AUTOMATED MONITORING OF EEG BACKGROUND AND EPILEPTIFORM ACTIVITY WITH SPECIAL REFERENCE TO ANTIEPILEPTIC DRUG TREATMENT

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1. Contents

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3. Abbreviations and terminology

ADHD	Attention - deficit - hyperactivity disorder
AED	Antiepileptic drug
AMF	Alpha mean frequency
ASD	Autism spectrum disorder
ASF	Automated alpha frequency determination by Short segment Fourier transform
ATD	Automated alpha frequency determination in Time Domain
AWF	Automated alpha frequency determination by Whole recording Fourier transfor
BRAC	Basic rest-activity cycle
CBZ	Carbamazepine
cm	Centimeter
CPT	Continuous performance test
CSD	Current source density
CSWS	Continuous spike wave during slow sleep
CV	Coefficient of variation
CZP	Clonazepam
DBS	Deep brain stimulation
DC	Direct current
DFT	Discrete Fourier transform
ECD	Equivalent current dipole
EEG	Electroencephalography
EPSP	Excitatory postsynaptic potentials
ERD	Event related desynchronization
ERS	Event related synchronization
ESES	Electric status epilepticus during sleep Encephalopathy with status epilepticus during sleep
ESI	Electric source imaging
FFT	Fast Fourier transform
fMRI	Functional magnetic resonance imaging
FMT	Frontal midline theta
FNEA	Focal nocturnal epileptiform activity
GABA	γ-aminobuteric acid
HV	Hyperventilation
Hz	Herz
IED	Interictal epileptiform discharges
IFSECN	International Federation of Societies for Electroencephalography and Clinical Neurophysiology
ILEA	International League Against Epilepsy
IPSP	Inhibitory postsynaptic potentials

ISI	Inter spike interval
LAURA	Local autoregressive averaging
LEV	Levetiracetam
LKS	Landau-Kleffner syndrome
LORETA	Low resolution brain electromagnetic tomography
LTG	Lamotrigine
LTM	Long term monitoring
MEG	Magnetoencephalography
MNI	Montreal neurological institute
MRI	Magnetic resonance imaging
ms	Millisecond
MST	Multiple subpial transections
MUSIC	Multiple signal classification
NMR	Nuclear magnetic resonance
NREM	Non rapid eye movement (sleep stages)
OXC	Oxcarbazepine
P	Macropotential
PAF	Peak alpha frequency
PCA	Principal component analysis
PET	Positron emission tomography
r	Dipole vector location
REM-sleep	Rapid eye movements-sleep (dream sleep)
ROI	Region of interest
s	Macropotential
SD	Standard deviation
SI	Spike index
SMAC	Spherical head model with anatomical constraints
t	Time
TCI	Transitory cognitive impairment
TDM	Therapeutic drug monitoring
TPM	Topiramate
VPA	Valproate
VFT	Visual detection and alpha determination through Fourier Transform
VMC	Visual detection and Manual Counting of alpha activity
w	Micro current vector
W	Tissue volume
α	Alpha band (8 Hz - 13 Hz)
β	Beta band (13 Hz - 30 Hz)
γ	Gamma band (30 Hz - 100 Hz)
δ	Delta band (0.5 Hz - 4 Hz)
θ	Theta band (4 Hz - 8 Hz)

Θ	Heaviside function

4. General introduction

Electroencephalography (EEG) is the only direct method for assessing brain activity of patients in clinical settings. EEG is mainly used in repeated brief recordings, typically lasting 20 minutes, resulting in short samples for assessing brain functions in disease and especially in epilepsy (Deuschl and Eisen, 1999; Mendez and Brenner, 2006; Noachtar and Rémi, 2009). However, there is an increased use of long-term EEG monitoring (LTM), lasting hours or days, often with synchronous video recording. LTM is used for diagnostic purpose (Wada and Rasmussen, 1960; Engel Jr et al, 1993), for monitoring acutely ill patients, surgical and anaesthetic procedures (Lopez, 1996; Lavine et al, 1997) and in the presurgical investigation in epilepsy. EEG has been a mandatory procedure in the follow up of patients with epilepsy and is used as a predictor of outcome in antiepileptic drug (AED) discontinuation (Shinnar et al, 1994). In epilepsy EEG is also used in monitoring variations in patients' disease and cerebral effects and side effects of AED intake. The EEG parameters used in the follow up of epilepsy patients have been related to the amount of interictal epileptiform discharges (IED) (Gotman and Gloor, 1976), increase in amount of slow activity (Niedermeyer and da Silva, 2005), and to a lesser extent, changes, mainly slowing, in background activity. Automatic assessment and quantification of EEG indicators in patients with epilepsy have only to a limited extent been used in clinical practice.

In the later years there has been an increased acceptance of IED, for instance in continuous spike wave activity during slow sleep (CSWS) as an importance element in genesis of cognitive impairment (Bureau, 1995; Casas-Fernandez et al, 2002; Holmes and Lenck-Santini, 2006; Tassinari et al, 2009). Attempts have been made to relate the degree of cognitive impairment to the amount of IED during sleep (Tassinari et al, 1985). However, published works have not or very superficially defined how to assess the amount of spikes or the influence of the spikes on the brain.

This thesis is a part of ongoing work to enhance the available EEG toolbox for clinical use by automated monitoring of both background activity and epileptiform activity, with special reference to AED treatment in patients with epilepsy and in patients with subclinical epileptiform activities.

4.1 EEG

The EEG is the applied method for assessing brain function in this thesis.

4.1.1 History

The first EEG recordings were reported in 1875 by Richard Caton and published in British Medical Journal in 1877 (Caton, 1875; Caton, 1877). The recordings, which were done in rabbits and monkeys, were accomplished by a galvanometer reflecting a light beam on to the wall. About 50 years later, Hans Berger in 1929, reported the first human EEG (Berger, 1929). He described different background entities and even activity seen during a tonic-clonic seizure. EEG has been a clinically applied method since. Berger probably recorded the first epileptiform potentials, but later he discarded the findings (Brazier, 1959). The first report of the importance of the epileptic spike came from the Berlin group by Fischer and Löwenbach in 1933 (Fischer and Löwenbach, 1933) working mainly with animals. They recorded corticograms assessing the effects of strychnine and picrotoxin in rabbits, cats, dogs and frogs. This seems to be the first EEG study monitoring drug effects on brain activity by first recording baseline activity, then giving a drug, and then monitoring the effect on the brain by means of EEG. The development of clinical EEG must be credited to many scientists and clinicians, including Grey Walter, who was the first to point out the importance of the slow activity (Walter, 1936), Gibbs et al. who initiated the use of EEG studies in patients with epilepsy (Gibbs et al, 1935), and Jasper et al. who contributed important work related to epilepsy and EEG (Jasper and Andrews, 1938; Jasper and Hawke, 1938). At the end of the 1930s, EEG was the leading method in human brain function assessment, including epilepsy.

4.1.2 EEG signals

The electric scalp potentials recorded in the EEG is a high level integration of electromagnetic oscillations in the brain with different temporal and spatial frequencies in different locations depending on the recording method, mirroring its electromagnetic activity (Creutzfeldt et al, 1966; Freeman, 1975; Nunez, 1989; Nunez et al, 1994; Steriade, 1999; Nunez and Silberstein, 2000; Nunez, 2000b; Nunez et al, 2001; Nunez and Srinivasan, 2006b). The origin of the electromagnetic oscillations are the postsynaptic return currents, mainly in the pyramidal cells (Speckmann and Walden, 1991), and to a lesser extent other sources. Thus, even the glia cells show modulated electromagnetic activity (Kuffler et al, 1966; Picker et al, 1981), but it's influence on scalp EEG is unclear (Amzica and Massimini, 2002; Amzica, 2002).

The operational physiological unit of the brain is the action potential. An action potential lasts for about 1 ms corresponding to 1000 Hz, with a recovery phase of up to 10 ms (Hodgkin and Huxley, 1939) corresponding to a frequency of about 100 Hz. Routine EEG is recorded from 0.5 Hz up to 70 Hz and hence, does not contain direct information about single action potentials. The EEG is routinely recorded according to the 10 - 20 system with 20 scalp electrodes (Nuwer, 1997; Nuwer et al, 1999; Deuschl and Eisen, 1999). Each electrode receives input from many hundred million neurons. The neurons have different distance to electrodes with different directions. The macropotential may be defined as:

$P(r',t) = \frac{1}{W} \iiint_{w} ws(r',w,t)dW(w)$ where W is the tissue volume, and s(r',w,t) is the local volume source inside a tissue volume (Nunez et al, 2001). The vector locations are defined by r', and w defines the micro current vector within a column. The time is denoted by t. Hence, the electromagnetic activities in the neurons contribute to the extra-cranial electromagnetic signal in a complex manner. Firing coherence, direction of propagation and active volume sums up to be the recorded EEG. The degree of connectivity, i.e. to what extent different source activities are related, will vary among the cell assemblies and as a function of time. As outlined above, the signal that is recorded has a very

complex relation to the electromagnetic activity within the brain. As a consequence of this, the representation of the EEG will vary with changes in the spatial frequency which changes with the recording montages (Nunez and Pilgreen, 1991; Nunez et al, 1994; Nunez, 1995).

EEG has been described as a stochastic signal due to its complexity. This is obviously not correct. Applying nonlinear mathematical methods the EEG has been shown to be deterministic and is estimated to have a fractal dimension of about 8 -10 in awake humans (Pereda et al, 1998; Lehnertz et al, 2001). As the signal is not stationary, but varies as a function of time, it is impossible to get exact values of the complexity of the signal. Analyses of the EEG have not brought conformity in our understanding of the signals (Palus 1996). Several groups are engaged in further defining the scalp EEG by means of linear and non linear mathematical methods, especially in patients with epilepsy (Van Quyen et al, 1999; Lehnertz et al, 2001; Litt et al, 2001; Kugiumtzis et al, 2006). However, there is a huge knowledge base in clinical reading of EEG, which still holds a leading role both in the clinic and in research. However, computer programs are now increasingly implemented to help in EEG reading, both for obtaining more objective criteria and quantifiable data available for further analyses.

4.1.3 Brain rhythms

In the first years of the EEG era, labelled frequency bands were called rhythms. This is mainly abandoned and activity is now the common label. Today the only entity where there is a clear distinction is alpha rhythm/activity. The alpha rhythm is more distinctly defined than the alpha activity (see 4.1.3.3).

The electromagnetic activity recorded through an EEG system is classically divided into different frequency bands: Clinically the different bands convey diverse information about the patient and this is to a large extent mirrored in EEG research.

Delta < 4 Hz

Theta 4 - 8 Hz
Alpha 8 - 13 Hz
Beta 13 - 30 Hz
Gamma >30 Hz

With the increased utilization of higher frequency activities in EEG analysis, the higher frequencies are named ‘gamma’. In the later years the fastest frequencies in intracranial recordings have been named ripples and fast ripples (100 – 500 Hz).

4.1.3.1 Delta activity

The name delta rhythm was introduced by Grey Walter in 1936 (Walter, 1936). He described slow EEG activity over brain tumours in patients, and coined the term delta (‘δ’) for ‘brevity’. A more exact reason for the labelling is unknown. Originally delta included all frequencies below alpha, but theta was eventually put in between (see 4.1.3.2). Under physiological conditions, delta activity is seen in deep sleep (Loomis et al, 1937; Dement and Kleitman, 1957) being the prominent activity in the deep sleep stages III and IV. In contrast, the delta is not seen in clinical EEG reading as a clearly defined rhythm in healthy awake adults, but nevertheless usually contributes to the low-frequency parts of EEG spectra during wakefulness. However, delta is commonly seen in patients with pathological conditions, such as brain tumours and encephalitis, as originally observed by Walter (Walter, 1936).

