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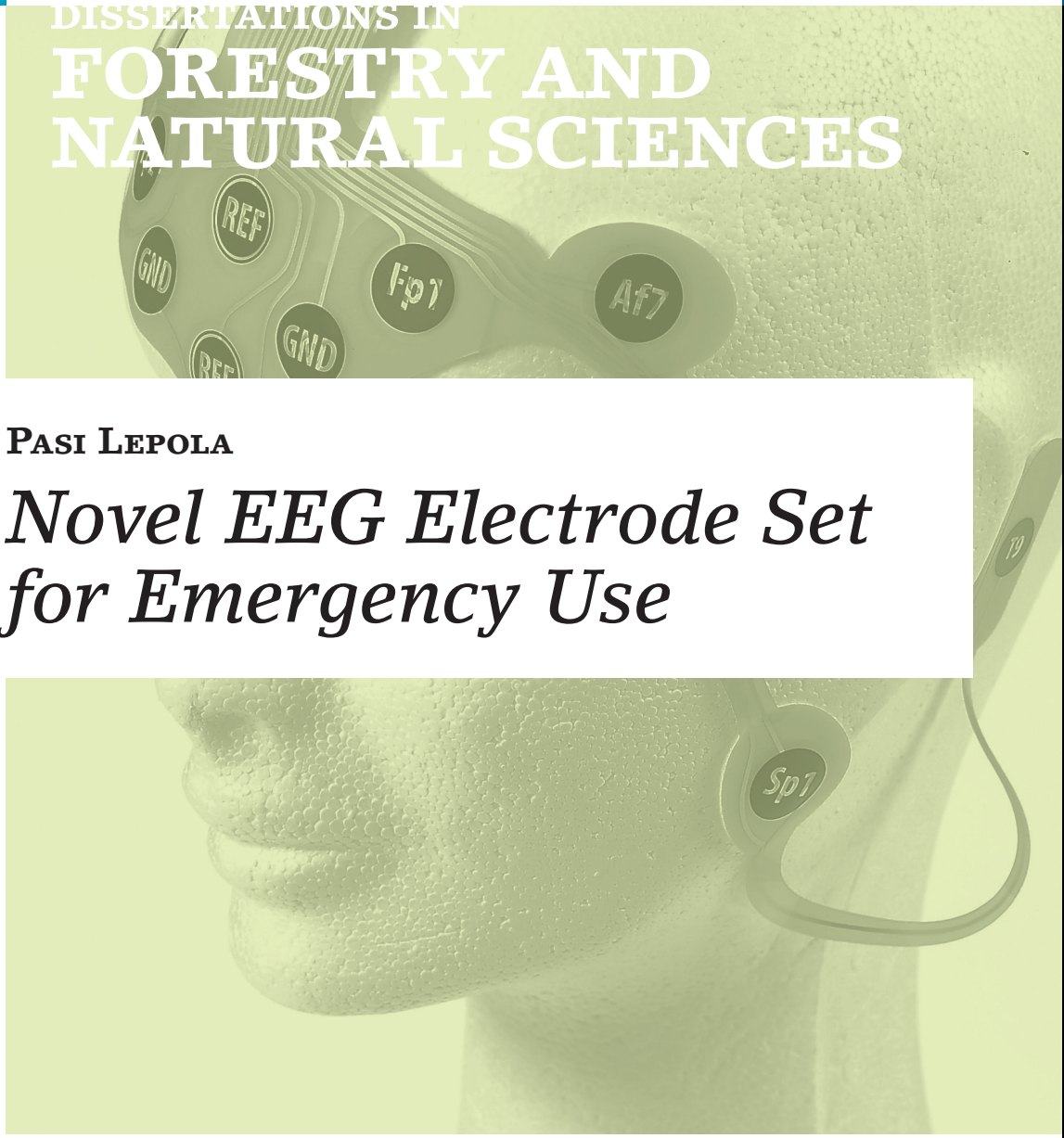

Pasi Lepola

Novel EEG Electrode Set for Emergency Use

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Dissertations in Forestry and Natural Sciences

UNIVERSITY OF
EASTERN FINLAND

PASI LEPOLA

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ABSTRACT

Recording of the electroencephalogram (EEG) in an emergency situation enables monitoring of electrical activity of the brain of a patient with an unexplained altered mental state in an early phase. If EEG monitoring can be started already in the emergency room or even in the ambulance, the diagnosis and patient access to the appropriate treatment will be speeded up. Although the benefits of emergency EEG are clear, acute EEG monitoring has not become a clinical routine mainly due to the lack of convenient electrode solutions. The current systems are cumbersome and time-consuming to attach to the patient's head.

The main aim of this thesis work was to design, fabricate and evaluate a rapid and simple-to-use disposable EEG electrode set for emergency use. The second aim was to investigate the opportunities to reduce electromagnetic interference pick-up of the screen-printed EEG electrode set with different shielding solutions, but still to allow magnetic resonance imaging and computed tomography without any signs of significant imaging artifacts.

The final prototype of the EEG electrode set was produced using screen printing technology. It consists of 16 hydrogel-coated electrodes (12 recording, 2 reference and 2 ground electrodes) embedded in a single flexible polyester film. The performance of the developed EEG electrode sets was evaluated *in vitro* and *in vivo* in several electrical tests, including impedance, noise and signal quality measurements. The EEG recordings revealed that in spite of skin-electrode impedances being higher, the signal quality was comparable with that obtained with traditional cup electrodes and the clinical question could be answered accurately in almost all patient cases. The effectiveness of proposed shielding layer solution was demonstrated. This reduced radio frequency interference in the standardized laboratory tests and the shielded electrodes showed better power-line interference immunity *in vivo*.

On the basis of the present results, it is reasonable to predict that the developed EEG electrode set, now commercialized as *BrainStatus* may be a solution for EEG registrations when the conventional 10–20 electrode setup is not available or feasible.

National Library of Medicine Classification: QT 36, WB 105, WL 150, WL 385

Medical Subject Headings: Electroencephalography/instrumentation; Electrodes; Hydrogel; Emergencies; Neurologic Manifestations; Seizures; Epilepsy; Status Epilepticus

Yleinen suomalainen asiasanasto: EEG; elektrodit; hätätilanteet; ensihoito; akuuttihoito; neurologiset oireet; kohtaukset; epilepsia

To Katri and Roosa

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Kuopio, September 2014

Pasi Lepola

LIST OF ABBREVIATIONS

AAMI	Association for the Advancement of Medical Instrumentation
AC	Alternating current
ACR	American College of Radiology
ACNS	American Clinical Neurophysiology Society
Ag/AgCl	Silver-silver chloride
AMS	Altered mental state
ANSI	American National Standards Institute
CBF	Cerebral blood flow
corr	Correlation
CJD	Creutzfeld-Jacob disease
CMRR	Common mode rejection ratio
CT	Computed tomography
DC	Direct current
ECG	Electrocardiography
ED	Epilepsy Department
EEG	Electroencephalography, Electroencephalogram
EIS	Electrical impedance spectroscopy
EMC	Electromagnetic compatibility
EMG	Electromyography
EN	European standards
EOG	Electrooculography
ER	Emergency room
EU	European Union
FDA	Food and Drug Administration
F	Female
FN	False negative
FP	False positive
FtF	Face-to-face
GND	Ground electrode
GmbH	Gesellschaft mit beschränkter Haftung
GPED	Generalized periodic epileptiform discharge
GRP	Ground reference plane
ICP	Intracranial pressure
IFCN	International Federation of Clinical Neurophysiology

ICU	Intensive care unit
Inc.	Incorporation
IEC	International Electrotechnical Commission
ISO	International Organization for Standardization
IR	Infrared
Ltd	Limited company
N	Negative instances
NCSE	Nonconvulsive status epilepticus
M	Male
MEMS	Microelectromechanical system
MR	Magnetic resonance
MRI	Magnetic resonance imaging
P	Positive instances
PET	Positron emission topography
PLED	Periodic lateralizing epileptiform discharges
PSD	Power spectral density
PTFOS	Polymer thick film organic substrate
REF	Reference electrode
RF	Radio-frequency
RMS	Root mean square
ROSC	Return of spontaneous circulation
SAH	Subarachnoid hemorrhage
SD	Standard deviation
SE	Status epilepticus
SNR	Signal-to-noise ratio
SPECT	Single-photon emission computed tomography
StE	Skin-to-electrode
T1W SE	T1 weighted spin-echo
T2W FLAIR	T2 weighted fluid attenuated inversion recovery
T2W TSE	T2 weighted turbo spin-echo
TBI	Traumatic brain injuries
TN	True negative
TNR	True negative rate
TM	Trademark
TP	True positive
TPR	True positive rate
ZIF	Zero insertion force

LIST OF SYMBOLS

C	Capacitance
C_d	Capacitance of the skin-electrode interface
C_e	Capacitance of the epidermis
dBW	Decibel Watt
E_{hc}	Half-cell potential
E_p	Potential difference over *stratum corneum*
E_{RMS}	Root mean square of the voltage
Δf	Frequency range
I_{RMS}	Root mean square of the current
k	Boltzmann's constant
n	Number of times/measurements/patients
p	Probability
R	Resistance
R_d	Resistance of the skin-electrode interface
R_e	Resistance of the epidermis
R_s	Resistance of the electrolyte
R_u	Resistance of dermis and other tissues under it

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on data presented in the following articles, referred to by the Roman numerals I-IV.

I Myllymaa S*, Lepola P*, Töyräs J, Hukkanen T, Mervaala E, Lappalainen R and Myllymaa K. New disposable forehead electrode set with excellent signal quality and imaging compatibility. *Journal of Neuroscience Methods, 215 (1), pp. 103-109, 2013.*

II Lepola P, Myllymaa S, Töyräs J, Hukkanen T, Mervaala E, Määttä S, Lappalainen R and Myllymaa K. A Handy EEG Electrode Set for patients suffering from altered mental state. Submitted.

III Lepola P, Myllymaa S, Töyräs J, Muraja-Murro A, Mervaala E, Lappalainen R and Myllymaa K. Screen-printed EEG electrode set for emergency use. *Sensors and Actuators A: Physical, 213, pp. 19 - 26, 2014.*

IV Lepola P, Myllymaa S, Töyräs J, Mervaala E, Lappalainen R and Myllymaa K. Shielded design of screen-printed EEG electrode set reduces interference pick-up. *IEEE Sensors Journal, 14 (8), pp. 2692 - 2697, 2014.*

*equal contribution

AUTHOR'S CONTRIBUTION

The publications selected for this dissertation concern the development, testing and evaluation of novel EEG electrode sets for emergency EEG. The original idea behind the EEG electrode set (publication **I**) was proposed by its inventors Esa Mervaala, Juha Töyräs, Katja Myllymaa, Sami Myllymaa and Reijo Lappalainen. The ideas behind other studies (**II-IV**) did arose during the development process of the electrode set and were based on discussions between the author (P. Lepola), co-authors and the project steering group.

The author had the main responsibility for writing for manuscripts, except of the publication **I** that has an equal contribution from S. Myllymaa. All publications were submitted after receiving constructive comments from supervisors (K. Myllymaa, J. Töyräs, R. Lappalainen and S. Myllymaa) and other co-authors.

The author carried out electrical impedance measurements (**I** and **III**) and EMC tests (**IV**), and analyzed their data together with S. Myllymaa. The author created the illustrations of EEG samples that were selected and interpreted by EEG specialists (E. Mervaala **I-IV**, S. Määttä **II** and A. Muraja-Murro **III**). The author performed the computed tomography and magnetic resonance imaging together with M. Könönen (**I** and **III**). The author was mainly responsible for all statistical analyses. The author was also responsible for the technical implementation of the EEG recordings (**I-IV**) and an experienced EEG technician (T. Hukkanen) performed the patient recordings. The author had a very significant role in the design of the electrode together with the other members of the study group. The author's fingerprints are visible especially in the final screen-printed EEG electrode set (**III-IV**), which was industrially produced based on his technical drawings.

Contents

1 Introduction

Although modern neuroimaging techniques such as magnetic resonance imaging (MRI), computed tomography (CT), and metabolic brain imaging by single-photon emission computed tomography (SPECT) and positron emission topography (PET) are becoming commonly available, electroencephalography (EEG) is still the method of choice for the detection of epileptic activity and nonconvulsive status epilepticus (NCSE) (Noachtar & Rémi 2009). EEG also plays an important role in the investigation of encephalitis, head trauma, coma, stroke and brain death (Khan et al. 2005, Praline et al. 2007, Varelas et al. 2003).

Many patients arriving in the emergency room (ER) display alterations in their mental status (Bautista et al. 2007). Since there are many possible causes for altered mental state (AMS), the origin and reason for acute changes in mental status may not be immediately obvious (Bearden & Nay 2011, Murphy et al. 1999, Ziai et al. 2012). The use of EEG recording in an emergency situation provides the possibility to investigate AMS at an early phase. Any lag in EEG monitoring leads to a delay in the diagnosis and this can jeopardize the patient's access to the most appropriate treatment (Ziai et al. 2012). Even better, if EEG monitoring can be started already in the ambulance, the diagnosis will definitely be speeded up.

Although the benefits of emergency EEG are clear, it is not yet a clinical routine (Baki et al. 2011) and its round-the-clock availability varies widely in different EEG laboratories (Quigg et al. 2001). The main reasons for this situation are the high costs of EEG recording systems, the difficulty to find storage space close to the patients, the general hurried tempo in ER as well as the lack of trained personnel to apply electrodes, to use the

recording systems, and to interpret the recordings (Baki et al. 2011). Traditional EEG electrodes require abrasion of the skin and the use of electrolytic paste to improve conductivity and to reduce skin-electrode impedance (Nunez & Srinivasan 2006). In addition, the correct positions of the electrodes based on standard 10–20 system are not easy to find on hair-bearing areas especially by a non-technologists (Kolls et al. 2012). Therefore the attachment of the traditional electrodes to the patient's head is both a cumbersome and a time-consuming procedure.

One solution to this time-consuming positioning problem is to utilize full-montage EEG templates specially designed for easy positioning by onsite personnel (Jordan & Schneider 2009, Kolls et al. 2012). These kinds of EEG templates have been claimed to shorten the time required to initiate EEG recording and they are well accepted by the personel in the intensive care unit (ICU) (Kolls et al. 2012). Although the quick positioning has been achieved, skin abrasion was still needed and the attachment with the separate electrodes can take more than a half an hour when performed by non-technologists (Kolls et al. 2012).

Recently, several electrode solutions that do not require skin preparation have been devised. These can be made in several techniques *e.g.* micromachined spikes (Forvi et al. 2012, Griss et al. 2001, 2002, Ng et al. 2009), carbon nanotubes (Ruffini et al. 2008), polymer foam (Lin et al. 2011) or hydrogel (Alba et al. 2010, Toyama et al. 2012). However, most of these electrode solutions are still under development. At present, only a few hydrogel-based solutions are commercially available *i.e.* HydroDot electrode (Hydrodot Inc., Westford, MA, USA) intended to be used with full-montages EEG templates and StatNet (Hydrodot Inc.), which is a full-montage electrode set with fixed electrodes. However, full-montage EEG electrode sets may not be attached if the patient's head is unmovable. This is a major disadvantage in ER where clinicians often suspect that there are head or neck injuries in an unconscious patient. Head trauma or the presense of other implanted measuring instruments at the head region may also complicate the

attachment of a full-montage. In an attempt to overcome the above-mentioned shortcomings related to the attachment of full-montage, some solutions in which a limited number of electrodes are attached below the hairline have been introduced (Bridgers & Ebersole 1988, Kolls & Husain 2007a, Young et al. 2009).

During the EEG monitoring, some patients may need to be imaged in CT or MRI. This may happen as soon as the patient arrives in ER or later in ICU, where CT and MRI are routinely used for the acute evaluation of patients (Mirsattari et al. 2009). Unfortunately, if the electrodes need to be removed before imaging, then important EEG data can be missed. This situation is especially problematic if the electrode set is known to be difficult and time consuming to attach. As a consequence, EEG recording may be postponed for many hours. Therefore, it would be practical if the patient could be imaged with the electrodes attached without any increased risk for patient safety or imaging artifacts (Mirsattari et al. 2009).

In this thesis, a disposable screen-printed EEG electrode set for emergency use was developed. The electrode positions were optimized to be placed on hairless areas in such a way that the signals would be reliable and provide a comprehensive picture of the electrical activity of the brain. The developed electrode set is easy-to-use, no skin abrasion is required and the electrode set attachment can be performed in only a few minutes without moving the patient's head. Different materials and manufacturing techniques were investigated in order determine the most suitable choices for commercial mass production and to allow MR and CT imaging without introducing clinically significant artifacts. The coupling of external electromagnetic fields to screen-printed circuits was investigated to devise optimal ways to reduce the interference pick-up. Moreover, the performance and suitability of the EEG electrode set were evaluated in electrical performance tests and clinical EEG recordings. The working hypothesis was that an easy-to-use below hairline EEG electrode set would be advantageous for

EEG registration when the conventional 10–20 electrode setup is not available or feasible.

