VĚDECKÉ SPISY VYSOKÉHO UČENÍ TECHNICKÉHO V BRNĚ

Edice Habilitační a inaugurační spisy, sv. 755

ISSN 1213-418X

Aamir Saeed Malik

DATA ANALYTICS AND BIOMARKER DEVELOPMENT FOR INVESTIGATION OF THE BRAIN DYNAMICS USING ELECTROENCEPHALOGRAM (EEG) SIGNALS

VYSOKÉ UČENÍ TECHNICKÉ V BRNĚ

Fakulta informačních technologií

Doc. Dr. Aamir Saeed Malik

DATA ANALYTICS AND BIOMARKER DEVELOPMENT FOR INVESTIGATION OF THE BRAIN DYNAMICS USING ELECTROENCEPHALOGRAM (EEG) SIGNALS

ANALÝZA DAT A VÝVOJ BIOMARKERŮ PRO ZKOUMÁNÍ DYNAMIKY MOZKU POMOCÍ SIGNÁLŮ ELEKTROENCEFALOGRAMU (EEG)

TEZE PŘEDNÁŠKY

K PROFESORSKÉMU JMENOVACÍMU ŘÍZENÍ

VYSOKÉ UČENÍ TECHNICKÉ V BRNĚ NAKLADATELSTVÍ VUTIUM

BRNO 2023

KEYWORDS
Neural Engineering, Neuroimaging, Brain, Mental Health, Electroencephalogram (EEG), Event Related Potential (ERP), Biomarker, Feature Extraction, Diagnosis, Treatment, Memory, Learning, Cognition

KLÍČOVÁ SLOVA
Neurové inženýrství, neurozobrazování, mozek, duševní zdraví, elektroencefalogram (EEG), potenciál související s událostmi (ERP), biomarker, extrakce funkcí, diagnostika, léčba, paměť, učení, kognice

ISBN 978-80-214-6160-4
ISSN 1213-418X

Contents

About the author 4

1 Introduction 7
1.1 Motivation, Scope and structure 7
1.2 Acknowledgements 8

2 Evolution of electroencephalogram (EEG) 10
2.1 History of EEG 10
2.2 From 1980 to 2000 11
2.3 What changed after 2000? 12

3 Biomarker development for clinical applications 16
3.1 Assessment of Mental Stress 16
3.2 Diagnosis of Major Depressive Disorder (MDD) 17
3.3 Treatment Efficacy for Major Depressive Disorder (MDD) 18
3.4 Classification of Alcohol Use Disorder (AUD) Patients 20
3.5 Prediction of Partial Epileptic Seizure 21

4 Targeting non-clinical applications 23
4.1 Proposing a New Biomarker 23
4.2 Long Term Memory Assessment 24
4.3 P300 and Fluid Intelligence 25
4.4 Cognitive Load Assessment 26
4.5 Influence of Color on Emotion and Memory 27

5 Conclusions and the Future 28

References 29

Abstract 33

About the author

Name: Aamir Saeed Malik

Born: 18-November-1969

Address: Faculty of Information technology, Brno University of Technology, Bozetechova 2, Brno, 61200

Email: malik@fit.vutbr.cz

Education

2004 – 2008: PhD (Information & Mechatronics), Gwangju Institute of Science & Technology, South Korea

1998 – 2000: MS (Information & Communication), Gwangju Institute of Science & Technology, South Korea

1993 – 1995: MS (Nuclear Engineering), Quaid-i-Azam University, Islamabad, Pakistan

1988 – 1993: BS (Electrical Engineering), University of Engineering & Technology, Lahore, Pakistan

Professional Experience

2021 – Present: Associate Professor, Faculty of Information Technology, Brno University of Technology, Czech Republic

2018 – 2021: Director Technical Team, Frack Technologies, Australia

2012 –2018: Associate Professor, Universiti Teknologi PETRONAS, Malaysia

2009 – 2012: Senior Lecturer, Universiti Teknologi PETRONAS, Malaysia

2008 – 2009: Assistant Professor, Yeungnam University, South Korea

2000 – 2004: Senior Instructor, IBM ACE, (IBM Center for Education - Advanced Career Education Services), Islamabad, Pakistan

Management & Academic Positions

- Head, Cognitive & Neural Engineering (CANE) Research Group at FIT (VUT), 2021-Present
- Head, HICOE CISIR (National Center on Neuroimaging in Malaysia), 2017-2018
- Chairman, CISIR (Centre for Intelligent Signal & Imaging Research) Management Committee, 2015-2017
- Editor-in-Chief, RESINNEX (Universiti Teknologi PETRONAS Research Newsletter), 2013-2015
- Director, Mission Oriented Research Biomedical Technology, Universiti Teknologi PETRONAS, 2011-2015
- Center Director, IBM ACE, Pakistan, 2000-2004

Editorial Committee Member

- Guest Editor, Frontiers in Psychology (Q1 Journal), 2022-2023
- Editor, Asia-Pacific Journal of Neuro-Therapy, 2019-Present
- Editor-in-Chief, Neuro-Eastern, Bi-Monthly Newsletter of Asia-Pacific Neurofeedback Association (APNA), 2016-2017
- Guest Editor, Special Issue, Electronic Imaging, 2016

Memberships

- Board Member, Asia-Pacific Neurofeedback Association (APNA)
- Senior Member, IEEE (Institute of Electrical & Electronics Engineers)
- Life Member, PEC (Pakistan Engineering Council)

Conference Committee / Society Member

- Committee Member (Forums, Workshops), IEEE EMBS Conference on Biomedical Engineering & Sciences, Malaysia, 2018

- Steering Committee Member, International Conference of Imaging, Signal Processing & Communication, Malaysia, 2017
- Committee Member (Forums, Workshops), IEEE EMBS Conference on Biomedical Engineering & Sciences, Malaysia, 2016
- Steering Committee Member, International Conference on Quality Control and Artificial Vision (QCAV), France, 2015
- Vice Chair, IEEE Consumer Electronics Society, Malaysia Chapter (2014)
- Executive Committee Member, IEEE Engineering in Medicine and Biology Society, Malaysia Chapter (2014)
- Committee Member, International Conference on Neural Information Processing, Malaysia, Nov 2014
- Executive Committee Member, IEEE Consumer Electronics Society, Malaysia Chapter (2013)
- Auditor, IEEE Engineering in Medicine and Biology Society, Malaysia Chapter (2013)
- Technical Committee Member, IEEE International Conference on Imaging Systems and Techniques (IST), Manchester, UK, 2012
- Technical Committee Member, IEEE International Instrumentation and Measurement Technology Conference (I2MTC), Graz, Austria, 2012
- Technical Committee Member, IEEE International Instrumentation and Measurement Technology Conference (I2MTC), Hangzhou, China, 2011

Invited Talks

- "Challenges for real time analysis of signals for brain computer interfaces", Conference on High Performance Computing in Sciences & Engineering (HPCSE), Roznov Pod Radhostem, Czech Republic, May 2022.
- "Contributions to Brain Research: From an Engineer's Perspective", Masaryk University, Czech Republic, 4th March, 2022.
- "Assessment of stress using machine learning", Asia Pacific Neurofeedback & Biofeedback Conference, Indonesia, October, 2021.
- "Factors Affecting Learning & Memory: Implications for Intervention", Applied Neuroscience Society of Australia (ANSA) Annual Conference & Workshops, Australia, August, 2019.
- "Simultaneous EEG-fMRI for cognitive processes & neurofeedback", Keynote Speaker, Asia Pacific Neurofeedback & Biofeedback Conference, Kuala Lumpur, October 2017.
- "How important is planning for the research?", Keynote Speaker, Symposium in Biomedical Engineering & Science, Kuala Lumpur, November 2015.
- "Effect of 3D Display Technologies on Human Brain", Keynote Speaker, International Conference on Neural Information Processing (ICONIP), Malaysia, November, 2014.
- "Development of EEG based predictive Biomarker for Major Depressive Disorder", Invited Speaker, Interdisciplinary Neuroscience Symposium, UPM, Kuala Lumpur, November, 2014.
- "EEG and ERP Signal Processing", University of Girona, Spain, 19 June 2013.
- Series of seminars on Medical Signal and Image Processing at University of Girona, Spain, 28 May – 8 June 2012.
- Series of seminars on 3D imaging at University of Burgundy, France, 25 January – 23 February 2011.
- "Introduction to 3D shape recovery using optical passive methods", University of Sharjah, UAE, 16 December, 2009.

Patents

- Tae-Sun Choi, Wook-Jin Choi, Aamir Saeed Malik, "Method and apparatus for classifying honeycombed lung image and computer-readable medium", Korea Patent Application No. 10-2009-0104465, Patent No. 10-1066468, filed 30-Oct-2009, Granted/Registered: 15-Sep-2011.
- Aamir Saeed Malik, Nidal Kamel, Mohd Zuki Yusoff, "Methodology of extracting brain ERP signals from background noise", Malaysia patent application (MYIPO) 2011000906, filed 28-Feb-2011, Granted: 15-Dec-2014, Registration No. MY-152983-A.
- Aamir Saeed Malik, Yasir Salih, Junaid Ahmad, "Depth estimation using triangulation from single image and its applications", Malaysia patent application (MYIPO) 2011004719, filed 30-Sep-2011, Granted: 15-Nov-2017, Registration No. MY-164003-A.
- Aamir Saeed Malik, Rafi Ullah, Humaira Nisar, Nidal Kamel, "Method of Obtaining Motion Vectors for Tracking EEG signals using Block-Based Motion Estimation Algorithm", Malaysia patent application (MYIPO) 2012701193, filed 15-Dec-2012, Granted: 28-Dec-2018, Registration No. MY- 168915-A.
- Aamir Saeed Malik, Wajid Mumtaz, "Methodology of using Electroencephalogram (EEG) for Major Depressive Disorder (MDD) Patient Diagnosis and Antidepressants Efficacy Prediction", Malaysia patent application (MYIPO) 2015701569, filed 15-May-2015, Granted: 20-Nov-2020, Registration No. MY-180034-A.

- Aamir Saeed Malik, Rana Fayyaz Ahmad, Jahangir Khan Kayani, “A System and Method for Functional Brain Imaging Using Microwave Radiometry”, Malaysia patent application (MYIPO) 2016700715, filed 01-Mar-2016, Granted: 28-Sep-2020, Registration No. MY- 177762-A.
- Aamir Saeed Malik, Uvais Qidwai, Mohamed Shakir, Nidal Kamel, “Wearable System for Indentification and Prediction of Partial Seizure”, Malaysia patent application (MYIPO) 2014703881, filed 18-Dec-2014, Granted: 18-Jan-2021, Registration No. MY- 182188-A.

Books

- Aamir Saeed Malik, Wajid Mumtaz, “EEG based experiment design for major Depressive Disorder”, ISBN: 9780128174203, Elsevier, 2019.
- Aamir Saeed Malik, Hafeezullah Amin, “Designing EEG Experiments for Studying the Brain: Design Code and Example Datasets”, ISBN: 9780128111406, Elsevier, 2017.
- Nidal Kamel, Aamir Saeed Malik, “EEG/ERP Analysis: Methods and Applications”, ISBN: 9781482224696, CRC Press, US, June, 2014.
- Aamir Saeed Malik, Tae-Sun Choi, Humaira Nisar, “Depth map and 3D imaging applications: Algorithms and technologies”, ISBN13: 9781613503263, ISBN10: 1613503261, IGI Global Publishers, US, 2012.
- Tae-Sun Choi, Aamir Saeed Malik, Book: “Vision & Shape -- 3D Recovery using Focus”, Sejong Publishing Company, ISBN# 978-89-86174-11-3, Korea, July 2008.

