Methadone Effects on Frontal Brain Lobe based EEG-P300 Waves in Drug Rehabilitation Patients

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Abstract: Drug abuse in various parts of the world is increasingly widespread. Therefore, a drug addict should immediately stop and must be recovered. To overcome the symptoms of addiction, the use of methadone as a synthetic drug to replace opioid type drugs is recommended. In this paper, an experiment with rehabilitation patients to identify the effect of the drugs on the brain activity in the frontal, central, temporal, and occipital lobes is proposed. The EEG data collection is performed using 18 channel electrodes, namely central: C3, C4; frontal: Fp1, Fp2, F3, Fz, F4, F7, F8; occipital: P3, Pz, P4, O1, O2; and temporal: T3, T4, T5, T6. In the brain signals record, subjects were asked to comfortably sit in a chair. The recording was done in three sessions: 5 minutes before drinking methadone, 10 and 60 minutes after drinking the methadone, respectively. To reduce background noise and artefacts removal, band pass filter (0.5-50 Hz) and wavelet method were applied, respectively. From this experiment it was found that a decrease in amplitude after methadone intake for average in four lobes is obtained. This results indicates that the use of methadone is highly effect on the entire brainwave activity which indicates a decrease in the level of desire to do activities.

1 INTRODUCTION

Drug abuse in various parts of the world is increasingly widespread. Various cases show material and non-material losses and even cause the death. Therefore, a drug addict should immediately stop and must be recovered. According to Indonesian law, narcotics addicts and victims of narcotics abuse must serve out medical rehabilitation and social rehabilitation (Undang-Undang Republik Indonesia No. 5 tentang Psikotropika, 1997). It regulates that narcotics addicts and narcotics abuse victims who are undergoing the process of investigation, prosecution and trial in court are supported with treatment and recovery in rehabilitation institutions (BNN Regulation 11/2014) (Badan Nasional Narkotika, 2007). By law, the state is responsible for recovering drug users through rehabilitation. Therefore, there should be no obstacles for rehabilitation programs, including regarding infrastructure or facilities for the recovery of drug addicts. Drug rehabilitation consists of three stages namely medical rehabilitation (detoxification), social or non-medical rehabilitation, and advanced development. Some detoxification techniques include cold turkey method where the patient is locked up in the addiction (*sakau*) phase, substitution or replacement therapy where the needs of opioid or heroin addicts are replaced with other types of drugs such as methadone, or symptomatic therapy where drug administration is adjusted to the user's complaints.

The therapeutic method with an effective medical approach that still recognized today is a drug switching program to another substance called methadone therapy (Wang, Kydd, Wouldes, Jensen, & Russell, 2015; Yang, et al., 2015; Turnip, et al., 2018; Turnip, Kusumandari, Hidayat, 2018; Hu, et al., 2017). There are a variety of positive benefits that allow patients to be able to carry out their normal activities, but methadone therapy also causes side effects and the dependence that can psychologically affect the patients' quality of life (Yang, et al., 2015; Maeyer, et al., 2011; Lin, et al., 2016; Malik, Adelson, Sason, Schreiber, Peles, 2019). Methadone is a therapy used for drug addicts from opioid groups

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such as heroin, morphine and codeine including methamphetamine. The methadone therapy must be routinely done. Methadone is a group of opiate analgesics that can be used to treat ongoing severe pain (such as pain due to the cancer). This substance works directly in the brain by changing how the body feels and how the body responds to the pain. Methadone is also used to treat dependence on narcotic drugs (such as heroin) as an approved therapy program. It can also help prevent withdrawal symptoms due to the drug withdrawal (Hu, et al., 2017; Wang, Kydd, Wouldes, Jensen, & Russell, 2015; Yang, et al., 2015; Malik, Adelson, Sason, Schreiber, Peles, 2019). The success of substitution therapy such as the methadone program for drug addicts is higher than rehabilitation without drugs or detoxification. Even with this therapy, the spread of HIV can be suppressed because the use is done by drinking. Some researchers have found that methadone maintenance can significantly reduce craving symptoms except in patients with heroin dependence. Long-term consumption of heroin causes adaptive changes in the brain system that may last for a long time (Li, 2012). Verdejo, et al. (2005) has found that methadone itself has the side effect of causing cognitive impairment. Other researchers have found that rehabilitation can effectively repair impaired cognitive function caused by buprenorphine, placebo, and methadone (Attou, Figiel, Timsit-Berthier, 2001).