2 Emergency EEG

EEG has been routinely used at least half a century for monitoring the electrical activity of the brain. Usually, the EEG is measured in departments of clinical neurophysiology, but it is often recorded also in ICU and ER. The term "emergency EEG" has traditionally referred to the EEG registration, which it has been mandatory to carry out immediately if there is any suspicion of a pathological condition that may be life-threatening or may lead to organ failure requiring thereby prompt diagnosis and correct treatment to avoid serious consequences (Praline et al. 2007). Although emergency EEG is available in most hospitals with EEG facilities, round-the-clock availability varies widely between EEG laboratories (Quigg et al. 2001). This usually means that outside of normal business hours, a technician always has to be on-call to respond to a physician's request if a patient is considered to need emergency EEG (Praline et al. 2007). Unfortunately, this causes a delay, which may be even longer than four hours (Kolls et al. 2012). In the worst case scenario, EEG registration can be delayed until the next business day and this delay in the diagnosis of NCSE may reduce the chance for successful treatment subsequently increasing the risk of permanent brain damage and death (Drislane et al. 2008, Kolls et al. 2012, Young et al. 1996). In addition, it may lead to unnecessary tests, procedures, admissions, and increased costs (Zehtabchi et al. 2013a).

The routine use of emergency EEG is very valuable in those patients with changes in their mental status without any obvious cause (Baki et al. 2011). Emergency EEG is most useful if the patient has a neurological disorder, but it also has an invaluable role in detecting or ruling out a possible NCSE or severe encephalopathies (Kaplan 2005, Zehtabchi et al. 2011). Utilization of EEG could also help to quantify traumatic brain injury while the patient is still in the ER (Naunheim et al. 2010).

Unfortunately, EEG has been underused for these patients and in fact emergency EEG cannot be considered as a clinical routine (Bautista et al. 2007). It is associated with expensive and difficult to use recording systems. In addition, the present electrodes are cumbersome and time-consuming to attach to a patient. The use of these systems requires expertise and a considerable amount of time, which is often difficult to find in the hectic and pressurized working environment of ER (Baki et al. 2011). During the last few years, several solutions have been presented in an attempt to resolve the above-mentioned challenges *e.g.* using shorter recording times, applying of EEG caps, templates or dry electrodes, as well as using the Internet for rapid interpretation of EEG data (Bautista et al. 2007, Ziai et al. 2012). Although the necessity of conducting emergency EEG is widely recognized, breakthroughs in emergency EEG have also been delayed partly due to the lack of international recommendations (Bautista et al. 2007, Ziai et al. 2012). Even finding a consensus on uniform terminology has been difficult (Praline et al. 2007).

2.1 ALTERED MENTAL STATE

Altered mental state (AMS) is a nonspecific manifestation of brain dysfunction where the consciousness of a patient is acutely impaired. AMS may appear in a variety of forms *i.e.* from a slight confusion to deep coma (Kanich et al. 2002). Some patients present in a sleep-like state with reduced mental and motor activities whereas others may be hyperactive (Murphy et al. 1999). On the other hand, some patients may appear to be awake and alert but are unable to respond to external stimuli (Murphy et al. 1999). AMS may be sudden or gradual in onset, transient, fluctuating, or sustained in progression and acute or chronic in duration (Kanich et al. 2002). Generally, the diagnosis of an altered level of consciousness is based on the knowledge of the patient's history (Murphy et al. 1999). Therefore, the clinical evaluation of AMS can be complicated if a complete medical history is not available or a friend or family member does not

accompany the patient. It has been estimated that from two to ten percent of patients in ER are suffering from AMS (Kanich et al. 2002, Wofford et al. 1996, Zehtabchi et al. 2013a). For example, millions of patients every year in the United States have AMS (Strange et al. 1992, Zehtabchi et al. 2013a). Moreover, it has been estimated that as many as 30 % of elderly patients in ER might suffer from AMS (Kanich et al. 2002).

The etiology of AMS is complicated and there is a large range of different causes (Murphy et al. 1999). The majority, up to one third of AMS is attributable to a neurological disorder and one fourth is caused by toxicological reasons (Kanich et al. 2002). Other common causes are based on trauma (14 %), psychiatric (14 %) infectious (10 %), endocrine/metabolic (5 %), pulmonary (3 %), oncologic (3 %), cardiovascular (1 %), gastrointestinal (1 %), and renal (1 %) reasons (Kanich et al. 2002). These estimations are based on research performed in a university hospital ER with 317 patients (mean age 49) (Kanich et al. 2002). Although, the origin of acute changes in mental status may not be immediately obvious in the ER, it is important to make the correct diagnosis as soon as possible (Bautista et al. 2007).

Since one third of AMS cases are caused by neurological disorders, EEG is often helpful in achieving the correct diagnosis in ER (Ziai et al. 2012). Ziai et al. (2012) enrolled 82 patients with AMS and based on the surveys completed by ER physicians, EEG helped to determine the diagnosis in the majority (51.3 %) of the patients. Furthermore, EEG registration also changed management in 3.9 % of the patients in ER. Emergency EEG can help to detect or rule out specific AMS etiologies including toxic-metabolic encephalopathy, hepatic or uremic encephalopathy, herpes encephalitis, and status epilepticus (Zehtabchi et al. 2013b). The benefits of EEG increase if the etiologically straightforward patient cases such as hypoglycemia, hypotension, hypothermia, hyperthermia, or narcotic overdose are excluded from the routine use of emergency EEG (Zehtabchi et al. 2013a). Zehtabchi et al. (2013b) recorded EEG from 259 patients with AMS and reported that 78

% of the AMS patients had abnormal EEG. These 150 cases showed slowing background activities, which may indicate underlying encephalopathy and 12 cases were NCSE (Zehtabchi et al. 2013b). These findings suggest that the prevalence of EEG abnormalities in ER patients with AMS is significant.

2.2 NONCONVULSIVE STATUS EPILEPTICUS

Nonconvulsive status epilepticus (NCSE) is a serious electrophysiological disorder of the brain where continuous seizure activity lasts at least 30 minutes (Kaplan 2007). In most cases, NCSE causes cognitive or behavioral changes and it occurs without any apparent convulsions (Kaplan 2005, Sutter et al. 2012). Therefore, it is impossible to diagnose NCSE without EEG registration (Brigo 2012, Kaplan 2005, 2007, Sutter et al. 2012).

NCSE is a common cause for AMS in ICU, particularly in patients with epilepsy (Kapadia et al. 2005, Privitera et al. 1994). The incidence of NCSE at ER is lower than that in ICU varying between 8–30 % (Claassen et al. 2004, Praline et al. 2007, Privitera et al. 1994, Towne et al. 2000). Zehtabchi et al. (2013b) enrolled a group of 259 patients from which the easily treatable cases of AMS (*e.g.* hypoglycemia) were excluded. They reported that nonconvulsive seizures (including NCSE) were detected in 5 % of these patients (Zehtabchi et al. 2013b). Although NCSE is more common in elderly patients, AMS caused by NCSE is also common among children (Saengpattrachai et al. 2006, Waterhouse & Delorenzo 2001). This is a challenging diagnostic problem, because changes in the mental state of child may not be noticed as readily as in adults. Diagnostic is important since NCSE requires immediate medical treatment (Zehtabchi et al. 2011).

NCSE is associated with epilepsy with a high risk of recurrence (Sutter et al. 2012). In addition, several electrolyte disturbances or chronic diseases may trigger NCSE including diffuse cerebral microangiopathy, autoimmune diseases,

paraneoplastic syndromes, inherited metabolic disorders, neurodegenerative disorders and brain tumors (Sutter et al. 2012).

Although EEG is essential for the detection of NCSE, there are no simple sets of numerical criteria with which to include or exclude the condition (Kaplan 2007). In particular, the frequency, amplitude, morphology or evolution of electrographic activity tends to vary from patient to patient (Kaplan 2007). Therefore, the diagnosis of NCSE relies on subjective interpretation (Brigo 2012, Sutter et al. 2012). The typical EEG findings related to NCSE may include repetitive focal or generalized spikes, polyspike, sharp waves, spike-and-wave as well as sharp- and slow-wave complexes at 2.5 Hz (Kaplan 2007, Sutter et al. 2012). Rhythmic waves at 0.5 – 1 Hz with different onset, evolution and location or post-periodic epileptiform discharges background slowing or attenuation are also typically distinguishable (Kaplan 2007, Sutter et al. 2012). Traditionally, NCSE is divided into focal NCSE or generalized NCSE often called absence status (Kaplan 2007). In technical terms, focal NCSE may be difficult to discern in the EEG. Therefore, the use of the full-montage is recommended in emergency EEG (Jordan & Schneider 2009, Kolls & Husain 2007a, Kolls et al. 2012). In contrast, generalized NCSE is often characterized by very drastic changes in the EEG and a few or even one EEG channel may well be enough to detect this condition (Bastani et al. 2005, Nitzschke et al. 2012, Young et al. 2009).

It is important that there is a correct and rapid diagnosis and then immediate treatment of NCSE. Since untreated NCSE carries a clear risk of permanent brain damage, delays diminish the likehood for successful treatment (Drislane et al. 2008, Young et al. 1996). Mortality increases by two percent per hour if the NCSE remains untreated (Jordan & Schneider 2009). Therefore, the need to rule out NCSE is one of the most common reasons for requesting emergency EEG (Praline et al. 2007). The mechanism explaining how NCSE causes mortality is complicated, but based on a publication, it is believed that

untreated NCSE causes increase in brain glutamate concentration above excitotoxic levels (Vespa 2005). NCSE also increases intracranial pressure and brain lactate and pyruvate levels after acute traumatic brain injuries (TBI) (Vespa et al. 2007). These phenomena can cause death of brain cells subsequently leading to brain damage (Jordan & Schneider 2009).

3 Recording of EEG

EEG can be thought as continuous noise originating from the electrical activity of the brain. This noise can be simply recorded by attaching a pair of electrodes onto the surface of the skull. This microvolt-scale signal recorded by electrodes is called EEG. Although the EEG is nearly a century old technique (Berger 1929), several decades of research were needed before the origin of the EEG was understood.

3.1 FROM CELLULAR LEVEL TO EEG SIGNAL

The brain consists of four main parts, *i.e.* the brainstem, thalamus, cerebellum, and cerebrum. The brainstem is a structure, which transmits sensory and motor action potentials between the spinal cord and the brain. The thalamus is responsible for the logistics of sensory inputs (except smell) to the cortex. The cerebellum includes the surface areas of the brain controls muscle movements and certain aspects of cognition. The outer edge of the cerebrum is called cerebral cortex. This is about two to five millimeters thick structure containing more than half a billion neurons per square centimeter. (Nunez & Srinivasan 2006)

The functional unit of the nervous system is the neuron, which transmits information between other neurons via synapses, which conduct electrical and chemical signals. The exchange of ions alters the membrane potential of the neuron. The neurons found in the cerebral cortex are called pyramidal cells (Nunez & Srinivasan 2006). Pyramidal cells are strongly interconnected; a single pyramidal cell may receive signal from more than 30,000 synapses (Megías et al. 2001). The EEG signal as recorded from the scalp reflects the summated postsynaptic potentials of billions of pyramidal cells at the cortex. The

interpretation of recorded signals is complicated by the structure of the cortex. The cortex is not flat, but rather it is intensely wrinkled. In practice, only signals from pyramidal cells oriented towards the surface of the skull are recordable. The voltage of the recorded signal also depends on the size of synchronically operating pyramidal cell group and the signal is invariably a combination of several signals originating from different cell groups. In addition, there is cerebrospinal fluid as well as the skull and the scalp lying between the pyramidal cells and the recording electrode. These fluids and tissues affect signals recorded from the scalp. (Nunez & Srinivasan 2006)

Typically, the amplitude of the EEG signal recorded from the scalp varies from 10 to 100 μV and it consists of frequencies below 70 Hz (Nuwer et al. 1999). Classically, this frequency range is divided into five bands, *i.e. alpha*, *beta*, *delta, gamma* and *theta*. These frequency bands are also called rhythms. The rhythms of EEG findings depend on the person's level of awareness and state of consciousness (Table 3.1.) (Constant & Sabourdin 2012). The main frequency in the normal EEG is the beta rhythm, which has a low amplitude (10–20 μV) when the subject is awake. With closing the eyes, alpha rhythm appears immediately and the amplitude rises up slightly (20–40 μV) (Claassen et al. 2004).

Table 3.1. *The EEG rhythms (Constant & Sabourdin 2012).*

EEG Rhythm	Frequency range (Hz)	Status of a subject
Delta (δ)	<3	In deep sleep
Theta (θ)	4-7	In light sleep
Alpha (α)	8-13	Awake with eyes closed and relaxed
Beta (β)	13-30	Awake and alerted, thinking actively
Gamma (γ)	>30	Awake. Involved in the processes of perception

3.2 TYPICAL EEG RECORDING SYSTEM

A modern EEG recording system consists of electrodes, an EEG amplifier and a computer unit. Based on the EEG characteristics and requirements of clinical use, the Council of

the International Federation of Clinical Neurophysiology (IFCN) and the American Clinical Neurophysiology Society (ACNS) have published recommendations for instrumentation of clinical EEG (ACNS 2006a, ACNS 2006b, Ebner et al. 1999, Klem et al. 1999, Nuwer et al. 1999).

Traditionally electrodes have been fabricated from platinum, silver or gold (Ebner et al. 1999). They are recommended to be attached to the patient's head according to a standard 10–20 electrode system (Figure 3.1) (ACNS 2006b, Klem et al. 1999). This system is based on standard landmarks on the skull where electrodes are placed at 10 % and 20 % intervals of the distance from nasion to inion (Klem et al. 1999).

The electrodes are connected to an EEG amplifier with flexible insulated wires. The EEG amplifier is a device in which measured tiny EEG signals are amplified and digitized. In addition, some pre-processing of the EEG signal may take place prior to the transmission of EEG data signals to the computer unit, which stores the EEG data (Ebner et al. 1999).

According to the international guidelines (ACNS 2006a, Nuwer et al. 1999), the EEG amplifier's sampling rate should be at least 200 Hz and the frequency band of recorded EEG at least 0.5 – 70 Hz. It is recommended, that the time constant of the high pass filter should be at least 0.016 s (ACNS 2006a, Nuwer et al. 1999). In addition, the common mode rejection ratio (CMRR) should be less than 80 dB for each EEG channel and noise in the recording less than 2 μV (ACNS 2006a, Nuwer et al. 1999). These recommendations are not technically challenging to achieve (Baki et al. 2011) and practically every commercial system meets these criteria.

Traditional EEG systems have been heavy and burdensome to move between departments. However, modern systems are becoming lighter and smaller. Nowadays, ambulatory recordings without the computer unit are common. The data stored on a server is immediately available for interpretation. (Baki et al. 2011)

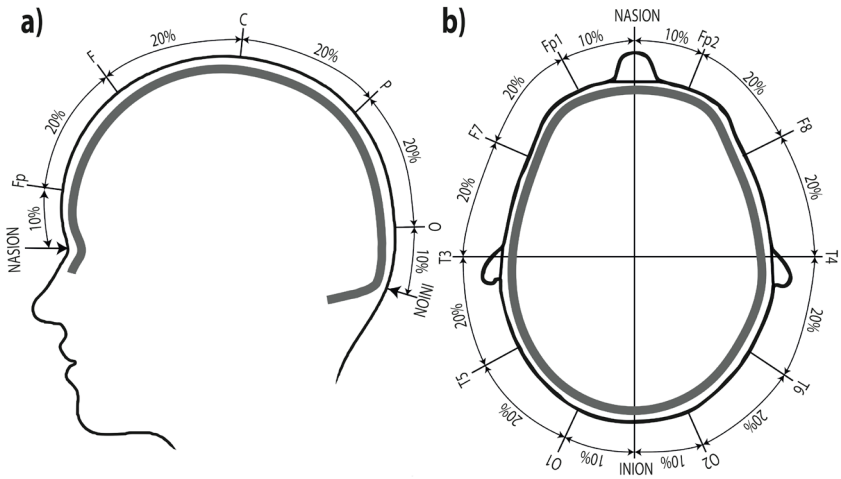
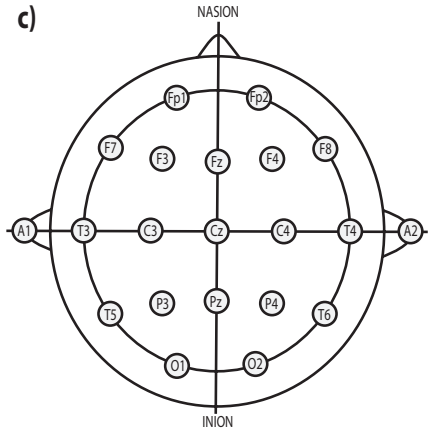


Figure 3.1. *A standard 10–20 electrode system. (a) Lateral and (b) superior views of head present a method to find correct electrode positions. (c) A plane projection of the 10–20 electrode system. The electrodes are named based on the region they represent i.e. the fronto polar (Fp), frontal (F), central (C), parietal (P), temporal (T) and occipital (O) areas. Two electrodes are placed on the auricles (A).*



4 Prerequisites for high quality EEG signal

As mentioned in chapter 3.2, the certain preconditions that the hardware for EEG recordings must meet are described in international guidelines (ACNS 2006a, Nuwer et al. 1999). In addition, before a medical device can be brought to the market, it has to fulfill certain prequisites, which are defined in standards for medical devices (Parvizi & Woods 2014). In the European Union (EU), these standards are described in Medical Devices Directive (93/42/EEC). The Notified Body is an organization that has been accredited to make a decision as to whether or not a product meets standards in the EU (McCulloch 2012). In the United States, this mandate has been delegated to the Food and Drug Administration (FDA) (Johnson 2012). The above-mentioned specifications are also commonly monitored by technicians or physicists while performing acceptance tests and in the annual quality control tests. Even though the EEG recorder may meet the criteria and is in good technical condition, this does not guarantee that one will obtain a high-quality signal. The signal may be contaminated by a variety of artifacts associated with hardware, the patient or the surrounding environment (Nunez & Srinivasan 2006).

