This study aims to introduce a new approach of a comprehensive paradigm to evaluate brain electrophysiological properties among addicts. Electroencephalographic spectral power as well as amplitudes and latencies of mismatch negativity (MMN), P300, and P600 components were evaluated among 19 male heroin addicts and 19 healthy nonsmoker subjects using a paradigm consisting of three subparadigms, namely (1) digit span Wechsler test, (2) auditory oddball, and (3) visual cue-reactivity oddball paradigms. Task 1 provided auditory P300 and P600 in association with working memory. Task 2 provided auditory P300 as well as small and large deviant MMN event-related potential (ERPs). Finally, task 3 provided visual cue-reactivity P300. Results show that beta power was higher among heroin addicts while delta, theta, and alpha powers were decreased compared with healthy subjects. ERP analysis confirmed the decline of brain-evoked potential amplitudes when compared with healthy subjects, thus indicating a broad neurobiological vulnerability of preattentive and attentional processing including attentional deficits and compromise of discrimination abilities. The prolonged latency of ERPs reflects poor cognitive capacity in the engagement of attention and memory resources. On the other hand, an increase of attention towards the heroin-related stimuli could be concluded from the increase of P300 in the cue-reactivity condition among heroin addicts. Findings suggest that applying this paradigm in addiction studies benefits comprehensive evaluation of neuroelectrophysiological activity among addicts, which can promote a better understanding of drugs’ effects on the brain as well as define new neuroelectrophysiological characteristics of addiction properties.
addition to EEG spectral analysis to examine the effects of heroin on brain functionality (Davydov and Polunina, 2004; Franken et al., 2004; Polunina and Davydov, 2004, 2006; Fingelkurts et al., 2006a, 2006b, 2007a, 2007b, 2008, 2009), brain event-related potential (ERP) components were evaluated as a reliable approach to study cognitive abilities related to information processing, selective attention, and memory updating of addicts (Motlagh et al., 2016). Among various ERP components, measuring the amplitude and latency of mismatch negativity (MMN), P300, and P600 components in standard condition has attracted special attention in ERP evaluation among addicts. These ERPs are associated with brain discrimination abilities, orientation of attention, response resolution, and executive working memory. Additionally, examining cognitive responses to drug-related stimuli showed promising results in providing better understanding of brain functional alterations during withdrawal and abstinence periods associated with addiction traits such as craving and anhedonia (Franken et al., 2003; Lubman et al., 2007, 2008, 2009; Jiang et al., 2011). For this purpose, various types of ERP paradigms have been designed to probe subjects’ evoked cognitive responses using deviant, affective, and drug-related stimuli (Motlagh et al., 2016).

MMN is attributed to preattentive processing for change detection associated with conscious discrimination ability (Kraus et al., 1995). It has been evaluated among heroin addicts to measure their deficiency in orienting their attention (Kivisaari et al., 2007; Yang et al., 2009; Morie et al., 2014). P300 is associated with selective attention, memory renewal, motivation, stimulus significance, activation of inhibitory processes (Tomberg and Desmedt, 1998), and attentional operations (Donchin, 1981; Donchin and Coles, 1988; Polich, 1998; McEvoy et al., 2001) and has been investigated among opioid dependents (Bauer, 2001; Marques-Teixeira and Barbosa, 2005; Lubman et al., 2007, 2009; Singh et al., 2009). P600 reflects attributes of second-pass parsing processes of information processing in association with working memory systems (Guillem et al., 1999; Frisch et al., 2003) and has been suggested to serve as a valuable investigative tool for a more comprehensive understanding of the neurobiological substrate of drug abuse and central executive working memory (Papageorgiou et al., 2001).

It is imperative to note that investigation of cognitive traits associated with striking features of addiction in a single study can help advance the understanding of neurological features of addiction. However, lack of a comprehensive evaluation of electrophysiological variables as a sensitive measure of impaired cognitive control in a single experiment is a major deficiency in the field (Buzzell et al., 2014; Motlagh et al., 2016). Investigating quantitative EEG (qEEG), MMN, P300, and P600 properties can lead to a better understanding of brain neurobiological feature alteration among heroin addicts and offer more insight for a reliable analysis of brain behavior relations related to preattentive processing, attentional deficit, and response inhibition related to the development and maintenance of addictive behaviors. This study aims to introduce a new approach consisting of a comprehensive paradigm to evaluate EEG power spectral density (PSD) and properties of MMN, P300, and P600 components simultaneously. In addition, for the first time in the field of addiction, a state-of-the-art signal-processing algorithm was applied for single-trial evaluation of ERP properties.

**MATERIALS AND METHODS**

**Subjects**

In this study, EEG power spectrum as well as ERP (MMN, P300, and P600) amplitude and latency of 26 heroin-dependent subjects were compared with those of 19 healthy subjects using this paradigm. Twenty-six male heroin-dependent subjects (age: mean = 39.3, standard deviation [SD] = 7.7; period of addiction: mean = 17.7, SD = 7.1) were recruited from the waiting list in the Substance Clinic at the University of Malaya Medical Center (UMMC). This study took place at the clinical engineering laboratory in the Department of Biomedical Engineering, University of Malaya. The inclusion criteria for this study were at least 1 year of documented heroin addiction and fulfillment of Diagnostic and Statistical Manual of Mental Disorders (DSM IV) criteria for heroin dependency, syndrome diagnosis, a minimum age of 18 years, and/or a minimum 6 years of drug abuse. In addition, 19 nonsmoking volunteers (age: mean = 34.3, SD = 7.5) were included as healthy control subjects and were recruited from the university’s portal e-mail broadcast. The exclusion criteria from this study were alcohol dependency, the presence of any acute psychiatric or neurological disorders (e.g. major head trauma), lifetime history of a major medical disorder, HIV infection, previous head injury resulting in loss of consciousness, seizures, history of methadone treatment, and record of polysubstance dependence. All subjects were informed that their last dose of heroin should be taken at least 6 hr prior to attending the assessment session. The study was approved by the ethics committee of UMCC (ethic number MEC 871.14), and written consent was obtained from each subject prior to enrollment.

