EEG ANALYSIS OF OPIOID-DEPENDENTS AFTER METHADONE MAINTENANCE

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This project paper is dedicated to my parents and my sister whom they give me good upbringing with whole of their kindness.

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ABSTRAK

Fungsi otak boleh jadi dapat diubah melalui penggunaan opioid. Kajian ini memuat analisis menyeluruh kuasa elektroensefalografik (EEG) daripada penagih opioid ke atas beberapa jalur frekuensi (Afla (8-12), Beta (13-24) dan Gama (25-45)). Analisis kuasa telah dilakukan untuk mengesan fungsi otak. Bermula-mula data mentah EEG ke atas 19 saluran mesin EEG diambil dengan menggunakan perisian imbas-saraf. Setelah itu, data mentah dipraproses untuk menghilangkan artifak melalui Analisis Komponen Merdeka (ICA). Data kajian ini juga dianalisis dengan menggunakan perisian SPSS. Selain dari pada itu, kajian ini menunjukkan perubahan komposisi tubuh daripada para penagih. Alat yang digunakan pada kajian ini adalah Bio Dynamics Model 450. Analisis ini telah dilakukan terhadap penagih heroin yang tengah bermula berhenti dengan menggunakan metadon. Kajian ini adalah kajian rintisan kerana analisis pada kajian sebelumnya hanya dijalankan ke atas subyek dengan pengekalan metadon. Analisis pada kajian ini dijalankan ke atas para penagih yang tengah bermula berhenti dengan menggunakan metadon dengan mengira perubahaan yang terjadi. Hasil daripada analisis menunjukan adanya peningkatan kuasa otak di jalur frekuensi Alfa dan frekuensi Gamma setelah penggunaan metadon. Sementara itu, frekuensi Beta mengalami penurunan. Berbanding dengan subyek yang sihat, perubahan ke atas kuasa otak dipengaruhi adanya aspek psikologi, yang bermakna bahawa subyek penagih di kajian ini dengan mengkonsumi metodon akan kembali ke keadaan semula. Hasil daripada Analisis Komposisi Tubuh (BIA) menunjukkan bahawa setelah penggunaan metodon didapati adanya peningkatan nyata pada Sudut Fasa (PA), Ketahanan (Res.), Kemuatan Tubuh (BC) dan Jisim Sel Tubuh (BCM).

ABSTRACT

Brain function could be changed by usage of opioids. This report presents electroencephalographic (EEG) power analysis across the several frequency bands (Alpha (8-12), beta (13-24) and Gamma (25-45)) for opioids. Power analysis is a feature has been used in this study for brain function examination. First of all the raw EEG data took by 19 channel EEG machine with the help of neuro-scan soft ware. After that the preprocessing has been done on raw data for removing artifact by Independent Component Analysis (ICA). Also data analysis has been done with Spss Software to compare the results. The body composition has measured for this project by Bio Dynamics Model 450.

The project been conducted on four heroin addicts' patients whom start to withdrawal by methadone. This was a pilot study because previous research just applied to the subjects who were under methadone maintenance (MM). This study works on the addicts' patients who just start to withdrawal by methadone and measured brain power alteration. The results show that changes in brain power in Alpha frequency band after taking methadone had been increased and also the same situation for Gamma frequency band had been occurred. But in case of Beta frequency band power had decreased. By comparison with the healthy subjects, this changes from the physiologically aspect means that our addicts subjects by administration of methadone going back to the normal situation. For Body Composition Analysis (BIA) result presents that after taking methadone there was significant increase in Phase Angle (PA), Resistance (Res.), Body Capacitance (BC) and Body Cell Mass (BCM).

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1 CHAPTER I: INTRODUCTION

1.1 Introduction

Signal processing on brain responses to the biologically or non-biologically stimulus have been made wide spread span to work on it for finding disorders in patients or brain affiliations (Onton & Makeig, 2006).

A wide range of researches have been demonstrated that withdrawal from drug like heroin has prominent effect in functional cortical connectivity. (Alexander A. Fingelkurts1, 2007) The change in this functional connectivity has been observed in alpha and beta EEG signals oscillation. We predict that this sign would be measured even by change in gamma EEG signal oscillation which should be monitored. We suppose that the relation between this functional connectivity by observed in the frequency spectrum of gamma signal and withdrawal of heroin by using methadone are so closed which during this study will be observed.

To be clear, we acclaim that the temporal and metastable group of cortical dynamics in opioid-addicted do not has vary from regular assessment of healthy patients. We take to mean these results as ability of the methadone to bring back a usual temporal and metastable construction of activity in brain within opioid-dependent subjects after taking it. On the whole the effects and penetration of methadone on temporal and metastable construction of EEG activity will be investigated through this study.

1.2 Problem Statement

The function of brain in normal situation is deadly depends on dynamical balance among some activity function like global integrative process and neurons assemblies. Each kind of disorders which lead to loss of this balance due to over order or independent order processing have result as a reflection of brain disease. Opioid people like heroin addicted could be categorized in brain metastable balance disease where from local and remote functional connectivity respectively increases and decreases. Whereas methadone has used in maintenance treatment of heroin addicted patients this study try to indicate that how methadone can plays this role and would influence on this brain balance by monitoring the EEG oscillation signal in brain frequency bands.

1.3 Objective of the Study

The objectives of the study are:

1) To compare the brain relative power before and after taking methadone in Alpha, Beta and Gamma frequency band and finding out the spectral pattern of them.
2) To evaluate of body composition analysis before and after taking methadone.

1.4 Scope of the Study

This study was carried out following scopes:

- EEG signals analysis in Alpha, Beta and Gamma frequency bands on four subjects.

- Analysis of the brain physiological effect before and after taking methadone.
- Analysis of the brain signals before and after methadone administration to calculation of the relative power and spectral pattern by Fast Fourier Transform (FFT) and Hanning windows 50%.

1.5 Significance of Study

Methadone has been used for withdrawal from drugs like heroin. Brain alteration before and after taking methadone have been shown in other literature. In this research reports that the brain changes in several frequency bands associated with power of brain in that special frequency bands. Also in other hands body composition would be changed after taking methadone especially in phase angle which has been increased and also in BC, Res., and BCM.

1.6 Outline of report

In this research report in five chapters the whole of project has been illustrated. Chapter one is goes for introduction and over view of the whole of study and also statement of the problem, objectives. Chapter two is a review and the works have been done before on methadone effects on brain and also on the technique they have used for this goal. In chapter three you can see the methodology that it been used in signal processing and body composition analysis. The results comes up in the forth chapter which in details depicted the answer of the study which is alteration of brain after taking methadone rather than before taking methadone. Chapter five whereas clarify the conclusion of the study, it shows the way for future work in our study.

2 Chapter II: LITERATURE REVIEW

2.1 Introduction

This chapter reviews the whole of the researches were done by other researcher in the area of brain response to the withdrawal by methadone on addicts. Focus was on the power alteration in the several frequency bands.

2.2 Physiology of Brain and Opioids

The special effects of both endogenous and exogenous substance dependent are created by opioids tie to opioid receptors scattered during CNS and gastrointestinal tract.

Addicts act at 3 different classes of receptors: kappa, delta, and mu and all of these receptors individually contributed in controlling altered brain functions (e.g. opiates and endorphins are able to block pain signals by binding to the mu receptor site).

