Event-Related Potential Correlates of Biased Cognitive Processing and Control in Substance Abusers: A Review

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Abstract
Purpose: Event-Related Potentials (ERPs) have been used in addiction studies to evaluate cognitive performance and craving in individuals with Substance Use Dependence (SUD). This paper reviews studies that used ERPs to investigate cue reactivity, inhibitory control and error processing in SUDs to integrate new findings.

Materials and Methods: Five abused substances are included in the investigation, i.e. alcohol, nicotine, cannabis, cocaine, and methamphetamine. For each substance, the main recent findings related to the ERPs are specifically discussed, according to the latency of ERPs.

Results: Individuals with SUD allocate more attention resources to the cognitive processing of substance related cues, indexed by increased amplitude of middle and late latency ERPs. Laboratory observations also show amplitude enlargement for early latency ERPs. Individuals with SUD reveal a deficiency in the inhibitory control and conscious error processing, indexed by attenuated N2 and Pe amplitude.

Conclusion: This study expands the findings of previous related reviews implying that substance abusers allocate more attention resources to drug cues indexed by enlarged P3 and LPP amplitude. Regarding P3 elicited in inhibitory control tasks, there is not still convergent results, while N2 and Pe become attenuated as reported in previous reviews. The cognitive and motor inhibitory component (P3) changes show a controversial result.

1. Introduction

There are six impaired brain networks in individuals with substance dependence (reward, habit, salience, executive, memory, and self-directed networks) during task performance, such as cue exposure and inhibitory control, and also during resting states. These networks have shown increased activity for drug relate-processing and decreased activity during non-drug-related processing [1]. These impairments cause failure to inhibit addict behaviors such as abstaining substance abuse, increased attention to drug-related cues, and failure to adaptively learn from previous harmful behaviors. Two important components of cognitive control are inhibitory control and error processing impaired in addiction: The first is associated with neural networks involved in inhibition of inappropriate behavior and the second is related to neural networks involved in monitoring the performance errors to prevent future mistakes [2]. Another important cognitive impairment is attentional bias leading to empowered cognitive processing of drug-

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related cues in addicts that has been associated with relapse and addictive behavior [3-6].

Addictions are chronic relapsing psychiatric disorders in which patients have shown affected neuronal reactivity when neutral environmental stimuli become drug-related (words, pictures, faces, sounds, etc.). This reactivity, known as cue reactivity, has been reported as a motivationally salient response increasing the risk of relapse to substance misuse [7]. This salience is associated with dopamine release in reward structures of the brain [8-10].

Substance and behavioral addiction studies have used cue reactivity paradigms to evaluate behavioral and neuronal responses to different stimuli. Cognitive processing of these stimuli has been explored by using electroencephalography (EEG) to measure event-related potentials (ERPs) at the neurophysiological level. The ERPs have generated brain waves in response to discrete events such as seeing a word or picture on a computer screen [11]. These waves comprise positive and negative deflections, called components, associated with perceiving and making sense of that event [12]. The components are often characterized by their latency (e.g., 300 ms) and polarity (e.g., negative), which illustrate the extent to which cognitive processing is occurred [13].

The ERP components, which are frequently investigated in addiction studies with cue reactivity, inhibitory control and error processing paradigms include error-related negativity (ERN), P1 (P100), N2 (N200), error positivity (Pe), P3 (also termed P300, having 2 subcomponents: P3a and P3b), late positive potential/complex (LPP/LPC) and slow positive wave (SPW). They are categorized into 3 groups according to the latency: early ERP components (ERN, P1, N2, and Pe <300 ms), middle ERP components (P3, 300_800 ms) and late ERP components (LPP, LPC &SPW, >800 ms), while the time intervals may differ to some extent in different studies.

The P3 and late positive ERP components are ERPs related to cue reactivity reflecting attentional processing and motivational tendencies with medial-central and parietal distribution for P3 and posterior scalp distribution for late ERP components [14] [15-17]. The late ERP components are thought to reflect a greater allocation of attentional resources to motivationally relevant, emotional stimuli [18, 19].

Oddball paradigm is frequently used to elicit P3 and LPP components in which the presentation of a sequence of a repetitive-non-target stimulus (standard stimuli) is infrequently interrupted by a deviant-target (oddball) stimulus. The reaction of participant to the target stimulus is recorded. There are several variants to the oddball paradigm used in addiction studies [20].

Regarding these components, a meta-analysis assessed the P3 and slow positive components (SP>800 ms) in drug cues relative to neutral cues at Fz and Pz electrode sites. Where, the P3 and SP amplitude effect sizes were significantly larger in individual with substance dependence (cocaine, nicotine, heroin, alcohol, and cannabis) than healthy controls, indicating an enhanced cognitive processing of drug cues in substance users [16]. Another meta-analysis also showed that regular cannabis users may experience moderate to extremely intense cue reactivity to cannabis cues relative to neutral cues [21].

The N2, P3, ERN, and Pe are ERP components which have been reported to reflect changes in brain activity related to inhibitory control and error processing, arising at the fronto-central and parietal-central locations [22] [23-26].