4.1 SKIN-ELECTRODE INTERFACE

When metal is located in an electrolyte solution, ion-electron exchange occurs. Metal ions will enter to the electrolyte and electrolyte ions will combine with the metal of the electrode. This results in a potential difference across the metal-electrolyte interface. The potential difference is also known as the half-cell potential, which results in an electric double layer, wherein a

positive or negative charge covers the surface of the metal and the opposite charge is present in the immediately adjacent electrolyte. A current may alter the half-cell potential with the difference being dependent on the polarization of the electrode. In theory, there are electrodes that are perfectly nonpolarizable or that are perfectly polarizable. Perfectly nonpolarizable electrodes allow current to pass freely over the electrode–electrolyte interface, without any energy input. Perfectly polarizable electrode acts like a capacitor. In these electrodes, no actual charge crosses the electrode-electrolyte interface, but instead there is a small displacement current. Both of these perfect electrode types are only theoretical and they are not actually manufacturable. However, some real-life electrodes are not far from the characteristics of the perfect electrodes. The commonly used silver-silver chloride electrode (Ag/AgCl) posesses characteristics that are close to the perfectly nonpolarizable electrode and some noble metals like platinum are close to the perfectly polarizable electrodes. (Webster 1998)

With traditional EEG electrodes, it is necessary to place a separate electrolyte (*e.g.* paste or gel) between the electrode and the scalp in order to achieve a stable and acceptable impedance level. Therefore, there are actually two interfaces: the first between the electrode and electrolyte and the second between electrolyte and the skin. The electrode-skin interface can be modeled as a simple electrical equivalent circuit (Figure 4.1).

Figure 4.1 represents an equivalent circuit for the skin-electrode interface. E_{hc} is the half-cell potential. R_d and C_d represent impedance and polarization effects of the interface. The series resistance R_s is associated with the effects of the electrolyte gel. The outermost layer of the epidermis, the *stratum corneum*, consisting of dead cells is only semipermeable to ions. Therefore, there is a difference in the ionic concentration across this membrane resulting in a potential difference marked as E_{se}. More specifically, the *stratum corneum* is a composite of protein rich corneocytes that are surrounded by lipid bilayers (Madison et al. 1987). The structure and low permeability of the lipid bilayers are responsible for its barrier properties and high

electrical impedance of the *stratum corneum* (Lackermeier et al. 1999). It is possible to reduce the effect of potential difference by removing the *stratum corneum* from under the electrode by wiping it with an ethanol soaked pad and scratching with a stick or an abrasive paper. However, the epidermis can be considered as a parallel interface where the first branch represents epidermis itself and the second branch is the sweat glands and ducts. The dermis and layers under it can be generalized as a single resistive component, R_u.

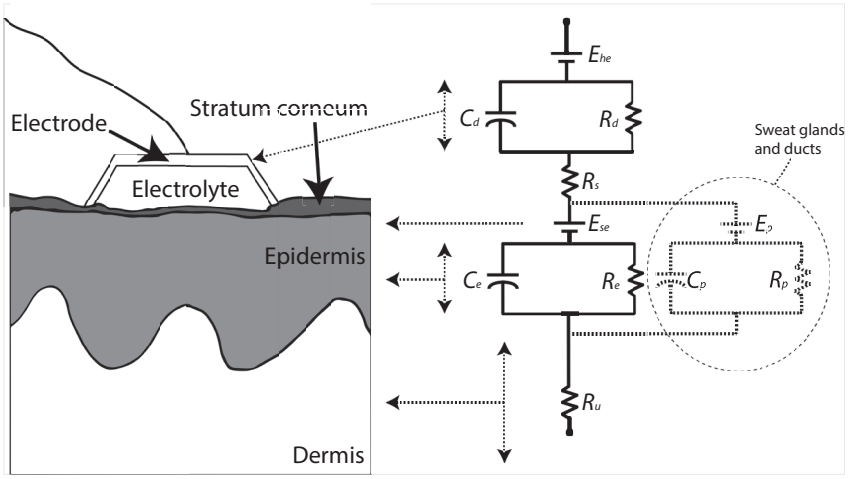


Figure 4.1. *Traditional Ag/AgCl electrode attached to the skin and its electrical equivalent circuit. E_{hc} is the half-cell potential, and R_d and C_d represent the impedance and polarization effects of the electrode–electrolyte interface. R_s is the resistance in the electrolyte. C_e and R_e represent the impedance and polarization effects of the epidermis and C_p and R_p those of the sweat glands and ducts. E_{se} and E_p represent potential differences over the stratum corneum. R_u is the overall resistance of dermis and other tissues under it. Figure is modified from Webster (1998).*

Since the equivalent circuit of the skin-electrode interface consists of three resistor-capacitor circuits, it is understood that the impedance is strongly dependent on the frequency of the signal to be measured (Webster 1998). The impedance of the unprepared skin (1 cm^2) varies from approximately 200 kΩ (1 Hz) to 200 Ω (1 MHz) (Rosell et al. 1988). In addition, it should be noted that the EEG signal is the voltage between the two electrodes. Thus, there are two similar skin-electrode interfaces connected in series (Webster 1998).

4.2 ARTIFACTS IN EEG

The EEG signal may be contaminated by a variety of artifacts arising from the patient, the hardware or the environment (Nunez & Srinivasan 2006). Hardware-related artifacts are typically associated with the skin-electrode interface or the hardware itself. The high electrode impedance may appear as an attenuation of the signal amplitude (Ferree et al. 2001). However, modern amplifiers with very high input impedance (over 200 MΩ) are capable of recording signals in even though there may be high skin-electrode impedance levels (Ferree et al. 2001). Ferree et al. (2001) demonstrated that the maximum signal loss was only 0.0025 % with scalp abrased electrodes having the skin-electrode impedance of 5 kΩ. Even without scalp abrasion (50 kΩ), the maximum amplitude attenuation was only 0.025 %, which was thought to almost be at a negligible level (Ferree et al. 2001).

In addition to the skin-electrode interface, also the bioamplifier itself and other components of the recording device may create noise in the EEG signal. There are two types of internal noise, thermal noise and integrated circuit noise (Gray et al. 1993). The electronic noise generated by the thermal agitation of the electrons in passive resistive elements is called thermal noise. In an ideal resistor, thermal noise is white and its power spectral density is nearly constant (Gray et al. 1993). The root-mean-square value (E_{RMS}, [V]) of the thermal noise can be calculated with the following equation:

$$E_{RMS} = \sqrt{4kRT\Delta f}, \qquad (4.1)$$

where k = Boltzmann's constant [1.3806488 × 10^{-23} J/K], R = resistance [Ω], T = temperature [K] and Δf = frequency range (Gray et al. 1993). Integrated circuit noise is a group of different low amplitude noises *i.e.* shot noise, flicker noise (1/f noise), burst noise (popcorn noise) and avalanche noise (Table 4.1) (Gray et al. 1993). Thermal noise and flicker noise are the most significant in the EEG frequency range in comparison with the

other noise sources in circuits (Gray et al. 1993). However, these low amplitude noises are not a problem in modern and well designed EEG devices. The internal noise may be also attributable to the electrodes *e.g.* the thermal noise of Ag/AgCl electrode has been estimated to be 0.1 – 1.5 μV and from 1 – 15 μV when placed on the skin (Fernández & Pallás-Areny 2000).

Table 4.1. *Characteristics of different integrated circuit noises (Gray et al. 2003).*

	Shot	**Flicker**	**Burst**	**Avalanche**
Associated	Direct-current flow	Direct-current flow	Presence of heavy-metal ion contamination	Zener or avalanche breakdown
Present in	Diodes, MOS transistors, and bipolar transistors	Active devices and some passive elements	Gold doped devices	Typically in Zener diodes
Dependence	Temperature and frequency independent	1/f frequency dependence	Popping sound, $1/f^2$ frequency dependence	Temperature and frequency independent

The most difficult problem associated with the skin-electrode interface is the motion artifact (Tam & Webster 1977). When the electrode moves, it may cause artifacts and these may result in unreadable signal traces or an amplifier may exceed its range. If skin abrasion and separate electrode paste are used to achieve sufficiently low and stable skin-electrode impedance, this may also reduce motion artifacts (Tam & Webster 1977).

The common physiological signals that may be contaminated to the EEG channels are electrocardiogram (ECG), electrooculogram (EOG), electromyography (EMG) and breathing (Klass 1995). While they are important signals in some situations, *e.g.* in polysomnography (Grigg-Damberger 2012), they can harmfully mask EEG. There is also a small chance to incorrectly interpret eye blinks or ECG artifacts as interictal epileptiform discharges or as periodic lateralized epileptiform discharges (Tatum et al. 2011b). The EOG and facial EMG artifacts can be readily diminished by asking a conscious and cooperative patient to "open your mouth and close your eyes" (Tatum et al. 2011b). Placing a small weight on the eyes can help a patient who has trouble keeping the eyes closed. ECG and EOG artifacts should be easily identifiable by synchronizing

EEG with the signals from EOG and ECG electrodes (Bearden 2007, Tatum et al. 2011b). The regularity of the rhythm of the heart helps to identify the ECG artifact and the symmetry in both hemispheres helps to separate the EOG artifact from the EEG (Bearden 2007, Klass 1995). Referential montages, especially with ear references are also often sensitive to physiological artifacts. On way to avoid this artifact is to change to bipolar montages, which will clean up the signal (Tatum et al. 2011b). Breathing and also sweat can be responsible for slow waveform artifacts (below 0.5 Hz) in the EEG signal, and these may complicate the detection of cerebral rhythm at the same frequencies (Klass 1995). A variety of algorithms for EEG clean-up for ECG and EOG artifacts have been developed, but they have not yet found their way into widespread clinical use (Fatourechi et al. 2007, Gross 2014, Shackman et al. 2009).

Environmental artifacts may also contaminate EEG signal. Intensive care units (ICU) and emergency rooms (ER) are electrically hostile environments for EEG recording (Tatum et al. 2011a). These environments are electrically active regions, in which many electrical devices and instruments are being employed. Alongside the EEG, several other modalities are available to investigate brain physiology in the ICU, *e.g.* intracranial pressure (ICP) monitoring, brain tissue oxygenation monitoring, cerebral blood flow (CBF) monitoring, and brain metabolism monitoring (Wartenberg et al. 2007). These different instruments may be used simultaneously and therefore environmental artifacts frequently encountered are difficult to eliminate (Tatum et al. 2011a). In addition, nearby ventilators, infusion pumps and intravenous drips may cause artifacts, which may be difficult to identify, because they are not common in routine recordings (Tatum et al. 2011b). The presence of static electricity may also produce artifacts when an invidual, *e.g.* a nurse or some other patient, moves near to the wires or recording electrodes (Tatum et al. 2011b). The most common source of environmental artifacts is power-line (50/60 Hz) interference from nearby power supplies, devices, or outlets.

4.3 POWER-LINE (50/60 HZ) INTERFERENCE

The power-line interference is a common problem encountered when recording biosignals (Huhta & Webster 1973). It occurs in the recorded signal at the same frequency as alternating current (AC) oscillates in power-lines. For example, that frequency is 50 Hz in Europe and 60 Hz in North America. The power-line interference is always present when the recording system is located in the vicinity of electronic devices and power-line interference can contaminate the recorded signal (Huhta & Webster 1973). This is particularly harmful, because its frequency (50/60 Hz) overlaps with the diagnostically important frequency range (0.5 − 70 Hz) of EEG (Nuwer et al. 1999).

A time-varying magnetic field accompanied by a spatially varying and non-conservative electric field in conductive loops can induce an electromotive force that results in power-line interference (Huhta & Webster 1973). This is consistent with the Maxwell–Faraday equation (a generalization of Faraday's Law). The time-varying electric field may also cause AC current that flows through the tissues and electrode impedances producing power-line interference. In fact, these currents are displacement currents that result from the capacitive coupling between the electromagnetic fields and the measurement system (Huhta & Webster 1973). It is also possible that power-line interference can be amplitude-modulated to a radio-frequency (RF) carrier wave (Huhta & Webster 1973). Although the radio-frequencies are not in the diagnostically important frequency range or even within the EEG amplifier's operation range, the amplitude modulated power-line interference can be converted back into its original form and cause 50/60 Hz interference in the EEG signal. This is readily understandable when converting the radio-frequencies (3 kHz to 300 GHz) to their wavelengths (100000 m to 0.001 m) and noting that all EEG wires, the short or long ones, surely fit in this range. This phenomenon can be explained by the operation of a conventional antenna, where induced standing waves are oscillating. In this case, the power-line interference can be considered as a radio broadcasting, which is amplitude

modulated to a carrier wave. In addition, power-line interference may result from a phenomenon where terminated two-wire transmission lines are excited by a nonuniform electromagnetic field (Linares Y Miranda et al. 2013, Taylor et al. 1965). The importance of this phenomenon will increase as screen-printed electronics and electrodes become more common (Linares Y Miranda et al. 2013).

The power-line interference is known to be directly proportional to the difference in skin-electrode impedance (Chimeno & Pallàs-Areny 2000). Therefore, it is important to achieve low skin-electrode impedance and to avoid large impedance differences between EEG electrodes (Metting van Rijn et al. 1990).

In modern EEG amplifiers, all EEG channels are connected to a dedicated common ground electrode, which is electrically isolated. In addition, amplifiers are equipped with components that achieve high input impedance and high CMRR. These features have been found to significantly reduce the power-line interference (Ferree et al. 2001). Although the present current differential amplifiers are rather effective at reducing electromagnetic interference, they do not eliminate it completely (Chimeno & Pallàs-Areny 2000).

Wires create small current loops that generate a changing magnetic flux that can magnetically couple (Fowler 2000). Twisting of wires is a commonly used method of avoiding magnetically induced power-line interference (Fowler 2000). Furthermore, this technique may reduce the common-mode current by reducing the loop area for inductive coupling (Fowler 2000). Electrode wires are typically twisted around each other and bundled next to the patient's head after electrode attachment (Ferree et al. 2001). An effective shielding technique against capacitive coupling is to utilize an appropriately placed shield that prevents the coupling between circuits by shunting the charge to the ground (Fowler 2000). Therefore, shielded cables are an effective way of avoiding power-line interference. However, the shielding effect may be limited, if the shielding does not cover the electrodes (Wood et al. 1995). Furthermore, in

the electrically most hostile locations, it has been recommended that the whole preamplifier part of an EEG recorder should to be shielded with aluminum foil (Sadafi et al. 2005).

Although all of the above mentioned preventive methods are in use, the signal can still contain a significant amount of power-line interference. In this case, notch filters are recommended to be used (Tatum et al. 2011b). Although notch filters are effective, they do remove some essential frequencies from the recorded EEG.

To summarize, there are several methods for reducing power-line interference when recording the EEG. In addition, medical devices must be designed carefully and equipped with electromagnetic shielding. The crucial electro-magnetic compatibility (EMC) tests for medical devices are defined in EU directives and the regulations of FDA (Calcagnini et al. 2007).

5 EEG electrode sets for emergency use

5.1 EMERGENCY EEG ELECTRODES

EEG can be recorded invasively or noninvasively. In invasive EEG, biopotentials are recorded with subdermal needles placed under the scalp or directly from the surface of the brain with subdural electrodes. Modern small and thin needle electrodes cause minimal discomfort to a patient (Schneider 2006). In addition, the signal-to-noise ratio (SNR) is considerably better than with noninvasive electrodes (Noachtar & Rémi 2009). However, due to the increased risk of local infections and hemorrhages, invasive electrodes are not recommended to be used before noninvasive EEG studies have been performed (Noachtar & Rémi 2009).

In noninvasive EEG, the electrodes are attached to the scalp individually or jointly in the form of an electrode array. EEG electrodes may be made of a variety of materials. In the first human EEG measurement, Hans Berger used two saline-soaked pads as electrodes (Berger 1929). Traditionally, electrodes are fabricated from suitable metals, compounds or metal alloys (*e.g.* silver, silver chloride or stainless steel) (Tyner et al. 1983).

When utilizing traditional electrodes, a separate conductive paste between the electrode and the scalp is required to achieve adequately low impedance level (Tyner et al. 1983). For this reason, these electrodes are commonly referred as wet electrodes. If too much conductive gel or paste is used, this may burst out from under the electrodes and cause short-circuits between the adjacent electrodes (Lin et al. 2011). Furthermore, the gel or paste may dry out during long-term EEG monitoring, which can lead to EEG signal attenuation or even its entire loss. These electrodes also require skin abrasion prior to attachment.

Although these operations usually lead to a good electrode contact with the skin, they may complicate the EEG recording. The abrasion is time-consuming and it can cause pain (Stjerna et al. 2010). Stjerna et al. (2010) introduced a standardized method (SurePrep) for the preparation of electrode–skin contact in neurophysiological recordings. SurePrep makes only a small incision through the skin while the traditional skin abrasion causes a shallower and larger epithelial damage (Sinisalo et al. 2012). However, epithelial penetration means that both methods (SurePrep and skin abrasion) are invasive (Sinisalo et al. 2012). SurePrep has been demonstrated to be a suitable alternative for skin preparation in neonatal EEG monitoring, but there are no publications describing its use in EEG recording in adults with long hair (Sinisalo et al. 2012).

