EFFECTS OF REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION ON ELECTROENCEPHALOGRAPHY, PHYSICAL ACTIVITY, SLEEP AND PSYCHOLOGICAL STATES OF MIGRAINE PATIENTS

By

SUPRIYATI BINTI ZAINUDDIN

Thesis Submitted to the School of Graduate Studies University Putra Malaysia, in Fulfilment of the Requirements for Master of Science

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Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfilment of the requirement for the Degree of Master of Science

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Migraine is one of the leading causes of morbidity in the world. This study is to explore repetitive transcranial magnetic stimulation (rTMS) as a preventive treatment of episodic migraine, analysing on its efficacy on headache days and other secondary health outcomes.

This study is part of the main clinical trial; MAGNET-EM; a double-blinded randomised, controlled trial which included seventy-six participants randomised into treatment arm and sham arm. Full protocol of the clinical trial was published and registered at clinicaltrial.gov. This study analyses the secondary health outcomes; on difference of electroencephalography (EEG), sleep, physical activities, sleep as well as mental health. The measures used for each outcome were observed EEG changes, GPAQ, PSQI, DASS-21 questionnaires were given to the participants pre- and post-RTMS respectively.

The study found a statistically significant difference in the proportion of photic driving response pre- and post-rTMS, $p = .0001$, $\eta p^2 = .336$) in the rTMS group vs. placebo. Sleep scores did not yield any significant changes but there was statistically significant improvement in physical activity ($p=0.015$.). In terms of mental health, there was reduction in the depression score ($X^2 = 9.60$, $p = 0.022$) and stress score, $p=0.052$ in the

rTMS group vs placebo. However, there is no significant changes of anxiety scores and sleep scores.

To conclude, the rTMS may have some beneficial effects on improving secondary health outcomes such as the photic drive responses, physical activity and depression in patient with episodic migraine. Although this is an early finding, the current rTMS study protocol could be used by clinician as an early adjunctive treatment for migraine patient with comorbid depression.

Keyword: Dorsolateral Prefrontal Cortex, Electroencephlography, Magnetic Stimulation, Migraine

SDG: GOAL 3: Good Health and Well-Being

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Master Sains

KESAN RAWATAN STIMULASI MAGNETIK KE ATAS BACAAN ELEKTROENSEFALOGRAFI, AKTIVITI FIZIKAL, TIDUR DAN STATUS PSIKOLOGI UNTUK PESAKIT MIGRAIN

Oleh

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Migrain merupakan antara salah satu faktor morbiditi tertinggi di dunia. Kajian ini bertujuan mengkaji kebarangkalian RTMS sebagai salah satu rawatan pencegahan untuk migraine episodic; mengakji keberkesanannya terhadap sakit kepala dan hasil-hasil sekunder lain. Kajian ini merupakan sebahagian daripada kajian percubaan klinikal utama; MAGNET-EM; kajian rawak terkawal rMTS berbanding placebo di mana tujuh puluh enam peserta kajian dibahagikan kepada kumpulan placebo dan kumpulan rawatan. Protokol penuh kajian percubaan klinikal ini diterbitkan diclinicaltrial.org. Kajian ini menganalisa hasil dapatan kajian sekunder; perbezaan bacaan elektroensefalografi (EEG), kualiti tidur, aktiviti fizikal dan kesihatan emosi. Ukuran kajian bagi setiap hasil dapatan adalah berdasarkan perbezaan bacaan EEG, GPAQ, PSQI dan DASS-21.

Kajian ini menemui perbezaan signifikan sebelum dan selapas rawatan pada respons rangsangan cahaya dalam kumpulan rawatan stimulasi rTMS, $p=0.001$, $np^2 =.0336$). Skor tidur tidak menghasilkan perubahan signifikan tetapig terdapat penemuan signifikan untuk aktiviti fizikal ($p=0.015$). Dalam sudut kesihatan emosi, terdapat pengurangan symptom depresi $X^2 = 9.60$, $p = 0.022$) dalam kumpulan rTMS berbanding placebo. Skor stress turut menunjukkan perbezaan signifkan secara statistik berbanding placebo, $p=0.052$ bagi analisa ITT. Meskipun begitu analisa kebimbangan melampau dan kualiti tidur tidak menunjukkan sebarang perbezaan statistik.

Konklusinya, rangsangan rTMS pada bahagian DLPFC dapat memberi efek positif dalam hasil dapatan kajian sekunder seperti respons rangsangan cahaya, meningkatkan aktiviti fizikal, mengurangkan symptom kemurungan dan stress. Walaupun ini adalah kajian awal, protokol kajian ini sesuai dijadikan rujukan awal bagi pengamal perubatan untuk rawatan sampingan bagi penderita migraine dengan komorbid depresi.

Kata Kunci: Kortex Dorsolateral Prefrontal, Electroensefalografi, Rangsangan Magnet, Migrain

SDG: Matlamat 3: Kesihatan yang baik dan sejahtera

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This thesis was submitted to the Senate of University Putra Malaysia and has been accepted as fulfillment of the requirement for the degree of Master Science. The members of the Supervisory Committee were as follows:

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LIST OF ABBREVIATIONS

EGG	Electroencephalography
rTMS	Repetitive Transcranial Magnetic Stimulation
CSD	Cortical Spreading Depression
IPS	Intermittent Photic Stimulation
Hz	Frequency
GPAQ	Global Physical Activity Questionnaire
PSQI	Pittsburgh Sleep Quality Index
DASS-21	Depression, Anxiety, Stress Score
BMI	Body Mass Index
MRI	Magnetic Resonance Imaging
DLPFC	Dorsolateral Prefrontal Cortex
GABA	Gama Aminobutyric Acid
TCD	Transcranial Doppler
TCC	Thalamocortical Cortex

CHAPTER 1

INTRODUCTION

Migraine comes from the Greek word 'hemicrania' which means half of the skull describing the unilateral characteristic of the headache. It was first used by Galenus, a Greek physician. (NS Kikkeri et al.,2021). Migraine has a significant impact on many aspects of patients' life such as physical activity, quality of sleep and negative emotions including depression, anxiety, and stress.

Mean percentage of productivity loss at workplace due to migraine is almost twenty-fold higher when compared to work time missed in Malaysia which means presenting at work during migraine attack is twenty times productive than did not coming to work (LP Wong et al 2020). This chapter describe the importance of sleep quality, psychological states, physical activity and neurophysiological study in repetitive transcranial magnetic stimulation (RTMS) treatment for migraine. Despite wide choices of preventive care, comorbidities in migraine is reported higher when compared to healthy population

1.1 Background

Work absenteeism among migraine patients and low productivity demonstrate social problems that require patient-centred approach. Employees miss 4.4 workdays per year on average due to migraine attacks and waste another 11.6 days of reduced productivity (OB Dhaem et al., 2021; M Von Korff et al., 1998). Nowadays, there is still lack of diagnostic tool that is able to sensitively be assessing migraine progression. Migraine was ranked sixth as the cause of disability based on Year Loss to Disability (YLD). In contrast, patients tend to ignore it as a simple headache to prevent being stigmatised by their colleague which may lead to disease progression and chronification.

Migraine is a multifactorial disease with multiple mechanisms involve in the initiation and progression including involvement of trigeminovascular system, cortical spreading depression, fluctuation of serotoninergic activity, increase in GABAergic activity and release of CGRP, PACAP 38, and proinflammatory molecules into the bloodstream (T Shiina et al., 2018; M Aggawal, Brown DA et al., 2009; Peroutka et al., 2007). Besides, current studies postulated cortical spreading depression as

one of the mechanism leading to migraine development (Leao et al 1944; Andrea Harrott et al., 2019).

Usually, migraine patients are prescribed with medications. However, introduction of neuromodulation techniques allow prophylaxis treatment to be carried out non-invasively and may reduce medications overused. There are few modulation techniques used during attack for example transcranial direct current stimulation (TDCS), single-pulse transcranial magnetic stimulation (sTMS), non-invasive vagal nerve stimulators (nVNS), and external trigeminal nerve stimulators (eTNS). Meanwhile, this study aims to use rTMS technique for prophylaxis which is delivered in two weeks within five sessions. The session is prolonged, and more pulses was given when compared to single-pulsed TMS. However, this study uses shorter treatment duration when compared to the treatment for other disease such as depression and obsessive-compulsive disorders (OCD).

According to 8th Congress of International Headache Society/13th IHC in Stockholm, migraine is introduced as hyperexcitability state of brain. RTMS added the noise frequency to reduce neuronal excitability. Thus, this study suggest use of rTMS to counterbalance the unilateral hyperexcitable state. Current studies postulated cortical spreading depression as one of the mechanisms developing migraine. At the same time, migraine is introduced as hyperexcitability state in the brain as discussed in XIII Congress of the International Headache Society/13th IHC 2007 in Stockholm, rTMS is seen as a promising neuromodulation technique to counterbalance the hyperexcitable state of migraine.

However, the pathophysiology of the disease remains debatable while the cause is believed multifactorial. Photophobia is one of the characteristics of migraine as described in International Headache Classification Disorders (ICHD-3). This study explored the possibility of using electroencephalography (EEG) to measure photic driving response (PDR) which is observed in electroencephalogram after photic stimulation. Electroencephalography has been widely used in the diagnosis of neurological diseases and used in the migraine for research purposes.

Extensive research is required to address all the possible factors to be taken into account during management of migraine patients. Migraine remains the diagnosis of exclusion when the other cause of headache has been ruled out. The disability caused by migraine however, is not small. While comorbidities such as psychiatric and sleep disorders are reported much more common in migraine as compared to healthy

population (Tsukasa Kato et al., 2015; Antonaci F et al., 2011; S Seidel et al., 2017; Pompili, M et al., 2010). Many migraine patients choose to avoid triggers to reduce the attacks frequency.

In contrast, suggesting to avoid risk factors and triggers is not the only option (Mayara- Mendonça et al 2012). For example, avoidance from physical activity have been one of maladaptive coping mechanism in migraine because the sufferers believe that the exercise and other trigger factors may initiate migraine and worsen the attack (SG Farris et al., 2018). In contrast, exercise benefits migraine patients by reducing the attacks frequency and intensity if it is correctly practiced (AG Martinez et al., 2013; Amin FM et al., 2018) In addition, the preventive suggestion recently, has switched towards better coping mechanism such as gradual exposure to triggering factors. For example, photic stimulation exposed migraine patients to repetitive light has been used to increase the threshold of migraine tolerance towards bright light.

At the same time, cortical spreading depression is more common in migraine (Fogang et al., 2015). Further study among migraine patients proposed that migraine with aura has lower photic driving response as compared to migraine without aura (Shiina et al., 2019; Coppola et al., 2019). However, a study postulated that migraine with aura has protective mechanism against migraine attack since photic stimulation test has done to both populations showed less photic driving response among migraine with aura. More study is needed to explore the mechanism underlying the photic driving response in migraine and its interaction with other factors.

Preventing migraine attack has become the focus of interest among researchers nowadays because progression towards chronification of the disease usually leads to unfavourable outcomes including medication overused, resistant to multiple medication increase in attack frequency, higher cardiovascular risk and tendency towards psychiatric comorbidities (Schwedtz TJ et al 2021; E Martinez- Pías et al 2021). Adjunctive therapies such as neuromodulation shades better hope to the future generation besides its mass production in the market recently. There is no longer need for taking medication as frequent and patients can avoid invasive procedure such as botulinum toxin injection or occipital nerve block.

1.2 Problem Statement

Globally, the prevalence of migraine is ranging from 9% to 14% (Stovner et al., 2022). While specifically in Malaysia, 9% of population is expected to have migraine (Alders et al. While 81% of them are women, 89.6% are having migraine without aura. Even though the value is underreported, migraine ranked sixth as cause of disability for Global Burden of Disease on 2016 jumping up from 19th within fifteen years despite mass introduction of medication and advanced disease intervention.

RTMS has been used in migraine during acute episode of migraine. However, moving toward preventive medicine, searching for a better prophylaxis treatment of migraine is very important. There is no randomised-controlled trial done sing rTMS treatment stimulated at the area of dorsolateral prefrontal cortex (DLPFC) area on episodic migraine. However, an open label trial found that rTMS has potential benefit on migraine when stimulated at DLPFC area. Arresting migraine chronification and disease progression is important to reduce medication overuse and development of comorbidities arising in chronic migraine.

Reduced quality of life, perceived stress and social problem had been reported in migraine (Eskin et al., 2013). However, rTMS treatment on depression and migraine requiring different prescription (O' Reardon JP et al., 2017). This study focus on positive predictors of treatment outcome and episodic migraine to arrest disease progression and to assess reduction of symptoms in comorbidities including stress, depression, anxiety and sleep disorders (S Giri et al 2022; Deghare AS et al 2022). Migraine has been introduced as multifactorial disease which has bidirectional relationship with lifestyle changes such as physical inactivity while dietery consumption affecting migraine attack is diversified (Gazerani et al., 2021). For example, some patients may complain of bloating and entering prodrome phase after eating crusciferous vegetables while, some not (Gupta J et ql 2022; M Nicole et al., 2022). However, some may avoid some food they perceived may induce migraine attack (P Gazerani et al 2021). In contrast, recent study showed that gradual exposure to triggers may reduce migraine better than avoidance as a maladaptive coping strategies (PR Martin et al., 2014). Avoidance behaviour reduce threshold of tolerant towards stimuli and triggers explaining different tolerance among migraine patients. Some migraine patients precipitate migraine attack in vigorous exercise while others in moderate exercise showing different tolerance (J Lemmens et al., 2014).

Avoidance from physical activity and photophobia is two added characteristics in International Classification of Headache 3 (ICHD-3) of

migraine. Photophobia has been unique characteristic of migraine and has a great impact on patients' social life and adaptability towards surrounding. While physical activity is recommended for migraine management, 80% of migraine patients reported intentional avoidance of physical activity (Farris SG et al., 2018). Preliminary findings in previous study correlates anxiety sensitivity may contribute to avoidance of physical activity in moderate and vigorous domains also correlates it with fear-based cognitions about exercise. (SG Farris et al., 2019).

To conclude, this study aims to measure the effect of rTMS on physical activity, sleep, EEG changes and psychological states of migraine and explore rTMS as a potential treatment as a prophylaxis for migraine.

1.3 Objectives

1.3.1 General Objectives

The general objective of this study is to evaluate the efficacy of rTMS stimulated at DLPFC area as prophylaxis treatment.

1.3.2 Specific Objectives

1. To determine the effect of rTMS on photic driving response in electroencephalography readings of migraine patients
2. To determine the effect of rTMS treatment on sleep quality of migraine patients.
3. To determine the effect of rTMS treatment on physical activity of migraine patients
4. To measure the effect of rTMS on psychological states of migraine patients.

1.4 Study Outcomes

This study aims to measure the efficacy of repetitive transcranial magnetic stimulation (rTMS) in the aspects of sleep quality, psychological states, electroencephalography changes and physical activity. This study is a part of a large study. Additionally, tolerability, safety, quality of life, evaluation of headache diaries is discussed in different studies.

The primary outcome measure of this trial is change from baseline in mean monthly migraine days. Meanwhile the secondary outcomes measures were

1. The changes in Depresion, Anxiety, Stress-21Score (DASS-21) in migraine patients in response to rTMS.
2. The changes in Pittsburgh Sleep Quality Index (PSQI) score in migraine in response to rTMS.
3. The changes in Global Physical Activity Questionnaire (GPAQ) score in migraine in response to rTMS
4. The changes in electroencephalograpy (EEG) readings in migraine in response to rTMS.

1.4 Research Hypothesis

Null Hypothesis: Repetitive transcranial magnetic stimulation delivered on dorsolateral prefrontal cortex has no effect on photic driving response (PDR), sleep quality, physical activity, depressive symptoms, anxiety, and stress.

Hypothesis 1: There is significant difference in photic driving response in migraine EEG pre- and post-rTMS

Hypothesis 2: The PSQI score correlates significantly with rTMS treatment.

Hypothesis 3: The GPAQ score correlates significantly with rTMS treatment in migraine patients**.**

Hypothesis 4: There is significant difference in psychological status pre- and post-rTMS treatment for migraine.

1.5 Scope of the Study

The following works are considered accomplishing the objectives of this study:

1. Photic driving response in interictal EEG is localised pre- and post-rTMS for any reduction of migraine.
2. Reduction of PSQI score post rTMS in treatment group marked positive predictive response to rTMS.

3. Reduction of depression score marked positive predictive response to rTMS treatment.
4. Increment in physical activity may predict positive outcome for rTMS treatment.

1.6 Definition of Terminology

This part discussed the contextual and subsequently operational definition of the terms used in this study.

Migraine

Episodic migraine is recurrent attacks of headache disorder manifesting in each attack that lasted for 4-72 hours with typical unilateral location, pulsating in nature, usually with moderate or severe intensity of at least five attacks with accompanying symptoms either nausea vomiting, and/or photophobia and phonophobia fulfilling ICHD-3 criteria. It may be preceded with or without aura. In this study, it requires the participant to fill up headache diary with satisfying migraine headache days less than 14 days per month.

Neurophysiological Changes

Based on the International Encyclopedia of the Social Sciences & Behaviour neurophysiology is the study of the functional properties of neurons, glia, and networks. BHIstory started with usage of electrophysiology—the electrical recording of neuronal events ranging from the molar (the electroencephalogram, EEG) to the cellular (intracellular recording of the properties of single neurons) (TJ Teyler, 2001). The electroencephalography (EEG) is used to measure neurophysiological changes of the brain used in this study. Electroencephalography changes observed is photic driving response (PDR). Photic driving response is characterised by spike higher than baseline waves after light stimulation in electroencephalogram. PDR changes recorded is transient and observed during interictal phase of migraine.

Sleep

Based on DSM-V sleep disorder is explained as predominant complaint

with dissatisfaction with sleep quantity or quantity. Sleep quality is measured by Pittsburgh sleep quality Index (PSQI) which consisted of 7 domains measuring subjective sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbance, use of sleep medication and daytime dysfunction.

Physical activity

Physical activity when performed at level more than recommended by WHO in which is significantly higher than what is needed for energy expenditure is considered physically active. Physical activity is quantified based on GPAQ questionnaires consisted of three domains measuring moderate, vigorous activity and sedentary lifestyle.

Psychological states

Psychological states refer to the state of mind with inclusion of experience of pain, perception, intention, emotion and memory (Martin, 1990). This study measures the psychological state in the aspects of perception of negative emotion using DASS-21. The questionnaire consisted of three component of negative emotions which is depression, anxiety and stress. DASS-21 is a self-evaluated questionnaire.

Depression is measured by 7 subscales: dysphoria, hopelessness, devaluation of life, self-deprecation, lack of involvement, and hedonia and inertia. Anxiety subscales includes autonomic arousal, skeletal muscle effects, situational anxiety and subjective experience of anxious feeling.

Lastly, stress parameter is measured based on sensitivity to levels of chronic non-specific arousal assessing difficulty on relaxation, nervous arousal and being easily agitated, irritable, over-reaction and impatience (Henry et al 2005; Musa et al 2007; Lovibond & Lovibond et al 1995).

Contributions

Based on the results of this study, contributions of the current work are as follows:

1. Promote the usage of EEG as evaluation for migraine progression of disease.

2. Promote rTMS as adjunctive therapy for migraine treatment in episodic group.
3. Using comorbidities, sleep quality and lifestyle as indicators for migraine chronification.

CHAPTER 2

LITERATURE REVIEW

2.1 Introduction

Prevalence of migraine ranging from 8% to 14% around the world (Yeh WZ et 2018). In Malaysia, 9.0 percent of people can expect a migraine with 10.6% of them are migraine with aura. This chapter provides a background about migraine, repetitive transcranial magnetic stimulation (rTMS) as the main intervention and factors affecting migraine that will be measured in this study which are sleep quality, physical activity, and migraine comorbidities (depression, anxiety and sleep) and photic driving response in electroencephalography (EEG) reading.

2.2 Conceptual Frame

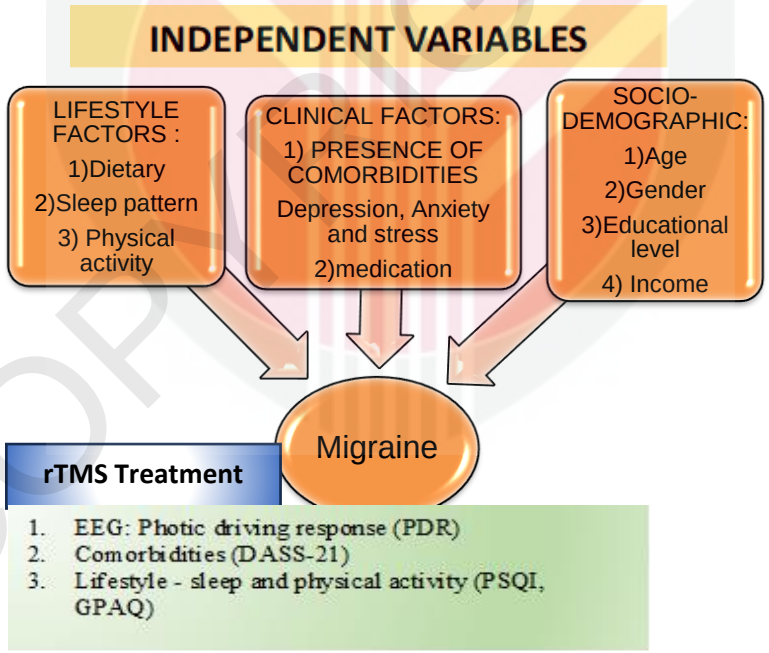

Figure 2.1: Conceptual Framework

2.3 Migraine and Phases

Figure 2.2 showed migraine phases. Migraine attack starts with prodromal state which may last for a few days. Some migraine patients may experience aura which takes up to 60 minutes before the attack. In postdrome state, migraine patients may experience common symptoms including fatigue, nausea, sensitivity to light, dizziness, body aches, and difficulty concentrating within one to two days. In between attack, which is called interictal stage, become the focus of recent studies aiming on preventive medicine. In addition, it allows us to study on pathophysiology of the disease. Resilience mechanism has been postulated happened during interictal stage in which migraine patient has no cognitive impairment and shows no epileptic properties or structural brain changes in functional MRI (FcMRI). Resilience in migraine brain was found in recent study. Resilience mechanism is described as decreased coherency in migraine brain during photic stimulation (M-Mendounca et al., 2012).

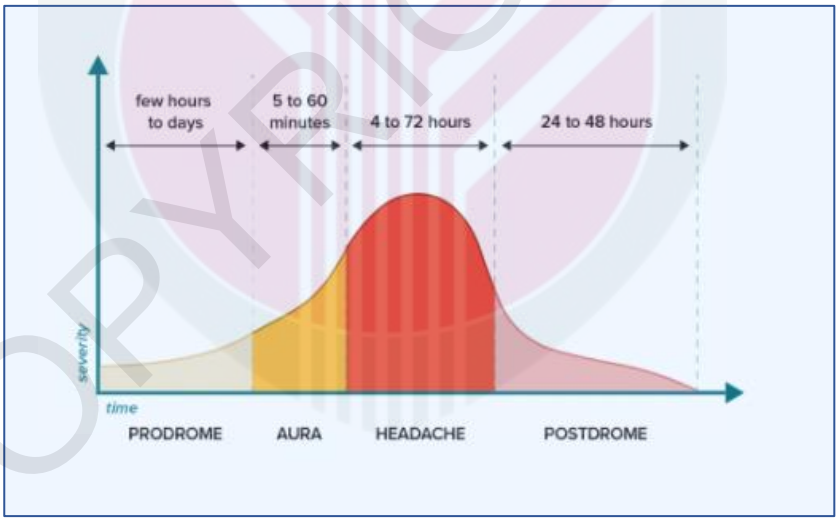

Figure 2.2: Migraine Phases (Source: headachedisorders.org)

Recent studies showed that there is anatomical relevance in migraine pathophysiology with the clinical symptoms including regulatory processing of emotion, memory, visuospatial, auditory, olfactory and visual perception in cortices, thalamus and nociceptive processing

explaining patients complaint on neurological disturbance, photophobia, and comorbid affective disorders (Zhang X et al., 2011).

Thalamocortical projection transmits nociceptive information from meninges to cortex. Involvement of trigeminal area, primary and secondary somatosensory cortex (S1 S2) and insula manifest in migraine is undeniable since there is evidence for hyperactivity after pain stimulation (Peyron et al 1998). However, role of posterior insula in migraine remains debatable. Scientist found that the insula is capable of manipulating other brain areas involve in nociceptive processing to perceive elevated pain affect (Starr et al 2009).

2.3.1 Pathophysiology of Migraine

Hyperexcitability had been postulated playing a role in unilateral aspect of migraine pathophysiology. Older theory stated that migraine may involve ions imbalance in the neuron leading to disturbed neuronal activity. Thus, some scientist agreed that migraine has a resemblance of epilepsy but not to the degree of occurrence of seizure. Furthermore, migraine showed unaltered cognitive function while, in epilepsy, cognitive function may deteriorate. Some study postulated that abnormal long-term cortical functional plasticity reducing thalamocortical activation which was observed during interictal period resulting in alteration in thalamic control (Pierelli et al., 2013). In other study, it was found that the lateral inhibition in the somatosensory cortex and cortical activity were reduced between attack supporting the postulated theory (Coppola et al., 2015).

Recent studies emphasis on the burden of migraine includes persistence of migraine in between attacks, or interchangeably referred as interictal phase. It occurs with accompanying associated symptoms including allodynia, hypersensitivity, photophobia, phonophobia, osmophobia, visual or vestibular disturbance and vertigo (M Vincent et al. 2022).

