Department of Electronics

A mobile recording system and an acquisition control method for average event-related potential measurements

Antti Paukkunen

Aalto University

DOCTORAL
DISSERTATIONS

Aalto University publication series
DOCTORAL DISSERTATIONS 35/2012

A mobile recording system and an acquisition control method for average event-related potential measurements

Antti Paukkunen

Doctoral dissertation for the degree of Doctor of Science in Technology to be presented with due permission of the School of Electrical Engineering for public examination and debate in Auditorium S1 at the Aalto University School of Electrical Engineering (Espoo, Finland) on the 25th of May 2012 at 12 noon.

Aalto University
School of Electrical Engineering
Department of Electronics
Applied Electronics Research Group

Supervisor
Prof. Raimo Sepponen

Instructor
Prof. Raimo Sepponen

Preliminary examiners
Prof. Mikko Sams, Aalto University, Finland
Prof. Jari Hyttinen, Tampere University of Technology, Finland

Opponents
Prof. Mikko Sams, Aalto University, Finland
Prof. Juha Voipio, University of Helsinki, Finland

Aalto University publication series
DOCTORAL DISSERTATIONS 35/2012

ISBN 978-952-60-4562-7 (printed)
ISBN 978-952-60-4563-4 (pdf)
ISSN-L 1799-4934
ISSN 1799-4934 (printed)
ISSN 1799-4942 (pdf)

Unigrafia Oy
Helsinki 2012

Finland

The dissertation can be read at http://lib.tkk.fi/Diss/

441 697
Printed matter

Aalto University

Abstract

Aalto University, P.O. Box 11000, FI-00076 Aalto www.aalto.fi

Author
Antti Paukkunen

Name of the doctoral dissertation
A mobile recording system and an acquisition control method for average event-related potential measurements

Publisher School of Electrical Engineering

Unit Department of Electronics

Series Aalto University publication series DOCTORAL DISSERTATIONS 35/2012

Field of research Applied Electronics

Manuscript submitted 1 June 2011 **Manuscript revised** 8 December 2011

Date of the defence 25 May 2012 **Language** English

☐ **Monograph** ☒ **Article dissertation (summary + original articles)**

Abstract

Event-related potentials (ERPs) are a result of the activity elicited in the brain during the performance of a cognitive task. They can be studied by using an EEG, and are used to investigate the brain functions related to the processing of sensory data, and memory. The technique is flexible, and affordable, and has various potential diagnostic applications. The clinical feasibility, however, is limited due to the low measurement reliability. In addition, performance of the tests could be enhanced if the recording devices were more robust.

The current study presents two ways of improving the performance of ERP measurements. The first deals with the improvement of the efficiency of the recording procedure and the second, with the optimization of the recording system design for clinical use. In addition, the discussion on improving the measurement reliability is contributed to by conducting a study with mismatch negativity (MMN) to determine the relationship between the measurement error and the test-retest reliability.

To improve the recording procedure, an acquisition control method is suggested which helps optimize the amount of data recorded in terms of its concurrent quality. It allows optimization of the recording time and control of the measurement error, which reduces subject discomfort and improves measurement repeatability. In the MMN study conducted, the effect varied, depending on the parameterization, and whether the deviant responses were studied separately or as a profile. It was, however, generally significant, and repeatability was estimated to keep improving until the error level went below 10% of the peak amplitude.

Second, a mobile ERP recording system design with an integrated audio stimulation unit is presented. It is easy to apply, and capable of performing online data analysis. It is also tolerant of external interference because of its compact size, close proximity to the measured target, and the average grounding arrangement it uses. This kind of design allows fluent performance of the measurements in applications where the target activity is well-defined, which is important in an attempt to allow clinical use to be made of them. Together with the application of the algorithm developed, it provides easy access to ERPs and makes the investigations efficient, and less inconvenient.

Keywords Electroencephalogram, event-related potential measurement, instrumentation, mismatch negativity, measurement error, signal-to-noise ratio, test-retest reliability

ISBN (printed) 978-952-60-4562-7 **ISBN (pdf)** 978-952-60-4563-4

ISSN-L 1799-4934 **ISSN (printed)** 1799-4934 **ISSN (pdf)** 1799-4942

Location of publisher Espoo **Location of printing** Helsinki **Year** 2012

Pages 102 **The dissertation can be read at** http://lib.tkk.fi/Diss/

Aalto-yliopisto

Aalto-yliopisto, PL 11000, 00076 Aalto www.aalto.fi

Tiivistelmä

Tekijä
Antti Paukkunen

Väitöskirjan nimi
Mobiili mittauslaitteisto ja signaalinkeruun ohjausmenetelmä keskiarvoistettuihin EEG-herätevastemittauksiin

Julkaisija Sähkötekniikan korkeakoulu

Yksikkö Elektroniikan laitos

Sarja Aalto University publication series DOCTORAL DISSERTATIONS 35/2012

Tutkimusala Sovellettu Elektroniikka

Käsikirjoituksen pvm 01.06.2011 **Korjatun käsikirjoituksen pvm** 08.12.2011

Väitöspäivä 25.05.2012 **Kieli** Englanti

☐ **Monografia** ☒ **Yhdistelmäväitöskirja (yhteenveto-osa + erillisartikkelit)**

Tiivistelmä

EEG-herätevasteilla (ERP:lla) tarkoitetaan sähköisiä signaaleja, joita syntyy kognitiivisen aivotoiminnan seurauksena. Niitä voidaan tarkastella aivosähkökäyrän avulla ja hyödyntää tutkittaessa aistiherätteiden synnyttämää aivotoimintaa sekä muistia. Menetelmä on joustava, edullinen ja kliinisten sovellusten kannalta monikäyttöinen. Käytettävyys on kuitenkin rajallista mittausten heikon luotettavuuden takia. Lisäksi tehokkuutta voitaisiin parantaa kehittämällä robustimpia mittalaiteratkaisuja.

Tässä työssä esitetään kaksi tapaa mittausten kehittämiseksi. Toinen näistä liittyy mittausprosessin ja toinen mittausjärjestelmien parantamiseen. Lisäksi tutkimuksessa otetaan kantaa keskusteluun mittausten luotettavuudesta tutkimalla mittausvirheen vaikutusta poikkeavuusnegatiivisuusvasteen (MMN) toistettavuuteen.

Mittausprosessin tehostamiseksi esitellään laadunhallintamenetelmä, joka auttaa optimoimaan mitatun aineiston määrää, sen laadun perusteella. Menetelmän avulla voidaan optimoida mittauksen kestoa ja hallita mittausvirheen suuruutta, mikä vähentää mittausten epämukavuutta sekä parantaa tulosten toistettavuutta. MMN-kokeissa vaikutus riippui vasteen parametrisoinnista sekä siitä, että tulkittiinko vasteita erillisinä vai toisiinsa suhteutettuina. Se oli kuitenkin yleisesti merkitsevä ja toistettavuuden arvioitiin parantuvan ainakin kunnes virhe laskisi alle 10%:iin vasteen huippuamplitudista.

Mittausjärjestelyjä ajatellen esitellään mobiili mittalaitetoteutus, jossa herätelähde on rakennettu osaksi mittausyksikköä. Toteutus on helppokäyttöinen ja kykenee suorittamaan aineistoanalyysiä mittauksen aikana. Lisäksi se sietää hyvin ulkoisia häiriöitä pienen kokonsa, mitatun kohteen läheisyyden, sekä käytetyn keskiarvomaajärjestelyn ansiosta. Kliinistä käyttöä ajatellen on tärkeää, että mittaukset kyetään suorittamaan mahdollisimman sujuvasti. Esitetynkaltainen laitteisto soveltuu erityisesti tunnettujen vasteiden mittaamiseen. Yhdessä laadunhallintamenetelmän kanssa, sellaisen arvioidaan helpottavan herätevasteiden tutkimista sekä vähentävän mittausten epämukavuutta.

Avainsanat Elektroenkefalografia, herätevastepotentiaalimittaus, instrumentointi, mittausvirhe, poikkeavuusnegatiivisuus, signaali-kohinasuhde, toistettavuus

ISBN (painettu) 978-952-60-4562-7 **ISBN (pdf)** 978-952-60-4563-4

ISSN-L 1799-4934 **ISSN (painettu)** 1799-4934 **ISSN (pdf)** 1799-4942

Julkaisupaikka Espoo **Painopaikka** Helsinki **Vuosi** 2012

Sivumäärä 102 **Luettavissa verkossa osoitteessa** http://lib.tkk.fi/Diss/

Preface

The research for this doctoral thesis has been carried out at the Department of Electronics, School of Electrical Engineering, Aalto University during 2006-2011. The work was funded by the Graduate School of Electrical and Communications Engineering (AALTO), Applied Electronics Unit (Electronics department, AALTO), and the Society of Electronics Engineers.

First of all, I want to express my gratitude to my supervisor Prof. Raimo Sepponen for his guidance and support throughout the project, and to the pre-examiners for their constructive comments during the preparation of the dissertation manuscript. I also want to thank my colleagues and co-workers in the Applied Electronics Unit, for the many inspiring discussions and helpful efforts they have presented.

I am especially grateful for Mr. Miika Leminen, who co-authored with me in many of the publications, and provided a valuable user's perspective for the study. I had the pleasure of working with him right from the beginning of this project, and he helped me to solve various problems during the progression of the work.

To my family, I want to express my warmest gratitude for their endless love, support, encouragement, and understanding. There have been many ups and downs during this project, and the past year has been particularly rough. Thank you for always being there for me. I also want to thank my dear friends, especially Markus, for the lasting friendship. I hope I will now have more time for fishing with you.

Finally, I want to thank all the volunteer subjects, for taking part to the study. Your contribution to this study has been very important.

Vantaa, May 14, 2012,

Antti Paukkunen

Contents

List of Publications

This thesis consists of this summary and the following articles, which are referred to in the text by their symbols ([P1] to [P4]).

[P1] Paukkunen, AK, Sepponen R. The effect of the ground electrode on the sensitivity, symmetricity and technical feasibility of scalp EEG recordings. *Medical & Biological Engineering & Computing,* 46(9), 933–938, 2008.

[P2] Paukkunen, AK, Leminen, MM, Sepponen, R. Development of a method to compensate for signal quality variations in repeated auditory event-related potential recordings. *Frontiers in Neuroengineering,* 3:2, doi:10.3389/fneng.2010.00002, 2010.

[P3] Paukkunen, AK, Kurttio, AA, Leminen, MM, Sepponen, RE. A compact EEG recording device with integrated audio stimulation system. *Review of Scientific Instruments*, 81(6):064301, doi:10.1063/1.3436634, 2010.

[P4] Paukkunen, AK, Leminen, M, Sepponen, R. The effect of measurement error on the test-retest reliability of repeated mismatch negativity measurements. *Clinical Neurophysiology*, 122(11), 2195–2202, 2011.

Author’s contribution

The publications included in this thesis are a result of teamwork carried out by the authors referred to. The manuscripts were written by the author and he had the main responsibility for the approach taken in all of them. He also performed the majority of the work related to the design and implementation of the methods and the technology, as well as the investigations required to evaluate the results.

The specifications for the recording system presented in publication [P3] and the online evaluation procedure presented in publication [P2] were defined in cooperation between R. Sepponen, M. Leminen, and the author. The author had the main responsibility for the decisions that were made, but R. Sepponen gave technical assistance and M. Leminen provided a practical point of view from the user’s perspective.

The design and implementation were performed by the author, and he also performed the simulations, measurements, and analyses presented in publications [P1] – [P4]. In addition, the author supervised a master’s thesis that dealt with the design of the online artifact detection method used in publication [P3].

The evaluation of the results was mainly performed by the author, but they were also commented on by M. Leminen, in publications [P2] – [P4], R. Näätänen and R. Hari, in publication [P4], and R. Sepponen, in publications [P1] – [P4].

Symbols and abbreviations

Δ	Change
N	Total number of trials to be recorded
p	Probability/statistical significance
s.d.	Standard deviation
V	Voltage

AC	Alternating current
A/D	Analog-to-digital
ADC	Analog-to-digital converter
AERP	Auditory event-related potential
CMRR	Common-mode rejection ratio
DC	Direct current
DRL	Driven-right-leg circuit
EEG	Electroencephalogram
EOG	Electro-oculogram
ERP	Event-related potential
IC	Integrated circuit
ICA	Independent component analysis
ICC	Intra-class correlation coefficient
MCU	Main control unit
MMC	Multimedia card
MMN	Mismatch negativity
Nxxx	Negative ERP waveform component, with latency of xxx ms
Pxxx	Positive ERP waveform component, with latency of xxx ms
PC	Personal computer
RMS	Root mean square
SNR	Signal-to-noise ratio
SPI	Serial peripheral interface
SOA	Stimulus onset asynchrony
UART	Universal asynchronous receiver-/transmitter
μC	Microcontroller

1 Introduction

1.1 Event-related potentials

Event-related potentials (ERPs) are electrical responses elicited in the brain by stimuli while the subject is performing a cognitive task [1]. They can be recorded from an electroencephalogram (EEG) and used to investigate the activity in the brain related to the processing of sensory information.

The first ERP recordings were published in the late 1930s by Davis [2, 3], who demonstrated a change in the EEG signal when subjects were presented with a sound. The data were obtained by using a six-channel EEG amplifier and recorded by using an ink recorder. The next big step was taken in the 1960s, when the first computerized measurements were reported [4]. Automated data processing allowed the handling of large datasets and more detailed analyses to be made of them. Today, the high level of performance of the measurement instrumentation, analysis tools, and investigative methods has made the measurements generally available. The applications have gained more and more professional interest, and ERPs have become a popular tool in the investigation of the psychological and neurological functions of the brain. [5, 6]

1.2 Measurement technique

1.2.1 General arrangements

The origin of ERPs lay in the sensory system, where a stimulus (auditory, visual, or somatosensory) triggers a series of events leading to the activation of the brain. A sound, for example, causes the auditory nervous system to activate (Fig. **1**, phases 1–2). The receptor cells (in the cochlear nerve) produce an electrical impulse which propagates to the sensory cortex (auditory cortex) (Fig. **1**, phase 3). This initiates neuronal activation (Fig. **1**, phases 4–5), and the synchronous activation/inhibition of different neuron populations generates positive/negative signals in the EEG (Fig. **1**, phase 6). [5, 7, 8, 9]

To study these signals in a controlled way, the test subject is presented with different stimuli while the responses are recorded with a synchronized EEG measurement system. The stimuli may be auditory (e.g., tones, sounds, phonemes, or changing rhythms), visual (e.g., changing figures or moving, flickering, and rotating forms), somatosensory (e.g., puffs of air), or combinations of them. Each type of stimulus is presented multiple times, and the responses are averaged to highlight the stimulus-related activity. In addition, the subject may be provided with a passive task (e.g., watching a silent movie with subtitles) to keep him focused and to distract him from attending to the stimuli, or an active one (e.g. the calculation of certain types of stimuli) in order to study the attention effect [10].

