THESIS ON NATURAL AND EXACT SCIENCES B146

Detection of the Effect of Weak Stressors on Human Resting Electroencephalographic Signal

ANNA SUHHOVA

TUT PRESS

TALLINN UNIVERSITY OF TECHNOLOGY
Technomedicum
Department of Biomedical Engineering

Dissertation was accepted for the defence of the degree of Doctor of Philosophy in Natural and Exact Sciences on November 13, 2012

Supervisors: Professor Emeritus Hiie Hinrikus, Department of Biomedical Engineering, Techomedicum, Tallinn University of Technology

Maie Bachmann, Ph.D., Department of Biomedical Engineering, Technomedicum, Tallinn University of Technology

Opponents: Professor Wlodzimierz Klonowski, Nalecz Institute of Biocybernetics and Biomedical Engineering Polish Academy of Sciences, Poland

Professor Jukka Juutilainen, University of Eastern Finland, Finland

Defence of the thesis: January 11, 2013

Declaration:
Hereby I declare that this doctoral thesis, my original investigation and achievement, submitted for the doctoral degree at Tallinn University of Technology has not been submitted for any academic degree.

Anna Suhhova

ISSN 1406-4723
ISBN 978-9949-23-411-0 (publication)
ISBN 978-9949-23-412-7 (PDF)

LOODUS- JA TÄPPISTEADUSED B146

Nõrkade stressorite mõju avastamine inimese puhkeoleku elektroentsefalograafilises signaalis

ANNA SUHHOVA

TTÜ
KIRJASTUS

CONTENTS

INTRODUCTION

The functions of the brain depend on the ability of brain neurons to transmit electrical and biochemical signals to other cells, and their ability to respond appropriately to signals received from other cells. The bioelectrical processes are fundamental in the brain functioning.

Any changes in the bioelectrical processes in the brain have impact on the physiological state of the brain and as a result on a human's life quality. Several psychiatric conditions with heightened stress and instability are associated with changes in the brain bioelectrical activity.

Not only mental disorders can affect brain activity. In modern society where the whole population voluntarily or involuntarily is being exposed to electromagnetic fields (EMF), the EMF should be considered as one of the external stressors producing effects on living organisms and brain due to thermal and non-thermal interactions [Hyland, 2000].

As the brain neurons can respond to the EMF and to different degrees of neurological and other kinds of alterations, the studies in brain electrical activity enable us to obtain more information about brain functioning and different states of the brain. The information about brain activity can be achieved noninvasively using electroencephalography (EEG).

The EEG signal has been frequently employed to assess the effect of microwave exposure and mental disorders on the human brain bioelectrical activity because of its sensitivity to immediate changes in neural processes. EEG has several clear advantages as a tool for exploring states of the brain because of its low cost, it is being widely used in clinical practice because it is, non-invasive, portable and when recording, EEG patients are not exposed to (electro-)magnetic fields. Another advantage of the EEG method is that brain electrical activity is being measured directly while other methods record changes in the blood flow (single-photon emission computed tomography (SPECT), functional magnetic resonance imaging (fMRI)) or metabolic activity (positron emission tomography (PET)), which are indirect markers of brain electrical activity. The major problem of EEG use to evaluate the effect of weak stressors on the brain bioelectrical activity is insufficient sensitivity of the EEG analysis methods to discover small changes in the EEG signal hidden in its high natural variability.

The present study is focused on the evaluation of changes in the resting EEG signal produced by microwave exposure and mental disorders.

In the first part of this thesis the characteristic changes in the EEG signal caused by microwave exposure have been investigated.

Effects of low-level modulated microwave radiation on the brain bioelectrical activity became a topic of major interest due to the wide use of telecommunication equipment. In traditional use, a mobile phone positioned close to the ear during transmission causes strongly asymmetric distribution of field power density and a specific absorption rate (SAR) inside the human head. The dosimetric data indicate that approximately 50-60% of the mobile phone output power is absorbed in the speaker head during conversation [Gandhi, 2002], but the impact of exposure is imperceptible to a mobile phone user. The growing public concern about the effects of mobile phone radiation on the central nervous system has initiated massive studies focused on its possible effects.

Experiments using human volunteers exposed to microwave radiation are restricted to the evaluation of a possible effect at the exposure level not exceeding recommendations developed by the International Commission on Non-Ionizing Radiological Protection (ICNIRP). The ICNIRP guidelines are based on reviews of current scientific knowledge in the field of radiation protection. According to the guidelines, the recommended localized SAR for general public exposure for head and trunk was set at 2 W/kg for radiofrequency fields and a field strength of 61 V/m [ICNIRP, 1998].

ICNIRP guidelines for exposure to microwaves have been based on thermal effects that are well understood and mainly associated with the absorption of the radiofrequency (RF) energy resulting from the electrical conductivity of a biological tissue. All interactions between RF fields and the biological tissue are likely to result in energy transfer to the tissue and this will ultimately lead to an increase in its temperature [Challis, 2005]. A major consideration of existing guidelines is the prevention of adverse biological effects resulting from electromagnetic exposures that could bring temperature rises on the order of 1°C in humans.

Despite the fact that many studies have suggested that microwave exposure at low levels may have biological effects, non-thermal (effects on low-intensity) mechanisms have not been considered for the regulation of exposure. One possible reason for that is that the significance of performed experimental studies for human health cannot be adequately assessed since they have not been consistently replicated. Ongoing scientific research has given more evidence for reasonable suspicion of existing risks based on clear evidence of bioeffects, which, with prolonged exposures, may reasonably be presumed to result in health impacts. Concerning the results of recent studies it was suggested that new guidelines based on non-thermal (low-intensity) effects from microwave exposure should be applied [Hardell and Sage, 2008].

The importance of the problem was pointed out by the Council of Europe who adopted Resolution 1815 in May 2011, which recommends a preventive threshold to be set for levels of long-term exposure to microwaves, in accordance with the precautionary principle, not exceeding 0.6 volts per metre. The need for further independent research and financing of the research on this topic is underlined in the Resolution [Council of Europe, 2011].

In recent years, numerous studies have focused on the evaluation of different impacts of EMF on humans, ranging from the effect on brain electrical activity, sleep and cognitive functions to EMF attributed symptoms [for review see van Rongen et al., 2009; Juutilainen et al., 2011; Kwon and Hämäläinen, 2011]. However, results appear contradictory, and therefore questions have been raised whether the concerns about the EMF impact on psychology or health are justified since the strength of evidence for many EMF outcomes remains inadequate [EFHRAN, 2010]. In a recent review, a conclusion was drawn confirming the lack of systematic data on the dependence of microwave effects on the level of the exposure [Juutilainen et al., 2011], therefore further studies should concentrate on dose-dependent effects of exposure.

The second part covers problems of how an EEG signal is affected by mental disorders like depression.

Today, depression is becoming one of the most prevalent psychiatric disorders affecting large proportions of population, World Health Organization (WHO) ranks depression as the 4th leading contributor to the global burden of disease in 2000. Depression is expected to rank second by 2020, behind ischemic heart disease, and current predictions indicate that by 2030 depression will be the leading cause of disease burden globally calculated for all ages, both sexes [WHO, 2012].

Tremendous expenses are associated with disabilities caused by depression. According to data disclosed by the National Institute of Mental Health, in the United States for the year 2002, the economic burden of depression was estimated at $317 billion: 32% related to direct medical costs, 8% to disability benefits like social security income and disability insurance, and 62% to workplace costs, including loss of earnings among people with mental illness. The total annual cost of depression in Europe by 2004 was estimated at Euro 118 billion, showing that the direct healthcare costs alone totaled at Euro 42 billion and indirect costs due to morbidity and mortality were estimated at Euro 76 billion [Sobocki et al., 2006]. Higher medical costs arise largely from non-response to treatment as initial treatments frequently do not lead to recovery [Simon et al., 2006]. Following the review of cost demonstrates that a global cost of depression outweighs far the cost to understanding it accurately and treating successfully those who suffer [Richards et al., 2011].

Up to now, the diagnosis of depression is based on the evaluation of the intensity of subjective and clinical symptoms by psychiatrists (M.I.N.I. interview, Hamilton test, and others). At the same time, the EEG analysis provides promising results in the diagnosing of nervous diseases. Several mental disorders (Alzheimer's disease, dementia) produce alteration in brain electrical activity [Abasolo et al. 2008; Henderson et al., 2006; Adeli et al., 2008]. However, only limited data are available about alterations in the EEG in a depressive disorder.

The presence of left frontal hypoactivation for depressed individuals has been shown in numerous studies [Allen et al., 2004; Knott et al., 2001; Lubar et al., 2003], but in some cases the expected left anterior hypoactivation was not observed [Flon-Henry et al., 2004]. One study suggests that absolute and relative power in the beta band appeared to differentiate patients and controls, with patients exhibiting more beta power than controls [Knott et al., 2001]. The results published do not lead to useful conclusions in depressive mode evaluation while distinguishing reactions to somatic diseases from depressive disorders whereas the treatment required is very complicated. Therefore, regarding the percentage of population suffering from mental illnesses and the global cost of depression, the demand for nonsubjective methods to determine depressive disorder based only on objective symptoms is justified.

Regarding to the potential effect of electromagnetic radiation on the central nervous system and the impact of depressive disorder on world economy and health of society, the need for methods to determine the effect on the brain on early stages is evident.

The aim of this work is to evaluate the capability of different analysis methods to detect small hidden changes in the human resting EEG signal caused by a) an external stressor such as microwave radiation and b) mental disorders such as depression.

This thesis reviews the author's work at the Department of Biomedical Engineering of the Technomedicum of Tallinn University of Technology during her doctoral studies. The thesis consists of the author's publications. The thesis presents the results of the studies focused on evaluating the impact of microwave radiation or depression on the human brain bioelectrical activity.

The present thesis is based on the following papers referred to in the text by their Roman numerals I-VII.

I. **Suhhova, A.,** Bachmann, M., Karai, D., Lass, J., Hinrikus, H. (2012). Effect of microwave radiation on human EEG at two different levels of exposure. *Bioelectromagnetics* (in press)

II. **Suhhova, A.,** Bachmann, M., Lass, J., Karai, D., Hinrikus, H. (2009). Effect of modulated microwave radiation on human EEG asymmetry. *The Environmentalist*, 29: 210-214.

III. **Suhhova, A.,** Hinrikus, H., Bachmann, M., Lass, J. (2009). Effect of modulated microwave exposure on spectral asymmetry of human EEG. *IFMBE Proceedings,* Volume 25/3, pp 406-409.

IV. Hinrikus, H., Bachmann, M., Lass, J., **Suhhova, A.,** Tuulik, V. Aadamsoo, K., Võhma, Ü., (2012). Method and device for determining depressive disorders by measuring bioelectromagnetic signals of the brain. US 8244341.

V. Hinrikus, H., **Suhhova, A.,** Bachmann, M., Aadamsoo, K., Võhma, Ü., Lass, J., Tuulik, V. (2009) Electroencephalographic spectral asymmetry index for detection of depression. *Med Biol Eng Comput,* 47:1291-1299.

VI. Hinrikus, H., **Suhhova, A.,** Bachmann, M., Aadamsoo, K., Võhma, Ü., Pehlak, H., Lass, J. (2010). Spectral features of EEG in depression. *Biomed Tech*, 55: 155-161.

VII. **Suhhova, A.,** Bachmann, M., Lass, J., Aadamsoo, K., Võhma, Ü., Hinrikus, H. (2012). EEG spectral asymmetry index for detection of depression at individual and fixed frequency bands. *IFMBE Proceedings*, 39:589-92.

Approbation

COST Action B27, Electrical Neuronal Oscillations and Cognition – ENOC, Goettingen Meeting, 12-14 October, 2007

14th North-Baltic Conference on Biomedical Engineering and Medical Physics, Riga, Latvia, June 16-20, 2008

5th International Workshop on Biological Effects on Electromagnetic Fields, Terrasini, Palermo, September 28 – October 2, 2008

4th European Conference of the International Federation for Medical and Biological Engineering, Antwerp, Belgium, November 23-27, 2008

COST Action B27, Electrical Neuronal Oscillations and Cognitions – ENOC, Advanced Workshop "Consciousness and its Descriptors", Crotone, Italy, March 27-28, 2009

COST Action B27, Electrical Neuronal Oscillations and Cognition – ENOC, Zurich Meeting, May 15-16, 2009

World Congress on Medical Physics and Biomedical Engineering, Munich, Germany, September 7-12, 2009

5th International Summer School on Emerging Technologies in Biomedicine "High Throughput Communication between Brain and Machine", University of Patras, Greece, September 26 – October 1, 2010

World Congress on Medical Physics and Biomedical Engineering, Beijing, China, May 26 – 31, 2012.

Author's own contribution

In all publications the author participated in planning the experiment, taking the EEG recordings and contributing to writing the paper. The major part of the EEG signal analysis was conducted by the author, except the statistical analysis part in Publication I and calculation of specific EEG bands for spectral asymmetry index.

Acknowledgements
I would like to express my appreciation to each associate who has contributed to the creation of this thesis.

I would like to express my deepest gratitude to my supervisor and research group leader Professor Emeritus Hiie Hinrikus for her guidance and motivation, which made this thesis possible. I am grateful to my supervisor Maie Bachmann, Ph.D., for her fruitful collaboration and advice during my studies at Tallinn University of Technology. I wish to thank Jaanus Lass and Deniss Karai for their valuable help and practical advice. Financial support from the Estonian Science Foundation, the Estonian targeted financing project SF0140027s07, from the European Union through the European Regional Development Fund, and Archimedes Foundation is appreciated.

1. EFFECT OF LOW-LEVEL MODULATED MICROWAVE EXPOSURE ON BRAIN BIOELECTRICAL ACTIVITY

1.1 Resting EEG studies

The growing public concern about potentially toxic effect of electromagnetic radiation on central nervous system has initiated a number of research programs that have evaluated physiological effect of microwave radiation. Results of the studies on the resting EEG signal have produced somewhat mixed results, although the majority of published results point to the existence of the effect of radiation, primarily to the alpha band of the EEG.

Croft et al. (2002) tested wheatear exposure to active mobile phone affects the EEG signal as a function of exposure duration. The results showed that mobile phone (Global System for Mobile Communications (GSM) 900) exposure altered the resting EEG, increasing alpha (8-12 Hz) activity and decreasing delta (1-4 Hz) activity as a function of time.

The effect of microwave radiation on the EEG waking activity and its temporal development was investigated by Curcio et al. (2005). The subjects (N=20) participating in the study were exposed to a 900 MHz GSM phone signal at SAR values of 0.5 W/kg after and during the EEG recording session. The recordings were performed in real exposure, baseline and sham conditions. The results show that microwave exposure increases power in the alpha (9-10 Hz) frequency band. At the same time, authors stress that regarding to a small sample and effect size, the strength of the presented data should be regarded with caution.

Consistent with Curcio et al. (2005), Croft et al. (2008) tested whether the alpha power would increase in response to mobile phone type radiation. Healthy participants (n=120) were tested using double-blind counterbalanced crossover design, recorded at an interval of 1 week. Alterations related to exposure (875 MHz GSM signal, SAR value of 0.11 W/kg) were demonstrated in the EEG alpha band (9-10 Hz) power, which was larger on the ipsilateral than on the contralateral side in posterior regions. Hence, previous reports of an overall alpha power enhancement during exposure were confirmed.

Decreased EEG alpha (8-12 Hz) and beta (13-20 Hz) power was found by D'Costa et al. (2003) in a single-blind study with mobile phone configured to be

enable transmission at a nominal average power of 250 mW with a 900 MHz carrier modulated at 217 Hz.

Hinrikus et al. (2008a, 2008b) detected an increase in the resting eyes closed EEG alpha (8-13 Hz), beta1 (15-20 Hz) and beta2 (22-38 Hz) power with 450 MHz radiation modulated at 7, 14, 21, 40, 70 or 217 Hz frequencies at the SAR value of 0.3 W/kg.

Regel et al. (2007a) reported an increase in the alpha band (10.5-11Hz) activity after the exposure to the pulsed 900 MHz signals at SAR 1 W/kg in the eyes-closed condition, while no effect was seen in the eyes-open condition.

The EEG alpha band power enhancement in the resting EEG recorded at SAR values of 1 W/kg at 900 MHz pulse modulated signal was observed by Huber et al. (2000, 2002).

Vecchio et al. (2007) suggested that prolonged mobile phone emission affects not only the cortical activity but also the spread of neural synchronizations conveyed by interhemispherical functional coupling of EEG, especially alpha rhythm. Two years later it was shown that compared to young subjects, elderly subjects develop significant increase in inter-hemispheric synchronization of frontal and temporal alpha bands following exposure to a GSM signal at 0.05 W/kg [Vecchio et al., 2010].

To study whether adolescents and/or elderly are more sensitive to mobile phone-related bioeffects than young adults, Croft et al. (2010) used the 2nd generation (SAR 0.7 W/kg) GSM, and the 3rd generation (SAR 1.7 W/kg) Wideband Code Division Multiple Access (W-CDMA) exposures. The data showed that the young adults' alpha wave activity was greater in the 2nd generation exposure than at the sham exposure. However, no effect was found in the adolescent or the elderly groups, and no effect of 3nd generation exposures was found in any group. No effect of UMTS (SAR 1.75 W/kg) exposure on the spectral power of different EEG frequency bands of spontaneous EEG was reported by Trunk et al. (2012). It should be noticed that in this experiment EEG was not recorded during the exposure, therefore possible short-term effect of radiation cannot be excluded.

Maby et al. (2006a) exposed healthy volunteers and epileptic patients to a signal from a 900 MHz GSM mobile phone. In the healthy volunteers, a decrease in the EEG power in the theta, alpha, and beta bands was observed (more precisely on occipital electrodes for the alpha-band) and a decrease in the variations in the delta band was noted. In contrast, in the epileptic patients, an increase in power in all EEG bands was observed.

On the other hand, some researchers were unable to detect any differences in the EEG spectra related to exposure to the signal of a mobile phone at SAR values of 1.56 W/kg and 1 W/kg [Perentos et al. 2007; Kleinlogel et al., 2008].

1.2 Studies at two different levels of exposure

It is assumed that EEG is affected in a dose-dependent manner by exposure to microwave radiation. Despite the fact that the estimation of the critical level of microwave exposure is crucial to preventing possible impairment of human nervous system, only a few studies have compared the effect of microwave radiation at two different levels of exposure.

Regel et al. (2007b) investigated the effects of microwaves on brain physiology using a GSM handset like signal with a 10 g-averaged peak SAR of 0.2 W/kg and 5 W/kg on three different cognitive tasks and on the sleep EEG. The analysis of the sleep EEG revealed a dose-dependent increase of power in the spindle frequency range in the non-REM sleep. Moreover, it was shown that reaction speed decelerated with increasing field intensity in the cognitive task, while accuracy remained unaffected in a dose-dependent manner.

Kleinlogel et al. (2008) investigated the effect of two types of exposure emitted by modern mobile phones, 1950 MHz Universal Mobile Telecommunications System (UMTS) at SAR of 0.01 W/kg and 1 W/kg and pulsed 900 MHz GSM at SAR of 1 W/kg on well-being of the resting eyes-closed EEG. Results of the study give no evidence for a deleterious effect on the either the UMTS or the GSM exposure on normal healthy mobile phone users.

1.3 Sleep EEG studies and neurobehavioural outcomes

According to various population surveys, sleep disturbances are the most common health complaints attributed to microwave exposure [Huss et al., 2004; Schreirer et al., 2006; Röösli et al., 2004]. In several studies the microwave effect on sleep was analyzed by means of the EEG signal.

No effect on sleep architecture and EEG was observed in the study of Wagner et al. (1998) using a GSM signal from a planar antenna (SAR 0.6 W/kg), where the healthy volunteers were exposed for an 8 h night sleep. In 2000 Wagner et al. employed much stronger exposure with SAR 1.8 W/kg. Sham and exposure conditions were applied continuously for 8 h on two consecutive nights. They observed no effect on sleep architecture or EEG spectral power density.

Huber et al. (2000, 2002) exposed healthy volunteers for 30 min to a 900 MHz GSM signal (SAR 1W/kg) immediately before sleep episode. They observed an increased spectral power in the alpha (9.75-11.25 Hz) and beta bands (12.5-13.25 Hz) during the non-REM sleep phase. No differences in the effect between the right or the left-sided exposure were found. No effect on sleep parameters or on

EEG power under exposure from a GSM signal with SAR 1 W/kg was reported by Fritzer et al. (2007).

Increased EEG alpha range in the sleep EEG was detected also at the SAR value of 1.4 W/kg [Lowden et al., 2011].

Dose-response increase in 10.75-11.25 Hz and 13.5-13.75 bands in the non-REM sleep has been observed by Regel et al. (2007a) who applied a GSM signal from a planar antenna with SAR 0.2 and 5 W/kg.

Danker-Hopde et al. (2011) studied possible effects of electromagnetic fields emitted by GSM 900 (SAR 2 W/kg) and WCDMA/UMTS (SAR 2 W/kg) mobile phones on the macrostructure of sleep. The experimental setup included an adaptation night, which served as a screening night for sleep disorders and as an adjustment night to the laboratory environment. The adaptation night was followed by nine study nights (separated by a two week interval) in which subjects were exposed to three exposure conditions (each condition for three nights: sham exposure, GSM 900 and WCDMA/UMTS in a randomized order). No evidence of a sleep-disturbing effect of GSM 900 and WCDMA exposure was demonstrated.

No significant change was observed between the exposure (GSM SAR: 0.11 W/kg) and sham conditions for either sleep latency, REM sleep latency, sleep duration or sleep efficiency by Loughran et al. (2012) who re-tested a subset of participants from a previous study applying the same exposure conditions [Loughran et al., 2005]. At the same time, the increase in the EEG spectral power was demonstrated in the 11.5-12.25 Hz frequency range in the first 30 min of non-REM sleep following exposure. This increase was more prominent in the participants that showed an increase in the original study [Loughran et al, 2005]. Furthermore, the observations that microwave induced effect is sensitive to individual variability provides a possible explanation for previous inconsistent results. It may be suggested that rather than effects being small or subtle, mobile phones may in fact have larger but differential effects on different people [Loughran et al., 2012].

Many studies regarding impact on neurobehavioural outcomes have been conducted in recent years.

In Freude et al. study (2000), subjects were exposed to a signal from a GSM 900 phone with SAR 0.88 W/kg for a duration of a series of cognitive tests. Analysis of the EEGs revealed a decrease of the EEG power in all regions except frontal during a visual monitoring task. These effects were stronger in the exposed hemisphere.

Maby et al. (2004) studied auditory ERPs in two groups of 14 subjects: healthy volunteers and epileptic patients (GSM signal, SAR 1.4 W/kg). They reported a reduction in the amplitude of the early sensory component of the auditory ERP in

the healthy subjects, and a decrease in the amplitude for the epileptic patients. They also observed an increase in the amplitude of a later component only in the healthy subjects.

Maby et al. (2006b) examined the effects of GSM (SAR 1.4 W/kg) exposure on auditory ERPs in both normal and epileptic subjects. In their experiment the epileptic patients showed a lengthening of fast response (100 ms latency) in the frontal area contralateral to the exposure. For the healthy subjects, an amplitude increase (200 ms latency) was identified in the frontal area.

No effect on cognition in performance between the exposure and the sham series was reported at SAR levels of 0.1 W/kg, 0.61 W/kg, SAR 0.74 W/kg, SAR 0.78 W/kg, SAR 2 W/kg [Hamblin et al., 2006; Hinrichs and Heinze, 2004; Krause et al., 2007; Haarala et al., 2007; Schmid et al., 2012]. The improvement in performance when exposed to EMFs was reported at SAR levels of 0.5 W/kg, 1.4 W/kg, 0.2 W/kg and 5 W/kg, 1 W/kg [Curcio et al., 2004; Vecchio et al., 2012; Wiholm et al., 2009; Regel et al., 2007; Regel et al., 2007a]. Impairments were shown at SAR 0.65 W/kg and SAR 0.87 W/kg [Krause et al., 2004; Hamblin et al., 2004].

None of the studies on 3G UMTS signal (SAR 0.0037 and 0.37 W/kg; 0.023 and 0.23 W/kg) found any significant effect on various cognitive functions [Schmid et al., 2005; Unterlechner at al., 2008].

1.4 Reasons for doubts and difficulties in the identification of microwave effects on the brain

Despite many investigations at different levels of exposure, the results provide insufficient systematic knowledge of how the reported effects depend on the level of exposure to microwave fields. For example, the alterations in the brain electrical activity have been reported at SAR levels below 1 W/kg or close to 1 W/kg [Huber et al., 2002, 2002; Curcio et al., 2005; Regel et al., 2007a, 2007b; Croft et al., 2008; Hinrikus et al., 2008a, 2008b; Vecchio et al., 2010]. On the other hand, no effects have been detected at SAR levels close to 1 W/kg or even higher [Wagner et al., 2000; Fritzer et al., 2007; Perentos et al., 2007; Kleinlogel et al., 2008; Croft et al., 2010; Trunk et al., 2012].

The majority of contradictory and null findings in the literature are unlikely to result from the low power level of mobile phones radiation applied, it is likely that the analysis methods used were not sensitive enough to discover small hidden changes in the EEG signal. It should be taken into account that the EEG signal has high natural variability, therefore the analysis of the changes in the brain bioelectrical activity is complicated and the effect may not be detected due to

natural characteristics of the EEG signal. Another explanation may be the variability of the states of the brain (including age, mental illnesses) that may cause different reactions to external stressors. In addition, the main problem is that data from different studies are incomparable due to different methods and experimental protocols as well as microwave and modulation frequencies. In a recent review, a conclusion was drawn confirming the lack of systematic data on the dependence of microwave effects on the level of the exposure [Juutilainen et al., 2011].

The aim of this thesis is to find out a possible dose-response relationship between the strength of the electromagnetic field and the effects on the brain, and to analyze sensitivity of signal analysis methods used to discover hidden changes in the EEG caused by microwave exposure.

To accomplish these objectives, three different methods were applied for the EEG analyses:

- integration of differences (ID) in the energy of the EEG segments with and without the exposure – Publication I;
- brain inter-hemispheric asymmetry (IhA) - Publication II;
- spectral asymmetry index (SASI) calculated as relative differences in the power of two EEG special frequency bands selected higher and lower EEG spectrum maximum – Publication III.

The results of the analyses have been presented for the group and separately for individuals.

2. EEG FINDINGS IN DEPRESSION

While depression is essentially associated with functional impairment [Ansseau et al., 2009], its underlying neural circuitry and pathosphysiology are not completely understood [Ricardo-Garcell et al., 2009; Townsend et al., 2010]. According to Fingelkurts et al. (2007), depression can be understood as re(dis)organization of the local and global oscillatory states in the cortex. The oscillatory states reflect the synchronization of neuronal assemblies evolving in different frequency ranges that might have their own different functional role [Takahashi, 2012]. The EEG provides a satisfactory scale for accessing the large-scale dynamic of the brain's oscillatory states [Fingelkurts et al., 2006] associated with health and disease [Hughes and John, 1999; Basar et al., 2004].

The changes in the power spectrum of the EEG signal have revealed important information about the electrical activity of the brain when suffering from depressive disorder.

Frontal asymmetry of the EEG alpha power has been studied as an individual difference variable rather than a variable associated with psychopathological condition. According to Allen et al. (2004), changes in asymmetry scores examined at 4-week intervals for 8 and 16 weeks were insignificantly related to changes in the clinical state, moreover depressives demonstrated stability that is comparable in magnitude to that seen in non–clinical populations.

Salustri et al. (2007) have demonstrated that the patient's parietal alpha is higher in the right than in the left hemisphere. It should be noted that the patients studied were not completely drug free. For this reason, it is impossible to rule out the possibility that results are an effect of drug assumption. Nevertheless, since all patients were well below the drugs' steady state levels when the data were recorded, their relation to the patients' clinical pictures suggests that an unbalance of the excitatory or inhibitory cortical activity, and especially a potentiation of the parietal afferent to the motor cortex, may be significant hallmarks of depression.

When studying resting frontal alpha asymmetry in 306 individuals aged 18-34 (31% male), using a current source density reference, Steward et al.(2010) concluded that major depressive disorder is linked relatively less to left frontal activity for both sexes. It was suggested that current source density referenced EEG asymmetry is a possible endophenotype for depression.

In their analysis of resting EEG stability, Vuga et al. (2006) concluded that the EEG alpha asymmetry reflects a stable individual difference that is robust to variation in the clinical state.

Smith et al. (2007) investigated whether the common genetic factor underlying the risk for depression is reflected in individual differences in the frontal asymmetry of the EEG alpha power. After the examination of the frontal asymmetry of the EEG alpha power of 732 twins and their singleton, the authors conclude that a significant relation between frontal asymmetry and risk for depression was only found in young adults (males 32% and females 37%). The evidence for alpha asymmetry to be a marker of vulnerability for a familiar form of depression was found by Bruder et al. (2012) as well as by Keune et al. (2011).

On the other hand, in the study of Debener et al. (2000), the depressed patients failed to show more left than right anterior alpha activity, whereas healthy controls had markedly more right than left anterior alpha activity, i.e. relatively greater activation of left anterior regions.

The results of studies of Henriques and Davidson (1990, 1991) demonstrated that depressed subjects have less left-sided anterior and less right-side posterior activation (i.e. more alpha power) than the subjects never depressed.

EEG activity of depressed subjects differs from that of healthy subjects in various brain areas, not only in the frontal region. Interhemisphere asymmetry in the whole cortex with right hyperactivity in frontal, parietal and occipital brain regions was observed by Fingelkurts et al. (2006). Although the frontal EEG asymmetry literature has traditionally focused on alpha power, it is important to examine actual brain oscillation in a wide frequency range, as this may provide additional information not reflected in the alpha band [Fingelkurts et al., 2006].

Knott et al. (2001) investigated the resting eyes-closed EEG collected from 70 unmedicated depressive male patients and 23 normal control male subjects. It was suggested that overall relative power and, at bilateral anterior regions, absolute power in the beta frequency band differentiated patients and controls, with the patients exhibiting more power than the controls; as compared to the depressive group, controls exhibited relatively reduced left hemisphere activation.

Yamada et al. (1995) noted that patients with anxiety type depression had greater beta1 and beta2 power than normal controls, and the differences were statistically significant over the parietal and occipital regions in the beta1 band.

In some cases the inter-hemispheric coherence analysis was applied. Coherence is a technique that quantifies the similarity between the EEG waveforms generated at a pair of electrodes and it is considered to be an indicator of independence between those sites [Sritharan et al., 2005]. The coherence analysis for alpha and beta bands revealed reduced intra-hemispheric coherence values for depressed subjects compared to healthy controls [Knot et al., 2001; Yamada et al., 1995].

Other studies have used a source localization method called Low Resolution Electromagnetic Tomography (LORETA) to examine changes in brain activity. LORETA has been used to evaluate different aspects in depression patients, such

as inter-hemispheric asymmetry or patterns of brain activation in depressed patients.

Pizzagalli et al. (2002) analyzed the resting EEG recorded in 38 unmedicated subjects with major depressive disorder and 18 normal comparison subjects. Depressed subjects showed more excitatory (beta3, 21.5-30.0 Hz) activity in the right superior and inferior frontal lobe than comparison subjects.

Lubar et al. (2003) compared the current density power and power asymmetry in 15 unmedicated chronically depressed females and age-matched healthy female controls. Increased alpha2 (10-12 Hz) current density in the left hemisphere as compared to the right hemisphere was observed in depressed individuals. Decreased current density in the delta band was observed in the right temporal lobe and the same trend was seen also in the theta, alpha and beta band.

Using LORETA, Flor-Herny et al. (2004) also compared the source-current densities from a group of 25 unmedicated male subjects with depression and a group of 65 matched controls. The current density from the right hemisphere in the delta, alpha and beta frequency bands both during the resting and cognitively challenged conditions was reported. The expected left anterior hypoactivation in depression (reflected by increased resting left frontal EEG power in the alpha band compared to controls) was not observed. The results suggested exactly the opposite, i.e., increased activation of the left frontal lobe and decreased activation of the right frontal lobe.

By use of LORETA, Saletu et al. (2010) demonstrated a decrease in power in the theta frequency band in a menopausal syndrome female with the diagnosis of a depressive episode compared to healthy controls.

Ricardo-Garcell et al. (2009) applied Variable Resolution Electromagnetic Tomography (VARETA) to estimate the source generators of the EEG data. The results suggested that any of the two hemispheres could be affected by depressive disorder, but abnormal EEG sources can be found more frequently in the right hemisphere, which demonstrated its maximum at the alpha and theta bands in frontal and parietal regions.

Using Independent Component Analysis, Grin-Yatsenko et al. (2010) showed an increase in power in depressed patients in theta (4-7.5Hz), alpha (7.5-14Hz), and beta (14-20Hz) in parietal and occipital brain regions.

A brief review of literature demonstrates that during the past decades frontal inter-hemispheric asymmetry has been considered to be almost the only indicator of depression and emotional effect [Henriques and Davidson, 1990, 1991; Steward et al., 2010; Allen et al., 2004; Bruder et al. 2011; Keune et al. 2010]. However, the results of the studies are often contradictory, showing first that remission of depression is not accompanied by changes in the frontal asymmetry [Henriques and

Davidson, 1990; Vuga et al., 2006] and second, the anterior asymmetry is not always related to depression [Reid et al., 1998; Debener et al., 2000]. Thus, considering mixed results of scientific studies not allowing us to draw useful conclusions regarding to the evaluation of depressive mode, the demand for modern methods for detection of depressive disorders is justified.

In this study sensitivity of the three EEG signal analysis methods to discover depression related changes in the signal were evaluated:

- inter-hemispheric asymmetry (IhA) as a traditional method – Publication V;
- inter-hemispheric coherence (IhC) as a traditional method – Publication V;
- spectral asymmetry index (SASI) as a novel method to evaluate depressive disorder based on the EEG frequency spectrum analysis - Publication IV, Publication V, Publication VI, Publication VII.

3. EXPERIMENTAL STUDIES: RESULTS AND DISCUSSION

3.1 Analysis methods

In order to evaluated the changes in EEG signal caused by microwave exposure and mental disorder the different methods were applied in this study.

The evaluation the microwave exposure induced changes was done using the three different EEG analysis methods.

The method of integration of differences (ID) was similar to that applied in studies performed by Hinrikus et al 2008 a, b. The relative changes in the recorded EEG signal between the cycle segments with and without exposure were selected as a measure to detect the microwave effect on the EEG power.

The average value of the EEG power s_i of an arbitrary comparison segment i was calculated as

$$s_i = \frac{1}{N}\sum_{r=1}^{N}[x(r)]^2 \qquad (1)$$

where x(r) is the amplitude of the recorded signal in a sample r and N is the number of samples. Parameter S_c as the relative changes in the power of the recorded segments with and without exposure for a cycle was calculated as follows:

$$S_c = \left(\frac{s_2}{s_1} - 1\right) \text{x } 100\% , \qquad (2)$$

where s_1 and s_2 are the average powers inside the comparison segments without and with exposure, respectively.

The second method applied was the inter-hemispheric asymmetry. The used methods imply 2 main steps: first, the alteration in EEG energies of the theta, alpha, beta1 and beta2 frequency bands caused by microwaves exposure were analyzed using method of ID. Finally, the intra-hemispheric asymmetry A was calculated as follows:

$$A = S_L - S_R \qquad (3)$$

where S_L and S_R are S-parameters calculated for left or right hemisphere symmetric channel, respectively.

The Spectral Asymmetry Index (SASI) was the third method applied. SASI is calculated as relative differences between the higher and the lower EEG frequency band power. The balance of the powers characterizes the EEG spectral asymmetry. Important aspect of the method is exclusion of the central (alpha) band frequencies from the analysis. Therefore, the boundary frequencies were adjusted taking into account the alpha frequency range in the EEG power spectrum.

Calculation of the SASI comprises four main steps:
(1) computing of power spectral density of the recorded EEG signal;
(2) selection of boundary frequencies of the lower and higher specific EEG frequency bands;
(3) calculation of the EEG signal power in the selected bands; and
(4) calculation of the SASI as a combination of the EEG powers in the selected bands.

At first, the frequency with the maximum spectral power f_{max} in the region of alpha band 8–13 Hz of the EEG signal should be estimated.

The frequency limits for the lower and the higher specific frequency bands are related to the estimated central alpha band and determined as follows: the lower frequency band from F1 = (fc – B - 4) Hz to F2 = (fc - B) Hz, and the higher frequency band from F3 = (fc + B) Hz to F4 = (fc + B + 24) Hz, where the B is half-width of the band..

The EEG signal powers W_{lmn} and W_{hmn} in the lower and in the higher EEG frequency bands, respectively, are calculated as follows:

$$W_{lmn} = \sum_{f=F1}^{F2} S_{mn}; \qquad W_{hmn} = \sum_{f=F3}^{F4} S_{mn} \qquad (4)$$

Finally, the SASI is calculated as

$$SASI_{mn} = \frac{W_{hmn} - W_{lmn}}{W_{hmn} + W_{lmn}} \qquad (5)$$

The changes in EEG signal caused by depressive disorder were evaluated using following methods.

The traditionally used inter-hemispheric (IhA) EEG asymmetry was calculated as relative EEG power in the left W_{Lmn} and the right W_{Rmn} hemisphere symmetric channels in each EEG frequency bands as follows

$$A_{mn}(f_1, f_2) = \frac{W_{Lmn} - W_{Rmn}}{W_{Lmn} + W_{Rmn}} \times 100 \qquad (6)$$

The traditionally used inter-hemispheric coherence (IhC) values for each EEG frequency band were calculated using the formula:

$$c_{xy}(f_1, f_2) = \frac{\left(\sum_{f=f_1}^{f_2} s_{xy}\right)^2}{\sum_{f=f_2}^{f_2} s_{xx}(f) \times \sum_{f=f_1}^{f_2} s_{yy}(f)} \qquad (7)$$

where s_{xy} is the power cross-spectral density of the two signals; s_{xx} *a*nd s_{yy} are the power spectral densities of each signal.

As the third method the SASI method was applied.

3.2 Changes in the EEG power caused by microwave radiation

In all experiments the 450 MHz microwave radiation pulse-modulated at fixed modulation frequency was used. The fixed modulation frequency of one-minute long periods was repeated for several times, each exposure minute was followed by a resting segment without exposure. In each experiment the EEG during 10 exposure cycles was recorded. The signal analyses were performed by summarizing the impact of all 10 exposure cycles. The microwave induced effect was evaluated by implementing different signal analysis methods.

A dose–response relationship between the EMF intensity and the magnitude of microwaves induced effect on the human brain activity has been discussed in *Publication I.* The 450 MHz microwave exposure modulated at 40 Hz frequency was applied to a group of 15 healthy volunteers at two different SAR levels: higher level of 0.303 W/kg and lower level of 0.003 W/kg. To evaluate the effect on pulse-modulated microwave radiation at different levels of exposure the method of ID was used.

The results of the experiment performed revealed the dose-dependence relationship of the modulated microwave effect: the average values of relative

changes were higher at the higher level of exposure than at the lower level. The microwave exposure caused an increase in relative changes in the EEG power between the exposed and the resting segments compared to reference recordings for the whole group and for individual subjects at both SAR levels.

Relative changes averaged over the whole group showed maximal increase of the EEG power in the EEG beta 2 frequency band: 157% at the SAR level of 0.303 W/kg and 39% at the SAR level of 0.003W/kg. The increase of the changes in the alpha band was about two times lower, 68 % at the SAR of 0.303W/kg and not evident at the lower SAR.