Electroencephalogram (EEG) is an activity that records spontaneous brain activity in the form of potential electrical signals along the scalp produced by interconnected neurons. Among the medical use of EEG, among others, for the diagnosis of diseases associated with brain and psychiatric disorders (Pastor, et al., 2019; Wang, Kydd, Wouldes, Jensen, & Russell, 2015; Turnip, et al., 2018; Hu, et al., 2017). EEG is also applied to detect a person's mind patterns or mental condition. Visual observation of the EEG signal directly is very difficult given the amplitude of the EEG signal is so low and the pattern is very complex. Besides that, EEG signals are strongly influenced by various variables, including mental condition, health, activity of the patient, recording environment, electrical disturbances from other organs, external stimulation, and age of the patient. The nature of EEG signals in general is non stationary and random so that adds complexity to the processing of EEG signals (Turnip, et al., 2018; Hu, et al., 2017; Iskandar, Kusumandari, Turnip, 2019; Turnip, Kusumandari, Pamungkas, 2018). However, the classification of EEG signals to changes in certain variables can explain the work function of the brain and capture changes in brain activity to the relevant variable.

EEG signal in a person, generally consists of wave components which are distinguished based on their frequency region, namely: Human brain waves have a range of frequencies and amplitudes - different so that it is divided into several types of waves, namely: delta waves (when deep asleep and without dreaming) have the frequency is less than 4 Hz with an amplitude of about 10 μV. Theta waves (occurring when light sleep or drowsiness) have frequencies between 4 –8 Hz with an amplitude of around 10 μV; Alpha waves (occur when relaxation or transition between conscious and unconscious states) have a frequency between 8-13 Hz with an amplitude of around 50 μV. Beta waves (in a state of thinking or in the activity) have a frequency between 13-19 Hz with an amplitude between 10-20 μV. Gamma waves (experiencing very high mental activity such as fear, very panic, appearing in public) have a frequency between 19-100 Hz (Motlagh, et al., 2018; Zhang, et al., 2017). Therefore, the representation of EEG signals into the frequency domain is mostly done in research related to EEG signal analysis. In this study, the use of EEG signals to observe the effect of methadone administration on changes in brain activity in the central, frontal, parietal, occipital, and temporal parts is proposed. So far, methadone experiments and observations of their effects on brain activity using brain waves from EEG signals are still rarely done.

2 METHODS

Experiments were carried out in a room that was conditioned away from noise and provided comfort for the subject (Figure 1). Before conducting an EEG signal recording session, the subjects first directed interviews with the medical team, filled out information of concern, and follow the urine tests. Then the subject is attached to an instrument in the form of an electro-cap on the head and also tied a belt to the chest of the subject so that the electro-cap does not shift. Subjects were briefed regarding the experimental scenario. The EEG signals are recorded through 19 channel electrodes, including Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1, and O2. The reference in this experiment uses electrodes mounted on the ear, the A1 and A2 channel electrodes, which are A1 for the left ear and A2 for the right ear. When installing electrodes, a gel is applied to each EEG sensor to increase conductivity while maintaining impedance between the scalp and electrodes below 5 kΩ. The electrode mounting position, the electrolyte liquid used in the form of an electro gel, and the impedance shown in Figure 2. The electrode impedance can be monitored in WinEEG software before the signal recording process is started. The dark color on the electrode indicator indicates a higher impedance, while the bright color indicates a low impedance level.

In addition to fix the electrode impedance, another thing to consider is setting the recording process in the WinEEG system. Settings include the sampling frequency used which is 500 Hz, the list of channels to be used and their references, and interconnection with PCs / laptops to display the stimuli used when recording EEG signals. During the recording process, subject was asked to sit relaxed while closing his eyes. Experimental time allocated for each trial is 1 hour and 10 minutes. The time is divided into 3 sessions, namely 5 minutes before, 10 minutes after, and 60 minutes after consuming methadone. After the recording session is finished, the recording of the EEG signal is exported into a file with EEG format, which the file can later be processed using a signal processor.

Figure 1: The experiment design.

