EEG ANALYSIS OF OPIOID DEPENDENTS DURING METHADONE TREATMENT

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ABSTRAK

Matlamat kajian ini adalah untuk mempelajari tentas perubahan struktur otak pada penagih heroin setelah penggunaan awal metadon dan menentukan peranan metodon dalam menormalkan kecelaruan psikofisiologik berkaitan kebergantungan kepada opioid. Untuk mengkaji kemampuan metadon dalam memulihkan semula struktur fungsi otak daripada penagih opioid, komposisi daripada ayunan elektroensefalografi (EEG) jalur frekuensi lebar (0.5Hz – 60Hz) dikaji. Analisis komponen merdeka (ICA) daripada isyarat EEG kulit kepala digunakan untuk mengesan kawasan kortikal dan aktiviti spektro-temporal yang didapati pada kebergantungan opioid dan pengubatan metodon. Hasil kajian ini menunjukkan bahawa, semasa keadaan kebergantungan opioid, aktiviti sumber otak yang responsif terhadap opioid terpumpun pada medial prefrontal cortex (mPFC) dan luasan sistem limbik, dan aktiviti-aktiviti ini nyata sekali menurun setelah penggunaan metadon. Analisis spektrum daripada akitiviti kortikal menunjukkan peningkatan akitiviti alfa, beta, dan gama semasa kebergantungan opioid, manakala sesaat selepas penggunaan metodon, berlaineudaripede aktiviti gama, aktifiti alfa dan beta menurun.

ABSTRACT

This study aims to explore the structural brain changes in heroin abusers after the first administration of methadone and therefore examine the role of methadone in normalizing the psychophysiological impairments associated with the state of opioid dependency. The ability of methadone to restore the normal cortical functioning in opioid dependents the composition of electroencephalographic (EEG) oscillations within a broad frequency band (0.5Hz – 60Hz) was explored. The Independent Component Analysis (ICA) was used to identify the cortical regions and their relevant spectro-temporal activities involved in opioid dependency and methadone therapy based on the information content of the scalp EEG signal. It has been shown that within the state of opioid dependency the majority of brain activities responsive to opioids are located within the medial prefrontal cortex (mPFC) and the extended limbic system, and these activities reduced significantly after methadone administration. Spectral activities of the brain within alpha, beta, and gamma frequencies increased during opioid dependency while, unlike the gamma spectrum, the alpha and beta spectral activities underwent a decline early after the onset of methadone administration.

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1 CHAPTER I: INTRODUCTION

1.1 Overview

Opioid dependency is a chronic brain syndrome associated with psychophysiological disorders. Although the possibility of relapsing back to state of opioid dependency is quite high particularly in early abstinence, neuropsychophysiological deficits during the state of opioid dependency or after opioid cessation are barely investigated. On the other hand, structural cortical alterations and their correlation with the onset age and duration of opioid abuse, remain unknown.

Methadone is known as a long term acting medication for opioid dependency. While oxycodone, morphine, heroin or other types of addictive drugs have a short term effect on the body and brain, methadone has long lasting effects. Like other opioids, methadone can cause dependence but since it has steadier effects on the Mu receptors, it produces less tolerance and withdrawal symptoms. Methadone treatment can also normalize the disruption of the hormones in opioid dependents. Effects of methadone on mediating the symptoms of opioid abuse are not limited to the physiological treatment. It also provides psychological medication like facilitating the behavioral therapy (White, 2007).

1.2 Problem Statement

Despite of a large number of advantages associated with methadone as an influential therapy for opioid dependency, still the efficiency of this treatment is highly dependent upon the prescription condition. Since methadone is considered as a long term medication with addictive effects, the risk of getting back opioid dependency is very high if the patient cannot meet the required period of the treatment while the methadone itself can cause dependency. Yet the optimal dosage of methadone administration has not been discovered.

Moreover the psychophysiological side effects of methadone therapy need to be considered. All of these facts about the methadone therapy make it of great importance to investigate different psychophysiological aspects of this treatment to identify the optimal therapy.

1.3 Objectives

The aim of this study is to investigate the efficiency of methadone treatment in the state of opioid dependency.

1.4 Scope of study

The main scopes of conducting this study include:

- Providing a novel and highly efficient method to process the electroencephalographic (EEG) signal while being able to accurately track cortical regions of the EEG.
- Spectral analysis of neurophysiological alteration through the state of opioid dependency and methadone-based treatment to investigate the effects of opioids and methadone on the brain structure.
- Evaluating the efficiency of methadone treatment in medication of opioid dependency.

1.5 Significance of Study

The effectiveness of this spatial filtering lies within the application of the information content of EEG signal itself rather than a predefined set of cortical locations to separate the scalp data into brain and artifact sources (Makeig *et al.*, 2002). Another major advantage of applying ICA for EEG source localization is that the locally coherent cortical activities which constitute one particular EEG source will be joint together making a single independent component (IC) which includes projection of those activities to all of the scalp

electrodes, whereas the unrelated EEG source activities will be eliminated from this IC and contributed to other ICs (Onton & Makeig, 2005).

1.6 Outline of the Report

This project is categorized in five chapters each investigating one aspect of the study. Statement of the problem, objectives of the study along with the scopes and significance of conducting the experiment are covered through the first chapter. Chapter II presents the wide range literature related to EEG analysis, opioid dependency and methadone medication while it tries to evaluate the most significant finding regarding the objectives of the present study. Chapter III deals with the theoretical and practical aspects of the methodology used in this study, and how it can be applied to obtain the most reliable results. Chapter IV represents the result of implementing the study and how they can be interpreted regarding the effects of methadone therapy in opioid abusers. Lastly, chapter V draws a conclusion on the efficiency of methadone medication based on the results of the previous chapter and also recommends the future work in this area.

2 Chapter II: REVIEW OF RELATED LITERATURE

2.1 Introduction

This chapter covers the literature regarding the neurophysiological and neuropsychological aspects of drug dependency, methadone treatment, and the methodological strategies of temporal and spectral analysis of the EEG signal focusing on the Independent Component Analysis (ICA) to investigate opioid dependent EEG signal.

2.2 Physiology of Brain

The following table gives an overview of the brain structures and their functions while their basic physiology is demonstrated in Figure 2.1 as follows.