2.3 Opioids Affect 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 opioids system is linked with utmost neurotransmitter networks through the whole of the body. The relation among the opioids system and the dopaminergic system seems to be tangled in addiction, broadmindedness, and abstinence symptoms. The applicable relations perform to happen beside the mesolimbic prognosis, mainly in the ventral tegmental area (VTA) and nucleus accumbens (NA). Opiates modify the limbic system to create amplified feelings of desire, relaxation and satisfaction. The brainstem controls things your body does spontaneously, like inhalation. Opiates have this capability to performance on the brainstem to stop coughing or relaxed inhalation. Ventral Tegmental Area (VTA) which is placed in the center of the brain and covers the dopaminergic neurons which is innervate the limbic system and the prefrontal cortex. Nucleus Accumbens (NA) or Ventral Striatum that is positioned in the septal region, innervated by the ventral tegmental area, and helps as an boundary amoung the limbic system and the motor system. Opiates works not just on the vital constructions of the reward circuit, but works on other constructions which are naturally controlled by endorphins counting:

- Amygadala
- Locus coeruleus
- Acuate nucleus
- Periaqueuctal grey matter
- Thalamus

2.4 The Mesolimbic Reward System

When opioids encourage mu opioid receptors in the brain, they cells in the ventral tegmental area (VTA) produce dopamine and release it into the nucleus accumbens (NAc), giving rise to feelings of pleasure. Feedback from the prefrontal cortex (PFC) to the VTA helps us overcome drives to obtain pleasure through actions that may be unsafe or unwise, but this feedback appears to be compromised in individuals who become addicted to drugs. The locus ceruleus (LC) is anarea of the brain that plays an important role in drug dependence (Ramage et al., 2005)

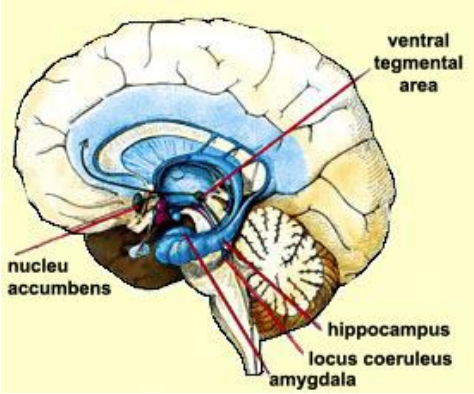


Figure 2.1: Region of effects under methadone (Figo d. , 2011)

2.5 Description of brain after methadone maintenance treatment

Methadone maintenance treatment brought the relative presence of 72-92% of spectral pattern types up to the level of that in healthy subjects. However, even after MM treatment, the probability of certain types of SPs occurring differed from the values for healthy subjects (Busto et al., 2000).

C > M				
Brain oscillation	SP type	Main peak(s) (Hz)	EEG channels (%)	Topographical distrbution
Alpha1	SP5	9	65	distributed across majority of brain lobes except frontal
	SP26	8.5 --10	70	distributed across all brain lobes
	SP27	9--10	55	distributed across all brain lobes
Alpha2	SP6	10.5	45	distributed across all brain lobes
	SP29	10.5--11.5	30	distributed across occipital and temporal brain lobes
Beta1	**SP9**	**15**	90	distributed across all brain lobes
C < M				
Delta-Theta1	SP16	3--4.5	25	distributed across temporal and frontal brain lobes
Theta1	SP2	4.5	45	distributed across majority of brain lobes except occipital
Theta1-Theta2	SP21	4--6	70	distributed across all brain lobes
Theta2-Alpha2	SP24	5.5--10.5	35	distributed across all brain lobes

2.1: EEG spectral pattern

Spectral power of deferent part of brain in different frequency bands, reproduce from (Alexander A. Fingelkurts1, 2007). Spectral pattern types which demonstrated statistically significant differences in methadone-mediated and control subjects in more than 20% of EEG channels have been shown in the table 6.1.

2.6 Temporal stabilization of EEG SPs after methadone maintenance treatment

The temporal stabilization of SPs in both the EEG of methadone maintenance patients and the EEG of healthy subjects were very similar. Methadone maintenance treatment normalized considerably the composition of EEG oscillations and their percentage ratio in EEG and restored the temporal structure of patients' EEG comparable with healthy subjects. Uncommon Adverse Effects of Opioid Abuse are Respiratory depression, Bad dreams, Hallucinations, Seizures, Urticaria, Urinary retention, Miosis, Urinary urgency (Bosker & Huestis, 2009).

2.7 EEG signal processing

This study is sort of research which is going to demonstrate the effect of methadone in heroin addicted people and how it proceed on reverting their brain activity back to its normal condition. In some previous literatures it has been demonstrated that the EEG of addicted during usage of opium and during its withdrawal is differentiated signal and their temporal behavior. (An.A., 2001)

Heretofore not so much research has been assigned to perform considering the EEG effects and its modification on heroin addicted and in relation to methadone. Researches demonstrated that the changes, in above seventy percent of heroin addicted which is revealed low voltage background activity in central regions.(Olivennes, 1983) (Polunina, EEG spectral power and mean frequencies in early heroin abstinence. , 2004).

In some research it has indicated that sober heroin addicted subject has an improved fast beta power in comparison with the control in healthy situation and this is synchronized with the other EEG research on other drugs subjects. (Franken I. H., 2004) (Herning, 1994) (Rangaswamy, 2004) (Roemer R. A., 1995)

In methadone maintenance (MM) for heroin addicted, a number of quantitative modifying has revealed as well. (Gritz E. R., 1975) (Shufman E. P.-H., 1996) They have indicated a considerable slowing of occipital alpha rhythm peak frequency in some MM patients and some sober heroin addicted patients. Polunina et al (2004) acclaims that the amount of heroin which is taken by the addicted is greatly associated to the slowing of slow alpha between eight to ten Hz frequencies before withdrawal. (Polunina, EEG spectral power and mean frequencies in early heroin abstinence., 2004) They also showed the frequency shifting in fast alpha range at the position of central and frontal recording areas.

In addition at the positions of central area, temporal sites and also at occipital situations of recording area there is shifting in slowing of slow alpha mean frequency in heroin addicted whom use it for more than eighteen month (Van Ruitenbeek, Vermeeren, & Riedel, 2010).

The information could be collected from the cortex layer of brain. (Koob, 2001) Result concluded the mean of the process of achieving stability which has gained homeostatic range through the changes. (McEwen, 1998) Before, within the frequency of 0.5 to 30, signals have been examined with some classification analysis like short term power spectral (SP) (Fingelkurts A. A., 2003). SP is the character that classified the collection of spectra and also Probability Classification Profile (PCP) has taken to account. There are lots of differences within PCP method and conventional method such as the limitation of conventional EEG analysis rather than the PCP analysis and it cannot characterize each of individual Power Spectra for each EEG part. (Fingelkurts A. F., 2004) In general in the whole of research associated with the opioid patient's EEG spectral analysis, entire bands frequencies were outlined in advance and were got isolated from each other. This action restrict researcher to test the performance of real EEG oscillation. According those researchers has utilized the PCP and they tested whether methadone treatment makes regular the EEG oscillation and their temporal treatment in addicted patients (Alexander A. Fingelkurts1, 2007).

In some other, the activity of diagnosis of the composition of EEG throughout the condition of opioid dependency has investigated and also there are some more about methadone treatment and effect of that on actual composition of EEG in that patient. (Alexander A. Fingelkurts1, 2007)(Weiskopf et al., 2011). Most of the studied have been worked in this field follow these methods:

- Subjects
- Trial design
- EEG registration
- Data processing

2.7.1 Subjects

This study needs 20 heroin-dependent patients which they are during withdrawal with methadone. They should been asked, when they had not access to the heroin, what they had used. They should been checked that in which stage after heroin administration they undergo the methadone treatment. The study should be accepted by Ethics Committees and all the subjects of study ought to give their written consent before participate in the project. The limitation of age is between 21 to 50 years old. The important thing which must be attended is the time priority in which they have used heroin and we try methadone for them because the effect of methadone in each stage is deferent. (Carina Graversen, 2010).

2.7.2 Trial design

For this goal it should make a situation in which patient has sense of comfort like chair and the room of experiment and comfortable position without movement to reduce the stress and movement artifact which is observed in the experiment if do not care about that the wrong response would be comes up. Also patients have been asked to watch straight or close their eyes. They are undergoing around 5 minutes to complete the EEG registration procedure. Automatic brain activities have to record within 0.05 to 75 Hz with 60 channel

electrode cap due to international 10/20 extended system (Frodl et al., 2010). The subjects whom are undergoing the treatment should be categorized in attention to time which they start to the MM treatment. For the withdrawal symptom management in subjects, the amount of methadone which is used should be taken in to the account (i.e.95 – 150 mg depend on the subjects). It is better to take EEG signal at noon because in that time muscle artifacts come down. Subjects should be asked to be comfort and even close here or his eyes. Do not allow the subject to have sleep spindles (Volkow et al., 2010).

2.7.3 EEG registration

EEG signal should recorded by electrode cap due to international 10/20 extended system and one electrode like nose electrode ought to be utilized as a reference. 19 channel EEG data acquisition and frequency of 0.05 to 95 Hz and more should be considered as our other references. The impedances should be taken to account for each electrode that is most of the time less than 10 KΩ (Lingford-Hughes, Daglish, Brooks, & Nutt, 2011).

2.7.4 Data processing

The EEG signals which is driven from the patient are not pure and it concluded some component which containing some artifacts such as movement, bold muscle activity and eye blinks. They are spontaneously removed by ICA (Independent Component Analysis) procedure. (Hyvarinen, Oja, & Karhunen, 2001)(C. Graversen, 2010).