Electrophysiological responses to successful inhibitions are N2 and P3 components. The N2, is a negative-going wave observed approximately 150–400 ms after stimulus onset, associated with the detection of response conflict appearing maximally in fronto-central regions [27, 28], and P3 is the later positive potential arising from sources close to the motor and premotor cortices [29]. The ERN arises 50–80 ms after making an error and is followed by the Pe, a positive deflection arising about 300 ms after incorrect responses [30, 31].

To measure the inhibitory capacity, Stroop [32], Eriksen Flanker [33] and Go/No-Go tasks are most commonly used, especially the later one. In the Go/No-Go paradigm, participants perform a binary decision on each stimulus to respond as quickly as possible to frequent Go stimuli, while inhibiting the responses to infrequent No-Go stimuli that require inhibitory control to prevail automatic response tendencies [34, 35].
Regarding the inhibitory control and error processing, a systematic review was carried out in SUD population. The results for P3 component were controversial, but the N2, ERN and Pe amplitudes were lower as compared to controls, indicting deficiencies in early cognitive processes of substance users, such as conflict detection [35].

However, the previous reviews reported that substance dependent individuals allocate more attention to drug cues compared to controls indexed by enhanced P3 and LPP amplitudes: inverse findings were also reported in some researches, for example in [36]. Hence, review of new findings is helpful to confirm the concatenation of previous reviews more. Furthermore, according to the review of Luijten et al. [26] the most consistent findings in addicted individuals relative to healthy controls were lower N2, while the corresponding findings about P3 were controversial. Hence, new findings of inhibitory control studies may help to get converged pieces of evidence about the P3. Therefore, here, we considered new studies about five most abused substances (alcohol, cigarette, cannabis, methamphetamine, and cocaine) to extract main results. Nevertheless, the older studies have also been considered in the discussion section to get converged pieces of evidence. All the included studies recruited human subjects and measured the ERPs to investigate their hypothesis in the domain of cue reactivity, inhibitory control and error processing [37].

Many of these studies used cue factors of emotional valence (negative or unpleasant, positive or pleasant) arousal level (low and high), stimuli type (drug-related and neutral) and category (target and non-targets) in combination with other factors such as gender, electrode sites and group (user, nonuser). The effects of these factors were measured by electrophysiological (ERP components) and behavioral measurements (e.g., accuracy and reaction time) in response to target stimuli.

2. Materials and Methods

In we have done the literature review on PubMed and Web of Science databases. The terms we searched were: “electroencephalography” or “EEG” or evoked potentials or event-related potentials and “psychiatric disorder” or “mental disorder” or "addiction" or "behavior, addictive" or “substance abuse” or "substance-related disorders" or “alcohol-related disorders” or "opioid-related disorders" or “nicotine-related disorders “ or "amphetamine-related disorders" or "cocaine-related disorders" or "alcoholism” or “cigarette smoking” and “cue reactivity” or "cue induced craving" or “visual task” or “picture viewing task” or” inhibitory control” or” error processing”.

To update the findings of past reviews, we applied a date restriction from January 1, 2012 to March 1, 2018 to report findings of recent research. Those studies have been selected for further investigation that examined ERPs in cue-reactivity research or in cognitive inhibitory control and error processing using Go/NoGo and Eriksen Flanker paradigms. Then, the studies that included alcohol, nicotine, cannabis, cocaine, or methamphetamine as a substance to the investigation on human subjects were selected. Table 1 summarizes the ERP measures, findings, and subjects of all new studies (after 2012). Next sections explain the major findings. According to the latency of ERPs, the new outcomes for each substance have been brought separately. Then, they have been discussed together in discussion section.

3. Results

3.1. Studies in Individuals with Cannabis Dependence

Two new studies have been conducted based on cannabis dependency [38, 39]. In the first [39], chronic marijuana-users and nonusers actively watched cannabis-related, negative and neutral images, during which three ERPs were recorded, EAP, P3, and LPP. In that study, Drug-related EAP modulation was present in the cannabis user group over the left fronto-central scalp in comparison to emotionally negative stimuli and neutral cues. P3 amplitude also significantly increased for substance cues relative to neutral stimuli, while the enhancement of LPP was not significant. It also reported a high correlation between LPP amplitude and self-report craving of cannabis use.
Table 1. New ERP studies in individuals with substance use dependence