4.1.3.2 Theta activity

In 1944 Walter and Dovey reported on EEG in patients with subcortical tumours (Walter and Dovey, 1944). They suggested splitting the delta activity in two parts naming the faster part theta. Theta was chosen to denote thalamus, as they assumed that this activity was of thalamic origin.

Theta activity is seen in children and young adults when awake and increases during drowsiness and sleep (Rechtschaffen et al, 1973). In healthy awake humans, theta has been seen up to the age of 30 years (Niedermeyer, 2005).

The theta activity is connected to a set of activities in healthy humans. There is a strong connection between theta phase and gamma activity in the brain (Canolty et al, 2006). Newer research have demonstrated that the place cells and the grid cells in the temporal lobe of rodents have gamma activity that is phase locked to the theta activity (Moser et al, 2008). It may be speculated that many systems in the brain would work in a similar way.

The frontal midline theta (FMT) activity has been connected to mental activity and problem solving (Niedermeyer, 2005). Niedermeyer et al. were not able to confirm this finding (Niedermeyer et al, 1989), but an increase in FMT in learning situations has been reported more recently by others (Laukka and Järvilehto, 1995). The FMT have been shown to correlate to working memory load (Jensen and Tesche, 2002). Asada and coworkers have located the origin of the activity to the prefrontal cortex and the anterior part of gyrus cingulus (Asada et al, 1999).

4.1.3.3 Alpha rhythm/activity

The alpha rhythm was first seen by Berger in 1924 and published in 1929 (Berger, 1929). The formal definition of the alpha rhythm from International Federation of Societies for Electroencephalography and Clinical Neurophysiology (IFSECN) as proposed in 1974 was: ‘Rhythm at 8-13 Hz occurring during wakefulness over the posterior regions of the head, generally with higher voltage over the occipital areas. Amplitude is variable but is mostly below 50 μV in adults. Best seen with eyes closed and under conditions of physical relaxation and relative mental inactivity. Blocked or attenuated by attention, especially visual, and mental effort’. The committee also pointed out that ‘alpha rhythm’ must be

restricted to rhythms fulfilling all of the above criteria, which have further been elaborated by Deuschl and Eisen (Deuschl and Eisen, 1999).

The genesis and the physiological behaviour of the alpha rhythm are poorly understood (Andersen and Andersson, 1968; Lopes da Silva and Storm van Leeuwen, 1977; Nunez et al, 1978; Nunez, 1989; Nunez, 2000b; Nunez et al, 2001; Nunez and Srinivasan, 2006a, Hughes and Crunelli, 2005). However, the variability of the alpha rhythm is well established in clinical EEG reading. The fact that alpha frequency changes as a function of age is central in the EEG literature (Eeg-Olofsson, 1970; Niedermeyer and da Silva, 2005). The rhythm shows physiological variation in amplitude and frequency as a function of changes in attention (Cole and Ray, 1985; Ray and Cole, 1985), as well as arousal and other factors, such as blood glucose levels (Brazier et al, 1944). Most studies on alpha frequency variability have been done in cognitive performance studies (Klimesch, 1997; Klimesch et al, 1999; Klimesch et al, 2001; Shaw, 2003; Hanslmayr et al, 2005).

The alpha rhythm has been reported to be influenced by drugs. In particular it has been reported that AED treatment can cause a general slowing of the EEG accompanied by slowing of the alpha rhythm (Salinsky et al, 1994; Frost Jr. et al, 1995).

In this thesis the alpha activity was chosen to be assessed due to well established empery.

4.1.3.4 Beta activity

The beta activity was first reported by Berger (Berger, 1929) as the next rhythm after alpha on the frequency scale. It is seen in almost every healthy adult, and is usually connected to high arousal and mental activity (Niedermeyer, 2005). Beta

activity is enhanced in some pathological conditions and in response to some drugs such as benzodiazepines (Brown et al, 1979)

4.1.3.5 Gamma activity

The term gamma activity was introduced by Jasper and Andrews in 1938 (Jasper and Andrews, 1938). Originally, the term was used for 30 - 40 Hz occipital activity superimposed on the alpha activity. Eventually, the gamma-activity was seen as part of the beta frequencies. In the 1990s however, the gamma band was reintroduced primarily as an induced rhythm and is now defined as activity between 30 Hz and 100 Hz. The rhythmic 40 Hz activity has been prototypic for the gamma activity and was early seen in motor cortex at self-paced voluntary movements (Pfurtscheller and Neuper, 1992). In the last years the gamma activity has been found in many systems (Canolty et al, 2006; Herrmann et al, 2010), to some extent phase locked to other activities.

After the possible relation between gamma activity and visual consciousness was reported, the visual system has been explored to increase our understanding of consciousness. Increased coherence in gamma activity between areas has been pointed to by some researchers as being indicative of consciousness in the visual system and it is seen as an important element in the visual binding (Crick and Koch, 1990). The issue is still under research and other frequencies, and the phase synchronization of theta and gamma activity are among hypotheses being suggested (Melloni et al, 2007).

4.1.3.6 Fast and ultrafast activities

The fast activities called ripples (100 – 200 Hz) and fast ripples (200 – 500 Hz) (Bragin et al, 1999) are hot topics and reports on the significance of these activities in different contexts are flourishing. The activity has been reported to be important as pathological and indicative element in EEG in epilepsy surgery (Jacobs et al, 2010a; Jacobs et al, 2010b), especially in conjunction with spike activity in the temporal lobe. Fast ripples seem to be a good indicator of the seizure onset zone (Urrestarazu et al, 2007).

4.1.4 Spike and spike wave

A spike is an EEG transient, clearly distinguished from the background activity, with a pointed peak at conventional paper speed and duration from 20 to 70 ms. Its genesis is unclear, but a brief hypersyncronization is often used as an explanation. The spike has variable morphology even in the same channel in the same patient. The spikes may occur in bursts as polyspikes and runs of rapid spikes (Niedermeyer and da Silva, 2005).

A sharp wave is defined by the IFSECN as the spike, except duration of 70 to 200 ms. Today spikes and sharp waves are often used synonymously.

A wave commonly trails the spike or sharp wave. Niedermeyer (2005) makes a point of the distinction between spike-wave and the spike wave complexes seen in classical 3 Hz spike and wave in absence seizures. In this thesis, the spike is used in calculation of SI. In the propagation study (Publ 2), also wave data was processed.

The spike is probably generated through different mechanisms. Most spikes have amplitudes requiring underlying cell populations to have coherent firing. Many studies have been carried out to elucidate the different possible mechanisms behind the hypersynchronization. The paroxysmal depolarization shift (PDS), where there is a lasting elevation of the membrane potential giving rise to trains of depolarizations, is one well studied mechanism (Schaul, 1998).

The spike activity is usually reported in a pseudo-quantitative way after visual inspection. This is an insufficient way of monitoring drug effects. A number of spike detectors have been designed and tested (Pfurtscheller and Fischer, 1978; Frost, Jr., 1979; Gotman and Wang, 1991; Gabor and Seyal, 1992; Flanagan et al, 2003; Ossadtchi et al, 2004), but they have only found limited use in clinical settings. This is to some extent due to low sensitivity or low specificity or both. In

the actual study a semiautomatic method was applied both to give a highly quantifiable assessment and as a quality insurance.

4.1.5 Montages

In this thesis the selection of montages are paramount in giving good results that are practically useful. Correct spatial filters will enhance the activity under assessment and simplifies further computation.

The EEG records the electrical component of the electromagnetic signal from the brain. It is measured as voltage which is a field difference and thus needs two electrodes for measurements. The EEG is classically set up either to record with a ‘reference electrode’ or with ‘bipolar’ electrode pairs. The reference electrode may be a real electrode or a calculated, virtual electrode. The recording of voltage differences increases the complexity of the signal as both the active and the reference electrodes will convey the same amount of information. The classical solutions to this were either to select the locations for both the recording and reference electrode to suit the clinical setting, e.g. longitudinal or transversal bipolar recordings or to find a ‘neutral’ location for a reference electrode as an earlobe. Eventually calculating a virtual reference electrode as the average reference electrode has gained popularity. Recording with a reference electrode calculated as the average of all, or almost all, electrodes in the set is now commonly used in clinical EEG. The calculated average reference electrode will still convey information that influences the recorded signal. The spatial filter function is almost the same using average reference or single electrode reference. To deal with the issue that there always was a reference electrode conveying signal into each EEG-channel, Hjorth (Hjorth, 1975; Hjorth, 1991) proposed to calculate the locale source activity. These methods have been further elaborated (Nunez and Pilgreen, 1991; Gevins et al, 1994). By transforming the data from voltage differences to currents, no reference electrode is needed. The methods as outlined by Nunez and Pilgreen are central in the spike detection algorithm used in this thesis.

Due to the high resistance in the skull and low resistance in the cerebrospinal fluid, there is a blurring of the signal (Nunez and Pilgreen, 1991; Nunez et al, 1994). The same source montage of Hjorth as mentioned above decreased these challenges. His ‘source derivation’ (Hjorth, 1975) and later ‘source distribution’ (Hjorth, 1991) gave every recording electrode a spatial filter function counteracting the blurring. Gevins et al. used a more advanced ‘deblurring’ algorithm to accomplish the spatial filter function (Gevins et al, 1994). With 124 channels it was possible to show the same activity distribution using scalp electrodes as seen in a recording with intracranial grid electrodes. Cubic spline and eventually the spherical spline with the calculated current source density (Nunez and Pilgreen, 1991) are now well established and the spherical spline is now probably the most commonly implemented method for spatial filtering. The spline function is a curve fitting function. The cubic spline will match a row of 3. degree polynomials to a signal. The spherical spline fits the signal as recorded on the scalp with a two dimensional cubic spline on a spherical surface.

It is important to understand spatial filtering in EEG and how it changes the weighting and the representation of the returned information from the recording (Nunez et al, 1994; Nunez et al, 2001; Srinivasan et al, 2006). In this project the spherical spline is an important part of the spike detection algorithm. On the other hand, the alpha rhythm is better recorded with a longitudinal or bipolar montage or an average reference than with a spherical spline montage as the rhythm often has a relatively low spatial frequency (Nunez et al, 2001).

Most publications on frequency based methods in the EEG have used ordinary montages, without implementing spatial filters. Most of the reported results have been disappointing as the analyzed data contained blurred signals from two locations, the recording electrode and the reference electrode.

In the studies that form the basis of this thesis, a single reference electrode was applied to record the alpha activity with its low spatial frequency. To get a better defined grapho-element of the spikes, current source density (CSD) was applied in the cognitive impairment studies with SI.

4.1.6 Source localization

Besides recording the EEG and characterizing the recordings by different grapho-elements, as alpha rhythms and spikes, localizing activity is important. Methods for source localization are in varying degree model dependant i.e. they require prior assumptions on what to find (Mosher et al, 1993; Lantz et al, 1996; Merlet and Gotman, 1999; Fuchs et al, 2004; Lopes da Silva, 2008).

There is no real filter in the skull in the common EEG frequency range (Nunez, 1995). The skull conductance, however, increases as a function of frequency (Akhtari et al, 2002; Akhtari et al, 2003). There are no filter based phase shifts in the EEG in its common frequency range, and this is a prerequisite for source localization in time domain. There are studies showing changes in source localization depending on the conductance parameters used in the model (Stinstra and Peters, 1998).

