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RESEARCH PAPER

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Acute effects of methadone on neural oscillations: an EEG study of theta, alpha, beta power, and frontal alpha asymmetry in opioid rehabilitation patients

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ABSTRACT

Methadone is a synthetic opioid that commonly employed in opioid substitution therapy (OST) to reduce withdrawal symptoms and suppress cravings in individuals with opioid use disorder. While its pharmacological effects are well-documented, the neurophysiological changes it induces—especially during acute administration—remain underexplored. This study aims to address that gap by investigating methadone-induced alterations in brain oscillatory activity through electroencephalography (EEG). Specifically, it examines changes in theta (4–8 Hz), alpha (8–12 Hz), and beta (12–30 Hz) frequency bands, along with frontal alpha asymmetry (FAA) for F4-F3 and F8-F7, a biomarker associated with emotional and cognitive processing. EEG data were collected from patients enrolled in opioid rehabilitation programs both prior to and one hour following oral methadone intake. The results revealed a significant global decrease in theta power, notably within the frontal, temporal, and occipital cortices. This reduction may reflect changes in executive functioning, emotional regulation, and increased sedation. In contrast, alpha power showed a marked increase, particularly in the central, parietal, and occipital regions, suggesting reduced sensory processing and heightened sedation or attentional disengagement. Meanwhile, beta power was consistently reduced across cortical regions, pointing toward decreased cortical arousal and cognitive alertness. FAA analysis revealed high variability among participants, indicating that methadone's influence on emotional valence and approach-avoidance behavior may differ significantly across individuals. These findings underscore methadone's sedative and stabilizing effects on neural activity and support its clinical role in managing opioid dependence. Further research into inter-individual differences in EEG responses may inform more personalized and effective OST protocols.

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1. INTRODUCTION

Methadone is a long-acting synthetic opioid commonly used in opioid substitution therapy (OST) for individuals undergoing rehabilitation from substance use disorders (SUD) [1]. As a μ-opioid receptor agonist, methadone helps relieve withdrawal symptoms and reduce opioid cravings, thereby facilitating long-term recovery [2]. However, methadone also exerts significant neurophysiological effects, altering brain function and cognitive processing, which can be assessed using electroencephalography (EEG) [3]. Understanding these effects is crucial for evaluating the impact of methadone on brain activity and its implications for cognitive function and behavioral regulation in patients undergoing rehabilitation.

EEG provides a non-invasive method to assess neural oscillatory activity across different frequency bands, each associated with distinct cognitive and behavioral states. In this study, the EEG analysis is focused on theta, alpha, and beta frequency bands due to their well-documented sensitivity to opioid effects, including methadone. Delta (0.5–4 Hz) and gamma (30–100 Hz) were excluded because they are either less relevant to methadone's cognitive effects or present higher variability in opioid research [3] [4] [5]. Theta (4–8 Hz) oscillations are linked to cognitive control, drowsiness, and inhibitory

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mechanisms [6]. Changes in theta power have been observed in opioid users, suggesting alterations in cognitive function and attentional control [7]. Alpha (8–12 Hz) activity is associated with relaxation, sensory inhibition, and cognitive idling [8]. Increased alpha power following methadone intake has been reported, reflecting its sedative effects [5]. Beta (12–30 Hz) waves are related to active cognitive processing, motor control, and attentional engagement [9]. Previous studies indicate a suppression of beta activity post-methadone administration, suggesting reduced cortical excitability and attentional focus [10]. Additionally, Frontal Alpha Asymmetry (FAA) serves as a biomarker of emotional and cognitive states, with shifts in FAA patterns indicating changes in mood and motivation [11]. Alterations in FAA following opioid administration may reflect emotional dampening and decreased approach motivation [5].

Several studies have investigated the effects of opioids, including methadone, on EEG activity. Authors [12] demonstrated that acute opioid administration leads to an increase in alpha power, correlating with subjective euphoria in heroin users. Similarly, study [3] observed abnormalities in EEG patterns in methamphetamine users, highlighting the impact of substance use on neural oscillatory dynamics. Paper [7] reviewed opioid-induced alterations in theta and beta activity, reporting significant reductions in cognitive processing efficiency. More recently, [5] examined FAA changes in opioid users, suggesting potential alterations in emotional regulation and cognitive control mechanisms. However, most previous studies have focused on chronic opioid effects rather than acute changes following a single dose of methadone. Furthermore, while FAA has been explored in opioid users, its specific alterations in response to methadone administration remain underexplored. Additionally, comparative analyses across multiple EEG frequency bands before and after methadone intake are limited, especially in the context of NAPZA rehabilitation programs.