The number of subjects statistically affected by microwave exposure was 40-60% higher (6 subjects in alpha, 4 subjects in beta1 and beta2 bands) at the higher SAR value of 0.303 W/kg compared to that (3 subjects in alpha, beta1 and beta2 bands) at the lower SAR of 0.003 W/kg. The same subjects were sensitive at the higher and lower level of exposure. For all subjects having significant difference between the reference and the microwave exposed series, the average relative changes were positive; consequently, the level of power in segments with exposure was higher than in segments without exposure.

The relative part of affected subjects was 40% for alpha and 27% for beta bands at the higher SAR and 20% for alpha and beta bands at the lower SAR.

The results are close to these in the study of Hinrikus et al. (2008a), where the same exposure conditions were applied (450 MHz, modulation frequency 40 Hz, SAR=0.303 W/kg), showing a relative part of affected subjects in parietal channels P3-P4 in the beta1 band to be 20% (3 subjects). This finding agrees with the results of Regel et al. (2007b) whose report provides evidence for a dose-response relationship: spectral power of the sleep EEG in the fast spindle frequency range increased by 7.7% after radiofrequency exposure at a SAR of 0.2 W/ kg, and 13.6% after exposure at 5 W/kg.

The traditional use of a mobile phone causes strongly asymmetric distribution of field power density inside the human head. Therefore, enhancement in the asymmetry of the EEG parameters between the brain hemispheres can be an indicator of the effect. Microwave exposure induced inter-hemispheric asymmetry has been discussed in *Publication II*. To analyze the energies for theta, alpha, beta1 and beta2 EEG frequency bands in different EEG channels the method of ID was applied. Finally, the intra-hemispheric asymmetry was calculated as relative differences between ID values in the right and left symmetrical channels. The quarter-wave antenna was located at 10 cm from the left side of the head. Differences in the calculated SAR values between the hemispheres were up to 20 dB.

The results of this study showed that 450 MHz microwave radiation modulated at 14 and 40 Hz (SAR = 0.303 W/kg) altered EEG asymmetry between hemispheres and increased the EEG energy from the left side, where the microwave power density was higher, and asymmetry scores are more positive in microwave exposed conditions. The demonstrated increase in the EEG power in the exposed hemisphere is in good agreement with the study of Hinrichs and Heinze (2004) who reported a difference in the total EEG power in the left (exposed) hemisphere applying the GSM type signal with the SAR value of 0.61 W/kg [Hinrichs and Heinze, 2004].

The greatest difference in the asymmetry values occurs in the temporal-parietal brain region. However, differences in asymmetry between the exposed and sham-exposed recordings were not statistically significant for a group. Statistical analysis performed for individuals revealed significant differences in the asymmetry between the exposed and the sham-exposed recordings for 2 subjects (15%) at 14 Hz and 5 subjects (35%) at 40 Hz modulation frequency.

The spectral asymmetry index (SASI) for the evaluation of small hidden changes in the EEG caused by microwave exposure was used in the study summarized in *Publication III*. The 450 MHz microwave exposure modulated at 40 Hz frequency with the SAR value of 0.303 W/kg was applied.

The experimental results showed negative average values of SASI in both microwave exposure and sham conditions, but average SASI values were more positive in the microwave exposed condition. The increase in SASI values indicates increased power in the higher beta band as a response to microwave radiation and it is in good agreement with the results reported in other studies [Huber et al., 2005; Hinrikus et al., 2008b; Curcio et al., 2005]. Changes in the EEG produced in the case of microwave exposure are very similar with the human nervous system reaction to such chemical (toxic) stressors like alcohol and cocaine: the increase in the beta EEG power has been reported in several studies [Herning et al., 1997; Costa et al., 1997; Rangaswamy et al., 2002].

The Student t-test revealed changes between the sham and the microwave conditions to be statistically significant for the whole group in parietal (P3, P4 channels), temporal (T3, T4 channels) and occipital (O1, O2 channels) brain areas.

The SASI values calculated for individual subjects were also more positive with the exposure for the majority of subjects. The percentage of the subjects showing more positive values as a reaction to microwaves was the same for all the analyzed channels.

In summary, it was reported that the ID and SASI methods revealed a significant increase in the EEG power for the group of subjects and for a number of individual subjects. However, the IhA method detected significant alterations only

for a smaller number of individual subjects. Thus, it can be concluded that the result of the evaluation of microwave induced effect depends on the EEG analysis procedure, pointing out that statistically significant changes may vary with the analysis method applied.

The observation that microwave induced alteration in the EEG signal were demonstrated at different non-thermal levels of exposure using different analysis methods provides strong evidence for the presence of the effect that has been a topic of debate for decades.

3.3 Evaluation of depressive disorder

Subjective symptoms of depression are accompanied by objective alterations in the brain activity and in the EEG signal.

As we proposed in *Publication IV*, the detection of depression can be based on the analysis of the EEG frequency spectrum. The proposed spectral asymmetry index (SASI) is calculated as relative differences in the power of two EEG special frequency bands selected higher and lower of the EEG spectrum maximum (beta and theta bands). The EEG central frequency band round the spectrum maximum (alpha band) was excluded from the calculations. The boundary frequencies of the bands, as related to the frequency of the EEG spectrum maximum, were selected for each individual. The selected beta and theta bands can be shifted in the case of low or high spectrum maximum.

In the study reviewed in *Publication V* the sensitivity of different well-known electroencephalographic indicators (IhA and IhC) for the detection of depression and introduced novel spectral asymmetry index SASI were compared using the database of EEG signals collected from the same subjects.

Previous papers conclude that the EEG beta band differentiates the depressive patients and the healthy controls [Yamada et al., 1995; Flor-Henry et al., 2004; Grin-Yatsenko et al., 2010] and that the EEG beta band is associated with mental depression [Sun et al, 2008].

The calculated EEG asymmetry between the left and right brain hemisphere was similar in both groups and no statistically significant differences between depressive patients and healthy controls were detected. Neither did the EEG coherence analysis reveal any significant differences between the depressive and the control group. The EEG IhC showed even an opposite direction of differences between depressive and healthy subjects in different brain regions.

At the same time, the difference in SASI between the depressive and the control group is remarkable in all channels, showing positive values for patients with depressive disorder (except for 2 of 18) and negative values for healthy subjects (except for 3 of 18). The changes in polarity of SASI were determined by the

balance of the higher and the lower EEG frequency band power. The SASI is well correlated with the 17-item Hamilton Depression Rating Scale scores traditionally applied for those diagnosed of depression. The SASI values calculated between the depressive and the healthy group differ significantly in all channels ($p<0.005$). Hence, it was suggested that the method is a promising measure for the evaluation of depression.

On the basis of the results it can be concluded that the introduced SASI provides better results in the detection of depression than the EEG inter-hemispheric asymmetry and coherence measures.

Results presented in *Publication VI* demonstrate the dependence of SASI on the EEG signal length of 1, 5 and 30 min. The results for the control group showed the same trend as reported by Maltez et al. (2004), demonstrating a decrease in the beta power towards the end of the recording session in resting conditions, whereas the theta power showed a systematic increase. At the same time, the stability of the SASI values for depressive subjects at different signal lengths indicate a constant high level of the EEG beta band power during long-term recordings.

In the SASI method the bandwidths of the higher and lower EEG frequency bands are selected depending on the EEG alpha maximum. The individual alpha frequency varies normally in the range of 8 to 12 Hz. The maximum alpha frequency changes over the lifespan, increasing up to adolescence and decreasing after that. The importance of evaluation on the individual alpha maximum was discussed in *Publication VII*. It was pointed out that individual tuning of the EEG frequency bands provides much more consistent results in the calculation of the spectral asymmetry index than by use of fixed traditional EEG frequency bands. Therefore, while applying the SASI method, the individual selection of EEG frequency bands is recommended.

CONCLUSIONS

The study explores the capability of different EEG signal analysis methods to detect changes in the human EEG signal produced by different stressors. In this thesis the alteration in the EEG signal produced by the microwave exposure and depressive disorders were evaluated. Grouped according to the research topic, the main conclusions are listed below:

Microwave radiation studies:

a) The effect of microwave radiation on the brain electrical activity depends on the level of exposure. The results showed that the decrease of the microwave field 20 dB reduces microwave related changes in the EEG signal 5-8 dB.
b) Microwave exposure induced effects were demonstrated using all three methods selected for the EEG analysis (the methods of integration of differences, inter-hemispheric asymmetry and spectral asymmetry index).
c) Resulting from microwave induced alterations in the EEG signal demonstrated by different analysis methods and at different non-thermal levels of exposure, strong evidence of the effect is demonstrated; to emphasize that it has been a topic of debate for decades.

Depressive disorder evaluation:

a) Traditional methods in the evaluation of depression induced changes in the EEG signal, like inter-hemispheric asymmetry and coherence, are not sensitive enough in the evaluation of disorder specific changes in the EEG signal.
b) The Spectral Asymmetry Index introduced provides promising results in evaluating depressive disorder. Results show positive SASI values for the depressive group and negative SASI values for the control group. The SASI is also well correlated with HAM-D scores traditionally applied for diagnoses of depression.

Overall conclusions:

1. The result of the evaluation of microwave induced effect and alterations produced by mental disorder depend on the EEG analysis procedure; statistically significant changes may vary with the analysis method applied.
2. SASI method is sensitive to evaluation changes in the EEG signals produced by modulated microwave radiation and depressive disorder implying that the method detects changes in the brain bioelectrical activity caused by different stressors.

REFERENCES

Abasolo, D., Hornero, R., Escudero, J., Espino, P. (2008). A study on the possible usefulness of detrended fluctuation analysis of the electroencephalogram background activity in Alzheimer's disease. *IEEE Trans Biomed Eng,* 55: 2171–2179.

Adeli, H., Ghosh-Dastidar, S., Dadmehr, N. (2008). A spatio-temporal wavelet-chaos methodology for EEG-based diagnosis of Alzheimer's disease. *Neurosci Lett,* 444:190–94.

Allen, J.B., Urry, H.L,, Hitt, S.K., Coan, J.A. (2004). The stability of resting frontal electroencephalographic asymmetry in depression. *Psychophysiology*, 41: 269–80.

Ansseau, M., Demyttenaere, K., Heyrman, J., Migeotte, A., Leyman, S., Mignon, A. (2009). Objective: remission of depression in primary care The Oreon Study. *Eur Neuropsychopharmacol,* 19(3):169-76.

Bruder, G.E., Bansal, R., Tenke, C.E., Liu, J., Hao, X., Warner, V., Peterson, B.S., Weissman, M.M. (2012). Relationship of resting EEG with anatomical MRI measures in individuals at high and low risk for depression. *Hum Brain Mapp*, 33(6):1325-33.

Challis, L.J. (2005). Mechanisms for interaction between RF fields and biological tissue. *Bioelectromagnetics,* Suppl 7:S98-S106.

Costa, L., Bauer, L. (1997). Quantitative electroencephalographic differences associated with alcohol, cocaine, heroin and dual-substance dependence. *Drug Alcohol Depend,* 46:87–93.

Council of Europe. (2011). The potential dangers of electromagnetic fields and their effect on the environment. Parliamentary Assembly, Resolution 1815. 27. May 2011. Strasbourg, France.

Croft, R.J., Chandler, J.S., Burgess, A.P., Barry, R.J., Williams, J.D., Clarke, A.R. (2002). Acute mobile phone operation affects neural function in humans. *Clin Neurophysiol,* 113: 1623–32.

Croft, R.J., Leung S., McKenzie, R.J. , Loughran, S.P., Iskra, S., Hamblin, D.L. , Cooper, N.R. (2010). Effects of 2G and 3G Mobile Phones on Human Alpha Rhythms:Resting EEGin Adolescents, Young Adults, and the Elderly. *Bioelectromagnetics,* 31(6):434-44.

Croft, R.J., Hamblin, D.L., Spong, J., Wood, A.W., McKenzie, R.J., Stough, C. (2008). The effect of mobile phone electromagnetic fields on the alpha rhythm of human electroencephalogram. *Bioelectromagnetics,* 29(1):1-10.

Curcio, G., Ferrara, M., De Gennaro, L., Cristiani, R., D'Inzeo,G., Bertini, M. (2004). Time-course of electromagnetic field effects on human performance and tympanic temperature. *Neuroreport*, 15(1):161–4.

Curcio, G., Ferrara, M., Moroni, F., D'Inzeo, G., Bertini, M., De Gennaro, L. (2005). Is the brain influenced by a phone call? An EEG study of resting wakefulness. *Neurosci Res*, 53:265–70.

D'Costa, H., Trueman, G., Tang, L., Abdel-rahman, U., Abdel-rahman, W., Ong, K., Cosic, I. (2003). Human brain wave activity during exposure to radiofrequency field emissions from mobile phones. *Australasian Phys Eng Sci Med,* 26(4):162-7.

Danker-Hopfe, H., Dorn, H., Bahr, A., Anderer, P., Sauter, C. (2011). Effects of electromagnetic fields emitted by mobile phones (GSM 900 and WCDMA/UMTS) on the macrostructure of sleep. *J Sleep Res,* 20:73-81.

Debener, S., Beauducel, A., Nessler, D., Brocke, B., Heilemann, H., Kavser, J.(2000). Is resting anterior EEG alpha asymmetry a trait marker for depression? Findings for healthy adults and clinically depressed patients. *Neuropsychobiology,* 41:31-37.

European Health Risk Assessment Network on Electromagnetic Fields Exposure Deliverable Report D2 - Risk analysis of human exposure to electromagnetic fields. (2010). http://efhran.polimi.it/docs/EFHRAN_D2_final.pdf

Fingelkurts, A.A., Fingelkurts, A.A, Rytsälä H., Suominen, K., Isometsä, E., Kähkönen, S. (2007). Impaired functional connectivity at EEG alpha and theta frequency bands in major depression. *Hum Brain Mapp,* 28(3):247-61.

Fingelkurts, A.A., Fingelkurts, A.A., Rytsälä, H., Suominen, K., Isometsä, E., Kähkönen, S. (2006). Composition of brain oscillations in ongoing EEG during major depression disorder. *Neurosci Res*, 56(2):133-44.

Flor-Henry, P., Lind, J.C., Koles, Z.J. (2004). A source-imaging (low-resolution electromagnetic tomography) study of the EEGs from unmedicated males with depression. *Psychiatry Res*, 109:191–207.

Freude, G., Ullsperger, P., Eggert, S., Ruppe, I. (2000). Microwaves emitted by cellular phones affect human slow brain potentials. *Eur J Appl Physiol,* 81(1-2):18-27.

Fritzer, G., Göder, R., Friege, L., Wachter, J., Hansen, V., Hinze-Selch, D., Aldenhoff, J.B. (2007). Effects of short- and long-term pulsed radiofrequency electromagnetic fields on night sleep and cognitive functions in healthy subjects. *Bioelectromagnetics,* 28(4):316-325.

Gandhi, O.P. (2002). Electromagnetic fields: human safety issues. *Annu Rev Biomed Eng,* 4:211-34.

Haarala, C., Takio, F., Rintee, T., Laine, M., Koivisto, M., Revonsuo, A., Hämäläinen, H. (2007). Pulsed and continuous wave mobile phone exposure over

left versus right hemisphere: effects on human cognitive function. *Bioelectromagnetics,* 28(4):289-95.

Hamblin, D,L., Wood, A.W., Croft, R.J., Stough, C. (2004). Examining the effects of electromagnetic fields emitted by GSM mobile phones on human event-related potentials and performance during an auditory task. *Clin Neurophysiol,* 115(1):171–178.

Hamblin, D.L., Croft, R.J., Wood, A.W., Stough, C., Spong, J. (2006). The sensitivity of human event-related potentials and reaction time to mobile phone emitted electromagnetic fields. *Bioelectromagnetics,* 27(4):265-27.

Hardell, L., Sage, C. (2008). Biological effects from electromagnetic field exposure and public exposure standards. *Biomed Pharmacother,* Volume 62, Issue 2, pp. 104–109.

Henderson, G., Ifeachor, E., Hudson, N., Goh, C., Outram, N., Wimalaratna, S., Del Percio, C., Vecchio, F. (2006). Development and assessment of methods for detecting dementia using the human electroencephalogram. *IEEE Trans Biomed Eng,* 53(8):1557–1568.

Henriques, J.B., Davidson, R.J. (1991). Left frontal hypoactivation in depression. *J Abnorm Psychol,* 100:535-545.

Henriques, J.B., Davidson, R.J. (1990). Regional brain electrical asymmetries discriminate between previously depressed and healthy control subjects. *J Abnorm Psychol,* 99(1):22-31.

Herning, R.I., Guo, X., Better, W.E., Weinhold, L.L., Lange, W.R., Cadet, J.L., Gorelick, D.A. (1997). Neurophysiological signs of cocaine dependence: Increased electroencephalogram beta during withdrawal. *Biol Psychiatry,* 41:1087–1094.

Hinrichs, H., Heinze, H.J. (2004). Effects of GSM electromagnetic field on the MEG during an encoding-retrieval task. *Neuroreport,* 15(7):1191-1194.

Hinrikus, H., Bachmann, M., Lass. J., Karai, D., Tuulik, V. (2008a). Effect of low frequency modulated microwave exposure on human EEG: individual sensitivity. *Bioelectromangenitcs,* 29(7):527-538.

Hinrikus, H., Bachmann, M., Lass, J., Tomson, R., Tuulik, V. (2008b). Effect of 7, 14 and 21 Hz modulated microwave radiation on human electroencephalographic rhythms. *Int J Radiat Biol,* 84(1):66-79.

Huber, R., Graf, T., Cote, KA., Wittmann, L., Gallmann, E., Matter, D., Schuderer, J., Kuster, N., Borbery, AA., Achermann, P. (2000). Exposure to pulsed high-frequency electromagnetic field during waking affects human sleep EEG. *NeuroReport*, 11:3321–3325.

Huber, R., Treyer, V., Borbely, AA., Schuderer, J., Gottselig, JM., Landolt, HP., Werth, E., Berthold, T., Kuster, N., Buck A, Achermann , P. (2002).

Electromagnetic fields, such as those from mobile phones, alter regional cerebral blood flow and sleep and waking EEG. *J Sleep Res,* 11:289–295.

Huss, A., Küchenhoff, J., Bircher, A., Heller, P., Kuster, H., Niederer, M., Scartazzini, G., Schwarzenbach, S., Waeber, R., Wegmann, L., Braun-Fahrländer, C. (2004). Symptoms attributed to the environment--a systematic, interdisciplinary assessment. *Int J Hyg Environ Health,* 207(3):245-54.

Hyland, G.J. (2000). Physics and biology of mobile telephony. *Lancet*, 356 (9244):1833–1836.

ICNIRP Guidelines. Guidelines for limiting exposure to time-varying electric, magnetic, and electromagnetic fields (up to 300 GHz). (1998). Health Physics 74: 484-522.

Juutilainen, J., Höytö, A., Kumlin, T., Naarala, J. (2011). Review of possible modulation-dependent biological effects of radiofrequency fields. *Bioelectromagnetics*, 32(7):511-34.

Keune, P.M., Bostanov, V., Hautzinger, M., Kotchoubey, B. (2011). Mindfulness-based cognitive therapy (MBCT), cognitive style, and the temporal dynamics of frontal EEG alpha asymmetry in recurrently depressed patients. *Biol Psychol,* 88(2-3):243-52.

Kleinlogel, H., Dierks, T., Koenig, T., Lehmann, H., Minder, A., Berz, R.(2008). Effect of weak mobile phone- electromagnetic fields (GSM, UMTS) on well-being and resting EEG. *Bioelectromagnetics,* 29(6):479-87.

Knott, V., Mahoney, C., Kennedy, S., Evans, K. (2001). EEG power, frequency, asymmetry and coherence in male depression. *Psychiatry Res,* 106: 123–140.

Krause, C., Haarala, C., Sillanmäki, L., Koivisto, M., Alanko, K., Revonsuo, A., Laine, M., Hämäläinen, H. (2004). Effects of electromagnetic field emitted by cellular phones on the EEG during an auditory memory task: a double blind replication study. *Bioelectromagnetics,* 25(1):33-40.

Krause, C.M., Pesonen, M., Haarala Bjornberg, C., Hamalainen, H. (2007). Effects of pulsed and continuous wave 902 MHz mobile phone exposure on brain oscillatory activity during cognitive processing. *Bioelectromagnetics,* 28(4):296–308.

Kwon, M., Hämäläinen, H. (2011). Effects of mobile phone electromagnetic fields: critical evaluation of behavioral and neurophysiological studies. *Bioelectromagnetics,* 32(4): 253-72.

Loughran, S.P., McKenzie, R.J., Jackson, M.L., Howard, M.E., Croft, R.J. (2012). Individual differences in the effects of mobile phone exposure on human sleep: rethinking the problem. *Bioelectromagnetics,* 33(1):86-93.

Loughran, S.P., Wood, A.W., Barton, J.M., Croft, R.J., Thompson, B., Stough, C. (2005). The effect of electromagnetic fields emitted by mobile phones on human sleep. *Neuroreport,* 16(17):1973-6.

Lowden, A., Akerstedt, T., Ingre, M., Wiholm, C., Hillert, L., Kuster, N., Nilsson, J.P., Arnetz, B. (2011). Sleep after mobile phone exposure in subjects with mobile phone-related symptoms. *Bioelectromagnetics,* 32(1):4-14.

Lubar, J.F., Congedo, M., Askew, J.H. (2003). Low-resolution electromagnetic tomography (LORETA) of cerebral activity in chronic depressive disorder. *Int J Psychopathol* 49: 175–85.

Maby, E, Le Bouquin Jeannes, R., Liégeois-Chauvel, C., Gourevitch, B., Faucon, G. (2004). Analysis of auditory evoked potential parameters in the presence of radiofrequency fields using a support vector machines method. *Med Biol Eng Comput,* 42(4):562-68.

Maby, E., Le Bouquin Jeanes, R., Faucon, G. (2006b). Scalp localization of human auditory cortical activity modified by GSM electromagnetic fields. *Int J Radiat Biol,* 82(7):465-72.

Maby, E., Le Bouquin Jeannès, R., Faucon, G. (2006a). Short-term effects of GSM mobiles phones on spectral components of the human electroencephalogram. *Conf. Proc. IEEE Eng. Med. Biol. Soc,* 1:3751–54.

Maltez, J., Hyllienmark, L., Nikulin, V., Brismar, T. (2004). Time course and variability of power in different frequency bands of EEG during resting conditions. *J Clin Neurophysiol* 34: 195–202.

Perentos, N., Croft, R.J., McKenzie, R.J., Cvetkovic, D., Cosic, I. (2007). Comparison of the effects of continuous and pulsed mobile phone like RF exposure on the human EEG. *Australas Phys Eng Sci Med,* 30(4):274-80.

Pizzagalli, D.A., Nitschke, J.B., Oakes, T.R., Hendrick, A.M., Horras, K.A., Larson, C.L., Abercrombie, H.C., Schaefer, S.M., Koger, J.V., Benca, R.M., Pascual-Marqui, R.D., Davidson, R.J. (2002). Brain electrical tomography in depression: the importance of symptom severity, anxiety, and melancholic features. *Biol Psychiatry,* 52(2):73-85.

Rangaswamy, M., Porjesz, B., Chorlian, D.B., Wang, K., Jones, K.A., Bauer, L.O., Rohrbaugh, J., O'Connor, S.J., Kuperman, S., Reich,T,, Begleiter. H. (2002) Beta power in the EEG of alcoholics. *Biol Psychiatry,* 52(8):831–42.

Regel. S.J., Gottselig, J.M., Schuderer, J., Tinguely, G., Rétey, J.V., Kuster, N., Landolt, H.P., Achermann, P. (2007a). Pulsed radio frequency radiation affects cognitive performance and the waking electroencephalogram. *Neuroreport*, 28 18(8):803-07.

Regel, S., Tinguely, G., Schuderer, J., Adam, M., Kuster, N., Landolt, H. (2007b). Pulse radio-frequency electromagnetic fields: dose-dependent effects on sleep, the sleep EEG and cognitive performance. *J Sleep Res*, 16, 253-58

Reid, S., Duke, L., Allen, J. (1998). Resting frontal electroencephalographic asymmetry in depression: Inconsistencies suggest the need to identify mediating factors. *Psychophysiology,* 35: 389–404.

Ricardo-Garcell, J., González-Olvera, JJ., Miranda, E., Harmony, T., Reyes, E., Almeida, L., Galán, L., Díaz, D., Ramírez, L., Fernández-Bouzas, A., Aubert, E. (2009). EEG sources in a group of patients with major depressive disorders. *Int J Psychophysiol*, 71(1):70-4.

Richards, D. (2011). Prevalence and clinical course of depression: A review. *Clinical Psychology Review,* 31: 1117-25.

Röösli, M., Moser, M., Baldinini, Y., Meier, M., Braun-Fahrländer C. (2004). Symptoms of ill health ascribed to electromagnetic field exposure--a questionnaire survey. *Int J Hyg Environ Health,* 207(2):141-50.

Saletu, B., Anderer, P., Saletu-Zyhlarz, G.M. (2010). EEG topography and tomography (LORETA) in diagnosis and pharmacotherapy of depression. *Clin EEG Neurosci,* 41(4):203-10.

Salustri, C., Tecchio, F., Zappasodi, F., Bevacqua, G., Fontana, M., Ercolani, M., Milazzo, D., Squitti, R., Rossini, P.M. (2007). Cortical excitability and rest activity properties in patients with depression. *J Psychiatry Neurosci,* 32(4):259-66.

Schmid, G., Sauter, C., Stepansky, R., Lobentanz, I.S., Zeitlhofer, J. (2005). No influence on selected parameters of human visual perception of 1970 MHz UMTS-like exposure. *Bioelectromagnetics,* 26(4):243–50.

Schmid, M.R., Loughran, S.P., Regel, S.J., Murbach, M., Bratic Grunauer,A., Rusterholz, T., Bersagliere, A., Kuster, N., Achermann, P. (2012). Sleep EEG alterations: effects of different pulse-modulated radio frequency electromagnetic fields. *J Sleep Res,* 21:50-58.

Schreier, N., Huss, A., Röösli, M. (2006). The prevalence of symptoms attributed to electromagnetic field exposure: a cross-sectional representative survey in Switzerland. *Soz Praventivmed,* 51:202–09.

Simon, G.E., Khandker, R.K., Ichikawa, L., Operskalski, B.H. (2006). Recovery from depression predicts lower health services costs. *J Clin Psychiatry,* 67(8):1226-31.

Sobocki, P., Jönsson, B., Angst, J., Rehnberg, C. (2006). Cost of depression in Europe. *J Ment Health Policy Econ,* 9(2):87-98.

Sritharan, A., Line, P., Sergejew, A., Silberstein, R., Egan, G., Copolov, D. (2005). EEG coherence measures during auditory hallucinations in schizophrenia. *Psychiatry Res*, 136:189-200.

Stewart, J., Bismark, A., Towers, D., Coan, J., Allen, J. (2010). Resting Frontal EEG Asymmetry as an Endophenotype for Depression Risk: Sex-specific Patterns of Frontal Brain Asymmetry. *Abnorm Psychol,* 119(3): 502–12.

Sun, Y., Li, Y., Zhu, Y., Chen, X., Tong, S. (2008). Electroencephalographic differences between depressed and control subjects: an aspect of interdependence analysis. *Brain Res Bull*, 76:559-64.

Takahashi, T. (2012). Complexity of spontaneous brain activity in mental disorders. *Prog in Neuropsychopharmacol Biol Psychiatry*, 2012 May 8. [Epub ahead of print]

Townsend, J.D., Eberhart, N.K., Bookheimer, S.Y., Eisenberger, N.I., Foland-Ross, L.C., Cook, I.A., Sugar, C.A., Altshuler, L.L. (2010). fMRI activation in the amygdala and the orbitofrontal cortex in unmedicated subjects with major depressive disorder. *Psychiatry Res*, 183(3):209-17

Trunk, A., Stefanics, G., Zentai, N., Kovács-Bálint, Z., Thuróczy, G., Hernádi, I.(2012). No effects of a single 3G UMTS mobile phone exposure on spontaneous EEG activity, ERP correlates, and automatic deviance detection. *Bioelectromagnetics,* Jun 4. doi: 10.1002/bem.21740. [Epub ahead of print]

Unterlechner, M., Sauter, C., Schmid, G., Zeitlhofer, J. (2008). No effect of an UMTS mobile phone-like electromagnetic field of 1.97 GHz on human attention and reaction time. *Bioelectromagnetics,* 29:145–53.

van Rongen, E., Croft, R., Juutilainen, J., Lagroye, I., Miyakoshi, J., Saunders, R., de Seze, R., Tenforde, T., Verschaeve, L., Veyret, B., Xu, Z. (2009). Effects of radiofrequency electromagnetic fields on the human nervous system. *J Toxicol Environ Health B Crit Rev,* 12(8):572-97.

Vecchio, F., Babiloni, C., Ferreri, F., Buffo, P., Cibelli, G., Curcio, G., van Dijkman, S., Melgari, J.M., Giambattistelli, F., Rossini, P.M. (2010). Mobile phone emission modulates inter-hemispheric functional coupling of EEG alpha rhythms in elderly compared to young subjects. *Clin Neurophysiol,* 121(2):163-71.

Vecchio, F., Babiloni, C., Ferreri, F., Curcio, G., Fini, R., Del Percio, C., Rossini, P. (2007). Mobile phone emission modulated interhemispheric functional coupling of EEG alpha rhythms. *Eur J of Neurosci*, 25:1908-13.

Vecchio, F., Buffo, P., Sergio, S., Iacoviello, D., Rossini, P.M., Babiloni, C. (2012). Mobile phone emission modulates event-related desynchronization of α rhythms and cognitive-motor performance in healthy humans. *Clin Neurophysiol,* 123(1):121-8.

Vuga, M., Fox, N., Cohn, J., George, C., Levenstein, R., Kovacs, M. (2006). Long-term stability of frontal electronecephalographic asymmetry in adults with a history of depression and controls. *Int J of Psychophysiol*, 59(2):107-15.

Wagner, P., Roschke, J., Mann, K., Fell, J., Hiller, W., Frank, C., Grozinger, M. (2000). Human sleep EEG under the influence of pulsed radio frequency electromagnetic fields. Results from polysomnographies using submaximal high power flux densities. *Neuropsychobiology,* 42(4):207-12.

Wagner, P., Roschke, J., Mann, K., Hiller, W., Frank, C. (1998). Human sleep under the influence of pulsed radiofrequency electromagnetic fields: a polysomnographic study using standardised conditions. *Bioelectromagnetics,* 19(3):199-202.

Wiholm, C., Lowden. A., Kuster, N., Hillert, L., Arnetz, B.B., Akerstedt, T., Moffat, S.D. (2009). Mobile phone exposure and spatial memory. *Bioelectromagnetics,* 30(1):59-65.

World Health Organization. (2012). Global burden of mental disorders and the need for a comprehensive, coordinated response from health and social sectors at the country level (PDF). Sixty-Fifth world health assembly. Provisional agenda item 13.2

Yamada, M., Kimura, M., Mori, T., Endo, S. (1995). EEG power and coherence in presenile and senile depression. Characteristic findings related to differences between anxiety type and retardation type. *Nippon Ika Daigaku Zasshi* 62, 176–185 (in Japanese).

Author's publications

I **Suhhova, A.,** Bachmann, M., Karai, D., Lass, J., Hinrikus, H. (2012). Effect of microwave radiation on human EEG at two different levels of exposure. *Bioelectromagnetics* (in press)

II **Suhhova, A.,** Bachmann, M., Lass, J., Karai, D., Hinrikus, H. (2009). Effect of modulated microwave radiation on human EEG asymmetry. *The Environmentalist*, 29: 210-214.

III **Suhhova, A.,** Hinrikus, H., Bachmann, M., Lass, J. (2009). Effect of modulated microwave exposure on spectral asymmetry of human EEG. *IFMBE Proceedings,* Volume 25/3, pp 406-409.

IV Hinrikus, H., Bachmann, M., Lass, J., **Suhhova, A.,** Tuulik, V. Aadamsoo, K., Võhma, Ü. (2012). Method and device for determining depressive disorders by measuring bioelectromagnetic signals of the brain. US 8244341.

V Hinrikus, H., **Suhhova, A.,** Bachmann, M., Aadamsoo, K., Võhma, Ü., Lass, J., Tuulik, V. (2009) Electroencephalographic spectral asymmetry index for detection of depression. *Med Biol Eng Comput,* 47:1291-1299.

VI Hinrikus, H., **Suhhova, A.,** Bachmann, M., Aadamsoo, K., Võhma, Ü., Pehlak, H., Lass, J. (2010). Spectral features of EEG in depression. *Biomed Tech*, 55: 155-161.

VII **Suhhova, A.,** Bachmann, M., Lass, J., Aadamsoo, K., Võhma, Ü., Hinrikus, H. (2012). EEG spectral asymmetry index for detection of depression at individual and fixed frequency bands. *IFMBE Proceedings,* 39:589-92.

List of author's publications related to the thesis

Bachmann, M., Hinrikus, H., Aadamsoo, K., Võhma, Ü., Lass, J., Rubljova, J., **Suhhova, A.,** Tuulik, V. (2007). Modulated microwave effects on individuals with depressive disorder. *The Environmentalist*, 27:505-510.

Suhhova, A., Bachmann, M., Aadamsoo, K., Võhma, Ü., Lass, J., Hinrikus, H. (2008). EEG coherence as a measure of depressive disorder. *IFMBE Proceedings,* Volume 22:353-355.

Suhhova, A., Bachmann, M., Aadamsoo, K., Võhma, Ü., Lass, L., Hinrikus, H. (2008). Effect of microwave radiation on EEG coherence. *IFMBE Proceedings*, Volume 20:331-334.

Suhhova, A., Bachmann, M., Aadamsoo, K., Võhma, Ü., Lass, J., Hinrikus, H. (2008). EEG coherence in female depression. *Revista Espanola de Neuropsicologia*, 10(1):151- 152.

Hinrikus, H., Bachmann, M., Lass, J., **Suhhova, A.,** Tuulik, V. (2009). Effect of modulated microwave radiation on brain electrical oscillations. *IFMBE Proceedings* Volume 25/3: 585-588.

Suhhova, A., Bachmann, M., Lass, J., Tuulik, V., Hinrikus, H. (2011). EEG spectral asymmetry index reveals effect of microwave radiation. *IFMBE Proceedings,* Volume 37:1206-1209.

Bachmann, M., Lass, J., **Suhhova, A.,** Hinrikus, H. (2011). Effect of low-level electromagnetic field on the balance of the EEG rhythms. *Toward a Science of Consciousness*: 107 – 108.

KOKKUVÕTE

Nõrkade stressorite mõju avastamine inimese puhkeoleku elektroentsefalograafilises signaalis

Käesolev töö hindab erinevate EEG analüüsi meetodite sobilikkust avastamaks väikeseid muutusi EEG signaalis, mis on põhjustatud a) mikrolainekiirguse või b) depressiooni poolt.

Esimeses osas esitatakse ülevaade madalasagedusliku pulss-moduleeritud mikrolainekiirguse mõjust inimajule. Vaadeldakse mõju puhkeoleku- ja une EEG-le. Lisaks antakse ülevaade teadustöödest, mille käigus uuriti efekti inimajule rakendades eri tasemega mikrolainekiirgust.

Töö teises osas on toodud ülevaade uurimustöödest, mille põhisuundadeks on depressioonist tingitud muutuste uurimine EEG signaalis. Samuti antakse kokkuvõttev ülevaade erinevatest depressioonist tingitud muutuste hindamistest kasutades signaali analüüsi meetodeid.

Kolmandas osas annab autor ülevaate teostatud eksperimentaalsetest uurimistöödest, esitletakse nelja signaali analüüsi meetodit ja hinnatakse nende võimekust väikeste muutuste avastamisel EEG signaalis.

Töö tulemusena leiti järgmist:

1. Mikrolainekiirguse mõju inimajule sõltub rakendatud kiirguse tasemest. Töö tulemused näitavad, et mikrolainekiirguse taseme vähendamine 20 dB vähendab muutusi EEG signaalis 5-8 dB.
2. Mikrolainekiirguse mõju EEG signaalile demonstreeriti kasutades kõiki kolme analüüsi meetodit (ID, IhA, SASI)
3. Depressiooni mõju EEG signaalile oli näidatud SASI meetodi abil, IhA ja IhC meetodiga jäid spetsiifilised muutused tuvastamata.

Kokkuvõtvalt saab väita, et erinevate stressorite poolt avaldatud mõju tuvastamine on sõltuvuses kasutatud analüüsimeetodist, statistiliselt oluliste muutuste arv võib varieeruda lähtuvalt kasutatud analüüsi meetodist. SASI meetodit kasutades saab hinnata EEG signaalis muutusi, mis olid esile kutsutud nii mikrolainekiirguse kui ka depressiooni poolt.

Võtmesõnad: mikrolainekiirguse mõju, EM-välja mõju, depressioon, EEG signaal, analüüsi meetodid.

ABSTRACT

Detection of the Effect of Weak Stressors on Human Resting Electroencephalographic Signal

The thesis focuses on the evaluation of the capability of different EEG analysis methods to detect small changes in human resting EEG signal caused by a) an external stressor such as microwave radiation and b) mental disorders such as depression.

Section 1 summarized the effects of low-level pulse-modulated microwave radiation on brain bioelectrical activity. The effects on resting and sleep EEG are discussed. In addition, comparison of the effect of microwave radiation at two different levels of exposure is reviewed.

Section 2 covers addresses the problems of how the EEG signal is affected by mental disorders like depression. Different analysis methods in the evaluation of depression related changes in brain bioelectrical activity are summarized.

Section 3 summarizes the results of the experimental studies of the author and reviews four different signal analysis methods and capability of the methods of evaluating small hidden changes in the EEG signal.

The results of the study add knowledge to understanding signal methods capability in evaluating different stressor impact on brain bioelectrical activity:

1. The effect of microwave radiation on the brain electrical activity depends on the level of exposure. The results showed that the 20 dB decrease of the microwave field reduces microwave related changes in the EEG signal 5-8 dB.
2. Microwave exposure induced effects were demonstrated using all three methods selected for the EEG analysis (ID, IhA, SASI).
3. Depression related alterations in the EEG signal were not detected using the IhA and IhC signal analysis methods, thus spectral asymmetry index provides promising results in evaluating depressive disorders.

In summary, it can be concluded that the result of the evaluation of the microwave induced effect and alteration produced by mental disorder depends on the EEG analysis procedure; statistically significant changes may vary with the analysis method applied. Changes in the EEG signals produced by modulated microwave radiation and depressive disorder were demonstrated using the SASI method, implying that the method detects changes in brain bioelectrical activity caused by different stressors.

Keywords: microwave effect, EMF effect, depressive disorder, EEG signal, analysis methods.