4.1.6.1 Equivalent current dipole

A common method is the use of equivalent current dipole (ECD) localization (Ebersole, 1991). The model assumes that the recorded activity comes from one or a few locations. This makes calculations of the signal as a function of time possible. However, the method is heavily model-dependent. When localizing a dipole you assume that the activity recorded comes from a single point. To exemplify this: When you see a wave rolling to the shore you may postulate that the wave comes from a stone thrown into the water. By exact observation of the wave at three places at the shore, you can calculate where the wave came from and the energy released when the stone hit the water. However, if the wave came from a passing boat, your model is totally wrong even though the

calculated results may seem convincing. The same applies to the calculation of point sources in EEG. To be visible in the EEG, an area of 6 cm^2 of cortex have to be synchronous. Hence, recording of EEG from a single point on the cortex is impossible from the scalp due to attenuation and signal blurring (Nunez and Srinivasan, 2006b), so the dipole model is wrong. Add to that, the EEG we record comes from the entire brain, and, hence, localizing activity to one location may be wrong. On the other hand, it has been shown scientifically and through empery that the dipoles usually are good indicators for focus or functional location (Ebersole, 1991; Scherg and Ebersole, 1993; Lantz et al, 1996; Merlet and Gotman, 1999).

4.1.6.2 Regional solutions

Instead of modelling sources as point in the brain as done with dipoles, regional solutions may be applied. These methods returns regional activities in the brain either by means of statistical probabilities as the deviation scans (Fuchs et al, 2004), multiple signal classification (MUSIC) (Mosher and Leahy, 1998) or calculating regional solutions as a minimal norm estimate (MNE) (Hämalainen and Ilmoniemi, 1994), minimal norm current estimate (MCE) (Uutela et al, 1999), local autoregressive averaging (LAURA) (Michel et al, 2004), low resolution brain electromagnetic tomography (LORETA) (Pascual-Marqui et al, 1999) or other methods. There is no obvious way to make time dependent plot with these methods, but the results may be given as videos showing the activity distribution over the resultant surface or volume as a function of time. These regional models will often be constrained to the cortex.

4.1.7 Region of interest

Another way to do spatial filtering and to scrutinize activity is to constrain the EEG sources to discrete regions in the brain or to the brain surface (Michel et al, 2004). The EEG may be calculated into a three - dimensional solution space and the resultant activity of each defined region of interest is returned. This is commonly denoted as ‘region of interest’ (ROI) calculations. ROIs may have

been defined manually or by other methods as fMRI (Bonmassar et al, 2001). ROI calculation may return the time variant signal as the ECD does, however, as the ECD tries to explain as much as possible of the scalp signal through the dipoles, the ROI calculations will constrain the activity in the model to activity with the origin within the ROI.

ROI calculation is used in the thesis in the propagation study for the assessment of the changes in propagation.

4.1.8 EEG monitoring

Monitoring brain function by means of EEG in patients is used both as part of a disease follow up and in drug effect evaluation. As huge amounts of information are generated, the review of the data is labour intensive and, hence, expensive. As computation power has become increasingly available, a series of methods have been tried, mainly in anaesthesia and intensive care units and some have gained clinical acceptance for cerebral brain monitoring (Prior et al, 1971; Nuwer, 1997; Vivien et al, 2002; Schumacher et al, 2010). Classically, most methods for monitoring brain functions have used only one or very few channels, limiting the yield and hence the general applicability in clinical medicine. The present study is an attempt to enhance the available toolbox of clinically useful methods for intermittent monitoring of patients with epileptiform activity and changes in background activity due to epilepsy or AED medication. The study was initiated as a demand for better methods and conveys a set of approaches to issues in a clinician's everyday work.

4.2 Connectivity in the brain

The human brain is an extremely complex structure. It has been called a 'connection machine' (Hillis, 1989). The brain is estimated to contain about 100 billion neurons. The neocortex is 1.5 to 4.5 mm thick. It has been thoroughly studied by Pakkenberg et al. (Pakkenberg and Gundersen, 1997; Pakkenberg et al, 2003). In young males they found an average of 22.8 billion neurons. There

are about 39 billion glia cells in the same volume. Each neuron connects to other neurons through synapses. Each neuron is estimated on average to have about 7000 thousands synapses, making the estimate of the total number of connections in the neocortex to be about 0.15×10^{15}. Most connections in the neocortex are through short axons - about 1 mm long. However, there are about 10 billion corticocortical fibers that are between 1 cm and 15 cm (Nunez and Srinivasan, 2006b). About 100 million of the fibers cross the midline through the corpus callosum.

The brain is assumed to work through action potentials passing down the axons and eventually propagate to new neurons through the synapses. An action potential will travel along an axon and jump to the next neuron at the synapse. Depending on the nature of the synapse this will either give an excitation (excitatory postsynaptic potential (EPSP)) or inhibition (inhibitory postsynaptic potentials (IPSP)) (Eccles, 1964). One potential alone will usually not be able to elicit a new action potential on the postsynaptic side. Depending on different factors, e.g. the synapse location on the neuron, the number of EPSPs needed to elicit a new action potential will vary. This arrangement makes the signal propagation highly nonlinear. The transfer is often modelled as a sigmoid function (Erb, 1993; Bartesaghi et al, 2006), and it varies as a function of synaptic plasticity (Triesch, 2005). The modification of the transfer function has been a central hypothesis for memory (Andersen et al, 1977; Bliss and Collingridge, 1993) and for dynamic factors (Fortune and Rose, 2001). Some CNS drugs have been shown to modify the transfer functions. (Alonso et al, 2010). According to Friston (Friston, 1994) connectivity may be seen as

- anatomical – related to how the nerve fibers are organized in the brain
- functional – related to statistical parameters used to calculate connectivity (e.g. correlations) between locations
- effective – related to information flow between locations, which assumes direction information

The connectivity is dynamic and varies both due to structural changes in the brain including changes in synapses and due to changes in excitation / inhibition homeostasis. The latter is among others influenced by medication.

The brain appears to adhere to fundamental principles of functional organization, functional integration and functional specialization, where the integration within and among specialized areas is mediated by connections among them (Deco et al, 2008). There are many studies that support the notion that processing of information takes place simultaneously on different spatial scales (Freeman, 1975). Our own experience is that spikes may need 10 - 12 ms to move from one layer of the cortex to the next, 6 ms to get to a point 1 cm away and 10 – 12 ms to get from one temporal lobe to the other (Figure 1).

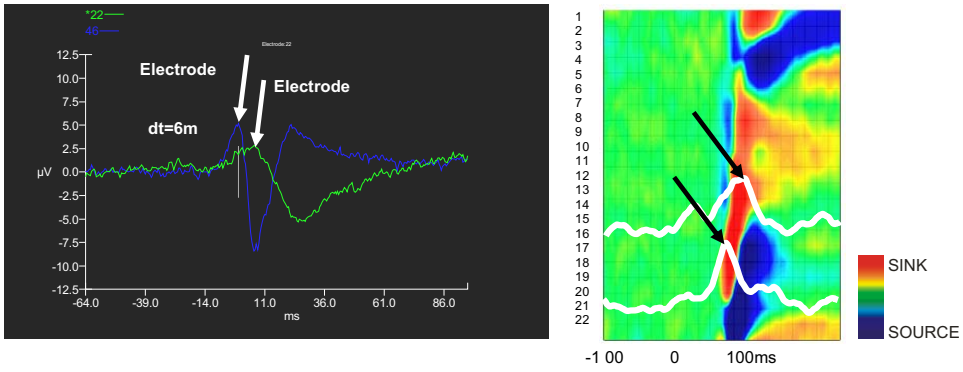

Figure 1. Intralaminar recording from human temporal lobe in vivo. The left panel gives the spike in two different intralaminar electrodes located 1 cm apart. The right panel shows the calculated current source density through cortex. It is about 3 mm from channel one to channel 22 and it reproduces the activity from 100 ms before the peak of the spike and up till 100 ms after. Illustration by Ulbert (unpublished study, Oslo 2004).

The cortex is organized in minicolumns each containing about 110 neurons except in striate cortex where there are about 260 neurons in a minicolumn. The minicolumns, but also the macrocolumns have been seen as functional units (Mountcastle, 1997). The columns connect through a mesh, mainly by corticocortical fibers. The mean length of the corticocortical fibers is about 4 cm. Hence, neighbouring macrocolumns are not expected to be in the same system.

Due to the anatomical build-up in minicolumns with many long corticocortical fibers the brain does work both locally and globally on the same information and to some extent at the same time scale (Nunez and Silberstein, 2000; Nunez, 2000a; Nunez, 2000b). The integration and specialization of the processing may be seen as elements of a local/global network with inhibition as an important element in segregation in information processing (Nunez 2010).

In this thesis the changes in effective connectivity as a function of AED treatment is central in the spike propagation study (Publ 2).

4.3 Epilepsy

4.3.1 Definition

Epilepsy is one of the most common chronic diseases (Hauser, 1994). The definition given by the International League Against Epilepsy (ILAE) is: ‘Epilepsy is the name of a brain disorder characterized predominantly by recurrent and unpredictable interruptions of normal brain function, called epileptic seizures. Epilepsy is not a single disease entity but a variety of disorders reflecting underlying brain dysfunction that may result from many different causes.’ (1981; 1989; Fisher et al, 2005). Until recently the definition of epilepsy required that the patient should have had two unprovoked seizures. According to the new ILAE proposal, only one epileptic seizure is now required for the diagnosis of epilepsy, with the precondition that it is in association with enduring disturbance of the brain, capable of giving rise to other seizures.

4.3.2 Incidence and prevalence

The incidence of epilepsy has internationally been estimated to 50 per 100 000 persons in developed countries (Sander, 2003). The incidence is higher in children and in the elderly than in the middle aged population (Hauser, 1994). In Norway, the prevalence is estimated to be 7 and 1000 inhabitants (Krohn, 1961). In a study from 2007 Svendsen et al reported 8.2 cases per 1000 inhabitants and pointed to using a narrower definition as laid out by ILAE, reduced the mean prevalence to 5.3 cases per 1000 inhabitants (Svendsen et al, 2007). The incidence has been reported from northern Norway to be 32.8 /100000 (Graaf, 1974).

4.3.3 Classification

The currently used seizure classification of epilepsies is the proposed classification of 1981 by ILAE with minor updates. A recent updated classification (Berg et al., 2010) defines generalized seizures as seizure with a focal start with fast spread and bilateral involvement. The partial seizures are now renamed focal seizures. For seizure classification see appendix A.
If a seizure does not fit into this classification, it should be considered unclassified.
The focal seizures are further described through the degree of impairment of consciousness during the seizure.
The epilepsy syndrome classification is based on the ILAE classification 1989. It builds on a combination of semiology and EEG. Berg et al. have now made a new ILAE proposition for classification of epilepsy (electroclinical) syndromes (Berg et al, 2010) (appendix B). A syndrome is defined as a complex of clinical features, signs, and symptoms and is further identified through typical age at onset, EEG characteristics and seizure types. Not all epilepsies are part of an electroclinical syndrome.

Due to the continuous gained knowledge on epilepsy, revision of the classification will always seem necessary and there have been scores of suggestions during the last years (Lüders et al, 1998; Engel, 2001; Fisher et al, 2005; Engel, Jr., 2006; Lüders et al, 2006), usually with little acceptance. The new proposal (Berg et al, 2010) seems to be accepted and is in the process of being adopted in clinical use.

4.4 Epileptiform activity and cognitive impairment

4.4.1 Background

It is well known and established that epileptiform activity in many patients increases during sleep (Rossi et al, 1984, Sammaritano et al, 1991). One characteristic pattern is ‘continuous spike and wave during slow sleep’. This was first described by Patry and collaborators (Patry et al, 1971) reporting six children, five with seizures of whom one lacked language and two had delayed language. The patient without seizures had no language. They called the pattern ‘Electrical Status Epilepticus Induced by Sleep’. In 1977 Tassinari et al. suggested the name ‘Electric Status Epilepticus during Sleep’ (ESES) (Tassinari et al, 1977), and in 1985 the name ‘Continuous Spike and Wave during Slow sleep’ (CSWS) was established (Tassinari et al, 1985). This abbreviation has also been used for a syndrome. This has created some confusion. Thus, the electrographic manifestation is ESES, while the syndrome is called epilepsy with CSWS according to the ILAE classification (1985; 1989; Berg et al, 2010). ‘Slow sleep’ is synonymous with NREM sleep. Tassinari has lately advocated the use of ESES for the EEG findings.