**Trial Design**

Each subject underwent routine clinical assessments by trained psychiatrists in the substance clinic in UMMC. Alcohol breath screening test, baseline blood investigations for HIV, viral hepatitis B/C screening, and a rapid urine drug test for illicit drug use were carried out as objective measures to verify the absence of alcohol and other substance abuse prior to the EEG procedures in addition to verbal information collected from the subjects. The Fagerstrom test was used to assess the intensity of physical addiction to nicotine among addicts. The Fagerstrom test evaluates the quantity of cigarette consumption, the compulsion to use, and dependence. In addition, the Mini-International Neuropsychiatric Interview (MINI) for DSM-IV for controlling the psychiatric premorbid effects was performed for both groups (Sheehan et al., 1998).

After the introductory assessment in the substance clinic and signing the written consent form, clinic staff brought the subjects immediately to the EEG recording room. Once the instruments were calibrated and the electrodes were placed on
the scalp, the subjects were lulled into a relaxed situation in a
dimmned, electromagnetically shielded recording room. Subjects
were instructed to be relaxed and comfortable without any
movement. These criteria reduced artifact effects that might be
derived from muscle tension during the EEG recording. Sub-
jects underwent 30 min of EEG recording from 19 channels
during the performance of the paradigm.

**Paradigm**

Each session of EEG recording consisted of two main
parts; the first was 5 min of eye-closed EEG recording for eval-
uation of qEEG properties, and the second was the ERP
recording part. ERPs occur in response to any stimuli of exper-
imental paradigms, and they are acquired within particular para-
digms that directly probe central attentional processes.
However, designing an effective paradigm for clinical research
should provide acquisition of high-quality ERPs. In this study,
a modified version of standard paradigms was designed based on
the guidelines of eliciting ERPs in clinical research (Duncan
et al., 2009), to evaluate EEG spectrum, P300, MMN, and
P600 as major ERP components in addiction studies. Hence,
auditory and visual oddball paradigms, as the most frequent
paradigms employed for evaluating MMN and P300 compo-
nents, were modified based on standard interstimulus intervals
to eliminate the probability effect on ERP polarity. The oddball
paradigm demonstrates a random sequence of neutral audio/
visual stimuli and rare deviant stimuli. This type of paradigm
has been used to analyze the brain’s responses to drug-related
stimuli (known as the cue-reactivity condition), compared with
neutral and arousal stimuli, to extract brain electrical activity
properties associated with heroin addiction properties. More-
over, it is believed that oddball paradigms reveal information
regarding cognitive processing, especially on processing the
probability and discrimination of stimuli.
The designed ERP paradigm is based on a combination
of a modified version of a computerized auditory digit span
Wechsler test and two multisimulus “oddball” paradigms as
standard auditory and heroin-related visual stimuli. The multi-
simulus “oddball” paradigm is appropriate for processing and
Evaluating focus of attention, or novelty processing for investi-
gation of P300 and MMN when each deviant stimulus is
unique, and includes probable standard stimuli, improbable tar-
target stimuli, and equally improbable deviant stimuli.

**Auditory digit span Wechsler test.** A forward
digit span Wechsler test was used to evaluate the ERPs associat-
ed with working memory (Conklin et al., 2000; Wechsler,
2000; Marchand et al., 2006). Therefore, the first part of the
ERP paradigm was designed to probe the P300 and P600 com-
nponents to assess working memory based on a computerized
modified version of the digit span Wechsler test (Fig. 1). Sub-
jects were required to sit in an armchair in a comfortable posi-
tion and follow the instructions presented binaurally via
earphones at a sound pressure level of 65 dB; they were asked
to close their eyes during the test to minimize eye movements
and blinks. Subjects were asked to memorize a series of num-
bers in a certain order (two to nine digits, starting from two
digits and increasing after each successful performance) follow-
ing a warning tone, and then repeated in the same order after

the subjects had heard the warning tone for the second time.
First, a single resonance of high frequency (3,000 Hz) was pre-
sented to the subject with a duration of 100 msec as the warn-
ing stimulus. Since the P300 component related to the subject’s
attention at the presentation time correlates with working
memory performance (Lefebvre et al., 2005; Pratt et al., 2011;
Betti, 2015), an interval of total silence was given for 1 sec to
record this component. Then the numbers to be memorized
were recited through the earphones. The recital of the numbers
was not timed as the digits were read out at a normal pace. At
the end of the number sequence presentation, the same warning
stimulus was repeated for 100 msec, and the subjects were asked
to recall the given numbers as quickly as possible. The ERPs
related to recall phase were recorded from the onset of the sec-
ond warning tone. This procedure was continued until the first
mistake occurred, which was usually not more than nine
rounds. The number of correct answers was summed to calcu-
late the working memory score.

**MMN and P300 auditory oddball.** This para-
digm was designed for the evaluation of MMN and novelty
P300 using four classes of auditory stimuli. The MMN compo-
nent can be elicited by the presence of a mismatching stimulus
in a series of identical stimuli, which can be different in pitch,
duration, or intensity (Duncan et al., 2009). MMN is calculated
by subtraction of the N2 elicited by the standard stimulus from
those elicited by the deviant stimulus when both of these

Fig. 1. Process of modified version of digit-span Wechsler test includ-
ing the precise timing and process of ERP recording. [Color figure
can be viewed at wileyonlinelibrary.com]
successive target stimuli can affect the polarity of elicited P300, randomly as described in Figure 2. Since a low interval between standard pictures including neutral pictures of trees and color pictures of heroin use were presented. A total of 100 stimuli (standard pictures including neutral pictures of trees and color pictures of heroin use) were presented in a random order based on ERP-eliciting guidelines (Duncan et al., 2009) with the following characteristics:

- Standard stimuli 80% (800 Hz, 65 db, 50 msec + 10 msec for rise and fall)
- Small deviant stimuli 6.6% probability (700 Hz, 65 db, 50 msec + 10 msec for rise and fall)
- Large deviant stimuli 6.6% probability (400 Hz, 65 db, 50 msec + 10 msec for rise and fall)
- Novel sound stimuli 6.8% probability (3,000 Hz, 65 db, 50 msec + 10 msec for rise and fall)