APPENDIX 1

PUBLICATIONS

Publication I

Suhhova, A., Bachmann, M., Karai, D., Lass, J., Hinrikus, H. (2012). Effect of microwave radiation on human EEG at two different levels of exposure. *Bioelectromagnetics* (in press)

BEM-11-0254.R5(21772)

Bioelectromagnetics 9999:1–11 (2012)

Effect of Microwave Radiation on Human EEG at Two Different Levels of Exposure

Anna Suhhova[Q2],* Maie Bachmann, Deniss Karai, Jaanus Lass, and Hiie Hinrikus

Department of Biomedical Engineering, Technomedicum, Tallinn University of Technology, Tallinn, Estonia

This study is aimed at evaluating the effect of microwave radiation on human brain bioelectric activity at different levels of exposure. For this purpose, 450 MHz microwave exposure modulated at 40 Hz frequency was applied to a group of 15 healthy volunteers at two different specific absorption rate (SAR) levels: a higher level of 0.303 W/kg (field strength 24.5 V/m) and a lower level of 0.003 W/kg (field strength 2.45 V/m). Ten exposure cycles (1 min off and 1 min on) at fixed SAR values were applied. A resting eyes-closed electroencephalogram (EEG) was continuously recorded. Results showed a statistically significant increase in the EEG power in the EEG beta2 (157%), beta1 (61%) and alpha (68%) frequency bands at the higher SAR level, and in the beta2 (39%) frequency band at the lower SAR level. Statistically significant changes were detected for six individual subjects in the EEG alpha band and four subjects in the beta1 and beta2 bands at the higher SAR level; three subjects were affected in the alpha, beta1 and beta2 bands at the lower SAR level. The study showed that decreasing the SAR 100 times reduced the related changes in the EEG three to six times and the number of affected subjects, but did not exclude the effect. Bioelectromagnetics 9999:1–11, 2012. © 2012 Wiley Periodicals, Inc.

Key words: microwave exposure; electroencephalogram; exposure level; dose-dependence; field strength

INTRODUCTION

The significant increase in wireless technology applications has caused public concern about possible microwave exposure effects on human health. Up to this time, the basic restrictions for limiting exposure are based on the International Commission on Non-Ionizing Radiation Protection (ICNIRP) guidelines [ICNIRP, 1998]. According to these guidelines, the recommended localized specific absorption rate (SAR) for the head and trunk is 2 W/kg for radiofrequency fields at a field strength of 61 V/m. However, experimental results reported by many authors have shown the effect of microwave radiation on human brain bioelectrical activity and cognitive behavior at exposure levels less than the recommended limits for SAR [Freude et al., 1998; Borbely et al., 1999; Huber et al., 2000, 2002; D'Costa et al., 2003; Maby et al., 2004; Curcio et al., 2005; Regel et al., 2007a; Hinrikus et al., 2008a, b; Croft et al., 2008, 2010; Vecchio et al., 2010]. Considering possible health effects, some countries have established more strict limitations on the exposure levels for the general public. The European Parliament in recently accepted resolutions recommends setting thresholds not exceeding 0.6 V/m for levels of long-term exposure to microwaves in all indoor areas, and reducing it to 0.2 V/m in the medium term [Council of Europe, 2011]. This is an alternative perspective that is not supported by any of the major expert bodies.

The electroencephalographic (EEG) signal has been frequently employed to assess the effect of microwave exposure on human brain bioelectrical activity because of its sensitivity to immediate changes in neural processes. Alterations related to exposure at 875 MHz frequency by Global System for Mobile Communications (GSM) technologies were demonstrated at an SAR value of 0.11 W/kg in the EEG alpha band (9–10 Hz) power, which was larger on the ipsilateral side in posterior regions compared to the contralateral side [Croft et al., 2008]. An increase in the resting EEG alpha (8–13 Hz), beta1 (15–

Grant sponsors: Estonian Project (SF0140027s07); European Union through the European Regional Development Fund.

*Correspondence to: Anna Suhhova[Q2], Department of Biomedical Engineering, Technomedicum, Tallinn University of Technology, 5 Ehitajate Road, EE19086 Tallinn, Estonia.
E-mail: anna@cb.ttu.ee

Received for review 8 November 2011; Accepted 17 November 2012

DOI 10.1002/bem.21772
Published online in Wiley Online Library (wileyonlinelibrary.com).

20 Hz) and beta2 (22–38 Hz) power was detected with 450 MHz radiation modulated at 7, 14, 21, 40, 70, or 217 Hz frequencies at an SAR value of 0.3 W/kg [Hinrikus et al., 2008a, b]. An increase in the alpha band power was also observed in a study using a GSM 900 phone at SAR values of 0.5 W/kg during and after exposure [Curcio et al., 2005]. An increase in the alpha band (10.5–11 Hz) activity was reported after exposure to pulsed 900 MHz signals at an SAR of 1 W/kg in the eyes-closed condition; no effect was seen in the eyes-open condition [Regel et al., 2007a]. The EEG alpha band power enhancement was observed in resting EEG recorded at SAR values of 1 W/kg in the case of a 900 MHz pulse-modulated signal [Huber et al., 2000, 2002]. Compared to young subjects, elderly subjects showed a significant increase in the inter-hemispheric synchronization of frontal and temporal alpha bands following exposure to a GSM signal at 0.05 W/kg [Vecchio et al., 2010].

Several studies reported an increase in the EEG spectral power during sleep when exposed to pulse-modulated 900 MHz microwaves at SAR values of 1 W/kg [Borbely et al., 1999; Huber et al., 2002]. An increased EEG alpha range in the sleep EEG was also detected at an SAR value of 1.4 W/kg (884 MHz GSM) [Lowden et al., 2011]. Microwave exposure at a lower SAR value of 0.29 W/kg emitted by a digital mobile phone increased the EEG spectral power in the 11.5–12.25 Hz frequency range during the initial part of sleep following the exposure [Loughran et al., 2005, 2012]. A strong dependence on the modulation frequency and individual variability were reported at an SAR value of 2 W/kg [Schmid et al., 2012]. On the other hand, a GSM signal from a planar antenna at an SAR value of 0.6 W/kg, and from a horn antenna at an SAR value of 1.8 W/kg, had no effect on sleep architecture and the EEG [Wagner et al., 1998, 2000].

The effects of GSM signals on cognitive performance and auditory event-related potentials have been reported at SAR levels of 1.4 W/kg [Maby et al., 2004] and 0.61 W/kg [Hinrichs and Heinze, 2004]. The exposure to GSM signals of 902 MHz at an SAR of 0.65 W/kg also caused changes in EEG signals during a visual working memory task [Krause et al., 2000a]. However, the authors were unable to replicate their previous findings in later studies [Krause et al., 2000b, 2004]. They concluded that the effects of microwave radiation on brain oscillatory responses may be subtle, variable, and difficult to replicate for unknown reasons [Krause et al., 2007]. Another possibility, and the consensus view at present, is that there is no detectable effect of microwave radiation on cognitive performance and the reported findings may have been caused by chance [Regel and Achermann, 2011]. Therefore, it is not reasonable to select cognitive tasks as a measure for the evaluation of a dose-dependent relationship.

Only a few studies were aimed at comparing the effect of microwave radiation at two different levels of exposure. The effect of a GSM handset-like signal with 10 g averaged peak SARs of 0.2 and 5 W/kg was investigated on three different cognitive tasks and the sleep EEG [Regel et al., 2007b]. The study revealed a dose-response relationship between field intensity and its effects on brain physiology as demonstrated by changes in the sleep EEG [Regel et al., 2007b]. No dose-response relationship was found for accuracy in the cognitive tasks [Regel et al., 2007b]. The effects of two types of exposure, 1950 MHz Universal Mobile Telecommunications System (UMTS) signals at SAR values of 0.1 and 1 W/kg, and pulsed 900 MHz GSM signals at an SAR of 1 W/kg, were tested on well-being and the resting eyes-closed EEG [Kleinlogel et al., 2008]. However, the results of the study did not give any evidence for an effect at SAR values of both 0.1 and 1 W/kg [Kleinlogel et al., 2008].

Despite many investigations at different levels of exposure, the results do not provide sufficient systematic knowledge about how the reported effects depend on the level of exposure to microwave fields. The main problem is that data from different studies are not comparable due to different methods and experimental protocols as well as microwave and modulation frequencies. The alterations in brain electrical activity have been reported at SAR levels below 1 W/kg [Regel et al., 2007b; Croft et al., 2008; Hinrikus et al., 2008a, b; Vecchio et al., 2010]. On the other hand, no effects have been detected at SAR levels close to 1 W/kg or even higher [Wagner et al., 1998, 2000; Kleinlogel et al., 2008]. In a recent review, a conclusion was drawn confirming the lack of systematic data on the dependence of microwave effects on the level of exposure [Juutilainen et al., 2011].

The aim of this study was to evaluate the dependence of microwave effects on the level of exposure. For this purpose, alterations in the human EEG signal caused by modulated microwave exposure were compared at two different levels of exposure, both lower than the existing health protection limit. An SAR value of 0.303 W/kg (field strength 24.5 V/m) was selected and was equal to that in our previous studies where an effect was detected [Hinrikus et al., 2008a, b]. Another SAR value was selected 100 times lower, equal to 0.003 W/kg (field strength 2.45 V/m).

MATERIALS AND METHODS

Subjects

The experiment was carried out on a group of volunteers consisting of 15 healthy subjects (aged 23–32), nine male and six female. Their physical and mental condition was evaluated by a questionnaire and clinical interview before the experiment. All subjects selected reported themselves to be in good health and without medical or psychiatric disorders. Those who declared themselves tired or sleepy before the experiment were excluded. After the recordings, the subjects were asked to describe how they felt during the experiment. They reported no effect on their alertness and no experience of any strain during the EEG recordings. Each participant was aware of the purpose of the experiments and gave a written consent.

During the experiments, the subjects were asked to lie in a relaxed position, with eyes closed and ears plugged. The experiments were performed in a dark laboratory room. All subjects participated in two EEG recording sessions. For each recording session, the exposure condition was randomly assigned. The subjects were not informed of the exposure power level during the recording session, however, they were aware of the possibility of being exposed. Both recording sessions were performed on the same day. The interval between the two sessions was at least 15 min.

The study was conducted in accordance with the Declaration of Helsinki and was formally approved by the Tallinn Medical Research Ethics Committee (Tallinn, Estonia).

Microwave Exposure

The 450 MHz electromagnetic radiation was generated by a signal generator (SML02, Rhode & Schwartz, Munich, Germany). The radiofrequency signal was 100% pulse modulated using a pulse modulator (SML-B3, Rhode & Schwartz) at a frequency of 40 Hz and a duty cycle of 50%. The signal from the generator was amplified using a power amplifier (MSD-2597601, Dage, Stamford, CT). The generator and amplifier were carefully shielded and did not cause artifacts during recordings. The 1 or 0.01 W electromagnetic radiation output power was guided by a coaxial lead to a 13-cm quarter-wave antenna (NMT450 RA3206, Allgon Mobile Communication, Stockholm, Sweden). The antenna was located 10 cm from the skin on the left side of the head close to ear; the angle between axis of the head and antenna was 45°. The spatial distribution of the electric field was measured with a field strength meter (CA 43 Fieldmeter, Chauvin Arnoux, Paris, France). The measurements were performed by the Central Physical Laboratory of the Health Board (Tallinn, Estonia) under real experimental conditions. During the experiments, the stability of the electromagnetic radiation level was monitored with a field strength meter (Digi-Field C, IC Engineering, Thousand Oaks, CA).

The SAR was calculated using SEMCAD software (Schmid & Partners Engineering, Zurich, Switzerland). The finite-difference time-domain computing method with the specific anthropomorphic mannequin (SAM) specified in the Institute of Electrical and Electronics Engineers (IEEE) Standard 1528–2003 [IEEE, 2003] was applied. The results of the SAR distribution calculations are shown in Figure 1. Maximal exposure occurred in the left central region of the head; in this area, the calculated spatial peak SAR averaged over 1 g was 0.303 W/kg for the microwave output power of 1 W, and 0.003 W/kg for the microwave output power of 0.01 W.

Recording Protocol and Equipment

Each subject participated in two EEG recording sessions. The protocol of each recording session consisted of one series of reference followed by two series of microwave exposure; each series included five experimental cycles (Fig. 2). One experimental cycle consisted of a 60-s resting segment without microwave exposure and a 60-s exposure segment with microwave exposure. Each microwave series was conducted at a constant field power density of the

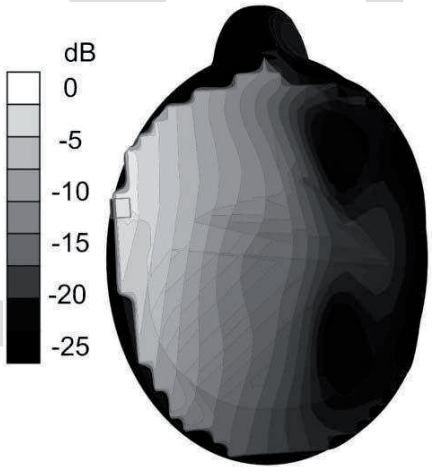


Fig. 1. Calculated SAR distribution in the SAM cross section. 0 dB corresponds to 0.003 W/kg averaged over 1 g for 0.01 W antenna input power and 0.303 W/kg for 1 W antenna input power.

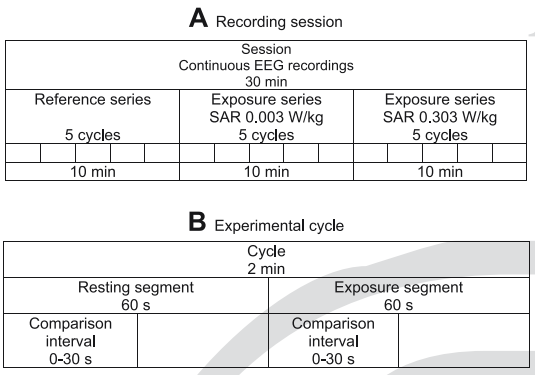


Fig. 2. Schedule of the recording protocol. **A**: Recording session; **B**: Experimental cycle.

modulated microwave radiation. The order of the two microwave exposures (SAR 0.303 and 0.003 W/kg) was randomized among subjects. However, the lower SAR level was selected in the first series and the higher SAR level in the second series in one session and vice versa in the other session for each subject. The reference series consisted of five cycles without exposure. One EEG recording lasted for 30 min, during which the EEG was continuously recorded while the subject was relaxed with eyes closed.

Cadwell Easy II EEG measurement equipment (Kennewick, WA) was used for the EEG recordings. The EEG was recorded using 19 electrodes, which were placed on the subject's scalp according to the international 10–20 system of electrode placement. EEG channels selected for analysis were identical to these in our previous studies [Hinrikus et al., 2008a, b]: frontal FP1, FP2; temporal T3, T4; parietal P3, P4; occipital O1, O2; and the reference electrode Cz. The raw data of the EEG recordings in the frequency band 0.5–48 Hz were stored on a computer at a 400 Hz sampling frequency. Signals for further analysis were selected in the frequency band 4–38 Hz. Such selection excluded the modulation frequency from analysis. Elliptical bandpass filters with an attenuation of 100 dB in the stopband were used. Preprocessing of the signals was performed in the LabVIEW (National Instruments, Austin, TX) programming and signal-processing environment using the analysis tool, Elliptic filter. An experienced neurologist examined the recorded EEG signals by visual inspection. Recordings made with drowsy subjects or recordings with apparent electrode artifacts were not used and the whole session was re-recorded on another day. To detect possible problems that could have occurred with electrodes, filtering, etc., the average group spectrum of recorded signals was calculated before further processing with the LabVIEW analysis tool.

Artifacts can be induced by parasitic demodulation of the radiofrequency electromagnetic components of the EEG electrodes and equipment. To detect possible parasitic interactions between the recording and radiofrequency equipment, the set-up was validated before the experiments. To conduct testing, an EEG cap was placed on a passive phantom of a human head [Hinrikus et al., 2008b]. The recordings of the phantom were conducted in accordance with the protocol of the present study. Multichannel recordings in the frequency band 0.5–48 Hz detected a spectral component of 40 Hz at the higher and lower SAR values. The component disappeared when the antenna was removed therefore it was not caused by the radiofrequency equipment but by the radiation from the antenna. No other spectral components were detected. The artifacts at the modulation frequencies were removed from the EEG signals by off-line filtering during the pre-processing of the signals.

EEG Analysis

The EEG analysis was similar to that applied in our previous studies [Hinrikus et al., 2008a, b]. Relative changes in the recorded EEG signals between the cycle segments with and without exposure were selected as a measure to detect the microwave effect on the EEG power.

The powers of the four basic EEG frequency bands, theta (4–7 Hz), alpha (8–13 Hz), beta1 (15–20 Hz), and beta2 (22–38 Hz), were extracted from the total EEG by filtering. Elliptical bandpass filters with an attenuation of 100 dB in the stopband were used.

The average powers of segments with and without exposure were compared. The comparison intervals were selected as 30 s from the beginning of the resting (unexposed) and microwave-exposed segments in one exposure cycle. The first half of the 60 s segment was selected considering possible physiological adaptations of the brain to exposure revealed in our previous study [Hinrikus et al., 2008a].

The average value of the EEG power s_i of an arbitrary comparison segment i was calculated as:

$$s_i = \frac{1}{N}\sum_{r=1}^{N}[x(r)]^2 \quad (1)$$

where $x(r)$ is the amplitude of the recorded signal in a sample r, and N is the number of samples;

during 30 s, $N = 12000$. Parameter S_c, the relative change in the powers of the recording segments with and without exposure for one cycle, was calculated as:

$$S_c = \left(\frac{s_2}{s_1} - 1\right) \times 100\% \quad (2)$$

where s_1 and s_2 are the average powers inside the comparison segments without and with exposure, respectively.

The effect of microwave exposure on a subject was estimated by averaging the values of parameter S_c over 10 cycles of exposure (five cycles from each recording session) at a fixed SAR value. Parameter S_n, the average relative change in the EEG power of the recording segments with and without exposure at a fixed SAR value for a subject n, was calculated as:

$$S_n = \frac{1}{10}\sum_{c=1}^{10} S_c \quad (3)$$

where S_c is the value of the parameter calculated according to Equation (2) for one cycle.

Statistical Analysis

The hypothesis is that the exposure causes differences between data at the three exposure conditions. To reveal the effect, which is expected to be small, it is important to minimize the influence of other factors such as possible differences between EEG sites, frequency bands, subjects, etc. Therefore, the differences between exposure conditions were compared at all other identical conditions, in the same EEG channel (channel 1 was compared only to channel 1, channel 2 only to channel 2, etc.), frequency band (alpha was compared only to alpha, beta only to beta, etc.) and for the same subject (subject 1 was compared only to subject 1, subject 2 only to subject 2, etc.). To avoid additional differences caused by factors other than exposure conditions, the comparisons were not performed between combinations of different channels, frequency bands, and subjects. The statistical analysis was performed for three exposure conditions at each of eight EEG channels and 24 (3×8) comparisons at each of four EEG frequency bands. In the case of individual subjects, the statistical analysis was planned separately for each of the 15 subjects.

The software package Statistica 6.0 (StatSoft, Tulsa, OK) was used in the statistical analysis. For the group analysis, a mixed-design ANOVA was employed whereby the 10 reference, 10 SAR1 (0.003 W/kg) and 10 SAR2 (0.303 W/kg) measurements (calculated parameter S_c for 10 cycles, degrees of freedom ($df = 9$) per participant were treated as independent (comprising three levels of the factor "Exposure Condition"), and the eight electrode sites were treated as levels of the within-subject factor "EEG Channel". The post hoc Bonferroni test was performed to evaluate the significance level of comparisons for the main effects of "Exposure Condition" (correction factor 3). Additionally, the planned Bonferroni correction was calculated for multiple comparisons in four EEG frequency bands (correction factor $3 \times 4 = 12$) and eight EEG channels (correction factor $3 \times 4 \times 8 = 96$). Finally, the initial P-values were multiplied by the correction factor 96 for all comparisons in the group analysis.

The averaging of relative changes in the EEG power over the whole group may mask larger effects for individual subjects. Therefore, individual changes in the EEG power for each subject were evaluated. The same analysis as for the whole group with the Bonferroni correction (correction factor 96) was applied for each individual subject, differing only in that the total number of independent measurements per test was 30 (as it only included one subject's data). An additional Bonferroni correction was applied for 15 subjects (correction factor 15). The total correction factor for each individual subject consisted of the correction for the group analyses (96) multiplied by the number of subjects ($96 \times 15 = 1440$).

RESULTS

The average group spectrum of recorded EEGs for the signal segments with and without exposure is shown in Figure 3. The spectra of the signal segments for further analysis selected by filtering in the 4–38 Hz band are similar. Small differences are caused by changes in the state of the brain at different times. Only a very small rise the in alpha band with exposure can be detected.

Figure 4 shows the relative changes in the EEG power caused by microwave exposure in the different EEG frequency bands. Microwave exposure at the higher SAR value of 0.303 W/kg caused an increase in the EEG average power changes compared to the reference series in the EEG alpha, beta1, and beta2 bands. No effect was detected in the theta band. At the lower SAR level of 0.003 W/kg, the obvious trend of increase was evident in the EEG beta1 and beta2 bands.

To demonstrate more clearly the dependence of the effect on exposure level, the values of changes in the exposed and reference series were compared. The graphs presented in Figure 5 show the relative difference of the changes in the exposed and reference

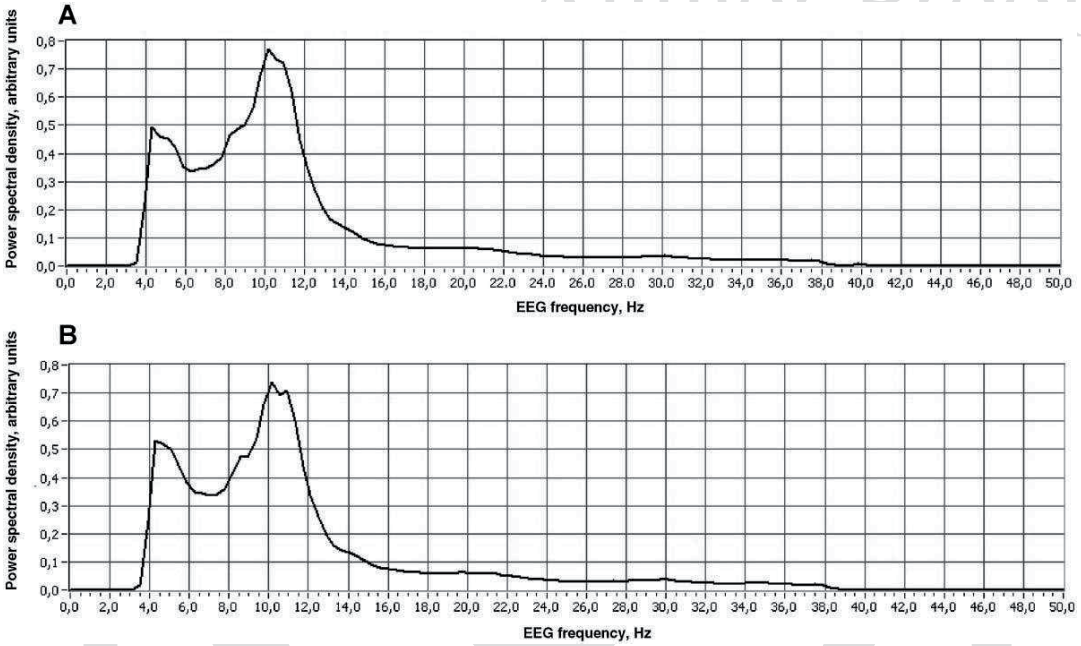


Fig. 3. Calculated EEG spectra selected by bandpass filtering in the frequency band 4–38 Hz averaged over the group of subject ($n = 15$) and all EEG channels. **A**: Spectrum of the segments of recorded signals with exposure; **B**: Spectrum of the segments of recorded signals without exposure.

series. Compared to EEG power changes in the reference series, the strongest increase in the changes at the SAR level of 0.303 W/kg occurred in the beta2 band (157%); the increases in the alpha (68%) and beta1 (61%) bands were somewhat smaller. A trend of increase in the EEG power changes at the SAR level of 0.003 W/kg was evident only in the beta2 (39%) and beta1 (23%) bands.

The results of the statistical evaluation for the whole group are presented in Table 1. These results revealed statistically significant differences between the reference and microwave-exposed series at the

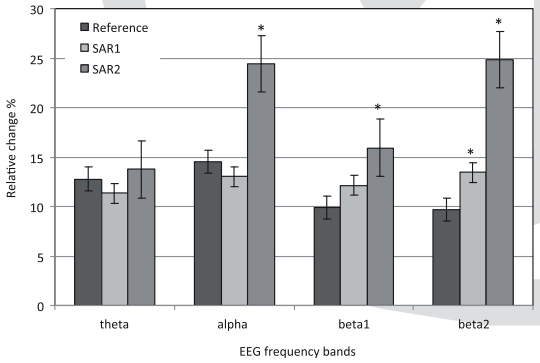


Fig. 4. Relative changes in the EEG power as parameter S_c values calculated for the theta, alpha, beta1 and beta2 EEG frequency bands averaged over 10 cycles and 15 subjects at three exposure conditions: reference without exposure; SAR1 = 0.003 W/kg; and SAR2 = 0.303 W/kg. **Vertical bars** denote standard error. *Significant difference between reference and exposed series indicated by Bonferroni corrected $P < 0.05$.

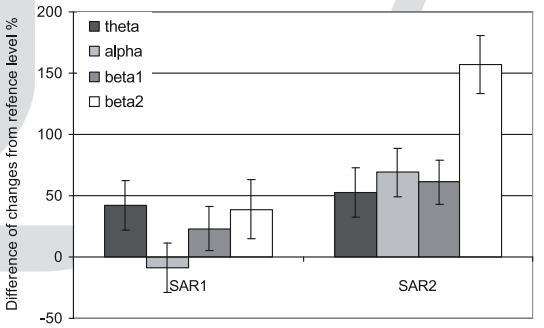


Fig. 5. Quantity of the microwave effect as the relative difference of change (parameter S_n) in the exposed (S_{ne}) and reference (S_{nr}) series for a subject n calculated as $S_{ne} - S_{nr}/S_{nr}$ for the theta, alpha, beta1 and beta2 EEG frequency bands averaged over 15 subjects at SAR1 = 0.003 W/kg and SAR2 = 0.303 W/kg. **Vertical bars** denote standard error.

TABLE 1. Results of the Post-Hoc Bonferroni Test for Comparison Between the Reference, Exposed at SAR1 (0.003 W/kg) and SAR2 (0.303 W/kg) Series for the Whole Group in the EEG Theta, Alpha, Beta1 And Beta2 Frequency Bands Calculated for 10 Cycles of Exposure Grouped for the eight EEG Channels

	P-values		
	Reference	SAR1	SAR2
Theta			
Ref	N/A	1.0000	1.0000
SAR1	1.0000	N/A	1.0000
SAR2	1.0000	1.0000	N/A
Alpha			
Ref	N/A	1.0000	**0.0002**
SAR1	1.0000	N/A	**0.0005**
SAR2	**0.0002**	**0.0005**	N/A
Beta1			
Ref	N/A	0.8573	**0.0030**
SAR1	0.8573	N/A	0.0732
SAR2	**0.0030**	0.0732	N/A
Beta2			
Ref	N/A	**0.0261**	**0.0008**
SAR1	**0.0261**	N/A	**0.0188**
SAR2	**0.0008**	**0.0188**	N/A

Significant values $P < 0.05$ in bold.

SAR level of 0.303 W/kg in the EEG alpha, beta1, and beta2 frequency bands. A significant difference was also revealed between the reference and exposed series at the SAR level of 0.003 W/kg in the EEG beta2 frequency band. Statistically significant differences were detected between exposure conditions at the higher and lower SAR levels in the EEG alpha and beta2 frequency bands.

The individual changes for each subject are shown in Figure 6. The graphs show relative alterations caused by microwave exposure in the EEG beta1 frequency band. The exposure caused a remarkable increase in changes for four subjects (2, 5, 12, and 15), whereas the increase occurred at both SAR levels for three of them (2, 12, and 15). Some trend of increase in changes compared with the reference series was evident at both SAR levels for an additional two subjects (11 and 14). A decrease in alterations related to exposure was mentioned for one subject (9) and the stability of alterations for two subjects (1 and 8). The values of bars lower than 10% (the level comparable with reference bars in Fig. 3) can be considered as natural variability in the EEG signal (six subjects: 3, 4, 6, 7, 10, and 13) and no trend of changes was revealed for these subjects.

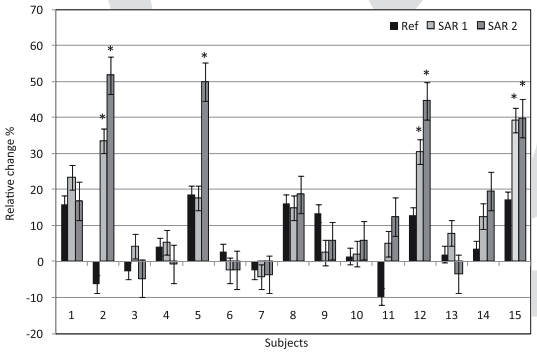


Fig. 6. Relative changes in the EEG power as parameter S_c values calculated for the beta1 frequency band averaged over 10 cycles for individual subjects ($n = 15$) at three exposure conditions: reference without exposure; SAR1 = 0.003 W/kg; and SAR2 = 0.303 W/kg. **Vertical bars** denote standard error. *Significant difference between reference and exposed series indicated by Bonferroni corrected $P < 0.05$.

Table 2 specifies results of the statistical analysis for individual subjects in the EEG alpha, beta1, and beta2 frequency bands. No statistically significant changes were detected in the EEG theta band. The statistical analysis results show that the subjects affected by exposure had significant changes simultaneously in several EEG frequency bands. Microwave exposure introduced statistically significant changes in all or the majority (except one) of the EEG frequency bands for three subjects (2, 12, and 15) at both SAR levels. The changes were evident for the same subjects at both SAR levels. In the alpha band, six subjects were affected at the higher SAR level (2, 5, 8, 11, 12, and 15), and three at the lower SAR level (2, 11, and 12); in the beta1 band, four subjects were affected at the higher SAR level (2, 5, 12, and 15) and three at the lower SAR level (2, 12, and 15); in the beta2 band, four subjects were affected at the

TABLE 2. Bonferroni-Corrected *P*-Values for Comparison Between the Reference, Exposed at SAR1 and SAR2 Series for Individual Subjects in the EEG Alpha, Beta1 and Beta2 Frequency Bands Calculated for 10 Cycles of Exposure

	P-values					
	SAR1 = 0.003 W/kg			SAR2 = 0.303 W/Kg		
Subject	Alpha	Beta1	Beta2	Alpha	Beta1	Beta2
1	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000
2	↑ **2×10^{-5}**	↑ **0.0025**	↑ **7×10^{-4}**	↑ **0.0455**	↑ **1×10^{-4}**	↑ **8×10^{-5}**
3	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000
4	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000
5	1.0000	1.0000	1.0000	↑ **2×10^{-4}**	↑ **0.0060**	0.1605
6	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000
7	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000
8	1.0000	1.0000	1.0000	↑ **2×10^{-5}**	1.0000	1.0000
9	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000
10	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000
11	↑ **0.0046**	0.8765	↑ **0.0321**	↑ **0.0465**	1.0000	↑ **1×10^{-5}**
12	↑ **0.0363**	↑ **0.0441**	0.8105	↑ **3×10^{-4}**	↑ **0.0063**	↑ **0.0321**
13	0.6462	1.0000	1.0000	1.0000	1.0000	1.0000
14	0.1052	0.6854	0.8064	0.1821	0.1915	0.5664
15	1.0000	↑ **0.0246**	↑ **0.0033**	↑ **0.0404**	↑ **0.0328**	↑ **0.0096**

Significant values $P < 0.05$ in bold; ↑ denotes an increase in the EEG power with exposure.

higher SAR level (2, 11, 12, and 15) and three at the lower SAR level (2, 11, and 15). The results show that the subjects affected at the lower SAR level were also affected at the higher SAR level in the same EEG frequency band.

For all subjects having a significant difference between the reference and microwave-exposed series, the average relative changes were positive; consequently, the level of power in segments with exposure was higher than in segments without exposure.

DISCUSSION

The experiments revealed the dose-dependent relationship of the modulated microwave effect: the average values of relative changes were higher at the higher level of exposure compared to those at the lower level. Microwave exposure caused an increase in the relative changes in the EEG power between exposed and resting segments compared to reference recordings for the whole group and for individual subjects at both SAR levels (Figs. 4–6).

The effect became evident in the EEG alpha, beta1, and beta2 frequency bands (Figs. 4–6). No effect was revealed in the EEG theta band. The increase in the EEG alpha band power caused by microwave exposure is in good accordance with findings reported by other research groups [Huber et al., 2002; Curcio et al., 2005; Croft et al., 2008, 2010]. The application of a more sensitive experimental method (repetitive cycles of exposure) made it possible to detect an increase in the EEG power not only in the alpha but also in the beta band. An increase in the EEG beta band power related to modulated microwave at similar exposure conditions was reported in our previous studies [Hinrikus et al., 2008a, b].

Several studies support the position that delayed effects may occur after 30–45 min of microwave exposure [Huber et al., 2002; Curcio et al., 2005]. The protocol of our experiment (comparison of 1 min exposed and 1 min resting EEG during 10 cycles) was not sensitive for detecting the outlasting effect of exposure. The presence of the effect during both exposed and resting segments could cause a decrease in the difference between them and a diminishing of the detected effect. Moreover, the selection of the first half of the 60 s segment for analysis was the most unfavorable choice regarding an outlasting effect. Nevertheless, statistically significant changes were detected and the impact of the outlasting effect did not seem important. However, if the microwave effect on the EEG persisted after the exposure, the detected effect was smaller than its real value.

Relative changes averaged over the whole group showed a maximal increase in the beta2 band: 157% at the SAR level of 0.303 W/kg, and 39% at the SAR level of 0.003 W/kg. The increase in the changes in the alpha band was about two times lower: 68% at the SAR level of 0.303 W/kg and not evident at the lower SAR level. It does not seem random that the major effect was evident in the EEG

beta band. According to the parametric model of excitation, modulated microwave radiation causes periodic changes in the brain electric susceptibility and leads to excitation of the EEG rhythms at parametric resonance frequencies [Hinrikus et al., 2011]. The linear model of parametric excitation determines a main resonance close to one-half of the external frequency (40 Hz modulation[Q3]) [Butikov, 2004]. Therefore, the strongest effect is expected at the EEG beta band frequencies close to 20 Hz. Moreover, according to the nonlinear model of parametric excitation of the brain, the excitation of additional EEG rhythm components at one-quarter and three-quarters of the modulation frequency is expected [Hinrikus et al., 2011]. These components (close to 10 and 30 Hz) cause an increase in the EEG alpha and beta band power.

EEG alterations at reference conditions are caused by natural variability in the signal related to neural activity in the brain. The time course of the EEG spectrum power in resting conditions has been reported to have monotonic alterations toward the end of the recordings [Maltez et al., 2004]. The monotonic changes in the EEG power during the recordings lead to changes in the reference data. However, these processes do not cause significant differences between signal segments.

The number of individual subjects significantly affected by exposure was 40–60% higher (six subjects in the alpha band, four subjects in the beta1 and beta2 bands) at the higher SAR value of 0.303 W/kg compared with the lower SAR value of 0.003 W/kg (three subjects in the alpha, beta1, and beta2 bands). The same subjects were sensitive at the higher and lower level of exposure. The relative part of affected subjects was 40% for the alpha band and 27% for the beta bands at the higher SAR value, and 20% for the alpha and beta bands at the lower SAR value. These results are close to those in our previous study, where at the same exposure conditions (450 MHz microwave radiation, modulation frequency 40 Hz, SAR = 0.303 W/kg) and number of subjects ($n = 15$), the relative percentage of affected subjects in the beta1 band was 20% (three subjects) [Hinrikus et al., 2008b]. However, those results were based on the analysis of the EEG only in parietal channels P3–P4 [Hinrikus et al., 2008b].

As expected, alterations caused by exposure increase with increasing SARs (Figs. 4–6). This finding agrees with the results achieved in another study where exposure to 900 MHz GSM-like radiation had been applied [Regel et al., 2007b]. The reported data in that study provided evidence for a dose-response relationship: the spectral power of the sleep EEG in the fast spindle frequency range increased by 7.7% after radiofrequency exposure at an SAR of 0.2 W/kg, and 13.6% after exposure at 5 W/kg [Regel et al., 2007b].

The dependence of the effect on the exposure level is obviously not linear; the reduction in the effect is much slower than expected according to the decreasing SAR. In our study, the level of SAR decreases 100 times (20 dB), while the effect (relative changes of EEG power between resting and exposed segments) decreased only three to six times (5–8 dB; Figs. 4 and 5). In our study, both exposure levels were lower than the exposure limit for the general public. In the case of comparison of the effect at exposure levels higher (5 W/kg) and lower (0.2 W/kg) than the exposure limit for general public, the level of SAR decreases 25 times but the spectral power of the EEG decreases only about 1.8 times [Regel et al., 2007b]. One reason for the slow decrease in the effect is a possible parametric mechanism of excitation of the EEG rhythms by modulated microwave radiation [Hinrikus et al., 2011]. According to the theory of parametric excitation, even a weak external periodic force can cause remarkable excitation of the oscillatory system [Butikov, 2004]. Consequently, the modulated microwave radiation as a periodic factor can cause excitation of EEG rhythms even at a low level of exposure and the dose-dependent relationship can be less critical than expected.

It is difficult to predict how effective a further decreasing of the field strength at lower SAR values is, and at which level the threshold of the effect is expected. A physical model in which cells are considered as possible detectors of very weak electric fields has been proposed and discussed [Weaver and Astumian, 1990]. The paradox is that according to experimental data, much smaller fields than the calculated thermal noise limit caused the effect and, according to the model, could be detected [Weaver and Astumian, 1990]. The parametric model of excitation can provide a threshold value lower than the thermal noise level of the system. However, there are still no data to estimate the threshold. Therefore, there is no certainty that reducing the preventive levels of exposure to microwaves down to 0.2 V/m, proposed by the Council of Europe, will fully eliminate the effect.

Further investigations, especially at lower levels of exposure, are needed to gain sufficient knowledge about the dependence of the microwave radiation effect on the level of exposure and the threshold of the effect.

CONCLUSION

The results of this experimental study confirm that exposure to 450 MHz microwave radiation modulated at 40 Hz has an effect on brain electrical activity depending on the level of exposure. A decrease in the exposure by 100 times reduces the effect, which results in a reduction in the relative changes of the EEG by three to six times and the number of subjects significantly affected by microwave exposure by 40–60%. However, a reduction in the effect is slower than expected according to the decrease in the level of exposure. This study showed that a decrease in the microwave field 100 times reduced but did not exclude microwave-related changes in the EEG.

REFERENCES

Borbely AA, Huber R, Graf T, Fuchs B, Gallmann E, Achermann P. 1999. Pulsed high-frequency electromagnetic field affects human sleep and sleep electroencephalogram. Neurosci Lett 275:207–210.

Butikov EI. 2004. Parametric excitation of a linear oscillator. Eur J Phys 25:535–554.

Council of Europe. 2011. The potential dangers of electromagnetic fields and their effect on the environment. Parliamentary Assembly, Resolution 1815, 27 May 2011, Strasbourg, France.

Croft RJ, Hamblin DL, Spong J, Wood AW, McKenzie RJ, Stough C. 2008. The effect of mobile phone electromagnetic fields on the alpha rhythm of human electroencephalogram. Bioelectromagnetics 29:1–10.