ESES is as EEG phenomenon. Usually, the activity shows a maximum in central or Rolandic regions. Dipole localization will then usually indicate a vertical dipole in the upper part of the temporal lobe (Paetau, 1994). Practically, all children with language impairment show a central maximum, with a temporal location of the dipole. Other cognitive impairment, as outlined below, may have a maximum at different scalp locations, but even in these groups the central maximum is common. Having different symptoms in patients with the same spike locations (Hughes et al, 2000; Wolff et al, 2005) and different spike locations with same disease as published by Lewine and collaborators in ASD patients (Lewine et al., 1999) indicates that the diseases are related to different, intermingled brain networks.

ESES is a characterizing phenomenon in the Landau – Kleffner syndrome (LKS), which was first described in 1957, as 'acquired aphasia with convulsive disorder in children'. LKS is a partial reversible encephalopathy manifesting with verbal auditory agnosia and other predominantly linguistic deficits and neuropsychological behavioural abnormalities in childhood (Bureau, 1995; Panayiotopoulos, 2007). ESES is compulsory in the specific syndrome 'Epilepsy with CSWS' (Deonna et al, 1977; Panayiotopoulos, 2005). It is related to LKS, but has more severe epilepsy manifestations and a more general neuropsychological decline (Panayiotopoulos, 2007).

ESES usually appears in ages 3 - 5 years, but may be seen before 2 years of age and disappears in adolescence probably in relation to puberty (Rossi et al, 1999a). The activity only occurs in children (figure 2). As there is a lag from patients get ESES to they are admitted to the centre, the left side of the diagram shows a shift towards higher ages.

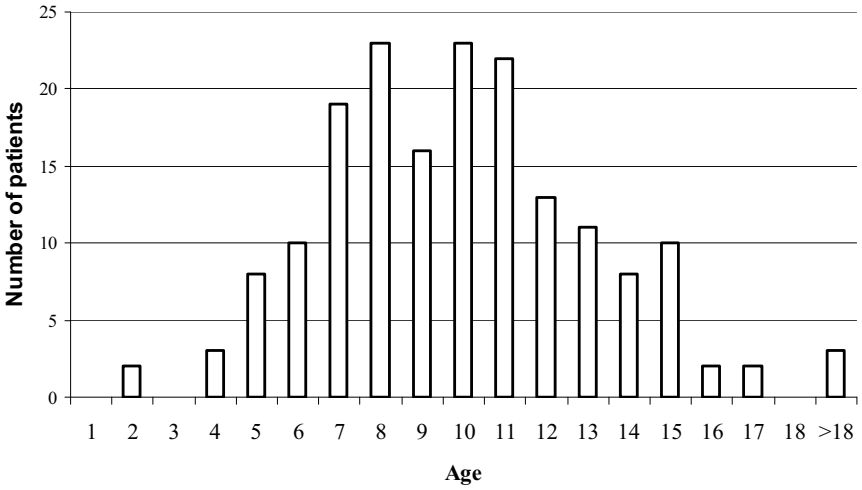

Figure 2. Age distribution of the first 175 patients admitted to the National center for Epilepsy after start of the CSWS study

Other disorders including benign focal epilepsies of childhood (Rolandic epilepsy) show activation or enhancement of epileptiform activity during sleep. There are reports, corroborated by our own experience, on the occurrence of epileptiform activity during sleep in children without a seizure history, but with behaviour and learning disorders (Deonna, 2000; Ballaban-Gil and Tuchman, 2000; Castaneda-Cabrero et al, 2003; Besag, 2004; Scholtes et al, 2005; Wilson et al, 2005; Larsson Wilson, 2005; Van Hirtum-Das et al, 2006; Chez et al, 2006; Silvestri et al, 2007).

The relation between the spike activity and the cognitive impairment is complex. The number of spikes is related to the spike frequency and the length of the spiking period. The spiking usually starts in preschool age. The night to night variation and variation over longer periods are unknown. The number of neurons in the activity is expected to be an important factor. This relates to the area with spikes on the scalp, but all related EEG parameters are heavily influenced by degree of synchrony.

The label ‘spike index’ is used, but has not been defined (Bureau, 1995). In the original work of Patry et al. (1971), it is stated that: ‘By continuous, we mean that they occupy at least 85% of the slow sleep tracing.’ (Patry et al, 1971). There is no further definition of the method. In the results they used ‘spike and wave index’ without further explanation. However, a ‘spike and wave index’ was defined in 1969 in a study by Guey et al., of ‘petit mal’ as (sum of durations of paroxysms per activity)/(total duration of the activity in question)x100 (Guey et al, 1969). The duration of paroxysmal activity was not defined. Later SI has been used with varying definitions. Among the SI definitions found in the literature, one expresses the total minutes with spike-waves multiplied by 100 and divided by the total number of minutes in non-REM sleep without spike activity (Holmes and Lenck-Santini, 2006) and another is based on dividing the number of spikes in each sleep stage by the time spent in that stage (Nobili et al, 1999).

Using 85 % as NREM sleep time as a limit is arbitrary. Lower values are also expected to influence the brain (Bureau, 1995). In our studies on children with cognitive impairment, SI down to 30 has been applied, and this is reflected in this thesis.

As ESES commonly has been associated with 85 % or more of epileptiform activity, a more general name, focal nocturnal epileptiform activity (FNEA) has been coined. Focal is in the name to stress that this activity starts in one focus, usually easy to localize, and commonly with a fast spread. As the most common amplitude maximum is central, where reference electrodes usually are located, the activity will often give a generalized expression. The name nocturnal epileptiform activity was suggested, but FNEA seems more appropriate.

4.4.2 Cognitive impairment

Epileptiform activity during sleep is associated with cognitive impairment (Deonna et al, 1997; Scholtes et al, 2005; Holmes and Lenck-Santini, 2006;

Nicolai et al, 2006; Pinton et al, 2006). The patients are usually diagnosed according to the major symptom e.g. challenges in language as in LKS, attention as in attention-deficit-hyperactivity disorder (ADHD) or in social interaction as in autism spectrum disorder (ASD), but most of these patients have additional co-morbidities with cognitive impairment besides the major trait reflected in their diagnosis. Patients with autism may show hyperactivity symptoms and patients with attention problems may have learning disabilities and so on. Hence, patients with ESES will commonly exhibit combined cognitive impairment.

Besides LKS and epilepsy with CSWS, ADHD and ASD are the best defined disorders sometimes having epileptiform activity during sleep. The recordings with FNEA in this thesis are from patients having different diagnoses with or without cognitive impairment. One study deals explicitly with patients having an ADHD diagnosis.

Attention - deficit - hyperactivity disorder is characterized by pervasive and impairing symptoms of inattention, hyperactivity, and impulsivity according to the DMS-IV. The prevalence has been reported to be between 1 % and almost 20 %, but in a pooled worldwide prevalence it has been estimated to 5.3 % (Polanczyk et al, 2007). The large variation may to some extent be due to geographical differences, but most of the variation has been suggested to be due to methodological differences with respect to diagnosis.

A relation between epilepsy and ADHD has been known for a long time. Clinical studies have reported 30 % to 40 % of children with epilepsy having ADHD symptoms (Hauser, 1994; Dunn and Kronenberger, 2005), inattention being more common than hyperactivity (Dunn and Kronenberger, 2005). Wannag and collaborators (Wannag et al, 2010) reported that in a group of children, 6 – 14 years, almost all with epilepsy, admitted to a tertiary epilepsy centre, 44 of 362 patients, had a confirmed ADHD diagnosis before admission. A further 79 were suspected of having ADHD. Forty-six in this group were thoroughly tested and 30

were diagnosed with ADHD. Thus, 20.4 % had a certain diagnosis of ADHD and a 9.1 % was suspected of having ADHD but not tested. Hence, the study indicated that about 25% of children with epilepsy, admitted to a tertiary centre have ADHD.

Only few reports deal with epileptiform activity in attention deficit disorders (Castaneda-Cabrero et al, 2003; Becker et al, 2004). The few small reports found 20 % to 30 % of patients having epileptiform activity in EEG during sleep (Hughes et al, 2000; Bernal Lafuente et al, 2004; Becker and Holtmann, 2006; Hamoda et al, 2009). Silvestri et al, 2007, reported that 53.1 % of children with ADHD referred to a sleep clinic had interictal epileptic discharges. In 42 children with ADHD and epileptiform activity the following comorbidities were reported: Dyslexia 33.3 %, language disorder 12.8 %, dyspraxia 12.8 % and eating disorder 7.6 %.

ASD is a group of disorders that comprises pervasive developmental disorders, Asperger syndrome, autism, Rett syndrome, and childhood disintegrative disorder. A wide range of prevalences have been reported, but most studies have estimated the prevalence in the population to about 6 patients with ASD per 1000 inhabitants (Newschaffer et al, 2007). However, Baird and collaborators found in a cohort study in London 11.6 patients per 1000 (Baird et al, 2006). Patients with ASD have an increased probability of having epilepsy (Ballaban-Gil and Tuchman, 2000). They often have epileptiform activity in their EEGs. In a study of ambulatory EEG recordings in 889 patients with ASD, Chez and coworkers found epileptiform activity in their EEG during sleep in more than 60 % of the patients (Chez et al, 2006). Lewine (Lewine et al, 1999) showed that 72% of children with ASD had an abnormal 24 hour EEG. Magnetencephalography (MEG) increased the yield and 81 % was found abnormal.

4.5 Treatment

Many antiepileptic drugs (AEDs) are used for treating patients with epilepsy. All drugs have one or more known molecular target (Rogawski and Löscher, 2004), but the relation between these targets and the antiepileptic effect is unclear. More than one mechanism of action of the different drugs are usually postulated. Many drugs have their assumed modes of action updated from time to time as the knowledge of the nervous system increases. Some drugs are designed to have a specific effect. Vigabatrin, a γ-aminobutyric acid (GABA) transaminase blocker and tiagabine, a GABA uptake inhibitor, were designed to be AEDs due to expected antiepileptic effects in the GABA system (Meldrum and Whiting, 2001). Levetiracetam was evolved from piracetam to be an AED. On the other hand, topiramate was initially developed for treatment of diabetes, but failed and was subsequently found to be an AED.

Due to the diversity both in the genesis of the epilepsies and in the effects of AEDs on epileptic seizures in different patients, a large number of AEDs are now available. Treatment is initiated by introducing a drug expected to be effective in that patient. If no effect is achieved, a second drug may be introduced either replacing the first or as add-on. If the combination is efficacious the first drug may be gradually tapered off, always striving for monotherapy whenever possible. This procedure may be repeated with more drugs. At the moment there are no shortcuts to this procedure. The propagation study in this thesis (Publ 2) is a promising method which eventually may help assessing drug effect early in the treatment period.

About 70 % of epilepsy patients will be seizure free on AEDs (Kwan and Brodie, 2001; Elger and Schmidt, 2008). Patients not becoming seizure free after using two AEDs in adequate doses for an adequate time are, eligible to be evaluated for epilepsy surgery. Other treatment methods as vagal nerve stimulation (VNS) or deep brain stimulation (DBS) may be applied, but only after failed epilepsy

surgery work-up. Diets, as the ketogenic diet, are used in patients with epilepsy with some success.

