Cortical Complexity Alterations in Methamphetamine, Cannabis, and Opioid Users: An EEG-Based Analysis

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ABSTRACT

Background: Drug abuse causes substantial psychological and physical harm to individuals, highlighting the critical need for advanced diagnostic and treatment methodologies.

Objective: This study aimed to develop a highly accurate automatic detection system for substance abuse, specifically targeting Methamphetamine (Meth), Cannabis (Can), and Opioid (Op) users.

Material and Methods: This descriptive study developed a drug abuse detection system based on nonlinear Electroencephalogram (EEG) signal analysis combined with a Support Vector Machine (SVM) classifier. It also examined changes in EEG signal complexity associated with Meth, Can, and Op abuse by extracting determinism and complexity parameters using Recurrence Quantification Analysis (RQA).

Results: The observed decrease in EEG complexity in the Op and Meth groups suggests that these substances may reduce cognitive or behavioral complexity. Conversely, increased complexity in the Can group compared to the Healthy Control (HC) group may indicate enhanced complexity associated with cannabis use. The classification system achieved 88.77% accuracy, 87.69% sensitivity, and 96.30% specificity.

Conclusion: The designed automatic diagnostic assistance system, leveraging nonlinear brain data analysis, effectively differentiates Meth, Op, and Can users from HC individuals.

Keywords

Electroencephalogram; Cannabis; Opioid-Related Disorders; Methamphetamines; Nonlinear Dynamics

Introduction

According to the United Nations Office on Drugs and Crime, drug use contributed to the deaths of 585,000 individuals in 2017 alone [1]. Substance abuse remains a critical global health issue, profoundly affecting individuals, families, and communities. The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) classifies substances into ten primary drug categories, with methamphetamines (Meth), cannabis (Can), and opioids (Op) standing out due to their high abuse prevalence and their impact on health [2]. In particular, Iran has experienced a notable rise in substance use, high-

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lighting the critical need for effective detection and intervention strategies to address this escalating public health challenge [1].

Drug abuse heavily influences the brain's reward circuitry, leading to the reinforcement of certain behaviors while undermining the motivation to engage in regular, essential activities [2]. Prolonged substance abuse inflicts extensive damage on brain structures [3-7] and disrupts functional processes, including cognitive, emotional, and behavioral regulation [8-17]. Thus, understanding and quantifying the functional brain alterations associated with substance abuse is crucial for developing objective and reliable diagnostic systems.

Traditional substance abuse detection methods, such as testing urine, blood, saliva, or hair, are widely used with some limitations, including the potential for manipulation and a lack of direct insight into neurological impact. On the other hand, a brain-based detection system could offer a direct and objective assessment of substance-related neural changes, presenting a robust alternative to traditional tests. With the growing availability of neuroimaging and electrophysiological technologies, there is an opportunity to harness these tools to create an advanced diagnostic approach that reflects real-time brain function.

Previous studies have explored various neurophysiological markers for substance dependence detection by examining functional brain connectivity [9,14-19], brain responses to external stimuli [10,11,20-24], and biomarker identification [25-31] using Electroencephalogram (EEG) signals. EEG, a non-invasive and cost-effective method with high temporal resolution, captures rapid neural activity, making it well-suited for real-time applications in clinical settings [17]. Given its advantages, EEG-based approaches have been instrumental in evaluating brain connectivity and identifying potential biomarkers associated with substance dependence. After reviewing the advantages and limitations of these approaches, biomarker identification emerged as the most promising method for reliable and quantifiable EEG-based assessments [30].

EEG signal analysis considers multiple hypotheses about the signal's underlying nature. In this study, we hypothesized that EEG signals exhibit chaotic properties, aligning with the concept that brain activity, particularly under the influence of substances, demonstrates complex, nonlinear dynamics. To analyze this complexity, Recurrence Quantification Analysis (RQA) was employed, leading to the detailed examination of phase-space properties in dynamic systems. RQA provides valuable metrics for capturing the complexity of EEG signals, resulting in the chaotic patterns linked to substance dependence [32]. This approach offers unique insights into the nonlinear dynamics of brain function, facilitating an in-depth understanding of how substance abuse may alter neural complexity.