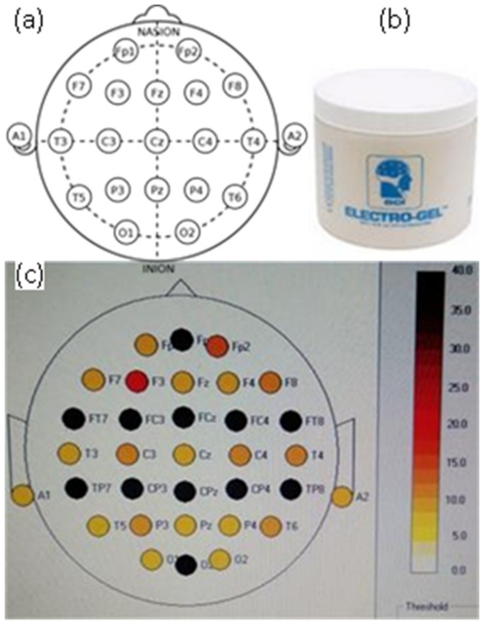
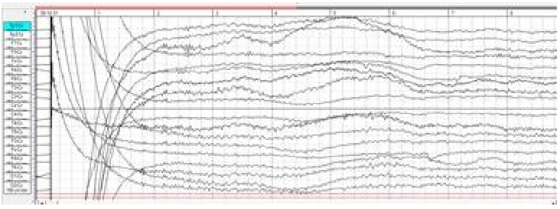


Figure 2: (a) Electrode position, (b) electrogel for conductivity, (c) electrode conductivity with around 5 kΩ impedance.

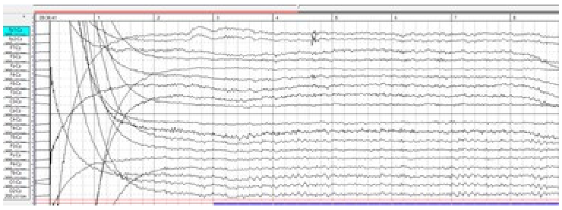
3 SIGNAL PROCESSING

EEG raw data is processed with C2 references using 18 channels from 8 subjects. The 18 channels that are used are grouped according to the brain lobes, namely Central: C3, C4; Frontal: Fp1, Fp2, F3, F2, F4, F7, F8; Parietal Occipital: P3, Pz, P4, O1, O2; Temporal: T3, T4, T5, T6. The average amplitude (after extraction) of each channel group is calculated. Before the data is processed montage reference is changed to the middle part of the brain with the Cz channel. Recording of each subject is done for ± 5 minutes per session. Data is taken from 10 seconds to 130 seconds because data processing will be more effective if taken 2 minutes of data that is clean and free of artefacts. Data recording before the 10th second is cut because the initial 10 seconds are considered to be still corrupted by noise where the subject is still adjusting to the experimental conditions.

From Figure 3 raw data generated, clearly visible on the EEG signal there are still many artifacts which make it difficult in understanding the character of the signal, therefore the next processes are needed.



(A)



(B)

Figure 3: Raw data of EEG in relax and close aye condition: before and (b) after Methadone intake.

To reduce background noise, the filtering process for EEG raw data is carried out. Bandpass filter is a circuit that is designed to pass the frequency within certain limits and reject other frequencies outside the desired frequency. And bandpass filter is a combination of highpass and lowpass filter. In the experiment, the cut off frequency used is 0.5 and 50 Hz. As for feature extraction, the wavelet method with the symlet model and the 5 level decomposition process is used.

Wavelet transform is a signal processing method by resembling signal analysis using Fourier transforms, namely by breaking the signal to be analyzed into several parts. The difference, if the Fourier transform signal is broken down into signal sinusioda with different frequencies, then the wavelet transformation of the analyzed signal is broken down into a number of signals resulting from shifting and scaling of a small signal called a wavelet. The wavelet transform method in Equation (1) (Jawabri & Sharma, 2019), mainly used to identify true components and remove noise from the raw data

$$W_f(j,k) = \int_{-\infty} f(t)\psi_{j,k}*(t)dt \text{ , with} \quad (1)$$

where, $\psi_{j,k}(t) = 2^{-j/2}\psi(2^{-j}t - k$, where $\psi(t)$ is the mother wavelet, $f(t)$ is the series analyzed, and t indicates the time; integer j indicates the decomposition level, and k indicates the time translation factor, and $\psi*(t)$ is the complex conjugate.

