Faculty of Electronic and Computer Engineering

OBJECTIVE QUANTIFICATION OF SELECTIVE ATTENTION IN SCHIZOPHRENIA: A HYBRID TMS – EEG APPROACH

Wan Amirah Binti W Azlan

Master of Science in Electronic Engineering

2017

© Universiti Teknikal Malaysia Melaka

OBJECTIVE QUANTIFICATION OF SELECTIVE ATTENTION IN SCHIZOPHRENIA: A HYBRID TMS – EEG APPROACH

WAN AMIRAH BINTI W AZLAN

A thesis submitted
in fulfillment of the requirements for the degree of Master of Science
in Electronic Engineering

Faculty of Electronic and Computer Engineering

UNIVERSITI TEKNIKAL MALAYSIA MELAKA

2017

© Universiti Teknikal Malaysia Melaka

DECLARATION

I declare that this thesis entitle "Objective Quantification of Selective Attention in Schizophrenia: A Hybrid TMS – EEG Approach" is the result of my own research except as cited in the references. The thesis has not been accepted for any degree and is not concurrently submitted in candidature of any other degree.

Signature : _____

Name : WAN AMIRAH BINTI W AZLAN

Date : _____

© Universiti Teknikal Malaysia Melaka

APPROVAL

I hereby declare that I have read this thesis and in my opinion this thesis is sufficient in terms of scope and quality for the award of Master of Science in Electronic Engineering.

Signature : _____

Name : DR LOW YIN FEN

Date : _____

© Universiti Teknikal Malaysia Melaka

DEDICATION

To my beloved family

© Universiti Teknikal Malaysia Melaka

ABSTRACT

Schizophrenia is a brain disorder that exhibits effects on perception, way of thinking and behavior. Often, schizophrenia patients suffer from attention deficiency. Currently clinical interview is used to diagnose schizophrenia by doctors. There is no alternative way to diagnose schizophrenia in present. Thus, an objective approach by employing transcranial magnetic stimulation combined with electroencephalogram (TMS-EEG) is proposed. The aim of the study is to quantify objectively the neural correlate of selective attention that reflected in auditory late responses (ALRs) using signal processing techniques. TMS provides a means of stimulating neuronal structures within the cortex using brief time-varying magnetic pulses generated by a coil positioned over the scalp. Integrating it with electroencephalogram provides real-time information on cortical reactivity and connectivity through the analysis of TMS evoked potentials or induced oscillations. In this project, auditory oddball paradigm was used throughout the experiment. The experiment involved three sessions; 1) without TMS, 2) single pulse TMS (sTMS) and 3) repetitive TMS (rTMS). All sessions were conducted in attended (attention) and unattended (no attention) conditions. It is found that the amplitude of the grand averaged of ALR (the N1-P2 wave) is higher in control compared to schizophrenia in without TMS session at both conditions. However, the amplitude of ALR in schizophrenia subjects is higher than control subjects in sTMS and rTMS at both conditions. The attention level measure, i.e., the Wavelet Phase Stability (WPS) was used to extract and quantify the neural correlates of auditory selective attention reflected in ALRs. In particular, Complex Morlet was implemented (scales 50-100 corresponding to 4-8Hz). There are significant differences of the ALR between schizophrenia and control groups in without TMS ($p<0.05$) and sTMS at the attended condition (frontal electrodes). Meanwhile at the unattended condition, Significance difference is found between two groups of the subjects in without TMS but no significant difference in sTMS (frontal electrodes). Particularly, the WPS of controls are larger than schizophrenia patients for without TMS and sTMS at attended for frontal electrodes. These results were consistent for temporal electrodes. It is worth to note that the phase stability of ALR in single pulse TMS is lower than without TMS for controls during attended but showed reversed pattern in unattended. Besides, it is found that a large phase stability difference between without TMS and sTMS in schizophrenia (frontal and temporal electrodes) at unattended compared to attended. For control subjects, this difference is small at frontal and temporal electrodes in both conditions. In a further investigation, the C4.5 decision tree algorithm was implemented to classify the N1-P2 wave of control and schizophrenia subjects elicited by sTMS and rTMS. Four features (energy, power, variance and entropy) were extracted by continuous wavelet transform (CWT). The result shows high classification accuracy which is above 83% in all three sessions at both attended and unattended conditions. In conclusion, the combined TMS-EEG approach shows a promising way to study the selective attention in schizophrenia. By successfully quantifying the neural correlates of auditory selective attention reflected in ALRs using the WPS and discriminating the control and patient groups using C4.5 decision tree provides an objective way to diagnose schizophrenia in compliment to the current subjective method.