We previously developed a substance abuse detection system that effectively distinguished between users of multiple drugs and a Healthy Control (HC) group [30]. Based on the positive results, this system was further enhanced to improve accuracy and specificity in identifying Meth, Op, and Can users.The primary aim of the current study is to enhance this diagnostic system, offering an advanced and EEG-based tool for substance abuse detection. Despite a descriptive phase, the findings provide a foundation for distinguishing substance addiction from other conditions and complement traditional chemical testing methods. Ultimately, this research represents a step toward developing a practical and objective diagnostic tool that addresses a critical public health need.

Material and Methods

In descriptive research, the drug abuse detection system can be structured through the following steps:

• Signal Acquisition: EEG signals are collected from participants, including Meth, Can, Opnusers, and HCs, all of whom meet specific

inclusion criteria [31-33].

• Preprocessing: The recorded EEG signals undergo filtering and preprocessing to remove noise and artifacts, ensuring high-quality data for analysis [31-33].

• Feature Extraction: RQA is applied to the preprocessed EEG signals. Key features, including Determinism (DET) and Complexity (CPX) indexes, are extracted to quantify signal complexity and capture nonlinear dynamics.

• Classification: An SVM classifier is utilized to develop a model identifying substance dependence. A 4-fold cross-validation scheme assesses the model's classification accuracy, sensitivity, and specificity.

RQA Analysis

Weber introduced the Recurrence Quantification Analysis (RQA) method [34], which is specifically designed for analyzing non-stationary and nonlinear signals. This makes it particularly effective for capturing the complex, chaotic dynamics often observed in EEG signals [35]. RQA quantifies phase-space features within a dynamical system by analyzing recurrence patterns and their durations. To reconstruct the phase space, the time series is projected into higher dimensions, based on time delay (τ) and embedding dimension (m) parameters [30].

A Recurrence Plot (RP) was used to visualize time series recurrence patterns, providing insights into the time-dependent behavior of the phase space trajectory [36]. Various features of RPs quantify signal characteristics, with the Determinism (DET) feature specifically applied here to assess complexity. DET represents the percentage of recurrence points aligned along diagonal lines within the RP, indicating deterministic structures in dynamic systems.

$$DET = \frac{Sum\ of\ diagonal\ line\ lengths\ above\ threshold}{Total\ number\ of\ recurrence\ points} \quad (1)$$

Here, the threshold eliminates diagonal lines caused by tangential phase-space movements.

Complexity (CPX) is then defined as an inverse function of DET to accentuate DET variations [37]:

$$CPX=-20\log(DET) \quad (2)$$

According to [32], periodic signals yield higher DET and lower CPX values, while random signals show the opposite trend. Biosignals, such as EEG, typically are between these extremes, with moderate CPX values reflecting a balance between deterministic and random components.

Classifier Model

Several algorithms, including K-Nearest Neighbors (KNN), Neural Networks (NN), Naive Bayes (NB), decision trees, and Support Vector Machines (SVM), address multi-class classification challenges. SVM's advantages over methods like KNN, NB, and decision trees include its use of kernel functions and its robust capacity to model nonlinear patterns. Although Neural Networks (NNs) also model nonlinear behaviors, they can be challenging to parameterize and are sensitive to initial conditions [38,39]. SVM, a well-established supervised classification technique, is widely used in biomedical applications, which effectively balances accuracy and overfitting avoidance. SVM achieves optimal class separation by constructing a hyperplane that maximally distinguishes groups while maintaining high generalization ability [38,40].

Evaluation Criteria

The effectiveness of the proposed method was evaluated using accuracy, sensitivity, and specificity metrics [30].

Statistical analysis

The normality of CPX distribution was assessed with the Kolmogorov-Smirnov test, while t-tests determined significant differences between substance abuse groups (Meth, Can, and Op) and the HC group, with a significance level set at 0.05.

Results

The study's findings are presented in two sections: (1) the evaluation of EEG signal complexity and (2) the classification performance of the automatic drug abuse detection system.

