UNIVERSITI PUTRA MALAYSIA

EXPLORING NEURONAL ACTIVATION IN RESPONSE TO REWARD THROUGH MRI CORRELATED WITH SIMULTANEOUS EEG AMONG MALE UNDERGRADUATES HAVING PROBLEMATIC SMARTPHONE USAGE

SHARIFAT HAMED

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EXPLORING NEURONAL ACTIVATION IN RESPONSE TO REWARD THROUGH fMRI CORRELATED WITH SIMULTANEOUS EEG AMONG MALE UNDERGRADUATES HAVING PROBLEMATIC SMARTPHONE USAGE

By

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Abstract of thesis presented to the Senate of Universiti Putr Malaysia in fulfilment of the requirement for the degree of Master of Science

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Smartphone usage among young Malaysian adults has increased dramatically in the past decade leading to smartphone addiction (SPA) particularly involving social networking applications such as Instagram. SPA prevalence has been noted to be as high as 47% among medical students in a Malaysian university. There is a need to objectively assess the cerebral mechanisms that respond to reward using electroencephalography (EEG)-informed functional magnetic resonance imaging (fMRI) also known as EEG-fMRI as a potential biomarker.

Therefore, after receiving ethical clearance, an observational study was conducted among 24 male UPM students using Smartphone Addiction Scale-Malay version (SAS-M) questionnaire, modified Instagram Addiction Scale (IAS) and EEG-fMRI. The subjects were recruited by simple random sampling from a Phase 1 cross sectional study comprising of 850 male UPM students who had been administered with the SAS-M questionnaire. Subjects with SAS-M scores ≥ 98 and IAS ≥ 37 were considered High scorers (HS) and deemed to be having SPA, whereas subjects with SAS-M scores < 98 and IAS < 37 were considered Low Scorers (LS) and deemed as healthy controls. A 64-channel EEG scalp electrode was placed on the participants (12 HS, 12 LS) and a task-based fMRI was performed with simultaneous EEG recordings.

Evoked response potential (ERP) derivatives of EEG namely the P300 peak waves and contingent negativity variance (CNV) were analyzed using Brain-Vision EEG analyzer and fMRI dataset were analyzed using Statistical Parametric Mapping (SPM). There was significant difference in the P300 wave

amplitude between HS and LS, which corresponded well with cerebral activations regions related to response to reward.

The combination of the high spatial resolution of fMRI with the high temporal resolution of EEG to correlate cerebral regional activation, in response to cue related reactivity during response to reward task among smartphone addicts, has the potential to be a surrogate biological marker for assessment of Instagram addiction.

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

KORELASI PENGAKTIFAN NEURONAL MENGGUNAKAN fMRI DALAM TINDAKBALAS TERHADAP GANJARAN DENGAN EEG-SERENTAK DI KALANGAN MAHASISWA YANG MENGALAMI PENGGUNAAN TELEFON PINTAR BERMASALAH

Oleh

SHARIFAT HAMED

Ogos 2020

Pengerusi : Profesor Madya Subapriya Suppiah, PhD, MD, MMed
Fakulti : Perubatan dan Sains Kesihatan

Penggunaan telefon pintar di kalangan generasi muda di Malaysia telah meningkat baru-baru ini dan mengakibatkan ketagihan telefon pintar ataupun penggunaan telefon pintar bermasalah (SPA) terutama yang melibatkan aplikasi rangkaian sosial seperti Instagram. SPA dijangka mempengaruhi hampir 47% di kalangan pelajar perubatan di salah sebuah universiti awam di Malaysia. Terdapat keperluan untuk mengkaji secara objektif untuk menilai mekanisma otak yang bertindakbalas terhadap ganjaran menggunakan pengimejan resonans magnetik yang berfungsi (fMRI) serta elektroencephalographi (EEG) serentak, yang juga dikenali sebagai EEG-fMRI sebagai biomarker yang berpotensi.