Funding

- A Novel Algorithm for Estimation of Depth in 3D Applications using Focus and Defocus Cues, EScience Grant, Ministry of Science, Technology & Innovation, Malaysia, 2010-2012.
- Investigation of Signal processing approach for low back pain analysis using fatigue loading, FRGS Grant, Ministry of Higher Education, Malaysia, 2011-2013.
- 3D Tracking Prototype using Single 2D Camera, PRGS Grant, Ministry of Education, Malaysia, 2012-2014.
- 3D mapping for robotic vision, University of Burgundy Grant, France, 2012-2014.
- Vegetation monitoring using satellite stereo for power lines in Malaysia, Electricity Trust Fund (MESITA), MESITA Grant, Ministry of Energy, Green Technology & Water (KeTTHA), Malaysia, 2013-2016.
- Design and analysis of 3D educational content for learning and memorization processes, National Plan for Science & Technology (NPST) grant, Saudi Arabia, 2014-2016.
- Robust Point Cloud Descriptors using Eigenvalue Decomposition for 3D Object Recognition, University of Burgundy Grant, France, 2014-2016.
- Development of QEEG module for EEG Data Analysis, CISIR HICOE Grant, Ministry of Education, Malaysia, 2014-2017.
- Prediction of treatment outcome for Major Depressive Disorder for SSRI class medicine, CISIR HICOE Grant, Ministry of Education, Malaysia, 2014-2017.
- Assessment of Psychosocial Stress levels and Stress Mitigation in Urban Workplace, CISIR HICOE Grant, Ministry of Education, Malaysia, 2014-2017.
- Investigation of 2D and 3D display technology for Long Term Memory, CISIR HICOE Grant, Ministry of Education, Malaysia, 2014-2017.
- Investigation of Brain Neuronal Mechanisms for the Effect of 3D Technology on Learning and Memorization Processes, FRGS Grant, Ministry of Education, Malaysia, 2014-2016.
- Intelligent Treatment Management System (ITMS) for Major Depressive Disorder (MDD), PRGS, Malaysia 2015-2017.

Summary of Research Record

H-Index (Google Scholar)	43	Books	5
Total No. of Citations (Google Scholar)	8455	Number of Journal Articles (Q1, Q2)	50
Patents (Granted)	7	Number of Conference Papers	60
Number of External Grants	10	PhD Students Supervision (Graduated)	14
Awards & Certificates	15	MS (by research) Students (Graduated)	21

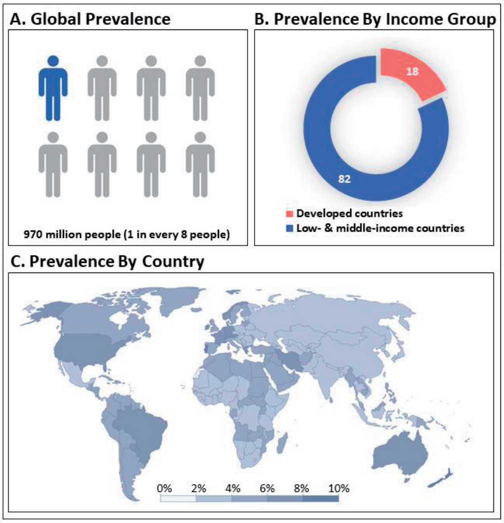
1. Introduction

I started my academic career with focus on biomedical signal and image processing. With time, I shifted and narrowed down my focus to neural imaging, that is, neural (brain) signal and image processing. This document details my various contributions in the field of neuroimaging (with focus on electroencephalogram - EEG) over the last fifteen years. During this period, I have the honor to serve as the head of the national center of neuroimaging in Malaysia, that is, Center for Intelligent Signal and Imaging Research (CISIR) at Universiti Teknologi Petronas (UTP) in Malaysia. My research involves analyzing and interpreting data acquired from four different neuroimaging modalities which include functional Magnetic Resonance Imaging (fMRI), electroencephalogram (EEG), magnetoencephalogram (MEG), and Functional Near Infrared Spectroscopy (FNIR). This document provides my contributions related to EEG research.

1.1 Motivation, Scope and Structure

From very early in my career, I was intrigued by what's going on in our brain. Some call the brain related research as a last frontier and probably rightly so. Our understanding of the human body is quite detailed and solid except the human brain. The brain, though being approximately 1400 grams organ, is hugely complex and provides us the identity of who we are. Unfortunately, it not only provides us an identity but is also the centerpiece of all our activities including what may be going wrong with us. Hence, my motivation stems from the fact that brain (neurological domain) and mental health (functional domain) issues, in some ways, affect every one of us. Hence, I want to make research contributions that can help alleviate the pain of various brain and mental health related issues, diseases and disorders.

According to World Health Organization (WHO), one in eight persons is severely affected by some mental health issue [1], that is, it amounts to almost a billion people on earth. A study published in JAMA Psychiatry [2] reports reduced life expectancy of up to 10 years for people suffering from severe mental health issues and 14.3% of all deaths worldwide. This further results in economic burden in terms of loss of productivity and the associated medical costs as well as resources [3]. Covid pandemic further exacerbated the situation with more than 25% increase in anxiety and depression cases [4]. World Economic Forum (WEF) has predicted the economic burden to cost up to US$ 16 trillion by 2030 [5]. In Europe, WHO reported that mental health affects 1 in 6 people. The associated costs are estimated to be more than 4% of GDP of EU countries. These are just the statistics from mental health issues. If brain health issues (neurological domain) are also included in the statistics then the numbers are staggering because that covers diseases and disorders like stroke, epilepsy and dementia. Therefore, a small contribution in this area can go a long way in impacting the lives of the people and improving their



quality of life. This is what motivates me and keep me awake and energetic to do more in neuroimaging research.

My emphasis is on studying the changes in brain signals and images due to the various underlying neuronal mechanisms associated with various brain and mental health issues, diseases and disorders. The target is to detect such changes before the onset of any issue, that is, early detection of changes occurring in the brain. As people do not seek help at earlier stages of brain and mental health issues, hence the early detection has to be based on a neuroimaging modality that is low cost, easily accessible, mobile, and provides interpretable results and which can be used both at home as well is affordable for smaller clinical setups. This eliminates functional Magnetic Resonance Imaging (fMRI), magnetoencephalogram (MEG), and Positron Emission Tomography (PET) because of their large size, high cost, immovability, restricted availability & accessibility, and specialized environment. This leaves us with two neuroimaging modalities, that is, electroencephalogram (EEG), and Functional Near Infrared Spectroscopy (FNIR). Though FNIR is promising, however, currently it has high cost as well as its an indirect measurement of the brain activity. This leaves us with EEG which is low cost, easily accessible, mobile, affordable, and provides interpretable results. Hence, this is my motivation for developing biomarkers for early detection of brain and mental health issues using EEG signals. Therefore, the scope of this document is limited to EEG.

This document is structured as follows: (i) Chapter 1 provides an introduction including motivation, scope, structure and acknowledgements, (ii) Chapter 2 gives an overview of EEG including its short history and evolution through two important periods, that is 1980’s to 2000 and post-2000, (iii) Chapter 3 discusses my contributions in the development of biomarkers in the clinical area, (iv) Chapter 4 discusses my contributions for the non-clinical applications, (v) Chapter 5 provides conclusions with discussion about the future aspects.

1.2 Acknowledgements

First of all, I would like thank all my teachers who shaped me for what I am today. I cannot forget my teachers from the school (primary, secondary, high school) who inculcated the culture of hard work and questioning while being very patient in their dealings with all the students. My special thanks to my supervisors at Gwangju Institute of Science and Technology (South Korea). My MS thesis supervisor Professor Zang-Hee Jo introduced me to neuroimaging research and my PhD supervisor Professor Tae-Sun Choi taught me, not only, how to do research but also how to aim for top publication in my domain.

I want to mention here about Professor Ahmad Fadzil who was heading the Center for Intelligent Signal and Imaging Research (CISIR) at Universiti Teknologi Petronas (UTP) in Malaysia when I joined that university. He proved to be a true mentor in all aspects. One of the most crucial and significant gain for me was to learn and experience the transformation of a research group to a national center in the country as I was part of the CISIR journey from the very beginning to the point when it was recognized as Malaysian National Center in Neuroimaging. Later, I had the honor of serving as CISIR head from 2017 to 2018. I also want to thank the whole CISIR group who were there for me during the decade long journey.

I want to especially thank FIT management for providing me the opportunity to come here and to all FIT colleagues. Though I joined in 2021 but I feel it as my second home. All the colleagues are very kind and helpful, and they assisted me throughout to make my stay comfortable as well as enjoyable. I especially want to mention Dean of FIT, Professor Pavel Zemcik, Vice Dean (Science & Research) Professor Tomas Vojnar, and Head of my Department (Computer Systems) Professor Lukas Sekanina.

Finally, acknowledgements are not complete without extending my thanks to my family for their patience and love, and to Almighty for making me believe in myself.

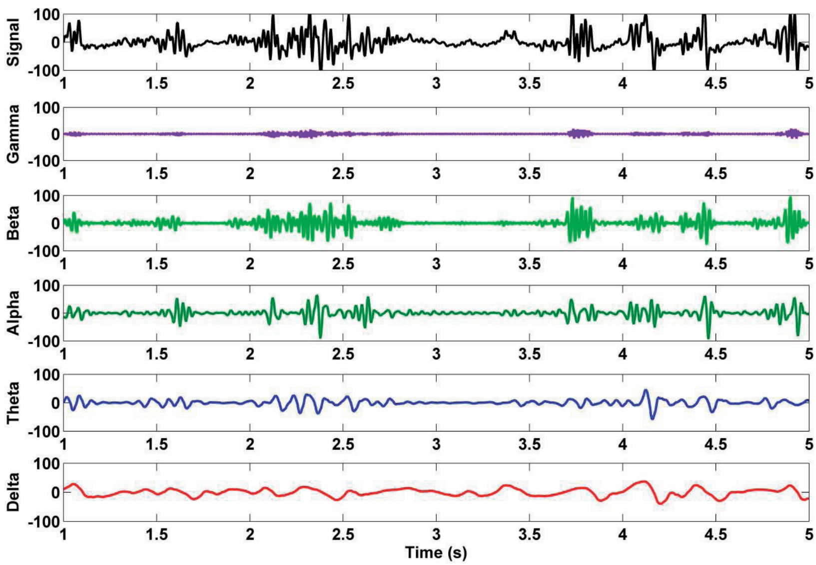
2 Evolution of electroencephalogram (EEG)

The human nervous system is divided into the central nervous system (CNS) and the peripheral nervous system (PNS). The former consisting of the brain and the spinal cord and the later connecting the brain and the spinal cord to the sensory system and the body organs. The neuron is the basic functional unit of the nervous system which carries information to and from the brain. A neuron consists of three main parts, the soma, the dendrites and the axons. The neurons communicate with each other through synaptic transmission—the point where the terminal part of the axon (part of the neuron) contacts another neuron. The axon carries electrical signals to other cells to make the information transmission. The flow of the electrical signals among the neurons produces an electrical field potential over the scalp. This electrical potential can be recorded in real time and hence the origin of the term electroencephalogram (EEG).[46].

