The duration was varied among trials within a range of 6 to 10 seconds. Tangential velocity v(t) was calculated as:

$$v(t) = (\pi / d)\ \{43.6\cos[z(t)]^2 + 1002.8\sin[z(t)]^2\cos[z(t)]^2\ \}^{0.5}$$

Start and stop positions were symmetrically to the left and right of the screen. Direction was randomly changed and balanced across trials. Acceleration resulted to be maximal at the start and decreased to zero as the disk reached 52% of its maximal height on the parabolic trajectory. In continuation the disk decelerated slightly, till it reached the maximum height. For the period of downward movement, the acceleration profile was reversed. Acceleration changed smoothly over all the movement time, making it feasible to the subject to re-enact the non-biological movement with the index finger (see below).

Further, the profile of tangential velocity reached maximum at the rising and falling edges of the parabolic trajectory. A local minimum was reached at the highest point of the trajectory (40% of maximum velocity). Hence, the velocity decreased slightly as the curvature of the trajectory increased, making the dynamics more similar to those of a biological movement.
For biological movements, subjects were asked to perform smooth movements without abrupt speed changes and to spontaneously vary the duration of their movements between 6 and 10 seconds, corresponding to the range of durations of the non-biological movements. Also the experimenter

varied the duration of his movements in the same range. Before starting the biological movement, the agent (i.e.: experimenter or subject) had to hold down a key of the keyboard with his/her right index finger. Movements had to be started spontaneously by releasing the key, and moving the index finger in a parabolic trajectory up and down to press a second key, symmetrically located at the other side of the keyboard.

The fact that the experimenter was sitting at the right side of the subject, and using his right hand, ensured that subjects could see the experimenter's index finger easily during the movement. Training for each movement type was conducted before starting the experiment, in order to familiarize subjects with the task. At the beginning of the experiment, the keyboard was covered, leaving free only the two keys reserved for the start and stop of the movements. Similar to the non-biological condition, the direction was randomly changed and balanced over trials. At the beginning of each trial, movement direction was indicated by an arrow in the center of the screen. Durations of biological movements were measured from the release of the start key to the pressing of the stop key.

In the second part of each trial, subjects were asked to either imagine (i) or overtly re-enact (r) the very same movement once again (i *vs.* r = response mode), indicating its start and stop. When subjects had to re-enact the movement, they had to use the same keys as were used before (in the biological condition), or the keys corresponding to the start/stop position of the disk on the screen (in the non-biological condition). The disk trajectory had to be reproduced with the tip of the index finger moving in the air. In order to indicate the start and stop of the imagined movements, subjects had to use the keys in the same manner as during the re-enactment, but with the difference that the left and right index fingers were used to operate the start and the stop key, respectively. Thus subjects did not have to lift and move hand and index finger from the start to the stop key (like they did during overt re-enactment).

Instead, both hands rested in a stable position until the completion of simulation process. Each of the six resulting conditions (i.e.: NBi, BSi, BOi, NBr, BSr, BOr) was repeated in ten randomly ordered trials.

Fig. 3 The experimental setup and the different experimental situations

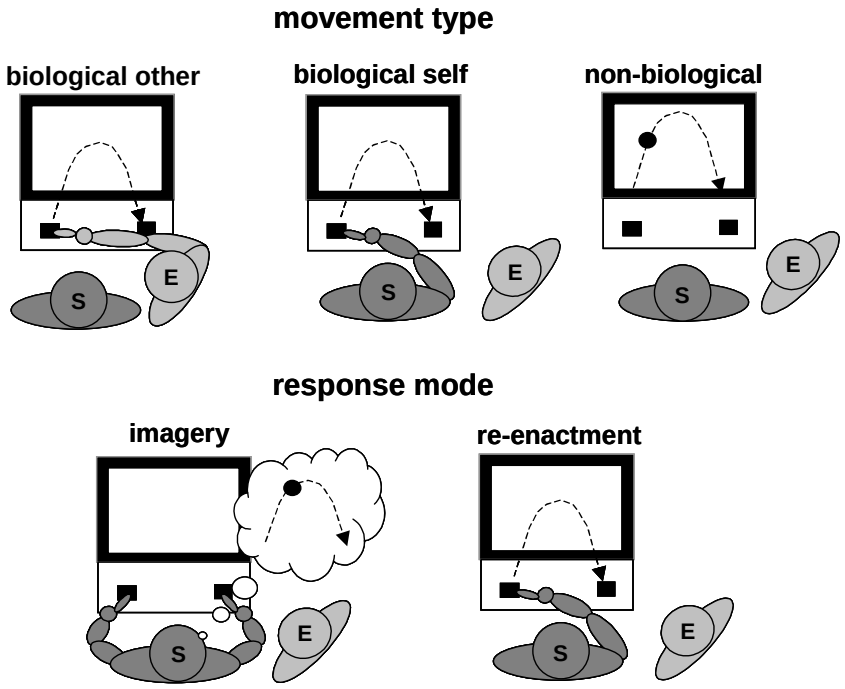


Fig 3. Schematic drawing of the experimental setup and the different experimental situations. Subjects (S) sat in front of a laptop with the experimenter (E) to their right. In the first part of each trial, subjects had to observe or execute one of three different movements (movement type, upper three panels) and immediately after to either imagine or re-enact the very same movement (response mode, lower two panels). *Biological other*: Demonstration of the movement by the experimenter. His index finger is on the start key and the dashed line indicates the movement's trajectory to the stop key. *Biological self*: Execution of the movement by the subject. *Non-biological*: Observation of a disk movement on the screen. *Imagery*: Mental simulation of the previously observed or executed movement. The subjects used both index fingers to indicate start and stop. *Re-enactment*: Re-enactment of the previously observed/executed movement.

Statistical Analysis for pilot study

Correspondence between the durations of the presented/executed and the related imagined movements were measured by the mean proportional error (MPE) calculated in each condition of each experimental session and all phases for each subject and compared respectively with schizophrenics' performance.

Statistical Analysis for longitudinal study

As different types of epilepsy affected patients, we analyzed data for each subject separately. Correspondence between the durations of the presented/executed and the related imagined movements was measured by the mean proportional error (MPE) calculated in each condition of each experimental session. A regression analysis was performed to determine possible correlations between absolute MPE values and temporal distance of the test sessions from the respectively preceding and succeeding seizure. The preictal and postictal delay of each behavioral test was defined as the time intervals between the administration of the test and the onset of the preceding seizure (postictal delay of test) as well as the onset of the subsequent seizure (preictal distance of test).