Complexity evaluation

To assess the complexity of EEG signals, each channel's data was segmented into one-second windows with a 50% overlap, followed by the calculation of the CPX index. This segmentation enabled a more detailed and temporally specific analysis of signal complexity, capturing variations across both time and brain regions. Figure 1 displays the mean CPX index values across different EEG channels, providing insights into the complexity patterns associated with each substance group.

Figure 2 displays the t-values for the comparisons between Meth vs. HC, Can vs. HC, and Op vs. HC, illustrating the statistical significance of CPX variations across different EEG channels. The Figure 2 highlights specific channels, where complexity differences are pronounced, thereby indicating regions of the brain potentially impacted by each substance.

The CPX values for the Meth, Op, Can, and HC groups showed a normal distribution according to the Kolmogorov-Smirnov test. A t-test compared CPX indices between each substance abuse group (Meth, Op, and Can) and the HC group, revealing statistically significant differences at an alpha level of 0.05.

Figure 3 shows topographic maps of the

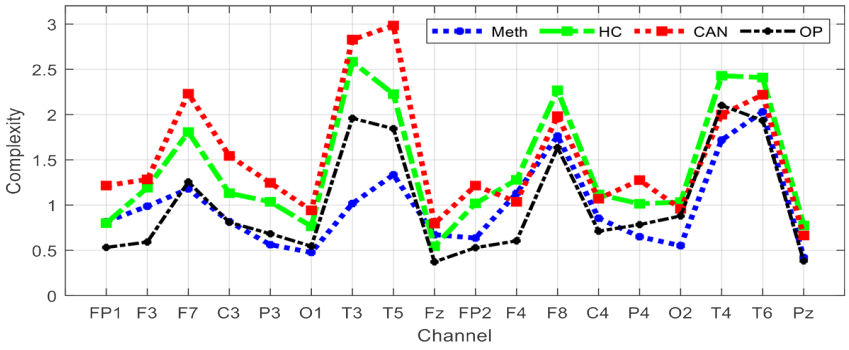

Figure 1: Mean complexity index values across EEG channels

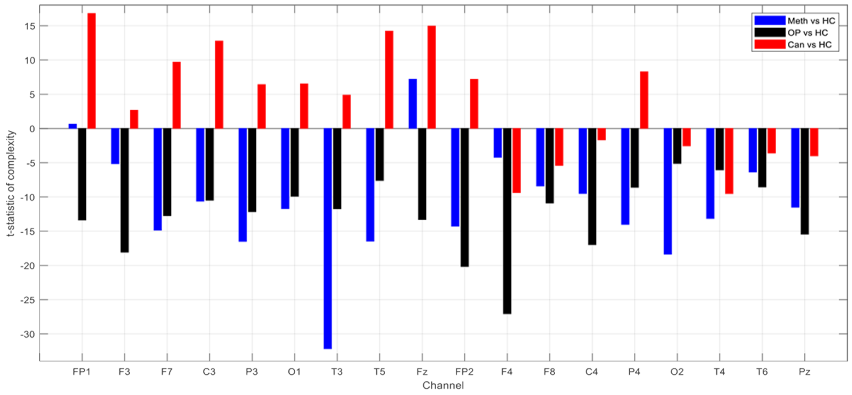

Figure 2: The t-values of the complexity index in all channels. Changes in complexity index in the Methamphetamines (Meth) vs. Healthy Control (HC) in the FP1; and Cannabis (Can) vs. HC in the C4 were not significant.

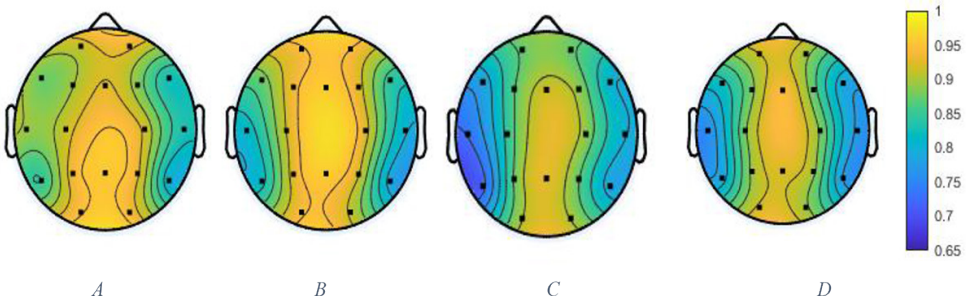

Figure 3: The topographic maps of the determinism parameters in the **A**: Meth, **B**: Opioids(Op), **C**: Can and **D**: HC groups.