**P300 visual oddball cue reactivity.** The three-stimulus "oddball" paradigm is appropriate for processing the focus of attention and novelty processing for investigation of P300 when each deviant stimulus is unique and includes probable standard stimuli, improbable target stimuli, and equally improbable deviant stimuli (Duncan et al., 2009). In this paradigm, three types of visual stimuli were presented as probable standard, improbable target, and equally improbable deviant stimuli. This paradigm was presented while the subject was looking at the computer screen; each subject was asked to press a key upon hearing a singular high-frequency tone. One thousand stimuli were binaurally delivered through earphones in a random order based on ERP-eliciting guidelines (Duncan et al., 2009) with the following characteristics:

- Standard stimuli 80% probability (neural pictures 500 msec for 500 msec in the middle of the screen, followed by 1,000 msec of a “crosshair” before the next image was presented. A total of 100 stimuli (standard pictures including neutral pictures from households, neutral pictures of trees and landscapes as deviant stimuli, and color pictures of heroin use and heroin paraphernalia as target stimuli) were presented randomly as described in Figure 2. Since a low interval between successive target stimuli can affect the polarity of elicited P300, 6 sec was set as the minimum successive target stimuli interval.

- Standard stimuli 80% probability (neural pictures 500 msec + 1,000 msec crosshair)
- Deviant stimuli 10% probability (nature pictures 500 msec + 1,000 msec crosshair)
- Target stimuli 10% probability (heroin-related pictures 500 msec + 1,000 msec crosshair)

**EEG Recording**

The Nicolet EEG diagnostics system (Care Fusion Corporation, San Diego, CA) was used to capture the EEG activities within a frequency band of 0.5 to 70 Hz (with a sampling rate of 256 Hz). Considering the technical limitations and reducing the complexity of the analysis, EEG signals were recorded from 19 electrodes (FP1/2, F7/8, Fz, F3/4, T3/4, T5/6, P3/4, Pz, O1/2) according to the 10–20 standard of electrode placement, with A1/2 (earlobes) as the reference. These electrodes were widely distributed across the scalp. Before data collection, the impedances of all the electrodes were monitored for each subject, to verify their value to be under 5 kΩ. Then, the paradigm timing system and the EEG recorder were synchronized, followed by 30 min of signal recording during the performance of the described paradigm.

**EEG Signal Processing**

In this study, 19 EEG channels and two additional channels (HOC, VOC) for recording horizontal–vertical eye movements and blinking were used. EEG recording is highly susceptible to various forms and sources of noise, which present significant difficulties and challenges in the analysis and interpretation of the EEG data. Different signal-processing techniques were applied for qEEG and ERP analysis; noisy epochs can be rejected from the recorded EEG for qEEG analysis, while artifacts should be detected and removed from EEG for ERP analysis. Therefore, preprocessing and analysis of the EEG spectrum and ERPs are explained in separate sections.

**qEEG artifact rejection.** Only resting-state eye-closed EEG recordings were used for qEEG analysis. To have a uniform and standard procedure for rejecting the EEG artifacts, all signals were divided into epochs with a duration of 2 sec. A uniform algorithm for identifying clean EEG epochs was applied to all recorded signals. All epochs that went through the same algorithms were subsequently labeled as clean or contaminated EEG epochs.

The signal mean, SD, skewness, kurtosis, and median were calculated, and the Kolmogorov–Smirnov test was applied for the estimation of distribution subsequently on raw data and processed signals after the artifact rejection. The result of this test at a significance level of $P \leq 0.05$ will indicate whether the data distribution of the signal was Gaussian or not. Also, in this step, empirical quantile–quantile plot was used to depict the quantiles of the data versus the quantiles of standard normal (Gaussian) distribution. The result of this step was used for validation of artifact rejection as a precondition evaluation in order to apply independent component analysis (ICA) for artifact removal in the next step. Manual inspection was applied to the signals if the explained examinations did not classify the artifact-free signals as a Gaussian distribution.

In this study, unlike the common practice in psychiatric studies (experts screening the signals to reject the contaminated epochs), an automated artifact rejection method was performed using the EEGLAB toolbox (Delorme and Makeig, 2004) in MATLAB. In the first step, epochs were rejected based on four criteria:

1. **Extreme values:** This method consists of defining the standard threshold of ± 75 µV for potential values. If the absolute value of any data points in the epoch exceeds this range, the epoch is labeled as artifactual.
2. **Linear trends:** Data points of each epoch must fit a straight line, and if the slope of the calculated line is more than 60 µV, it is deemed an artifactual epoch.
3. **Data improbability:** Transient odd or unexpected value points in each epoch are identified by the comparison of the epoch values and normal statistical values.
recorded during the whole trial using the probability density function of all data points for each electrode.

4. Spectral pattern: The Slepian multitaper spectrum is computed for all trials and channels, using the MATLAB “pmtm” function defaults (four orthogonal tapers; FFT length of 500 data points for each data epoch). Subsequently, the average power spectrum of the whole trial over each channel is subtracted from the calculated epoch spectrum. If the subtraction value exceeds a value of \(65\) dB in the range of 0.5 to 2 Hz and \(125\) or \(2100\) dB for 20 to 45 Hz, then the epoch is labeled as a contaminated epoch and is selected for rejection. The purpose of using 0.5 to 2 Hz and 20 to 30 Hz is to help single out eye movements and muscle activities.

These four steps of epoch rejection can partially remove some types of artifacts (e.g., line noise or muscle artifact). Therefore, as an alternative approach, the scalp EEG data are separated into active cortical and artifact sources based on the physiology and statistically acceptable assumption of the ICA (Ball and Ross, 1991; Delorme and Makeig, 2004; Delorme et al., 2007). The runica algorithm from EEGLAB (Delorme and Makeig, 2004) was used in this study to calculate the ICA components (the same criteria were used for automatic epoch rejection of ICA components). Based on the dipoles of the head model provided by EEGLAB (Delorme and Makeig, 2004), the artifactual components were rejected from the ICA results, and the EEG signals were then reconstructed based on the remaining components. By automatically eliminating noisy epochs and rejecting the artifactual independent components, EEG signals can be used for spectral analysis.