CONTROL

8. Control of epileptic seizures by means of Neurofeedback: the experimental set up

SCP self regulation

For three (C.B, D.M., C.V.) of four patients affected by epilepsy (described in detail, in paragraph 6.2 in Table 3) 30 training sessions were established, subdivided into a three-week phase of 20 sessions and a two-week phase of 10 sessions, respectively. Each session consisted of 145 trials and lasted about 90min. The two phases were separated by an eight-week phase during which the people were instructed to practice at home the strategies they had learned during the first training phase. During a training session, the patient' SCPs were recorded at the vertex (Cz), referred to as the average potential of the two mastoid electrodes measured separately. The time constant was set to 16s. Mean EEG amplitudes over 500ms intervals sliding with a 100ms moving average were presented as a moving cursor on a computer screen over a period of 8s in each trial. They were corrected on-line for blinks and verti. Each trial began with the presentation of the letter "A" or "B", chosen in a pseudo-randomized order, that served as a discriminative signal informing the subject whether the cortical potential should be changed to a negative ("A") or positive ("B") polarity compared to baseline (first 500 ms of each trial) (Fig.4B).

Fig. 4 The BCI system

A **B**

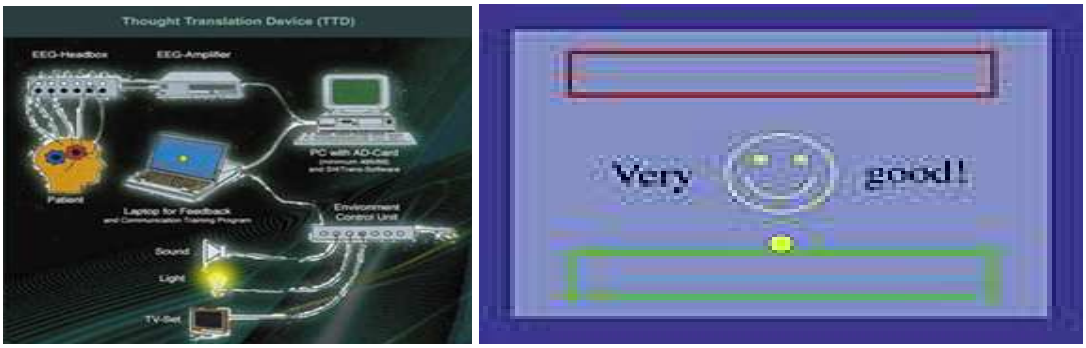


Fig. 4 (A**)** Basic design and operation of any BCI system. Signals from the brain are acquired by electrodes on the scalp, the cortical surface, or from within the brain and are processed to extract specific signal features (e.g., amplitudes of evoked potentials or sensorimotor cortex rhythms, firing rates of cortical neurons) that reflect the user's intent. (B) Features are translated into commando that operate a device. (drawings from Wikipedia Web Site).

Rightward movements of the feedback cursor indicated an SCP change in the required direction, and leftward movement changes in the opposite direction (i.e. a positive SCP shift, when negativity was required, or vice versa). After 8 s, the letter and feedback signal disappeared, indicating the end of the trial. Inter-trial intervals varied randomly between 2s and 5s. To assist the transfer of the acquired self-regulation skill to every day life, "transfer trials" were employed where the participants were prompted by the letters "A" and "B" but received no feedback .

RESULTS

9. PE as a suitable measure for detection of changes in vigilance states.

Since median AUC values diverge significantly from 0.5 (i.e. the value obtained when distributions are non-separable), results of ROC analysis indicate an efficacy of PE in seizure prediction. Interestingly, however, the correlation between PE and vigilance state was found to be significant in all three patients [Patient 1: rho=-0.6771; $p<0.001$; Patient 2: rho=-0.426; $p<0.001$; P3: rho=-0.6187; $p<0.001$]. Fig. 5c shows for one day EEG recording of Patient 1 the profile of PE and the corresponding vigilance states. In this figure, it can be observed that the seizure occurred when PE amplitude was consistently low; however, low values of PE amplitude corresponded also to low levels of vigilance, as the simultaneous evaluation of the vigilance states shows. Seizures tended to occur at the transition from low to higher levels of vigilance. These evidences suggest that in our patients PE could reliably detect oscillations of vigilance and transitions from one state to the other. Regarding seizure anticipation, PE did not provide false prediction, however, at present our data do not allow to demonstrate a specific sensitivity of PE for this task.

Fig. 5 Best AUC values determined for each channel of patient P1 under both hypotheses

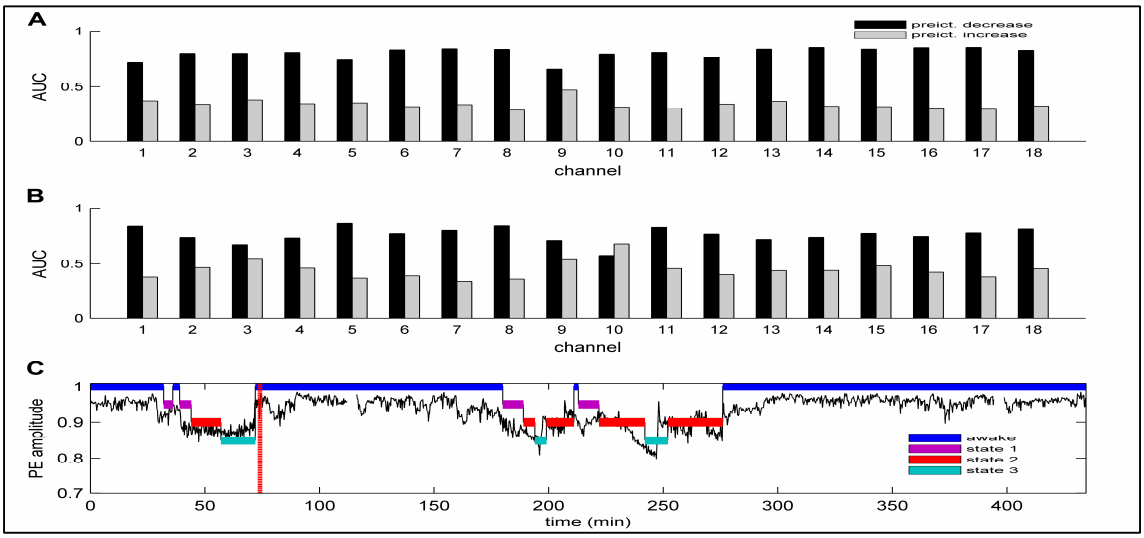


Fig. 5(**A**) Best AUC values determined for each channel of patient P1 under both hypotheses: preictal decrease [black bars] and preictal increase [gray bars] of PE. (**B**) Best AUC values for patient P2, visualized like in panel a. (**C)** Time profiles of PE amplitude and vigilance states shown for one day recording of patient P1. Black line represents the time profile of PE, while vigilance states are indicated by lines in different colours. Horizontal steps between different vigilance states are arbitrarily chosen to indicate their depth. The gray vertical line indicates the onset of one seizure.