Setelah menerima kelulusan etika, kajian observasi telah dijalankan di kalangan 24 pelajar siswa UPM menggunakan borang soal selidik versi Bahasa Melayu - Skor Ketagihan Smartphone-Melayu (SAS-M) serta Skala Instagram Addiction yang dimodifikasi (IAS) dan EEG-fMRI. Para subjek dijemput untuk kajian Fasa ke-2 melalui kaedah pensampelan mudah rawak dari Kajian Fasa Pertama yang terdiri daripada 850 pelajar siswa ijazah UPM yang menjawab boring kajiselidik SAS-M. Subjek-subjek dengan skor SAS-M ≥ 98 serta IAS ≥ 37 dianggap Penilai Tinggi atau 'High Scorer' (HS) dan dianggap mempunyai SPA, manakala subjek dengan skor SAS-M <98 serta IAS < 37 dianggap 'Low Scorer' (LS) dan dianggap sebagai subjek kawalan yang sihat. Elektrod kulit kepala EEG yang mempunyai 64 saluran diletakkan pada 24 peserta (12 HS, 12 LS) dan fMRI berasaskan tugasan melihat imej yang dipapar di skrin dilakukan dengan rakaman EEG serentak.

Derivatif potensi respons yang teruja (ERP) terutamanya gelombang P300 dan variasi contigen negatif (CNV) telah dianalisa dengan menggunakan penganalisis EEG Brain-Vision dan dataset fMRI dianalisa menggunakan Pemetaan Statistik Parametrik (SPM). Terdapat perbezaan yang signifikan dalam ERP yang ditimbulkan pada amplitud gelombang P300 antara HS dan LS; yang sesuai dengan pengaktifan serebrum wilayah yang berkaitan dengan tindak balas terhadap ganjaran. Gabungan resolusi spatial tinggi fMRI dengan resolusi temporal yang tinggi EEG untuk mengaitkan pengaktifan serantau, sebagai tindakbalas kepada rangsangan berkaitan reaksi semasa tindakbalas kepada tugasan ganjaran di kalangan pelajar dengan SPA, berpotensi menjadi penanda biologi tumpuan untuk penilaian ketagihan telefon pintar, khususnya kepada Instagram.

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

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Declaration by graduate student

I hereby confirm that:

- this thesis is my original work;
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Declaration by Members of Supervisory Committee

This is to confirm that:

- the research conducted and the writing of this thesis was under our supervision;
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AC	Anterior Commissure
BOLD	Blood Oxygen Level Dependent Imaging
CFA	Confirmatory Factor Analyses
CNV	Contingent Negative Variation
DCM	Dynamic Causal Modelling
Deoxy-Hb	Deoxy hemoglobin
DLPFC	Dorso-lateral Prefrontal Cortex
DRARSF	Data Processing Assistant for Resting-State fMRI
EEG	Electroencephalography
EFA	Exploratory Factor Analyses
EP	Evoked Potentials
ERP	Event Related Potentials
E-SAPS	Estonian Smartphone Addiction Proneness Scale
FFT	Fast-Fourier Transform
fMRI	Functional Magnetic resonance Imaging
GLM	General Linear Model
HC	Healthy Cases
HRF	Haemodynamic Response Function
IAS	Instagram Addiction Scale
KMO	Kaiser-Meyer-Olkin
LIOG	Left Inferior Occipital Gyrus
LLG	Left Lingual Gyrus
LMOG	Left Middle Occipital Gyrus

LORETA	Low-resolution Brain Electromagnetic Tomography
LS	Low Scorer
MPFC	Medial Prefrontal Cortex
OCD	Obsessive Compulsive Disorder
OFC	Orbito Frontal Cortex
Oxy-Hb	Oxy hemoglobin
PC	Posterior Commissure
PET	Positron Emission Tomography
PFC	Prefrontal Cortex
PIGU	Problematic Instagram Usage
PPDN	Centre for Diagnostic Nuclear Imaging
PSC	Percentage Signal change
RC	Right Cuneus
Rc	Right Cerebellum
RFG	Right Fusiform Gyrus
RITG	Right Inferior Temporal Gyrus
ROI	Region of Interest
SAS	Smartphone Addiction Scale
SAS-M	Smartphone Addiction Scale- Malay Version
SNAs	Social Networking Applications
SPA	Smartphone Addiction
tb-fMRI	Task-based fMRI
TE	Time to Echo
TR	Time to Repeat
UPM	Universiti Putra Malaysia

CHAPTER 1

INTRODUCTION

1.1 Background of Study

Nowadays, when we talk about modern technology, we are referring to the application of scientific knowledge for practical purposes to help us in our daily lives. Technology is vital because it is used for nearly everything. The fact that human beings cannot stay apart from technologies such as computer systems, televisions, mobile phones cannot be denied anymore. The usage of technological innovations and devices have slowly taken an indispensable role in people’s everyday lives; hence being without them would be unimaginable to some of us. Invention of mobile technology is one of those technology that has brought us closer than ever. Smartphones have evolved and developed swiftly over the past few years. Indeed a cell phone device has actually turned from being a simple pager to a smartphone device that provides tools such as GPS navigation, web browser, communication by instant messaging and also perform as a handheld gaming console (Patil & Karhe ,November 2012).