© Universiti Teknikal Malaysia Melaka

ABSTRAK

Skizofrenia adalah satu penyakit otak yang mempengaruhi cara berfikir dan tingkahlaku seseorang. Kebiasaannya, pesakit mengalami masalah tidak dapat menumpukan sepenuh perhatian terhadap sesuatu seperti bunyi. Teknik semasa yang digunakan untuk mengdiagnosis pesakit skizofrenia ialah melalui temubual. Oleh itu, kaedah objektif menggunakan TMS – EEG dicadangkan. Tujuan kajian ini adalah untuk mengkaji secara objektif hubungan neural pada selektif perhatian dalam ALR menggunakan teknik pemprosesan signal. TMS mengeluarkan daya magnetik di dalam kortex. Gabungan elektroencephalogram memberikan informasi dalam waktu yang sebenar. Kaedah auditory oddball digunakan dalam eksperimen. Eksperimen ini melibatkan tiga sesi iaitu; 1) tanpa TMS, 2) nadi tunggal TMS dan 3) pengulangan TMS. Semua sesi tersebut dijalankan dalam keadaan fokus dan tidak fokus. Amplitud keseluruhan ALR (N1-P2) lebih tinggi bagi normal subjek berbanding skizofrenia tanpa TMS sesi untuk kedua-dua keadaan. Tetapi, amplitud ALR bagi skizofrenia lebih tinggi berbanding subjek normal dalam nadi tunggal TMS dan pengulangan TMS bagi kedua-dua keadaan. Fasa Kestabilan Wavelet digunakan untuk mencari hubungan neural pada perhatian selektif auditori dalam ALR. Complex Morlet yang berskala 50-100 bersamaan dengan 4-8Hz telah digunakan. Terdapat perbezaan ALR antara skizofrenia dan normal subjek pada sesi tanpa TMS ($p<0.05$) dan nadi tunggal TMS bagi keadaan fokus (frontal elektrod). Terdapat perbezaan antara kedua-dua kumpulan pada sesi tanpa TMS tetapi tidak ada perbezaan pada nadi tunggal TMS (frontal elektrod) bagi keadaan tidak fokus. Fasa Kestabilan Wavelet bagi normal subjek adalah lebih besar daripada skizofrenia untuk tanpa TMS dan nadi tunggal TMS bagi keadaan fokus di frontal elektrod. Keputusan ini adalah selari dengan temporal elektrod. Fasa kestabilan ALR untuk nadi tunggal TMS adalah rendah berbanding tanpa TMS bagi normal subjek semasa fokus tetapi menunjukkan keputusan yang sebaliknya pada keadaan tidak fokus. Selain itu, terdapat perbezaan yang besar pada fasa kestabilan antara tanpa TMS dan nadi tunggal TMS bagi skizofrenia (frontal dan temporal elektrod) dalam keadaan tidak fokus berbanding fokus. Bagi normal subjek, perbezaan ini adalah kecil di frontal dan temporal elektrod dalam kedua-dua keadaan. C4.5 decision tree digunakan untuk mengelaskan N1-P2 dari normal subjek dan skizofrenia. Empat ciri (tenaga, kuasa, varian dan entropi) diperolehi dari ubahan wavelet berterusan. Keputusan menunjukkan klasifikasi ketepatan yang tinggi iaitu lebih daripada 83% untuk semua sesi bagi kedua-dua keadaan. Kesimpulannya, kaedah TMS-EEG dapat digunakan untuk mengkaji perhatian selektif auditori pada skizofrenia. Oleh itu, kaedah objektif untuk mendiagnosis skizofrenia mempunyai keupayaan sebagai alternatif kepada kaedah subjektif.