Hence, this study provides a comprehensive analysis of acute methadone-induced EEG changes across multiple frequency bands (theta, alpha, beta) and frontal alpha asymmetry (FAA) in patients undergoing opioid rehabilitation. Unlike previous studies that focused on chronic opioid effects, this research specifically examines neural oscillatory changes before and one hour after oral methadone administration, offering insights into the immediate neurophysiological impact of methadone. We specifically analyze spectral power changes in theta, alpha, and beta bands before and one hour after oral methadone administration, to provides a targeted investigation into methadone's acute effects on cognitive control, relaxation, and attentional processing, which are crucial aspects of opioid rehabilitation [5] [7]. The inclusion of FAA analysis adds a novel perspective on emotional and cognitive regulation, which is rarely explored in the context of methadone treatment. By examining these neural oscillatory changes, this research seeks to provide insights into the neurophysiological impact of methadone on brain function, which may have implications for cognitive performance, emotional regulation, and treatment outcomes in opioid-dependent individuals. This study is also bridging the gaps in existing literature by contributing valuable information for understanding methadone's acute effects on brain function, which may help optimize treatment strategies in opioid rehabilitation programs.

This study is structured as follows: section II discusses the subjects (dataset), data recording, and data processing. Section III displays the results of PSD calculation and frontal alpha asymmetry. Section IV discusses the interpretation and comparison of results with other studies and limitations. Section V, conclusions, which rewrite the objectives, main findings and future works.

2. MATERIALS AND METHOD

A. Subjects

Twenty participants undergoing methadone maintenance treatment at the rehabilitation center of Hasan Sadikin Hospital were recruited for this study. The participants ranged in age from 28 to 45 years (mean ± SD: 39.93 ± 6.15) and their daily methadone dosage varied between 25 and 205 mg (mean ± SD: 85.18 ± 49.77). Methadone dosage among participants was determined based on individual clinical assessments conducted by healthcare professionals, taking into account factors such as body weight, opioid dependency history, and metabolic response. The inclusion criteria included all the participants had a minimum education level of senior high school (to obtain more homogeneous data distribution to enhance the reliability of statistical analyses and technical considerations as a more uniform dataset and ensuring that participants can follow instructions more easily during the experiment), all participants were required to have the ability to communicate both verbally and in writing, and the participants had been receiving methadone treatment consistently for at least six months. Exclusion criteria included recent drug or alcohol use within the past 30 days, as well as the presence of physical illnesses, epilepsy, or any mental disorders. The subjects with excessive noise of EEG signal recording will also exclude for data processing.

B. Data Recording

This study received ethical approval from Hasan Sadikin Hospital (RSHS) with the number of 0819091273. Prior to obtaining informed consent, participants were provided with an informational session regarding the study two weeks in advance, in accordance with the ethical clearance approved by the Ethics Committee of RSHS. This session was conducted collectively in a group setting at the Methadone Maintenance Therapy Clinic of RSHS.

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Patients who expressed interest in participating in the study were instructed to contact the designated physician or liaison officer to schedule the experimental session and formally sign the written informed consent form. The participants were assigned to sessions randomly to reduce selection bias and improve the reliability of results. EEG recordings were conducted using the Mitsar-EEG System, with electrode caps in line to the International 10/20 system. A total of 19 EEG channels were utilized, including the prefrontal (Fp1, Fp2), frontal (F7, F3, Fz, F4, F8), central (C3, Cz, C4), temporal (T3, T4, T5, T6), parietal (P3, Pz, P4), and occipital (O1, O2) regions. The sampling rate was set at 500 Hz, and electrode impedance was maintained below 5 kΩ for all channels. The experimental protocol was five minutes eyes open in a relaxed state. EEG data were collected at two time points: before methadone administration and an hour post-administration