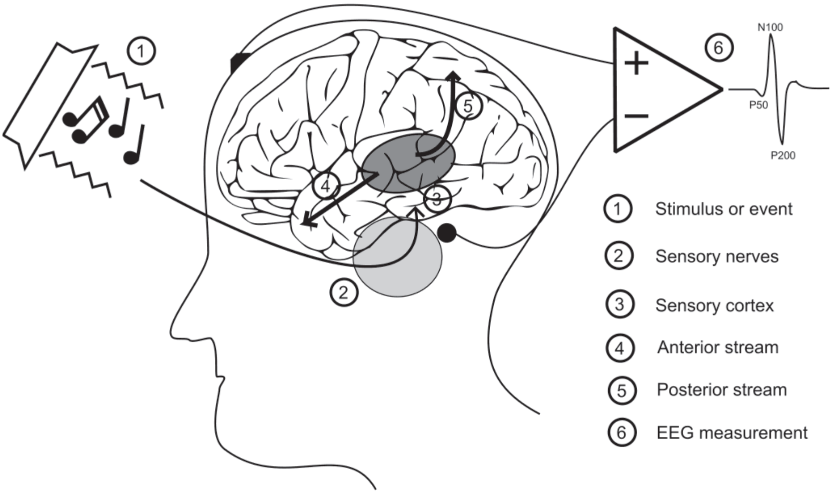


Fig. **1**. A schematic example of the generation of ERPs (in auditory modality). The stimulus (i.e., event) triggers an electrical signal that activates the brain (1-5) and initiates neuronal activity which is reflected in the EEG waveform (6). Being recorded from the surface of the scalp, the responses are weak and temporally flattened, but they still provide specific information on the processes going on in the brain.

1.2.2 Data acquisition

Being obtained from the surface of the scalp, the responses are greatly attenuated by the resistive skull [9, 11, 12, 13, 14] and the remaining amplitude is typically on a microvolt scale [15]. Thus, to bring the amplitude up to a convenient scale, the signals have to be amplified by 60–80 dB prior to sampling [16, 17, 18]. The frequency band reaches up to about 100 Hz (0 Hz excluded), and the signals are typically sampled at a rate of at least 200 Hz/channel, or four times the cutoff frequency of the low-pass filter [10, 19].

Prior to digitalization the signals are filtered to block the DC offset, to reduce the noise level [18, 20], and to prevent aliasing [19]. Furthermore, to reduce the 50/60-Hz power line interference [21, 22], active feedback circuits (i.e., a driven right-leg circuit, DRL) and notch filters may be used [16, 18, 23, 24, 25, 26, 27]. However, they are often unnecessary as a result of the high common-mode rejection ratio (CMRR) of the measurement amplifier circuits (>100 dB at 50/60 Hz) [10, 18, 28]. Notch filters may even be harmful, as they might distort the signal [10, 18, 29].

1.2.3 Digital signal processing

After digitizing, the data are further processed by using digital signal processing methods. Typically, they are first filtered and cleaned of artifacts. Then they are averaged to further improve the signal-to-noise ratio (SNR) [10, 30, 31].

Filtering

The filtering of noise is typically performed with a continuous zero-phase low-pass filter, and the DC offset decoupled by subtracting the baseline individually from each epoch [32]. The baseline may be computed by calculating the mean signal amplitude at an interval of 50–100 ms before the onset of the stimulus. Alternatively, the baseline may be removed by using a high-pass filter, but it may cause data loss as a result of the long settlement time of the filter [33].

Furthermore, after the epochs have been extracted, a tailored wavelet filter can also be used to bring up the morphology of the underlying response [34, 35, 36, 37]. Unlike conventional filters, wavelet filtering allows the consideration of the temporal signal features, and can be used to make the key signal features stand out better [38, 39, 40, 41]. At best, it may even allow the investigation of the responses from single trials [42, 43, 44].

Artifact rejection

Artifact rejection is performed to reduce the contribution of activity of non-cerebral origin (physiological or extraphysiological activity) to the data [45]. Common sources of such interference are eye and mouth movement, and muscle activity. The amplitude of the artifacts typically exceeds the ERPs, and they need to be eliminated in order for it to be possible to analyze the data.

The simplest way to reduce artifacts is to detect them by analyzing the signal amplitude at certain scalp locations, or the electro-oculogram (EOG) channels, and to reject them by discarding the data relating to the respective time interval [46]. This mainly works for the rejection of ocular defects, but it may be adequate in many cases, since they are the most common source of artifacts in ERP studies. On the other hand, a coarse rejection criterion may cause severe loss of data [47, 48, 49], and the remaining part may not be sufficient.

To improve the process advanced test criteria can be used, or mathematical models that allow more detailed investigation of the underlying sources [50, 51, 52, 53]. For example, if the electrode density is high enough, blind source separation (BSS) algorithms can be applied to detect artifacts on the basis of their presumed location and polarity, and a model of the anatomy of the brain [54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64]. In this way, the artifacts can be extracted from the data, and at least a part of the data can be made available for analysis [65]. On the downside, the modeling typically requires intensive computing and a large computation capacity to process the data. The performance of the method depends on the selection of the algorithm [61, 66], and versions that are feasible online have been suggested [67].

Averaging

Based on the assumption that the underlying signal remains essentially stable throughout the experiment, averaging is commonly performed simply by direct summing [68]. However, variations in the signal quality and the subject's mental state (e.g., vigilance, attention, and learning) may cause variation in the data and affect the direct averages [69, 70]. Thus, modified averaging methods which allow compensation for the latency jitter [71, 72, 73] and variation in the signal quality [74, 75, 76, 77, 78, 79] have been suggested. Single-trial investigations are also becoming available, and may be used to study the variations in the signals to be averaged [80, 81, 82].

1.3 Applications

The practical usage of ERPs covers a large variety of applications, which are typically based on the analysis of the average waveform parameters, the magnitude of which is compared to normative data from healthy subjects [10, 32]. Typical parameters studied are the magnitude, latency, and morphology of the waveform. The orientation and location of the underlying sources may also be modeled on the basis of the measured scalp surface potential distributions [32].

ERPs are particularly useful in the investigation of cognitive processes, and typical responses measured with such investigations are, e.g., P50, N100, P300, N400, P600, and MMN. Physiologically, Px/Nx are positive/negative ERP components peaking at a latency of x ms from the stimulus onset, and MMN a negative one peaking at approximately +100s to +250ms [83]. P50 is thought to be the first cortical ERP component which indicates a reaction to a stimulus. It may be used e.g., to study the reduced gating effect related to schizophrenia [84]. N100, MMN, and P300 reflect the cognitive processes related to, e.g. sensory memory and attention. They may be used to study, e.g., cognitive dysfunctions [83, 85, 86, 87, 88]. N400 and P600 reflect the integration of semantic and syntactic information and structures, particularly in the language context. They may be used to investigate e.g., semantic memory and the processing of syntactic anomalies [89, 90, 91, 92].

Table 1. Examples of clinical applications for event-related potential measurements and their prevalence within the Finnish population according to statistics collected in 2008 [93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104].

CONDITION	OCCURRENCE	ERP INDICATORS
Dyslexia	10% of children have some difficulties 2% of children have severe difficulties	Reduced amplitude of MMN for deviating syllables and frequency changes
Alzheimer's disease	36% risk (age > 65) 25% risk (age > 85)	Increased latency of auditory P300 Reduced amplitude of visual P300
Mild cognitive impairment	4% (ages: 65–74) 10% (ages:75–84) 33% (age > 85)	Reduced auditory P600 in word repetition test
Schizophrenia	1% of population 500 new cases yearly	Unchanged auditory P50 in a double-click test
Cognitive dysfunction	6% of babies are born prematurely	Absence of auditory MMN
Epilepsy	1% of the population	Longer auditory/visual P300 latency
Coma outcome	15,000-20,000 head injuries yearly	Appearance of the auditory MMN for large-frequency deviant tone

Currently, the use of ERPs is focused on general brain research applications, but they are a tempting option for clinical use, too (for examples, see Table 1). The instrumentation is rather inexpensive, their temporal resolution good, and their application flexible, as they do not require any specific infrastructure [9, 32, 105].

The greatest potential probably lies in the diagnosis of different cognitive dysfunctions and memory disorders such as Alzheimer's syndrome, involving the occupation of the auditory MMN [106, 107], P300 [108, 109, 110], and N400 [111] components [112]. Dyslexia, for example, may be treated by therapy if diagnosed early enough. ERP investigations could allow the detection of the related symptoms at an early age, and early rehabilitation might prevent displacement in schools and reduce the costs of remedial education [113, 114].

On the other hand, the number of patients with mild cognitive impairments or Alzheimer's disease is constantly rising [93]. Thus, more and more efficient diagnostic tools are needed to maintain a sufficient investigation volume and to prevent the issues related to delayed treatment. ERP investigations might be well suited to use here [115]. Furthermore, ERPs might be useful in the evaluation of patients' progress during therapy.

1.4 Current state of technology

1.4.1 Performance of the measurements

To be feasible in practical applications, the performance of the ERP measurements should be robust, and the results they produce reliable and reproducible. At the moment, this condition is not always met. Differences can be identified between diagnostic groups, but the results show too much variation for single-subject diagnosis (for examples, see Table 2). This makes the determination of the intermediate phenotype complex and the interpretation of the results hard [113, 114, 116]. A part of this variation is caused by the changes in the subjects' mental state, but the variation in the data quality between sessions also accounts for a large part of these changes [33, 70, 82, 117, 118, 119, 120, 121, 122, 123].

Table 2. Some test-retest reliabilities reported for the amplitude and latency of auditory ERPs, between repeated measurements, in single-subject recordings with healthy test subjects. [113, 117, 118, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140]

ERP	Test-retest reliability (between sessions)		Test-retest reliability (within session)	
	amplitude	latency	amplitude	latency
N100	~0.75	0.40–0.53	0.09–0.40	0.27–0.75
P200	0.75–0.8	0.15–0.45	0.23–0.47	0.50–0.73
P300	0.31–0.81	0.07–0.48	0.48–0.93	0.32–0.8
MMN	0.37–0.87	0.32–0.78	-	-

Physiological and psychological constraints

The way the brain reacts to the stimuli, depends on the subjects' sensory and cognitive abilities, which is reflected in the amplitude and latency of the ERPs. Musicians, for example, can generally detect, and react to, smaller details in auditory stimuli than a normal subject. With them, the amplitude of the ERPs is typically higher and the latency shorter [141, 142]. Elderly subjects, on the other hand, tend to produce weaker and slower responses, as their sensory abilities have declined with age [117, 134, 143]. In addition, the anatomy of the brain, handiness, gender, health, and external factors, such as medication, may cause individual differences in the responses [10, 112, 117, 119, 144, 145].

The subject's mental state and its variations also modulate the responses. Fatigue, habituation, and changes in attention may affect the amplitude and latency of the signals, and elicit brain activity unrelated to the phenomenon being studied [117, 118, 120, 135, 138, 146]. While the personal characteristics can be taken into account in the experimental design (test group selection, testing and compensation of sensory abilities, etc.), the fluctuations in the mental state are more difficult to control. They are considered to be one of the major reasons for the low measurement reliability [e.g. 117].

Body artifacts and other sources of interference

Furthermore, as ERPs are weak signals, they are easily distorted by different artifacts and other sources of interference [33, 70, 82, 117, 118, 119, 120, 121, 122, 123]. This will reduce the data quality, make the responses more difficult to detect, affect the validity of the results, and reduce the reliability of the measurements [33, 113, 117, 118, 138]. Typical forms of interference are power-line interference, amplifier noise, stimulus jitter, body artifacts, and background EEG activity. Amplifier noise and power-line interference couple with the signals and reduce the SNR, while jitter will affect the timing of the ERPs causing the averaged responses to flatten. Jitter may also elicit changes in the ERPs themselves, if the asynchrony is high [10, 131]. Body artifacts typically exceed the ERP amplitude and hide the signal of interest. Background EEG activity may also do the same (e.g., the alpha waves in an eyes closed condition) [10].

Current best practices

Currently, the best way to secure reliable recordings is to optimize the signal quality, to use proper stimuli, and to apply an efficient investigation paradigm [19, 33, 112, 147]. Proper stimulus design can optimize the quality of the responses, and high signal quality will reduce the distortion in the measurement outcome [9, 33, 117]. An efficient investigation paradigm, on the other hand, allows a large amount of data to be collected during the session. In this way, it permits efficient denoising through averaging and robust rejection of contaminated data, while not causing unnecessary stress for the subject [148]. Furthermore, providing a task for the subject may reduce the modulation of the responses resulting from changes in the attention condition [10, 146]. It may also prevent fatigue, and help the subjects to relax, which may reduce artifacts.

The application of these methods allows reduction of the issues related to the physiological and psychological constraints, and the signal quality variations. However, they will only work to a certain extent, and since the investigations are based on recording a fixed number of trials, it can not always be guaranteed that the amount of data is sufficient [31]. Longer measurements perform better, but also increase the fatigue and stress caused for the subjects [19]. As the quality of the data and the amount of artifacts can not be reliably defined in advance [31], it might be more efficient to define the number of trials to be recorded online. This would allow compensation for the variations in data quality, and optimization of the session length, without risking the sufficiency of the data.

1.4.2 Instrumentation design

A basic ERP recording system consists of an EEG amplifier, a stimulus presentation system, a data acquisition and processing system, a user interface, and measurement electrodes. In addition, extra devices, such as reaction buttons, or EOG goggles, may be added. Implementation depends on the intended use, and the available solutions vary from complex laboratory systems, to highly integrated special function devices.

Laboratory recording systems are intended for multipurpose use, and the design is typically modular and flexible. Amplifier and electrode cap interface are separate units, and the stimuli are provided either from the interface PC or by using a specific stimulation unit. The number of electrodes is typically high, and can reach up to 1024, which allows high-resolution mapping of the activity of the brain. If needed, integration of extra sensors and other devices is typically easy. Examples of such systems are e.g., Synamps (Compumedics Neuroscan, USA, neuroscan.com), QuickAmp (Brain Products, Germany, brainproducts.com), ActiveTwo (Biosemi, Netherlands, biosemi.com), and Nation7128W (Shanghai Nation Medical Equipment Co, China, cnnation.com).

Mobile recording systems are typically more compact than the laboratory systems. The design often features a wireless communication channel, a smaller channel count, and typically provides fewer options for adding external devices. It may not be as flexible as a laboratory system, but application is faster and more robust. Conventional mobile designs are simplified versions of laboratory systems. Examples of these are NuAmps (Compumedics Neuroscan, USA, neuroscan.com), ASA-lab (ANT, Netherlands, ant-neuro.com), and NeuExpert-ERP-E32 (Shinova Systems Co, China, shinova.com). More integrated solutions are also available, such SmartEP (Intelligent Hearing systems, USA, ihsys.com), and BoxEMG (Shinova Systems Co, China, shinova.com), and highly integrated special function systems, such as Cognision (Neuronetrix, USA, neuronetrix.com). Furthermore, a number of portable designs have been presented for different clinical applications, such as sedation level measurement [149], and long-term monitoring [150].

Alternatively, it is possible to perform the recordings by using a mobile EEG recording unit and a separate stimulation system. Mobile EEG units typically provide a fixed, fast-to-apply electrode grid and an integrated amplifier with wireless data transmission. In addition, they typically come with data acquisition software that allows external stimulus keys to be acquired, and linked to EEG data. This kind of system can be made compact, but it also requires the user to be able to configure the system to make the application work. Examples of portable EEG systems are, e.g., BAlert X10/24 (Advanced Brain Monitoring, USA, b-alert.com), Mynd (Neurofocus, USA, neurofocus.com), Epoch (Emotiv, Australia, emotiv.com), or MindWave (Neurosky, USA, neurosky.com).

Practical usability

Regarding the practical applications, the use of the laboratory recording systems is convenient. They can easily be configured to suit the needs of the investigator, and are particularly well suited for general research purposes. In clinical use, the tests tend to be more established. Thus, rather than being highly configurable, it may be more important that the recording system is straightforward to use and fast to set up [149, 150]. Mobile recording systems are usually optimized for robust performance of the measurements. Thus, they might provide a practical and cost-efficient solution for these kinds of applications. In addition, the greater mobility makes it possible to have more flexibility in the selection of the recording site, and to perform investigations outside the laboratory premises.