9.1 Mental simulation task for seizure prediction.

Motor imagery task with Paranoid schizophrenics

The results applying motor imagery task in schizophrenics and healthy subjects are the followings Strong effects of movement type (healthy subjects: $F(2,9) = 63.442$, $p < .001$; schizophrenics: $F(2,9) = 92.550$, $p < 0.001$) and response mode (healthy subjects: $F(1,9) = 386.598$, $p < .001$; schizophrenics: $F(1,9) = 175.994$, $p < .001$), as well as a strong interaction between both factors (healthy subjects: $F(2,9) = 87.778$, $p < .001$; schizophrenics: $F(2,9) = 106.578$, $p < .001$) were present in both groups (Fig. 6). Post hoc testing (Bonferroni; $\alpha = 1\%$) in schizophrenic patients, showed no difference between the BSi and the BOi condition, but in both conditions MPEs were significantly larger than in all other conditions (NBi, NBr, BSr, BOr, in all cases $p < .001$). For healthy subjects, instead, MPEs were significantly larger in condition NBi compared to all other conditions (in all cases $p < .001$), whereas all other comparisons were not significant. Comparisons between group revealed significant differences ($\alpha = 1\%$) in all three conditions, in which the movements had to be imagined. Whereas in the NBi condition, the MPEs were larger in healthy subjects ($t(10.4) = -15.531$, $p = .001$), in the biological movement conditions, BSi and BOi, MPEs were larger in schizophrenic subjects (BSi: $t(9.7) = 10.816$, $p = 0.001$; BOi: $t(9.9) = 10.547$, $p = .001$).

Fig. 6 Mean proportional errors in healthy subjects and schizophrenics

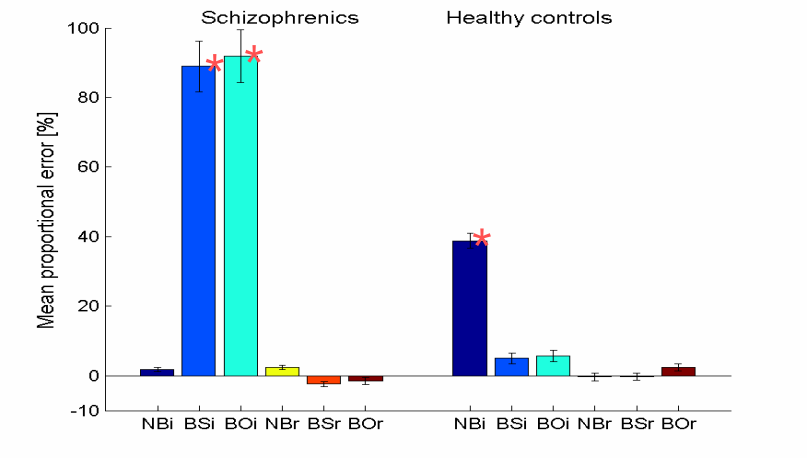


Fig. 6 Mean proportional errors in healthy subjects and schizophrenics. It has been shown both means and s.e. m. for all conditions. NBi: non-biological, imagined; BSi: biological self, imagined; BOi: biological other, imagined; NBr: non-biological, re-enacted; BSr: biological self, re-enacted; BOr: biological other, re-enacted.

The pilot study with epileptic patients

Performance of epileptic patients changed over the different phases. In the non-biological movement condition, the error was larger in the interictal as in the preictal phase (Fig. 7A; Table 3), while for the biological movement condition the opposite was found. The errors in both biological movement conditions were again smaller in the postictal phase 2 compared to the preictal phase. Intriguingly, in epileptic patients the effects depended on the patients' history. In the preictal phase the found effects were similar to that in schizophrenic patients, whereas in the interictal phase effects corresponded to that in healthy controls (Fig.7 A, B). The errors in both biological movement conditions were again smaller in the postictal phase 2 compared to the preictal phase. Intriguingly, the comparison between healthy subjects and epileptics showed the biggest differences for all three-movement conditions in the preictal phase (Table 4). In contrast, comparison between schizophrenics and epileptics revealed different errors in all conditions in the interictal phase, but no differences either for the error or for their variability in the preictal phase.

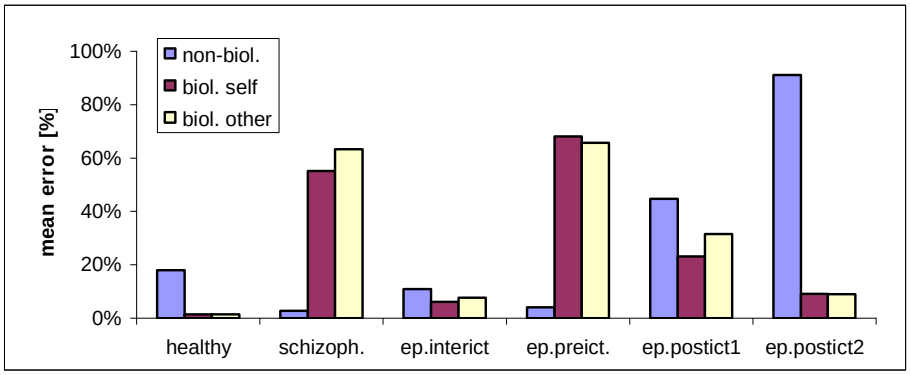
Table 3. Comparison of mean proportional error and standard deviation (SD) between different movement conditions and within the same subject groups and phases in epileptics.

Subject groups	Mean error			Mean SD		
	NB *vs* BS	**NB *vs* BO**	**BS *vs* BO**	**NB *vs* BS**	**NB *vs* BO**	**BS *vs* BO**
Hls.	<0.001 **	<0.001 **	0.868	<0.001 **	<0.001 **	0.225
Schiz.	<0.001 **	<0.001 **	0.499	<0.001 **	<0.001 **	0.832
Ep. interict	0.385	0.424	0.795	0.226	0.759	0.118
Ep. preict	0.009 **	0.0097 **	0.878	0.004 **	0.004 **	0.77
Ep. post 1	0.289	0.516	0.382	0.14	0.192	0.0096 **
Ep. post 2	0.067	0.06	0.967	0.213	0.311	0.077

Paired two-tailed t-test was used. Abbreviations: NB: non-biological movement; BS: biological movement, self; BO: biological movement, other; Hls: healthy subjects; Schiz: schizophrenics; Ep: Epileptics; interict: interictal phase; preict: preictal phase; post 1: postictal phase 1; post 2: postictal phase 2.

Fig. 7 Mean proportional errors and mean standard deviations in the different movement conditions, and subject groups.