C. Data Processing

Six out of twenty subjects were excluded from the analysis due to excessive noise in their EEG signals, so the data processing was conducted for only fourteen subjects. The data processing was conducted as in Fig. 1. The data was processed using EEGlab. The raw EEG data for each participant were removing the first and last minutes to eliminate potential instability in the relaxation state. A fourth-order Butterworth bandpass filter was then applied with a cut-off frequency range of 4–30 Hz, along with a 50 Hz notch filter to remove the power line interference. Following filtering, Independent Component Analysis (ICA) was performed to remove noise artifacts, such as eye blinks and muscle activity. Subsequently, the Short-Time Fourier Transform (STFT) was utilized to compute the power spectrum. The STFT is mathematically expressed as shown in Eq. (1):

$$F(\omega,\tau) = \int_{-\infty}^{\infty} f(t)\varphi(t-\tau)e^{-j\omega t} \quad (1)$$

where $f(t)$ is the EEG signal in the time domain, $\varphi(t-\tau)$ is the window function (in this study use Hanning-Window), ω and τ are modulations and translation parameters. The power spectra were calculated for theta (4-8 Hz), alpha (8-13 Hz), and beta (13 - 30 Hz) frequency ranges and were averaged for each electrode position. Furthermore, it was averaged for each region.

For the calculation of frontal alpha asymmetry (FAA) equation (2), a natural logarithm transformation was applied to all power density values to ensure a normalized distribution. This study specifically examined the F4, F3, F8, and F7 electrode sites, which are widely utilized in the literature on frontal alpha asymmetry [13] [14] [15]. FAA scores were derived by subtracting the natural-log-transformed alpha power of the right frontal electrodes from that of the left electrodes (e.g., F4 - F3, F8 - F7) [13] [14]. The FAA calculation is expressed as Eq. (2):

$$FAA = \ln(alpha_{right}) - \ln(alpha_{left}) \quad (2)$$

A positive FAA score indicates greater alpha power in the right frontal, corresponding to reduced cortical activity in that region, whereas a negative FAA score reflects greater alpha power in the left frontal, signifying reduced cortical activity on the left hemisphere.

Statistical analysis was conducted using a paired t-test to assess the acute effect of methadone before and after administration. The paired t-test was chosen because it is appropriate for comparing two related samples, ensuring that differences observed are within the same subjects rather than between independent groups. The significance level was set at $p < 0.05$, which is a commonly accepted threshold in biomedical research for determining statistical significance. Since only a single paired comparison was made (before vs. after administration), no additional correction for multiple comparisons was necessary.

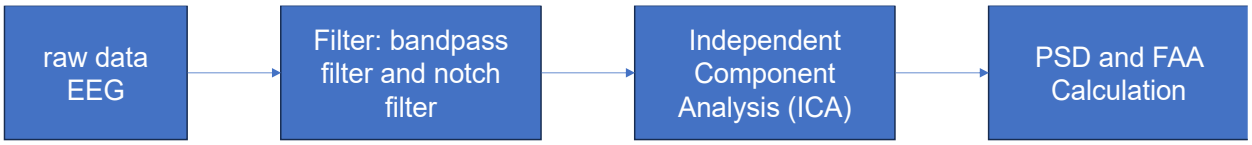

Fig. 1. The workflow of data processing for acute effects of methadone treatment

Table 1. The effect size and post hoc power of sample size for theta band

Brain Region	Differences (post-pre)	Stdev of differences	Cohen's d	Power
Frontal	-1.58	2.61	-0.61	0.86
Temporal	-0.94	1.55	-0.61	0.86
Central	-1.06	1.72	-0.62	0.87
Parietal	-0.97	1.70	-0.57	0.79
Occipital	-0.95	1.61	-0.59	0.82

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3. RESULT

A. Theta

The mean theta power across all brain regions shows a general decrease after methadone administration, suggesting a potential reduce effect on brain activity as shown in Fig. 2. This effect is particularly pronounced in the frontal (Pre: 3.07 ± 2.75, Post 1h: 2.01 ± 1.23), temporal (Pre: 1.79 ± 1.51, Post 1h: 1.16 ± 0.88), and occipital (Pre: 1.69 ± 1.82, Post 1h: 1.22 ± 0.95) with the reduction rate were 34.4%, 35.4%, 27.5% respectively. The central region also exhibits a notable reduction in theta power (Pre: 2.12 ± 1.42, Post 1h: 1.74 ± 1.11) with the percentage of reduction was 17.7 %. The least reduction was in the parietal region (Pre: 1.96 ± 1.83, Post 1h: 1.67 ± 1.03) with the percentage of reduction was 15.2%. This result aligns with [16] which also shows a decrease of theta power of acute methadone administration.