Croft RJ, Leung S, McKenzie RJ, Loughran SP, Iskra S, Hamblin DL, Cooper NR. 2010. Effects of 2G and 3G mobile phones on human alpha rhythms: Resting EEG in adolescents, young adults, and the elderly. Bioelectromagnetics 31:434–444.

Curcio G, Ferrara M, Moroni F, D'Inzeo G, Bertini M, De Gennaro L. 2005. Is the brain influenced by a phone call? An EEG study of resting wakefulness. Neurosci Res 53:265–270.

D'Costa H, Trueman G, Tang L, Abdel-rahman U, Abdel-Rahman W, Ong K, Cosic I. 2003. Human brain wave activity during exposure to radiofrequency field emissions from mobile phones. Australas Phys Eng Sci Med 26:162–167.

Freude G, Ullsperger P, Eggert S, Ruppe I. 1998. Effects of microwaves emitted by cellular phones on human slow brain potentials. Bioelectromagnetics 19:384–387.

Hinrichs H, Heinze HJ. 2004. Effects of GSM electromagnetic field on the MEG during an encoding-retrieval task. NeuroReport 15:1191–1194.

Hinrikus H, Bachmann M, Lass J, Tomson R, Tuulik V. 2008a. Effect of 7, 14 and 21 Hz modulated 450 MHz microwave radiation on human electroencephalographic rhythms. Int J Radiat Biol 84:69–79.

Hinrikus H, Bachmann M, Lass J, Karai D, Tuulik V. 2008b. Effect of low frequency modulated microwave exposure on human EEG: Individual sensitivity. Bioelectromagnetics 29:527–538.

Hinrikus H, Bachmann M, Lass J. 2011. Parametric mechanism of excitation of the electroencephalographic rhythms by modulated microwave radiation. Int J Radiat Biol 87: 1077–1085.

Huber R, Graf T, Cote KA, Wittmann L, Gallmann E, Matter D, Schuderer J, Kuster N, Borbery AA, Achermann P. 2000. Exposure to pulsed high-frequency electromagnetic field during waking affects human sleep EEG. NeuroReport 11: 3321–3325.

Huber R, Treyer V, Borbely AA, Schuderer J, Gottselig JM, Landolt HP, Werth E, Berthold T, Kuster N, Buck A, Achermann P. 2002. Electromagnetic fields, such as those from mobile phones, alter regional cerebral blood flow and sleep and waking EEG. J Sleep Res 11:289–295.

ICNIRP. 1998. Guidelines for limiting exposure to time-varying electric, magnetic, and electromagnetic fields (up to 300 GHz). Health Phys 74:484–522.

IEEE. 2003. Standard 1528–2003. Recommended practice for determining the peak spatial-average specific absorption rate (SAR) in the human head from wireless communications devices: Measurement techniques. New York, NY, USA: IEEE.

Juutilainen J, Höytö A, Kumlin T, Naarala J. 2011. Review of possible modulation-dependent biological effects of radiofrequency fields. Bioelectromagnetics 32:511–534.

Kleinlogel H, Dierks T, Koening T, Lehmann H, Minder A, Berz R. 2008. Effects of weak mobile phone-electromagnetic fields (GSM, UMTS) on well-being and resting EEG. Bioelectromagnetics 29:479–487.

Krause CM, Sillanmäki L, Koivisto M, Häggqvist A, Saarela C, Revonsuo A, Laine M, Hämäläinen H. 2000a. Effects of electromagnetic fields emitted by cellular phones on the electroencephalogram during a visual working memory task. Int J Radiat Biol 76:1659–1667.

Krause CM, Sillanmäki L, Koivisto M, Häggqvist A, Saarela C, Revonsuo A, Laine M, Hämäläinen H. 2000b. Effects of electromagnetic field emitted by cellular phones on the EEG during a memory task. NeuroReport 11:761–764.

Krause CM, Haarala C, Sillanmäki L, Koivisto M, Alanko K, Revonsuo A, Laine M, Hämäläinen H. 2004. Effects of electromagnetic field emitted by cellular phones on the EEG during an auditory memory task: A double blind replication study. Bioelectromagnetics 25:33–40.

Krause CM, Pesonen M, Haarala C, Björnberg C, Hämäläinen H. 2007. Effects of pulsed and continuous wave 902 MHz mobile phone exposure on brain oscillatory activity during cognitive processing. Bioelectromagnetics 28:296–308.

Loughran SP, Wood AW, Barton RJ, Croft RJ, Thompson B, Strough C. 2005. The effect of electromagnetic field emitted by mobile phones on human sleep. NeuroReport 16:1973–1976.

Loughran SP, McKenzie RJ, Jackson ML, Howard ME, Croft RJ. 2012. Individual differences in the effect of mobile phone exposure on human sleep: Rethinking the problem. Bioelectromagnetics 33:86–93.

Lowden A, Åkerstedt T, Ingre M, Wiholm C, Hillert L, Kuster N, Nilsson JP, Arnetz B. 2011. Sleep after mobile phone exposure in subjects with mobile phone-related symptoms. Bioelectromagnetics 32:4–14.

Maby E, Le Bouquin Jeannes R, Liégeois-Chauvel C, Gourevitch B, Faucon G. 2004. Analysis of auditory evoked potential parameters in the presence of radiofrequency fields using a support vector machines method. Med Biol Eng Comput 42:562–568.

Maltez J, Hyllienmark L, Nikulin VV, Brismar T. 2004. Time course and variability of power in different frequency bands of EEG during resting conditions. J Clin Neurophysiol 34:195–202.

Regel SJ, Achermann P. 2011. Cognitive performance measures in bioelectromagnetic research—critical evaluation and recommendations. Environ Health 10:10.

Regel SJ, Gottselig JM, Schuderer J, Tinguely G, Rétey JV, Kuster N, Landolt HP, Achermann P. 2007a. Pulsed radio frequency radiation affects cognitive performance and the waking electroencephalogram. NeuroReport 18:803–807.

Regel SJ, Tinguely G, Schuderer J, Adam M, Kuster N, Landolt HP, Achermann P. 2007b. Pulsed radio-frequency electromagnetic fields: Dose-dependent effects on sleep, the sleep EEG and cognitive performance. J Sleep Res 16:253–258.

Schmid MR, Loughran SP, Regel SJ, Murbach M, Grunauer AB, Rusterholz T, Bersagliere A, Kuster N, Achermann P. 2012. Sleep EEG alterations: Effects of different pulse-modulated radio frequency electromagnetic fields. J Sleep Res 21:50–58.

Vecchio F, Babiloni C, Ferreri F, Buffo P, Cibelli G, Curcio G, van Dijkman S, Melgari JM, Giambattistelli F, Rossini PM. 2010. Mobile phone emission modulates inter-hemisphere functional coupling of EEG alpha rhythms in elderly compared to young subjects. Clin Neurophysiol 121: 153–171.

Wagner P, Röschke J, Mann K, Hiller W, Frank C. 1998. Human sleep under the influence of pulsed radiofrequency electromagnetic fields: A polysomnographic study using standardized conditions. Bioelectromagnetics 19:199–202.

Wagner P, Roschke J, Mann K, Fell J, Hiller W, Frank C, Grozinger M. 2000. Human sleep EEG under the influence of pulsed radio frequency electromagnetic fields. Results from polysomnographies using submaximal high power flux densities. Neuropsychobiology 42: 207–212.

Weaver J, Astumian R. 1990. The response of living cells to very weak electric fields: The thermal noise limit. Science 247:459–462.

PUBLICATIONS

Publication II

Suhhova, A., Bachmann, M., Lass, J., Karai, D., Hinrikus, H. (2009). Effect of modulated microwave radiation on human EEG asymmetry. *The Environmentalist*, 29: 210-214.

Environmentalist (2009) 29:210–214
DOI 10.1007/s10669-009-9214-8

Effect of modulated microwave radiation on human EEG asymmetry

Anna Suhhova · Maie Bachmann · Jaanus Lass · Deniss Karai · Hiie Hinrikus

Published online: 18 January 2009

Abstract This study is aimed to investigation of the effect of modulated 450 MHz microwave radiation on the EEG inter-hemispheric asymmetry. Ten cycles of the microwave exposure (1 min off and 1 min on) at fixed modulation frequency were applied on two groups of healthy volunteers. The first group of 13 subjects was exposed to microwave radiation modulated at 14 Hz and the second group of 15 subjects at 40 Hz frequency. The peak specific absorption rate (SAR) average over 1 g was 0.303 W/kg. Differences in SAR between hemispheres were up to 20 dB. Rod antenna was located from the left side of the head. Differences of relative changes in EEG energy between symmetric channels FP1–FP2, T3–T4, P3–P4 and O1–O2 in exposed and sham conditions were analysed. The results showed increase in EEG energy from the left side caused by microwave exposure. Statistical analysis done for the whole group of subjects didn't reveal significant differences in inter-hemispheres asymmetry between exposed and sham conditions. However, statistical analysis performed for individual subjects detected significant differences in asymmetry caused by exposure for 15–35% of individuals.

Keywords Microwave radiation · Modulation · EEG analysis · Inter-hemispheric asymmetry · Individual sensitivity

A. Suhhova (✉) · M. Bachmann · J. Lass · D. Karai · H. Hinrikus
Department of Biomedical Engineering, Technomedicum of Tallinn University of Technology, 5 Ehitajate Rd, 19086 Tallinn, Estonia
e-mail: anna@cb.ttu.ee

1 Introduction

Effects of low-level modulated microwave radiation on human brain became important due to wide use of telecommunication equipment. A number of investigators have reported that exposure to a low-level microwave produces alterations in the resting or sleep electroencephalographic (EEG) signal and/or brain behaviour (Borbely et al. 1999; Huber et al. 2000, 2002; Krause et al. 2000a; Lass et al. 2002; Hinrikus et al. 2004; Curcio et al. 2005). Difficulties experienced in replication of experimental findings have caused doubts concerning these effects (Krause et al. 2000b). Despite of many investigations, the observed effects of low-level microwave were subtle and the underlying mechanisms remain still unknown.

The traditional use of mobile phones causes strongly asymmetric distribution of field power density and specific absorption rate (SAR) inside the human head. Therefore, enhance in asymmetry of the EEG parameters between the brain hemispheres caused by microwave exposure can be an indicator of the effect. Results of our previous study (Suhhova et al. 2008), where 450 MHz microwave exposure modulated at 1,000 Hz was applied, did not reveal significant changes in the EEG between hemispheres. Possible reason is absence of the effect at 1,000 Hz modulation frequency (Hinrikus et al. 2008a). On the other hand, it has been reported that the microwave exposure causes increase in the EEG power in the frequency bands that are close to or lower than the modulation frequency of microwaves (Hinrikus et al. 2008b).

This study is aimed to evaluate the possible effect of microwave radiation modulated at low frequencies inside the EEG spectrum on asymmetry of EEG rhythms between brain hemispheres. In our study we tested the hypothesis that inter-hemispheric EEG asymmetry is affected by

microwave exposure which level is much higher from the left side of the head.

2 Materials and methods

2.1 Subjects

The experiments were carried out on two groups of volunteers: 13 healthy volunteers (aged 21–30) were exposed to 450 MHz microwave radiation modulated at 14 Hz (Group A) and 15 healthy volunteers (aged 21–24) were exposed to 450 MHz modulated at 40 Hz (Group B). All the subjects selected had no medical or psychiatric disorders. All subjects passed the experimental protocols with exposure and sham. During each double-blind test session, the exposed and sham-exposed subjects were randomly assigned by computer.

The study was conducted in accordance with the Declaration of Helsinki and has approved by the local Medical Research Ethics Committee.

2.2 Microwave exposure

The microwave radiation was generated by the Rhode & Swartz signal generator model SML02. The 450 MHz radiation was 100% pulse modulated at 14 and 40 Hz frequency (duty cycle 50%). The generator signal was amplified and the 1 W microwave output power was guided by coaxial to the quarter-wave antenna NMT450 RA3205, located at 10 cm from the left side of the head. The spatial distribution of the microwave power density was measured by the Fieldmeter C.A 43 field strength meter. The field power density from the left side of the head was 0.16 mW/cm^2. The SAR was calculated using SEMCAD software. The finite difference time domain (FDTD) computing method with specific anthropomorphic mannequin (SAM) specified in IEEE Standard 1528 was applied. Results of calculations are presented in Fig. 1. The calculated spatial peak SAR averaged over 1 g was 0.303 W/kg. Differences in calculated SAR values between hemispheres were up to 20 dB.

2.3 Experimental procedure and EEG recording equipment

The experimental studies were performed according to the recording protocol identical for all subjects. All subjects completed the sessions with microwave and sham exposure during which the resting eyes closed EEG were continuously recorded. Ten cycles of modulated microwave exposure (1 min radiation off, 1 min radiation on) at each fixed modulation frequency were applied. Sham recording session used the same protocol, except that the microwave power was switched off.

The Cadwell Easy II EEG measurement equipment was used for the EEG recordings. The EEG was recorded using nine electrodes placed on the subject's head: frontal—FP1, FP2, parietal—P5, P4, temporal—T3, T4, occipital—O1, O2 and the reference electrode Cz. The EEG recordings were stored on a computer with a 400 Hz sampling frequency.

The energies of the four basic EEG rhythms theta (4–7 Hz), alpha (8–13 Hz), beta1 (15–20 Hz) and beta2 (22–38 Hz) were extracted from the total EEG signal (0.5–48 Hz) by filtering. Such a selection of the EEG bands excluded possible modulation frequency artifacts.

2.4 EEG analysis

The EEG energies of the theta, alpha, beta1 and beta2 frequency bands were analysed separately. The method of integration of differences was applied.

The relative change in the energy of the recording segments with and without exposure was selected for

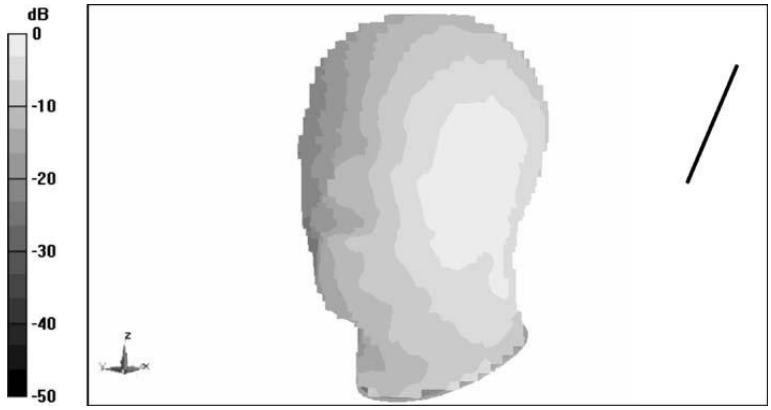


Fig. 1 Distribution of SAR values in SAM head

analysis. At first, the average energy of an arbitrary comparison interval was calculated as follows:

$$s_i = \frac{1}{N}\sum_{r=1}^{N}[x(r)]^2, \quad (1)$$

where x is the amplitude of the recorded signal and N is the number of samples. At second, parameter S as a relative change was calculated:

$$S = \left(\frac{s_2}{s_1} - 1\right) \times 100\%, \quad (2)$$

where s_1 and s_2 are the average energies inside the 30 s comparison intervals in the beginning of cycle segments without and with exposure, respectively.

Finally, the intra-hemispheric asymmetry A was calculated as:

$$A = S_L - S_R, \quad (3)$$

where S_L and S_R are S-parameters calculated for left or right hemisphere symmetric channel, respectively.

The asymmetry values were calculated for FP1–FP2, T3–T4, P3–P4 and O1–O2 channel pairs. The asymmetry for a subject was calculated as the value of the parameter A averaged over ten exposure cycles at fixed modulation frequency.

Signal processing and calculation of parameters were performed in the LabView programming and signal processing environment.

The statistical analysis of calculated parameter for group and individuals was performed. The two-tailed paired Student t-test for group was applied. The ratio of computed asymmetry differences to the standard deviation (calculated on the basis of sham signals) was used for evaluation of individual changes for a subject. Post-host Bonferroni correction was applied. The confidence level of 0.05 was considered statistically significant.

3 Results and discussion

Asymmetry values were calculated for channel pairs FP1–FP2, T3–T4, P3–P4 and O1–O2 for all subjects and all EEG frequency bands.

Average asymmetry values for Group A at 14 Hz modulation frequency are presented in Fig. 2.

The visual comparison of results presented in Fig. 2 shows, according to formula (3), increase of energy from the left side caused by microwave exposure in all analysed channel and all EEG rhythm, except alpha rhythm. The biggest differences in values occur in temporal–parietal brain region.

Results of t-test performed for comparison of sham and exposed conditions revealed no significant changes for the group.

Average asymmetry values calculated for Group B at 40 Hz modulation frequency are presented in Fig. 3. The microwave exposure increases EEG energy from the left side and asymmetry scores are more positive in microwave exposed conditions in all rhythms, except theta rhythm. Theta rhythm is not affected by the microwave exposure also in our previous study (Hinrikus et al. 2008b).

The character of graphs in Fig. 3 is similar to the results seen in case of microwaves modulated at 14 Hz in Fig. 2: microwave exposure increases the EEG power from the left side, where the field power density is higher. Standard deviation is about twice higher in exposed compared to sham conditions. However, the t-test performed for the groups revealed no significant differences between sham and exposed conditions. This effect can be explained by SAR distribution in the human brain: SAR values from the left side are higher but really the microwave field is present in both hemispheres and the asymmetry values are reduced.

Our previous results showed that the effect of microwave exposure differs for individuals (Hinrikus et al.

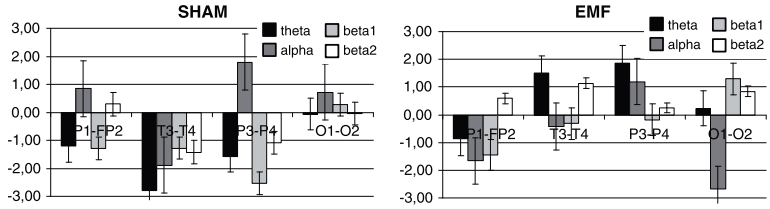


Fig. 2 The average asymmetry values calculated for different EEG rhythms for the group A (13 subjects) at 14 Hz modulation frequency in unexposed and microwave exposed conditions

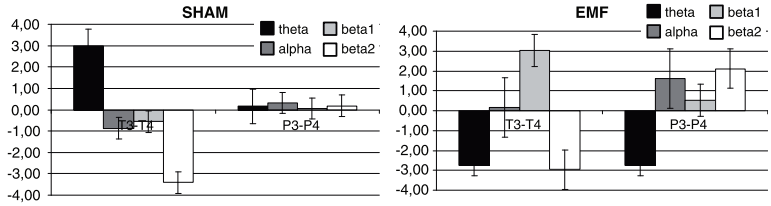


Fig. 3 The average asymmetry values calculated for different EEG frequency bands for the group B (15 subjects) at 40 Hz modulation frequency in sham and microwave exposure condition

Table 1 Numbers of subjects with statistically significant changes in EEG asymmetry values caused by microwave exposure

	14 Hz modulation				40 Hz modulation				Sham			
	F1–F2	T3–T4	P3–P4	O1–O2	F1–F2	T3–T4	P3–P4	O1–O2	F1–F2	T3–T4	P3–P4	O1–O2
Theta	–	–	1	–	–	2	3	–	–	–	–	–
Alpha	2	–	–	1	–	5	–	–	–	–	–	–
Beta1	–	–	–	–	–	1	–	–	–	–	–	–
Beta2	–	–	1	1	–	2	3	–	–	–	–	–

2008a), some of the subjects under investigation may be significantly affected and the others not. Variations in sensitivity to microwave exposure lead to increased variability of the results between individuals in exposed conditions (Lass et al. 2002). The idea about different sensitivity to exposure is supported by increased variability in exposed conditions in this study. Sensitivity of some subjects to microwave exposure is most likely related not to hypersensitivity of these individuals but to variability of the physiological state of the brain. Human brain is highly complicated system and affected simultaneously by hundreds of physical, chemical, psychological etc. stressors. Microwave exposure is one of these stressors. Effect of the microwave exposure as a weak stressor depends on combination of the other stressors and initial state of the brain. Therefore, despite that the effect of microwave exposure appears to be not statistically significant for the whole group, however, it can be significant for some individuals.

The differences between exposed and sham conditions in the asymmetry in all channel pairs and EEG rhythms for each subject were evaluated using the ratio of computed asymmetry differences to the standard deviation of differences (calculated on the basis of sham signals). The results are presented in Table 1.

Most of significant changes occur in temporal–parietal area. The rate of subjects affected by microwave exposure was lower at 14 Hz modulation, 15% (2 subjects) and higher at 40 Hz modulation, 35% (5 subjects). Such difference can be caused by variability of results in groups of different subjects. There were no significant differences in sham conditions.

In previous studies the individual sensitivity to microwave exposure was evaluated based on relative changes in the EEG power (*S*-parameter) (Hinrikus et al. 2008a; Bachmann et al. 2007). The results of this study are in good agreement with the rate of individual sensitivity 13–31% reported in our previous publications (Hinrikus et al. 2008a; Bachmann et al. 2007). It seems that inter-hemispheric asymmetry as a measure for evaluation of the microwave effect on EEG has about the same sensitivity as relative changes in the EEG power.

4 Conclusions

The results of this study showed that 450 MHz microwave radiation modulated at 14 and 40 Hz altered EEG asymmetry between hemispheres and increased the EEG energy from the left side where the microwave power density was higher. However, differences in asymmetry between exposed and sham-exposed recordings were not statistically significant for a group.

Evaluated sensitivity to microwave exposure for individuals revealed significant differences in asymmetry between exposed and sham-exposed recordings for two subjects (15%) at 14 Hz and 5 subjects (35%) at 40 Hz modulation frequency.

Acknowledgments This research was supported by the European Union through the European Regional Development Fund and by the Estonian Science Foundation grant No 6632.

References

Bachmann M, Kalda J, Säkki M, Tomson R, Lass J, Tuulik V, Hinrikus H (2007) Individual changes in human EEG caused by 450 MHz microwave modulated at 40 and 70 Hz. Environmentalist 27:511–517. doi:10.1007/s10669-007-9069-9

Borbely AA, Huber R, Graf T, Fuchs B, Gallmann E, Achermann P (1999) Pulsed high-frequency electromagnetic field affects human sleep and sleep electroencephalogram. Neurosci Lett 275:207–210. doi:10.1016/S0304-3940(99)00770-3

Curcio G, Ferrara M, Moroni F, D'Inzeo G, Bertini M, De Gennaro L (2005) Is the brain influenced by a phone call? An EEG study of resting wakefulness. Neurosci Res 53:265–270. doi:10.1016/j.neures.2005.07.003

Hinrikus H, Parts M, Lass J, Tuulik V (2004) Changes in human EEG caused by low-level modulated microwave stimulation. Bioelectromagnetics 25:431–440. doi:10.1002/bem.20010

Hinrikus H, Bachmann M, Lass J, Karai D, Tuulik V (2008a) Effect of low frequency modulated microwave exposure on human EEG: individual sensitivity. Bioelectromagnetics 29:527–538. doi:10.1002/bem.20415

Hinrikus H, Bachmann M, Lass J, Tomson R, Tuulik V (2008b) Effect of 7, 14 and 21 Hz modulated 450 MHz microwave radiation on human electroencephalographic rhythms. Int J Radiat Biol 84:66–79. doi:10.1080/09553000701691679

Huber R, Graf T, Cote KA, Wittmann L, Gallmann E, Matter D, Schuderer J, Kuster N, Borbery AA, Achermann P (2000)

Exposure to pulsed high-frequency electromagnetic field during waking affects human sleep EEG. NeuroReport 11:3321–3325. doi:10.1097/00001756-200010200-00012

Huber R, Treyer V, Borbely AA, Schuderer J, Gottselig JM, Landolt HP, Werth E, Berthold T, Kuster N, Buck A, Achermann P (2002) Electromagnetic fields, such as those from mobile phones, alter regional cerebral blood flow and sleep and waking EEG. J Sleep Res 11:289–295. doi:10.1046/j.1365-2869.2002.00314.x

Krause CM, Sillanmäki L, Koivisto M, Häggqvist A, Saarela C, Revonsuo A, Laine M, Hämäläinen H (2000a) Effects of electromagnetic field emitted by cellular phones on the EEG during a memory task. NeuroReport 11:761–764. doi:10.1097/00001756-200003200-00021

Krause CM, Sillanmäki L, Koivisto M, Häggqvist A, Saarela C, Revonsuo A, Laine M, Hämäläinen H (2000b) Effects of electromagnetic fields emitted by cellular phones on the electroencephalogram during a visual working memory task. Int J Radiat Biol 76:1659–1667. doi:10.1080/09553000050201154

Lass J, Tuulik V, Ferenets R, Riisalo R, Hinrikus H (2002) Effects of 7 Hz-modulated 450 MHz electromagnetic radiation on human performance in visual memory tasks. Int J Radiat Biol 78:937–944. doi:10.1080/09553000210153934

Suhhova A, Bachmann M, Aadamsoo K, Võhma Ü, Lass J, Hinrikus H (2008) Effect of microwave radiation on EEG coherence. IFMBE Proc 20:331–334. www.springerlink.com. doi:10.1007/978-3-540-69367-3_88

PUBLICATIONS

Publication III

Suhhova, A., Hinrikus, H., Bachmann, M., Lass, J. (2009). Effect of modulated microwave exposure on spectral asymmetry of human EEG. *IFMBE Proceedings,* Volume 25/3, pp 406-409.

Effect of Modulated Microwave Exposure on Spectral Asymmetry of Human EEG

A. Suhhova, H. Hinrikus, M. Bachmann, J. Lass

Department of Biomedical Engineering, Technomedicum of the Tallinn University of Technology, Tallinn, Estonia

Abstract— **This study was aimed to investigate the effect of modulated low-level microwave radiation on the human electroencephalographic (EEG) signal. The 450 MHz microwave exposure 100% pulse-modulated at 40 Hz frequency was applied to a group of 14 volunteers. The field power density at the scalp was 0.16 mW/cm^2. Ten cycles of the exposure (1 min on and 1 min off) were applied. The resting 9 channels EEG was recorded during 20 minutes in exposed and sham conditions. The EEG spectral asymmetry index was calculated as a relative difference in powers of high and low EEG frequency bands. The analysis revealed statistically significant changes caused by microwave exposure for the whole group in temporal, parietal and occipital EEG channels. The exposure caused increase in the calculated EEG spectral asymmetry index values related to increase in the EEG beta power.**

Keywords— **non-ionizing radiation, microwave effect, human EEG, spectral asymmetry.**

I. Introduction

Wide use of telecommunication equipment causes increasing interest to the effects of low-level modulated microwave radiation on human brain. A number of investigators have reported that exposure to a low-level microwave radiation produces alterations in the resting electroencephalographic (EEG) signal and/or brain behaviors [1 – 7]. Despite of many investigations, the observed effects of low-level microwave were subtle and the underlying mechanisms remain still unknown. Difficulties experienced in replication of experimental findings have caused doubts concerning these effects. Therefore new and more sensitive measures for detection of the microwave effect on EEG would be useful.

In our previous studies the modulated at different low frequencies microwave exposure was shown to increase the EEG power in the EEG alpha and beta frequency bands in all EEG channels. Most regular increase occurred in the EEG beta band power and no significant changes were revealed in the EEG theta band power [3, 7]. Based on these findings, we can assume that relative changes in the EEG power spectrum can characterize the effect of microwave exposure. On the other hand, a new indicator for depressive disorder, spectral asymmetry index (SASI), was recently proposed and investigated [8].

The aim of this study was to apply the spectral asymmetry index SASI to evaluate the specific changes produced by microwave exposure in human resting EEG.

II. Materials and methods

A. Subjects

Experiments were carried out on a group of healthy volunteers, consisting of 14 young healthy persons (aged 21–24): eight male and six female. All the subjects selected had no medical or psychiatric disorders. During the experiments, the experimenter and the subjects were in the dark laboratory room. The subjects were lying in a relaxed position, eyes closed and ears blocked during the experiments. All the subjects passed two recording sessions — with microwave exposure and sham exposure. For each recording session, the exposure conditions were randomly assigned. The subjects were not informed of their exposure during a session, however, they were aware of the possibility of being exposed.

The study was conducted in accordance with the Declaration of Helsinki and has formally approved by the local Medical Research Ethics Committee.

B. Microwave exposure

Electromagnetic radiation of 450 MHz was generated by a Rhode & Swartz signal generator (model SML02), The microwave radiation was 100% pulse-modulated at 40 Hz frequency (duty cycle 50%). The output power of 1 W was guided by a coaxial lead to the 13 cm quarter-wave antenna located at 10 cm from skin on the left side of head.

The spatial distribution of the electromagnetic radiation power density was measured by the Fieldmeter C.A 43 field strength meter. The measurements were performed by the Central Physical Laboratory of the Estonian Health Protection Inspection. The calibration curves of the dependence of field power density on the distance from the radiating antenna were obtained from these measurements, performed under real experimental conditions. Estimated

O. Dössel and W.C. Schlegel (Eds.): WC 2009, IFMBE Proceedings 25/III, pp. 406–409, 2009.
www.springerlink.com

from the measured calibration curves field power density at skin was 0.16 mW/cm^2. During the experiments a Digi Field C field strength meter was used to monitor the stability of the electromagnetic radiation level. The specific absorption rate (SAR) was calculated using SEMCAD software. The calculated spatial peak SAR averaged over 1 g was 0.303 W/kg.

C. Experimental procedure and EEG recording equipment

Our experimental study was performed according to the recording protocol identical for all subjects. All subjects completed the session with microwave exposure and sham.

In exposed recordings for the duration of every even minute of the recording the subject was exposed to microwave. The pair of successive reference minute followed by exposed minute was an exposure cycle. All subjects passed 10 cycles of exposure. EEG was continuously recorded during 20 minutes. Sham recording session used the same protocol, except that the microwave power was switched off. For each recording session, the exposure conditions (exposed or sham) were randomly assigned between subjects.

The Cadwell Easy II EEG measurement equipment was used for the EEG recordings. The EEG was recorded using 9 electrodes, which were placed on the subject's head according to the international 10-20-electrode position classification system. The channels for analysis were chosen to cover the entire head: frontal – FP1, FP2; parietal – P3, P4, temporal – T3, T4; occipital – O1, O2 and the reference electrode Cz. The EEG recordings were stored on a computer at a 400 Hz sampling frequency.

Artifacts can be induced by parasitic demodulation of the radio-frequency electromagnetic components on the EEG electrodes and equipment. To detect possible parasitic interaction between the recording and radio-frequency equipment, the set-up was validated before the experiments. The recordings on phantom were conducted in accordance with the procedure of the study. Multichannel recordings in frequency band 0.5-48 Hz detected spectral components at the modulation frequency 40 Hz. No other spectral components were detected. The artifacts at the modulation frequencies were removed from the EEG signals by off-line filtering during the pre-processing of the signals in the LabVIEW programming and signal-processing environment. Elliptic bandstop filters with an attenuation of 50 dB in the stopband were used.

The pre-processing of the signals was performed in the LabVIEW programming and signal-processing environment. The EEG spectrum 0.5 - 39 Hz was selected for the analysis. Such a selection excluded possible modulation frequency artifacts.

D. EEG analysis

The spectral asymmetry index was calculated using comparison of EEG powers in two selected EEG frequency bands. The EEG analysis comprises of four main operations: 1) estimation of power spectral density of the recorded EEG signal; 2) selection of boundary frequencies of high and low EEG frequency bands; 3) calculation of the EEG power in the selected bands; and finally 4) calculation of spectral asymmetry as a combination of the EEG powers in the selected frequency bands.

1) The power spectral density of the recorded EEG signal was estimated by means of Welch's averaged periodogram method. The signal was divided into overlapping sections (50%), with the length of 1024 points and windowed by the Hanning window.

2) The frequency limits of the high and low EEG frequency bands were selected as follows. The first step was estimating the central frequency band with the maximum spectral power f_{max} in the region of alpha band 8-13Hz of the recorded EEG signal. Thereafter the best parabolic fit was calculated to the ($f_{max} \pm a$) Hz spectrum, where a was half-width of the EEG central frequency (alpha) band. The maximum point of the fitted parabola fp_{max} was taken as a centre of the central band. This frequency is different for individual subjects.

The frequency limits for low and high frequency bands for an individual subject were determined as follows: low frequency band from F1= (fp_{max} – 6) Hz to F2= (fp_{max} – 2) Hz and high frequency band from F3= (fp_{max} + 2) Hz to F4= (fp_{max} + 26) Hz.

In this study the fixed boundary frequencies averaged for the whole group were applied: low frequency band from F1=4 Hz to F2=8 Hz and high frequency band from F3=14 Hz to F4=38 Hz.

3) Afterwards, the EEG signal power W_{lmn} in the low EEG frequency band (F1-F2) Hz and the power W_{hmn} in the high EEG frequency band (F3-F4) Hz was computed for each subject (indexed by $n \in [1,14]$) and channel (indexed by m=1,8) as the area under the spectrum for the corresponding frequency band (integral of the power spectral density over the band).

4) Finally, the spectral asymmetry index SASI was calculated as relative difference between powers of the high and low frequency bands

$$SASI = \frac{W_{hmn} - W_{lmn}}{W_{hmn} + W_{lmn}} \quad (1)$$

The Student t-test was applied for statistical comparison of the results between depressed and healthy subjects

separately in each EEG channel. The Bonferroni correction for multiple comparisons was used. The confidence level of 0.05 was considered statistically significant to the Bonferroni corrected *p*-values.

III. Results and discussion

Parameter SASI values were calculated in each EEG channel (8) for all subjects.

Calculated SASI values averaged over a group for recordings in microwave exposure and sham conditions are presented in Fig.1.

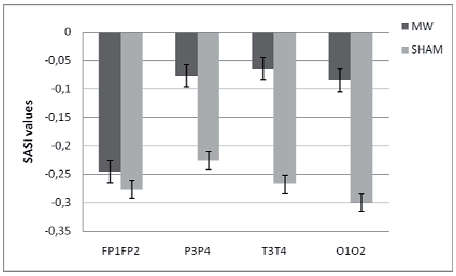


Figure.1. The calculated SASI values averaged over 10 exposure cycles, 14 subjects and 2 symmetric EEG channels in frontal, temporal, parietal and occipital brain regions for recordings in microwave exposure (MW) and sham condition.

Table 1. Results of *t*-test performed for evaluation of differences between the calculated SASI values in microwave exposure and sham conditions

Channel	FP1	FP2	T3	T4	P3	P4	O1	O2
P-values	0,91	0,36	0,03	0,02	0,02	0,03	0,01	0,02

As can be seen in Fig.1 the microwave exposure reduces averaged SASI parameter values in all analyzed channels compared to sham condition. The biggest differences occur in occipital channels, the changes in frontal channels are minimal.

The Student t-test performed for sham and microwave conditions reveals the changes to be statistically significant in all analyzed channel, except FP1 and FP2. (Table1).

Calculation of SASI values performed for exposed and reference minutes during recordings in microwave exposed conditions showed also negative SASI values averaged over 10 cycles in exposed compared to reference minutes. The biggest differences occur in P3 channels. No significant differences in SASI values during recordings in sham conditions.

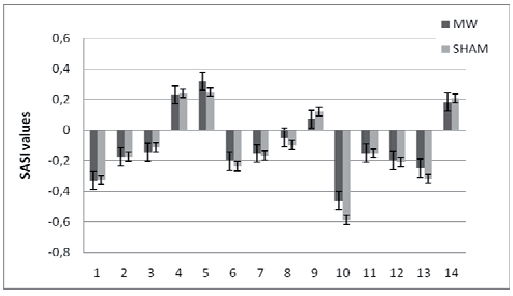


Fig.2. The calculated SASI values for individual subjects in P3 channels averaged over 10 exposure cycles.

The changes in SASI produced by microwave exposure for individual subjects are shown in Fig.2.

The results show negative average values of SASI in both microwave expose and sham conditions, but average SASI values are more positive in the case of microwave exposure.

The applied in this study spectral asymmetry index becomes more positive in the case of increased power in the high EEG (beta) band. Our experimental results showed more positive average SASI values in microwave exposed conditions (Fig. 1). The SASI values calculated for individual subjects are also more positive with exposure for majority of subjects (Fig. 2). These findings confirm increase in the power of higher EEG frequency bands in microwave exposed conditions and are in a good agreement with the results reported in other studies [2, 3, 6].

On the other hand, higher beta power has been shown characteristic for depressive disorder [9, 10]. Microwave exposure seems to disturb brain activity but only by a soft manner.

As can be seen from Fig. 2, about 28% of subjects involved in experiment showed positive SASI parameter values and are not affected by microwave exposure. The percentage of subjects not affected by microwave exposure was the same for all analyzed channels. Individual sensitivity to microwave exposure has been shown to be different [7]. Correlation of polarity of the SASI parameter with individual sensitivity to microwave exposure would be of interest and need further investigation.

IV. Conclusion

Our results suggest that the spectral asymmetry index as a combination of powers of high and low EEG frequency bands is promising for distinction of the effect of microwave radiation on the EEG. The proposed SASI parameter differs significantly between exposed and sham exposed conditions. The increase in the calculated EEG spectral asymmetry index values is related to increase in the EEG beta power.

Acknowledgement

This study was supported by the Estonian Science Foundation Grant No 6632, by the Estonian targeted financing project SF0140027s07, and by the European Union through the European Regional Development Fund.

References

1. Cook C, Saucier D, Thomas A, Prato F (2006) Exposure to ELF magnetic and ELF-modulated radiofrequency fields: the time course of physiological and cognitive effects observed in recent studies. Bioelectromagnetics 27: 613-627
2. Huber R, Treyer V, Schuderer J et al (2005) Exposure to pulse-modulated radio frequency electromagnetic fields affects regional cerebral blood flow. Eur J Neurosci 21:1000–1006
3. Hinrikus H, Bachmann M, Lass J et al (2008) Effect of 7, 14 and 21 Hz modulated 450 MHz microwave radiation on human electroencephalographic rhythms. International Journal of Radiation Biology 84:69-79
4. Bachmann M, Säkki M, Kalda .J et al (2005) Effect of 450 MHz microwave modulated with 217 Hz on human EEG in rest. The Environmentalist 25: 165-171
5. Huber R, Treyer V, Borbely A et al (2002) Electromagnetic fields, such as those from mobile phones, alter regional cerebral blood flow and sleep and waking EEG. J Sleep Res 11: 289–295
6. Curcio G, Ferrara M, Moroni F et al (2005). Is the brain influenced by a phone call? An EEG study of resting wakefulness. Neurosci Res 53: 265–270
7. Hinrikus H, Bachmann M, Lass J et al (2008) Effect of low frequency modulated microwave exposure on human EEG: Individual sensitivity. Bioelectromagnetics 29: 527-538
8. Hinrikus H, Bachmann M, Lass J et al (2008) Method and device for determining depressive disorders by measuring bioelectromagnetic signals of the brain. US12/196335
9. Knott V, Mahoney C, Kennedy S, Evans K (2001) EEG power, frequency, asymmetry and coherence in male depression. Psychiatry Research: Neuroimaging. 106:123 – 140
10. Sun Y, Li Y, Zhu Y et al (2008) Electroencephalographic differences between depressed and control subjects: an aspect of interdependence analysis. Brain Res Bull 76:559-564

Author: Anna Suhhova

- Institute: Technomedicum of the Tallinn University of Technology
- Street: Ehitajate road 5
- City: Tallinn
- Country: Estonia
- Email: anna@cb.ttu.ee

PUBLICATIONS

Publication IV

Hinrikus, H., Bachmann, M., Lass, J., **Suhhova, A.,** Tuulik, V. Aadamsoo, K., Võhma, Ü. (2012). Method and device for determining depressive disorders by measuring bioelectromagnetic signals of the brain. US 8244341.