<table>
<thead>
<tr>
<th>Study</th>
<th>Individuals</th>
<th>ERPs</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Piasecki, 2016</td>
<td>SU Ni</td>
<td>ERPs</td>
<td>Significant reduced Nogo P300</td>
</tr>
<tr>
<td>Luijten, 2016</td>
<td>CO: 18 (all male, M age: 16.92, current); CO: 18 (all male, M age: 17.23)</td>
<td>N2, P3</td>
<td>Not different between smokers and non-smokers. They were significantly higher in Nogo than in Go, and found in Go RTs. No significant difference was found in Go-No RTs.</td>
</tr>
<tr>
<td>Yin, 2016</td>
<td>CO:</td>
<td>N2, P3</td>
<td>Reduced Post-Error Slowing was related to an increased relapse risk as well as increased smoking.</td>
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<td>Reduced Post-Error Slowing was related to an increased relapse risk as well as increased smoking.</td>
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<td></td>
<td>Smaller P3 were related to increased smoking, but N2 was not predictive.</td>
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<td>Smaller P3 and ERN were associated with an increased relapse chance at a trend level.</td>
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<td>Smaller P300 and LPP were not predictive neither for relapse nor for smoking increase.</td>
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<td></td>
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<td></td>
<td>Smaller P3 were related to increased relapse risk as well as increased smoking.</td>
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<td></td>
<td>Increased Nogo/Go P300 amplitude and shorter Nogo/Go P300 latency were observed in adolescents smokers.</td>
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<td>Passive three-stimulus picture viewing</td>
<td>Passive two-stimulus picture viewing</td>
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<tr>
<td>Preceding high ER GWLs reduced the P3 elicited by smoking cues, significantly more than preceding low ER GWLs or neutral pictures.</td>
<td>Carbon monoxide sample and time since the last cigarette were uncorrelated with LPP amplitude.</td>
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<tr>
<td>Preceding high ER GWLs reduced the subjective rating of cigarette craving.</td>
<td>Carbon monoxide sample and time since the last cigarette were uncorrelated with LPP amplitude.</td>
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<tr>
<td>Carbon monoxide sample and time since the last cigarette were uncorrelated with LPP amplitude.</td>
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<tr>
<td>Event</td>
<td>Relat</td>
<td>Potential Correlates of Biased Cognitive Processing and Control in Substance Abusers: A Review</td>
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<td>This journal is © Tehran University of Medical Sciences</td>
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<td></td>
<td></td>
<td>Ern: 31</td>
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<td></td>
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<td>Versace, 2012</td>
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<td></td>
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<td>Bloom, 2013</td>
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<td></td>
<td></td>
<td>Ab: 31</td>
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<td></td>
<td></td>
<td>Intermittent smokers (12 male, M age: 23.9, current); Daily smokers (13 male, M age: 25.2, current); CO: 30 (14 male, M age: 25.2); Ab: 21 (13 male, current, M age: 34.3); CO: -</td>
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<tr>
<td></td>
<td></td>
<td>ERN, Pe, P2a, P3, LPP</td>
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<tr>
<td></td>
<td></td>
<td>ERN: 42 (3.3) CO: 2.2</td>
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<td>No main results</td>
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<td>No main results</td>
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<tr>
<td>Condition</td>
<td>RT (ms)</td>
<td>Age</td>
<td>P3 Amplitude</td>
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<tr>
<td>-----------------</td>
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<td>--------------</td>
</tr>
<tr>
<td>Alcohol</td>
<td>21.5±4</td>
<td>21</td>
<td>30.0±5</td>
</tr>
<tr>
<td>Non-Alcohol</td>
<td>21.2±3</td>
<td>20</td>
<td>28.0±4</td>
</tr>
</tbody>
</table>

**Summary:**

- **P3 Amplitude:** Greater for alcohol-related stimuli than for non-alcohol-related stimuli.
- **N2 Amplitude:** No significant difference between alcohol and non-alcohol conditions.
- **P100 Amplitude:** Greater for alcohol-related stimuli than for non-alcohol-related stimuli.

**Neuroimaging Studies:**

- **PET:** 
  - **P3:** Greater in the orbitofrontal cortex for alcohol-related stimuli compared to non-alcohol-related stimuli.
  - **N2:** No significant difference between alcohol and non-alcohol conditions.