The complexity of migraine pathophysiology remained debatable but the advancement in research at molecular level allowed us to see the involvement of neurotransmitters such as serotonin and calcitonin gene-related peptide (CGRP) activity in migraine (Arulmozhi et al., 2005). Some migraine patients responded well to triptans which act on 5-HT1a. While, some other respond to enerumab which is monoclonal antibodies that bind on calcitonin gene-related peptides (CGRP). Histological study done on migraine-preconditioned rat showed that CGRP increases in

blood vessels during preictal state of migraine attack during vasoconstriction that decreases blood flow to meningeal vessels.

However, migraine pain is not caused by a single mechanism. Trigeminovascular pathway is also affected in the initiation of the migraine attack. Figure 2.3 showed projection of trigeminovascular pathways. There is axonal arbors of trigeminovascular thalamic neuron associating cortical areas and migraine symptoms including somatosensory, insular cortex and projection from thalamus in transmission of nociceptive signals (Noseda et al., 2011).

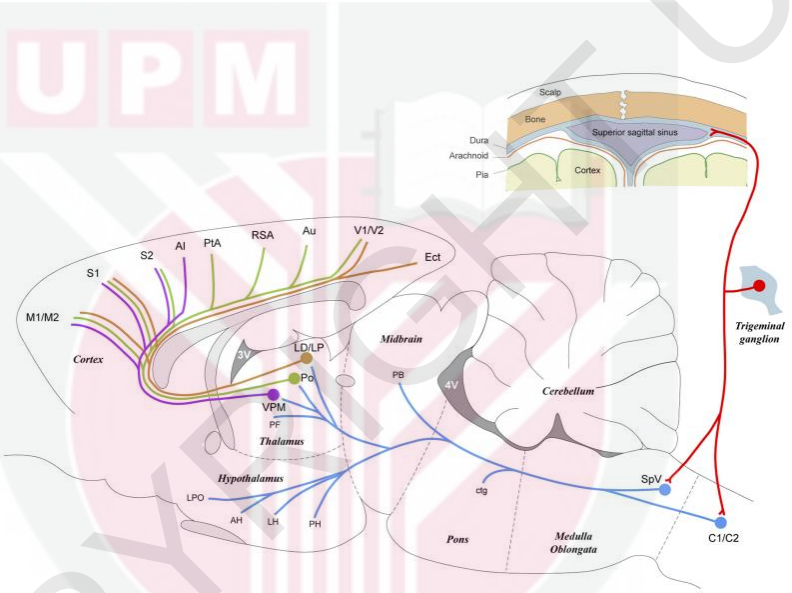

Figure 2.3: Illustration of Trigeminovascular Pathway.
(Source: Noseda et al., 2011)

Therapeutic trial on ketamine showed that a type of glutamate receptor on the membrane of neurons, N-methyl-aspartate (NMDA) receptor antagonist and non-selective AMPA/KA receptor antagonist LY293558 indicated that glutamatergic activity may be involved in reduction of migraine attack. While glutamic acid increases neuronal hyperexcitability (Giovanni Ie Andreaa et al., 2001).

Hypothalamic dysfunction in migraine has also been found in previous study. It was found that abnormal pattern of hypothalamic hormone was secreted in migraine brain (Peres et al., 2001). It is postulated that chronobiologic dysregulation and high dopaminergic activity are more

common in migraine when compared to healthy volunteers, while melatonin level was lower suggesting frequent case of insomnia among migraine patients. In this study, low metabolic by-products of melatonin were measured in their urine (A Zdunska et al.,).

Other factors affecting migraine may include depression, anxiety, exercise and alcohol (Ruben et al, 2019). While few other studies found sleep disorders is also affecting migraine condition(Kim et al., 2018). The focus of this study is to find whether these factors (sleep disorders, depression, anxiety, stress and exercising) play a role in predicting the positive outcome of rTMS treatment.

2.4 Electroencephalograpy (EEG)

Hans Berger, a psychiatrist from Germany introduced EEG on July 1924. The EEG was done on neurosurgical patient but the waves were considered artifacts until it was described by H. and P. Davies, F. and E. Lenox and Jaspers, thus pioneering EEG analysis. Advancement in EEG was continued forty years later skipping World War II after it was banned during years of conflicting political turmoil. Thus, invention of Computed Tomography (CT) bridging the forgotten EEG contribution on neurology.

Figure 2.4 illustrates the mechanism of signal detection from using various in neuroimaging technique. Electroencephalography has been widely used in migraine research. Combination with the other neuroimaging device such as MRI, steady state evoked potential (SSVEP) yields anatomical relevance. However, EEG has been known with the non-radioactive, non-invasive characteristics make it an interesting device to assist migraine study. Advancement in technological knowledge has transformed it into various types with different functional purposes including economical, portable simpler-sized device with lesser electrodes or more complex, higher amount of electrodes to appreciate greater anatomical coverage. In addition, more studies can be done with advancement in machine learning which can measure coherence, amplitude and assist in assessing functional connectivity in cortical area. While, understanding in signal processing allow researcher to compute greater amount of signals thus found correlation and discoveries in photic driving response, alpha asymmetry and hyperexcitability with migraine.

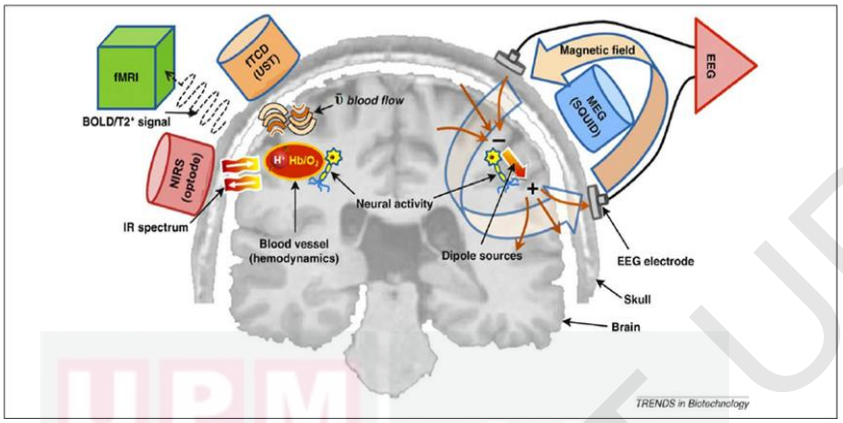

Figure 2.4: Schematic diagram of mechanisms of signals detection from brain.
(Cortical neural activity generates electrical potential that can be measured by EEG.
(Source: Byoung-Kyoung Min, et al., 2010))

2.4.1 EEG Band

The study done at rest showed that the electrical activity generated is from intrinsic activity which now called brainwaves (Biswal et al., 1995) consisted theta, alpha, beta and delta band. Functional magnetic resonance Imaging (FcMRI) has demonstrated intrinsic activity correlation known as functional connectivity (BP Roger et al., 2007). Based on relativity, waves are compared from one brain region to the other representing both hemispheres for occipital, parietal, frontal and temporal region which are represented by numbers as shown by Figure 8. Echo-planar MRI shows low frequency fluctuation, low oxygen and hand have movement has connectivity with sensorimotor cortex. However, extended version of EEG may cover whole brain including cerebellum, while its application may extend towards deeper brain structures such as thalamus which play a big role in migraine.

2.4.2 Neural Transmission and Electrical Signals

Neuron transmits information from its axon in the brain to the other part of brain cells called dendrites. The process is called synapse. The presynaptic part release neurotransmitters called chemical synapse. The postsynaptic part is the receiving end. The process may not occur

spontaneously. It requires pre-excitation process to allow electrical synapse. The nerve may be induced in several mechanisms, activated by different molecules such as AMK, Calcium ions (Ca), GABA or neurotransmitters (Zdunska et al., 2022; DK Arulmozhi et al., 2005). Thus, ions exchange at the base of the neurons allowing electrical activity to take place. This weak neural activity occurs simultaneously throughout the brain cells producing stronger electrical activity. The summation of electrical activity of the collective nerve cells allow it to be detected producing brainwaves which are represented relative to each electrode and which can be visualised in EEG monitor. Brainwaves are grouped based on their frequencies consist of delta, theta, alpha and beta waves.

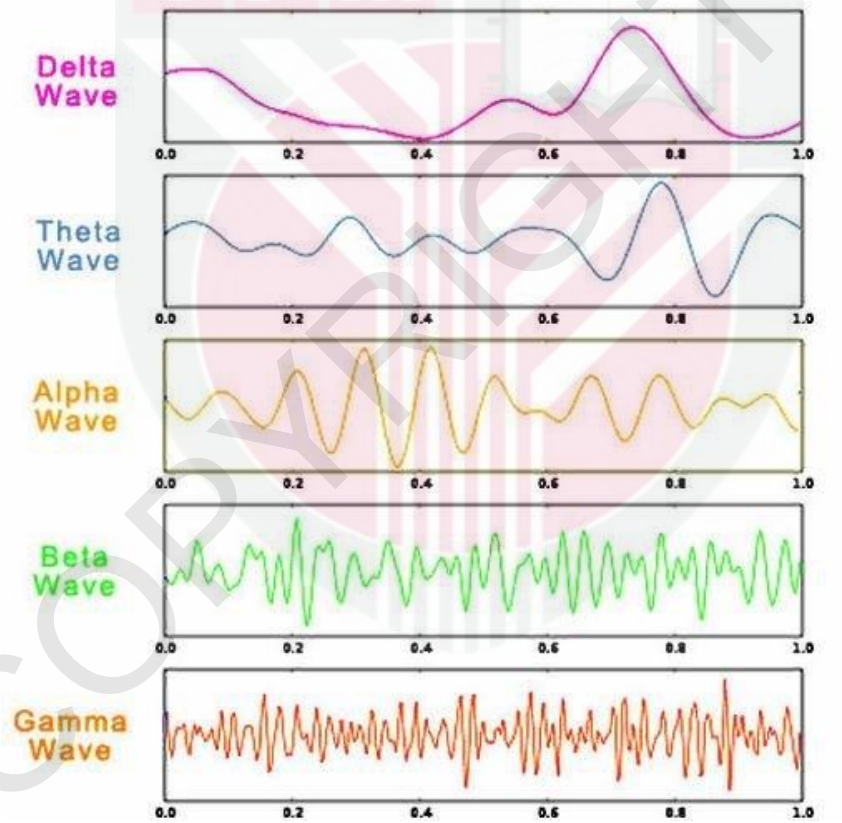

Figure 2.5: Brainwaves
(Sources: international Conference on Technics Technologies and Education by S. Buyukgoze et al., 2019)

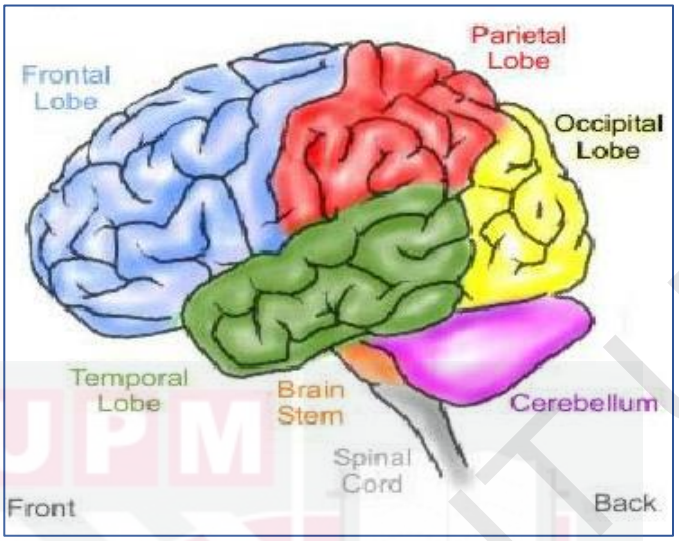

Figure 2.6: Regions (lobes) of the human brain, along with other major anatomical landmarks
(Source: Epilepsy Waikato)

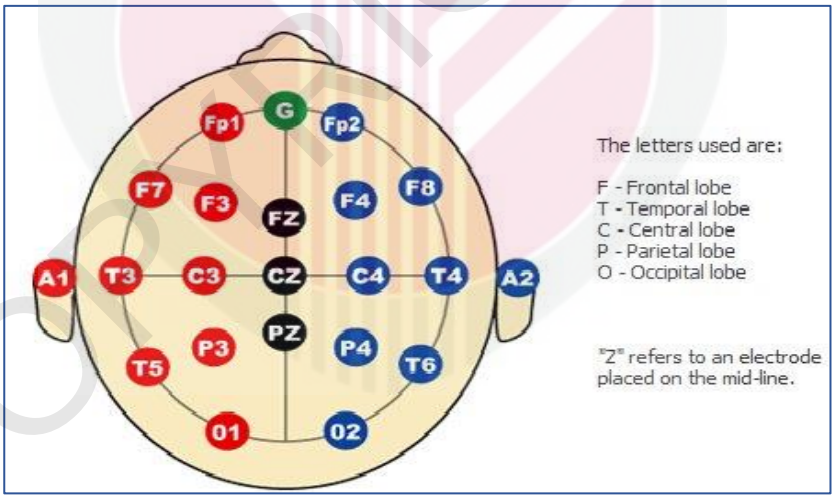

Figure 2.7: Placement of electrodes in 10-20 system
(Source: Roushdy et al., 2012)

2.4.3 Matching Clinical Representation of Brain Cortex Topography

Standardising the position and nomenclature of scalp electrode arrays was an important step in the development of electroencephalography. First, the 10–20 system of the International Federation was developed by Herbert H. Jasper and his co-workers (Jasper, 1958), resulting in the first published guidelines in 1999 (Klem et al., 1999). Early on the lack of proper coverage of the temporal lobe was criticized, resulting in the proposition of the 'Maudsley electrodes' to sample the temporal pole (Binnie et al., 1982). Large study had been done to find functional connectivity and managed to produced Seven Yeo Networks (Thomas Yeo et al., 2011).

2.4.4 EEG Montage

The types of EEG montage are either bipolar or referential. Longitudinal montage is linking anteroposterior lines. While transverse bipolar montage crosses the head from left to right side. Meanwhile, referential montage is monopolar linking each electrode to a common point.

This study uses double banana montage. Double banana montage is a longitudinal bipolar montage, considering distance between electrodes ranging 10% to 20% of maximum length whereby maximum length is distance between inion and nasion (Benbadis, 2005).

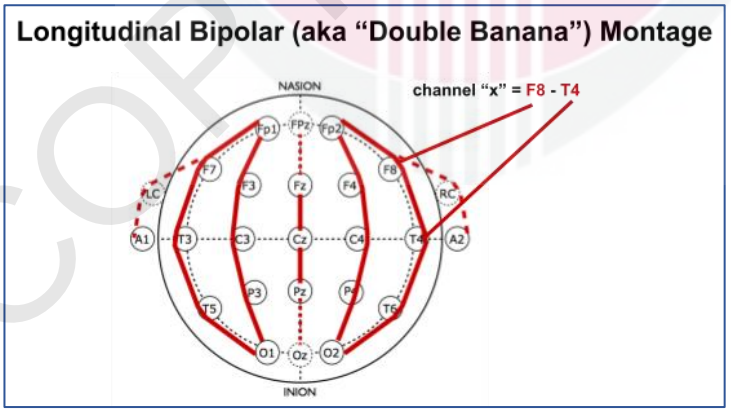

Figure 2.8: Montage of Bipolar double-banana EEG
(Source: https://eegatlas-online.com/index.php/en/)

Electroencephalography has been widely used in clinical research to study migraine pathophysiology and disease progression. Some studies found that photic driving response in migraine is higher than general population starting from 18 Hz stimulation and higher (Gantenbein et al., 2014; Hitomi et al., 2017). While some study referred it as 'h response', the study showed that at 20 Hz, migraine patients differed significantly a when compared to general population (Biallas & Hagmann, n.d.)(Pasqua, 2014). Other than that, some studies found theta activity and frontal intermittent rhythmic delta activity (FIRDA) in migraine patients significantly more common than general population during hyperventilation (Sand et al., 2010; Tan et al., 2007). Advancement in machine learning, introduced new approach in electroencephalography study where decrease in cortical coherence after photic stimulation but is found in migraine while increment found in controls (Neuroscience et al., 2012). It is postulated that the resilience mechanism occurs in pain-free interictal period. It may explain the increment in cortical coherence before photic stimulation, but when a stimulation started, it showed the decrement in coherency.

2.5 Artifacts

There are physiologic artifacts such as muscle activity as simple as yawning, eye-blinking, coughing, teeth clenching and shivering which are recorded by EEG but not generated by brain. Some study proved that thinking of physical activity may also give out artifact of perceived muscle activity. Non-physiologic artifacts may include drowsiness represented by rolling of eyes, sleep spindles, positive occipital sharp transients of sleep (POSTS), hypognagogic hypersynchrony characterized as paroxysmal burst of rhythmic waves located centrally at prefrontal areas. Therefore, performing all these unnecessary activities must be avoided during EGG testing in this trial.

2.6 EEG in Migraine

Studies done in interictal stage of migraine showed that there are seven findings of electroencephalography (EEG) changes in migraine found in literatures. Some may be unique in migraine while other findings are universally found.

Photic driving response (PDR) is higher in migraine patients when compared to healthy population. Photic driving response is the brain

response after light stimulation recorded in EEG as a spike. In laboratory, light stimulation can be adjusted based on different frequencies and the response from migraine patients will be recorded in EEG. In contrast, in real life situation, studies on the link between migraine and light stimulation is still inadequate Even though in real life migraine is not always preceded by photophobia, photophobia is reported one of the most common characteristics of migraine. Therefore, more research is needed to study the underlying pathophysiology explaining mechanism of photophobia in migraine. During inter-ictal phase of migraine, migraine patients are headache-free, however hypersensitivity to light stimulation might occur at this phase or concurrent pre-ictal phase. Some study postulated resilience mechanism explained the 'momentary' state of migraine symptoms. Photic stimulation test experimented in the study assessing resilience mechanism at frequency 9Hz (Neuroscience et al., 2012).

Table 2.1: EEG findings in migraine

No	Articles	Articles
1	'H'- response / photic driving response	3 (De Tommaso et al., 1999; Gantenbein et al., 2014; Pasqua, 2014; Fogang et al., 2014)
2	Non- specific Focal-slowing	2 (Hamad et al., 2014; Rho et al., 2020)
3	Peculiar, non-diagnostic EEG	1 (Sownthariya & Anandan, 2017)
4	Diffuse / lateralised abnormal slow activity	1 (F Pisani & C Fusco et al.,)
5	FIRDA	1 (Tan et al., 2007)
6	Transitory brain dysfunction with similar EEG features	1 (Merlino et al., 2007)
7	Increased delta and theta power	2 (Bjørk et al., 2009; Wu et al., 2016)
8	Alpha rhythm synchronization	2 (Angelini et al., 2004; de Tomasso et al., 2013)

While some other studies ran the EEG in different frequencies found photic driving response in migraine (De Tommaso et al., 1999;

Gantenbein et al., 2014; Pasqua, 2014; Tekin et al., 2009). However, photic driving response may interfere with mood and act as a confounding factor as its role may not be ruled out (Bjork et al., 2011). Other study mentioned photic stimulation triggers hypersensitivity and photophobia (Von Gizycki et al., 1998) while different study reported that the photic driving response may affect migraine in different way. Increase in visual imagery and decrement of psychological status were reported when related to photic driving response. The purpose of this study is to evaluate the changes in EEG pre- and post rTMS.

Prior studies have extensively explored the pathophysiology of migraine but little is known about the mechanism behind photophobia in migraine population. In this study we assess migraine brain response to light at different frequency through photic driving response in EEG pre- and post-rTMS treatment. Anatomically, the projection of lights input through retinal and trigeminal nociceptive input is sent to the occipital cortex and processed in thalamus, pons, primary and secondary somatosensory cortices, S_1 S_2. Trigeminal nerves mediate allodynia (Goadsby et al., 2017).

2.7.0 Repetitive Transcranial Magnetic Stimulation (rTMS)

The first modern technique of transcranial magnetic resonance device was introduced to stimulate human brain on motor cortex in 1985 by Dr Anthony Barker in attempt of disease treatment. This study proved the alteration of brain electrical signals under influence of magnetic fields applied by transcranial magnetic stimulation (TMS).

Study done on non-invasive brain stimulation including transcranial direct current stimulation (TDCS), rTMS, paired associative stimulation (PAS) and navigated brain stimulation (NBS) stimulated at somatosensory area showed modification of somatosensory processing thus facilitate cortical excitatory and tactile activity (Song & Sandrini et al., 2011). This study uses rTMS on DLPFC area for modifying pain processing. Earlier study done in this area showed promising results but since it is an open—label study, further study is needed to prove the efficacy (Kumar et al., 2018).

2.7.1 Nuclear magnetic resonance in transcranial magnetic stimulation (TMS): Principle definition

Based on the concept of resonance, the spinning on nuclei happens

when it achieves resonance frequency under sufficient electromagnetic field application. Nuclei spinning behaviour is explained in figure 9. When a condition is met, where $\nu = \gamma H0/2\pi$, thus resonance state is achieved.

[ν — frequency of radiation associated with transition from one state to the other; γ = proportionality constant and H_0 = magnetic field]'.

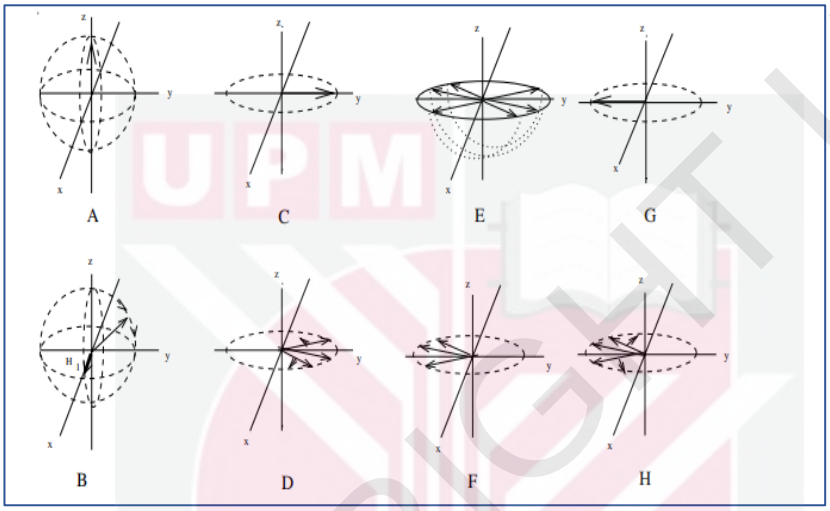

Figure 2.9: Nuclear spin based on angle in magnetic resonance
(The formation of a spin echo using the Carr-Purcell pulse sequence in the rotating frame. In A, spins are aligned and produce a net magnetization in the plus z direction, parallel to the external field. In B, using a 90 pulse, the spins are precessed down to the y-axis (C). In D, they start to de-phase due to variations in the external field. In E, a 180 pulse is applied to flip the spins around the x-axis so that they re-phase as in F and produce an echo in G. In H, the spins begin to de-phase again. (Source: Carr and Purcell (Phys. Rev. Vol 94, pg 630, 1954)).

2.7.2 Electromagnetic Induction in TMS

Different stimulation frequency may result in different physiological and behavioural effect. Recently researchers found that different frequencies of TMS despite from high or low frequencies may either increase or reduce excitation of cortical neurones (Li et al., 2016; Schwarzkopf et al., 2011; Silvanto & Cattaneo, 2017). This study uses high frequency rTMS.

There are few types of stimulations on brain. These include single-pulse (spTMS), paired-pulse (ppTMS), repetitive (rTMS), deeper stimulation (dpTMS) and theta-burst TMS while stimulation towards brain may include transcranial direct current stimulation (TDCS), and nerve conduction study (NCS). Study done comparing single-pulsed TMS, repetitive TMS, and paired pulse TMS found that RTMS has low risk of adverse events which is 0.040 (95% CI: 0.029-0.053) per patients and there is no seizure reported (Matthew VonLoh et al., 2013).

Deep brain stimulation requires invasive procedure where the electrode placement located directly to the brain tissue. RTMS is less invasive when compared to DBS technique and dpTMS. The calculation of percentage of how far each electrode precisely located to each other has been discussed in few congress and international conference.

Theta-burst stimulation is delivered in theta range, while high frequency rTMS is delivered in high frequency around 20 Hz. Low frequency rTMS is however delivered in low frequency around 1 Hz. There are few successful treatments in literature for migraine attacks but for episodic migraine the evidence is scarce. Even though the adverse effects of theta burst are not reported in vast studies, the safety is otherwise not sufficiently proven in literature. Transcranial direct current (TDCS) study in migraine found conflicting results. Even though the positive results are reported in eleven studies, the adverse events are equally reported in treatment and sham groups (Hong Pi et al. 2022). Therefore, theta-burst stimulation and TDCS were not chosen in this study.

While sTMS and rTMS differ in duration of treatment. Compared to repetitive TMS which is given for few sessions in several days, as a prophylaxis purpose, single-pulsed TMS is delivered in a session during migraine attack. Single-pulsed TMS has been widely used during migraine attack in hospital. However, there is no current guideline or protocol for rTMS as a prophylaxis stimulated on dorsolateral prefrontal cortex area. rTMS has been used in other neurological problem such as depression, obsessive compulsive disorder (OCD). While the area of stimulations done in previous studies varies. It includes motor cortex M1, somatosensory cortex (S_1S_2) and occipital cortex. The exact mechanism through which rTMS exerts beneficial effects in episodic migraine is however not clearly established.

The postulated theory is neurostimulation techniques such as single-pulsed TMS and paired-pulse TMS on dorsolateral prefrontal cortex (DLPFC) relieves pain through inhibitory effects acting on pain perception by resetting or reducing the fronto-limbic dysfunction (Lorenz

J et al 2003, Rome JD 2001), thus selection of DLPFC might be beneficial for migraine patients. Single-pulsed TMS might be used for temporary relief, but rTMS which is delivered repetitively might provide longer lasting inhibitory effects on pain perception.