Based on statistics, in year 2016, an expected 62.9% of the population worldwide already owned at least one smartphone device and this figure is estimated to pass the five billion mark by the end of 2019 (Samaha & Hawi, 2016). It can be seen that smartphones have changed the manner in which we cooperate with one another significantly. Those changes first arose on social media networks and that is why social applications or apps are so important these days. Social apps like Facebook, Instagram and WhatsApp with 2.5 billion, 1.5 billion and 1 billion respectively, have the highest number of active users among all social apps (Salinas, 2018, August 08). Despite of the advantages of smartphones, using them injudiciously could bring many disadvantages to our daily life.

In fact, mobile dependency or smartphone addiction (SPA) is a kind of dependence syndrome that is observed among smartphone users in the younger generation. It can be seen as a spectrum of problematic smartphone usage with SPA being in the far end of the spectrum. According to Gazelle survey, "More than 25% of respondents reported that they 'almost always' use their smartphone while in a social setting such as during a meal or during a party and 58% said they use it 'usually' during these settings" (Belardi, 15 October 2013). Another study took place at the Alabama State University regarding the consequences of smartphone usage on the students, which stated that “we are not addicted to smartphones themselves, but that we are addicted to the information, entertainment, and personal connections that a smartphone delivers" (Emanuel, 2015). Scientific evidence indicate that users often relate using smartphones with impaired concentration, reduced short term memory retrieval, concentration, tiredness, dizziness, disturbance in sleep pattern and also headaches (Al-Khlaiwi & Meo, 2004). Exorbitant mobile phone usage could result in a chain reaction, influencing one factor of the individual's life and progresses to involve other aspects of their being, which begins with problems in social interactions that can then lead to stress and depression, and in the long run can cause a negative impact on habits of daily living that involve eating and sleeping right (Thomée, Härenstam, & Hagberg, 2011).

The past researches on smartphone addiction or problematic smartphone usage have emphasized on the factors contributing to smartphone addiction. In this study, the response to reward and the brain dopaminergic reward system assessment via task-based fMRI with simultaneous acquisition of EEG recordings in the fMRI scanner (EEG-fMRI) will be conducted to investigate the correlation of the two parameters with smartphone addiction among male UPM undergraduate students.

FMRI measures the brain activity in such way that we can identify the alterations, which are linked with blood flow and oxygen supply in the brain. This technique is based on the certainty that whenever a region of the brain is being used, brain blood flow and neuronal activation are combined and blood stream to that particular region will increase (Thomée et al., 2011). Basically, the functional MRI utilizes the blood-oxygen-level dependent (BOLD) imaging inherent contrast that was initially discovered by the research team headed by Ogawa (Nikos K. Logothetis, Pauls, Augath, Trinath, & Oeltermann, 2001). fMRI scanning will map out activity of the neural in the cerebrum and / or the spinal cord by the means of imaging blood flow changes; known as hemodynamic response factor (HRF) that corresponds to energy utilized by the neurons (Huettel, Song, McCarthy, G.(2009), & 2009). Functional MRI technique can be joined with other brain imaging procedures such as near-infrared spectroscopy (NIRS) to have perfected information about both oxyhemoglobin and deoxyhemoglobin or with electroencephalography (EEG) to measure the functional brain activity along with electrical activity of the cerebral neurons.

Additionally, electroencephalography (EEG) performs as a non-invasive medical test that records the neuronal electrical impulse activity, using small metallic discs known as electrodes which are positioned on the scalp. As a rule, the neuronal cells in the brain communicate through electrical impulses that are constantly active, notwithstanding the patient or the participant is in sleep mode. Henceforth, EEG estimates the changes in electrical voltage that are generated by ionic currents within the cerebral neuronal cells (Schomer, L., da Silva, & Lopes, 2011). In clinical terms, EEG ordinarily means storing of the brain's spontaneous electrical activity within a given time period (Schomer et al., 2011). EEG diagnostic applications center either on its spectral content or on the event related potentials (ERP). The EEG recording result is utilized to investigate the kind of neural motions or what we know as “brain waves" that are observed in the frequency domain of EEG signals. In recent years, fMRI with simultaneous

EEG have turned to be a perfectly strong techniques combination, in which both functional MRI and electroencephalography have complementary strengths, one with high spatial resolution and the another one with a very high temporal resolution (Huettel et al., 2009). Therefore, this study aims to explore the regions of neuronal activations and patterns of EEG waveforms during response to reward task among undergraduate students in Universiti Putra Malaysia, particularly male students with problematic Instagram usage using simultaneous EEG-fMRI imaging.

