The characteristics of epileptiform activity and their implications for EEG background activity studied through a novel comprehensive EEG database

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Contents

1. Scientific environment

The present work was carried out at the Department of Clinical Medicine, Section of Neurology and Section of Clinical Neurophysiology, Department of Neurology, Haukeland University Hospital.

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3. Terms and abbreviations

Terms:

Alpha rhythm	The dominant posterior EEG-rhythm with frequency 8–13 Hz that is blocked or attenuated by eye opening
Background activity	Any EEG activity representing the setting in which a given normal or abnormal pattern appears and from which such a pattern is distinguished
Database	A filing system organised to provide fast access to desired pieces of data
Epilepsy	A disorder characterized by spontaneous recurrent episodes of paroxysmal brain dysfunction due to a sudden, disorderly, and excessive neuronal discharge
Focal epileptiform activity	Epileptiform activity that is not generalised
General background activity	The background activity apart from the alpha rhythm
Generalised epileptiform activity	Epileptiform activity appearing in three or more out of five brain regions at both sides at the same time and with not more than moderate asymmetry
Hyperventilation provocation	A procedure implying intentional overbreathing for 3 minutes
Hyperventilation sensitivity	Epileptiform activity being more than doubled during hyperventilation provocation
Photic stimulation	A procedure implying intermittent light flashes in a predefined sequence of different frequencies
Photoparoxysmal response	Generalised epileptiform activity being more than doubled during photic stimulation

Abbreviations:

aEEG	amplitude-integrated EEG
AM	annotation module
API	application programming interface
AR	alpha rhythm
ASTM	American Society for Testing and Materials
BA	background activity
BOLD	blood-oxygen-level-dependent
CBRDEE	current brain-related disease except epilepsy
COM	component object model
DM	database module
EAS	EEG annotation system
EEG	electroencephalography
EEGer	electroencephalographer
FEA	focal epileptiform activity
Fig	Figure
fMRI	functional magnetic resonance imaging
GBA	general background activity
GEA	generalised epileptiform activity
HVS	hyperventilation sensitivity
Hz	Hertz
ICD-9	International Classification of Diseases, Ninth Revision
ICD-10	International Classification of Diseases, Tenth Revision
IGE	idiopathic generalised epilepsy
JME	Juvenile myoclonic epilepsy
LTM	Long term monitoring
MEG	Magnet encephalography
MFPM	multivariate fractional polynomial model
MPM	multivariate polynomial model
MRI	magnetic resonance imaging
MS	Microsoft

ODBC	open database connectivity
OR	odds ratio
p	probability
PET	positron emission tomography
PPR	photoparoxysmal response
PSPs	postsynaptic potentials
RBS	regular bilateral synchronous
RGM	report generator module
sec	second
SPECT	single photon emission tomography
SQL	structured query language
TMS	transcranial magnetic stimulation
μV	micro-volt

4. Introduction

4.1 EEG

EEG represents the measurement of fluctuating electrical activity generated from the brain. This activity is usually obtained by recording from electrodes placed on the scalp, but can also be obtained from electrodes placed directly on the brain cortex or inside the brain cortex. The scalp EEG provides an inexpensive, non-invasive measurement of brain state fluctuations with high temporal resolution in the range of milliseconds, but, compared to modern imaging techniques, with rather low spatial resolution in the range of centimetres (Ritter and Villringer, 2006; Tao et al., 2007).

4.1.1 EEG history

Already in the late 19th century electrical currents from the surface of exposed brains of monkeys and rabbits were reported (Caton R, 1875). Hans Berger published in 1929 the first scalp EEG recording from humans (Berger, 1929). The first epileptiform spikes were published in 1935 (Kornmuller, 1935). In the 1980s and 1990s the digital computer technique was introduced for EEG recordings. This enabled user-selected montages, vertical and horizontal scaling, filter adjustments, a far better storage, and faster retrieval of EEGs (Burgess, 1993; Nuwer, 1997; Swartz, 1998; Quinonez, 1998; Blum, 1998; Epstein, 2006). Such technology also makes it possible to record multi-channel EEG and polygraphic data for ambulant patients. Digital video can be simultaneously recorded with EEG, known as video EEG telemetry.

4.1.2 Physiological basis of EEG

Convoluted dipole layers of pyramidal neurons in the cortical gray matter are the principal EEG generators of scalp EEG recordings (Schaul, 1998b). The recorded oscillations originate from postsynaptic potentials (PSPs) rather than action potentials. Although action

potentials are higher in amplitude, PSPs are longer in duration and involve a larger membrane surface allowing both temporal and spatial summation of excitatory and inhibitory PSPs. Using simultaneous scalp and intracranial recordings a recent study has demonstrated that 10-20 cm^2 of gyral cortex is commonly required to generate scalp-recognisable inter-ictal spikes. The phenomenon of temporal and spatial summation may explain the general relationship between frequency and amplitude. Oscillations with higher frequency are more liable to strict synchronisation between adjacent PSPs to produce high amplitudes recorded from a distant localisation leading to lower amplitudes compared to oscillations with lower frequencies (Singer, 1993; Schaul, 1998a; Pfurtscheller and da Silva, 1999; Smit et al., 2006). The physiological basis for oscillatory EEG behaviour, for example the underlying time constants responsible for specific frequency ranges, is poorly understood although several mechanisms have been proposed (Pedley TA, Traub RD, 1990; Nunez et al., 2001).

Epileptogenesis

Hypersynchrony is probably a crucial factor of epileptogenesis and may involve either excitatory or recurrent inhibitory innervation (Binnie and Stefan, 1999c). Neither bursting nor synchrony depends, however, on synaptic transmission, as synchronous bursting can also be demonstrated in tissue slices after complete synaptic blockade, presumably on the basis of ephaptic transmission. In idiopathic generalised epilepsy (IGE) it is understood that the cortex is abnormally and unevenly hyperexitable and responds by spike-wave activity to essentially physiologic afferents from the thalamus and reticular-activating system, while the associated subcortical component becomes secondarily involved in the thalamocortical oscillations that maintain the discharge (Avoli and Kostopoulos, 1982; Koutroumanidis and Smith, 2005). Long-term potentiation by high frequency stimulation and the converse process for long-term depression are the most studied models for memory formation in mammals (Cooke and Bliss, 2006). The long-term potentiation mechanism of memory is similar to the mechanism underlying focal epileptogenesis by kindling (Meador, 2007). Kindling involves repeated administration of brief, low-intensity trains of electrical stimuli that result in a permanent state of increased susceptibility and even spontaneous seizures. The hippocampus contributes both through its role in memory formation and its low seizure threshold. Transition from normal to epileptiform behaviour of neuronal networks is probably caused by greater spread and neuronal recruitment secondary to a combination of

enhanced connectivity, enhanced excitatory transmission, a failure of inhibitory mechanisms, and changes in intrinsic neuronal properties (Duncan et al., 2006).

4.1.3 Basic elements of visually assessed EEGs

Visual EEG assessment can be separated into several specific elements. Each element has its own significance, but usually all elements, together with clinical information, should be brought together to draw a conclusion.

The EEG background activity (BA) is defined as any EEG activity representing the setting in which a given normal or abnormal pattern appears and from which such a pattern is distinguished (Chatrian et al., 1983). The alpha rhythm (AR) is a separate part of the BA. The AR is defined as the dominant posterior rhythm with frequency 8–13 Hz that is blocked or attenuated by eye opening. Alpha variant rhythm is defined as with AR characteristics but with frequency outside the 8–13 Hz alpha band (Chatrian et al., 1983). We defined the BA apart from the AR (or AR variant) as the general background activity (GBA). Low GBA frequency and high GBA amplitude are generally interpreted as EEG background slowing and is indicative of CNS pathology (Dustman et al., 1993; Babiloni et al., 2006). Most of the cerebral activity observed in the scalp EEG falls in the range of 1-20 Hz. EEG activity is separated into frequency bands; delta (< 4 Hz), theta (4-8 Hz), alpha (8-13 Hz), beta (>13 Hz, usually 13-40 Hz).

EEG findings occur as normal or abnormal patterns appearing from, and distinguished from, the BA. The EEG findings can be separated into four groups: Epileptiform pathology, non-epileptiform pathology, normal findings and variants, and extra cerebral activity.

4.1.4 Factors affecting EEG activity

EEG activity can be affected by numerous endogenous and exogenous factors. Age, and thereby the maturation of the brain, is crucial for the appearance of EEG activity. Knowledge about the normality at different ages is essential to separate pathology from normality. In general, there are slower frequencies and higher amplitudes found in EEGs from children compared to EEGs from adults. When it comes to pathology, a usual effect in adult EEGs is the reappearance of slow activities, appearing diffusely in general pathology

and localised in focal pathology. Consciousness, the degree of alertness, sleep-wake cycles, and drugs acting in the brain are furthermore critical for the appearance and assessment of the EEG.

4.1.5 EEG techniques

Long term monitoring (LTM)

Some diagnostic problems cannot be adequately addressed by inter-ictal routine EEG recordings, but require monitoring over a long period of time lasting for hours to weeks. If the visual inspection of clinical events is presumed to be essential, EEG with synchronous digital video-monitoring is to prefer, otherwise ambulatory EEG with a portable recording and storage unit is suitable. The clinical applications of EEG monitoring are:

- diagnosis of paroxysmal neurological attacks
- differentiation between nocturnal epilepsy and parasomnias
- diagnosis of psychogenic non-epileptic seizures
- characterisation of seizure type
- quantification of inter-ictal epileptiform discharges or seizure frequency
- evaluation of candidates for epilepsy surgery (Smith, 2005).

Amplitude-integrated EEG (aEEG)

aEEG is a LTM technique where the EEG data recorded with a reduced number of electrodes is visualised as a time-compressed amplitude-integrated trend measure. aEEG has become increasingly acknowledged as a method for continuous evaluation of brain function in neonates (Hellstrom-Westas and Rosen, 2006). One reason for this was the finding that the very early background pattern is sensitive for predicting outcome in asphyxiated full-term infants even during the first postnatal hours (Hellstrom-Westas et al., 1995; Eken et al., 1995). aEEG has also proved to predict outcome after cardiac arrest and induced hypothermia in an adult population (Rundgren et al., 2006).

Intracranial EEG

Intracranial EEG recordings are performed in the presurgical evaluation of patients with drug-resistant focal epilepsy where non-invasive techniques have not been able to locate the epileptogenic zone. Implanted subdural electrodes allow recording from large superficial cortical areas, but provide limited coverage of deep-seated structures, such as the hippocampus, as well as of the cortex within sulci (Cossu et al., 2005). Stereotactically inserted intracerebral electrodes have the advantage of excellent sampling from mesial structures and from intrasulcal cortex, but with the disadvantage of providing information from a limited volume of tissue. Such electrocortigography is used peroperatively to identify the location and borders of the epileptogenic area, to guide the extent of resection, and to secure its completeness (Kuruvilla and Flink, 2003).

EEG source imaging

EEG source imaging attempts to visualise the origin of scalp EEG recordings. This represents "the inverse problem". EEG can only measure the electrical dipole current components perpendicular to the surface where it is measured. The EEG signal reflects the sum of the electrical dipoles from the recorded tissue. The dipoles located near the surface contribute more than the distant ones. Only synchronized electrical activities sum up, whereas non-phase locked sources may cancel each other out and contribute only as statistical fluctuations (i.e., imperfect cancellation) to the EEG (Ritter and Villringer, 2006). The exact relation between intracranially and extracranially recorded epileptiform activity, however, has been the subject of considerable debate (Lantz et al., 2003). Numerous models have been applied to solve the inverse problem, but by introducing reasonable a priori constraints EEG source imaging can be a useful tool (Michel et al., 2004).

4.1.6 EEG applications

Even though epilepsy is a clinical diagnosis, EEG plays a major role in evaluating epilepsy, the single most studied patient diagnosis in nearly all EEG laboratories, and the area in which EEG is of greatest clinical value (Binnie and Stefan, 1999b; Flink et al., 2002a). Such investigations serve three main purposes: to support the general diagnosis of epilepsy, to aid deciding if the seizure is generalized or focal, and to aid syndrome classification (Binnie and

Stefan, 1999a; Fowle and Binnie, 2000). Despite advances in neuro-imaging techniques over the past three decades that have helped identifying structural lesions of the central nervous system, EEG continues to provide valuable insight into brain function by demonstrating nonepileptiform focal or diffuse abnormalities and epileptiform abnormalities (Markand, 2003). EEG facilitates differentiating between epileptic and non-epileptic seizures, seizure types, epilepsy syndromes, focal or generalised epilepsies, and symptomatic versus idiopathic epilepsies. Thereby EEG also facilitates the choice of antiepileptic medication and prediction of prognosis. EEG is furthermore useful in the evaluation of focal and diffuse encephalopathies, comatose conditions and cerebral disorders affecting neonates and infants (Markand, 2003).

Quantitative EEG (qEEG)

The most commonly used quantitative representation of EEG is the estimation of power density of selected EEG frequency bands Fast Fourier Transform (Barry et al., 2003). The EEG is usually first visually inspected, and a period with a minimum of artefacts is chosen. The frequency range has traditionally been transformed into delta (1.5-3.5 Hz), theta (3.5-7.5 Hz), alpha (7.5-12.5 Hz), and beta (12.5-20 Hz). Results from each electrode can be represented as absolute power in each band (total μV^2), relative power in each band (percentage of total power), coherence (a measure of synchronisation between activity in two channels), or symmetry (the ratio of power in each band between a symmetrical pair of electrodes) (Hughes and John, 1999).

4.1.7 Functional neuroimaging

MRI/fMRI

MRI is the mainstay of brain imaging in elective clinical practice, and should be used in all patients who develop epilepsy as adults, in whom focal onset is suspected, or in whom seizures persist (Duncan et al., 2006). An increase of neuronal activity is accompanied by an increase of the metabolic rate of oxygen consumption and a much larger increase in the local blood flow. This result in a change in the proportion of oxygenated vs. deoxygenated haemoglobin and thereby a change of magnetic properties. These principles are exploited in the fMRI blood-oxygen-level-dependent (BOLD) contrast technique. Simultaneous fMRI

and EEG is being investigated for its possibilities of combining the high temporal millisecond resolution of EEG with the high spatial resolution of fMRI. When the temporal pattern from events such as epileptiform discharges is known, fMRI may provide an anatomical map of the corresponding physiologic activity with a spatial resolution of less than 5 mm^3 (Stern, 2006; Benar et al., 2006). The most widely used technique for such integration is spike-triggered imaging. However, both theoretically and empirically there will be situations where fMRI signals occur without any EEG correlates and vice versa. The mismatch between electrophysiological and haemodynamic signals provide challenges for the integration of EEG and fMRI (Ritter and Villringer, 2006).

Magnet encephalography (MEG)

The MEG-technique measures oscillations of the magnetic fields arising arise from the same sources in the brain as in EEG (Sharon et al., 2007). The signals are recorded from sensors outside the scalp, and share the same high temporal millisecond resolution as in EEG. Magnetic fields are insensitive to tissue connectivity differences, resulting in simpler calculations of the reverse problem compared to EEG, which in turn increases localisation accuracy (Rampp and Stefan, 2007). Each electrical current will produce a magnetic field perpendicular to the electrical current. The EEG and MEG techniques are thus complementary, and the combination of the two could yield the most accurate localisation (Sharon et al., 2007).

Cerebral blood flow tracers

Positron emission tomography (PET)

PET has been an important tool in the mapping of all aspects of brain function, not just neuronal activation, and depending on the agent used (Savoy, 2001). PET scanning utilizes an exogenously administered agent that is tagged with a positron emitter, usually with a very short half-life. An emitted positron will travel a short distance, and as it collides with an electron two high-energy gamma rays are emitted that travel in exactly opposite directions (Shin, 2000). The coincident detection of this pair of photons on opposite sides of the head, thus defining a line along which is the likely source of the gamma rays, forms the basic data for PET (Savoy, 2001).

Single photon emission tomography (SPECT)

SPECT uses a principle similar to that of PET, but the radioactive isotope used in SPECT emits only a single photon, and so the localisation of the photon cannot be calculated as a pair as in PET scan. This results in a lower spatial resolution (Shin, 2000). The radioactive isotope used is, however, much easier available and has a longer half-life, making SPECT the only modality, except for EEG, practically suited for imaging brain activity changes during a spontaneously occurring seizure (Knowlton, 2006). Subtracting inter-ictal SPECT from ictal SPECT and co-registered with MRI has further improved the ability of localising the seizure focus in patients with partial epilepsy (O'Brien et al., 1998).

Transcranial magnetic stimulation (TMS)

Transcranial magnetic stimulation (TMS) is a method for activating the brain by modulating the voltage over the cell membrane of cortical neurons. This is performed by applying magnetic fields generated by short current pulses driven through a coil, which is placed against the subject's head (Barker and Jalinous, 1985). The transient magnetic fields induce corresponding electrical fields in the tissues of the head, thus stimulating cortical neurons. The main critical issue of the TMS technique has been the precise and reliable positioning of the applied magnetic field according to the cortical region of interest (Schonfeldt-Lecuona et al., 2005; Sparing et al., 2008). This problem is addressed through newly introduced stereotactic neuronavigational strategies according to the subject’s MRI, fMRI, or the use of functional neuroimaging data from the literature, a so-called “probabilistic approach”. Stimulation of different cortical areas evokes remote EEG activity. The recently combined use of TMS and EEG has provided means for the detailed study of the reactivity of any cortical region in the intact brain; also the reactivity of non-motor cortical areas related to higher-order functions (Komssi and Kahkonen, 2006).

4.1.8 Future EEG applications

The temporal millisecond resolution of EEG (and MEG) studying cerebral neuronal activity is unique and can never be achieved by the techniques based on indirect measurements such as altered cerebral metabolism, O_2 consumption, or blood flow (Ebersole, 2000). Other imaging techniques, however, provide far better spatial resolution with millimetre accuracy.

Thus, future applications will probably to a greater extent combine EEG data with imaging techniques with higher spatial resolution.

Independent component analysis (ICA) is a statistical method to extract independent signals from a linear mixture of sources (Comon, 1994). As long as the EEG can be considered a linear mixture of electric brain activities, ICA might be able to isolate those activities. A joint ICA model combining the high temporal resolution of EEG with the spatial resolution of haemodynamic activation has recently been proposed as a promising general framework of combining multiple modalities (Eichele et al., 2005; Moosmann et al., 2007; Eichele et al., 2007).

Brain computer interface provides communication between neural activity and external devices. The most widely applied and advanced current use of brain computer interface is the cochlea implants, bringing the perception of sound to thousands of deaf individuals by means of electrodes implanted in the cochlea. Similar attempts are under way to provide images to the visual cortex and to allow the brains of paralyzed patients to control the external environment via recording electrodes (Mussa-Ivaldi and Miller, 2003).

4.2 Epilepsy

Epilepsy is a disorder characterized by spontaneous recurrent episodes of paroxysmal brain dysfunction due to a sudden, disorderly, and excessive neuronal discharge (Adams et al., 1997). The incidence of epilepsy in developed countries is around 50 per 100 000 people per year, and is higher in infants and elderly people (MacDonald et al., 2000; Sander, 2003; Forsgren et al., 2005; Duncan et al., 2006). Epilepsy lifetime prevalence is 4-6 per 1000 (MacDonald et al., 2000; Kelvin et al., 2007).

4.2.1 Etiology

Most commonly epilepsies probably represent complex traits with environmental effects acting on inherited susceptibility, mediated by common variation in particular genes (Duncan et al., 2006; Meador, 2007). Reported etiological factors for epilepsy are listed in Table 1 (from (Forsgren et al., 2005).

Table 1

Estimated proportions (%) of presumed causes of epilepsy in population-based incidence studies.

	Range (%)
Vascular	14-21
Ischemia	16-18
Haemorrhage	3-4
Trauma	0-16
Neoplasm	6-10
Infection	0-2
Degenerative	1-5
Congenital	4-7
Other	0-13
Remote or progressive symptomatic[a]	31-56
Unknown	44-69

[a]Summary of all etiologies mentioned above.

