General introduction

Our body is a very complex machine, in which many chemical, electrical and physical processes take place. Only a small part of these processes is known and understood. The human body is even more complex than the most complex man-made machine. If our machine, the body, is damaged or isn’t functioning well, we go to the hospital. There a medical specialist tries to make a diagnosis. To come up with the correct diagnosis, anamnesis, physical examination as well as different medical tests or imaging procedures might be required. These imaging procedures and medical tests are often performed with high-tech medical devices, such as imaging systems that visualize structures and physiological processes in the body and systems that can measure blood flow, electrical activity or the concentration of certain components in the blood.

Finally, if a diagnosis is made the specialist may prescribe a drug, another way of life or plan a surgery. The drug can be packaged in an advanced drug delivery system. The latter administers drugs through controlled delivery in the body so that the optimum amount reaches the desired body location. On the other hand, during surgery again many advanced medical devices can be used, for example to monitor the state of the patient or to better visualize the intervention. In addition, a robot may be used to perform very precise actions or a high-tech prosthesis can be implanted.

Accordingly, many engineers are needed in the field of health care; in the hospital to work with all the high-tech devices and to develop new applications, in business to develop new medical devices and techniques and in fundamental research to learn more about chemical, electrical and physical processes in the body. These fields of research and development have fascinated me since I started to study Biomedical Engineering in Eindhoven. During my studies I did a variety of projects from developing a mechanical and electrical model of the heart to investigating the response of cells to different mechanical loads. After these projects, I found out that one of my fields of interest is biosignal analysis for direct clinical applications. Electroencephalogram (EEG) is an electrical biosignal used for diagnosis of neurological disorders and for monitoring. This thesis aims to investigate new diagnostic applications of multichannel EEG, in particular evoked potentials (EPs) and event-related potentials (ERPs), by developing new analysis techniques.
EEG is a non-invasive technique that measures the electrical activity produced by nerve cells in the brain with electrodes placed on the scalp. EEG activity was first recorded by Hans Berger in 1924. He discovered that different waves or rhythms are present in the normal brain and that alterations of these brain waves occur in neurological disorders like epilepsy. Around 1950, EEG started to be used in hospitals for clinical diagnostic purposes. At that time EEG recordings were analog paper recordings and evaluation was mainly based on visual inspection. During the 1970s, computers were increasingly used for EEG recording and advanced EEG signal analysis became possible. At that time, EPs were also applied for the first time for clinical diagnosis and ERPs were used for research purposes. EPs and ERPs are electrical brain potentials that are responses to a certain stimulus (visual, auditory, sensory) or action. EPs are exogenous potentials with a short latency that are insensitive to attention and subject performance. On the other hand, ERPs are endogenous long latency potentials elicited by cognitive processes that are influenced by the level of attention and subject performance. With the development of CT, MRI and PET between 1970 and 1990, it became possible to image the inside of the body noninvasively. These developments had great impact on individual diagnosis, treatment and prognosis in neurology and for a few decades the interest in EEG as a clinical diagnostic tool decreased. However, a major advantage of EEG compared to MRI, CT, SPECT and PET remains its low cost and high temporal resolution; whereas functional MRI and PET have a time resolution in the order of seconds, for EEG this is in the order of milliseconds. Furthermore, EEG can directly measure brain electrical activity, while fMRI, SPECT and PET measure brain electrical activity indirectly by assessing metabolic changes or blood flow. Because of these advantages EEG is still used nowadays as a diagnostic tool for epilepsy and sleep disorders, for monitoring during surgery and for the diagnosis of brain death. Evoked potentials are still used clinically as well, for clinical diagnosis of demyelinating-, visual- or hearing disorders, for the prognosis of comatose patients and for intraoperative monitoring.