While the aim of delivering the rTMS as a neuromodulation technique is to provide secondary prevention by arresting the pain for longer duration, we also aim to achieve minimal side effects. TMS done on motor cortex and somatosensory area were reported with side effects including seizure. Seizure may deteriorate brain cognition temporarily and chronically if the management is poor. In this study we choose dorsolateral prefrontal cortex area (DLPFC) area which has no reported case of seizure in the previous study. However, any case of seizure will be reported in order to maintain the fidelity of this study.

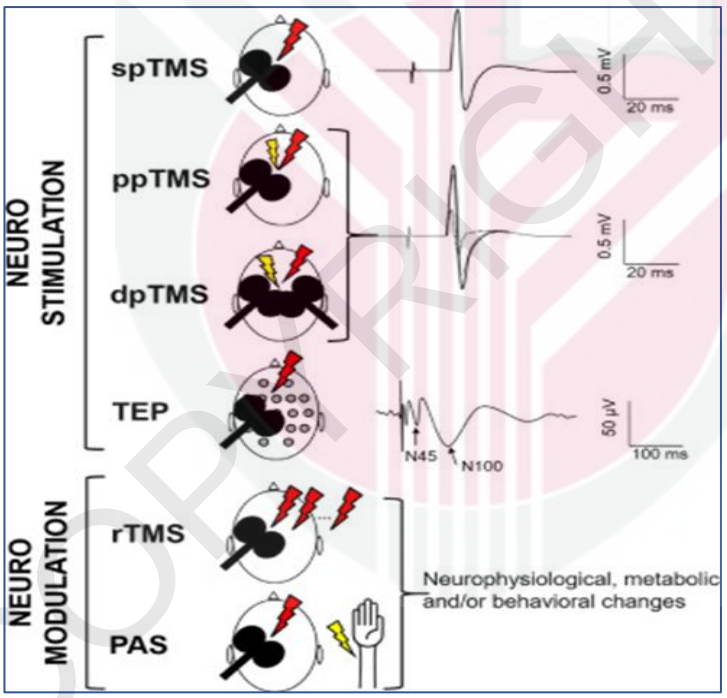

Figure 2.10: TMS application in neuroscience
(Source: Cuypers & Marsman, 2020)

2.7.3 Molecular Resonant Frequency Determination Using rTMS in Migraine Neuromodulation Technique

Recent studies showed that single-pulse migraine could relieve headache during attack. It could be suggested that low-frequency rTMS is associated with intracortical fascilitation (ICF) than intracortical inhibition (ICI) (Ziemann et al. 1995; Schwenkreis et al. 2000). Alternatively, GABAergic slow γ-aminobutyric acid GABA B receptor, mediates late cortical inhibition (i.e., interstimulus interval (ISI) later than 2–5 ms). It might be affected more easily than fast GABA A receptors, mediating early cortical inhibition (McCormick 1989; Martinez F et al., 1993). Thus, the rTMS train effect on ICF is a result of an initiation of inhibitory late mechanisms as suggested by (Romero et al. 2002). If this is the case, the inefficiency of late as well as early cortical inhibitory circuits in migraine patients would not allow their upregulation by low frequency rTMS. It is believed that the mechanism that play behind the rTMS effect on behaviour acting on the neuronal activity is the stochastic resonance effect (Schwarzkopf et al., 2011). Stochastic resonance effect is observed when increased in random noise cause increase in metric of the quality of signal transmission or detection performance rather than decrease. Thus, when rTMS is delivered, the pulse increase random noise leads to increase in quality of electrical transmission in nerves.

Recent study found that at a higher stimulation, TMS may has facilitatory effect on behaviour if the neuron is inhibited by ongoing task-related or preconditioning situation (Silvanto & Cattaneo, 2017). It was observed that the shifted activity from inhibitory to facilitatory may happen in inhibited neuronal excitability or changes occur for instance adaptation called “virtual lesion” paradigm. This may contribute to the positive effect on the migraine comorbidities such as depression, anxiety and sleep disorders. MRI done on post-TMS patients, shows the activation of prefrontal cortex, while some other study involving BOLD technique showed activation at the other associated brain area at cortical-to-subcortical network such as thalamus (Hanlon et al., 2013).

2.7.4 Safety of RTMS

Side effects of TMS has been reported in pilot study in few other countries is headache, nausea and vomiting (Matthew VanLoh et al., 2013). Post-TMS seizures has been reported in rare cases with predisposition. Nausea and vomiting may be treated with metoclopramide, while simple headache can be prescribed with paracetamol. Reported headache complaint is short-lasting and less severe when compared to migraine characters. While seizures, can be treated with benzodiazepines intravenously. Thus, it is suggested that

the patient undergo TMS treatment in neurology clinic under supervision of trained medical staff (Jiang et al., 2013).

Up to date, a few studies on single-pulsed TMS treatment during migraine attack have been performed to investigate the association between migraine patients with psychological states. To our knowledge, there has been no study on psychological effects of rTMS stimulated at prefrontal cortex for episodic migraine as a prophylaxis treatment. The current study will study the effect of rTMS on different factors related to migraine including psychological states, EEG changes, physical activities and sleep quality.

2.8 Sleep Quality

Sleep quality among migraine patients are reported poorer than controlled population especially in daytime sleepiness and sleep disturbance. (Eskin et al., 2013; Sengul et al., 2015; Song et al., 2018). Further study categorized migraine patients into smaller group and found that migraine patients with eight or more migraine days per month has higher PSQI score as compared to migraine patients with lesser than eight migraine days per (Sadeghniiat et al., 2013). However, some studies did not found sleep disorders as a mediators to predict the positive outcome of RTMS treatment stimulated on somatosensory cortex (Lindholm et al., 2016).

Poor sleep quality is reported with disability, worsening cognitive ability in retaining memory and poor task-switching skill. Higher level of orexin has been reported in poor sleeper, while neurotransmitters circulating cerebral glymphatic system which usually removed during sleep may be the reason behind the reported complaints accompanying sleep disorders. However, research on glymphatic system has divided results. Pilot study showed that there is no significant impairment of glymphatic system when compared to control. Animal study showed cortical spreading depression which also underlies migraine pathophysiology may impair glymphatic system (Sehain et al., 2017). The other study characterized difficulty in initiating and maintaining the sleep, insomnia thus interfering with daily functioning (Peres et al., 2001). Significant delayed in melatonin peak was found among migraine patients but not in controls. While lower prolactin and higher cortisol concentrations were found among migraine patients with no correlation with medication overuse and insomnia. Meanwhile free-floating neurotransmitters in cerebrospinal fluids may bind in brain tissues affecting excitability of neurons creating transient hyperexcitability state of brain through

GABAergic activity. For instance, 'virtual lesions' has been proposed in migraine condition.

A study showed that in susceptible arousal system, migraine patient sleep has low wave and less K-burst. Decreased arousability increases sleep deprivation during the daytime while in robust arousal system where arousability is preserved has higher risk to develop sleep disturbance (Engstrøm et al., 2014). While recently in animal study exposed to single-prolonged stress and sleep deprivation showed that sleep deprived rats exhibited fear-associated memory processing (Davis et al., 2021).

Overlapping in anatomical structures between migraine and sleep might have been the reason linking poor sleep quality and migraine (Tiseo et al., 2020). In brainstem, rapid eye movement (REM) sleep is inhibited by noreadrinergic and serotoninergic neurons, whereas pain is transmitted from afferent fibers of thalamocortical cortex (TCC) to the thalamus. While at the same time, pain modulation occurs through descending inputs from thalamus and hypothalamus. Orexinergic neurons in hypothalamus facilitate or inhibit TCC nociception by receptor-specific pathway. While, in sleep mechanism, waking state is stabilised by receiving orexinergic excitatory projections and send inhibitory inputs to the sleep promoting ventrolateral preoptic nucleus (VLPO) to reinforce wakefulness. The transition of sleep-wake is also controlled in hypothalamus by participation to flip-flop mechanism of sleep-wake transition. Hypothalamus also regulates circadian rhythm.

In addition, low dopaminergic tone may be the shared pathophysiological factor in sleep disorders and migraine condition. Other than that, low dopamine leads to sleep deprivation (AJ Kasner 2011). The dopaminergic A11 nucleus play a role in premonitory migraine symptoms. While other study found rTMS modulate dopamine (S. Jakelanein, Lindholm et al., 2014). This study will look for improvement in sleep disorders after migraine treatment with rTMS.

2.9 Physical Activity

Hypersensitivity towards stimuli has been proposed causing avoidance coping behaviour among migraine patients. While another study found that kinesophobia is significantly higher in migraine as compared to general population (Martins et al., 2006). Strong belief on physical activity may cause migraine attack or worsening the symptoms has been proposed causing avoidance coping behaviour towards exercise among

migraine patients (Farris et al., 2018). Avoidance to physical activity is higher among migraine patients as compared to general population caused by perception of physical activity may act as a triggers to migraine attacks Splenings MD et al.,1988).

Recent study showed that there is association between moderate exercise and migraine attack in episodic migraine while no significant different with vigorous exercise was reported from the same study (Kobina K Hagan et al., 2021). Study showed that exercise as a social determinant of migraine favouring aerobic exercise as a predictive factor of reduction in migraine attack even though the pathophysiological mechanism remains understudied (Hammond & Stinchcombe, 2019).

However, molecular study showed that there is a genetic linkage between harm avoidance personality and serotoninergic synaptic neurotransmission in migraine without aura(Jeong et al., 2006). The study found that variable number tandem repeat (VNTR) genotype STin2.12/STin2.12 was more significant (90%) among Harm avoidant in migraine without aura as compared to healthy volunteers (77%) which is the gene for serotonin transporter protein. It acts as modulator for neurotransmission involving serotoninergic synapses. Thus, negative attitude towards modifiable lifestyle risk factors is inversely proportional to migraine treatment succession.

2.10 Negative emotions: Depression, Anxiety and Stress

A lot of studies have been done to assess neuropsychological condition of headache population. The relationship is bidirectional which it may affect each other. Those with depressive symptoms and anxiety had increased odd of migraine (Berhane & Williams, 2012). For example, a study shows that management of comorbidity in migraine by cognitive behaviour therapy is able to lower the level of depression, stress and migraine symptom compared to control group (Hamedi et al., 2013). While a few studies had been done on rTMS effect on migraine, some studies focused on migraine with psychiatric comorbidities which reported reduction in symptoms among migraine patients with comorbid depression (Kumar et al., 2018). However, it is an open-label study which require further research to validate the study. Thus, in this study, we used randomised controlled trial which has straight-forward cause-effect relationship buy minimising bias.

Treating patient as an individual with multiple conditions not solely on one disease have been research interest in the modern medicine.

Multiple correlation between comorbidities and migraine has been proven since centuries. Functional magnetic resonance imaging (FcMRI) showed that both depression migraine brain exhibited increase activity of left prefrontal cortex (Zhang et al., 2019). Based on figure 11, default mode network (DMN) was insufficiently suppressed when intrinsic activity in the left medial prefrontal cortex increase. Other than that, insufficient DMN suppression interchangeably caused depression. At the same time, DMN suppression insufficiency cause increase in functional connectivity with thalamus, insula and left postcentral gyrus which led to headache.

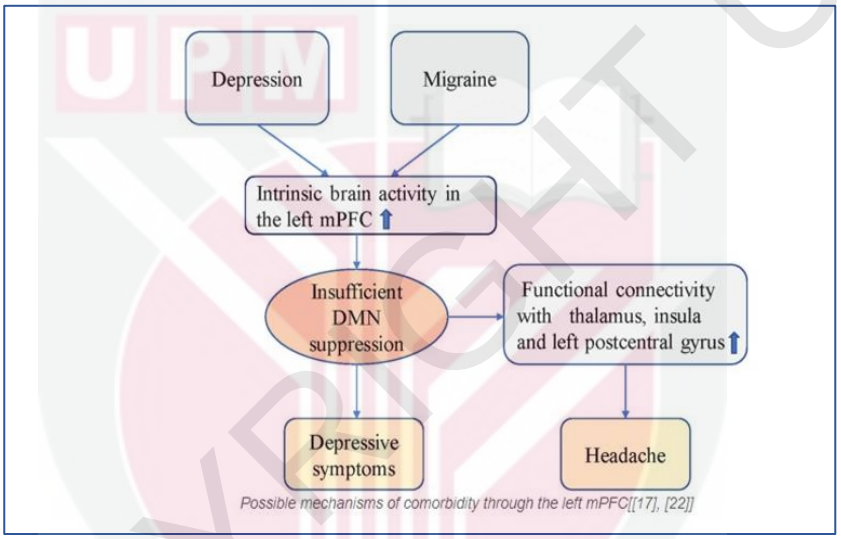

Figure 2.11: Possible mechanism of comorbidity between depression and migraine
(Source: Zhang et al., 2011)

The exact pathophysiology that correlates migraine and depression is not sufficiently established. Some studies postulated that higher level of photophobia in migraine with comorbid depression may be linked to pupillary dysfunction (Seidel et al., 2017). Genetic study done on serotonin transporter gene-linked polymorphic region (5-HTTPLR) and brain derived neurotrophic factor (BDNF) Val66met gene which encode serotonin transporter gene and are related to depression and migraine showed that those genes are positive predictive factor towards successful rTMS treatment for depression (Bocchio-Chiavetto et al., 2008).

Cognitive behavioural therapy showed significant positive result showing that psychological wellbeing plays an important role in reduction of migraine pain. While some studied showed that locus of control and positive attitude towards healing contribute toward arresting disease chronification. In addition, study on perceived stress, social problem-solving and life satisfaction showed that depressive migraine patients has lower level of problem solving skills when compared to healthy volunteers (Eskin et al., 2013).

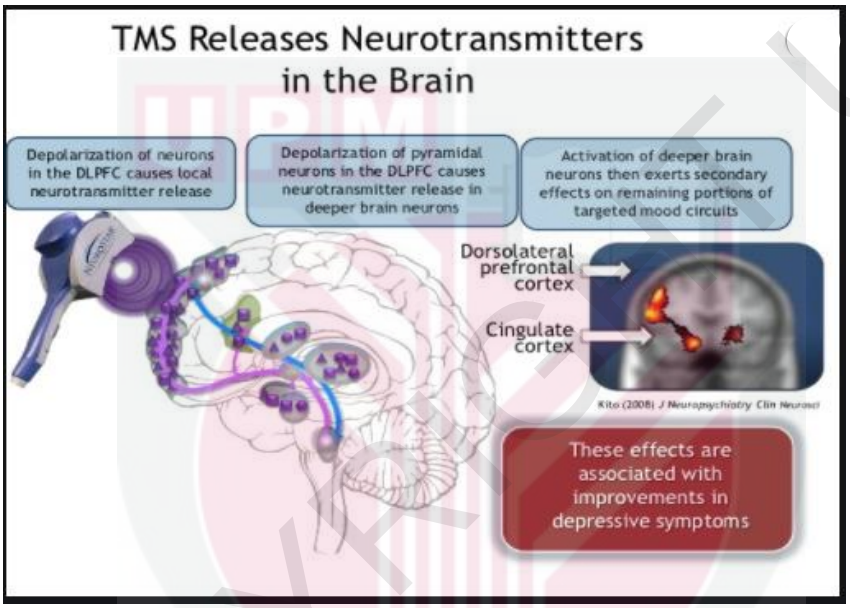

Figure 2.12: TMS in depression
(Source: Kito et al., 2008)

Study done on effect of TMS to depression shows that stimulation on DLPFC area may activate deeper structures of brain and exerts secondary effects on mood cuircuit (Kito et al., 2008). Figure 12 describe the mechanism behind reduced depressive symptoms when treated with TMS. Neurotransmitters are released when neurons are depolarized by TMS. Targeted mood circuit in deeper brain structures is activated by the release of neurotransmitters causing reduced depressive symptoms.
RTMS has been used for the treatment of major depressive Disorders (MDD) and generalised anxiety disorders (GAD) specifically and as secondary treatment for other diseases. For example, a meta-analysis has described rTMS treatment for anxiety as secondary disease and

found that both left and right sided DLPFC has been targeted for treatment of anxiety (PA Rodrigues et al. 2019).

Classification of anxiety includes generalised anxiety disorders (GAD), Social anxiety disorder, panic disorder, agoraphobia, seperation anxiety disorder, selective mutism and specific phobias. Anxiety can be a symptom or accompanying other disease as a comorbidity. A few studies reported comorbid anxiety coexists with other diseases including MDD (Kaur et al 2019;Durmaz et al 2017; Tovar-Pordomo et al 2017, Diefenbachet al 2013; Pretallie et al 212; Berlim et al 2011;George et al 2000) and also Post stress Traumatic Disorders (PTSD) (Oznur et al 2014; Watts et al 2012; Baggio et al 2010; Cohen et al 2004) and other pathologies such as obsessive compulsive disorders (OCD), tinnitus, borderline, schizophrenia, pain tourette syndrome, restless leg syndrome and migraine. However, pathophysiology linking migraine and anxiety is unknown. However, there is evidence of anxiety is associated with increased cerebral blood flow (G Hasler 2007). Increased cerebral blood flow or known as interictal hyperperfusion is also reported in migraine. Increased blood flow might be one of the shared pathology between migraine and anxiety that leads to higher percentage of anxiety symptoms in migraine when compared to general population. Thus, usage of rTMS in this study targeting migraine might be a promising candidate to effectively reduce comorbid anxiety symptoms.

Based on meta-analysis study, fourteen articles reported delivering stimulation at the left side while three articles reported that the area of stimulation is at the right side (PA Rodrigues et al 2016). Thus, high frequency stimulation at left sided DLPFC which is targeted in our study has been supported by previous study compared to the right side. Even though rTMS protocols used different frequencies tailored based on the primary disease, reduction in anxiety symptoms and stress score are reported. A study reported reduction of anxiety symptoms in GAD after 25 sessions (Dilkov et al 2017). Similarly, PTSD has been effectively treated with rTMS. There is evidence based on open label study that targeting motor cortex may elucidate symptoms of PTSD. Motor cortex has been targeted for treatment of few diseases including migraine, PTSD, anxiety and OCD.

Previous study showed that rTMS influence on stress (Amalia Badawi et al 2022). However, some studies used low frequency rTMS instead of high frequency which is used in migraine and anxiety. On contrary, even though the rTMS treatment is tailored for depression, participant anxiety and stress scores is also reduced significantly. It is an important finding as stress is a trigger to migraine. In this case, ‘allostatic load’ is a concept used in literature describing repeated stressors may alter

normal response to stress and lower the threshold towards stressors. The brain identify stress as a threat and develop migraine as a maladaptive response (Nasim Maleki et al. 2013). It is supported by other studies reporting migraine attacks has responses which are mediated through excess of normal adaptive prosesses including pain, stress hormones, affective changes nausea and vomiting (McEwen BS et al. 2006; McEwen BS et al 2007).

Stress and posttraumatic stress disorder (PTSD) is twice more common in women compared to men and has a lifetime prevalence of 8% in general population. The most common cause of PTSD are traumas such as physical and sexual abuse with childhood abuse as a factor is that associates with migraine (Goodwin RD et al 2003; Tietjen GE et al. 2007). While other study reported 41.7 % of episodic migraine sufferers reported history of physical and sexual abuse. Thus, it is important to screened stress, anxiety and depression for migraine treatment.

Even though the exact pathology that links migraine and stress is unknown, there are evidences from the literature that oestrogen may play a role that links migraine and stress (Martin VT et al 2006; Denuelle M et al 2007, Solomon MB e al 2009, Walf AA et al 2006). For example, menstrual migraine marked hormonal fluctuation with accompanying premenstrual symptoms of mood disorders including dysphoria, depression, anxiety and stress. Oestrogen is not specifically affects women and it is important to take note that oestrogen and its receptors also exist in men. Oestrogen modulate neurotropic factors and neuropeptides which also affecting migraine and mood (Grigoriadis S et al 2002; Martin VT et al 2006). Therefore, neuropeptide Y, corticotrophin-releasing hormone (CRH) and neurotransmitters such as serotonin, dopamine and glutamate are the shared pathology that may explain high prevalence of stress in migraine.

CHAPTER 3

METHODOLOGY

3.1 Introduction

The study is a double-blinded randomized controlled trials and adhering to Consolidated Standards of Reporting Trials (CONSORT) statement. The aim of the current study is to evaluate the effectiveness of repetitive Transcranial Magnetic Stimulation (rTMS). This study intends to explore the effect on neurophysiological, psychological states, physical activity and sleep. All participants were among Malaysian population who resides in Serdang, Selangor. This chapter will describe the flow of this study. This chapter describes the methodology of the process evaluation which was conducted alongside the main clinical trial as a secondary outcome of the overall MAGNET-EM study. It presents the data collection and analysis methods in detail. Selection of methods for monitoring, measuring and assessing intervention fidelity are discussed.

3.2 Study Design

Table 3.1: Study Design

Study Type:	Interventional (Clinical Trial)
Actual Enrollment:	76 participants
Allocation:	Randomised
Interventional model description:	Two-arm parallel assignments involve two group of participants. One group receives rTMS and the other group receives sham placebo rTMS.
Masking:	Quadruple (Participant, Care Provider, Investigator, Outcomes assessor
Masking description:	Double-blinded
Primary Purpose:	Treatment

Table 3.1: Continued

	Electroencephalography, Physical Activity, Sleep and Psychological States of Migraine Patients
Actual started Date:	15th April 2019
Actual Primary Completion Date:	4th February2021
Actual Study Completion date:	1st April 2022

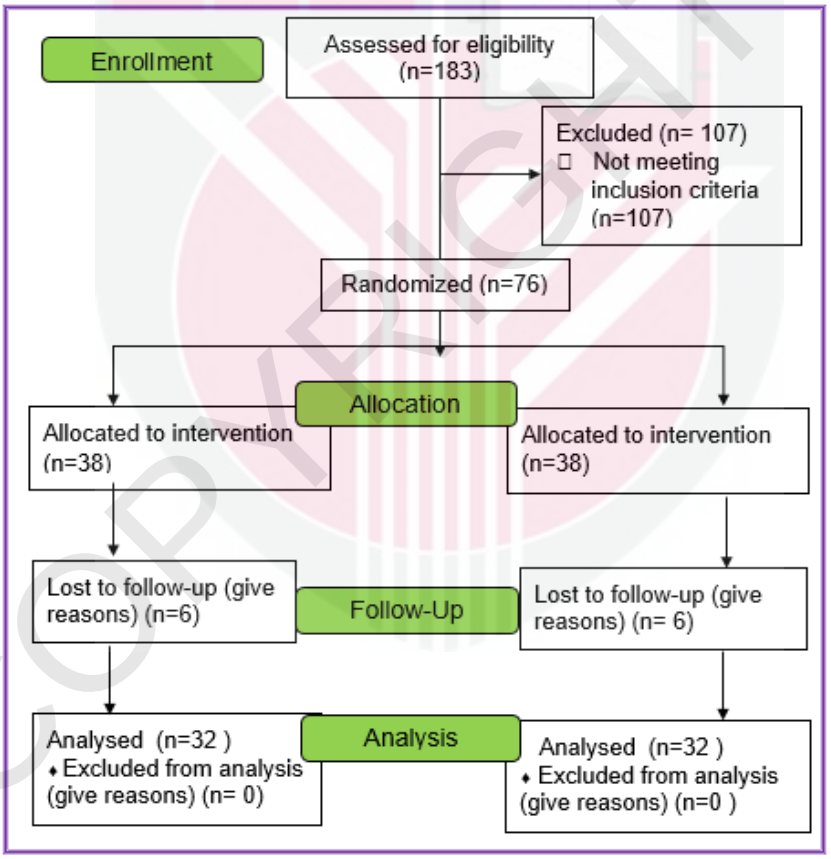

Figure 3.1: Schematic diagram of the CONSORT flowchart for study design

3.2.1 RTMS and sham procedure

1. Single-pulse stimulation was delivered with gradual increment until muscle twitching was observed either by contralateral limb muscles or ipsilateral facial muscle to find the threshold.
2. After motor threshold is obtained, only 80% of the motor threshold is delivered to the participants.
3. RTMS treatment was stimulated at DLPFC area from 90° angle. Eighty percent from threshold was delivered. Each session of RTMS consisted of 2000 pulses. The pulses will be given in 40 trains, each train duration is 5 seconds consisting of 50 pulses at 20 Hz with inter-train interval of 25s.

3.2.2 Control

Figure 3.2: Indistinguishable look between rTMS coil stimulator and sham.
(Source: www.medicalexpo.com)

Controlled group received sham treatment. The sham treatment I a placebo with without producing any stimulation. The appearance is the similar to the device mimicking the rTMS coil in shape, size and its look. It is indistinguishable from the rTMS stimulator. The duration of session is the same as for rTMS group. However, sham coil does not stimulate the brain. Controlled group is received same procedures and questionnaires as rTMS group. The staff who deliver the rTMS and procedures is blinded.

3.2.3 Blinding & emergency unblinding procedures

This study is a double-blinded study. The participants and outcome

assessor of the study is blinded about the allocation status of the participants. The rTMS and sham coil stimulator is labelled as A and B which are unknown by the staff who deliver the stimulation. If adverse effects (AE) is reported or pregnancy occurs for which knowledge of the identity of the test drug is necessary to manage the subject's condition, the sealed emergency code key for that subject may need to be broken and medical monitor will identify the test. The medical monitor will have a set of sealed emergency code keys (one for each subject) kept in a secured location and he/she will be accessible at all times by telephone. In the event of emergency unblinding is required, the investigator will call the medical monitor who will break the emergency code key for that subject, identify the test coil and inform the primary investigator. A report with detail information including date and reason for identifying the study drug will be prepared by the medical monitor and attached to the case report form (CRF). This report must be signed by the medical monitor and the investigator. Counting all the unused sealed code keys will be done at the end of the study. Except in the case of emergency, maintaining treatment blind is necessary until all subjects have completed the treatment and the database has been cleaned and locked. Justifying for any broken code is compulsory and with explanation by a comment on the case report form, along with the date on which the code was broken.