4.2.2 Diagnosis and classification

There are two dichotomies dividing the epilepsies and epileptic syndromes into main categories; generalised versus localisation-related, and idiopathic versus symptomatic (Commission on Classification and Terminology of the International League Against Epilepsy, 1989; Wolf, 2006). Generalised epilepsies comprise widespread morphological or functional pathology. Genetic factors causing, for example, channelopathies are presumed to have a major causative role in the development of seizures (Pitkanen et al., 2007). Localisation-related epilepsies and syndromes are epileptic disorders in which seizure semiology or findings at investigation disclose a localised origin of the seizures. The lesion can be genetically programmed cellular alterations like neuronal migration disorders in the cortex, or an acquired lesion like traumatic brain injury or stroke. Epilepsies are furthermore categorised into epileptic syndromes on the basis of age, type of seizures and EEG findings (Commission on Classification and Terminology of the International League Against Epilepsy, 1989).

Epilepsy is a clinical diagnosis, but EEG and brain imaging techniques play a major role in evaluating epilepsy (Flink et al., 2002b; Duncan et al., 2006). Persistent focal epileptiform activity suggests localisation-related epilepsy whereas generalised epileptiform activity suggests generalised epilepsy (Pillai and Sperling, 2006). Non-epileptiform pathology suggests symptomatic etiology whereas the idiopathic epilepsies usually have normal BA. The 3/sec spike-slow-wave activity is the hallmark of idiopathic epilepsy whereas similar activity with lower frequency is associated with symptomatic generalised epilepsies.

Imaging techniques can visualise structural lesions underlying symptomatic epilepsies. Such investigations are especially important in individuals with refractory partial seizures who would be possible candidates for surgical treatment, and in those with progressive neurological or psychological deficits (Duncan et al., 2006; Commission on Neuroimaging of the International League Against Epilepsy, 2008).

4.3 Databases

A database is a filing system organised to provide fast access to desired pieces of data, the term being mostly used for computerised systems. The development of the computer industry has dramatically increased the possibilities of generating and collecting data, and likewise the need of appropriate data storage and retrieval. Modern databases address these challenges, and provide tools for personal needs, laboratory solutions, as well as for large scale multidisciplinary database applications. Storing data in a well organised database thus provides a powerful tool for clinical, educational and scientific purposes.

Different areas within human science have exploited these new possibilities to a variable extent. The field of genomics has embraced information technology much more effectively than neuroscience (Koslow, 2000). The Human Genome Project is a successful example (Collins and McKusick VA, 2001). Geneticists agreed long ago on the value of storing reproducibly generated DNA sequences, but not images of their sequencing gels (Chicurel, 2000). This illustrates the problem of complex data structures. Electrophysiological data comprises a wide variety of large and complex data sets, and there is no widely accepted standard way for the data to be stored or described (French and Pavlidis, 2007). Consensus on what should be including in databases is needed. In addition, the technical difficulty of

collating and relating such disparate types of information must be solved to be able to globally share the data (Chicurel, 2000).

Progress in neuroscience might be faster if researchers shared their results in a network of databases (Chicurel, 2000; Koslow, 2000). The Human Brain Project, the neuroscience counterpart of the Human Genomic Project, has been a major principal funding source for such initiatives (Huerta et al., 1993; Shepherd et al., 1998; Van Horn JD et al., 2004). A number of scientific journals have now mandated that authors of accepted papers are willing to provide access for other scientists to the raw data upon which the paper was based (Van Horn JD et al., 2004; Gordon E and Konopka LM, 2005).

5. List of publications

I. Aurlien H, Gjerde IO, Gilhus NE, Hovstad OG, Karlsen B, Skeidsvoll H. A new way of building a database of EEG findings. Clin Neurophysiol 1999;110:986-995.

II. Aurlien H, Gjerde IO, Aarseth JH, Eldoen G, Karlsen B, Skeidsvoll H, Gilhus NE. EEG background activity described by a large computerized database. Clin Neurophysiol 2004;115:665-673.

III. Aurlien H, Aarseth JH, Gjerde IO, Karlsen B, Skeidsvoll H, Gilhus NE. Focal epileptiform activity described by a large computerised EEG database. Clin Neurophysiol 2007;118:1369-1376.

IV. Aurlien H, Gjerde IO, Eide, GE, Brøgger JC, Gilhus NE. Characteristics of generalised epileptiform activity. In press.

6. Aims of the study

I. To develop a new computerised EEG annotation system and then to build a database of EEG findings.

II. To study the age-related development of the EEG BA.

III. To study the age-related topographical tendency of expressing epileptiform activity.

IV. To study the age-related occurrence of specific generalised epileptiform activity (GEA) features and GEA subtypes, and to study the correlation between specific GEA features.

V. To study the effect of epileptiform activity on the EEG BA.

VI. To study the effect of specific features of GEA on the EEG BA.

7. Materials and methods

7.1 Platform and software

The digital EEG software Nervus® has 3 main components: the `study room', the recorder and the editor. This software was used for all EEG recordings. Using the 'study room', one can schedule and record EEG tests, review, mark and annotate them and review patients' records stored in individual folders. With this EEG software as a core I developed the EEG annotation system (EAS) including 3 main components; the database module (DM) for data storage, the annotation module (AM) for visual EEG analysis, and the report generator module (RGM). The DM was developed using Microsoft Access, the AM using Microsoft Visual Basic programming language, and the RGM using Visual Basic and Visual Basic for Applications.

7.2 Inter-system communication

Direct input to the EAS from the EEG editor was initially accomplished by Windows Application Programming Interface (API) calls. Output to the EEG editor was executed by sending keystrokes from the annotation module to the editor. In a later version, the Nervus® software provided a more comprehensive Component Object Model (COM) interface, permitting all communication between the Nervus software and the EAS to be replaced by this technology (Microsoft, 2008) (Fig. 1). The DM was also linked to the hospital's patient administrative system using an open database connectivity (ODBC) link to an ORACLE database.

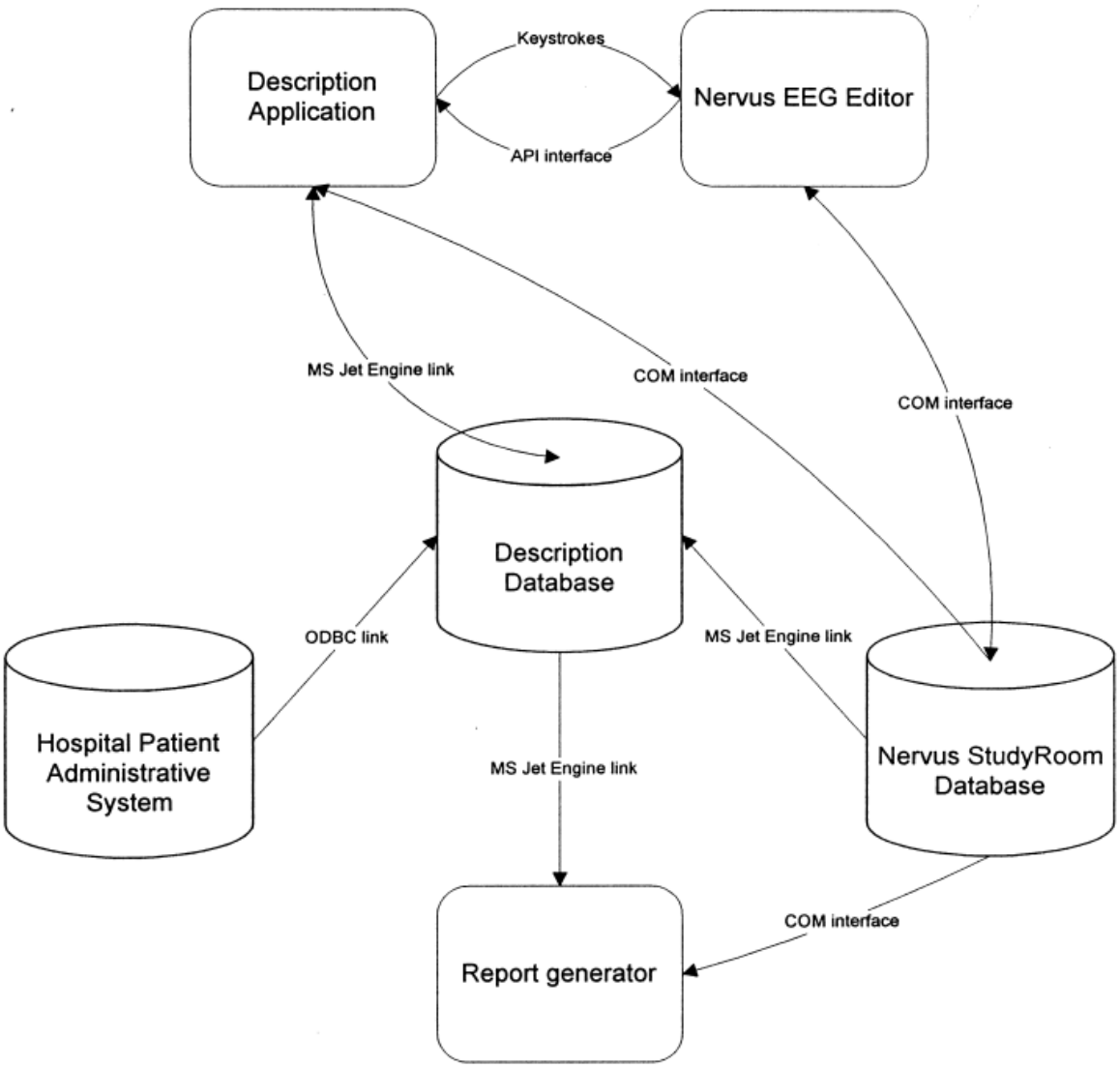

Fig. 1. Overview of the EEG annotation software (EAS) and its communication with the Nervus® EEG system including Nervus EEG editor, Nervus StudyRoom Database (a database connected to the Nervus EEG editor), and the hospital's patient administrative system. COM: Component Object Model, ODBC: Open Database Connectivity, MS: Microsoft®

7.3 Standards

EEG waveforms and activities were in our work categorized according to the American Society for Testing and Materials; ASTM (1994) standard (Table 2). These categories were further divided into 4 groups: `epileptiform pathology', `nonepileptiform pathology', `normal variants', and `extra-cerebral activity' (Westmoreland and Klass, 1990). A single waveform category could be placed in more than one of the 4 groups; for example the category `sharp

waves' was simultaneously placed in the groups `epileptiform pathology', `non-epileptiform pathology', and `normal variants' because a sharp wave could comply with all these characteristics. Some of the ASTM categories were omitted because they could be replaced by another category combined with parameters for localization or pattern. A few new categories were added (Table 2). Epileptic seizures were categorized according to the `Proposal for Revised Clinical and Electroencephalographic Classification of Epileptic Seizures' (Commission on Classification and Terminology of the International League Against Epilepsy, 1981). International Classification of Diseases, Ninth Revision (ICD-9) was initially used for coding EEG related patient diagnoses, i.e. the reason for referral to EEG. This ICD-9 coding was, however, replaced by the International Classification of Diseases, Tenth Revision (ICD-10), which was used during the study period.

Table 2

Categorization of EEG waveforms/activity based on the ASTM 'Standard specifications for transferring digital neurophysiological data between independent computer systems' and with a few categories added (marked with an asterix). All categories are further divided into 4 groups: 'epileptiform pathology', 'non-epileptiform pathology', 'normal variants', and 'extra-cerebral activity.

Code	Mother Code	Description
1		**Epileptiform Pathology**
1.D	1	**Sharp Appearing Activity Identifiers**
1.D.30	1.D	Unspecific epileptiform discharges
1.D.31	1.D	Sharp transients
1.D.41	1.D	Sharp waves
1.D.42	1.D	Spikes
1.D.43	1.D	Polyspikes
1.D.44	1.D	Spike and wave complexes
1.D.45	1.D	Poly spike and wave complexes
1.D.46	1.D	Atypical spike and wave complexes
1.D.47	1.D	Sharp and slow wave complexes
1.D.49	1.D	Hypsarrhythmia
1.F	1	**Periodic/Rhythmic Cerebral Activity Identifiers**
1.F.11	1.F	Beta activity
1.F.12	1.F	Alpha Activity
1.F.14	1.F	Theta activity
1.F.16	1.F	Delta activity
1.G	1	**Suppressions**
1.G.58	1.G	Bursts with suppressions
1.G.581	1.G	Suppression/desynchronisation*
1.H	1	**Eye-related Activity Identifiers**
1.H.68	1.H	Photoparoxysmal activity

2		**Nonepileptiform Pathology**
2.B	2	**Background and Slow Wave Activity Identifiers**
2.B.11	2.B	Beta activity
2.B.12	2.B	Alpha activity
2.B.13	2.B	Mu activity (continuous asymmetric)
Code	**Mother Code**	**Description**
2.B.14	2.B	Theta activity
2.B.16	2.B	Delta activity
2.B.19	2.B	Slow fused transients
2.B.191	2.B	Hyperventilation response (pathological) *
2.B.1A	2.B	Intermittent rhythmic delta activity (FIRDA etc)
2.D	2	**Sharp Appearing Identifiers**
2.D.31	2.D	Sharp transients
2.D.34	2.D	Zeta waves
2.D.35	2.D	Triphasic waves
2.D.41	2.D	Sharp waves
2.D.46	2.D	Atypical spike and wave complexes
2.G	2	**Suppressions**
2.G.58	2.G	Bursts with suppressions
2.G.581	2.G	Suppression/desynchronisation*
3		**Normal variants**
3.A	3	**Sleep and Wake Stage Identifiers**
3.A.01	3.A	Unstageable activity
3.A.02	3.A	Stage W (wake) activity
3.A.03	3.A	REM sleep activity
3.A.04	3.A	REM-spindle activity
3.A.05	3.A	Stage I sleep activity
3.A.06	3.A	Stage II sleep activity
3.A.07	3.A	Stage III sleep activity
3.A.08	3.A	Stage IV sleep activity
3.A.09	3.A	Alpha-delta sleep activity
3.A.091	3.A	Drowsiness*
3.A.092	3.A	Trace alternant*
3.B	3	**Background and Slow wave Activity Identifiers**
3.B.11	3.B	Beta activity
3.B.12	3.B	Alpha activity
3.B.13	3.B	Mu activity
3.B.14	3.B	Theta activity
3.B.141	3.B	Occipital slow waves of youth*
3.B.16	3.B	Delta activity
3.B.19	3.B	Slow fused transients
3.B.191	3.B	Hyperventilation response (normal)*
3.B.1A	3.B	Intermittent rhythmic delta activity
3.C	3	**Sleep Activity and Event Identifiers**
3.C.20	3.C	Sleep activity
3.C.21	3.C	Sleep spindles
3.C.22	3.C	V waves (vertex sharp transients)

3.C.23	3.C	F waves
3.C.24	3.C	K complexes
3.C.25	3.C	Positive occipital sharp transients (POSTS)
3.C.26	3.C	Saw tooth waves
3.C.27	3.C	Sleep stage shifts
3.C.28	3.C	Arousals
3.C.29	3.C	Awakenings
3.D	3	**Sharp Appearing Identifiers**
3.D.31	3.D	Sharp transients
3.D.32	3.D	Wickets
3.D.33	3.D	Small sharp spikes
3.D.34	3.D	Zeta waves
3.D.36	3.D	Phantom spike and wave activity
3.D.37	3.D	14 and 6 Hz positive bursts
3.D.38	3.D	Lambda waves
Code	**Mother Code**	**Description**
3.D.39	3.D	Rhythmic theta of drowsiness
3.D.3A	3.D	Subclinical rhythmic electrographic discharge of adults
3.D.41	3.D	Sharp waves
3.G	3	**Suppressions**
3.G.581	3.G	Suppression/desynchronisation*
3.H	3	**Eye-related Activity Identifiers**
3.H.66	3.H	Photic driving activity
4		**Extracerebral activity**
4.H	4	**Eye-related Activity Identifiers**
4.H.60	4.H	Unspecific eye movements
4.H.61	4.H	Eye blinks
4.H.62	4.H	Nystagmoid eye movements
4.H.63	4.H	Slow eye movements
4.H.64	4.H	Fast irregular eye movements
4.H.65	4.H	Rapid eye movements
4.H.67	4.H	Photomyogenic activity
4.H.69	4.H	Electroretinogram
4.I	4	**Myogenic Noncerebral Activity Identifiers**
4.I.70	4.I	Unspecified myogenic activity
4.I.72	4.I	Myokymia
4.I.73	4.I	Facial synkinesis
4.I.74	4.I	Hemifacial spasms
4.I.75	4.I	Extraocular muscle activity
4.I.76	4.I	Tremor activity
4.I.77	4.I	Myoclonic activity
4.I.78	4.I	Periodic movements of sleep
4.I.79	4.I	Periodic movements of sleep with arousals
4.J	4	**Artefactual Activity Identifiers**
4.J.80	4.J	Unspecified artefacts
4.J.81	4.J	Electrode/instrumental artefacts
4.J.82	4.J	Movements artefacts

4.J.83	4.J	Sweat or galvanic skin artefacts
4.J.84	4.J	Pulse artefacts
4.J.85	4.J	EKG artefacts
4.J.86	4.J	Respiratory artefacts
4.J.87	4.J	Glossokinetic artefacts
4.J.88	4.J	Swallowing/chewing/sucking artefacts
4.J.89	4.J	External interference artefacts
4.K	4	**Special Respiratory and Cardiovascular Event Identifiers**
4.K.90	4.K	Unspecified cardiorespiratory events
4.K.91	4.K	Apneas or hypopneas with ventilatory effort
4.K.92	4.K	Apneas or hypopneas with little or no ventilatory effort
4.K.93	4.K	Oxygen desaturations
4.K.94	4.K	Sinus dysrhythmias
4.K.95	4.K	Sypraventricular dysrhythmias
4.K.96	4.K	Ventricular dysrhythmias or asystoles
4.K.961	4.K	Normal one channel ECG*
4.K.97	4.K	Systolic hypotensive episodes
4.K.98	4.K	Diastolic hypotensive episodes

7.4 EEG recordings

All routine EEGs recorded at Haukeland University Hospital from March 1st 2000 to December 31st 2005 were visually evaluated and described using the EAS. This included 17 723 EEGs from 12 511 patients. Long-term registrations, EEGs during general anaesthesia, and during Wada tests and Tilt tests were not included in this study (Wada and Rasmussen, 1960; Low et al., 1983).

Paper II included the first EEG from consecutive patients recorded from March 1st 2000 to March 1st 2002 comprising 4651 EEGs from 2228 females and 2423 males.

Paper III included the first EEG containing focal epileptiform activity (FEA) from consecutive patients recorded from March 1st 2000 to December 31st 2005 comprising 1647 EEGs from 852 females and 795 males.

Paper IV recruited patients from patients recorded from March 1st 2000 to December 31st 2005. Critically ill patients were excluded due to the lack of consensus regarding the assessment of rhythmic and periodic EEG patterns encountered in this group (Hirsch et al., 2005). EEGs with suppression-burst complexes, triphasic waves and paroxysmal flattening

can in some cases appear as an epileptiform phenomenon but were excluded in this study due to the controversy about the nature and etiology of such activity (Raegrant et al., 1991; Husain et al., 1999). The first EEG containing GEA from each patient was selected for this study. EEGs marked in routine coding as having GEA were re-evaluated. 325 EEGs, 181 from females and 144 from males, were found to have GEA. These 325 EEGs were scored for the following GEA features: Waveform, bilateral synchronicity, regularity, frequency, amplitude of the sharp component, photoparoxysmal response (PPR), and hyperventilation sensitivity (HVS).

In paper III and IV a control group consisting of all first EEGs from drug-free outpatients with no EEG pathology from the study period were included (N = 3268).

7.5 Statistics

In paper II and III age-related amplitude and frequency variation were described using polynomial regression models with age as the independent variable. Multivariate polynomial models were applied where 3 or more variables were included in the model at the same time. For some of the tests, the number of individuals at high age was low. The polynomial models therefore became unstable. Individuals above the age of respectively 85 and 60 years in publication II and III were excluded from these polynomial regression analyses. The chi-square test was used to test age dependency for the localisation of FEA in topographical regions as well as for FEA asymmetry and for association between the EEGers and asymmetry. S-Plus 6.0 and SPSS 13.0 were used for the analyses.

In paper IV continuous and binomial dependent variables were described using multiple linear and logistic fractional polynomial regression models, respectively (Royston and Sauerbrei, 2005). Age-related changes in the occurrence of specific GEA-types were described using multinomial logistic regression analysis. Pairwise correlation analyses were calculated with Spearman's correlation test. Stata 9.2 was used for the analyses.