The first step of the wavelet application starts from the original signal then the coefficients set is approximated on each level. In each step except the first one, only the approximated coefficients are analyzed. The wavelet used must meet the regularity of order N condition in Eq. (2)

$$\int_{-\infty} t\ \psi(t)dt = 0,\ k = 1,\cdots, N-1 \quad (2)$$

Under the level of j, the original signals can be reconstructed using Eq. (3).

$$f_j(t) = \sum W_f(j,k)\psi*(2^{-j}t - k) \quad (3)$$

By increasing the decomposition level j, the detailed information of signals at larger temporal scales would obtained. The more contribute information we have, the better performance of the model is achieved. However, more input could reduce the computing efficiency and decrease the stability of the model. Therefore, it is important to select an appropriate decomposition level for wavelet modeling.

4 RESULTS AND DISCUSSION

Drugs provide a dominant effect on the functioning of the four brain lobe: frontal, parietal, temporal, and occipital lobes. These effects can be observed if brain activities is record and processed. In the experiment of brain activity record, a group of subject is asked to sit in relax while closing their eyes. The brain wave is recorded about three times: before, 10 minutes, and 60 minutes after taking methadone. Assumption that subjects who are follow the rules of experiment will fill craving in the first record, starts to comfort after 10 minutes, and feel comforts after 60 minutes of consuming methadone. The differences in the amplitude of the extracted EEG before and 1 hour after the subject consume the methadone in four region of brain is observed. Subjects who have not been given methadone have a higher level of interest in methadone (craving), consequently the amplitude after consuming methadone must be lower. The decrease in amplitude value is also supported by the influence of methadone which tends to make the subject sleepy where theta waves increase and beta waves decrease.

The cerebral cortex of the brain can be divided into four lobes (see Figure 4): The frontal, parietal, occipital, and temporal lobes. They are associated with different functions into the body ranging from reasoning to auditory perception. The frontal lobe is associated with motivation, thinking, movements, cognition, and expressive language. Damage to the frontal lobe can lead to changes in sexual habits, socialization, and attention as well as increased risk-taking. The parietal lobe is associated with processing tactile sensory information such as pressure, touch, and pain. The temporal lobe is important for interpreting sounds and the language. Damage to the temporal lobe can lead to problems with memory, speech perception, and language skills. The occipital lobe is associated with interpreting visual stimuli and information. Damage to this lobe can cause visual problems such as difficulty recognizing objects, an inability to identify colors, and trouble recognizing words (Jawabri & Sharma, 2019).

Because drugs affect the work of brain, drugs can change the mood of feelings, ways of thinking, awareness, and behavior of the wearer. That is why narcotics are called psychoactive substances. There are several kinds of effects of drugs on the brain, such as inhibiting the work of brain, called depression. This state could reduce awareness resulting in drowsiness. Drugs can also stimulate the work of the brain or what is often called a stimulant, so that arises a sense of freshness and enthusiasm, increased confidence, and relationships with others become close. However, this can cause inability to sleep, restlessness, faster heart palpitations, and increased blood pressure. Some drugs could cause delusions, or what are often called hallucinogens. Narcotics abuse has an influence on the work of the nervous system, including: Sensory nerve disorders (central and occipital lobes) that cause numbness and blurred vision that can cause blindness; Autonomic nerve disorders (frontal lobe) that cause unwanted movements through motor motion. Impaired motor nerves (central and frontal lobes) that cause loss of coordination with the motor system. Vegetative nerve disorders (frontal, temporal, and central lobes) cause language to come out of consciousness and cause fear and lack of confidence.

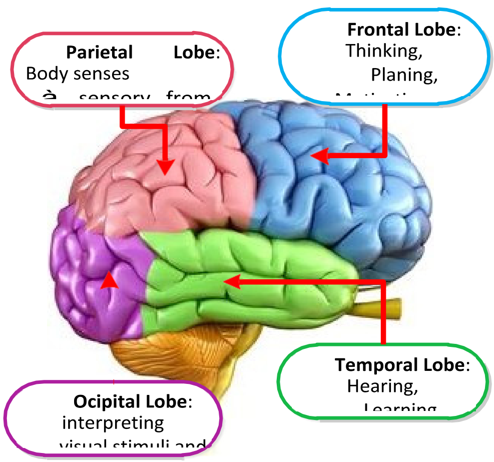


Figure 4: Brain lobe effected by Methadone.