US008244341B2

(12) **United States Patent**
Hinrikus et al.

(10) **Patent No.: US 8,244,341 B2**
(45) **Date of Patent: Aug. 14, 2012**

(54) **METHOD AND DEVICE FOR DETERMINING DEPRESSIVE DISORDERS BY MEASURING BIOELECTROMAGNETIC SIGNALS OF THE BRAIN**

(75) Inventors: **Hiie Hinrikus**, Tallinn (EE); **Maie Bachmann**, Saku vald (EE); **Jaanus Lass**, Tallinn (EE); **Anna Suhhova**, Pärnu (EE); **Viiu Tuulik**, Tallinn (EE); **Kaire Aadamsoo**, Tallinn (EE); **Ülle Võhma**, Tallinn (EE)

(73) Assignees: **Tallinn University of Technology**, Tallinn (EE); **North Estonia Medical Centre**, Tallinn (EE)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 994 days.

(21) Appl. No.: **12/196,335**

(22) Filed: **Aug. 22, 2008**

(65) **Prior Publication Data**

US 2009/0054801 A1 Feb. 26, 2009

Related U.S. Application Data

(60) Provisional application No. 60/957,514, filed on Aug. 23, 2007.

(51) **Int. Cl.**
A61B 5/04 (2006.01)

(52) **U.S. Cl.** **600/544**

(58) **Field of Classification Search** 600/300–301, 600/544–545

See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

5,083,571 A * 1/1992 Prichep 600/544
5,230,346 A 7/1993 Leuchter et al.
6,021,346 A 2/2000 Ryu et al.
6,622,036 B1 9/2003 Suffin
2003/0181821 A1 * 9/2003 Greenwald et al. 600/544

OTHER PUBLICATIONS

Knott et al. EEG power, frequency, asymmetry, and coherence in male depression. Psychiatry Research Neuroimaging. Elsevier Science. Apr. 10, 2001.pp. 123-140.*

Glass and Kwiatokowski. Power Spectral Density Changes in EEG during Mental Arithmetic and Eye-Opening. Pyschol. Forsch. 1970. pp. 85-99.*

Saletu, B. et al., "EEG Mapping and Low-Resolution Brain Electromagnetic Tomography (LORETA) in Diagnosis and Therapy of Psychiatric Disorders: Evidence for a Key-Lock Principle", Clinical EEG and Neuroscience, 2005, pp. 108-115, vol. 36, No. 2.

Knott, V. et al., "EEG Power, Frequency, Asymmetry and Coherence in Male Depression", Psychiatry Research: Neuroimaging, 2001, pp. 123-140, vol. 106.

Allen, J.B. et al., "The Stability of Resting Frontal Electroencephalographic Asymmetry in Depression", Psychophysiology, 2004, pp. 269-280, vol. 41.

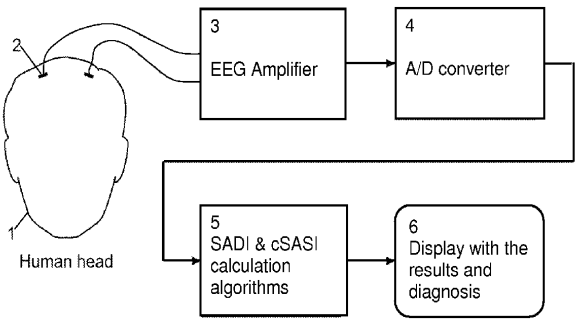
(Continued)

Primary Examiner — Michael Kahelin
Assistant Examiner — Tiffany Weston
(74) *Attorney, Agent, or Firm* — Maine Cernota & Rardin

(57) **ABSTRACT**

The present invention provides a method and device for determining depressive disorders or other mental disorders related to similar brain imbalances when the combination of powers of specific frequency bands in quantitative EEG has a certain positive or negative value. The present invention performs a signal-processing task to resting EEG recording, calculates the power of two specific frequency bands, finds the combination of the powers and evaluates the result. The method can be used as quick and easy noninvasive tool for diagnosing depression related problems in different patients as separate algorithm, as a part of an EEG recording and analysis device and as a separate device.

17 Claims, 7 Drawing Sheets



OTHER PUBLICATIONS

Flor-Henry, P. et al., "A Source-Imaging (Low-Resolution Electromagnetic Tomography) Study of the EEGs From Unmedicated Males With Depression", Psychiatry Research: Neuroimaging, 2004, pp. 191-207, vol. 130.

Lubar, Joel et al., "Low-Resolution Electromagnetic Tomography (LORETA) of Cerebral Activity in Chronic Depressive Disorder", International Journal of Psychophysiology, 2003, pp. 175-185, vol. 49.

Maltez, J. et al., "Time Course and Variability of Power in Different Frequency Bands of EEG During Resting Conditions", Clinical Neurophysiology, 2004, pp. 195-202, vol. 34.

Rangaswamy, M. et al., "Beta Power in the EEG of Alcoholics", Society of Biological Psychiatry, 2002, pp. 831-842, vol. 52.

Bachmann, M. et al., "Effect of 450 MHz Microwave Modulated with 217 Hz on Human EEG in Rest", The Environmentalist, 2005, pp. 165-171, vol. 25.

Hinrikus, Hiie et al., "Electroencephalographic Spectral Asymmetry Index for Detection of Depression", Med. Biol. Eng. Comput., Mar. 9, 2009, 9 pages.

* cited by examiner

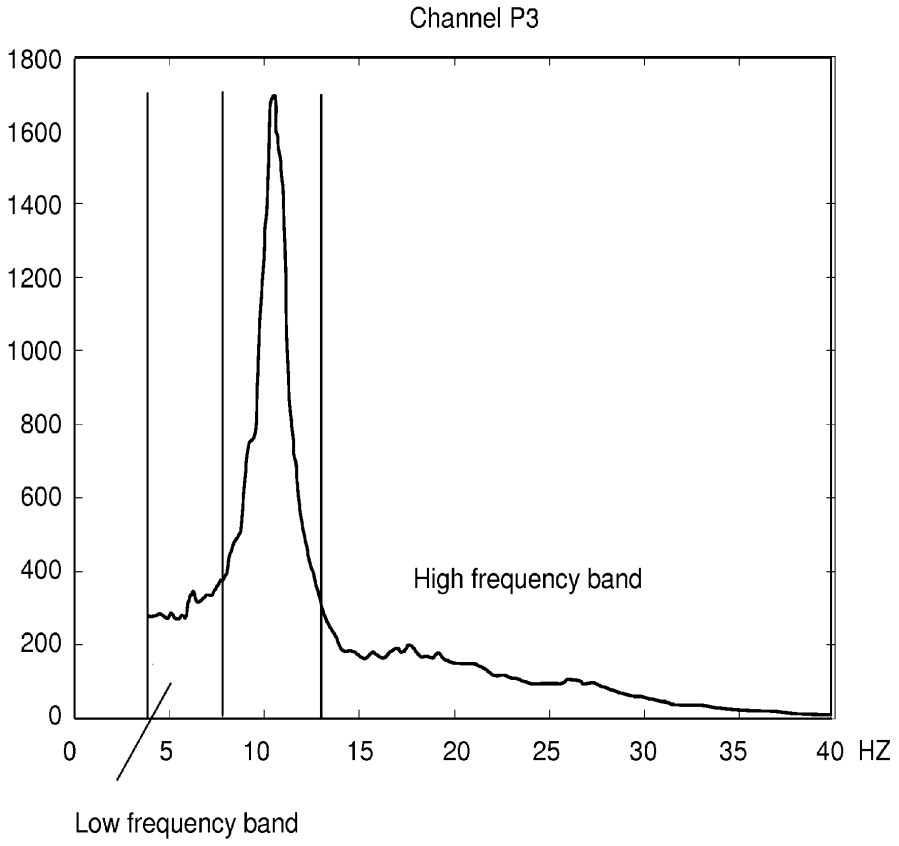

Channel P3
1800
1600
1400
1200
1000
800
600
400
200
0
0
5
10
15
20
25
30
35
40 HZ
High frequency band
Low frequency band

FIG. 1

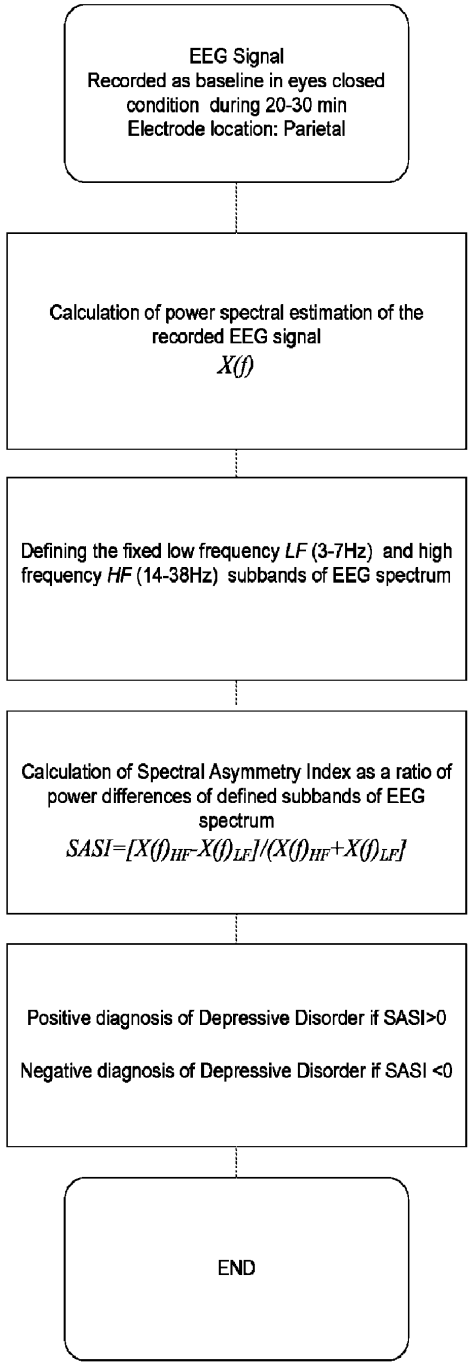

EEG Signal
Recorded as baseline in eyes closed condition during 20-30 min
Electrode location: Parietal
Calculation of power spectral estimation of the recorded EEG signal
X(f)
Defining the fixed low frequency LF (3-7Hz) and high frequency HF (14-38Hz) subbands of EEG spectrum
Calculation of Spectral Asymmetry Index as a ratio of power differences of defined subbands of EEG spectrum
SASI=[X(f)HF-X(f)LF]/(X(f)HF+X(f)LF]
Positive diagnosis of Depressive Disorder if SASI>0
Negative diagnosis of Depressive Disorder if SASI <0
END

FIG. 2

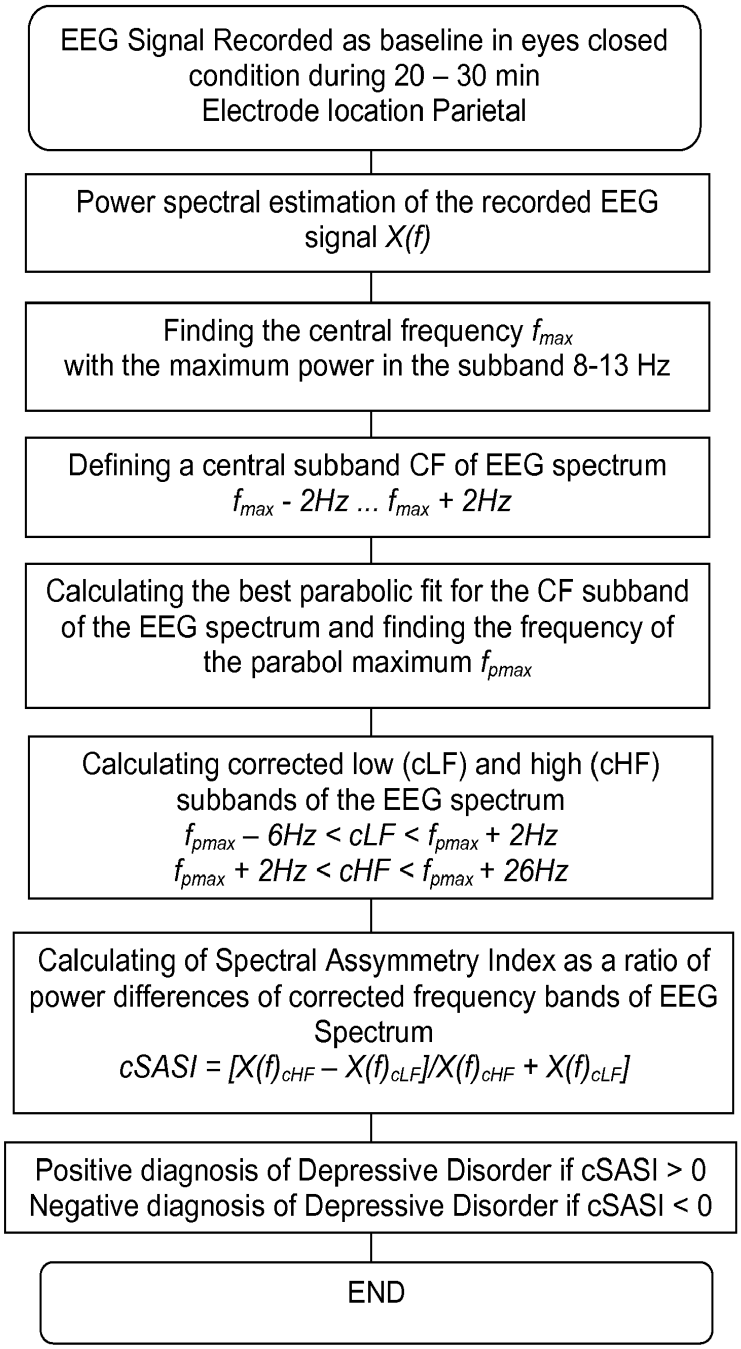

EEG Signal Recorded as baseline in eyes closed condition during 20 – 30 min Electrode location Parietal
Power spectral estimation of the recorded EEG signal X(f)
Finding the central frequency f_{max} with the maximum power in the subband 8-13 Hz
Defining a central subband CF of EEG spectrum f_{max} - 2Hz ... f_{max} + 2Hz
Calculating the best parabolic fit for the CF subband of the EEG spectrum and finding the frequency of the parabol maximum f_{pmax}
Calculating corrected low (cLF) and high (cHF) subbands of the EEG spectrum f_{pmax} – 6Hz < cLF < f_{pmax} + 2Hz f_{pmax} + 2Hz < cHF < f_{pmax} + 26Hz
Calculating of Spectral Assymmetry Index as a ratio of power differences of corrected frequency bands of EEG Spectrum $cSASI = [X(f)_{cHF} – X(f)_{cLF}]/X(f)_{cHF} + X(f)_{cLF}]$
Positive diagnosis of Depressive Disorder if cSASI > 0 Negative diagnosis of Depressive Disorder if cSASI < 0
END

FIG. 3

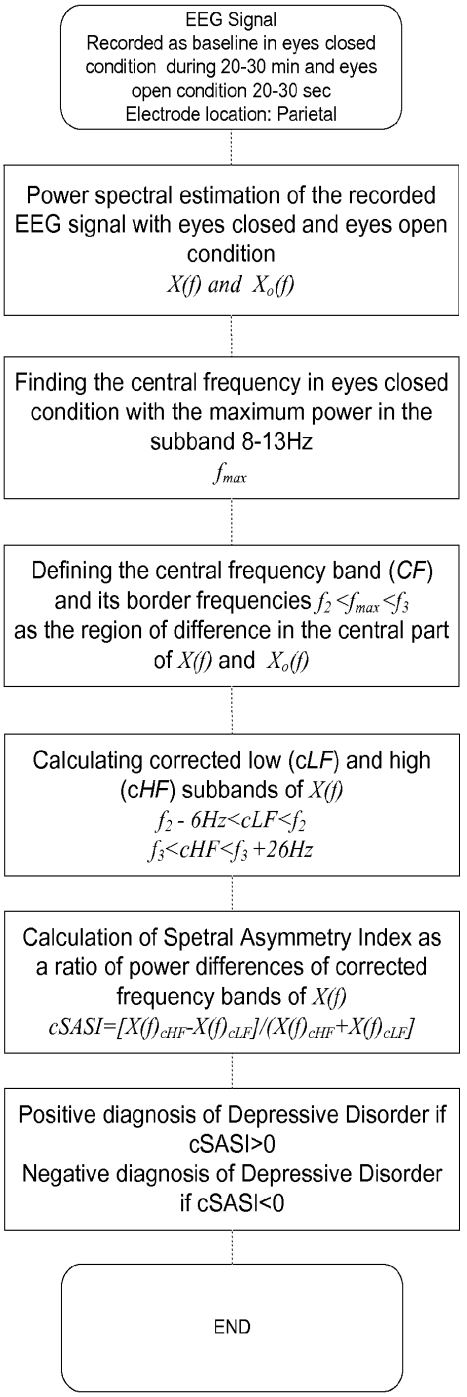

EEG Signal
Recorded as baseline in eyes closed condition during 20-30 min and eyes open condition 20-30 sec
Electrode location: Parietal
Power spectral estimation of the recorded EEG signal with eyes closed and eyes open condition
X(f) and Xo(f)
Finding the central frequency in eyes closed condition with the maximum power in the subband 8-13Hz
fmax
Defining the central frequency band (CF) and its border frequencies f2 <fmax <f3 as the region of difference in the central part of X(f) and Xo(f)
Calculating corrected low (cLF) and high (cHF) subbands of X(f)
f2 - 6Hz<cLF<f2
f3<cHF<f3 +26Hz
Calculation of Spetral Asymmetry Index as a ratio of power differences of corrected frequency bands of X(f)
cSASI=[X(f)cHF-X(f)cLF]/(X(f)cHF+X(f)cLF]
Positive diagnosis of Depressive Disorder if cSASI>0
Negative diagnosis of Depressive Disorder if cSASI<0
END

FIG. 4

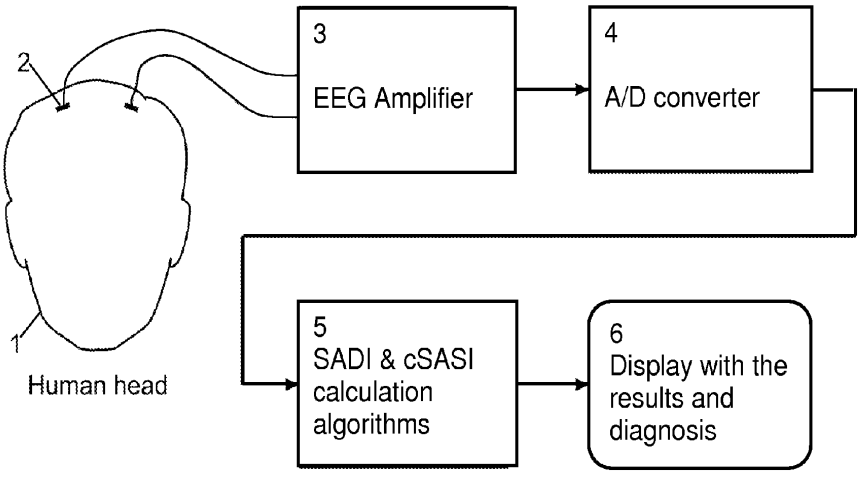

2
1
Human head
3
EEG Amplifier
4
A/D converter
5
SADI & cSASI calculation algorithms
6
Display with the results and diagnosis

FIG. 5

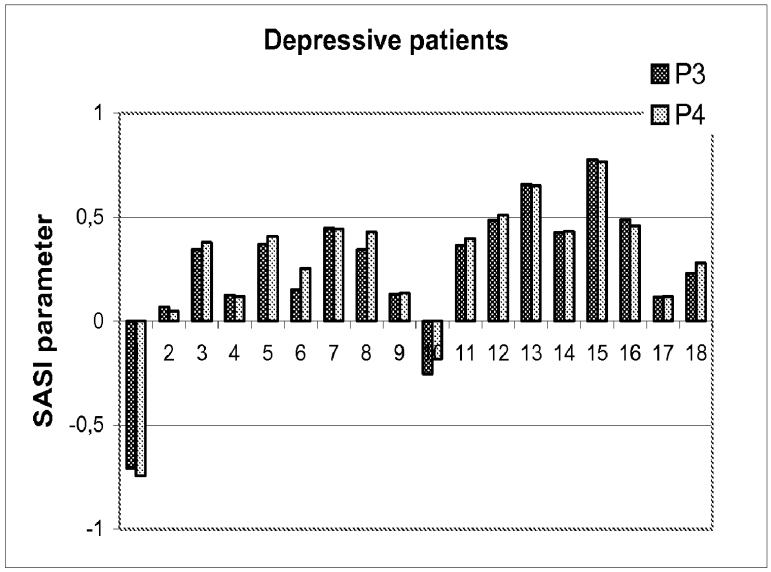

Depressive patients
P3
P4
SASI parameter
1
0,5
0
-0,5
-1
2 3 4 5 6 7 8 9 11 12 13 14 15 16 17 18

FIG. 6A

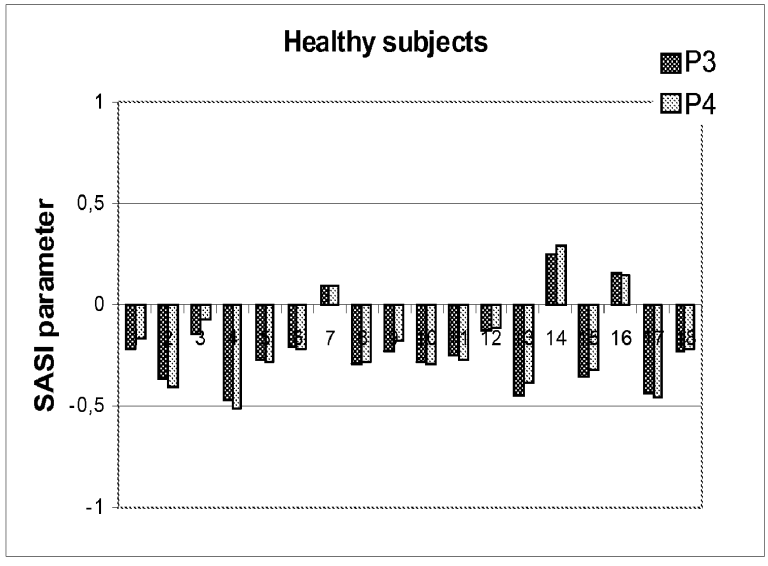

Healthy subjects
P3
P4
SASI parameter
1
0,5
0
-0,5
-1
7 14 16

FIG. 6B

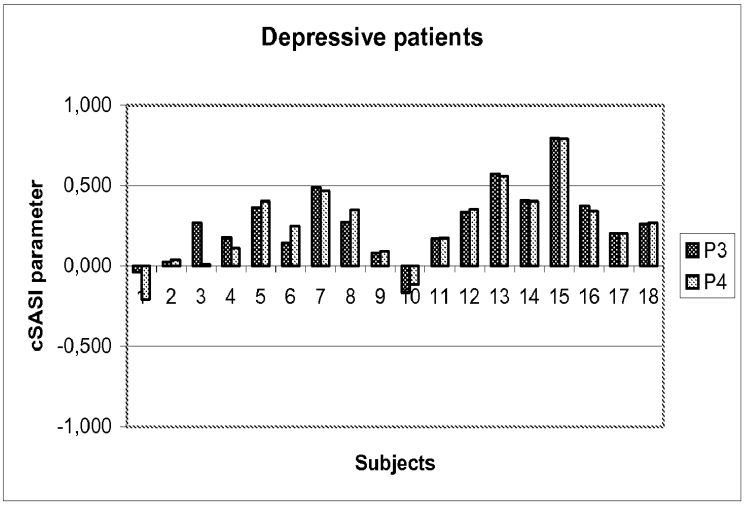

Depressive patients
1,000
0,500
0,000
-0,500
-1,000
cSASI parameter
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18
Subjects
P3
P4

FIG. 7A

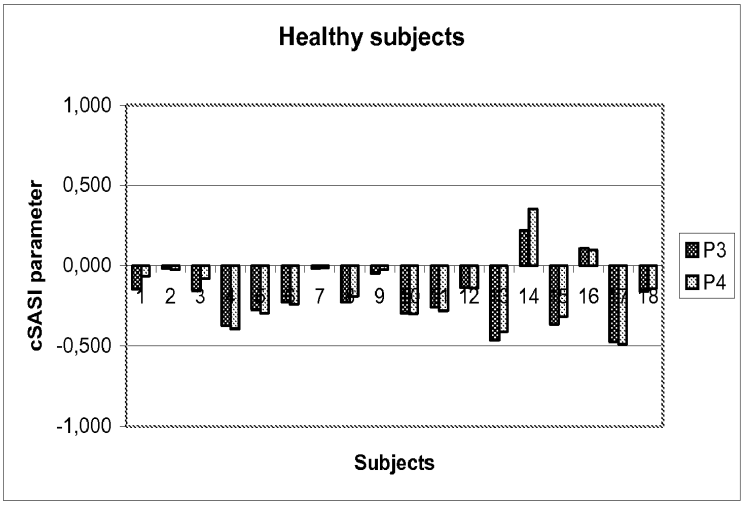

Healthy subjects
1,000
0,500
0,000
-0,500
-1,000
cSASI parameter
1 2 3 7 9 12 14 16 18
Subjects
P3
P4

FIG. 7B

METHOD AND DEVICE FOR DETERMINING DEPRESSIVE DISORDERS BY MEASURING BIOELECTROMAGNETIC SIGNALS OF THE BRAIN

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. provisional patent application No. 60/957,514, filed on Aug. 23, 2007, incorporated herein by reference in its entirety for all purposes.

TECHNICAL FIELD

The invention relates to the field of medical diagnosis and more specifically, to methods and devices for determining mental disorders such as depression by measuring and monitoring the bioelectromagnetic signals of the brain, e.g., by electroencephalogram (EEG).

BACKGROUND OF THE INVENTION

Fast rhythm of life and everyday stress has raised significantly the role of mental diseases and disorders in our society. Depression and other mental disorders are more and more frequent. About 340 million people (6 percent of total population of the world) suffer from deep depression. According to study performed by NIH (National Institute of Health), USA, during last 10 years the number of diagnosed depression increased about 40 times.

Even though depression and other mental disorders are more frequent, the physiological mechanisms of these are not finally clear yet. As a cause of depression, biochemical changes in brain can be considered as disturbance of the function of catecholamines and serotonin in the brain. According to another theory, depression is related to the imbalance of neurotransmitters in brain.

The diagnosis for depression is based on evaluation of the intensity of subjective and clinical symptoms by psychiatrists (M.I.N.I. interview, Hamilton test, and others). Distinguishing reactions to somatic diseases from depressive disorders requiring treatment is very complicated in psychiatric diagnostics. Therefore, there is a great need for methods for determining depression based on objective symptoms. There is a further need for objective monitoring of possible appearance of depressive conditions or other mental disorders of high-risk or high-stress workers such as military personnel, police, rescue workers.

Without doubt, changes in physiological state of the brain do occur together with mental illness and analysis of such changes can provide objective information. Changes in rhythms of bioelectrical activity of the brain, related to the changes in EEG, have been successfully used for diagnosing several neurological and psychiatric diseases (epilepsy, schizophrenia and others). However, only limited data are available about changes in neurophysiological state of the brain in depressive disorders.

Based on previous studies it was supposed that left frontal hypoactivation is distinctive for depressed individuals, being characterized by relatively more left alpha activity [1-4]. Moreover, frontal alpha asymmetry seems to characterize also recovered depressives [1, 3]. The results of the studies showed that EEG alpha asymmetry in depressives demonstrates stability that is comparable in magnitude to that seen in non-clinical populations and the stability is apparent despite rather substantial improvements in clinical state [2].

No relationship between depression severity and EEG asymmetry could be proven [3]. In addition, absolute and relative power in beta band appeared to differentiate patients and controls, with patients exhibiting more power than controls [1]. One of the studies employing LORETA (low-resolution electromagnetic tomography) observed in depressed individuals a pattern of more central, temporal, superior fronto-lateral and medial frontal asymmetry (increased alpha2 current density in the left hemisphere as compared to the right hemisphere) [4], which correlates with previous findings. Decreased current density in delta band was observed in right temporal lobe and the same trend was seen also in theta, alpha and beta band [4].

The results of the other study, employing the same method, showed increased source-current density underlying the EEG from the right hemisphere in the delta, alpha and beta frequency bands both during the resting and cognitively challenged conditions [3]. The expected left anterior hypoactivation in depression (reflected by increased resting left frontal EEG power in the alpha band compared to controls) was not seen [3]. The results suggested exactly the opposite, increased activation of the left frontal lobe and decreased activation of the right frontal lobe. Results showed significantly reduced delta band source-current density in depressed individuals compared to controls during the resting condition in most of the brain volume [3].

The following references were addressed:

[1] V. Knott, C. Mahoney, S. Kennedy, K. Evans, "EEG power, frequency, asymmetry and coherence in male depression," *Psychiatry Research: Neuroimaging*, vol. 106, pp. 123-140, 2001.

[2] J. B. Allen, H. L. Urry, S. K. Hitt, and J. A. Coan, "The stability of resting frontal electroencephalographic asymmetry in depression," *Physiology*, vol. 41, pp. 269-275, 2004.

[3] P. Flor-Henry, J. C. Lind, Z. J. Koles, "A source-imaging (low-resolution electromagnetic tomography) study of the EEGs from unmedicated males with depression," *Psychiatry Research: Neuroimaging*, vol. 109, pp. 191-207, 2004.

[4] J. F. Lubar, M. Congedo, J. H. Askew, "Low-resolution electromagnetic tomography (LORETA) of cerebral activity in chronic depressive disorder," *International Journal of Psychopathology*, vol. 49, pp. 175-185, 2003.

From the review above we can conclude that published results about changes in EEG caused by depression are contradictory and do not allow to make useful conclusions to evaluate the depressive mode.

In U.S. Pat. No. 6,021,346 a method for determining positive and negative emotional states by using a relative power in a subband of a specific frequency band increases or decreases in the course of time. The invention determines positive and negative emotional states by using a relative power in a subband of a specific frequency band increases or decreases with the lapse of time. The invention performs a Fourier transform for a unit time not an entire response time regarding a stimulus, and can be used in real time by using a time-frequency analysis method continuously executed with the lapse of time.

In U.S. Pat. No. 6,622,036, neurophysiologic information such as quantitative electroencephalography is used in a method for classifying, diagnosing, and treating physiologic brain imbalances, including for remotely assessing and treating patients with physiologic brain imbalances.

In U.S. Pat. No. 5,230,346, determining the brain condition of a human between normal and abnormal as determined by dementia, and selectively between dementia of the Alzheimer's-type and multi-infarct dementia is effected. Measures

of electrical output, spectral ratio and coherence value of the brain are determined. Selected scores are applied to the electrical output, spectral ratio and coherence values. A relationship between the scores and additionally the scored value of a coherence ratio are effected to obtain a diagnostic evaluation.

Depression has been shown to cause asymmetry and decreased coherence between brain hemispheres. However, published results about depression caused changes in EEG asymmetry are contradictory and cause doubts in hemispheric asymmetry based indicators to evaluate the depressive mode. Nevertheless, subjective symptoms of depression should be accompanied by changes in bioelectrical activity of the brain and in the EEG signal. Comparisons of the EEG signals of healthy persons and patients with depressive disorder may allow to detect characteristic features in the EEG produced by depression and to find objective criteria and measures for evaluation of depression and other mental disorders. By the present invention, there is provided a method and device based on the analysis of combination of the EEG selected bands power for distinction of characteristic features in the EEG caused by depression and other mental disorders.

OBJECTS AND SUMMARY OF THE INVENTIONS

The invented method is based on the notion that combination of the EEG beta and theta band power provides distinction of characteristic features in the EEG caused by depression.

The present invention is directed to a method for determining depressive disorders or other similar brain inbalances from EEG/QEEG (quantative EEG), which substantially obviates the above-described problem due to limitations and disadvantages of the related art. It is an object of the present invention to provide a method for calculating and combining the changes in EEG power at theta and beta frequency bands and to provide parameters characterizing the existence or non-existence of depressive disorder for a subject.

In one embodiment, the method uses an algorithm where different power spectral components of bioelectromagnetic activity signal of the brain are calculated by filtering or by Fourier analysis, namely a spectral asymmetry index (SASI) is calculated from two special frequency bands lower (theta band) and higher (beta band) of the EEG spectrum maximum and excluding central frequency band round EEG spectrum maximum (alpha band) from calculations. The polarity of the index value is the main indicator of the depressive or other mental disorder.

The limiting frequencies of beta and theta band have a role in SASI index calculation and can be defined in different ways. One aspect of the invention is excluding of central (alpha) frequencies from analysis. The limiting frequencies can be fixed or adjusted taking into account alpha frequency range in power spectrum of a particular subject. In last case the parameter is called a corrected spectral asymmetry index (cSASI).

For SASI and cSASI calculation resting EEG recording (eyes closed) is needed, preferably for 10 to 30 minutes. Single channel recording is sufficient for the index calculations. In one embodiment, one of the P channels in international classification system of 10-20-electrode position is used.

The SASI and cSASI calculation algorithms can be used for analysis of recorded EEG data, as a tool for EEG analysis in EEG recording and analyzing device and in a separate wearable device for EEG recording and analysis. The separate wearable device uses at least two electrodes for EEG recordings, amplifier, processor for SASI and cSASI calculations, an indicator-display and a power supply.

It is to be understood that both the foregoing brief description and the following detailed description are exemplary and explanatory and are intended to provide further explanation of the invention as claimed.

BRIEF DESCRIPTION OF THE DRAWINGS

The present invention will become more fully understood from the detailed description given herein below and the accompanying drawings which are given by way of illustration only, and thus are not limitative of the present invention, and wherein:

FIG. **1** is an EEG spectrum, showing the locations of higher frequency (beta) and lower frequency (theta) bands according to present invention.

FIG. **2** is a block diagram of a method for determining depressive disorder by calculating SASI.

FIG. **3** is a block diagram of a method for determining depressive disorder by calculating corrected SASI (cSASI).

FIG. **4** is a block diagram of a further method for determining depressive disorder by calculating corrected SASI (cSASI).

FIG. **5** is a structural scheme of a device for measurement of SASI and cSASI and for determining depressive disorder.

FIG. **6** is a graph that shows calculated values of SASI for individual subjects in symmetric EEG channels. FIG. **6**A represents data of 18 patients with clinically diagnosed depressive disorder and FIG. **6**B represents data of healthy subjects.

FIG. **7** is a graph that shows calculated values of cSASI for individual subjects in symmetric EEG channels. FIG. **7**A represents data of 18 patients with clinically diagnosed depressive disorder and FIG. **7**B represents data of healthy subjects.

DETAILED DESCRIPTION OF THE INVENTIONS

Reference is now made in detail to the preferred and other embodiments of the present invention, examples of which are illustrated in the accompanying drawings.

The present invention is based on calculating a Spectral Asymmetry Index (SASI) from the power spectra of two frequency bands. The formula can be generally presented as:

$$SASI = \frac{\int_{f_3}^{f_4} X(f)df - \int_{f_1}^{f_2} X(f)df}{\int_{f_3}^{f_4} X(f)df + \int_{f_1}^{f_2} X(f)df}$$

where X(f) is power spectrum of bioelectromagnetic activity signal of the brain (measured by EEG, MEG or others). One of the frequency bands f_3 to f_4 is selected higher (beta band B, also HF) and the other f_1 to f_2 is selected lower (theta band T, also LF) than the spectrum maximum of the activity signal of the brain. Values of signal powers within selected bands B and T characterize asymmetry of the spectrum. An important feature defining the B and T bands is excluding central frequency band around spectral maximum (alpha band A, also CF) from the analysis. The precise definition of B and T bands limiting frequencies is performed using several ways. Three embodiments are described here but it is clear that the invention is not limited to these three definitions of band values.

According to one embodiment, the limiting frequencies are chosen as follows: f_1=4 Hz, f_2=7 Hz, f_3=14 Hz and f_4=38 Hz for calculating SASI.

According to another embodiment, determining the limiting frequencies for B and T band for a particular subject is based on assumption that often the alpha band of the subject is shifted from its conventional frequencies (low-alpha or high-alpha). In this case a corrected SASI (cSASI) index can be calculated by modifying the frequencies f_1, f_2, f_3, and f_4. One possible way is described here. The first step is estimating the frequency with the maximum spectral power f_{max} in the region of 8-13 Hz of the recorded EEG. Thereafter the best parabolic fit is calculated to the f_{max}±2 Hz spectrum. The maximum point of the fitted parabola f_{pmax} is taken as a centre value for the alpha band. Reference points for corrected frequency bands (cHF and cLF) for cSASI are determined as follows: $f_1=f_{pmax}-6$ Hz, $f_2=f_{pmax}-2$ Hz, $f_3=f_{pmax}+2$ Hz, $f_4=f_{pmax}+26$ Hz. It should be also understood that this way of excluding alpha frequencies from cSASI calculation is exemplary and different approaches are possible that are still in the scope of current invention.

The third way for determining the limiting frequencies for HF and LF band is based on defining the central frequency band as an alpha frequency band which power significantly decreases when a subject opens eyes. In this case lower frequency f_3 of higher frequency band HF is equal to higher limit of decreased EEG power and higher frequency f_2 of lower frequency band LF is equal to lower limit of decreased EEG power.

EXAMPLE

The experiments were carried out on two groups of volunteers: a group of patients with major depressive disorder and a group of healthy comparison subjects. Each group consisted of 18 female persons, mean age 39 years, standard deviation 10 years. Subjects with major depressive disorder were selected from hospital inpatient unit. Subjects with non-psychotic major depressive disorder as defined by ICD-10 criteria and determined by 17-item Hamilton Depression Rating Scale (HAM-D) score more than 14 were eligible. The average HAM-D score for the group was 21 (SD 3.3). Subjects were without antidepressant treatment. Concomitant treatments for current general medical conditions were permitted on the basis of clinical judgment (patients receiving medication with known side effects on central nervous system were not eligible). The study was conducted in accordance with the Declaration of Helsinki and was formally approved by the local Medical Research Ethics Committee.

Experimental Protocol and EEG Analysis

The experimental procedure consisted of continuous resting eyes closed EEG recording during 30 minutes. The experimenter and the subjects were in the dark laboratory room during the experiments. The subjects were lying in a relaxed position, eyes closed and ears blocked during the experiments. The Cadwell Easy II EEG measurement equipment was used for the EEG recordings The EEG was recorded using 19 electrodes, which were placed on the subject's head according to the international 10-20-electrode position classification system. The channels for analysis were chosen to cover the entire head: frontal—FP1, FP2; parietal P5, P4, temporal—T3, T4; occipital O1, O2 and the reference electrode Cz. The EEG recordings were stored in a computer using 400 Hz sampling frequency. The power spectral density (PSD) of the recorded EEG signal was estimated by means of Welch's averaged periodogram method. The signal was divided into overlapping sections (50%), with the length of 2048 points and windowed by the Hanning window.