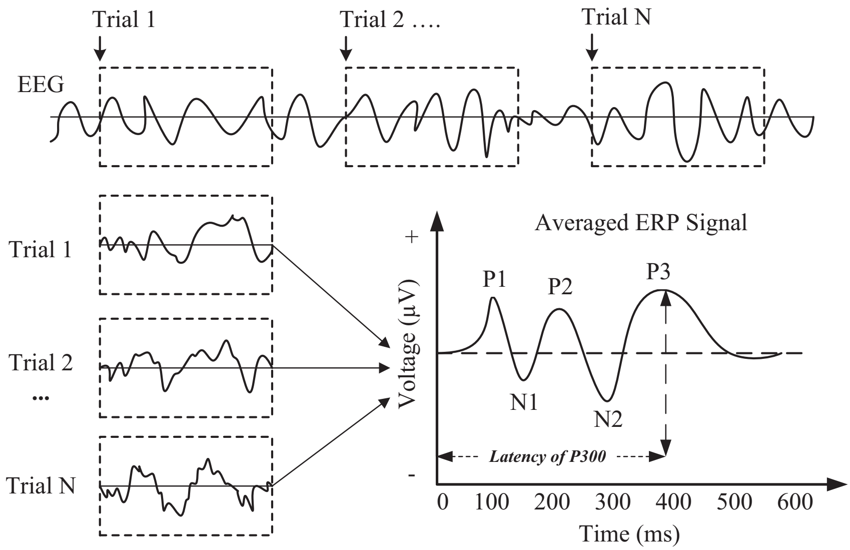
2.1 History of EEG

In 1929, a German psychiatrist Hans Berger, discovered electroencephalography (EEG), which was a historical breakthrough in the neurologic and psychiatric fields. The EEG is a technique to record the electrical potential induced due to neuronal communication. Since its discovery, EEG has been widely adopted in brain research. With the passage of time, researchers divided the EEG waves into different frequency bands associated with different brain functions. These frequency bands mainly include delta, theta, alpha, beta and gamma. [46].

In the beginning, EEG researchers focused on studying the brain oscillations (various frequencies) and investigated their relationship with cognitive functions. Frequency bands (delta, theta, alpha, beta, gamma) were defined for various ranges. Those bands were investigated for relationship with brain structure and functions. For example, the alpha and beta waves were discovered by Hans Berger. A typical example of EEG waves can be seen in figure [46] below.



There is another concept related to EEG called Event Related Potentials (ERPs). ERP signal is buried within EEG and hence is extracted from EEG. The first recording of ERPs was done by Pauline and Hallowell Davis in 1935 [6]. ERPs are time-locked voltage fluctuations in EEG recordings that are sensitive to cognitive events. One example of a cognitive event is some visual stimulus, for example, when a visual stimulus, such as an event, is presented on a computer screen, it evokes an EEG activity. The ERP signal is extracted by analyzing the time-locked small portion of the EEG activity that is evoked by the event of the visual stimulus. As the amplitude of the ERP signal is small, the visual stimulus presentation is repeated, and the time-locked EEG activity is averaged. The ERP signal in response to cognitive events consists of many peaks (positive or negative), which normally occur around the 100ms, 200ms and 300ms time points after the onset of the stimulus, and are referred to as ERP components, such as P100, N100, P200, N200 and P300 [7]. These components are analyzed by their time of occurrence (latency) and their strengths (amplitude). Figure [8] below shows the concept of ERP. [46].



2.2 From 1980 to 2000

During the twenty years from 1980 to 2000, main EEG research was restricted to frequency analysis of the EEG signal and the associated ERP analysis. For EEG, researchers decomposed EEG signals into various frequency bands and associated them with various human cognitive functions. The five main categories included delta, theta, alpha, beta and gamma bands. The range of frequencies within each of these bands has remained an open discussion based on experiences of individual researchers. However, a consensus is present among the research community regarding the existence of these frequency bands and their association with human cognitive functions. A brief overview of these bands is provided in the following paragraph.

EEG delta waves (generally categorized up to 4 hz) are high amplitude and low frequency brain waves and they have been observed in various sleep stages. In addition to the various sleep stages, the delta waves are associated with different brain functions; for example, delta waves occurring in the frontal region during the awake condition may indicate boredom. Theta waves (generally categorized from 4 to 8 hz) are related to self-introspection and are observed during the meditation state. They are also observed in the drowsy state. In the absence of any cognitive activity or any task related activity, high theta activity is considered abnormal. High theta activity can occur in brain disorders, e.g., high frontal theta is linked with the non-response to antidepressant treatment in depression patients. Alpha waves (generally categorized from 8 to 13 hz) can be observed spontaneously in normal adults during wakefulness and a relaxed state, especially when there is no mental activity. During the eyes closed condition, alpha waves are prominent at parietal and occipital locations. Attentional processing or cognitive tasks cause the attenuation of the alpha waves. Alpha waves are subdivided into lower alpha and upper alpha. Beta waves (generally categorized from 13 to 30 hz) have lower amplitudes than the alpha, delta and theta waves. It has been observed that beta activity increases during problem solving and thinking activities and this increase is in the frontal and central regions of the brain. Traditionally, beta waves are subdivided into low beta (from 13 to 21 hz) and high beta (from 21 to 30 hz). Gamma waves (generally categorized above 30 hz) are fast oscillations and usually found during conscious perception. Gamma waves have not been as widely studied as compared to the other slow brain waves. High gamma activity at temporal locations is associated with the memory process. [46].

For the ERP, the researchers looked at the latency and amplitude of the peaks within the ERP signal. They associated those peaks and their associated changes in terms of latency and amplitude with deterioration of various cognitive functions. The variations in latency and the amplitude of the ERP components were found to be sensitive to the brain dynamics and useful to understand the neural processing. The P100 and P200 components were found in the frontal regions of the brain during visual task performance after the onset of stimulus 100ms and 200ms, respectively. The early visual sensory processing within the dorsal stream reflected the amplitude of P100 component, while the amplitude of P200 was associated with the patients of major depression [9]. The N100 and N200 are negative components of ERP and occurred around 100ms and 200ms after the onset of stimulus. The amplitude of N100 was proposed as a potential trait marker of schizophrenia patients [10]; while the N200 was related to stimulus identification [11]. However, the important and most widely used ERP component discovered was the P300 [10]. The P300 (P3) component of the ERP was the most reported component in studies for the assessment of the brain’s neuronal system during mental activities. The P3 component was suggested to closely relate to attentional resource allocation and working memory at the frontal and parietal regions. P3 can be extracted from the ERP signal occurring between 250ms to 500ms after the stimulus onset. It was found that P3 reflects cognitive information processing, including the stimulus detection, perception and occurrence of novel stimulus. The amplitude and latency of the P3 component were considered as indicators of the attention resource allocation and thus, were taken to be the measures of the strength of the cognitive processes. [46].

2.3 What changed after 2000?

The EEG research till 2000 was restricted due to the EEG hardware that was required for EEG signal acquisition from the scalp. The EEG equipment was bulky, expensive, low density (generally up to 19 electrodes supporting 10-20 electrodes placement) and required specialized training to set up the EEG electrodes on the scalp. However, with the technological advancements in the hardware as well as the software, there were significant improvements in the EEG equipment that lead to the wide availability of EEG equipment with lower costs, smaller size, higher density (systems became available with 32, 48, 64, 128, 256 and higher number of electrodes), better amplifiers with good signal to noise ratio, lower setup times (from gel based to saline water based electrodes, dry electrodes), and wireless (from wired to wireless) systems. This development led to a large number of academic, clinical and industrial researchers entering EEG research. As these researchers came from various backgrounds (like mathematics, computer science, various engineering disciplines, clinical disciplines etc.), they brought with them diverse knowledge that resulted in tremendous extension of analysis of EEG signals. The EEG analysis now incorporate new features (like time based (in addition to traditional frequency based), time-frequency based, connectivity, microstates, ERP, etc.) that provide detailed analysis of underlying neuronal mechanisms and hence the comprehensive interpretability which is significant for diagnosis and treatment efficacy in the clinical domain. The following paragraphs summarize some of the EEG related research post 2000.

The EEG related research has been employed for the diagnosis and treatment efficacy of various brain and mental health issues like mental stress, major depression disorder, anxiety, dementia, autism, epilepsy etc. For example, assessment of mental stress is a significant and hot topic in EEG related research. Stress is the negative emotional and physical response that occurs due to a low control of a person over meeting demands in daily life. A prolonged episode of stress turns into chronic stress, which permanently keeps the body aroused for danger, that takes its toll on the body by endangering it to disease [12]. An electroencephalogram (EEG)-based study [13] had shown promising outcomes to classify stress levels. In this study, 23 subjects were recruited. All of them were male and their ages were between 18 to 28 years. All of them were exposed to a stress test. Data was recorded for three different conditions, that is, recording was made before the start of the stress test, immediately after the stress test and finally twenty minutes after the test. During these 3 conditions, EEG data as well as salivary cortisol level were recorded. The authors used a functional connectivity measure, that is synchronization likelihood (SL). Brain networks were studied using SL connectivity measure. The computation of SL was done for the four EEG bands, namely, delta, theta, alpha, and beta band. The brain networks were found using weighted connectivity as well as binary connectivity matrices (using thresholding). Four network parameters, namely, transitivity, modularity, characteristic path length, and global efficiency were computed by the authors. Then compensation distance evaluation technique (CDET) was employed for selection of the optimal features. The classification was done with multi-class support vector machine (SVM) for classifying the multiple states of stress. The results show that multiple levels of stress can be classified with good accuracy.

Depression and anxiety are two significant mental health disorders that account for almost 70% of all the mental health issues. Their timely diagnosis and treatment efficacy are important for a patient to recover from these disorders. The researchers are hence involved in trying to find EEG based biomarkers that can be used for the diagnosis and treatment efficacy for these two disorders. For the diagnosis of major depression disorder (MDD) as well as anxiety patients, the traditional method used by physicians and psychiatrists is the clinical questionnaire-based assessment, which is primarily determined by patients' responses and behavioral activities [14]. Thus, it is highly susceptible to human subjectivity, which impairs the objectivity of the diagnosis process. Consequently, numerous studies have been conducted to advance the traditional models' competency as well as develop better replaceable strategies for diagnosing depression and anxiety.

The classification of major depression disorder (MDD) patients from EEG data is done in two steps; first, some feature extraction techniques are used to extract features from EEG data, and then some classification technique is used on the extracted features to classify the MDD patients. For feature extraction, several methods have been put forth in the literature, including source localization, frequency analysis, time series analysis, time-frequency analysis, connectivity measures, and microstate analysis [15]. Furthermore, based on the extracted features, several classification techniques have been proposed in the literature such as logistic regression (LR), artificial neural networks (ANN), support vector machines (SVM), and convolutional neural networks (CNN) [16]. Because of superior classification performance, Deep learning (DL) techniques have also been proposed for MDD classification [17].