Recently, several preparation-free electrodes have been introduced. Some of these advanced electrode solutions based on hydrogels can be classified as wet electrodes (Alba et al. 2010). However, some novel approaches do not require electrolytes. These dry concepts are typically based on micromachined spikes, carbon nanotubes or polymer foam (Table 5.1). These concepts have been designed to reduce the above-mentioned shortcomings associated with traditional wet electrodes.

Table 5.1. *Studies dealing with preparation-free EEG electrodes.*

Study	Electrode type	Impedance (kΩ)	Impedance Tested on	Volunteers/ Electrodes
Griss et al. 2002	Micromachined spikes	<25	Forehead	12/3
Ruffini et al. 2008	Carbon nanotubes		Forehead	1/1
Ng et al. 2009	Micromachined spikes	7-25	Haired area	1/1
Alba et al. 2010	Hydrogel	9-12	Forehead/ Haired area	2/2
Lin et al. 2011	Polymer foam	4-26	Forehead / Haired area	5/2
Forvi et al. 2012	Micromachined spikes	≈13	Forehead / Haired area	1/4
Toyama et al. 2012	Hydrogel	3-25	Forehead / Haired area	1/9

Most of the dry electrodes are based on microneedles that pierce the outermost layer of the epidermis, *i.e. stratum corneum* in order to reach the electrically more conductive tissue layer, *stratum germinativum*. The majority of the microneedles are fabricated by microelectromechanical system (MEMS) techniques (Ruffini et al. 2006). They are designed to not to break of the dermis layer in order to avoid pain or bleeding (Chang et al. 2010). However, the thickness of the epidermis varies from one person to the next and it is also highly dependent on the patient's age (Pouradier et al. 2013). Therefore, there may be a risk for local infections and sensations of the pain (Ferree et al. 2001). In addition, there is also the possibility breaking of microneedles during extended recording periods (Dias et al. 2010). Carbon nanotubes have been introduced to enable a shallow penetration of the *stratum corneum.* This, together with small diameter of carbon nanotubes, has been proposed to result in a lower risk of infection (Ruffini et al. 2006). However, manufacturing costs and the lack of physical strength during the skin penetration are major drawbacks of MEMS and carbon nanotube electrodes (Lin et al. 2011).

Conductive hydrogels are commonly used in biomedical applications due to their ease of use and low impedance (Green et al. 2012). Hydrogel-based disposable electrodes have performed well in electrical tests and have displayed excellent suitability for long time-constant AC coupled recording (Tallgren et al. 2005). They have many excellent properties *e.g.* low offset voltage, resistance, polarization, rate of drift, and noise (Tallgren et al. 2005). In the literature, hydrogel is defined as a polymeric cross-linked network structure, which has the capacity to hold water within its structure (Hoffman 2012, Laftah et al. 2011). This confers on hydrogels similar characteristics to soft tissues and therefore they are well suited for biomedical applications (Hoffman 2012). Although hydrogels have characteristics comparable to those of soft tissues, they are not usually able to hydrate the skin completely and therefore, skin abrasion is needed. Recently, hydrogels capable for adequate skin hydration without abrasion were

introduced (Alba et al. 2010, Kleffner-Canucci et al. 2012, Toyama et al. 2012). Alba et al. (2010) described a hydrogel electrode consisting of urea, a natural component of healthy skin. Kleffner-Canucci et al. (2012) developed an adhesive hydrogel consisting of a NIPAm (N-isopropyl acrylamide:acrylic acid) co-polymer. Toyama et al. (2012) described a solid-gel chip electrode, which was made of carboxymethylcellulose sodium salt, calcium chloride dihydrate, glycerol and pure water. These solutions included components that play key roles in skin hydration.

Furthermore, some methods to reduce the impedance of the *stratum corneum* have been presented. Lin et al. (2011) introduced a novel dry polymer foam electrode, which was made of urethane. The polymer foam creates a strong capacitive component for the skin-electrode impedance and the EEG could be recorded by using the inductive method (Lin et al. 2011, Webster 1998). In addition, active electrodes, in which preamplification is imported to the immediate vicinity of an electrode, have been developed (Fonseca et al. 2007, Morikawa et al. 2013, Taheri et al. 1994). The main advantages of these active electrodes are their good tolerance of high impedance levels and the lower sensitivity to be disturbed by power-line (50/60 Hz) noise (Taheri et al. 1994). However, there is a major drawback, active electrodes are expensive (Mota et al. 2013).

When comparing the characteristics of different preparation-free electrode types, one can discern that recording is possible from the forehead as well as from haired area, in fact the impedances at these areas are at the same level (Table 5.1). Although, impedances are high in comparison with the recommendations (5 kΩ), but they are at such a level (typically less than 40 kΩ), that they should not represent a problem for modern amplifiers capable of operating at high impedance conditions (Ferree et al. 2001, Nuwer et al. 1999). However, dry electrodes suffer from certain significant drawbacks (Table 5.2). Dry electrodes are expensive to manufacture and invasive (Lin et al. 2011). Flexible hydrogel electrodes can also be designed to be adhesive (Kleffner-Canucci et al. 2012). This is a major

advantage, because dry electrodes need a solid EEG cap or a template, which has to provide a sufficient pressure to keep the electrodes in contact with the skin.

Table 5.2. *Comparison of common characteristics of different electrode types.*

Electrode type	Noninvasive/ Invasive	Adhesive	Price
Trad. surface electrode	Noninvasive	No	Cheap
Trad. needle electrode	Invasive	No	Cheap
Micromachined spikes	Invasive	No	Expensive
Carbon nanotubes	Invasive	No	Expensive
Hydrogel	Noninvasive	Yes	Average
Polymer foam	Noninvasive	No	Average

Trad. = traditional

5.2 COMMERCIAL EMERGENCY EEG ELECTRODE SETS

Full-montage EEG templates and caps designed for easy positioning are recommended for emergency use (Jordan & Schneider 2009, Kolls et al. 2012). The template is an elastic net-like applicator that can be easily applied to the patient's head (Kolls et al. 2012). The electrode sites are typically marked with color codes that assist the user to attach the cup or needle electrodes to the correct positions. Typically both, the template and electrodes are disposable. However, since the template does not provide pressure on the electrodes, adhesive paste or collodion glue is needed with cup electrodes (Kolls et al. 2012). Nonetheless, the setting up and placement of electrodes using templates is easier and faster than using the conventional bridge electrodes with a silicone net (Jordan & Schneider 2009).

EEG caps typically include fixed electrodes positioned according to the standard 10–20 system. In contrast to templates, the EEG cap is not disposable and needs to be carefully cleaned after use. The electrolyte gel or paste should be dosed before the setting of the cap or alternatively after setting up the cap through the hole in the electrode with a syringe. There are several commercial EEG templates and caps currently on the market (Table 5.3).

Table 5.3. *Examples of commercially available EEG templates, EEG caps and emergency electrode sets. Possible weaknesses of the device are also listed.*

Name	Type	Number of electrodes	Electrode material and type	Recom-mended electrolyte	Supplier	Weaknesses A	B	C	D	E
BraiNet	Template	14-21	Ag/AgCl passive	EC2 cream collodion glue	Jordan NeuroScience, Inc.	x	x	x	x	x
Neuroband	Template	2-19	Sn or Ag/AgCl passive	ElectroMist gel	Dr. Diane Brain Health	x	x	x	x	x
EazeNet	Template	19	Ag/AgCl passive	Gel pre-attached	Hydrodot, Inc.	x			x	x
MultiCap	Cap	21	Ag/AgCl passive	ECI electrode gel	GVB-geliMED KG		x	x	x	x
EasyCap	Cap	19-40	Ag/AgCl passive	Abrassive gel (Abrylat 2000)	EASYCAP GmbH		x	x	x	x
EasyCap Active	Cap	19-40	Ag/AgCl active	SuperVisc Hydrogel	EASYCAP GmbH		x		x	x
QuickCap	Cap	19-256	Sn, Au, Ag/AgCl passive	QuikCell Hydrogel	Compumedics USA Inc.		x	x	x	x
WaveGuard	Cap	21-256	Ag/AgCl passive	Gel	ANT Neuro		x	x	x	x
BrainCap	Cap	up to 256	Ag/AgCl passive	Various	Brain Products GmbH		x	x	x	x
ActiCap	Cap	up to 64	Ag/AgCl Active	SuperVisc Hydrogel	Brain Products GmbH		x		x	x
StatNet	Set	18	Ag/AgCl passive	Gels pre-attached	Hydrodot, Inc.				x	x

A = Separate electrodes, B = Separate gel/paste, C = Skin abrasion needed, D = Hairy area related problems, E = Need to move the head during setup

The most common templates and caps listed in Table 5.3 except for EazeNet (HydroDot, Inc. Westford, MA, USA), EASYCAP Active (EASYCAP GmbH, Woerthsee-Etterschlag, Germany) and ActiCap (Brain Products GmbH, München, Germany) are based on passive metal or compound electrodes. These solutions are intended to help the user to find the right electrode positions, but separate electrode gel/paste and skin abrasion are still needed. EazeNet's electrodes, called Hydrodot Biosensors, contain incorporated hydrogel, which can shorten the setting time. However, Hydrodot's manual recommends parting the hair to expose the scalp under the EzeNet sockets and to prepare the skin as usual. The skin abrasion phase is time-consuming and it can cause pain (Stjerna et al. 2010). ActiCap and

EASYCAP Active are designed to reduce the need for the abrasion. The electronic components (*i.e.* preamplification) are directly fitted into the electrode housing, which may help to achieve a sufficient signal quality also at higher electrode-skin impedances. It is believed that this solution may reduce both noise and motion artefacts. The manufacturer claims that when using a specific electrolyte gel, the abrasion may be replaced by mild scratching with a blunted needle or even completely abandoned. Unfortunately, the manufacturer has not provided any peer-reviewed article to back up this claim.

Currently, there is only one commercial electrode set in the market intended for emergency use. StatNet (Hydrodot, Inc.) offers whole set of electrodes, pre-attached hydrogel and a template in the same package. It has been fabricated with screen printing technology. Pregelled Ag/AgCl sensors and silver ink tracings are embedded in a flexible headpiece. Because of predetermined locations for electrode placement, according to the webpage of the manufacturer (http://www.hydrodot.net/), it is claimed that StatNet requires on average only five minutes applying. In addition it does not require skin preparation. The manufacturer provides instruction videos on its website, where StatNet is placed on the sitting volunteer with long hair in five minutes. However, the manufacturer does not mention how much experience is needed to perform attachment so quickly. Unfortunately, the manufacturer does not provide any peer-reviewed references for setting times or achieved impedance levels.

Although the current commercial templates, caps and sets facilitate the placing of the electrodes in emergency care, they are still difficult and time-consuming to apply, especially for patients with long curly hair. The problem may be accentuated if the patient's head cannot be moved due to head or neck injuries conditions that are often clinically suspected in an unconscious patient. There are still no any below-the-hairline attachable solutions on the market, but some interesting patents or applications can be found (Table 5.4).

Table 5.4. *Patent application review of below-the-hairline electrode sets (Patent database Espacenet was used at May 2014. Used keywords were EEG electrode, EEG headset, electrode array, forehead and sensor arrangement).*

Patent name	Number of electrodes (locations)	Patent number Applicant	Date of publication (yyyy-mm-dd)
Electrode array system for measuring electrophysiolocical signals	3-4 (Forehead)	EP1350462 Devlin et al Aspect Medical Systems, Inc.	1997-10-10
Sensor mask and method of making same	5 (Forehead) 2 (Chin) 2 (Neck)	US6032065 Brown	2000-02-29
Frontal electrode array for patient EEG signal acquisition	3-5 (Forehead)	US2002019588 Marrow	2002-02-14
Configurable sensor system for measuring biopotentials	3 (Forehead)	US2003009096 Lähteenmäki Instrumentarium corp	2003-01-09
Physiological sensor combination	3 (Forehead)	US2003225323 Kiani et al	2003-12-04
Sensor arrangement	3-5 (Forehead) 1 (EOG) 1 (Behind ear)	US2005085741 Hoskonen et al GE Finland	2005-04-21
Method of positioning electrodes for central nervous system monitoring	5-7 (Forehead)	US6950698 Särkelä et al Instrumentarium corp	2005-09-27
Electrode configuration for central nervous system monitoring	2-3 (Forehead) 1-4 (EOG) 0-1 (Ear)	US2007255164 Viertiö-Oja et al GE Finland	2007-11-01
Detection of Focal Epileptiform Activity	6 (Forehead) 2 (Behind ears)	US2008021340A Särkelä et al GE Finland	2008-01-24
Modular electrode arrays for EEG measurement	4 (Forehead) 2 (Behind ears)	GB2447354 Rantala et al GE Finland	2008-09-10
Flexible headset for sensing brain electrical activity	6 (Forehead) 2 (Behind ears)	US2010041962A Causevic et al BrainScope co Inc.	2010-02-18

Some of these patents have been applied for with respect to the electrode arrangement or method and the electrode materials have been left open (Hoskonen et al. 2005, Lähteenmäki 2003, Rantala 2008, Särkelä 2008, Särkelä & Vieriö-Oja 2005, Vieriö-Oja & Sampson 2007). There are claims in five patents that the bodies of electrode sets can be fabricated with screen printing or comparable technology (Brown 2000, Causevic et al. 2010, Devlin et al. 2003, Kiani et al. 2003, Marro et al. 2002). Hydrogel

is mentioned in two of these patents (Kiani et al. 2003, Marro et al. 2002), whereas the others refer commonly to the usage of some gel or electrolyte. The electrode array system presented by Devlin et al. (2003) consists of a gel that is self-adherent and self-prepping.

Although some of the above-mentioned patented electrode sets are already commercialized as anesthesia monitoring systems, they have not made yet breakthroughs in the recording of emergency EEG. The version of Causevic et al. (2010) may be the closest to success, because their electrode set named BrainScope B-Ahead II (BrainScope Inc., Bethesda, MD, USA) is currently undergoing FDA validation trials for the assessment of EEG in ER patients with brain injury. In addition, they have published several studies in the peer-reviewed journals that support the potential of their electrode set together with a standalone recording device to evaluate sport related concussion, to detect epidural hematoma, to quantify traumatic brain injury and to identify several abnormalities in the emergency department (Jacquin et al. 2007, McCrea et al. 2010, Naunheim & Casner 2010, Naunheim et al. 2010, 2011). These results will be reviewed in more detail in the next chapter of this thesis. One major drawback of the BrainScope's electrode set is its compatibility only with their own EEG recorder.

5.3 BELOW-THE-HAIRLINE EMERGENCY EEG SETS

The attachment of traditional EEG electrodes according to the 10–20 electrode system is a difficult and time-consuming process (Kolls et al. 2012). Therefore, investigations have been performed to determine whether a reduced number of electrodes would suffice to obtain comparable findings as with the full-montage. As early as 1985, Ebersole and Bridgers enrolled 30 patients for a cassette EEG recording and claimed that three electrodes could achieve results comparable with those obtained with eight electrodes (Ebersole & Bridgers 1985). Although all seizures, which were detected, using the eight-

channel EEG, were also detected with three electrodes, there were some false-positive findings. Despite the promising performance, this solution did not remove the requirement for the electrodes to be located in the areas with hair.

A few years later, Bridgers & Ebersole (1988) introduced a below-the-hairline EEG electrode arrangement and montage for the detection of epileptiform abnormalities (Figures 5.1). Their preliminary results were promising; the sensitivity to epileptiform abnormalities was 96 % (Bridgers & Ebersole 1988). Subsequently, this below-the-hairline arrangement has been thoroughly investigated and compared with the full-montage in several studies (Table 5.5). The results are congruent; excellent specificity, but poor sensitivity regardless of what kind of montage has been used (Karakis et al. 2010, Kolls & Husain 2007a, Tanner et al. 2014, Young et al. 2009). Based the results of these studies, one can conclude that the below-the-hairline EEG arrangement seldom gives false positive finding but often does produce false negative findings.

Kolls & Husain (2007) also attempted to devise an optimal montage for the below-the-hairline EEG arrangement presented by Bridges & Ebersole but without success. Based on their results, Kolls & Husain did not recommend further research into below-the-hairline EEG as a screening tool for NCSE. However, Bubrick et al. (2007) remarked that it might be dangerous to draw final conclusions about the potential of the below-the-hairline EEG, since these systems may represent a solution to the management of seriously ill patients especially if other viable options are not available. Nonetheless, the publications highlighting the poor sensitivity values suggest that there is a need for optimizing the electrode layout (Bubrick et al. 2007).

Bubrick et al. (2010) published their experience with below-the-hairline EEG recordings in ER with NCSE patients. They reported that EEG signal recorded with below-the-hairline electrodes showed status epilepticus related patterns in 41 % of the time with NCSE patients (Bubrick et al. 2010). There is also one published patent where the below-the-hairline EEG arrangement presented by Bridges & Ebersole is mentioned.

This patent describes the method and an apparatus for detection of focal epileptiform activity (Särkelä 2008) (Figure 5.1b).