To justify the sample size, a post-hoc power analysis was performed using G*Power application with the observed effect sizes (Cohen's d) from this study. Effect size is around 0.6 across different brain regions. Using a paired t-test with N = 14 and α = 0.05, the statistical power for detecting these effects was calculated to be around 0.8 across all regions as in Table 1, which indicates an acceptable power. These results confirm that the sample size was sufficient for detecting significant changes in brain activity following methadone administration.

Then, the t-test was conducted in Matlab and Table 2 shows that frontal, temporal, and occipital theta power showed significant reductions ($p < 0.05$), while central and parietal reductions were not statistically significant ($p > 0.05$).

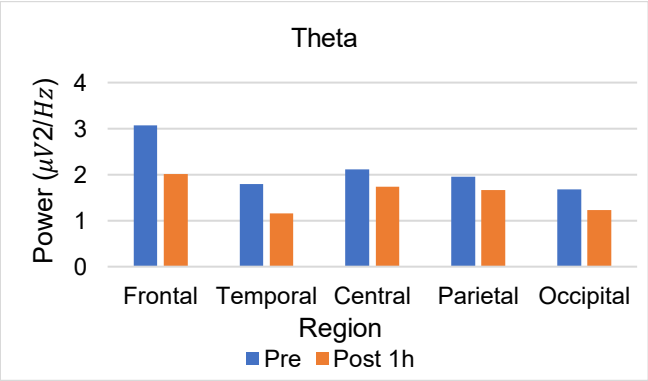

Fig. 2. Mean of theta power per region for pre and post methadone administration

Table 2. Statistical measurement t-test result of mean theta power per region

Brain Region	t-value	p-value
Frontal	2.37	0.036
Temporal	2.65	0.021
Central	1.92	0.078
Parietal	1.56	0.144
Occipital	2.12	0.048

B. Alpha

The mean alpha power across all brain regions shows a general increase after methadone administration as shown in Fig. 3. This effect is particularly pronounced in the central (Pre: 1.59 ± 1.28, Post 1h: 2.58 ± 2.78) and parietal (Pre: 1.61 ± 1.52, Post 1h: 2.76 ± 2.92) with the percentage increase were 61.9% and 71.6% respectively. The frontal (Pre: 1.52 ± 1.13, Post 1h: 1.83 ± 1.63), temporal (Pre: 1.14 ± 1.01, Post 1h: 1.57 ± 1.63), and occipital (Pre: 1.22 ± 1.17, Post 1h: 1.71 ± 1.94) region also exhibits a notable increase in alpha power with the percentage of increase were 20.38 %, 37.96%, and 39.71% respectively. This result is consistent with the study [17] [18] that methadone administration increases the alpha power.

Similar to the theta power, the sample size was justified using a post-hoc power analysis, utilizing G*Power application with the observed effect sizes (Cohen's d) from this study. Effect size is around 0.6 across different brain regions. Using a paired t-test with N = 14 and α = 0.05, the statistical power for detecting these effects was calculated to be around 0.8 across all regions, except for frontal, which is 0.92, as in Table 3, which indicates an adequate power. These results confirm that the sample size was sufficient for detecting significant changes in brain activity following methadone administration.

The results of the paired t-tests shows in Table 4 indicate that the parietal region showed a significant increase in alpha power ($p=0.050$), indicating that methadone administration may have a measurable impact on neural activity in this area. The central region exhibited a marginally significant increase in alpha power ($p=0.059$), suggesting a potential effect that approaches statistical significance. While the frontal, temporal, and occipital regions did not show significant changes before and after administration ($p>0.05$).