PSD. A low-pass FIR filter was used to filter the signal in the range of 0.5 to 30 Hz. Evaluation of PSD within the 0.5- to 30-Hz frequency range was done for delta (0.5–4 Hz), theta (4–8 Hz), alpha (8–13 Hz), and beta (13–30 Hz). PSD of each trial was computed using the Pwelch function of MATLAB with 0.5-Hz resolution without overlapping. The Pwelch function applied four orthogonal tapers of 500 data points (2 sec) for
each trial using the Hanning window. The estimation of the PSD values of each trial consisted of 59 values for 0.5 to 30 Hz with resolution of 0.5 Hz. The PSD modality was evaluated for each group based on 2 × SD of PSD (as the selection boundary), and the mean and SD were recalculated after eliminating the outliers; then, data were scaled to reduce the skewness.

**ERPs.** Since timing is a dominant aspect of ERPs, a different preprocessing algorithm was used to remove noise from the EEG signal during the ERP paradigm presentation. A uniform novel method of ERP signal processing used in this study removed the artifacts instead of a direct rejection of epochs. It should be noted that all channels were used for the preprocessing phase to provide artifact-free signals; however, based on the guidelines for eliciting, recording, and quantifying ERPs in clinical research (Duncan et al., 2009), four active channels (Cz, Fz, Pz, Fcz) were used for extracting ERP properties. Each channel’s signal was band-pass filtered between 0.1 and 45 Hz using the Slepian multitaper spectrum (MATLAB “pmtm” function) by applying four orthogonal tapers (a combination of high-pass and low-pass filters), to remove power line, high-frequency noises, and DC biases. The ICA algorithm was used to remove the artifacts, eye movements, and blinking using “runica infomax” from MATLAB (described in Li et al., 2006; Schlögl et al., 2007). After removing the artifact-independent components, the remaining signals were used for reconstruction of the channels’ EEG. In the next phase, each signal should be synchronized with the stimuli onset timing of the paradigm; therefore, 256 samples (1 sec) from the onset of the stimuli were selected as a single trial.

Typically, averaging is the common approach for ERP detection in clinical experiments. However, in spite of the convenience of this method, summation of various latencies of trials results in wide peaks and valleys, which reduce the accuracy in latency and amplitude detection of the ERPs that might subsequently influence the statistical inferences. Given the importance of the exact value of amplitude and latency of ERPs in addiction study, as well as the lack of Fourier transform in analyzing time-transient signals, a newly established method of ERP detection was used. In this study, a combination of a continuous wavelet transform (CWT) and discrete wavelet transform (DWT) was used for feature extraction from each trial. Wavelet transform, as an optimal convolution for nonstationary signals like the EEG (Quiroga and Garcia, 2003; Xu et al., 2004; Bostanov and Kotchoubey, 2006; Motlagh et al., 2012, 2013), provides coefficients that indicate the similarity of signal with shifted wavelet functions at different scales. Contracted scales of wavelet function match the signal’s high-frequency components, and the expanded scales match the low-frequency oscillations. Wavelet transform maps each trial from time domain (one independent variable) to a function in time and scale domains. Therefore, correlation coefficients provide a hierarchical scheme called multiresolution decomposition. ERPs are time-locked amplitudes in low frequency, and Wavelet transform provides access to both of these domains simultaneously.

In the first phase, DWT was used for decomposition of signals into “details” and “approximation” (high-frequency and low-frequency) components. Quadratic B-spline functions have a high similarity to ERPs and have optimal time-frequency resolution (Quiroga and Garcia, 2003; Motlagh, 2012). Therefore, these functions were chosen as the wavelet in this study. The first level of DWT decomposition transformed the trials into approximations (A) and detailed (D) components; another four levels of DWT decomposition of each level of approximations provide six decompositions of D1–5 and A5. DWT time-frequency decompositions were relative to frequencies of 64 to 128 Hz (D1); 32 to 64 Hz (D2); 16 to 32 Hz (D3); 8 to 16 Hz (D4); 4 to 8 Hz (D5); and 0.1 to 4 Hz (A5). Thanks to the low frequency of evoked potentials, A5 and D5 decompositions were used for signal reconstruction.

In the next step, CWT was applied on the reconstructed trials using Mexican hat wavelet. Different scales of wavelet swept each trial, and their correlation was calculated for each time scale as a similarity coefficient. Calculated CWT coefficients were averaged over different scales, and extremum values of obtained vector were stored. The amplitude and latency of each trial were stored in a new matrix, and for each subject the N2, P300, and P600 amplitudes and latencies were extracted for each subparadigm. The trials in which their ERP attributes were not detected were eliminated from the final comparison.

Wavelet analysis results provide the latency and polarity of each single-trial ERP. It is assumed that the absolute maximum of the ERP curve has an amplitude of \( A_0 \) at time \( T_0 \); two local extremums—i.e., one just after \( A_0 \) and another just before \( A_0 \), with amplitudes of \( B_1 \) and \( B_2 \), respectively (Eq. 1)—were extracted. \( T_0 \) was the latency of the ERP and was assumed to be near 150 msec for MMN, 300 msec for P300, and 500 msec for P600. Therefore, in Equation 2 the ideal latency of each ERP (shown as ERP latency) was subtracted from the real latency of the ERP, and then it was scaled by the ideal latency to have a similar latency ratio. Using Equations 1 and 2, two heuristic features were defined as amplitude and latency (“A” is the similarity amplitude, and “T” is the ratio of latency). Following this, the results were averaged over the number of trials to have a final amplitude and latency ratio for each of the subjects per task. The mean values of recorded ERP amplitude and latency ratio from all tasks were stored in a MAT file for statistical analysis.

\[
A = |A_0 - B_1| + |A_0 - B_2| \tag{1}
\]

\[
T = |T_0 - ERP_{\text{latency}}|/ ERP_{\text{latency}} \tag{2}
\]

**Statistical Analysis**

Initial group comparisons for demographic and clinical characteristics (Table 1) were performed using one-way ANOVA. A Lilliefors test (two-sided goodness-of-fit test) was used to check the normality assumption of the demographic characteristics and electrophysiological properties of groups. An alcohol breath-screening test, baseline blood investigations for HIV, viral hepatitis B/C screening, and urine rapid drug test for illicit drug use, as well as the Fagerstrom and MINI, were performed for both groups. To decrease the intergroup differences and with regard to the influence of smoking on EEG and ERP properties, the heroin-dependent subjects with scores of 1 to 4 on the Fagerstrom test were not included in the final
analysis (the final number of heroin addicts included was 19, who were recognized as moderately or highly nicotine dependent).