Afterwards, the power in the LF (4-7 Hz) and HF (14-38 Hz) band was computed for each subject as the area under the spectrum for the corresponding frequency band (integral of the band). SASI was calculated for all subjects according to formula above.

Parallel the cSASI was calculated. The frequency of the maximum spectral power f_{max} was estimation in the region of 8-13 Hz. Thereafter the best parabolic fit was calculated to the f_{max}±2 Hz spectrum. The maximum point of the fitted parabola f_{pmax} was taken as a centre value of the band CF. Frequency bands HF and LF for cSASI were determined as follows: $f_1=f_{pmax}-6$ Hz, $f_2=f_{pmax}-2$ Hz, $f_3=f_{pmax}+2$ Hz, $f_4=f_{pmax}+26$ Hz.

Parameter cSASI for a subject was calculated according to the formula described above. Signal processing and calculation of parameters were performed in the MatLab and LabVIEW programming and signal processing environment.

Results

Parameters SASI and cSASI values were calculated in each EEG channel (8) for each subject in the groups of patients with depressive disorder and healthy subjects. Values of SASI and cSASI parameters for each subject in P3 and P4 channels are presented in FIGS. **3** and **4**. Results in frontal, temporal and occipital channels were similar. As can be seen from the FIGS. **3** and **4** positive values of SASI prevail for patients with depressive disorder and negative values prevail for healthy subjects.

Hamilton test scores for patients with depressive disorder and values of calculated SASI and cSASI parameters are presented in Table 1.

TABLE 1

Calculated SASI and cSASI values in P3 and P4 EEG channels and Hamilton test scores for patients with depressive disorder.

SASI		CSASI		Hamilton
P3	P4	P3	P4	test
−0.70976	−0.74408	0.096	−0.071	17
0.068861	0.048907	0.117	0.182	17
0.344449	0.378201	0.374	0.075	20
0.123771	0.118723	0.177	0.135	20
0.368606	0.406663	0.410	0.443	22
0.149337	0.252144	0.130	0.244	22
0.447907	0.442863	0.506	0.478	20
0.343162	0.429961	0.310	0.372	20
0.129796	0.134331	0.199	0.155	22
−0.25406	−0.18257	−0.088	−0.013	18
0.364769	0.396001	0.243	0.261	19
0.484125	0.509341	0.449	0.489	24
0.658612	0.649608	0.587	0.556	27
0.425472	0.430825	0.444	0.445	27
0.776882	0.764701	0.798	0.795	26
0.486627	0.45839	0.433	0.400	26
0.114486	0.119744	0.227	0.200	24
0.229875	0.279593	0.296	0.302	22

Coefficients of correlation r were calculated between all different parameters in Table 1: between SASI and cSASI parameters, between Hamilton test scores and SASI/cSASI values, between parameters in P3 and P4 channels.

TABLE 2

Calculated correlation coefficients between calculated parameters and Hamilton test scores for patients with depressive disorder

	SASI	cSASI	Ham. test	P3	P4
SASI		0.85337 P4 channel	0.673161 P4 channel		
CSASI	0.842326 P3 channel		0.727817 P4 channel		
Ham. test	0.69724 P3 channel	0.713079 P3 channel			
P3					0.902166 cSASI
P4				0.993286 SASI	

Calculated values of SASI and cSASI parameters are well correlated in two symmetric EEG channels (r>0.9), between themselves (r>0.8) and finally with Hamilton test score (r>0.67 for SASI and r>0.71 for cSASI).

SASI values in two symmetric EEG channels (FIGS. **6** and **7**) are close to each other. Statistical comparisons of symmetric channels did not reveal significant differences between hemispheres (p>0.05).

Calculated SASI/cSASI values for depressive and healthy subjects (FIGS. **6** and **7**) differ significantly. Two-sample unequal variance t-test for differences between the groups of healthy and depressive subjects resulted in p=1.3 E-7.

The invention claimed is:

1. A method for determining a mental condition of a subject by measuring bioelectromagnetic signals of the brain and calculating a spectral asymmetry index representing the mental condition, the method comprising:

obtaining a recorded bioelectromagnetic signal from only one site on the subject's brain during a predetermining period of time;

performing, on a processor, a power spectral calculation on said recorded bioelectromagnetic signal;

defining a lower frequency band of said bioelectromagnetic signal, said lower frequency band having a second limiting frequency that is below a lower limiting frequency of an alpha band of said bioelectromagnetic signal of the brain, and a first limiting frequency chosen below said second limiting frequency, and calculating a first power of said bioelectromagnetic signal within said lower frequency band;

defining a higher frequency band of said bioelectromagnetic signal, said higher frequency band having a third limiting frequency that is above a higher limiting frequency of an alpha band of said bioelectromagnetic signal of the brain, and a fourth limiting frequency chosen above said third limiting frequency, and calculating a second power of said bioelectromagnetic signal within said higher frequency band;

calculating a spectral asymmetry index by subtracting the first power value from the second power value and dividing the result with the sum of the first power value and the second power value; and

defining a positive determination of the mental condition when the spectral asymmetry index is in the first predetermined range and defining a negative determination of the mental condition when the spectral asymmetry index is in the second predetermined range.

2. The method as in claim **1**, wherein said bioelectromagnetic signal is an EEG signal, a quantitative EEG signal, or a MEG signal.

3. The method as in claim **2**, wherein said predetermined period of time is from 5 to 30 minutes.

4. The method as in claim **3**, wherein said first limiting frequency is about 4 Hz.

5. The method of claim **4**, wherein said second limiting frequency is about 7 Hz.

6. The method of claim **5**, wherein said third limiting frequency is about 14 Hz.

7. The method of claim **6**, wherein said fourth limiting frequency is about 38 Hz.

8. The method as in claim **7**, wherein said first predetermined range is less than zero and said second predetermined range is larger than zero.

9. The method as in claim **8**, wherein said mental condition is a depressive disorder or a mental disorder similar to a depressive disorder.

10. The method as in claim **8**, wherein said spectral asymmetry index represents subject's response to a treatment of a mental condition.

11. The method as in claim **1**, wherein said spectral asymmetry index represents subject's suitability for inclusion in drug trials.

12. The method as in claim **1**, wherein said spectral asymmetry index is used to determine early symptoms of depression or other mental disorders of a subject.

13. The method as in claim **1**, wherein said alpha band is a corrected alpha band, said corrected alpha band determined by following steps:

determining a local maximum frequency in the region of 8 to 13 Hz, corresponding to a maximum of the power spectrum;

defining said corrected alpha band as having band width 4 Hz, wherein said local maximum frequency is a center frequency of said corrected alpha band;

calculating a best parabolic fit to said corrected alpha band and taking the maximum point of said best parabolic fit as a corrected center frequency of said corrected alpha band.

14. The method as in claim **13**, wherein said first limiting frequency is about 6 Hz less than said corrected center frequency and said second limiting frequency is about 2 Hz less than said corrected center frequency.

15. The method as in claim **14**, wherein said third limiting frequency is about 2 Hz more than said corrected center frequency and said fourth limiting frequency is about 26 Hz more than said corrected center frequency.

16. The method as in claim **1**, wherein said alpha band is a corrected alpha band, said corrected alpha band determined by the following steps:

obtaining a second recorded bioelectromagnetic signal from the subject's brain with the patient's eyes open;

performing a power spectral calculation on said second recorded bioelectromagnetic signal; and

defining said corrected alpha band as a frequency range where the power significantly decreases for the patient's eyes open compared to the patient's eyes closed.

17. The method as in claim **16**, wherein said second limiting frequency is equal to a lower limiting frequency of said corrected alpha band and said first limiting frequency is about 3 Hz less than said second limiting frequency and said third limiting frequency is equal to a higher limiting frequency and fourth limiting frequency is about 24 Hz higher than said third limiting frequency.

* * * * *

PUBLICATIONS

Publication V

Hinrikus, H., **Suhhova, A.,** Bachmann, M., Aadamsoo, K., Võhma, Ü., Lass, J., Tuulik, V. (2009). Electroencephalographic spectral asymmetry index for detection of depression. *Med Biol Eng Comput,* 47:1291-1299.

Med Biol Eng Comput (2009) 47:1291–1299
DOI 10.1007/s11517-009-0554-9

ORIGINAL ARTICLE

Electroencephalographic spectral asymmetry index for detection of depression

Hiie Hinrikus · Anna Suhhova · Maie Bachmann · Kaire Aadamsoo · Ülle Võhma · Jaanus Lass · Viiu Tuulik

Received: 9 March 2009 / Accepted: 2 November 2009 / Published online: 13 November 2009

Abstract This study is aimed to compare sensitivity of different electroencephalographic (EEG) indicators for detection of depression. The novel EEG spectral asymmetry index (SASI) was introduced based on balance between the powers of two special EEG frequency bands selected lower and higher of the EEG spectrum maximum and excluding the central frequency from the calculations. The efficiency of the SASI was compared to the traditional EEG inter-hemispheric asymmetry and coherence methods. EEG recordings were carried out on groups of depressive and healthy subjects of 18 female volunteers each. The resting eight-channel EEG was recorded during 30 min. The SASI calculated in an arbitrary EEG channel differentiated clearly between the depressive and healthy group ($p < 0.005$). Correlation between SASI and Hamilton Depression Rating Scale score was 0.7. The EEG inter-hemispheric asymmetry and coherence revealed some trends, but no significant differences between the groups of healthy controls and patients with depressive disorder.

Keywords EEG analysis · Spectral asymmetry · Inter-hemispheric asymmetry · Coherence · Depression

H. Hinrikus (✉) · A. Suhhova · M. Bachmann · J. Lass · V. Tuulik
Department of Biomedical Engineering, Technomedicum of the Tallinn University of Technology, Ehitajate Rd 5, 19086 Tallinn, Estonia
e-mail: hiie@cb.ttu.ee

K. Aadamsoo · Ü. Võhma
Clinic of Psychiatry, North Estonia Regional Hospital, 13419 Tallinn, Estonia

1 Introduction

During last decades understanding of the brain activity became a topic of major interest. Fast rhythm of life and everyday stress raised significantly the role of mental disorders in our society. Nowadays the modern methods of brain imaging are applied to get objective information about changes in brain physiology characteristic for mental diseases and disorders. Some steps toward understanding and assessment of mental fatigue and dementia [1, 2] have been reported. The electroencephalogram (EEG) analysis provided promising results for evaluation of Alzheimer's disease [3–5]. However, only limited data are available about alterations in the EEG in depressive disorders.

The diagnosis for depression is traditionally based on evaluation of the intensity of subjective and clinical symptoms by psychiatrists (M.I.N.I. interview, Hamiltoni test). Distinction of reactions to somatic diseases from depressive disorders required treatment is very complicated in psychiatric diagnostics. Therefore, the demand is justified for objective diagnostic methods in depressive disorders.

Electroencephalographic (EEG) studies have found abnormal regional hemispheric asymmetries in depressive disorders, which have been hypothesized to be vulnerability markers for depression. It has been reported that depressed patients show left frontal hypoactivation compared to healthy controls [6–10]. Some recent studies have focused on abnormalities of regional hemispheric asymmetries, as measured by the EEG alpha power over the left and right hemisphere sites [11]. The abnormal EEG sources are most frequently found in the right hemisphere showing increase in current power densities in the alpha and the theta EEG bands [12]. However, not all studies have found the frontal asymmetry to be always related to emotions and depression [13]. Some studies have found frontal EEG

asymmetry in both the depressed patients and the healthy controls [14]. Evidence of changes in the EEG alpha asymmetry scores have been not significantly related to changes in depressive severity and clinical state [6].

The second measure for analyzing the EEG in depression has been the inter-hemispheric coherence. The depression has been characterized by the reduced coherence values in each EEG frequency band [8].

It was also demonstrated that absolute and relative power in the EEG beta band appeared to differentiate the depressive patients and the controls with the patients exhibiting more power than the controls [8]. Recently, anomalies in the EEG beta waves have been found to be associated with mental depression [15]. This finding confirms previous results [8] and creates expectation that alterations in the EEG spectral bands power can include information useful for evaluation of depression.

The review above shows that published results reporting characteristic features in the EEG related to depressive disorder are contradictory and do not allow making final selection of indicators for evaluation of depression. Nevertheless, subjective symptoms of depression are accompanied by objective alterations in the brain bioelectrical activity and in the EEG signal. Therefore, the indicators based on the EEG analysis can be fruitful for diagnostics of depression.

Several measures based on the EEG analysis have been successfully employed for evaluation of the brain physiological state and different diseases [16–19]. The EEG spectral mean frequency was used to provide computational sleep depth analysis [16]. The mean frequency represents the center of gravity of the EEG amplitude spectrum 0.58–30.1 Hz [16]. An epileptic abnormality index was constructed from the EEG frequency band power and power inter-hemispheric asymmetry parameters comparing powers of the low (delta and theta) and high (alpha and beta) frequency bands between the brain hemispheres [17]. The revised extended brain symmetry index has been proposed to detect interhemispheric asymmetry, in particular with an emphasis on the detection of cerebral ischaemia [18]. Nonlinear method of length distribution of low variability periods (LDLVP) provided high sensitivity for detection of small alterations in the EEG caused by microwave exposure [19]. However, the LDLVP method revealed no significant differences between the normal and depressive EEG during our previous study [20].

From the review above, we can conclude that the measures employed in published studies are based on inter-hemispheric asymmetry of different EEG parameters and on analysis of the EEG frequency spectrum including all the EEG frequency bands. The EEG alpha band has been shown to play a crucial role in detection of inter-hemispheric asymmetry in depression [6, 8, 21]. Nevertheless, based on recent results, it seems promising to explore the EEG beta band for evaluation of depression [15].

In this article, we introduce a new method for detection of depressive disorder based on analysis of the EEG frequency spectrum, whereas balance of different spectral band powers can be evaluated in an arbitrary EEG channel and hemisphere [22]. The presumption is that the EEG beta band includes useful information for evaluation of depression, whereas the EEG theta band is stable and not affected by a disease. A spectral asymmetry index (SASI) is calculated as a relative differences in power of two EEG special frequency bands selected higher and lower of the EEG spectrum maximum. The EEG central frequency band round the spectrum maximum (alpha band) is excluded from the calculations. The boundary frequencies of the bands are specially selected for each individual and related to the frequency of the EEG spectrum maximum. The selected for calculation frequency bands are close to the traditional beta and theta bands but can be shifted in the case of low or high alpha frequency. The efficiency of the developed new method is compared to the EEG inter-hemispheric asymmetry and coherence methods using the same database.

2 Materials and methods

2.1 Subjects

The experiments were carried out on two groups of volunteers: a group of patients with depressive disorder and a control group of healthy subjects. The depression, usually considered separately for male and female patients, is more frequent for females; therefore female subjects were selected for investigation in this study [23]. Both groups consist of 18 female subjects at a mean age of 35 years, a standard deviation of 11 years.

The study was conducted in accordance with the Declaration of Helsinki and has formally approved by the local Medical Research Ethics Committee.

Subjects with depressive disorder without antidepressant treatment were selected for a hospital inpatient unit. Subjects with nonpsychotic depressive disorder as defined by ICD-10 criteria and determined by 17-item Hamilton Depression Rating Scale (HAM-D) score higher than 14 were eligible. The average score for the group was 22.8 (standard deviation 3.3).

2.2 Experimental procedure and EEG recording equipment

During the experimental procedure the continuous resting eyes closed EEG was recorded during 30 min. The measurements were performed in dark laboratory room; to

exclude the auditory stressors the ear plugs were used. During the experimental procedure participants were lying in relaxed position with closed eyes.

The Cadwell Easy II EEG measurement equipment was used for the EEG recordings. The EEG was recorded using nine electrodes, which were placed on the subject's head according to the international 10–20-electrode position classification system. In addition, two EOG electrodes were sited on the outer side of the eyes. Raw EEG signals were recorded using the Cadwell Easy data acquisition system with a frequency band of 0.3–70 Hz. The impedance of recording electrodes was monitored for each subject prior to data collection and it was always below 5 kΩ. The channels for analysis were chosen to cover the entire head: frontal—FP1, FP2; parietal—P5, P4; temporal—T3, T4; occipital—O1, O2 and the reference electrode Cz. The EEG signal was band-pass filtered 0.5–48 Hz and stored on a computer at the sampling frequency of 400 Hz.

2.3 EEG analysis

2.3.1 Spectral asymmetry index

The proposed SASI was calculated as a relative difference between the higher and the lower EEG frequency band power. The balance of the powers characterizes the EEG spectral asymmetry.

In order to achieve the balance a comparability of the powers in the bands is required. The EEG spectrum has much higher power spectral density in lower (delta, theta) than in higher (beta) frequencies. Therefore, to provide required balance, bandwidth of the higher frequency band should be selected much wider than the bandwidth of the lower frequency band. The 4 Hz bandwidth (close to traditional theta bandwidth) was selected for the lower EEG frequency band and the 24 Hz bandwidth (close to the traditional beta bandwidth) for the higher band.

Important aspect of the method is exclusion of the central (alpha) band frequencies from the analysis. Therefore, the boundary frequencies were adjusted taking into account the alpha frequency range in the EEG power spectrum of a particular subject.

Calculation of the SASI comprises four main steps: (1) computing of power spectral density of the recorded EEG signal; (2) selection of boundary frequencies of the lower and higher specific EEG frequency bands; (3) calculation of the EEG signal power in the selected bands; and (4) calculation of the SASI as a combination of the EEG powers in the selected bands.

(1) The power spectral density of the recorded EEG signal was calculated by means of Welch's averaged periodogram method. The signal was divided into overlapping epochs (50%), with the length of 1,024 and extracted through a Hanning window. The power spectral density s_{mn} was computed for each EEG channel (indexed by $m \in [1, 8]$) and subject (indexed by $n \in [1, 18]$).
(2) The boundary frequencies of the higher and lower specific EEG frequency bands were selected as follows (Fig. 1).

At first, the frequency with the maximum spectral power $f_{\max}$ in the region of alpha band 8–13 Hz of the recorded EEG signal was estimated. Thereafter the parabolic approximation was applied to the spectrum of the EEG central frequency band ($f_{\max} \pm B$) Hz, where B was

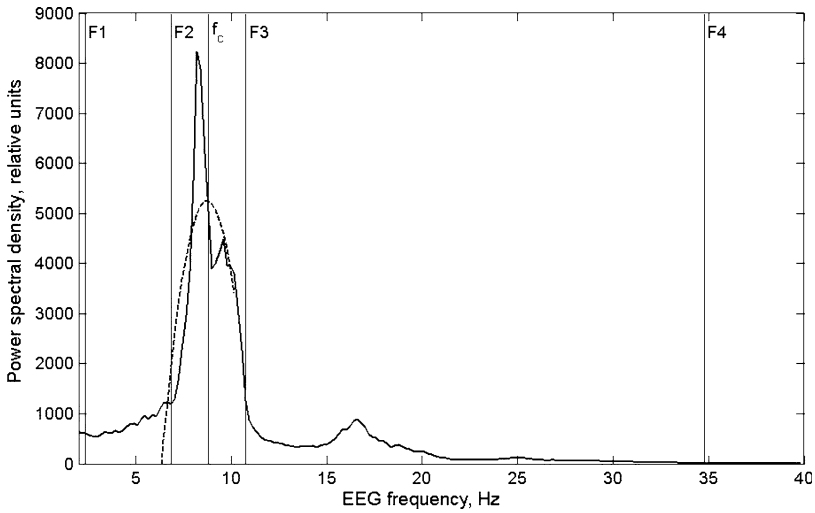


Fig. 1 Positions of the boundary frequencies for calculation of SASI. The parabolic approximation maximum (the centre of the excluded EEG central band) is marked as f_c; F1 and F2 denote lower and higher boundary frequencies of the lower EEG frequency band; F3 and F4 denote lower and higher boundary frequencies of the higher EEG frequency band. *Continuous line* denotes an EEG spectrum; *disconnected line* denotes a parabolic approximation

half-width of the band. The best parabolic fit was calculated by applying the Matlab POLYFIT tool, which finds the coefficients of a polynomial function that fits the data in a least-squares sense. The maximum point of the fitted parabola f_c was taken as a centre of the central band.

The frequency limits for the lower and the higher specific frequency bands were related to the estimated central band and determined as follows: the lower frequency band from F1 = ($f_c - B - 4$) Hz to F2 = ($f_c - B$) Hz, and the higher frequency band from F3 = ($f_c + B$) Hz to F4 = ($f_c + B + 24$) Hz. The value of the central bandwidth $2B$ was varied during preliminary calculations. The value of $B = 2$ Hz was finally determined.

(3) The EEG signal powers W_{lmn} and W_{hmn} in the lower and in the higher EEG frequency bands, respectively, were calculated for each EEG channels (indexed by $m \in [1, 8]$) and subject (indexed by $n \in [1, 18]$) as

$$W_{lmn} = \sum_{f=F1}^{F2} s_{mn}; \quad W_{hmn} = \sum_{f=F3}^{F4} s_{mn} \tag{1}$$

(4) Finally, the SASI was calculated as

$$\mathrm{SASI}_{mn} = \frac{W_{hmn} - W_{lmn}}{W_{hmn} + W_{lmn}} \tag{2}$$

The calculations of the SASI were performed for each subject and EEG channel.

2.3.2 Inter-hemispheric asymmetry

Asymmetry scores were calculated separately in the EEG theta (4–8 Hz), alpha (8–13 Hz), beta1 (13–20 Hz) and beta2 (20–40 Hz) frequency bands for the frontal, temporal, parietal, and occipital brain regions.

At first, relative EEG signal power in the left W'_{Lmn} and in the right W'_{Rmn} hemispheric symmetric channels (indexed as L and R) were calculated in each EEG frequency band as

$$W'_{Lmn} = \sum_{f=f_1}^{f_2} s_{Lmn} \Big/ \sum_{f=0.5\ \mathrm{Hz}}^{48\ \mathrm{Hz}} s_{Lmn}; \quad W'_{Rmn} = \sum_{f=f_1}^{f_2} s_{Rmn} \Big/ \sum_{f=0.5\ \mathrm{Hz}}^{48\ \mathrm{Hz}} s_{Rmn}, \tag{3}$$

where f_1 and f_2 are the lowest and the highest frequency of the selected EEG frequency band, respectively.The inter-hemispheric EEG asymmetry was calculated for each EEG frequency band, channel and subject as

$$A_{mn}(f_1, f_2) = \frac{W'_{Lmn} - W'_{Rmn}}{W'_{Lmn} + W'_{Rmn}} \cdot 100. \tag{4}$$

The higher asymmetry scores reflect higher relative left hemisphere activation. The asymmetry analysis was performed to FP1–FP2, T3–T4, P3–P4, and O1–O2 symmetric EEG channels.

2.3.3 Inter-hemispheric coherence

Inter-hemispheric coherence values for each EEG frequency band were computed using the formula:

$$C_{xy}(f_1, f_2) = \frac{\left(\sum_{f=f_1}^{f_2} s_{xy}\right)^2}{\sum_{f=f_1}^{f_2} s_{xx}(f) \cdot \sum_{f=f_1}^{f_2} s_{yy}(f)}, \tag{5}$$

where s_{xy} is the power cross-spectral density of two signals; s_{xx} and s_{yy} are the power spectral densities of each signal. The calculations of coherence were performed separately in the EEG theta (4–8 Hz), alpha (8–13 Hz), beta1 (13–20 Hz), and beta2 (20–40 Hz) frequency bands. The coherence values were calculated for FP1–T3—FP2–T4, T3–P3—T4–P4 and P3–O1—P4–O2 channel pairs.

Signal processing and calculation of parameters were performed in the MatLab (Signal Processing Toolkit) and LabVIEW Full Development System (Mathematics and Signal Processing modules) environment.

The Student t test was performed and the Bonferroni correction for multiple comparisons applied to evaluate differences between depressive and control group in each EEG channel. The confidence level of 0.05 was considered statistically significant to the Bonferroni corrected p values.

3 Results

3.1 Spectral asymmetry index

Calculated frequencies of parabolic maximum and boundary frequencies of the lower and the higher EEG frequency bands for all subjects in the depressive and the healthy group are presented in Table 1. As expected, the selected lower frequency band appeared to be close to the traditional EEG theta and the higher frequency band close to the beta frequency band. Differences compared with the traditional EEG band frequencies become evident for subjects with low or high alpha frequency (about half from total number of subjects). A relatively small shift of the central frequency band can lead to remarkable changes in the higher and lower bands power due to the high EEG power spectral density within the central band (Fig. 1).

SASI values were calculated in each EEG channel for all subjects in the group of patients with depressive disorder and in the control group of healthy subjects. Averaged over a group values of calculated SASI in different

Table 1 Boundary frequencies for the lower and the higher EEG frequency bands estimated for the EEG P3 channel

	Depressive patients					Healthy subjects				
	f_c	F1	F2	F3	F4	f_c	F1	F2	F3	F4
1	10.0	4.0	8.0	12.0	36.0	9.4	3.4	7.4	11.4	35.4
2	10.4	4.4	8.4	12.4	36.4	8.0	2.0	6.0	10.0	34.0
3	10.2	4.2	8.2	12.2	36.2	9.8	3.8	7.8	11.8	35.8
4	9.8	3.8	7.8	11.8	35.8	8.8	2.8	6.8	10.8	34.8
5	9.6	3.6	7.6	11.6	35.6	9.0	3.0	7.0	11.0	35.0
6	8.0	2.0	6.0	10.0	34.0	10.2	4.2	8.2	12.2	36.2
7	9.6	3.6	7.6	11.6	35.6	12.1	6.1	10.1	14.1	38.1
8	10.5	4.5	8.5	12.5	36.5	11.3	5.3	9.3	13.3	37.3
9	10.4	4.4	8.4	12.4	36.4	9.0	3.0	7.0	11.0	35.0
10	10.9	4.9	8.92	12.9	36.9	10.2	4.2	8.2	12.2	36.2
11	10.9	4.9	8.9	12.9	36.9	10.0	4.0	8.0	12.0	36.0
12	10.9	4.9	8.9	12.9	36.9	10.0	4.0	8.0	12.0	36.0
13	11.9	5.9	9.9	13.9	37.9	10.4	4.2	8.4	12.4	36.4
14	10.7	4.7	8.7	12.9	36.7	10.0	4.0	8.0	12.0	36.0
15	11.1	5.1	9.7	13.1	37.1	10.0	4.0	8.0	12.0	36.0
16	9.2	3.2	7.2	11.2	35.2	11.5	5.5	9.5	13.5	37.5
17	11.3	5.3	9.3	13.3	37.3	10.5	4.5	8.5	12.5	36.5
18	9.8	3.8	7.8	11.8	35.8	8.0	2.0	6.0	10.0	34.0

EEG channels are presented in Fig. 2. The calculated SASI average values are positive for the depressive and negative for the control group in all EEG channels. The values are approximately equal in the symmetric channels in the left and the right brain hemispheres.

Distinction ability of the index is determined by the difference in SASI values between the depressive and the healthy subjects. The differences in SASI between the depressive and the control group are remarkable in all channels; a slight maximum occur in the parietal channels.

Calculated SASI values for individual subjects in the depressive and the control group in P3 and P4 channels are presented in Fig. 3. Positive values of SASI prevail for patients with depressive disorder (except two patients, 11%) and negative values for healthy subjects (except three subjects, 17%). Calculation of SASI based on the fixed traditional EEG theta and beta band frequencies was performed for comparison. Calculation without individual tuning of the selected frequency bands resulted in 5 (28%) negative SASI values in the depressive and 7 (39%) positive SASI values in the control group.

The calculated SASI values in all EEG channels as well as Hamilton test scores for the patients with depressive disorder are presented in Table 2. Positive values of SASI appear for the majority of depressive subjects. The values are negative in all EEG channels only for two depressive subjects (6 and 16). SASI becomes negative for one

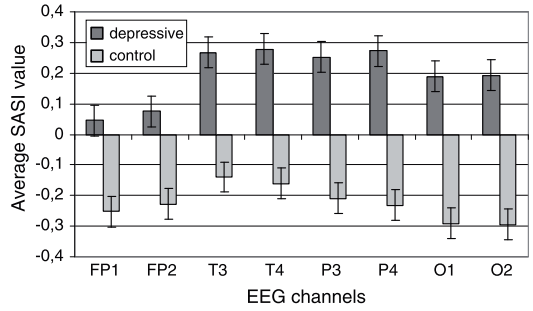


Fig. 2 Calculated SASI values averaged over a group of depressive and control subjects ($n = 18$) in different EEG channels. *Vertical bars* denote standard deviation

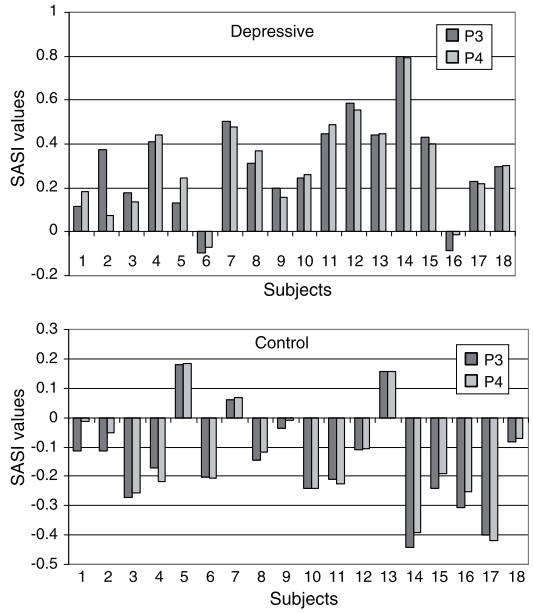


Fig. 3 Calculated SASI values in the EEG P3 and P4 channels for individual subjects in the group of depressive patients and healthy controls

additional subject in the frontal and the temporal channels and for three additional subjects only in the frontal channels. Negative SASI values prevail for the majority of the healthy control subjects. Only for three subjects these values are positive at least in four EEG channels.

Results of calculations of correlation between SASI values in different EEG channels as well as Hamilton Depression Rating Scale score are summarized in Table 3. Correlation between SASI values is highest between the symmetric EEG channels in different brain hemispheres (0.94–0.99). Correlation between SASI values is higher for

Table 2 Calculated SASI values in different EEG channels and Hamilton Depression Rating Scale score (HAM-D) for patients with depressive disorder

Subject	FP1	FP2	T3	T4	P3	P4	O1	O2	HAM-D
1	−0.044	−0.046	0.137	0.138	0.068	0.048	0.158	0.103	17
2	−0.541	−0.342	0.266	0.314	0.344	0.378	0.173	0.167	20
3	−0.075	−0.057	0.313	0.451	0.123	0.118	0.051	−0.123	20
4	0.401	0.424	0.433	0.468	0.368	0.406	0.184	0.209	22
5	0.512	0.533	0.476	0.273	0.149	0.252	−0.091	−0.036	22
6	−0.381	−0.381	−0.563	−0.596	−0.091	−0.074	−0.759	−0.769	17
7	0.391	0.388	0.333	0.342	0.447	0.442	0.131	0.214	20
8	0.475	0.413	0.473	0.516	0.343	0.429	0.215	0.289	20
9	0.058	0.086	0.223	0.224	0.129	0.134	0.078	0.027	22
10	0.061	0.021	0.142	0.231	0.364	0.396	0.347	0.411	19
11	0.056	0.043	0.171	0.201	0.484	0.509	0.503	0.501	24
12	0.587	0.644	0.703	0.766	0.658	0.649	0.667	0.665	27
13	0.118	0.143	0.314	0.761	0.425	0.431	0.414	0.445	27
14	0.633	0.871	0.781	0.703	0.776	0.764	0.716	0.728	26
15	0.141	0.145	0.323	0.258	0.486	0.458	0.566	0.459	26
16	−0.612	−0.574	−0.338	−0.315	−0.254	−0.182	−0.178	−0.173	18
17	−0.131	−0.128	−0.101	−0.101	0.114	0.119	0.051	0.058	24
18	0.294	0.131	0.308	0.369	0.229	0.279	0.181	0.283	22

the EEG channels located in the close brain areas and decreases for the channels located in the farther brain areas. The lowest correlation 0.53 was calculated between SASI in the frontal and the occipital channels. Correlation between calculated SASI values and Hamilton test scores showed its lowest value about 0.55 in the frontal and achieved values about 0.7 in the parietal and occipital channels.

Results of statistical evaluation of differences in SASI values between the depressive and the healthy group for different EEG channels are presented in Table 4. Calculated SASI values differ significantly in all channels ($p < 0.005$). Statistical comparisons of SASI in the symmetric EEG channels did not reveal significant difference between the brain hemispheres ($p > 0.05$).

Table 3 Correlation coefficients between calculated SASI values in different EEG channels and Hamilton Depression Rating Scale scores

	FP1	FP2	T3	T4	P3	P4	O1	O2
FP1								
FP2	0.974							
T3	0.817	0.875						
T4	0.709	0.751	0.935					
P3	0.658	0.727	0.876	0.873				
P4	0.666	0.729	0.884	0.867	0.993			
O1	0.542	0.605	0.772	0.793	0.947	0.931		
O2	0.596	0.651	0.777	0.796	0.956	0.949	0.982	
HAM-D	0.534	0.566	0.591	0.625	0.697	0.673	0.725	0.708

3.2 Inter-hemispheric asymmetry and coherence

The asymmetry between the brain hemispheres and inter-hemispheric coherence were calculated in each EEG frequency band for patients with depressive disorder and healthy control subjects.

Asymmetry values for the theta, alpha, beta1, and beta2 frequency bands between different EEG channels averaged over a group of depressive and healthy subjects are presented in Fig. 4. The average asymmetry values behave quite similar for both groups. In the majority of cases the depressive group shows higher asymmetry scores compared to the control group. This trend is more noticeable in the theta and the alpha frequency band. In the beta band differences between the depressive and the healthy group varied in different channels. Nevertheless, the *t* test revealed no significant differences in asymmetry between the depressive and the control group.

The coherence values calculated for the fronto-temporal, the tempora-parietal, and the parieto-occipital EEG channels in the theta, alpha, beta1, and beta2 frequency bands are presented in Fig. 5.

Coherence values show similar behavior for the group of patients with depressive disorder and the control group. The largest differences between two groups occur in the

Table 4 Bonferroni corrected p values for differences in spectral asymmetry between depressive and control groups in different EEG channels

EEG channel	FP1	FP2	T3	T4	P3	P4	O1	O2
p Values	0.005	0.004	2E−04	1E−04	3E−05	7E−05	2E−05	2E−05

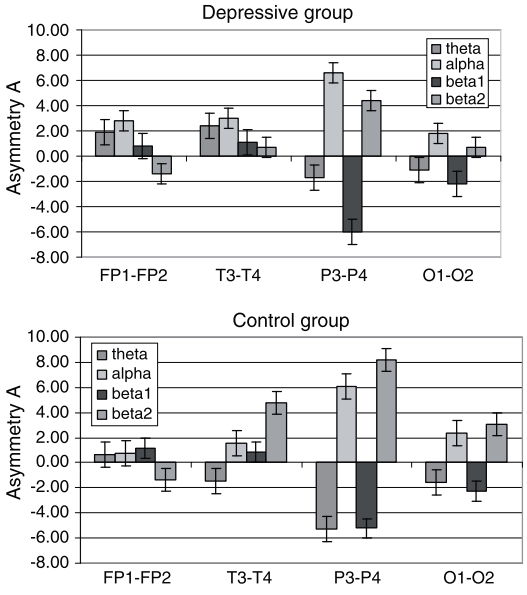


Fig. 4 Calculated inter-hemispheric asymmetry values between FP1 and FP2, T3 and T4, P3 and P4, and O1 and O2 EEG channels averaged over all subjects ($n = 18$) within the depressive and control group in the theta, alpha, beta1 and beta2 EEG frequency bands. *Vertical bars* denote standard deviation

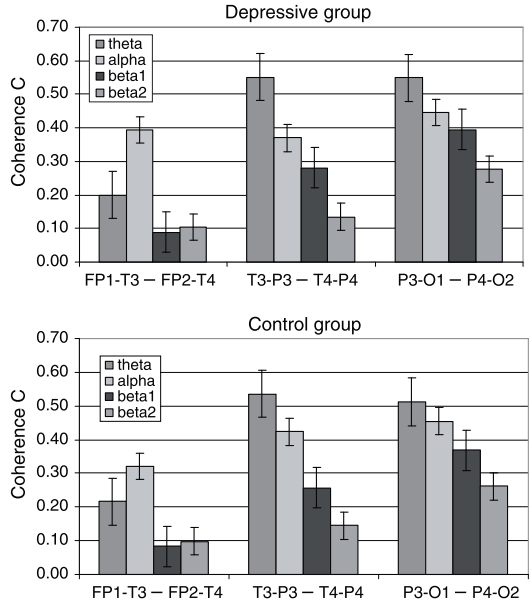


Fig. 5 Calculated coherence values for FP1–T3—FP2–T4, T3–P3—T4–P4, and P3–O1—P4–O2 channel pairs averaged over all subjects ($n = 18$) within the depressive and control group in the theta, alpha, beta1, and beta2 frequency band. *Vertical bars* denote standard deviation

alpha band in the fronto-temporal brain region where the coherence values were about 20% higher in the depressive group compared to the control group. In the tempora-parietal channel pairs T3–P3—T4–P4 the average coherence value in the alpha band was about 12% higher in the control group. The coherence values in the parieta-occipital channels pairs P3-01—P4-02 were nearly equal in the depressive and the control group.

Coherence values in the fronto-temporal channel pairs FP1–T3—FP2–T4 and the tempora-parietal channel pairs T3–P3—T4–P4 in the alpha frequency band for individual subjects are presented in Fig. 6. Opposite trends appeared in coherence values between the depressive and the healthy subjects in the fronto-temporal and the tempora-parietal brain regions. However, these trends were not statistically significant for the group. Statistical comparison did not reveal significant differences between the healthy subjects and the depressed patients for any EEG frequency band ($p > 0.05$).

4 Discussion and conclusions

Three measures for detection of depressive disorder, spectral asymmetry, inter-hemispheric asymmetry and coherence, were compared utilizing the databases of the EEG signals collected from the same subjects.

The calculated EEG asymmetry between the left and right brain hemisphere was similar in both groups and no statistically significant difference between depressive patients and healthy controls was detected (Fig. 4).

Performed EEG coherence analysis also revealed no significant differences between the depressive and control group (Fig. 5). The EEG inter-hemispheric coherence showed even opposite direction of differences between depressive and healthy subjects in different brain regions (Fig. 6).

Contradictive data on EEG asymmetry and coherence in depression have been reported also by other authors [9, 10,

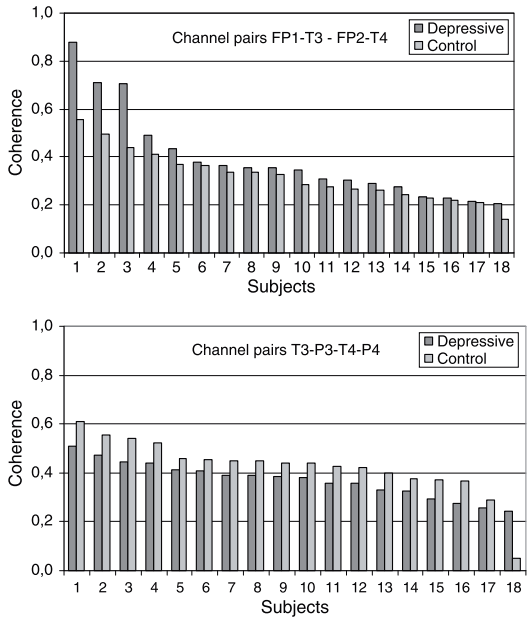


Fig. 6 Calculated coherence values in the EEG alpha band for FP1–T3—FP2–T4 and T3–P3—T4–P4 channel pairs for individual subjects in the group of depressive patients and healthy controls

13, 24]. The diminished left frontal activation compared to healthy controls was shown in some studies [10, 24]. However, our results supported rather the reports where left frontal hypoactivation in depressed patients was not confirmed [9, 13]. No significant differences in frontal activation emerged between depressed and healthy participants were detected [13]. The between groups comparison revealed decreased activity in the right middle temporal gyrus in the depressed group in the whole frequency spectrum analyzed (2–32 Hz), although it reached significance in the delta (2–3.5 Hz) band only [9].