In a study related to severity assessment of social anxiety disorder (SAD) using deep learning models on brain effectivity connectivity focused on trait anxiety [18]. EEG signals of 88 participants were recorded during resting state. Dataset contained balanced distribution of classes, in particular of 22 healthy group, 22 having mild SAD, 22 having moderate SAD, and 22 with severe SAD. This grouping into different classes was based on self-assessment of the SIAS (Social Interaction Anxiety Scale). Data were collected using ANT Neuro EEG system (32 electrodes). Feature used was effective connectivity of the DMN (Default mode network), particularly PDC (Partial directed coherence) for each frequency band (delta, theta, alpha, beta, gamma). These were fed into CNN, LSTM and CNN + LSTM. The highest accuracy of 93 % was obtained using CNN + LSTM. In addition to classification accuracy, authors also located cortical sources of activity using effective connectivity features, and were able to demonstrate the differences in the brain activity between healthy and SAD participants, during resting state.

For brain (neurological) health issue like epilepsy, researchers have invested time and resources in identifying the location of epileptic seizures in long recording (multiple days) of EEG signals as well as attempted to develop models for the prediction of epileptic seizures. Epilepsy is defined as a disorder and it is chronic in nature. The daily routine of an epileptic patient is affected (and for some it is severely affected) because of the epileptic seizures. The epileptic seizure is sudden and hence the patient may fall immediately with the onset of the seizure. Therefore, a seizure prediction scheme can be extremely beneficial for the epileptic patients. In a study [19], the authors proposed an automatic epileptic seizure technique based on a deep learning algorithm, that is, spectral feature-based two-layer LSTM network model. Generally, for an epileptic patient, their EEG recordings are available and they are long term recordings (spanning many days). Hence, a deep learning model can be used in such a scenario where lot of data is available. The authors proposed to use power and mean amplitude features extracted from all EEG bands including delta, theta, alpha, beta, and gamma band. The dataset consisted of 24 epilepsy patients whose EEG data was recorded from a 23 channels EEG machine. The authors used single-layer and two-layer LSTM models with EEG segments whose durations were in the range of 5 to 50 seconds. It was found that 30 seconds duration segment resulted in accurate seizure prediction when two-layer LSTM model was used. For comparison purposes, traditional machine learning (ML) approaches were employed including random forest, decision tree, k-nearest neighbor, support vector machine, and naive Bayes classifiers. The proposed two-layer LSTM model with EEG spectral features outperformed the traditional ML approaches and accurately predicted epileptic seizures in real time. The proposed technique achieved average classification accuracy of 98.14%, average sensitivity of 98.51%, and average specificity of 97.78%.

There is lot of EEG related research done for non-clinical applications too including learning and memory, brain computer interfaces, cognitive skills enhancement etc. For learning and memory, classification of the type of learner had been an active topic of research, for example to classify visual learner from a non-visual learner. Visual learning style is essential as most learners are visual learners. Many things come under this heading, such as pictures, graphs, videos, and images. It also includes words and written material. In [20], the visual and reading part of the Visual, Audio, Reading, Kinesthetic (VARK) test was used along with P200 amplitude to measure event-related potential at the occipital site on the scalp. The participants recruited for the study were divided into two groups; visual learners (learn by looking at pictures) and verbal learners those who learn by reading (books, articles, flashcards). The study concluded that there was a psychological difference between students who were visual learners and who were readers. The visual learner's students had a higher peak of P200 compared to the readers. In another study [21], the visual-verbal styles for a person were investigated to see the changes in brain dynamics when an individual was exposed to a learning style that does not matches his/ her style. They examined the difference between a visual learner and a verbal learner and how their brain performed when a visual learner was asked to process a verbal task. One hundred and thirty-five healthy students were recruited for the experiment; all were right-handed and healthy individuals. The learning style of the recruited subjects was analyzed using the indexed learning style test. This test is a subjective measure and it provides information about the learning style of a person. During the EEG recording session, the participants in the study were shown different pictures of animals. The data were analyzed using the Wilcoxon signed-rank test for categorizing students into visual or verbal learners. After further analysis of the EEG theta and beta bands from overall brain, it was observed that the visual learner's theta waves decreased, and beta waves increased. For verbal learners, theta waves were higher, and beta waves were lower. The authors concluded that the concentration of visual learners decreased when they were asked to perform another task which was a verbal task in their study.

The above-mentioned are some examples from the EEG related research which has been published for the various clinical and non-clinal applications. The next two chapters summarize my contributions in this field with focus of chapter 3 on clinical applications while the focus of chapter 4 on non-clinical applications.

3 Biomarker development for clinical applications

This chapter summarizes my EEG related research for mental stress, major depressive disorder (diagnosis and treatment efficacy), alcohol addiction, and epilepsy (prediction of partial epileptic seizures). The following sub-sections present details of my contributions for these topics.

3.1 Assessment of Mental Stress

My research related to mental stress involves developing of methods and biomarkers for early detection of stress, predictions for treatment efficacy, and classification of the four levels of stress (mild, moderate, severe, very severe) [22, 23, 24, 25].

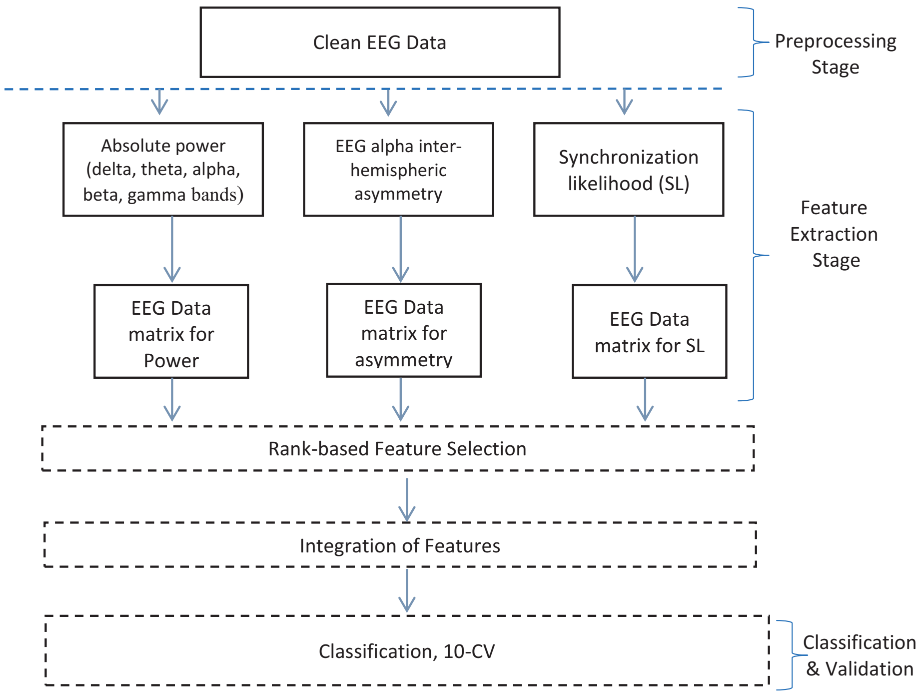
The early detection of mental stress is critical for efficient clinical treatment. As compared with traditional approaches, the automatic methods presented in literature have shown significance and effectiveness in terms of diagnosis speed. Unfortunately, the majority of them mainly focus on accuracy rather than predictions for treatment efficacy. This may result in the development of methods that are less robust and accurate, which is unsuitable for clinical purposes. In our study, we proposed a comprehensive framework for the early detection of mental stress by analyzing variations in both electroencephalogram (EEG) and electrocardiogram (ECG) signals from 22 male subjects (mean age: 22.54 ± 1.53 years). The significant contribution of this study was that the presented framework was capable of performing predictions for treatment efficacy, which was achieved by defining four stress levels and creating models for the individual level. The features that were used included relative power, relative power ratios (like delta/theta etc.), coherence, phase lag, amplitude asymmetry, heart rate, and heart rate variability. Feature reduction was performed by principal component analysis (PCA). The following table [24] shows the features before and after application of PCA.

Features	Number of features at each level before paired t-test	Number of selected features after paired t-test			
		Level 1	Level 2	Level 3	Level 4
Relative power	95	5	8	12	20
Relative power ratio	114	14	24	33	62
Coherence	256	12	43	55	47
Phase lag	256	5	12	23	18
Amplitude asymmetry	256	5	13	21	18
HR and HRV	7	1	1	1	1
Total Variables	984	42	101	145	166
Variables after applying PCA		18	23	26	26

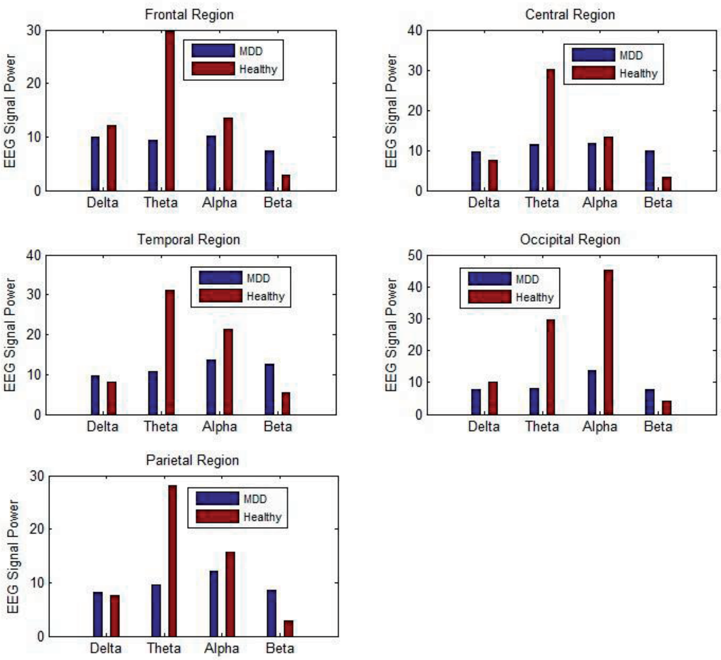
The experimental results from SVM classifier indicated that the framework has realized an accuracy, a sensitivity, and a specificity of 79.54%, 81%, and 78%, respectively for classification of four levels of stress. Moreover, the results indicated significant neurophysiological differences between the stress and control (stress-free) conditions at the individual level.

3.2 Diagnosis of Major Depressive Disorder (MDD)

Major Depressive Disorder (MDD), a leading cause of functional disability worldwide, is a mental illness and commonly known as unipolar depression. The clinical management of MDD patients has been challenging that includes an early *diagnosis* and antidepressant's *treatment selection*. This subsection deals with the diagnosis of MDD patients. In our study [14, 26, 27, 28], our hypothesis was that the MDD patients and healthy controls could be discriminated based on integrating the EEG band powers, alpha asymmetry and synchronization likelihood (the EEG measure to quantify the brain functional connectivity). The proposed method for MDD diagnosis included a general machine learning (ML) framework for EEG feature extraction, the selection of most noteworthy features that could give high-performance classification models. The proposed method was validated with EEG data involving 34 MDD patients (medication-free) with a confirmed diagnosis of depression and a group of 30 age-matched healthy controls. In addition, the proposed method was validated with 10-fold cross validation (10-CV). Consequently, the EEG features selected for diagnosis included the power of various frequency bands, alpha interhemispheric asymmetry, and synchronization likelihood which were extracted from the frontal and temporal regions. The following figure [14] shows the block diagram of the proposed method.