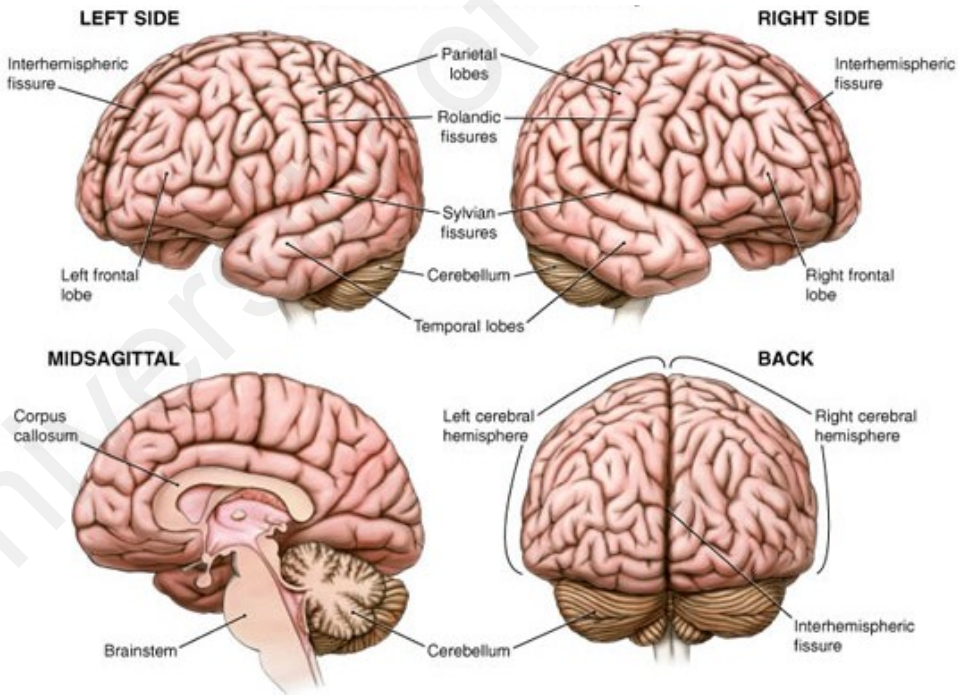


Figure 2.1 Basic Physiology of Brain (Swanson, 2011).

Table 2.1 Cortical Regions and Their Functions

CORTICAL AREA	FUNCTION
Cerebral Cortex	Controlling voluntary movements, perception, thinking, and language
Cerebellum	Controlling posture, coordination, and movement balance
Hypothalamus	Controlling emotions, digestion, sleep, body temperature
Mid Brain	Controlling reflexes of swallowing and breathing
Thalamus	Controlling sensory and motor integration
Hippocampas	Controlling learning and memory

2.3 Opioid Dependency

2.3.1 Neurobiology

The effects of both endogenous and exogenous opiates are produced by opioids binding to opioid receptors distributed throughout CNS and gastrointestinal tract. Opioids act at three distinct classes of receptors: kappa, delta, and mu, each of these three receptors is involved in controlling different brain functions like opiates and endorphins are able to block pain signals by binding to the mu receptor site (Goddard *et al.*, 2001).

Opioids affect the sites along:

- Pain pathways.
- Respiratory center.
- Cough center in the medulla (which leads to a reduction in the cough reflex).
- Vomiting center (stimulation of chemoreceptor trigger zone in area postrema of the medulla causing nausea and vomiting).
- Hormonal (endocrine) system (cause release of antidiuretic hormone which may explain the fluid retention).
- Hypothalamus (which leads to an increase in body temperature during opioid use).

- Immune system (there may be a degree of immunosuppression due to these drugs and this can lead to increased susceptibility to infections in vulnerable patients. Whether this is a problem with prescribed doses is unclear).

The opioid system is connected with most neurotransmitter networks in the body. The interaction between the opioids and the dopaminergic system appears to be involved in addiction, tolerance, and withdrawal symptoms (Grace, 2000). The relevant interaction appears to occur along the mesolimbic projection, particularly in the ventral tegmental area (VTA) and nucleus accumbens (NAc) (Walwyn *et al.*, 2010). The limbic system controls emotions. Opiates change the limbic system to produce increased feelings of pleasure, relaxation and contentment (Kreek, 1992). The brainstem controls things your body does automatically, like breathing or coughing. Opiates can act on the brainstem to stop coughing or slow breathing. The spinal cord transmits pain signals from the body. By acting here, opiates block pain messages and allow people to bear even serious injuries.

Opiates act not only on the central structures of the reward circuit (the VTA and the NA), but also on other structures that are naturally modulated by endorphins including the amygdale, locus coeruleus, arcuate nucleus, periaqueductal grey matter which also influence dopamine levels, though indirectly, and thalamus which would explain their analgesic effect (Kosten, 1990).

The brain pleasure centers affected by drugs:

- Ventral Tegmental Area (VTA) which is located in the midbrain and contains the dopaminergic neurons that innervate the limbic system and the prefrontal cortex.
- Nucleus Accumbens (NA) or Ventral Striatum which is located in the septal region, innervated by the ventral tegmental area, and serves as an interface between the limbic system and the motor system.

- Prefrontal Cortex whose role in the processes of attention and motivation is well established (Robinson & Berridge, 2000). The following figure demonstrates these three regions within the cortex.

2.3.2 Neuropsychological changes

Neuropsychological research reported short term disfunction in visual and verbal memory, attention, working memory and concentration through the state of opioid dependency. Even a general intellectual decline has been shown while intoxicated or very recently detoxified (Khantzian *et al.*, 1984; Prosser *et al.*, 2006). It has been shown that after rapid detoxification heroin abusers who had shown a deficit in attention, working and episodic memory, and verbal fluency during abuse did not differ from controls after one to two weeks of abstinence. It seems that opioid abuse induces partially transient alterations of cognitions. On the other hand, after long term abstinence a consistent deficit in executive functioning, especially in impulse control has been found (Davis *et al.*, 2002; Fu *et al.*, 2008; Mintzer *et al.*, 2005). The prefrontal cortex is involved in cognitive functions such as planning, anticipation and establishment of goals, organization and motivation of behavior, defined as executive functions (Fellows, 2007). The functional imaging studies of substance abusers also point to those frontal pathways related to cognition (Ghodse & Galea, 2010; Volkow *et al.*, 2002).