SASI makes clear differentiation between the depressive and control group based on EEG signal analysis in an arbitrary EEG channel (Fig. 2). The changes in polarity of SASI are determined by balance of the higher and the lower EEG specific frequency band power. Selection of boundary frequencies is critical for polarity of SASI. Applied selection of the bands seems to be matched better in the parieta-occipital than in fronto-temporal channels (Table 2). Nevertheless, the SASI values calculated for different EEG channels are well correlated (Table 3) and provide distinction of depression in each of the channels (Table 4). The SASI is also well correlated with HAM-D scores traditionally applied traditionally for diagnoses of depression (Table 3).

The polarity of SASI is different for majority of depressed and control subjects (Fig. 3). The method of calculation of SASI leads to positive values of the calculated parameter in the case of increased power in the higher EEG (close to beta) band. Our results showed positive SASI values for depressive group and for the majority of individuals within the group (Figs. 2, 3). The values of calculated SASI become negative for control group at lower level of the EEG higher frequency band power (normal beta power). This finding confirms evident of the higher beta power in depression. Our results are in a good agreement with the findings reported by other authors where relative beta was found to be greater in depressive patients than in controls [8, 15].

The introduced SASI based on balance between the powers of two special EEG frequency bands selected lower and higher of the EEG spectrum maximum provides better results in detection of depression compared to the EEG inter-hemispheric asymmetry and coherence measures. Our results suggest that the SASI is a promising measure for evaluation of depression.

Acknowledgments This study was supported by the Estonian Science Foundation Grant No 6632, by the Estonian targeted financing project SF0140027s07, and by the European Union through the European Regional Development Fund.

References

1. Henderson G, Ifeachor E, Hudson N et al (2006) Development and assessment of methods for detecting dementia using the human electroencephalogram. IEEE Trans Biomed Eng 53:1557–1568
2. Shen KQ, Li XP, Ong CJ, Shao SY, Wilder-Smith EP (2008) EEG-based mental fatigue measurement using multi-class support vector machines with confidence estimate. Clin Neurophysiol 119:1524–1533
3. Adeli H, Ghosh-Dastidar S, Dadmehr N (2008) A spatio-temporal wavelet-chaos methodology for EEG-based diagnosis of Alzheimer's disease. Neurosci Lett 444:190–194
4. Abasolo D, Escudero J, Hornero R, Gomez C, Espino P (2008) Approximate entropy and auto mutual information analysis of the electroencephalogram in Alzheimer's disease patients. Med Biol Eng Comp 46:1019–1028
5. Lehmann C, Koenig T, Jelic V, Prichep L, John R (2007) Application and comparison of classifications algorithms for recognition of Alzheimer's disease in electrical brain activity (EEG). J Neurosci Methods 161:342–350
6. Allen JB, Urry HL, Hitt SK, Coan JA (2004) The stability of resting frontal electroencephalographic asymmetry in depression. Psychophysiology 41:269–275
7. Henriques JB, Davidson RJ (1991) Left frontal hypoactivation in depression. J Abnorm Psychol 100:535–545
8. Knott V, Mahoney C, Kennedy S, Evans K (2001) EEG power, frequency, asymmetry and coherence in male depression. Psychiatry Res Neuroimaging 106:123–140
9. Lubar JF, Congedo M, Askew JH (2003) Low-resolution electromagnetic tomography (LORETA) of cerebral activity in chronic depressive disorder. Int J Psychopathol 49:175–185

10. Mathersul D, Williams L, Hopkinson P, Kemp A (2008) Investigating models of affect: relationships among EEG alpha asymmetry, depression, and anxiety. Emotion 8:560–572
11. Pop-Jordanova N, Pop-Jordanov J (2005) Spectrum-weighted EEG frequency ("brain-rate") as a quantitative indicator of mental arousal. Prilozi 26:35–42
12. Ricardo-Garcell J, Gonzalez-Olvera J, Miranda E et al (2009) EEG sources in a group of patients with major depressive disorder. Int J Psychophysiol 71:70–74
13. Reid SA, Duke LM, Allen JJB (1998) Resting frontal electroencephalographic asymmetry in depression: in consistencies suggest the need to identify mediating factors. Psychophysiology 35:389–404
14. Debener S, Beauducel A, Nessler D, Brocke B, Heilemann H, Kavser J (2000) Is resting anterior EEG alpha asymmetry a trait marker for depression? Findings for healthy adults and clinically depressed patients. Neuropsychobiology 41:31–37
15. Sun Y, Li Y, Zhu Y, Chen X, Tong S (2008) Electroencephalographic differences between depressed and control subjects: an aspect of interdependence analysis. Brain Res Bull 76:559–564
16. Huupponen E, Saunamäki T, Saastamoinen A, Kulkas A, Tenhunen M, Himanen S-L (2009) Improved computational frontocentral sleep depth parameters show differences between apnea patients and control subjects. Med Biol Eng Comput 47:3–10
17. Temuçin CM, Tokçaer AB, Bilir E (2005) Detection of EEG background abnormalities in epilepsy by a new spectral index. Clin Neurophysiol 116:933–947
18. Van Putten MJ (2007) The revised brain symmetry index. Clin Neurophysiol 118:2362–2367
19. Bachmann M, Kalda J, Lass J, Tuulik V, Sakki M, Hinrikus H (2005) Non-linear analysis of the electroencephalogram for detecting effects of low-level electromagnetic fields. Med Biol Eng Comp 43:142–149
20. Bachmann M, Hinrikus H, Aadamsoo K, Võhma Ü, Lass J, Rubljova J, Suhhova A, Tuulik V (2007) Modulated microwave effects on individuals with depressive disorder. Environmentalist 27:505–510
21. Towers DN, Allen JJ (2009) A better estimate of the internal consistency reliability of frontal EEG asymmetry scores. Psychophysiology 46:132–142
22. Hinrikus H, Bachmann M, Lass J, Suhhova A, Tuulik V, Aadamsoo K, Vohma Y (2009) Method and device for determining depressive disorders by measuring bioelectromagnetic signals of the brain. US 2009/0054801/A1 from Feb 26, 2009
23. National Institute of Mental Health (2008) The numbers count: mental disorders in America. Describes statistics about mental disorders. http://www.nimh.nih.gov/health/publications/the-numbers-count-mental-disorders-in-america
24. Flor-Henry P, Lind JC, Koles ZJ (2004) A source-imaging (low-resolution electromagnetic tomography) study of the EEGs from unmedicated males with depression. Psychiatry Res Neuroimaging 109:191–207

PUBLICATIONS

Publication VI

Hinrikus, H., **Suhhova, A.,** Bachmann, M., Aadamsoo, K., Võhma, Ü., Pehlak, H., Lass, J. (2010). Spectral features of EEG in depression. *Biomed Tech*, 55: 155-161.

Biomed Tech 2010; 55:155–161 © 2010 by Walter de Gruyter • Berlin • New York. DOI 10.1515/BMT.2010.011

Spectral features of EEG in depression

Hiie Hinrikus[1,*], Anna Suhhova[1], Maie Bachmann[1], Kaire Aadamsoo[2], Ülle Võhma[2], Hannes Pehlak[3] and Jaanus Lass[1]

[1] Department of Biomedical Engineering, Technomedicum of Tallinn University of Technology, Tallinn, Estonia
[2] Clinic of Psychiatry, North Estonia Regional Hospital, Tallinn, Estonia
[3] Institute of Agricultural and Environmental Sciences, Estonian University of Life Sciences, Tartu, Estonia

Abstract

The aim of this study was to find distinctions of the EEG signal in female depression. Experiments were carried out on two groups of 18 female volunteers each: a group of patients with depressive disorder who were not on medication and a group of control subjects. Patients who had Hamilton depression rating scores higher than 14 were selected. Resting EEG was recorded for the duration of 30 min. Spectral asymmetry (SA) of the EEG spectrum was estimated as relative difference in the selected higher and lower EEG frequency band power. Calculated SA values were positive for depressive and negative for healthy subjects (except for 2–3 subjects). The values behaved similarly in all EEG channels and brain hemispheres. Differences in SA between depressive and control groups were significant in all EEG channels. Dependence of SA on EGG signal length appeared not to be identical for depressive and healthy subjects. Our results suggest that SA based on balance between the powers of the higher and the lower EEG frequency bands seems to enable characterization of the EEG in depression.

Keywords: depressive disorder; EEG analysis; EEG frequency; spectral asymmetry.

Introduction

Traditional diagnostic methods for mental disorders are mainly based on the evaluation of the intensity of subjective and clinical symptoms by psychiatrists. During the past years the methods for understanding brain activity have become a topic of major interest. Modern neuroimaging methods (PET, fMRI, EEG, etc.) enable us to acquire objective information about changes in brain physiology related to mental diseases and disorders [4, 5]. EEG analysis provides promising results in diagnosing several nervous diseases which produce alterations in EEG waveforms (epilepsy, schizophrenia, dementia and others) [1, 8, 11, 18]. However, the majority of EEG signals are normal in depression and abnormalities in waveforms are generally mild [10]. Compared with more sophisticated methods, spectral analysis has been shown to provide very good ability to distinguish such signals [1]. The diagnostic value of EEG in depression is still a topic under discussion [2, 12].

Depression is becoming increasingly frequent, but its physiological mechanisms are not yet entirely clear [15, 17]. EEG analysis has been reported to enable detection of changes in inter-hemispheric asymmetry and coherence of signals in depressive disorder [12]. A modified computing method has been proposed to improve reliability estimates for frontal alpha inter-hemispheric asymmetry [21].

Previous studies have given some evidence that left frontal hypoactivation is distinctive for depressed individuals, being characterized by relatively higher left alpha activity [2, 12, 13]. Moreover, frontal alpha asymmetry also seems to characterize recovered depressives [2]. Results of the studies showed that EEG alpha inter-hemispheric asymmetry in depressives demonstrates stability that is comparable in magnitude to that seen in non-clinical populations, with stability being apparent despite rather substantial improvements in clinical state [2]. No relationship between depression severity and EEG asymmetry could be proven [7]. In addition, absolute and relative power in the beta band appeared to differentiate patients and controls, with patients exhibiting more beta power than controls [12]. Making use of LORETA (low-resolution electromagnetic tomography) a pattern of more central, temporal, superior fronto-lateral and medial frontal asymmetry (increased alpha current density in the left hemisphere compared to the right hemisphere) was observed in depressed individuals [13], which correlates with previous findings. Decreased current density in the delta band was observed in the right temporal lobe and the same trend was also found in the theta, alpha and beta bands [12].

Unfortunately, these results have not been confirmed in several other studies. The results reported showed an increased source-current density underlying EEG from the right hemisphere in the delta, alpha and beta frequency bands both during resting and cognitively challenged conditions [7]. The expected left anterior hypoactivation in depression (reflected by increased resting left frontal EEG power in the alpha band compared to controls) was not observed [7]. Results suggest exactly the opposite, i.e., increased activation of the left frontal lobe and decreased activation of the right frontal lobe [7]. Results showed a significantly reduced delta band source-current density in depressed individuals compared to controls during the resting condition in most of the

*Corresponding author: Hiie Hinrikus, Department of Biomedical Engineering, Technomedicum of Tallinn University of Technology, Ehitajate Rd 5, 19086, Tallinn, Estonia
E-mail: hiie@cb.ttu.ee

brain volume [7]. Despite the fact that compared to healthy elderly, depressive elderly subjects showed relatively greater right frontal alpha activity and relatively greater left parietal activity; this difference was not significant [6]. In our preliminary study, no significant differences were found in EEG inter-hemispheric asymmetry and coherence in a comparison of depressed patients and healthy controls [19].

From the above-mentioned studies, we can conclude that published results outlining specific changes in EEG in depression are contradictory and do not lead to useful conclusions in depressive mode evaluation. By contrast, anomalies in the beta waves have been found to be associated with mental depression [20]. This result confirms findings reported by other researchers [12]. Compared with controls, patients evidenced greater overall relative beta power and, at bilateral anterior regions, greater absolute beta power and faster mean total spectrum frequency [12]. Alterations in spectrum-weighted EEG frequency have been proposed as a quantitative indicator of mental state [16]. In our previous study, a combination of EEG beta and theta band powers was successfully applied to detect the electromagnetic field effect on depression [3].

Based on the studies above, it appears reasonable to analyze spectral characteristics of the EEG signal for the evaluation of depression. To find distinctions of EEG in depression it might be useful to explore the EEG beta band. A supposition is that the best way to find the distinction of depression is to compare EEG beta power (as most altered) to theta power (as most stable). Such an approach requires that alpha band high level power (not including useful information) be excluded from the analysis. Therefore, the approach is expected to be superior to a relative power method including all EEG frequency bands. In this study, we performed a comparative analysis of combination of powers in EEG frequency bands higher and lower than the spectral maximum for patients with depressive disorder and for healthy controls.

Materials and methods

Subjects

The experiments were carried out on 18 female volunteers with depressive disorder, with a mean age of 36 years, and a standard deviation (SD) of 10 years. Male and female depression is considered separately in the majority of publications. We selected female depression, because depressive disorder is more prevalent in women than in men [15]. Subjects with depressive disorder were selected from a hospital inpatient unit and the experiments were performed before any treatment. Subjects with non-psychotic depressive disorder as defined by ICD-10 criteria and determined by 17-item Hamilton depression rating scale (HAM-D) score higher than 14 were eligible. The average HAM-D score for the group was 21 (SD 3.3). Subjects were without antidepressant treatment; most of the subjects had never used antidepressant drugs. Drug-free period was at least 2 months for others. Concomitant treatments for current general medical conditions were permitted on the basis of clinical judgment. Patients receiving medication with known side effects on the central nervous system were not eligible. Our main concern was to exclude anticonvulsive properties (valproic acid, lamotrigin, carbamazepin) or lithium.

The control group for comparison consisted of 18 healthy female volunteers, with a mean age of 35 years, and a SD of 10.5 years. The volunteers in the control group were diagnosed as healthy subjects using a psychiatric interview carried out by a psychiatrist.

Subjects in both groups were evaluated before an investigation by an experimenter using a questionnaire. All subjects selected abstained from alcohol for a week before and coffee on the day of the experiment. Tired or sleepy candidates were excluded.

Investigations in our current and recent studies were performed on different groups of depressive and control subjects selected according to similar criteria [9].

The study was conducted in accordance with the Declaration of Helsinki and was formally approved by the Tallinn Medical Research Ethics Committee.

Experimental procedure and equipment

Distinction of EEG in depression requires information about spectral features of EEG in different brain areas and about the time course of the signals. Therefore, EEG channels were selected to cover the entire head in recordings. Continuous EEG recordings were analyzed using three fixed lengths of the signal from the beginning of the recording.

The experimental procedure consisted of continuous resting eyes closed EEG recording for the duration of 30 min. The experimenter and the subjects were in a dark laboratory room during the experiments. The subjects were lying in a relaxed position, eyes closed and ears blocked during the experiments.

The Cadwell Easy II EEG measurement equipment was used for EEG recordings. EEG was recorded using 19 electrodes, which were placed on the subject's head according to the international 10–20-electrode position classification system. The channels for the analysis were chosen from different brain areas: frontal, FP1, FP2; parietal P5, P4, temporal, T3, T4; occipital O1, O2 and the reference electrode Cz. EEG signals within the frequency band of 0.5–48 Hz were stored on a computer at a sampling frequency of 400 Hz.

EEG analysis

Spectral asymmetry was calculated by comparing EEG powers in two frequency bands selected higher and lower than the spectral power maximum in the alpha band. The selected bands can be shifted compared with the traditional beta and theta bands to avoid influence of possible low or high alpha frequency.

EEG analysis comprised four main operations: (i) estimation of power spectral density of the recorded EEG signal; (ii) selection of the boundary frequencies of two EEG frequency bands; (iii) calculation of EEG power in the selected bands; and finally (iv) calculation of spectral asymmetry as

a combination of EEG powers in the selected frequency bands.

Power spectral density (PSD) of the recorded EEG signal was estimated by means of the Welch averaged periodogram method. The signal was divided into overlapping sections (50%), with the length of 2048 points and windowed by the Hanning window. To achieve better averaging of the spectrum shape the length of the window selected was longer than in our recent study (1024 points) [9].

The frequency limits of the bands were selected as follows (Figure 1). The first step was to estimate the frequency with the maximum spectral power f_{max} in the region of the alpha band 8–13 Hz of the recorded EEG signal. Thereafter, parabolic approximation was applied to the ($f_{max} \pm b$) Hz spectrum, where b was half-width of the EEG central frequency (alpha) band. The best parabolic fit was calculated by applying the MatLab POLYFIT tool to find the coefficients of a polynomial function that fits the data in a least-squares sense.

The maximum point of the fitted parabola f_{pmax} was considered as the fixed center of the central band for each EEG channel.

The frequency limits for lower and higher frequency bands were related to the estimated central band and obtained as follows: the lower frequency band from F1 = (f_{pmax}-b-4) Hz to F2 = (f_{pmax}-b) Hz, and the higher frequency band from F3 = (f_{pmax} + b) Hz to F4 = (f_{pmax} + b + 24) Hz. EEG power spectral density is much higher at the frequencies lower than the maximum (alpha band) and much lower at the frequencies higher than the maximum. To ensure balance between the EEG powers of the lower and the higher bands, the higher band must have much wider bandwidth (24 Hz) than the lower band (4 Hz). These values were selected close to traditional EEG theta and beta bandwidths. The value of the central (alpha) bandwidth 2b was varied during preliminary calculations based on the experimental data of our previous study and the optimal value was selected [3]. The optimal value of $b = 2$ Hz was applied in this study.

Afterwards, the EEG signal power W_{lmn} in the lower EEG frequency band (F1–F2) Hz and the power W_{hmn} in the higher EEG frequency band (F3–F4) Hz were computed for each subject (indexed by $n \in [1,18]$) and EEG channel (indexed by $m = 1,8$) as the area under the spectrum for the corresponding frequency band (integral of the band).

Finally, spectral asymmetry (SA) was calculated as:

$$SA = \frac{W_{hmn} - W_{lmn}}{W_{hmn} + W_{lmn}} \quad (1)$$

Advantage of the difference of the corresponding band powers selected in the formula over the ratio appears in change of polarity of the calculated SA caused by different directions of unbalance of the powers.

Calculations were performed for each EEG channel for signal lengths from the first 1, 5 and 30 min of the recording.

Signal processing and calculation of parameters were performed in the MatLab (Signal Processing Toolkit) and LabVIEW Full Development System (Mathematics and Signal Processing Modules) environment under proprietary software licenses.

The nonparametric Mann-Whitney U-test was applied for the statistical comparison of the results between the depressed and control subjects separately in each EEG chan-

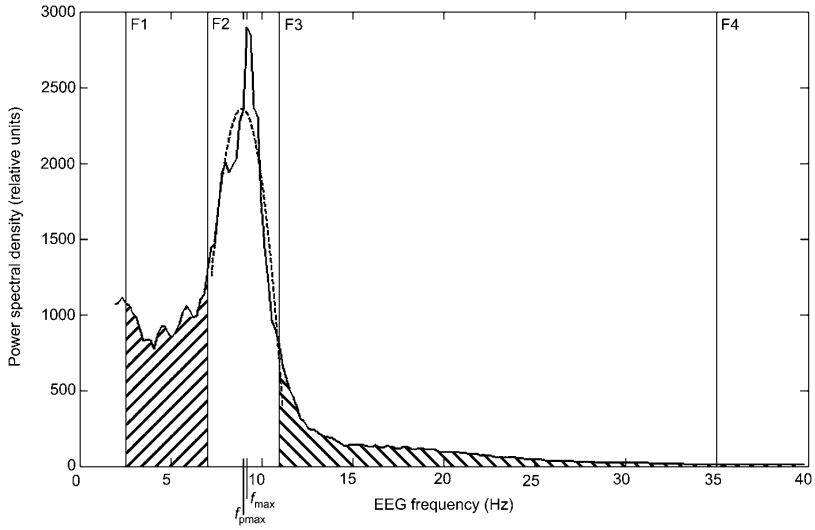


Figure 1 Schematic selection of EEG frequency bands for the calculation of SA.
The EEG spectrum maximum is marked as f_{max}; parabolic approximation maximum as f_{pmax}. F1 and F2 denote lower and higher boundary frequencies of the lower EEG frequency band; F3 and F4 denote lower and higher boundary frequencies of the higher EEG frequency band. Streaked areas represent the lower and higher frequency bands powers.

nel. The Bonferroni correction for multiple comparisons was used (8 channels, 3 lengths of recording segments). The confidence level of 0.05 was considered statistically significant to the Bonferroni corrected p-values.

Results

The lower EEG frequency band (from F1 to F2, Figure 1) and the higher EEG frequency band (from F3 to F4, Figure 1) powers computed for each subject in the depressive and the control group are presented in Figure 2. An unbalance related to slightly higher power in the higher frequency band for the depressive and in the lower frequency band for the control group is evident for the majority of subjects. Averaged over the depressive and control group power values are closer in the lower frequency band (6.6 and 7.1 relative units, respectively). Average power in the higher frequency band is approximately 1.8 times higher for the depressive group compared with the control group (9.7 and 5.5 relative units, respectively).

Average values of SA calculated for all EEG channels and signal lengths of 1, 5 and 30 min are presented in Figure 3. Average values of SA are negative for the group of control subjects and positive for the group of depressive subjects on all EEG channels and signal lengths.

Values of SA in the control group decreased with the increase of the signal length (Figure 3). A decrease of the calculated SA values with an increase of the signal length can be produced by a decrease of the EEG beta or an increase of the theta power during long-term EEG recordings. However, a decrease of SA for the control group appears more clearly in the temporal, parietal and occipital channels and it is hidden in the frontal channels owing to the unbalance of the EEG powers in the selected EEG frequency bands (Figure 3). No dependence on the signal length appeared in the depressive group. Stability of the calculated SA values for the depressive subjects at different signal lengths presumes a constant high level of EEG beta power during long-term recordings.

Calculated SA values for individual subjects within a depressive and a control group at 30 min EGG signal are presented in Figure 4. Calculated SA values have the same polarity in both hemispheres. SA behaves similarly in the temporal, parietal and occipital channels. In these channels the majority of depressive subjects showed positive SA value; except two subjects: 1 and 10. Negative values of the calculated SA for these two subjects were caused by a very low alpha frequency in their EEG spectrum. Unbalance between the powers of the higher and lower EEG frequency bands leads to more negative values of the calculated SA in the case of increased power in the lower frequency band [see Eq. (1)]. Very low alpha frequency causes an abnormal

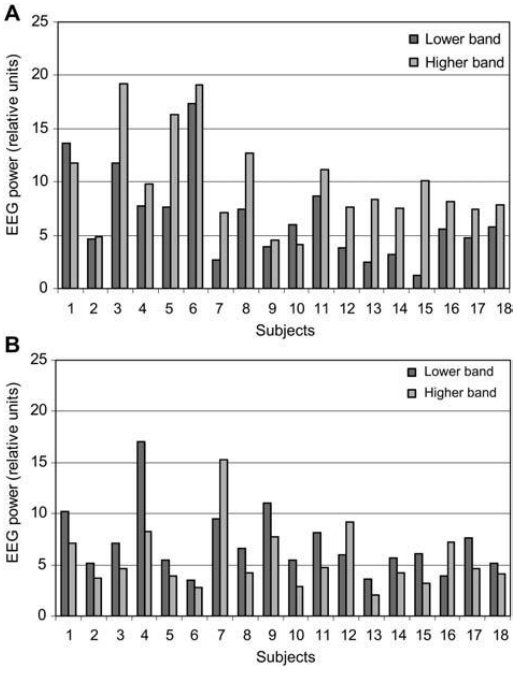


Figure 2 Calculated EEG power values in the lower and higher EEG frequency bands in P3 channel for individuals in (A) depressive and (B) control group at 30-min length of the EEG signal.

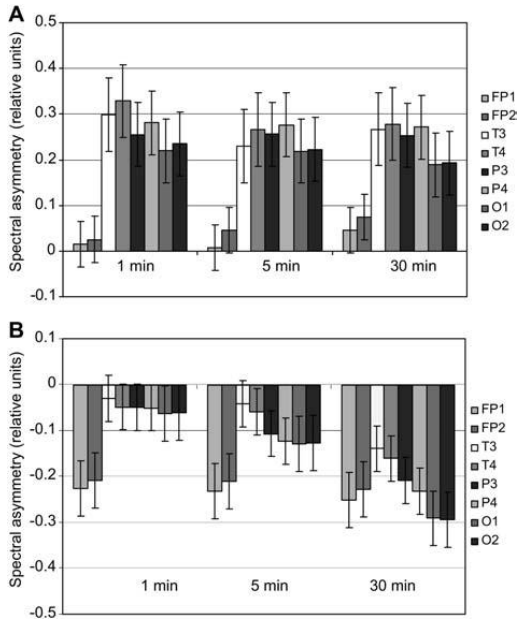


Figure 3 Average values of the calculated spectral asymmetry (as relative differences in the selected higher and lower EEG frequency band powers) in different EEG channels at 1-, 5- and 30-min lengths of the EGG signal for (A) depressive and (B) control group (n = 18). Vertical bars denote ± standard deviations.

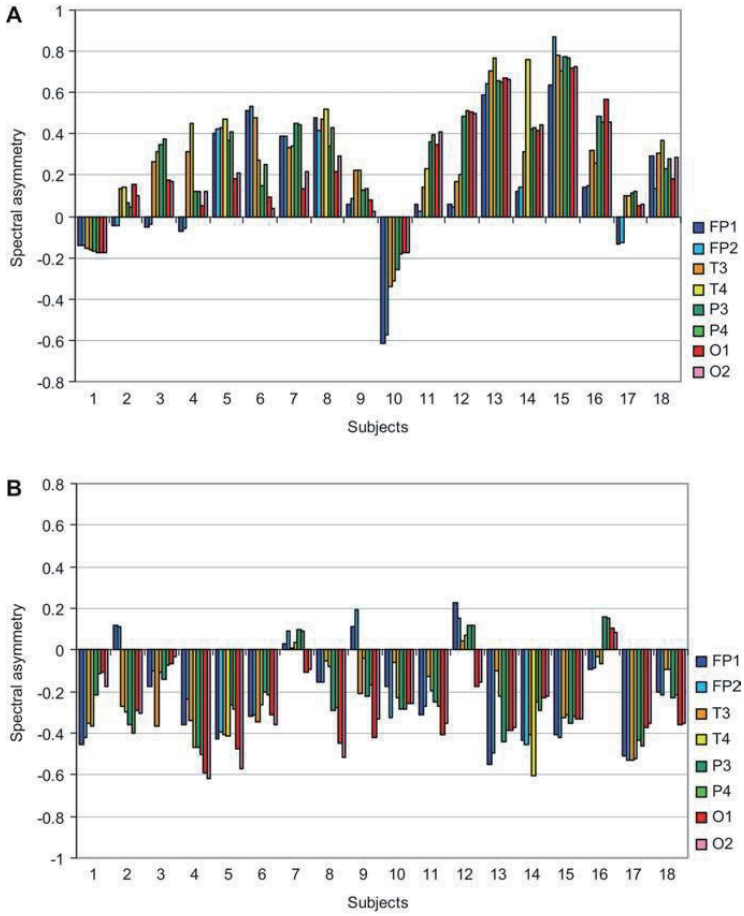


Figure 4 Calculated spectral asymmetry values (as relative differences in the selected higher and lower EEG frequency band powers) for individual subjects in (A) depressive group and (B) control group in different EEG channels at 30-min length of the EGG signal.

increase of EEG power in the lower EEG frequency band and consequently negative SA values. In addition, four depressive subjects (subjects 2, 3, 4 and 17) had negative SA values only in the frontal channels. Such a distinction of the SA is caused by the higher relative theta power measured in the frontal channels compared with other channels. The majority of control subjects had negative SA values. However, three control subjects (7, 12 and 16) had positive SA values in the temporal-parietal channels and four control subjects (2, 7, 9 and 12) in the frontal channels.

SA values for each individual subject within the depressive and control groups at different lengths of the EEG signal were calculated. As shown in Figure 3 the calculated SA behaves similarly in the temporal, parietal and occipital EEG channels. Therefore, as an example in Figure 5 individual results are presented only in one (P3) channel at the signal lengths of 1, 5 and 30 min. No changes were found in individual scores of SA at different signal lengths for the depressive subjects. Two depressive subjects had negative SA values at 1 and 5 as well as at 30 min recordings. However, SA values decreased at longer signal lengths for the control subjects. The number of subjects with positive SA values varies at different signal lengths in the control group: five subjects at 1 and 5 min and three subjects while the signal length was 30 min.

Results of the statistical evaluation of differences in SA between the depressive and healthy groups are presented in Table 1. The Bonferroni corrected p-values confirm a significant difference in the calculated SA values between the depressive and control groups in all EEG channels and at all signal lengths (Table 1). However, calculated p-values are much lower for longer EGG signals (Table 1). Longer time of EEG recordings increases the differences between the calculated SA for the depressive and control subjects owing to the decrease of SA for the control subjects, whereas SA for the depressive subjects is constant.

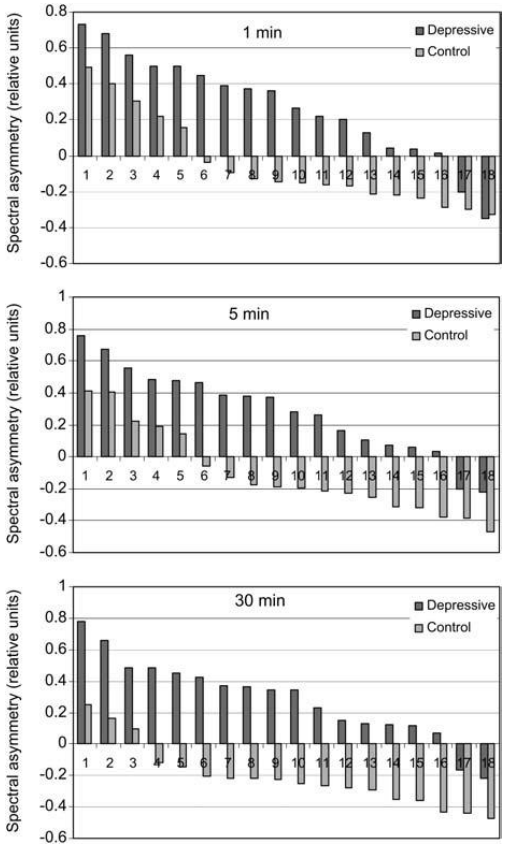


Figure 5 Calculated spectral asymmetry values (as a relative differences in the selected higher and lower EEG frequency band powers) in P3 channel for individual subjects in depressive and control groups at 1-, 5- and 30-min lengths of the EGG signal arranged in descending order.

Discussion

Most critical in the calculations of SA is the balance between EEG powers in the lower (close to theta) and higher (close to beta) EEG frequency bands [Eq. (1), Figure 2].

Our results showed positive values of the calculated SA and consequently an increased relative EEG beta power for the depressive group compared with negative SA values in the control group at the normal beta level (Figure 3). This finding confirms a higher beta power in depression and is in good agreement with the results reported by other authors where relative beta was found to be greater in the depressive patients than in the controls at all scalp sites [12, 20].

A similar SA parameter, a relative difference of the fixed theta and beta band powers, was used in our previous study to evaluate the electromagnetic field effect on 18 depressive subjects [3]. The calculated parameter was positive for 14 and negative for 4 subjects. Such a small variation in the results between two experiments on groups of a limited number of subjects can be caused by chance. Nevertheless, the effect of the low alpha frequency on SA was obvious and correction of the theta and beta frequency bands regarding alpha maximum during preliminary calculations led to positive values of the parameter for 17 depressive subjects.

Table 1 Bonferroni corrected p-values for differences in calculated spectral asymmetry values between depressive and control groups (n = 18) in different EEG channels at different EEG signal lengths *t*.

EEG channel	p-Values		
	t = 1 min	*t* = 5 min	*t* = 30 min
FP1	0.011	0.009	0.005
FP2	0.007	0.009	0.007
T3	0.003	0.024	0.001
T4	0.001	0.010	0.001
P3	0.003	0.001	1E-04
P4	0.001	0.001	2E-04
O1	0.003	0.001	2E-04
O2	0.003	0.001	2E-04

A decrease of the SA values in the control group with an increase of the EGG signal lengths (Figure 3) can be produced only by a decrease of EEG beta or an increase of theta power during long-term EEG recordings. Our results for the control group showed clearly the same trend as reported by other authors [14]. Maltez et al. demonstrated that alpha and beta power decreased towards the end of the recording session during resting conditions, whereas delta and theta power showed a systematic increase [14].

The slightly modified method applied for SA calculation in our recent study used decreased length of the window for calculations of the EEG spectrum and adaptation of the selected frequency bands to different EEG channels [9]. The results achieved in another group of subjects were in good agreement with the current study and additionally confirmed the ability of SA to discriminate between depressive and healthy subjects better than inter-hemispheric asymmetry or coherence [9].

The balance between the higher and the lower EEG frequency bands is sensitive to a number of other factors besides depression. Therefore, the SA method has some limitations in its use in evaluating depression.

The main concern is a possible side effect of drugs. Several antidepressant drugs can cause changes in the EEG spectrum and therefore lead to false unbalance between the EEG powers in the higher and the lower frequencies of the spectrum. Therefore, the SA method can be applied only for persons not on medication or persons not on long-term medication before the investigation. Furthermore, individuals under investigation should avoid alcohol, coffee and other chemical, physical or psychological stressors before EEG recordings.

Another important limitation is the diversity of the EEG frequency spectrum for individuals. In the proposed method, the bandwidths of the higher and lower EEG frequency bands are selected tuned to the EEG alpha maximum. It takes into account individual low or high alpha frequency. Nev-

ertheless, in some cases even such a tuning is not effective enough (subjects 1 and 10 in the depressive group). According to our results, the individual diversity of the EEG spectrum appears even more clearly in the control group. Our results also revealed alterations in the EEG spectrum between the different EEG channels: the higher relative theta power was measured in the frontal channels.

Further investigations are required to select optimal bandwidths for the higher and the lower EEG frequency bands and EEG channels based on extended databases and several independent groups. It is very challenging to apply nonlinear methods for the analysis of EEG with very mild abnormalities in the waveforms.

Our results suggest that SA based on the balance between the powers of the higher and the lower EEG frequency bands seems to enable characterization of EEG in depression.

Acknowledgements

This study was supported by the Estonian Science Foundation Grant No. 6632, by the Estonian targeted financing project SF0140027s07, and by the European Union through the European Regional Development Fund.

References

[1] Abasolo D, Hornero R, Escudero J, Espino P. A study on the possible usefulness of detrended fluctuation analysis of the electroencephalogram background activity in Alzheimer's disease. IEEE Trans Biomed Eng 2008; 55: 2171–2179.

[2] Allen JB, Urry HL, Hitt SK, Coan JA. The stability of resting frontal electroencephalographic asymmetry in depression. Psychophysiology 2004; 41: 269–280.

[3] Bachmann M, Hinrikus H, Aadamsoo K, et al. Modulated microwave effects on individuals with depressive disorder. The Environmentalist 2007; 27: 505–510.

[4] Bandettini PA. What's new in neuroimaging methods? Ann N Y Acad Sci 2009; 1156: 260–293.

[5] Calhoun VD, Maciejewski PK, Pearlson GD, Kiehl KA. Temporal lobe and ''default'' hemodynamic brain modes discriminate between schizophrenia and bipolar disorder. Hum Brain Mapp 2008; 29: 1265–1275.

[6] Deslandes AC, de Moraes H, Pompeu FA, et al. Electroencephalographic frontal asymmetry and depressive symptoms in the elderly. Biol Psychol 2008; 79: 317–322.

[7] Flor-Henry P, Lind JC, Koles ZJ. A source-imaging (low-resolution electromagnetic tomography) study of the EEGs from unmedicated males with depression. Psychiatry Res 2004; 109: 191–207.

[8] Henderson G, Ifeachor E, Hudson N, et al. Development and assessment of methods for detecting dementia using the human electroencephalogram. IEEE Trans Biomed Eng 2006; 53: 1557–1568.

[9] Hinrikus H, Suhhova A, Bachmann M, et al. Electroencephalographic spectral asymmetry index for detection of depression. Med Biol Eng Comp 2009; 47: 1291–1299.

[10] Holschneider DP, Leuchter AF. Clinical neurophysiology using electroencephalography in geriatric psychiatry: neurobiologic implications and clinical utility. J Geriatr Psychiatr Neurol 1999; 12: 150–164.

[11] Jordan D, Schneider G, Hock A, Hensel T, Stockmanns G, Kochs EF. EEG parameters and their combination as indicators of depth of anaesthesia. Biomed Tech 2006; 51: 89–94.

[12] Knott V, Mahoney C, Kennedy S, Evans K. EEG power, frequency, asymmetry and coherence in male depression. Psychiatry Res 2001; 106: 123–140.

[13] Lubar JF, Congedo M, Askew JH. Low-resolution electromagnetic tomography (LORETA) of cerebral activity in chronic depressive disorder. Int J Psychopathol 2003; 49: 175–185.

[14] Maltez J, Hyllienmark L, Nikulin VV, Brismar T. Time course and variability of power in different frequency bands of EEG during resting conditions. J Clin Neurophysiol 2004; 34: 195–202.

[15] National Institute of Mental Health. The numbers count: mental disorders in America. Describes statistics about mental disorders. 2008; http://www.nimh.nih.gov/health/publications/the-numbers-count-mental-disorders-in-america.

[16] Pop-Jordanova N, Pop-Jordanov J. Spectrum-weighted EEG frequency (''brain-rate'') as a quantitative indicator of mental arousal. Prilozi 2005; 26: 35–42.

[17] Rost K. Disability from depression: the public health challenge to primary care. Nord J Psychiatry 2009; 63: 17–21.

[18] Saletu B, Anderer P, Saletu-Zyhlarz GM, Pascual-Marqui RD. EEG mapping and low-resolution brain electromagnetic tomography (LORETA) in diagnosis and therapy of psychiatric disorders: evidence for a key-lock principle. Clin EEG Neurosci 2005; 36: 108–115.

[19] Suhhova A, Bachmann M, Aadamsoo K, Võhma Ü, Lass J, Hinrikus H. Coherence as measure of depressive disorder. IFMBE Proc 2008; 22: 353–355.

[20] Sun Y, Li Y, Zhu Y, Chen X, Tong S. Electroencephalographic differences between depressed and control subjects: an aspect of interdependence analysis. Brain Res Bull 2008; 76: 559–564.