8. Results

8.1 Paper I

8.1.1 EEG annotation

Each EEG was analysed visually by the EEGer according to standard procedures. The current EEG test in the editor was automatically linked to the corresponding description in the description module. All patient demographic data and administrative test parameters were thereby set directly. Start and stop of events later to be described were manually marked in the EEG editor. From the referral, the interpreter set one or more relevant ICD-10 diagnoses. The interpreter could simultaneously see a table with all previous hospital diagnoses for this patient.

EEG background activity (BA)

The alpha rhythm was evaluated for frequency, amplitude, asymmetry, and reactivity (Fig. 2). The frequency and amplitude range were drawn graphically with the mouse and could thereby be determined in one operation. Numerical values were automatically denoted in separate boxes. If asymmetric, the amplitude could be set separately for the left and right side. Reactivity was marked by clicking `suppressed by eye opening'.

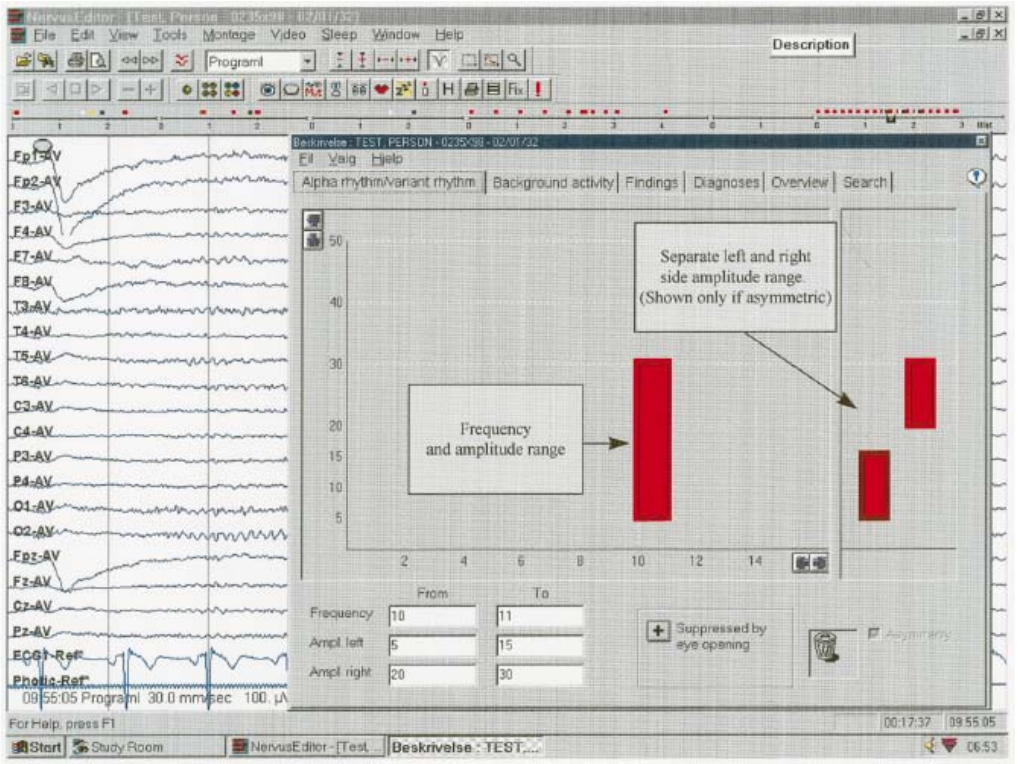

Fig. 2. Input interface for alpha rhythm (AR), frequency along the X-axis, amplitude along the Y-axis.

The BA was described for frequency and amplitude and was marked graphically in the same way as the alpha rhythm (Fig. 3). As recommended in `Guidelines for writing EEG reports' (American Electroencephalographic Society, 1994), the frequency was given in Hertz and the amplitude in micro volts, both with the possibility of describing a range of values. Several different rhythms that together constituted the BA could be marked separately. If this activity was focal or asymmetric, it was marked as an EEG event rather than as BA. BA was defined as any activity representing the setting in which a given normal or abnormal pattern appears and from which such a pattern was distinguished (Chatrian et al., 1983). However, the alpha rhythm or alpha variant rhythm was described separately, as mentioned previously, because the impact of this specific rhythm differs from the rest of the BA. For instance a 7 Hz rhythm has a completely different meaning if it represents the alpha variant rhythm or if it is part of the non-alpha BA.

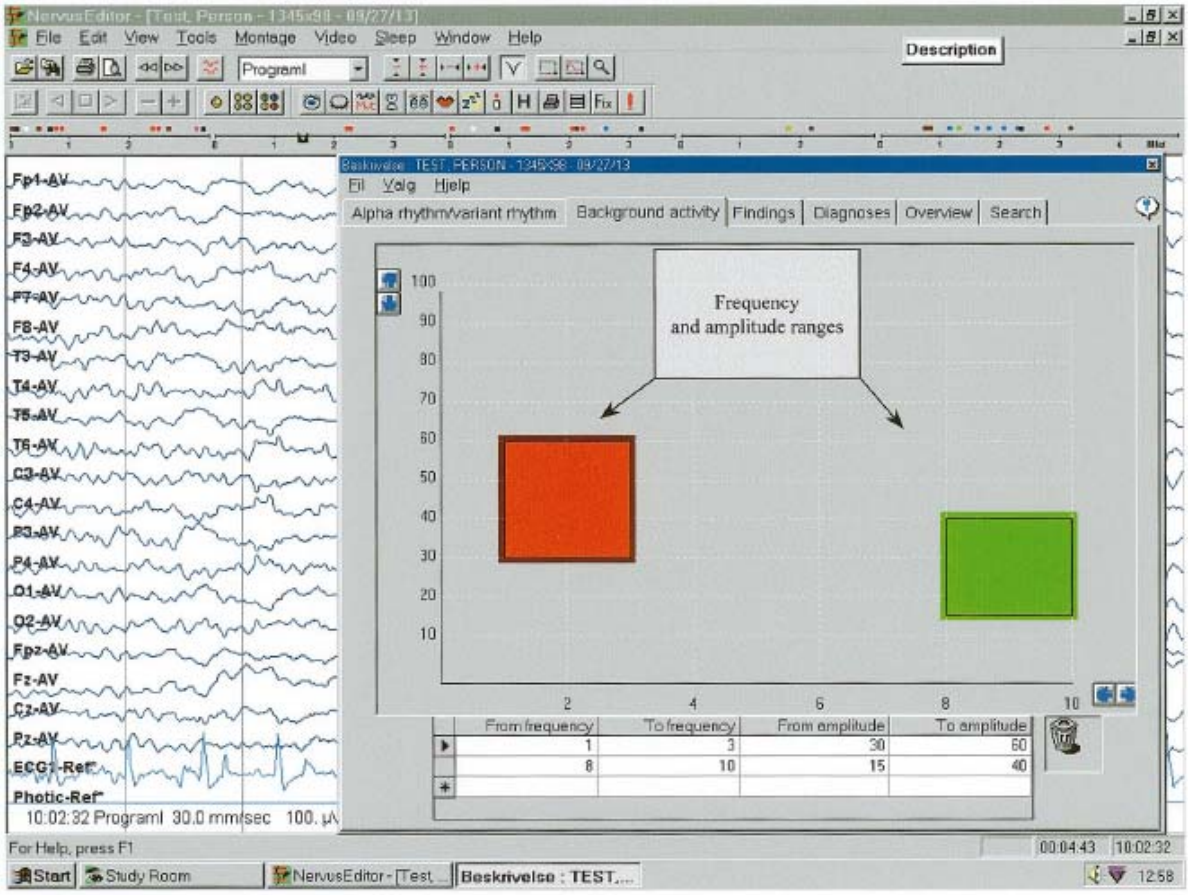

Fig. 3. Input interface for general background activity (GBA), frequency along the X-axis, amplitude along the Y-axis.

EEG findings

The description module automatically picked up EEG fragments already marked (see above). All such fragments were categorized by clicking the suitable category (Fig. 4). By clicking an event in the description module, the EEG editor automatically navigated to the corresponding part of the EEG. The waveform/activity categories were arranged in a hierarchical tree view with the 4 main groups: `epileptiform pathology', `non-epileptiform pathology', `normal variants', and `extra-cerebral activity' as the main branches. The interpreter could in addition grade the probability of epileptogenic origin as `definite', `probable', or `possible'. Activity branched as `non-epileptiform pathology' could still be characterized as `epileptogenic origin not excluded'. To provide data consistency, this grading of epileptogenic probabilities was restricted to categories that could possibly be epileptogenic. The localization of the EEG activity was determined by clicking the traces where the EEG event occurred. In the monopolar montage, the corresponding electrode was

directly marked, whereas in bipolar montages, the system automatically determined the electrodes engaged on the basis of the marked traces. Maximum localization could similarly be marked. According to the electrodes engaged, the system proposed `no asymmetry', `mild asymmetry', `moderate asymmetry', `marked asymmetry', or `left/right side only'. This grading could be overruled by the interpreter, with the exception of `left/right side only'.

Each event could be quantitatively determined as `rare', `intermittent', `frequent', or `continuous'. The event pattern could be evaluated as `scattered', `paroxysmal', `rhythmical', or `periodical'. A free text annotation could be attached to any EEG event.

Events marked from the EEG editor could also be defined as a seizure. Seizures were further classified according to the international classification system, presented in a tree-view structure like the EEG waveform/activity classification table (see above). Free text description could be attached to all seizure events.

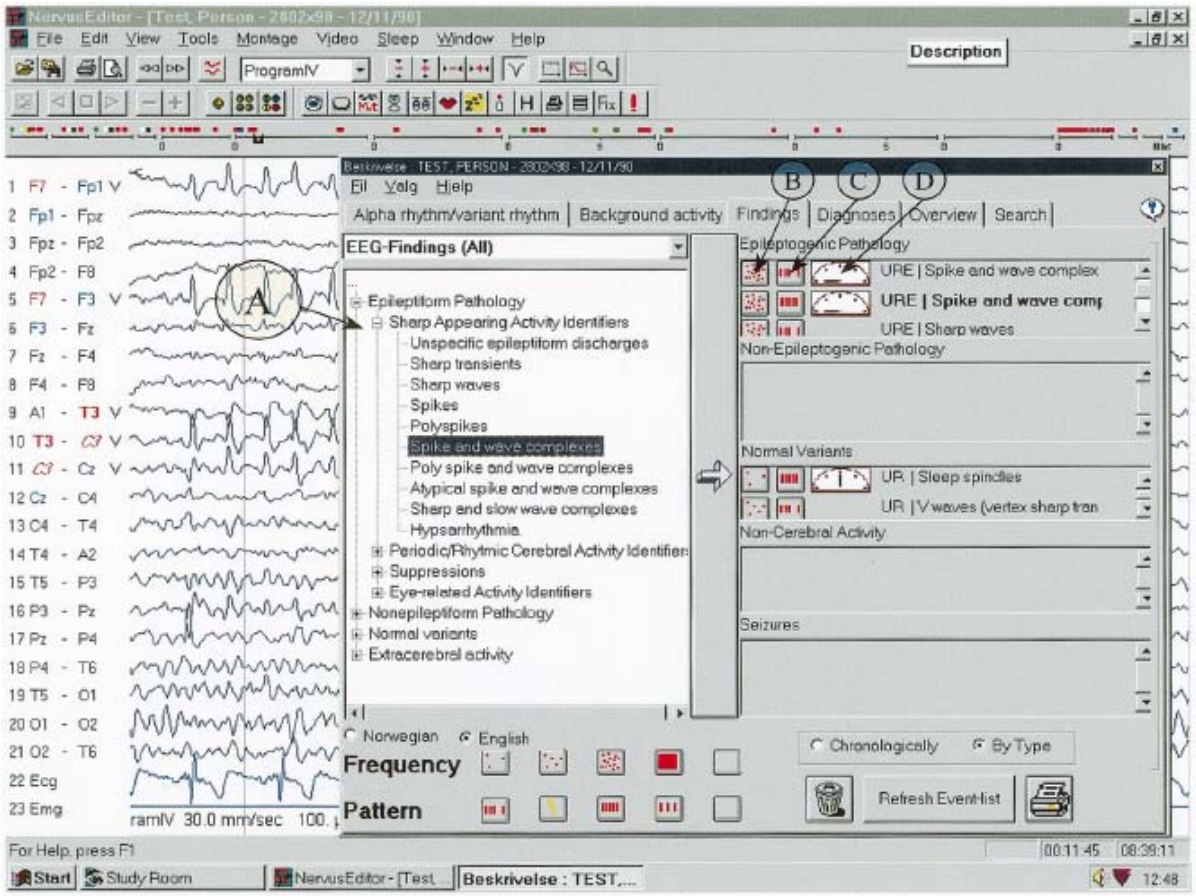

Fig. 4. Input interface for describing EEG events/findings. Waveform/activity categories are organized in a tree view (A). EEG findings are supplied with quantity- (B), pattern- (C), and asymmetry- (D) identifiers. Traces clicked by the interpreter are marked with a `V'. Electrodes engaged are automatically marked as red.

8.1.2 Report generator

After completing the EEG description, the system generated a report from the information collected in the database (Fig. 5). The report was made as a MS Word document that could be edited directly and was automatically saved and linked to the EEG recording. The main conclusion was based on the EEG events described. A pathological EEG was defined as a test that contained events of either `epileptiform pathology' or `non-epileptiform pathology'. This proposal for a conclusion made by the system was not itself a part of the database, but produced as a syntax of the database information. The conclusion could be edited and corrected by the EEGer. Finally, the EEGer was supposed to manually fill in an overall assessment in light of the clinical question. During the recording session, the EEG nurse or technician filled in `test notes', `patient notes' and `medication' in the EEG recorder. This information was automatically transferred to the report. If the marked events occurred during a period of hyperventilation or photo-stimulation, this was automatically noted by the system. The localization of all pathological findings was visualized on a head model with different patterns for epileptogenic and non-epileptogenic pathology (Fig. 5).

HORDALAND COUNTY

HAUKELAND UNIVERSITY HOSPITAL
SECTION OF CLINICAL NEUROPHYSIOLOGY
DEPARTMENT OF NEUROLOGY

EEG REPORT

Bergen 18. January 1999

REFERAL DOCTOR:

xxxxxxxx
xxxxxxxx

PATIENT:

Name:	Test Person
Personal ID:	010252 12345
Age:	66
Address:	5009 Bergen
Test date:	26.01.1998
Test ID:	4321x98

Reason for referral:
345.4 Partial (focal) epilepsy with reduced consciousness.
Medication:
Paracetamole 500mg 2x4
EEG type:
Routine EEG-registration with hyperventilation and photo-stimulation.
Patient state:
Alert.
Notes:
Good hyperventilation effort.

Alpha rhythm:
10-11Hz., 20-30 uV amplitude. Suppressed by eye opening.
Background activity:
4-6Hz. 20-40 uV amplitude and 15-20Hz. 10-15 uV amplitude.

DESCRIBED EVENTS:
Epileptiform pathology:
Sharp transients
Located in the left fronto-temporal region (Fp1, F7, T3). Maximum left lateral frontal area (F7).
Scattered, moderate frequent. Probable epileptiform activity.
Normal variants:
Hyperventilation response (normal)
Location not stated.

CONCLUSION:
- Pathological EEG.
- Cerebral dysfunction with probable epileptogenic features located in the left side fronto-temporal region and maximum in the left lateral frontal area.
- There is abundant beta activity. Benzodiazepine effect?
- Clinical comment.....

(Signature)
EEGer's name

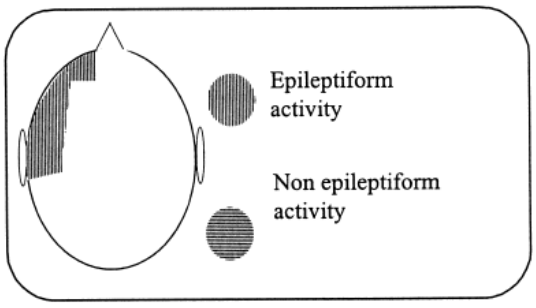

Fig. 5. EEG report generated from the EEG database. This report was generated automatically except from the last sentence where the EEGer filled in relevant clinical comments.

8.1.3 Search engine

A search engine was developed to provide easy access to all the relevant variables in the database. The user was guided through a stepwise procedure choosing; the parameters to be viewed, criteria, and sorting order. This resulted in a structured query language (SQL)-string that was sent to the database. The patient's previous hospital diagnoses as well as the EEG referral diagnoses could be included in the query. The result was presented in a tree-view, where the EEG-test or EEG activity of interest could be chosen and the actual EEG opened.

8.2 Paper II

8.2.1 AR

Estimated mean AR frequency increased gradually until age 20 years and to a value of 10 Hz (Fig. 6A). The frequency remained stable until age 45 years and then declined. Higher AR frequencies were recorded for females ($P < 0.001$) (Fig. 6B). AR frequencies were significantly higher for EEGs without non-AR pathology ($P < 0.001$), being less pronounced in children (Fig. 6C). Medication reduced the AR frequency ($P < 0.001$), most pronounced for patients with non-AR pathology (P interaction = 0.029).

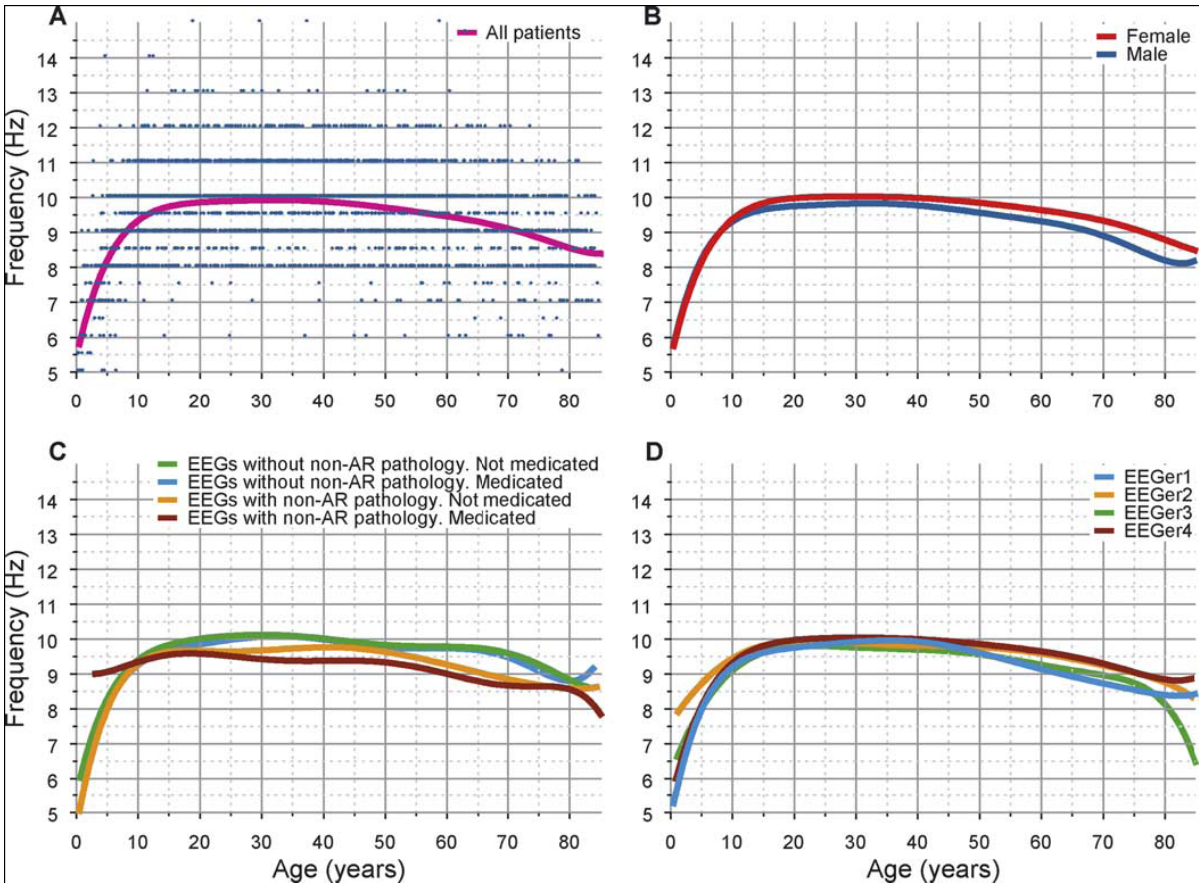

Fig. 6. AR frequency as a function of age for (A) all patients with registered alpha rhythm, each dot representing one patient, (B) females and males, (C) EEGs without and with non-AR pathology and without

and with medication, and (D) 4 different EEGers. The estimated means are based on a polynomial regression model of 7th order.