2.4 EEG Studies

The signal recorded at each scalp electrode is the sum of activities originating in nearly all cortical sources and artifact source domains from movements, muscles, eyes, electrodes, and the electrical environment. So far most of the EEG studies are based on the analysis of electrical potential time series receiving at each scalp electrode, which reveals little information regarding the type, number and spatial distribution of the brain sources

generating them. So EEG recordings are usually considered to have low spatial resolution. Furthermore, different patterns of cortical folding across individuals may cause the spatially equivalent brain source areas to have different orientations, relative amplitude, and distances across most of the cortex, making significant differences in their projections to the scalp electrodes. Thus, comparing EEG signals of the subjects across equivalent scalp electrodes may not be accurate.

2.5 Methadone Treatment

Methadone is considered to be the standard agonist substitution therapy for heroin abusers. Recent findings in clinical neuroscience reveal the importance of methadone to decrease craving for opioids (Greenwald *et al.*, 2007) while it can also prime craving and opioid cue response (Curran *et al.*, 2001; Gerra *et al.*, 2003; Shaham *et al.*, 1996). Although many studies have already supported the efficiency of methadone treatment as a medication for opioid abuse (Ball & Ross, 1991; Simpson *et al.*, 1997). Still some issues remain. Methadone prevents symptoms of withdrawal through affecting the same opioid receptors as opioids. While it is associated with physical dependency, it causes less psychological dependency as compared with other opioids like heroin since it does not give the same sense of euphoria.

Methadone treatment can affect brain cognitive function; as compared to abstinent subjects methadone subjects have shown considerably poorer performance in learning tests and also immediate recall (Gritz *et al.*, 1975). It has been reported that that patients underwent methadone treatment have shown some impairments in attention tests and psychomotor speed (Mintzer & Stitzer, 2002). Furthermore a significant alteration in levels of cerebral phospholipid metabolite (Silveri *et al.*, 2004)and also higher production of interleukins (IL-6) (Zajocov *et al.*, 2004) was observed in methadone treatment subjects.

It has been shown that while a long period (minimum of three months) of abstinence may significantly or even completely normalize the EEG of opioid-dependent patients(Bauer, 2001; Costa & Bauer, 1997; Gekht *et al.*, 2003; Shufman *et al.*, 1996) methadone treatment can recover the temporal structure of EEG oscillations in the opioid abusers (with slight slowing down of EEG dynamics) (Gritz, Shiffman*, et al.*, 1975) comparable to the healthy subjects. The electroencephalographic signal of opioid dependents during withdrawal and opioid abuse is reorganized significantly in terms of EEG oscillations and their temporal activity (Fingelkurts, Kivisaari, Autti, Borisov, Puuskari, Jokela, & Kahkonen, 2006) Methadone can restore these structural changes

which extensively distribute over the cortex back to the normal level of healthy subjects (Fingelkurts *et al.*, 2007).

2.6 Independent Component Analysis (ICA)

As an alternative approach to simultaneously monitoring field activities of the brain sources, independent component analysis (ICA) (Bell & Sejnowski, 1995; Cardoso & Laheld, 1996)was applied. Each subject scalp EEG data was separated into the active cortical and artifact sources based on the physiologically and statistically reasonable assumption of the ICA that these cortical activities should be nearly temporally independent of each other (Makeig *et al.*, 1996; Makeig *et al.*, 1999).

3 CHAPTER III: METHODOLOGY

3.1 Introduction

This chapter discusses in detail what methodological and experimental steps were taken to conduct this study and also describes the rationale of applying them. These steps are summarized as the following chart.

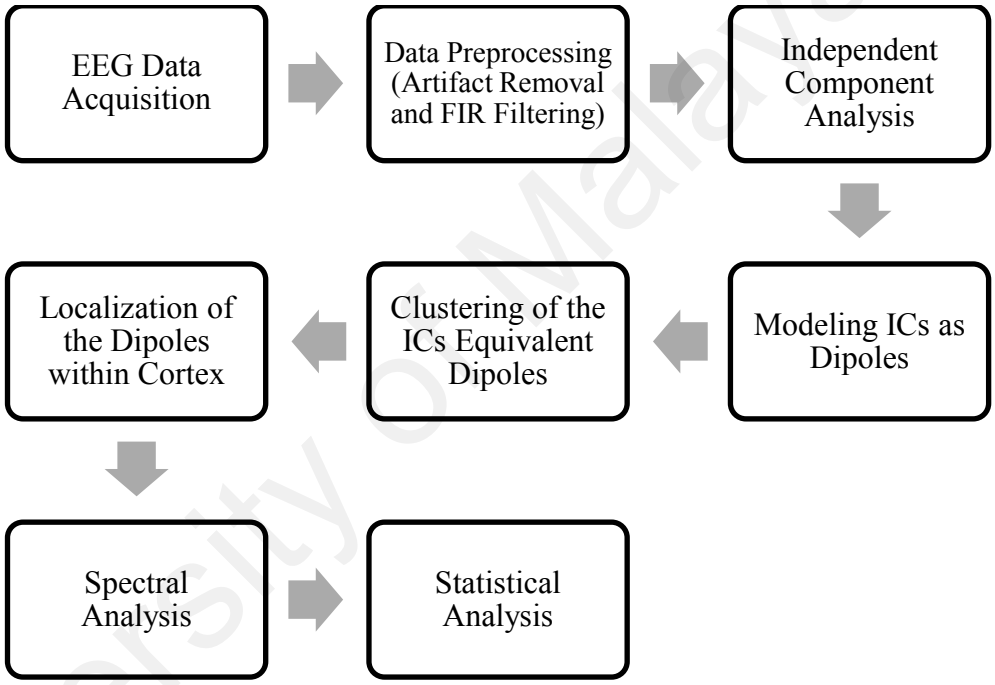


Figure 3.1 Overview of the methodology

3.2 Subjects

This study involved a total number of four opioid-abuser patients (aged 25 ± 2 years, 4 males). The inclusion criteria for this study which took place at University Malaya Biomedical Engineering Laboratory were at least 4 years of documented opioid dependency, a minimum age of 20 years, and negative test of methadone abuse at least 2 months before starting the treatment. The criteria for exclusion from this study were alcohol dependency, any kind of psychiatric, neurological (major head trauma) or physical

(vascular pathology) disease which can have adverse effects on the routine therapy, and any records of poly-substance abuse. All of the patients have been abusing heroin for at least 6 years and none of them had used methadone before. None of them reported any episodic (irregular) use of alcohol, benzodiazepines, cannabis, and amphetamines while heroin and street buprenorphine were reported as the only drugs taken daily (regularly) for the past few years (at least 3 years). The study was approved by the Ethics Committees of University Malaya Hospital and all of the patients submitted their consent form before being enrolled in the study.