This stage starts with the channel which has the best performance and is continued with addition of other channels. By this way the most significance channels are chosen with minimum of redundancy. (A. Maitrot, 2005). In this stage the features before, during and after taking methadone has been analyzed and find out the best channel which has answer

for our target. (O. F. do Nascimento, 2008). This stage is sort of recovery and analysis to omit the unclear and low classified channel in stage three which is come back to our volunteers. (H. Peng, 2005). The whole EEG steams take 10 min for corrected to get rid of artifacts for each of patient. The EEG data split into 4 distinct groups:

- Control subjects
- Current opioid dependency
- Withdrawal
- Methadone maintenance treatment

After this stage by mean re-modeling to the spectral analysis, each of EEG signals should be filtered by band pass-filtering between 8-12Hz for alpha and between 13-24Hz for beta and in our case study 25 to 45 Hz for gamma frequency band. According to lots of studies it has been confirmed the liability and efficacy of methadone maintenance (MM) treatment for usage of drugs and opioids. (Simpson, 1982), MM treatment has been shown itself as normalize experiment in lots of countries (Maremmani, 1995). On the other hand, there are several problems. In correlation between the same opioid receptors as opioids, methadone averts extraction symptoms that take place in the time that administration of opioids is halts. Methadone is deal with lesser troubles of psychological addiction because it does not give the same euphoria sense that arise from, for example, heroin. There are lots of study in this filed which statement. (Silveri, 2004) The actions of people who are uses methadone are not considerably as different from sober subjects. (Gritz E. S., 1975). Indeed it has proposed that the oscillatory system of brain carry out the possible contact networks with functional associations to the brain with functions which are integrative. (Basar, 2001) It has been supposed that EEG is one of the fundamental importances for arbitrate and deal

out “higher-level” action in the human brain. (Basar, 2001) (Klimesch, 1999). All the characteristics have been shown the importance of operation more effort into the importance of MM treatment on the continuing brain activity in opioid users. Whereby, the EEG makes a desire amount of the large-scale dynamics of brain activity (due to milliseconds) and reacts in the integrative brain and cognitive functions deal with health and pathology (Levy, 1987).

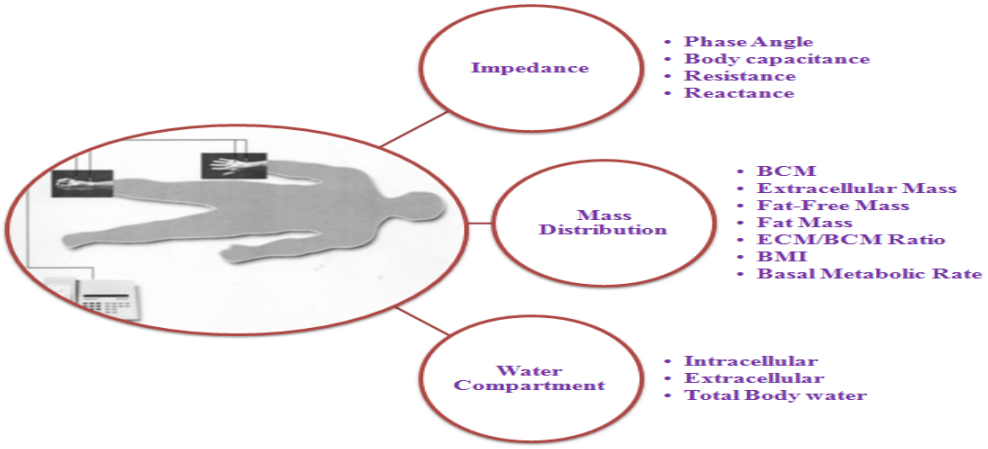
On the whole, several studies (Bauer, Predicting relapse to alcohol and drug abuse via quantitative electroencephalography., 2001) (Bauer, Differential effects of alcohol, cocaine, and opiod abuse on event-related potentials recorded during a response competition task., 2002) (Costa, 1997) (Papageorgiou, 2004) (Polunina, EEG spectral power and mean frequencies in early heroin abstinence., 2004) (Shufman E. P.-H., 1996) demonstrated that EEG’s spectral power tries to regularize brain signal response to the methadone approximately after more than a few weeks of sober. The significant modifies in EEG of heroin addicts patient have been reported in alpha and beta frequencies. It is involved a shortfall in alpha activity and an overload of fast beta activity in early heroin sober. The relation among beta and theta frequencies shifts and neurotransmitter imbalances features for heroin withdrawal looks ambiguous. Research on useful functional connectivity among heroin addicted patients in case of drug withdrawal has been limited to a few researches on inconsistency of the EEG signal in sober heroin addicted (Fingelkurts A. A., 2006) (Franken I. H., 2003) active heroin abusers (Fingelkurts A. A., 2006) and in sober poly material addicted. (Roemer R. A., 1995).

In special, (Fingelkurts A. A., 2006) found out that the amount and power of remote functional connections among the variety of cortical regions was predicted by EEG

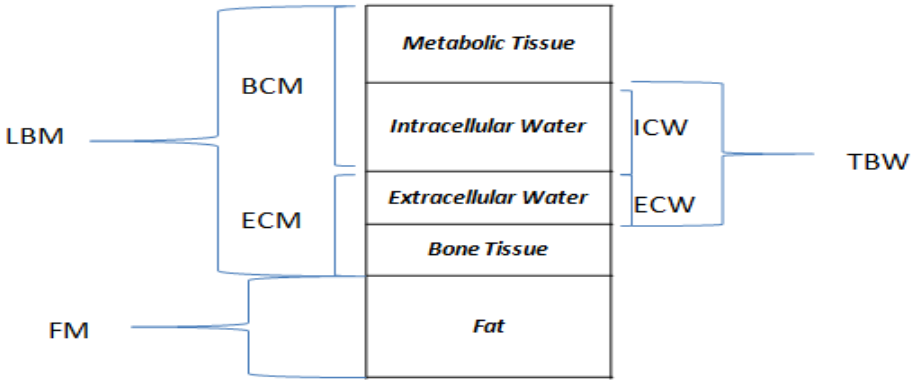
synchrony which is prominently more higher in addicted in severe heroin withdrawal rather than in healthy people for the majority types of functional connections . While this consequence is indicated in the alpha like beta frequency, it is very significant for the beta collection. Another study with the same situation of samples underneath sever opioid pressure (Fingelkurts A. A., 2006) demonstrated the reverse: a prominent induce the amount and power of remote functional connections, when evaluated with healthy controls. Consequently, the growth of remote synchronicity between cortical sections within the short-term withdrawal time might observe the distinguished attentional concentrates on prompts and memories associated with drugs while ignoring neutral prompts. (Franken I. H., 2000) (Sokhadze, 2007).

2.8 Body Composition Analysis

BIA: The evaluation of alteration in electrical tissue conductivity that points out altered body composition. Resistance is element if Impedance associated to the debauchery of energy in a conductive medium. Reactance is component of Impedance associated to the storage of energy in a conductive medium. Phase Angle is time delay between a stimulating current and the voltage generated by an alternative current in a conductive medium. Is base on the principle that the resistance, or the conductivity of a tissue to a low amplitude electrical current depends on its water and electrolyte content. Fat rich tissues have less water and electrolytes thus less conductivity than fat-free tissues. Some of criteria are changes slowly and it needs a time to show their effect on body of addicted whom taking methadone like change in fat, muscle, metabolic and non-metabolic tissues and so forth. In the other side we are going to show that some of the criteria have early response to the taking methadone such as phase angle resistance or reactance of the body.



2.2 Body and Bio-Impedance relation



2.3 Relation of mass and water components by Bio-impedance analysis

Intracellular Water is water enclosed within the cell. Healthy cells preserved their integrity and hold their fluid inside. Alteration in this technique can helps us to identify the body response of our subjects. (Where as our patients using drinking kind of Methadone, we cannot talk about this character) Body Capacitance is the ratio of alteration to potential. It is a pointer of the body's energy storage characteristics.

3 CHAPTER III: DESIGN, METHODS AND PROCEDURE

3.1 Introduction

This chapter focuses was on the procedure and following methods of data collection and ways of analysis of our data. First of all it has been talked about the state of subjects and their situations then the instruments which was needed and we have used it for our research, after that the procedure of this experimental study has been illustrated and finally statistic which we applied to our study have mentioned.