Estimated mean AR amplitude declined from 50 µV in the very young to 30 µV at 35–40 years of age (Fig. 7A). It then remained stable, except for a small increase in the very old. Females had higher AR amplitudes than males ($P < 0.001$), but not in children (Fig. 7B). The difference increased with age ($P < 0.001$).

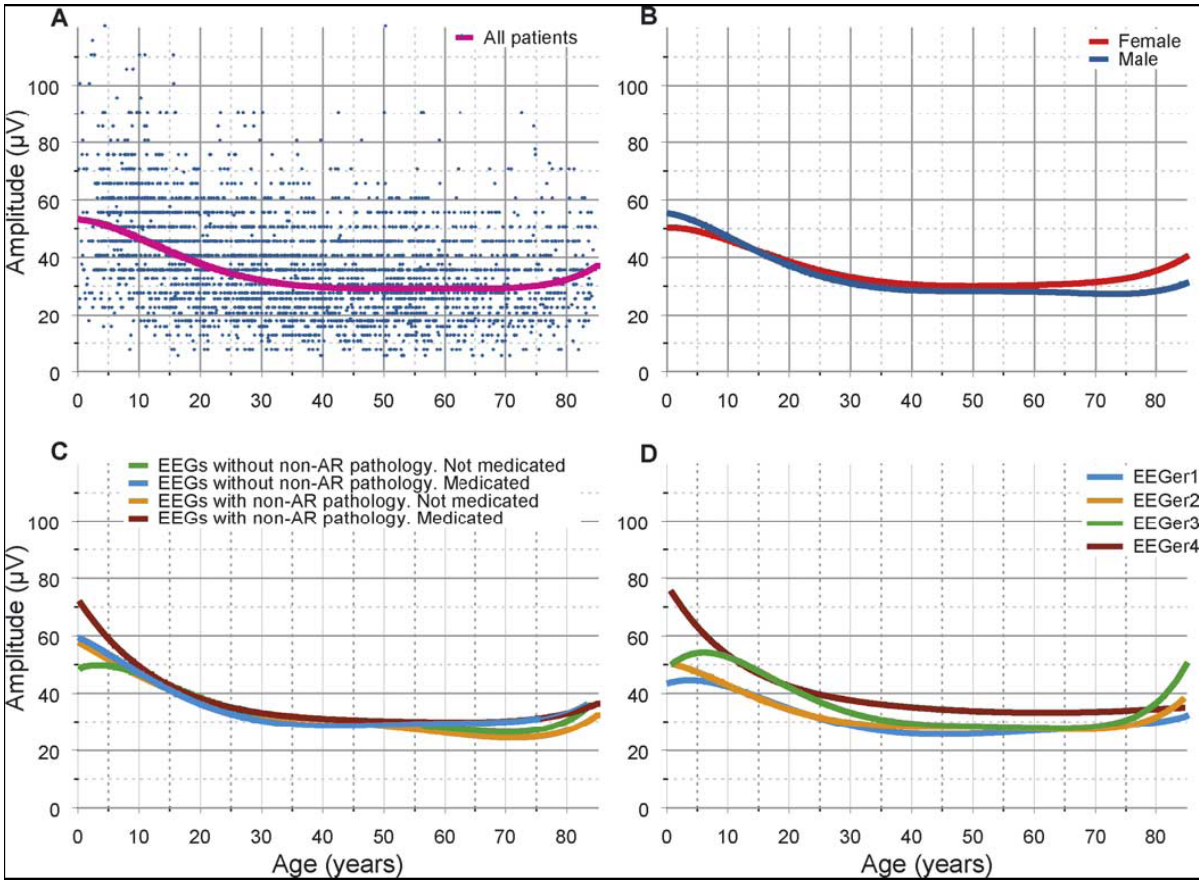

Fig. 7. AR amplitude as a function of age for (A) all patients with registered alpha rhythm, each dot representing one patient, (B) females and males, (C) EEGs without and with non-AR pathology and without and with medication, and (D) 4 different EEGers. The estimated means are based on a polynomial regression model of 5th order.

8.2.2 GBA

Delta activity never occurred in EEGs evaluated as normal in individuals over age 26 years. At age 15–25 years such activity occurred only rarely and then together with low amplitude

(Fig 8). For the 4–7 Hz GBA activity, the 95th percentile was below 31 mV at ages over 20 years, and for the 8–11 Hz activity it was below 25 mV.

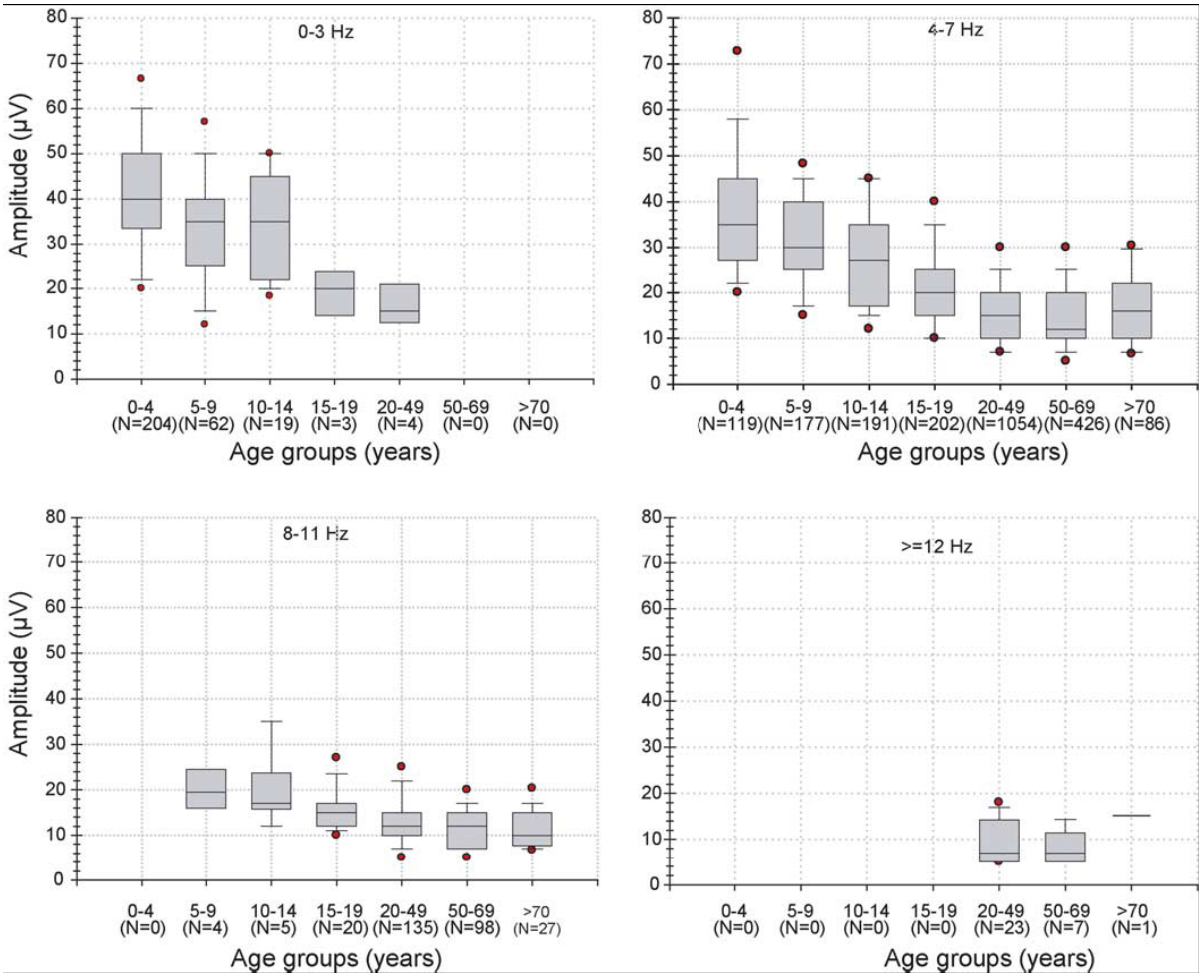

Fig. 8. Relationship between GBA frequency, amplitude, and patient age in all EEGs evaluated as normal. The boxes indicate the 25th and 75th percentiles, lines within the boxes mark the median. Whiskers indicate the 10th and 90th percentiles, and red circles indicate the 5th and 95th percentiles.

Estimated mean GBA frequency increased from 3 Hz under the age of 5 years to 5 Hz at age 30 years and with only a small decrease afterwards (Fig. 9A). EEGs with non-GBA pathology had lower GBA frequencies than those without ($P < 0.001$) (Fig. 9C). Medication significantly reduced the GBA frequency ($P < 0.001$).

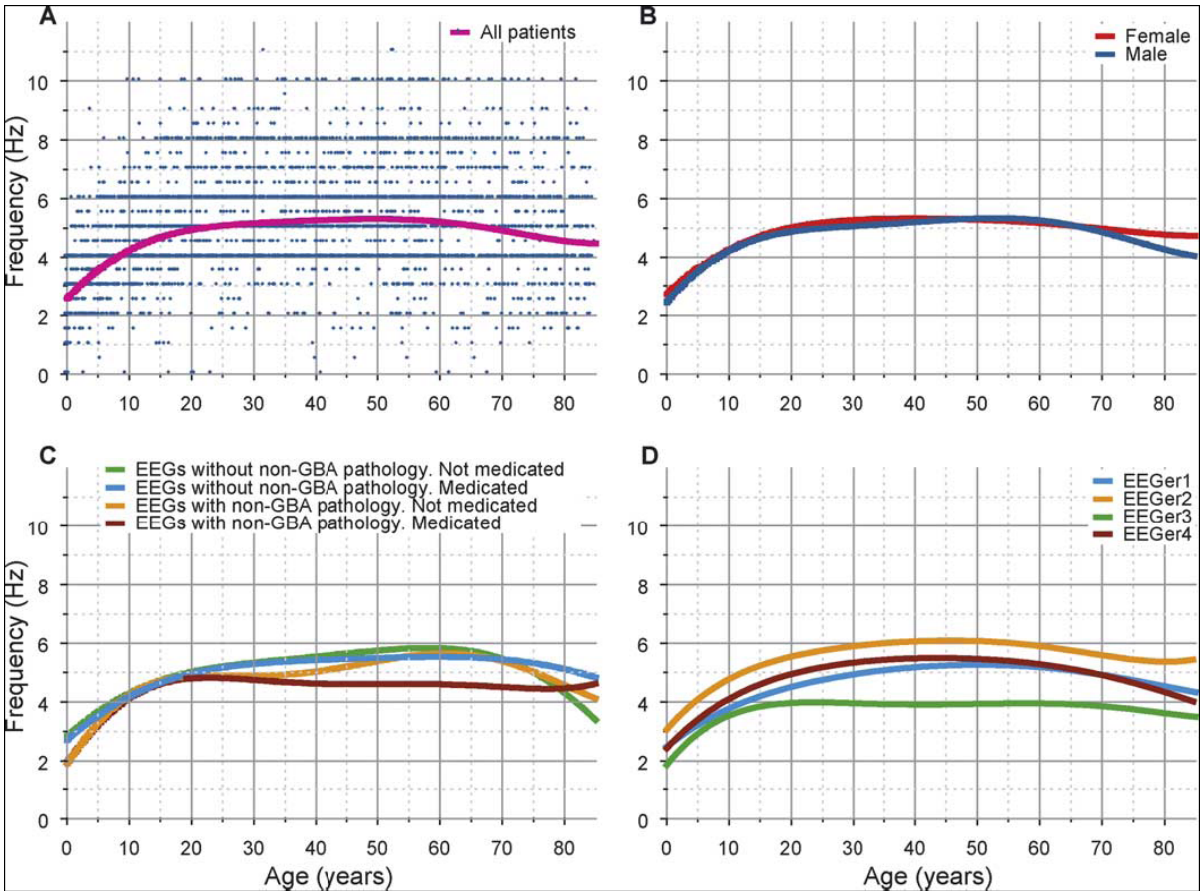

Fig. 9. GBA frequency as a function of age for (A) all patients with registered GBA, each dot representing one patient, (B) females and males, (C) EEGs without and with non-GBA pathology and without and with medication, (D) 4 different EEGers. The estimated means are based on a polynomial regression model of 5th order.

The estimated mean GBA amplitudes declined from 40 μV at birth to 15 μV at age 30 years from where it remained stable with a small increase over 70 years (Fig. 10A). EEGs with non-GBA pathology had higher amplitudes than EEGs without such pathology ($P < 0.001$) (Fig. 10C). Medication significantly increased the GBA amplitude ($P < 0.001$).

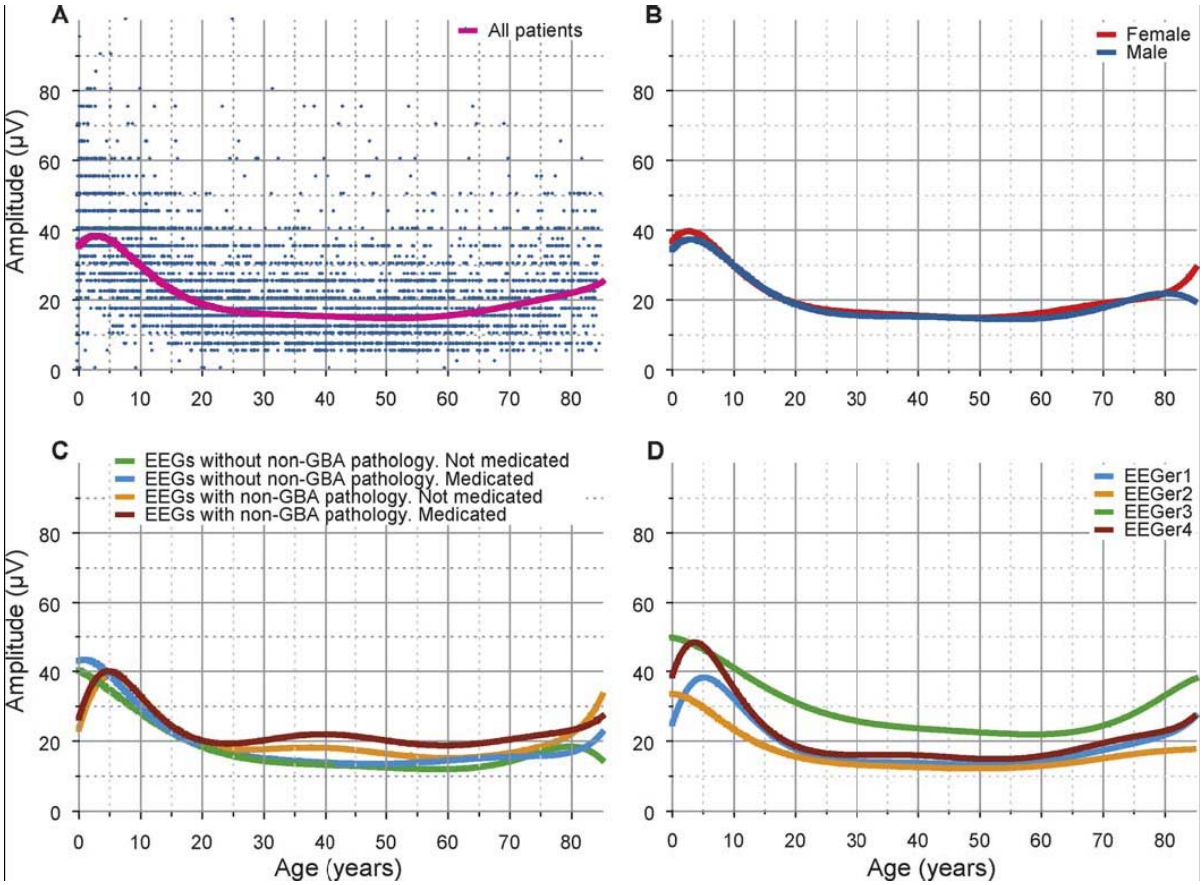

Fig. 10. GBA amplitude as a function of age for (A) all patients with registered GBA, each dot representing one patient, (B) females and males, (C) EEGs without and with non-GBA pathology and without and with medication, and (D) 4 different EEGers. The estimated means are based on a polynomial regression model of 7th order.

8.2.3 Agreement between EEGers

The agreement between the EEGers in AR and GBA assessment showed significant ($P < 0.001$) minor to moderate differences in absolute values, but always with the same trends for all EEGers (Fig. 6C, Fig. 7C, Fig. 9C, Fig. 10C).

8.3 Paper III

8.3.1 FEA topographical distribution

Topographical distribution of FEA was age-dependent for all brain regions ($p < 0.0005$) except for the temporal ($p = 0.17$) (Fig. 11).

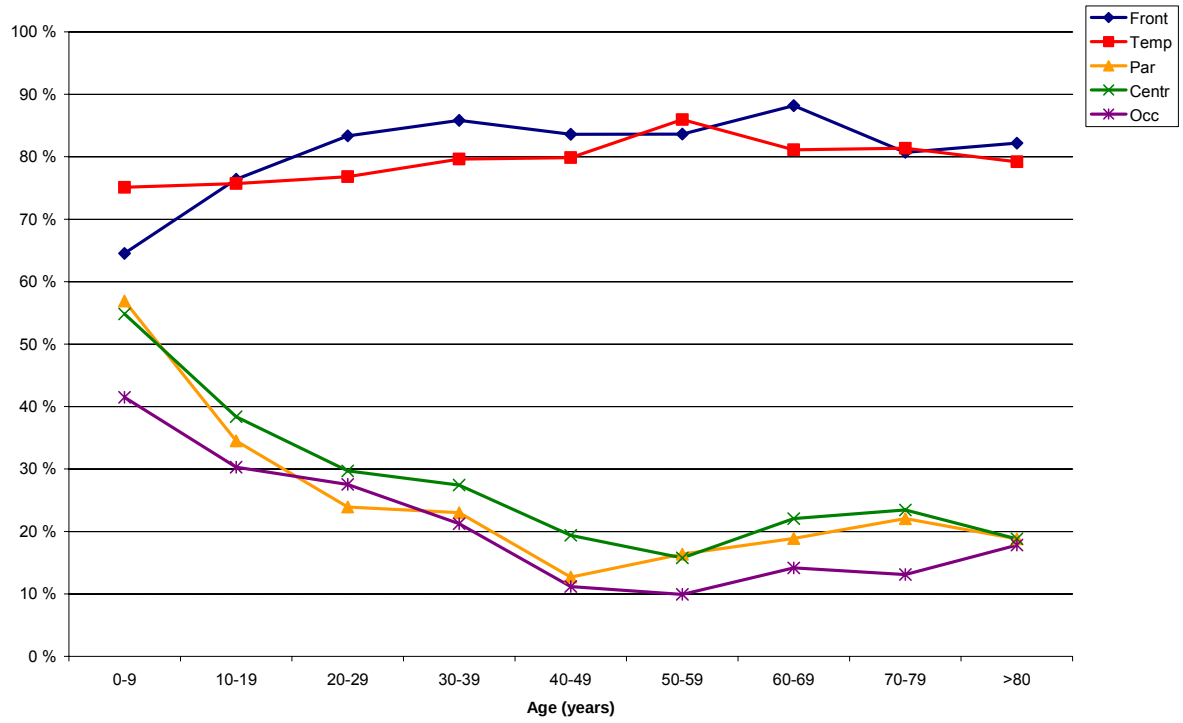

Fig. 11. Age-related topographical distribution of FEA in 1647 consecutive patients with EEGs containing FEA. FEA could be located in more than one region.

8.3.2 FEA asymmetry

FEA lateralised more often to the left side of the brain compared to the right; 565 (34%) vs. 487 (30%) ($p = 0.018$). 595 EEGs (36%) had no side asymmetry. The left–right result did not vary significantly between the 6 EEGers ($p = 0.18$). There was still more left than right FEA asymmetry when only EEGs with completely unilateral FEA were included; 444 vs. 381 (27% vs 23%) ($p = 0.031$). Left and right FEA asymmetry varied significantly between age groups ($p = 0.013$) (Fig. 12).