3.2.4 Study Outcomes

3.2.4.1 Primary Outcome Measure

The primary outcome of this study is the change from baseline in mean monthly migraine days.

3.2.4.2 Secondary Outcomes Measure

1. The DASS-21 score changes in migraine patients in response to rTMS. [Time Frame: 4 months after first session of rTMS]. Mean score changes from baseline for depression, anxiety and stress category.
2. The PSQI score changes in migraine in response to rTMS. [Time Frame: 4 months after first session of rTMS]. Mean scores change from baseline.
3. Electroencephalography (EEG) pattern change in migraine in response to rTMS. [Time Frame: Baseline and after treatment sessions (4 months after session).

4. The GPAQ score change in migraine in response to rTMS. [Time Frame: 4 months after first session of rTMS]. Mean score changes from baseline.

3.3 Study Location

This study is a single-centred study. The treatment and all procedures are delivered in neurophysiology laboratory of Faculty of Medicine and Health Sciences, Universiti Putra Malaysia which located in Serdang, Malaysia. Participants We adhered to rules and regulations of Ethics Committee.

3.4 Study Population

Migraine patients 18 to 60 years old based on International Classification of Headache Disorders 3 (ICHD-III) having episodic migraine.

3.5 Sample

Seventy-six samples were recruited, however only 64 subjects completed the study.

3.6 Sample Size Calculation

Based on Lemeshow et al., (1990), the formula for estimating sample size, hypothesis testing for comparing two means is used with significance value less than 0.05 and study power 80%. All of the previous study use primary outcome for sample size calculation. Based on previous paper, Misra et al., (2013), we assumed a 50% reduction in migraine days per month with standard deviation (SD) 50% for sample size calculation for the main study. Power analysis calculated at least 32 cases mandated per group (11) with α (the probability of type I error) as 0.05, and β (the probability of type II error [1- power of the test]) as 0.20. Considering a 30% dropout rate, a final sample size of 38 subjects in each treatment arm was estimated.

The formula is for sample calculation is:

$$\frac{(\sigma_1^2 + \sigma_2^2)\left(z_{1-\frac{\alpha}{2}} + z_{1-\beta}\right)^2}{\Delta^2}$$

where σ: Variance of mean; Δ: Absolute difference between two means; z: Critical value for a given α or β.

3.7 Sampling Method

This study practised non-probability consecutive sampling method was in this study which is fast, easy and inexpansive. It is widely used in RCT which considered the best. It give a better insight into the number of eligible subjects (Thewes et al., 2018). Advertisements were circulated in HSAAS, Hospital Serdang, UPM and Serdang area. Emails were aslo sent among UPM students and staff. Moreover, after patients with a history of migraine headaches were identified during a series of health screenings done for the Serdang community, these patients were contacted and invited to come to Neurophysiology Laboratory, UPM. Those who met the eligibility criteria were invited to participate to the study.

3.8 Inclusion and Exclusion Criteria

Screening failures were the patients who failed to meet the inclusion and exclusion criteria. The investigator maintained a Screening Log which includes screen failures. The log documented the subject number, subject initials, demographics and the reason(s) for excluding the patient from the study. This log was kept in the Investigator's Study File.

Patients who withdrew from the study for other reasons had previously consented to follow-up in the study. Data up to this time can be included in the study if was anonymous. Subjects who withdrew or were withdrawn from the study should:

1. Have the reason(s) for their withdrawal recorded.

2. Be asked about the presence of any adverse events (AEs) and if so should be followed up by regular scheduled visits, telephone contact, correspondence, or home visits until satisfactory clinical resolution of AEs is achieved.

3. Be seen by an investigator and all final assessments will be performed and recorded in the Termination page of CRF.

4. Be encouraged to continue coming for regular visits and assessments.

5. Have at least one follow-up contact (scheduled visit, telephone contact, correspondence or home visit) for safety evaluation during the 30 days following the last administration of study treatment.

6. In the event of suspicion of pregnancy, the subject should be monitored until conclusion of the pregnancy and the outcome of pregnancy reported.

3.8.1 Inclusion Criteria Using ICHD-III Criteria

Episodic migraine complaint by the participant must satisfy on ICHD-III criteria:

A. Migraine attack must be five attacks or more fulfilling criteria B-D

B. The headache attacks lasting 4-72 hours (untreated or unsuccessfully treated)

C. The headache must at least have two of the following four characteristics:
   1) the location is unilateral or affect one hemisphere
   2) pulsating quality
   3) The pain intensity is moderate or severe
   4) the pain is aggravated by or causing the sufferers to avoid routine physical activity (e.g., walking or climbing stairs)

D. During headache at least one of the following:
   1) complaint of nausea and/or vomiting
   2) photophobia and phonophobia

E. Not better accounted for by another ICHD-3 diagnosis.

Migraine with aura diagnostic criteria:

I. At least two attacks fulfilling criteria B and C

II. One or more of the following fully reversible aura symptoms:

1. visual
2. sensory
3. speech and/or language
4. motor

5. brainstem
6. retinal

F. At least three of the following six characteristics:
1. at least one aura symptom spreads gradually over ≥5 minutes
2. two or more aura symptoms occur in succession
3. each individual aura symptom lasts 5-60 minutes
4. at least one aura symptom is unilateral
5. at least one aura symptom is positive
6. the aura is accompanied, or followed within 60 minutes, by headache

G Not better accounted for by another ICHD-3 diagnosis.

Based on above ICHD-3, these are the inclusion criteria:

1. Subjects with age ranging between 18 to 60 years.
2. Subjects is fulfilling the criteria of episodic migraine according to ICHD-3 for at least one year.
3. The frequency of headache is 2 to 8 per month and not over fifteen days per month. More than fourteen days is considered chronic migraine.
4. The subject is compliant to headache diary with minimum of 80% compliance during the run-in period.
5. The informed consent form is signed and dated by the subject indicating that he/she had been informed and acknowledged all aspects and potential risks or benefits of the study.

3.8.2 Exclusion Criteria

1. Any individuals with history of receiving RTMS treatment.
2. The onset of headache at age 50 years or more.
3. Organic secondary headache or any red flags or symptoms suggested to it.
4. Lactating or pregnant women.
5. Proof of contraindication to TMS based on the Screening 13-items Questionnaire for rTMS candidates (Rossi et al., 2011).
6. Individuals with underlying severe medical conditions such as severe hypertension, cardiovascular or cerebrovascular disease, infection, malignancy, epilepsy, degenerative central nervous system disease, renal failure, hepatic failure, bleeding diathesis and serious mental illness.

3.9 Instruments

3.9.1 Electroencephalography Test

Electroencephalography (EEG) is used to run photic test. EEG is safe and does not produce radiation when compared to x-ray and computed tomography. Stimulation with increasing frequency is delivered to the participants and photic driving responses (PDR) observed in the graph displayed by the monitor. PDR has amplitude higher than baseline is. PDR is easily observed in EEG and the most discussed findings in literature about EEG of migraine patients. For data analysis, the absence of PDR is marked as 'No', while the presence of PDR is marked as 'Yes'. Figure 15 showed the example of PDR.

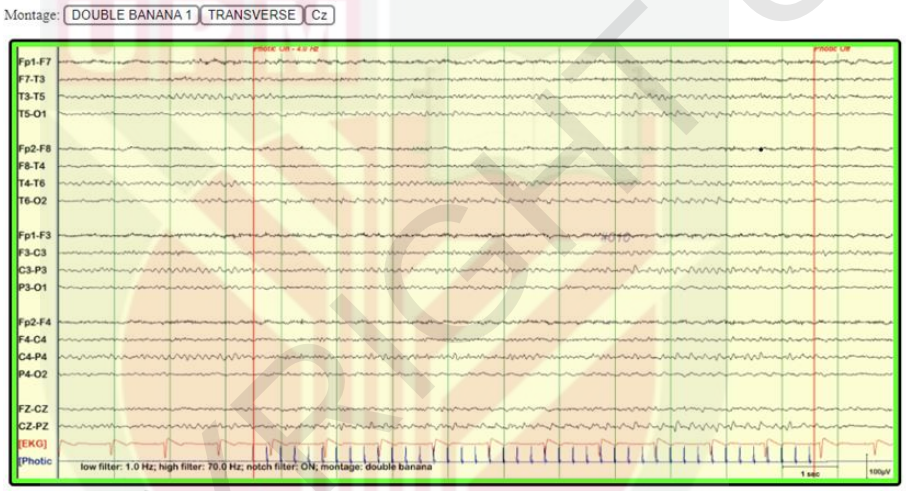

Figure 3.3: Photic driving response.
(Source: https://eegatlas-online.com/index.php/en/alphabetical-index/photic-driving-guest)

3.9.2 Questionnaires

This study used Pittsburgh Sleep Quality (PSQI) to measure sleep quality, Global Physical Activity Questionnaires (GPAQ) and DASS-21 questionnaires to assess negative emotions which are depression, anxiety and stress.

3.9.3 Sleep (Pittsburgh Sleep Quality Index)

Pittsburgh Sleep Quality Index (PSQI) will be used to measure quality of sleep among migraine patient. The evaluated parameter in 19-item self-reported questionnaire PSQI consists of 7 component scores to measure sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbance, use of medication and daytime dysfunction. The score of more than 5 showing low sleep quality. PSQI is developed by Daniel J. Buysse. The reliability of Malay version is tested by Nor Mf Farah et al on 2019 with Cronbach alpha: 0.74. The questionnaire showed acceptable reliability and is valid for Malaysian population. This study also reported sleep-related complaints by the subjects. While higher prevalence of poor sleep quality and complaints of sleep disturbance was reported in migraine, this questionnaire is needed in this study. Its utility is proven for clinical settings and non-clinical purpose such as research activity.

In scoring the PSQI, there are seven component scores. Subject must rate the symptoms from 0 to 3 as '0' represent no difficulty and '3' is severe difficulty. The component scores are summed to produce a global score ranging from 0 to 21. Score more than 5 is considered poor sleeper. Higher scores indicate worse sleep quality. Figure 16 summarised the distribution of the scoring system based on the component.

Component 1: Subjective sleep quality—question 9
Response to Q9

Component 1 score:

Very good =0
Fairly good =1
Fairly bad =2
Very bad =3

Component 1 score:_____

Component 2: Sleep latency—questions 2 and 5a
Response to Q2

Component 2/Q2 subscore < 15 minutes 0 16-30 minutes 1 31-60 minutes 2 > 60 minutes 3 Response to Q5a

Component 2/Q5a subscore
Not during past month
0 Less than once a week
1 Once or twice a week
2 Three or more times a week
3 Sum of Q2 and Q5a subscores

Component 2 score 0 0 1-2 1 3-4 2 5-6 3

Component 2 score:_____

Component 3: Sleep duration—question 4 Response to Q4

Component 3score
> 7 hours =0
6-7 hours =1
5-6 hours =2
< 5 hours =3

Component 3 score:_____

Component 4: Sleep efficiency—questions 1, 3, and 4

Sleep efficiency = (# hours slept/# hours in bed) X 100% # hours slept—question 4 # hours in bed—calculated from responses to questions 1 and 3 Sleep efficiency

Component 4
score > 85% = 0
75-84% 1 65-74% = 2
< 65% = 3

Component 4 score:_____

Component 5: Sleep disturbance—questions 5b-5j Questions 5b to 5j should be scored as follows:

Not during past month =0
Less than once a week =1
Once or twice a week =2
Three or more times a week =3

Sum of 5b to 5j scores Component 5 score 0 0 1-9 1 10-18 2 19-27 3

Component 5 score:_____

Component 6: Use of sleep medication—question 6 Response to Q6

Component 6 score:____

Not during past month = 0
Less than once a week = 1

Once or twice a week = 2
Three or more times a week = 3

Component 6 score: _____

Component 7: Daytime dysfunction—questions 7 and 8
Response to Q7

Component 7/Q7 subscore

Not during past month 0
Less than once a week 1
Once or twice a week 2

Three or more times a week 3 Response to Q8

Component 7/Q8 subscore
No problem at all 0
Only a very slight problem 1
Somewhat of a problem 2
A very big problem 3
Sum of Q7 and Q8 subscores

Component 7 score 0 0 1-2 1 3-4 2 5-6 3

Component 7 score: ____

Global PSQI Score: Sum of seven component scores: _____

Figure 3.4: PSQI calculation based on components
(Source: Daniel J. Buysse 1989)

3.9.4 Global Physical Activity Questionnaires (GPAQ)

Global Physical Activity Questionnaires (GPAQ) consisted of three domains evaluating sedentary lifestyle, moderate and vigorous physical activity (endorsed by World Health Organization 2002). The validity of Malay version is assessed by Arma Noor et al., 2017 with Cronbach alpha: 0.84. However, even though it is low-to-moderate validity and acceptable reliability, GPAQ is suitable to use in different cultures around the world.
The GPAQ consisted of sixteen questions asking about the physical activity whether it is carried out at work, travel to and from places, and

recreational activities. The duration of vigorous and moderate-intensity physical activities are recorded for workplaces and leisure activities sections. and moderate-intensity physical activity (walking, bicycling) is asked in the travel to and from places section. The duration of the sedentary period is in additional section.
Metabolic speed (MET) is used for calculation of physical activity. The MET is the metabolic speed in a person at basal metabolic rate or rest which require no activity other than needed for cell survival such as respiration. A MET is defined as the energy spent while sitting in relaxation and is equivalent to 1 kcal/kg/h caloric expenditure. The GPAQ measures how many MET-min of physical activity is engaged during a typical week. The MET-min per week obtained from the GPAQ is a scale-type variable. Moderate-intensity physical activity corresponds to 4 MET/min, and vigorous-intensity physical activity corresponds to 8 MET/min. During the calculation of weekly total MET-min, the durations of each type of physical activity are multiplied by these coefficients. Moderate activity multiplied by 4 while vigorous activity multiplied by 8.

To sum up, the formula is:

Total weekly MET-min: (Minutes engaged in moderate-intensity activity each week X 4 MET) + (Minutes engaged in vigorous-intensity activity each week X 8 MET)

Example: If one person walks 3 hours and plays 1 hour of basketball a week: 180 min X 4 + 60 min X 8 = 1200 MET-min is calculated.

Levels below 600 MET-min weekly were accepted as physically inactive.

3.9.5 Psychological States (Depression, Anxiety, Stress Score (DASS-21) Questionnaires)

The DASS-21 is the short version of DASS-42 which is set of self-perceived questionnaires consisted of three subscales to quantitatively measure the negative psychological states which is depression, anxiety, and stress (SH Lovibond et al 1995; Inga Marijanovic et al 2022). The scale is suitable for clinical and non-clinical setting for screening purpose. It has 21 items which is a list of questions for the subjects to rate each of the three negative affective states within the past four weeks on a four-point scale to be graded ranging from: (0) not at all, (1) some of the time, (2) a good part of the time, and (3) most of the time. Scores range from 0 to 21 in each of the three domains. Since DASS-21 is the short version, the value must be multiplied by two to reach final score matching DASS-42. Table 3.1 showed the validated cut-offs were used

to categorize DASS scores Depression subscale with Cronbach alpha Depression: 0.95, Anxiety: 0.85, Stress: 0.86 – The validity of Malay version is asssessed by Musa et al 2007 while English version is developed by Lovibond & Lovibond in1995. The three scale has high internal consistency which has meaningful discrimination thus suitable for research purpose of this study and even for clinician. It can be used to monitor perceived symptoms over time and in the case of this study is for assessing treatment response.

Table 3.2: DASS-21 scoring.

	DEPRESSION	ANXIETY	STRESS
Normal	0-9	0-7	0-14
Mild	10-13	8-9	15-18
Moderate	14-20	10-14	19-25
Severe	21-27	15-19	26-33
Extremely severe	28+	20+	34+

3.9.5 Intervention Module

In this trial, there are two groups of interventions; the subjects are divided into the rTMS group and the sham group. On this basis, each subject has a 50% chance to get either sham or rTMS treatment but nevertheless, all subjects are required to undergo the same procedures. Subjects has to undergo run-in period, baseline, treatment period, follow-up, and final visit. The timeline for the trial subjects were shown in Figure 17. Using a similar setting and study design of the trial, the neurophysiological component is also examined using an electroencephalogram (EEG). While psychological states of subjects are analysed using DASS-21, sleep quality and disturbance is analysed using PSQI while physical activity is measured by GPAQ. RTMS applied over left DLPFC area.

The procedure is described as follows:

1. A subject is instructed to sit on the chair, relax and maintain head position throughout the study.
2. Ag-AgCl surface electrodes with diameter 0.9 cm are placed 3 cm apart over the belly and tendon of the abductor pollicis brevis muscle.
3. For searching the motor threshold, single pulse focal TMS was applied over motor cortex by using a figure-of-eight coil

connected to two Magstim 200 stimulators through a Bistim module (Magstim Co., Dyfed, UK) while observing for any contralateral finger movement (if stimulated at left brain hemisphere, finger movement is at the right side).

4. When finger movement is observed, the resting motor threshold is recorded.
5. Eighty percent from the motor threshold is calculated, recorded and set for the stimulation.
6. RTMS treatment is stimulated at dorsolateral prefrontal cortex (DLPFC) area from 90° angle.
7. Eighty percent from threshold was delivered.
8. Each session of r-TMS consisted of 2000 pulses. The pulses will be given in 40 trains, each train duration is 5 seconds consisting of 50 pulses at 20 Hz with intertrain interval of 25 seconds.
9. The session is repeated five times in two weeks. Three sessions are delivered in in three consecutive days in first week and two sessions is done in second week.

3.9.7 Checklist Reminder

A checklist is shown to the participants for clear picture of the sequence of the study design. While a self-report checklist is done by facilitator. Figure 17 showed the summary of the procedures in sequence. The advantages if this checklist is that it may remind facilitator about the key components to be delivered and encourage the facilitator to adhere to the study protocol.

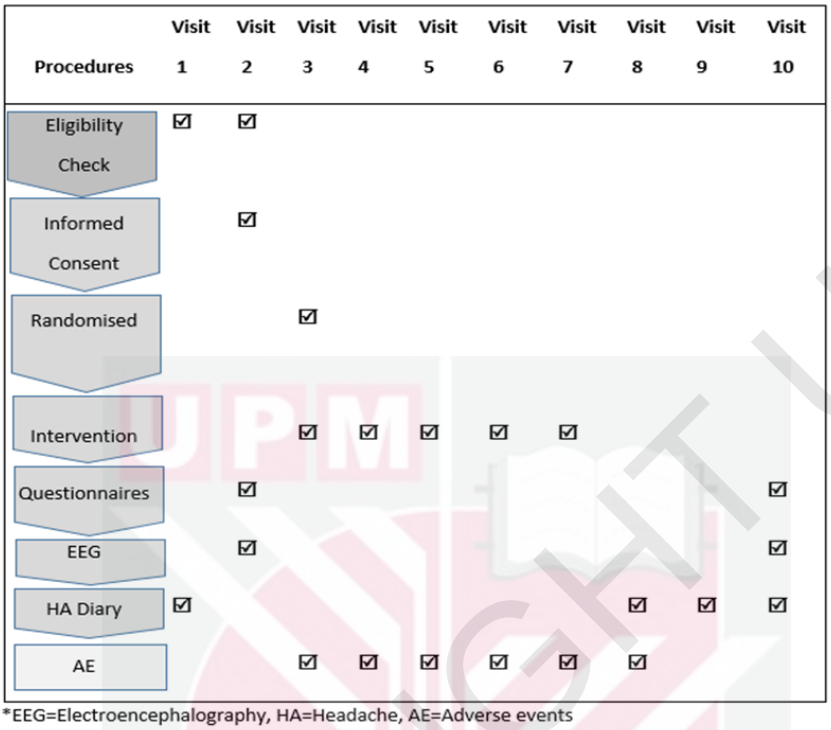

Figure 3.5: Summary of Procedures

3.10 Data Collection

During the baseline assessment, all procedures with the possible risks and benefits of rTMS treatment were explained to the participants. They were allowed to ask questions and given more. They were asked to sign an Informed consent were signed after they make decision to participate into the study. They were informed that they would receive cash as an honorarium after completion of the study and they are allowed to leave whenever they are intended to not commit to the study and for any reason. The schedule of the sessions was informed and discussed with the participants.

After the baseline assessment, an assistant randomly assigned the participants into two different groups by using block randomisation developed by a web (randomizer.org). A computer-generated randomised groups were assigned and typed in the papers which then were folded, sealed and kept in an envelope for each participant following the randomisation patterns. All the sealed envelopes were

given to the assistant who did the measurement. The envelope was only individually opened when a subject wanted to start the treatment. The researchers who conducted the intervention and assistant received the treatment group in sealed envelope to deliver to the subjects. Both could not access to the randomisation pattern. While, subjects are also blinded in which they did not know whether they were receiving treatment or sham. Subjects were supposed to complete the rTMS treatment, however if there is any missing session, they were subjected to a discussion with the researcher to reschedule the missing session.

Recruitment of 183 subjects was done from April 2019 to September 2020. Hundred and seven from them had to be excluded. While 55 of them is not eligible. 26 subjects did not consent and withdrew, while there were 26 subjects who were uncontactable thus lost to follow up. As per the calculated sample size, 76 subjects enrolled in this trial for randomisation. The subjects were randomised into rTMS intervention (n = 38) and sham (n = 38).

In the rTMS group, five subjects withdrew from the study before intervention due to a busy schedule thus unable to comply to the treatment schedule resulting in only 33 subjects received the rTMS intervention. After intervention, there were no subjects lost to follow-up. However, one subject made a complaint of serious migraine attack and terminated from the study. Therefore, the final analysis only includes 32 subjects in treatment arm.

Meanwhile, only two subjects who were randomised into the placebo group, withdrew from this trial before intervention. One of them transferred to another location for working purpose. Another dropped out subject is due to busy schedule thus unable adhere to the treatment schedule. Therefore, only thirty-six subjects received the intervention. However, four subjects discontinued the treatment from this group. Three of them has busy schedule while another one was terminated after a complaint of severe migraine attack. Thus, only thirty-two subjects completed the intervention in placebo arm. For analysis purpose, ITT analysis includes all randomised subjects randomised thus thirty-eight subjects were analysed in each arm. For PP analysis, all subjects who completed the intervention are analysed which are thirty-two subjects for each group.

3.10.1 Research providers

Following ICH-GCP, a Principal Investigator is Associate Professor Dr

Wan Aliaa Wan Sulaiman. She is a qualified consultant neurologist at Hospital Sultan Abdul Aziz Shah (HSAAS). At the same time, all investigators had attended the compulsory training of Malaysian Good Clinical Practice (GCP). The investigators were also trained on all the related procedures involved in this clinical trial. The training was given promptly before the investigators were due to perform the delegated tasks.

3.10.2 Recruitment, Screening, Consent and Baseline Data

International Classification of Headache Disorders (ICHD-III) criteria were used to screen the headache diary. If satisfying the criteria, subjects is allowed to go for visit 2 which is the baseline appointment. Information sheet containing details of the study was given for reading and subject is allowed to ask questions and provided enough information. If they are agreed to the study, then inform consent was given in two copies, one copy was given to the subject and another copy was kept together with the case report form. This copy was kept in a file. Subject's study number was labelled. The file was kept within a locked cabinet inside a secure room in the Headache Research Clinic in Neurophysiology Laboratory, UPM.

Recruitment was carried out from 15th April 2019 until the end of September 2020. Recruited subjects were screened International Classification of Headache Disorder 3rd Edition (ICHD-3) for migraine at visit 1. The details of the study were described to the subjects. Subjects with episodic migraine were asked to self-monitor their headache attacks and fill in a headache diary for a month which is a run-in period. After a month, text message or a call was made to schedule for visit 2. 80% compliance to headache diary is considered a compliant subject. They were given an appointment date for the baseline appointment. Any uncontactable subjects were considered lost to follow-up after three attempt of contacting them results in failure. At baseline, few procedures are carried out which are for primary study and this study. For this study, subject has to undergo electroencephalography and fill up questionnaires before rTMS intervention.

3.10.3 Randomisation

The participants are assigned to either in rTMS intervention or a sham control arm in a parallel intervention mode. In order to randomise the participants, randomisation sequence is generated by web-based

randomiser (www.randomizer.org). Random allocation is employed to assign the participants to an intervention and a control arm. To achieve an unbiased comparison group and to have a balanced randomization, this study used permuted block randomization with a varying block size. The sample size estimated for the study is 76. Hence, there are ten blocks with a block size of four participants each and ten blocks with a block size of two participants each with one-to-one allocation ratio is used. A trial member is assigned for the randomisation process and to label the treatment into A and B. Preparation of the sealed envelope containing randomisation group is prepared by the same person. The trial members who is assigned to prepare the data of randomisation with envelope is unblinded, while the staffs who have to deliver the treatment, sham and other procedures remains blinded. The team members that ran the statistical analysis is also blinded from the study.

3.10.4 Safety Analysis

The safety analysis of this trial was conducted by the primary study. The summaries of adverse events include all patients who received any study treatment; those who did not receive study treatment are not included in these summaries. The safety population comprised of all randomized patients who received at least one treatment dose and was based on the actual treatment received.

3.10.5 The Intervention

Figure 3.6: Photo of rTMS
(Source: www.magstim.com)

Randomisation process took place during visit 3. They received their respective treatment intervention as either '**Treatment A'** or '**Treatment B'** for five sessions within two weeks regardless of their group. The treatment is scheduled as three consecutive days in the first week and two consecutive days in the following week. Then the subjects will start the first intervention. Figure 18 showed the rTMS treatment. Intervention sessions were scheduled for visit 3 to visit 8. After randomisation process, motor threshold measurement was determined before the rTMS was delivered. All subjects were reminded to come for their treatment visits via text messages. Earplug is recommended throughout the session. On the last day of the treatment session, subjects received three sets of headache diaries for them to fill in within the next three months (reported in other study).