Epilepsy surgery is a set of different procedures. The most common procedure is lobectomy, where a part of a lobe in the brain is removed after thorough focus localization. This procedure requires a well defined focus in an area not expected to leave a sequel after surgery. The outcome varies from about 80 % seizure free patients in temporal lobe epilepsy with hippocampal sclerosis to less than 50 % in extratemporal epilepsy without a MRI lesion. In eloquent cortex, multiple subpial transections (MST) may be tried (Morrell et al, 1989) to avoid or minimize post surgical functional deficits.

With respect to patients with ESES both drugs and surgery have been applied (Mikati and Shamseddine, 2005; Campos and de Guevara, 2007). Treatment with benzodiazepines (Rossi et al, 1999b; Kawakami et al, 2007) and other AEDs (Hirsch et al, 2003) as well as steroids (Sinclair and Snyder, 2005), have been reported often with good effects. Lately, levetiracetam (LEV) has been suggested as the drug of choice (Hoppen et al, 2003; Capovilla et al, 2004; Aeby et al, 2005; Wheless, 2007; Bakke et al, 2011).

In 1995 Morrell et al. reported the first 14 cases with MST in LKS patients (Morrell et al, 1995). He found that 50 % recovered age-appropriate language and 29 % had a marked improvement in language. His results have been hard to reproduce by others. This may be due to patient selection, surgery procedure or post surgery follow-up and treatment.

Resective surgery in patients with cognitive impairment have been reported both anecdotally (Neville et al, 1997; Roulet et al, 1998) and as part of studies (Lewine et al, 1999; Cross and Neville, 2009). Lewine reported reduction in autistic features and improvement in language skill in 12 of 18 cases who had a surgical resection (Lewine et al, 1999).

VNS have been applied in patients with epilepsy with CSWS (Hallböök et al, 2005). The results have reflected the use in seizure treatment and not as ESES-treatment.

Drug treatment is classically monitored by blood samples, therapeutic drug monitoring (TDM), to give quantitative blood levels for AED (Elger and Schmidt, 2008; Johannessen and Landmark, 2008), TDM gives information on compliance and individual pharmacodynamic and pharmacokinetic properties.

4.6 Moore's law

In 1965 Intel's cofounder Gordon E. Moore observed that they were able to double the number of transistors on an integrated circuit every 18 month (Moore, 1965) and from about 1970 it was called Moore's law. In 1970 he adjusted the estimate and said that the component count doubled every two years, which even today is seen as a good estimate. In consumer electronics and in computer systems this shows up as continuous reduction in equipment size, lower price, and higher performance. The law is a self-fulfilling prophecy; if a company wants to make a new product ready for the market in two years, it has to comply with Moore's law – either half price or double performance to survive when it reaches the market (Wikipedia).

In research it has been noted that the complexity of neuroscience studies correlates linearly with Moore's law giving double complexity in published studies every second year. It has been estimated that the practical limit in neuroscience are studies that require more than about 14 days of computer time. Results from neuroscience research do continuously spill over to clinical medicine. This is one of the driving forces in our ability to increase yield and refine methods in clinical medicine by means of implementing computer algorithms.

Through the centuries a huge amount of ingenious mathematical and physical formulas and algorithms have been crafted. With the introduction of the digital

computers some of the earlier works were immediately applied in computer systems and with the increased power in computer systems, as outlined by Moore, more and more algorithms have been implemented. The fast Fourier transform (FFT) was probably implemented in computer systems in the 1950s, and soon after implemented in medical research, however, initially with minor clinical acceptance. In 1973 FFT was suggested implemented as the method for making images from nuclear magnetic resonance (Lautenbur, 1973), and it soon became the standard method (Song et al, 1982). The nonlinear aspects of EEG were addressed about the same time (Basar, 1981) and in 1986 the calculations of fractal dimension in EEG was first suggested (Broomhead and King, 1986).

The computer evolution is continuously bringing more mathematical methods within reach of clinical medicine as this thesis shows.

5 Aim and scope of the thesis

5.1 Aim

This thesis was made to enhance the ability of digital systems to help human expert in EEG assessment.

The aim of this thesis is to describe and show how to use new automated EEG methods to investigate patients with epilepsy and patients without epilepsy but with epileptiform activity during sleep. This is pursued following two ideas:

1. Assessing nocturnal epileptiform activities in EEGs
2. Assessing the background activities and its variability

Ad 1.

The assessment of the epileptiform activity was performed with the aim of making available a single number that reflected the effect of the spiking upon the brain. As no approved or de facto standard was available, the method was set up on the background findings in transitory cognitive impairment (TCI) (Aarts et al, 1984; Aldenkamp and Arends, 2004) and changes in the brain activity in physiological settings such as reported in the event related synchronisation (ERS) desynchronization (ERD) research (Pfurtscheller and Silva, 1999). The definition of the method and the parameters used are described in publication 1. From the methodological side the study was followed up by a study on changes in spike propagation/spread as a function of AED use (Publ 2). Four clinical studies (Larsson et al 2010, Wannag et al 2010, Bakke et al 2011 and one in preparation) were started partly as clinical assessment and as method feasibility studies where one is part of the thesis (Publ 3).

Ad 2.

The alpha activity has the special feature of partly being defined in the time domain with a set of features – the alpha rhythm. The alpha activity may be assessed by means of FFT. The time domain constrains laid on the alpha rhythm

by definition will then be impossible to implement. Therefore, a new algorithm was constructed as a base for further time domain analyses after an initial study on the feasibility of using alpha frequency information clinically (Publ 4). The algorithm was then compared to frequency domain methods and visual inspection methods for alpha activity definition (Publ 5).

Monitoring brain functions by means of EEG have been implemented for decades. According to Moore's law there is continuous evolvement of computer based methods that become available for application in clinical use, as the computers gain power and speed. In this thesis, computer intensive methods for monitoring the brain have been tested and implemented with the goal of clinical acceptance.

In this context the monitoring may approach the problem from two sides; monitoring epileptiform activity and monitoring non-epileptiform activity. Monitoring epileptiform activity is more obvious with the activity's close relation to epilepsy. On the other hand, interictal epileptiform activity and ictal activity is usually sparse in the EEG. This form of analysis requires long recordings accumulating huge amount of data to collect enough usable information for analysis. The limited amount of applicable data and the huge amount of non related activity will hamper the deductive value. However, the non-epileptiform activity is seen through most of the recordings even in patients without epilepsy. Extracted features from non-epileptiform activity will to a large extent return unspecific results due to the dynamic character of brain activity which is reflected in the EEG. The huge amount of applicable information will statistically give very distinct results, but due to the large amount of unspecific EEG data the deductive value will be constrained. This thesis was set up to establish new tests in both; one set for the epileptiform activity and one for the non-epileptiform activity. In the latter case, the alpha activity was chosen as parameter because it is well defined and seen in almost all recordings.

Up to now, the lack of computer power for calculation and hence objective assessment of the impact of a disease or drug on brain function, information has had little impact on clinical EEG reading.

5.2 Scope of the thesis

These studies forming the basis of this thesis were performed examining patients either admitted to the National Center for Epilepsy at Oslo University Hospital, or having an EEG examination as outpatients at this centre. Patients are referred to the centre either because they have difficult-to-treat epilepsy, or if they are in a diagnostic work up where epilepsy is one probable diagnosis. Children with cognitive impairment and/or with known ESES are to an increasing extent referred for over night EEG examination and some of the patients in the studies are from this group.

The EEG analyses were done as described above.

6. Publications

6.1 Publication 1

A New Method for Quantification and Assessment of Epileptiform Activity in EEG with Special Reference to Focal Nocturnal Epileptiform Activity
Pål G. Larsson, John Wilson, Orvar Eeg-Olofsson. Brain Topography 2009;22: 52-59

6.1.1 Background

Evaluation of SI has been reported in the literature since the seventies (Guey et al, 1969; Beaumanoir et al, 1974; Watanabe, 1989; Hommet et al, 2000; Holmes and Lenck-Santini, 2006). The calculations have been performed differently and are usually not described in the publications. The methods have been labour intensive and reproducibility have been moderate and not been meant for clinical application. The need for quantification of the epileptiform activity for clinical use has been increasing both in patient follow up and in AED monitoring especially in the context of cognitive impairment work up.

This study deals with the development of a new way to assess and calculate the SI. The first requirement to accomplish a high reproducibility is a spike detector which must have a high sensitivity, above 90 %, and a very high specificity. E.g. muscle artefacts must be excluded, which implies specificity above 99 % in such instances.

The SI calculations should reflect the pathophysiology of the spiking. Transient cognitive impairment due to interictal spiking is well established clinically. Neuropsycholgical testing has shown that even brief bursts affect cognition (Schwab, 1939; Aarts et al, 1984; Binnie et al, 1984; Matricardi et al, 1989; Rugland, 1990; Binnie and Marston, 1992; Aldenkamp, 1997; Aldenkamp et al, 2001). In epileptic bursts Mirsky and Vanburen have in a group of patients showed reduced performance on continuous performance test (CPT) up to 5 s before the burst (Mirksy and Vanburen, 1965). The effect of spiking has been studied by Holmes et al. (2006). They concluded that the spiking is the reason for the cognitive impairment. One clinical argument used, was that removing the spiking by means of surgery diminishes the cognitive symptoms.

To calculate the SI, the spikes must be detected. This should ideally be done automatically or with a minimal interaction. Both a high sensitivity and specificity is required. In this study a new method was crafted with a set of parameters for reproducible SI calculation.

6.1.2 Methods

Spikes were detected by template matching of the principal components of the current source density estimate. Different correlation thresholds were tested. For this study, 75 % was initially used to make a good template and subsequently, 50 % was used for the following detection of spikes in the full recording. Epoch lengths of 120 s and 600 s have been tested. These epoch lengths constitute the limits of acceptable epoch length – 120 s the shortest to give a good spike count and 600 s to be the longest practical useable epoch length still giving good

detection of REM phases. The threshold value for inter spike interval (ISI) have been tested from 1 s to 7 s.

As part of the study, ten consecutive 19 channels ambulatory recordings were used for blind evaluation of inter reader variability.

6.1.3 Results

In this study a new method to calculate spike index was tested and parameters tested to optimize results.
Continuous spiking was tested with ISI between 1 s and 7 s. The study defined continuous as the instances where there were less than 3 s between spikes. An epoch length of 10 minutes was chosen for clinical use. There was a good inter user correlation.

6.1.4 Conclusion

The new method works well and has been implemented both in the clinic and in research (Larsson et al, 2010; Wannag et al, 2010; Bakke et al, 2011).

6.2 Publication 2

Decrease in Propagation of Interictal Epileptiform Activity After Introduction of Levetiracetam Visualized with Electric Source Imaging
Pål G. Larsson, Orvar Eeg-Olofsson, Christoph M. Michel, Margitta Seeck, Göran Lantz.
Brain Topography 2010;23: 269 – 278

6.2.1 Background

Different neuroimaging techniques (fMRI, Spectroscopy, PET) are used to evaluate candidate drugs in pharmacological development. In patients with epilepsy fast propagation of the epileptiform activity between different brain areas may occur. Electric Source Imaging (ESI), in contrast to the aforementioned techniques, has a millisecond time resolution, allowing visualization of this fast propagation. The purpose of the current project was to use ESI to investigate

whether introduction of an antiepileptic drug (levetiracetam, LEV) would change the propagation patterns of the interictal epileptiform activity during sleep.

6.2.2 Methods

Thirty patients with epilepsy were subject to an EEG recording before (Pre-LEV) and after introduction of LEV (In-LEV). Interictal spikes with similar topographic distribution were averaged within each subject, and a distributed source model was used to localize the EEG sources of the epileptiform activity. The temporal development of the activity within 20 regions of interest (ROIs) was determined, and source propagation between different regions was compared between the Pre-LEV and In-LEV recordings.