1.2 Problem Statement and Justification

Problematic smartphone usage has been linked with poor sleep quality, impaired daytime functioning as well as depressive signs (Lemola, Perkinson-Gloor, Brand, Dewald-Kaufmann, & Grob, 2015). Thus, it is alarming that the usage of smartphones among the young adults has become increasingly prevalent. As matter of fact, the prevalence of problematic smartphone usage among public university students in a medical faculty in Malaysia has been observed to be as high as 47% (Ching et al., 2015). In truth, the matter of problematic smartphone usage could pose a serious problem among the young adults of this generation predominantly due to excessive usage of social networking applications (SNAs), particularly SNAs such as Facebook or Instagram, which are widely available on smartphones (Kross et al., 2013). There is a neural evidence of dopaminergic response to reward disorder among other types of substance addiction but not much is known regarding the neural correlates of smartphone addiction. Therefore, this study will aim to detect the neuropsychological changes among undergraduate students in UPM who have problematic smartphone usage with regards to response to reward towards Instagram cues.

The assessment of problematic smartphone usage and digital addiction is conventionally conducted using validated questionnaires such as the Chen Internet Addiction Scale (CIAS), Smartphone Addiction Scale, Smartphone Addiction Scale – Malay version (SAS-M) and previously Instagram Addiction Scale (IAS) (Chen, Weng, Su, Wu, & Yang, 2003) (Ching et al., 2015).

With regards to the SAS-M questionnaire, the students with problematic smartphone usage can be identified with cutoff scores, whereby high scorers (HS) can be differentiated from low scorers (LS) for the identification of subjects with problematic smartphone usage. We can also assess SNA pathological usage, particularly related to pathological Instagram usage by utilizing the modified Instagram Addiction Scale (IAS) questionnaire (Lancy D'Souza, Samyukta A, & Tevin John Bivera, July 2018). This method can help to identify subjects with Problematic Instagram Usage (PIGU). Nevertheless, these methods sometimes have a limitation on objectively assessing problematic smartphone usage.

Combining functional MRI and EEG techniques is a novel initiative way that is able to objectively determine the activation of neurons and lay out patterns of the brain wave in different segments of it (C.-Y. Wee et al., 2014). Functional MRI utilizes blood oxygenation level dependent (BOLD) imaging technique that gives different signals in the brain based on oxygen utilization whether in resting-state or task-based activity that is seen in a task-based fMRI (tb-fMRI). It's worthwhile to mention that, addiction have impact on the modulation of dopaminergic activity in the meso-corticolimbic circuitry, particularly in the hypothalamus and amygdala, which can be objectively evaluated using fMRI (Goldstein et al., 2007).

Considering that addiction is caused by several domains namely development of dependence, tolerance, withdrawal, etc. we aimed to focus on the development of tolerance towards rewarding cues based on Instagram upload. Visual stimuli have been known to cause arousal based on the emotional valence elicited by the pictures (Gerdes et al., 2010). For instance images that are positive/ pleasant was correlated with emotional arousal and fMRI activations in the right caudate nucleus, nucleus accumbens and left dorsolateral prefrontal cortex and negative/ unpleasant images elicited stronger activations in the amygdala (Gerdes et al., 2010).

Furthermore, a study by Nitschke et al, 2004 identified mothers viewing rewarding pictures of their newborn had higher activations of their orbitofrontal cortex (Nitschke et al., 2004). The importance of predicting a reward for a group of individuals is based on a positive or negative value assigned by the group for a stimulus, whereby increased activity can be observed in the prefrontal cortex indicating stimulation of the dopaminergic reward system (Lena et al., 2005, Perogamvros & Schwartz, 2012) by utilizing a task that presents the subject with images of negative emotional valence or 'Risky' images, we believe we can identify differences of brain reward system activation in subjects with PIGU. Conversely, images with positive emotional valence or referred to as 'Participant' images are expected to elicit pleasant feelings and response in both PIGU and Control groups and should not overly stimulate the prefrontal cortex, orbitofrontal cortex and amygdala in the brain reward system.