3.10.6 Follow-up

The follow-up phase was ended on 2nd February 2021. All subjects were followed up until three months. Calculation was made from the last session of the intervention. All conversation regarding the schedule for visit was made via text messages.

Subjects were contacted after three months for Visit 10. The subjects had to repeat the same procedures done on visit 2 which is EEG for this study and fill up the same questionnaires which are DASS-21, PSQI and GPAQ for this study. for measurement of post-intervention. The three sets of the headache diaries were inspected and all entries regarding their headache attacks were asked for further clarification (which are analysed by other study). All subjects were reimbursed with RM100 for transportation cost. Certificate of participation was given as a token of appreciation for commitment until the end of the study.

3.10.7 Adverse Event and Unblinding

Assessment of migraine attack is recommended by using a simple attack report form for the primary objective in the clinical trials. During the attack, the simple, detail form is recommended compared to the complicated form (Tfelt-Hansen et al., 2000). In case of any adverse event, JKEUPM must be informed within 24 hours and action must be taken accordingly. Two cases of severe migraine attacks were reported in this study warranted for unblinding. The patients were referred to the neurology clinic. The unblinding process is taken over by the trial

member who keep the randomization detail and the information about their intervention whether it is a sham or Rtms is passed over to clinician without informing the trial members who deliver the procedures to the subjects. Thus they remained unblinded.

3.10.8 Evaluation

The important difference between intention-to-treat and per-protocol analyses -and their impact on how we interpret and share results. In the real world, people may not follow an ideal protocol, drop out cases will be high. In this trial, both intentional to treat (ITT) and per protocol (PP) were used. Intention-to-treat (ITT) was the primary analysis which includes all subjects that had been randomised to their allocated treatment regardless of their adherence to the treatment or the entry criteria and regardless of the protocol deviation or subsequent withdrawal from the trial (Peace, 1989). Overestimation of treatment efficacy could be prevented that often resulted when non-compliance subjects were removed from the analysis. The probability of non-adherence and protocol deviation is acceptable as in the actual clinical settings (Heritier et al., 2003).

ITT analysis is usually the preferable method of analysis. The strength of randomisation is preserved by assuming that the rate of non-adherence is equal in both intervention groups (Wang & Bakhai, 2006). However, underestimation of the effect of the intervention might occur and cause an intervention to look safer when incomplete compliance had occurred but was not taken into consideration. Therefore, maximal efficacy could be achieved in per-protocol (PP) where only completed subjects' data is taken into account. It also prefers patients's decision whether or not to use the treatment (Hernán & Robins, 2017; Wang & Bakhai, 2006). Therefore, in this study PP analysis was also performed.

A few methods are available for handle missing data including complete case analysis, single value imputation either using simple mean imputation or replacing the value using the subject's last observed value or multiple imputations. For example, multiple imputation was proposed by Rubin on 1987 in which *D* imputed values for each of the missing observation is generated and hence we get *D* complete data set. From each of the complete data set an estimate of the parameter of interest θ is obtained by using a standard technique, assuming no non-response is present. Valid statistical inferences will be obtained that properly reflect the uncertainty due to missing values (R. Arnab 2017). Multiple imputations technique was considered valid and the preferred method for imputing plausible missing values (Jakobsen et al., 2017;

Sterne et al., 2009), even though it could not provide the pooled F test following the analysis of variance (ANOVA) in SPSS statistical software (van Ginkel & Kroonenberg, 2014). In this RCT, the mean imputation method was used to replace missing data in ITT analysis.

By using the Kolmogorov-Smirnov test to normality was assessed and graphical approach through a histogram with a normal curve. Frequency, percentage, mean and standard deviation were reported for baseline demographic measures. All results were analysed using IBM SPSS statistical software version 26.0 by a researcher and a statistician blinded to the treatment intervention. For analysing continuous data of photic driving response, McNemar's test was chosen. A significant value was considered as a p-value of less than 0.05.

For other secondary outcome measures which were PSQI, DASS-21 and GPAQ score, within-group comparisons were conducted using the inter-group comparisons were tested using the Kruskal-Wallis H test. Kruskal-Wallis H test on DASS-21 score which is non-parametric test. Non-parametric test of pair-wise rank test is superior than ANOVA if the data does not follow normal distribution. We run Kolmogorov-Smirnov test, the data is not normally distributed. Therefore, instead of ANOVA which requires normal distribution, we use Kruskal-Wallis H test. The reason why the data is not normally distributed is because the data is skewed. The p-value less than 0.05 is chosen as the level of signficance.

3.11 Validity and Reliability

The first questionnaire used was a validated DASS-21 questionnaire which had been designed to assess psychological states consisted of 3 set of subscales measuring three negative emotion Depression, anxiety and Stress. Depressive symptoms are measured with a set of questions asking seven subscales which are dysphoria, hopelessness, devaluation of life, self-deprecation, lack of involvement, anhedonia and inertia. Anxiety subscales include set of questions asking about autonomic arousal, skeletal muscle effects, situational anxiety and subjective experience of anxious feeling. While, stress parameter is evaluated based on sensitivity to the levels of chronic non-specific arousal assessing difficulty on relaxation, nervous arousal and being easily agitated, irritable, over-reaction and impatience. The original English version was developed in 1995 and its reliability had been tested and validated (Lovibond & Lovibond et al., 1999). The translated Malay version has been validated in the Malaysian population by Musa et al. 2007). Cronbach alpha Depression: 0.95, Anxiety: 0.85, Stress: 0.86.

The second questionnaire is Global Physical Activity Questionnaires (GPAQ) consisted of three domains evaluating sedentary lifestyle, moderate and vigorous physical activity. This questionnaire is endorsed and recommended by world Health Organization in 2002. The questionnaire is suitable for cross-culture and different settings. The original English version was validated by CL Cleland et al on 2014. The Malay version has been validated by Arma Noor et al., on 2017 with Cronbach alpha: 0.84. This study concluded that GPAQ has high psychometric properties and valid for Malaysian population.

Pittsburgh Sleep Quality Index (PSQI) was the last questionnaire. It was validated by Evaluated parameters in PSQI: sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbance, use of medication, Daytime dysfunction. The translated Malay version by Nor Mf Farah et al on 2019 with Cronbach alpha: 0.74.

3.12 Data Analysis

Analysis will include all randomised subjects. Importantly, Baseline Comparability True randomisation, concealed location and adequate sample size in this study will ensure enough baseline comparability between groups (r-TMS and placebo group). Collectively, we include a table of baseline characteristics of participants in each group, without between-group statistical comparisons. This table will be analysed to decide whether any characteristics were imbalanced enough to influence the outcomes of the study.

The primary analysis of this study is intention-to-treat (ITT) analysis. All randomized subjects from placebo and treatment arm are included in the study without taking into account their compliance towards the treatment, protocol deviation or even trial study withdrawal (Peace, 1989). An overestimation of treatment efficacy could be avoided in case of attrition. It considers actual clinical environment where protocol deviation and non-compliance is not constraint (Heritier et al., 2003).

Even though attrition from the study is allowed at any time, the missing data is taken into account. This study use mean amputation method to replace missing data. However, there are few methods to compute missing data. For instance, multiple imputations. Multiple imputations are preferable and has validity (Jakobsen et al., 2017; Sterne et al., 2009). However, pooled F test could not be provided for the primary

study in this trial.

This study complies with the CONSORT guidelines on analysis and data reporting while statistician was blinded to the treatment status (Schulz et al., 2010). Kolmogorov-Smirnov test was used to for normality test. Baseline demographic and primary outcome measures were reported using frequency, percentage, mean and standard deviation. In primary study, categorical data were analysed using Chi-square test and Fisher's exact test and continuous data were analysed using an independent T-test. While in this study, Kruskal-Wallis H test was used which is non-parametric rank-based test. Kruskal-Wallis test were developed by William H. Kruskal and W. Allen Wallis in 1952 to determine whether more than two samples come from the same or different populations. Kruskal-Wallis H test do not assume the data to be normally distributed (Carver & Nash, 2011). Kruskal-wallis can analyse ordinal data from DASS-21, GPAQ and PSQI which is arranged based on severity of the symptoms when Kolmogorov-smirnov test showed the data is not normally distributed. All results were analysed using IBM SPSS statistical software version 26.0. This study is a double-blinded study where participants and researchers are blinded. For analysis purpose, statistician is also blinded. Some of the data from this large trial was analysed by other study.

3.13 Ethical Considerations

The study will be conducted in compliance with the protocol and standard operating procedures guided by *"JawatanKuasa Etika Penyelidikan UPM*" (JKEUPM) or known as Ethics Committee for Research involving Human Subjects and already receive JKEUPM approval. These are designed to ensure adherence to the ethical principles that have their origin in the "World Medical Association Declaration of Helsinki", "Malaysian Guidelines for Good Clinical Practice" and applicable regulatory Requirements. Applicable government regulations and Universiti Putra Malaysia research policies and procedures will also be followed.

Submission of protocol and any amendments will be directed to the JKEUPM for formal approval to conduct the study. The investigator will receive the decision of the JKEUPM concerning the conduct of the study in writing form. All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval

by the JKEUPM. The formal consent of a subject, using the JKEUPM - approved consent form, will be obtained before that subject is submitted to any study procedure.

3.13.1 Ethical Approval

This study is a secondary analysis from MAGNET-EM study. It is a single-centred, double-blinded randomised, controlled trial registered with clinicaltrial.gov (ClinicalTrials.gov NCT03556722) and to Universiti Putra Malaysia Ethics Committee for Human Research (JKEUPM-2018-397)). General guidelines set up by ICH-GCP were followed and this research upholds the principles of the Declaration of Helsinki. Ethical clearance was renewed annually since approval date 22nd March 2019. Written consent will be obtained from each subject involved in the study. If it is not possible, oral consent can be obtained by a signed statement from one or more persons not involved in the study as witness. Reason for inability to sign must be stated. The informed consent form must receive must be approved by IEC prior to the study.

3.13.2 Reporting Severe Adverse Events (SAE)

Severe adverse events (SAE) will be recorded with all the necessary information on the Serious Adverse Event Page of the CRF and must be reported within 24 hours to the (JKEUPM)/sponsor by fax. Waiting for additional information to fully document the SAE before notifying (JKEUPM) which will cause delay must be avoided. A fax SAE form should follow telephone report of SAE. Compliance with the applicable regulatory requirements related to the reporting of unexpected serious drug reactions to the regulatory authorities is a must. The information from relevant medical records and autopsy reports should be obtained where applicable. Any death or congenital abnormality within 6 months after cessation of study treatment, whether considered treatment related or not should be reported to JKEUPM.

3.14 Summary

This chapter describes the study methodology. All measurements used in this study were explained, ethical concerns have been addressed and limitations were presented.

Table 3.3: Summary of the study

Study Element	Study Component	Key Literature
Population	Episodic migraine	Lack of effective interventions for those with comorbidity despite the negative impact on individuals in terms of functioning, sleep quality, psychological health and healthcare system in terms of utilisation and cost.
Intervention	Repetitive transcranial magnetic stimulation	Lack of prophylaxis treatment and management for comorbidities. **Pre-Intervention:** Study Location Study design Sample size Sampling method Inclusion Criteria Statistical Analysis Method Ethical approval Recruitment Screening sessio
Comparison	Sham	Baseline Data Collection Randomisation **Intervention:** Intervention & Post Test **Post-Intervention:** Follow-up and Statistical Analysis
Outcome	Quality of Life	Sham treatment was given and usual primary care is appropriate for management in primary care.
		Primary outcome: Treatment efficacy was determined using four common outcome measures; mean changes of migraine days, mean changes in migraine frequency, mean changes of pain score and mean changes in medication intake

Table 3.3: Continued

		between pre and post-intervention [in primary study] **Secondary outcomes**: EEG changes, Sleep Quality, Psychological states (Depression, anxiety, stress), Physical Activity [described in this study].

CHAPTER 4

RESULTS

4.1 Overview

This chapter describes the descriptive study of the socio-demographic data of the participants. The effectiveness of the repetitive transcranial magnetic stimulation (RTMS) in reducing DASS-21 scores, PSQI scores and GPAQ scores of migraine patients are also presented. DASS-21 measure negative emotions, PSQI measures sleep quality and GPAQ measures physical activity as described in previous chapter. It recommended by CONSORT guidelines to report the baseline data for subjects in randomised controlled trial (Moher et al., 2012). Table 4.1 and 4.2 describe the baseline demographic data of this trial.

April 2019 to September 2020, recruitment for this study was done on 183 subjects. However, 107 were excluded from the study. The reason of exclusion of 55 subjects is not meeting eligibility criteria while 26 subjects were lost to follow-up. Randomisation was carried out for 76 subjects. 38 of them were randomised into placebo group, while another 38 into RTMS treatment group. Five subjects from rTMS group withdrew from the study before intervention visit due to busy schedule. No subject loss to follow-up While, one subjects reported severe migraine attack thus, result in termination of the study. The remaining 32 subjects cooperated towards the end of the study. Meanwhile, two subjects from placebo group withdrew from the study before intervention visit. One of them transferred out of town for working purpose. Another one dropped-out due to busy schedule. Thus, thirty-six of them started the intervention. However, three subjects withdrew due to busy schedule and another one subject was terminated due to severe migraine attack. Therefore, each arm received thirty-two subjects. Data of all subjects randomised in this study is analysed using intervention-to-trat (ITT) analysis, while data of the subjects who completed the trial is analysed using per protocol (PP) analysis.

4.2 Sociodemographic data (Aura, gender, educational status and working status)

Baseline characteristics of all of the randomised subjects is demonstrated in Table 4.1, while the baseline data of the subjects who completed the study is summarised in Table 4.2. The ratio in gender,

race, marital status, and employment status in both groups is similar. While most of the subjects reached tertiary education. while based on descriptive study result, 81-78% of subjects has migraine without aura which is close to the prevalence of migraine in Malaysia which is 89.6%. In addition, 81% among them are female thus fit the findings in this study which is 81.3% are female subjects with remaining 18.8% are males. The distribution of races is slightly different. While Malays range from 84-94% which is higher than general population. Hospital Sultan Abdul Aziz Shah (HSAAS) is a university hospital which is located in urban area, a human settlement with high population density and an infrastructure of built environment. This condition may explain why the percentage of Malay respondents is high. Besides that, representing labour force participation rate in Malaysia (which is 68.6% in 2021). In this study, the working subjects is ranging from 65% to 70%. The unemployed subjects are mostly students and housewives. As much as 78.1% subjects finished tertiary education, while remaining 21.9% is not which may include undergraduate students pursuing the study.The Mean Monthly Migraine Days is the primary outcome of the clinical trial which had been analysed in a different study (Nabil et al 2023). The Mean Monthly Migraine Days is the primary outcome of the clinical trial which had been analysed in a different study (Nabil et al 2023).

Table 4.1 Baseline characteristics of all of the trial subjects

		Total	Treatment				
			RTMS		Placebo		
			n	(%)	n	(%)	P
Types	Without aura	59	28	(73.7)	31	(81.6)	0.41
	With aura	17	10	(26.3)	7	(18.4)	
Gender	Female	63	32	(84.2)	31	(81.6)	0.76
	Male	13	6	(15.8)	7	(18.4)	
Race	Malay	69	33	(45.6)	36	(94.7)	0.43
	Non-Malays	7	5	(113.2)	2	(5.3)	
Work status	Working	56	27	(44)	29	(76.3)	0.60
	Not-working	20	11	(28.9)	9	(23.7)	
Education status	Lower than tertiary	20	8	(21.1)	12	(31.6)	0.30
	Higher than tertiary	56	30	(78.9)	56	(73.7)	

*Significant p-value < 0.05

Table 4.2: Baseline characteristics of all of the subjects who completed the trial

		Treatment						
		Total		rTMS		Placebo		
		n	%	n	%	n	%	P
Aura	Without aura	50	78.1	24	75	26	81.2	0.55
	With aura	14	21.9	8	25	6	18.8	
Gender	Female	51	79.7	26	81.2	25	78.1	0.76
	Male	13	2.3	6	18.8	7	21.9	
Race	Malay	57	89.1	27	84.4	30	93.8	0.43
	Non-Malays	7	1.9	5	15.8	2	6.3	
Working status	Working	46	71.9	21	65.6	25	78.1	0.27
	Not working	18	28.1	11	34.4	7	21.9	
Education	< Tertiery	18	28.1	7	21.9	11	34.4	0.27
	> Tertiery	46	71.9	25	78.1	21	65.6	

*significant p-value < 0.05, rTMS= repetitive transcranial magnetic stimulation, < = less than, > = more than

4.3 Electroencephalography changes

The photic driving response (PDR) is measured from EEG readings. McNemar's test is used to analyse the non-parametric data of paired sample test. McNemar's test is used to analyse this data because the data is non-parametric data and the dependent variable is dichotomous data. For the dependent variable, the absence of PDR is marked as 'No', while the presence of PDR is marked as 'Yes'. ITT analysis and PP analysis reported similar result. Seventy-six subjects were randomised into rTMS and placebo arm. In ITT analysis, seventy- six subjects randomised in the study. An exact McNemar's test determined that there was statistically significant difference in the proportion of the PDR pre and post intervention, p=0.0001.

While in PP analysis, sixty-four subjects took part in the intervention study designed for migraine prophylaxis. An exact McNemar's test determined that there was statistically significant difference in the proportion of the PDR pre and post intervention, p=0.005. Figure 18 showed the histogram representing result of PDR analysis.

4.4 Comparison between ITT and PP analysis for PDR

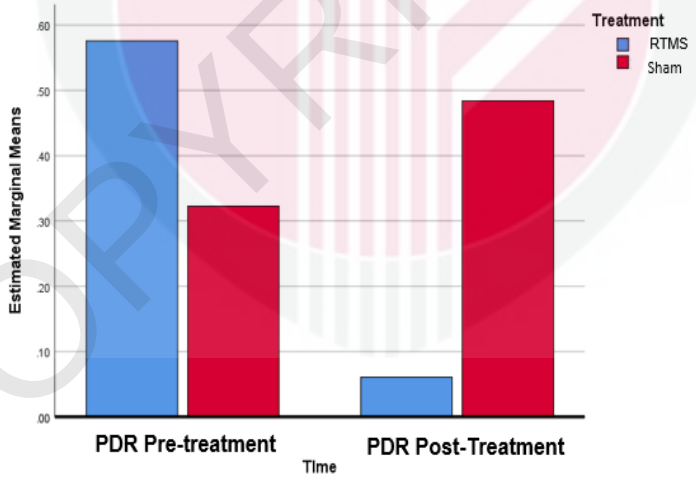

Figure 4.1: ITT analysis for PDR
*PDR=photic driving response

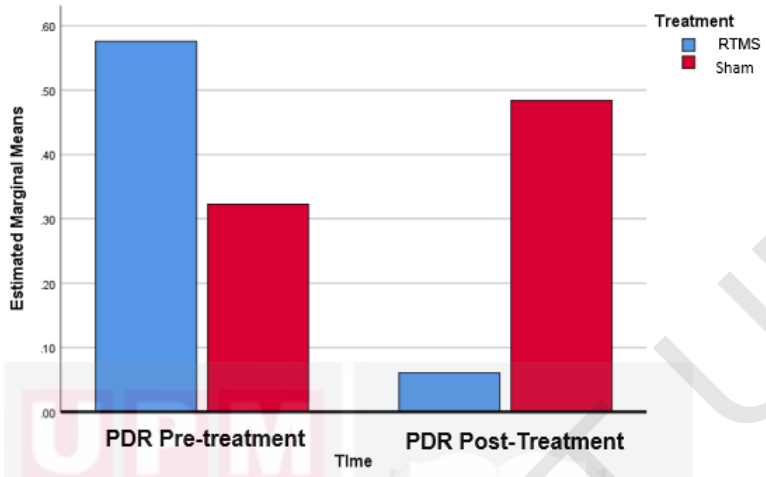

Figure 4.2: PP analysis for PDR

***PDR=** Photic driving response

4.5 Sleep Quality

Pittsburgh Sleep Quality Index measure sleep quality and daytime disturbance. The data is ordinal. In PSQI questionnaires, subjects were required to complete all components. The summation of all components yield a total of score ranging from 0 to 21. The score higher than 5 is considered poor sleeper. We run Kolmogorov-Smirnov test on the PSQI score and the data was not normally distributed. The significant p-value, 0.0001 in PSQI scores was obtained. Since 0.0001 is less than 0.05. The data is considered not following normal distribution.

Wilcoxon Rank test has computed to examine physical activity pre- and post-treatment. The findings demonstrated in table 4.5a showed that there was a significant different in PSQI score between pre- and post-treatment in rTMS and placebo group for ITT analysis, For rTMS group (*Z*= -3.484, p=0.0001), while for placebo (Z = -3.301, p=0.001). While in PP analysis, there was no significant difference between pre-and post-treatment.

Therefore, Kruskal-Wallis H test was chosen as it is suitable rank-based non-parametric test for two or more groups. The results of PSQI score are summarised in table 4.5b. ITT analysis reported no significant difference in PSQI score between RTMS group and placebo but not in PP analysis. ITT analysis showed that there was a significant difference

in physical scored by RTMS and placebo group, *H(1) = 1.19, P= 0.756* with median of 6.50 for placebo group and 6.00 for RTMS group. Since the significant value is 0.756 which was higher than 0.05, the difference between two group was not statistically significant in ITT analysis. The median was 6 and 6.5 which is higher than 5. This indicated poor sleeper, thus half of the subjects reported having sleep problems in both group.

PP analysis showed that there was no significant difference in PSQI scored by RTMS and placebo group with *H(1)= 1.89, P= 0.596* with median 5.00 for placebo group and 5.50 for RTMS group. The significant value was 0.596 which was higher than 0.05. Thus we can conclude that there was no significant difference between rTMS and placebo group. Thus, null hypothesis was retained.

Table 4.5a: Comparison between ITT and PP analysis in PSQI pre- and post-treatment

ITT analysis rTMS group (n = 38)

	Median		Negative Ranks		Positive Ranks			
Variables Pair	Pre	Post	Mean	Sum	Mean	Sum	Z	P value
SQ Post-SQ Pre	5	4	20.03	581	15.25	122	-3.484[c]	0.0001*

PP analysis rTMS group (n = 32)

	Median		Negative Ranks		Positive Ranks			
Variables Pair	Pre	Post	Mean	Sum	Mean	Sum	Z	P value
SQ Post-SQ Pre	6	5	13.97	251.50	15.45	154.50	-1.113[b]	0.266

ITT analysis placebo group (n = 32)

	Median		Negative Ranks		Positive Ranks			
Variables Pair	Pre	Post	Mean	Sum	Mean	Sum	Z	P value
SQ Post-SQ Pre	5	5	18.86	415	9	81	-3.301[c]	0.001*

Table 4.5a: Continued

PP analysis placebo group (n = 32)

	Median		Negative Ranks		Positive Ranks			
Variables Pair	Pre	Post	Mean	Sum	Mean	Sum	Z	P value
SQ Post-SQ Pre	6	5	13.97	251.50	15.45	154.50	-1.113[b]	0.266

Table 4.5b: Comparison of ITT and PP analysis of PSQI in between groups

ITT analysis

Factors	Group	N	50th (Median)	Mean Rank	Kruskal-Wallis H	P
PSQI	Pre-RTMS	38	6.67	73.26	1.19	0.756
	Pre-Placebo	38	6.67	72.15		
	Post-RTMS	38	6.00	80.97		
	Post-Placebo	38	6.50	79.74		

*Significant P<0.05

PP analysis for PSQI

Factors	Group	N	Median	Mean Rank	Kruskal-Wallis H	P
PSQI	Pre-RTMS	32	6.00	69.11	1.89	0.596
	Pre-Placebo	32	6.00	68.38		
	Post-RTMS	32	5.50	58.31		
	Post-Placebo	32	5.00	62.20		

*Significant P<0.05, PSQI=Pittsburgh Sleep Quality Index, RTMS=repetitive transcranial magnetic stimulation

4.6 Physical Activity

Physical activity was measured using GPAQ questionnaire. GPAQ measure physical activity (PA). It has three domains which was vigorous exercise (VE), moderate exercise (ME) and sedentary life style which was physical inactivity. We run Kolmogorov-smirnov test on the GPAQ scores and significant value of 0.0001 is obtained. Since 0.0001 is lower than 0.05, the data was not normal distributed. The reason iwa the histogram was skewed.

Wilcoxon Rank test has computed to examine physical activity pre- and post-treatment. The findings demonstrated in table 4.6a showed that there was no a significant different in physical acitivity score between pre and post treatment in rTMS group for both ITT and PP analysis. For ITT analysis (*Z*= -1.177, p=0.239), while for PP analysis (Z = -1.177, p=0.239). However, vigorous and moderate physical activity showed significant difference between pre- and post-treatment in RTMS group.

Kruskal-Wallis H test was chosen as it was suitable rank-based non-parametric test for two or more groups. The reason for the data is not normally distributed is because the subject scores was skewed. The results of physical activity score were summarised in table 4.6b. ITT analysis reported statistically significant difference in physical activity between RTMS group and placebo but not in PP analysis. ITT analysis showed that there was a significant difference in physical scored by RTMS and placebo group with mean *rank (H(1)= 10.50, P= 0.015* with mean rank of 93.08 for rTMS group and 81.26 for placebo group post-treatment. The significant value was 0.015 which was lower than 0.05. Therefore, there was a significant difference between placebo and rTMS group. While in PP analysis, significant value was 0.73. The value was higher than 0.05 thus, there was no significant difference between rTMS group and placebo in PP analysis.