3.3. Trial Design

On the day of admission, each subject underwent breath screening, blood test and urine samples to verify a). Heroin abuse within 12 hours prior to the EEG recording, b). Abstinence of methadone (this allowed us to examine the exact instantaneous effect of methadone), and c). Absence of any withdrawal symptoms (subjects required to be on their daily dosage to avoid these symptoms). Methadone was used in dosage of 90-120 mg (depending on the subject) in the morning.

Once the instruments were calibrated and the scalp electrodes located on the scalp, the subject was placed in a comfortable situation in a dimmed electromagnetically shielded recording room and the whole procedure was explained. Subjects were instructed to look straightly forward (even while their eyes were closed) and have a very comfortable position without any movement. These considerations reduce artifacts originating from eye movement and muscle tensions. Subjects underwent 10 minutes of EEG recording before and a few minutes after taking methadone, 5 minutes with their eyes opened and 5 minutes closed. Subject behavior through the experiment was monitored using a TV camera.

3.4. Data Acquisition (EEG Recording)

EEG recording carried out in an electrically and magnetically shielded recording room in the BIOMEDICAL Laboratory of the UNIVERSITY MALAYA Engineering Faculty. EEG activities were captured using 32-channel EEG data acquisition equipment within a frequency band of 0.5Hz to 85Hz (256Hz sampling rate). We applied the standard international 10/20 electrode system with the Cz electrode as the reference. Before data collection, for each subject we monitored the impedance of all the electrodes to verify its value to be under 5 kΩ. Based on the physiologically plausible facts regarding the cortical areas which are most affected by drugs, and also to reduce the complexity of the analysis we analyzed EEGs from 19 ($F_{7/8}$ .F_z . $F_{3/4}$. $T_{7/8}$. $C_{5/6}$. $C_{3/4}$. C_z . $P_{7/8}$. $P_{3/4}$ .P_z .$O_{1/2}$) electrodes widely distributed across the scalp allowing us to accurately capture the brain signals.

3.5. Data Pre-Processing

A clean decomposition of EEG signal by ICA which can yield highly accurate and reliable results is dependent upon two main factors; first the number of time points in each EEG channel data and second applying the universal rule of GIGO "garbage in, garbage out" to ICA.

3.5.1 Duration of EEG Signal

Number of Time Points: Assuming to have *n* channels of EEG data, the number of time points which are required for a clean decomposition is related to the number of channels squared (Onton & Makeig, 2006). Running so many trials and errors, we considered the best value for K to be 25. While the number of channels was 19 and K being equal to 25 the sufficient number of data points needed for a clean decomposition would be:

$$Number\ of\ time\ points = K.n^2 = 25 \times\ 19^2 = 9025$$

With a sampling frequency of 256 Hz (f_s= 256 *Hz*) the time duration is:

$$\Delta t = \frac{K.n^2}{f_s} = \frac{9025}{256} = 35.25\ Sec. \approx 30\ Sec$$

Thus we need 30 seconds of each channel EEG data to perform a clean decomposition. Further analysis of the EEG data was then implemented individually for each 30 Seconds portion of the signal. Following this strategy effectively enhanced the statistical confidence of the results.

3.5.2 Artifact Removal:

Two main classes of EEG artifacts considered '*garbage*' or undesirable for ICA; stereotyped artifacts like eye blinks, eye movements, muscle tensions, and non-stereotyped artifacts caused by scalp electrode movement arising from large muscle activities. The latter can highly reduce the efficiency of the ICA decomposition due to highly variable spatial distribution which produces a great number of distinctive scalp maps, resulting in a few ICs to be left for capturing cortical activities (Onton *et al.*, 2006).

To identify artifact components, we combined temporal and spatial features of each type of artifact prototypes using five different algorithms (Table 3.1). These features then optimized to capture generic discontinuities, blinks, and eye movements.

Table 3.1 Algorithms of Artifact Removals and Their Index of Sensitivity

ARTIFACT	REMOVAL ALGORITHM	SENSITIVITY OF THE APPLIEDALGORITHM
Eye Blink	Spatial Average Difference (SAD)	Higher amplitude in frontal areas
	Temporal Kurtosis (TK)	Outliers in the amplitude distribution typical of blinks
Horizontal Eye Movement	Spatial Eye Difference (SED)	Large amplitudes in frontal channels near the eyes typical of horizontal eye movements
	Maximum Epoch variance (MEV)	Slower fluctuations typical of vertical eye movements
Vertical Eye Movement	Spatial Average Difference (SAD)	Higher amplitude in frontal areas
	Maximum Epoch variance (MEV)	Slower fluctuations typical of vertical eye movements
Generic Discontinuities	Generic Discontinuities Spatial Feature (GDSF)	Local spatial discontinuities
	Maximum Epoch variance (MEV)	Slower fluctuations typical of vertical eye movements

Pruned ICs completely corrected from the artifact effects then back projected together by ICA (Makeig *et al.*, 1997) to make the clean brain activities ready for further analysis.

EEG streams, fully corrected from the influence of artifacts, contained a continuous 5-min signal (with eyes closed) for each patient and control subject. Due to the technical requirements of the tools which were later used to process the data, EEGs from 20 electrodes (F7/8, Fz, F3/4, T3/4, C5/6, Cz, C3/4, T5/6, Pz, P3/4, Oz, O1/2) were analyzed with a converted sampling rate of 128 Hz.

Prior to the spectral analysis, each EEG signal was band pass filtered within the 0.5-30 Hz frequency range. This frequency range was chosen because approximately 98% of spectral power lies within it (Collura *et al.*, 2008).