6.2.3 Results

Patients with epileptic seizures showed propagation in 22/24 identified spike types in the Pre-LEV recordings. In the In-LEV recordings only 7/15 spike types showed propagation, and six of these seven propagating spikes were recorded in patients with poor effect of treatment. Also in patients without seizures LEV tended to suppress propagation.

6.2.4 Conclusion

We conclude that the observed suppression of source propagation can be considered as an indicator of effective antiepileptic treatment. ESI might thus become a useful tool in the early clinical evaluation of new candidate drugs in pharmacological development.

6.3 Publication 3

Levetiracetam reduces the frequency of interictal epileptiform discharges during NREM sleep in children with ADHD

Kristin A. Bakke, Pål G. Larsson, Ann-Sofie Eriksson, Orvar Eeg-Olofsson. European Jorunal of Pediatric Neurology 2011; E-pub.

6.3.1 Background

Symptoms of attention – deficit - hyperactivity disorder (ADHD) are more common in children with epilepsy than in the general population. Epileptiform discharges may be seen in children with ADHD, also in those without a seizure disorder. Sleep enhances these discharges, which may be suppressed by LEV. This work was performed to assess the effect of LEV on focal epileptiform discharges during sleep in children with ADHD.

6.3.2 Methods

Thirty-five children with ADHD, 17 with focal epilepsy, one with generalized epilepsy and 17 with no seizures were included in this retrospective study. They all had a 24 - hour ambulatory EEG-recording when admitted to the hospital and a 24 – hour follow up recording after a median time of 4 months. All recordings were analyses with the semi-automated method described in publication one.

6.3.3 Results

Mean spike index was reduced from 50 before LEV - treatment to 21 during treatment. Seventeen children had no focal interictal epileptiform activity in EEG at follow up. Five children had more than 50 % reduction in spike index. Thus, a more than 50 % reduction in spike index was found in 22/35 children (63 %). Out of these an improved behaviour was noticed in 13 patients (59 %).

6.3.4 Conclusion

This study shows that LEV reduces interictal epileptiform activity discharges in children with ADHD.

6.4 Publication 4

Lower frequency variability in the alpha activity in EEG among patients with epilepsy

Pål G. Larsson, Hrisimir Kostov. Clinical Neurophysiology 2005;116:2701-2706

6.4.1 Background

Clinically, intra-subject variability of the alpha frequency is well known, but sparsely documented and practically not used in the evaluation of the electroencephalogram (EEG). In cognitive science, however, the peak alpha frequency (PAF) variations are implemented. The aim of the present study was to document the clinical notion of differences in alpha frequency and the alpha frequency variability in patients with epilepsy compared to a control group.

6.4.2 Methods

Standard EEG recordings from 28 patients, 18 with epilepsy and 10 patients having EEG for other reasons were included. Ten seconds of artifact free EEG were sampled from F3, F4, T5, T6, O1 and O2 at the beginning, after hyperventilation and at the end of a 20 minutes recording and Fast Fourier transforms was applied to these epochs of each recording.

6.4.3 Results

The study showed a lower frequency in the epilepsy group (frontal 9.22 vs. 10.24 Hz, temporal 9.18 vs. 9.88 Hz and occipital 9.42 vs. 10.30 Hz) and lower frequency variability, with lower values in the epilepsy group in occipital (0.8 vs. 1.44 Hz) and temporal leads (0.89 vs. 1.39 Hz). Frontally, the variability was not significant (0.71 vs. 1.18 Hz, p=0.0824). Within the groups, there was no relation between frequency and variability.

6.4.4 Conclusions

There is PAF variability in the alpha activity. This variability is compromised in patients with epilepsy. Lower alpha frequency is observed in the epilepsy group. This is to some extent dependent on antiepileptic drug treatment. The lower

alpha frequency variability is probably due to a different mechanism as there is no relation between the frequency and its variability within the two groups.

6.5 Publication 5

Alpha frequency estimation in patients with epilepsy.
Pål G. Larsson, Orvar Eeg-Olofsson, Göran Lantz. Submitted Clinical EEG and Neuroscience

6.5.1 Background

This study on the variability of the alpha activity showed variations on different time scales. A new method was developed which should be able to monitor wave to wave frequency variations to assess the both the fast changes in the alpha frequency which could not be assessed with standard frequency based methods, and the slow changes. This method was applied to a set of adult patients with and without epilepsy and compared with four other methods for alpha frequency assessment.

6.5.2 Method

Fifty six consecutive 20 minute routine recordings each in normally functioning patients between 16 and 70 years of age with and without epilepsy were used for assessment in this study. The use of antiepileptic drugs was recorded and changes in alpha frequency and its variability was assessed by two visual guided methods and two automated frequency methods and the new time domain based fully automated method.

The visually based methods were counting of alpha waves as seen by visual inspection and estimation through FFT of 3 -10 s epochs at the beginning, in the middle and at the end of the recording. The epochs were chosen by visual inspection as having good alpha rhythm with little artifacts as described in publication 4 (Larsson and Kostov, 2005).

The two automated FFT-based methods, one assessing alpha frequency for every second of the recording returning the mean of all values and the other calculated one FFT for the full length of the recording.

In the new method the EEGs was automatically analyzed by means of a Matlab script using a time based peak detector. Only occipital alpha activity was analyzed.

6.5.3 Results

The fully automated method calculating one FFT over the full length of the recording turned out overall best. It preformed marginally better than classical visual estimating when it came to discriminating groups of patients with and without epilepsy.

The new time domain based method did generally underestimate the high frequencies probably due to a regression towards the mean.

6.5.4 Conclusions on alpha frequency estimation

Our results show that automated analyses of alpha frequency is a clinically applicable procedure with results comparable to or even slightly better than the visual techniques. In this study the automated fast Fourier transform of the whole EEG in one segment (AWF) seems to do overall better than the other automatic methods, which is surprising considering that the other two automatic methods are more advanced. In standard 20 minutes EEG recordings the AWF calculates the mean alpha frequency very similar to the visual counting method, and the AWF does a decent job in discriminating the patient groups. The method is simple, fast and easily implemented and well suited for support in clinical EEG assessment.

7. Conclusions

This thesis is part of an ongoing work on using automatic assessment of elements from EEG analyses for clinical applications. The use of computer based methods in clinical evaluation of patients is increasing, bringing higher quality, saving labour and to some extent access to new information. In the studies, the methods for estimating the background activity and the interictal epileptiform activity have been further developed and tested for feasibility in clinical use.

The new method for estimating SI (Publ 1) has rapidly gained acceptance and is in daily use, clinically and in research in Norway (Larsson et al, 2010; Wannag et al, 2010; Bakke et al, 2011; Publ 3). It is also spreading internationally. The method has made it feasible both to assess individual patients and to compare groups of patients with objective, well reproducible values. The SI is both robust, only moderately sensible to the characteristics of the underlying spike detector, and it mirrors the cerebral load of the epileptiform activity. Due to the reproducibility of the method, a double blind cross over placebo controlled treatment study with LEV is now being conducted, applying SI as a main parameter. This study would not have been possible without a good quantitative method. Yielding further information from the spikes by assessment of spike activity propagation open up the possibility for AED effect assessment (Publ 2).

The alpha activity was chosen as it shows changes in frequency as a function of diseases and treatment. The initial study (Publ 4) quantified the differences between patients at the group level. To optimize the yield of the alpha activity assessment, five different assessment methods were tested (Publ 5). The results indicated that FFT of the whole recording was the best method for assessing the alpha frequency in discriminating the patient groups. This method is expected to give enough clinically useful information and is expected to be clinically implemented.

In conclusion, this thesis has resulted in a new method to assess SI, which has already gained clinical acceptance in individual patient work up. The other method, the alpha activity analysis, still needs more elaboration to become part of the clinical armamentarium, but one of the fully automated methods shows results at the same level as the classical visual alpha rhythm assessment when discriminating between patients with and without epilepsy.

8. Appendixes

8.1. Appendix A. Epileptic seizure classification

(Berg et al, 2010)

- Generalized seizures
  - Tonic-clonic (in any combinations)
  - Absence
    - Typical
    - Atypical
    - Absences with special features
      - Myoclonic absences
      - Eyelid myoclonia
  - Myoclonic
    - Myoclonic
    - Myoclonic atonic
    - Myoclonic tonic
- Focal seizures
- Unknown
  - Epileptic spasms

8.2. Appendix B. Electroclinical syndromes and other epilepsies

(Berg et al, 2010)

Electroclinical syndromes arranged by age at onset

Neonatal period

- Benign familial neonatal epilepsy (BFNE)
- Early myoclonic encephalopathy (EME)
- Ohtahara syndrome

Infancy

- Epilepsy of infancy with migrating focal seizures
- West syndrome
- Myoclonic epilepsy in infancy (MEI)
- Benign infantile epilepsy
- Benign familial infantile epilepsy
- Dravet syndrome
- Myoclonic encephalopathy in nonprogressive disorders

Childhood

- Febrile seizures plus (FS+) (can start in infancy)
- Panayiotopoulos syndrome
- Epilepsy with myoclonic atonic (previously astatic) seizures
- Benign epilepsy with centrotemporal spikes (BECTS)
- Autosomal-dominant nocturnal frontal lobe epilepsy (ADNFLE)
- Late onset childhood occipital epilepsy (Gastaut type)
- Epilepsy with myoclonic absences
- Lennox-Gastaut syndrome
- Epileptic encephalopathy with continuous spike-and-wave during sleep (CSWS)
- Landau-Kleffner syndrome (LKS)
- Childhood absence epilepsy (CAE)

Adolescence – Adult

- Juvenile absence epilepsy (JAE)

Juvenile myoclonic epilepsy (JME)

Epilepsy with generalized tonic–clonic seizures alone

Progressive myoclonus epilepsies (PME)

Autosomal dominant epilepsy with auditory features (ADEAF)

Other familial temporal lobe epilepsies

Less specific age relationship

Familial focal epilepsy with variable foci (childhood to adult)

Reflex epilepsies

Distinctive constellations

Mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE with HS)

Rasmussen syndrome

Gelastic seizures with hypothalamic hamartoma

Hemiconvulsion–hemiplegia–epilepsy

Epilepsies that do not fit into any of these diagnostic categories can be distinguished first on the basis of the presence or absence of a known structural or metabolic condition (presumed cause) and then on the basis of the primary mode of seizure onset (generalized vs. focal)

Epilepsies attributed to and organized by structural-metabolic causes

Malformations of cortical development (hemimegalencephaly, heterotopias, etc.)

Neurocutaneous syndromes (tuberous sclerosis complex, Sturge-Weber, etc.)

Tumor

Infection

Trauma

Angioma

Perinatal insults

Stroke

Etc.

Epilepsies of unknown cause

Conditions with epileptic seizures that are traditionally not diagnosed as a form of epilepsy per se

- Benign neonatal seizures (BNS)
- Febrile seizures (FS)

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I

II

III

IV

Alpha frequency estimation in patients with epilepsy

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Introduction

The alpha activity in human was first observed by Hans Berger in 1924 [1] with the findings published in 1929 [2]. The alpha rhythm is classically defined as a rhythmic activity in the EEG during wakefulness with a frequency between 8 Hz and 13 Hz. The rhythm is predominant in the posterior regions of the head and is blocked by eye opening [3]. The aetiology as well as the physiological behaviour of the alpha rhythms is poorly understood [4-10]. However, the variability of the alpha rhythm is well established in clinical EEG interpretation [1, 11-13]. The fact that alpha frequency changes as a function of age is important. The rhythm varies in amplitude and frequency due to changes in attention, [14 -17] arousal [18] and other factors, e.g. blood sugar levels [19]. Most studies on short term alpha frequency variability have been performed in cognitive performance studies [20 - 26]. Also in patients with epilepsy, decreased variability of the alpha frequency have been reported [2].