Table 1 shows the mean amplitude of each lobe before and after consuming Methadone. The results of previous studies show that drug use automatically affect brain performance in each lobe such as disturbing vision for the occipital, movement, and language for central and frontal, emotions for temporal. In theory, if someone who is craving is given Methadone then the subject should feel more comfortable after an hour. Based on the experimental results in Table 1, except for subjects 5 and 6, the average amplitude in each lobe has decreased. Individually, subjects 2, 3, 4, 7, and 8 have their respective amplitudes increasing at central, occipital, frontal & temporal, occipital, central, and frontal parts.

When compared with subjects 5 and 6, the increase is not that significant. Subjects 5 and 6 had lobes of increased amplitude after taking Methadone. Based on the history of substance use, the two subjects used almost the same drugs and the most compared to other subjects. Both have almost the same age with few mental disorders and a relatively high value of impulsivity. They also took high doses of Methadone even though they had been undergoing rehabilitation for a long time (subject 5 had rehab for 11 years). Subjects 5 and 6 also consumed benzodiazepines during the experiment.

Based on the demographic conditions of two subjects, it can be understood that the increase in the amplitude value of brain activity in each lobe is the result of impaired brain function in the related area. The highest increase was seen in subject, 6 which is about 6.5 times the time of craving. Meanwhile, the increase in subject 5 is only about 2.5 times from the condition at craving. Based on demographic conditions, subject 6 still consumed very high doses of methadone or the maximum dose during the experiment. It is suspected that subject 6 does not follow routine and adequate rehabilitation. Meanwhile, subject 5 had obtained a significant reduction in dose to the maximum dose. However, because the age of using the drug is quite long, which is 11 years, it is likely that a lot of brain nerve tissue has been damaged so that even though it has been given Methadone, brain function cannot return to normal.

Subjects 4 and 8 both had two lobes in which the amplitude of brain activity did not decrease. Both subjects had the second-highest history of substance use than other subjects, and the dose was almost the same as the maximum dose. When viewed as a whole, changes in the brain activity amplitude after consuming Methadone are closely related to history of substance use and decreased Methadone dose.

When compared with subjects 2 and 3, subject 7 experienced a significant increase in the amplitude of the occipital region, which is almost 4 times compared to the craving condition. Based on the results of urine tests, subject 7 is suspected to consume benzodiazepines and methamine during the experiment. These conditions sufficiently state the reasons for the increase in the associated amplitude.

Table 1: Amplitude of brain activity in the lobe of central, frontal, occipital, and temporal: before, 10 minutes, one hours of methadone intake.

Amplitude				
S	**Lobes**	**Before**	**10 m**	**1 hours**
1	Central	28.29	20.82	10.01
	Frontal	119.80	63.73	8.34
	Ocipital	48.23	37.78	15.40
	Temporal	69.81	63.78	20.52
2	Central	7.80	5.82	18.12
	Frontal	10.08	12.06	9.10
	Ocipital	9.85	14.40	3.27
	Temporal	10.55	17.04	2.71
3	Central	216.88	131.25	55.29
	Frontal	84.02	61.15	33.26
	Ocipital	89.55	105.08	124.45
	Temporal	36.77	31.04	11.39
4	Central	42.69	28.47	32.42
	Frontal	26.47	28.07	29.34
	Ocipital	34.85	17.94	32.73
	Temporal	8.70	8.46	9.34
5	Central	14.46	28.87	49.23
	Frontal	15.17	21.83	50.79
	Ocipital	20.55	59.43	25.65
	Temporal	4.58	7.32	18.28
6	Central	24.49	20.47	120.79
	Frontal	24.50	22.86	122.04
	Ocipital	13.93	22.32	197.58
	Temporal	16.74	5.6	92.36
7	Central	40.58	11.69	5.498
	Frontal	38.51	11.85	8.81
	Ocipital	1.25	6.76	5.46
	Temporal	16.65	3.37	3.49
8	Central	27.05	28.41	33.38
	Frontal	23.26	23.49	31.73
	Ocipital	16.40	14.85	16.89
	Temporal	7.93	9.83	7.53

5 CONCLUSIONS

Methadone intake by the drug rehabilitation patients causes a decrease in the brain's impulsivity to given stimuli, which indicates a decrease in the level of desire for drugs after being given Methadone. The main results of present analysis indicated that the subjects have a longer P300 latency and a lower P300 amplitude after consuming Methadone. This study revealed that drug patients have abnormalities in the P300 component, which may reflect deficits in cognitive function.

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