DET index across groups, representing complexity patterns within each brain region.

According to Figures 1, 2, and 3, the Meth group exhibited a reduction in CPX and an increase in DET in nearly all brain channels except Fz and Pz, indicating decreased complexity compared to the HC group. Specifically, t-statistic changes in the parietal, left temporal, and occipital lobes were significant. Additionally, increasing DET in the Meth and Op groups suggest decreased complexity in the left temporal, parietal, and occipital regions.

CPX values were lower across all brain areas in the Meth and Op groups compared to the HC group, while the Can group showed an increase in complexity (Figures 2 and 3). Significant CPX changes were observed in the Can group's left hemisphere, anterior frontal, and parietal regions compared to HC. The topographic maps support the pattern of reduced complexity in the Meth and Op groups and increased complexity in the Can group.

Classification evalution

The SVM classifier was trained with CPX and DET indices from each EEG segment across all channels and subjects. A 4-fold cross-validation approach was used to generalize findings, addressing inter-subject variation. The data was classified into four subgroups in each fold, with the model trained on three subsets and tested on the remaining one. This process was repeated four times, with each subset as the evaluation set once. Table 1 presents the mean classification performance metrics.

Table 2 compares the performance of the current method with previous studies on drug abuse detection. The proposed system demonstrates an enhanced ability to identify and distinguish between different substance groups and HC, showing either superior or comparable accuracy to earlier methods. This improvement underscores the robustness of the current approach in reliably detecting substance-specific EEG signal patterns and advancing the field of automated substance abuse detection.

Discussion

The recent descriptive study introduces an innovative EEG-based model for substance abuse detection. It employs RQA to capture nonlinear dynamic patterns in EEG signals and utilizes an SVM classifier for group differentiation. The model analyzes brain dynamics using fundamental phase-space properties, DET, and CPX. DET indirectly reflects the regularity of EEG signals, while CPX provides a direct measure of signal complexity, offering an objective view into neural activity alterations associated with substance use.

Findings from this study revealed a significant reduction in brain complexity across all regions in Meth users. Supporting this, Jaeseung et al. [8] observed decreased brain complexity in Meth users, evidenced through

Table 1: Classification performance metrics for binary and multi-group classification.

Groups	Accuracy (%)	Sensivity (%)	Specificity (%)
Opioids & Healthy Control	91.71	91.17	92.23
Cannabis & Healthy Control	89.07	86.92	91.17
Methamphetamines & Healthy Control	94.88	95.23	94.45
Methamphetamines & Cannabis & Opioids & Healthy Control	88.77	87.69	96.30

Despite minor classification differences among the drug abuse groups and HC, all binary and multi-group classification accuracy levels were above random chance.

Table 2: Comparison with previous studies on drug abuse detection.

Research	Group	Number of groups	Accuracy (%)
[17]	Methamphetamine & Healthy Control	2	93
[14]	Opioids & Methadone	2	86
[15]	Opioids & Healthy Control	2	90
[26]	Mild & moderate & severe drug addicts	3	63.15
[19]	Methamphetamine & Healthy Control	2	82.8
[28]	Opioids & Healthy control	2	97
[30]	Multidrug & Healthy Control	2	90
Current Study	Opioids & Healthy Control	2	91.71
	Cannabis & Healthy Control	2	89.07
	Methamphetamine & Healthy Control	2	94.88
	Methamphetamine & Cannabis & Opioids & Healthy control	4	88.87

Approximate Entropy (ApEn) in resting-state EEG data. The t-statistic highlighted substantial changes in the left temporal, parietal, and occipital lobes, critical for auditory and visual processing. Additionally, Chen et al. [27] reported disruptions in phonological processing and visual networks in Meth users using microstate analysis. Investigations by Khajehpour et al. using graph theory further corroborated the impaired functional connectivity in Meth users, notably in delta and gamma frequency bands [16,17,19]. These alterations in connectivity may be a driving factor behind the reduced brain complexity observed in Meth abusers.