Additionally, EEG patterns can defect brain waveform in response to addictive behaviors, particularly in response to a rewarding stimulus (Boecker-Schlier et al., 2017). EEG patterns are shown as peaks and troughs in a recording sheet with the amplitudes of fluctuations referred to as evoked response potential (ERP) i.e. it is the measurement of the electrophysiological responses particularly of the central nervous system to a myriad of stimuli. Specifically, we can measure the P300 response based on EEG readings, which is a peak that is elicited during decision-making and it represents an endogenous ERP that mirrors the participant's response to a given cue (van Dinteren, Arns, Jongsma, & Kessels, 2014). Contingent negativity variance (CNV) is another EEG parameter that is closely related to response to a given stimulus. We generally refer to the time between an imperative stimulus and the behavioral response as the reaction time. With reference to EEG, the equivalent to response time is the CNV, which is referred as thus due to the timing of the variation of the negatively deflected wave that depicts the elicited response, is contingent on the statistical relationship between the cue/ warning to stimulate anticipation and the imperative presentation of stimuli to assess response to reward. (Walter, Cooper, Aldridge, McCallum, & Winter, 1964).

Hence, combining these two techniques, fMRI BOLD-imaging with simultaneous-EEG can potentially to be an alternative and non-invasive biological marker for the evaluation of problematic smartphone usage.

1.3 Objectives

General Objective: The key objective is to correlate fMRI activation with EEG data, in response to cue related reactivity during response to reward among PIGU group.

Sub-Objectives:

i. To identify the subjects' demographic data (age, gender, frequency of smartphone usage, SAS-M scores, modified IAS scores)
ii. To identify percentage signal change (PSC) in regions of interest in tb-fMRI study during response to reward (PIGU group vs Control group)
iii. To compare the time of onset of CNV during response to reward (PIGU group vs Control group)
iv. To compare the amplitude height of P300 peak wave during response to reward (PIGU group vs Control group)
v. To correlate subject demographic data with EEG findings of P300 amplitude and PSC on tb-fMRI respectively
vi. To correlate the EEG findings of P300 amplitude with PSC on tb-fMRI

1.4 Hypothesis

Hypothesis (H) and Null hypothesis (H0) for this thesis:

H1: There is a significant difference between the demographic data i.e., age, gender, and frequency of smartphone usage among the PIGU and controls.

H0: There is No significant difference between the demographic data i.e., age, gender, and frequency of smartphone usage among the PIGU and controls.

H2: There is a significant difference between the percentage signal change (PSC) in regions of interest in tb-fMRI study during response to reward among the PIGU group compared to the Control group.

H0: There is No significant difference between the percentage signal change (PSC) in regions of interest in tb-fMRI study during response to reward among the PIGU group compared to the Control group.

H3: There is a significant difference between the time of onset of CNV during response to reward among PIGU group compared to the Control group.

H0: There is No significant difference between the time of onset of CNV during response to reward among PIGU group compared to the Control group.

H4: There is a significant correlation between the subject demographic data with EEG findings of P300 amplitude and PSC on tb-fMRI in the PIGU group compared with the control group.

H0: There is No significant correlation between the subject demographic data with EEG findings of P300 amplitude and PSC on tb-fMRI in the PIGU group compared with the control group.

H5: There is a significant difference between the amplitude height of P300 peak wave during response to reward among the PIGU group compared to the Control group.

H0: There is No significant difference between the amplitude heights of P300 peak wave during response to reward among the PIGU group compared to the Control group.

H6: There is a significant correlation of the EEG findings of P300 amplitude with PSC on tb-fMRI during viewing 'Risky' cues in the PIGU group.

H0: There is No significant correlation of the EEG findings of P300 amplitude with PSC on tb-fMRI during viewing 'Risky' cues in the PIGU group.

1.5 Organization of Thesis

The outline of this thesis is as follows:

The first chapter explains the concepts for this response to reward study and Figure 1.1, gives the conceptual framework of this study.

In the following chapter, we provide the literature review from precedent works in studying types of assessments for smartphone addiction and Instagram addiction as well as fMRI and EEG studies related substance addiction, behavioral addictions and problematic smartphone usage. We will provide sufficient explanation from previous studies in order to answer, why this study focuses mainly on undergraduate male students in Malaysia and in particular to Instagram application. We will also discuss the significant EEG and fMRI findings from various addiction studies and also discuss the significance of using tb-fMRI in addiction studies. We will also debate the significance of using simultaneous EEG-fMRI in this study. We will highlight the relationship between problematic smartphone usage particularly PIGU, among male undergraduate students, with fMRI percentage signal change (PSC) in areas of the cerebrum involved in responding to reward stimuli and correlate this with simultaneous-EEG detected P300 wave and CNV.