3.5.3 Filtering

Considering the fact that the natural brain activities are represented by different types of simultaneous oscillations (Basar *et al.*, 2000), spectral filtering and isolating EEG data into different frequency bands would mask the natural composition of cortical activities (Fingelkurts, Kivisaari, Autti, Borisov, Puuskari, Jokela, & Kähkönen, 2006) Temporal activity of each independent component is the resultant of instantaneous and thus broad band filtering of EEG scalp data, therefore it represents the synchronous segment of activity within a single or two connected cortical patches. This fact also supports the drawbacks of applying spectral filtering to the EEG data prior to the main analysis (Fingelkurts & Kahkonen, 2005).

Therefore we considered a broad frequency band (0.5Hz – 45Hz) for our analysis knowing that also 98% of the whole power of the EEG signal lies within this spectrum (Fingelkurts *et al.*, 2000) which makes it easier to capture and monitor the activities of brain sources. This broad band-pass filtering enhanced the efficiency of ICA decomposition as well (Delorme & Makeig, 2004)since it efficiently minimized the appearance of 50Hz or 60Hz linear trends. We applied EEGLAB toolbox of the MATLAB software to implement the Finite Impulse Response (FIR) Butterworth band-pass filtering of the data. The advantages of this non-linear filtering algorithm arise from its flat band passing which is excellent in simulating the band pass of an ideal filter.

3.6 Independent Component Analysis (ICA)

As the next step, we performed ICA decomposition using infomax ICA algorithm (provided in EEGLAB Toolbox of MATLAB) which requires a few matrix inversion and therefore runs very fast. The main advantage of this algorithm is that it can detect not only supergaussian (peaky) sources of activities but also subgaussian distributions.

This feature of infomax algorithm is of great importance while detecting artifacts (Lee *et al.*, 1999).Experimental trials and errors revealed that for our analysis applying the infomax ICA yields cleaner decompositions.

3.7 Components Source Modeling

As we have previously seen in this study, low spatial resolution of the EEG scalp signals makes it so difficult to indicate the location of even the most intensive underlying sources in the cortex. Therefore, we directly applied an inverse modeling of cortical source locations from distribution of EEG potentials on the scalp. But this approach might be quite intractable since almost the entire EEG scalp signals are sum of the activities of multiple cortical and non-cortical sources. ICA has paved the way to solve this problem by applying inverse modeling of ICs scalp maps rather than their projection to each of the scalp electrodes.

3.8 Modeling Components Equivalent Dipoles

The most realistic approach to this inverse modeling tries to match each ICs scalp map with the closest projection of a single equivalent dipole(Scherg & Von Cramon, 1985).We used DIPFIT plug-in of EEGLAB toolbox to localize the equivalent dipoles of ICs. We applied the standard four shell (Skin, Skull, CSF, and Cortex) spherical head model to simulate the brain. To make the coordinates of the dipoles returned by DIPFIT, meaningful channel were co-registered to the surface of the selected head model. After fine fitting of the dipoles, for each subject we were able to find single equivalent dipole models for 20 ICs whose projection patterns across scalp significantly (with no more than 15% residual variance (R.V.) between the scalp projection of the dipole and the actual IC scalp

map) match the observed IC map. To have a highly accurate modeling if an IC scalp map didn't adequately modeled by a single equivalent dipole we would exclude it from the analysis. Performing further analysis requires adequate identification of physiologically plausible components originating from the cortical sources. A workable criterion to distinguish between cortical and non-cortical ICs is that the cortical independent component should match adequately to a single (or bilateral) equivalent dipole(s) *(R.V. < 15%)* which localized inside the volume of the head. Modeling ICs to the best-fitting equivalent dipoles not only provide localization of cortical activities to a certain brain region; but also paves the way to evaluate and visualize the spatial uniformity of clusters which include functionally comparable or equivalent IC activities across subjects.

3.9. Components Clustering

To identify and correlate equivalent ICs across subjects we applied a clustering approach. We analyzed and compared independent components from different subjects and found ICs which were functionally or spatially equivalent, these equivalent components then were grouped together as one cluster. In other words, ICs representing the same functional activities were spatially modeled as equivalent dipoles in one single cluster. Clustering independent components according to their equivalent dipoles 3D locations we were able to analyze brain activities in almost all cortical areas or at least in cortical regions having adequate densities of dipoles across subjects. We used K-means distance-based algorithm to run the clustering of ICs equivalent dipoles. Physiological differences of cortical structures in location and orientation of gyrus, sulci, and also the brain shape may reduce the reliability and confidence in the results achieved by comparing cortical areas of ICs equivalent dipoles across subjects. Therefore, to normalize 3D locations of equivalent

dipoles across subjects, we performed a spatial normalization of each subject head shape to a standard four shell head model learned from 3D locations of each subject scalp electrodes. To this end, we performed a true comparison of dipoles 3D locations across the subjects.

3.10 Spectral Analysis

Although clustering of independent components across subjects to find the most significant functional or spatial correlation among different cortical activities is itself a statistical approach, to put more confidence in our analysis regarding the source localization of the cortical activities involved in states of opioid dependency and methadone treatment, we also compared broad band (0.5Hz-120Hz) relative power across three clusters of ICs in alpha, beta, and gamma frequencies.

4 CHAPTER IV: RESULTS AND INTERPRETATIONS

4.1 Introduction

This chapter provides the results of EEG source localizations along with the spectral and statistical analysis of the results. We applied ICA for localizing the EEG sources within the cortex while these cortical sources were modeled as equivalent dipoles of the independent components (ICs). Spectral analysis of the clustered dipoles was implemented in alpha, beta, and gamma frequencies. Finally we applied t-test for statistical analysis of the results.

4.2 Dipoles Localization

3D Spatial localization of dipoles, whose location and orientation within the cortex represents the synchronous brain source activities in that specific region of the brain, across subjects before and after methadone administration distinctly characterized the cortical areas responsive to methadone (FIG. 4.1). The following figure demonstrates the cortical concentration of the dipoles before and after taking methadone in four subjects, according to this figure it is quite clear that mid prefrontal cortex and the extended limbic system (NAc, VTA, and LC) are the brain regions mostly affected by methadone while the cortical activities within these regions reduced after receiving methadone. These results are highly acceptable considering methadone as one type of addictive drugs with protective or normalizing effects that can affect the same cortical regions as opioids do. It has been shown that prefrontal cortex and limbic system or more specifically ventral tegmental area (VTA), nucleus accumbens (NA), and lucus ceruleus (LC) (Kosten & George, 2002) are highly involved in opioid dependency, and our results also support this fact while showing that methadone significantly reduced the cortical dynamics within those areas.