In the Op user group, reduced CPX parameters across all lobes suggest a decline in overall brain complexity. This aligns with the known impact of opioids on neural function. However, TT et al. [28] found increased brain complexity in heroin users using entropy measures, suggesting variability in opioid effects on brain dynamics. Capecci and Doborjeh [14,15] explored neural connectivity in opiate addicts undergoing methadone treatment, revealing reduced connectivity in high-dose users compared to low-dose users and broader functional pathways in HC [14,15]. This decline in connectivity could underlie the reduction in brain complexity noted in OP users in this study.

Can users exhibited increased complexity, particularly in the left hemisphere and channels FP2 and P4. Vincent Laprevote's study

using the Lempel-Ziv index found heightened brain complexity in regular Can users [29]. This increase in complexity may stem from heightened connectivity within the salience and central executive networks, as noted by Imperatori et al. [18] particularly involving the dorsal anterior cingulate cortex and right posterior parietal cortex.

Topographic DET maps revealed complexity reductions primarily in the right hemisphere across all substance groups, suggesting that this region's involvement in substance use affects neural dynamics. Given the right hemisphere's role in imagination and emotional processing, its reduced complexity may be linked to users' altered emotional and perceptual experiences. CPX results indicated a shift from chaotic to periodic neural activity in Meth and Op users. In contrast, Can users displayed a trend towards random neural activity, suggesting distinct EEG signal behaviors across substance types [33].

Finally, a two-class model was created alongside the primary four-class model to facilitate comparison with prior studies. In detecting Meth abuse, the model achieved a notable accuracy of 94.2%, surpassing that of previously developed models [17,19]. For OP detection, this study's model demonstrated an accuracy of 91.3%, performing comparably to work earlier [15]. Ultimately, the multi-class model effectively distinguished among Meth, Can, OP, and HC groups, providing an accurate and robust EEG-based diagnostic alternative for substance abuse detection.

The study has limitations, notably the participant sample size. Although a power analysis determined a sample size of 17 per group, recruitment and data collection challenges during COVID-19 may have impacted generalizability. Despite these constraints, the study's findings remain promising.

Developing an accurate, substance-specific diagnostic system has important clinical implications, as it can guide targeted treatment approaches. Unlike traditional tests, urine, blood, saliva, and hair samples, this system may offer a tamper-resistant, objective substance detection method. Furthermore, tracking brain complexity changes across regions during substance use could provide a means of quantifying drug-induced brain damage.

Conclusion

The primary aim of this study was to develop an EEG-based diagnostic method for detecting drug abuse. Assuming the chaotic nature of EEG signals, we utilized the RQA approach to analyze data from Meth, Can, and Op abusers, along with HC. The extracted DET and CPX indices effectively highlighted distinctions between these substance-abusing groups and the HC group. The classification model showed high accuracy in differentiating drug abusers from the HC group and achieved performance above chance in recognizing the four distinct groups of Meth, Can, Op abusers, and HC. These findings suggest that the proposed method can serve as an objective and reliable test for identifying both substance abuse and the specific type of substance used with promising accuracy.

Authors' Contribution

N. Marvi, J. Haddadnia, MR. Fayyazi Bordbar, and, F Davarinia: Conceptualization; N. Marvi, and J. Haddadnia: Methodology; N. Marvi and, F Davarinia: Data collection; MR. Fayyazi Bordbar: Supervision of data collection; N. Marvi: Formal analysis; N. Marvi: Software; N. Marvi and, F Davarinia: Writing - Original Draft; N. Marvi, and, F Davarinia: Validation; N. Marvi, J. Haddadnia, and, MR. Fayyazi Bordbar: Review & Editing; All the authors read, modified, and approved the final version of the manuscript.

Ethical Approval

The Behavioral and Psychiatric Sciences Research Center ethics committee of Mashhad University approved this research (Ethic cod: IR.MUMS.MEDICAL.REC.1400.027).

Informed Consent

All the participants have written informed consent in the project.

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Conflict of Interest

None

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