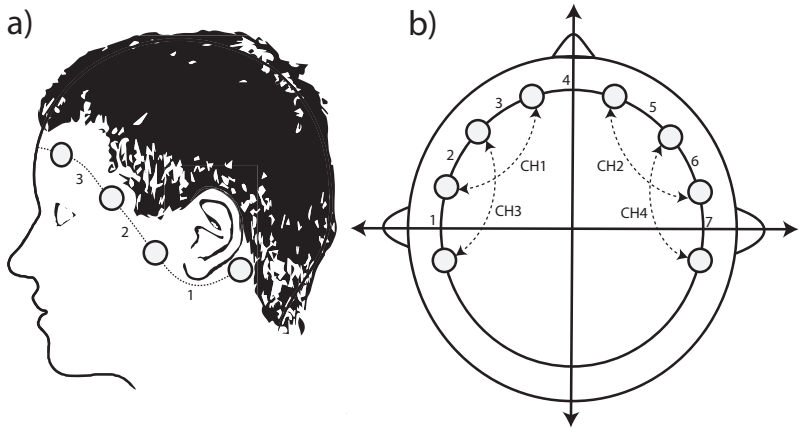


Figure 5.1. *a) The sites of electrodes in the below-the-hairline EEG electrode arrangement introduced by Bridges & Ebersole (1988). b) The eight-channel electrode arrangement allows a couple of montage variations to review EEG. The seven channel montage described by Bridges & Ebersole is marked with numbers 1-7. The four channel montage divised by Särkelä (2008) and Young et al. (2009) is marked with labels of CH1, CH2, CH3, and CH4.*

Table 5.5. *EEG studies based on the below-the-hairline EEG arrangement introduced by Bridges & Ebersole (1988).*

Study	Findings	Number of patients / Unit	Sensitivity (%) / Specificity (%)
Kolls et al. 2007	Normal	18 / ICU	88 / 96
	Diffuce Slowing	23 / ICU	82 / 84
	Burst suppression	15 / ICU	81 / 98
	Seizures	27 / ICU	68 / 93
	GPED	10 / ICU	55 / 92
	PLED	27 / ICU	62 / 97
	Overall	120 / ICU	72 / 93
Young et al. 2009	Seizures	70 / ICU or ED	68 / 98
Karakis et al. 2010	Seizures	38 / ICU	85 / 97
Tanner et al. 2014	Seizures	170 / ICU	54 / 100
	Abnormalities	170 / ICU	60 / 94

ICU = Intensive Care Unit, ED = Epilepsy Department. Values obtained in the study of Kolls et al. (2007) are visually approximated from graph.

Karakis et al. (2010) compared the below-the-hairline montages presented by Bridges & Ebersole (1988) and Kolls & Husain (2007) with reduced EEG array with seven electrodes (Fp1, Fp2, T3, T4, O1, O2, and Cz). They proposed that these electrodes could be easily applied by using only anatomic landmarks (pupils, ears, vertex, and inion). The average values of sensitivity and specificity of the reduced EEG arrangement for seizure detection were 92.5 % and 93.5 %, respectively (Karakis et al. 2010). The achieved sensitivity was slightly better than that with below-the-hairline EEG montages (85 %). However, when the study was repeated with hundred EEG recordings (50 ictal and 50 non-ictal), sensitivity and specificity for detection of seizures were 70 % and 96 %, respectively (Rubin et al. 2014).

As mentioned in chapter 5.2, one below-the-hairline electrode set named as BrainScope B-Ahead II (BrainScope Inc., Bethesda, MD, USA) is close to commercialization (Causevic et al. 2010, McCrea et al. 2010). This electrode set is based on a slightly different placement of the electrodes compared to the above-mentioned below-the-hairline EEG arrangement described by Bridges & Ebersole. It consists of five EEG electrodes (Fp1, Fp2, AFz, F7, F8) and two reference electrodes located behind the ears. BrainScope has also developed a device, which uses a mathematical algorithm, including symmetry, power spectrum, and coherence of EEG signals to calculate an index of abnormality by comparing it with age-expected normal values (Jacquin et al. 2007, Naunheim & Casner 2010). As a result, the device computes the probability that the patient's EEG is not different than that of the normal population. According to their preliminary studies, this mathematical algorith showed very promising results in terms of sensitivity and specificity for providing as seizure alert in patients with NCSE (Jacquin et al. 2007). This electrode set has not been yet thoroughly compared with the below-the-hairline EEG arrangement devised by Bridges & Ebersole, although a few studies have been published in peer-reviewed journals (McCrea et al. 2010, Naunheim et al. 2010, 2011).

Naunheim et al. (2010) enrolled 105 patients with head injury, of those of 53 and 52 had positive and negative CT findings, respectively. Furthermore, 50 ER patients were selected for controls. They reported that BrainScope traumatic brain injury related index appeared to provide a sensitive index of brain function. In addition they speculated that the index might be used to decide whether a patient with altered mental status requires a CT scan (Naunheim et al. 2010). In McCrea et al. (2010), 28 football players with concussion and 28 matched controls were investigated. Based on quantitative offline EEG analyses, as well as postconcussive symptons, postural stability and cognitive function they could detect a significant difference between the group suffering concussions and the matched controls (McCrea et al. 2010). One year later Naunheim et al. (2011) published a study with 153 patients suffering from headache or altered mental status. They stated that the sensitivity and specificity of diagnosis based on EEG recording with the BrainScope were 96 % and 87 %, respectively (Naunheim et al. 2011).

To summarize, the reports in literature provide a hope that the below-the-hairline electrodes may be useful in emergency medicine, especially in situations where the full-montage EEG is not available or not possible to be used. However, further development of these systems is clearly demanded.

6 Aims of the present study

Although the clinical importance of emergency EEG is widely recognized, there are still impediments to the routine use of EEG in emergency medicine. One major obstacle is related to impractical electrode solutions available on market. It was hypothesized that an easy-to-use below-the-hairline EEG electrode set could represent a solution for EEG registrations when the conventional 10–20 electrode setup was not available or feasible. The main aims of this thesis were:

1. to design the optimal construction and layout for a below-the-hairline EEG electrode set and to evaluate its performance and suitability through rigorous electrical performance tests and clinical EEG recordings,

2. to investigate materials and manufacturing techniques for an EEG electrode set to allow artifact free MR and CT imaging and suitability for commercial mass production,

3. to investigate the coupling of external electromagnetic fields to screen-printed circuits and to determine optimal ways to reduce the interference pick-up.

7 Materials and methods

The present thesis consists of four studies (**I**-**IV**). A summary of the materials and methods used in these studies is presented in Table 7.1. In addition, some unpublished results are included. The below-the-hairline EEG electrode sets developed in studies **I-IV** are called Disposable Forehead Electrode Set (Study **I**), Handy EEG Electrode Set (Study **II**), Screen-printed EEG electrode set (Studies **III** and **IV**) and BrainStatus (Study **III**). In this thesis, the electrode set is called the handmade EEG electrode set or the screen-printed EEG electrode set depending on the manufacturing method.

Table 7.1. *Overview of the materials and methods used in the thesis.*

Study	Manufacturing method	Electrodes included in the set	Methods
I	Handmade	12 EEG (REF, GND, 2xEOG, Fp1, Fp2, Af7, Af8, F7, F8, Sp1 and Sp2)	EEG, DC offset voltage, EIS, internal noise, MRI and CT
II	Handmade	16 EEG (2xREF, 2xGND, 2xEOG, Fp1, Fp2, Af7, Af8, F7, F8, Sp1, Sp2, T9 and T10) + ECG	EEG
III	Screen-printed	16 EEG (2xREF, 2xGND, 2xEOG, Fp1, Fp2, Af7, Af8, F7, F8, Sp1, Sp2, T9 and T10) + ECG	EEG, Impedance testing, MRI and CT
IV	Screen-printed (Shielded)	16 EEG (2xREF, 2xGND, 2xEOG, Fp1, Fp2, Af7, Af8, F7, F8, Sp1, Sp2, T9 and T10) + ECG	EEG, EMC tests
Unpublished data	Screen-printed (Shielded)	16 EEG (2xREF, 2xGND, 2xEOG, Fp1, Fp2, Af7, Af8, F7, F8, Sp1, Sp2, T9 and T10) + ECG	MRI and CT

CT = Computed tomography, EEG = Electroencephalography, EIS = Electrical impedance spectroscopy, EMC = Electromagnetic compatibility, MRI = Magnetic resonance imaging

7.1 EEG ELECTRODE SET CONSTRUCTIONS

The EEG electrode set was developed into a fully functional solution over a 4-year trial period. During the development process, numerous prototype generations were produced (Figure 7.1). Each generation was further developed from the previous one, with improvements achieved in material selection and optimizations in the sensor layout. A summary of the materials used in the handmade and the screen-printed EEG electrode sets is shown in Table 7.2. Optimized electrode positions in the final prototype of the EEG electrode set are presented in Figure 7.2.

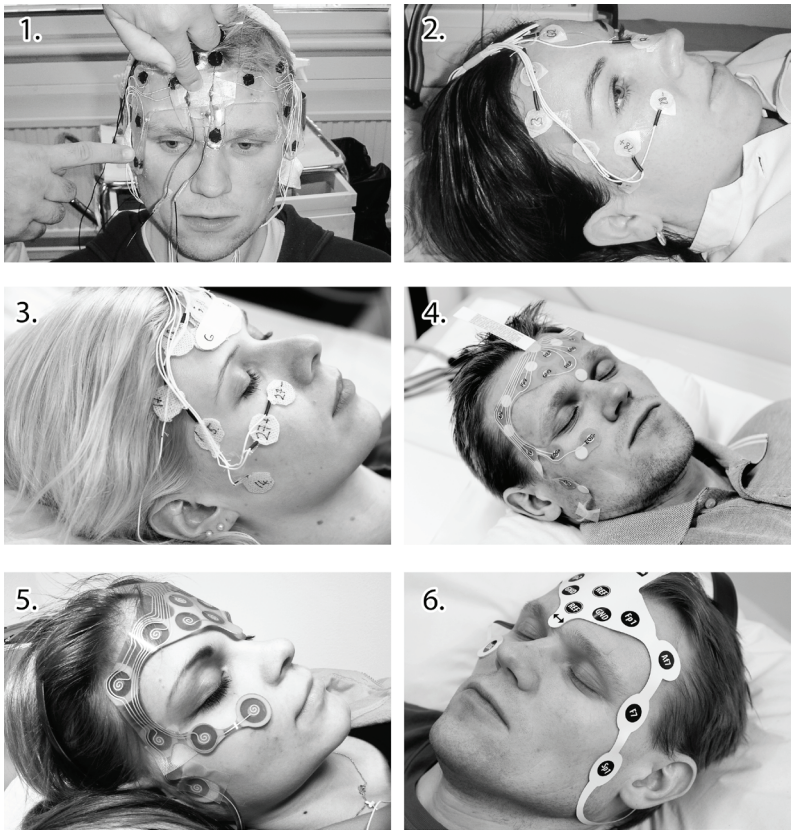


Figure 7.1. *These images illustrate the evolution of the developed electrode set during the last four years. Prototype generations are presented in numerical order. Images 1-3 represent prototypes of handmade EEG electrode set and 4-6 show prototypes of the screen-printed EEG electrode set. The use of these photographs has been approved by the volunteers.*

Table 7.2. *Summary of the materials and solutions applied in the handmade and screen-printed EEG electrode sets.*

	Handmade	**Screen-printed**
Electrodes	Spiral shaped silver wire	Screen-printed spiral (silver ink)
Electrolyte	Hydrogel	Hydrogel
Wires	Electrode cables	Screen-printed traces (silver ink)
Body	Tied electrode cables and flexible polyester film	Flexible polyester film
Adhesion	Hydrogel and medical tape	Hydrogel and non-conductive foam

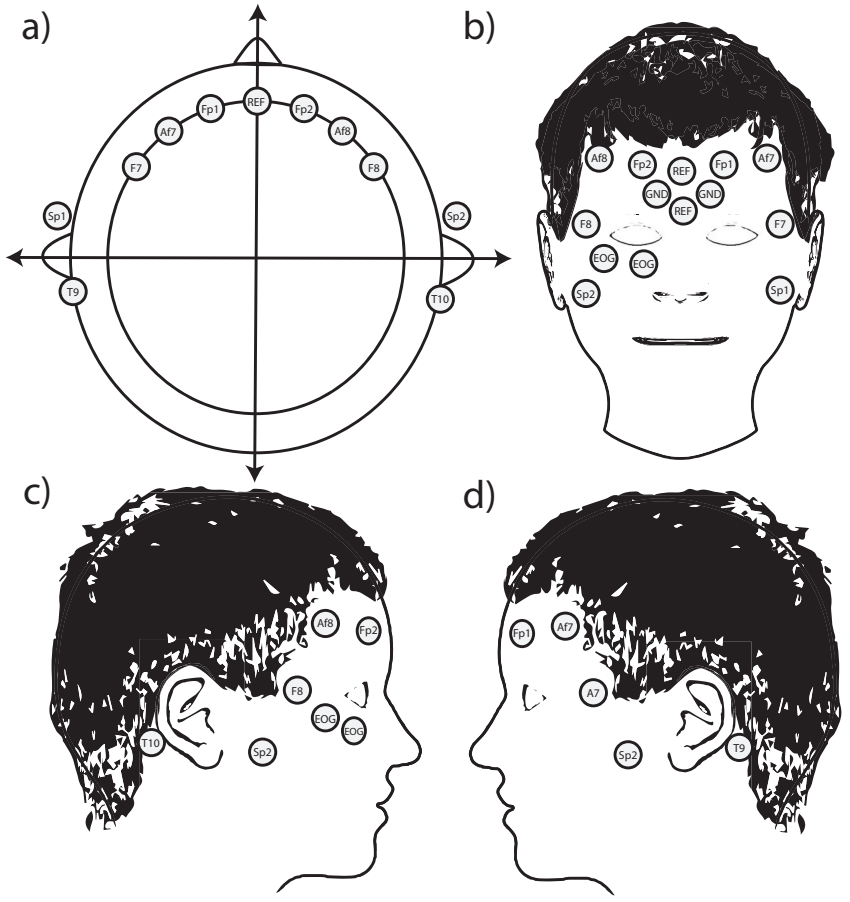


Figure 7.2. *The sites of electrodes used in the final prototype of the EEG electrode set. a) A plane projection of the electrode sites. b) Front, c) right and d) left view of the head with marked electrode sites.*

Electrodes of the handmade EEG electrode sets (Studies **I** and **II**) were constructed from spiral shaped silver wire (Ag 99.9 %, Ø: 0.4 mm). The silver spirals were covered with round-shaped (diameter 18 mm) pieces of adhesive hydrogel (AG602, Amgel Technologies, Fallbrock, CA, USA). The silver spirals were attached to the ends of electrode cables (Ambu A/S, Ballerup, Denmark), widely used in biosignal monitoring. The polyester film protects the electrode from drying out and facilitated attaching. Although the hydrogel is self-adhesive, Omnifix medical grade tape (Hartmann Inc., Rock Hill, SC, USA) was used to ensure the skin attachment.

The screen-printed EEG electrode set (Studies **III** and **IV**) is presented in Figure 7.3. It was embedded into a flexible polyester film (Autostat CT4, MacDermid Autotype Ltd, Wantage, UK). Electrodes and conduction traces were printed with silver (XCMS-015 Polymer thick film silver ink, Spray-lat Electronic Materials Group, Mt. Vernon, NY, USA) directly to the polyester film (Autostat CT4, MacDermid Autotype Ltd, Wantage, UK) in a flat-bed sheet silk screen printing unit (Screentec Oy, Oulu, Finland). The silver paste was infrared-(IR) and air-dried at 120 °C before the encapsulation of conduction traces. The encapsulation was printed with insulation paste (Acheson Electrodag 452 SS, D-MAX technologies CO., Ltd, Shenzhen, China) with the same screen printing unit.

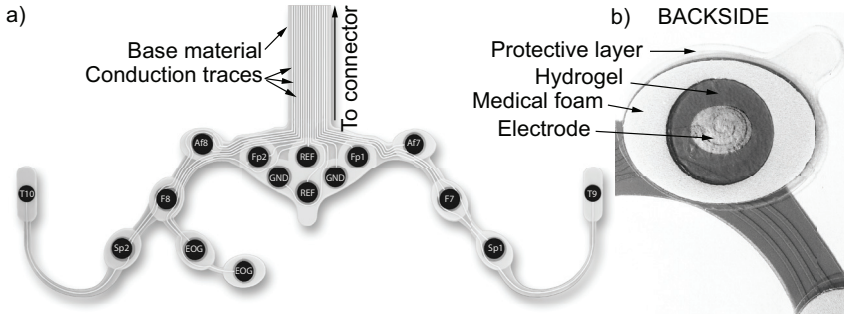


Figure 7.3. *a) A schematic figure of the screen-printed electrode consisting of ten electroencephalography (EEG) electrodes, two electro-oculography (EOG) electrodes, two common ground electrodes and two reference electrodes. b) Closeup picture of an individual electrode.*

The electrode positions of the screen-printed EEG electrode set were covered with an adhesive hydrogel membrane (AG602, Amgel Technologies, Fallbrock, CA) to improve contact with the skin. Skin attachment was secured with non-conductive foam (Venture 7432M, Venture Tape, MA, USA) surrounding the hydrogel circles, which also prevents the gel from drying out. The final outshaping was performed with a laser cutting technique to the pre-designed shape to allow a good fit onto the face. A connection cable terminating to 16-channel zero insertion force (ZIF) connector were used. The connection cable could be easily attached and detached when necessary. In study **IV**, silver-shielded and graphite-shielded versions of the screen-printed EEG electrode set were also fabricated. The shielding layer was printed on the front side of the polyester film (Figure 7.4).