The alpha rhythm is also prone to frequency changes in some disorders as epilepsy, dementia and some tumours, and in treatment with antiepileptic drugs [27-35]. This knowledge is rarely taken into consideration in the assessment of clinical EEG. With the advent of stronger computer systems the availability to new automated analyses and hence, better statistical analyses, pushes for the development of new quantification tools. One of these will be a method for automated assessment of the alpha rhythm in clinical settings.

Quantification of the alpha-rhythm is a difficult task. According to the definition by International Federation of Clinical Neurophysiology (IFCN) [3] the alpha rhythm is

defined mainly as a set of features in time domain but without a clear definition in the frequency domain except for the main frequency band. That the activity is within the alpha frequency band is not enough to make it an alpha rhythm. The alpha rhythm proper is impossible to assess through FFT. Even so, Fast Fourier transform (FFT) is to some extent implemented to find alpha rhythm frequencies in short segments (a few seconds), but fully automatic analysis is not commonly applied clinically.

The lack of clinical impact of the alpha frequency in EEG reading may be attributed to two issues; the inter- and intra-individual physiological variability in frequency and amplitude and the lack automated methods for high reproducibility. Hence, the reports of pathological findings in the alpha rhythm are usually rather coarse such as asymmetries in amplitude and frequencies and dominant frequency.

The aim of the present study was to compare different methods for automatic analysis of the alpha activity using time domain and frequency domain based methods to assess the applicability of these automatic techniques in clinical EEG reading, and compare the results with standard visual interpretation. It has been demonstrated that there is a difference in alpha frequency between people with and without epilepsy [27, 36] and the ability of the methods to detect these differences was used as an indicator of their efficiency.

Methods

Fifty - six consecutive patients between 16 and 78 years of age, each having a 20 minute routine EEG recording, were included in the study. The patients were divided

in groups, with epilepsy (Ep) and without epilepsy (nEp). For grouping, patient information was collected from the referral information and from the patient record when applicable. Among the 56 patients, there were 36 with an epilepsy diagnosis and 20 with an unclear diagnosis, e.g. headache and dizziness.

The EEGs were recorded according to the 10 – 20 system with added “low rows” (F9, F10, T9, T10, P9, P10) with a total of 25 channels at 256 samples per second filtered 0.5 – 70 Hz. The reference electrode was according to protocol located at CP1. All analyses were commenced using a single reference montage. For this study the alpha rhythm in the six channels O1, O2, P3, P4, T5 and T6 was analyzed.

The alpha frequency was assessed in five different ways.

Visual inspection and manual counting (VMC)

The VMC was implemented by counting alpha waves approximately one minute after the start of the recording, 3 minutes after the end of hyperventilation and one minute after the end of intermittent light stimulation in artifact free segments (Larsson and Kostov, 2005). The protocol required counting at least one second of alpha activity at each location in each applicable channel. With this technique the frequency resolution was approximately 0.5 Hz. The method was only applied to O1 and O2.

Visual inspection and FFT in same segments as the manually counted (VFT)

For the epoch used in the VMC, FFT was applied on 3 s to 6 s artifact free segments. The frequency with the highest amplitude between 8 Hz and 13 Hz was taken as the alpha frequency. The frequency resolution was 0.25 Hz. The method was only applied to O1 and O2.

Three fully automated methods were applied.

Automatic assessment of alpha waves in time domain (ATD)

This time domain method was crafted to enable assessment of frequency variability down to consecutive waves. The algorithm used a moving time window for detection. The algorithm was set to find both positive and negative peaks in the EEG. When a peak was found, the sign was changed and the algorithm looked for a peak with the opposite sign. The time window comprised 17 sample points for each half cycle which corresponds to 7.5 Hz (period time: (17 samples *2)/256= 0.1328s). The algorithm looked for the most extreme value within the time window. Before accepting a point as a peak, the next 17 samples from the peak were checked for more extreme values. If no more extreme value was found, the peak candidate was accepted as a peak. The search was then continued for consecutive half waves. Peak-to-peak intervals outside the alpha band (20 -36 sample points; 7.1 Hz – 12.80 Hz (period time: 0.0781s - 0.1406s)) and peaks with amplitude difference below 10 μV in two consecutive half waves were discarded.

The inverse of the median value for every inter peak time in the full recording was returned as the alpha frequency for the given channel.

The algorithm used in the ATD alpha frequency assessment has an implicit filter function that influences the returned values. In figure 1 the influence of the time window length (i.e. the search window to look for higher peaks) on the returned alpha frequencies are visualized in two patients. The tested time window length range is from 10 to 20 sample points. Given a sampling rate of 256 Hz, the corresponding time window length is from 39 ms to 78 ms for each half wave which corresponds to

a frequency range from 6.4 Hz to 12.8 Hz. A factor 2 change in time window length gives here only about 4 % change in returned median alpha frequency (10.24 Hz to 9.85 Hz and 9.85 Hz to 9.48 Hz in the two patients, respectively). Consequently, the impact of time window length on the frequency is rather limited, and in all further calculations a 17 points look a head window have been applied.

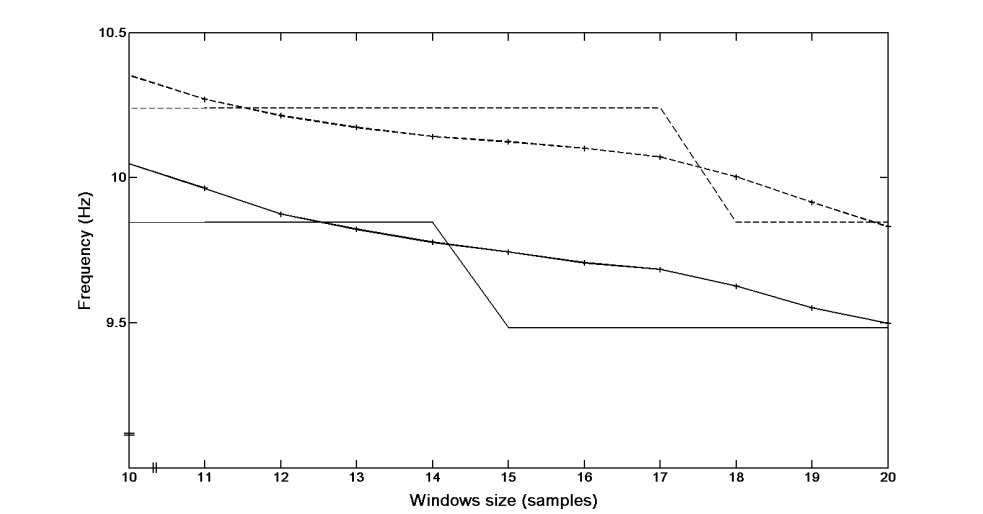

Figure 1. Plot of estimated alpha frequency in Herz as a function of length of the look ahead window, in two patients. Both mean (line with markers) and median (line without markers) were plotted in both patients.

Automatic assessment of whole EEG by one FFT of the full recording (AWF)

The AWF was calculated by doing one single FFT calculation on the full recording. This returned 153600 frequency values from each 20 minute recording. The returned alpha frequency was the frequency with the highest amplitude in the FFT between elements 9600 and 15600 (8 Hz – 13 Hz). To increase robustness, a 50 point moving average was applied to the calculated FFT. Subsequently a linear detrend as applied by Matlab (Mathworks) was applied to the alpha range before finding the highest

amplitude which corresponded to the alpha frequency. The function removes the mean or linear trend from analyses FFT segment. FFT was calculated by means of the FFT function in Matlab.

Automatic assessment of EEG segments by FFT (ASF)

The FFT was calculated with four second windows with one second increments. A linear detrend of the returned FFT in the alpha range was applied before the frequency at the highest amplitude was returned for each segment. The median value for all segments was returned as the alpha frequency.

To test for variability within each recording, mean absolute deviation (MAD) was calculated. MAD is calculated as the mean absolute deviation from the mean: $\frac{1}{n}\sum_{i=1}^{n}|x_i - mean(x)|$. MAD weights extreme values less than standard deviation does as there is no squaring of the numbers before adding.

Within the patient groups means were calculated and differences between groups were tested by two sided Student T-tests. Comparison of methods was done by Bland-Altman plot where the differences in values between two methods are plotted against the mean value from the two methods.

Results

VMC

The VMC gives a mean frequency of 9.97 Hz in group nEp (Table 1a). In group Ep the mean frequency is 9.35 Hz. In both groups O1 and O2 show almost identical values. The difference between the groups for each channel is almost significant, p=0.065 and p=0.061 respectively. Pooling the values from the two occipital channels gives a significant difference (p=0.008).

The variability between the three observations, as measured by MAD, gives no clear tendencies (Table 2 a), but there might be a tendency to lower variability in the group without epilepsy.

	VMC			**VFT**		
a	**Ep**	**nEp**	**p**	**Ep**	**nEp**	**p**
O1	9.31	9.94	0.065	9.44	9.89	0.136
O2	9.38	10	0.061	9.49	9.88	0.166
Mean	9.35	9.97	0.008	9.47	9.89	0.04

	ATD			AWF			ASF		
b	Ep	nEp	p	Ep	nEp	p	Ep	nEp	p
O1	9.15	9.29	0.240	9.11	10.16	<0.001	9.61	9.82	0.384
O2	9.17	9.34	0.450	9.14	10.12	0.003	9.63	9.83	0.401
P3	9.19	9.31	0.107	9.36	9.82	0.064	9.66	9.88	0.371
P4	9.18	9.33	0.242	9.24	9.90	0.143	9.72	9.93	0.386
T5	9.21	9.45	0.138	9.30	9.91	0.063	9.73	9.96	0.344
T6	9.28	9.54	0.054	9.40	10.1	0.008	9.73	10.16	0.086
Mean	9.20	9.38	0.002	9.26	10.00	0.003	9.68	9.93	0.011

Table 1. Calculated alpha frequency and probability (p) with the automated methods (panel a) and visually guided methods (panel b). 'Ep' denotes the epilepsy group, 'nEp' the control group. The p-values given in the last line ('Mean') are calculated on pooled data. VMC = Visual inspection and manual counting , VFT = Visual inspection and FFT in same segments as the manually counted, ATD = Automatic assessment of alpha waves in time domain, AWF = Automatic assessment of whole EEG by one FFT of the full recording, ASF = Automatic assessment of EEG segments by FFT.

	VMC			VFT		
a	**Ep**	**nEp**	**p**	**Ep**	**nEp**	**p**
O1	0.879	0.377	0.250	0.421	0.411	0.926
O2	0.439	0.589	0.318	0.494	0.385	0.228
Mean	0.659	0.483		0.458	0.398	

	ATD			ASF		
b	**Ep**	**nEp**	**p**	**Ep**	**nEp**	**p**
O1	1.28	1.30	0.597	0.787	0.910	0.677
O2	1.29	1.31	0.566	0.785	0.816	0.687
P3	1.28	1.30	0.666	0.770	0.811	0.572
P4	1.29	1.30	0.739	0.771	0.819	0.532
T5	1.29	1.30	0.657	0.783	0.835	0.454
T6	1.29	1.32	0.442	0.770	0.813	0.553
Mean	1.29	1.31		0.78	0.83	

Table 2. The alpha frequency variability and the probability (p) calculated by visually guided methods (panel a) and the fully automated methods (panel b). 'Ep' denotes the epilepsy group, 'nEp' the patient group without epilepsy. VMC = Visual inspection and manual counting , VFT = Visual inspection and FFT in same segments as the manually counted, ATD = Automatic assessment of alpha waves in time domain, ASF = Automatic assessment of EEG segments by FFT.

VFT

The VFT method shows similar values to those returned by VMC in the Ep group and the nEp group (9.47 Hz versus 9.89 Hz). Pooling the alpha frequencies from the two occipital channels gave a significant difference between the groups (p=0.040)

The variability between the three observations is similar to the VMC values, but eventual differences are even less impressive.