© Universiti Teknikal Malaysia Melaka

ACKNOWLEDGEMENTS

First and foremost, I would like to take this opportunity to express my sincere acknowledgement to my supervisor Dr. Low Yin Fen from the Faculty of Electronic and Computer Engineering Universiti Teknikal Malaysia Melaka (UTeM) for her essential supervision, support and encouragement towards the completion of this thesis.

I would also like to express my greatest gratitude to Dr. Choo Yun Huoy from Faculty of Information & Communication Technology and Dr Hazli Zakaria, co-supervisors from HUKM of this research for their advice and suggestions throughout the completion of the project. Special thanks to ERGS grant funding (ERGS/2013/FKEKK/TK02/UTEM/02/03 E00019) for the financial support throughout this project.

Particularly, I would also like to express my deepest gratitude to Mr. Ahmad Syafiq and other HUKM staffs from Psychiatric Department, HUKM for their assistance and efforts during the experiment and in recruiting the participants.

Special thanks to all my colleagues, my beloved mother and siblings for their moral support in completing this degree. Lastly, thank you to everyone who had been associated to the crucial parts of in this project.

© Universiti Teknikal Malaysia Melaka

TABLE OF CONTENTS

© Universiti Teknikal Malaysia Melaka

© Universiti Teknikal Malaysia Melaka

LIST OF TABLES

© Universiti Teknikal Malaysia Melaka

© Universiti Teknikal Malaysia Melaka

LIST OF FIGURES

© Universiti Teknikal Malaysia Melaka

© Universiti Teknikal Malaysia Melaka

LIST OF APPENDICES

© Universiti Teknikal Malaysia Melaka

LIST OF ABBREVIATION

ALR	-	Auditory Late Response
CWT	-	Continuous Wavelet Transform
EEG	-	Electroencephalogram
N1	-	N100
P2	-	P200
STMS	-	Single pulse Transcranial Magnetic Stimulation
RTMS	-	Repetitive Transcranial Magnetic Stimulation
TMS	-	Transcranial Magnetic Stimulation
WEKA	-	Waikato Environment for Knowledge Analysis
WPS	-	Wavelet Phase Stability

© Universiti Teknikal Malaysia Melaka

LIST OF PUBLICATIONS

The research papers produced and published during the course of this research are as follows:

1. **W Azlan, W.A.** and Low, Y.F., 2014. Feature Extraction of Electroencephalogram (EEG) Signal – A Review. In: *IEEE Conference on Biomedical Engineering and Sciences*. pp. 801-806.
2. **W Azlan, W.A.,** Liew, S-H., Choo, Y-H., Zakaria, H. and Low, Y.F., 2016. Wavelet feature extraction and J48 decision tree classification of auditory late response (ALR) elicited by transcranial magnetic stimulation. *ARPN Journal of Engineering and Applied Sciences*, 11(10), pp.6319-6323.
3. **W Azlan, W.A.,** Zakaria, H. and Low, Y.F., 2016. Quantification of Neural Correlates of Selective Attention in Schizophrenia with a Hybrid TMS-EEG Setup. (*Submitted to Asian Journal of Psychiatry*)

© Universiti Teknikal Malaysia Melaka

CHAPTER 1

INTRODUCTION

1.0 Background

Electroencephalography is a technique used to record the brain activity across the scalp while electroencephalogram (EEG) refer to the electrical potential resulted from the summation of thousands of firing neurons in the brain. As the matter of fact, the EEG signal is known as auditory evoked potential (AEP), visual evoked potential (VEP) and somatosensory evoked potential. This study focused on the Auditory Late Response (ALR), i.e., a variation of AEP, of control and schizophrenia groups. The advantages of EEG in brain research are less costly, noninvasive and it offers high temporal resolution. However, EEG is lack of spatial resolution and easily distracted by noise. Thus, EEG can be integrated with other imaging modalities such as Magnetic Resonance Imaging (MRI), Positron Emission Tomography (PET) and Magnetoencephalography (MEG) to obtain robust result. Integration of EEG with brain stimulation so called Transcranial Magnetic Stimulation (TMS – EEG) brings many advantages. In inductive approach, the cortical excitability and connectivity are evaluated (Miniussi *et.al,* 2012). Conducting TMS-EEG experiments while the subjects are performing a task is referring to interactive approach. Interaction of TMS with the oscillatory brain activity can be referred as rhythmic approach. The specific frequencies in specific brain area can be evaluated through this approach.