**Subjective Reports:**

- **Craving:** Higher for alcohol-related stimuli than for non-alcohol-related stimuli.
<table>
<thead>
<tr>
<th>Event</th>
<th>Related Potential Correlates of Biased Cognitive Processing and Control in Substance Abusers: A Review</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Go/No-Go</strong></td>
<td><strong>Go</strong></td>
</tr>
<tr>
<td><strong>RTs</strong></td>
<td>No significant effect.</td>
</tr>
<tr>
<td><strong>ERN</strong></td>
<td>Negative N2 amplitude only to alcohol cues.</td>
</tr>
<tr>
<td><strong>P3d</strong></td>
<td>Statistically different P3d between groups.</td>
</tr>
<tr>
<td><strong>P3</strong></td>
<td>Enhanced P3 in response to low-probability inhibition trials cued by alcohol but not non-alcohol cues.</td>
</tr>
<tr>
<td><strong>N2 (A)</strong></td>
<td>No-Go N2 for the alcohol cues was larger than the neutral cues in both placebo and acute alcohol groups.</td>
</tr>
<tr>
<td><strong>ERN</strong></td>
<td></td>
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<tr>
<td><strong>RTs</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Error rate</strong></td>
<td></td>
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<tr>
<td><strong>Omission error rates</strong></td>
<td></td>
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<tr>
<td><strong>Commission error rates</strong></td>
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<tr>
<td><strong>RTs</strong></td>
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<td><strong>Commission error rates</strong></td>
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<tr>
<td>Group</td>
<td>Condition</td>
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<tr>
<td>N170 (A): Larger occipital NoGo N170 in response to alcohol-related stimulus was associated with relapse in 3 months following detoxification.</td>
<td>No significant results for both ERP. NoGo-Go/NoGo N170 C: 3.0 (5)</td>
</tr>
<tr>
<td>P100 &amp; N170 (latency): No significant results for both ERP. NoGo-Go/NoGo N170 C: 3.0 (5)</td>
<td>AB: 6.7</td>
</tr>
<tr>
<td>RTs of the alcohol-target were shorter relative to neutral target. NoGo-Go N170 C: 3.0 (5)</td>
<td>AB: 6.7</td>
</tr>
<tr>
<td>No main results.</td>
<td></td>
</tr>
<tr>
<td>Alcohol-related conflict P3: amplitude of P3 was reduced in subjects with AUD.</td>
<td>NoGo-Go N2 amplitude in patients was trendily lower than controls. N2: NoGo-Go N2 was trendily lower in subjects with strong craving.</td>
</tr>
<tr>
<td>N2 (A): Stress enhanced N2 amplitudes to drug-related and nonrelated stimuli regardless of their target status.</td>
<td>N2 (latency): It significantly decreased following the stressor. P3 (A): It was not enhanced by stress, P3 amplitudes were enhanced for alcohol targets. P3 (latency): It was decreased following the stressor. P3 (A): it significantly decreased by stress beyond practice effects.</td>
</tr>
<tr>
<td>P3: amplitude of P3 was reduced in subjects with AUD.</td>
<td>P3 (latency): It was decreased by stress following the stressor.</td>
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<tr>
<td><strong>Go-No-Go (A)</strong></td>
<td>Moderate intensity exercisers showed shorter reaction time compared to controls.</td>
</tr>
<tr>
<td><strong>P3 amplitude</strong></td>
<td>In decreased craving, the higher intensity exercisers showed larger amplitudes than controls.</td>
</tr>
<tr>
<td><strong>RT &amp; error rate</strong></td>
<td>There were no significant differences between groups in RT or error rate at baseline and 6 months after detoxification.</td>
</tr>
<tr>
<td><strong>Go/NoGo N2 (A)</strong></td>
<td>Moderate intensity exercisers showed larger N2 amplitudes than controls.</td>
</tr>
<tr>
<td><strong>Go/NoGo N2 (latency)</strong></td>
<td>Moderate intensity exercisers had shorter latencies than controls.</td>
</tr>
<tr>
<td><strong>Go/NoGo N2 (A)</strong></td>
<td>Moderate intensity exercisers had larger amplitudes than controls.</td>
</tr>
<tr>
<td><strong>N2 (latency)</strong></td>
<td>No significant exercise effect.</td>
</tr>
<tr>
<td><strong>Go/NoGo N2 (A)</strong></td>
<td>Only for MA-related task, Nogo-N2 were significantly larger than Go-N2.</td>
</tr>
<tr>
<td><strong>Go/NoGo N2 for exercisers</strong></td>
<td>Were significantly larger than controls.</td>
</tr>
<tr>
<td><strong>P3: No alterations in the P3 amplitude or latency following acute exercise.</strong></td>
<td></td>
</tr>
<tr>
<td><strong>RT &amp; error rate</strong></td>
<td>There were no significant differences between groups in RT or error rate at baseline and 6 months after detoxification.</td>
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</tbody>
</table>
ERN, Pe, N2, P3 amplitudes were smaller in addicts than in controls. 10R allele group: Cocaine minus pleasant LPPs of CUD+ was larger than healthy controls. 9R allele group: Cocaine minus pleasant LPPs of CUD+ was larger than CUD-. 10R/10R vs 9R allele: Cocaine minus LPPs of 10R/10R CUD+ were larger than 9R allele CUD-. In both CUD groups, Cocaine cue LPPs was larger than pleasant cue LPPs. N2 amplitude was associated with duration of drug use. Controls were smaller in addicts than in non-cocaine users. RT: Cocaine users were generally slower errors. RT: Cocaine users were more accurate. Cocaine users earned more points. Cocaine users were more accurate, but commission errors were only in controls. Commission and reaction time were correlated, but inhibition control and accuracy were not associated. N2 amplitude was associated with duration of drug use.
null
In the second study [38], the relationship between cannabis cue reactivity and craving was examined in a large sample of 353 participants, varying in self-reported cannabis use: never, infrequent and heavy cannabis users. P3 during neutral, exercise, and cannabis cue presentation were recorded and found that enhancement of P3 amplitude to cannabis related cues becomes intensified with continued use of cannabis (number of days used) showing a linear relation between use and reactivity. Whereas, neither of previous studies found a relation between P3 cannabis cue reactivity and craving that may be due to small sample size (<15) and craving range [40-42].

In conclusion, the larger P3 amplitude to cannabis-related cues relative to neutral cues in new studies is in line with findings of pioneer cannabis studies [40-42] reflecting deployment of more attentional resources to cannabis-related cues between cannabis users. In this regard, early and late latency ERPs are required to be more studied among cannabis users. On the other hand, controversial results of correlation between LPP and self-report craving have been found between cannabis studies. The change of LPP amplitude and craving result of [31] was highly correlated while the findings of pioneer cannabis studies [32, 35, 36] were uncorrelated. This may indicate that craving can be sometimes an unconscious phenomenon.

3.2. Studies in Individuals with Nicotine Dependence (IND)

3.2.1. Early Latency ERPs

Among new studies recruited (IND), two studies measured P2 and two other studies measured N2, ERN and Pe by conducting inhibitory control task. Their findings show that these components may be modulated by target, non-target but drug-related stimuli and also associative learning and could have partial association with relapse.