EEG measurements were used as the primary outcomes to define the electrophysiological differences between addicts and healthy subjects. Group comparisons for PSD and ERP features were performed using repeated-measure ANOVA, while the group of subjects was chosen as a between-subject factor. To reduce multiple testing and evaluation of statistical differences of PSD among the controls and addicts, as a common approach (Brickman et al., 2005; Liddell et al., 2007; Whitford et al., 2007; Gatt et al., 2008; Wang et al., 2015), averaged PSD of channels over certain brain regions (frontal [Fp1/2, F3/4, F7/8, and Fz], central [C3/4 and Cz], temporal [T3/4 and T5/6], and occipital-parietal [P3/4, Pz, O1/2]) were used for further analysis. For fitting the data into a repeated-measure model, the frequency band (delta/theta/alpha/beta) and the brain region (frontal/central/temporal/occipital-parietal) were within-subjects factors.

Furthermore, to explore the differences in cognitive response features among the addicts and controls, ERP data of each task were fitted into a repeated-measure ANOVA model to evaluate if the model terms were significant in their effect on the response by measuring how they contribute to the overall covariance. The multivariate responses for each subject were a vector of repeated measures, and ERP features (amplitude/latency) were within-subjects factors. Based on the described paradigms, task 1 provided auditory P300, and P600 in association with the working memory task; task 2 provided auditory P300 as well as small and large deviant MMN components; and finally task 3 provided visual cue-reactivity P300.

For accurate P value calculations in the repeated-measure ANOVA models, the Mauchly test was used for sphericity assessment, and if the compound symmetry assumption was not satisfied, the P value was adjusted using three different correction methods (Greenhouse–Geisser/Huynh–Feldt/lower bound adjustment). Based on the results of repeated-measure mix models, significant main effects were followed up with post hoc pairwise analysis of variance using the Tukey–Kramer correction method.

RESULTS

The demographic and clinical characteristics of the two groups are shown in Table I. The healthy control subjects had higher education (years) ($F_{(1,36)} = 51.68$, $P < 0.001$) and lower age ($F_{(1,36)} = 5.68$, $P = 0.02$) compared with the addicts. The digit-span Wechsler score for subjects showed that healthy controls achieved higher scores in this test ($F_{(1,36)} = 39.6$, $P < 0.001$) compared with the addicts. Furthermore, Pearson r and Spearman rho correlations showed no significant correlation ($P < 0.05$) between the EEG and ERP measurements and duration of addiction. Since these electrophysiological features were extracted during the performance of different tasks, the results of each subparadigm were analyzed separately. The results of this study are shown in separate sections including the PSD of resting EEG, digit-span P600, auditory MMN, and P300.

### Table I. Demographic and Clinical Characteristics (Mean and SD) of Each Group of Subjects

<table>
<thead>
<tr>
<th>Variable</th>
<th>Heroin addicts ($n = 19$)</th>
<th>Healthy controls ($n = 19$)</th>
<th>$F_{(1,36)}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>39.3 (7.7)</td>
<td>33.2 (8.1)</td>
<td>5.68*</td>
</tr>
<tr>
<td>Duration of opioid addiction (years)</td>
<td>17.7 (7.1)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Education (years)</td>
<td>8.1 (5.3)</td>
<td>12.8 (5.1)</td>
<td>51.68**</td>
</tr>
<tr>
<td>Fagerstrom score</td>
<td>6.2 (1.4)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Digit-span score</td>
<td>4.4 (1.1)</td>
<td>6.7 (1.2)</td>
<td>39.6*</td>
</tr>
<tr>
<td>Sex (F/M)</td>
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<td>19/0</td>
<td>—</td>
</tr>
<tr>
<td>Ethnicity (Malay/others)</td>
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<td>19/0</td>
<td>—</td>
</tr>
<tr>
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<td>19/0</td>
<td>—</td>
</tr>
<tr>
<td>Hepatitis B (positive/negative)</td>
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<td>19/0</td>
<td>—</td>
</tr>
<tr>
<td>Hepatitis C (positive/negative)</td>
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<td>19/0</td>
<td>—</td>
</tr>
<tr>
<td>Alcohol (positive/negative)</td>
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<td>19/0</td>
<td>—</td>
</tr>
<tr>
<td>Drug (cannabis/ATS/benzo)</td>
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<td>0/0/0</td>
<td>—</td>
</tr>
<tr>
<td>Employment status (yes/no)</td>
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<td>19/0</td>
<td>—</td>
</tr>
<tr>
<td>Marital status (married/divorced)</td>
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<td>19/0</td>
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</tr>
<tr>
<td>Major depressive episode</td>
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<td>—</td>
</tr>
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<td>Dyshymnia/suicidality</td>
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<td>0/0</td>
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<tr>
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<tr>
<td>Manic episode (current/past)</td>
<td>0/0</td>
<td>0/0</td>
<td>—</td>
</tr>
<tr>
<td>Panic disorder (current/past)</td>
<td>1/1</td>
<td>0/0</td>
<td>—</td>
</tr>
<tr>
<td>Agoraphobia</td>
<td>0</td>
<td>0</td>
<td>—</td>
</tr>
<tr>
<td>Social phobia</td>
<td>2</td>
<td>0</td>
<td>—</td>
</tr>
<tr>
<td>Obsessive compulsive disorder</td>
<td>2</td>
<td>0</td>
<td>—</td>
</tr>
<tr>
<td>Posttraumatic stress disorder</td>
<td>3</td>
<td>0</td>
<td>—</td>
</tr>
</tbody>
</table>

Note: Group comparison was performed using the one-way ANOVA with continuous variables. * $P < 0.01$; ** $P < 0.001$; SD indicates standard deviation.
was higher among addicts at all locations (compared with the healthy subjects. Figure 3 illustrates the alpha power was significantly lower only at the frontal and central regions (\(t(3,108)=65.32\)) regions.

P300 in all three tasks, the results for the P300 component are described in a separate section.