These features were found significant for the MDD diagnosis and an example of power-based features is shown in the figure [14, 27] below. It can be seen that the difference in power in theta bands is obvious between the MDD patients and controls.

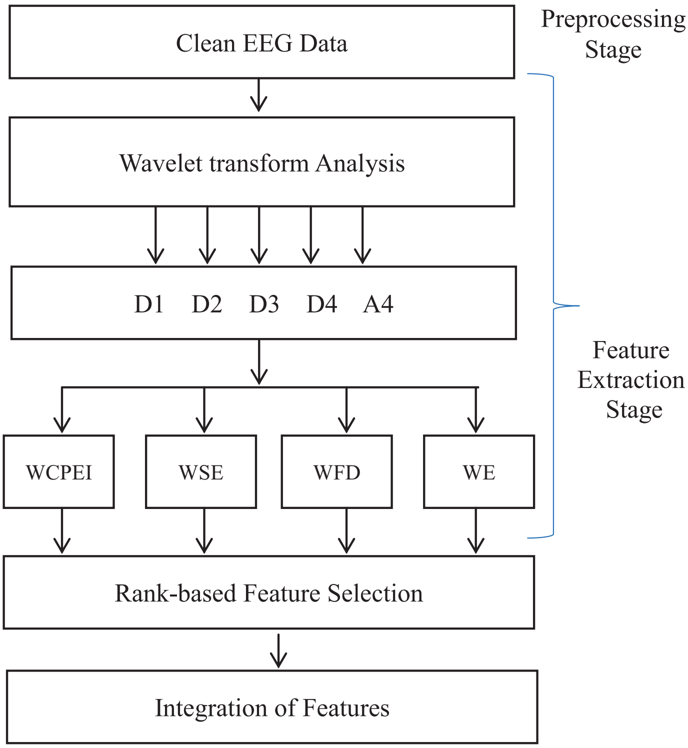


The proposed method with SVM classifier exhibited diagnosis accuracy=98.8%, sensitivity=98.6%, specificity=99.4%, and F1-score=0.98. Comparison was made with other methods and the proposed method showed better performance as shown in the table [14] below.

Method	Accuracy	Sensitivity	Specificity	F-measure
Delta Power	84.5	82	87.4	81.4
Theta Power	87.5	88.6	87	85.6
Alpha Power	95.1	96.6	94.3	94.4
Beta Power	90.1	90.3	92.4	89.7
Alpha Asymmetry	97.1	97	98	96.2
Synchronization Likelihood (SL)	94.38	97	92.4	92.1
Proposed Method	**98.8**	**98.6**	**99.4**	**98.3**

3.3 Treatment Efficacy for Major Depressive Disorder (MDD)

In continuation from the previous subsection, this one provides details of our research related to antidepressant's treatment selection. In our study [14, 29, 30], our hypothesis was that the integration of the time and frequency information involving wavelet transform (WT) analysis and EEG signal complexity measures (composite permutation entropy index, sample entropy, and fractal dimension) could discriminate the antidepressants treatment response and non-response. The proposed method can classify during antidepressant's treatment selection such as classifying MDD patients as either respondents or non-respondents to treatment with selective serotonin re-uptake inhibitors (SSRIs): Escitalopram (E), Fluvoxamine (F), Sertraline (S), Fluoxetine (Fl). Consequently, the EEG features selected for treatment selection included wavelet-based signal energy, wavelet-based sample entropy, wavelet-based fractal dimension, and wavelet-based composite permutation entropy index which were extracted from the frontal and temporal regions. The following figure [14] shows the block diagram of the proposed method. After the integration of the features, next step was classification and validation. In the figure, D1 to D4 are detail components of the wavelet for the 4 levels of decomposition, A4 is the approximate component of the wavelet for the 4th level of decomposition, WCPEI is Wavelet-based Composite Permutation Entropy Index, WSE is Wavelet-based Sample Entropy, WFD is Wavelet-based Fractal Dimension, and WE is Wavelet-based signal energy.



These features were found significant for the antidepressant's treatment selection and the proposed SVM method predicted the treatment outcome with an accuracy=89.1%, sensitivity=91%, specificity=88.7%, and F1-score=0.90. Comparison was made with other methods and the proposed method showed better performance as shown in the table [14] below.

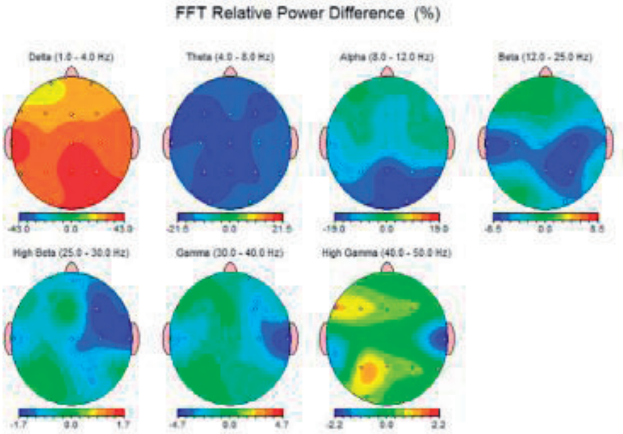
Method	Accuracy	Sensitivity	Specificity
Alpha Power	62.2%	64.7%	60%
Theta Power	58.71%	64.7%	52.14%
Alpha Asymmetry	65%	62.38%	68.5%
ATR Index	61.68%	70%	54%
Theta Cordance	70.7%	75.7%	65.7%
Coherence	76.3%	81.9%	69.5%
P300 Intensities	74.16%	70%	75%
Proposed Method	**89.1%**	**91%**	**88.7%**

3.4 Classification of Alcohol Use Disorder (AUD) Patients

Screening alcohol use disorder (AUD) patients has been challenging due to the subjectivity involved in the process. Hence, robust and objective methods are needed to automate the screening of AUD patients. In our study [31, 32, 33, 34, 35], a machine learning method was proposed that utilized resting-state electroencephalography (EEG)-derived features as input data to classify the AUD patients and healthy controls and to perform automatic screening of AUD patients. In this context, the EEG data were recorded during 5 minutes of eyes closed and 5 minutes of eyes open conditions. For this purpose, 30 AUD patients and 15 aged-matched healthy controls were recruited. After preprocessing the EEG data, EEG features such as inter-hemispheric coherences and spectral power for EEG delta, theta, alpha, beta and gamma bands were computed involving 19 scalp locations according to 10-20 system. The selection of most discriminant features was performed with a rank-based feature selection method assigning a weight value to each feature according to a criterion, i.e., receiver operating characteristics curve. For example, a feature with large weight was considered more relevant to the target labels than a feature with less weight. Therefore, a reduced set of most discriminant features was identified and further was utilized during classification of AUD patients and healthy controls.

As for the results, the inter-hemispheric coherences between the brain regions were found significantly different between the study groups and provided high classification efficiency (accuracy = 80.8, sensitivity = 82.5, and specificity = 80, F-Measure = 0.78). In addition, the power computed in different EEG bands were found significant and provided an overall classification efficiency as accuracy = 86.6, sensitivity = 95, specificity = 82.5, and F-Measure = 0.88. Further, the integration of these EEG feature resulted into even better results (accuracy = 89.3 %, sensitivity = 88.5 %, specificity = 91 %, and F-Measure = 0.90). Based on the results, it was concluded that the EEG data (integration of the theta, beta, and gamma power and inter-hemispheric coherence) could be utilized as objective biomarkers to screen the AUD patients and healthy controls.

AUD can further be categorized in to two classes, that is alcohol abuse and alcohol dependent (also called alcoholics). We found that relative power can be used as a biomarker for classification between the two classes of AUD. Figure [34] below shows the difference in relative power between alcohol abusers and alcoholics. It can be seen from the figure that there appears to be observable differences between the two classes in various frequency bands.



The t-test confirms that features extracted using relative power are significant in delta, theta, alpha and beta bands. The table [34] below shows the t-test results. In the table, EC is Eyes Closed condition, EO is Eyes Open condition, AP is Absolute Power, RP is Relative Power, and the entries in the table indicate the electrodes location (for example O1 is from left occipital region).

Selected features using T-test between alcoholics and alcohol abusers ($p < 0.01$).

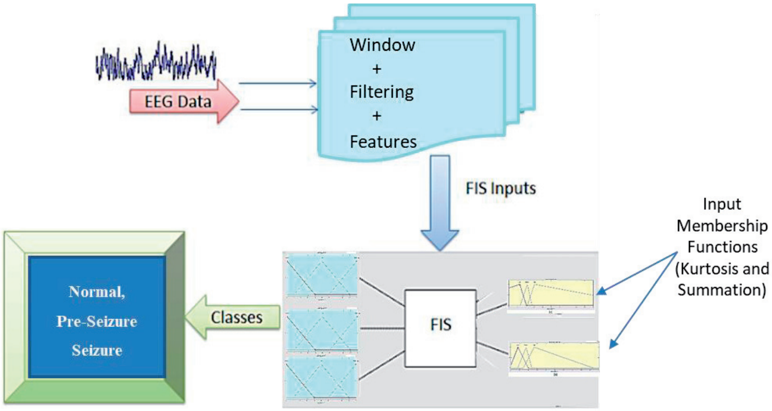
Band	EC AP	EC RP	EO AP	EO RP
Delta	FP1, FP2, C3, P3, O2, T3, T4	All regions	P4, O2, T3, T4, T6, Cz, Pz	FP2, F3, F4, C3, C4, P3, P4, O1, O2, F7, F8, T3, T4, T5, T6, Fz,, Cz, Pz
Theta	–	F3, F4, O1, F7, Fz, Cz	–	F3, O1, O2, Fz, Cz, Pz
Alpha	–	P4, O2, T3, Pz	–	F3, C3, C4, P3, P4, O2, F7, T3, T6, Fz, Pz
Beta	–	P4, Pz	–	C4, P4, Pz
High Beta	–	–	–	–
Gamma	–	–	–	–
High Gamma	–	–	–	–

–: No feature is selected (left blank)

Using the relative power features, Logistic Model Tree (LMT) classifier was used for the classification of the two classes of AUD, that is, alcohol abusers and alcoholics. The classification results were 93% accuracy, 94% sensitivity, 92% specificity, and F-score of 0.94.

3.5 Prediction of Partial Epileptic Seizure

Epilepsy, a diverse set of chronic mental disorders, has been characterized by spontaneous and recurrent epileptic seizures. The epileptic seizures could occur any time during daily activities that could cause convulsions or loss of consciousness. Therefore, an epileptic seizure may become a potential hazard for epileptic patients and his/her surroundings. The epileptic seizures need to be controlled immediately through medication and by adopting an effective strategy to predict well-before the occurrence of the epileptic seizures. Hence, the knowledge about occurrence of an epileptic seizure may help the patients and doctors to take necessary actions. In our study [36, 37, 38, 47], we considered partial epileptic seizure for the development of the prediction method for the seizure. We proposed an algorithm to detect the early occurrence of epileptic partial pre-seizures in a cost-effective, embedded, wearable system. The algorithm was designed using Fuzzy Inference System based classification technique with Kurtosis and Summation as the input feature. These features further were fed to a classification model that can distinguish normal, pre-seizure and seizure signals. Centered on the Fuzzy Inference System, three 'rules' were developed by using the degree of membership, for which logic high or low was performed for a specific type of input feature, and produced a result that was either normal, pre-seizure or seizure. The figure [47] below shows the block diagram of the proposed model.