A



B

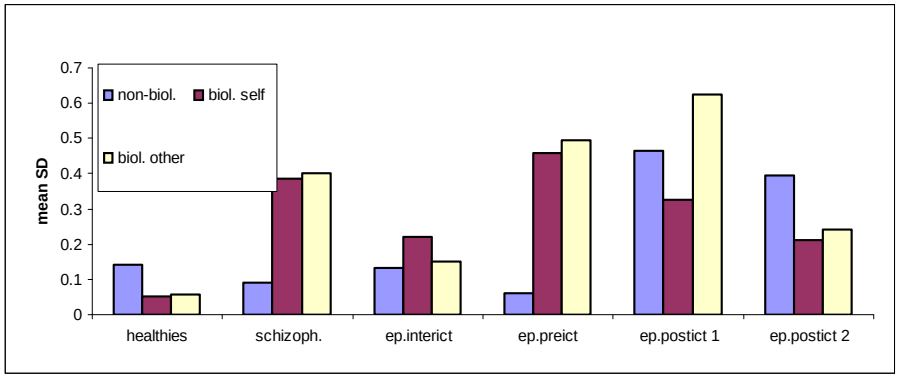


Fig. 7(A) Mean proportional errors and (B) mean standard deviations in the different movement conditions, and subject groups: healthy controls, schizophrenics and epileptics in four different phases of epilepsy (interictal, preictal, postictal 1 and 2).

Table 4. **Comparison of mean proportional error and standard deviation (SD) between different subject groups and phases in epileptics**.

Comparisons	Mean error			Mean SD		
	NB	**BS**	**BO**	**NB**	**BS**	**BO**
Hls. *vs* Schiz.	<0.001 **	<0.001 **	<0.001 **	0.068	<0.001 **	<0.001 **
Hls. *vs* Ep. interict	0.046 *	0.095	0.018 *	0.864	0.031 *	0.019 *
Hls. *vs* Ep. preict	<0.001 **	0.006 **	0.008 **	0.002 **	0.003 **	0.004 **
Hls. *vs* Ep. post 1	0.146	0.132	0.069	0.038 *	0.001 **	0.002 **
Hls. *vs* Ep. post 2	0.093	<0.001 **	0.049 *	0.116	<0.001 **	<0.001 **
Schiz. *vs* Ep. interict	0.03 *	<0.001 **	<0.001 **	0.434	0.041 *	<0.001 **
Schiz. *vs* Ep. preict	0.277	0.392	0.872	0.308	0.382	0.289
Schiz. *vs* Ep. post 1	0.047 *	0.048 *	0.058	0.023 *	0.321	0.038 *
Schiz. *vs* Ep. post 2	0.057	<0.001 **	<0.001 **	0.072	0.005 **	0.001 **
Ep. interict *vs* Ep.preict	0.013 *	0.012 *	0.01 *	0.151	0.052	0.003 **
Ep. interict *vs* Ep. post 1	0.114	0.244	0.148	0.089	0.248	0.009 **
Ep. interict *vs* Ep. post 2	0.087	0.277	0.756	0.186	0.874	0.04 *
Ep. preict *vs* Ep. post 1	0.06	0.029 *	0.151	0.027 *	0.028 *	0.408
Ep. preict *vs* Ep. post 2	0.064	0.008 **	0.013 *	0.074	0.033 *	0.031 *

Two-tailed heteroschedastic t-test was used for between group comparisons and two-tailed t-test for repeated measures for comparisons between different epileptic phases. Abbreviations like in table 3.

The longitudinal study: Reliability of the motor imagery task for prediction of seizures motor imagery task.

For each patient the means of all MPE values resulting from all test sessions in the different experimental conditions are reported in table 5. The ranges of temporal distances of the test sessions from the next preceding/succeding seizure are indicated as well. Correlations were found in subject 1 between the distance of test sessions to the succeeding seizure and MPEs resulting for conditions NB (F (1,16)=33.74; p<0.01; ß=0.82) and BO (F (1,16)=5.18; p=0.04; ß=-0.49). Likewise, in patient s2 a correlation was found between the distance of test sessions to the succeeding seizure and MPE values, but only in condition NB (F (1,15) =8.43; p=0.01; ß=0.6). No correlations were found both in patients s3 and s4. For the both patients, s1 and s2 MPEs were plotted against the preictal delay of test (Fig. 9). These graphs show that MPEs in condition NB were smaller in both patients when the behavioral test was closer to the forthcoming seizure. Moreover, in patient s1, MPEs were bigger in the condition BO when the behavioral test was closer to the next seizure (Fig. 8A). Although the latter finding could be shown to be statistically significant only in condition BO, the same tendency seemed to be present also in condition BS (Fig. 8A).

A further inspection of the MPE values in the condition NB revealed for the two patients s1 and s2 a clear separation of the ranges spanned by MPE values resulting from test sessions being close to a forthcoming seizure and values being measured with bigger distance to the next following seizure. A threshold in the two graphs in figure 9 indicates this segregation. However, test sessions were always conducted at the same time of the day and frequency of seizure occurrence was particularly high for certain phases of the circadian cycle. Hence, there was a gap of some hours between the population of small MPEs and that of large MPEs. Consequently, the duration of the preictal phase associated with reduced MPEs in the condition NB could not be determined definitively. Nevertheless, the gap between the two populations of MPEs allowed deducing that the preictal phase lasts at least 8 hours in patient s1 and 3.25 hours in patient s2. The means were calculated separately for all MPE values falling within this minimum preictal phase and those being measured outside this phase (see table 5).

Table 5. **MPE values resulting from all test sessions (ALL) in the different experimental conditions.**

PZ.	PHASE	NB	BS	BO	AFTER SEIZURE (h)	BEFORE SEIZURE (h)
S1	ALL	13.46 (3.92)	29.32 (5.95)	38.03 (7.13)	16 - 304.5 (18; 72.5; 17.1)	3.8 – 264 (18; 55.5; 13.1)
	PREICTAL	0.98 (0.19)	38.29 (8.63)	53.09 (9.02)	16.5 – 304.5 (11; 59.3; 17.9)	3.8 – 8 (11; 6.7; 2)
	INTER-/POSTICTAL	33.08 (2.66)	15.21 (2.95)	14.37 (2.17)	16 – 208.5 (7; 98.8; 37.3)	30 – 264 (7; 132.1; 49.9)
S2	ALL	15.61 (2.39)	16.69 (4.21)	33.62 (3.61)	10 – 143(17; 57.2; 13.9)	0.5 – 104 (17; 39.7; 9.6)
	PREICTAL	2.46 (0.74)	30.07 (10.13)	29.19 (4.96)	10 – 82 (5; 57.7; 25.8)	0.5 - 3.25 (5; 1.4; 0.6)
	INTER-/POSTICTAL	21.09 (1.55)	11.11 (3.38)	35.47 (4.70)	10 – 143 (12; 57; 16.4)	23 -104 (12; 55.7; 16.1)
S3	ALL	22.35 (5.21)	44.07 (8.64)	47.55 (9.78)	18 – 209 (18; 71.5; 16.9)	1.8 - 189.5 (18; 52.6; 12.4)
S4	ALL	35.48 (4.80)	42.02 (13.88)	41.13 (12.18)	9 – 95 (18; 45.3; 10.7)	1 – 100 (18; 44.4; 10.5)

All conditions (columns NB, BS, BO) were averaged for each patient (S1, S2, S3, S4). Standard errors are indicated in brackets. In addition, for patients S1 and S2, means were calculated for MPE values resulting from test sessions within preictal phase (PREICTAL) and interictal/postictal phases (INTER-/POSTICTAL). Range of temporal distances of test sessions from the preceding (AFTER SEIZURE) and succeeding seizure (BEFORE SEIZURE) are indicated in hours (h). In brackets, the number of test sessions, as well as mean and standard error of temporal distance of test sessions to seizures are indicated.