C. Beta

The data indicates an overall reduction in beta power across all brain regions after one hour of methadone administration as shown in Fig. 4. The mean and percentage of beta power decreased for each brain region is pronounced in all brain region: frontal (Pre: 1.10 ± 1.51, Post 1h: 0.49 ± 0.27), temporal (Pre: 1.00 ± 1.65, Post 1h: 0.37 ± 0.21), central (Pre: 1.13 ± 1.50, Post 1h: 0.57 ± 0.35), parietal (Pre: 1.08 ± 1.54, Post 1h: 0.54 ± 0.29), and occipital (Pre: 0.97 ± 1.55, Post 1h: 0.35 ± 0.17) with the reduction rate were 55.9%, 63.5%, 49.4%, 49.6%, and 64.3% respectively. This result is aligned with [19] [20] that acute methadone administration decrease the beta power.

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Table 4. The effect size and post hoc power of sample size for alpha band

Brain Region	Differences (post-pre)	Stdev of differences	Effect size	Post hoc power
Frontal	0.788	1.19	0.66	0.92
Temporal	0.65	1.09	0.59	0.82
Central	0.99	1.78	0.55	0.75
Parietal	1.15	1.99	0.58	0.81
Occipital	0.74	1.26	0.59	0.82

Similar to the previous frequency band, the sample size was justified using a post-hoc power analysis, utilizing G*Power application with the observed effect sizes (Cohen's d) from this study. Effect size is around 0.6 across different brain regions. Using a paired t-test with N = 14 and α = 0.05, the statistical power for detecting these effects was calculated to be around 0.8 across all regions, as in Table 5, which indicates an enough power. These results confirm that the sample size was sufficient for detecting significant changes in brain activity following methadone administration. However, the change of beta power before and after methadone administration was not statistically significant in all brain region.

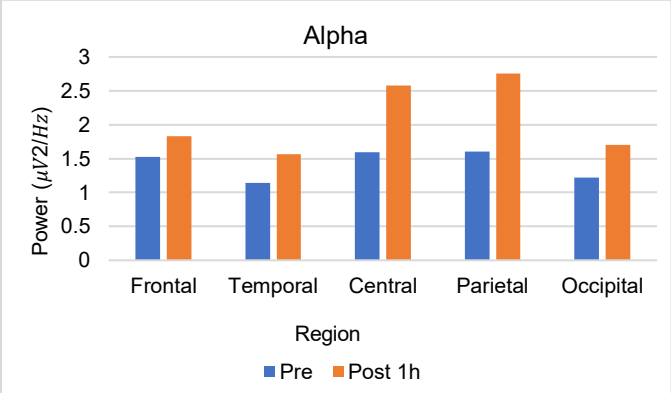

Fig. 3. Mean of alpha power per region for pre and post methadone administration

Table 3. Statistical measurement t-test result of mean alpha power per region

Brain Region	t-value	p-value
Frontal	-0.969	0.350
Temporal	-1.477	0.164
Central	-2.072	0.059
Parietal	-2.162	0.050
Occipital	-1.446	0.172

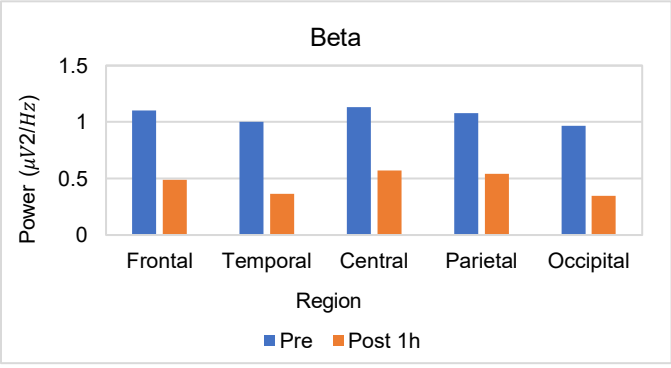

Fig. 4. Mean of beta power per region for pre and post methadone administration

D. FAA

The analysis of frontal alpha asymmetry (FAA) is conducted for the F3-F4 and F7-F8 regions as shown in Fig. 5, reveals notable changes after one hour of methadone administration. In the F3-F4 region, the mean asymmetry value increased from -0.2987 (pre-administration) to -0.5218 (post-administration), indicating a 74.70% increase.