**Resting EEG PSD**

Group comparisons for PSD of resting-time EEG recording showed significant differences for the between-subjects factor (\(F_{(1,36)} = 5.08, P = 0.03\)), as well as interactions between the within-subjects and between-subjects factors (frequency band [\(F_{(3,108)} = 99.34, P < 0.001\]), brain location [\(F_{(3,108)} = 3.71, P = 0.03\]), and band/location [\(F_{(9,324)} = 15.23, P < 0.001\)]. Within-group correlations (Pearson \(r\) and Spearman rho) showed no significant correlation \((P < 0.05)\) between the EEG bands’ PSD and education or duration of addiction. The results of repeated-measure ANOVA and the post hoc analysis of PSD measurements are shown in Table II. Results showed that delta and theta band activities were lower among addicts in all locations \((P < 0.001)\), while their alpha power was significantly lower only at the frontal and central regions \((P < 0.05)\). In contrast, beta power was higher among addicts at all locations \((P < 0.01)\) compared with the healthy subjects. Figure 3 illustrates the PSD comparison (mean and standard error) of each frequency band of each region for both groups.

**Digit-span P600**

ANOVA analysis of the P600 features showed significant differences between two groups \((F_{(1,36)} = 28.49, P < 0.0001)\), and follow-up within-factor analysis showed higher amplitude \((F_{(1,36)} = 43.80, P < 0.0001)\) and lower latency \((F_{(1,36)} = 133, P < 0.0001)\) of the P600 component among the healthy controls compared with the addicts. There was also a significant correlation between the digit-span score of subjects and P600 amplitude \((r = 0.47, P = 0.002)\), as well as its latency ratio \((r = -0.66, P < 0.0001)\). Moreover, correlation was observed between the P600 and the P300 recorded at both attention \((r = 0.65, P < 0.0001)\) and recall phases \((r = 0.66, P < 0.0001)\).

**Auditory MMN**

MMN amplitude and latency for small and large deviant auditory stimuli were fitted into a repeated-measure ANOVA model with subjects’ group as the between-subjects factor, and stimuli types were chosen as within-subjects factor. Results showed that there was a significant difference in between-subjects factor \((F_{(1,36)} = 22.09, P < 0.001)\), and MMN amplitude was lower among addicts for both small and large deviant stimuli \((P < 0.001)\) compared with the healthy subjects. The latency ratio of MMN components was also longer among addicts compared with the controls \((P < 0.0001)\). There was also a significant correlation between both MMN amplitudes \((r = 0.52, P = 0.0007)\) and novel P300 amplitude extracted from this task \((r = 0.40, P = 0.012)\).

**P300**

To analyze the P300 features recorded during the paradigm performance, data were fitted into a repeated model while tasks and features (amplitude/latency) were chosen as within-subjects factors. Results showed that the P300 amplitude of addicts was lower compared with the healthy controls \((F_{(1,36)} = 25.97, P < 0.001)\), while their latency was longer \((F_{(1,36)} = 492, P \approx 0.000)\). Results indicated that task type had a significant effect on between-group differences of P300 amplitude \((F_{(3,108)} = 20.32, P < 0.001)\), and the post hoc analysis confirmed diminished P300 amplitude among the addicts during digit-span \((P < 0.0001)\) and auditory oddball \((P = 0.0007)\) tasks, while it was higher for cue-reactivity condition \((P = 0.009)\) compared with the healthy controls. Although the effect of group X task for P300 amplitude was significant \((F_{(3,108)} = 20.32, P < 0.001)\), task type had no effect on the latency of P300 \((F_{(3,108)} = 1, P = 0.39)\). In addition, a correlation was observed between the P300 recorded at attention and recall phases during the performance of the digit-span test \((r = 0.53, P = 0.0006)\). Table III shows the mean and standard deviations of electrophysiological measurements of the two
Fig. 4. Scatter plots depict the ERP amplitude versus latency ratio for comparison of both groups in each task (top two scatter plots depict the auditory MMN and P300, the middle plots show the ERPs recorded during the digit-span task, and the lowest scatter plot illustrates the visual P300 related to drug stimuli). The figure shows that the ERP amplitude of addicts is lower than that of the controls in standard conditions, and they take a longer time to occur compared with controls. However, P300 of addicts in response to heroin-related pictures was greater than controls. [Color figure can be viewed at wileyonlinelibrary.com]
groups. The group comparison is shown in Figure 4 based on the amplitude and latency of ERP components.

**DISCUSSION**

In this study, an integration of paradigms was introduced to probe the MMN, P300, and P600 components during standard and cue-reactivity conditions. This paradigm was designed based on modification of well-known paradigms in electrophysiological studies of the addiction field and follows the methodological recommendations for eliciting and recording ERP in clinical trials (Duncan et al., 2009). The paradigm consists of various tasks related to salient brain electrophysiological features of addiction studies. Closed-eye qEEG and ERPs (MMN, P300, and P600) associated with brain discrimination abilities, orientation of attention, response resolution, and working memory were assessed among chronic heroin addicts and healthy control subjects.

The PSD analysis showed the significant increase of beta and decrease of delta, theta, and alpha among heroin addicts compared with healthy subjects. The PSD alteration was shown to be more significant across all cortex locations for delta and beta bands. These results were in line with previous studies, which reported the increase of beta activity (Roemer et al., 1995; Costa and Bauer, 1997; Herning et al., 1997; Rangaswamy et al., 2002) among heroin addicts. Previous studies among alcohol addicts also showed the increase of beta activity (Rangaswamy et al., 2002; Ceballos et al., 2009) and decrease in alpha, delta, and theta band activities (Saletu et al., 2004). It was also believed that heroin addicts’ long-term memory, working/short-term memory, problem-solving abilities, and psychomotor speed performance were associated subsequently with delta, theta, alpha, and beta band properties (Polunina and Davydov, 2004). It is thought that low-frequency activities (delta and theta) are inhibitory, while alpha activity as an expression of normal brain functioning and beta activities is excitatory (Sokhadze et al., 2008). Notably, cognitive dysfunctions measured by alteration of EEG spectral power are associated with chronic heroin-related thoughts, heroin craving, and heroin abuse history (Davydov and Polunina, 2004; Franken et al., 2004; Polunina and Davydov, 2004). It was also believed that heroin addicts’ long-term memory, working/short-term memory, problem-solving abilities, and psychomotor speed performance were associated subsequently with delta, theta, alpha, and beta band properties (Polunina and Davydov, 2006). The increase of beta power has been attributed to psychomotor speed (Polunina and Davydov, 2006), and it has been found to be superior in gauging illness severity (Bauer, 1994; Costa and Bauer, 1997). In addition, the results indicate that qEEG power alteration is more significant in the frontal and central regions of the brain, which supports the hypothesis that