3.2 Materials and methods

This section included of four parts to explain the materials and methods which have been used. They are subjects, instruments, procedure, statistics and signal processing.

3.2.1 Subjects

Four male subjects which they have been addicted to heroin between 6 to 10 years have been recruited from University of Malaya Medical Center (UMMC). All participants wanted to start abstinent from heroin and they just want to start it with our program. At the time of our experiment did not take any medication. The subjects had been checked for urine drug test of methadone usage. No one was positive on urine methadone test. If any of them was positive test it has omitted from our research. Ten healthy subjects whom they never used drug had been recruited from student of University of Malaya. If any situation of withdrawal symptoms, disorders, mental hold back or prominent symptom revealed (Parkinson, schizophrenia, epilepsy) the subject immediately was excluded. Whole of our control subjects were male and with the high educational level in the Malay educational system. The mean age of control subjects were between 26 to 30 years (mean

28.87+_1.31). In other side our heroin-dependent subjects were 24, 25, and 26 and 38 years old and also they had middle level of education. Heroin-dependent subject did not have history of other additional drug and alcohol. But two of them one times had been on methadone withdrawal. They started for the first session of methadone treatment with 20 mg/d and 30 mg/d for two other more, by drinking way. They way to usage of heroin were by smoking the heroin for three of them and one other more was by intravenous administration. This study has been approved by the Ethical Committee of the University of Malaya Medical Center and also all of the subjects have been filled the consent form and whole of them inform clearly about the experiment they had right to withdrawal from the study whenever they wants and they were informed about the situation of the study and they inform that:

- Inoffensive and does not involve any hazard
- Necessitate their cooperation
- They cooperated voluntarily.

3.2.2 Instruments

The EEG was measured with a digital Nervous Scan amplifier which it has uses the cap with 19 electrode channel of Ag/AgCl at 19 place on the brain area due to international 10/20 system. Channel which has been used according to the our literature were F3, F4, F7, F8, Fz, C3, C4, C5, C6, Cz, T7, T8, P3, P4, P7, P8, Pz, O1, O2. Ground was placed at the Oz and also reference has been placed in front of Fz. Whole of the signals were become digitized by the nervous study software and no filtering was used on raw digital signals. The sampling rate was 256 Hz and with 32-bit A/D conversion. Each of the electrodes was adjusted with conductive past at whole of the nineteen locations of the cap and brain gap.

Additionally frequency had been cut off for below 1 Hz and over 90 Hz by Butterworth band pass filter. The impedance of the electrodes was kept below 10 KΩ. One epoch with length of ten minute were included this signal recording. Other instrument which has been used for our survey was bio-impedance analyzer. Bio-dynamics model 450. Bioelectric Impedance Analyzer or BIA works as a measurement of the resistance of body tissues through, the following a small electrical current and computing of this signal. The quantity of body fat could be computed as the current which has been passed between the portion of the body that are included typically of water (such as blood, urine & muscle) rather than it does within air, fat or bone. It has this capability to calculate how much body fat each body has by merging the bioimpedance scale with age, fitness, weight, gender and height. EEGLAB soft ware is a toolbox which freely could be found it out in http://www.cis.hut.fi/projects. EEGLAB is a sort of interactive Matlab toolbox for processing continuous and event-related EEG, MEG and other electrophysiological data incorporating independent component analysis (ICA) time/frequency analysis, artifact rejection event-related statistics, and several useful modes of visualization of the averaged and single-trial data. EEGLAB provides an interactive graphic user interface (GUI) allowing users to flexibly and interactively process their high-density EEG and other dynamic brain data using independent component analysis (ICA) and/or time/frequency analysis (TFA), as well as standard averaging methods. Whereas our project mainly comes back to the relations of brain local regions and justification of local/ remote area of brain, the merit of this interactive GUI make its flamboyant for our survey (Olbrich, Jödicke, Sander, Himmerich, & Hegerl, 2011).

3.2.3 Procedure

3.2.3.1 EEG

After signal acquisition we went for signal processing. There were two session of signal acquisition. Ten minute with one epoch data acquisition had been done which first five minute were eyes open and next five minute was close eyes. The subjects were sited on the comfort chair in a calm room, without any disruption one times before taking methadone and the second round was after 30 minute to one hour after drinking methadone in the same situation. Third round of EEG acquisition was around two month after first administration, when the patient are on methadone and they reaches to the optimum amount of methadone dosage. The relative power has been measured in three frequency band Alpha (8-12) frequency band, Beta (13-24) frequency band and Gamma (25-45) frequency band.

First of all before taking EEG signal the urine test was taken to be informed about other type of methadone, that if it was positive the whole of procedure would be stopped. Then oral methadone had been administered by addict's subjects after first session of the EEG signal acquisition (Larsen, 2011). Raw EEG data included lot of artifact such as eye blinks, muscle activity, eye movement which should be removed from our data to reach the pure and good data for analysis. We have done this stage with help of ICA (Independent Component Analysis). After removing this kind of artifact the analysis had been done with FastICA toolbox for Matlab which freely available online at http://www.cis.hut.fi/projects/ica/fastica. This toolbox added to the EEGLAB windows in MATLAB. Whole of the EEG signals separated from artifacts effects which were five minute eye close and five minute eye open for each subject. After that additional analysis and processing had been applied to the each 30 second of our data. It made good statistical

confidence in our results. We had chosen 19 channel for our goal because of the place in which methadone has effect on brain and with the help of this channel it can be easily illustrated. After this, the band pass filter applied to the signals for separation of each band frequency span (Alpha, Beta, and Gamma). Alpha had chosen 4 to 12, Beta 13 to 24 and Gamma 25 to 45 Hz. In this frequency our feature was spectral power. Indeed EEG signals goes to the non-stationary signals with lots of individuality and it seems to be dynamics. To catch these alternative dynamics we tried to separate our data to the windows which they have overlapped together. Then after individually for each interval the power spectral were computed in the range of 8 to 12, 13 to 24 and 25 to 45. For this target Fast Fourier Transform (FFT) with Hanning windows and 50% overlap has been used. This procedure applied to the each of the 19 channel separately and also each epoch for this range was 30 second. Basically according to our findings and also other study in this field this procedure revealed the prototype for oscillation from signals. This kind of procedure has two important benefits. It means that it is sort of recompense for the property of windowing. It can develop the assurance of our statistical analysis. Moreover shift in samples give us this capability to a good resolution of the overleaping boundaries of EEG portion with temporally steady oscillatory movement.

Output of this, has been shown in the fig 7.1. One hundred forty nine was the general number of each of spectral patterns for 30 second of each of the channels. In continuous the mixture of our signal oscillation base on the spectral power by using the probability classification of EEG spectral pattern has been forecasted. Indeed this kind of analysis has been experienced and illustrated in other studies which have been published

but we just highlighted the important part which we had used in our study (Baillet, Friston, & Oostenveld, 2011).