Transcranial magnetic stimulation (TMS) is a biomedical equipment applied to study the brain behavior and plays a role as a treatment tool. Especially, TMS has great potential as a diagnostic tool for psychiatric disorders. The magnetic stimulation excites

© Universiti Teknikal Malaysia Melaka

the neurons in the brain. The current is produced under the coil when is placed at the head. However, the use of TMS in Malaysia is still in early stage. Back to 2008, Food and Drug Administration (FDA) has approved the first TMS machine to treat major depression in people who fail on antidepressant. Later, in 2013, a new TMS machine to relieve migraine patients is approved by FDA (Weir K., 2015). This indicates that the development and recognition of TMS as a tool for therapeutic approach is known and expands through the years.

Schizophrenia is a brain disorder that exhibits effects on perception, way of thinking and behavior. DSM – IV is a guideline book used by doctors or psychiatrists to diagnose psychiatric patients. The core sign of a person who suffer on schizophrenia is cognitive impairment. They have attention deficit and memory deficit which refer to unstable mental state (Aleman A., 2014). Schizophrenia is a long term mental disorder which can occur in early adulthood or late adolescences; however it can also begin during childhood. The diagnosis of schizophrenia is based on subjective method – clinical interview. This method is more toward the questionnaires to the patients; the answers which cannot be sensed by observation.

Feature extraction is a process whereby extracting the relevant information or characteristics from the signal so that the features can be interpreted by humans. Therefore, it is a substantial process in interpreting an input signal. The information extracted reflects the physiology and anatomy of the activity going on within the brain. It involved a number of variables in a large set of data, which require a large amount of memory or powerful algorithm for analyzing. In this context, feature extraction method is needed in order to resolve these variables or information to be interpreted in a simple way and accurately.

© Universiti Teknikal Malaysia Melaka

1.1 Problem Statement

In present, doctors and psychiatrists follow the 'Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition (DSM-IV)' published by the American Psychiatric Association to diagnose schizophrenia patient. They follow the DSM-IV guidelines in conducting the clinical interview or also known as history taking. They prepare the surveys and questionnaires to the patients or relatives of patients'. However, this method has its limitation due to the result only depends on the surveys and interview. Moreover, the results is solely based on the behavioral changes and physical appearances of a patient. Till now, there is no alternative method that are sufficiently reliable and conclusive to confirm and examine schizophrenia patients. Related to this, an objective method is needed to complement the current practice. Therefore, an approach based on EEG combined with transcranial magnetic stimulation (TMS) is suggested. In addition, classification methods can be applied to discriminate the patients from controls. Meanwhile, the common analysis technique of EEG is depending on the averaging of event related potential of schizophrenia. This method relies on assumption that ERP consist of an invariant pattern time locked to stimulus (Quiroga and Garcia, 2002). Besides, the oscillations may cancel out when averaging across multiple subjects (Hermann *et.al*, 2004). To overcome these problems, a trial-to-trial analysis method, i.e., wavelet phase stability is proposed.

© Universiti Teknikal Malaysia Melaka

1.2 Objectives

This research work embarks on the following objectives:

- To design and develop experiment paradigms that combines TMS and EEG in analyzing the brain activity in schizophrenia patients with selective attention deficiency.
- To quantify objectively the neural correlates of selective attention reflected in ALRs using Wavelet Phase Stability (WPS) and C4.5 Decision Tree algorithm as the classification technique.
- To analyze the difference of auditory late response (ALR) that elicited by control and schizophrenia patients.
- To study the effects of TMS in the control and schizophrenia patients.

1.3 Research Scope

Based on the objectives mentioned earlier, the project is confined within the scopes identified as below:

- Auditory selective attention was the subject of investigation. Particularly, pure tones with three different frequencies (1 kHz, 1.5 kHz and 2 kHz) arranged in randomized order and with randomized interstimulus interval (ISI) at 1 – 3s were used as the auditory stimulation. There were two sessions of experiment which are without the use of TMS and with TMS. Types of TMS used are single pulse TMS and repetitive TMS. The oddball paradigm was applied in the experiment that required subjects to respond by clicking the mouse due to target tones (called as attended condition) or just relax (called as unattended condition).