There is a good correlation between the two visually guided methods as demonstrated in figure 2.

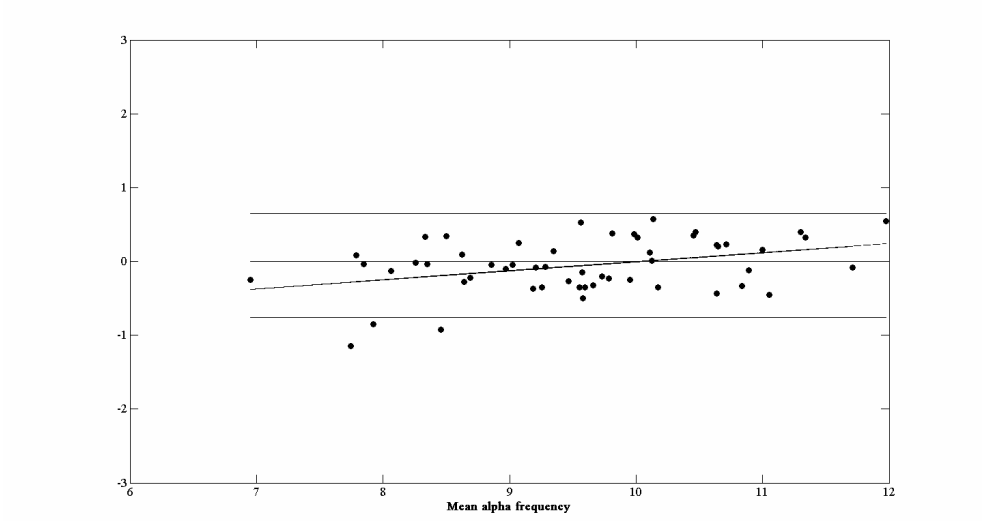

Figure 2. Bland - Altman plot of differences between the two visually guided methods

ATD

Estimating the alpha frequency by means of ATD gives a mean frequency of 9.38 Hz in the nEp group and 9.20 Hz in the Ep group (Table 1b). The difference between the groups is not significant. Generally this method calculates values closer to the mean,

and hence does not reflect good estimates for very high or very low alpha frequencies. Pooling all six channels gives a significant difference between the groups (p=0.002). This method underestimated high frequencies and to some extent overestimated low frequencies (fig. 3)

The variability in the calculated alpha frequencies in each patient is not different between the groups (Table 2 b).

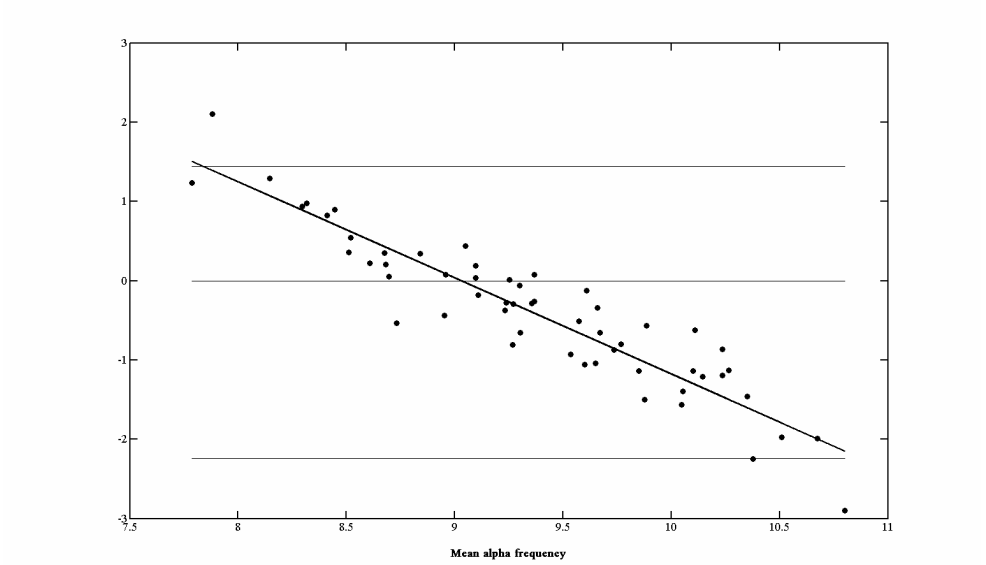

Figure 3. Bland – Altman plot of differences between the automated time domain method (ATD) and classically assessment (VMC)

AWF

The mean alpha frequency in the nEp group is 10.00 Hz versus 9.26 Hz in the Ep group (p=0.043). In the occipital channels the difference is highly significant (O1 10.16 Hz vs. 9.11 Hz, p<0.001 and O2 10.12 Hz vs. 9.14 Hz, p=0.003). As one FFT is calculated for the full length of each electrode, there is only one number returned for each patient and electrode, variability can not be calculated.

ASF

ASF provides small differences between the groups; 9.93 Hz and 9.68 Hz respectively in the control and the epilepsy group.

All methods indicate lower alpha frequencies in the Ep group than in the nEp group. With VMC and the AWF these differences are in the order of 0.5 Hz, and the differences are statistically significant for most of the analyzed electrodes, (Table 1 a, Table 1 b). The significances are somewhat stronger for AWF compared to VMC.

The variability in the alpha frequency within each recording did not help discriminating the patient groups (table 2). Both in the ASF and the ATD analysis for the ultradian rhythms, the basic rest-activity cycle (BRAC) [37] could sometimes be seen. This was not analysed further.

Discussion

This study was set up to compare different methods for estimation of the alpha frequency in a clinical setting as a follow up on our former study [27]. The goal was to assess different automated methods' ability to deliver clinically valuable information and compare the methods to the conventional visual EEG reading (VMC).

Estimating the alpha frequency by a Fourier transform will by definition return a different alpha activity than visual inspection. Not only visible alpha waves but also

elements from complex waveforms where the alpha components are not recognized by the naked eye are included. Some of these waves do not have the same source as the alpha rhythms proper. On the other hand, the FFT may include elements with the same sources as the alpha rhythm proper, which is not recognized by visual inspection and thus not included in the visual estimate.

Automatic analysis of the alpha rhythm can be established with two different primary goals. The first is to match all features in time domain to mimic the classical, visual interpretation. This is still out of clinical range. The other goal is to optimize the information yield to include information of clinical relevance that has not been appreciated in classical EEG interpretation.

Among the automated FFT methods, the AWF discriminated best between the epilepsy and the no epilepsy groups, better than any of the manual methods. The visual VMC method performed almost as good as the AWF method. The VFT returned values similar to VMC and AWF, but this method was slightly inferior to the two abovementioned when it came to discriminating between patient groups. This was unexpected as VFT uses the strength of the visual methods when selecting area for analysis and the computer strength of reproducible results.

The rational for setting up the ATD was to have results mimicking parts of the visual interpretation. The method applied is crude in the sense that it only looks for peaks to estimate the alpha rhythm. Invisible elements in the alpha range will not be recorded and accordingly no subelements of complex grapho-elements will be included. There

were no extra criteria used to mimic the clinically used selection routines for the alpha rhythm proper e.g. recognizing the spindle shape. ATD returns a frequency value for every single wave and hence has the ability also to return information on ultradian rhythms as the 90 minutes rhythm seen in sleep or the 20 – 50 seconds BRAC rhythm. However, the irregular occurrence of alpha waves, gives rise to some extra challenges in the analysis especially with the requirement of using discrete Fourier transform for non-uniform sampling.

Despite the similarity to visual inspection and the large amount of available information, the ATD method did not prove very good to discriminate between the groups. It is not a good alternative to VMC when it comes to reporting on absolute alpha frequencies. ATD reports too low mean frequency in patients with high alpha frequencies. This is not due to the look forward window length. The calculated alpha frequencies hardly changes when the window length is changed as shown in figure 1. The reported lower alpha frequencies in patients with alpha frequencies well above the mean may be explained by a regression toward the mean. There will always be waves at most frequencies within the alpha band. When the dominating alpha frequency is close to the border of the alpha band the median will be calculated with a bias towards the middle of the alpha band. This phenomenon was less pronounced at the lower frequency border than the upper, which may be attributed to a more general slowing and hence less fast activity going in to the calculations of the mean in patients with lower alpha frequencies.

The alpha frequency variability as calculated by the different methods, did not help discriminating the patient groups. Even though they weight the information of the variability differently; none of the methods where effective. The VMC and VFT returns 3 values – one from the start, one from the middle and one from the end of the recording. This weights in the slow variability as reported in the prior paper. The ATD calculates the frequency distribution from between 1372 and 7474 values. These values are a mix of the wave to wave variability of the alpha and, in this context, noise. The noise contains peaks from interfering waves and potentials from extracranial artifacts. The ATD is insensitive to slow variations in opposition to the visual methods as there are more values returned every second The variability, calculated as absolute deviation of the 1197 samples do not turn out as a good discriminating parameter. This may be due to artifacts being added to the calculations or that there is no second to second variability difference between the groups. The AWF does only return one value so variability could not be reported for this modality.

The intra recording alpha frequency variability in this study is less impressive than the findings in the former article [27]. This may be attributed to chance or to differences in the patient sample. In this study, 56 consecutive patients were selected prospectively and either defined as having or not having epilepsy. In the former study, we retrospectively sampled two groups with clear differences, which may have enhanced the differences between the groups in this study. It would be expected that this sample bias would contribute to the difference between the studies. Barna et al. [38] directly challenged the findings of Larsson and Kostov [27] in a study where they compared 20 children with “mild epilepsy” and 20 controls. They concluded that it is

unlikely to differentiate between normal children and children with “mild epilepsy” based on peak frequency and mean voltage distribution. However, studying children and using different methods, implies a weak inference power relative our prior study. The results of the three studies together support the hypothesis that there are some changes in the slow variability, but it seems to have no clinical applicability as implemented. The differences are small and not significant even in moderate sized groups.

In many of the statistical inferences done, combining data from more channels was necessary to reach significance levels. This is not a standard way of handling groups of data in ordinary statistical inference and was only done to help discriminating too low power in the study from lack of effect. More significant differences when combining data from more channels was attributed to too small samples, as random differences is expected to cancel out when increasing the sample size.

Estimation of the alpha frequency at symmetrical positions gives almost the same results. This is an indicator of the robustness of the tested algorithms and indicates that the reported variabilities are related to intra- and inter patient variations.

In summary, the different visual and automatic methods show strong and weak sides. The VMC is the old well studied standard giving the definition of the alpha rhythm and hence, the only to comply with the formal definition. However, this method is prone to subjective influence. The VFT, with its automatic calculation of the alpha frequency in segments visually determined to be alpha rhythm, was expected to return as good as or even better results than VMC, but this was not the case.

Among the automatic methods, the ASF, estimating alpha frequency from a large number of segments seems ideal for automated analyses. However, the method does perform slightly inferior both to the visual VFT and the automatic AWF. The automatic ATD method, estimating the alpha frequency in time domain, was expected to be equivalent to VMC. The method generally returned lower alpha frequencies, and, despite some discriminating abilities, still seems inferior to the other methods. The automatic AWF, on the other hand, returned frequencies very similar to the visual VMC and, despite its simplicity, also discriminated well between the patient groups.

To conclude, our results show that automated analyses of alpha frequency is a clinically applicable procedure with results comparable to or even slightly better than the visual techniques. The AWF seems to do overall better than the other automatic methods, which is surprising considering that the other two automatic methods are much more advanced. In standard 20 minutes EEG recordings the AWF calculates the mean alpha frequency very similar to the VMC, and the AWF does a decent job in discriminating the patient groups. The method is simple, fast and easily implemented and well suited for support in clinical EEG assessment.

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