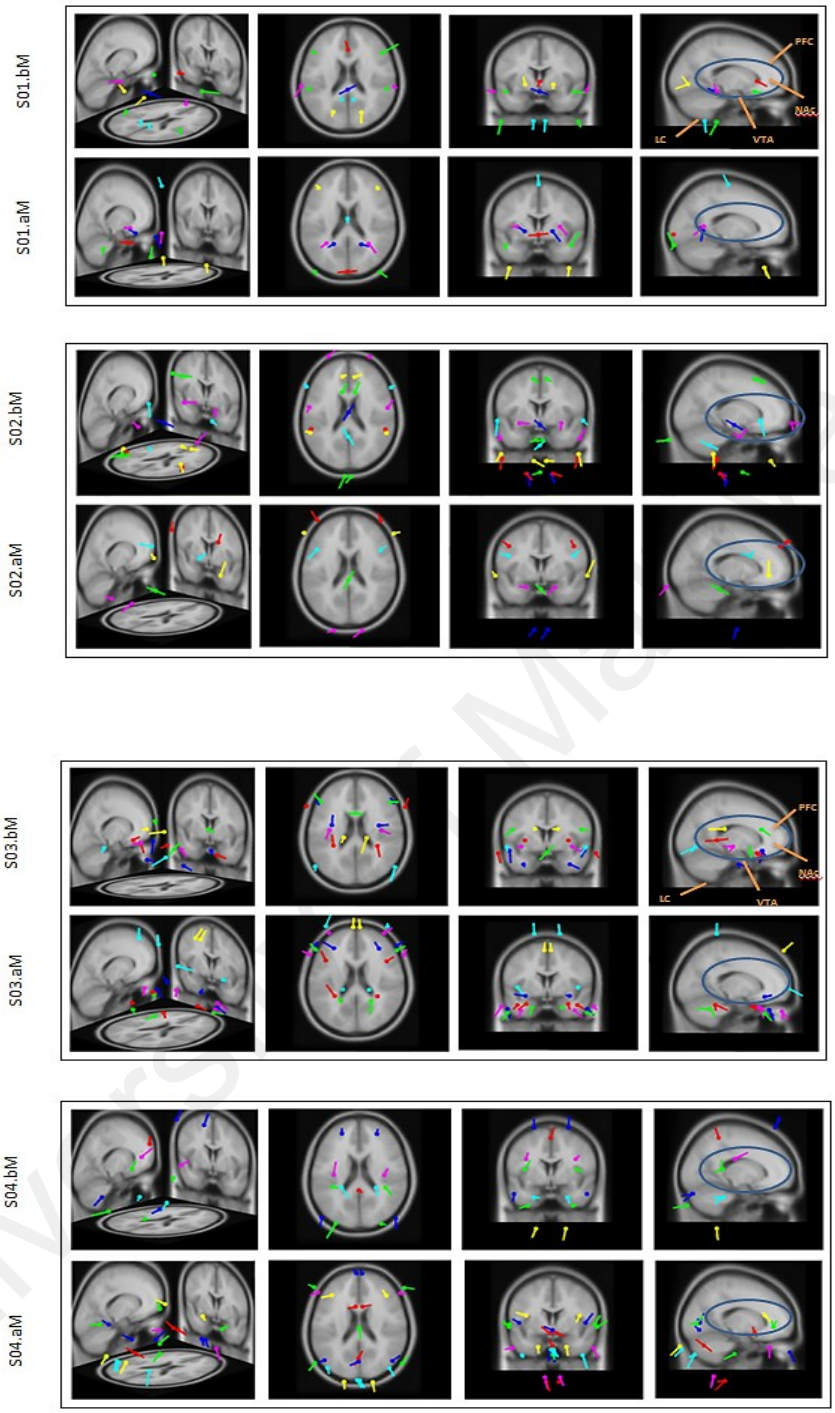


Figure 4.1 Clustering ICs from 4 subjects based on their functional consistency and common spatial projection of their equivalent dipoles

We identified 3 homogenous clusters of 20 ICs whose equivalent dipoles accurately *(R.V. <15)* project to the scalp map of those ICs (Figure 4.2). Spatial 3D localization of these dipoles within 3 clusters precisely demonstrated the concentration of the locally coherent cortical activities in medial prefrontal cortex (mPFC) and extended limbic system through the state of opioid dependency and methadone-based treatment in all 4 subjects. Since the clustering algorithm which was used in our analysis (K-Means) efficiently finds the functionally and spatially coherent activities across the cortex, therefore it provides more accurate and plausible results as compared to the analysis of single subjects in the previous section. So it is quite clear that the concentration of coherent cortical activities across the mid prefrontal cortex and extended limbic system (VAT, NAc) is more distinct across the clusters rather than the subjects. These findings also support the efficiency and precision of our clustering algorithm.