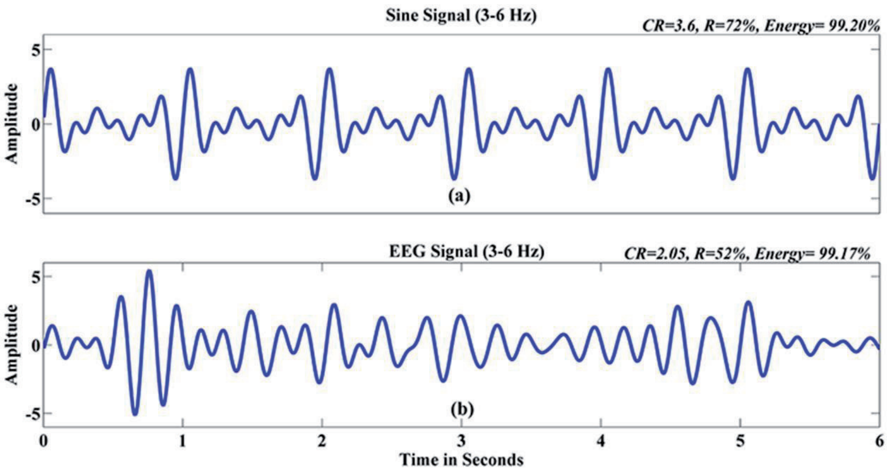
The algorithm was optimized for an individual based on their pre-existing EEG data. This embedded system fuzzy classifier yielded results of 93.47% accuracy of correct recognition of pre-seizure state from the EEG dataset with a pre-seizure detection latency of 30 seconds in duration, specificity of 93%, and sensitivity of 93.9%.

4 Targeting non-clinical applications

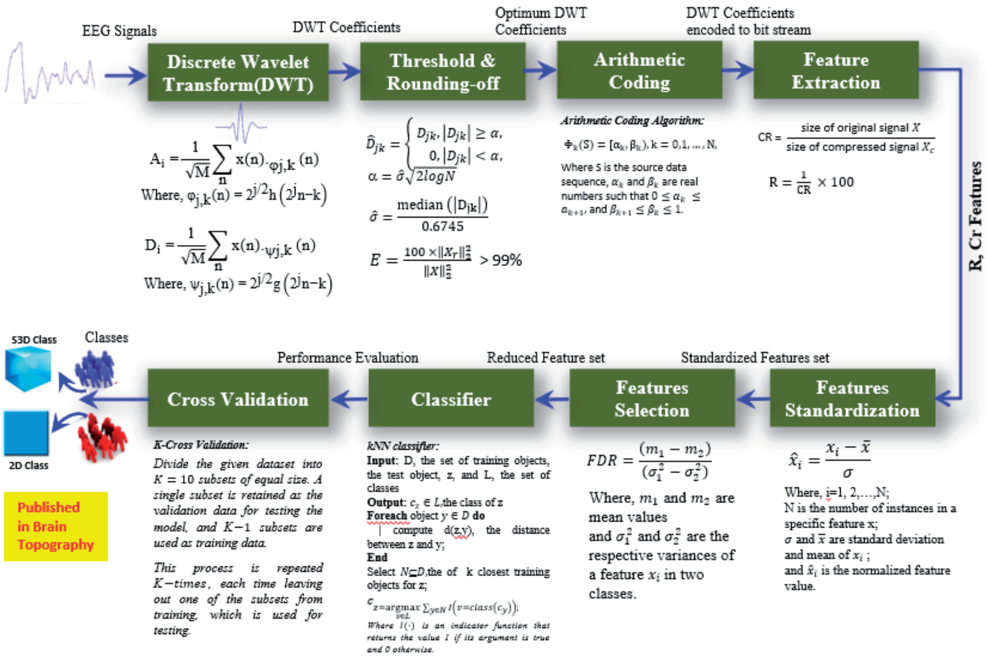
This chapter summarizes my EEG related research for non-clinical applications including learning, memory, cognitive load, and emotions. The following sub-sections present details of my contributions to these topics.

4.1 Proposing a New Biomarker [39, 46]

In signal processing, a completely periodic signal repeats itself with a constant period and can be mathematically defined, such as sin(x). However, in case of EEG signal, it is not completely periodic like sin(x), but there is some periodicity. Such periodicity can introduce redundancy in the information. In our study [39], we proposed a new EEG based feature and consequently a biomarker based on the redundant information of the EEG signals. The figure [39, 46] below shows that while a periodic sine signal in the range 3 to 6 hz has 72% redundant information, an EEG signal in the same range (for a specific subject in eyes closed condition) can have 52% redundant information.



The information redundancy of EEG signals and the brain neuronal processing are related. It is obvious that the EEG signals recorded over the scalp are dependent on whatever neural process is occurring inside the brain and reflecting directly the electrical activity of the neuronal communications. Our hypothesis was that if the active neuronal networks of the brain during certain task fire with constant rate over time, for example EEG in resting state eyes closed condition, then there will be fewer fluctuations in the electrical potential, resulting in high periodic information in the EEG signal. However, if the active neuronal networks of the brain during certain task firing with rapid changes over time, for example EEG in problem solving task, then there will be high fluctuations in the electrical potential, which lead to very low periodicity of EEG signal. It can be interpreted as when an individual is feeling relaxed during certain situation or the brain is not involved in complex processing such as cognition, the recorded EEG signal will have high amount of redundant information; reverse of such situation will lead to very minimum redundant information in the EEG signal, because the brain will be involved in complex processing and many brain regions will be coordinating with each other to perform a particular task. The details of the proposed biomarker are shown in figure [39, 46] below.

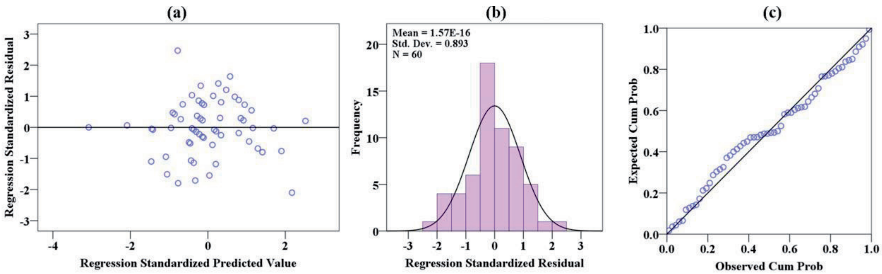


We tested this biomarker with three different datasets, the results of which are shown in the table below. The table [39, 46] shows the accuracy comparison and it can be seen that the proposed method outperforms all other methods. The sensitivity, specificity and F-Score computations also provided superior performance for our method.

Feature Methods	Dataset-1 Memory Recall vs. EO	Dataset-2 Intelligence Test vs. EO	Dataset-3 S3D vs. 2D
Proposed Method	96.07	95.58	90.45
Delta Power	94.67	91.17	69.34
Theta Power	92.85	80.88	71.28
Alpha Power	89.1	67.64	69.29
Beta Power	87.35	73.52	69.78
Gamma Power	87.48	67.64	67.35
ApEn	68.75	87.5	53.46
SamEn	86.75	83.82	53.68
CPEI	68.5	75	60.81
Hjorth Complexity	73.5	75	65.51
Fractal Dimension	75	58.82	61.76

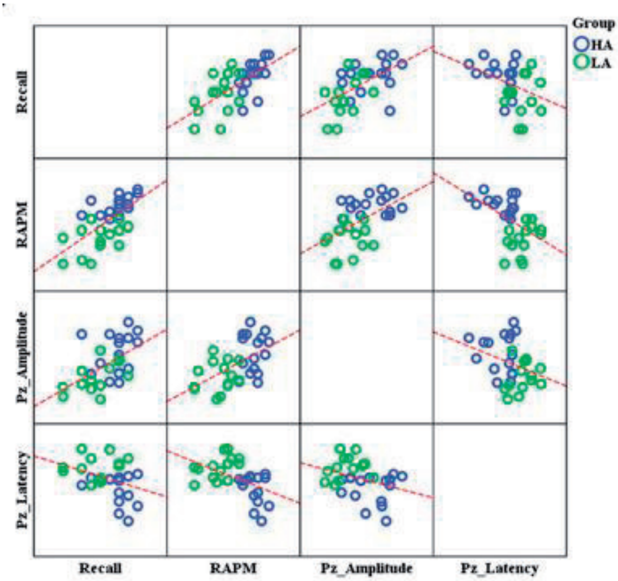
4.2 Long Term Memory Assessment [40]

Long-term memory (LTM) assessment is a challenging task to both the educationists and clinicians. The existing assessment tools are based on subjective assessment or manual cognitive tests, which requires a population norm and services of expert psychologists. Presently, there is no quantitative tool for LTM assessment. Hence, a quantitative measurement and grading tool for LTM remains an elusive goal for educationists, clinicians and even psychologists. Therefore, to address these issues, our study [40, 46] proposed an electroencephalogram (EEG) based quantitative assessment scheme for LTM assessment. A sample of 68 healthy young adults (age range: 23.66±3.63 years) was recruited for this study. In the first session, the participants were tested for LTM immediately after thirty minutes of learning task; while in the last three sessions, the retention duration was two months long. Our proposed method for LTM assessment was based on resting state EEG and event-related potentials (ERPs) features. First, a network of resting state eyes open EEG, based on absolute phase delay measure, was identified in twelve pairs of electrodes (Fp2-F7, Fz-C4, T3-Pz, T5-P4, T6-T4, Fp2-P3, F7-F4, C3-O1, Fp2-P3, F3-C3, F7-C3 and T3-O2) across theta, alpha and gamma frequency bands correlated with the LTM score. The absolute phase delay values of theta, alpha and gamma in the identified pairs of electrodes were used as an input to multiple linear regression (MLR) model that successfully predicted the LTM score. The prediction results of MLR model for LTM after 30 minutes retention were, $F(12,51)=4.421$, $p\text{-value}<0.0001$, $R=0.714$, $R2=0.510$, and for LTM after 2 months retention was, $F(12, 47)=4.994$, $p\text{-value} <0.0001$, $R=0.749$, $R2=0.560$. In conclusion, it was experimentally proved that resting state EEG network in theta, alpha and gamma bands, and P300 component at Pz site can be used to assess one's LTM ability quantitatively. The figure [46] below shows the (a) scatter plot of regression standardized residual against the regression standardized predicted values of memory recall, (b) the normal distribution of residual, and (c) normal P-P plot of regression standardized residual.