The performance of modern instruments is high and they can be used to perform credible ERP measurements in an efficient fashion. However, to judge from the designs studied, there is also room for further development. Many of the current systems are not very compact, and the integrated ones are typically optimized for single types of applications. Further integration would allow better mobility and improved interference tolerance. This could also involve integration of the stimulation unit. It would reduce the complexity of the system and the load on the interface computer.

In addition, not all the systems do perform online analysis for the data recorded, but it is left for the investigator to do offline. Automated cleaning, averaging, and parameterization of the data would reduce the amount of manual work required. In addition, visualization of the accumulation of the resulting waveforms would allow the investigator to detect possible issues and preview the results during the measurement. These might allow more convenient access to ERPs, and optimize the time to reach the diagnosis.

Referencing strategy

In addition to the system design, it is also important to consider the implementation of the measurement setup. What is of particular importance is the selection of a proper referencing strategy, which ultimately defines the measurement sensitivity and the way the interference couples with the data [12, 13]. Optimally, the signal ground would be symmetric about the recording sites, and the recording reference completely silent. This would allow high common-mode interference reduction, minimal reference effect, and low signal distortion.

A customary solution is to position the ground and the recording reference to a silent site, such as either of the cheeks, nose, or either of the mastoids. None of these sites are symmetric, but the low activity at these sites helps keep the referential noise low. Linked-ears, or linked-mastoids references, may also be used. They provide a more symmetric coupling, but are sensitive to the imbalance between the channels [151, 152]. In addition, building a low-impedance path between distant scalp locations, involves a risk of distorting the scalp potential distribution [153]. The third common option is to choose the sites at the centre of the recording montage. This may provide better common-mode interference rejection, but typically increases the level of reference noise.

Currently, the best option probably is to use any proper recording strategy, and re-reference the data to the common average reference. Common average reference is computed by calculating the average signal over all the recording channels. If the coverage of the scalp surface is complete enough, it will produce an accurate estimation of the scalp surface integral (i.e., the null potential of the head) [10, 151, 154, 155, 156, 157, 158, 159]. Thus, the re-referencing will remove the common-mode interference from the data. On the other hand, the use of this method is not recommended for small recording setups [151]. In such cases, it may be better to use a physical common average ground arrangement, formed by tying the amplifier inputs together with an averaging resistor network [160, 161]. As the signals to-be-averaged are unamplified, the possible imbalance is smaller, and the average computed is a better representation of the common-mode signal at the recording sites.

While it may not be a perfect reconstruction of the scalp surface integral, in small setups [151] it is probably more symmetric about the recording sites than any single site on the scalp surface. On the downside, the circuit implementation loads the amplifier inputs increasing the voltage divider effect, and magnifies the common-mode voltage formed between the subject and the amplifier ground. These will have to be taken into account, and they may limit the feasibility in some applications. However, if the electrical isolation of the amplifier is high, it may be possible to fit the circuit in such way that measurements with wet electrodes would become feasible. According to current recording standards, this would require tolerating contact impedances of at least 5kΩs [10].

2 Purpose of the study

This study has the following aims:

1. To design and realize a method for reducing quality variation in averaged ERP recordings.

Variation in the quality of the recorded data affects the outcome of ERP measurements, and the measurement reliability [33, 117]. Extended recordings cope better [132, 139], but also cause more fatigue and stress for the subject. The variations could be tolerated better if the amount of data recorded were not fixed, but adjusted according to the prevailing signal quality. This would also optimize the session length, which could make the investigation more efficient and less inconvenient. This kind of approach has provided promising results in auditory brainstem response (ABR) measurements [162, 163, 164, 165, 166, 167]. Both the efficiency and the diagnostic value of the investigations were improved [166, 168]. Its implementation for ERP measurements would require consideration of the special characteristics of the signals.

2. To design and realize a prototype of a compact, mobile ERP measurement system with an in-built stimulation unit, that allows robust, high-quality ERP measurements, and online data analysis.

The measurement electronics and stimulation system are integrated into a compact head box with a wireless computer interface. Data processing is automated, and the system is made to provide the user with information on the progress of the measurement. This kind of design should allow robust performance of the measurements in applications where the target activity is well-defined. In addition, the integration of the stimulation system releases resources from the interface computer, and simplifies the system construction.

Furthermore, to improve the electromagnetic compatibility, and to reduce signal distortion, grounding is performed by using a common average ground arrangement, based on [160, 161]. It is sensitive to the contact impedance variations., but should provide a symmetric ground signal in normal conditions, if only the electrical isolation of the amplifier is good, and the network impedance is fitted properly. When finished, the system prototype is used to study the use of the quality control algorithm, *in vivo*.

3. To demonstrate the use of the new approach to recording ERPs and to investigate the impact of the reduced quality variation on the measurement test-retest reliability.

The variability of the quality of the data affects the measurement repeatability in ERP investigations. A part of this is due to the natural variation in the physiological signals, but the variation of the measurement error has also been found significant [e.g., 33, 70, 117, 118, 119, 120, 121, 122, 123]. However, to the best of our knowledge, results from systematic investigations presenting this effect have not been reported, and the extent to which the error level is relevant has not been properly evaluated. Thus, a measurement series is performed to study this effect *in vivo*. In addition, it is expected to provide new information on the application of the quality control algorithm developed.

The testing is done by performing measurements with auditory the mismatch negativity (MMN) component of the ERP waveform. The repeatability analyses are performed for the amplitude, mean amplitude, and latency of the waveform component. MMN was chosen as an example as it is a widely used ERP component the detection of which is known to be distorted as a result of the variation in the data quality [33, 117, 138]. Thus, for the particular waveform component, a successful method could allow greater measurement reliability and improve clinical feasibility [114, 121]. In addition, MMN and other ERP components share the same basic characteristics, thus allowing the results to be generalized. Finally, the selection was also supported by the cooperators' long experience of working with MMN.

3 Materials and methods

3.1 Structure of the study

The study was conducted in three parts. First, a prototype of the recording system and the quality control algorithm were designed and realized, and their technical performance was tested by performing simulations and offline measurements. Investigation of the use of the common average ground arrangement was conducted as a part of the hardware development process. Then, how they performed in practice was studied and a small measurement series was performed with volunteer test subjects to demonstrate the application *in vivo*. The last part dealt with the estimation of the impact of the methods, and a larger series of repeated measurements was performed to investigate their influence on the quality of the results and the test-retest reliability.

The design of the recording system (Chapter 3.2, Fig. 2A) is presented in publications [P1] and [P3]. Publication [P1] dealt specifically with the implementation of the common average ground arrangement, and publication [P3] with the whole recording system design. The design of the quality control algorithm (Chapter 3.3, Fig. 2B) is presented in publication [P2].

Methods used to study the feasibility of the common ground arrangement in the present setup (Chapter 3.4.1), and the respective results (Chapter 4.1) are presented in publication [P1]. Test arrangements for the evaluation tests and demonstration measurement series (Chapters 3.4.2, and 3.4.3) and the respective results (Chapters 4.2, and 4.3) are presented in publications [P2] and [P3]. The arrangements (Chapter 3.4.4) and results (Chapter 4.4) of the impact study are presented in publication [P4].

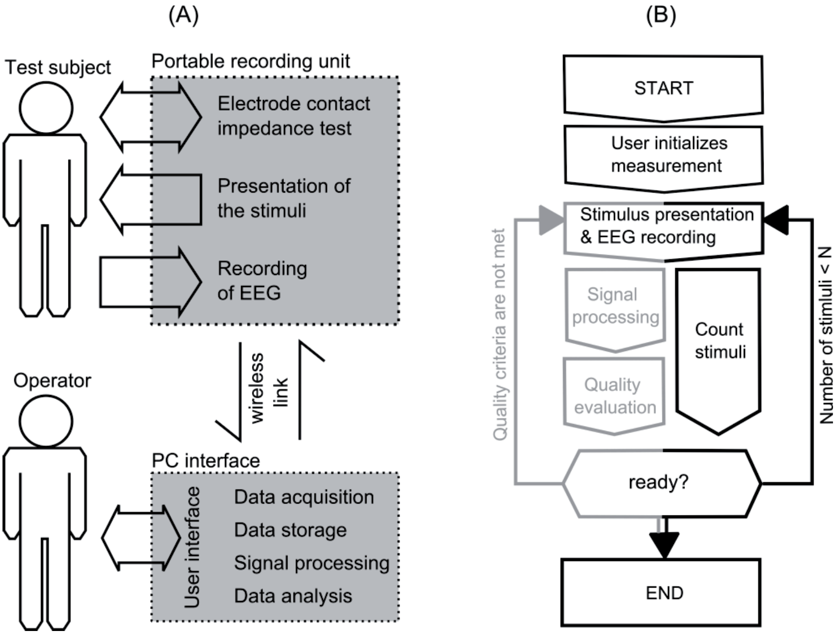


Fig. **2**. Concept design of the prototype recording system (A) and the adaptive recording procedure (B) realized in this study. In (B), the conventional work flow is presented in black and the phases that were changed in gray.

3.2 Development of the recording system

3.2.1 Design requirements

The reference for the development of the new design was taken from the commercial measurement systems currently in use in general research applications. In comparison to that, the basic functionality and the functional block design were kept unchanged, but the system construction and implementation were reconsidered to promote practicality and easy access to ERPs. [P3]

First, to make the operation of the recording system efficient and convenient, it was specified that the system should be compact and its construction simple, so that it would be fast to set up and easy to use. Thus, the functional blocks directly related to the measurement procedure (stimulation system, measurement amplifier, and data conversion block) should be integrated into a single recording unit. Data acquisition and signal processing should be performed by using a PC with a user interface.

Furthermore, the number of electrode channels was defined to be small and only eight electrodes were used in the design. The use of such a small array would require careful design of the recording setup. However, it was considered to be enough for the target applications, where the appearance of the target activity would be quite predictable. The benefits of using such a small setup were shortened preparation time and improved CMRR. It also reduced the amount of data collected during the session, making the processing of the results faster.

Second, to reduce the coupling of external interference and to further simplify the design, it was specified that the device should be made battery-powered and the amount of external wiring minimal. In addition, it should be made wearable. This would reduce the common-mode voltage level and also the need for active electrodes, because the electrode wires could be made short (~20 cm).

The technical requirements were a high signal quality, a reasonable operating time, and the capability to perform stimulus presentation with sufficient accuracy. Furthermore, the system should be capable of performing online signal analysis. Detailed specifications are presented in Table 3.

Table 3. Technical specifications for the recording system prototype.

#	**Parameter**	**Criteria**
1	Noise level [μVrms]	< 0.5
2	Measurement resolution [nV]	< 100
3	Sample rate [Hz/channel]	≥ 200
4	Stimulus jitter (s.d.) [ms]	< 2.5
5	Operating time [min]	≥ 60

Meeting these criteria was expected to enable high quality recording of common ERPs, such as N100, MMN, and P300. The stimulus jitter criterion was defined in terms of the sampling rate, and better performance would reduce the risk of causing changes to the physiological responses.

3.2.2 Implementation

Following the specifications, the implementation consisted of two parts: a measurement unit (Fig. **3**) and a PC interface (Fig. **4**). The measurement unit performed the measurement tasks and handled the collection of the data, which were transmitted to the PC interface for processing. The PC interface acquired the data, performed processing and data storage, and also provided a wireless user interface. Communication took place through a Bluetooth connection (WT12, Bluegiga Technologies Oy, Finland).

Measurement unit

The compact, wearable, battery-powered recording unit included all of the measurement electronics. It performed three functions: stimulus presentation, recording of the EEG, and testing of contact impedance.

Control of the operations was performed by using a µC MCU (Atmega2560, Atmel Corp., USA).

Generation of the stimuli was performed by using a specific decoder IC (VS1011e, VLSI Solutions Oy, Finland). The sounds were stored on a separate memory card (MMC) in a wave sound file format, and the MCU used the decoder to load and play them according to the investigation paradigm. As the presentation was controlled directly by the embedded processor, this setup was expected to allow accurate timing of the stimuli. The MCU could perform at the same accuracy with the crystal oscillator, but the jitter could increase if there would be variation in the play-to-sound delay of the encoder IC.

EEG recording was performed by using an 8-channel amplifier with Ag/AgCl electrodes and a high-resolution A/D converter (LTC2449, Linear Technology Corp., USA). The nominal gain was 60 dB, the passband 0.16 – 70 Hz, and the dynamic range 2.5 Vdc ± 250 mVac. Digitalization (24 bits, Vref = ±2.5 V) was performed at a 200-Hz sample rate per channel. Grounding was performed by using a common average ground arrangement, where the ground electrode was replaced by a 2-MΩ resistor network. It was sensitive to the selection of the value of the network resistance, but also expected to improve the symmetry of the recording setup, and the integrity of the data that were obtained [P1]. According to the simulations made, it could tolerate contact impedances up to 20kΩ [P1], which was enough for measurements performed with wet electrodes [10].

Contact impedance testing was performed by feeding a test signal to the test electrode site while measuring the attenuation from the measurement channels. The test signal was a 300-mV_{rms}, 23.2-Hz sine wave which was generated by using the PWM output of the MCU, and a low pass filter. The test electrode was placed on the left cheek and the signal was fed to it through a 2-MΩ serial resistor. The resistor was added to secure the balance of the average ground-referenced setup and to make the test electrode appear as normal electrode input [P3].

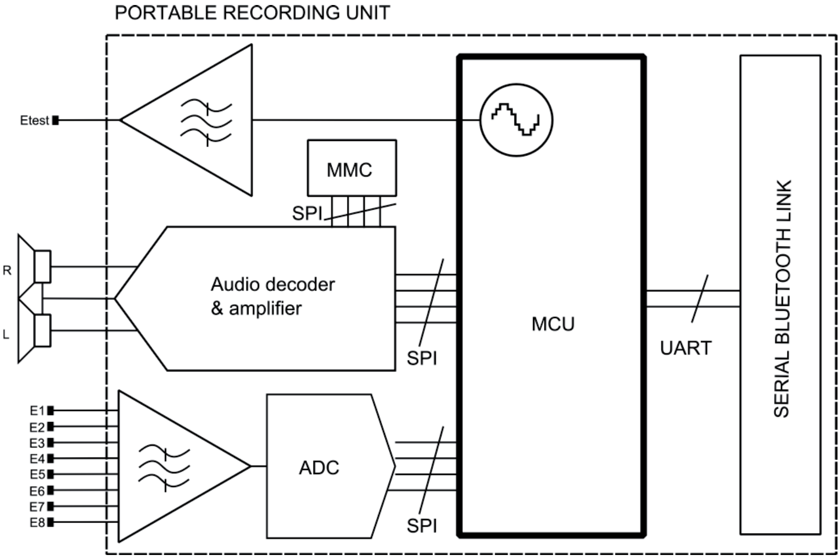
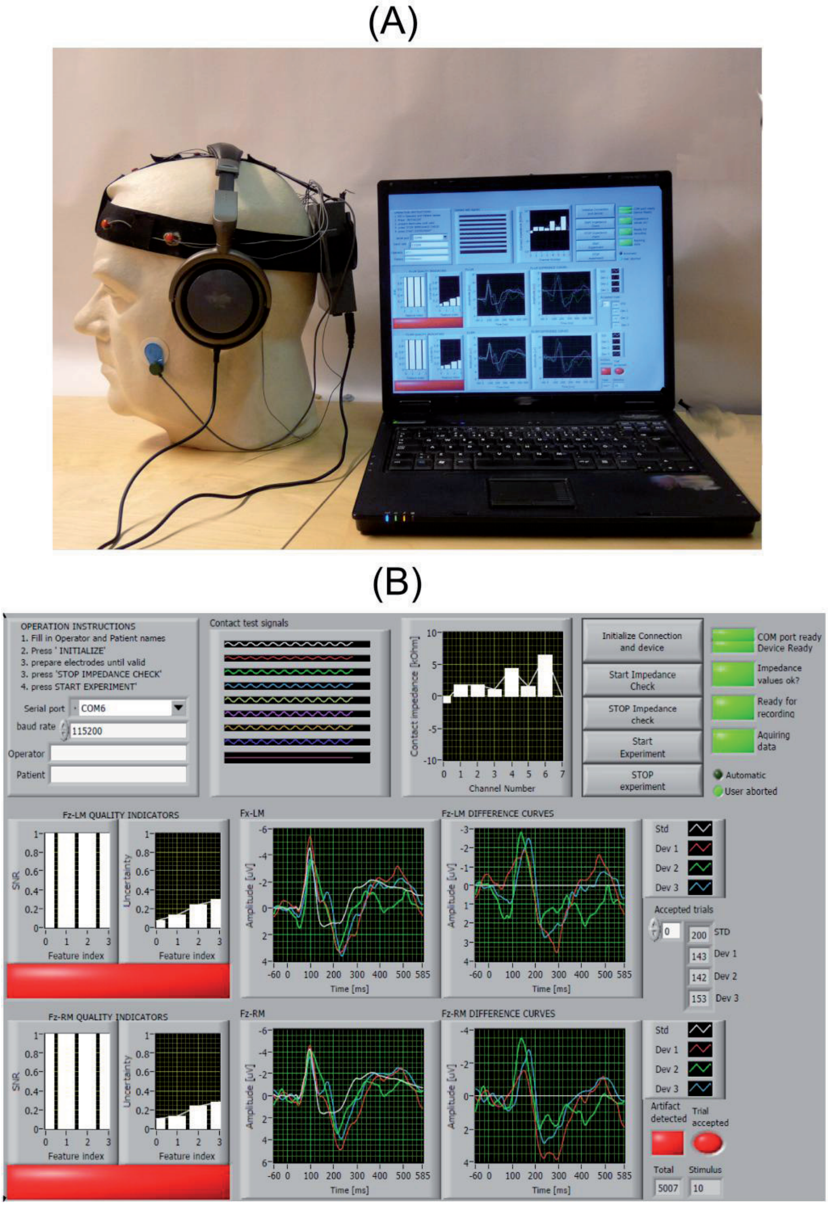