In ITT analysis, pairwise comparison using Dunn test indicated that the rTMS group physical activity scores were observed to be significantly different from those of placebo group (p=0.024). The higher mean rank in physical activity was also observed when compared to placebo group post-treatment. Thus, subjects in rTMS group was physically more active than placebo group.

We also ran Kruskal-Wallis test on two domains of GPAQ which are vigorous and moderate exercise. In ITT analysis, both vigorous and moderate activity had significant findings. ITT analysis reported

statistically significant difference in vigorous physical activity between RTMS and placebo group, (H(1)= 9.33, P= 0.025 with mean rank 86.44 for RTMS group and 87.85 in placebo group. For moderate exercise, there was also statistically significant difference in moderate physical activity done by RTMS group and placebo group with mean rank *(H(1)= 14.28, P=0.003* with mean rank 87.25 for RTMS group and 91.36 in placebo group. Only moderate activity was reported had significant difference between placebo and rTMS group in both ITT and PP analysis.

Table 4.6(a): ITT Analysis and PP analysis in PA pre- and post-treatment

ITT analysis for rTMS

	Median		Negative Ranks		Positive Ranks			
Variables Pair	Pre	Post	Mean	Sum	Mean	Sum	Z value	P value
PA Post - PA Pre	600.000	600.000	6	24	6.75	54	-1.177[b]	0.239
ME Post - ME Pre	260	360	17.29	207.50	19.10	458.50	-1.981[b]	0.05*
VE Post -VE Pre	200	260	15.95	175.50	19.62	490.50	-2.483[b]	0.01*

PP analysis for rTMS

	Median		Negative Ranks		Positive Ranks			
Variables Pair	Pre	Post	Mean	Sum	Mean	Sum	Z value	P value
PA Post - PA Pre	140	600	6	24	6.75	54	-1.177[b]	0.239
ME Post - ME Pre	52.5	135	2.75	11	6.25	25	-.981[b]	0.326
VE Post -VE Pre	115	70	4	16	4	12	-.339[b,c]	0.734

Table 4.6(a): Continued

ITT analysis for placebo

	Median		Negative Ranks		Positive Ranks			
Variables Pair	Pre	Post	Mean	Sum	Mean	Sum	Z value	P value
PA Post - PA Pre	597.5	600	5.5	16.5	6.19	49.5	-1.468[b]	0.142
ME Post - ME Pre	260	360	16.60	83.00	19.38	620.00	-4.059[b]	0.00
VE Post -VE Pre	200	260	18.07	126.50	15.40	15.40	-2.388[b]	0.017*

PP Analysis for Placebo

	Median		Negative Ranks		Positive Ranks			
Variables Pair	Pre	Post	Mean	Sum	Mean	Sum	Z value	P value
PA Post - PA Pre	597.50	600.00	5.5	16.5	6.19	49.5	-1.468[b]	0.142
ME Post - ME Pre	210	360	13.80	69.00	15.84	396.00	-3.366[b]	0.001*
VE Post -VE Pre	180	240	11.07	77.50	13.09	222.50	-2.074[b]	0.038*

*significant value<0.05, PA=Physical activity, ME=moderate exercise, VE=vigorous exercise

Table 4.6(b): Comparison between ITT and PP analysis for physical Activity

ITT analysis of Physical activity (PA) in rTMS group

Factors	Group	N	50th (Median)	Mean Rank	Kruskal-Wallis H	P
Vigorous PA	Pre-RTMS	38	200.00	68.38	9.33	0.025*
	Pre-Placebo	38	200.00	63.51		
	Post-RTMS	38	260.00	86.44		
	Post-Placebo	38	260.00	87.85		
Moderate PA	Pre-RTMS	38	260.00	68.17	14.28	0.003
	Pre-Placebo	38	260.00	59.46		
	Post-RTMS	38	360.14	87.25		
	Post-Placebo	38	360.14	91.36		
Physical Activity	Pre-RTMS	38	609.75	69.07	10.50	0.015*
	Pre-Placebo	38	609.75	63.50		
	Post-RTMS	38	672.95	93.08		
	Post-Placebo	38	672.95	81.26		

*Significant P<0.05, PA= Physical Activity

Table 4.6(b): Continued

PP analysis of PA in placebo group

	Group	N	Mean Rank	Kruskal-Wallis H	P
Physical activity	Pre-RTMS	32	63.17	1.30	0.730
	Pre-Placebo	32	60.41		
	Post-RTMS	32	63.94		
	Post-Placebo	32	70.48		
Vigorous PA	Pre-RMTS	33	59.05	4.10	0.251
	Pre-Placebo	31	56.82		
	Post-RMTS	33	70.29		
	Placebo Post	31	71.82		
Moderate PA	Pre-RMTS	33	63.36	9.84	0.020
	Pre-Placebo	31	47.98		
	Post-RMTS	33	71.77		
	Post-Placebo	31	180.00		

*Significant P<0.05, PA= Physical Activity

4.7 DASS-21

DASS-21 measure negative emotions which are depression, anxiety and stress.

There are 21 items that need to be answered by the subjects as discussed in the previous chapter. It evaluates the severity of associated mental disorder symptoms and the global scores will fall into a few categories which are mild, moderate or severe result. Each of the questions is rated based on severity from 0 to 3. Therefore, each of the axes presents partial scores of 0 to 18-24 depending on the number of questions assigned. Validated cut-offs were used to categorize DASS-21 scores which are summarised in table 3 from previous chapter. We ran Kolmogorov-Smirnov test on the DASS-21 for normality test. The significant p-value obtained was is 0.0001 in depression, anxiety and stress scores pre- and post-treatment which is less than 0.05. Therefore, the data were not normally distributed.

Wilcoxon Rank test had computed to examine the depression, anxiety and stress score for pre- and post-treatment. The findings demonstrated in Table 4.7a showed that there was a significant different between pre and post treatment in rTMS group for both ITT and PP analysis. For ITT analysis (Z= -2.828, p=0.026), while for PP analysis (Z = -2.239, p=0.025). By looking at the median, the score of depression post-treatment in PP analysis is 6 which is significantly lower than pre-treatment which was 8. RTMS treatment might have positive effect on the improvement of depressive symptoms. There was no significant difference in placebo group between pre- and post-treatment.

For inter-group analysis, Kruskal-Wallis H test was performed on DASS-21 score which was non-parametric test to compare two or more samples (Kruskal WH 1952). Non-parametric test of pair-wise rank test is superior than ANOVA if the data does not follow normal distribution. Therefore, instead of ANOVA which requires normal distribution, we used Kruskal-Wallis H test. Kruskal-Wallis H test does not assume normal distribution (Carver & Nash 2011). Kruskal-Wallis can also be used in unequal samples. Median is used for comparison in kruskal-Wallis test (Zhang and Zhang 2019). Depression, anxiety and stress are self-reported questionnaire where the score is dependent on the answer provided by subjects which most likely unequal. The reason why the data was not normally distributed was because the data was skewed. After running Kruskal- Wallis H test, post hoc Dunn test was run to data with significant result for confirmation. The result was significant for depression score in ITT analysis. Seventy-six patients with migraine were assigned to either RTMS treatment group A (n=38) or placebo group B(n=38). After 3 months of treatment, patients underwent EEG test, while DASS-21, GPAQ and PSQI questionnaire were given.

The results of DASS-21 score were summarised in table 4.7b. In ITT analysis, there was a significant difference in depression scored by RTMS and placebo group with mean *rank H (1) = 9.60, P= 0.022* with median of 5.50 for placebo group and 4.00 for RTMS group. The significant value between group were 0.022. Since the value was less than 0.05, there was a significant different between group. While in PP analysis, there was a significant difference in depression scored by RTMS and placebo group with mean *rank H (1)= 10.2, P= 0.018* with median of 4.50 for placebo group and 3.00 for RTMS group. For depressive symptoms, higher median score was reported in placebo post-treatment when compared to rTMS group post-treatment and higher sum rank in placebo group compared to rTMS. This means that subjects in placebo group scored higher depressive symptoms compared to RTMS group.

4.7.1 Post-Hoc Test

In ITT analysis, pairwise comparison using Dunn test indicated that the rTMS group depression scores were observed to be significantly different from those of placebo group (p=0.0001). Therefore, null hypothesis was rejected and we could conclude that there was a significant different in the depression scores between rTMS group and placebo group. However, in PP analysis, pairwise comparison using Dunn test indicated that the rTMS group depression scores were observed to be not significantly different from those of placebo group.

Meanwhile for anxiety score there were no significant different between groups in both ITT and PP analysis. In ITT analysis, there was no significant difference in anxiety scored by rTMS and placebo group, *(H(1)= 3.54, P= 0.315* with mean rank of 68.99 for placebo group and 74.28 for RTMS group. While in PP analysis, there was also no significant difference in anxiety scored by RTMS and placebo group with mean *rank (H(1)= 10.2, P= 0.693* with mean rank of 63.92 for placebo group and 60.48 for RTMS group. Significant value was 0.315 and 0.693 which was higher than 0.05, showing that there was no significant difference between placebo and rTMS. Therefore, null hypothesis was retained.

Stress scores had different result in ITT analysis and PP analysis. In ITT analysis, there was a significant difference in stress scored by RTMS group and placebo group, *(H(1)= 7.73, P= 0.052* with mean rank of 67.28 for placebo group and 76.03 for RTMS group. Since significant value was close to 0.05, there was a significant difference between

placebo and rTMS group. The mean rank post-treatment in placebo group was lower than rTMS group means that subjects in rTMS group reported higher stress score. While in PP analysis, there was no significant difference in anxiety scored by RTMS and placebo group with mean *rank (H(1)= 1.45, P= 0.693* with mean rank of for placebo group and 66.67 for RTMS group. Since significant value was 0.693, which was higher than 0.05, there was no significant difference between groups.

4.7.2 Post-Hoc Analysis

In ITT analysis, pairwise comparison using Dunn test indicated that the rTMS group stress scores were observes to be significantly different from those of placebo group (p=0.0001). ITT was the primary study analysis in this trial. Therefore, null hypothesis was rejected and we can conclude that there was asignificant different in the stress scores between rTMS group and placebo group.

Table 4.7(a): Comparison between ITT and PP analysis of DASS-21 pre- and post-treatment

ITT analysis rTMS group (n = 38)

	Median		Negative Ranks					
Variables Pair	Pre	Post	Mean	Sum	Mean	Sum	Z	P value
DS Post – DS Pre	54.3	68.8	17.41	383	14.5	624	-2.232	0.026*
AS Post – AS Pre	7.11	6	14.28	285.5	20.21	459.5	-.405[c]	0.686
SS Post – SS Pre	8	7.3	15.24	320	17.6	402.5	-1.414c	0.157

PP analysis rTMS group (n = 32)

	Median		Negative Ranks		Positive Ranks			
Variables Pair	Pre	Post	Mean	Sum	Mean	Sum	Z	P value
DS Post – DS Pre	8	6	14.82	281.50	12.06	96.50	-2.239[b]	0.025*
AS Post – AS Pre	8	6	13.16	210.50	15.23	167.50	-.530[b]	0.569
SS Post – SS Pre	8	6	13.19	211.00	13.19	211.00	-.903[b]	0.366

Table 4.7(a): Continued

ITT analysis rTMS group (n = 38)

	Median		Negative Ranks		Positive Ranks			
Variables Pair	Pre	Post	Mean	Sum	Sum	Mean	Z	P-value
DS Post – DS Pre	7.6	4.7	16.23	357	171	17.1	-1.745c	0.08
AS Post – AS Pre	6	85	15.77	80.5	248	20.67	-.850c	0.396
SS Post – SS Pre	8	7.3	16.86	371	295	21.07	-.599c	0.0549

*Significant P<0.05, ITT=intention-to-treat, DS= Depression score, AS=Anxiety score, SS=Stress score

PP analysis placebo group

	Median			Positive Ranks				
Variables Pair	Pre	Post	Mean	Sum	Mean	Sum	Z	P value
DS Post – DS Pre	6	4	12.38	198.00	14.11	127.00	-.966[b]	0.334
AS Post – AS Pre	6	6	13.34	127.00	14.95	164.50	-.595[b]	0.552
SS Post – SS Pre	6	7	14.25	228.00	15.84	396.00	-.228[b]	0.820

*significant value <0.05

Table 4.7b: Comparison between ITT and PP analysis for DASS-21 between groups

ITT Analysis for DASS-21

Factors	Group	N	50th (Median)	Mean Rank	Kruskal-Wallis H	P-value
Depression	Pre-RTMS	38	7.69	81.15	9.60	0.022*
	Pre-Placebo	38	7.69	91.83		
	Post-RTMS	38	4.00	62.09		
	Post-Placebo	38	5.50	72.01		
Anxiety	Pre-RTMS	38	7.12	87.40	3.54	0.315
	Pre-Placebo	38	6.56	76.20		
	Post-RTMS	38	6.00	74.28		
	Post-Placebo	38	6.00	68.99		
Stress	Pre-RTMS	38	8.00	93.28	7.73	0.052*
	Pre-Placebo	38	6.00	71.05		
	Post-RTMS	38	7.00	76.03		
	Post-Placebo	38	7.00	67.28		

*Significant P<0.05, ITT=intention-to-treat, DASS-21=Depression, Anxiety, Stress Scores

Table 4.8: Comparison between ITT and PP analysis for DASS-21 between groups

ITT Analysis for DASS-21

Factors	Group	N	50th (Median)	Mean Rank	Kruskal-Wallis H	P-value
Depression	Pre-RTMS	38	7.69	81.15	9.60	0.022*
	Pre-Placebo	38	7.69	91.83		
	Post-RTMS	38	4.00	62.09		
	Post-Placebo	38	5.50	72.01		
Anxiety	Pre-RTMS	38	7.12	87.40	3.54	0.315
	Pre-Placebo	38	6.56	76.20		
	Post-RTMS	38	6.00	74.28		
	Post-Placebo	38	6.00	68.99		
Stress	Pre-RTMS	38	8.00	93.28	7.73	0.052*
	Pre-Placebo	38	6.00	71.05		
	Post-RTMS	38	7.00	76.03		
	Post-Placebo	38	7.00	67.28		

*Significant P<0.05, ITT=intention-to-treat, DASS-21=Depression, Anxiety, Stress Score

Table 4.8: Continued

PP Analysis for DASS-21

	Group	N	%0th (Median)	Mean Rank	Kruskal-Wallis H	P
Depression	Pre-RTMS	32	5.00	64.36	10.02	*0.018
	Pre-Placebo	32	9.00	79.67		
	Post-RTMS	32	3.00	50.69		
	Post-Placebo	32	4.50	63.28		
Anxiety	Pre-RTMS	32	7.00	65.56	0.71	0.870
	Pre-Placebo	32	6.00	68.03		
	Post RTMS	32	5.00	63.92		
	Post-Placebo	32	4.00	60.48		
Stress	Pre-RTMS	32	9.00	69.23	1.45	0.693
	Pre-Placebo	32	6.00	63.33		
	Post-RTMS	32	6.00	66.67		
	Post-Placebo	32	6.00	58.77		

*Significant P<0.05, ITT=intention-to-treat, DASS=Depression, Anxiety, Stress Scores

CHAPTER 5

DISCUSSION

5.1 Overview

This chapter comprises of the discussion on the effectiveness of rTMS on migraine in the scope of psychological states, physical activity, sleep quality and electroencephalography changes of participants with migraine. A total of 76 subjects were randomised in this study. However, only sixty-four p subjects with episodic migraine (EM) completed the study.

5.2 Descriptive study

Based on descriptive study result, 84.4% of subjects are having migraine without aura and remaining 15.6% have migraine with aura which is almost reaching percentage in Malaysian population 89.6%. Following 81% of female migraine prevalent, this study has percentage of 81.3% are female subjects while 18.8% are males. The races are unevenly distributed which are 87.5% Malays, 12.5% non-Malays. Representing labour force participation rate in Malaysia (which is 68.6% in 2021), in this study 62.5% of the subjects are working full-time, 9.4% working part-time and followed by 28.1% of non-working students or housewives. As much as 78.1% subjects finished tertiary education, while remaining 21.9% is not which may include undergraduate students pursuing the study.

Based on meta-analysis, depression is prevalent in migraine ranging from 8.6% to 47.9% (K Rammohan et al. 2019 from J of Neuroscience) While in this study the percentage is 37.5%. The prevalence of anxiety is ranging from 16-83% (Leila Karimi et al 2020, from Frontiers Neurology) and the percentage in this study is 71.8%. Stress prevalent can be up to 71 % while sleep disturbance 47% (AR Rafi et al., 2022 from BMC Neurology). While, other study demonstrated higher prevalent of poor sleep in migraine which is 66.7% (TJ Song et al 2018). Stress prevalent in this study 21.9%, and poor sleeper percentage is 87.5 which is higher than range. Meanwhile depression and anxiety match the range.

The primary outcome of this trial which used migraine days is aligned with the International Headache Society (IHS) recommendation for a clinical trial of preventive treatment of migraine attacks where it is recommended to use change from baseline in MD. Besides that, the IHS guideline also suggested the alternative primary endpoint, which should be the 50% responder rate, while any other percentages (i.e., 25% or 75%) of the responder rate are not recommended (Diener et al., 2020).

5.3 Electroencephalography

There were limited neurophysiological studies done to investigate EEG changes in migraine. The most frequently described in literature is photic driving response (PDR). Some literature used different terms such as 'H response' and enhanced photic driving. Recent study found that photic driving response is related to the trigger sensitivity in migraine (Bjørk M et al., 2022). Photophobia or sensitivity to light stimulation is one of the migraine feature as discussed in literature section.

Recent study also reported there is significant difference in PDR for migraine without aura (MWOA) as compared to migraine with aura (MWA) when photic stimulation is delivered interictally at frequency 5, 8, 15 and 20 Hz. The stimulation is stronger in MWOA (Tomohiko Shiina et al. 2019). While other study done reported PDR may be related to ictal phase (M Bjork et al 2010). This study also reported driving power of 12 Hz increase before attack. However, this study is a longitudinal, controlled study on migraine population only. Headache-free subjects are needed for clinical and statistical comparison.

However, there is still lack of evidence on the pathophysiology behind photophobia in migraine. We suggest further research to be done to explore the pathophysiology behind photophobia in migraine to understand this unique symptoms of migraine and how the manipulation of rTMS may affect brain response on photic stimulation. Photophobia in migraine is not well understood in migraine.

In this study, there was a significant different in photic driving response between group after receiving rTMS treatment $F(1, 62) = 33.05$, $p = .0001$, $\eta p^2 = .35$). We cannot rule out the possibility of using photic driving response in evaluating migraine progression in the future work. Despite being one of the cardinal rule to characterise migraine, recent study reported photophobia as a predictor of depressive symptoms

level, thus may act as a confounding factor(Seidel et al., 2017). Even though the evidence in literature to support this study result is still scarce, this study may become a basis for future research work. Previous studies on rTMS were tremendous but more focus on safety, efficacy and quality of life.

However, interest on clinical neurophysiology is increasing among researcher due to the discovery of machine learning for efficient and faster data analysis. While, advancement in technology through EEG-fMRI contributes better understanding about migraine and rTMS. For example, this combination allowed us to understand that we must respect the individual variability in functional connectivity of human brain to be taken into account when facing different outcomes of rTMS (Mueller et al., 2012). The variability in connectivity architecture is not only represented by MRI in this study, but it is also observed in our daily approach to life in decision making, action and behaviour.

5.4 Sleep Quality

In general population sleep disorders are common (Ohayon 2011; Murphy and Peterson 2015). While in migraine, the reported complaints are higher. Improved sleep quality in rTMS treatment has been reported in several studies on various conditions such as major depressive disorders (MDD), general anxiety disorders (GAD) and insomnia (Van Dijk et al. 2009; Sanchez-Escadon et al. 2016). The electroencephalography (EEG) study with combined polysomnography (PSG) were done in rTMS treatment resulted in decrease in the frequency of EEG abnormalities and significant improvement in sleep efficiency and total sleep time. “Limbic symptoms” such as sleeps disorders are common in migraine. While stimulation on DLPFC area may activate this area and reset the fronto-limbic dysfunction.

A Kruskal-Wallis H test showed that in pp analysis, there was no statistically significant difference in PSQI score between the different rTMS treatment and placebo, $\chi^2(2) = 8.520$, $p = 0.59$, with a mean rank PSQI score of 69.11 for rTMS, 34.83 for placebo. While ITT analysis also showed no significant difference between groups, p= 0.756. While this study did not use polysomnography which can measure sleep pattern and disturbance at night, PSQI might be inadequate to report on sleep disturbance. Subjects might have interrupted sleep but unaware of the situation. Besides that, this study uses high frequency rTMS while, previous study uses low frequency rTMS for treatment of insomnia (Valero -Cabre et al 2017). Even though there were six studied used high frequency, eight studies reported usage of low frequency

which should not be overlooked (Ricardo Oroz et L. 2021). Low frequency rTMS deliver 1 Hz while high frequency may be delivered from 18 Hz and higher. The mechanism of action might be different from cortical inhibition to mechanism of sleep disorders is complex and multifactorial. Further research including somnograph and REM-sleep EEG are needed to explore how migraine correlates with sleep disorders. Meanwhile, research on targetting deeper structures of brain which has shared anatomical relation between migraine and sleep disorders may open up to knowledge on vast possibility of rTMS as adjunctive treatment of migraine.

Cortical hyperexcitability is a shared pathology reported both in migraine and primary insomnia. While, mechanism of action of rTMS is by altering hyperexcitability states of brain, rTMS may become a potential candidate for treatment of both conditions or migraine with comorbid sleep disorders. Fronto-limbic. However, there is lack of evidence in this study to prove the impact of rTMS on the aspects of sleep quality. Further research is needed to design a suitable study protocol in finding the right frequency of stimulation and other related parameters.

5.5 Physical Activity

Physical exertion is used to be known as a common triggers of migraine attack (Chen SP et al 2009). However, following correct exercise regime is needed for management of migraine (Stronks DL et al. 2004; Varkey et al. 2009; Mauskop A et al. 2012; Verrotti A et al. 2013). In the meantime, some studies reported benefits of both vigorous and moderate exercise (Lemstra M et al. 2002; Strelniker YM et al. 2009). The long-term benefit of exercise is they may develop tolerance towards the pain thus, increase the pain threshold triggered by exercise (Hindiyeh NA et al. 2013).

Swedish population study reported low physical activity related to higher prevalence of self-reported migraine when compares to physically active subjects (Molarius et al. 2008). this study result was supported by few studies on pain intensity and headache frequency. The studies reported reduction in migraine attack frequency and significant reduction of pain intensity (Osun Narin S et al. 2003, Dittrich SM et al 2008; Overath CH et al. 2014).

Even though there were contrasting results in vast studies on exercise, in depth studies and exploration of the underlying mechanism may provide a clearer picture of the dynamic impact of exercise. For

example, in one study, mean peak of oxygen uptake was found lower in migraine when compared to headache-free subjects. However, after 12-week regular exercise intervention, the mean peak oxygen uptake increased (Hagen K et al 2015). Besides, impaired autonomic control of vasoreactivity have been reported in migraine (Wallasch TM et al 2011). While at the same time, exercising may regulate vascular tone (Darling M et al. 1991).

This study aimed to measure rTMS impact on the aspect physical activity aspect. ITT analysis reported statistically significant difference in GPAQ score between rTMS group and placebo group. However, in PP analysis there is a lack of evidence to support that there is significant improvement of physical activity after rTMS treatment. The reason might be the small sample size due to study attrition. However, moderate physical activity domain showed significant difference between groups in ITT and PP analysis. Improvement in moderate exercise is recommended and supported by evidence. Besides that, some literature reported reduction in migraine attack after moderate exercise regime (Pairo Z et al 2016; Giuseppi Lippi et al 2018). Pairo compared continous moderate exercise group with control group who did not exercise and reported reduced migraine intensity, frequency and duratin within a month. The regime in this study is 40 minutes of moderate exercise for three times a week. While G Lippi provided a narrative review on collected articles consisted of epidemiogic studies and intervention studies and recommended moderate exercise for migraine as a preventive measure.

5.6 Psychological states related to depression, anxiety and stress

Depression is twice more common in migraine than healthy population. Reducing depressive symptoms may increase quality of life of migraine patients and reduce burden of disease(B. Lee Peterlin et al., 2014). This study showed that rTMS may reduce depression symptoms perceived by migraine patients. A Kruskal-Wallis H Test showed that there was statistically significant difference in depression score between rTMS treatment group and the placebo in the ITT analysis $X^2 = 9.60$, $p = 0.022$. A possible explanation is prefrontal cortex play a critical role in emotional regulation(Dixon et al., 2017). Stimulation on DLPFC region has been showing significant result on affective disorders such as depression and anxiety. In contrary, conflicting outcomes reported by different studies may be caused by different frequencies. This study cannot evict the possibility that rTMS targeting prefrontal region may reduce perceived depressive symptoms. However, this study used self-reported

questionnaires in which the symptoms were based on participants' own perception.

Referring to other previous studies, rTMS was effective to treat anxiety symptoms and depressive symptoms (Chen L et al., 2019). Few protocols were used in this study. It involves left-sided, right-sided and bilateral which were all correlated with improvement in symptoms. Interestingly, some patients showed no improvement after unilateral stimulation. However, other study showed improved symptoms in this group of patients when the area of stimulation is directed bilaterally after not responding to unilateral stimulation of the brain.

Even though, anxiety is more prevalent than depression in migraine, this study shows no significant changes in anxiety score when treated with rTMS. On contrary, this study shows no significant difference in stress score for the ITT analysis even though the PP analysis reported no significant finding. Meanwhile, relationship between stress and migraine is bidirectional, post-traumatic stress disorders (PTSD) is reported higher in chronic migraine than other type of headaches thus explaining the importance of evaluating and managing stress level in migraine patients (Zarei et al., 2016). However, this study does not demonstrate significant relationship might be caused by the targeted subjects are episodic migraine rather than chronic. Previously, researcher found that the higher frequency of stress is demonstrated in chronic migraine subjects when compared to episodic migraine (Corchs et al., 2011).