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**TABLE II. Results of the Repeated-Measure ANOVA Model for Resting EEG PSD Measurements**

<table>
<thead>
<tr>
<th>Effect</th>
<th>F statistics</th>
<th>P value</th>
<th>Location</th>
<th>Difference</th>
<th>Standard error</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group</td>
<td>F(1,36) = 5.08</td>
<td>0.03</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group/band</td>
<td>F(3,108) = 99.34</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group/region</td>
<td>F(3,108) = 3.70</td>
<td>0.03</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group/band/region</td>
<td>F(9,324) = 15.23</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: There are two groups of subjects, four regions, and four frequency bands. Repeated-measure ANOVA computes three P values using Greenhouse-Geisser (Pgg), Huynh-Feldt (Phf), and lower bound (Pn) corrections, respectively. Estimated difference between the mean values of addicts and controls and standard errors are shown in this table.
neurophysiological abnormalities of heroin addicts in the frontal and central regions may be an indicator of brain atrophy and chronic brain damage.

In addition to qEEG, ERPs consisting of time-locked components related to information-processing operations are able to monitor cognitive responses with high temporal resolution. The precision of ERPs provides the cognitive resolution attribute of the brain to identify affection or disruption of information-processing properties. The assessments of ERP features showed prolonged MMN, P300, and P600 amplitudes among heroin addicts compared with healthy subjects in standard tasks. These results confirm a decrement of attentional processing and cognitive dysfunction induced by chronic heroin abuse. MMN as an attention-independent component is related to neural aspects of preattentive auditory processing and assesses discrimination abilities of subjects. Therefore, diminished amplitude of MMN among chronic heroin users might be related to their preattentive processing deficits. In addition, MMN latency inversely reflects the speed of deviance detection (Stefanics et al., 2014), and prolonged occurrence of MMN among opioid addicts was in line with previous studies and was suggested to be related to deficits of attentional bias (Kivisaari et al., 2007; Yang et al., 2009; Morie et al., 2014).

MMN is elicited by shifting attention to deviant stimuli among standard ones, which is followed by the P300 component when the stimulus is novel. MMN and P300 are the most studied ERPs in the assessment of discrimination ability and attentional bias among addicts. The P300 component is thought to comprise the activation of inhibitory processes over widespread cortical areas (Tomberg and Desmedt, 1998), and it may reflect the decisional process of memory updating (Polich and Herbst, 2000) and cognitive closure (Verleger, 1988). Evaluation of P300 amplitude among opioid addicts was suggested by Bauer (2001) as an index of CNS recovery from opioids. P300 also has been advocated to be a neuropsychological marker in correlation with addiction properties (Lubman et al., 2007, 2009). Investigation of P300 and N2 among heroin addicts (Bauer, 2001; Marques-Teixeira and Barbosa, 2005; Kivisaari et al., 2007; Singh et al., 2009; Yang et al., 2009; Morie et al., 2014) and smokers (Anokhin et al., 2000; Neuhaus et al.,

### TABLE III. Electrophysiological Measurements (Mean and SD) of Both Groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Heroin addicts (n = 19)</th>
<th>Healthy controls (n = 19)</th>
<th>F statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
</tr>
<tr>
<td>Delta</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frontal</td>
<td>4.0</td>
<td>2.1</td>
<td>9.1</td>
</tr>
<tr>
<td>Central</td>
<td>3.3</td>
<td>2.1</td>
<td>7.8</td>
</tr>
<tr>
<td>Temporal</td>
<td>2.9</td>
<td>1.7</td>
<td>5.5</td>
</tr>
<tr>
<td>Occipital/parietal</td>
<td>3.9</td>
<td>2.6</td>
<td>8.1</td>
</tr>
<tr>
<td>Theta</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frontal</td>
<td>1.9</td>
<td>0.9</td>
<td>3.4</td>
</tr>
<tr>
<td>Central</td>
<td>1.8</td>
<td>0.8</td>
<td>3.2</td>
</tr>
<tr>
<td>Temporal</td>
<td>1.3</td>
<td>0.6</td>
<td>1.8</td>
</tr>
<tr>
<td>Occipital/parietal</td>
<td>1.6</td>
<td>0.8</td>
<td>2.5</td>
</tr>
<tr>
<td>Alpha</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frontal</td>
<td>2.6</td>
<td>1.3</td>
<td>3.9</td>
</tr>
<tr>
<td>Central</td>
<td>3.8</td>
<td>3.2</td>
<td>6.5</td>
</tr>
<tr>
<td>Temporal</td>
<td>2.2</td>
<td>1.2</td>
<td>2.5</td>
</tr>
<tr>
<td>Occipital/parietal</td>
<td>3.3</td>
<td>2.6</td>
<td>4.7</td>
</tr>
<tr>
<td>Beta</td>
<td></td>
<td></td>
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<tr>
<td>Frontal</td>
<td>5.9</td>
<td>1.4</td>
<td>2.7</td>
</tr>
<tr>
<td>Central</td>
<td>7.6</td>
<td>1.9</td>
<td>3.1</td>
</tr>
<tr>
<td>Temporal</td>
<td>4.7</td>
<td>0.6</td>
<td>2.6</td>
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<tr>
<td>Occipital/parietal</td>
<td>5.8</td>
<td>1.2</td>
<td>2.8</td>
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<tr>
<td>ERP amplitude</td>
<td></td>
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</tr>
<tr>
<td>MMN</td>
<td></td>
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</tr>
<tr>
<td>Small</td>
<td>1.21</td>
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</tr>
<tr>
<td>Large</td>
<td>3.56</td>
<td>0.81</td>
<td>4.99</td>
</tr>
<tr>
<td>P300</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Task 1 attention phase</td>
<td>11.66</td>
<td>2.20</td>
<td>17.72</td>
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<tr>
<td>Task 2 recall phase</td>
<td>13.89</td>
<td>1.84</td>
<td>16.74</td>
</tr>
<tr>
<td>Auditory</td>
<td>11.98</td>
<td>2.73</td>
<td>16.17</td>
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<tr>
<td>Visual cue reactivity</td>
<td>20.77</td>
<td>1.78</td>
<td>18.75</td>
</tr>
<tr>
<td>P600</td>
<td>9.51</td>
<td>1.73</td>
<td>12.66</td>
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<tr>
<td>ERP latency</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMN</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small</td>
<td>0.76</td>
<td>0.15</td>
<td>0.27</td>
</tr>
<tr>
<td>Large</td>
<td>0.76</td>
<td>0.15</td>
<td>0.22</td>
</tr>
<tr>
<td>P300</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Task 1 attention phase</td>
<td>0.75</td>
<td>0.13</td>
<td>0.24</td>
</tr>
<tr>
<td>Task 2 recall phase</td>
<td>0.77</td>
<td>0.15</td>
<td>0.24</td>
</tr>
<tr>
<td>Auditory</td>
<td>0.81</td>
<td>0.12</td>
<td>0.22</td>
</tr>
<tr>
<td>Visual cue reactivity</td>
<td>0.79</td>
<td>0.13</td>
<td>0.19</td>
</tr>
<tr>
<td>P600</td>
<td>0.79</td>
<td>0.14</td>
<td>0.25</td>
</tr>
</tbody>
</table>