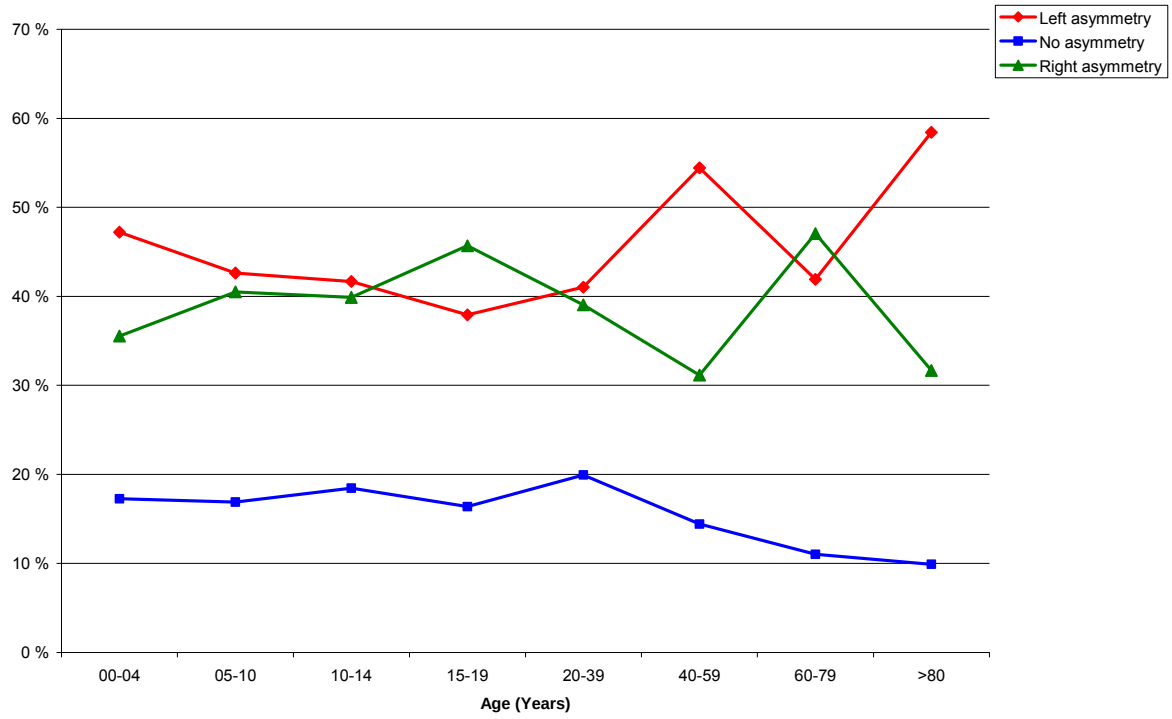

Fig. 12. Side asymmetry of FEA in 1647 consecutive patients with EEGs containing FEA.

Also FEA asymmetry independent of left or right side varied between age groups ($p < 0.0005$). The relative risk for asymmetric FEA was highest in patients over the age of 80 years (94 asymmetric vs. 7 symmetric), and lowest at age 20–39 years (171 asymmetric vs. 80 symmetric) (Fig. 13).

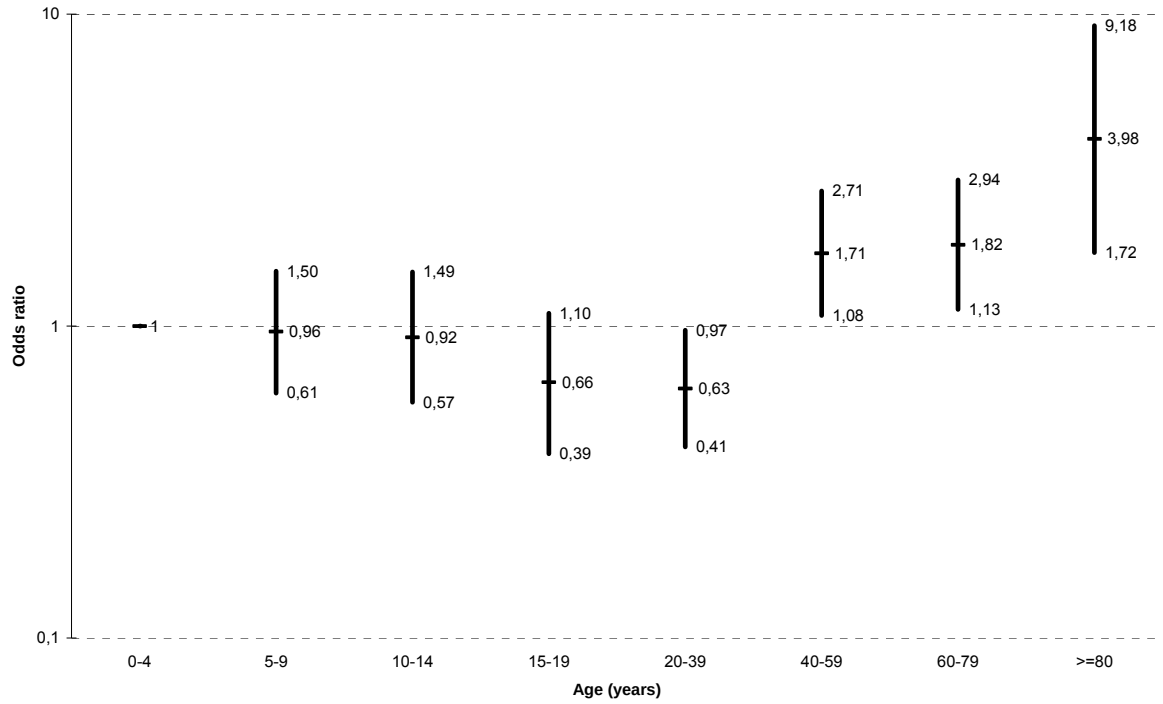

Fig. 13. Probability of more than moderate FEA asymmetry independent of left or right side in different age groups, as compared to the age group 0–4 years where the probability is defined as 1. The middle mark shows the odds ratio, while the upper and lower marks define the 95% confidence interval.

8.3.3 FEA and AR

The total group of patients with FEA had lower AR frequency ($p < 0.0005$) and higher amplitude ($p < 0.0005$) compared to the drug-free outpatient controls (Fig. 14a and b). The subgroup of drug-free outpatients with FEA had lower AR frequency ($p = 0.0041$) and higher amplitude ($p = 0.0023$) compared to the outpatient controls (Fig. 14c and d).

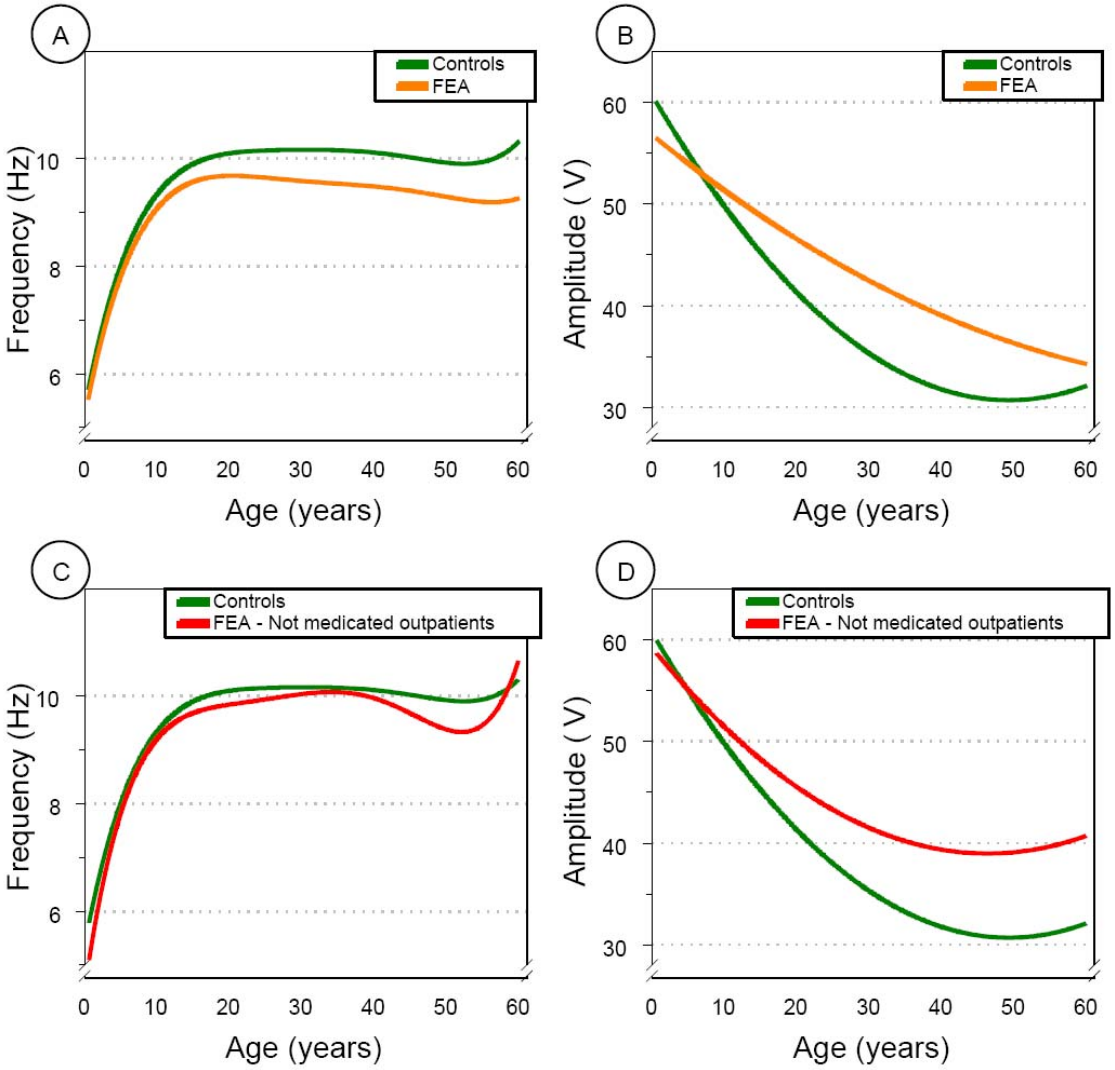

Fig. 14. AR frequency (a) and AR amplitude (b) from all patients with FEA and from drug-free outpatient controls. AR frequency (c) and AR amplitude (d) from drug-free outpatients with FEA and from drug-free outpatient controls.

8.3.4 FEA and GBA

The total group of patients with FEA had lower GBA frequency ($p < 0.0005$) and higher amplitude ($p < 0.0005$) compared to the drug-free outpatient controls (Fig. 15a and b). The subgroup of drug-free outpatients with FEA had higher amplitude ($p < 0.0005$) compared to the outpatient controls, while GBA frequency was the same ($p = 0.96$) (Fig. 15c and d).

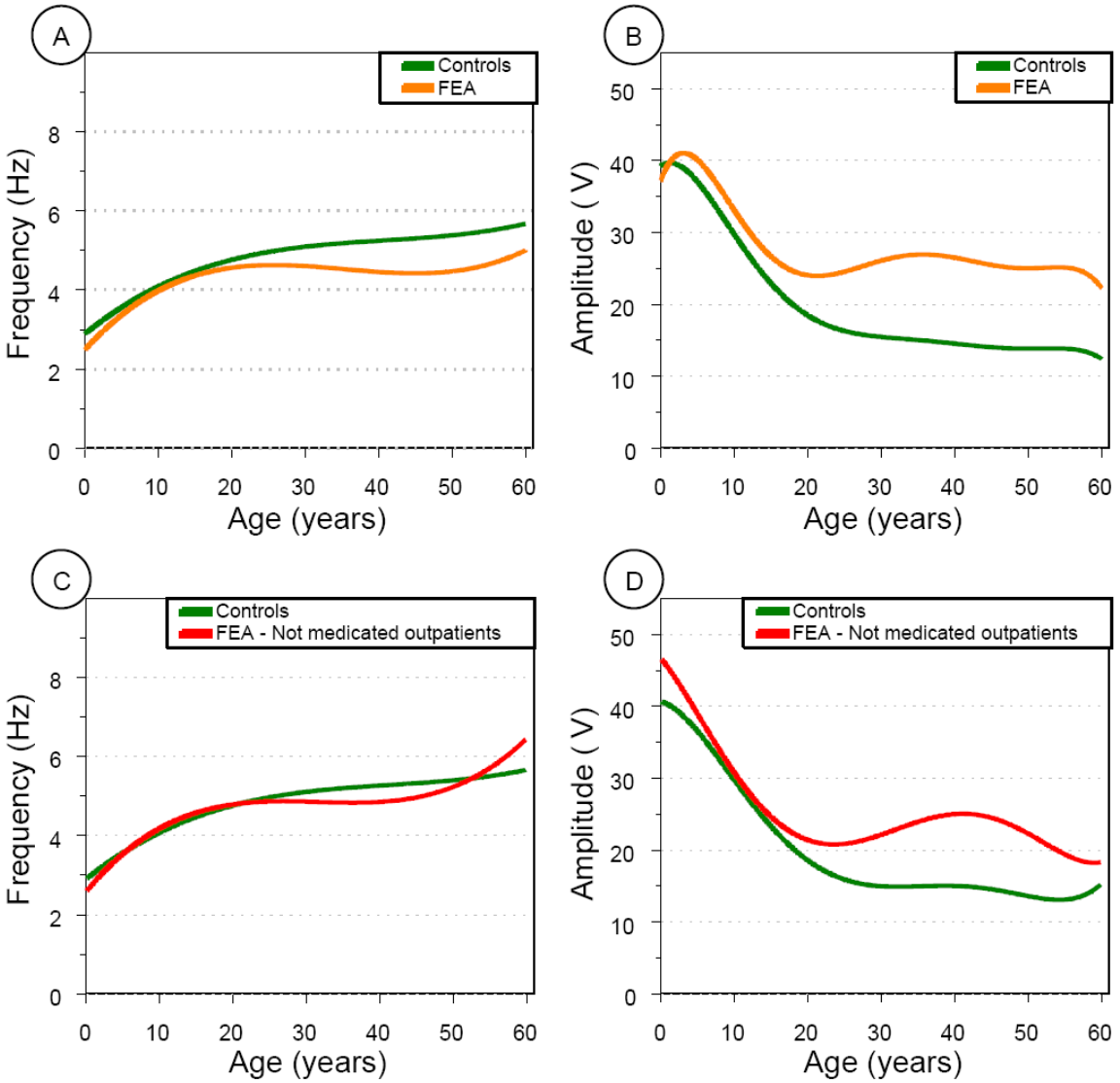

Fig. 15. GBA frequency (a) and GBA amplitude (b) from all patients with FEA and from drug-free outpatient controls. GBA frequency (c) and GBA amplitude (d) from drug-free outpatients with FEA and from drug-free outpatient controls.

8.4 Paper IV

8.4.1 GEA and BA

All EEG background parameters were clearly affected in EEGs with GEA compared to controls, as shown in Figure 16 and Table 2. The effects of other GEA-related variables are

also shown in Table 2.

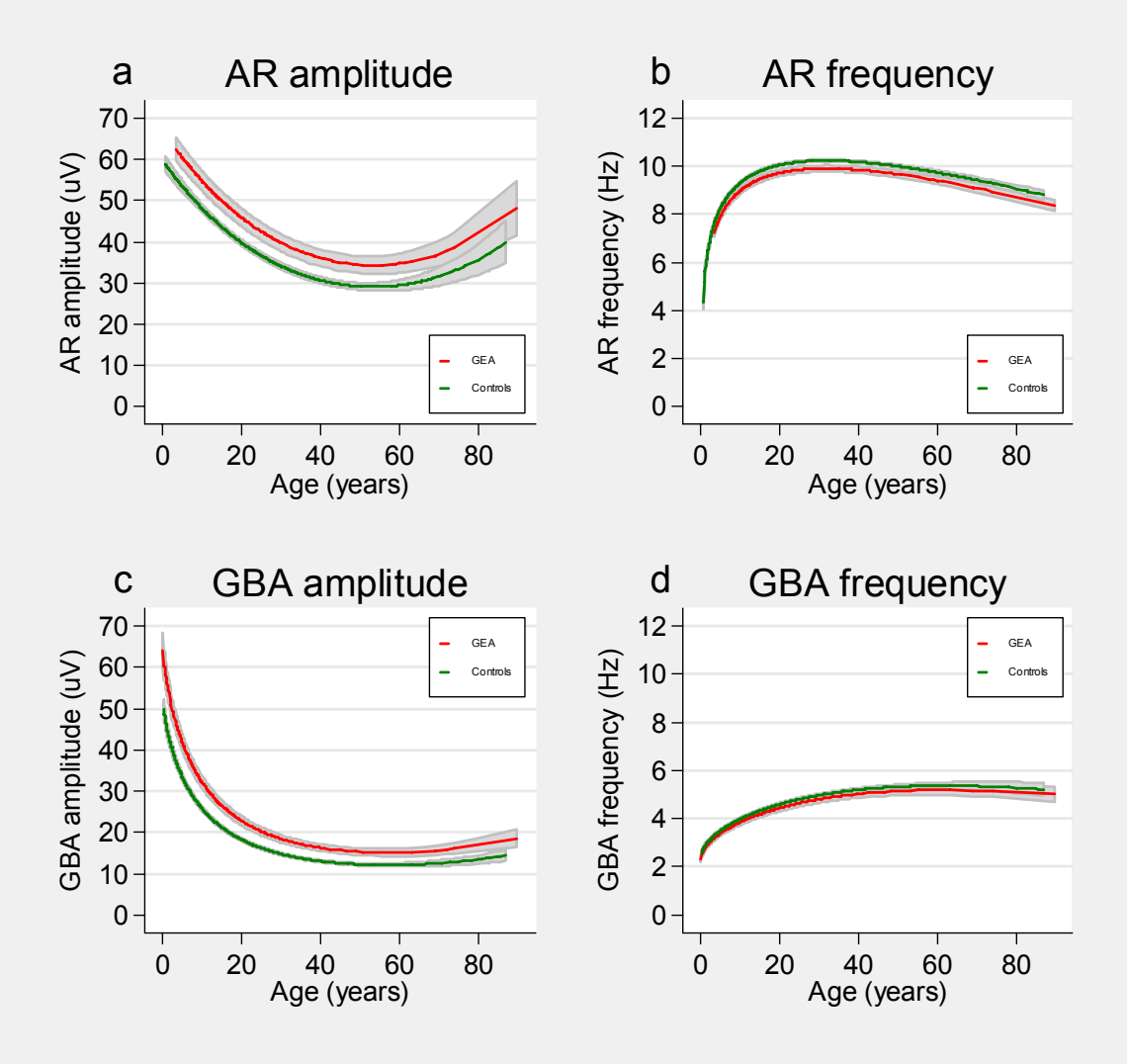

Figure 16 Fitted values for alpha rhythm (AR) amplitude (a), AR frequency (b), general background activity (GBA) amplitude (c), and GBA frequency (d) by age in 325 patients with generalised epileptiform activity (GEA) and in 3268 drug-free outpatient controls. Shaded areas are fitted values ± 1.96 SE.

Table 2 Association between GEA-related variables and EEG BA, measured as AR -and GBA amplitudes and frequencies.

Study groups	Independent variable	Effect variable for EEG background activity	Significance
GEA patients (N = 325) and controls (N = 2368)	GEA present	↑ AR amp	p < 0.001
		↓ AR freq	p < 0.001
		↑ GBA amp	p < 0.001
		↓ GBA freq	p = 0.038
	Male gender	↓ AR freq	p = 0.002
		↓ GBA freq	p = 0.002
GEA patients (N = 325)	'Polyspike'	↑ AR amp	p = 0.037
	'Hypsarrhythmia'	↑ GBA amp	p = 0.001
		↓ GBA freq	p < 0.001
	'Ictal'	↓ AR amp	p = 0.040
		↑ AR freq	p = 0.042
		↓ GBA freq	p = 0.004
	'Post-ictal'	↓ GBA freq	p = 0.004
	↑ GEA amp	↑ AR amp	p = 0.003
		↑ GBA amp	p = 0.006
	Male gender	↓ GBA freq	p = 0.009
	CBRDEE	↑ GBA amp	p = 0.018
		↓ GBA freq	p = 0.004
Patients with RBS GEA (N = 57)	↓ GEA freq	↓ GBA freq	p = 0.005
	'Post-ictal'	↓ AR freq	p = 0.004
	Male gender	↓ AR freq	p = 0.033

↑ = higher. ↓ = lower. Amp = amplitude. Freq = frequency. CBRDEE = current brain related disease except epilepsy

AR amplitude, AR frequency, GBA amplitude, and GBA frequency were all pairwise correlated ($p < 0.001$) (Fig. 17). Lower AR frequency correlated with higher AR amplitude, higher GBA amplitude, and lower GBA frequency.