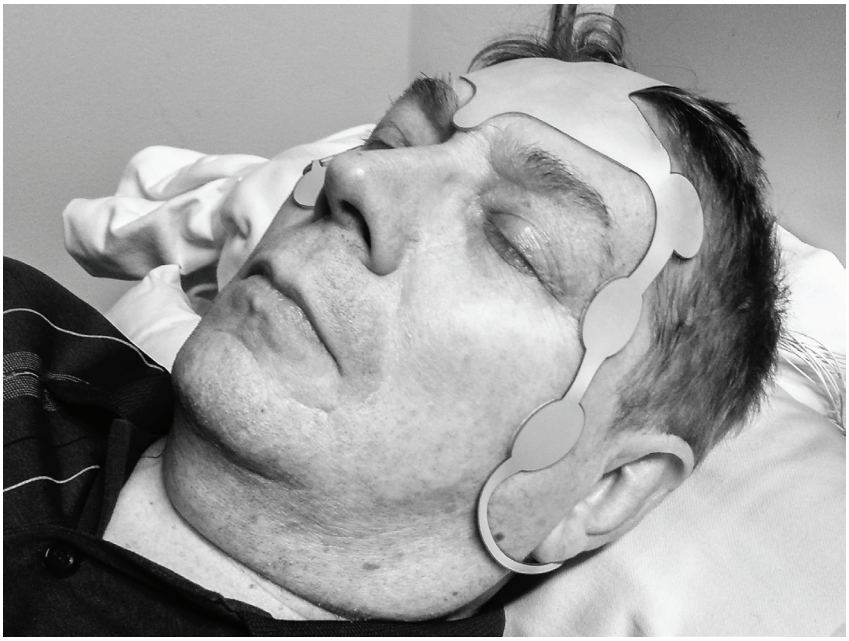


Figure 7.4. *A silver-shielded EEG electrode set attached to a volunteer's head. The silver layer was printed on the front side of the polyester film to protect the electrode set from enviromental electromagnetic artefacts. The use of this photograph has been permitted by the volunteer.*

7.2 ELECTRICAL PERFORMANCE

In study **I**, the electrical performance of the electrodes was determined with several measurements following the guidelines of the American National Standards Institute and Association for the Advancement of Medical Instrumentation (ANSI/AAMI) EC-12:2000 standard for disposable electrocardiography (ECG) electrodes). The characteristics of three commercially available disposable electrodes were compared with the handmade silver spiral electrode. The electrodes used in the comparison were a conventional Ag/AgCl cup electrode (Neuroline 726, Ambu A/S) with OL electrode paste (Berner Ltd., Helsinki, Finland), a self-adhesive solid gel surface electrode (Neuroline 700, Ambu A/S) and a wet gel ECG electrode (Blue Sensor SU, Ambu A/S). All measurements in study **I** were carried out with a Solartron 1260 impedance/gain-phase analyser coupled to a Solartron 1287 electrochemical interface (Solartron Analytical, Farnborough, UK). Data acquisition and analysis were carried out with CorrWare, CorrView, ZPlot and ZView (Scribner Associates Inc., Southern Pines, NC, USA) software.

In study **III**, measurements were carried out in the Department of Clinical Neurophysiology, Kuopio University Hospital (Kuopio, Finland) with a healthy adult volunteer. The SIGGI II (BrainProducts GmbH, Gilching, Germany) impedance meter was used in measurements.

7.2.1 DC offset voltage

In study **I**, the face-to-face and skin-to-electrode DC offset voltage of electrodes was measured. In the face-to-face measurements, the electrodes were placed in opposition to each other. With the skin-to-electrode measurements, the forearm was selected due to its accessibility and the electrode placement site was wiped gently with an ethanol-soaked (80 %) cotton pad. The DC offset voltage was measured for 5 min starting from the placing of the electrodes.

7.2.2 Impedance measurements

Impedance spectrum can be measured from the voltage differences of the electrode pair when supplying an alternating current through an electrode pair (Hewson et al. 2003). In study **I**, impedance measurements were carried out in the frequency range between 0.1 Hz and 10 kHz for the face-to-face electrodes and electrode–skin interfaces. The sinusoidal current was 50 μA without any DC offset. Three measurements were performed per each pair of electrodes after a stabilisation period of 10 min.

In study **III**, the impedance measurements were carried out by passing a sinusoidal (15 Hz and 30 Hz) currents through electrodes. Before the measurement, the skin was wiped carefully with an ethanol-soaked (80 %) cotton pad. Then five of the electrode sites were selected from the forehead to remain unprepared whereas beneath the other five electrodes the skin was abraded enabling a comparison of impedances between unprepared and abraded skin.

7.2.3 Internal electrode noise

In study **I**, internal electrode noise was measured by using a three-electrode configuration. Two identical working electrodes (the outermost electrodes) and a reference electrode (in the middle) were attached to a plastic sheet covered with electrically conductive hydrogel (AG602, Amgel Technologies, Fallbrock, CA, USA). The plastic sheet was placed inside a Faraday cage. Transient current flow and the potential difference between the working electrodes were recorded simultaneously for 5 minutes with a sampling frequency of 5 Hz. CorrWare and CorrView software (Scribner Associates Inc., Southern Pines, NC, USA) were used to calculate the root mean square (RMS) values for the noise in voltage and current.

7.3 ELECTROMAGNETIC COMPATIBILITY TESTS

In study **IV**, standardized electromagnetic compatibility (EMC) tests (Medical device standard EN 60601-1-2) were carried out in

an audited and certified (ISO/IEC 17025) EMC laboratory (Savonia University of Applied Sciences, Kuopio, Finland).

For testing purposes a silver-, graphite- and unshielded version of the screen-printed EEG electrode sets were glued to five-liter polypropylene measuring jugs (Kartell, Milano, Italy) with a conductive hydrogel sheet (AG602, Amgel Technologies) (Figure 7.5). The Medical device standard (EN 60601-1-2) describes tests for immunity to powerline frequency (50 Hz) magnetic field test (EN 61000-4-8) and Immunity to radiated radio-frequencies (RF) tests (EN 61000-4-3).

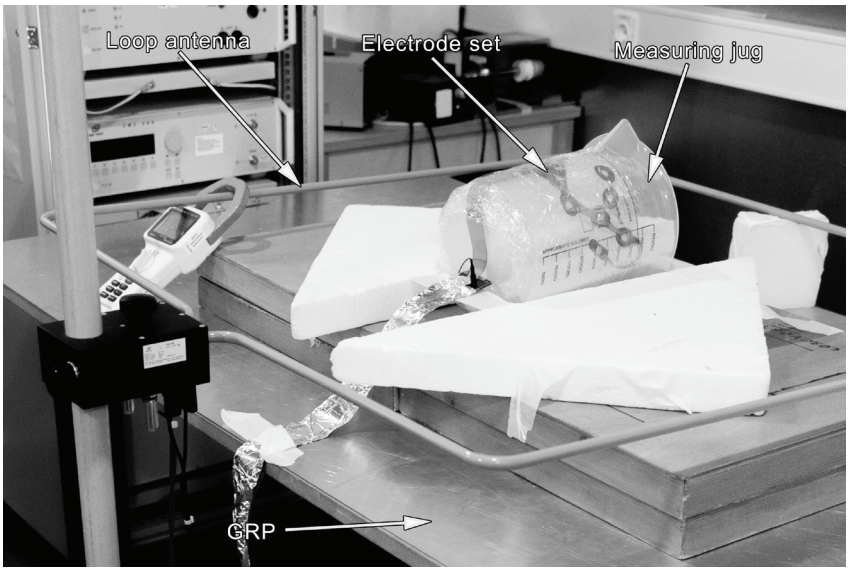


Figure 7.5. *Measuring jug attached screen-printed EEG electrode set were placed 10 cm above the ground reference plane (GRP) inside a loop antenna in a pulsed immunity test system.*

7.3.1 Magnetic field tests

The immunity to powerline frequency (50 Hz) magnetic field was carried out inside a shielded chamber. During the test, the measuring jugs and attached electrodes were placed 10 cm above the ground reference plane (GRP) inside a loop antenna. GRP consisting of an insulating support was connected with the laboratory safety earth. The tests, one-minute in duration, were carried out with a pulsed immunity test system (EM TEST

GmbH, Reinach, Switzerland) with two current density levels (3 A/m^2 and 30 A/m^2). The power-line interference was recorded with a TREA ambulatory EEG amplifier (Grass Technologies, Warwick, RI, USA) positioned outside the magnetic field of the loop antenna. All electrodes were tested in three different orientations (X, Y and Z).

7.3.2 Radiated radio-frequencies (RF) tests

In the Immunity to radiated radio-frequencies (RF) tests (EN 61000-4-3), the measuring jugs and attached electrodes were moved to a semi-anechoic chamber, where a floor and walls were covered with absorbers, and placed on a non-conductive table 0.8 m above GRP. The distance between the field generating antenna (height 1.55 m) and the measuring jug was adjusted to 3.0 m. The antenna was turnable which allowed testing of the vertical and horizontal polarizations of the RF-signal. The RF-signal was driven from 80 MHz to 300 MHz and was amplitude modulated (80 %) with 2 Hz signal. The working hypothesis was that the RF signal would appear as 2 Hz waves in the recorded signals. The recording was carried out with the TREA ambulatory EEG amplifier (Grass Technologies), which was positioned outside of the semi-anechoic chamber.

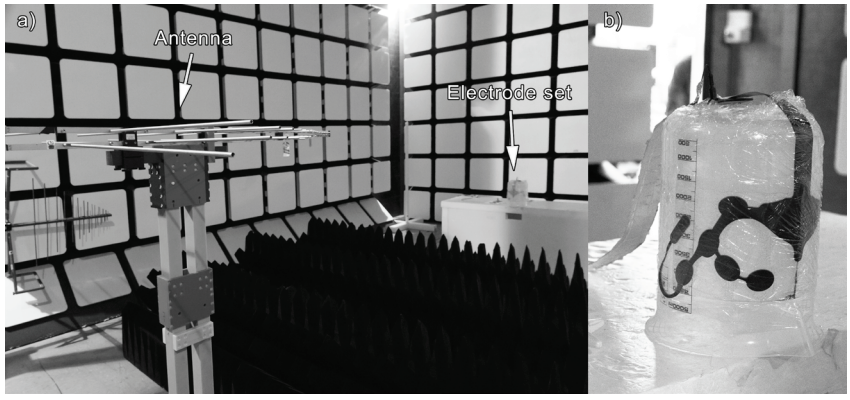


Figure 7.6. *a) Field generating antenna facing towards and electrode set attached to a measuring jug. b) The graphite-shielded EEG electrode set attached to the measuring jug.*

7.4 TESTING OF CT AND MRI COMPATIBILITY

Magnetic resonance imaging (MRI) and computed tomography (CT) tests of the handmade (Study **I**) and the screen-printed (Study **III**) EEG electrode sets were performed in Kuopio University Hospital. EEG electrode sets were attached to the surface of an imaging phantom (ACR MRI Phantom, The American College of Radiology, Reston, VA) (Figure 7.6). MRI experiments were performed in a whole-body MRI scanner (Philips Achieva 3T, Philips Medical Systems, Best, The Netherlands) equipped with a head matrix coil using typical head imaging sequences (Table 7.3). CT experiments were performed in a clinical CT scanner (Siemens Syngo CT 2010B, Siemens AG, Erlangen, Germany) using a routine head imaging program (100 kV; 192 mAs). Finally, an experienced specialist in neuroradiology assessed the presence of imaging artifacts. CT and MR images of silver-, graphite- and unshielded EEG electrode are previously unpublished.

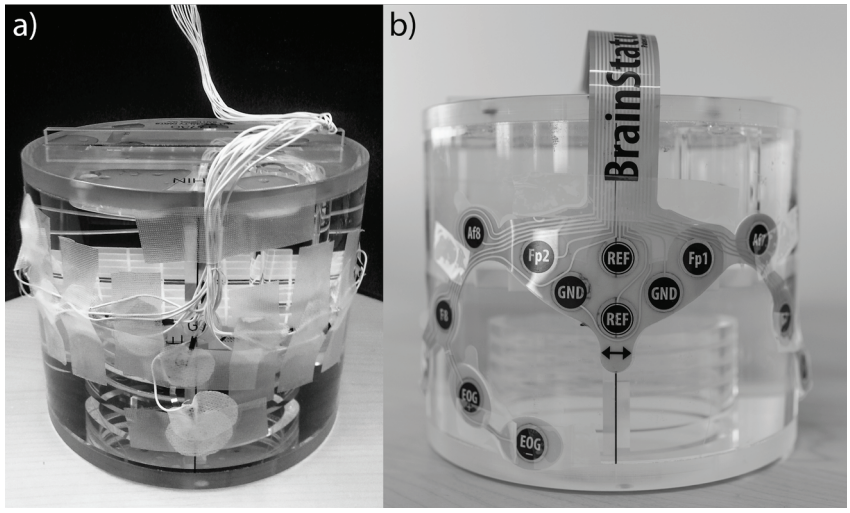


Figure 7.6. *a) The handmade and b) the screen-printed EEG electrode set attached to an ACR MRI Phantom.*

Table 7.3. MRI sequence parameters applied in compatibility tests.

Parameter	T2W TSE	T2W FLAIR	T1W SE
Field of view (mm x mm)	230 x 230	230 x 230	230 x 230
Matrix (pixel x pixel)	512 x 512	512 x 512	512 x 512
Slice thickness (mm)	3	3	4
Echo train length	15	40	-
Repetition time (ms)	4132	11000	600
Echo time (ms)	80	120	10
Inversion time (ms)	-	2800	-
Number of averages	1	2	1

7.5 EEG RECORDINGS

All patient EEG recordings were carried out in the Kuopio University Hospital under the supervision of an experienced specialist in clinical neurophysiology. Skin was prepared for the recording by wiping it with ethanol soaked cotton pad. The EEG electrode set was attached below the hairline of the patient. For comparison purposes, conventional electrodes (Grass Technology, West Warwick, RI, USA) affixed with EC2 electrode cream (Grass Technologies) were positioned according to the international 10–20 system. In study **I**, EEG with conventional electrodes was recorded just before placing the handmade EEG electrode set.

Four commercial EEG recorders, Comet XL (Grass Technologies) (Studies **I**, **II** and **III**) SystemPlus LTM (Micromed S.p.A., Treviso, Italy) (Study **II**), Aura (Grass Technologies) (Study **II**) and TREA Ambulatory EEG amplifier (Grass Technologies) (Study **IV**), were used in the present thesis. Sampling frequencies were 200 Hz in Grass and 256 Hz in Micromed devices. EEG was recorded with similar pass band (0.3 – 70 Hz) in all devices. Patient EEG recordings lasted from twenty minutes up to two days depending on the question in the referral. In studies **II** and **III**, EEG signals were simultaneously recorded with EEG electrode sets and conventional electrodes. Although recordings were acquired simultaneously they were reviewed separately; EEG electrode

set recordings were reviewed first and the recordings with the conventional electrodes a few days later.

There were a total of 17 patient cases in present thesis (Table 7.4). The most common clinical question in the referrals was to rule-out whether a patient was in status epilepticus (SE) (15 cases out of 17). In case #2, the clinical question in the referral was to clarify suspected Creutzfeld-Jacob disease (CJD) and in case #12 it was wished to rule out isoelectric EEG. In study II, 12 cases out of 13 were selected to be reviewed by two experienced specialists in clinical neurophysiology. One case was excluded because of the use of reduced EEG electrode set without the behind-ear electrodes. A summary of the EEG experiments carried out during this thesis work is presented in Table 7.4.

Table 7.4. *Overview of EEG experiments included in the present thesis.*

Study	Electrode set type	Reference EEG method	Volunteers /Patients	Departments
I	Handmade	Previous 10–20	-/2	ER
II	Handmade	Simultaneous 10–20	-/13	ICU, ER, Clinical Neurophysiology and Neurology
III	Screen-printed	Simultaneous 10–20	1/2	ICU and Clinical Neurophysiology
IV	Screen-printed (shielded)	None	6/-	Clinical Neurophysiology

In addition, EEG was recorded from six healthy adult volunteers for five minutes in study **IV**. In this study, the quality of EEG recording obtained with silver-, graphite- and unshielded screen-printed EEG electrode sets were compared. All three types of electrodes were attached as many times as first, second or third in order to eliminate electrode attachment order related effects on the quality of EEG signal.

The attachment times of the screen-printed EEG electrode set were measured by placing the EEG electrode set on four randomly selected patients (Study **III**). First, an EEG technician measured the width of the patient's forehead in order to choose the most suitable size of the EEG electrode set. Second, the technician cleaned up the skin by wiping it gently with an

ethanol soaked cotton pad. Next, the technician took the EEG electrode set out of the package and removed the protective layer from the middle of the EEG electrode set and placed the EEG electrode set on the forehead. As the last step of the attachment procedure, the technician removed the protective layer from other electrodes and attached to the skin one by one. Finally, the electrode was connected to the recording device.