Note: One-way ANOVA with continuous variable was used for calculating the F statistics. * P < 0.01; ** P < 0.001; *** P = 0; SD indicates standard deviation.
addicts when compared with healthy subjects. Moreover, the response inhibition, decrement of preattentive processing speed among addicts. Although increased latency of P300 and P600 among heroin addicts in all tasks. P300 amplitude is influenced by attentional variables, while processing of the stimulus evaluation affects its latency. Moreover, the amplitude of the P300 component has been thought to increase when more attention is oriented by the participant or required by the task. As such, higher amplitude of P300 among addicts encountering heroin-related stimuli shows the increase of their attention toward this type of stimuli compared with standard novel stimuli. However, prolonged P300 latency in the cue-reactivity condition resulted in deficiencies in attentional processing speed among addicts. Although increment of visual P300 amplitude gives ground to the postulation of using P300 as an opioid carving index, the failure of addicts to pay attention to stimulus sources, as well as in directing attentional resources to environmental stimuli, thus reflecting gray matter abnormalities (Bauer, 2001; Marques-Teixeira and Barbosa, 2005; Singh et al., 2009).

In this study, analyzing the P300 properties has further confirmed declined P300 amplitude in addicts for auditory standard stimuli, while it was higher for visual drug stimuli compared with controls. On the other hand, P300 latencies were prolonged among addicts in all tasks. P300 amplitude is influenced by attentional variables, while processing of the stimulus evaluation affects its latency. Moreover, the amplitude of the P300 component has been thought to increase when more attention is oriented by the participant or required by the task. As such, higher amplitude of P300 among addicts encountering heroin-related stimuli shows the increase of their attention toward this type of stimuli compared with standard novel stimuli. However, prolonged P300 latency in the cue-reactivity condition resulted in deficiencies in attentional processing speed among addicts. Although increment of visual P300 amplitude gives ground to the postulation of using P300 as an opioid carving index, the failure of addicts to pay attention to stimulus sources, as well as in directing attentional resources to environmental stimuli, thus reflecting gray matter abnormalities (Bauer, 2001; Marques-Teixeira and Barbosa, 2005; Singh et al., 2009).

The results of the digit-span task and, with regard to the differences of P300 and P600 related to working memory (Frisch et al., 2003), diminished amplitude and prolonged latency of P300 and P600 among heroin addicts, reflect their difficulty in second-pass parsing in information processing in association with working memory systems. These abnormalities have been suggested to be related to the impairment of working memory and attention involving the right prefrontal areas of the brain (Papageorgiou et al., 2003, 2004). It is worth mentioning that the amplitude of P300 diminishes with increasing working memory load (Gaspar et al., 2011); therefore, lower amplitude of P300 in the working memory task can be attributed to both attentional deficits and task difficulty. It is in agreement with the correlation of the P300 amplitude index at both attention and recall phases of the working memory test.

Taken together, these findings lead to the conclusion that various brain activity abnormalities and dysregulation related to information processing are present among chronic heroin addicts, which are attributed to a variety of cognitive dysfunctions. Comparison of various neurophysiological attributes of both groups confirmed dysregulation of brain activity and cognitive abnormalities, response inhibition, decrement of preattentive processing, and central executive working memory among addicts when compared with healthy subjects. Moreover, attentional bias associated with P300 properties was found among addicts confronting heroin-related stimuli. Dysfunction of these brain structures may contribute to the identification of basic cognitive processes that could account for the cognitive deficits in addiction.

Based on the findings of this study, integration of resting EEG spectral activity at frontal and central regions as well as MMN and P300 latency can be used as an index of addiction severity. Furthermore, the efficiency of alternative addiction treatment methods can be evaluated through assessment of these ERP properties. It is significant that simultaneous evaluation of P300 and N2 components, as a sensitive measure of impaired cognitive control, improves neurophysiological elucidation of addiction. MMN does not require participants’ attention to be acquired, which makes it appropriate as an index of cognitive deterioration among addicts. P300 as an index of information processing is appropriate as a sensitive index for the ability allocate attentional resources. The P600 component, which is modulated by the basal ganglia and cingulate area, has been considered an index of the completion of any synchronized operation after target detection, rather similar to working memory operation. This observational study showed that using this paradigm together with advanced signal-processing techniques could provide more robust electrophysiological features during withdrawal and abstinence periods associated with addiction traits such as craving and anhedonia. This comprehensive investigation of cognitive traits associated with craving features of addiction could effectively contribute to improving the understanding of neurological features of addiction, and it is speculated that ERP properties can be used as an index for severity of addiction and a reliable objective assessment for recovery evaluation.

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ROLE OF AUTHORS

All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: F.E.M., F.I., R.A.R., and H.H. Acquisition of data: F.E.M., R.A.R. Analysis and interpretation of data: F.E.M. and F.I. Drafting of the manuscript: F.E.M., F.I., T.S. Critical revision of the manuscript for important intellectual content: R.R., F.I, T.S. Obtained funding: H.H. Study supervision: F.I., H.H.

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no competing interests.

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