Fig. 8 MPE values of patient s1 and patient s2 plotted against the temporal distance of test sessions from next forthcoming seizure (preictal distance).

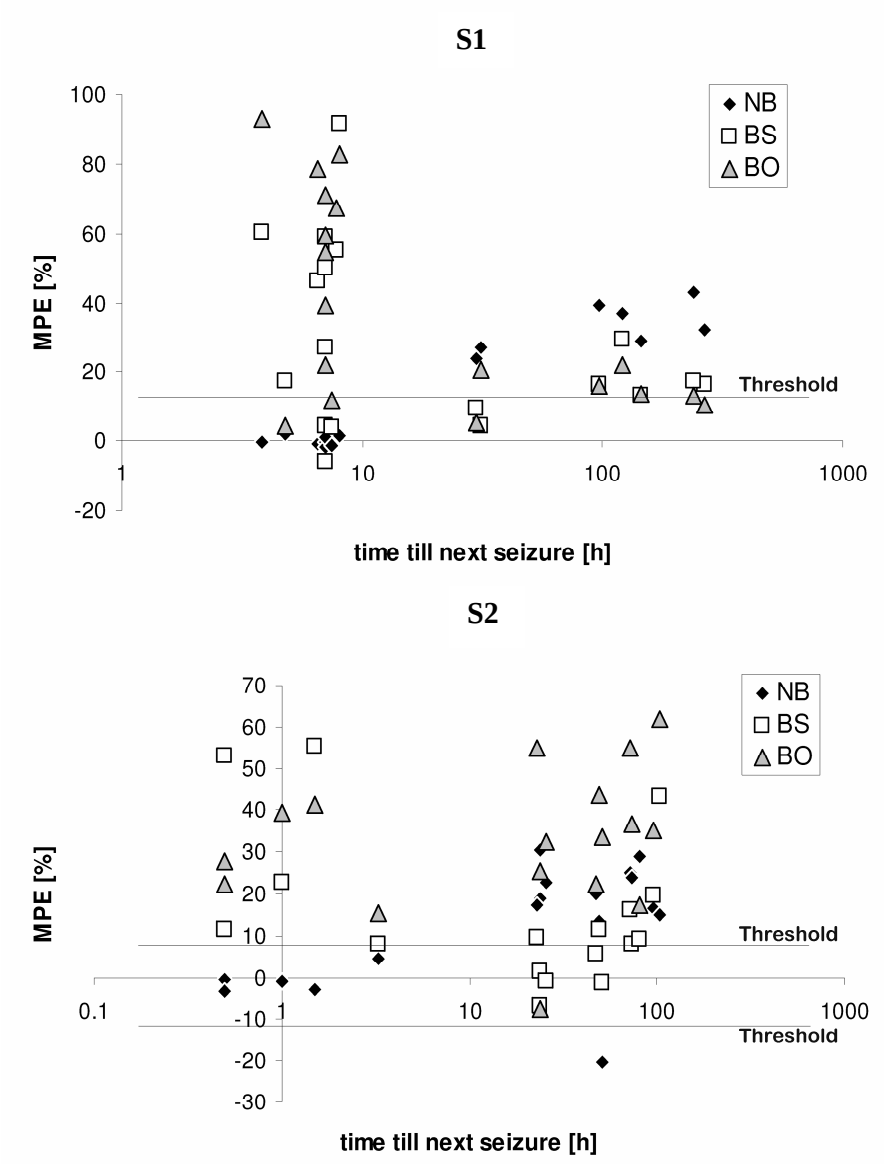


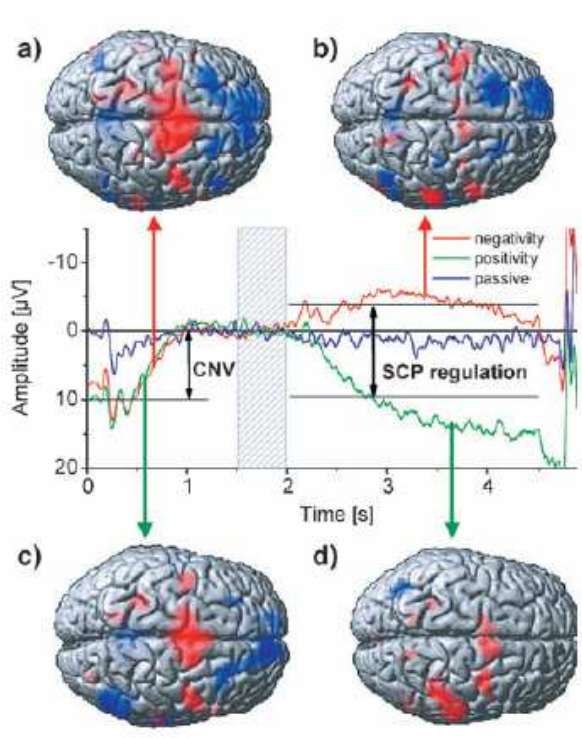
Fig. 8. MPE values of patient s1 and patient s2 plotted against the temporal distance of test sessions from next forthcoming seizure (preictal distance). Thresholds indicate the segregation between small/large MPE values being measured with short/long distance to the next upcoming seizure.

9.2 Modulation of slow cortical potentials in epilepsy.

Analysis of electroencephalogram data

The percentage of SCP shifts in the correct polarity (percentage of correct responses) served as performance measure for SCP selfregulation. The effect size of the SCP differentiation provided an additional measure defined by the difference of the mean potential during all trials from the task to produce a positive potential shift and the mean of all negativity tasked trials normalized to the SD. While the percentage of correct responses expresses the precision of the potential shifts in the desired direction, the effect size expresses the ability to create different potentials. Usually both measures are highly correlated ($r > 0.9$). One sample t-tests (one-tailed) were performed on the percentage of correct responses to test for them being significantly greater than 50%. The SCP shifts were tested for being greater or smaller than zero depending on the expected polarity.