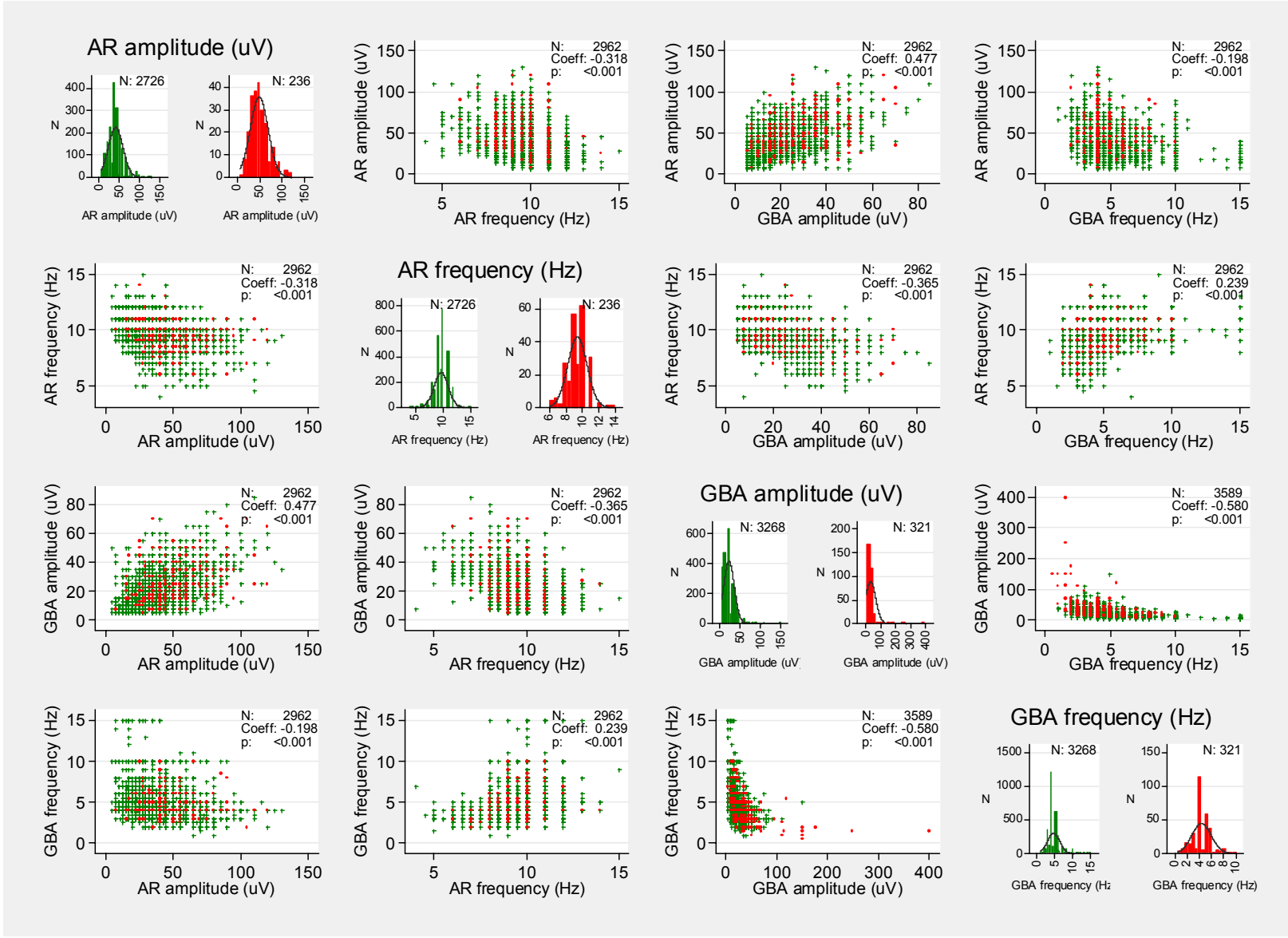

Figure 17 Pairwise correlation (Spearman's) between AR amplitude, AR frequency, GBA amplitude, and GBA frequency in 325 consecutive GEA patients (red) and 3268 controls (green). Each background activity variable is plotted against the other ones. Histograms show the number of EEGs with identified AR/GBA amplitude/frequency in EEGs with GEA and in controls. The black lines in the histograms indicate the normal distribution.

8.4.2 GEA –and GEA-related features

GEA amplitude and GEA frequency were not correlated (p = 0.35), nor was the probability of HVS and PPR (p = 0.54).

GEA amplitude

GEA amplitude changed with age in GEA patients (p<0.001) (Fig. 18a), also if adjusted for other significant covariates (p < 0.001). 'Ictal' EEG and EEG with RBS GEA correlated with higher GEA amplitude (p < 0.001). GEA amplitude changed with age also in the RBS GEA subgroup (p < 0.001). In this subgroup EEGs with 'polyspike slow wave' correlated with higher GEA amplitude (p = 0.029).

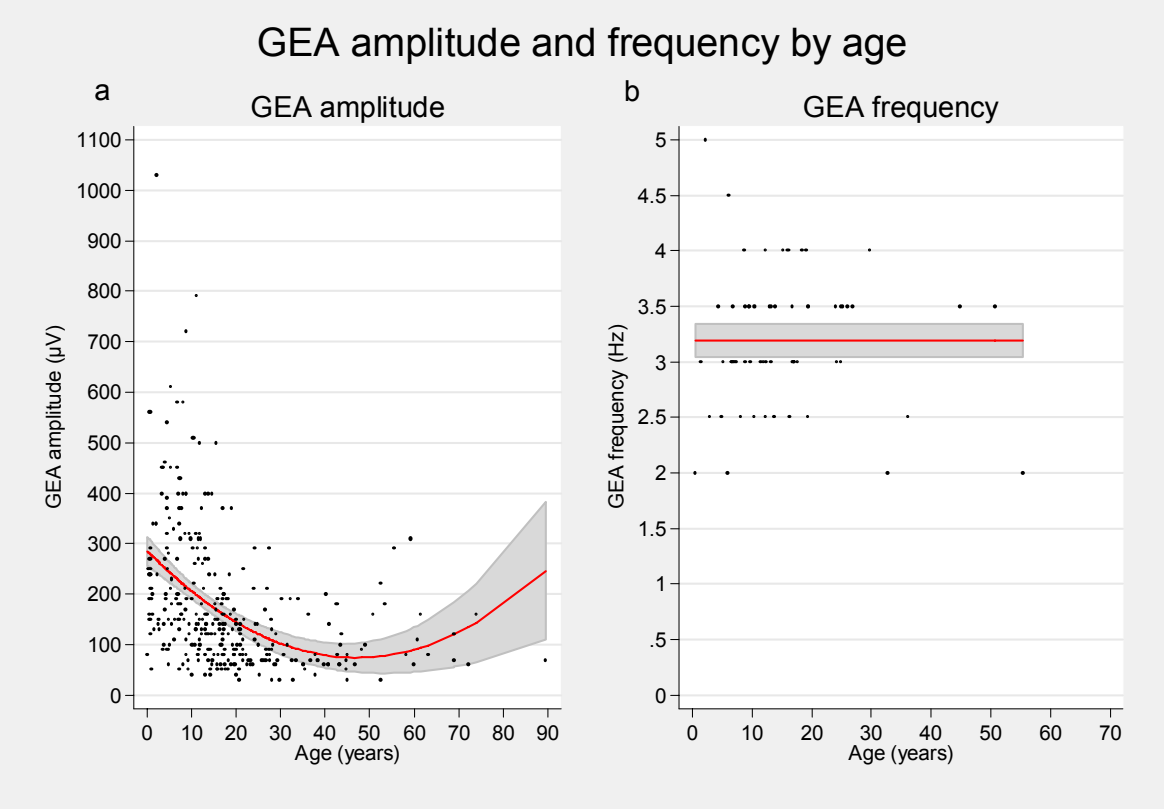

Figure 18 Fitted values for GEA amplitude (a) and GEA frequency (b) by age in 325 patients with GEA. Shaded areas are fitted values ± 1.96 SE.

GEA frequency

GEA frequency did not change with age (Fig. 18 b). This was true also when adjusted for significant covariates, and also in the RBS GEA subgroup. ‘Polyspike’ correlated with higher GEA frequency ($p < 0.001$), while ‘ictal’ correlated with lower GEA frequency ($p = 0.002$). In the RBS GEA subgroup no other GEA-features correlated with GEA frequency.

Hyperventilation sensitivity (HVS)

The probability for HVS did not change with age, even if adjusted for other GEA features. RBS GEA increased the probability for HVS (OR = 12.7, $p < 0.001$).

In the RBS GEA subgroup the probability for HVS did not change with age, neither if adjusted for other significant GEA features. Higher probability for HVS correlated with the GEA-type ‘spike/sharp slow wave’ compared to ‘polyspike slow wave’ (OR = 9.0, $p = 0.005$).

Photoparoxysmal response (PPR)

The probability for PPR changed with age with a maximum probability at 11 years, but only after adjustments for other significant GEA features ($p = 0.011$) (Fig. 19). Higher probability for PPR correlated with ‘polyspike slow wave’ (OR = 4.9, $p = 0.002$), ‘poly-spike’ (OR = 32, $p < 0.001$), female gender (OR = 3.8, $p = 0.001$), and no medication (OR = 3.0, $p = 0.003$).

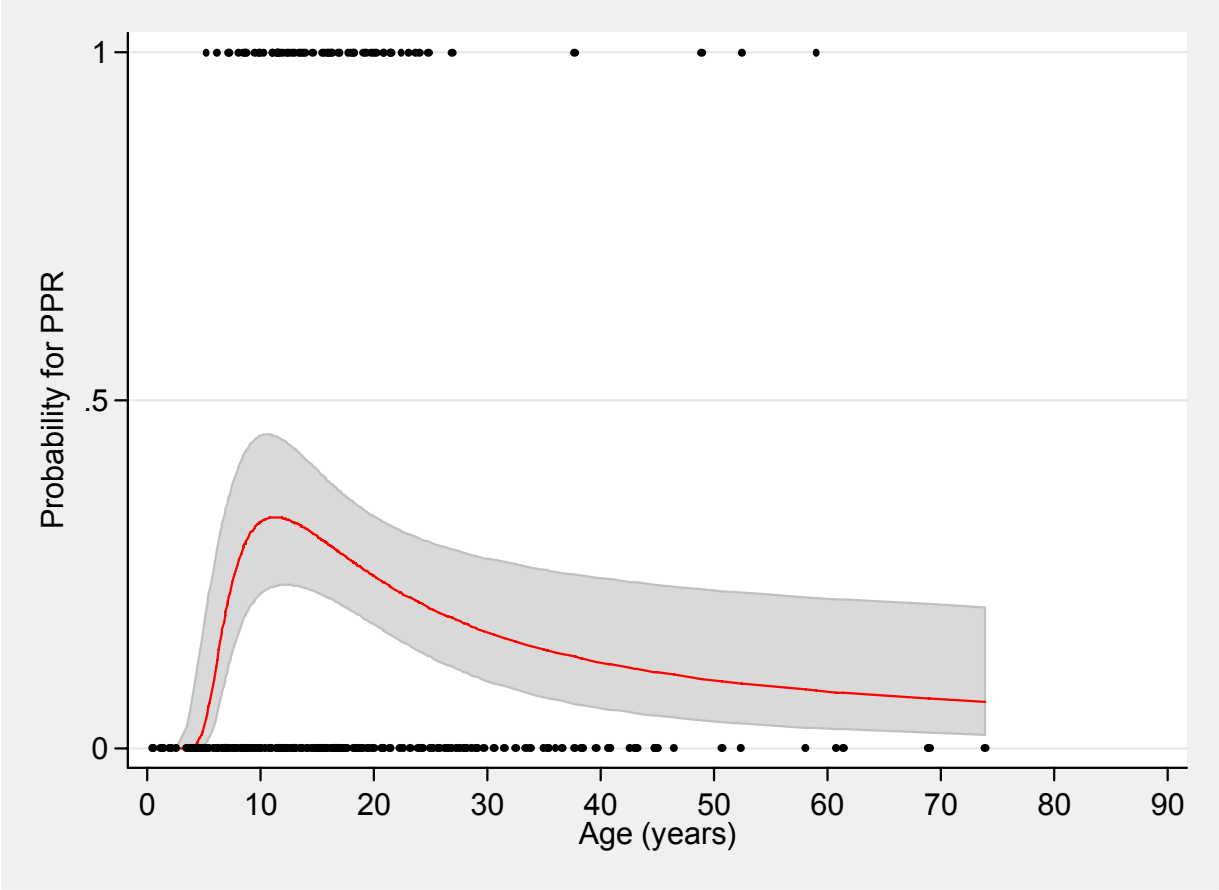

Figure 19 Age-related predicted probability for PPR in 259 GEA patients who had been provoked with flicker stimulation. The predicted probabilities are adjusted for significant predictors such as 'polyspike slow wave', 'poly-spikes' 'gender', and 'medicated'. Shaded areas are predicted values ± 1.96 SE.

Regular bilateral synchronous (RBS) GEA

The probability for RBS GEA changed with age ($p = 0.021$) with maximum probability at 11 years (Fig. 20). This age-related probability was also present when adjusted for other significant covariates ($p = 0.002$). Higher probability for RBS GEA correlated with higher GEA amplitude ($p < 0.001$).

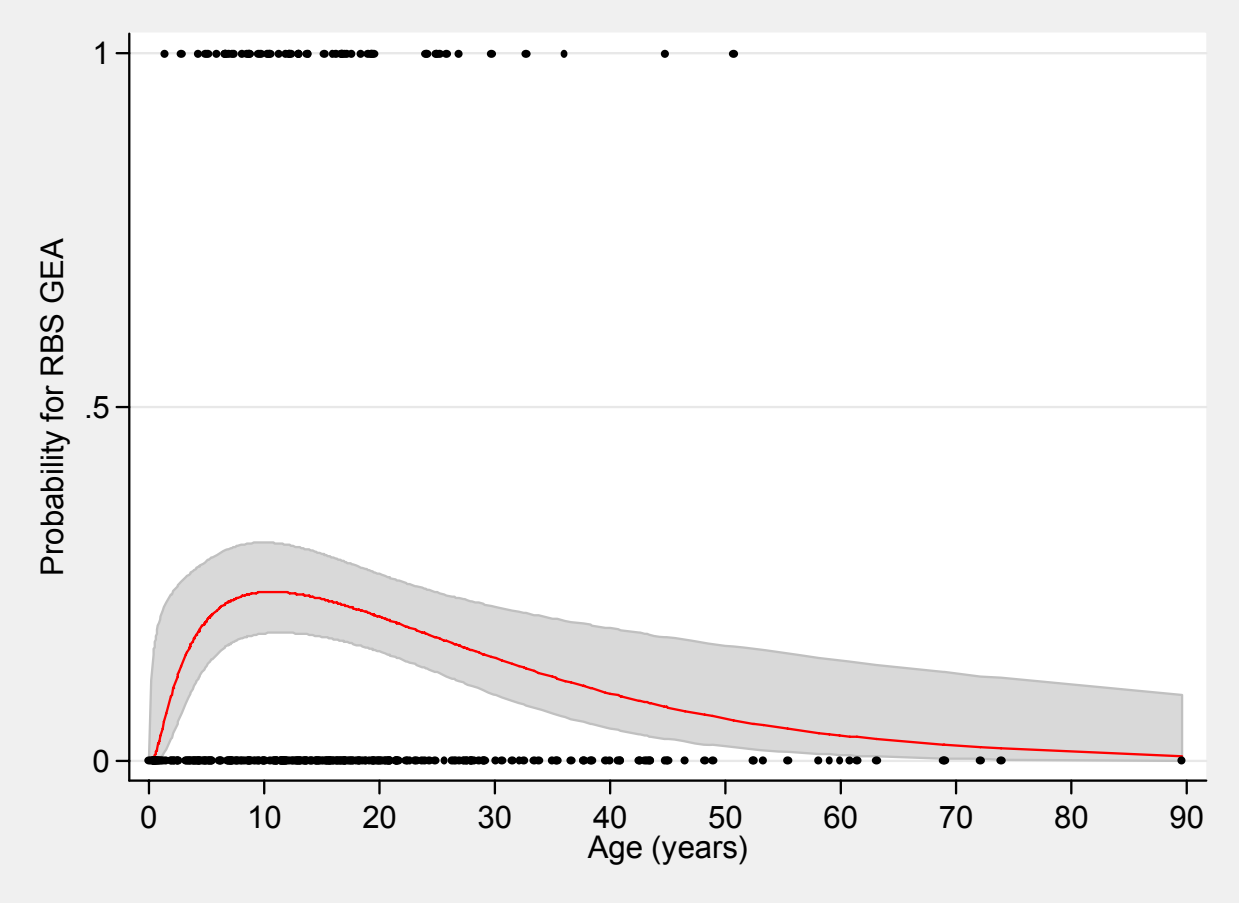

Figure 20 Predicted probability for RBS GEA by age in 325 GEA patients. Shaded areas are predicted values ± 1.96 SE.

Focal epileptiform activity (FEA)

The probability for FEA did not change with age. Lower probability for FEA correlated with 'polyspike slow wave' compared to 'spike slow wave' (OR = 0.43, p = 0.026).

GEA-types

The occurrence of 'irregular spike/sharp slow wave' pattern increased with age (p = 0.003) compared to the reference-group 'spike/sharp slow wave' (Fig 21). 'Hypsarrhythmia' decreased with age (p = 0.016) and was not seen after age 1 year. The other GEA-types were not age-related compared to the reference-group 'spike/sharp slow wave'.

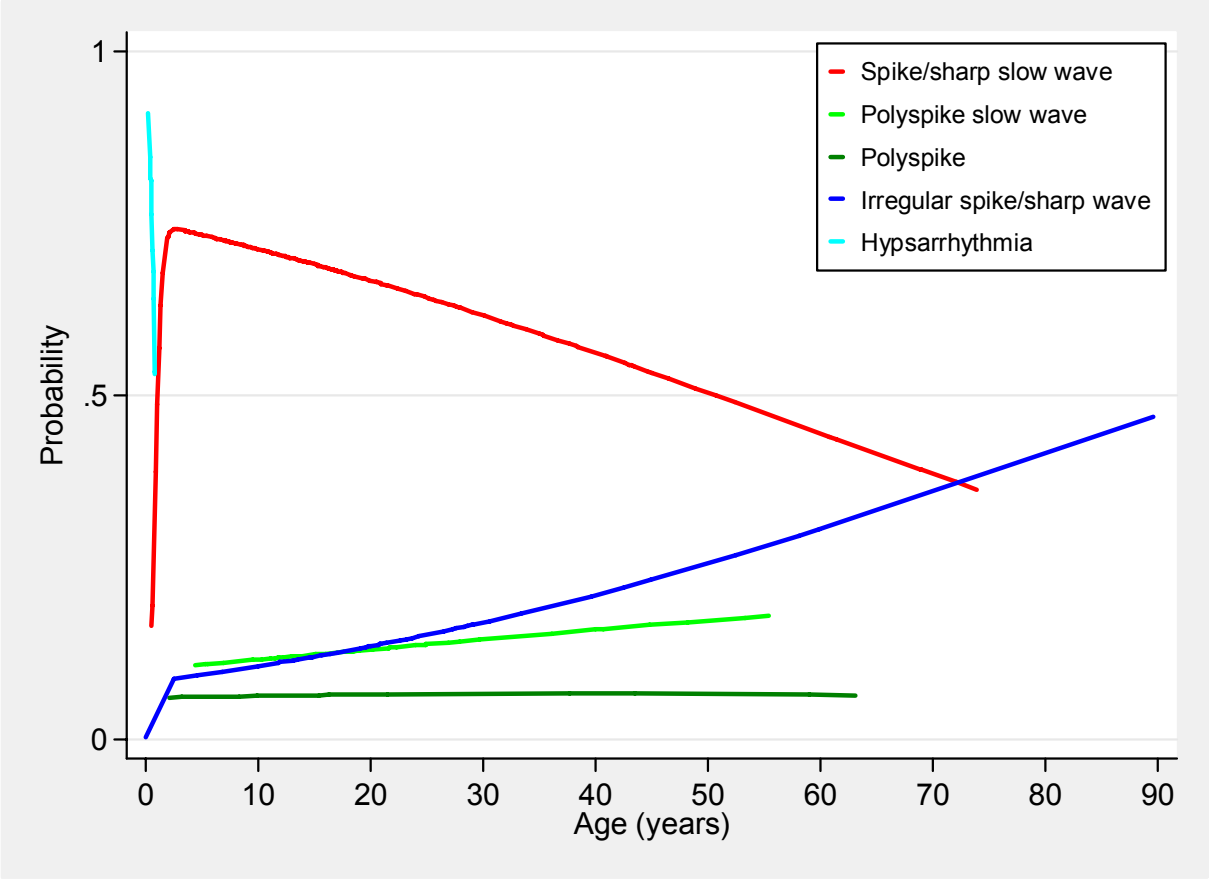

Figure 21 Age-related probability of different GEA types in 325 consecutive GEA patients.