Fig. **3**. Block diagram of the prototype of the portable recording unit developed in this study. Stimulus presentation was performed by using a specific audio decoder chip (VS1011e, VLSI Solutions, Finland) and the EEG recorded by using an amplifier and a high-resolution A/D converter (LTC2114, Linear Technology Corp., USA). The system was controlled by an 8-bit µC MCU (AT2560, Atmel Corp., USA), which also generated the PWM sine signal applied for the electrode contact check. The wireless communication with the PC interface was made through Bluetooth by using a serial Bluetooth link module (WT12, Bluegiga Oy, Finland).

PC interface

The PC interface was implemented on a regular laptop PC with a graphical programming language (Labview® 8.2, National Instruments Corp., USA). It performed the processing and the storing of the data. In addition, it provided the user with the controls for selecting the measurement functions and run-time displays that showed the progress of the experiment. In the contact impedance check mode, the signals obtained from each channel were lowpass filtered, and the amplitude (RMS) of the test signal was used to estimate the attenuation of the test signal and the contact impedances. The results were presented in a bar plot where the user could observe the inter-channel differences. In the recording mode, the data were first cleaned of artifacts and averaged to prepare them for the analysis. Then, after the addition of a new trial, the quality of the updated average was evaluated to estimate the concurrent level of uncertainty and the maturity of the results. The analysis results were presented in graphs in which the operator could follow the accumulation of the averages and the estimated quality parameters online.



OPERATION INSTRUCTIONS
1. Fill in Operator and Patient names
2. Press ' INITIALIZE'
3. prepare electrodes until valid
3. press 'STOP IMPEDANCE CHECK'
4. press START EXPERIMENT'

Serial port COM6
baud rate 115200
Operator
Patient

Accepted trials 0
200 STD
143 Dev 1
142 Dev 2
153 Dev 3

Total 5007
Stimulus 10

Fig. 4. (A) An example test setup for the application of the recording system that was developed. The recording electrodes and the portable recording unit were attached to a custom electrode cap made of spring fabric. Separate electrodes were used for the contact impedance test electrode and the mastoids. Stimuli were presented through stereo headphones. (B) A screenshot of the wireless user interface captured during an ongoing experiment. The accumulation of the average responses could be monitored from the displays, and the quality parameters estimated were presented in bar plots on the left. When the quality parameters met the predefined criteria, the LED indicators turned green and the experiment stopped automatically. Reprinted with permission from [P3]. Copyright 2010, American Institute of Physics.

3.3 Development of the quality control algorithm

3.3.1 Design requirements

The algorithm was based on performing two basic tasks. First, the accumulation of the average responses was monitored and the respective error level estimated to indicate the quality. Then, the estimate that had been computed was compared to a predefined threshold criterion, and the experiment was automatically concluded only when the quality was high enough. To implement the tasks, a method had to be chosen for producing the estimate and tests performed to define feasible threshold criteria for practical use. In addition, an online data cleaning procedure was needed in order to able to reduce the influence of artifacts and to improve the stability and efficiency of the algorithm.

To be able to produce a proper error estimate, the computation method had to be defined in a way that was concurrent with the responses being studied. Neither the level of interference nor the signal strength could be assumed to be either temporally stationary or spatially uniform. Therefore, it required consideration of both the temporal and spatial characteristics of the signal [70, 169]. In addition, the ERP quantification method had to be taken into account to conform to the different behaviors of the different parameters (peak amplitude, mean amplitude, and peak latency) under interference.

To be able to define proper test criteria, the effect of the error on the validity of the results had to be quantified. As the actual underlying response was unknown, it could not be computed directly, but had to be done by studying the impact on the measurement repeatability. This gave an indication of the validity [129], and allowed the determination of the criteria that would have to be met to ensure sufficient quality for the results.

In addition, the feasibility also had to be considered, which required investigation of the influence on the required number of trials. In typical settings, the recording time was not supposed to exceed one hour and the data rejection ratio was expected to vary between 10 and 50%. Thus, depending on the stimulus presentation rate and the number of different stimulus types, obtaining 200–600 good trials was considered to be feasible.

3.3.2 Implementation

Artifact rejection

In the investigations presented in publications [P2] and [P4], the artifact rejection was performed on the basis of a single threshold predefined for the data, but in the demonstration study [P3] a specific algorithm was applied. In short, it was based on testing the presence of the typical artifacts from specific scalp locations by comparing the signal magnitudes to partly adaptive threshold criteria. Blinks were detected from the frontal electrodes Fp1 and Fp2 (re-reference to the mean of the mastoids) and eye saccades from the differential signal between F7 and F8. Bites were detected on the basis of the increased variance of the signals at the mastoids (M1, and M2) and the possible yawns from the mean of Fp1 and Fp2 (re-referenced to the mean of the mastoids). A more detailed description is given in the Master's Thesis of A. Kurttio [170], which was supervised as a part of the present study.

Quality analysis

After the artifact rejection had been performed, the accepted trials were analyzed to estimate the concurrent quality and averaged to prepare them for further parameterization. The quality estimation was based on calculating the SNR and the remaining measurement error. The SNR indicated when the signal could be detected from the noise, while the measurement error was used as a measure of the stability of the results.

The SNR was computed from the difference between two successive responses (cf. [31]), and linked to the one-sample t-test in order to be able to define criteria for the test. On the basis of the simulations that were made [P2], an SNR of 0.69 (linear scale) corresponded approximately to the significance criterion of the t-test ($p<0.05$). Thus, it was chosen as the threshold used in the practical applications.

The measurement error was estimated by calculating the difference between the odd and the even epochs included into the sum (c.f. [162]). It was linked to the test-retest reliability in order for it to be possible to use it as an estimator for the validity of the response. Other alternatives were also considered (e.g., pair-vice difference, correlation coefficient, etc.), but this method was chosen for its good computational efficiency and robustness [P2].

From the odd and the even averages, the error estimate was produced by computing their mean difference in a time window of +100 ms to +200 ms (from the stimulus onset). Alternatively, it could also have been produced by computing the point-vice difference of the averages at the MMN peak latency, or by determining the maximum difference at the time interval. However, the point-vice estimator would have been hard to define reliably as a result of the difficulty of locating the peak when the SNR is low. It would also have only been valid for the peak parameter. The maximum difference was considered to be a proper estimator for the maximum error. It would have been usable for indicating the quality of the data in general, but also prone to overestimating the error.

As an exception from the procedure described above, the quantification of the error was performed differently during the concept evaluation phase [P2, P3]. There, the time window covered the whole trial and the magnitude was quantified on the basis of the peak maximum at that interval. This was considered to be appropriate for the inspections performed there, but also very general, and later it was modified to make it more specific to MMN.

3.4 Tests

3.4.1 Fitting of the common average ground circuit

To study the feasibility of the common average ground arrangement, simulations were performed with a simple 3-concentric spheres head model [12]. The effect on the symmetricity of the setup was studied, and the performance compared to two alternative grounding arrangements. In the first alternative, the ground site located near to the recording sites. In the second, it was set to a maximally distant site. Furthermore, the fitting of the network resistance was studied in terms of the interferences, system isolation, and electrode contact impedances.

3.4.2 Technical performance

To verify the proper operation of the recording system that was developed, the prototype was tested with respect to the requirements that had been defined. The tests included verification of the characteristics of the recording system (gain per channel, noise level, and dynamic area), the operating time (power consumption versus battery capacity), and the accuracy of the stimulation system (inter-stimulus interval jitter).

The quality control algorithm was evaluated by performing simulations which demonstrated the effect on the measurement repeatability and feasibility. The simulations were made by using stored data originally used in [171]. From those data, the largest dataset (the responses to the standard tone) was chosen and used to create small datasets (N=600, random samples). These data were treated as if they had been obtained separately and used to simulate repetitive measurements. This approach was considered to be useful because the variability of the underlying responses was minimal in the simulated data. In effect, the repeatability was mainly affected by the variation in average signal quality over simulated sessions, and the effect of the quality control could be clearly expressed.

From the results obtained, it was first determined how the SNR and statistical significance correlated and how large an SNR would guarantee the significance of the response. Then, a study was performed of how the measurement error affected the measurement repeatability, and how the choice of the criterion affected the measurement feasibility.

3.4.3 Practical feasibility

To test the practical performance and to investigate the limitations of the technique, a pilot measurement series was performed with three healthy volunteers. They each attended a 1-hour recording session, during which they sat on a chair watching a silent movie with subtitles while being presented with different auditory stimuli.

The stimuli used in the experiment were presented by using an Oddball paradigm where every fifth sound (p=0.2) was a deviant tone followed by four standard tones (p=0.8). The standard stimulus was a 75-ms, 523-Hz, sinusoidal tone with two harmonics (1046 and 1569 Hz). It was presented at 40 dB above the individual hearing threshold. The deviants were different with respect to the frequency (Freq, 573 Hz), duration (Dur, 25 ms), and temporal composition (Gap, 5 ms silent period in the middle of the tone). The stimulus onset asynchrony (SOA) was 1014 ms.

The purpose of the experiment was to demonstrate the use of the system that had been built and the algorithm. Thus, the classic Oddball paradigm was chosen to avoid complications related to the paradigm. For the same reason, the deviants were also rather conservative, and their characteristics chosen so that detection would not produce complications. [171] was used as a design reference.

Further on, both the presentation of the stimuli and the EEG recording were performed by using the prototype system. The EEG was acquired from eight channels (F7, Fp1, Cz, Fz, Fp2, F8, and the mastoids), and ERPs to the different stimulus types were extracted from the data to determine MMN. Furthermore, the PC interface was also occupied and the quality analysis performed online. The adaptive artifact rejection method [170] was used to clean the data, which were then averaged and evaluated by using the quality control algorithm that had been developed.

As a change from the original idea, the conclusive error criterion was not applied online, but after the series had been performed, a commonly reached error threshold criterion was determined and the corresponding responses were extracted from the data. This indirect approach had to be taken as there was no prior knowledge of the feasible error levels. This was not considered to influence the results of the feasibility test, as there was no difference in the way the quality was estimated.

3.4.4 Test-retest reliability

On the basis of earlier studies [e.g., 33, 117], it was known that a smaller error would yield higher repeatability, but the limit to where the effect would be relevant had not been determined. To gain further information on the subject, a series of repeated recordings was performed to determine the effect of the measurement error on the test-retest reliability in repeated ERP recordings. The results were also expected to help determine a proper criterion for the measurement error test. This had been found to be difficult in the experiments that had been performed earlier [P2, P3].

The measurements were performed with 13 healthy volunteers who all attended five repeated 1-hour recording sessions. During the sessions, they sat on a chair watching a silent movie with subtitles, and they were presented with auditory stimuli while the EEG was recorded from eight channels (F7, Fp1, Cz, Fz, Fp2, F8, and the mastoids). To reduce the variation in the subjects' mental state, the sessions were scheduled at the same time of day. Vigilance was tested and documented prior to each session by asking the subjects to fill in a short query.

The stimuli were presented by using a multi-feature paradigm where every standard tone ($p=0.5$) was followed by a deviant one ($p=0.2$). The standard stimulus (Std) was a harmonic 75-ms, 523-Hz sinusoidal tone with two harmonics (1046 Hz and 1569 Hz). It was presented at 40 dB above the individual hearing threshold. The deviants had a different frequency (Freq, low: 450/609 Hz), location (Loc, ±90°), intensity (Int, ±10 dB), duration (Dur, −48 ms), and temporal composition (Gap, 5-ms silent period in the middle of the tone). The location deviant was produced by introducing a 700-µs inter-aural difference between the left and right audio channels. SOA was 500ms. A multi-feature paradigm was chosen to optimize the amount of data recorded. Stimuli were chosen to be such that the amplitude of the signal would be optimized. [112] and [171] were used as design references.

From the data obtained, ERPs to different stimulus types were first analyzed to extract the MMN waveform in the different stimulus conditions and the respective measurement error as a function of N. Then the measurement error and the MMN variability were studied together, and the effect of the error on the repeatability of the waveform components (peak amplitude, peak latency, and mean amplitude) was determined. Quantification of the error was performed by computing the mean deviation of the (+/-) average in the time window of 100 to 200ms, which is typical for MMN [83, 112], and the data extracted from a single channel where the SNR was generally found to be the highest (Fz).

4 Results

4.1 Fitting of the common average ground circuit

The choice of the ground arrangement was found to influence the symmetricity of the measurement setup (Fig. 5). When the ground electrode located near to the recording sites, the lead field was largely different for the close-by sites and the distant sites. This effect was reduced when the ground was located farther away, but the resulting field was still not symmetric. The lead field was the least disturbed, when the common average ground arrangement was used. Neither was this a perfect reconstruction of the scalp surface integral, but the electrical symmetricity allowed the common-mode interference to be efficiently reduced.

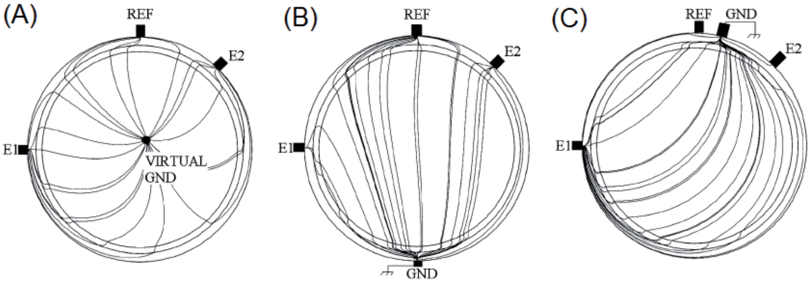


Fig. 5. Simulated lead field in arrangements where (A) common ground, (B) physical distant ground, or (C) physical near-by ground, is used. Reprinted with kind permission from Springer Science+Business Media: [P1], figure 2. © International Federation for Medical and Biological Engineering 2008.