Specifically, different protocol has been approved by United States Food and Drug Administration (FDA) for generalised anxiety disorders and major depression. However, these disorders usually occur concomitantly with other disorder including migraine. This study is tailored to test the efficacy of its protocol on migraine and its comorbid condition including depressive symptoms, anxiety symptoms and stress. Even though migraine and psychiatric disorders are separate disease, they My share similar mechanisms including hormonal fluctuation, genetics, neurotransmitter dysregulation and underlying biology. It is undeniable that migraine is influenced by psychological factors (Helen Broen et al., 2012). Reduction in migraine attacks was reported after behavioural management. This is supported by other successful studies on psychological interventions in migraine which yields positive outcomes (Andrew Sullivan et al 2016; Sharpe L et al., 2019).

5.7 Findings and Implication of the Study

Migraine is a debilitating disease which reducing productivity worldwide thus, vast amount of researches have been done to find the best treatment that fit all. However, there is still no cure for migraine. Wide range of treatment options are available which include pharmacological approach, nerves block injections, and stimulation. Unfortunately, they may suit certain patients only and undesirable in certain cases. For example, consumption of medications may not suitable in pregnancy and lactation. While usage of rTMS has no contraindication in pregnancy, rTMS may become a promising treatment option in the future if there are continuous efforts to search for a correct protocol and for further understanding of the mechanism of the treatment.

The current study protocol assessed the effectiveness of rTMS on neurophysiological, clinical aspects and psychological states of migraine. However, it did not yield the sufficient results to support rTMS as an effective prophylaxis for migraine. However, there is a notable finding for EEG application in migraine to measure photic driving response and in depressive symptoms. This finding may serve as a basis for future research with the help of advanced current knowledge in machine learning and other types of brain imaging for instance functional MRI. However, this study also

CHAPTER 6

CONCLUSION AND FUTURE STUDY

6.1 Overview

In conclusion, the rTMS may have some beneficial effects on improving secondary health outcomes such as the photic driving response, physical activity and emotional states in patient with episodic migraine.

6.2 Limitation of the Study

Problems inherent in the nature of single-centred trial is that this trial may have been contradicted when tested in other settings. Besides that, this study is a quantitative study, which bind to usage of mathematical models which are derived from a collective assumption which may not be relevant to some problems if caution is not taken into consideration. To reduce this error, we consulted with statistician. Apart from that, this study is done within less than two years. Longer study duration may yield better result on preventive treatment purposes.

In addition, there are also missing data due to the participant dropouts, thus reduce the accuracy of the results. Mean imputation method has to replace the missing data. Besides that, the technique for placing coil on DLPFC area is less precise because neither neuronavigation nor TMS cap is not used. Head movement is minimised by supervision and instructions alone. Meanwhile for electroencephalography (EEG) electrodes placement, EEG cap is also not used. The chances of subjects not to commit is higher because of the long duration of session for each procedures and to answer lengthy questionnaires.

6.3 Strength of the Study

Demographic picture illustrates the data is representative to the migraine prevalence population in Malaysia. Besides that, it is known that in this RCT, we use gold standard placebo for testing interventions which reducing bias of error to occur by chance. By using community-based participatory research, we could increase recruitment in this trial.

REFERENCES

Mohamad Safiai NI, Mohamad NA, Basri H, Inche Mat LN, Hoo FK, Abdul Rashid AM, Yusof Khan AHK, Loh WC, Baharin J, Fernandez A, Samsudin IN, Mohamed MH, Siew MC, Lee KW, Ramachandran V, Pozo-Rosich P, Wan Sulaiman WA. High-frequency repetitive transcranial magnetic stimulation at dorsolateral prefrontal cortex for migraine prevention: A protocol for a systematic review of controlled trials. PLoS One. 2021 Jun 17;16(6):e0251528. doi: 10.1371/journal.pone.0251528. PMID: 34138860; PMCID: PMC8211237.

Vincent Maurice, Viktrup Lars, Nicholson Robert A., Ossipov Michael H., Vargas Bert B. The not so hidden impact of interictal burden in migraine: A narrative review. Frontiers in Neurology VOL. 13 2022 DOI=10.3389/fneur.2022.1032103

Tsukasa Kato (2015). Effects of Flexibility in Coping with Chronic Headaches on Depressive Symptoms. National Library of Medicine - Int J Behav Med 2015 Aug;22(4):506-11. doi: 10.1007/s12529-014-9443-1.

Antonaci, F. et al. Migraine and psychiatric comorbidity: a review of clinical findings. The Journal of Headache and Pain, [s. l.], v. 12, n. 2, p. 115–125, 2011.

Aggarwal M, Puri V, Puri S. Serotonin and CGRP in migraine. Ann Neurosci. 2012 Apr;19(2):88-94. doi: 10.5214/ans.0972.7531.12190210. PMID: 25205974; PMCID: PMC4117050.

Brown DA, PASSMORE GM (2009). Neural KCNQ (Kv7) channels. Br J Pharmacol 156: 1185–1195. 009). https://doi.org/10.1111/j.1476- 5381.2009.00111

D Arulmozhi Veeranjaneyulu, A. Bodhankar, S. L. Migraine: Current concepts and emerging therapies. Vascular Pharmacology 2005 Vol. 43 Issue 3 p.176-187.

Leao, AAP. Pial circulation and spreading depression activity in cerebral cortex. J Neurophysiol 1944;7:391

Andreas R Gantenbein , Peter S Sandor 2, Peter J Goadsby et al. (2014) Chirp stimulation: H-response short and dynamic. Cephalalgia 2014 Jun;34(7):554-8.doi: 10.1177/0333102413517777. Epub 2014 Jan 3.

Seidel, S., Beisteiner, R., Manecke, M., Aslan, T. S., & Wöber, C. (2017). Psychiatric comorbidities and photophobia in patients with migraine. The journal of headache and pain, 18(1), 18. https://doi.org/10.1186/s10194-017-0718-1

S. Farris, J. Thomas, A. Abarantes et al Intentional avoidance of physical activity in women with migraine. Cephalalgia Reports 2018 Vol. doi: 10.1177/2515816318788284

Y. Fogang, P. Gerard, V. De Pasqua. Analysis and clinical correlates of 20 Hz photic driving on routine EEG in migraine. *Belgian Neurological Society* (2014) DOI 10.1007/s13760-014-0309-8

T Shiinaa, R Takashimaa RD. Pascual-Marqui et al Evaluation of Electroencephalogram Using Exact Low-Resolution Electromagnetic Tomography During Photic Driving Response in Patients with Migraine. *Neuropsychobiology* 2018 DOI: 10.1159/000489715

G Coppola, Martina Bracaglia, Davide Di Lenola et al (2015) Lateral inhibition in the somatosensory cortex during and between migraine without aura attacks: Correlations with thalamocortical activity and clinical features. Cephalalgia 2016 May;36(6):568-78. doi:10.1177/0333102415610873. Epub 2015 Oct 6.

Schwedt TJ, Buse DC, Argoff CE et al,. Medication Overuse and Headache Burden: Results From the CaMEO Study. Neurol Clin Pract. 2021 Jun;11(3):216-226. doi: 10.1212/CPJ.0000000000001037. PMID: 34476122; PMCID: PMC8382341.

Martínez-Pías E, García-Azorín D, Trigo-López J, et al. Migraña crónica con cefalea diaria. Revisión de la bibliografía [Chronic migraine with daily headache. Literature review]. Rev Neurol. 2021 Feb 16;72(4):133-140. Spanish. doi: 10.33588/rn.7204.2020583. PMID: 33570160.

Eskin, M., Akyol, A., Cßelik, E. Y. & G€ultekin, B. K. Social problem-solving, perceived stress, depression and life-satisfaction in patients suffering from tension type and migraine headaches. (2013) Scandinavian Journal of Psychology 54, 337–343. Doi:10.1111/sjop.12056

O'Reardon JP, Solvason HB, Janicak PG et al. Efficacy and safety of transcranial magentic stimulation in the acute treatment of major depression: a multisite randomized controlled trial. Biol. Psychiatry62(11), 1208–1216 (2017)

Bloch, Y., Grisaru, N., Harel, E.V., et al. (2008). Repetitive transcranial magnetic stimulation in the treatment of depression in adolescents: An open-label study. The Journal of ECT, 24, 156–159. doi: 10.1097/YCT.0b013e318156aa49

Gazerani P. A Bidirectional View of Migraine and Diet Relationship. Neuropsychiatr Dis Treat. 2021 Feb 11;17:435-451. doi: 10.2147/NDT.S282565. PMID: 33603381; PMCID: PMC7884951.

Giri, S., Tronvik, E.A. & Hagen, K. The bidirectional temporal relationship between headache and affective disorders: longitudinal data from the HUNT studies. *J Headache Pain* **23**, 14 (2022). https://doi.org/10.1186/s10194-022-01388-x

Dhengare AS, Fulmali DG. The Development of Psychiatric Illness and Chemoprophylaxis of Botulinum Toxin in Migraine: A Narrative Review. Cureus. 2022 Dec 27;14(12):e32998. doi: 10.7759/cureus.32998. PMID: 36712737; PMCID: PMC9879228.

Berlim, M.T., Van den Eynde, F., Tovar-Perdomo, S., & Daskalakis, Z.J. (2014). Response, remission and drop-out rates following high-frequency repetitive transcranial magnetic stimulation (rTMS) for treating major depression: A systematic review and meta-analysis of randomized, double-blind and sham-controlled trials. Psychological Medicine, 44, 225–239. doi: 10.1017/S0033291713000512.

Coarckin, P.E., Wall, C.A., Nakonezny, P.A., Buyukdura, J.S., Husain, M.M., Sampson, S.M., … Kozel, F.A. (2012). Increased cortical excitability with prefrontal high-frequency repetitive transcranial magnetic stimulation in adolescents with treatment-resistant major depressive disorder. Journal of Child and Adolescent Psychopharmacology, 22, 56–64. doi: 10.1089/cap.2011.0054

Desmyter, S., Duprat, R., Baeken, C., Bijttebier, S., & van Heeringen, K. (2014). The acute effects of accelerated repetitive transcranial magnetic stimulation on suicide risk in unipolar depression: Preliminary results. Psychiatria Danubina, 26, 48–52.

Donaldson, A.E., Gordon, M.S., Melvin, G.A., Barton, D.A., & Fitzgerald, P.B. (2014). Addressing the needs of adolescents with treatment resistant depressive disorders: A systematic review of rTMS. Brain Stimulation, 7, 7–12. doi: 10.1016/j.brs.2013.09.012. https://journals.sagepub.com/doi/full/10.1177/2515816318788284

Kedzior, K.K., Reitz, S.K., Azorina, V., & Loo, C. (2015). Durability of the antidepressant effect of high-frequency repetitive transcranial magnetic stimulation (rTMS) in the absence of maintenance treatment in major depression: A systematic review and meta-analysis of 16 double-blind, randomized, sham-controlled trials. Depression and Anxiety, 32, 193–203. doi: 10.1002/da.22339.

Levkovitz, Y., Isserles, M., Padberg, F., Lisanby, S.H., Bystritsky, A., Guohua, X., Zangen, A. (2015). Efficacy and safety of deep transcranial magnetic stimulation for major depression: A prospective multicenter randomized controlled trial. World Psychiatry, 14, 64–73. doi: 10.1002/wps.20199.

Wall, C.A., Croarkin, P.E., Moroney-Smith, M.J., Haugen, L.M., Baruth, J.M., Frye, M.A., … Port, J.D. (2016). Magnetic resonance imaging- guided, open-label, high-frequency repetitive transcranial magnetic stimulation for adolescents with major depressive disorder. Journal of 15

Mongini, F. et al. Personality traits, depression and migraine in women: a longitudinal study. Cephalalgia: An International Journal Of Headache, [s. l.], v. 23, n. 3, p. 186–192, 2003.

Turner, D. P.; HOULE, T. T. Psychological evaluation of a primary headache patient. Pain Management, [s. l.], v. 3, n. 1, p. 19–25, 2013.

Nordenskjöld, A. et al. Effects of Hesel-coil deep transcranial magnetic stimulation for depression - a systematic review. Nordic Journal Of Psychiatry, [s. l.], v. 70, n. 7, p. 492–497, 2016.

Henry JD; Crawford JR. The short-form version of the Depression Anxiety Stress Scales (DASS-21): Construct validity and normative data in a large non-clinical sample. British Journal of Clinical Psychology, [s. l.], v. 44, n. 2, p. 227–239, 2005.

Silberstein, S. D.; Lipton, R. B.; Breslau, N. Migraine: association with personality characteristics and psychopathology. Cephalalgia: An International Journal Of Headache, [s. l.], v. 15, n. 5, p. 358–369, 1995.

Visens, L. S. [New physiopathological knowledge applied to migraine therapy and prophylaxis]. Medicina, [s. l.], v. 74, n. 2, p. 147–157, 2014.

Antony MM et al. Psychometric properties of the 42-item and 21 item versions of the Depression Anxiety Stress Scales in clinical groups and a community sample. Psychological Assessment, [s. l.], v. 10, n. 2, p. 176–181, 1998.

Renner, K.-H. et al. Differentiating anxiety and depression: the State-Trait Anxiety-Depression Inventory. Cognition & Emotion, [s. l.], v. 32, n. 7, p. 1409–1423, 2018.

Silberstein, S. D.; Lipton, R. B.; Breslau, N. Migraine: association with personality characteristics and psychopathology. Cephalalgia: An International Journal of Headache, [s. l.], v. 15, n. 5, p. 358–369, 1995.

Peres, M. F. P. et al. Anxiety and depression symptoms and migraine: a symptom-based approach research. The Journal Of Headache And Pain, [s. l.], v. 18, n. 1, p. 37, 2017.

Turner, D. P.; Houle, T. T. Psychological evaluation of a primary headache patient. Pain Management, [s. l.], v. 3, n. 1, p. 19–25, 2013.

Gupta J, Gaurkar SS. Migraine: An Underestimated Neurological Condition Affecting Billions. Cureus. 2022 Aug 24;14(8):e28347. doi: 10.7759/cureus.28347. PMID: 36168353; PMCID: PMC9506374.

Martin PR, Reece J, Callan M, MacLeod C, Kaur A, Gregg K, Goadsby PJ. Behavioral management of the triggers of recurrent headache: a randomized controlled trial. Behav Res Ther. 2014 Oct;61:1-11. doi: 10.1016/j.brat.2014.07.002. Epub 2014 Jul 16. PMID: 25108482.

J Lemmens, Joke De Pauw, TV Soom et al. The effect of aerobic exercise on the number of migraine days, duration and pain intensity in migraine: a systematic literature review and meta-analysis. J Headache Pain. 2019; 20(1): 16. doi: 10.1186/s10194-019-0961-8

Mendonça-De-Souza, Mayara Monteiro, Ubirakitan M et al., Resilience in migraine brains: decrease of coherence after photic stimulation. Frontiers in Human Neuroscience 2012 Vol. 6 July 1-6. doi: 10.3389/fnhum.2012.00207

SG Farris, J Graham Thomas, Ana M Abrantes et al (2019). Anxiety sensitivity and intentional avoidance of physical activity in

women with probable migraine. Cephalalgia International Headache Society 2019 Article reuse guidelines: sagepub.com/journals-permissions DOI: 10.1177/0333102419861712

Gil-Martínez A, Kindelan-Calvo P, Agudo-Carmona D et al. Ejercicio terapéutico como tratamiento de las migrañas y cefaleas tensionales: revisión sistemática de ensayos clínicos aleatorizados [Therapeutic exercise as treatment for migraine and tension-type headaches: a systematic review of randomised clinical trials]. Rev Neurol. 2013 Nov 16;57(10):433-43. Spanish. PMID: 24203665.

Amin FM, Aristeidou S, Baraldi C, Cet al. European Headache Federation School of Advanced Studies (EHF-SAS). The association between migraine and physical exercise. J Headache Pain. 2018 Sep 10;19(1):83. doi: 10.1186/s10194-018-0902-y. PMID: 30203180; PMCID: PMC6134860.

Yeh WZ, Blizzard L, Taylor BV. What is the actual prevalence of migraine? Brain Behav. 2018 Jun;8(6):e00950. doi: 10.1002/brb3.950. Epub 2018 May 2. PMID: 30106228; PMCID: PMC5991594.

Peng KP; Wang SJ. Migraine diagnosis: Screening items, instruments, and scales. Acta Anaesthesiologica Taiwanica, [s. l.], v. 50, n. 2, p. 69–73, 2012.

Mongini, F. et al. Personality traits, depression and migraine in women: a longitudinal study. Cephalalgia: An International Journal Of Headache, [s. l.], v. 23, n. 3, p. 186–192, 2003.

Aarre, T. F. et al. Efficacy of repetitive transcranial magnetic stimulation in depression: a review of the evidence. Nordic Journal Of Psychiatry, [s. l.], v. 57, n. 3, p. 227–232, 2003.

Osman, A. et al. The Depression Anxiety Stress Scales-21 (DASS-21): further examination of dimensions, scale reliability, and correlates. Journal Of Clinical Psychology, [s. l.], v. 68, n. 12, p. 1322–1338, 2012.

Hamel, E. Serotonin and migraine: biology and clinical implications. Cephalalgia: An International Journal Of Headache, [s. l.], v. 27, n. 11, p. 1293–1300, 2007.

Galletly, C. A. et al. A Comparison of Right Unilateral and Sequential Bilateral Repetitive Transcranial Magnetic Stimulation for Major Depression: A Naturalistic Clinical Australian Study. Journal of ECT, [s. l.], v. 33, n. 1, p. 58–62, 2017.

Wang, M. et al. Visual cortex and cerebellum hyperactivation during negative emotion picture stimuli in migraine patients. Scientific Reports, [s. l.], v. 7, p. 41919, 2017.

Katzman, M. A. et al. Canadian clinical practice guidelines for the management of anxiety, posttraumatic stress and obsessive-compulsive disorders. BMC Psychiatry, [s. l.], v. 14, p. 1–83, 2014.

Kumar, S. et al. The Effects of Repetitive Transcranial Magnetic Stimulation at Dorsolateral Prefrontal Cortex in the Treatment of Migraine Comorbid with Depression: A Retrospective Open Study. Clinical Psychopharmacology & Neuroscience, [s. l.], v. 16, n. 1, p. 62–66, 2018.

Pompili, M. et al. Psychiatric comorbidity and suicide risk in patients with chronic migraine. Neuropsychiatric Disease and Treatment, [s. l.], v. 6, p. 81–91, 2010.

Martinez F, Castillo J, Rodriguez JR, Leira R, Noya M. Neuroexcitatory amino acid levels in plasma and cerebrospinal fluid during migraine attacks. Cephalalgia. 1993;13:89-93

Li, J., Meng, X. M., Li, R. Y., Zhang, R., Zhang, Z., & Du, Y. F. (2016). Effects of different frequencies of repetitive transcranial magnetic stimulation on the recovery of upper limb motor dysfunction in patients with subacute cerebral infarction. *Neural regeneration research*, *11*(10), 1584–1590. https://doi.org/10.4103/1673-5374.193236

Silvanto, J., & Cattaneo, Z. (2017). Common framework for "virtual lesion" and state-dependent TMS: The facilitatory/suppressive range model of online TMS effects on behavior. *Brain and cognition*, *119*, 32–38. https://doi.org/10.1016/j.bandc.2017.09.007

D.Schulz, A.Aksoy, R.Canbeyli (2008). Behavioral despair is differentially affected by the length and timing of photic stimulation in the dark phase of an L/D cycle. Elsevier Progress in Neuro-Psychopharmacology and Biological Psychiatry Volume 32, Issue 5, 1 July 2008, Pages 1257-1262.

NG Hammond, A Stinchcombe (2019) Health Behaviors and Social Determinants of Migraine in a Canadian Population-Based

Sample of Adults Aged 45-85 Years: Findings From the CLSA. The Joirnal of Headache and Face Pain. https://doi.org/10.1111/head.13610

MJ McDermott , JC Fulwiler , Todd A Smitherman et al (2016). The relation of PTSD symptoms to migraine and headache-related disability among substance dependent inpatients. J Behav Med 2016 Apr;39(2):300-9. doi: 10.1007/s10865-015-9697-3. Epub 2015 Nov 26.

Navratilova E., Porreca, F. (2014). Reward and motivation in pain and pain relief. *Nature neuroscience*, *17*(10), 1304–1312. https://doi.org/10.1038/nn.3811

M Kanno, M Matsumoto, H Togashi (2003) Effects of Acute Repetitive Transcranial Magnetic Stimulation on Extracellular Serotonin Concentration in the Rat Prefrontal Cortex. Journal of Pharmacological Sciences Volume 93, Issue 4, 2003, Pages 451-457.

M De Tommaso, V Sciruicchio, R Bellotti (1999) Photic driving response in primary headache: diagnostic value tested by discriminant analysis and artificial neural network classifiers. Ital J Neurol Sci 1999 Feb;20(1):23-8. doi: 10.1007/s100720050006.

CL Cleland, Ruth F Hunter, Frank Kee et al (2014) Validity of the global physical activity questionnaire (GPAQ) in assessing levels and change in moderate-vigorous physical activity and sedentary behavior. BMC Public Health 2014 Dec 10;14:1255. doi: 10.1186/1471-2458-14-1255.

SB Akben, Deniz Tuncel, Ahmet Alkan (2016) Classification of multi-channel EEG signals for migraine detection. Biomedical Research (2016) Volume 27, Issue 3

SR Jahromi, Mansoureh Togha, Zeinab Ghorbani et al. The association between dietary tryptophan intake and migraine. *Neurological Sciences* (2019) volume 40, pages2349–2355

M Bjørk, K Hagen, Lj Stovner et al (2011) Photic EEG-driving responses related to ictal phases and trigger sensitivity in migraine: a longitudinal, controlled study. Cephalalgia 2011 Mar;31(4):444-55. doi: 10.1177/0333102410385582. Epub 2010 Nov 22.

Hong P, Liu Y, Wan Y, Xiong H, Xu Y. Transcranial direct current stimulation for migraine: a systematic review and meta-analysis of randomized controlled trials. CNS Neurosci Ther. 2022 Jul;28(7):992-998. doi: 10.1111/cns.13843. Epub 2022 Apr 19. PMID: 35437933; PMCID: PMC9160451.

V Hamedi, A Asghari, MR Sheeri (2013). An Investigation of The Effectiveness of a Composed Model of Cognitive-behavior Headache Management on the Treatment of Anxiety, Depression, Stress and Migraine Symptoms. Procedia - Social and Behavioral Sciences 84:1850-1855

Dixon, M. L., Thiruchselvam, R., Todd, R., & Christoff, K. (2017, June 15). Emotion and the Prefrontal Cortex: An Integrative Review. Psychological Bulletin. Advance online publication. http://dx.doi.org/10.1037/bul0000096

MR Zarei, M Shabani, G Chamani et al (2016): Migraine patients have a higher prevalence of PTSD symptoms in comparison to chronic tension-type headache and healthy subjects: a case–control study, Acta Odontologica Scandinavica, DOI: 10.1080/00016357.2016.1232435

Corchs F, Mercante JP, Guendler VZ et al. Sensitivity to aversive stimulation, posttraumatic symptoms and migraines: what do they have in common? Med Hypotheses. 2011;77(4):534–535. doi: 10.1016/j.mehy.2011.06.024.

Zhang X, Levy D, Kainz V, Noseda R et al. Activation of central trigeminovascular neurons by cortical spreading depression. Ann Neurol. 2011 May;69(5):855-65. doi: 10.1002/ana.22329. Epub 2011 Mar 17. PMID: 21416489; PMCID: PMC3174689.

Noseda, Rodrigo & Jakubowski, Moshe & Kainz et al,. Cortical Projections of Functionally Identified Thalamic Trigeminovascular Neurons: Implications for Migraine Headache and Its Associated Symptoms. The Journal of neuroscience : the official journal of the Society for Neuroscience. 31. 14204-17. 10.1523/JNEUROSCI.3285-11.2011.

Christopher J. Starr, Lumy Sawaki, George F. Wittenberg et,. Roles of the Insular Cortex in the Modulation of Pain: Insights from Brain Lesions Coghill Journal of Neuroscience 4 March 2009, 29 (9) 2684-2694; DOI: 10.1523/JNEUROSCI.5173-08.2009

Dooley JC, Krubitzer LA. Alterations in cortical and thalamic connections of somatosensory cortex following early loss of vision. J Comp

Neurol. 2019 Jul 1;527(10):1675-1688. doi: 10.1002/cne.24582. Epub 2018 Dec 9. PMID: 30444542; PMCID: PMC6465163.

Min, Byoung-Kyong & Marzelli, Matthew & Yoo, Seung-Schik. (2010). Neuroimaging-based approaches in brain-computer interface. Trends in biotechnology. 28. 552-60. 10.1016/j.tibtech.2010.08.002.

Zduńska A and Joanna Cegielska and Izabela Domitrz ,The Pathogenetic Role of Melatonin in Migraine and Its Theoretic Implications for Pharmacotherapy: A Brief Overview of the Research}, Journal Nutrients 2022}, vol. 14

Buyukgoze, Selma. (2019). THE BRAIN-COMPUTER INTERFACE. International Conference on Technics, Technologies and Education. 133-138. 10.15547/ictte.2019.02.094.

Buskila Y, Bellot-Saez A, Morley JW. Generating Brain Waves, the Power of Astrocytes. Front Neurosci. 2019 Oct 18;13:1125. doi: 10.3389/fnins.2019.01125. PMID: 31680846; PMCID: PMC6813784.

Abdourrahman S,M Roushdy 2013. Support Vector machine Aparoach for Human Identification based on EEG signals. J Mech Contin Math Sci 15(2):270-280.