Current brain-related disease except epilepsy (CBRDEE)

The probability of having CBRDEE increased by age ($p = 0.013$) (Fig. 22), also if adjusted for other significant covariates ($p < 0.001$). Patients with 'polyspike slow wave' had lower probability of having CBRDEE compared to 'spike slow wave' (OR = 0.18, $p = 0.006$). Lower GBA frequency correlated with higher probability of having CBRDEE ($p < 0.001$).

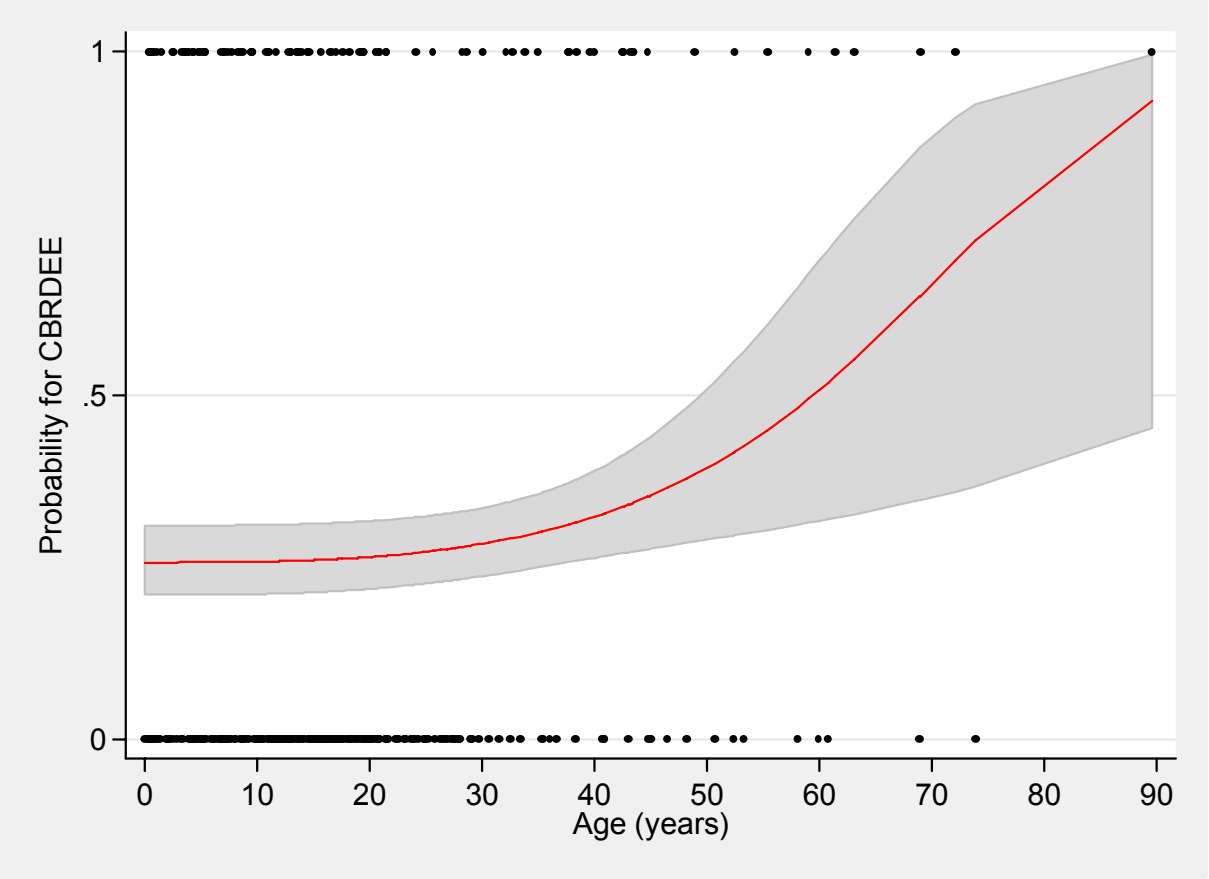

Figure 22. Age-related probability of current brain-related disease except epilepsy (CBRDEE) in 325 consecutive GEA patients.

9. Discussion

9.1 Methodological considerations

9.1.1 Inter-system communication

At the start of the project, there was no standard way of communicating with the actual EEG Editor. Windows API calls were therefore used to get information from the editor, whereas commands to the editor were accomplished by sending keystrokes. An automation interface provided by the EEG software vendor was later applied to meet these needs (Fig. 23). This made the EAS more robust.

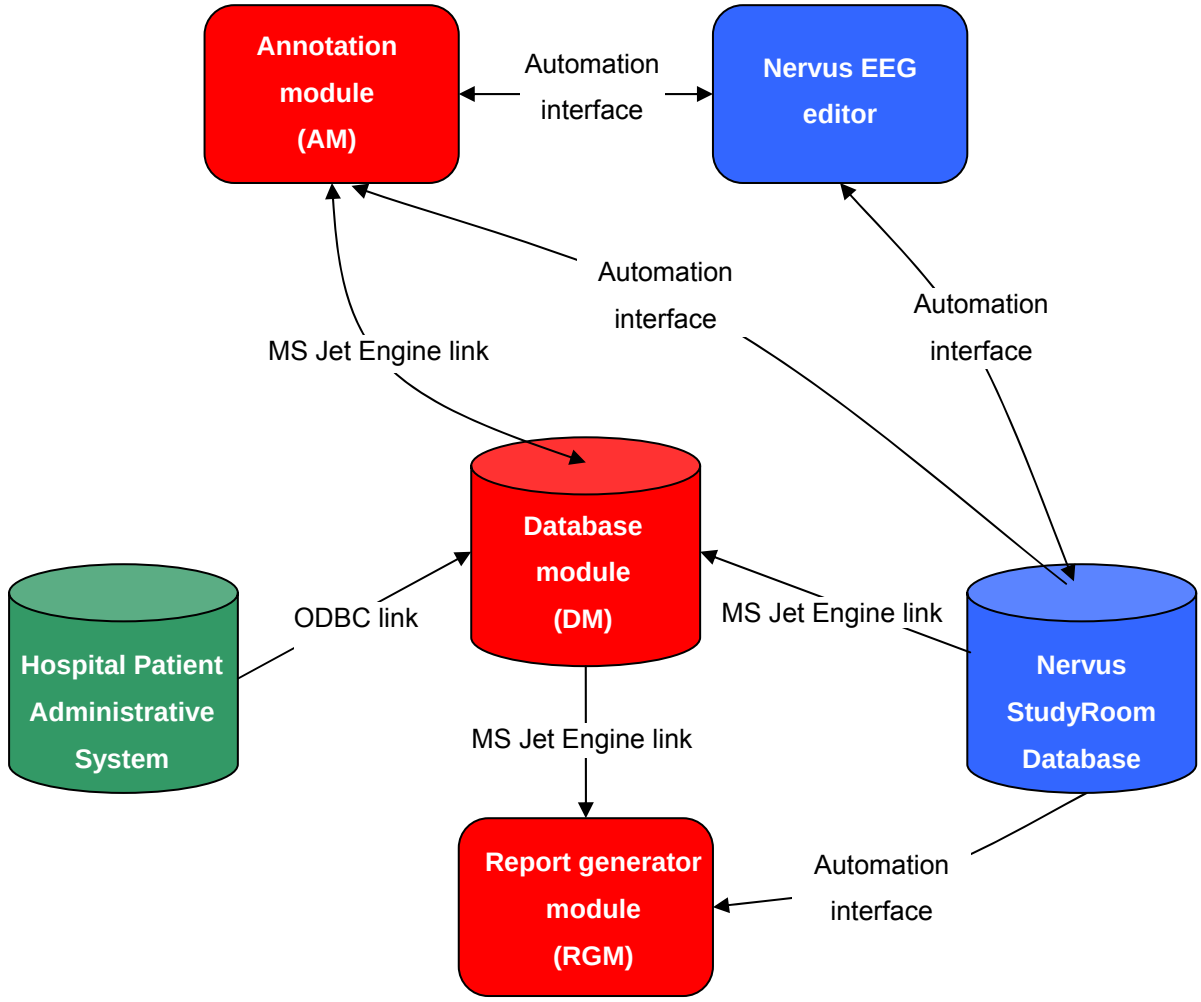

Fig. 23. Overview of the EEG annotation system (EAS) (red) and its communication with the Nervus® EEG system (blue) including Nervus EEG editor, Nervus StudyRoom Database (a database connected to the Nervus EEG editor), and the hospital patient administrative system (green). ODBC: Open Database Connectivity, MS: Microsoft®

9.1.2 Definitions

Assessment of the EEG BA is essential in EEG evaluation as slowing is indicative for brain pathology (Dustman et al., 1993; Babiloni et al., 2006). The term "EEG background activity" is, however, not uniformly used in international EEG literature. "Background activity" or "background rhythm" is sometimes used synonymously with AR (Adamis et al., 2005; Rodriguez et al., 2007). This is, according to authoritative standards, explicitly not an encouraged terminology (Chatrian et al., 1983). AR is a separate part of the EEG BA. We accordingly defined the GBA as the BA apart from the AR. The GBA activity is a more complex entity to describe compared to the AR. GBA is not a stable rhythm or frequency,

but rather a combination of several frequencies and amplitudes. The evaluation of the GBA in visually assessed EEGs is in previous EEG literature based upon categorisation into categorical groups (Ueberall et al., 1997; Londos et al., 2003). Such categorical variables are dependent on relating the BA to what is "appropriate for age", which has previously never been established in objective terms. We therefore chose to measure the GBA directly according to frequencies and amplitudes. The GBA amplitude and frequency had previously not been described in a large EEG material, and therefore no established consensus on how to measure these parameters was available. GBA amplitude and frequency was measured as one or more amplitude and frequency ranges. However, for use in the present scientific studies, the lowest GBA frequency and the mean of the lowest and highest value for the GEA amplitude were chosen. The lowest GBA frequency was chosen because this was assumed to be most relevant for assessing EEG pathology (Gloor et al., 1977). This choice, however, implied that higher GBA frequencies were highly under-reported.

9.1.3 Data collection

The data collection was accomplished through routine assessment of EEGs in a busy clinical practice. This study-design provided a very large dataset, but could at the same time result in less accuracy compared to a focused assessment of a limited numbers of EEGs. As shown in paper II, there were some systematic differences between the different EEGers, but always with the same trends. We have therefore no reason to suspect that systematic assessment bias has affected the results.

The BA often varies considerably through a routine EEG registration, with the degree of alertness as a main factor determining this variation. The AR was therefore measured in a segment where it was most distinctly appearing, and the GBA was measured during the most alert part of the registration. If drowsy, the patients were activated by activation procedures.

9.1.4 Control group

There are no established age-adjusted normal values established for the AR and GBA amplitudes and frequencies. In paper III and IV we therefore used a control group established from EEGs from not medicated outpatients without EEG pathology. This was

thus a sample of normal EEGs based on EEG findings, and not on clinical criteria. We excluded inpatients and medicated patients from the control sample to minimize confounding influence from medical effects and from complicating medical disorders.

9.1.5 Statistics

In paper II and paper III we used a multivariate polynomial model (MPM) to analyse age-related amplitude and frequency variation. The MPM appeared unstable at high patient age due to few registrations. Individuals above the age of respectively 85 and 60 years in publication II and III were therefore excluded from these analyses. This was thus a problem in paper III, but not to the same degree in paper II. To avoid excluding the older part of the population we applied another and more recent statistical model in paper IV; the multivariate fractional polynomial model (MFPM) (Royston and Sauerbrei, 2005).

(Royston and Sauerbrei, 2005) describe a dichotomy between nonparametric local-influence models and parametric global-influence models. The fit at a given point in the nonparametric local-influence model is strongly influenced by the neighbour points, but hardly affects the fit at remote points. Such models are highly flexible, but are also prone to artefactual behaviour with small neighbourhood sizes. These models are, however, constricted for "smoothing function" and cannot be used for comparing individual selections. By contrast, parametric global-influence models may be less responsive locally to true variations of the response as well as to perturbations, but the fit at distant points can be affected, in some cases considerably affected. High-order polynomials are especially prone to this affection of remote parts of the fits, and this explains our experience of instability of the model used in papers II and III. Both MPM and MFPM are examples of parametric global-influence models. The MFPM also exhibits global influence, but is more flexible than the MPM, and may provide satisfactory fits where high-order MPM may fail (Royston and Altman, 1994).

By using MFPM in paper IV, we avoided excluding the oldest part of our population even though the number of observations were lower than in paper III. The MFPM is in this thesis also applied on the data from paper III (Fig. 24 and Fig. 25) (unpublished data). However, all the conclusions were the same using this new statistical method, irrespective of the patients above the age of 60 years being excluded or not. The fitted curves were comparable, but with less local variations using the MFPM compared to MPM. This shows the superiority of

MFPM to MPM in describing our datasets, but in our case without affecting the conclusions. The MPM model had, on the other hand, an advantage compared to the MFPM in the way we used it by including the possibility for interaction between variables. This possibility has recently been included also in the MFPM model, but too late to be included in paper IV (Sauerbrei et al., 2007).

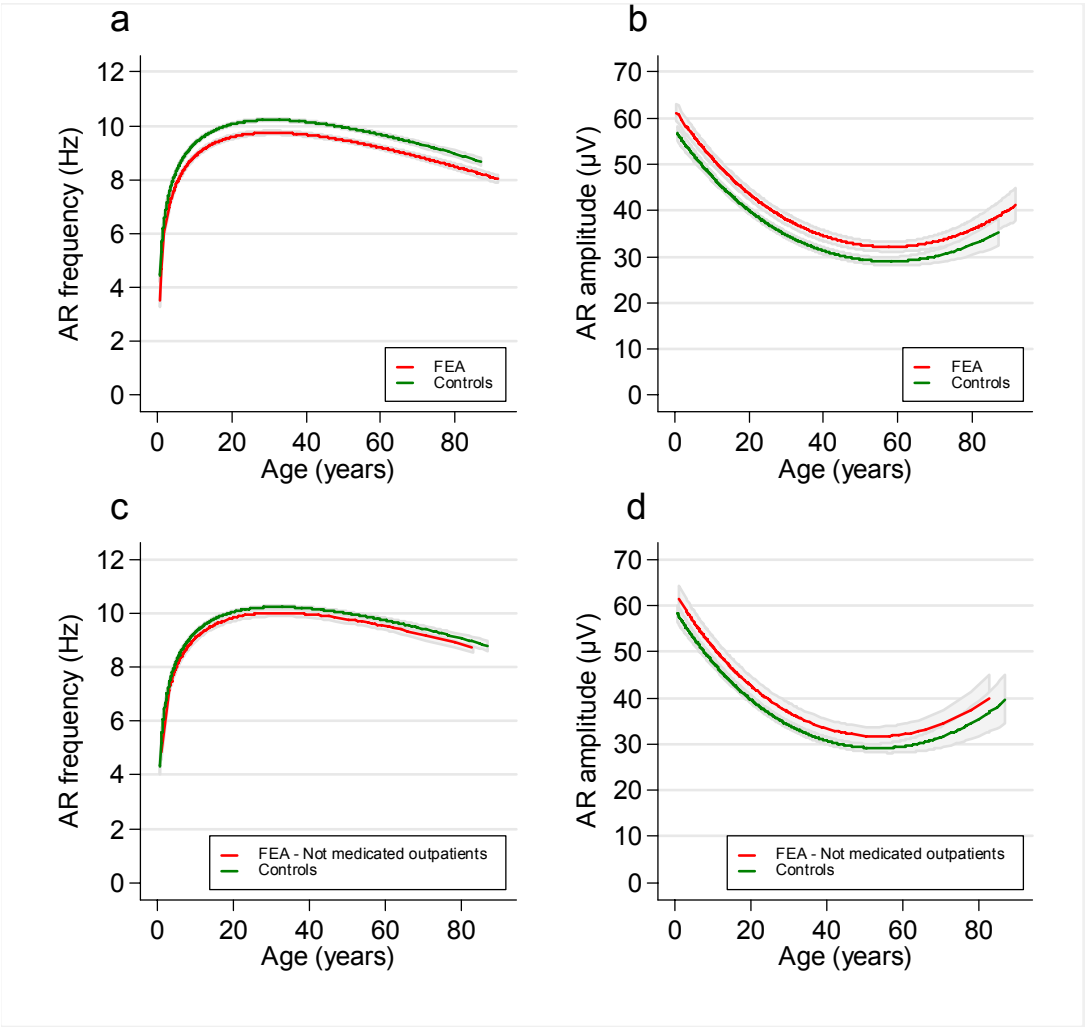

Fig. 24 AR frequency (a) and AR amplitude (b) from all patients with FEA and from drug-free outpatient controls. AR frequency (c) and AR amplitude (d) from drug-free outpatients with FEA and from drug-free outpatient controls. (Unpublished data)

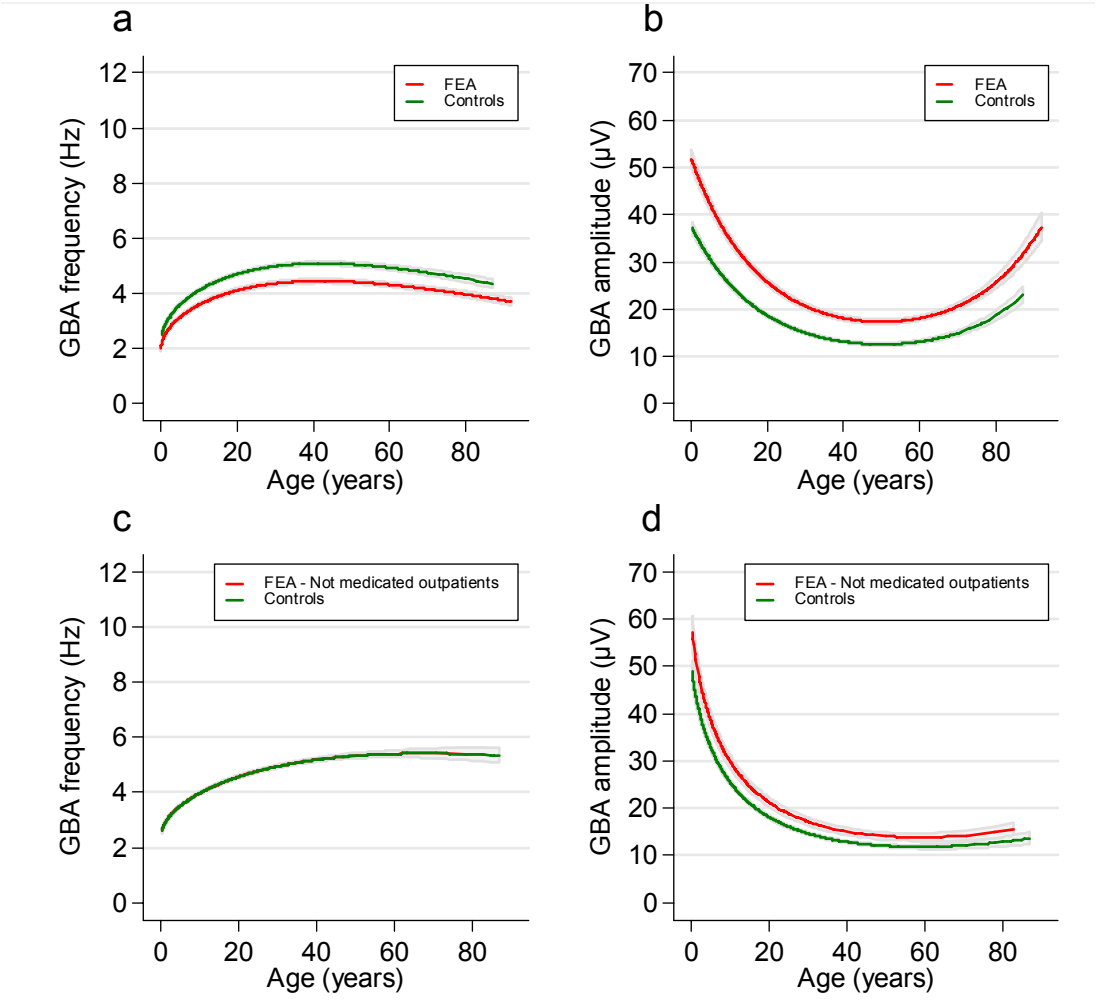

Figure 25. GBA frequency (a) and GBA amplitude (b) from all patients with FEA and from drug-free outpatient controls. GBA frequency (c) and GBA amplitude (d) from drug-free outpatients with FEA and from drug-free outpatient controls. (Unpublished data)

9.2 General discussion

9.2.1 The EEG annotation system (EAS)

The described EAS provided storage of EEG-findings in a structured and standardized way without significant extra time consumption for the EEGers. Description databases of categorized EEG findings had previously been established (Webber et al., 1989; Chung and Clancy, 1991; Lesser et al., 1993). Subsequent EEG databases have also been reported

(Finnerup et al., 1999; Hunter et al., 2005; Loddenkemper et al., 2007). However, none of them had direct communication to the EEG software and thereby direct linkage of database-stored categorized EEG epochs to the raw data (Penzel et al., 2002). Another new quality of the EAS is the method for data input and for automatic data retrieval. The same database could have been obtained without the inter-system communication described, but this would demand far more parameters to be manually determined, and thereby much more time used. The explicit numerical representation of the BA described by the frequencies and amplitudes was instrumental for papers II-IV. The dichotomy of the BA divided into the AR and the GBA was furthermore crucial to be able to assess the BA in papers II-IV.