In comparison to applying a physical ground electrode, the implementation of the common average ground arrangement was found to be more challenging. The resistance network caused load on the amplifier front-end, and increased the impedance between subject's body and amplifier ground. In effect, the contact impedance tolerance was decreased, and the common-mode voltage increased. To cope with this, the amplifier isolation had to be made high, and the network resistance optimized. On the basis of the calculations performed, a value of 2MΩ was found to be a reasonably good compromise for small montages. In a well-isolated setup, it would tolerate contact impedances up 20kΩ, which would be adequate for measurements with wet electrodes [10].

4.2 Technical performance

Regarding the recording system, the performance tests were successful, except for the noise level, which slightly exceeded the specifications. That, however, was not considered to be a problem and the technical performance was considered to be acceptable. The results from the tests are summarized in Table 4.

Table 4. Technical performance of the prototype.

#	Parameter	Test result	Specification
1	Gain per channel [dB]	60.6 ± 0.13	< ± 0.42
2	Dynamic range ($V_{ac} \pm V_{dc}$) [mV]	2.3 ± 250	> 1 ± 150
3	Noise level@ 0.16-70 Hz [μVrms]	0.64 ± 0.08	< 0.5
4	Stimulus jitter (s.d.) [ms]	0.4 ± 0.1	< 2.5
5	Power consumption [mW]	730-1100	< 1470

Regarding the control method, the test gave a positive indication of the usefulness of the technique. With respect to SNR, the magnitude of 0.69 (linear scale) was found to match the statistical significance criterion ($t<0.05$) [P2]. The measurement error never went very low, and an error of 1–2 μV was found to be the lowest feasible value (Fig. **6**). There, the respective repeatability was about 0.6. Further improvement would have required a more dedicated artifact rejection mechanism.

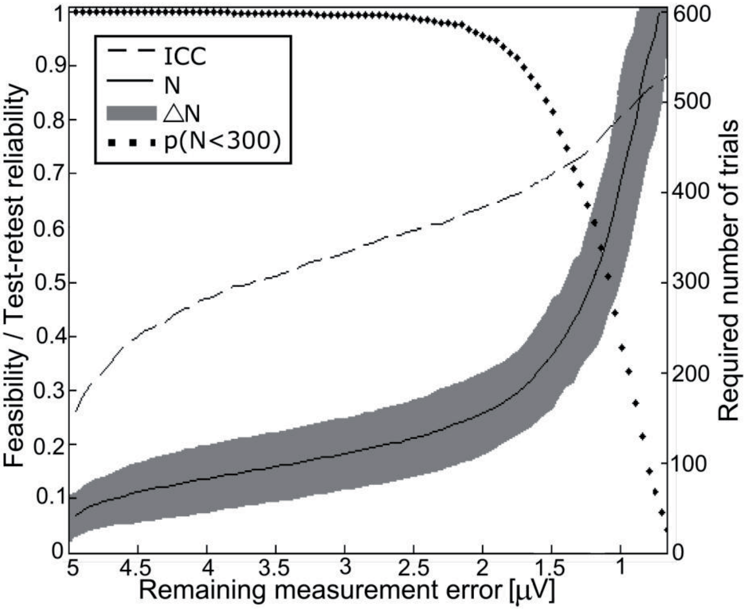


Fig. **6**. Results from the simulations conducted with the first version of the online evaluation algorithm presented in publication [P2]. Test-retest reliability (ICC) increases with a decreasing measurement error. However, it also affects the feasibility (p[N<300]) of the test because the number of epochs (N) required is increased. Reprinted with permission from [P2]. Copyright 2010, Paukkunen, Leminen, and Sepponen.

4.3 Practical feasibility

As a whole, the demonstration measurement results were promising and clear responses were obtained from all the test subjects. Representative results from one test subject are presented in Fig. 7.

With respect to the recording system, the tests showed that the design was feasible and could be used to conduct credible ERP recordings. The construction of the system was simplified, which made the installation easy, and the preparation of the test subject was also fast since the number of electrodes was small. At first, the weight of the head box was experienced as being too heavy and the test subjects felt pressure on the back of their head as a result of the tight headband. This, however, could be fixed by adjusting the attachment and adding padding. Furthermore, the integrated impedance check option was also found to be useful when verifying the balance of the electrode contacts. However, a specific contact impedance meter was still used because it saved the batteries. The use of the common ground arrangement was not found to cause any issues.

With respect to the analysis method, the specified tasks could be performed successfully and the quality of the data could be monitored online. However, the original intention was to also perform the testing of the criteria online (the maximum recording time would have been 1 hour), but it could not be done. The definition of the criterion for the measurement error test proved to be problematic without knowledge of the feasibility issues in practice, and, thus, the final comparison had to be left out of the online analysis cycle. Consequentially, all the recordings were made 1 hour long, and the demonstrative waveforms were reconstructed from the data only after the feasible criterion for the error test had been found.

On the other hand, as the data were kept untouched, the reconstructed results did not differ from what would have been obtained if the comparison had also been made online. Thus, the demonstration measurements still served their purpose, and the method was also proven to be feasible. Further investigations would still be needed to find out how the error criterion should generally be defined.

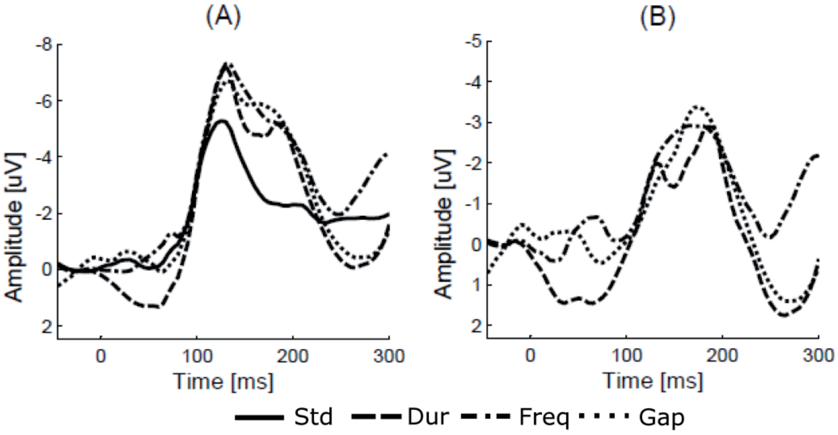


Fig. 7. Representative results from the demonstration measurements made with the prototype recording system. (A) Average responses to the standard tone (Std), duration deviant (Dur), frequency deviant (Freq), and gap deviant (Gap). (B) Difference in the responses to the deviants and the standard stimuli. MMN is the negative peak appearing in the difference waveform at about 100 to 200 ms from the stimulus onset.

4.4 Test-retest reliability

In the first part of the analysis, the data were digitally filtered (0–30 Hz), compensated for voltage offset, cleaned of artifacts, and then analyzed to extract MMN and the measurement error as a function of the number of trials (N). Then, the parameters were linked and the magnitude of MMN was expressed in terms of the measurement error (e.g., Fig. **8**). These empirical models that were created were applied to assess the test-retest reliability at different error levels (Fig. **9**). The assessment was first made for each stimulus type (Freq, Loc, Int, Dur, and Gap). Then, it was repeated for the auditory discrimination profile [171], i.e., the pattern formed of the responses to different stimulus types.

The results from the analysis showed that the contribution of the error was relevant, regardless of the stimulus type, the investigation method, and the parameterization. It was particularly clear when the error was moderate (2-3 µV), and it was estimated to be relevant at least until it went below 9–17% of the magnitude of the MMN peak amplitude. The data did not allow direct assessment of the level where the error became insignificant, but the threshold was estimated by extrapolation.

Furthermore, the parameters that were studied also had an effect on the repeatability. In comparison to the MMN peak latency, the amplitude parameters were slightly less affected when the error was high (>2–3µV). At small error levels, on the other hand, the repeatability of the peak latency was better as a result of the higher SNR. In addition, the repeatability of the auditory discrimination profile was found to be better than the repeatability of the single deviant responses.

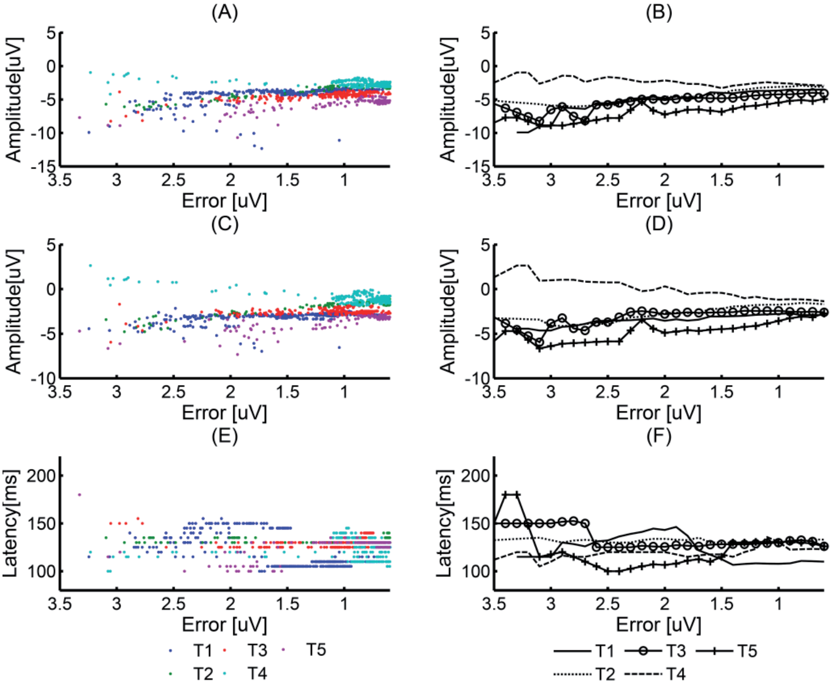


Fig. **8**. An example of the model created of the progression of MMN as a function of the measurement error (subject 11, responses to the frequency deviant tone), across test sessions (T1–T5). The original data representing the progression of the MMN peak amplitude, peak latency, and mean amplitude are presented in Figures A, C, and E. The model created on the basis of these data is presented in Figures B, D, and F. Reprinted from [P4], with permission from Elsevier. Copyright 2011 International Federation of Clinical Neurophysiology.

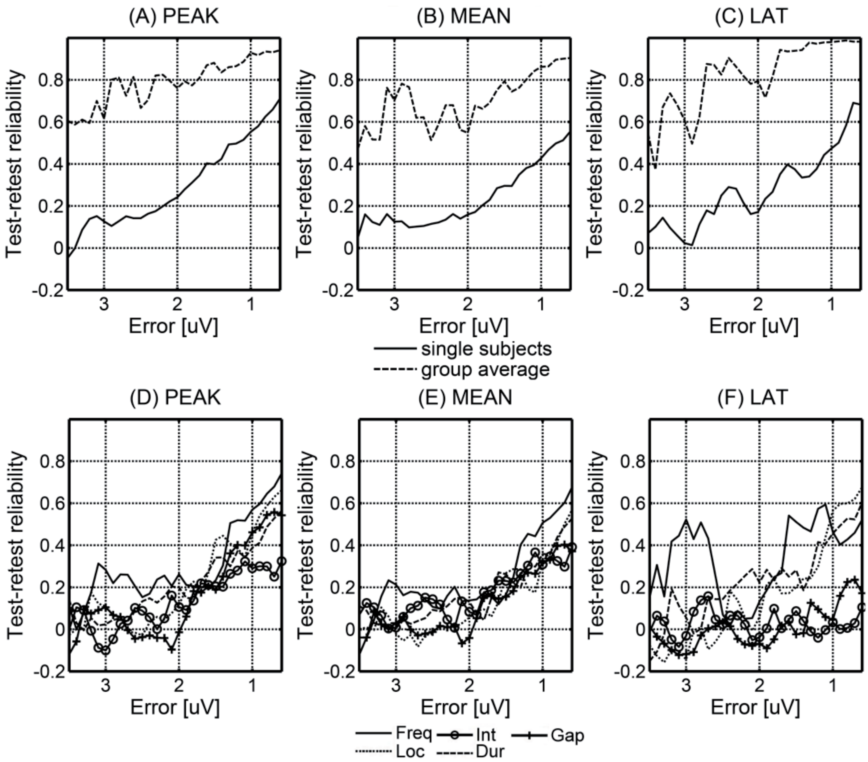


Fig. **9**. The effect of the measurement error on the test-retest reliability of MMN. The effect on the auditory discrimination for peak amplitude, mean amplitude, and peak latency is presented in Figures (A) – (C), respectively. The effect on the single deviant types is presented in Figures (D) – (F), respectively. Reprinted from [P4], with permission from Elsevier. Copyright 2011 International Federation of Clinical Neurophysiology.

5 Discussion

The overall aim of the current thesis was to develop methods to improve the performance of ERP measurements, increase the quality of the recordings, and to reduce the stress caused for the subjects. To achieve this, changes were made to the conventional recording system design and the recording procedure. In addition, the use of a common ground reference in small montages was studied in order to further enhance the electromagnetic compatibility and eliminate some of the interfering signals.

5.1 Design of the mobile recording system

The basic functionality of the system was kept conventional, but the system construction and hierarchy were optimized for applications where the measurement arrangements and the target activity would be well defined. The new design consisted of two parts. The measurement unit handled the stimulus presentation, EEG recording, electrode contact impedance checking, and wireless data transmission. It was packed into a compact (96x128x32 mm^3), light weight (374 g), battery-operated head box. The PC interface performed the data processing and provided a wireless user interface. The number of recording channels was eight and the electrical ground reference was implemented with a 2-MΩ resistor network connected to the amplifier input.

The design allowed the recording of high-quality AERP data, while providing the advantage of good mobility and easy, fast application. According to the technical tests, the noise level slightly exceeded the requirements (about 0.1 µVrms @ 0.16-70 Hz), but it could be improved by different component selections. In addition, even though the specifications were met, the power consumption was relatively high (730–1100 mW), because of the wireless communication channel, and the onboard audio amplifier. If necessary, this could be reduced by 20–30%, by reducing wireless communication and performing a larger part of the data analysis in the MCU. The channel count was small, and, therefore, fast to apply. It would be inadequate for source mapping applications, but was considered to be enough for investigating the most common responses, such as N100, P300, N400, P600, and MMN.

As the presentation of the stimuli was performed under the control of the embedded processor, the stimulus jitter was small (<1 ms), and the use of the computer resources efficient. Maintaining synchrony is typically not a big problem in modern recording systems, but in this way it could be done without using any specific software, or additional hardware. The resources saved were allocated to performing online data analysis. The system cleaned the data recorded online and calculated the quality parameters shown to the user. This allowed the progression of the test to be monitored, and the results to be pre-evaluated prior to the maturation of the experiment. It was convenient for the operator, as the accumulation of the results could be followed, and the experiment stopped if the data were not converging normally. In practical applications, it would help decrease the time needed to reach the diagnosis.

The interference tolerance of the system was good, as the measurement unit could be brought into close proximity to subject’s head. In addition, it was further enhanced by using a common average ground circuit [160], specifically fitted for a small montage. Even though it did not fully correspond to the true scalp surface integral [151, 155, 156, 157, 158, 159], it was still found to provide a more symmetric reference for the measurement than any physical site [P1]. Additionally, unlike linked references [152], it did not risk distorting the scalp potential distribution, as the network resistance was high. Furthermore, the reduction of the electrode count by one made the setup slightly more robust and faster to apply.