Like the other signals, the sample size was justified using a post-hoc power analysis, utilizing G*Power application with the observed effect sizes (Cohen's d) from this study. Effect size is close to 0.6 for the F4-F3 and F7-F8. Using a paired t-test with N = 14 and α = 0.05, the statistical power for detecting these effects was calculated to be marginally close to 0.8 across all regions, as in Table 6, which indicates an acceptable power. These results confirm that the sample size was sufficient for detecting significant changes in brain activity following methadone administration.

However, statistical analysis using the paired t-test resulted in a t-statistic of 0.5065 and a p-value of 0.6210, suggesting that this increase is not statistically significant.

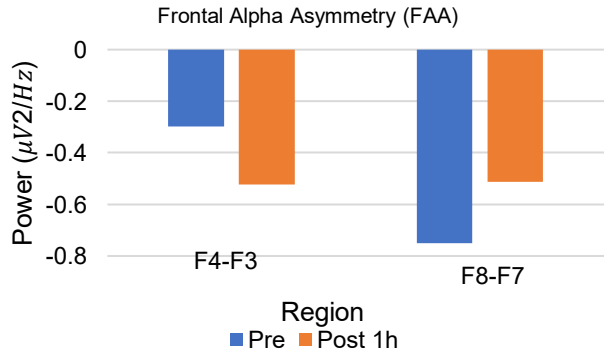

Fig. 5. Comparison of frontal alpha asymmetry (FAA) for pre and post methadone administration

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Similarly, in the F7-F8 region, the mean asymmetry value decreased from -0.7505 to -0.5125, reflecting a 31.71%

4. DISCUSSION

A. Theta

Methadone administration leads to a global decrease in theta power, with the most significant reductions observed in the frontal, temporal, and occipital lobes. These changes are associated with cognitive control, emotional regulation, and drowsiness, consistent with previous studies [21]. The reduction in frontal theta power suggests alterations in executive functions and inhibitory control, potentially suppressing craving-related neural activity [22]. Changes in temporal theta power may reflect modifications in memory and emotional processing, contributing to the stabilization of brain function in opioid-dependent individuals [23]. The occipital theta power reduction likely reflects sedative effects, reduced attentional engagement, and diminished craving-related mental imagery, supporting methadone's role in modulating both cognitive and sensory processes in opioid-dependent individuals [24] [25]. Further, decreases in central and parietal theta power suggest alterations in sensorimotor integration and attentional regulation, consistent with reports of cognitive slowing and reduced reward sensitivity in methadone-treated patients [26].

B. Alpha

Following methadone administration, alpha power increased overall, particularly in the central and parietal lobes. The observed increase in alpha power may serve as a biomarker for opioid-induced sedation and cognitive slowing, which could be valuable for monitoring treatment effects and optimizing methadone dosages [26]. The increase in central and parietal alpha power may indicate suppressed sensorimotor processing and attentional disengagement, effects commonly reported following opioid administration [27]. Additionally, occipital alpha power increased, which is often linked to reduced visual processing and drowsiness [21]. This finding is consistent with methadone's sedative effects, leading to diminished sensory awareness and attentional focus [28]. The frontal and temporal lobes exhibited notable increases in alpha power, reflecting reduced cognitive engagement and heightened sedation effects, consistent with methadone's role as a central nervous system depressant [21].

C. Beta

Methadone administration reduces beta power across all cortical regions, indicating a global sedative effect and diminished cognitive processing. This supports beta oscillations as biomarkers for opioid-induced cognitive suppression, useful for monitoring treatment responses and optimizing dosage [21]. These findings align with previous studies showing that opioids suppress beta activity linked to cognitive engagement and arousal [29] [30]. This decline was particularly notable in the frontal and temporal lobes, suggesting diminished executive function, attention, and emotional regulation, which is consistent with prior research suggesting that opioids reduce neural activity in these regions, leading to impaired decision-making and inhibitory control [22]. Beta power reductions in the central and parietal regions point to impaired sensorimotor integration and attentional focus, which isalign with findings that opioid-induced sedation disrupts sensorimotor processing, which may contribute to the slowed reaction times and motor impairments often reported in opioid-treated individuals [26]. While, decreases in the occipital lobe indicate weakened visual processing and environmental awareness awareness associated with methadone usev [21]. This supports previous evidence that opioids modulate occipital activity, leading to altered visual perception and attentional disengagement [27].