Fig. 9. Task-specific grand average of electroencephalogram (EEG) and the corresponding blood oxygen level-dependent (BOLD) activation maps.



The grand average of the EEG signal over all trials of all subjects is shown for the feedback electrode (Cz vs. mastoids) in one of the 3 patients trained. Five seconds of a trial are depicted separately for each task condition. Each condition contains about 900 trials of unfiltered EEG. The 'no-task' reveals no significant slow wave changes as expected. Due to the task presentation at the beginning of the trial a contingent negative variation (CNV) of about 10 lV emerged until the feedback started. After the imperative auditory signal (at second zero) the patients were required to produce a self-controlled potential shift of 13 lV between the negativity and positività task. The corresponding BOLD activation patterns are illustrated in the four brains. Red areas indicate higher BOLD activation in the task vs. the no-task condition. The riverse contrast is depicted in blue. The left two brains illustrate the A scan which represents the preparatory interval of the trial where the CNV is seen in the neuroelectric response. The right two brains represent the BOLD response during feedback of the B scans.
The upper brains contain only trials with the negativity task whereas the lower graphs show the brain response for the positivity task. (from Hinterberger *et al.* 2003).

Fig. 10 Slow cortical potential during training of self-regulation

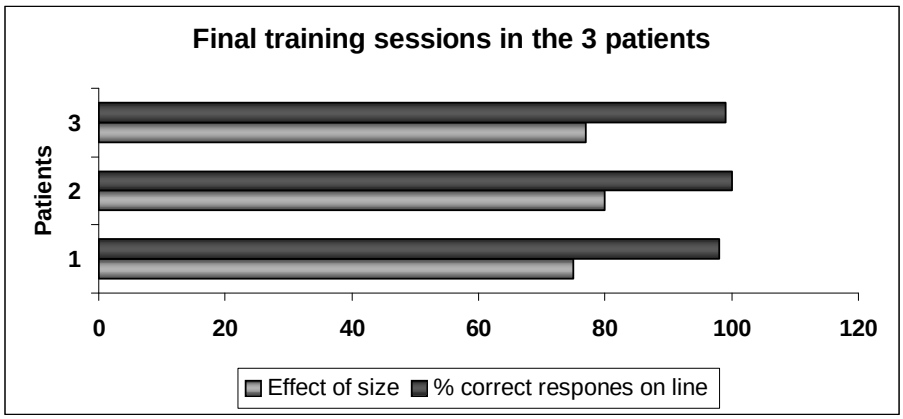


Fig. 10 Slow cortical potential during training of self-regulation The individual participants' SCP regulation performance. On the last training day the average online correct response rate was 77.3% for the whole group ($t_{2,\ 0.67}$ =4.4, p< 0.01, one tailed). The average effect size of the SCP differentiation between the negativity and positivity task served as an alternative measure for the SCP regulation skill. The last training session resulted in a significant mean effect size of 0.77 over all three subjects ($t_{2,\ 3.6}$ p < 0.01).

As can be seen in the table 6 above, the seizure rate changed between baseline and 6 month-follow-up phase (only in the patient s1 was not significant), but there was a decrease both in patients s2 and s3.

Table 6. Number of seizures for month in the three patients (s1, s2, s3). Pre, during the 6 month period before the beginning the NF treatment; post , during the 6 month-follow-up phase.

Patients	Pre	post
S1	18	16
S2	7	2
S3	6	0

In this two patients s2 and s3, there was a significant decrease of the overall seizure rate (Wilcoxon test with raw data, all tests were two tailed): p = 0.032; t test with logarithmic data: t = 4.03, p = 0.051, as well as the rate of simple partial seizures (Wilcoxon test with raw data: p = 0.044; t test with logarithmic data: t = 2.75, p = 0.023).

Personality variables

As compared with the baseline phase, all patients after treatment were less depressive (MMPI scale: $p = 0.077$; Beck Depression Inventory, $p = 0.098$). Further, at the end of the therapeutic program, all patients were better able to use relaxation for coping with stress ($p = 0.046$), and less able to recognize similarities between the actual stress situations and those that already occurred in the past ($p = 0.54$). Similarly, the tendency to extrapunitive responses to stress significantly decreased ($t = 3.11$, $p = 0.042$) in patient s1 and s3 only, leading to a marginally significant Patients × Time interaction ($F(3.72, 82.42) = 2.37$, $p = 0.063$).

Reported strategies

All of three participants reported using thoughts and mental imagery to control their brain responses. For the negativity task motor imagery or imagination of several emotional situations was reported most frequently. Most subjects reported the use of relaxing imagery for creating positive SCP shifts.

DISCUSSION AND CONCLUSION

10. Better Prediction Could Mean Better Control over Epileptic Seizures

Aim of my research was to establish whether PE is a sensitive method for seizure-prediction and for the detection of fluctuation of vigilance states. The ROC analysis showed a good separability of interictal and preictal phases for both patients, suggesting that PE could be sensitive to EEG modifications, not visible on visual inspection, that might occur well in advance respect to the EEG and clinical onset of seizures. However, the simultaneous assessment of the changes in vigilance showed that: a) all seizures occurred in association with the transition of vigilance states; b) PE was quite sensitive in detecting vigilance fluctuations, independently by the occurrence of seizures. Hence, the good separability between pre- and interictal phases might depend exclusively on the coincidence of epileptic seizure onset with a transition from a state of low vigilance to a state of increased vigilance. Since all our seizures occurred during vigilance transitions, it could be suspected that PE in our cases detected simply vigilance instead of changes in seizure onsets. Therefore, at variance with a recent report (Schelter *et al.,* 2006), PE algorithm did not provide false negatives; indeed, what emerged from our analysis is that PE seems to be sufficient specific to discriminate fluctuations of vigilance; its capability to identify preictal states cannot be definitely ruled out, since in our patients we did not obtain seizures onsets independent from vigilance transitions. Changes in EEG dynamics in the preictal state, preceding seizure onset by minutes or hours, have been reported (Lehnertz & Elger, 1998; Le Van Quyen *et al.,* 2001; Litt & Echauz, 2002). Moreover, sleep is largely reported to modulate epileptic EEG activity and epileptic seizures occurrence (Billiard, 1982; Crespel et al., 1998). However, the issue of the relationships between preictal EEG changes and vigilance transitions has been rarely addressed. In fact it might be that preictal EEG variations are associated more often than expected with fluctuations of alertness, drowsiness or even sleep.