Bloom et al. found that P2 component elicited by target stimuli is significantly more positive than non-targets across both smokers and non-smokers, showing a global target detection effect [43]. Their study showed that there is an enhanced early attentional bias to cigarette stimuli relative to non-cigarette stimuli between smokers [43]. The P2 component is also modulated by associative learning [44]. In this study, geometrical figures that were paired with smoking stimuli elicited significantly larger P2 wave than those paired with neutral stimuli.

Luijten et al. have shown that N2 reflecting inhibitory control is not correlated with the chance of relapse, while other early ERPs reflecting error processing, i.e. Pe and ERN, are associated with smoking relapse and resumption at trend levels [26]. Their study also showed that women might have a higher chance of relapse than men. The error processing ERPs also were studied among intermittent and daily smokers. The outcomes showed greater Pe amplitude in intermittent subjects than that of daily ones which reflect cognitive processes that may prevent the transition to dependent smoking [45]. However, as individuals with SUDs have shown lower Pe amplitude compared to healthy controls [26], the Pe is expected to be more pronounced in daily smokers than in intermittent subjects; while Rass et al.’s conclusion is in contrast with this finding. Therefore, error inhibitory assessment is required to be more studied in IND with different level of dependency.

3.2.2. Middle Latency ERPs

Most recent studies in IND, evaluated changes in these ERPs. Their findings show enhanced attentional bias to smoking cues, indexed by amplified P3 and LPP amplitude, and deficiency in inhibitory control in IND indexed by attenuated P3 amplitude, respectively. Some studies also found that late latency ERPs might be associated with relapse and dose of consumption in IND.

In this regards, increased processing of smoking cues results in increased P3 amplitude more than neutral cues [26, 43, 46, 47].

The amount of smoking (daily or occasional) did not moderate the P3 reactivity, while the gender differences modulated this early decisional component; men’s P3 reactivity was lower than women’s [48]. The P3 amplitude to visual cues also was modulated by preceding graphic warning cues. Highly emotional...
graphic warning labels reduced P3 response when showing the smoking-related cues between non-treatment-seeking smokers. This indicates that these labels could potentially reduce the number of smoking-related deaths [47]. In addition, some other studies show that alcohol sensitivity may be a modulator of P3 component in smokers. In these studies, lower alcohol sensitivity is associated with larger P3 amplitude in young adult smokers [48, 49]. Two new studies have evaluated the association between middle ERP with smoking relapse and cigarettes per day (CPD) [46] [26]. In Cheng’s [46] study, there was a significant positive association between CPD and the peak of P3 amplitude in young adult smokers. In another study, a Go/No-Go task has been conducted and the reduction of the P3 amplitude was associated with increased risk of the relapse reflecting an inhibitory control deficiency.

In addition to Luijten’s [26] study, the compromised P3 amplitude also was found in two other inhibition control study, where adolescent/satiated smokers and overnight nicotine-deprived smokers revealed less P3-inhibitory response compared to controls [50, 51]. This finding suggests that reduced P3 amplitude may be a marker of inhibition control deficits in IND.

Little et al. showed that associative learning might occur between young adult smokers. They used a conditioning task in which ERPs were recorded during the pairing of smoking-related and neutral stimuli with two geometrical figures. They revealed that the P3 amplitude of geometrical figures jointed with smoking-related cue is amplified relative to those jointed with neutral stimuli [44].

Regarding late latency ERPs, modulation of LPP amplitude in smokers by different visual stimuli, i.e., pleasant, unpleasant [52], and cigarette stimuli [26, 46, 52] was larger than that of neutral stimuli, reflecting a facilitated processing of motivationally relevant (or emotional) stimuli in smokers.

In Minnix’s study, cigarette-related images containing people in contrast to the images containing objects had no differences in LPP amplitude, while this difference in the case of emotional images does exist, denoting that cigarette objects may be highly relevant for smokers than emotional objects.

Among different types of stimuli, gender difference was found for pleasant type such that females showed a less attentional bias to pleasant cues, as they exhibited significantly smaller LPPs to pleasant stimuli than those of males [52].

Few studies assessed the association between late ERPs with smoking relapse, abstinence, and CPD [26, 46, 53]. Smokers showing blunted LPP responses to intrinsically pleasant stimuli had significantly lower rates of long-term smoking abstinence [53]. Luijten et al. also found that smaller Pe amplitude, reflecting conscious processing of errors, may be related to an increased chance of smoking relapse, they also reached to a larger LPP amplitude for smoking cues than neutral cues which was not associated with relapse [26]. A significant positive correlation was also found between the CPD and the SPW amplitudes, indicating more CPD is related to enhanced cognitive processing to smoking-related cues [46].