A disadvantage of EEG compared to the other imaging techniques is its low spatial resolution. However, with the development of multichannel EEG systems (> 64 electrodes) around 1990 spatial resolution has increased considerably. Initially, multichannel EEG was thought to be infeasible for clinical use, because of its long preparation times. Though, by using electrode caps, clinical application of multichannel EEG, EPs and ERPs has become possible. The question that directly arises from this development is if the extra amount of data obtained with multichannel recordings provides additional benefits compared to conventional techniques that employ fewer electrodes. So far, multichannel EEG has proven to be useful in the study of healthy brain physiology (Huber et al., 2004; Jackson et al., 2004; Massimini et al., 2004; Sabbagh et al., 2004) and has given new
insights in psychiatric diseases (Pae et al., 2003; Ruchsow et al., 2003; Youn et al., 2003). In contrast to what may be expected of a technique that has demonstrated its value in diagnostic neurology when using a few electrodes, only a limited number of studies report clinical neurological applications of multichannel EEG (Elting et al., 2005; Lantz et al., 2003a,b; Michel et al., 2004a). First applications were in pre-operative localization of epileptogenic lesions (Lantz et al., 2003a,b; Michel et al., 2004a). More recently, results from Elting et al. (2005) suggest that multichannel ERP can improve diagnosis and quantification of cognitive disorders after acute brain injury. These clinical applications are based on source localization, a signal analysis technique that can only be applied accurately to multichannel recordings. The hypothesis of the work in this thesis is that the number of clinical applications of multichannel EEG can be further extended partly by using new analysis techniques.

Before a new technique can be used for diagnostic purposes its usefulness must be tested (evidence based diagnostics); 1) the normal range and reproducibility of values must be determined, 2) its sensitivity and specificity for a certain disease must be estimated, 3) the benefits for the patients that undergo the diagnostic test must be evaluated and 4) its feasibility must be tested. Subsequently, one has to decide if the benefits outweigh the (additional) costs and burden for the patient. In this thesis, new analysis techniques are developed and applied to a large group of healthy subjects to determine its normal values and reproducibility. In addition, the techniques are applied to different patient groups to assess their diagnostic value. Furthermore, feasibility in patients is examined for a technique that has already been used for fundamental research in healthy subjects.

1.1 Outline of this thesis

The aim of this thesis is thus to investigate if multichannel EPs and ERPs can improve differential diagnosis of neurological disorders by introducing new analysis techniques.

A standard clinical analysis technique for EPs and ERPs is estimating peak amplitudes and latencies. However, also other analysis techniques can be applied, of which most are currently mainly used for research purposes. Chapter 2 and chapter 3 give an overview of these analysis techniques, where chapter 3 focuses on the wide range of source localization techniques.

In contrast to latency, E(R)P amplitude is hardly used for diagnostic purposes, because of its large variability among healthy subjects and patients. Only extremely high peaks or absent peaks are defined as abnormal. The variability among healthy subjects might at least partly be due to a combination of anatomical variation and the limited number of electrodes on specific positions used. Therefore, in chapter 4 we investigate if 128-channel recordings reduce the intersubject variability of
median nerve somatosensory EPs (SEPs), by using topographic mapping and the highest amplitude over all electrodes. In addition, in this chapter normal values are determined and the reproducibility of this approach is investigated.

While intersubject variability is large, the intrasubject variability between left and right hemispheres is relatively small. Therefore, for unilateral neurological disorders, it may be interesting to compare SEP activity in both hemispheres. So far, only peak amplitudes or peak source strengths of left and right SEPs have been compared. However, each subject has a specific SEP waveform and therefore also features other than SEP peaks might be interesting to compare. In chapter 5 we introduce a new method to quantify SEP symmetry. In this method, we compare left and right median nerve SEP waveforms. Furthermore normal values and reproducibility are determined for this technique.

In chapter 6 the methods introduced in chapters 4 and 5 are applied to SEPs of patients with different parkinsonian disorders to investigate whether the use of these techniques can improve the differential diagnosis. Previous studies with a limited number of electrodes already found some abnormalities in median nerve SEPs obtained from patients with different parkinsonian disorders. However, so far these abnormalities were too small or present in too few patients to be clinically useful.

Another SEP recording that is often used clinically is the tibial nerve SEP. It is already known that one of the peaks in the tibial nerve SEP differs enormously in position among subjects. Therefore, 128-channel amplitude estimation might be of additional value especially for this peak. In chapter 7 the amplitude of tibial nerve SEP in healthy subjects is investigated by using 128-channel recordings. Again normal values and reproducibility are estimated.

In contrast to EPs, ERPs have so far mainly been used for research purposes, but they might also be clinically relevant. A disadvantage of ERPs is that they depend on subject performance. In chapter 8, we investigate the feasibility for patients with Parkinson’s disease of a particular paradigm that is used to assess spatial attention and motor preparation.

Chapter 9 summarizes the results in this thesis and in chapter 10 future perspectives are given.