In addition, in previous studies, it is possible that inclusion criteria that excluded a certain amount of seizures and interictal EEG data, and that required a stable level of vigilance might have introduced several biases that render difficult to establish the reliability of the different algorithms in a clinical setting. In a study combining analysis of the preictal state by similarity measure and visual inspection of EEG to detect seizure onset and changes of vigilance, it has been reported that preictal EEG modifications, identified by the seizure prediction algorithm, were visually detectable in about 79% of electroclinical seizures (Navarro *et al.,* 2005); however, 81,5 % of preictal dynamic

changes were correlated with vigilance transitions or behaviour modifications; in addition, sometimes, fluctuations of the dynamics were not necessarily followed by seizures.

This quite striking relationship between preictal state and vigilance changes was interpreted postulating that the preictal state might be related to physiologic variations: as in reflex epilepsies (Lopes da Silva *et al.*, 2003), a diffuse physiologic change, such as a vigilance transition may induce a dynamic change that might trigger the sudden onset of the ictal state.

According to this hypothesis, preictal physiologic variations might represent a "facilitating state", in which the probability that a seizure may occur is higher. If this interpretation were proved to be correct, it could be helpful to reliably detect "higher probability states for seizure occurrence" (such as changes of vigilance), although without being able to accurately predict the seizure onset.

The study suggests that PE could satisfy this requirement. In addition, the dependency of PE on vigilance states is an original finding, not described for other algorithms reported in the literature.

In fact, most of the algorithms used, do not specifically distinguish pathologic from physiologic preictal variations, and the lack of data on the specificity of these methods limit their clinical applicability to the patients. It should be highly desirable that seizure prediction strategies should be insensitive to circadian physiologic changes.

In conclusion, PE is suggested as a strong tool to classify vigilance states in an automated and objective way. However, at present, the dependency of PE on the vigilance state restricts its possible application for seizure prediction and future work has to be done to clarify the origin of PE changes in the preictal phase.

10.1 A common behavioral side of paranoid schizophrenia and temporal lobe epilepsy: Could motor imagery be a key for seizures prediction?

The behavioral test employed in the longitudinal study revealed the presence of phase dependent changes in mental simulation of biological and non-biological movements in the two RTLE patients. This phase dependency makes effects particularly reliable, as there is no possibility to explain findings by the effects of anti-epileptic drugs. The same dose of drugs was assumed each day and always at the same time. In both RTLE patients timing precision during simulation of non-biological movements increased in the temporal vicinity of a forthcoming seizure (both in patients s1 and s2), while the timing precision during simulation of biological movements decreases near to the upcoming seizure (only in patient s1). As I recently reported (Bruzzo *et al.*, 2007), schizophrenic patients showed large errors in the same task, when simulating biological movements. However, they were almost perfect and significantly better than healthy subjects, when simulating non-biological movements. Hence, when comparing to these recent findings, the two studied RTLE patients showed a strong similarity to the behavioral performance of schizophrenic patients in the preictal phase, while being more similar to healthy subjects in the interictal phase. This similarity was particularly evident for the non-biological movement condition.

Although no phase dependent changes could be found in the two patients, s3 and s4, it is interesting to note that in these two subjects the timing errors were on average remarkable large in the biological movement conditions (mean MPE > 40% in all cases, see Table 5). This means that, similar to schizophrenic patients, the timing precision was reduced in simulation of biological movements, but in a phase-independent way. A correlation between the MPE magnitude and the temporal distance to the preceding seizure could not be found in any of the patients. This finding could have been due to the fact that sessions were in no case closer then 9 hours to the preceding seizure. This in turn could have been due to the fact that sessions were scheduled everyday at the same time, while seizures didn't occur with the same probability over the cycle of the day.

The differences found between the patients could be due to the different types of their epilepsy. Both, phase dependent changes in performance and very precise timing in simulating non-biological movements were found only in the two subjects with RTLE, but not in the patients with generalized epilepsy and with idiopathic epilepsy. These differences between types of epilepsy should be studied more in detail in future studies recruiting a bigger sample of subjects.

Also, varying the time of test administration over the day or even repeating it several times over the day should test the presence of postictal changes in performance.

However, this study shows certain similarities between the performance of all tested epileptic patients and that of schizophrenic patients, tested in my recent study (Bruzzo *et al.,* 2007). The increased timing error during motor imagery in the epileptic patients could be explained similarly as in the schizophrenic patients by disturbed forward models for the simulation of the effects of motor plans (Jeannerod, 1995). This finding could also explain the presence of symptoms like illusions of agency (Blakemore *et al,* 2002; Frith *et al*., 2000; Frith & Done, 1989) during psychotic episodes in epilepsy (Sachdev, 1989; Taylor, 2003; Trimble, 1977**;** Umbricht *et al.,* 1995). Even more intriguing is the finding of enhanced timing precision during simulation of non-biological movements in the preictal phase in the two RTLE patients. Already in the recent study on schizophrenia, an enhanced precision during mental simulation of non-biological movements was found.

The recurrence of this effect in epileptic patients, in which the tendency of having psychotic episodes is an often reported finding (Sachdev, 1989; Taylor, 2003; Trimble, 1977**;** Umbricht *et al.,* 1995), suggests that these effect reflects changes in brain state being important for the genesis of psychotic symptoms. Further, the performance in the non-biological movement condition was more predictive for an impending seizure then changes in the other conditions.

10.2 Seizure reduction by SCPs Neurofeeback

The hypothesis of a large decrease of number of seizures succeeding the application of SCPs self-regulation training in all three patients has been tested in the second part of my research project. This hypothesis was only partially supported. Firstly, the achievement of statistically significant SCP control during the first training sessions by none of the patients indicates their particular difficulties in SCP self-regulation. The corresponding ability was significantly enhanced during training (linear trend: $p = 0.04$). For patient s1 the seizure rate did not change between the baseline phase and the follow-up in the RES group, but there was a decrease in patients s2 and s3. No difference was found in the magnitude of seizure decrement after treatment between the SCP and the waiting list patients. Anyway the optimistic result on patients s 2 and s3 may indicate that, even though the SCPs training did not surpass the new drug therapy, SCPs self-regulation treatment can be recommended for patients who have excessive side effects or do not respond to medication. Negative side effects do not exist in psychophysiologic treatment methods such as the one used. Moreover, the changes in cognitive and personality variables observed in the course of treatment could explain the positive dynamics of seizures in patient s2 and s3. The decrease of depressive tendencies, the shift of control attributions from "powerful others" toward more internality, and the

increasing ability for relaxation response in stress conditions all indicate positive changes in the patients' psychologic state. It may be suggested that they are the result of positive therapeutic interactions, which were, albeit in quite different forms, realized in all three groups. Other psychological changes differed between patients.