Yeo BT, Krienen FM, Sepulcre J, Sabuncu MR, Lashkari D, Hollinshead M, Roffman JL, Smoller JW, Zöllei L, Polimeni JR, Fischl B, Liu H, Buckner RL. The organization of the human cerebral cortex estimated by intrinsic functional connectivity. J Neurophysiol. 2011 Sep;106(3):1125-65. doi: 10.1152/jn.00338.2011. Epub 2011 Jun 8. PMID: 21653723; PMCID: PMC3174820.

Rojas, Gonzalo & Alvarez, Carolina & Montoya Moya, Carlos & de la Iglesia Vaya, Maria & Cisternas, Jaime & Gálvez, Marcelo. (2018). Study of Resting-State Functional Connectivity Networks Using EEG Electrodes Position As Seed. Frontiers in Neuroscience. 12.10.3389/fnins.2018.00235.

Benbadis, S.R., Beniczky, S., Bertram, E., MacIver, S. and Moshé, S.L. (2020), The role of EEG in patients with suspected epilepsy. Epileptic Disorders, 22: 143-155. https://doi.org/10.1684/epd.2020.1151

Britton JW, Frey LC, Hopp JLet al., authors; St. Louis EK, Frey LC, editors. Electroencephalography (EEG): An Introductory Text and Atlas of Normal and Abnormal Findings in Adults, Children, and Infants [Internet]. Chicago: American Epilepsy Society;

2016. Appendix 2. Principles of Digital EEG. Available from: https://www.ncbi.nlm.nih.gov/books/NBK390353/

Bjørk MH, Stovner LJ, Engstrøm M, Stjern M, Hagen K, Sand T. Interictal quantitative EEG in migraine: a blinded controlled study. J Headache Pain. 2009 Oct;10(5):331-9. doi: 10.1007/s10194-009-0140-4. Epub 2009 Aug 25. PMID: 19705061; PMCID: PMC3452093.

Hitomi T, Inouchi M, Takeyama H, Kobayashi K, Sultana S, Inoue T, Nakayama Y, Shimotake A, Matsuhashi M, Matsumoto R, Chin K, Takahashi R, Ikeda A. Sleep is associated with reduction of epileptiform discharges in benign adult familial myoclonus epilepsy. Epilepsy Behav Case Rep. 2018 Oct 16;11:18-21. doi: 10.1016/j.ebcr.2018.09.010. PMID: 30591883; PMCID: PMC6305661.

Meritam Larsen P, Wüstenhagen S, Terney D, et al,. Photoparoxysmal response and its characteristics in a large EEG database using the SCORE system. Clin Neurophysiol. 2021 Feb;132(2):365-371. doi: 10.1016/j.clinph.2020.10.029. Epub 2021 Jan 12. PMID: 33450559.

Kim De, Shin JH, Kim YH, Eom TH, Kim SH, Kim JM. Source localization of intermittent rhythmic delta activity in a patient with acute confusional migraine: cross-spectral analysis using standardized low-resolution brain electromagnetic tomography (sLORETA). Neurol Sci. 2016 Jan;37(1):89-95. doi: 10.1007/s10072-015-2367-y. Epub 2015 Aug 21. PMID: 26292789.

Coppola, G., Di Lorenzo, C., Parisi, V. *et al.* Clinical neurophysiology of migraine with aura. *J Headache Pain* **20**, 42 (2019). https://doi.org/10.1186/s10194-019-0997-9

De Tommaso M. An update on EEG in migraine. Expert Rev Neurother. 2019 Aug;19(8):729-737. doi: 10.1080/14737175.2019.1586534. Epub 2019 Mar 7. PMID: 30806101.

Sownthariya R, Heber Anandan. Study of EEG abnormalities in migraine. International Journal of Contemporary Medical Research 2017;4(8):1743-1744.

Tan HJ, Suganthi C, Dhachayani S, Rizal AM, Raymond AA. The electroencephalogram changes in migraineurs. Med J Malaysia. 2007 Mar;62(1):56-8. PMID: 17682573.

Merlino, Giovanni & Valente, Mariarosaria & Anna, Sebastiano & Gigli, Gian & D'Anna, Sebastiano. (2007). Seizures With Prolonged EEG Abnormalities During an Attack of Migraine Without Aura. Headache: The Journal of Head and Face Pain. 47. 919 - 922. 10.1111/j.1526-4610.2007.00829.x.

MD Tommaso, D Marinazzo Marco Guido et al,. Visually evoked phase synchronization changes of alpha rhythm in migraine: correlations with clinical and Giuseppe Libro and Sebastiano Stramaglia and Luigi Nitti and Gianluca Lattanzi and Leonardo Angelini and Mario Pellicoro. International journal of psychophysiology : official journal of the International Organization of Psychophysiology 2005, vol. 57 p. 203-10

De Tommaso M,Stramaglia S,Marinazzo D, Functional and effective connectivity in EEG alpha and beta bands during intermittent flash stimulation in migraine with and without aura. Cephalalgia : an International Journal of Headache, 25 Feb 2013, 33(11):938-947. DOI: 10.1177/0333102413477741 PMID: 23439574

E Tekin, M Engin, T Dalbastı, E Z Engin. The evaluation of EEG response to photic stimulation in normal and diseased subjects,Computers in Biology and Medicine,Vol. 39, Issue 1,2009,Pages 53-60,https://doi.org/10.1016/j.compbiomed.2008.11.001.

HV Gizycki, G Jean-Louis, M Snyder, F Zizi, et al,. The effects of photic driving on mood states,Journal of Psychosomatic Research, Vol. 44, Issue 5, 1998, p. 599-604, https://doi.org/10.1016/S0022-3999(97)00204-3.

Barker AT, Jalinous R, Freeston IL. Non-invasive magnetic stimulation of human motor cortex. Lancet. 1985 May 11;1(8437):1106-7. doi: 10.1016/s0140-6736(85)92413-4. PMID: 2860322.

Carr, H. Y. and Purcell EM, Effects of Diffusion on Free Precession in Nuclear Magnetic Resonance Experiments}, Journal of Phys. Rev., Vol. 94, issue 3,p. 630-638,1954,May,doi=10.1103/PhysRev.94.630}, https://link.aps.org/doi/10.1103/PhysRev.94.630}

Schwarzkopf DS, Silvanto J, Rees G. Stochastic resonance effects reveal the neural mechanisms of transcranial magnetic stimulation. J Neurosci. 2011 Mar 2;31(9):3143-7. doi: 10.1523/JNEUROSCI.4863-10.2011. PMID: 21368025; PMCID: PMC3059801.

Silvanto J, Cattaneo Z. Common framework for "virtual lesion" and state-dependent TMS: The facilitatory/suppressive range model of

online TMS effects on behavior. Brain Cogn. 2017 Dec;119:32-38. doi: 10.1016/j.bandc.2017.09.007. Epub 2017 Sep 28. PMID: 28963993; PMCID: PMC5652969.

Hanlon, Colleen & Canterberry, Melanie. (2012). Hanlon CA, Canterberry M. The use of brain imaging to elucidate neural circuit changes in cocaine addiction. Subst Abuse Rehabil 3: 115-128. Substance abuse and rehabilitation. 3. 115-128. 10.2147/SAR.S35153.

Stultz DJ, Osburn S, Burns Tet al,. Transcranial Magnetic Stimulation (TMS) Safety with Respect to Seizures: A Literature Review. Neuropsychiatr Dis Treat. 2020 Dec 7;16:2989-3000. doi: 10.2147/NDT.S276635. PMID: 33324060; PMCID: PMC7732158.

Jiang R, BH. Jansen, BR. Sheth et al,. Dynamic Multi-Channel TMS With Reconfigurable Coil. Ieee Transactions On Neural Systems And Rehabilitation Engineering, Vol. 21, No. 3, May 2013. http://ieeexplore.ieee.org. Digital Object Id: 10.1109/TNSRE.2012.2226914

Martins IP, RG Gouveia, E Parreira et al. Kinesiophobia in Migraine. The Journal of Pain, Vol 7, No 6 (June), 2006: pp 445-451

Hagan KK, Li W, Mostofsky E, Bertisch SM et al,.. Prospective cohort study of routine exercise and headache outcomes among adults with episodic migraine. Headache. 2021 Mar;61(3):493-499. doi: 10.1111/head.14037. Epub 2020 Dec 21. PMID: 33349935; PMCID: PMC7987744.

Lemmons J, De Pauw J, Van Soom T, et al. The effect of aerobic exercise on the number of migraine days, duration and pain intensity in migraine: a systematic literature review and meta-analysis [published online February 14, 2019]. J Headache Pain. doi.org/10.1186/s10194-019-0961-8.

Park, J.W., Han, S.R., Yang, D.W., Kim, Y.I. and Lee, K.S. (2006), Serotonin Transporter Protein Polymorphism and Harm Avoidance Personality in Migraine without Aura. Headache: The Journal of Head and Face Pain, 46: 991-996. https://doi.org/10.1111/j.1526-4610.2006.00439.x

Peres MFP, Mercante JPP, Tobo PR, Kamei H, Bigal ME. Anxiety and depression symptoms and migraine: a symptom-based approach research. J Headache Pain. 2017 Dec;18(1):37. doi: 10.1186/s10194-017-0742-1. Epub 2017 Mar 21. PMID: 28324317; PMCID: PMC5360747.

Hamedi, Vajihe & Asghari, Ali & Sheeri, Mohammad. (2013). An Investigation of The Effectiveness of a Composed Model of Cognitive-behavior Headache Management on the Treatment of Anxiety, Depression, Stress and Migraine Symptoms. Procedia - Social and Behavioral Sciences. 84. 1850-1855. 10.1016/j.sbspro.2013.07.046.

Bae JY, Sung HK, Kwon NY, Go HY, et al,. Cognitive Behavioral Therapy for Migraine Headache: A Systematic Review and Meta-Analysis. Medicina (Kaunas). 2021 Dec 28;58(1):44. doi: 10.3390/medicina58010044. PMID: 35056352; PMCID: PMC8777662.

Kumar, Saurabh & Singh, Swarndeep & Parmar, Arpit & Vermaet al,. Effect of high-frequency repetitive transcranial magnetic stimulation (rTMS) in patients with comorbid panic disorder and major depression. Australasian Psychiatry. 26. 103985621877151. 10.1177/1039856218771517.

Hitomi S, Okada-Ogawa A, Sato Y, et al,. Enhancement of ERK phosphorylation and photic responses in Vc/C1 neurons of a migraine model. Neurosci Lett. 2017 Apr 24;647:14-19. doi: 10.1016/j.neulet.2017.03.023. Epub 2017 Mar 18. PMID: 28323089.

Okamoto K, Thompson R, Tashiro A, Chang Z, Bereiter DA. Bright light produces Fos-positive neurons in caudal trigeminal brainstem. Neuroscience. 2009 Jun 2;160(4):858-64. doi: 10.1016/j.neuroscience.2009.03.003. Epub 2009 Mar 11. PMID: 19285114.

Bocchio-Chiavetto L, C Miniussi, Roberta Zanardini et al,. 5-HTTLPR and BDNF Val66Met polymorphisms and response to rTMS treatment in drug resistant depression. Neuroscience Letters 437 (2008) p. 130–134. doi:10.1016/j.neulet.2008.04.005.

Aydinlar EI, Dikmen PY, Tiftikci A et al,. IgG-based elimination diet in migraine plus irritable bowel syndrome. Headache. 2013 Mar;53(3):514-25. doi: 10.1111/j.1526-4610.2012.02296.x. Epub 2012 Dec 6. PMID: 23216231.

Schnedl, Wolfgang & Queissner, Robert. (2019). Migraines appear more likely to be caused by histamine rather than ethanol. European Journal of Neurology. 26. 10.1111/ene.14003.

Kurth T, Rohmann J L, Shapiro R E. Migraine and risk of cardiovascular disease *BMJ* 2018; 360 :k275 doi:10.1136/bmj.k2

Chu, M.K. Sleep apnoea and poor sleep quality in patients with chronic migraine. *Nat Rev Neurol* **15**, 130–131 (2019). https://doi.org/10.1038/s41582-018-0124-6

Bjørk M, Hagen K, Stovner Lj, Sand T. Photic EEG-driving responses related to ictal phases and trigger sensitivity in migraine: a longitudinal, controlled study. Cephalalgia. 2011 Mar;31(4):444-55. doi: 10.1177/0333102410385582. Epub 2010 Nov 22. PMID: 21098109.

Sharpe L, Dudeney J, Williams ACC, Nicholas M, McPhee I, Baillie A, Welgampola M, McGuire B. Psychological therapies for the prevention of migraine in adults. Cochrane Database Syst Rev. 2019 Jul 2;7(7):CD012295. doi: 10.1002/14651858.CD012295.pub2. PMID: 31264211; PMCID: PMC6603250.

Tiseo, C., Vacca, A., Felbush, A. *et al.* Migraine and sleep disorders: a systematic review. *J Headache Pain* **21**, 126 (2020). https://doi.org/10.1186/s10194-020-01192-5

Sengul, Y., Sengul, H.S., Bakim, B., Yucekaya, S.K., Yucel, S. and Akgun, M. (2015), Sleep disturbances in migraine. Sleep and Biological Rhythms, 13: 76-84. https://doi.org/10.1111/sbr.12087

Sadeghniiat, Khosro & Rajabzadeh, Alaleh & Ghajarzadeh, Mahsa & Ghafarpour, Majid. (2013). Sleep Quality and Depression among Patients with Migraine. Acta Medica Iranica. 51. 784-8.

Lindholm P, Lamusuo S, Taiminen T et al,. The analgesic effect of therapeutic rTMS is not mediated or predicted by comorbid psychiatric or sleep disorders. Medicine (Baltimore). 2016 Nov;95(44):e5231. doi: 10.1097/MD.0000000000005231. PMID: 27858874; PMCID: PMC5591122.

Chen L, Hudaib AR, Hoy KE, Fitzgerald PB. Is rTMS effective for anxiety symptoms in major depressive disorder? An efficacy analysis comparing left-sided high-frequency, right-sided low-frequency, and sequential bilateral rTMS protocols. Depress Anxiety. 2019 Aug;36(8):723-731. doi: 10.1002/da.22894. Epub 2019 Apr 8. PMID: 3095890

APPENDICES

Appendix 1

DASS-21 Questionnaires

DASS21 Name: Date:

Please read each statement and circle a number 0, 1, 2 or 3 which indicates how much the statement applied to you *over the past week.* There are no right or wrong answers. Do not spend too much time on any statement.

The rating scale is as follows:

0 Did not apply to me at all
1 Applied to me to some degree, or some of the time
2 Applied to me to a considerable degree, or a good part of time
3 Applied to me very much, or most of the time

1	I found it hard to wind down	0 1 2 3
2	I was aware of dryness of my mouth	0 1 2 3
3	I couldn't seem to experience any positive feeling at all	0 1 2 3
4	I experienced breathing difficulty (eg excessively rapid breathing, breathlessness in the absence of physical exertion)	0 1 2 3
5	I found it difficult to work up the initiative to do things	0 1 2 3
6	I tended to over-react to situations	0 1 2 3

7	I experienced trembling (eg in the hands)	0	1	2	3
8	I felt that I was using a lot of nervous energy	0	1	2	3
9	I was worried about situations in which I might panic and make a fool of myself	0	1	2	3
10	I felt that I had nothing to look forward to	0	1	2	3
11	I found myself getting agitated	0	1	2	3
12	I found it difficult to relax	0	1	2	3
13	I felt down-hearted and blue	0	1	2	3
14	I was intolerant of anything that kept me from getting on with what I was doing	0	1	2	3
15	I felt I was close to panic	0	1	2	3
16	I was unable to become enthusiastic about anything	0	1	2	3
17	I felt I wasn't worth much as a person	0	1	2	3
18	I felt that I was rather touchy	0	1	2	3
19	I was aware of the action of my heart in the absence of physical exertion (eg sense of heart rate increase, heart missing a beat)	0	1	2	3
20	I felt scared without any good reason	0	1	2	3
21	I felt that life was meaningless	0	1	2	3

Appendix 2

Pittsburgh Sleep Quality Index (PSQI)

Kualiti Tidur Pittsburgh (PSQI)

The following questions relate to your usual sleep habits during the past month only. Your answers should indicate the most accurate reply for the majority of days and nights in the past month. **Please answer all questions.**

Soalan-soalan berikut berkaitan dengan tabiat tidur biasa anda sepanjang bulan lalu sahaja. Anda perlu menyatakan jawapan yang paling tepat bagi kebanyakan hari dan malam pada bulan lalu. ***Sila jawab semua soalan.***

1.	During the past month, what time have you usually gone to bed at night? *Pada bulan yang lalu, pukul berapakah anda lazimnya tidur pada waktu malam?*	
2.	During the past month, how long (in minutes) has it usually taken you to fall asleep each night? *Pada bulan yang lalu, berapa minitkah biasanya diambil oleh anda untuk tertidur setiap malam?*	
3.	During the past month, what time have you usually gotten up in the morning? *Pada bulan yang lalu, pukul berapakah anda lazimnya bangun pada waktu pagi?*	
4.	During the past month, how many hours of actual sleep did you get at night? *(This may be different than the number of hours you spent in bed).* *Pada bulan yang lalu, berapa jamkah anda mendapat tidur sebenar pada waktu malam?* *(Ini mungkin berbeza daripada bilangan jam yang anda baring di atas katil).*	

Bagi soalan yang selebihnya, sila periksa respons yang terbaik. Sila jawab semua soalan.

5. During the past month, how often have you had trouble sleeping because you *Pada bulan yang lalu berapa kerapkah anda mempunyai masalah tidur kerana anda*	Not during the past month *Tidak pada bulan lalu* (0)	Less than once a week *Kurang daripada sekali seminggu* (1)	Once or twice a week *Sekali atau dua kali seminggu* (2)	Three or more times a week *Tiga kali atau lebih seminggu* (3)
A. Cannot get to sleep within 30 minutes *Tidak boleh tidur dalam masa 30 minit*				
B. Wake up in the middle of the night or early morning *Bangun di tengah malam atau awal pagi*				
C. Have to get up to use the bathroom *Perlu bangun untuk menggunakan bilik air*				
D. Cannot breathe comfortably *Tidak boleh bernafas dengan selesa*				
E. Cough or snore loudly *Batuk atau berdengkur kuat*				
F. Feel too cold *Rasa terlalu sejuk*				
G. Feel too hot *Rasa terlalu panas*				
H. Have bad dreams *Mengalami mimpi buruk*				
I. Have pain *Mempunyai kesakitan*				
J. Other reason (s), please describe, including how often you have had trouble sleeping because of this reason (s): *Sebab-sebab lain, sila terangkan:* *Berapa kerap pada bulan yang lalu, anda mempunyai masalah tidur kerana ini?*				

6. During the past month, how often have you taken medicine (prescribed or "over the counter") to help you sleep? *Pada bulan yang lalu, berapa kerapkah anda mengambil ubat untuk membantu anda tidur (atas arahan doktor atau beli sendiri di farmasi)?*				
7. During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity? *Pada bulan yang lalu, berapa kerapkah anda mempunyai masalah untuk kekal berjaga semasa memandu, makan makanan, atau melibatkan diri dalam aktiviti sosial?*				
8. During the past month, how much of a problem has it been for you to keep up enthusiasm to get things done? *Pada bulan yang lalu berapa banyakkah masalah kepada anda untuk mengekalkan semangat yang cukup dalam menyiapkan sesuatu perkara?*				

Appendix 3

Travel to and from places			
The next questions exclude the physical activities at work that you have already mentioned. Now I would like to ask you about the usual way you travel to and from places. For example to work, for shopping, to market, to place of worship. [insert other examples if needed]			
7	Do you walk or use a bicycle (*pedal cycle*) for at least 10 minutes continuously to get to and from places?	Yes 1 No 2 *If No, go to P 10*	P7
8	In a typical week, on how many days do you walk or bicycle for at least 10 minutes continuously to get to and from places?	Number of days ⌊_⌋	P8
9	How much time do you spend walking or bicycling for travel on a typical day?	Hours : minutes ⌊_⌋⌊_⌋ : ⌊_⌋⌊_⌋ hrs mins	P9 (a-b)
Recreational activities			
The next questions exclude the work and transport activities that you have already mentioned. Now I would like to ask you about sports, fitness and recreational activities (leisure), [insert relevant terms].			
10	Do you do any vigorous-intensity sports, fitness or recreational (*leisure*) activities that cause large increases in breathing or heart rate like [*running or football,]* for at least 10 minutes continuously? *[INSERT EXAMPLES] (USE SHOWCARD)*	Yes 1 No 2 *If No, go to P 13*	P10
11	In a typical week, on how many days do you do vigorous-intensity sports, fitness or recreational (*leisure*) activities?	Number of days ⌊_⌋	P11
12	How much time do you spend doing vigorous-intensity sports, fitness or recreational activities on a typical day?	Hours : minutes ⌊_⌋⌊_⌋ : ⌊_⌋⌊_⌋ hrs mins	P12 (a-b)

GPAQ, Continued

Physical Activity (recreational activities) contd.			
Questions		**Response**	**Code**
13	Do you do any moderate-intensity sports, fitness or recreational (*leisure*) activities that causes a small increase in breathing or heart rate such as brisk walking (*cycling, swimming, volleyball*) for at least 10 minutes continuously? *[INSERT EXAMPLES] (USE SHOWCARD)*	Yes 1 No 2 *If No, go to P16*	P13
14	In a typical week, on how many days do you do moderate-intensity sports, fitness or recreational (*leisure*) activities?	Number of days ⌊_⌋	P14
15	How much time do you spend doing moderate-intensity sports, fitness or recreational (*leisure*) activities on a typical day?	Hours : minutes ⌊_⌋⌊_⌋ : ⌊_⌋⌊_⌋ hrs mins	P15 (a-b)
Sedentary behaviour			
The following question is about sitting or reclining at work, at home, getting to and from places, or with friends including time spent [sitting at a desk, sitting with friends, travelling in car, bus, train, reading, playing cards or watching television], but do not include time spent sleeping. *[INSERT EXAMPLES] (USE SHOWCARD)*			
16	How much time do you usually spend sitting or reclining on a typical day?	Hours : minutes ⌊_⌋⌊_⌋ : ⌊_⌋⌊_⌋ hrs min s	P16 (a-b)

Appendix 4

Screening 13-items Questionnaire for RTMS subject
(Source: Rossi et al)

VI. **TMS Screening questionnaire**

1. Do you have epilepsy or have you ever had a convulsion or a seizure? ☐
2. Have you ever had a fainting spell or syncope? If yes, please describe in which occasion(s) ☐
3. Have you ever had severe (i.e., followed by loss of consciousness) head trauma? ☐
4. Do you have any hearing problems or ringing in your ears? ☐
5. Are you pregnant or is there any chance that you might be? ☐
6. Do you have metal in the brain/skull (except titanium)? (e.g., splinters, fragments, clips, etc.) ☐
7. Do you have cochlear implants? ☐
8. Do you have an implanted neurostimulator? (e.g., DBS, epidural/subdural, VNS) ☐
9. Do you have a cardiac pacemaker or intracardiac lines or metal in your body? ☐
10. Do you have a medication infusion device? ☐
11. Are you taking any medications? (Please list) ☐
12. Did you ever have a surgical procedures to your spinal cord? ☐
13. Do you have spinal or ventricular derivations? ☐
14. Did you ever undergo TMS in the past? ☐
15. Did you ever undergo MRI in the past? ☐

* Affirmative answers to one or more of questions 1–13 do not represent absolute contraindications to TMS, but the risk/benefit ratio should be carefully balanced by the Principal Investigator of the research project or by the responsible (treating) physician.

Appendix 5

Informed consent

JAWATANKUASA ETIKA UNIVERSITI UNTUK PENYELIDIKAN MELIBATKAN MANUSIA (JKEUPM)
UNIVERSITI PUTRA MALAYSIA, 43400 UPM SERDANG,
SELANGOR, MALAYSIA

FORM 2.4: RESPONDENT'S INFORMATION SHEET AND INFORMED CONSENT FORM

Please read the following information carefully and do not hesitate to discuss any questions you may have with the researcher.

1. **STUDY TITLE :**

Effectiveness and Tolerability of Repetitive Transcranial Magnetic Stimulation for preventive treatment of episodic migraine: a single centre, randomised, double-blind, sham-controlled phase 2 trial (MAGNET-EM).

2. **INTRODUCTION:**

You are invited to participate in a research study because you have migraine that requires treatment of a non invasive device that delivers pulsed magnetic fields on the scalp. The treatment with the device is called repetitive transcranial magnetic stimulation (r-TMS) because it is done repetitively in several sessions. The details of the research trial are described in this document. It is important that you understand why the research is being done and what it will involve. Please take your time to read through and consider this information carefully before you decide if you are willing to participate. Ask the study staff if anything is unclear or if you like more information. After you are properly satisfied that you understand this study, and that you wish to participate, you must sign this informed consent form. To participate in this study, you may be required to provide your doctor with information on your health history, you might harm yourself if you are not being truthful with the information provided.

Your participation in this study is voluntary without any compensation or emolument. You do not have to be in this study if you do not want to. You may also refuse to answer any questions you do not want to answer. If you volunteer to be in this study, you may withdraw from it at any time. If you withdraw, any data collected from you up to your withdrawal will still be used for the study. Your refusal to participate or withdrawal will not affect any medical or health benefits to which you are otherwise entitled.

This study has been approved by the Jawatankuasa Etika Universiti Melibatkan Manusia (JKEUPM).

3. **WHAT WILL YOU HAVE TO DO?**

1. You are required to be present at the Neurophysiology Laboratory located at the Faculty of Medicine and Health Sciences UPM as described above.

2. You will be "randomized" into one of the study groups described below. Randomization means

PUBLICATION

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