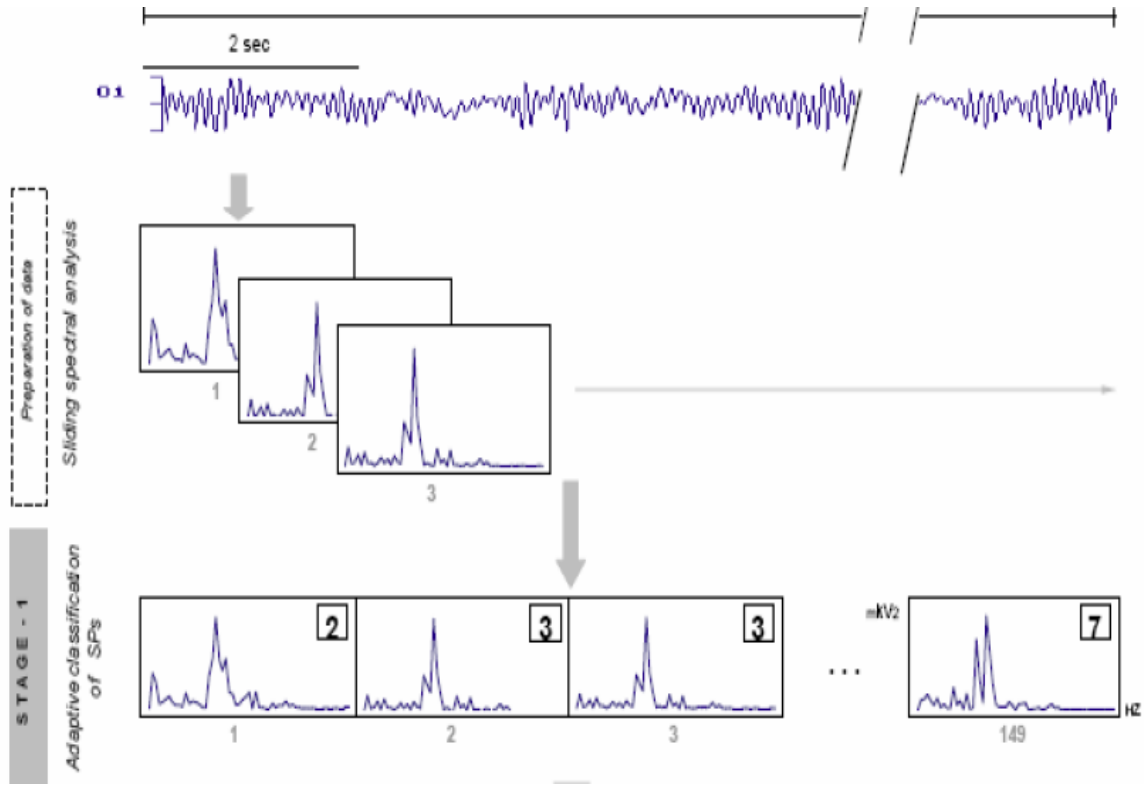


Figure 3.1. Sliding spectral analysis (Alexander A. Fingelkurts1, 2007)

By generated data among the first step, chronological EEG spectral patterns had been classified accurately within each of the 30 second of EEG. With Use of this kind of technique, each of the present spectral patterns was tagged due to which class it had belonged to. Thus for each of the EEG signals the reduction to the series of independently classification of spectral pattern are observable. In the second step, probability classification profiles of spectral patterns for each one of the 30 second of EEG channel in whole of the subjects were computed in the fig.. These probability classification profiles were computed by the relative amount of case of a spectral pattern, like a percentage of the

whole of spectral powers of the entire number among each channel. This has been depicted like a histogram by label of relative company of each of spectral patterns. Probability classification profiles had been averaged for ninety five for heroin dependent subjects and fifty for started to withdrawal subjects and 20 for methadone maintenance subject and 45 for healthy subjects the thirty second EEG for each channel individually. It had been projected that these probability classification profiles would demonstrate in specific the EEG composition oscillations (Delorme et al., 2011). Furthermore 3 other indices were computed individually for each of channels and also for each of situations of thirty second EEG oscillations as follow, brings the polyrhythmic activity in percentage which shown with polyrhythmic SPs. PSPs includes a pattern where reaches to the maximum inhabit a mass of the frequency ranges. This kind of SPs demonstrates the composition of activity of rare amount of neural populations. The other forecasting for ratio of the numbers of spectral pattern diagnosing of 30 second EEG to the entire number of standard set is the nonhomogeneity classification profile. This one shows that the deferent spectral pattern kind have been investigated in the probability classification profile.

Nonstability of the classification profile (NSCP) is shown that the set of separate spectral pattern type vary along the 3 EEG segments of 10 second of whole complete 30 second.

———— 3-1

In which n_i, is the number of separate spectral pattern type that has been found in a 10 second EEG part i; n_s is the number of spectral pattern type which has been found in whole of the 3 ten second EEG segments.

3.2.3.2 BIA

3.2.3.2.1 Pre-Test Preparation

They have to be asked do not drink of alcohol within 24 hours before the test. 4 hours before taking BIA the subjects should not do exercise drink caffeine or food and they have to drink two to four glasses of water two hours before test.

Water plays in role of conductive medium in the body. Normalizing prior-test preparation of subjects will dedicate the effects of impermanent dehydration on the answer of the test.

3.2.3.2.2 Positioning the Subjects

As the Bio Impedance Analysis tool is measuring the resistance of body tissues to the flowing of a narrow electrical current, the subject whom being measured should be isolated from other conducting instrument situation or surfaces. Also the subject should be with legs and arms away from each other and the body. Some instruments necessitate a pair of electrodes located on the hand and wrist, and another pair located on the ankle and foots meanwhile other instruments just needs to stand on two foot plates. Due to adhere the electrodes to the body of the subjects the succeeding steps can be gone after:

- Train the subjects to take away their right shoe and stocking.
- The subjects should be lain down on their back.
- Subject should be on the comfort situation and location and put the head to the back.
- Placing the Sensor Pads

For this goal 2 pairs of this kind of pads should be placed on the hand and foot of subjects. One of the pads should be mounted on the wrist and other should be located on

the hand and in case of leg pads one should be placed on the ankle and the other on the foot. To place the wrist pad, draw or imagine a line connecting the 2 bold wrist bones from the radius heads and also from the ulna heads. The pads should be put in the middle among the bones of wrist with one-half above and one-half below the line. Attention that the positive wire should be near to the heart rather than the other lead. The hand pad should be put with the border of the pad concerning one-half inch above the knuckle line in the direction of the center of the hand. The tab faces external from the body. To put the ankle pad, sketch or imagine a line above the top of the ankle and concerning the bold ankle bones. Position the pad on this line at the ankle top with one-half of the pads under the line and one-half the pad higher than the line. Position the foot pad with the rim about one inch on top of the toe line in the direction of the center of the foot. The tab faces external from the body. The following picture depicts the electrodes attachment.

Figure 3.2 position of subject and electrode installation (john, 2011)

It is also essential to attention the two points; put the two Red leads nearby to the heart and the other point is that all measurements should be carried out on the RIGHT part of the body.

3.2.4 Statistic

In our strategy, pair sample t-test has been used for the comparison of each of our data. The state of before taking methadone with the state of after taking methadone and also for each of Alpha, Beta and Gamma frequency band were in attention for this analysis. For whole of our comparison the amount of *p-value* was less than 0.05. Which this character shows us that in our comparison weather is significant or not. We have done it by the help of Spss which is Statistical Package for the Social Sciences(Beaver et al., 2011).

3.2.5 Data Analysis

The EEG signals were analyzed by MATLAB software version 7.2 (by University of Malaya) and EEGLAB software which is free access. The data was filtered by band pass filter Finite Impulse Response (FIR) between 1 to 66.6 Hz. Also FFT based on Hanning windows 50% calculated the power of the 30 second of each epoch. And also the relative power and total power in range of Alpha, Beta and Gamma computed.

3.2.6 Filtering

FIR filter is a kind of filter whose impulse response (or reply to any finite length input) is of finite duration, because it settles to zero in finite time. This is different to IIR filters. IIR filter has internal feedback and may carry on reacting indefinitely. FIR filters need more calculating power rather than the IIR filters. Their filter response can be adjusted so that it is superior to IIR filters.

- The use of a FIR filter is appropriate when the phase characteristic should be flat.
- When the demands on the filter are not very high, this is the easy solution to go for.

In the context of EEG measurements this filter could be used as high pass or low pass filters. The EEG signal is not degraded by a variable phase characteristic and yet a sharp fall-off can be attained by picked a filter with a high order, since a large delay is allowed for the off-line application. These filters are especially well suited if the phase characteristic of the signal is very important and can thus be used for coherence and synchrony measures.

4 CHAPTER IV: RESULTS AND DISCUSSIONS

4.1 Introduction

This chapter is presents the results which came out of the experiments and the consequences of the methodology which had been used.

4.2 Relative power

For each subject the 30 s continuous epoch of artifact free was selected by visually detection and then data filtered by band pass filter Finite Impulse Response (FIR) between with the 10% Hanning windows. The Fast Fourier Transform (FFT) then applied for calculation of power (μV^2) Gamma band (25-45), Beta (13-23) and Alpha (8-12). After that relative power for this three bands frequency has been calculated. Then the mean of relative power for two situation of before and after taking methadone was calculated. Pair t-test was used to show the significance of the alteration of mean relative power before and after methadone administration at *p-values <0.05* at whole of the electrodes and patients.