D. FAA

The analysis of frontal alpha asymmetry (FAA) in F3-F4 and F7-F8 regions before and after methadone

Table 5. The effect size and post hoc power of sample size for beta band

Brain Region	Differences (post-pre)	Stdev of differences	Effect size	Post hoc power
Frontal	-0.94	1.59	-0.59	0.82
Temporal	-0.97	1.65	-0.59	0.82
Central	-0.88	1.60	-0.55	0.75
Parietal	-1.03	1.63	-0.63	0.89
Occipital	-0.93	1.56	-0.60	0.84

Table 6. The effect size and post hoc power of sample size for frontal alpha asymmetry (FAA)

Brain Region	Differences (post-pre)	Stdev of differences	Effect size	Post hoc power
F4-F3	-0.91	1.65	-0.55	0.75
F8-F7	-2.20	3.93	-0.56	0.77

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administration provides insight into the drug's effects on emotional regulation, approach-avoidance behavior, and cognitive processing. Alpha asymmetry in F3-F4 is commonly associated with emotional regulation and motivation, where greater left frontal activity (negative FAA values) is linked to withdrawal-related emotions, while greater right frontal activity (positive FAA values) is associated with approach motivation and positive affect [31]. The observed post-methadone reduction suggests a potential increase in withdrawal-related emotions, such as sedation or decreased motivation, aligning with findings that opioids can blunt emotional responses and reduce reward sensitivity [29].

The F7-F8 region is involved in social-emotional processing and response inhibition, where lateral frontal alpha asymmetry has been linked to impulsivity and emotional reactivity [32]. The result of FAA in F3-F4 and F7-F8 are not statistically significant due to high variability across individuals and it suggests that methadone's effect on FAA is not uniform and may depend on individual neurobiological differences, opioid use history, or psychological state. These findings align with prior research showing that methadone can modulate emotional and cognitive processing, but its impact on frontal asymmetry remains complex and subject-dependent [33].

While the findings provide insights into the acute neurophysiological effects of methadone, certain limitations should be acknowledged. One key limitation of this study is the relatively small sample size (N=14), which may affect the generalizability of the results to a broader population of opioid-dependent individuals undergoing methadone maintenance therapy. The observed EEG changes, including reductions in theta and beta power, increases in alpha power, and the change in FAA may vary across individuals due to factors such as opioid use history, genetic predisposition, and psychological state.

Additionally, this study focused on acute effects measured one hour post-administration. While this timeframe captures short-term neural alterations, it does not account for long-term neurophysiological adaptations to methadone.

Despite these limitations, this study contributes to the understanding of methadone's acute neurophysiological impact and its important implications for opioid rehabilitation programs. The observed EEG changes suggest that neural oscillatory activity could serve as an objective biomarker to assess methadone's effects on cognitive and emotional processes. Clinically, this could support the development of personalized treatment strategies, where EEG monitoring helps adjust methadone dosage to optimize therapeutic benefits while minimizing cognitive impairment.

Future research should explore the long-term neurophysiological effects of methadone, investigating how treatment duration, opioid use history, and individual differences influence neural adaptation over time. Additionally, integrating EEG-based assessments into rehabilitation protocols may improve patient monitoring, offering a neurophysiological perspective to enhance treatment efficacy and relapse prevention strategies.