[21] Towers DN, Allen JJ. A better estimate of the internal consistency reliability of frontal EEG asymmetry scores. Psychophysiology 2009; 46: 132–142.

Received February 22, 2009; accepted December 2, 2009; online first April 26, 2010

PUBLICATIONS

Publication VII

Suhhova, A., Bachmann, M., Lass, J., Aadamsoo, K., Võhma, Ü., Hinrikus, H. (2012). EEG spectral asymmetry index for detection of depression at individual and fixed frequency bands. *IFMBE Proceedings*, 39:589-92.

EEG Spectral Asymmetry Index for detection of depression at Individual and Fixed Frequency Bands

A. Suhhova[1], M. Bachmann[1], J. Lass[1], K. Aadamsoo[2], Ü. Võhma[2], and H. Hinrikus[1]

[1] Department of Biomedical Engineering, Technomedicum of the Tallinn University of Technology, Tallinn, Estonia
[2] Clinic of Psychiatry, North Estonia Regional Hospital, Tallinn, Estonia

Abstract— **This study is aimed to compare the electroencephalographic (EEG) spectral asymmetry index (SASI) calculated at fixed and individual frequency bands. In addition, the possible age effect on SASI is analyzed. SASI is based on balance between the powers of two special EEG frequency bands selected lower and higher of the EEG spectrum maximum and excluding the central frequency from the calculations.**

EEG recordings were carried out on a group of 18 depressive subjects, a group of 18 age matched controls and two groups of young controls (15 subjects in each). The individual and fixed SASI was calculated for 10 minute resting EEG signals from channel P3.

The individual SASI differentiated the depressive subjects from all the other control groups. Fixed SASI was not so consistent and performed at poorer quality. The obvious age effect on SASI was not found, however, variances of results between control groups of different age decreased with individual tuning of frequency bands. Therefore, while using spectral asymmetry index for detection of depression or other mental disorders, the individual selection of EEG frequency bands is recommended.

Keywords— **EEG analysis, spectral asymmetry, depression, mental disorder.**

I. Introduction

The methods of diagnosis of mental disorders have been traditionally based mainly on evaluation of the intensity of subjective and clinical symptoms by psychiatrists. Nevertheless, subjective symptoms of disorders are accompanied by objective changes in the brain bioelectrical activity in the electroencephalographic (EEG) signal. Therefore the indicators based on the EEG analysis can be fruitful for diagnostics of depression and other mental disorders [1].

The spectral asymmetry index (SASI) was proposed in our previous study for evaluation of depression [2]. SASI is based on balance between the powers of two special EEG frequency bands selected lower and higher of the EEG spectrum maximum (alpha band). It provides good results in detection of depression [2]. The results of additional experiments suggest that the SASI is a promising measure for evaluation not only of depression but also the effect of microwave radiation on human brain [3].

While analyzing EEG the majority of studies are using the classical fixed band system of EEG frequencies. However, the individual mean alpha frequency varies normally in the range 9.5-11.5 Hz [4]. It is also recognized that the maximum alpha frequency changes over the lifespan, increasing until to puberty [5] and decreasing after that [6, 7]. In addition the variations in the EEG measures are explained by genetic factors [8, 9].

Could it be that inter and intra personal differences in EEG frequency bands are small enough not to obscure the results? If that is the case, there is no need to detect and calculate the individual frequency bands and the calculations could be more robust and quick. If not, the lower and higher frequency band limits, calculating SASI, must be chosen according to the individual alpha maximum.

This study is aimed to comparison of SASI calculated at fixed and individual EEG alpha frequency bands as well as estimation of possible age effect on the SASI.

II. Materials and methodsiting

A. Subjects

The data analysis was performed on 4 groups of human volunteers. The first two groups having 18 subjects in each: a group of female patients with depressive disorder and aged matched control group (mean age 35 years ± 11 years). The last 2 groups consisted of 15 young healthy subjects (mean age 22 years ± 1 year; mean age 27 years ± 4 years).

Subjects with depressive disorder and without antidepressant treatment were selected from a hospital inpatient unit. Subjects with nonpsychotic depressive disorder as defined by ICD-10 criteria and determined by 17-item Hamilton Depression Rating Scale (HAM-D) score higher than 14 were eligible. The average score for the group was 22.8 (standard deviation 3.3).

The study was conducted in accordance with the Declaration of Helsinki and was formally approved by the local Medical Research Ethics Committee.

M. Long (Ed.): World Congress on Medical Physics and Biomedical Engineering, IFMBE Proceedings 39, pp. 589–592, 2012.
www.springerlink.com

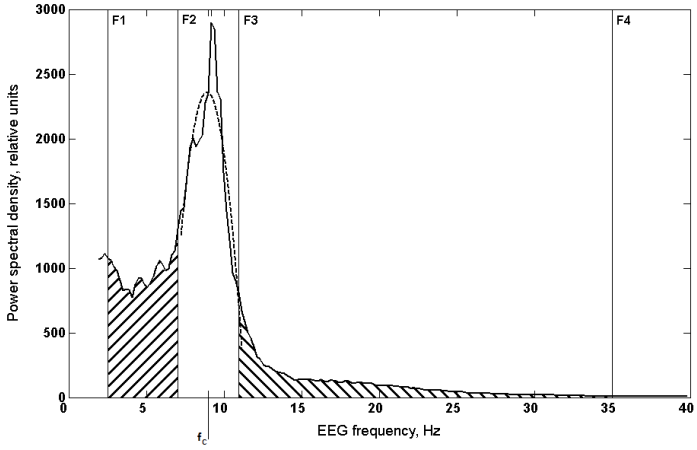


Fig. 1 EEG spectrum and positions of the boundary frequencies of the higher and lower specific EEG frequency bands for calculation of SASI. The parabolic approximation maximum is marked as f_c; F1 and F2 – lower and higher boundary frequencies of the lower EEG frequency band; F3 and F4 – lower and higher boundary frequencies of the higher EEG frequency band.

B. Experimental procedure and EEG recording equipment

During the experimental procedure the continuous resting eyes closed EEG was recorded during 30 min. For the analysis only the first 10 minutes were used. The measurements were performed in dark laboratory room; to exclude the auditory stressors the ear plugs were used.

During the experimental procedure participants were lying in relaxed position with closed eyes.

Cadwell Easy II EEG measurement equipment was used for the EEG recordings. The EEG was recorded using 19 electrodes, which were placed on the subject's head according to the international 10–20-electrode position classification system. Parietal channel P3 was chosen for analysis. Raw EEG signals were recorded using the Cadwell Easy data acquisition system with a frequency band of 0.3–70 Hz. The impedance of recording electrodes was monitored for each subject prior to data collection and it was always below 5 kΩ. The EEG signal was band-pass filtered 0.5–39 Hz and stored on a computer at the sampling frequency of 400 Hz.

C. EEG Analysis

The previously developed SASI was calculated as a relative difference between the higher and the lower EEG frequency band power. The balance of the powers characterizes the EEG spectral asymmetry.

In order to achieve the balance a comparability of the powers in the bands is required. The EEG spectrum has much higher power spectral density in lower (delta, theta) than in higher (beta) frequencies. Therefore, to provide required balance, bandwidth of the higher frequency band should be selected much wider than the bandwidth of the lower frequency band. The 4 Hz bandwidth (close to traditional theta bandwidth) was selected for the lower EEG frequency band and the 24 Hz bandwidth (close to the traditional beta bandwidth) for the higher band.

Important aspect of the method is exclusion of the central (alpha) band frequencies from the analysis. While considering individual frequency bands, the boundary frequencies were adjusted taking into account the alpha frequency range in the EEG power spectrum of a particular subject.

Calculation of SASI comprises four main steps: (1) computing of power spectral density of the recorded EEG signal; (2) selection of boundary frequencies of the lower and higher specific EEG frequency bands; (3) calculation of the EEG signal power in the selected bands; and (4) calculation of the SASI as a combination of the EEG powers in the selected bands.

• The power spectral density of the recorded EEG signal was calculated by means of Welch's averaged periodogram method. The signal was divided into overlapping epochs (50%), with the length of 1,024 and extracted through a Hanning window. The power spectral density s_n was com-

puted for each subject in each group (indexed by n ∈ [1, 18] or n ∈ [1, 15]).

• The boundary frequencies of the higher and lower specific EEG frequency bands for individual SASI are shown on Figure 1 and were selected as follows.

At first, the frequency with the maximum spectral power f_{max} in the region of alpha band 8–13 Hz of the recorded EEG signal was estimated. Thereafter the parabolic approximation was applied to the spectrum of the EEG central frequency band (f_{max} ± B) Hz, where B was half-width of the band. The best parabolic fit was calculated by applying the Matlab POLYFIT tool, which finds the coefficients of a polynomial function that fits the data in a least-squares sense. The maximum point of the fitted parabola f_c was taken as a centre of the central band.

The frequency limits for the lower and the higher specific frequency bands were determined as follows: the lower frequency band from F1 = (f_c – B - 4) Hz to F2 = (f_c - B) Hz, and the higher frequency band from F3 = (f_c + B) Hz to F4 = (f_c + B + 24) Hz. The value of B was 2 Hz.

For the fixed EEG frequency bands, the central band, f_c, was 10 Hz. Consequently, the lower frequency band was 4-8 Hz and the higher frequency band 12-36 Hz.

• The EEG signal powers W_{ln} and W_{hn} in the lower and in the higher EEG frequency bands, respectively, were calculated for each subject (indexed by [1, 18] or [1, 15]) as

$$W_{\ln} = \sum_{f=F1}^{F2} s_n; \qquad W_{hn} = \sum_{F3}^{F4} s_n \quad (1)$$

• Finally, the SASI was calculated as

$$SASI_n = \frac{W_{hn} - W_{\ln}}{W_{hn} + W_{\ln}} \quad (2)$$

Signal processing and calculation of parameters were performed in the MatLab (Signal Processing Toolkit) and LabVIEW Full Development System (Mathematics and Signal Processing modules) environment.

III. RESULTS & DISCUSSION

Figure 2 shows the results for the original SASI method employing the individual frequency bands. All subjects are sorted according to the SASI value. The figure clearly differentiates the depressive group from the healthy groups. While the depressive subjects have positive SASI values, except one, a remarkable number of healthy subjects have negative SASI values. Differences between age matched and younger controls are smaller than between depressed and age matched controls.

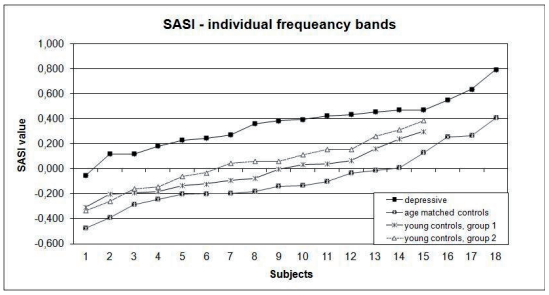


Fig. 2 Sorted SASI values calculated for all four groups using each person's individual frequency band.

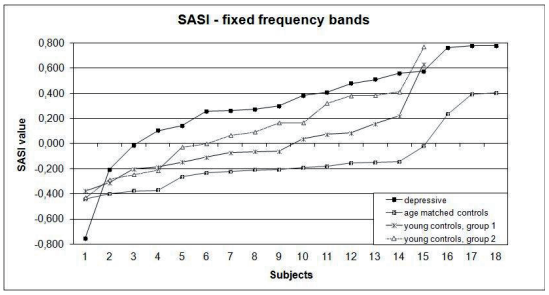


Fig. 3 Sorted SASI values calculated for all four groups using fixed frequency bands for all subjects

Figure 3 illustrates the data of SASI values while fixed frequency bands were used. The values for depressive subjects are still higher than for healthy subjects, however the difference is not as clear as with individual frequency bands. It is also possible to see that the results are not as consistent as those with individual frequency bands. The range of SASI values for depressive subjects starts from -0.8 and goes up to 0.8. While looking at the control groups, more positive SASI values appear and the group differences between healthy controls is also higher.

The average SASI values for groups are presented in Table 1. While looking at the averaged individual SASI values, only the depressed subjects have positive results, while all the healthy subjects have negative SASI. With fixed frequency bands the results of SASI are more ambiguous. The level of SASI value for depressed subjects is closer to the healthy groups. In addition, SASI for group 2 of young subjects is positive, therefore moving closer to the results of depressed subjects and more far from the other young group.

The corresponding p-values calculated by the Student t-test are presented in Table 2. Here we can see, the individu-

al SASI can differentiate depressive subjects from all the other groups. The results stay significant after Bonferroni correction. The difference between various healthy groups is not significant though. The fixed SASI could differentiate the depressive group from age matched controls and young controls from group 1, however it could not differentiate depressive subjects from the young controls in group 2.

Table 1 Average SASI values for two different calculation methods (individual and fixed bands) and four different groups: depressive subjects, age matched controls, first group of young subjects and second group of young subjects.

SASI	Individual fc	Fixed fc
Depressive	0,36	0,31
Age matched	-0,09	-0,14
Young, group 1	-0,03	-0,02
Young , group 2	-0,04	0,11

Table 2 *p*-values of a Student t-test for two different calculation methods (individual and fixed bands) and four different groups: depressive subjects, age matched controls, first group of young subjects and second group of young subjects. Significant after Bonferroni correction are marked Bold.

Individual fc	Age matched	Young, group 1	Young , group 2
Depressive	**6,01E-07**	**1,74E-06**	**8,98E-05**
Age matched		0,466	0,121
Young, group 1			0,327
Fixed fc	Age matched	Young, group 1	Young , group 2
Depressive	**1,65E-04**	**0,006**	0,107
Age matched		0,174	0,018
Young, group 1			0,234

It is clear that by calculating SASI using fixed frequencies the results are more obscured and the ability of SASI to differentiate depressive subjects from controls is of poorer quality. Therefore, we can conclude that inter-individual EEG spectral changes are too big for calculations with fixed frequency bands and the individual frequency bands are necessary for calculations of SASI. In case of attention-deficit/hyperactivity disorder subjects, it was also found that the increased theta activity and increased theta/beta ratio largely depended on a subgroup of children with ADHD who had slow alpha peak frequencies rather than increased theta activity [10].

The age related differences in SASI are obviously smaller than these caused by depression. However, variances of results between control groups of different age decrease with individual tuning of frequency bands.

IV. CONCLUSIONS

Our results showed that individual tuning of the EEG frequency bands provides much more consistent results in calculation of spectral asymmetry index compared to using of fixed traditional EEG frequency bands. Therefore, while using spectral asymmetry index for detection of depression or other mental disorders, the individual selection of EEG frequency bands is recommended.

ACKNOWLEDGMENT

This study was supported by the Estonian targeted financing project SF0140027s07, and by the European Union through the European Regional Development Fund

REFERENCES

1. Knott V, Mahoney C, Kennedy S, Evans K (2001) EEG power, frequency, asymmetry and coherence in male depression. Psychiatry Res. 106:123-40
2. Hinrikus H, Suhhova A, Bachmann M, Aadamsoo K, Võhma Ü, Lass J, Tuulik V (2009) Method and device for determining depressive disorders by measuring bioelectromagnetic signals of the brain. US 2009/0054801.
3. Suhhova A, Bachmann M, Lass J, Tuulik V, Hinrikus H (2011) EEG Spectral Asymmetry Index Reveals Effect of Microwave Radiation, IFMBE Proc. vol. 37, 5th European Conference of the International Federation for Medical and Biological Engineering, Budapest, Hungary, 2011, pp 1206 - 1209.
4. Klimesch W (1999) EEG alpha and theta oscillations reflect cognitive and memory performance: a review and analysis. Brain Res Brain Res Rev. 29(2-3):169-95.
5. Epstein HT (1980) EEG developmental stages. Dev. Psychobiol. 13: 629–631
6. Köpruner V, Pfurtscheller G, Auer LM (1984) Quantitative EEG in normals and in patients with cerebral ischemia. Prog. Brain Res. 62:29–50
7. Saletu B, Grünberger J (1985) Memory dysfunction and vigilance: neurophysiological and psychopharmacological aspects. Ann. N. Y. Acad. Sci. 444:406–427
8. Smit DJ, Posthuma D, Boomsma DI, Geus EJ (2005) Heritability of background EEG across the power spectrum. Psychophysiology 42:691 – 697
9. Tang Y, Chorlian DB, Rangaswamy M, Porjesz B, Bauer L, Kuperman S, O'Connor S, Rohrbaugh J, Schuckit M, Stimus A, Begleiter H (2007) Genetic influences on bipolar EEG power spectra. International Journal of Psychophysiology 65:2-9
10. Lansbergen MM, Arns M, van Dongen-Boomsma M, Spronk D, Buitelaar JK (2011) The increase in theta/beta ratio on resting-state EEG in boys with attention-deficit/hyperactivity disorder is mediated by slow alpha peak frequency. Progress in Neuro-Psychopharmacology & Biological Psychiatry 35:47-52

Author: Anna Suhhova
Institute: Technomedicum of the Tallinn University of Technology
Street: Ehitajate Rd 5
City: Tallinn
Country: Estonia
Email: anna@cb.ttu.ee

APPENDIX 2

ELULOOKIRJELDUS

1. Isikuandmed

Ees- ja perekonnanimi	Anna Suhhova
Sünniaeg ja -koht	30.09.1982, Sindi, Pärnumaa, Eesti
Kodakondsus	eestlane

2. Kontaktandmed

Aadress	Uue-Maailma, 24-24, 10131, Tallinn
Telefon	+ 372 6202203
E-posti aadress	anna@cb.ttu.ee

3. Hariduskäik

Õppeasutus (nimetus lõpetamise ajal)	Lõpetamise aeg	Haridus (eriala/kraad)
Tallinna Tehnikaülikool	2005	Infotehnoloogia teaduskond/tehnikateaduste bakalaureus
Tallinna Tehnikaülikool	2007	Matemaatika-loodusteaduskond/ loodusteaduste magister
Tallinna Tehnikaülikool		Matemaatika-loodusteaduskond/doktorant

4. Keelteoskus (alg-, kesk- või kõrgtase)

Keel	Tase
Eesti	Kõrgtase
Inglise	Kõrgtase
Vene	Kõrgtase

5. Teenistuskäik

Töötamise aeg	Tööandja nimetus	Ametikoht
2005–2007	Tallinna Tehnikaülikool	Tehnik
2006 –	Põhja-Eesti Regionaalhaigla	Medistiinitehnika vanemhaldur
2007 – k.a	Tallinna Tehnikaülikool	Erakorraline teadur
2012 –	Põhja-Eesti Regionaalhaigla	Meditsiinitehnika vaneminsener

7. Teadustegevus
   Madala tasemega elektromagnetkiirguse mõju uurimine inemese EEG-le
8. Teadustöö põhisuunad
   SF0142084As02, Bioelektriliste signaalide interpreteerimine, 2002–2006
   SF0140027s07, Biosignaalide interpreteerimine meditsiinitehnikas, 2007–2012
   ETF6632, Elektromagnetvälja mõju aju rühmidele, 2006–2009

APPENDIX 3

CURRICULUM VITAE

1. Personal data

Name	Anna Suhhova
Date and place of birth	30.09.1982, Sindi, Estonia

2. Contact information

Address	Uue-Maailma, 24-24, 10131 Tallinn
Phone	+ 372 6202203
E-mail	anna@cb.ttu.ee

3. Education

Educational institution	Graduation year	Education
Tallinn University of Technology	2005	Faculty of Information Technology/BSc.
Tallinn University of Technology	2007	Faculty of Science/MSc.
Tallinn University of Technology		Faculty of Science/PhD Student

4. Language competence/skills (fluent; average, basic skills)

Language	Level
Estonian	Fluent
English	Fluent
Russian	Fluent

5. Professional Employment

Period	Organisation	Position
2005–2007	Tallinn University of Technology	Technician
2006 –	North Estonian Medical Centre	Senior manager of medical devices
2007 –	Tallinn University of Technology	Researcher
2012 –	North Estonian Medical Centre	Senior engineer

6. Scientific work

Effect of low-level microwave radiation on human EEG

7. Main areas of scientific work/Current research topics

SF0142084As02, Interpretation of Bioelectrical Signals, 2002–2006
SF0140027s07, Interpretation of Biosignals in Biomedical Engineering, 2007–2012
ETF6632, Effect of electromagnetic radiation on brain oscillations, 2006–2009

DISSERTATIONS DEFENDED AT TALLINN UNIVERSITY OF TECHNOLOGY ON *NATURAL AND EXACT SCIENCES*

1. **Olav Kongas**. Nonlinear Dynamics in Modeling Cardiac Arrhytmias. 1998.

2. **Kalju Vanatalu**. Optimization of Processes of Microbial Biosynthesis of Isotopically Labeled Biomolecules and Their Complexes. 1999.

3. **Ahto Buldas**. An Algebraic Approach to the Structure of Graphs. 1999.

4. **Monika Drews**. A Metabolic Study of Insect Cells in Batch and Continuous Culture: Application of Chemostat and Turbidostat to the Production of Recombinant Proteins. 1999.

5. **Eola Valdre**. Endothelial-Specific Regulation of Vessel Formation: Role of Receptor Tyrosine Kinases. 2000.

6. **Kalju Lott**. Doping and Defect Thermodynamic Equilibrium in ZnS. 2000.

7. **Reet Koljak**. Novel Fatty Acid Dioxygenases from the Corals *Plexaura homomalla* and *Gersemia fruticosa.* 2001.

8. **Anne Paju**. Asymmetric oxidation of Prochiral and Racemic Ketones by Using Sharpless Catalyst. 2001.

9. **Marko Vendelin**. Cardiac Mechanoenergetics *in silico*. 2001.

10. **Pearu Peterson**. Multi-Soliton Interactions and the Inverse Problem of Wave Crest. 2001.

11. **Anne Menert**. Microcalorimetry of Anaerobic Digestion. 2001.

12. **Toomas Tiivel**. The Role of the Mitochondrial Outer Membrane in *in vivo* Regulation of Respiration in Normal Heart and Skeletal Muscle Cell. 2002.

13. **Olle Hints**. Ordovician Scolecodonts of Estonia and Neighbouring Areas: Taxonomy, Distribution, Palaeoecology, and Application. 2002.

14. **Jaak Nõlvak**. Chitinozoan Biostratigrapy in the Ordovician of Baltoscandia. 2002.

15. **Liivi Kluge**. On Algebraic Structure of Pre-Operad. 2002.

16. **Jaanus Lass**. Biosignal Interpretation: Study of Cardiac Arrhytmias and Electromagnetic Field Effects on Human Nervous System. 2002.

17. **Janek Peterson**. Synthesis, Structural Characterization and Modification of PAMAM Dendrimers. 2002.

18. **Merike Vaher**. Room Temperature Ionic Liquids as Background Electrolyte Additives in Capillary Electrophoresis. 2002.

19. **Valdek Mikli**. Electron Microscopy and Image Analysis Study of Powdered Hardmetal Materials and Optoelectronic Thin Films. 2003.

20. **Mart Viljus**. The Microstructure and Properties of Fine-Grained Cermets. 2003.

21. **Signe Kask**. Identification and Characterization of Dairy-Related *Lactobacillus*. 2003

22. **Tiiu-Mai Laht**. Influence of Microstructure of the Curd on Enzymatic and Microbiological Processes in Swiss-Type Cheese. 2003.

23. **Anne Kuusksalu**. 2–5A Synthetase in the Marine Sponge *Geodia cydonium*. 2003.

24. **Sergei Bereznev**. Solar Cells Based on Polycristalline Copper-Indium Chalcogenides and Conductive Polymers. 2003.

25. **Kadri Kriis**. Asymmetric Synthesis of C_2-Symmetric Bimorpholines and Their Application as Chiral Ligands in the Transfer Hydrogenation of Aromatic Ketones. 2004.

26. **Jekaterina Reut**. Polypyrrole Coatings on Conducting and Insulating Substracts. 2004.

27. **Sven Nõmm**. Realization and Identification of Discrete-Time Nonlinear Systems. 2004.

28. **Olga Kijatkina**. Deposition of Copper Indium Disulphide Films by Chemical Spray Pyrolysis. 2004.

29. **Gert Tamberg**. On Sampling Operators Defined by Rogosinski, Hann and Blackman Windows. 2004.

30. **Monika Übner**. Interaction of Humic Substances with Metal Cations. 2004.

31. **Kaarel Adamberg**. Growth Characteristics of Non-Starter Lactic Acid Bacteria from Cheese. 2004.

32. **Imre Vallikivi**. Lipase-Catalysed Reactions of Prostaglandins. 2004.

33. **Merike Peld**. Substituted Apatites as Sorbents for Heavy Metals. 2005.

34. **Vitali Syritski**. Study of Synthesis and Redox Switching of Polypyrrole and Poly(3,4-ethylenedioxythiophene) by Using *in-situ* Techniques. 2004.

35. **Lee Põllumaa**. Evaluation of Ecotoxicological Effects Related to Oil Shale Industry. 2004.

36. **Riina Aav**. Synthesis of 9,11-Secosterols Intermediates. 2005.

37. **Andres Braunbrück**. Wave Interaction in Weakly Inhomogeneous Materials. 2005.

38. **Robert Kitt**. Generalised Scale-Invariance in Financial Time Series. 2005.

39. **Juss Pavelson**. Mesoscale Physical Processes and the Related Impact on the Summer Nutrient Fields and Phytoplankton Blooms in the Western Gulf of Finland. 2005.

40. **Olari Ilison**. Solitons and Solitary Waves in Media with Higher Order Dispersive and Nonlinear Effects. 2005.

41. **Maksim Säkki**. Intermittency and Long-Range Structurization of Heart Rate. 2005.

42. **Enli Kiipli**. Modelling Seawater Chemistry of the East Baltic Basin in the Late Ordovician–Early Silurian. 2005.

43. **Igor Golovtsov**. Modification of Conductive Properties and Processability of Polyparaphenylene, Polypyrrole and polyaniline. 2005.

44. **Katrin Laos**. Interaction Between Furcellaran and the Globular Proteins (Bovine Serum Albumin β-Lactoglobulin). 2005.

45. **Arvo Mere**. Structural and Electrical Properties of Spray Deposited Copper Indium Disulphide Films for Solar Cells. 2006.

46. **Sille Ehala**. Development and Application of Various On- and Off-Line Analytical Methods for the Analysis of Bioactive Compounds. 2006.

47. **Maria Kulp**. Capillary Electrophoretic Monitoring of Biochemical Reaction Kinetics. 2006.

48. **Anu Aaspõllu.** Proteinases from *Vipera lebetina* Snake Venom Affecting Hemostasis. 2006.

49. **Lyudmila Chekulayeva**. Photosensitized Inactivation of Tumor Cells by Porphyrins and Chlorins. 2006.

50. **Merle Uudsemaa**. Quantum-Chemical Modeling of Solvated First Row Transition Metal Ions. 2006.

51. **Tagli Pitsi**. Nutrition Situation of Pre-School Children in Estonia from 1995 to 2004. 2006.

52. **Angela Ivask**. Luminescent Recombinant Sensor Bacteria for the Analysis of Bioavailable Heavy Metals. 2006.

53. **Tiina Lõugas**. Study on Physico-Chemical Properties and Some Bioactive Compounds of Sea Buckthorn (*Hippophae rhamnoides* L.). 2006.

54. **Kaja Kasemets**. Effect of Changing Environmental Conditions on the Fermentative Growth of *Saccharomyces cerevisae* S288C: Auxo-accelerostat Study. 2006.

55. **Ildar Nisamedtinov**. Application of ^{13}C and Fluorescence Labeling in Metabolic Studies of *Saccharomyces* spp. 2006.

56. **Alar Leibak**. On Additive Generalisation of Voronoï's Theory of Perfect Forms over Algebraic Number Fields. 2006.

57. **Andri Jagomägi**. Photoluminescence of Chalcopyrite Tellurides. 2006.

58. **Tõnu Martma**. Application of Carbon Isotopes to the Study of the Ordovician and Silurian of the Baltic. 2006.

59. **Marit Kauk**. Chemical Composition of $CuInSe_2$ Monograin Powders for Solar Cell Application. 2006.

60. **Julia Kois**. Electrochemical Deposition of $CuInSe_2$ Thin Films for Photovoltaic Applications. 2006.

61. **Ilona Oja Açik**. Sol-Gel Deposition of Titanium Dioxide Films. 2007.

62. **Tiia Anmann**. Integrated and Organized Cellular Bioenergetic Systems in Heart and Brain. 2007.

63. **Katrin Trummal**. Purification, Characterization and Specificity Studies of Metalloproteinases from *Vipera lebetina* Snake Venom. 2007.

64. **Gennadi Lessin**. Biochemical Definition of Coastal Zone Using Numerical Modeling and Measurement Data. 2007.

65. **Enno Pais**. Inverse problems to determine non-homogeneous degenerate memory kernels in heat flow. 2007.

66. **Maria Borissova**. Capillary Electrophoresis on Alkylimidazolium Salts. 2007.

67. **Karin Valmsen**. Prostaglandin Synthesis in the Coral *Plexaura homomalla*: Control of Prostaglandin Stereochemistry at Carbon 15 by Cyclooxygenases. 2007.

68. **Kristjan Piirimäe**. Long-Term Changes of Nutrient Fluxes in the Drainage Basin of the Gulf of Finland – Application of the PolFlow Model. 2007.

69. **Tatjana Dedova**. Chemical Spray Pyrolysis Deposition of Zinc Sulfide Thin Films and Zinc Oxide Nanostructured Layers. 2007.

70. **Katrin Tomson**. Production of Labelled Recombinant Proteins in Fed-Batch Systems in *Escherichia coli*. 2007.

71. **Cecilia Sarmiento**. Suppressors of RNA Silencing in Plants. 2008.

72. **Vilja Mardla**. Inhibition of Platelet Aggregation with Combination of Antiplatelet Agents. 2008.

73. **Maie Bachmann**. Effect of Modulated Microwave Radiation on Human Resting Electroencephalographic Signal. 2008.

74. **Dan Hüvonen**. Terahertz Spectroscopy of Low-Dimensional Spin Systems. 2008.

75. **Ly Villo**. Stereoselective Chemoenzymatic Synthesis of Deoxy Sugar Esters Involving *Candida antarctica* Lipase B. 2008.

76. **Johan Anton**. Technology of Integrated Photoelasticity for Residual Stress Measurement in Glass Articles of Axisymmetric Shape. 2008.

77. **Olga Volobujeva**. SEM Study of Selenization of Different Thin Metallic Films. 2008.

78. **Artur Jõgi**. Synthesis of 4'-Substituted 2,3'-dideoxynucleoside Analogues. 2008.

79. **Mario Kadastik**. Doubly Charged Higgs Boson Decays and Implications on Neutrino Physics. 2008.

80. **Fernando Pérez-Caballero**. Carbon Aerogels from 5-Methylresorcinol-Formaldehyde Gels. 2008.

81. **Sirje Vaask**. The Comparability, Reproducibility and Validity of Estonian Food Consumption Surveys. 2008.

82. **Anna Menaker**. Electrosynthesized Conducting Polymers, Polypyrrole and Poly(3,4-ethylenedioxythiophene), for Molecular Imprinting. 2009.

83. **Lauri Ilison**. Solitons and Solitary Waves in Hierarchical Korteweg-de Vries Type Systems. 2009.

84. **Kaia Ernits**. Study of In_2S_3 and ZnS Thin Films Deposited by Ultrasonic Spray Pyrolysis and Chemical Deposition. 2009.

85. **Veljo Sinivee**. Portable Spectrometer for Ionizing Radiation "Gammamapper". 2009.

86. **Jüri Virkepu**. On Lagrange Formalism for Lie Theory and Operadic Harmonic Oscillator in Low Dimensions. 2009.

87. **Marko Piirsoo**. Deciphering Molecular Basis of Schwann Cell Development. 2009.

88. **Kati Helmja**. Determination of Phenolic Compounds and Their Antioxidative Capability in Plant Extracts. 2010.

89. **Merike Sõmera**. Sobemoviruses: Genomic Organization, Potential for Recombination and Necessity of P1 in Systemic Infection. 2010.

90. **Kristjan Laes**. Preparation and Impedance Spectroscopy of Hybrid Structures Based on $CuIn_3Se_5$ Photoabsorber. 2010.

91. **Kristin Lippur**. Asymmetric Synthesis of 2,2'-Bimorpholine and its 5,5'-Substituted Derivatives. 2010.

92. **Merike Luman**. Dialysis Dose and Nutrition Assessment by an Optical Method. 2010.

93. **Mihhail Berezovski**. Numerical Simulation of Wave Propagation in Heterogeneous and Microstructured Materials. 2010.

94. **Tamara Aid-Pavlidis**. Structure and Regulation of BDNF Gene. 2010.

95. **Olga Bragina**. The Role of Sonic Hedgehog Pathway in Neuro- and Tumorigenesis. 2010.

96. **Merle Randrüüt**. Wave Propagation in Microstructured Solids: Solitary and Periodic Waves. 2010.

97. **Marju Laars**. Asymmetric Organocatalytic Michael and Aldol Reactions Mediated by Cyclic Amines. 2010.

98. **Maarja Grossberg**. Optical Properties of Multinary Semiconductor Compounds for Photovoltaic Applications. 2010.

99. **Alla Maloverjan**. Vertebrate Homologues of Drosophila Fused Kinase and Their Role in Sonic Hedgehog Signalling Pathway. 2010.

100. **Priit Pruunsild**. Neuronal Activity-Dependent Transcription Factors and Regulation of Human *BDNF* Gene. 2010.

101. **Tatjana Knjazeva**. New Approaches in Capillary Electrophoresis for Separation and Study of Proteins. 2011.

102. **Atanas Katerski**. Chemical Composition of Sprayed Copper Indium Disulfide Films for Nanostructured Solar Cells. 2011.

103. **Kristi Timmo.** Formation of Properties of $CuInSe_2$ and $Cu_2ZnSn(S,Se)_4$ Monograin Powders Synthesized in Molten KI. 2011.

104. **Kert Tamm**. Wave Propagation and Interaction in Mindlin-Type Microstructured Solids: Numerical Simulation. 2011.

105. **Adrian Popp**. Ordovician Proetid Trilobites in Baltoscandia and Germany. 2011.

106. **Ove Pärn**. Sea Ice Deformation Events in the Gulf of Finland and This Impact on Shipping. 2011.
107. **Germo Väli**. Numerical Experiments on Matter Transport in the Baltic Sea. 2011.
108. **Andrus Seiman**. Point-of-Care Analyser Based on Capillary Electrophoresis. 2011.
109. **Olga Katargina**. Tick-Borne Pathogens Circulating in Estonia (Tick-Borne Encephalitis Virus, *Anaplasma phagocytophilum*, *Babesia* Species): Their Prevalence and Genetic Characterization. 2011.
110. **Ingrid Sumeri**. The Study of Probiotic Bacteria in Human Gastrointestinal Tract Simulator. 2011.
111. **Kairit Zovo**. Functional Characterization of Cellular Copper Proteome. 2011.
112. **Natalja Makarytsheva**. Analysis of Organic Species in Sediments and Soil by High Performance Separation Methods. 2011.
113. **Monika Mortimer**. Evaluation of the Biological Effects of Engineered Nanoparticles on Unicellular Pro- and Eukaryotic Organisms. 2011.
114. **Kersti Tepp**. Molecular System Bioenergetics of Cardiac Cells: Quantitative Analysis of Structure-Function Relationship. 2011.
115. **Anna-Liisa Peikolainen**. Organic Aerogels Based on 5-Methylresorcinol. 2011.
116. **Leeli Amon**. Palaeoecological Reconstruction of Late-Glacial Vegetation Dynamics in Eastern Baltic Area: A View Based on Plant Macrofossil Analysis. 2011.
117. **Tanel Peets**. Dispersion Analysis of Wave Motion in Microstructured Solids. 2011.
118. **Liina Kaupmees**. Selenization of Molybdenum as Contact Material in Solar Cells. 2011.
119. **Allan Olspert**. Properties of VPg and Coat Protein of Sobemoviruses. 2011.
120. **Kadri Koppel**. Food Category Appraisal Using Sensory Methods. 2011.
121. **Jelena Gorbatšova**. Development of Methods for CE Analysis of Plant Phenolics and Vitamins. 2011.
122. **Karin Viipsi**. Impact of EDTA and Humic Substances on the Removal of Cd and Zn from Aqueous Solutions by Apatite. 2012.
123. **David Schryer**. Metabolic Flux Analysis of Compartmentalized Systems Using Dynamic Isotopologue Modeling. 2012.
124. **Ardo Illaste**. Analysis of Molecular Movements in Cardiac Myocytes. 2012.
125. **Indrek Reile**. 3-Alkylcyclopentane-1,2-Diones in Asymmetric Oxidation and Alkylation Reactions. 2012.
126. **Tatjana Tamberg**. Some Classes of Finite 2-Groups and Their Endomorphism Semigroups. 2012.
127. **Taavi Liblik**. Variability of Thermohaline Structure in the Gulf of Finland in Summer. 2012.
128. **Priidik Lagemaa**. Operational Forecasting in Estonian Marine Waters. 2012.

129. **Andrei Errapart**. Photoelastic Tomography in Linear and Non-linear Approximation. 2012.

130. **Külliki Krabbi**. Biochemical Diagnosis of Classical Galactosemia and Mucopolysaccharidoses in Estonia. 2012.

131. **Kristel Kaseleht**. Identification of Aroma Compounds in Food using SPME-GC/MS and GC-Olfactometry. 2012.

132. **Kristel Kodar**. Immunoglobulin G Glycosylation Profiling in Patients with Gastric Cancer. 2012.

133. **Kai Rosin**. Solar Radiation and Wind as Agents of the Formation of the Radiation Regime in Water Bodies. 2012.

134. **Ann Tiiman**. Interactions of Alzheimer`s Amyloid-Beta Peptides with Zn(II) and Cu(II) Ions. 2012.

135. **Olga Gavrilova**. Application and Elaboration of Accounting Approaches for Sustainable Development. 2012.

136. **Olesja Bondarenko**. Development of Bacterial Biosensors and Human Stem Cell-Based *In Vitro* Assays for the Toxicological Profiling of Synthetic Nanoparticles. 2012.

137. **Katri Muska**. Study of Composition and Thermal Treatments of Quaternary Compounds for Monograin Layer Solar Cells. 2012.

138. **Ranno Nahku**. Validation of Critical Factors for the Quantitative Characterization of Bacterial Physiology in Accelerostat Cultures. 2012.

139. **Petri-Jaan Lahtvee**. Quantitative Omics-level Analysis of Growth Rate Dependent Energy Metabolism in *Lactococcus lactis*. 2012.

140. **Kerti Orumets**. Molecular Mechanisms Controlling Intracellular Glutathione Levels in Baker's Yeast *Saccharomyces cerevisiae* and its Random Mutagenized Gluthatione Over-Accumulating Isolate. 2012.

141. **Loreida Timberg**. Spice-Cured Sprats Ripening, Sensory Parameters Development, and Quality Indicators. 2012.

142. **Anna Mihhalevski**. Rye Sourdough Fermentation and Bread Stability. 2012.

143. **Liisa Arike**. Quantitative Proteomics of *Escherichia coli*: From Relative to Absolute Scale. 2012.

144. **Kairi Otto**. Deposition of In_2S_3 Thin Films by Chemical Spray Pyrolysis. 2012.

145. **Mari Sepp**. Functions of the Basic Helix-Loop-Helix Transcription Factor TCF4 in Health and Disease. 2012.