Good access to appropriate information is essential for quality and effectiveness in daily routine work for the EEGer. In a later version of the EAS I have also implemented an overview tool providing a resume of previous EEG findings for the actual patient. The previous recordings are presented in a hierarchical view with the patient as the root, the individual recordings as branches, and the findings from each recording as sub-branches (Fig. 26). Marking the patient at the root will provide a graphical overview with all findings of the actual patient superimposed on a head model. The graphical overview will change according to the marked element; marking a recording will provide an overview of all findings of that recording, whereas marking of a finding will provide a graphical presentation of that single finding. Using this tool the EEGer can get a quick but still comprehensive overview of the patient's EEG history, and also retrieve appropriate EEGs and EEG reports for comparison.

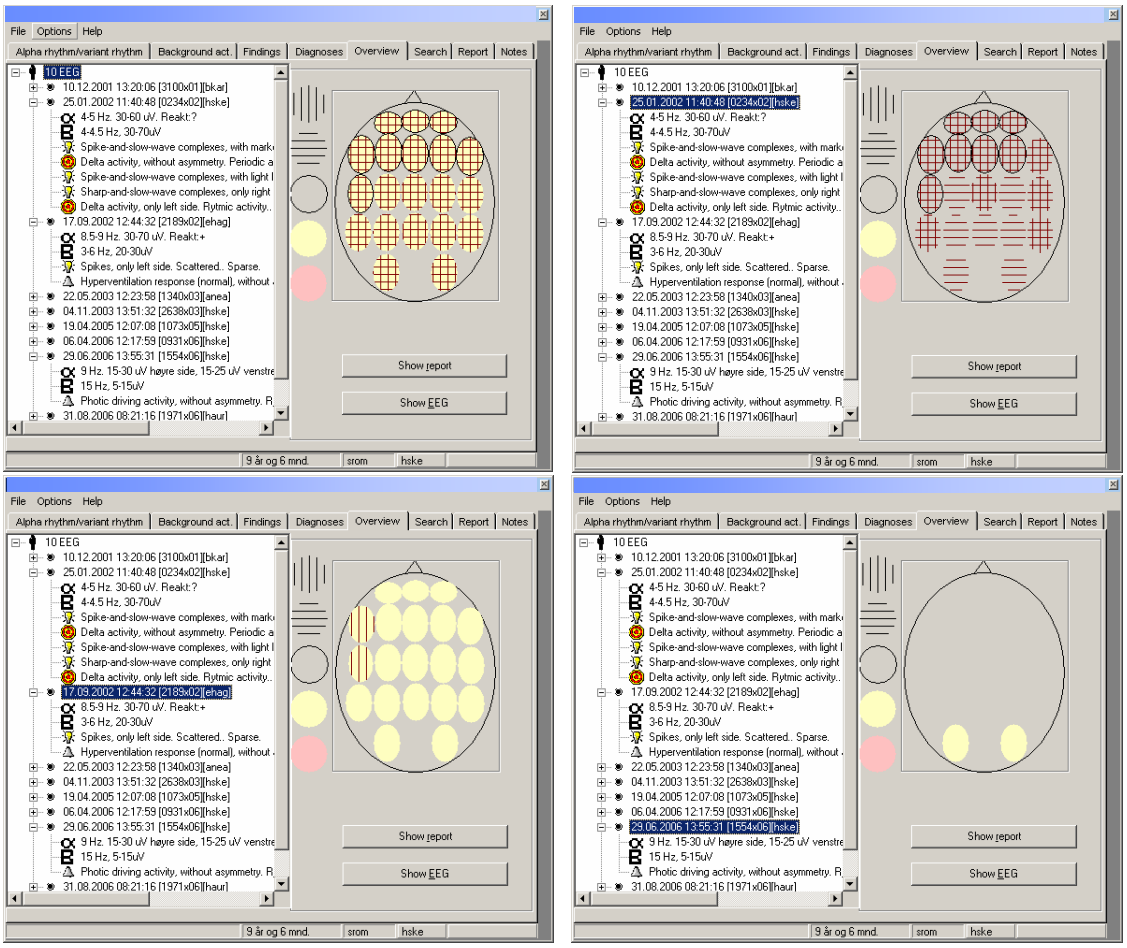

Fig. 26. Overview tool from the EEG annotation system (EAS) showing the graphical resume on a head model of all the patient's EEG recordings, dynamically changing as the patient or individual EEG recordings are selected (marked with a blue horizontal bar). Vertical lines indicate epileptiform pathology. Horizontal lines indicate non-epileptiform pathology. Yellow colour indicates normal findings and variants. Black circles indicate maximum electrodes.

9.2.2 EEG background activity (BA)

Evaluation of the BA, represented by AR and GBA, is an important part of visual EEG evaluation as BA slowing indicates CNS pathology (Guerrini, 2006; Pillai and Sperling, 2006; Smit et al., 2006; Tedrus et al., 2006a). GBA, assessed as frequencies and amplitudes, was for the first time collected and analyzed from a large number of EEGs from infancy to old age in paper II. These variables proved to be different in drug-exposed and drug-free patients, and in patients with and without non-GBA pathology in their EEGs.

EEG BA is often described as "appropriate for age" or not. Background slowing is often mentioned without any defined amplitude limits (Hughes and Cayaffa, 1977; Raymond et

al., 1995; Loddenkemper et al., 2007). No standards exist for appropriate GBA frequencies and amplitudes in visually assessed EEGs. As there was no available control group of documented healthy volunteers, no normal values in the strict sense could be established from our database. The age-related values from our not medicated patients without AR and GBA pathology, did, however, describe typical values at different ages. Furthermore, analysing the EEGs described as normal, maximal amplitudes at different ages could be suggested as the 95 percentile for each frequency band. According to these findings, the mean GBA amplitude in the theta frequency range should for example not exceed 30 μV in a normal EEG in subjects above the age of 20 years, and mean delta GBA amplitude should not exceed 60 μV in children aged 0-4 years (Fig. 8). The lowest GBA frequency was always chosen for this analysis, so higher GBA frequencies were grossly under-reported. The selection of the lowest frequency was, however, not necessary in this setting as the different frequency bands were described separately. In this thesis, I have therefore reanalysed the mean GBA amplitudes of all the frequency ranges from the control group from paper III and paper IV (N=2368) (Fig. 27) (unpublished data). These reanalyzed data gave a better representation of higher GBA frequencies.

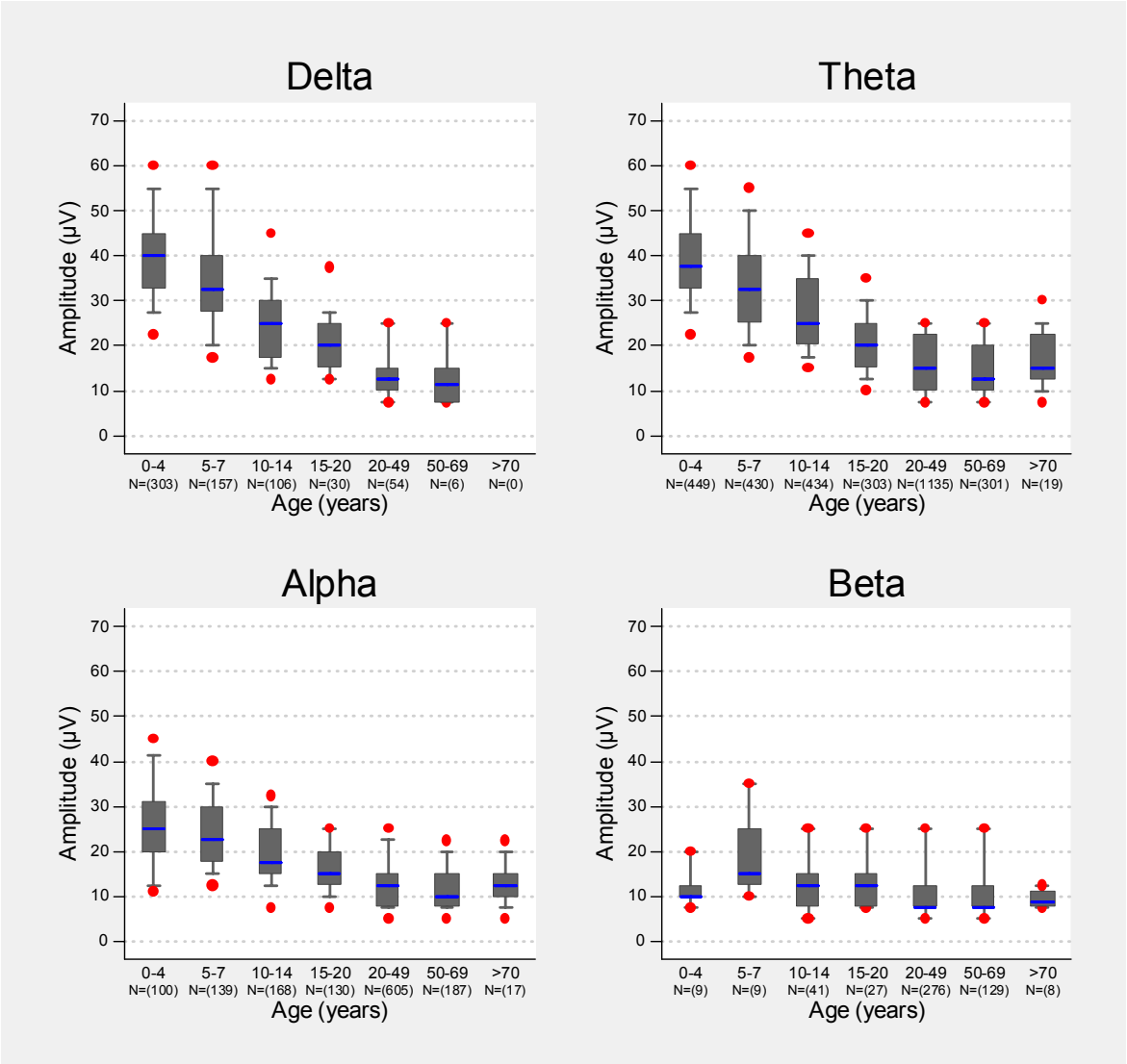

Fig. 27. Relationship between GBA frequency bands (delta, theta, alpha, and beta), amplitude, and patient age in 3268 not medicated outpatients without EEG pathology. The boxes indicate the 25th and 75th percentiles, blue lines within the boxes mark the median. Whiskers indicate the 10th and 90th percentiles, and red dots indicate the 5th and 95th percentiles.

Life span age-specific GBA frequency and amplitude have previously not been published. There has therefore until now not been any scientific basis for 'GBA appropriate for age.' Paper II and the modification in Fig. 27 indicate such values, and should be useful in the education of EEG interpreters.

The physiological background for the life-span changes of the frequencies and amplitudes of the BA is not evident. Mechanisms such as changes in bone density and corresponding increase in electrical impedance of the intervening tissue have been proposed (Dustman et

al., 1999). A recent study demonstrated gray matter volume decrease in the frontal and parietal cortex, with the greatest change occurring in adolescence, and suggested that the corresponding elimination of active synapses was responsible for the observed reduction in EEG power (Whitford et al., 2007). (Boord et al., 2007) found in a lifespan study a correlation between decreased EEG power and decreased cerebral metabolic rate. This supports the view that the reduced EEG power by age is due to reduced synaptic activity.

Paper III and IV showed BA slowing in patients with epileptiform activity compared to the control group. As a general principle, we first compared the total study group with the controls adjusted for age and gender only. Subsequently subgroups were compared to the same controls trying to identify confounding factors. Such confounding factors could be medication and complicating medical disorders. In paper III the subgroup of drug-free outpatients with FEA was therefore compared with the control group. This comparison still revealed BA slowing in the FEA group. The drug-free outpatients with FEA could, however, still have complicating medical disorders, and more or less so than the controls. To further investigate this possibility I have now also analysed the subset of drug-free outpatients and controls from the paper III study after all the individuals with brain-related ICD10-diagnoses other than epilepsy were excluded, retaining 146 drug-free outpatients with FEA and 1559 controls (unpublished data). The patients with FEA still had higher GBA amplitude compared to controls ($p < 0.001$), while there was no difference in GBA frequency, AR frequency, and AR amplitude. Another weakness regarding the comparison between the FEA group and the control group was that presence of non-epileptiform pathology by definition lead to exclusion in the control group, but not in the FEA group. I have therefore now analysed the subset of drug-free outpatients and controls from the paper III study where all individuals with brain-related ICD10-diagnoses other than epilepsy were excluded, and also excluded all EEGs with non-epileptiform pathology, retaining 106 drug-free outpatients with FEA and 1559 controls (unpublished data). The patients with FEA still had higher GBA amplitude compared to controls ($p < 0.014$), while there was no difference in GBA frequency, AR frequency, and AR amplitude. This finding supports the association between FEA per se and EEG BA slowing and is consistent with quantitative EEG studies (Diaz et al., 1998; Tedrus et al., 2006b). It should, however, be emphasised that our study is EEG centred, and not a clinical study directly applicable to specific epilepsy types.

High GEA amplitude was found to correlate with GBA slowing. The amplitude of the GEA spikes has to the best of my knowledge not previously been studied. The amplitude of scalp recorded epileptiform spikes and ictal rhythms depends on multiple factors such as the size of the cortical area involved, localisation of this area, orientation of the electrical field, degree of synchrony, and the amplitude of the original cortical signals (Ebersole and Hawes-Ebersole, 2007). The correlation between high GEA amplitude and GBA slowing could indicate larger cortical areas involved with high GEA amplitudes.

Even though the group with GEA showed more EEG BA slowing compared to the control group, this could be due to confounding factors as mentioned above. Because of the limited number of EEGs with GEA compared to FEA, and limited statistical power, a similar subgroup of not medicated outpatients was not applied for the GEA EEGs. We are therefore not able to correlate GEA and EEG BA slowing as specifically as for FEA. The distinct GEA characteristics could, however, be studied within the whole group of patients with GEA to weight the individual components' influence on the EEG BA.

Even though quantitative EEG (qEEG) measures are used in most EEG studies, the visually assessed EEG is still most used in daily clinical practice. The next step for the functionality of the EAS should be to incorporate the use of qEEG in the same system, and thereby combine the use of visually assessed EEG with qEEG. The different methods could then be compared, and the gain of each modality could be evaluated.

There is also a need for more accurate clinical information in the database. The referral diagnoses and the clinical ICD10 diagnoses set by the doctors treating the patients in the hospital are not always sufficiently sensitive and specific for exact disorders. Good clinical endpoints are necessary to correlate EEG findings to clinical settings. Standardised comprehensive and accurate clinical descriptions of normal individuals as well as of selected patient groups at different ages should therefore be included.

9.2.3 Characteristics of epileptiform activity

The age-related topographical distribution of FEA was described in paper III. Age-related epilepsies, such as occipital epilepsies and benign partial epilepsy in childhood explain some of the observed variation. Migration of epileptic foci could also contribute to such age-

related change of distribution, although this phenomenon has been debated (Blume, 1990; Andermann and Oguni, 1990). The amplitude maximum of spikes recorded from scalp EEG does not necessarily correspond directly to the underlying focus in the cerebral cortex due to neuronal propagation from distant areas as well as to peculiarities in the brain coverings such as skull holes (Torre et al., 1999). This has to be taken into consideration when applying the topographical distribution of FEA in clinical practice.

Paper IV demonstrated accurately the age-related occurrence of individual GEA-types.

Higher GEA amplitude and lower GEA frequency correlated with slowing of the EEG BA, and slowing of the EEG BA correlated with CBRDEE. This was in accordance with the generally accepted theorem that low-frequency GEA indicates symptomatic epilepsy (Markand, 2003; Smith, 2005; Pillai and Sperling, 2006). The amplitude of scalp recorded epileptiform spikes and ictal rhythms depends on multiple factors such as the size of the cortical area involved, localisation of this area, orientation of the electrical field, degree of synchrony, and the amplitude of the original cortical signals (Ebersole and Hawes-Ebersole, 2007). The electrical potentials decrease in inverse proportion to the square of the distance from the origin, and conduction through various tissues with different conduction rates attenuate the amplitudes (Hashiguchi et al., 2007). Our study showed that EEGs with RBS GEA and with ictal manifestations had higher GEA amplitudes. This could be a direct effect of a higher degree of synchrony or of a larger cortical area involved (Tao et al., 2007; Ebersole and Hawes-Ebersole, 2007). The decrease of GEA amplitude with age could in part be due to less synchrony related to a higher proportion of ‘irregular spike/sharp wave’. However, higher GEA amplitudes remained correlated with GBA slowing also after adjusting for these factors. This shows that high GEA amplitude is correlated to a general affection of cortical activity independent of age and other GEA-related features. This knowledge extends our understanding of GEA and helps the EEGer in weighing the various GEA components.

The probability for PPR changed with age, while the probability of HVS did not. The probabilities for PPR and HVS were not correlated. This indicated that HVS and PPR were complimentary in increasing the yield of the EEG registration. A consequence of these findings is that there should be no upper age-limit for HVS.

10. Conclusions

We have developed a comprehensive EAS providing storage of EEG-findings in a structured and standardized way. This system provided improved accessibility of EEG data for clinical, educational, and scientific use.

The age-related development of the AR and GBA was described, and also the association with gender, medication, non-AR pathology, and non-GBA pathology.

Topographical distribution of FEA was age-dependent for all brain regions except for the temporal region. Frontal FEA was more frequent in adults, whereas central, parietal, and occipital FEA were more frequent in children.

GEA amplitude changed by age, whereas GEA frequency did not. Higher GEA amplitudes and lower GEA frequencies correlated with GBA slowing. GEA amplitudes and GEA frequencies did not correlate.

The probability for PPR and for RBS GEA changed with age with a maximum at 11 years. The probability for HVS did not change with age, nor did the probability for FEA combined with GEA. The probability for HVS and PPR did not correlate. HVS and PPR are thus complimentary in increasing the yield of the EEG registration. There should be no upper age-limit for HVS.

FEA was associated with slowing of the EEG BA. Slowing remained significant in the subgroup of not medicated outpatients, suggesting that the association was due to the FEA per se. Also GEA was associated with slowing of the EEG BA. Due to confounding factors such as medication and complicating medical disorders, the exact association between GEA per se and this slowing of the EEG BA could not be established.

The age-related probability for specific GEA-types was established.

11. References

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12. Errata

1. Paper I, page 988: Code 3.A.95 should be corrected to 3.A.05
2. Paper I, page 992: Age should be 46 (not 66)
3. Paper II, page 666: The study period should be March 1, 2000 to March 1 2002 (not January 1, 2000 to March3, 2002)