### 3.2.3. Middle Latency ERPs

The main findings of behavioral results in nicotine dependence are as follows. Regarding the behavioral results in smokers, reduced post-error slowing and increased P3 amplitude elicited in cue reactivity paradigm were related to an increase in smoking behavior over time [26]. This relationship was also observed concerning the dependence level, i.e. the higher dependence the higher P3 [48]. Smokers were higher error in No-Go paradigm among smokers compared with non-smokers [50]. A positive correlation between CPD and P300/SPW amplitude was observed in young smokers [46]. Craving was significantly higher for a geometrical figure that was paired with smoking stimuli than for the geometrical figure that was paired with neutral stimuli [44]. Reaction time and accuracy in inhibitory control task was not different between smokers and non-smokers [43]. Most previous studies reported that smokers are less accurate on No-Go tasks and their inhibitory control is generally impaired in the way that their behavioral deficit is revealed during drug related and neutral cues [35]. In conclusion, it seems that cognitive deficits in nicotine-dependent individuals is reflected in their accuracy in inhibitory task by measuring accuracy rate but not in reaction time, however,
converged evidence are not still plenty. Moreover, the dependence/craving and dose of consumption are reflected in more pronounced P3 in cue induced craving tasks and this ERP when elicited in inhibitory paradigm has the potential to predict relapse.

3.3. Studies in Individuals with Cannabis Dependence

3.3.1. Early Latency ERPs

New researches in IAD show that the Early ERP (P100) may be modulated by drug-related cues. Moreover, N2 and P100 components may also have associations with relapse and dose of consumption.

In this regards, early automatic sensory processing (P100) revealed that processing of alcohol-related stimuli can be modulated by binge drinking [54]. In Petit et al.’s study, the P100 amplitudes elicited by alcohol-related pictures were significantly larger than those elicited by non-alcohol pictures where, latencies of the ERP component yielded no significant results which are in line with those of [55]. Two studies assessed the correlation between the relapse, dose consumption and the early ERP components [55, 56] in which larger amplitude of the P100 has a significant correlation with the duration of binge drinking habits and doses consumed per week [54]. Petit et al. showed that lower reactivity to addiction-related stimuli could be correlated with abstinence success. In line with this finding, No-Go N170 amplitude to substance cues was more elicited in patients who relapsed in 3 months following detoxification in response to the alcohol cues as compared to those who remained abstinent [55].

3.3.2. Middle Latency ERPs

Findings of new research assessing P3 changes show that the more alcohol consumption may be related to the increased P3 amplitude in both cue reactivity and inhibitory control paradigms.

In this regards, alcohol cues elicited larger P3 amplitude in binge drinkers compared to light drinkers with a greater effect among men, while P3-latency analyses did not reveal any significant effect between the drinkers [59]. The P3 amplitude enhancement shows that alcohol-related stimuli capture more attentional resources of binge drinkers relative to light drinkers. On the other hand, the potency of drug stimuli has been found not stronger than that of negative valence stimuli. In this regard, petit et al. [54] found that negative stimuli, independent of the stimulus type (alcohol or non-alcohol), elicit larger P3b amplitudes than positive (alcohol or non-alcohol) and neutral stimuli. Their finding is in line with previous studies among healthy population that showed the aversive information processing [60].

Increased P3 component in a Go/No-Go task shows that LS subjects confront with more conflict when they inhibit to respond to alcohol cues compared to their HS peers, reflecting more neural deficits in LS in contrast to HS alcoholic patients [58]. In [61] based on an inhibitory control task, it was shown that P3d amplitude (computed by subtracting Go P3 from No-Go P3) is the only variable that significantly predicts the chance of relapse between relapsed and non-relapsed alcohol-dependent participants; they found that the P3d is larger in relapsed subjects compared to the non-relapsed peers.

Stress effect on the P3 reactivity was assessed by recording ERPs in two states: stress state and non-stress state [62]. The results showed that the standard “oddball” effect has occurred in the non-stress condition unlike the stress condition. This finding suggests that the participants’ ability to ignore task-irrelevant stimuli is affected by the stress.

3.3.3. Behavioral Findings

Behavioral results among alcoholics have shown converged evidence on RT by performing visual oddball tasks, but these results were not considerably converged in inhibitory control studies. Studies that used visual oddball tasks [56, 59, 62] showed that the reaction time of alcoholics for alcohol images is shorter than that for neutral images. But in Go-NoGo tasks the results are not converged, as in some studies shorted RT for drug related cues is reported [58, 63] or no significant difference was observed for RT [58, 61]. Accuracy and error rates also had not significant differences between alcoholics and controls. However, Kamarajan et al. [64] and Petit et al. [61] found that individuals with alcohol dependence were
less accurate than controls during task performance. accuracy differences were not observed in six other studies. [35].

3.4. Studies in Individuals with Methamphetamine Dependence (IMD)

Among four new studies in IMD, three studies assessed early latency ERPs and one considered P3 changes by a visual oddball paradigm. Regarding early ERPs, a study has shown that cognitive performance improves following exercise [65]. Where, N2 amplitude was greater in one-session-moderate intensity exercise than other one-session exercisers (light/high intensity and control) indicating that moderate intensity exercise is optimal for facilitating neutral inhibition in the IMD. This finding is in line with that of [66] which assessed the effect of acute aerobic exercise on cognitive deficit of IMD, and also with a meta-analysis about the exercise effect on cognitive performance [67].