Successful implementation of the common average circuitry required proper isolation and the network resistance to be properly fitted. Too high a value would have increased the common-mode voltage, while too low value would have loaded the amplifier front-end, and attenuated the signals. In the current design, a value of 2MΩ was used. In the original study [160], values between 500kΩ and 2MΩ were suggested, but according to the results, at least the smaller values would be too low. The current setup was estimated to tolerate contact impedances up to 20kΩ, which is enough for measurements performed with wet electrodes [10]. It was not found to cause any issues in the practical measurements that were performed. Thus, the results suggest that the implementation was successful.

5.2 Comparison to the commercial systems

In diagnostic applications, the important qualities of a recording system are good mobility, fast set-up time, fast preparation, and straightforward use [149, 150]. Thus, compact size, wireless operation, simple construction, robust operation, and an intuitive user interface are important factors in a design. In addition, high isolation, short wiring, and proper reference arrangement will improve the interference tolerance of the system [22, 24, 172]. These qualities are particularly useful in measurements outside laboratory premises, but can also be useful in a clinical environment [173].

In comparison to commercial laboratory systems, such as Synamps (Compumedics Neuroscan, USA, neuroscan.com), QuickAmp (Brain Products, Germany, brainproducts.com), ActiveTwo (Biosemi, Netherlands, biosemi.com), and Nation7128W (Shanghai Nation Medical Equipment Co, China, cnnation.com), the current design had similar functionality, but lower configurability, simpler construction, and a more compact size. The laboratory systems suit all kinds of applications, but the mobility is not good. Thus, the current system is more practical particularly in field applications. In addition, it may be faster to apply, which makes the investigations more comfortable for both the investigator and the subject. This is particularly important in the investigation of children, or subjects that are otherwise restless. Number of recording channels is small in the present design, which may limit the use in some applications. It should, however, allow the measurement of the typical ERP components.

In comparison to commercial mobile systems, such as SmartEP (Intelligent Hearing systems, USA, ihsys.com), BoxEMG (Shinova Systems Co, China, shinova.com), NuAmps (Compumedics Neuroscan, USA, neuroscan.com), ASA-lab (ANT, Netherlands, ant-neuro.com), or NeuExpert-ERP-E32 (Shinova Systems Co, China, shinova.com), the construction of the current system is at least as simple, and its size more compact. In addition, very few of the commercial designs are wearable, or have the stimulus unit integrated. There are also more integrated devices available for ERP/EEG measurements, the construction of which is closer to the current design, like Cognision (Neuronetrix, USA, neuronetrix.com), BAlert X10/24 (Advanced Brain Monitoring, USA, b-alert.com), Mynd (Neurofocus, USA, neurofocus.com), Epoch (Emotiv, Australia, emotiv.com), or MindWave (Neurosky, USA, neurosky.com). However, most of these require the addition of an external stimulus system, or have a very focused application area.

Finally, the commercial designs typically make use of some physical ground arrangement. This allows high input impedance, which reduces the voltage divider effect. The present design does not allow the use of dry electrodes, which might have been useful in long-term monitoring applications [150]. On the other hand, the ground arrangement used should provide a more symmetric ground signal, which will be even better if the number of electrodes is high [P1, 151]. If the number of electrodes is high, also common average reference can also be used. However, the validity of such arrangement will depend on the amplifier channel mismatch, and the symmetricity of the measurement setup.

5.3 Design of the adaptive recording procedure

To allow the use of ERPs in practical applications, the results from the measurements need to be reliable [e.g., 114, 121]. At the moment, this is mainly achieved at group level. It has been suggested that the main reasons for this are the variation in the quality of the data, and the subject's mental state, which modulates the underlying signals [33, 70, 82, 117, 118, 119, 120, 121, 122, 123]. Changes in the subject's state can be relieved by experimental design [e.g., 10, 138, 146], but quality variations are hard to avoid unless they are compensated for in the recording procedure [e.g. 31, 33].

To allow better control of measurement data quality, the conventional recording procedure was modified by the addition of an adaptive algorithm, which helped optimize the amount of data to be recorded according to the prevailing data quality (SNR, and measurement error). A similar approach had been successfully used earlier in auditory brainstem response recordings [163, 164, 167]. The methods, however, could not be adopted directly [70, 169], but the quality estimation scheme had to be fitted for the responses studied.

The method was tested first by making simulations, and then by performing MMN measurements *in vivo*. According to the results, it allowed compensation for signal quality variations. This improved the tolerance of interference and noise, and had a positive impact on the measurement repeatability. In addition, as the conclusion of the measurement was defined in qualitative terms, the session length was optimized without risking the sufficiency of the data. This reduces the stress caused for the subject, issues related to a long investigation time, and the number of experiments that fail because of the lack of data.

These findings are in line with the earlier studies suggesting that a smaller error would yield higher repeatability [e.g., 33, 117]. A negative result would have indicated a poor choice of error estimates, or that the variation in the responses would have been very high. At the group level, the repeatability of the parameters was now converging at a level above 0.9, which suggests that the response did not vary much. Regarding clinical use of MMN, this suggests that it can be measured reliably if the measurement error can be made small enough. However, this could not be verified, as the same limit could not be reached at single-subject level.

Furthermore, the results of the study also stressed the importance of choosing the parameterization and investigation methods properly. In contrast to earlier results [e.g, 117], MMN peak amplitude was found to be the most repeatable parameter, in general. MMN peak latency became repeatable only when the error was moderate or small, because the peak could not be accurately detected before. Discrimination profile was found to be more repeatable than the single responses. This may be a result of its better tolerance of systematic changes in the amplitude of the responses. Such might occur, if the vigilance of the subject changes between sessions, for example. The use of the profile is also more robust as the diagnosis can be made by comparing the relative amplitudes of different response types. Analysis of the single response types requires some other reference, which may be difficult to produce.

The practical implementation of the method proved to be challenging. It requires careful balancing between the feasibility of the test criteria and the target quality that is required. They have to be set high enough to allow credible investigations, but not so high as not to be feasible. In the test measurements that were performed, the effect of the error was found relevant at the group level (N=13, discrimination profile) until it went below 0.7–1.3 µV. At the single-subject level, the threshold was estimated to be 0.2–0.4 µV (approximately 9–17% of the MMN peak amplitude, discrimination profile).

These criteria are stringent, particularly in single-subject studies, and hardly feasible unless the signal quality is high enough. In the investigations that were performed, the electrode contacts were carefully prepared, the artifact rejection threshold was properly defined, and the quality of the measured data was proper. Still, the lowest error level reached was about 1 µV. The results suggest that the application of the technique will benefit from the application of more efficient online signal processing, and artifact rejection. Making use of more efficient paradigms, would also improve the usability of the technique. For example, a recently published method allows the standard stimulus to be omitted in MMN studies, which almost doubles the recording rate [174].

5.4 General implications

The investigations performed in the current study were made for auditory MMN. Thus, in order for the same methods to be applied in other kinds of applications, the test specifications have to be reconsidered.

First, it has to be verified that the error estimation scheme is specific to the responses being studied. It is particularly important to consider the temporal and spatial characteristics of the responses, because they define the time frame and electrode sites where the error should be measured [70, 169]. In addition, different ERP parameters behave differently under interference [117], which should also be taken into account when choosing the estimator.

Second, the threshold criteria would have to be defined in compliance with the application. The limit for the error level depends on the application and the effect on the diagnostic sensitivity should be considered prior to making the final choice. In addition, the feasibility of the criterion has to be considered in terms of the available investigation time.

The device platform, on the other hand, converts more easily. The number of channels is already high enough for many applications and the designer is left with the task of choosing the recording sites. Changing the stimulus modality would require more work, and the 200-Hz sampling rate may also set limitations to some applications.

6 Conclusions

The changes made to the recording procedure allowed better control of the remaining measurement error. This had a significant influence on the measurement repeatability. It also helped in minimizing the session length without risking the validity of the results, which made the investigation more convenient. As the optimization can only be performed reliably online [31, 33], the present method provides a unique way of improving the performance of the ERP measurements. The estimators used were configured for MMN, but the method itself can be extended to other applications as well.

On the other hand, practical application of the method will require further investigation. The measurements that were performed showed that the repeatability would increase with smaller error, and it was estimated that it would keep improving until the error went below 10% of the response peak amplitude. Reaching this level would be a very stringent requirement. Thus, the application of efficient artifact rejection, advanced signal processing, and optimization of the paradigm will be necessary to make it feasible.

A prototype of a mobile, integrated ERP measurement system with an integrated stimulation unit was designed and realized. Its simple construction made it fast to set up and easy to use. It was tolerant of external interference because of its compact size, and close proximity to the measured target. The use of the common average ground arrangement also reinforced this. It caused load on the amplifier front-end, but was not found to affect the performance of the system. Application of dry electrodes, however, would be infeasible.

In an attempt to enable routine clinical use to be made of ERPs, the fluent performance of the measurements is very important. This kind of design would allow the robust performance of the measurements in applications where the target activity is well-defined. Together with the application of the algorithm developed, it provides easy access to ERPs, and makes the investigations efficient and comfortable. Regarding the future development, the use of the common average ground should be studied further by using a more realistic head model to gain information on the effect on measurement sensitivity. In larger setups, it can also be made more tolerant of contact impedances.

References

---

1 Nunez, PL, Srinivasan, R. Electric fields of the brain – the neurophysics of EEG. Oxford University Press. Oxford, NY, 611 p, 2006.

2 Davis, H, Davis, PA, Loomis, AL, Harvey, EN, Hobart, G. Electrical reactions of the human brain to auditory stimulation during sleep. *Journal of Neurophysiology*, 2(6), 500–514, 1939.

3 Davis, PA. Effects of acoustic stimuli on the waking human brain. *Journal of Neurophysiology*, 2(6), 494–499, 1939.

4 Galambos, R, Sheatz, GD. An electroencephalography study of classical conditioning, *American Journal of Physiology*, 203(1), 173–184, 1962.

5 Luck, SJ. *An introduction to the event-related potential technique*. MIT Press. Cambridge, MA, 388 p, 2005.

6 Woodman, GF. A brief introduction to the use of event-related potentials in studies of perception and attention. *Attention, Perception, & Psychophysics,* 72(8), 2031–2046, 2010.

7 Allison, T, Wood, CC, McCarthy, GM. *The central nervous system*. In: Coles, MGH., Donchin, E, Porges, SW (Eds.). Psychophysiology: systems, processes, and applications. Guilford Press, New York, NY, 5–25, 1986.

8 Coles, MGH, Rugg, MD. 1 *Event-related potentials: an introduction*. In: Rugg, MD, Coles, MGH. (Eds.). Electrophysiology of the mind. Oxford University Press, Oxford, NY, 1–23, 1996.

9 Kropotov, JD. *Quantitative EEG, event-related potentials and neurotherapy*. Elsevier, Burlington, MA, 542 p, 2009.

10 Picton, TW, Bentin, S, Berg, P, Donchin, E, Hillyard, SA, Johnson, R Jr, Miller, GA, Ritter, W, Ruchkin, DS, Rugg, MD, Taylor, MJ. Guidelines for using

human event-related potentials to study cognition: recording standards and publication criteria. *Psychophysiology*, 37(2), 127–152, 2000.

11 Rush, S, Driscoll, DA. EEG electrode sensitivity – an application of reciprocity. *IEEE Transactions on Biomedical Engineering*, 16(1), 15–22, 1969.

12 Malmivuo, J, Suihko, V, Eskola, H. Sensitivity distributions of EEG and MEG measurements. *IEEE Transactions on Biomedical Engineering*, 44(3), 196–208, 1997.

13 Malmivuo, J, Suihko, V, Eskola, H. Corrections to "Sensitivity Distributions of EEG and MEG measurements". *IEEE Transactions on Biomedical Engineering*, 44(5), 430, 1997.

14 Malmivuo, J, Suihko, V. Effect of skull resistivity on the spatial resolutions of EEG and MEG. *IEEE Transactions on Biomedical Engineering,* 51(7), 1276–1280, 2004.

15 Sörnmo, L, Laguna, L Chapter 4: Event-related potentials, in: Sörnmo, L, Laguna, L. *Bioelectrical signal processing in cardiac and neurological applications*. Elsevier, Burlington, MA, 181–329, 2005.

16 Metting van Rijn, AC, Peper, A, Grimbergen, CA. Amplifier for bioelectric events: a design with a minimal number of parts. *Medical & Biological Engineering & Computing*, 32(3), 305–310, 1994.

17 Prutchi, D, Norris, M. *Design and development of medical electronic instrumentation*. Wiley, Hoboken, NJ, 461 p, 2005.

18 Kandpur, RS. *Biomedical instrumentation – Technology and applications*. McGraw Hill, New York, NY, 924 p, 2005.

19 Pikvik, RT, Broughton, RJ, Coppola, R, Davidson, RJ, Fox, N, Nuwer, MR. Guidelines for the recording and quantitative analysis of electroencephalographic activity in research context. *Psychophysiology*, 30(6), 547–558, 1993.

20 Nuwer, MR, Comi, G, Emerson, R, Fuglsang-Frederiksen, A, Guérit, JM, Hinrichs, H, Ikeda, A, Luccas, FJ, Rappelsberger, P. IFCN standards for digital recording of clinical EEG. *Electroencephalography and Clinical Neurophysiology*, 106(3), 259–261, 1998.

21 Huhta, JC, Webster, JG. 60-Hz Interference in Electrocardiography. *IEEE Transactions on Biomedical Engineering*, 20(2), 91–101, 1973.

22 Fernandez, M, Pallas-Areny, R. A comprehensive model for powerline interference in biopotential measurements. *IEEE Transactions on Instrumentation and Measurement*, 49(3), 535–540, 2000.

23 Winter, BB, Webster, JG. Driven-Right-Leg Circuit Design. *IEEE Transactions on Biomedical Engineering*, 30(1), 62–66, 1983.

24 Metting vanRijn, AC, Peper, A, Grimbergen, CA. High-quality recording of bioelectric events – Part 1: Interference reduction, theory and practice. *Medical & Biological Engineering & Computing*, 28(5), 389–397, 1990.

25 Yoo, SK, Kim, NH, Kim, SH, Kim, JL. The development of high precision EEG amplifier for the computerized EEG analysis. *17th Annual Conference of the IEEE Engineering in Medicine and Biology Society*, Montreal, 2, 1651–1652, 1995.

26 Virtanen, J, Parkkonen, L, Ilmoniemi, RJ, Pekkonen, E. Biopotential amplifier for simultaneous operation with biomagnetic instruments. *Medical & Biological Engineering & Computing*, 35(4), 402–408, 1997.

27 Degen, T, Jackel H. Enhancing interference rejection of preamplified electrodes by automated gain adaption. *IEEE Transactions on Biomedical Engineering*, 51(11), 2031–2039, 2004.

28 Piipponen, KVT, Sepponen, R, Eskelinen, P. A biosignal instrumentation system using capacitive coupling for power and signal isolation. *IEEE Transactions on Biomedical Engineering*, 54(10), 1822–1828, 2007.

29 Nagel, JH. *Biopotential amplifiers*. In: Bronzino, JD (ed.). Biomedical Engineering handbook. IEEE Press, Boca Raton, FL, 1185–1195, 1995.

30 Malmivuo, J, Plonsey, R. *Chapter 13: Electroencephalography*. In: Malmivuo, J, Plonsey, R. Bioelectromagnetism - principles and applications of bioelectric and biomagnetic fields. Oxford University Press, New York, NY, 257–264, 1995.

31 Möcks, J, Gasser, T, Köhler, W. Basic statistical parameters of event-related potentials. *Journal of Psychophysiology*, 2(1), 61–70, 1988.