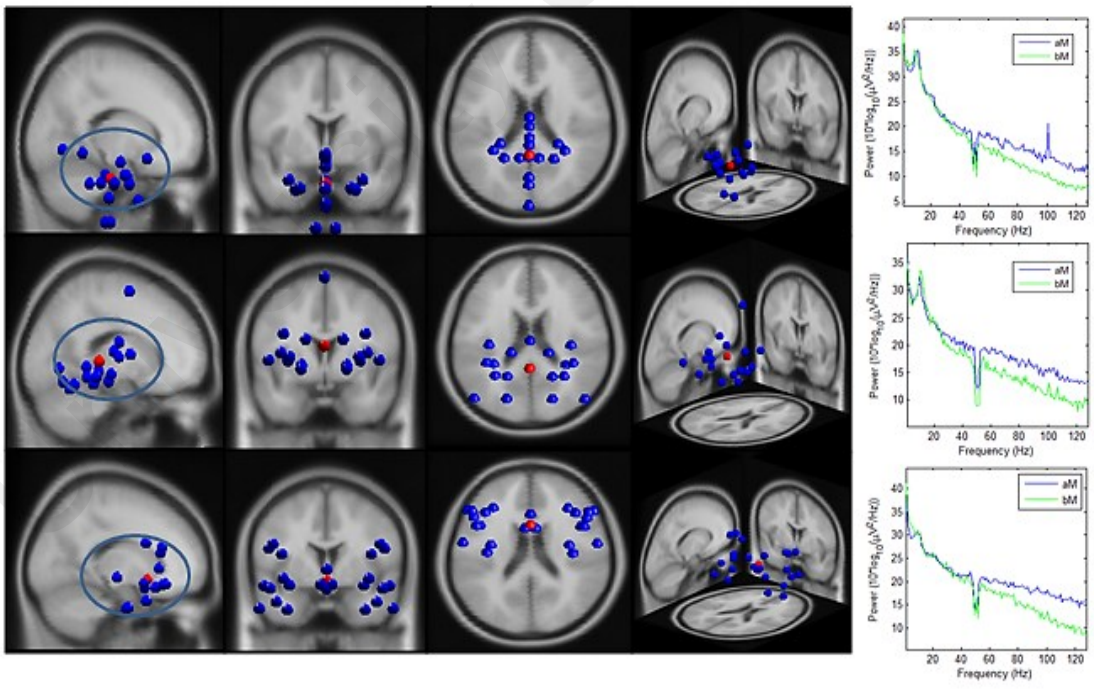


Figure 4.2 . Localization of the most functionally and spatially coherent cortical activities across the clusters and their corresponding spectrum

4.3 Spectral Analysis

To put more confidence in our results, we perform spectral analysis across the clusters in the state of opioid dependency (before receiving methadone therapy) and methadone treatment. The results (Figure 4.3) revealed a significant increase in the brain source activities within gamma spectrum while the cortical activities of the alpha and beta rhythms decreased after early onset of methadone treatment. These findinge were of great consistency across all three clusters while they highly agree with the results of statistical analysis as well.

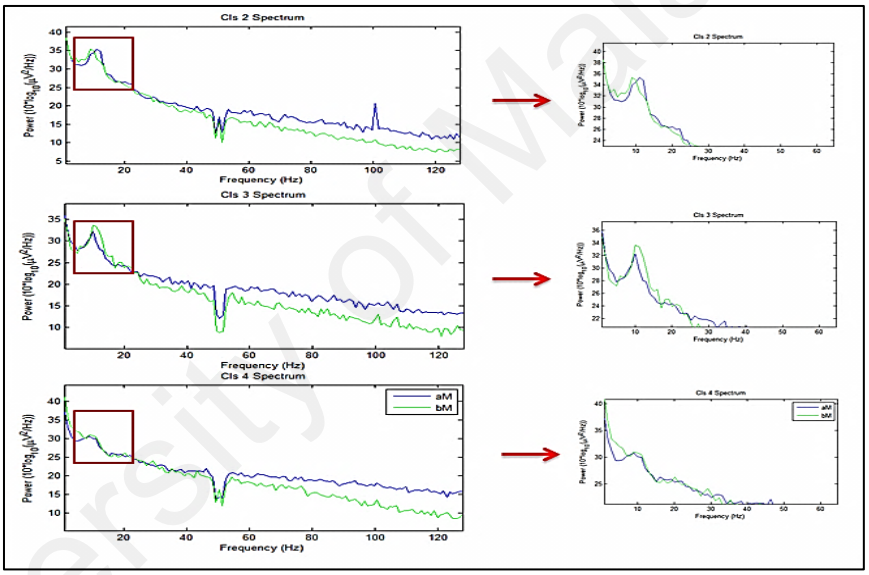


Figure 4.3 Clusters spectrum

Finally we compared the results of spectral analysis within the healthy state, opioid dependency and methadone treatment to investigate the effectiveness of methadone to restore the normal structural functioning of the brain comparable to the healthy subjects. This comparative approach revealed that through the state of opioid dependency and methadone treatment spectral activity of cortical sources has changed considerably in alpha, beta, and gamma frequency bands. These spectral activities underwent an upward trend through the state of opioid dependency and then dropped almost to the level of control

subjects (with a slight slowing down) after methadone administration in all three spectrums. This slight difference between the spectral activity of brain sources in control subjects and the subjects who take methadone treatment may arise from the duration and dosage of opioid abuse. The results (Figure 4.4) supported the ability of methadone to normalize the cortical activity of opioid dependents nearly to that of healthy subjects.