For middle latency ERPs, in the study of [68], performed in the abstinent IMD, the P300 reactivity was increasingly modulated by methamphetamine-related words over left-anterior electrode for IMD in comparison to healthy controls. This increase was correlated with patients’ craving for methamphetamine, measured by the Visual Analogue Scale (VAS). This implies that the P3 amplitude over left-anterior sites may be developed as an indicator of subjective craving. Their follow-up results revealed that attentional bias for methamphetamine-related cues declined after abstinence leading to a significant reduction trend in P3 amplitude within the first 3 months of abstinence.

3.4.1. Behavioral Findings in Stimulant Users (Methamphetamine and Cocaine)

Stimulant dependent individuals who used cocaine showed greater error rate with slower RT [39], while two other studies have not reported significant results in this regard [69, 70]. Among methamphetamine users, none of them reported significant differences in RT between control and methamphetamine users. The common finding of methamphetamine studies is that the exercise decreases RT and methamphetamine craving [65, 66]. Altogether the reports of stimulant drug studies are not converged on accuracy and RT differences between stimulant dependent individuals and controls.

3.5. Studies in Individuals with Cocaine Dependence (ICD)

3.5.1. Early and Middle Latency ERPs

Some of the recent studies in ICD have shown a neural deficit in inhibitory control and error processing of cocaine users. Morie et al. [71] investigated cognitive control in current cocaine users and found that the amplitude of inhibitory control (N2, P3) and error processing (ERN, Pe) components are lower than that of healthy controls. This finding corresponds to the findings of preceding studies in cocaine users who were abstinent for at least one month [72] and also in current cocaine users [73].

Sokhadze et al. [74] carried out a study among three groups: only cocaine dependent patients, cocaine dependent patients with comorbid Post-Traumatic Stress Disorder (PTSD), and healthy subjects. In their study, both groups of recruited individuals with ICD showed an enhanced cognitive processing to drug-related and negative valence (trauma) cues compared to neutral cues indexed by P3a and P3b. It happened while the deployment of attentional resources to both drug and trauma cues for cocaine dependent patients with PTSD was more than addiction-only group.

3.5.2. Late Latency ERPs

Regarding late ERPs, study of [75] showed that current cocaine abusers and abstinent peers allocate more attentional resources to the cognitive processing of cocaine cues and emotionally pleasant and unpleasant stimuli relative to neutral stimuli, indexed by early (400-1000 ms) and late LPP (1000-2000 ms). By the later LPP, enhanced processing of the cocaine pictures was apparent in abstinent users but not current users. This difference shows that abstinent cocaine users are stronger in retaining of attention to drug-related cues as compared to current users.

Moeller et al. [76] performed a study by recruiting 3 categories of participants: intact insight cocaine users,
impaired insight cocaine users and healthy controls. They used a passive picture-viewing task, during which early LPP and late LPP were recorded. Their result shows that late LPP elicited by cocaine cues predicted cocaine image choice in cocaine abusers with impaired insight better than pleasant/unpleasant and neutral cues, denoting that the late LPP may be used as a biomarker to forestall drug-related choice.

A more recent study [70] explored genetic factor (carriers of one 9R-allele of DAT1 vs. homozygote carriers of the 10R-allele) between ICDs. They computed the correlation between the number of days of cocaine abstinence and LPP reactivity. Their results showed that 72-hours- abstinent users with 9R-allele exhibit more enhanced relativity (LPP) to cocaine cues than neutral cues. This result may indicate that 9R-allele can be considered as a risk factor for relapse.

4. Discussion

In this study, we reviewed most recent studies that used ERPs to investigate cue reactivity, inhibitory control and error processing in individuals with SUDs. These works have often investigated the effect of different cue factors such as valence and stimulus type in their cue reactivity paradigms. Here, we discuss about the main findings of these factors in the recent studies and compare them with the results of similar older ones. The findings associated to inhibitory paradigms are also separately discussed.

4.1. Early Latency ERPs

A number of studies have shown no differences in automatic attention bias in abstinent and cocaine current users indexed by early posterior negativity (EPN) [75]; in abstinent alcoholic patients indexed by P100 [61] and in young binge drinkers indexed by the later cognitive processing component, N2b [54]. On the other hand, a significant difference has been found in chronic cannabis users and young binge drinkers demonstrated by the enhanced amplitude of early ERP components. The cannabis users allocate more attention to drug relative to negative valence stimuli as indexed by EAP [39], and this occurs among binge drinkers for alcohol-related cues in comparison to non-alcohol cues, indexed by P100 [54, 77]. The early ERP modulation also was significant in [78], where EPN was more elicited to passive viewing tobacco stimuli and positive valence compared to negative valence stimuli. Altogether, the results of studies investigating the early ERP components show an enhanced early cognitive processing to drug-related cues in the individual with SUD. However, more studies are required in individuals with MA-dependence.

Another consistency in outcomes of more recent works is concerning the relapse to substance abuse. Reduction in the amplitude of ERPs which reflects the inhibitory control [46] and error processing [26, 54] is associated with increased risk of relapse, among nicotine and alcohol users. This association proposes that the approaches which could increase the inhibitory control, e.g. exercising [47, 67] in smokers and alcohol drinkers, are worth of further investigation to make cessation interventions better.