32 Handy, TC. *Event-related potentials: a methods handbook*. MIT Press, Cambridge, MA, 404 p, 2005.

33 Sinkkonen, J, Tervaniemi, M. Towards optimal recording and analysis of the mismatch negativity. *Audiology and Neurotology*, 5(3–4), 235–246, 2000.

34 Quiroga, RQ. Obtaining single stimulus evoked potentials with wavelet denoising. *Physica D: Nonlinear Phenomena* 145(3–4), 278–292, 2000.

35 Markazi, SA, Qazi, S, Stergioulas, LS, Ramchurn, A, Bunce, D. Wavelet filtering of the P300 component in event-related potentials. 28th *Annual International Conference of the IEEE Engineering in Medicine and Biology Society*, New York, 1, 1719–1722, 2006.

36 Markazi, SA, Stergioulas, LK, Ramchurn, A, Bunce, D. Latency Corrected Wavelet Filtering of the P300 Event-Related Potential in Young and Old Adults. 3rd *International IEEE Engineering in Medicine and Biology Society Conference on Neural Engineering*, Kohala Coast, 582–586, 2007.

37 Burger, M, Hoppe, U, Kummer P, Lohscheller J, Eysholdt U, Döllinger M. Wavelet-based analysis of MMN responses in children. *Biomedizinische Technik/Biomedical Engineering*, 52(1), 111–116, 2007.

38 Daubechies, I. *Ten Lectures on Wavelets*. Society for Industrial and Applied Mathematics, Philadelphia, PA, 357 p, 1992.

39 Burrus, CS, Gopinath, RA, Guo, H. *Introduction to wavelets and wavelet transforms: A primer*. Prentice Hall, Upper Saddle River, NJ, 268 p, 1998.

40 Quiroga QR, Sakowitz OW, Basar, E, Schürmann M. Wavelet Transform in the analysis of the frequency composition of evoked potentials. *Brain Research Protocols*, 8(1), 16–24, 2001.

41 Wiltschko, AB, Gage, GJ, Berke, JD. Wavelet Filtering before Spike Detection Preserves Waveform Shape and Enhances Single-Unit Discrimination. *Journal of Neuroscience Methods*, 173(1), 34–40, 2008.

42 Effern, A, Lehnertz K, Fernandez G, Grunwald, T, David, P, Elger, CE. Single trial analysis of event related potentials: non-linear de-noising with wavelets. *Clinical Neurophysiology*, 111(12), 2255–2263, 2000.

43 Quiroga, RQ, Garcia, H. Single-trial event-related potentials with wavelet denoising. *Clinical Neurophysiology*, 114(2), 376–390, 2003.

44 Quiroga, RQ. Single trial event-related potentials with wavelet denoising: method and applications. *International Congress Series*, 1278, 429–432, 2005.

45 Benbadis, S, Rielo, D. EEG artifacts. *EMedicine Neurology*, 2010, http://emedicine.medscape.com/article/1140247-overview, cited: 13.5.2011.

46 Croft, RJ, Barry, RJ. Removal of ocular artifact from the EEG: a review. *Clinical Neurophysiology*, 30(1), 5–19, 2000.

47 Joyce, CA, Gorodnitsky, IF, Kutas, M. Automatic removal of eye movement and blink artifacts from EEG data using blind component separation, *Psychophysiology*, 41(2), 313–325, 2004.

48 Krishnaveni, V, Jayaraman, S, Anitha, L. Ramadoss, K. Removal of ocular artifacts from EEG using adaptive thresholding of wavelet coefficients, *Journal of Neural Engineering*, 3(4), 338–346, 2006.

49 Jung, TP, Humphries, C, Lee TW, Makeig, S, McKeown, M, Iragui, V, and Sejnowski, TJ. *Extended ICA removes artifacts from electroencephalographic recordings*. In: Jordan, MI, Kearns, MJ, Solla, SA. (Eds.). Advances in Neural Information Processing Systems 10, MIT Press, Cambridge, MA, 894-900, 1998.

50 Van de Velde, M, Van Erp, G, Cluitmans, PJ. Detection of muscle artefact in the normal human awake EEG, *Electroencephalography and Clinical Neurophysiology*, 107(2), 149–158, 1998.

51 He, P, Wilson, G, Russel, C. Removal of ocular artifacts from electro-encephalogram by adaptive filtering. *Medical & Biological Engineering & Computing*, 42(3), 407–412, 2004.

52 Croft, RJ, Barry, RJ. EOG correction: a new aligned-artifact average solution. *Electroencephalography and Clinical Neurophysiology*, 107(6), 395–401, 1998.

53 Boudet, S, Peyrodie, L, Gallois, P, Vasseur, C. A robust method to filter various types of artifacts on long duration EEG recordings. *2nd International Conference on Bioinformatics and Biomedical Engineering*, Shanghai, 2357–2360, 2008.

54 Hyvärinen, A, Oja, E. A fast fixed-point algorithm for independent component analysis. *Neural Computation*, 9(7), 1483–1492, 1997.

55 Hyvärinen, A. Fast and robust fixed-point algorithms for independent component analysis. *IEEE Transactions on Neural Networks* 10(3), 626–634, 1999.

56 Hyvärinen, A, Oja, E. Independent component analysis: algorithms and applications. *Neural Networks*, 13(4–5), 411–430, 2000.

57 Hyvärinen, A, Karhunen, J, Oja, E. *Independent component analysis*. Wiley, New York: NY, 504 p, 2001.

58 Vigário, R, Särelä, J, Jousmäki, V, Hämäläinen, M, Oja, E. Independent component approach to the analysis of EEG and MEG recordings. *IEEE Transactions on Biomedical Engineering*, 47(5), 589–593, 2000.

59 Zhou, W, Gotman, J. Removal of EMG and ECG artifacts from EEG based on wavelet transform and ICA. *26th Annual International Conference of the IEEE Engineering in Medicine and Biology Society,* San Fransisco, 392–395, 2004.

60 Särelä, J, Valpola, H. Denoising source separation. *Journal of Machine Learning Research*, 6(2005), 233–272, 2005.

61 Fitzgibbon, SP, Powers, DM, Pope, KJ, Clark, CR. Removal of EEG noise and artifact using blind source separation. *Journal of Clinical Neurophysiology*, 24(3), 232–243, 2007.

62 Delorme, A, Sejnowski, T, Makeig, S. Enhanced detection of artifacts in EEG data using higher-order statistics and independent component analysis. *Neuroimage*, 34(4), 1443–1449, 2007.

63 Brookes, MJ, Mullinger, KJ, Stevenson, CM, Morris, PG, Bowtell, R. Simultaneous EEG source localisation and artifact rejection during concurrent fMRI by means of spatial filtering. *Neuroimage*, 40(3), 1090–1104, 2008.

64 Grech, R, Cassa, T, Muscat, J, Camilleri, KP, Fabri, SG, Zervakis, M, Xanthopoulos, P, Sakkalis, V, Vanrumste, B. Review on solving the inverse problem in EEG source analysis. *Journal of NeuroEngineering and Rehabilitation*, 5:25, doi: 10.1186/1743-0003-5-25, 2008.

65 Vigário, RN. Extraction of ocular artefacts from EEG using independent component analysis. *Electroencephalography and Clinical Neurophysiology*, 103(3), 395–404, 1997.

66 Huang, HS, Pal, NR, Ko, LW, Lin, CT. Automatic identification of useful independent components with a view to removing artifacts from EEG signal. *International Joint Conference on Neural Networks*, Atlanta, 1267–1271, 2009.

67 Halder, S, Bensch, M, Mellinger, J, Bogdan, M, Kübler, A, Birbaumer, N, Rosenstiel, W. Online Artifact Removal for Brain-Computer Interfaces Using Support Vector Machines and Blind Source Separation. *Computational Intelligence and Neuroscience*, 2007:82069, doi: 10.1155/2007/82069, 2007.

68 Glaser, EM, Ruchkin, DS. *Principles of neurobiological signal analysis*. Academic Press, New York, NY, 471 p, 1976.

69 Ruchkin, DS. *Measurement of event-related potentials: signal extraction*. In: Picton, TW (Ed). Human event-related potentials: EEG Handbook. Elsevier, Amsterdam, 7–43, 1988.

70 Picton, TW, Lins, OG, Scherg, M. *The recording and analysis of event-related potentials*. In: Boller F, Grafman J (Eds), Handbook of neuropsychology. Elsevier, Amsterdam, 3–73, 1995.

71 Woody, CD. Characterization of an adaptive filter for the analysis of variable latency neuroelectric signals. *Medical & Biological Engineering & Computing*, 5(6), 539–554, 1967.

72 Wang, K, Begleiter, H, Porjesz, B. Warp-averaging event-related potentials. *Clinical Neurophysiology*, 112(10), 1917–1924, 2001.

73 Gibbons, H, Stahl, J. Response-time corrected averaging of event-related potentials. *Clinical Neurophysiology*, 118(1), 197–208, 2007.

74 Davila, CE, Mobin, MS. Weighted averaging of evoked potentials. *IEEE Transactions on Biomedical Engineering*, 39(4), 338–345, 1992.

75 Mühler, R, von Specht, H. Sorted averaging – principle and application to auditory brainstem responses. *Scandinavian Audiology*, 28(3), 145–149, 1999.

76 John, MS, Dimitrijevic, A, Picton, TW. Weighted averaging of steady-state responses. *Clinical Neurophysiology*, 112(3), 555–562, 2001.

77 Leonowicz, Z, Karvanen, J, Shishkin, S. Trimmed estimators for robust averaging of event-related potentials. *Journal of Neuroscience Methods*, 142(1), 17–26, 2005.

78 Rahne, T, von Specht, H, Mühler, R. Sorted averaging--application to auditory event-related responses. *Journal of Neuroscience Methods*, 172(1), 74–78, 2008.

79 Joutsen, A, Puumala, P, Lyytikäinen, L-P, Pajulo, O, Etelämäki, A, Eskola, H, Jäntti, V. EEG sources of noise in intraoperative somatosensory evoked potential monitoring during propofol anesthesia. *Journal of Monitoring and Computing*, 23(4), 237–242, 2009.

80 Jaskowski, P, Verleger, R. Amplitudes and latencies of single-trial ERP's estimated by a maximum-likelihood method. *IEEE Transactions on Biomedical Engineering*, 46(8), 987–993, 1999.

81 Jung, TP, Makeig, S, Westerfield, M, Townsend, J, Courchesne, E, Sejnowski, TJ. Analysis and visualization of single-trial event-related potentials. *Human Brain Mapping*, 14(3), 166–185, 2001.

82 Thornton, AR. Evaluation of a technique to measure latency jitter in event-related potentials. *Journal of Neuroscience Methods*, 168(1), 248–255, 2008.

83 Schröger, E. Application of ERP measures in psychological research. *Behavior Research Methods, Instruments, & Computers*, 30(1), 131–145, 1998.

84 Clementz, BA, Geyer, MA, Braff, DL. P50 Suppression among schizophrenia and normal comparison subjects: A methodological analysis. *Biological Psychiatry*, 41(10), 1035-1044, 1997.

85 Polich, J. *Overview of P3a and P3b*. In: Polich, J (Ed). Detection of change: event-related potential and fMRI findings. Kluwer Academic Press, Boston, 83–98, 2003.

86 Comerchero, MD, Polich, J. P3a and P3b from typical auditory and visual stimuli. *Clinical Neurophysiology*, 110 (1), 24–30, 1999.

87 Shaul, S. *Event-related potentials (ERPs) in the study of dyslexia*. In: Breznitz, Z (Ed). Brain Research in Language. Springer, New York, NY, 51–92, 2008.

88 Hansenne, M. The P300 event-related potential. II. Interindividual variability and clinical application in psychopathology. *Clinical Neurophysiology*, 30(4): 211–231, 2000.

89 Kutas, M, Federmeier, KD. Thirty years and counting: finding the meaning in the N400 component of the event-related brain potential. *Annual Review of Psychology*, 62(1), 621–647.

90 Kutas, M, Federmeier, KD. Electrophysiology reveals semantic memory use in language comprehension. *Trends in Cognitive Sciences*, 4(12), 463–470, 2000.

91 Coulson, S, King, JW, Kutas, M. Expect the unexpected: event-related brain response to morphosyntactic violations. *Language & Cognitive Processes*, 13(1), 21–58, 1998.

92 Leinonen, A, Brattico, P, Järvenpää, M, Krause, CM. Event-related potential (ERP) responses to violations of inflectional and derivational rules of Finnish. *Brain Research*, 1218(1), 181–193.

93 Keinänen, L-M. *Herätevastemittauksen sovellukset ja diagnostiikan tarve*. Bachelor’s thesis, Faculty of Electronics, Communications, and Automation, Helsinki University of Technology, 25 p, 2008.

94 Alonso-Búa, B, Díaz, F, Ferraces, MJ. The contribution of AERPs (MMN and LDN) to studying temporal vs. linguistic processing deficits in children with reading difficulties. *International Journal of Psychophysiology*, 59(2), 159–167, 2006.

95 Jackson, CE, Snyder, PJ. Electroencephalography and event-related potentials as biomarkers of mild cognitive impairment and mild Alzheimer's disease. *Alzheimer's & Dementia*, 4(1), 137–143, 2008.

96 Gironell, A, García-Sánchez, C, Estévez-González, A, Boltes, A, Kulisevsky, J. Usefulness of p300 in subjective memory complaints: a prospective study. *Journal of Clinical Neurophysiology*, 22(4), 279–284, 2005.

97 Pokryszko-Dragan, A, Słotwiński, K, Podemski, R. Modality-specific changes in P300 parameters in patients with dementia of the Alzheimer type. *Medical Science Monitor*, 9(4), 130–134, 2003.

98 Olichney, JM, Morris, SK, Ochoa, C, Salmon, DP, Thal, LJ, Kutas, M, Iragui, VJ. Abnormal verbal event related potentials in mild cognitive impairment and incipient Alzheimer's disease. *Journal of Neurology, Neurosurgery & Psychiatry*, 73(4), 377–384, 2002.

99 Olichney, JM, Iragui, VJ, Salmon, DP, Riggins, BR, Morris, SK, Kutas, M. Absent event-related potential (ERP) word repetition effects in mild Alzheimer's disease. *Clinical Neurophysiology*, 117(6), 1319–1330, 2006.

100 Bramon, E, Rabe-Hesketh, S, Sham, P, Murray, RM, Frangou, S. Meta-analysis of the P300 and P50 waveforms in schizophrenia. *Schizophrenia Research*, 70(2–3), 315–329, 2004.

101 Fellman, V, Kushnerenko, E, Mikkola, K, Ceponiene, R, Leipala, J, Näätänen, R. Atypical auditory event-related potentials in preterm infants during the first year of life: a possible sign of cognitive dysfunction? *Pediatric Research*, 56(2), 291–297, 2004.

102 Gokcay, A, Celebisoy, N, Gokcay, F, Atac, C. Cognitive functions evaluated by P300 and visual and auditory number assays in children with childhood epilepsy with occipital paroxysms (CEOP). *Seizure*, 15(1), 22–27, 2006.

103 Kane, NM, Curry, SH, Butler, SR, Cummins, BH. Electrophysiological indicator of awakening from coma. *Lancet*, 341(8846), 688, 1993.

104 Kane, NM, Curry, SH, Rowlands, CA, Manara, AR, Lewis, T, Moss, T, Cummins, BH, Butler, SR. Event-related potentials--neurophysiological tools for predicting emergence and early outcome from traumatic coma. *Intensive Care Medicine*, 22(1), 39–46, 1996.

105 Guttorm, TK, Leppänen, PH, Poikkeus, AM, Eklund, KM, Lyytinen, P, Lyytinen, H. Brain event-related potentials (ERPs) measured at birth predict later language development in children with and without familial risk for dyslexia. *Cortex*, 41(3), 291–303, 2005.