5. CONCLUSION

This study investigated the effects of methadone administration on cortical oscillatory activity, focusing on theta, alpha, and beta power, as well as frontal alpha asymmetry (FAA). Methadone administration led to a global reduction in theta power, particularly in the frontal, temporal, and occipital lobes, with the reduction rate were 34.4%, 35.4%, 27.5% respectively, which may reflect altered executive function, emotional regulation, and sedation effects. Conversely, alpha power increased, particularly in the central, parietal, and occipital lobes, with the percentage increase were 61.9%, 71.6%, and 39.71% respectively suggesting reduced sensory awareness, attentional disengagement, and sedation effects. Additionally, beta power decreased across all brain regions with the reduction rate of 55.9%, 63.5%, 49.4%, 49.6%, and 64.3% respectively for frontal, temporal, central, parietal, occipital. This reduction indicates reduced cortical excitability, impaired executive function, and diminished cognitive alertness. For FAA analysis, F3-F4 increased 74.70%, while F8-F7 decreased 31.71%. Analysis of FAA revealed high inter-individual variability, suggesting that methadone's impact on emotional processing and approach-avoidance behavior is not uniform and may depend on individual neurobiological differences, opioid use history, or psychological state. While some individuals exhibited increased FAA, indicative of approach-related tendencies, others showed reductions associated with withdrawal-related emotional states. Overall, the observed electrophysiological changes reinforce methadone's sedative and cognitive effects, aligning with prior research on opioid-induced neurophysiological alterations. Future research with larger sample sizes and longitudinal designs is needed to validate these findings and explore the sustained effects of methadone on neural oscillations. Furthermore, incorporating additional demographic, clinical variables (e.g., age, treatment duration, opioid use history, and methadone dosage), and psychological variables may help clarify inter-individual difference responses.

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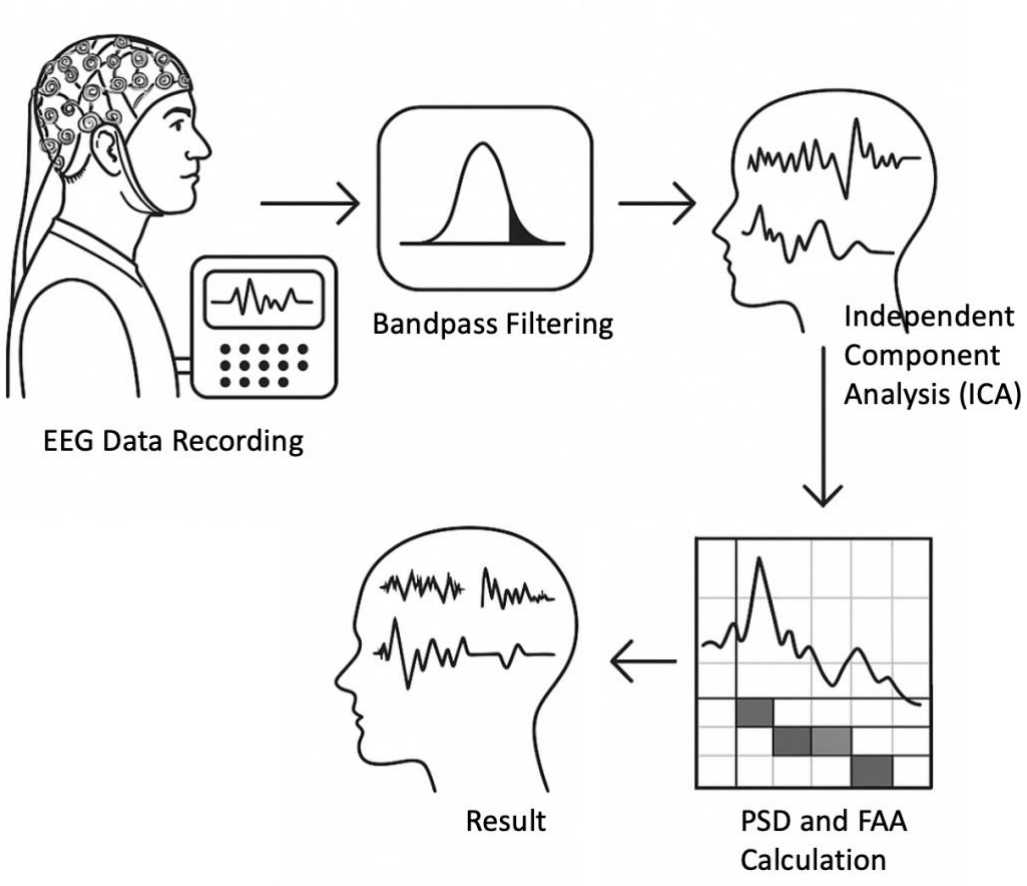

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