4.2. Middle and Late Latency

In the most cue reactivity based studies, it has been shown that ERP amplitude is increased by drug-related stimuli compared to neutral stimuli in individuals with substance dependence:

The amplitudes of the middle [46, 78, 79] or late latency components in cigarette smokers [46, 52, 53] and in cannabis users [80] [40] significantly increased, while non-significant increase has been found in cannabis users [39] and alcohol drinkers [59, 81, 82]. In this regard, drug-related stimuli had no significant effect on the LPP amplitude of abstinent-cocaine users [70], while it was significantly increased in current cocaine users with and without PTSD, indexed by P3a, P3b [74], LPP [83] and N300 [84].

Between-group (users, non-users) analysis also has shown that drug stimuli elicit larger neuronal reactivity in users than non-users: in cigarette users indexed by P3, SPW and LPP [46, 52]; in cannabis [38] and alcohol users [82, 85] index by P3.

In other word, these findings show that individuals with SUDs allocate more attentional resources for substance-related cues than neutral cues. In addition, drug stimuli capture the drug-dependent patient’s attention more than healthy controls, indexed by increased amplitude of
middle ERPs. Moreover, findings demonstrate that individuals with SUDs are stronger in retaining the attention to drug-related stimuli, indexed by increased amplitude of late ERPs. The new research outcomes are totally in line with previous meta-analysis findings [16].

Some studies have shown that the amplitude of ERPs increase in the case of valence stimuli (pleasant, unpleasant) relative to neutrals in cocaine and cigarette users, indexed by P3 and LPP components [53, 73, 78, 79]. As emotional events tend to be memorized and processed better than non-emotional events [86], it may be concluded that individuals with cigarette/cocaine dependence have no considerable deficiency in their emotional processing.

A number of studies have shown that the targets capture more attentional resources than non-targets [20, 43, 55, 87]. It shows that individuals with SUDs are vulnerable to addiction-related stimuli, even when occurring outside the focus of their directed attention. However, this vulnerability may be moderated among smokers by less attention to instructed targets compared to healthy controls [48, 88].

4.3. Inhibitory Control and Error Processing

In new studies regarding early stage of inhibitory control process, N2-amplitude (especially those induced in No-Go trials) has been shown to be related to relapse [55], enhanced by exercise [65, 66, 89] and is smaller in individuals with SUDs [71, 90]. However, the N2 amplitude was not significantly different between adolescent smokers vs. nonsmokers [50]. The new and pervious findings [35] both recognized the N2 component as a sensitive index of impairment in early stages of inhibitory control process in individuals with substance abuse.

Regarding the late stage of the inhibitory control process in individuals with SUD, a recent study [35] overall reached to controversial results, especially for alcohol users. Although some studies found smaller No-Go P3 amplitude in alcohol [91-93], cocaine [73] and nicotine users [88], other studies did not find any significant cognitive deficits in individuals with alcohol dependence [94, 95] and in cigarette smokers [96]. In recent studies, reduced P3 amplitude has been reported in cigarette smokers [50] and cocaine users [71]. In contrast, P3 amplitude enhancement was more pronounced between alcoholic patients than healthy controls [61]. Also Wang et al. did not observe significant differences between methamphetamine users and controls [47]. The findings of recent studies along with previous research, shows that the results related to the early stage of inhibitory control process are controversial, especially in alcohol and cocaine users. However, the results of studies between cigarette smokers have approximately shown that these patients show a deficiency in the late stage of inhibitory control process, indexed by lower No-Go P3 amplitude.

Two studies have indicated that more conscious processing of errors is less pronounced in individuals with nicotine and cocaine dependence [45, 71], indexed by lower Pe amplitude. The findings about initial error detection are controversial; the studies between nicotine users did not detect impaired initial error processing [45, 72], but another study showed that initial error detection is less pronounced in subjects with cocaine dependence, indexed by lower ERN amplitude. The latter corresponds to findings of Luitjen's study [35].

In conclusion, regarding to the predictive role of ERPs, it is expected that individuals with successful abstinence allocate less attention resources to drug-related cues to be abstained resulting in lower ERP amplitudes of cue reactivity and also those patients with less deficiency in inhibitory control resulting in less attenuated N2 amplitude may be more successfully abstained. In two studies by cue reactivity paradigm, Petit et al. [59] observed this attenuation in P3 of drug pictures in patients with alcohol dependence, but Luitgen et al. [35] reported no such relationship for cigarette smokers, or [78] observed it to P3 of emotional cues but not to that of drug cues. Also, [55] reported that relapsed individuals with alcohol dependence exhibits higher N2 amplitude. Hence, these findings show that there may be a relationship between relapse and ERP amplitude changes, but more studies are needed to find out if the changes have a decreasing or increasing trend.

In conclusion, new studies expand the findings of pioneer studies noting that individuals with SUD allocate more attentional resources to drug-related cues, indexed by increased amplitude of middle and late latency ERPs.
in comparison to healthy controls. New studies also show that this increase may also occur for early latency ERPs, reflecting enhanced automatic attention to drug-related cues in SUD individuals. In addition, their inhibitory control and conscious processing of error are deficient, shown by lower No-Go N2 and Pe amplitude. This deficiency in inhibitory control may predict relapse to substance abuse.

References


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