All study protocols in the thesis were reviewed by the local ethical committee (Kuopio University Hospital Ethical Committee, favorable opinions 10/2011 and 71/2012) and VALVIRA (Finnish National Supervisory Authority for Welfare and Health, permissions 166/2011 and 220/2013).

7.6 SIGNAL PROCESSING AND STATISTICAL ANALYSES

Signal processing was performed using custom written programs in Matlab R2011a (Mathworks, Natick, MA, USA) (Studies **III** and **IV**). In study **III**, power spectral density (PSD) was calculated from a sliding window (length 1 s) over recorded EEG samples (length 8 s). The correlation coefficients between PSDs recorded for the hydrogel electrode pairs and the cup electrode pairs were determined to evaluate the signal quality.

The power (Decibel-Watt, dBW) of the frequency of interest was calculated from a 1 s sliding window (Study **IV**). The frequencies of interest in RF immunity tests and in magnetic field tests were 2 Hz and 50 Hz, respectively. In magnetic field tests, the power used in statistical analyses was the average of the one-minute recording. In RF field tests, the value used in statistical analyses was the maximum power. Mann-Whitney U test (SPSS 21, IBM SPSS Statistics, Armonk, NY, USA) was used to investigate the statistical significance of the differences observed between the electrode types. $P < 0.05$ was set as the limit for statistical significance.

In the present thesis, sensitivity and specificity for detection of status epilepticus were determined for each reviewer and averaged to represent combined sensitivity and specificity. A

similar method has been used in previous studies (Karakis et al. 2010, Kolls & Husain 2007a, Rubin et al. 2014). Sensitivity (true positive rate (TPR)) was calculated with the following equation:

$$TPR = TP/P = TP/(TP + FN), \quad (7.1)$$

where TP = true positive (correctly identified), P = positive instances, FN = false negative (incorrectly identified). Specificity (true negative rate (TNR)) was calculated with the following equation:

$$TNR = TN/N = TN/(TN + FP), \quad (7.2)$$

where TN = true negative (correctly identified), N = negative instances and FP = false positive (incorrectly identified).

8 Results

The main results of the thesis are presented in the following chapters. They also include previously unpublished CT and MR images of shielded EEG electrode sets.

8.1 ELECTRICAL CHARACTERISTICS

The handmade EEG electrode set met the requirements stated in the AAMI standard (Study **I)**. The DC-offset of the handmade electrodes was found to be very stable and noiseless. The face-to-face impedance at 10 Hz was less than 2 kΩ (AAMI standard). The skin to electrode impedance was comparable to those of disposable cup electrodes (Neuroline 726), solid gel surface electrodes (Neuroline 700) and pre-wet-gel electrodes (Blue Sensor SU). Handmade electrodes performed well in the noise tests. In particular, the level of voltage noise was lower than that obtained with the reference electrodes described above. The results of the face-to-face and skin-to-electrode impedances as well as voltage and current noises are presented in Table 8.1. In study **III,** the skin to electrode impedance of hydrogel electrodes were also compared as measured on unprepared and abraded forehead skin (Table 8.2).

Table 8.1. *Summary of impedance and noise test results (mean ± SD).*

	Impedance FtF (at 10 Hz) (kΩ)	**Impedance StE (at 10 Hz) (kΩ)**	**Voltage noise E_{RMS} (μV)**	**Current noise I_{RMS} (pA)**
Handmade	0.79 ± 0.09	5.6 ± 2.6	9.3 ± 4.4	75 ± 11
Cup	0.07 ± 0.01	1.8 ± 0.2	48.8 ± 58.3	103 ± 11
Solid gel	0.27 ± 0.04	9.8 ± 3.4	48.3 ± 38.3	101 ± 34
Pre-wet-gel	0.65 ± 0.11	1.6 ± 0.1	31.5 ± 40.0	78 ± 11

FtF = face-to-face, StE = skin-to-electrode

Table 8.2. *The skin-to-electrode impedance on unprepared and abraded skin (mean ± SD).*

	Impedance at 15 Hz (kΩ)	Impedance at 30 Hz (kΩ)
Unprepared	53.1 ± 8.6	44.6 ± 8.0
Abraded	1.8 ± 1.2	1.8 ± 1.3

8.2 EEG SIGNAL QUALITY

In all studies (**I**-**IV**), the EEG signal quality was evaluated visually by experienced specialists in clinical neurophysiology. According to the specialists, the recorded EEG did not contain any clinically significant interference even when recorded on unprepared skin with the higher impedance values (≈ 50 kΩ, Study **III**). The EEG signal recorded with screen-printed EEG electrode set on unprepared and abraded skin was reported to be almost identical to the EEG signal recorded with cup electrodes. In addition, power spectral densities (PSD) of EEG recorded with hydrogel electrodes and cup electrodes correlated strongly (correlations were 97.3 % and 98.5 % for abraded skin and non-abraded skin, respectively).

8.3 INTERFERENCE PICK-UP

The reduction of electromagnetic interference pick-up with the silver-, graphite- and unshielded versions of the screen-printed EEG electrode sets was investigated in electromagnetic compatibility tests and EEG recordings (Study **IV**). Silver and graphite shielding reduced interference significantly in RF tests ($p < 0.001$ and $p < 0.001$) and EEG recordings ($p = 0.011$ and $p = 0.018$) (Table 8.3). Silver provided significantly better shielding than graphite in RF tests ($p = 0.029$), but in EEG recordings there was not difference between the silver and graphite layers ($p = 0.406$).

Table 8.3. *Calculated interference powers in magnetic field tests, radiated RF tests and EEG recordings (mean ± SD).*

	Magnetic field (dBW) (*n* = 33)	**Radiated RF (dBW) (*n* = 22)**	**EEG Recordings (dBW) (*n* = 66)**
Unshielded	8.5 ± 8.4	0.4 ± 6.6	10.9 ± 8.9
Silver-shielded	7.3 ± 6.9	-11.9 ± 6.0	7.0 ± 8.0
Graphite-shielded	6.1 ± 7.2	-8.6 ± 6.7	7.3 ± 7.0

8.4 MRI AND CT ARTIFACTS

When comparing the CT images of the phantoms with the handmade and screen-printed EEG electrode sets, there were some barely detectable star-like artifacts near to electrodes in the images of the handmade electrode set. However, based on the opinion of the radiologist, these artifacts were not clinically significant. In MR images, the situation was reversed.

MR images with handmade electrodes were completely free of artifacts, but with screen-printed EEG electrode sets, there was barely a noticeable signal loss on the surface of the phantom (up to a depth of 1 – 2 cm). That was noticeable particularly with the silver-shielded electrode (Figure 8.1). However, based on the opinion of the radiologist, these artifacts would not be clinically significant.

8.5 EEG RECORDINGS

In study **III**, the attachment times of the screen-printed EEG electrode set were measured by placing the EEG electrode set on four randomly selected patients. The attachment took 3 min 14 s ± 49 s (mean ± SD, n = 4), respectively.

In study **II**, two specialists in clinical neurophysiology replied correctly to the referral question in 11 or 12 cases out of 12 based purely on the handmade EEG electrode set recordings. In studies **I** and **III**, one specialist replied correctly to the referral question in all cases based purely on the handmade (Study **I**)

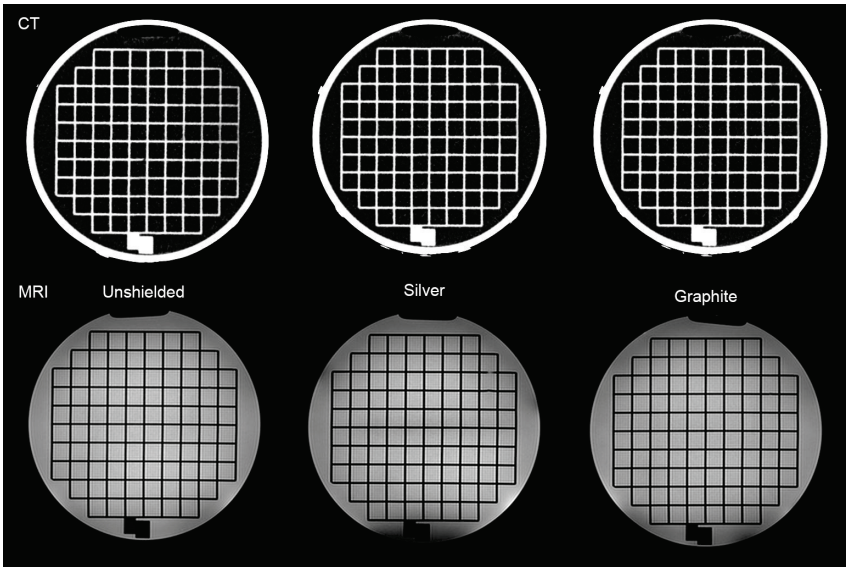


Figure 8.1. *Previously unpublished example of CT (Routine emergency head) and MRI (T2W FLAIR SENSE sequence) images of the phantom with the shielded electrodes. CT images (above) are clear from the artifacts in the phantom area, although the electrodes may be seen on the surface of the phantom. In MR images (bottom), there are no clinically significant artifacts, but there is a hardly noticeable signal loss in the vicinity of the attached electrode sets.*

and the screen-printed (Study **III**) EEG electrode set recordings. The individual results of all cases are presented in Table 8.4.

Findings are marked as true positive (TP) if a positive finding was correctly identified as compared to findings obtained with the reference (10–20) method. They were marked as true negative (TN) if correctly identified as negative. If the finding was incorrectly identified, it would be designated as a false positive (FP) or false negative (FN). In cases #3 – #15, the findings are marked twice, because there were two independent reviewers. The individual results of the reviewers are presented in Table 8.5. The results from reviewers #1 and #2 were used in the calculation of average sensitivity and specificity for status epilepticus. The average sensitivity and specificity for detecting status epilepticus based on EEG electrode set recordings were 65 % and 100 %, respectively. Note that there were no FP cases. If case #3 was excluded, then the sensitivity increased to 83 %. The exclusion is justifiable since in this case the reduced EEG

Table 8.4. *Summary of the patient EEGs in present thesis including referral questions and findings. A positive finding was confirmed in six times out of nine based purely on the EEG electrode set recordings. None of the findings were misinterpreted as positive.*

Patient	Referral	EEG electrode set findings
#1, F/18	Refractory focal epilepsy with very frequent seizures. Rule out SE.	**TP.** Very frequent ictal EEG discharges, SE confirmed.
#2, M/57	Suspected CJD. Clarify CJD.	**TN.** EEG background abnormalities, but no specific EEG features indicative for CJD.
#3, M/83	SAH. AMS and occasional left hand and eyelid jerks. Rule out SE.	**FN + FN.** Discharges at occipital regions that were not seen (EEG electrode set without the behind-ear electrodes).
#4, M/50	In EEG-confirmed SE, treated, SE resolved?	**TN + TN.** Diffuse slowing of background activity, periodic bursts or theta/delta activity. Hemispheric asymmetry. No SE.
#5, M/50	Clinically in SE, treated, SE resolved?	**TP.** Strongly abnormal. Continuous discharge at T9. Still in SE. **FN.** Reviewer 2: Too bad SNR to rule out SE.
#6, M/69	Clinically in SE, treated with general anesthesia, SE resolved?	**TN + TN.** Diffuse slowing of background activity. No SE.
#7, F/79	Alzheimer's disease with right ICH. Rule out SE.	**TN + TN.** Diffuse slowing, encephalopathic abnormalities, no discharges. No SE.
#8, F/62	Large SAH. Craniotomy, posterior fossa decompression. Rule out SE.	**TN + TN.** Diffuse slowing of background activity. No SE.
#9, M/64	Found in asystole, resuscitated. Left cheek fasciculation. Rule out SE.	**TN + TN.** Monotonic GPED. Anoxic brain injury, but not SE.
#10, M/34	Infratentorial glioma operated, shunt. Rule out SE.	**TN + TN.** Diffuse slowing of background activity and hemispheric asymmetry. No SE.
#11, F/74	Left limbs weak, in CT right acute ischemic lesion. Rule out SE.	**TN + TN.** Diffuse slowing of background activity. No SE.
#12, M/62	Resuscitated, ROSC 28 min. Hypothermic treatment. Rule out isoelectric EEG.	**TP + TP.** Burst-suppression EEG, with left-sided attenuation. Jerks during bursts.
#13, F/80	Acute confusion, intermittent eye deviation. Rule out SE.	**TP + TP.** Continuous bilateral epileptic discharges. Reacts to medication (i.v. benzodiazepine). SE confirmed.
#14, M/81	Intermittent aphasia or jargon. Rule out SE.	**TN + TN.** Diffuse slowing of EEG. No SE.
#15, F/55	Operated frontal malignant tumor, speech difficulties. Rule out SE.	**TN + TN.** Hemispheric asymmetry, frontally slowing over left side. No SE.
#16, M/74	Carcinoma surgery one week earlier. Fluctuating consciousness. Rule out SE.	**TN.** Diffuse slowing, but epileptiform discharges were not observed. No SE.
#17, F/73	Successfully treated due to SE with improved condition. Still slightly aphasic. Rule out SE.	**TN.** Repeated epileptiformic spikes and sharp waves in left temporal lobe. No SE.

F = Female, CJD = Creutzfeld-Jacob disease, CT = Computed tomography, EEG = Electroencephalography, FN = False negative, FP = False positive, GPED = Generalized periodic epileptiform discharge, M = Male, ROSC = Return of spontaneous circulation, SAH = Subarachnoid hemorrhage, SE = Status epilepticus, TN = True negative and TP = True positive

electrode set without behind-ear electrodes was used. For this reason, the presence of EEG discharges in posterior quadrant were missed.

Table 8.5. *Summary of all EEG electrode set findings compared to EEG recorded with 10–20.*

Reviewer	Cases	TP	FP	TN	FN
#1	#1 - #15	4	0	10	1
#2	#3 - #15	2	0	9	2
#3	#16 - #17	2	0	0	0

FN = False negative, FP = False positive, TN = True negative and TP = True positive

In addition to the main clinical question in the referrals several EEG phenomena and abnormalities could be detected with the EEG electrode set: hemispheric asymmetry, diffuse slowing of background activity, spike-slow-wave complexes, periodic lateralizing epileptiform discharges (PLED), triphasic waves and burst-suppression pattern. The electrode set showed its effectiveness for generalized nonconvulsive SE (*e.g.* case #13, Figure 8.2) as well as in the detection of focal findings (*e.g.* case #17, Figure 8.3).

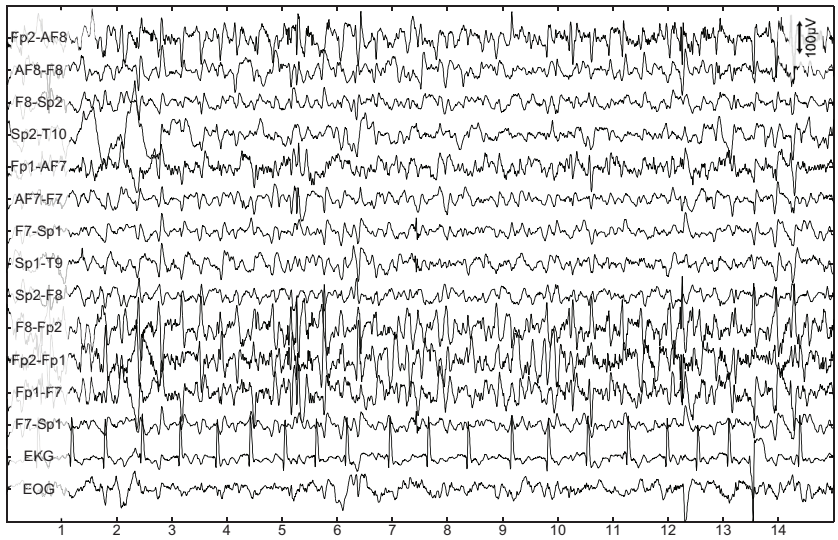


Figure 8.2. *EEG of a 73-year-old female (Case #13) with handmade EEG electrode set revealing continuous bilateral epileptic discharges.*

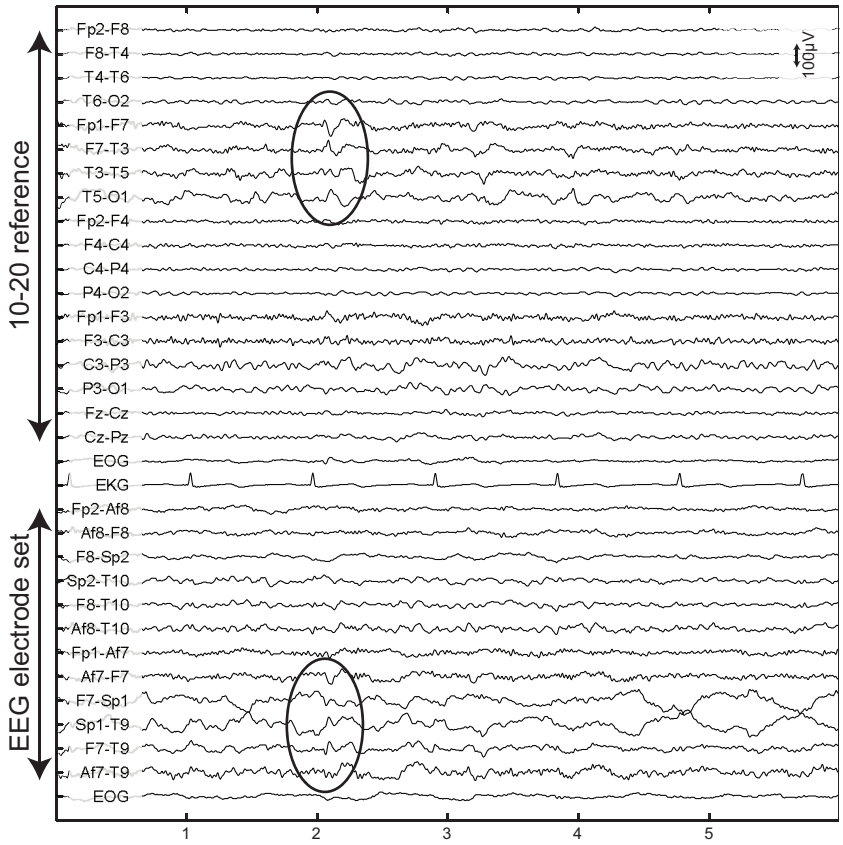


Figure 8.3. *Simultaneously recorded EEGs of 73-year-old female (Case #17) with conventional electrodes positioned according to the international 10–20 system (above) and the screen-printed EEG electrode set. Epileptiformic spikes and sharp waves (circled areas) are visible in the left temporal lobe.*

9 Discussion

The present thesis describes the design and evaluation of novel EEG electrode sets intended for emergency use. Their performance and suitability for emergency use were investigated through electrical performance tests, electromagnetic compatibility tests, CT and MR imaging and clinical EEG recordings. A final prototype of the screen-printed EEG electrode set is capable of providing sufficient EEG signals even without skin abrasion. It was demonstrated that several EEG abnormalities could be detected and that the clinical question could be answered based solely on the recordings with the EEG electrode set in most cases included in this thesis. Furthermore, the EEG electrode set was demonstrated to allow MRI and CT imaging without any signs of significant imaging artifacts.