4.3 P300 and Fluid Intelligence [41]

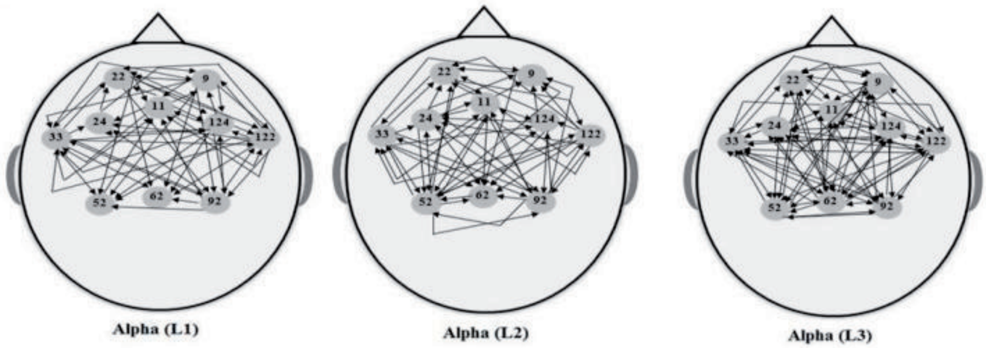
Educational psychology research has linked fluid intelligence with learning and memory abilities and neuroimaging studies have specifically associated fluid intelligence with event related potentials (ERPs). The objective of our study [41] was to find the relationship of ERPs with learning and memory recall and predict the memory recall score using P300 (P3) component. A sample of 34 healthy subjects between twenty and thirty years of age was selected to perform three tasks: (1) Raven's Advanced Progressive Matrices (RAPM) test to assess fluid intelligence; (2) learning and memory task to assess learning ability and memory recall; and (3) the visual oddball task to assess brain-evoked potentials. These subjects were divided into High Ability (HA) and Low Ability (LA) groups based on their RAPM scores. A multiple regression analysis was used to predict the learning & memory recall and fluid intelligence using P3 amplitude and latency. Behavioral results demonstrated that the HA group learned and recalled 10.89 % more information than did the LA group. ERP results clearly showed that the P3 amplitude of the HA group was relatively larger than that observed in the LA group for both the central and parietal regions of the cerebrum; particularly during the 300–400 ms time window. In addition, a shorter latency for the P3 component was observed at Pz site for the HA group compared to the LA group. The figure [41] below shows the scatter plots representing the relationship of learning & memory (Recall), Cognitive Ability (RAPM), P3 Amplitude (APz), and P3 Latency (LPz). (Recall; RAPM:R2 = 0.427, Recall; APz:R2 = 0.307, Recall; LPz:R2 = 0.133, RAPM; APz:R2 = 0.291, RAPM; LPz:R2 = 0.245, APz;LPz: R2 = 0.107)



These findings agreed with previous educational psychology and neuroimaging studies which reported an association between ERPs and fluid intelligence as well as learning performance. Our results also suggested that the P3 component is associated with individual differences in learning and memory recall and further indicated that P3 amplitude might be used as a supporting factor in standard psychometric tests to assess an individual's learning & memory recall ability; particularly in educational institutions to aid in the predictability of academic skills.

4.4 Cognitive Load Assessment [42, 43]

Cognitive load or cognitive workload is the name given to the load on cognitive resources of the mind generated due to cognitive demand of the task. The cognitive or working memory load reflects task difficulty and the associated mental effort. Hence, assessing cognitive load during a learning phase is important, as it assists to understand the complexity of the learning task. It can help in balancing the cognitive load of post-learning and during the actual task. In our study [42, 43], we used electroencephalography (EEG) to assess cognitive load in multimedia learning task. EEG data were collected from 34 human participants at baseline and a multimedia learning state. The proposed method was based on feature extraction measures of partial directed coherence (PDC) which is an effective connectivity measure. The proposed method of cognitive load assessment using the effective connectivity was integrated with the graph theory network analysis. The partial directed coherence (PDC), a frequency domain technique of effective connectivity was used to generate the adjacency matrices of different mental sates. Later, the network analysis was done on the extracted adjacency matrices to generate the different performance metrics of the brain network. The extracted performance metrics were path length, clustering coefficient, global and local efficiency, degree distribution and network density. The analysis was performed on the extracted metrics to assess the cognitive load of different mental states. The figure [42] below shows the connectivity among EEG channels during learning (L1) and rehearsal states (L2, L3).



Results revealed that the EEG frequency bands and activated brain regions that contribute to cognitive load differed depending on the learning state. We concluded that cognitive load during multimedia learning can be assessed using feature extraction measures of effective connectivity (PDC). The results further showed that the proposed method not only assessed the cognitive load but it also provided the details of the information flow from one area of the brain to another one during the cognitive task.

4.5 Influence of Color on Emotion and Memory [44, 45]

Color is a perceptual stimulus that has a significant impact on improving human emotion and memory. Studies have revealed that colored multimedia learning materials (MLMs) have a positive effect on learner's emotion and learning where it was assessed by subjective measurements. In our study [45], we aimed to quantitatively assess the influence of colored MLMs on emotion, cognitive processes during learning, and long-term memory (LTM) retention using electroencephalography (EEG). The dataset consisted of 45 healthy participants, and MLMs were designed in colored or achromatic illustrations to elicit emotion and that to assess its impact on LTM retention after 30-min and 1-month delay. The EEG signal analysis was first done to estimate the effective connectivity network (ECN) using the phase slope index and then expanded to characterize the ECN pattern using graph theoretical analysis. EEG results showed that colored MLMs had influences on theta and alpha networks, including (1) an increased frontal-parietal connectivity (top–down processing), (2) a larger number of brain hubs, (3) a lower clustering coefficient, and (4) a higher local efficiency, indicating that color influences information processing in the brain, as reflected by ECN, together with a significant improvement in learner's emotion and memory performance. This was evidenced by a more positive emotional valence and higher recall accuracy for groups who learned with colored MLMs than that of achromatic MLMs. Our method demonstrated how the EEG ECN parameters could help quantify the influences of colored MLMs on emotion and cognitive processes during learning.

5 Conclusions and the Future

More than a billion people are affected by brain and mental health issues worldwide. Hence, the adequate treatment cannot be provided due to lack of clinical resources including the lack of trained clinicians who are specialists in this field. Therefore, in order to address this problem, the future of brain and mental health lies in the transformation of the current landscape of clinical practice, that is, shifting from treatment to preventive health paradigm. To support such a shift, the only neuroimaging modality available is electroencephalogram (EEG) due to its low cost, small size, high mobility, easy setup, high temporal resolution, direct measurement of brain activity, and affordability. Hence, the focus of this document is on data analytics and biomarker development using EEG for investigation of brain dynamics.

In this document, I have provided details of my EEG related research done over the last fifteen years. It covers both clinical and non-clinical applications. For clinical applications, my most significant research output has been related to Major Depressive Disorder (MDD) which resulted in a number of publications, a patent and a book. Algorithms and biomarkers were developed for both the diagnosis as well as the treatment efficacy of MDD. The next step of this research is to go for clinical trials with large sample size so that the proposed method can be implemented in clinical practice at the GP (General Practitioner/ Family Doctor) level. In addition to MDD, I have also developed algorithms for detection of 4 levels of mental stress, prediction of epileptic seizures, and classification of Alcohol Use Disorder (AUD) patients. Out of these topics, chronic mental stress can further result in anxiety, depression, cardiovascular issues etc. Hence, I have a strong conviction that mental stress is the most significant topic because addressing it early can result in significant improvements in quality of life. The future of brain and mental health lies in early detection of chronic mental stress and continuous monitoring of the associated cognitive skills.

For the non-clinical applications, I presented my research which included assessment of long-term memory, new EEG biomarker development, assessment of fluid intelligence and cognitive load, and delving into emotions and memory. All of my research has resulted in three books related to EEG, six EEG related patents, and a number of publications in well renowned journals and conferences. I was also successful in getting many grants related to EEG research.

Finally, I want to say a few words about my future directions for teaching and research. For teaching, I plan to offer courses related to neural engineering, neurocomputation, and neuroimaging. After joining FIT, I have already offered and executed a master course on brain computer interface (BCI) in winter semester of 2022 and a PhD course on neuroimaging in summer semester of 2023. My future plan is to continue developing further teaching courses in this field. Additionally, I plan to prepare courses for FIT summer school as well as support the establishment of a BCI student club. I further plan to strengthen my network through both local and international collaborations which can be useful for both teaching and research activities. As for the research component, my focus will be on EEG research for early detection of mental stress, monitoring of cognitive skills, and new brain computer interfaces. Last but not the least, I want to start clinical trials for the diagnosis of major depressive disorder (MDD) which can lead to commercialization of a MDD Diagnosis Device.

References

[1] WHO (Accessed: 2023, Apr. 20). *Mental Disorders* [Online]. Available: https://www.who.int/news-room/fact-sheets/detail/mental-disorders

[2] E. R. Walker, R. E. McGee, B. G. Druss, “Mortality in mental disorders and global disease burden implications: a systematic review and meta-analysis,” *JAMA Psychiatry*, vol. 72, no. 4, pp. 334-341, 2015.

[3] P. E. Greenberg, et al., “The economic burden of adults with major depressive disorder in the United States (2010 and 2018),” *Pharmacoeconomics*, vol. 39, no. 6, pp. 653-665, 2021.

[4] D. F. Santomauro, et al., “Global prevalence and burden of depressive and anxiety disorders in 204 countries and territories in 2020 due to the COVID-19 pandemic,” *The Lancet*, vol. 398, no. 10312, pp. 1700–1712, 2021.

[5] WEF (Accessed: 20 April 2023). *This is the world’s biggest mental health problem - and you might not have heard of it* [Online]. Available: https://www.weforum.org/agenda/2019/01/this-is-the-worlds-biggest-mental-health-problem/

[6] H. Davis, P. A. Davis, A. L. Loomis, E. N. Harvey, G. Hobart, “Electrical reactions of the human brain to auditory stimulation during sleep,” *Journal of Neurophysiology*, vol. 2, pp. 500-514, 1939.

[7] S. Tong and N. V. Thakor, *Quantitative EEG analysis methods and clinical applications*, 1st ed. New York: Artech House, 2009.

[8] H. Alhaj, G. Wisniewski, R. H. McAllister-Williams, "The use of the EEG in measuring therapeutic drug action: focus on depression and antidepressants," *Journal of Psychopharmacology*, vol. 25, pp. 1175-1191, 2011.

[9] E. Vandoolaeghe, F. van Hunsel, D. Nuyten, M. Maes, "Auditory event related potentials in major depression: prolonged P300 latency and increased P200 amplitude," *Journal of Affective Disorders*, vol. 48, pp. 105-113, 1998.

[10] T. Rosburg, N. N. Boutros, J. M. Ford, "Reduced auditory evoked potential component N100 in schizophrenia — A critical review," *Psychiatry Research*, vol. 161, pp. 259-274, 2008.

[11] S. H. Patel, P. N. Azzam, "Characterization of N200 and P300: Selected Studies of the Event-Related Potential," *International Journal of Medical Sciences*, vol. 2, pp. 147-154, 2005.

[12] S. Cohen, M. L. Murphy, A. A. Prather, "Ten surprising facts about stressful life events and disease risk," *Annual review of Psychology*, vol. 70, pp. 577-597, 2019.

[13] S. Lotfan, S. Shahyad, R. Khosrowabadi, A. Mohammadi, B. Hatef, "Support vector machine classification of brain states exposed to social stress test using EEG-based brain network measures," *Biocybernetics and Biomedical Engineering*, vol. 39, no. 1, pp. 199-213, 2019.

[14] A. S. Malik and W. Mumtaz, EEG-based experiment design for major depressive disorder: machine learning and psychiatric diagnosis, 1st ed. London: Academic Press, 2019.