These differences could be explained by (a) mood and personality changes reflecting differential placebo effects; or (b) differences in the initial prebaseline level of the corresponding variables. If (a) is correct, larger before-to-after changes in placebo variables such as positive expectations would be observed in all patients. This was not the case, though. The option (b) may be correct for the external locus of control variable. Although all patients demonstrated similar tendencies to more internality, less chance, and powerful others control over time, these changes were more manifested in patients s2 and s3. To summarize, this psychological improvement and increased emotional stability were only an unspecific by-product of the attention experienced in a treatment regimen using positive interaction with the therapists; they were not related to the reduction of seizures. Therefore, the differential clinical effect seems to be independent of the dynamics of the psychological variables.

10.3 Running the future: full self-management of seizures.

The results obtained by the behavioral paradigm developed by Bruzzo *et al.*, 2007, for seizure prediction in RTLE patients, encourages the use of a simplified form based only on the non-biological condition. With this simplification the test could easily be applied by the patient, without any supervision, in order to assess the risk of seizure occurrence within hours in advance. Due to its simplicity and briefness, the test could be applied even repeatedly over the day and in the case of an alarm the subject would have enough time to counteract the underlying changes in brain state or to avoid dangerous situations.

Future research, recruiting larger samples of patients and including different types of epilepsy, should assess the value of the test in seizure forecasting in different types of epilepsy.

10. 4 Summary and outlook.

In this thesis I firstly report that, the changes of PE occur during the preictal phase and at seizure onset coincided with changes in vigilance state, restricting in this way, its possible use for seizure prediction on scalp EEG data extremely, even if it is encouraging for an automated classification of vigilance states.

Secondly, using a novel mental imagery paradigm on paranoid schizophrenics in comperison of a healthy control group, I give strong evidences for the existence of dissociation in timing of biological and non-biological movements. Furhter, applying the same task on a small sampleof epileptic patients, I describe a severe impairment of interval timing for biological movements, similarly in paranoid schizophrenic patients closely before a seizure coming (preictal-state) only. Nevertheless, I note that interval timing for non-biological movements is extremely precise in the two patients' groups. I interprete deficits in mental imagery as a consequence of impaired forward models.

Finally, the novel behavioural paradigm described in these pages being able to detect a transitory similarity in performance between epileptic patients before a seizure and in paranoid schizophrenics, emerges for the first time as a reliable a seizures prediction method on a purely behavioural level.

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APPENDIX A

BIOGRAPHICAL SKETCH

Birth date: 27/08/1979

Birth place: Turin (Italy)

Citizenship: Italian

Languages: Italian, English, German.

Hobbies: Swimming, Nordic Walking.

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From January 2005 to December 2007 - PhD. candidate - III ys' PhD. Program in General and Clinical Psychology-option address Experimental. Ph.D. dissertation on "*Seizure prediction and control in epilepsy*". Supported by a MIUR grant.

15/03/2004 -14/09/2004 Practicum in Experimental Psychology at the Institute of Medical Psychology and Behavioral Neurobiology of Tuebingen- Germany. Supervisor: Prof. Dr. Niels Birbaumer

15/09/2003-14/03/2004 Practicum in Clinical Psychology at the Institute of Neuroscience in Florence. Supervisor: Prof. Dr. Pallanti Stefano.

July 10th 2003: Master degree in Psychology- *summa cum laude*. Supervisor Prof. Dr. Vittorio Gallese (Full Professor in Human Physiology-Faculty of Medicine - University of Parma, Italy) Experimental Thesis in Neurophysiology.

1998-2003: V years' Academic program in Psychology-University of Parma.

1993-1998: V years' Academic Scientific High School.

APPENDIX B

LIST OF PUBLICATIONS

1. **Bruzzo**, A, Gesierich, B., & Wohlschlaeger, A. (2007). *Simulating biological and non-biological motion.* Brain and Cognition. (in press).

2. **Bruzzo**, A. (2007). *The chaotic nature of Self.* Dialeghestai online. Rivista telematica di filosofia.

3. **Bruzzo**, A., & Vimal, R.L.P. (2007). *Self: An adaptive pressure arising from self-organization, chaotic dynamics, and neural Darwinism.* Journal of Integrative Neuroscience. 6(4): 541-566.

4. **Bruzzo**, A., Gesierich, B., Santi, M., Tassinari, C.A., Birbaumer, N., & Rubboli, G.(2007). *Permutation Entropy to detect vigilance changes and preictal states from scalp EEG in epileptic patients. A preliminary study*. Revisions being processed in Neurological Sciences.

5. Gesierich, B., **Bruzzo**, A., Ottoboni, G., & Finos, L. (2007). *Human gaze behaviour during action execution and observation.* Revisions being processed in Acta Psychologica.

6. **Bruzzo, A.,** Gesierich, B., Rubboli, G., & Vimal, R.L.P. (2007). *Predicting epileptic seizures by a mental imagery task: a preliminary study.* Submitted.

7. **Bruzzo**, A., Borghi, A.M., & Ghirlanda, S. (2007). *Hand-object interaction in perspective.* Submitted.

POSTERS

1. Singapore, 8-12 June 2007. 27th International Congress of Epileptology, *Prediction of epileptic seizures by means of behavioural task.* **Bruzzo**, A., Gesierich, B., Rubboli, G., Tassinari, C.A. & Birbaumer, N. published in *Epilepsia Suppl.48 p516*

2. Rovereto, 19 April 2007. *Human gaze behaviour during action execution and observation,* Gesierich, B., **Bruzzo**, A., Ottoboni, G. & Finos, L.

3. Helsinki, 2-9 July 2006. 7th European Congress of Epileptology, *Seizure prediction algorithm is sensitive to changes in vigilance states.* **Bruzzo**, A., Gesierich, B., Rubboli, G., Tassinari, C.A. & Birbaumer, N. published *in Epilepsia Suppl 47.*

4. Canberra, 2-9 June 2006. The Australian National University, AAP 2006*, The chaotic nature of Self.* **Bruzzo**, A.

5. Cagliari, 18-22 September 2005. Associazione Italiana di Psicologia-Sezione sperimentale *Dare un senso alle azioni*. **Bruzzo**, A., Borghi, A.M. & Ghirlanda, S.

6. Tucson, Arizona, 4-8 April 2005. Centre for Consciousness studies, *The chaotic epigenesis of Self.* **Bruzzo**, A. Published on line.

7. Freiburg im Breisgau, 23 April 2004. Neurocortex- Meeeting. *Extracting behavioral components by data segmentation from multineuronal recordings in the premotor area (F4/F5)* Krüger, J., Engel, B., Dalla Volta, R., Grammont, F., Intskirveli, I., & **Bruzzo, A.**

8. Roma, 5-8 December 2003. Società Neurologica Italiana. *Multidimensional Scaling analysis: a prospective to clusterise mirror neurons.* Krüger, J., Dalla Volta, R., Engel, B., Grammont, F., & **Bruzzo**, **A.**