Based on the present results, this EEG electrode set might become a potential firstline screening tool for NCSE. Further, several EEG phenomena and abnormalities were successfully detected including hemispheric asymmetry, diffuse slowing of background activity, spike-slow-wave complexes, periodic lateralizing epileptiform discharges (PLED), triphasic waves and burst-suppression pattern. Since one third of the altered mental status (AMS) cases are caused by neurological disorders (Ziai et al. 2012), the simple electrode system developed in this thesis, may be particularly helpful in achieving the correct diagnosis in ER.

A number of studies related to below-the-hairline electrode sets and reduced EEG montages have been carried out in recent decades (Bridgers & Ebersole 1988, Ebersole & Bridgers 1985, Karakis et al. 2010, Kolls & Husain 2007a, Rubin et al. 2014, Tanner et al. 2014, Young et al. 2009). These studies have particularly focused on the below-the-hairline EEG electrode arrangement introduced by Bridgers & Ebersole (1988). These

studies have reported excellent specificity and the only moderate sensitivity of that electrode arrangement. Kolls & Husain (2007) even declared that based on the moderate sensitivity, further pursuit of that electrode arrangement of screening tool for NCSE was not recommended. This caused a heated debate in the journal (Bubrick et al. 2007, Kolls & Husain 2007b). Bubrick et al. (2007) stated that it might be dangerous to draw such final conclusions, since the below-the-hairline electrode sets may be sometimes the only solution for seriously ill patients especially if other viable options are not available. Bubrick et al. (2007) also commented that they were routinely trained neurology residents who could perform and interpret below-the-hairline EEGs, and they had found it useful (Bubrick et al. 2007, Milligan & Bromfield 2005). Kolls & Husain (2007b) did not accept this criticism and declared that although below-the-hairline EEG sets could be quicker and easier to use, they did not appear to represent an adequate substitute.

The excellent specificity of the below-the-hairline EEG when using electrode arrangement introduced by Bridgers & Ebersole (1988) means that it gives only seldom false positive findings. Accordingly, the positive findings can be trusted and the appropriate treatment can be started immediately after the positive finding. This may significantly reduce patient recovery time and reduce costs, because untreated NCSE increases the risk of permanent brain damage and diminishes the chance for successful treatment (Drislane et al. 2008, Young et al. 1996).

One commercial below-the-hairline EEG electrode set called B-Ahead II (BrainScope Inc.) is based on the slightly different placement of electrodes as compared to the arrangement presented by Bridges & Ebersole (1988). B-Ahead II consists of five EEG electrodes (Fp1, Fp2, AFz, F7 and F8) and two reference electrodes located behind the ears. In several studies, it has been demonstrated to possess a good clinical performance (Jacquin et al. 2007, McCrea et al. 2010, Naunheim et al. 2010, 2011). It has provided very promising results in terms of sensitivity and specificity (83 % and 96 %, respectively) for seizure alert with patients having NCSE (Jacquin et al. 2007).

Furthermore, BrainScope B-Ahead II displayed also good sensitivity and specificity (96 % and 87 %, respectively) for detecting abnormalities in the EEG (Naunheim et al. 2011). Furthermore, when taking into account that the addition of one electrode on the vertex (Cz) and two on occipital region (O1 and O2), does not significantly improve the sensitivity (Rubin et al. 2014), further pursuit of hairline EEG as a "quick and easy" screening tool for emergency use is meaningful.

The screen-printed EEG electrode set developed in this thesis work showed promising results in signal quality tests even without the abrasion of the skin. The specialists in clinical neurophysiology stated that the technical quality of EEG recorded with the screen-printed EEG electrode set was adequate even with higher skin-electrode impedance values. In addition, the power spectral density (PSD) correlation results between hydrogel electrode pairs and traditional cup electrode pairs support this observation. The determined skin-electrode impedance values were also comparable with those published in previous studies (Alba et al. 2010, Ferree et al. 2001, Kleffner-Canucci et al. 2012, Lin et al. 2011). Even on unprepared skin, the impedances were at a level (≈ 50 kΩ) that has been reported to be achievable for modern amplifiers with a very high input impedance (over 200 MΩ) (Ferree et al. 2001). Actually, in present studies, a relatively old EEG amplifier Comet XL (Grass Technologies), whose input impedance is only 10 MΩ resulted in a satisfactory signal quality. However, the high-performance EEG amplifier is a crucial component in the EEG recording system when using electrodes without skin preparation.

Short setting time, achieved with the developed screen-printed EEG electrode set is a major advantage in emergency situations where time matters. An experienced EEG technician could attach the screen-printed EEG electrode set in 3 min 14 s ± 49 s (mean ± SD, n = 4) (Study **III**). For comparison, it has been reported that when using BraiNet™ EEG template (Jordan NeuroScience), only 29 % of non-technologists were able to set up the 10–20 montage in less than 30 minutes (Kolls et al. 2012). Comparison with the results of Kolls et al. (2012) may sound

unfair, but based on their article 63 % of non-technologists used the templates one to five times, and 25 % had used it six to ten times during the trial period. Based on the present usability studies, this number of training sessions should suffice to reduce the setting time of the screen-printed EEG electrode set to below five minutes for non-technologists. Thus, it can be concluded that the setting times with the screen-printed EEG electrode are significantly shorter than with BraiNet. The developed electrode set is a compromise between the number of electrodes and the short setting time. Reducing the number of electrodes from 16 would not significantly shorten the setting time, but it could well reduce sensitivity or/and specificity. In addition, doubled number of electrodes allows multiple montage variations compared with the other introduced below-the-hairline arrangements (Bridges & Ebersole 1988, Jacquin et al. 2007). However, it is impossible to declare an optimal montage with the patient population used in the present thesis and further studies will be needed with a larger number of patients.

As mentioned in Chapter 4.3, shielded cables have been found to be an effective way to minimize power-line interference. However, the effect may be limited if the shielding does not cover the electrodes (Wood et al. 1995). In study **IV,** an effective method was devised to shield screen-printed electrode sets against interference pick-up. Silver and graphite shielding printed on the front side of the electrode set provided effective interference protection when used together with a shielded measurement cable. Silver and graphite shielding reduced interference significantly in radio frequency (RF) tests ($p < 0.001$ and $p < 0.001$) and in EEG recordings ($p = 0.011$ and $p = 0.018$). Most likely, the shielding layer prevents the capacitive coupling between circuits by shunting charge to common ground. This is a common shielding technique used in electrical devices to reduce induced voltage in a capacitive circuit (Fowler 2000).

It was somewhat surprising that in the magnetic field tests, the performance of shielded electrodes did not differ from unshielded electrodes significantly. This suggests that the 50 Hz

noise in EEG recorded by screen-printed electrodes was largely due to interference modulated in the RF signal. This is supported by recent studies, in which screen-printed circuits have been reported to show very good RF performance (Salvado et al. 2012, Scarpello et al. 2012). Therefore, a screen-printed electrode could be acting as antenna in the presence of electromagnetic energy of RF fields (Linares Y Miranda et al. 2013). Moreover, it should be taken into account that a certain part of the power-line interference due by RF signals may be resulted from terminated two-wire transmission line excited by a nonuniform electromagnetic field (Linares Y Miranda et al. 2013, Taylor et al. 1965). Thus, interference is dependent on the lengths of the traces and the direction in which the trace is oriented with respect to the polarization of the RF signal. These above-mentioned reasons may explain the relatively high standard deviations in Table 8.3. In the modern world, there is a wide range of artificial RF sources (*e.g.* powerful radio transmitters, wireless network devices and mobile phones) and many natural sources (atmosphere, lightning, electrostatic discharges) around us (Linares Y Miranda et al. 2013). Therefore, it is understandable that shielding of screen-printed electrodes is important especially if emergency EEG recordings are to be performed in ambulance or in field conditions. Silver shielding, which achieved a significantly better performance in the radiated RF tests ($p = 0.029$), is easy and cheap to realize with the screen printing technique. Therefore, it is easy to recommend the use of silver shielding in all printed electrodes. This is further emphasized when measuring microvolt scale signals in interfering conditions.

The materials used in the presented EEG electrode set were carefully selected during the development, testing and evaluation process. All of materials were selected such that the final prototype is biocompatible and well suited for emergency use. Screen-printed electrodes have been previously reported to be well suited for recording different biosignals (Karaguzel et al. 2009, Merritt et al. 2009, Paul et al. 2014, Rattfält et al. 2011, Yoo et al. 2009). In addition, precise pattern control and fully

automated printing unit with the laser cutting technique permit the fabrication of electrodes without the need for any manual steps. Therefore, screen printing is an economic technology suitable for mass production (Tymecki et al. 2006), too. Surprisingly, only a few screen-printed EEG electrodes are currently on the market (see Chapter 5.3.). At the moment, the major costs of the screen-printed EEG electrode set arise from the manual steps needed for setting of the hydrogels and sterile packaging of the product. However, when the above-mentioned shortcomings will be successfully resolved the selling price will be acceptable.

The flexible polyester body of the screen-printed electrode set follows smoothly the surface and movements of the skin. The adhesive hydrogel electrodes achieve a tight contact to the skin, which can significantly reduce the motion artifacts usually caused by the patient's movements or patient transfer. Hydrogels can also be easily affixed to the electrode surface, without increasing the manufacturing costs significantly. In contrast, dry electrodes are not adhesive. For this reason, it needs a solid template, which keeps them in contact to the skin (Lin et al. 2011). In addition, MEMS and carbon nanotubes are expensive techniques, which increasing the manufacturing costs of the dry electrodes (Lin et al. 2011). Finally, dry electrodes based on microneedles or carbon nanotubes are classified as invasive, which may complicate process to obtain permission for clinical use (Ruffini et al. 2008).

The nonconducting foam that surrounds the hydrogel in the present screen-printed EEG electrode set has an important role. The foam improves the adhesion to the skin and protects the hydrogel against drying or short-circuiting with adjacent hydrogel electrodes. For these many reasons, it is expected that flexible pregelled screen-printed electrode sets will become more popular in the future.

EEG electrodes are routinely removed prior to MRI and reattached after scanning (Mirsattari et al. 2009). This may lead to the situation, where important EEG data can be missed. It may also cause scheduling conflicts between MRI and EEG

protocols (Mirsattari et al. 2009). Therefore, safe and artifact-free MR and CT imaging of patient with attached EEG electrodes is increasingly demanded. All versions of the present EEG electrode set exhibited good performance in MRI and CT artifact tests. Even when the outer surface of the electrode set was covered with a continuous layer of silver or graphite, a specialist in neuroradiology did not notice any clinically significant artifacts in the images. In order to avoid issues related to the ferromagnetic materials in connectors, a 16-channel zero insertion force (ZIF) connector was used and this can be promptly attached and detached when necessary.

The MRI and CT compatibility of the screen-printed electrodes has not been widely investigated. In a recent study, Bonmassar et al. (2012) demonstrated that their flexible intracranial electrode set PTFOS (The Polymer Thick Film Organic Substrate flexible electrode set), did not cause any artifact in MR images (Bonmassar et al. 2012). PTFOS consists of electrodes made of silver ink and leads made of carbon ink isolated by a dielectric layer. Although the shielded screen-printed EEG electrode set contains more silver than PTFOS, no significant MRI or CT artifacts were detected. This is probably due to the fact that the silver shielding layer in the electrode sets was only 20 μm ± 5 μm thick. Although there did not appear to be any heating of the electrode surfaces during MRI sequences, the comprehensive temperature monitoring tests will be needed prior to patient use (Vanhatalo et al. 2014). In addition, further official standard tests will be needed to guarantee the true MRI compatibility and safety.

Although results obtained in the present thesis are promising, it should be noted that the clinical experience is limited. Therefore, further studies with a larger number of patients are warranted to clarify the true diagnostic sensitivity and specificity of the present screen-printed EEG electrode set. Further studies will be also required to clarify the true clinical benefit of using shielded electrodes.

In addition to emergency use, there are several other potential applications for the screen-printed EEG electrode set in

medicine. Since, the hydrogel retained its functionality for days without drying out, it could be very useful in long-term monitoring, especially with patients at a high risk of suffering repeated seizures or NCSE in ICU. In addition, EEG recorded with the screen-printed electrode set would help in making the prognosis after cardiac arrest. In particular, burst-suppression phenomenon in EEG, which can be seen with the screen-printed EEG electrode, is predictive of a brain injury after experimental hypothermic circulatory arrest (Pokela et al. 2003).

The screen-printed EEG electrode set may also be very suitable for sleep research in ambulatory use. It is easy to use and its lightweight construction does not interfere with a patient's sleep. However, it may be necessary to optimize the electrode sites to be more appropriate for these studies. An interesting application area may be found in the emerging field of the brain-computer or brain-machine interfaces (Lebedev 2014). The screen-printed EEG electrode set is flexible and lighter than most of the current commercially available brain-computer solutions. This could be useful not only in medicine but also in the fields of entertainment and computer game industry.

During the development process, a number of prototype generations were manufactured. Each generation was further developed from its predecessors, *e.g.* improvements and optimizations of material selection and sensor layout. The screen-printed EEG electrode set, which is almost ready for commercialization, is a result of the four-year trial period. In addition, national patent application "Järjestely ja menetelmä elektrodimittausten suorittamiseksi (The arrangement and method for performing electrode measurements, #20126186)" is pending in the National Board of Patents and Registration of Finland. Mega Electronics Ltd (Kuopio, Finland) bought the rights to the invention on 9 October 2013, and is currently launching the commercial production of the forehead EEG electrode set named BrainStatus.

10 Conclusions

In the present thesis, a disposable EEG electrode set for emergency use was successfully developed. Its performance and suitability for emergency use were investigated through electrical performance tests, EMC tests, CT and MR imaging, and clinical EEG recordings. The main conclusions are summarized with respect to the aims of the thesis as follows:

1. The EEG electrode set achieved good performance in signal quality tests even without skin abrasion. The clinical question could be answered based solely on recordings with EEG electrode set in most cases. The sophisticated screen-printed electrode structure with adhesive hydrogels enables stepwise attachment of electrode set within a few minutes.

2. The screen printing technology allows low-cost mass production of disposable electrode sets. Hydrogels and medical foams can also be easily affixed to the electrode surface without increasing the manufacturing costs significantly. MRI and CT images did not suffer from clinically significant artifacts arising from the EEG electrode set, even when equipped with a silver-shielding layer.

3. The shielding layer, particularly silver ink, printed on the front side of the EEG electrode set effectively reduced interference pick-up from external electromagnetic fields.

To conclude, the EEG electrode set developed in this thesis work may be a solution for EEG registrations when the conventional 10–20 electrode setup is not available or feasible. In addition, the knowledge about shielding of screen-printed electrodes obtained in the present thesis is applicable for in similar screen-printed electrodes when measuring microvolt scale signals under interfering conditions.

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Pasi Lepola

Novel EEG Electrode Set for Emergency Use

If electroencephalogram (EEG) monitoring can be started already in the emergency room or even in the ambulance, the patient access to the appropriate treatment will be speeded up. However, acute EEG monitoring has not become a clinical routine mainly due to the lack of convenient electrode solutions. In this thesis, a disposable EEG electrode set for emergency use was successfully developed. Its performance was investigated through electromagnetic tests, medical imaging techniques and clinical EEG recordings. To conclude, the EEG electrode set may be a solution for EEG registrations when the conventional 10–20 electrode setup is not available or feasible.

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