4.2.1 Relative Power graphs

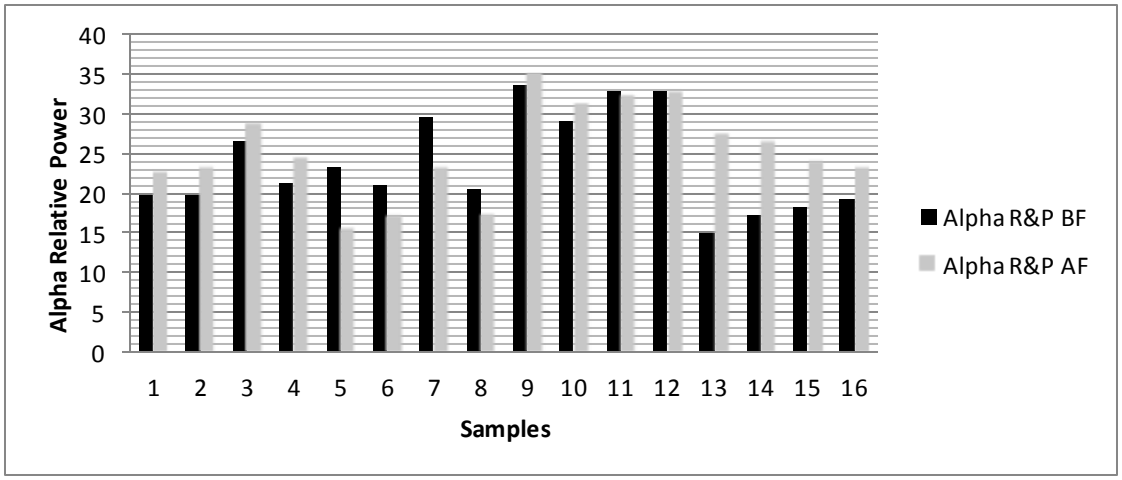


Figure 4.1 Alpha relative power

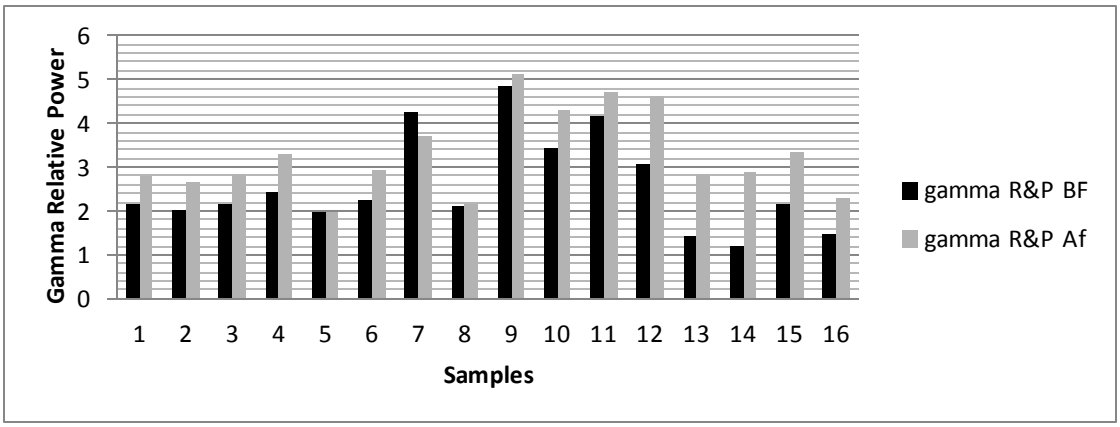


Figure 4.2 Beta relative power

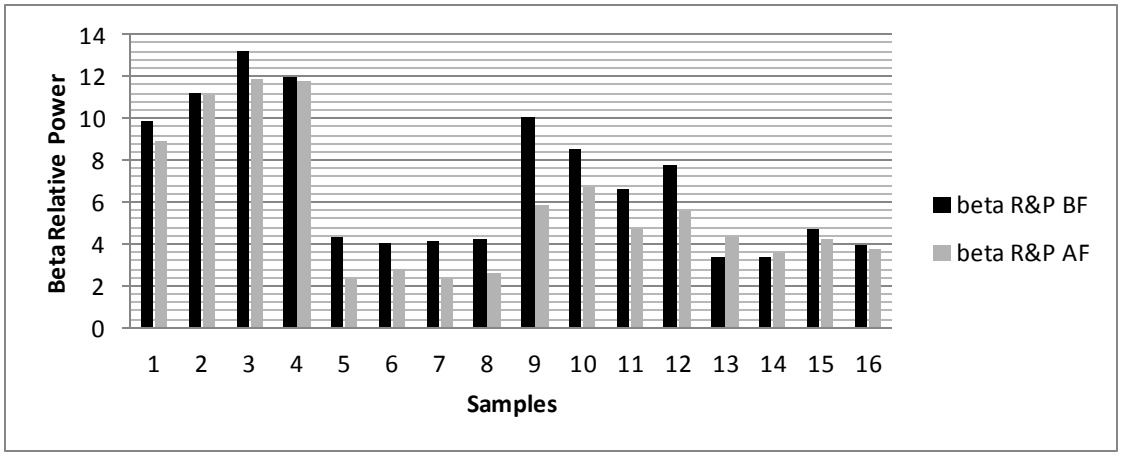


Figure 4.3 Gamma relative power

Statistical Analysis			
	Mean	Std.Deviation	Sig.
Power Alpha BF	23.7522	6.14	0.312
Power Alpha AF	25.1489	5.75	
Power Beta BF	6.9657	1.40715	0.002
Power Beta AF	5.7877	1.36401	
Power Gamma BF	2.5712	0.97886	0.00
Power Gamma AF	3.2848	0.95076	

4. 1: Statistical analysis

By the analysis of Alpha, Beta and Gamma pair t-test (Table 8-2) has been reveal that first of all it has remarkable change after taking methadone rather than the before taking methadone for heroin-dependent subject whom just start to heroin withdrawal by methadone. Further analysis shows that the relative power in heroin dependence after taking methadone were increased in Alpha (Before: Mean 23.7522, Std.Deviation 6.14 and P=0.0612), ((After: Mean 25.1489, Std.Deviation 5.75 and P=0.0612) and Gamma (Before: Mean 6.9657, Std.Deviation 1.4 and P=0.002), ((After: Mean 5.7877, Std.Deviation 1.36 and P=0.002) and it has decreased in Beta (Before: Mean 2.5712, Std.Deviation 0 .9788 and P<0.000), ((After: Mean 3.2848, Std.Deviation 0.9505 and P<0.000) frequency range and also this change was in comparison with healthy subjects (Fig.8-1, 8-2, 8-3). Our finding illustrate that Gamma frequency range had biggest significance in this analysis. These Findings are also in the wavelength with other EEG research on cocaine and alcohol.

4.3 Channels location

Alpha frequency slowdown was most bolded in central, occipital and temporal part of brain map which included CZ, O1, C5, and O2, F1. Meanwhile according to the statistical analysis, the induce of relative power was depicted in Gamma band at most of site map of opioids' brain especially in Fz, Cz, Pz, C3, C6, T7, P3, P7, T7 ($P<0.05$) (Binienda, Beaudoin, Thorn, & Ali, 2011). For beta this channel location and connectivity goes through frontal area of brain map. Totally relative power can be seen at O1 and CZ.

4.4 Mean Power of Frequency Bands

Another important thing was the change in power of Gamma, alpha and Beta for control subject, opioid and abstinent. According our results (Statistical analysis) had significant effect on power of Gamma [(mean SD, P-value<0.05) ;(Bf: 0.53 0.05642 AF: 0.7685 0.18503, P<0.05)] and also power of Beta [BF: 1.6879 1.35132, AF: 1.5506 1.3236, P<0.05). This significance of change for Gamma had upward movement and increased. For Beta the trend has downward movement and decreased. Another approach of our study come backs to the age of subjects and the duration of their drug usage in which, subjects with higher period of heroin usage have higher mean power especially in Alpha and gamma bands (Polunina & Davydov, 2004) (Hodgkinson et al., 2010).