[15] K. Lorenz, I. Rejer, “Feature selection with NSGA and GAAM in EEG signals domain,” in *8th International Conference on Human System Interaction (HSI)*, Warsaw, Poland, 2015, pp. 94–98.

[16] M. C. Guerrero, J. S. Parada, H. E. Espitia, “EEG signal analysis using classification techniques: Logistic regression, artificial neural networks, support vector machines, and convolutional neural networks,” *Heliyon*, vol. 7, no. 6, pp. e07258, 2021.

[17] C. Uyulan, T. T. Ergüzel, et al., “Major Depressive Disorder Classification Based on Different Convolutional Neural Network Models: Deep Learning Approach,” *Clinical EEG and Neuroscience*, vol. 52, no. 1, pp. 38–51, 2021.

[18] A. A. Ezzi, N. Yahya, N. Kamel, I. Faye, K. Alsaih, et al., “Severity Assessment of Social Anxiety Disorder Using Deep Learning Models on Brain Effective Connectivity,” *IEEE Access*, vol. 9, pp. 86899–86913, 2021.

[19] K. Singh, J. Malhotra, “Two-layer LSTM network-based prediction of epileptic seizures using EEG spectral features,” *Complex and Intelligent Systems*, vol. 8, pp. 2405–2418, 2022.

[20] S. Thepsatitporn, C. Pichitpornchai, "Visual event-related potential studies supporting the validity of VARK learning styles' visual and read/write learners," *Advances in Physiology Education*, vol. 40, no. 2, pp. 206-212, 2016.

[21] E. Kim, I. Yang, S. Lim, "An EEG Study on Visual Learners’ Performance a Scientific Classifying Task Composed of Pictures and Words," *Education*, pp. 86-91, 2015.

[22] A. R. Subhani, L. Xia, A. S. Malik and Z. Othman, "Quantification of physiological disparities and task performance in stress and control conditions," *2013 35th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC)*, Osaka, Japan, 2013, pp. 2060-2063.

[23] A. R. Subhani, W. Mumtaz, M. N. M. Saad, N. Kamel, A. S. Malik, "Machine Learning Framework for the Detection of Mental Stress at Multiple Levels," *IEEE Access*, vol. 5, pp. 13545-13556, 2017.

[24] L. Xia, A. S. Malik, A. R. Subhani, “A physiological signal-based method for early mental-stress detection,” *Biomedical Signal Processing and Control*, vol. 46, pp. 18-32, 2018.

[25] F. A. Hamid, M. N. M. Saad, A. S. Malik, “Characterization stress reactions to stroop color-word test using spectral analysis,” *Materials Today Proceedings*, vol. 16, pp. 1949-1958, 2019.

[26] W. Mumtaz, A. S. Malik, S. S. A. Ali, M. A. M. Yasin, H. Amin. "Detrended fluctuation analysis for major depressive disorder," in *2013 37th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC)*, milan, Italy, pp. 4162-4165, 2015.

[27] W. Mumtaz, L. Xia, S. S. A. Ali, M. A. M. Yasin, M. Hussain, A. S. Malik, "Electroencephalogram (EEG)-based computer-aided technique to diagnose major depressive disorder (MDD)," *Biomedical Signal Processing and Control*, vol. 31, pp. 108-115, 2017.

[28] W. Mumtaz, A. S. Malik, “A Comparative Study of Different EEG Reference Choices for Diagnosing Unipolar Depression,” *Brain Topography*, vol. 31, pp. 875–885, 2018.

[29] W. Mumtaz, A. S. Malik, M. Azhar, L. Xia, “Review on EEG and ERP predictive biomarkers for major depressive disorder,” *Biomedical Signal Processing and Control*, vol. 22, no. 2, pp. 85-98, 2015.

[30] W. Mumtaz, L. Xia, M. A. M. Yasin, S. S. A. Ali, A. S. Malik, "A wavelet-based technique to predict treatment outcome for Major Depressive Disorder," *PloS ONE*, vol. 12, no. 2, pp. e0171409, 2017.

[31] W. Mumtaz, P. L. Vuong, A. S. Malik, R. A. Rashid, “A review on EEG-based methods for screening and diagnosing alcohol use disorder,” *Cognitive Neurodynamics*, vol. 12, pp. 141–156, 2018.

[32] W. Mumtaz, M. N. M. Saad, N. Kamel, S. S. A. Ali, A. S. Malik, “An EEG-based functional connectivity measure for automatic detection of alcohol use disorder,” *Artificial Intelligence in Medicine*, vol. 84, pp. 79-89, 2018.

[33] W. Mumtaz, P. L. Vuong, L. Xia, A. S. Malik, R. A. Rashid, "An EEG-based machine learning method to screen alcohol use disorder," *Cognitive Neurodynamics*, vol. 11, no. 2, pp. 161-171, 2017.

[34] W. Mumtaz, P. L. Vuong, L. Xia, A. S. Malik, R. A. Rashid, "Automatic diagnosis of alcohol use disorder using EEG features," *Knowledge-Based Systems*, vol. 105, pp. 48-59, 2016.

[35] S. Jawed, A. S. Malik, “Deep learning-based diagnosis of alcohol use disorder (AUD) using EEG,” in *IEEE 12th International Conference on Consumer Electronics (ICCE-Berlin)*, Berlin, Germany, 2022, pp. 1-5.

[36] A. Shahid, M. A. Jatoi, N. Kamel, A. S. Malik, J. M. Abdullah, “Singular Value Decomposition (SVD) as a Detector of Epileptic Seizures in EEG Signals,” in *ICME International Conference on Complex Medical Engineering*, Beijing, China, 2013, pp. 652-655.

[37] M. Shakir, A. S. Malik, N. Kamel, U. Qidwai, "Rule-Base Wearable Embedded Platform for Seizure Detection from Real EEG Data in Ambulatory State," *IEEE REGION 10 SYMPOSIUM*, Kuala Lumpur, Malaysia, 2014, pp. 45-49.

[38] M. Shakir, U. Qidwai , A. S. Malik, N. Kamel, “Electroencephalography Simulation Hardware for Realistic Seizure, Preseizure and Normal Mode Signal Generation,” *Journal of Medical Imaging and Health Informatics*, vol. 5, no. 1, pp. 43-49, 2015.

[39] H. Amin, A. S. Malik, N. Kamel, M. Hussain, "A novel approach based on data redundancy for feature extraction of EEG signals," *Brain Topography*, vol. 29, no. 2, pp. 207-217, 2016.

[40] S. Hanouneh, H. Amin, M. N. M. Saad, A. S. Malik, “EEG power and functional connectivity correlates with semantic long-term memory retrieval,” *IEEE Access*, vol. 6, pp. 8695-8703, 2018.

[41] H. Amin, A. S. Malik, N. Kamel, W. T. Choi, M. Hussain, “P300 correlates with learning & memory abilities and fluid intelligence,” *Journal of NeuroEngineering and Rehabilitation*, vol. 12, no. 87, pp. 77, 2015.

[42] M. Mazher, A. Abd Aziz, A. S. Malik, H. Ullah Amin, "An EEG-Based Cognitive Load Assessment in Multimedia Learning Using Feature Extraction and Partial Directed Coherence," *IEEE Access*, vol. 5, pp. 14819-14829, 2017.

[43] M. Mazher, I. Faye, A. Qayyum, A. S. Malik, "Classification of Resting and Cognitive States using EEG-based Feature Extraction and Connectivity Approach," in *IEEE-EMBS Conference on Biomedical Engineering and Sciences (IECBES)*, Sarawak, Malaysia, 2018, pp. 184-188.

[44] M. T. Chai, H. Amin, M. N. M. Saad, A. S. Malik, "The influences of emotion on learning and memory," *Frontiers in Psychology*, vol. 8, pp. 1454, 2017.

[45] M. T. Chai, H. Amin, L. I. Izhar, M. N. M. Saad, M. A. Rahman, A. S. Malik, T. B. Tang, “Exploring EEG effective connectivity network in estimating influence of color on emotion and memory,” *Frontiers in Neuroinformatics*, vol. 13, pp. 66, 2019.

[46] H. Amin, “Long-term memory: Assessment and effects of stereoscopic 3D educational contents using EEG”, Ph.D. dissertation, Dept. of Electrical & Electronic Eng., Universiti Teknologi Petronas, Malaysia, 2017.

[47] M. Shakir, “Early detection of pre-seizure using electroencephalography for wearable embedded system,“ Ph.D. dissertation, Dept. of Electrical & Electronic Eng., Universiti Teknologi Petronas, Malaysia, 2018.

Abstract

The focus of this document is on one neuroimaging modality which is electroencephalogram (EEG). The main reason for this selection is that EEG is the only modality (with current technological advancements) that can be employed in frontend clinical practice (general practitioner/ family doctor) as well as by the end user (at home) for direct measurement of brain dynamics leading to assessment and early detection of brain and mental health issues. The various methods and results presented in this document show the promise of EEG being employed in future for the diagnosis and prognosis of various conditions like mental stress, depression, addiction, and epilepsy etc. The reported results in the literature are very encouraging with high accuracy, sensitivity and specificity (many reaching 90% and above) which are acceptable for a clinical application. The next step is to go for clinical trials with large sample size for the implementation of these methods in clinical practice.

In addition to clinical applications, this document also highlights the promise of employing EEG for non-clinical applications like assessment of long-term memory, and cognitive load measurement. Both of these topics are significant in educational setups. The implementation of long-term memory assessment and cognitive load measurement can lead to personalized learning, that is, the teaching methods and contents can be optimized for an individual. Again, what is required is the validation of the proposed methods through a large sample size that can lead to commercialized products for their implementation in the educational settings.

Abstrakt

Tento dokument se zaměřuje na jednu neurozobrazovací modalitu, kterou je elektroencefalogram (EEG). Hlavním důvodem pro tento výběr je, že EEG je jedinou modalitou (se současným technologickým pokrokem), kterou lze použít ve frontendové klinické praxi (praktický/rodinný lékař) i koncovým uživatelem (doma) pro přímé měření mozku. dynamika vedoucí k posouzení a včasné detekci problémů mozku a duševního zdraví. Různé metody a výsledky uvedené v tomto dokumentu ukazují příslib využití EEG v budoucnu pro diagnostiku a prognózu různých stavů, jako je duševní stres, deprese, závislost a epilepsie atd. Výsledky uváděné v literatuře jsou velmi povzbudivé s vysokou přesností senzitivitu a specificitu (mnoho z nich dosahuje 90 % a více), které jsou přijatelné pro klinickou aplikaci. Dalším krokem je jít do klinických studií s velkým vzorkem pro implementaci těchto metod do klinické praxe.

Kromě klinických aplikací tento dokument také zdůrazňuje příslib využití EEG pro neklinické aplikace, jako je hodnocení dlouhodobé paměti a měření kognitivní zátěže. Obě tato témata jsou významná ve vzdělávacích systémech. Implementace hodnocení dlouhodobé paměti a měření kognitivní zátěže může vést k personalizovanému učení, to znamená, že metody a obsah výuky lze optimalizovat pro jednotlivce. Opět je potřeba ověřit navržené metody prostřednictvím velkého vzorku, což může vést ke komercializovaným produktům pro jejich implementaci ve vzdělávacím prostředí.