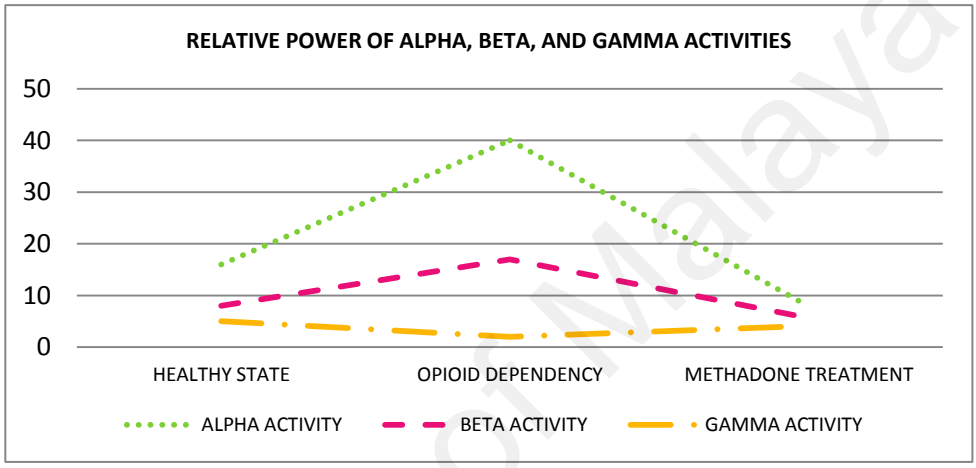
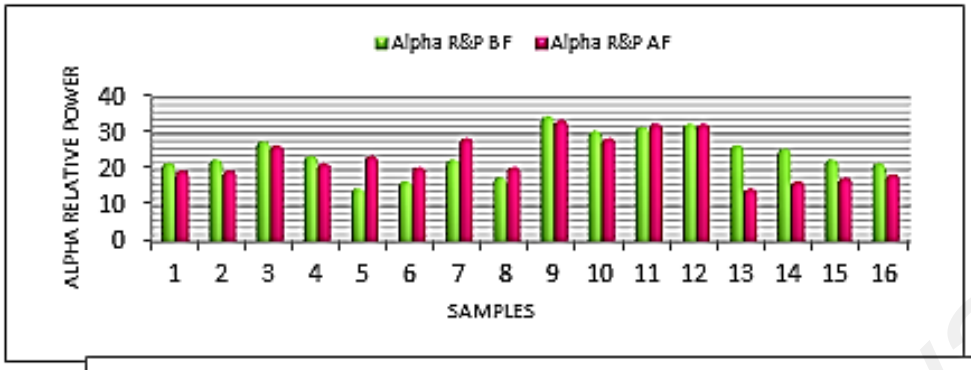
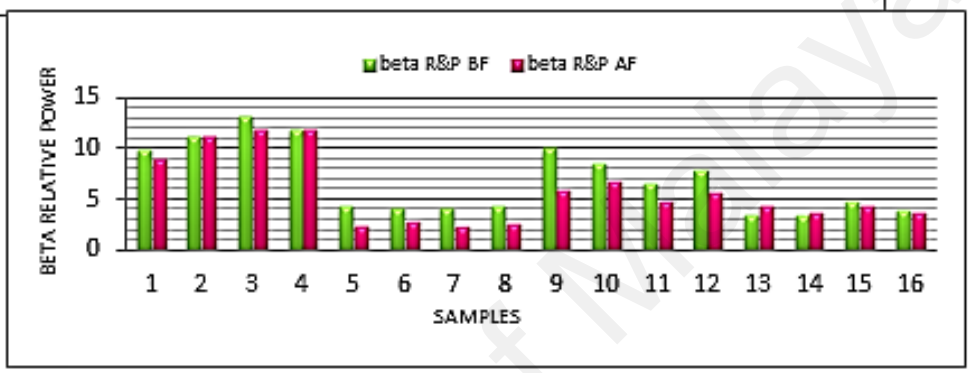


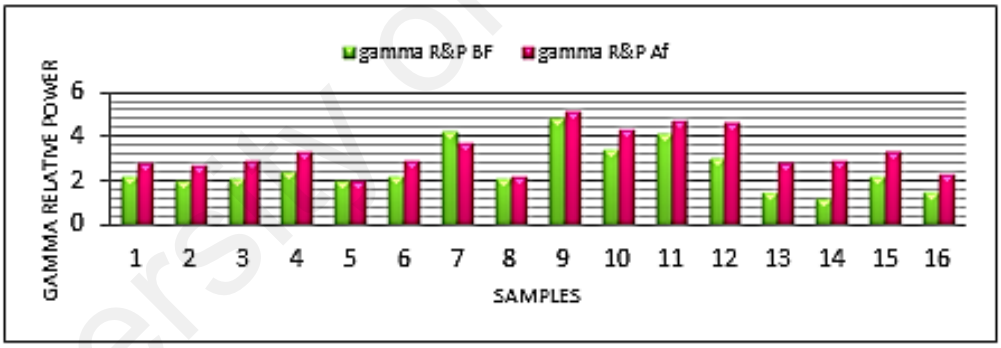
Figure 4.4 comparison of relative power in alpha, beta, and gamma frequency bands through healthy state, opioid dependency, and methadone – based treatment

4.4 Statistics

Assuming the statistical significance to be where $P < 0.05$, to investigate the actual effect of methadone on brain activities we applied paired t-test to compare the relative power of each cluster before and after methadone administration. Statistically significant *($p < 0.05$)* changes in relative power of clusters was observed in alpha, beta, and gamma spectrums. While after taking methadone the relative power of alpha and beta activities decreased, gamma activities exhibited an increase in the values of relative power (Figure 4.5).







FREQUENCY BANDS	BEFORE TAKING METHADONE			AFTER TAKING METHADONE		
	Mean	S.D.	P (< 0.05)	Mean	S.D.	P (< 0.05)
ALPHA	25.1489	5.75	0.0612	23.7522	6.14	0.0612
BETA	3.2848	0.9505	< 0.000	2.5712	0.9788	< 0.000
GAMMA	5.7877	1.36	0.002	6.9657	1.4	0.002

Figure 4.5 .Statistical Analysis of Relative Power Values within Alpha, Beta, and Gamma Frequency Bands Before and After Methadone Administration

5 Chapter V: CONCLUSION AND FUTURE WORK

5.1 Introduction

In this chapter the contribution of the results to optimal methadone treatment will be discussed.

5.2 Conclusion

Considering the allostatic state of opioid dependency defined as a chronic deviation from the normal structural functioning of the brain, the main finding of this study supports the important role of methadone to restore the normal cortical activities in opioid dependents comparable to healthy subjects (FIG. 4.4). Reorganization of the brain temporal activity within the state of opioid dependency which is contributed to the disorganization syndrome in drug dependency and reward regulation (Fingelkurts, Ermolaev*, et al.*, 2006; Haig *et al.*, 2000) reveals the significant role of psychotropic drugs to normalize the temporal structure of the brain.

Source localization of the cortical activities provides a potent approach to accurately investigate the actual cortical sources involved in opioid dependency which in return makes it easier to identify the most effective therapy for opioid abuse. Most of the research contributing to the temporal and spatial analysis of brain dynamics, apply advanced image processing techniques like MRI or CT, from this perspective the significance of this study derives from the efficient methodology used for brain source localization based on independent component analysis (ICA). This study is the first of its kind since it represent a completely novel approach to characterize the capability of methadone treatment in normalizing the cortical functions of opioid dependents.

Despite of the effectiveness of methadone treatment which has been proven in this study, these physiological medications still need to be conjugated with the psychological treatment knowing that opioid addiction is a psychophysiological disorder.

5.3 Future Work

Further analysis is required to estimate the optimal dosage of methadone which is highly dependent on brain dynamics of individuals and also the duration of treatment. Since investigation of the actual cortical activities is highly complex, there may be many contributing factors while analyzing the structural brain dynamics, therefore a plausible examination of all the contributing factors to the opioid addiction may require more sample data.

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