Chapter 3 brings a concise explanation on the methods employed to design our study protocol. We will clarify our study materials and method used. We will underscore the procedures associated with tb-fMRI along with simultaneous-EEG data analysis and describe the statistical methods that we utilized in analyzing the study results.

In Chapter 4, we present our results from simultaneous EEG-fMRI study in the form of tables, graphs, MRI image figures as well as EEG signal recordings.

In Chapter 5, we emphasize on the discussion related to the simultaneous EEG-fMRI study that was conducted among male undergraduate students in Universiti Putra Malaysia in relation to PIGU. We also contrast our results based on the simultaneous EEG-fMRI findings from other types of addiction studies and activation findings based on other task-based studies pertaining to addictions and response to reward. In this chapter, we will also give a synopsis of the thesis as well as expound on the important observations made in this study and the path for future works.

In Chapter 6, we will summarize this thesis and conclude our limitations and the recommendations for future works. A brief biodata of student is provided at the end.

1.6 Conceptual Framework

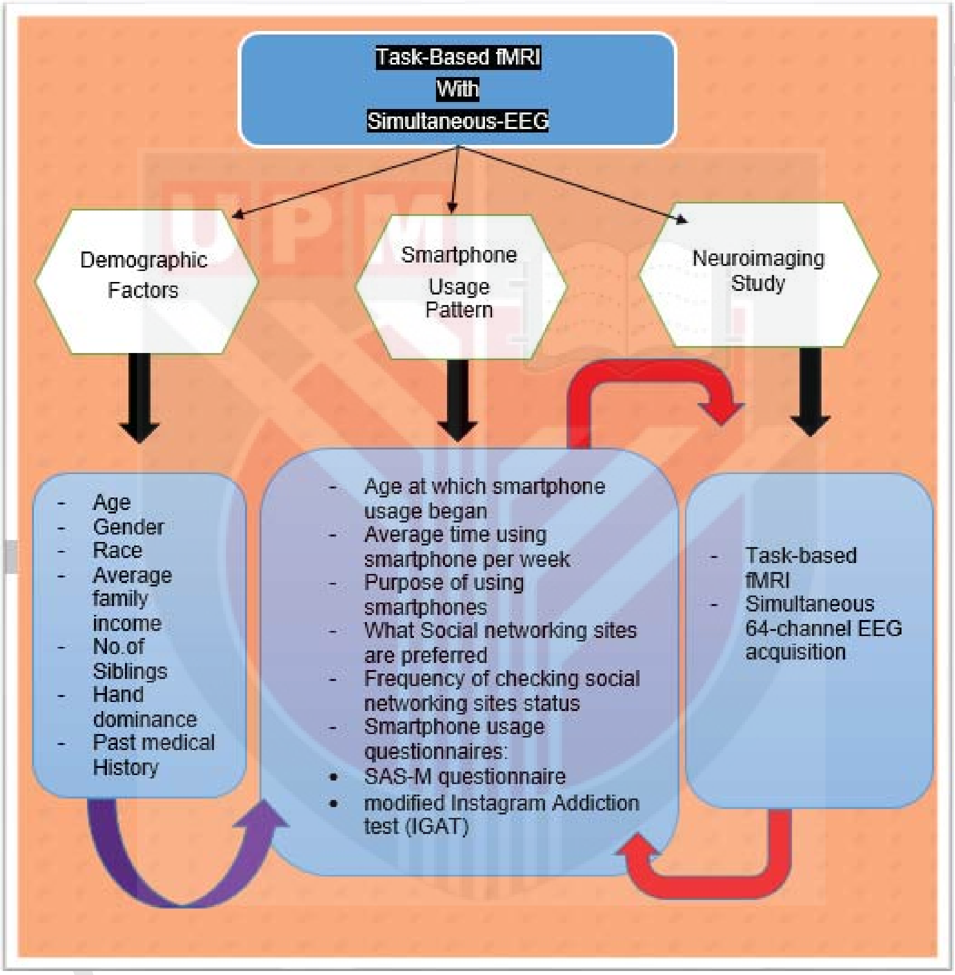

Figure 1.1 : The conceptual framework for simultaneous EEG-fMRI response to reward study

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