© Universiti Teknikal Malaysia Melaka

- Human subjects recruited in the study were divided into two different groups: controls and schizophrenia patients. Specifically, schizophrenia subjects are the outpatients, chronic patients while control subjects are the healthy individuals which do not experiences any psychiatric disorder. Ethical clearance application for the study has been sent to the Research Ethics Committee, the National University of Malaysia (UKM) for approval. (UKMREC approval number: UKM 1.5.3.5/244/FF-2015-321)
- The auditory late response (ALR) was studied for the extraction of neural correlates of selective attention. The N1 – P2 wave at 0.07 – 0.24s is investigated in the study for both control and schizophrenia patients. This wave is anatomically associated with the auditory cortex.
- Signal processing methods involved in the study are continuous wavelet transform (CWT) and the wavelet phase stability (WPS). For classification, C4.5 Decision tree algorithm is used.

1.4 Research Contribution

The major contributions of the thesis are described as below:

- The proposed experimental paradigms were able to elicit the N1 – P2 from both schizophrenia and control subjects at frontal and temporal electrodes.
- Implementing the proposed signal processing techniques which were CWT and WPS able to analyze the elicited ALR which regards to auditory attention. These methods able to improve the conventional averaging method whereby both able to extract the N1-P2 peaks from the EEG. Thus, the neural correlates of selective attention that reflected in ALR between control and schizophrenia could be quantify objectively using both proposed signal processing methods. C4.5 decision

© Universiti Teknikal Malaysia Melaka

tree algorithm is applied in the research. The differences of N1 and P2 peaks between both groups during attention and no attention were able to be observed.

- In particular, the proposed techniques have the potential to be used as objective method instead of clinical interview to diagnose the patients. This may contribute in providing the objective way of quantification the neural correlates of selective attention.
- Despite of that, the study provides better understanding on the effect of single pulse TMS and repetitive TMS on schizophrenia patients and controls in auditory selective attention. Particularly, the difference in cortical reactivity due to magnetic stimulation was reflected in the N1-P2 wave.
- Overall, this study offers beneficial insights regarding the deficit encountered by schizophrenia patients as well as to study and analyzed the neural correlates of selective attention reflected in ALR especially for schizophrenia patients by implementing the signal processing methods.

1.5 Thesis Organization

This thesis consists of five chapters. Chapter 1 presents a brief yet essential description of the project background. It includes the problem statement, objectives, research scope and research contribution. In Chapter 2, reviews on TMS – EEG, feature extraction and classification methods, schizophrenia and selective attention are discussed in details. Methodologies used to achieve the goal of the project are explained thoroughly in Chapter 3. Meanwhile in Chapter 4, results as well as discussions that based on the results are presented. In addition, interpretation and justification of the results are discussed in details. Lastly, in Chapter 5 a summary regarding the project is given. Besides that, recommendations and suggestions for future improvements are elaborated too.

© Universiti Teknikal Malaysia Melaka

CHAPTER 2

LITERATURE REVIEW

2.0 Introduction

The use of transcranial magnetic stimulation (TMS) is gaining attention from researchers in investigating the human brain. It is known to possess ability for diagnosis and also for therapeutic approach especially in neuropsychiatric disorder. Hence, many researchers try to find out the impact of the TMS on human brain. Human brain is a complex organ however, provide us with beneficial information through the so called EEG signal. The implementation of TMS – EEG is able to contribute on the knowledge of brain activities. This method is used in different area such as neurological (Alzheimer), brain damage and psychiatric disorder (schizophrenia). Signal processing methods are employed in order to extract the information content in the recorded EEG signal.

This chapter emphasizes the main topics related to the research. They are transcranial magnetic stimulation – electroencephalogram (TMS – EEG) and feature extraction methods. There will be brief history, detailed explanations and applications based on past research on each topic mentioned above. Besides, review on schizophrenia and selective attention will be discussed here.

© Universiti Teknikal Malaysia Melaka