106 Näätänen, R, Gaillard, AWK, Mäntysalo, S. Early selective attention effect on evoked potential reinterpreted. *Acta Psychologica*, 42(4), 313–329, 1978.

107 Näätänen, R. *Attention and Brain Function*. Erlbaum, Hillsdale, NJ, 494 p, 1992.

108 Snyder, E, Hillyard, SA. Long-latency evoked potentials to irrelevant deviant stimuli. *Behavioral Biology*, 16(3), 319–331, 1976.

109 Näätänen, R, Simpson, M., Loveless, N.E. Stimulus deviance and evoked potentials. *Biological Psychology*, 14(1–2), 53–98, 1982.

110 Sams, M, Paavilainen, P, Alho, K, Näätänen, R. Auditory frequency discrimination and event-related potentials. *Electroencephalography and Clinical Neurophysiology*, 62(6), 437–447, 1985.

111 Kutas, M, Hillyard, SA. Brain potentials during reading reflect word expectancy and semantic association. *Nature*, 307(5947), 161–163, 1984.

112 Duncan, CC, Barry, RJ, Connolly, JF, Fischer, C, Michie, PT, Näätänen, R, Polich, J, Reinvang, I, Van Petten, C. Event-related potentials in clinical research: guidelines for eliciting, recording, and quantifying mismatch negativity, P300, and N400. *Clinical Neurophysiology*, 120(11), 1883–1908, 2009.

113 Kujala, T, Karma, K, Ceponiene, R, Belitz, S, Turkkila, P, Tervaniemi, M, Näätänen, R. Plastic neural changes and reading improvement caused by audiovisual training in reading-impaired children. *The Proceedings of the National Academy of Sciences of the USA*, 98(18), 10509–10514, 2001.

---

114 Näätänen, R, Paavilainen, P, Rinne, T, Alho, K. The mismatch negativity (MMN) in basic research of central auditory processing: a review. *Clinical Neurophysiology*, 118(12), 2544-2590, 2007.

115 Polikar, R, Topalis, A, Green, D, Kounios, J, Clark, CM. Comparative multiresolution wavelet analysis of ERP spectral bands using an ensemble of classifiers approach for early diagnosis of Alzheimer's disease. *Computers in Biology and Medicine*, 37(4), 542–558, 2007.

116 Rentzsch, J, Jockers-Scherübl, MC, Boutros, NN, Gallinat, J. Test-retest reliability of P50, N100 and P200 auditory sensory gating in healthy subjects. *International Journal of Psychophysiology*, 67(2), 81–90, 2008.

117 Lang, AH, Eerola, O, Korpilahti, P, Holopainen, I, Salo, S, Aaltonen, O. Practical issues in the clinical application of mismatch negativity. *Ear and Hearing*, 16(1), 118–130, 1995.

118 Hall, MH, Schulze, K, Rijsdijk, F, Picchioni, M, Ettinger, U, Bramon, E, Freedman, R, Murray, RM, Sham, P. Heritability and reliability of P300, P50 and duration mismatch negativity. *Behavior Genetics*, 36(6), 845–857, 2006.

119 Petrek, J. ERPs to words – effect of gender and site of recording electrode. *Biomedical Papers of the Medical Faculty of the University Palacký, Olomouc, Czechoslovakia*, 148(2), 145–152, 2004.

120 Boksem, MAS, Meijman, TF, Lorist, MM. Effects of mental fatigue on attention: An ERP study. *Brain Research. Cognitive Brain Research*, 25(1), 107–116, 2005.

121 Kujala, T, Tervaniemi, M, Schröger, E. The mismatch negativity in cognitive and clinical neuroscience: Theoretical and methodological considerations. *Biological Psychology*, 74(1), 1–19, 2007.

122 Ding, HY, Ye, DT. The extraction of MMN modulated by attention. *2003 International Conference on Neural Networks and Signal Processing*, 1, 121–124, 2003.

123 Muller-Gass, A, Stelmack, RM, Campbell, KB. "...and were instructed to read a self-selected book while ignoring the auditory stimuli": the effects of task demands on the mismatch negativity. *Clinical Neurophysiology*, 116(9), 2142–52, 2005.

124 Polich, J. Normal variation of P300 from auditory stimuli. *Electroencephalography and Clinical Neurophysiology*, 65(3), 665–669, 1986.

125 Fabiani, M, Gratton, G, Karis, D, Donchin, E. *Definition, identification and reliability of measurement of the P300 component of the event-related brain potential*. In: Ackles, PK, Jennings, JR, Coles, MGH. (Eds.). Advances in Psychophysiology, JAI Press, 1987. London, 1–78, 1987.

126 Segalowitz, SJ, Barnes, K. The reliability of ERP components in the auditory oddball paradigm. *Psychophysiology*, 30(5), 451–459, 1993.

127 Kinoshita, S, Inoue, M, Maeda, H, Nakamira, J, Morita, K. Long-term patterns of change in ERPs across repeated measurements. *Physiology & Behavior*, 60(4), 1087–1092, 1996.

128 Sandman, CA, Patterson, JV. The auditory event-related potential is a stable and reliable measure in elderly subjects over a 3 year period. *Clinical Neurophysiology*, 111(8), 1427–1437, 2000.

129 Walhovd, KB, Flell, AM. One-year test-retest reliability of auditory ERPs in young and old adults. *International Journal of Psychophysiology*, 46(1), 29–40, 2002.

130 Chertoff, ME, Goldstein, R, Mease, MR. Early Event-Related Potentials with Passive Subject Participation. *Journal of Speech and Hearing Research*, 31(3), 460–465, 1988.

131 Pekkonen, E, Rinne, T, Näätänen, R. Variability and replicability of the mismatch negativity. *Electroencephalography and Clinical Neurophysiology,* 96(6), 546–554, 1995.

132 Escera, C, Grau, C. Short-term replicability of the mismatch negativity. *Electroencephalography and Clinical Neurophysiology*, 100(6), 549–554, 1996.

133 Frodl-Bauch, T, Kathmann, N, Möller, HJ, Hegerl, U. Dipole localization and test-retest reliability of frequency and duration mismatch negativity generator processes. *Brain Topography*, 10(1), 3–8, 1997.

134 Joutsiniemi, SL, Ilvonen, T, Sinkkonen, J, Huotilainen, M, Tervaniemi, M, Lehtokoski, A, Rinne, T, Näätänen, R. The mismatch negativity for duration decrement of auditory stimuli in healthy subjects. *Electroencephalography and Clinical Neurophysiology*, 108(2), 154–159, 1998.

135 Kathmann, N, Frodl-Bauch, T, Hegerl, U. Stability of the mismatch negativity under different stimulus and attention conditions. *Clinical Neurophysiology*, 110(2), 317–323, 1999.

136 Tervaniemi, M, Lehtokoski, A, Sinkkonen, J, Virtanen, J, Ilmoniemi, RJ, Näätänen, R. Test-retest reliability of mismatch negativity for duration, frequency and intensity changes. *Clinical Neurophysiology*, 110(8), 1388–1393, 1999.

137 Escera, C, Yago, E, Polo, MD, Grau, C. The individual replicability of mismatch negativity at short and long inter-stimulus intervals. *Clinical Neurophysiology*, 111(3), 546–551, 2000.

138 Dalebout, SD, Fox, LG. Reliability of the mismatch negativity in the responses of individual listeners. *Journal of the American Academy of Audiology*, 12(5), 245–253, 2001.

139 Lew, HL, Gray, M, Poole, JH. Temporal stability of auditory event-related potentials in healthy individuals and patients with traumatic brain injury. *Journal of Clinical Neurophysiology*, 24(5), 392–397, 2007.

140 Light, GA, Braff, DL. Stability of mismatch negativity deficits and their relationship to functional impairments in chronic schizophrenia. *The American Journal of Psychiatry*, 162(9), 1741–1743, 2005.

141 Tervaniemi, M, Ilvonen, T, Karma K, Alho, K, Näätänen, R. The musical brain: brain waves reveal the neurophysiological basis of musicality in human subjects. *Neuroscience Letters*, 226(1), 1–4, 1997.

142 George, EM, Coch, D. Music training and working memory: an ERP study. *Neuropsychologia*, 49(5), 1083–1094, 2011.

143 Kisley, MA, Davalos, DB, Engleman, LL, Guinther, PM, Davis, HP. Age-related change in neural processing of time-dependent stimulus features. *Cognitive Brain Research*, 25(3), 913–925, 2005.

144 Nagy, E, Potts, GF, Loveland, KA. Sex-related ERP differences in deviance detection. *International Journal of Psychophysiology*, 48(3), 285–292, 2003.

145 Ypparila, H, Karhu, J, Westeren-Punnonen, S, Musialowicz, T, Partanen, J. Evidence of auditory processing during postoperative propofol sedation. *Clinical Neurophysiology*, 113(8), 1357–1364, 2002.

146 Näätänen, R. The mismatch negativity: a powerful tool for cognitive neuroscience. *Ear and Hearing*, 16(1), 6–18, 1995.

147 Näätänen, R, Pakarinen, S, Rinne, T, Takegata, R. The mismatch negativity (MMN): towards the optimal paradigm. *Clinical Neurophysiology*, 115(1), 140–144, 2004.

148 Pakarinen, S, Lovio, R, Huotilainen, M, Alku, P, Näätänen, R, Kujala, T. Fast multi-feature paradigm for recording several mismatch negativities (MMNs) to phonetic and acoustic changes in speech sounds. *Biological Psychology*, 82(3), 219–226, 2009.

149 Tiihonen, P, Kinnunen, J, Töyräs, J, Mervaala, E, Pääkkönen, A. A portable device for intensive care brain function monitoring with event-related potentials. *Computer Methods and Programs in Biomedicine*, 89(1), 83–92, 2008.

150 Gargiulo, G, Calvo, RA, Bifulco, P, Cesarelli, M, Jin, C, Mohamed, A, van Schaik, A. A new EEG recording system for passive dry electrodes. *Clinical Neurophysiology*, 121(5), 686-693, 2010.

151 Dien, J. Issues in the application of the average reference: Review, critiques, and recommendations. *Behavior Research Methods, Instruments & Computers*, 30(1), 34–43, 1998.

152 Miller, GA, Lutzenberger, W, Elbert, T. The linked-reference issue in EEG and ERP recording. *Journal of Psychophysiology*, 5(3), 273–276, 1991.

153 Katznelson, R. *EEG recording, electrode placement, and aspects of generator localization*. In: Nunez, PL (Ed.). Electric fields of the brain: The neurophysics of the EEG. Oxford University Press, New York, NY, 176–213, 1981.

154 Rosenfeld, JP. Theoretical implications of EEG reference choice and related methodology issues. *Journal of Neurotherapy*, 4(2), 77–87, 2000.

155 Bertrand, O, Perrin, F, Pernier, J. A theoretical justification of the average reference in topographic evoked potential studies. *Electroencephalography and Clinical Neurophysiology*, 62(6), 462–464, 1985.

156 Junghöfer, M, Elbert, T, Tucker, DM, Braun, C. The polar average reference effect: a bias in estimating the head surface integral in EEG recording. *Clinical Neurophysiology*, 110(6), 1149–1155, 1999.

157 Desmedt, JE, Chalklin, V, Tomberg, C. Emulation of somatosensory evoked potential (SEP) components with the 3-shell head model and the problem of “ghost fields” when using an average reference in brain mapping. *Electroencephalography and Clinical Neurophysiology*, 77(4), 243–258, 1990.

158 Osselton, JW. Acquisition of EEG data by bipolar, unipolar and average reference methods: a theoretical comparison. *Electroencephalography and Clinical Neurophysiology*, 19(5), 527–528, 1965.

159 Rappelsberger, P. The reference problem and mapping of coherence: a simulation study. *Brain Topography*, 2(1–2), 63–71, 1989.

160 Offner, FF. The EEG as potential mapping: the value of the average monopolar reference. *Electroencephalography and Clinical Neurophysiology*, 2(2), 213–214, 1950.

161 Goldman, D. The clinical use of the "average" reference electrode in monopolar recording. *Electroencephalography and Clinical Neurophysiology*, 2(2), 209–212, 1950.

162 Schimmel, H. The (±) reference: accuracy of estimated mean components in average response studies. *Science*, 157(784), 92–94, 1967.

163 Lowy, K, Weiss, B. Assessing the significance of averaged evoked potentials with an on-line computer: the split-sweep method. *Electroencephalography and Clinical Neurophysiology*, 25(2), 177–180, 1968.

164 Wong, PKH, Bickford, RG. Brain stem auditory evoked potentials: The use of noise estimate. *Electroencephalography and Clinical Neurophysiology*, 50(1–2), 25–34, 1980.

165 Elberling, C, Don, M. Quality estimation of averaged auditory brainstem responses. *Scandinavian Audiology*, 13(3), 187-197, 1984.

166 Özdamar, Ö, Delgado, RE. Measurement of signal and noise characteristics in ongoing auditory brainstem response averaging. *Annals of Biomedical Engineering*, 24(6), 702–715, 1996.

167 Van de Velde, M, De Beer, NAM, Cluitmans, PJM. Evaluation of automatic quality assessment of auditory evoked potentials in clinical data. *18th Annual International Conference of the IEEE Engineering in Medicine and Biology Society*, Amsterdam, 4, 1520–1521, 1996.

168 Stecker, MM, Robertshaw, J. Factors affecting reliability of interpretations of intra-operative evoked potentials. *Journal of Clinical Monitoring and Computing*, 20(1), 47–55, 2006.

169 Gerull, G, Graffunder, A, Wernicke, M. Averaging evoked potentials with an improved weighting algorithm. *Scandinavian Audiology*, 25(1), 21–27, 1996.

170 Kurttio, A. *Development of an Adaptive Algorithm for Online Artefact Rejection in Electroencephalographic Recordings*. Master's thesis, Faculty of Information and Natural Sciences, School of Science and Technology, Aalto University, 36 p, 2010.

171 Pakarinen, S, Takegata, R, Rinne, T, Huotilainen, M, Näätänen, R. Measurement of extensive auditory discrimination profiles using the mismatch negativity (MMN) of the auditory event-related potential (ERP). *Clinical Neurophysiology*, 118(1), 177–185, 2007.

172 Martins, R, Selberherr, S, Vaz, FA. A CMOS IC for portable EEG acquisition systems. *IEEE Transactions on Instrumentation and Measurement*, 47(5), 1191–1196, 1998.

173 Järvenpää, M. *Optimization of the event-related potential recording unit*. Master's thesis, Faculty of Electronics, Communications and Automation, Helsinki University of Technology, 60 p, 2009.

174 Pakarinen, S, Huotilainen, M, Näätänen, R. The mismatch negativity (MMN) with no standard stimulus. *Clinical Neurophysiology*, 121(7), 1043–1050, 2010.

Event-related potential (ERP) measurements have a large potential in diagnostic applications. They are relatively simple to obtain, the instrumentation is inexpensive, and the application area is wide. The technique is widely adopted in general research use, but many of the clinical applications would benefit from higher measurement reliability and more robust performance. The current study presents ideas and technical solutions to enhance the performance of these measurements. The focus is on the optimization of the instrumentation and the measurement process. Their impact on measurement reliability and practical feasibility are discussed.

Aalto-DD 35/2012

9 789526 045627

ISBN 978-952-60-4562-7
ISBN 978-952-60-4563-4 (pdf)
ISSN-L 1799-4934
ISSN 1799-4934
ISSN 1799-4942 (pdf)

Aalto University
School of Electrical Engineering
Department of Electronics
www.aalto.fi

BUSINESS +
ECONOMY

ART +
DESIGN +
ARCHITECTURE

SCIENCE +
TECHNOLOGY

CROSSOVER

DOCTORAL
DISSERTATIONS