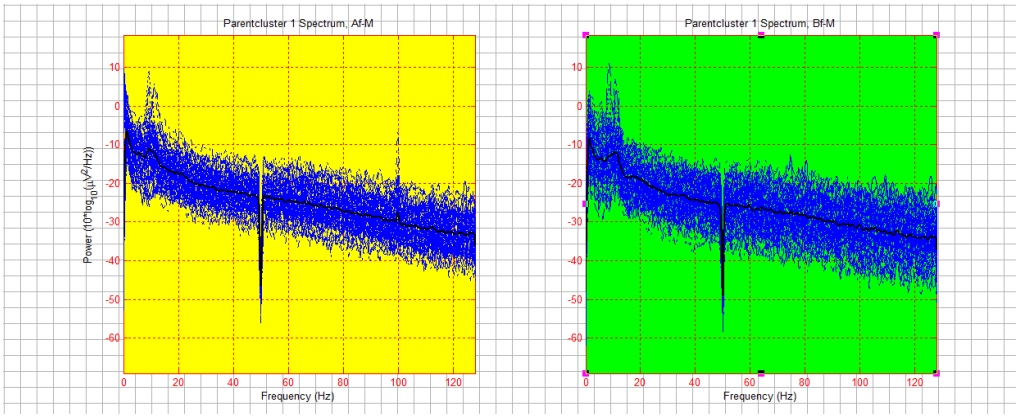


Figure 4.4 Total power of brain, before and after taking methadone

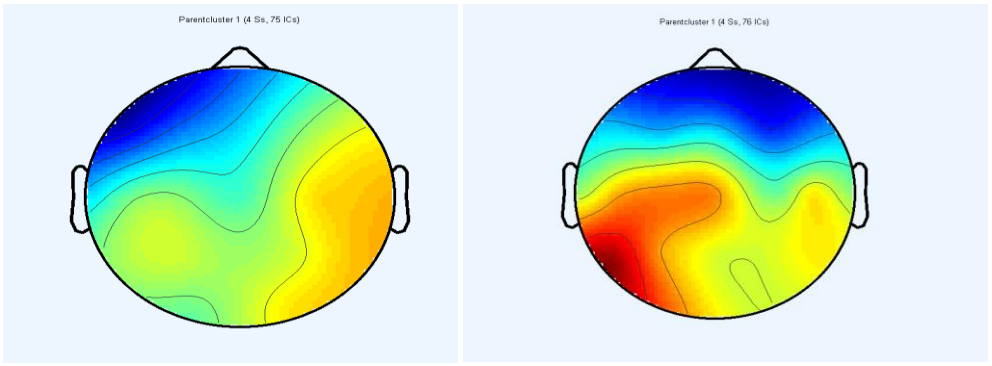


Figure 4.5 Average of components and subjects Bf and AF taking methadone

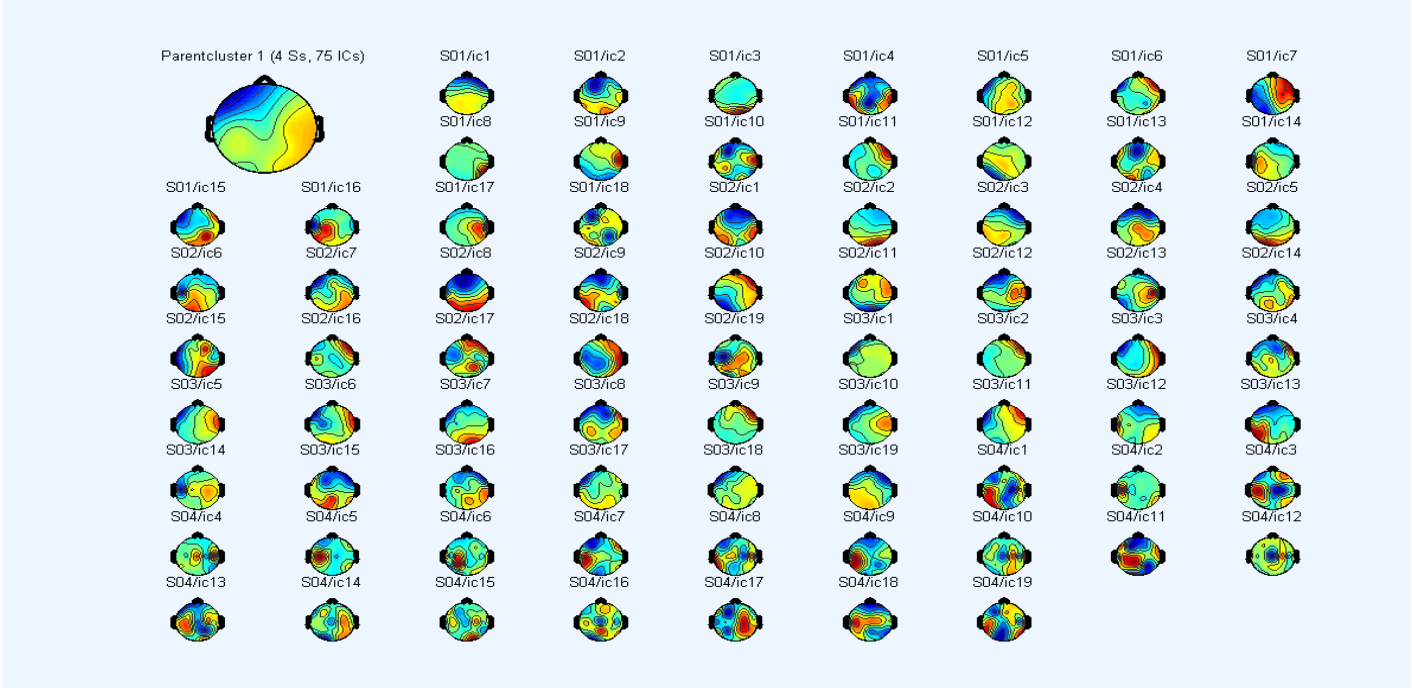


Figure 4.7 All components for all subjects before taking methadone

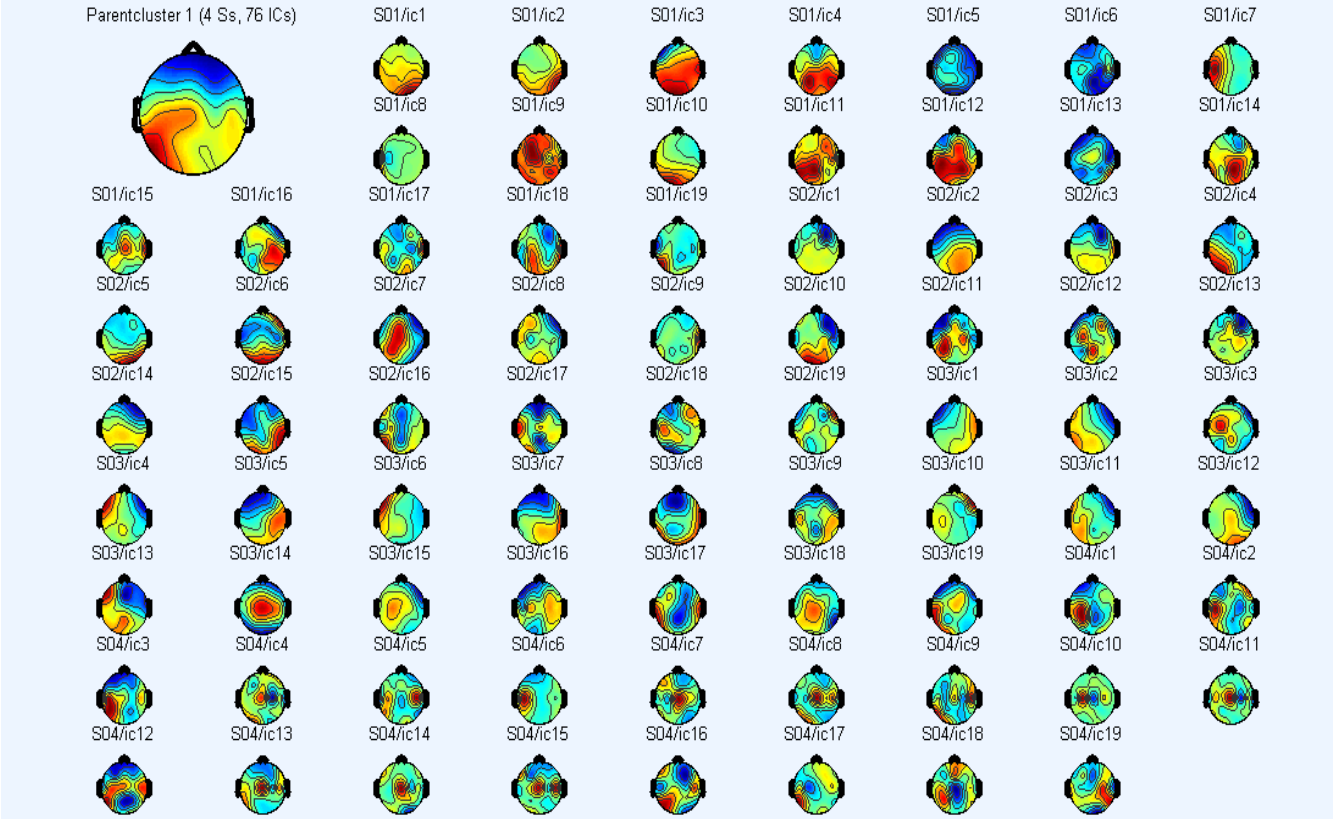


Figure 4.6 All components for subjects after taking methadone

Attention to the change of activity in the brain, slow activity in frontal and high activity in occipital which have been observed in Fig. 8-6, 8-7. As can be seen in Fig 8-8, 8-9 for heroin addicts we have abnormality in frontal-temporal cortex and also heroin make disruption and damages frontal and astrocytes has been mentioned in another studies(Sastre, Ventayol, & García-Sevilla, 1996) (Polunina, Davydov, & Briun, 2005). As it has been shown in above Fig. 8-9 for before taking methadone, it provides a courtesy that heroin addict's patient's increases brain activities and changes. The slowing cognitive potential components are significantly appeared in right-frontal after taking methadone Fig.8-8 at the first time of methadone administration (Parvaz, Alia-Klein, Woicik, Volkow, & Goldstein, 2011).

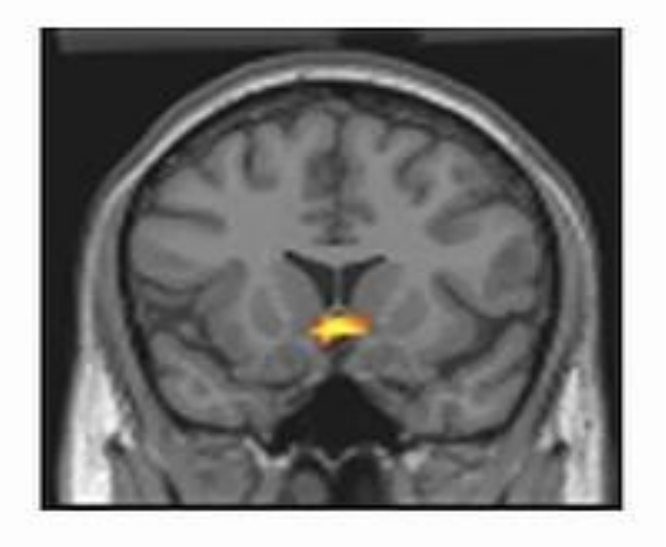


Figure 4.8 fMRI image of limbic system (john, 2011)

Some of studies have been reported that heroin addicts the brain face with decrease in DA D2 receptors which located in striatum (Fig. 8-10) and alteration and irregularity in metabolism and also the flowing of the cerebral blood in orbit frontal cortex. Ventral Striatum has a key role in pleasure-lauther-addiction effect which is associated with limbic system.

4.5 BIA descriptive analysis

The following table presents the characteristic of Body Composition Analysis (BCA) before and after taking methadone. According to the four of our patients, the results came up as follow:

Four Subjects	Before	After	changes
PA	5.6	6.4	PC
BC	609	661	PC
Res.	558.65	534.025	PC
Reac.	60.15	59.8	NC
BCM	22.425	23.375	PC
ECM	24.65	24.85	PC
LBM	47.075	48.225	PC
FM	6.05	4.9	NC
(ECM/BCM)	1.1	1.0675	PC

4.2: Comparison for BIA analysis (Positive Changes: PC, Negative changes: NC)

BMI did not change. The results shows that PA, BC, Res, BCM, ECM, LBM had positive changes and in Reac and Fm the negative changes has been observed from before to after taking methadone. In view of phase angle we had increase but because of this four subjects we are not able to acclaim that it is significant.

4.6 Discussion

Spectral power of brain frequency bands has close relation with the length of the withdrawal because in our four subjects. Thus this study gives this ground that maybe it can be said that long term drug users make the high oscillation of the brain frequency bands and it leads to the asocial behavior and sort of perturbation of memory in this patients. As it has been depicted in the graph the duration of the power spectral characteristic tend to be normalized during period of time of withdrawal (Osborne, Chou, & Shen, 2011).

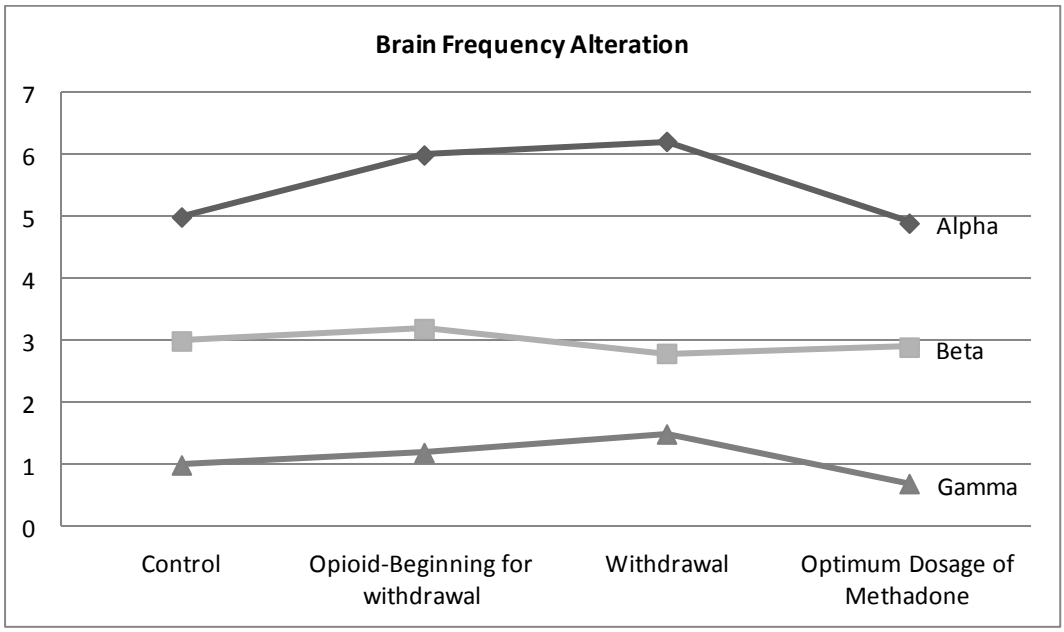


Figure 4.9 : Brain frequency alteration

Here we explain the situation in comparison with control subjects. As can be seen, for Gamma and Alpha frequency band the power for opioid are more than control subjects. By first time administration of methadone these increasing trends are still moving ahead. But after a while of usage of methadone and increase of the methadone amount this trends became downward to the control state. The interesting thing is the amount of power that

becomes a little lower than control subject. Meanwhile these ups and downs for Beta frequency band are in other way. Opioid state has bigger beta rather than the control, but after first time administration of methadone the power does not increase as what happened in Gamma and Alpha, and it has goes down. Then after reaching to the optimum amount of methadone dosage the power comes back to the state of control subjects. We can find out the roughly amount of this power in these frequency band and then reach to the optimum dosage for each subject(Van Someren, 2011).

For realization of BIA analysis we can mention points like follow:

If we come into the conclusion we can say that in body capacitance(BC), body resistance(Res.) and body fat mass(BCM) the significance of difference is observable($p<0.005$). BC and BCM have increasing trend and Resistance has decreasing trend. Each of which of this trends goes to become close to the normal (healthy) position. The other methods somehow have this capability to identify as a significant comparison between two steps of methadone administration (before/after). But it needs more data to shows weather our results are correct or not.

5 Chapter V: CONCLUSIONS AND RECOMMENDATION

5.1 Conclusion

In conclusion this chapter concludes the findings of the study. it has been shown that relative and mean power after taking methadone have been increased significantly in frequency range of Alpha and Gamma band and decreases in the range of Beta. This kind of decrease in Beta frequency band is sign of calmness. Because with increase of Beta the arousal will be comes up. In general in compare with healthy subjects' addicts' people brain's map, the high activity has been observed and also it is pointed out that there is bioelectric changes in the oscillation pattern of neural network of brain.

5.2 Future work

According to our finding in statistical analysis by comparison between Methadone Maintenance (MM) brain power signals (Beta & Gamma) with their situation in state of opioid, starting for withdrawal and control state as it has been shown in the graph it is plausible to reach to the stable algorithm which able to shows the optimum amount of administration of methadone. By just one subject whom reaches to the optimum dosage of the methadone we catch this result. To find a stable algorithm more patients is needed to do classification and training of the artificial intelligence for this matter.

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