Review Article

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

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Abstract

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. 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.

The results show that individuals with SUDs 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. SUDs reveal a deficiency in the inhibitory control and conscious error processing, indexed by attenuated N2 and Pe amplitude. The cognitive and motor inhibitory component (P3) changes show a controversial result.

This study expands the findings of previous related reviews implying that substance abusers allocate more attentional 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 outcomes also show that the chance of relapse to substance abuse could be predicted by recording ERPs reflecting inhibitory control and error processing.

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

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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 abusers with SUDs

Study	SU	Individuals	ERPs	Main electrophysiological results	Main behavioral results	paradigm
Piasecki, 2016	Ni	Ab: 90 (42 female, DS:46, OS: 44, age:18-29, current); CO: -	P3	P3 (A): Cigarette & straw cues elicited greater P3 compared to neutral stimuli. Increased cigarette craving elicited larger P3. Lower alcohol sensitivity elicited larger P3 to smoking cues. Neither smoking status (DS vs. OS) nor tobacco dependence moderated P3 reactivity to smoking cues. Lower sensitivity in combination with higher dependence was especially related to pronounced P3 reactivity to smoking cues.	No main results	Active-three stimulus-visual oddball
Luijten, 2016	Ni	Ab: 62 (30 males, current, M age: 43.035);CO: -	P300, LPP, N2 , P3 , ERN , Pe	P300 & LPP (A): They were not predictive neither for relapse nor for smoking increase. P3 & N2 (A): Smaller P3 were related to an increased relapse risk as well as increased smoking, but N2 was not predictive. ERN & Pe (A): Smaller Pe and ERN were associated with an increased relapse chance at a trend level.	Reduced Post-error slowing was related to an increase in Smoking behavior over time. NoGo accuracy: It has no association with relapse and smoking behavior	Passive-two stimulus-picture viewing ; Go/No-Go ; Eriksen Flanker
Yin, 2016	Ni	18(all male, M age:16.92,current);CO: 18(all male, M age: 17.23)	N2, P3	P3 (A & latency): Significantly reduced NoGo P300 amplitude and longer P300 latency were observed in adolescent smokers. N2 (A): They were not different between smokers and nonsmokers. They were significantly higher in NoGo trials than Go trials.	Error: Adolescent smokers made more NoGo RT: No significant difference was found in Go RTs.	Go/No-Go

Wang, 2015	Ni	Ab: 25 (9 female, current, M age: 33);CO: -	P3	P3 (A): Preceding high ER GWLs reduced the P3 elicited by smoking cues, significantly more than preceding low ER GWLs or neutral pictures.	Craving: Preceding high and low ER GWLs significantly reduced subjective the rating of cigarette craving.	Passive-three stimulus-picture viewing
Minnix, 2013	Ni	Ab: 180 (117 male, current, M age : 45.1);CO: 40(20 female, M age : 46.2)	LPP	LPP (A): In smokers, pleasant, unpleasant, and cigarette cues significantly elicited LPP larger than neutral stimuli, but did not differ from one another. Males had significantly enhanced LPP to pleasant stimuli than females and marginally larger LPPs to unpleasant stimuli. Nonsmokers had significantly smaller LPPs in response to erotic and cigarette stimuli relative to smokers.	Carbon monoxide sample and time since the last cigarette were uncorrelated with LPP amplitude.	Passive-three stimulus-picture viewing
cheng, 2016	Ni	Ab: 19(male, M age:21.0, 12h abstinent);CO: 19(male, M age 20.5)	P3 , SPW	P3 & SPW (A): The SPW of smoking-related cues was enhanced in young smokers compared with nonsmokers, P3/SPW of smoking-related cues was larger than neutral cues in young smokers.	A positive correlation between CPD and P300/SPW amplitude was observed in young smokers.	Passive-two stimulus-picture viewing

Rass, 2014	Ni	Ab: 31 Intermittent smokers(12 male, M age:23.9,current) ;22 Daily smokers (13 male, M age:25.2,current);CO: 30(14 male, M age:25.2)	ERN , Pe	ERN (A): In both tasks, ERN measures did not differ between groups. Pe (A): it was significantly largest for intermittent smokers.	No main results	Flanker ; Go/No-Go
Bloom, 2013	Ni	Ab: 21 (13 male, current, M age : 34.3);CO: 21(10 male, M age: 32.5)	P2a , P3	P2a (A): Cigarette stimuli elicited larger reactivity than the non-cigarette stimuli. P2a to the targets was larger than non-target. P3 (A): posterior P3 to the cigarette targets was significantly larger than other targets.	RT & Accuracy: No significant differences between smokers and non-smokers.	Active-three stimulus-picture viewing
Versace, 2012	Ni	Ab: 180 (63 male ,current , M age: 45.13);CO: -	LPP	LPP (A): Smokers with blunted LPPs in response to pleasant cues had lower rates of long-term smoking abstinence. The LPP for pleasant pictures was highly significant between two clusters, automatically clustered by k-means (k=2).	–	Passive-four stimulus-picture viewing

Little, 2012	Ni	Ab: 30 (current,5 males, M age: 21.9);CO: 31 (5 males, M age: 20.5)	P3 ,P1 , N2 , and P2	P2 & P3 (A): a geometrical figure that was paired with smoking stimuli elicited significantly larger P2 and P3 waves than the geometrical figure that was paired with neutral stimuli. P1 (A): It had no significant effect.	Craving: It was significantly higher for a geometrical figure that was paired with smoking stimuli than for the geometrical figure that was paired with neutral stimuli.	Higher order conditioning task(subjects responses by pairing smoking related and neutral stimuli)
Petit, 2013	Al	Ab: 29(15 male, current, M age: 21);CO: 27(10 male a, M age: 21)	P3	P3 (A and Latency): Greater P3 reactivity to alcohol cues relative to non-alcohol cues with a greater effect among men.P3 latency analyses did not show any effect.	RT: All participants have speeder response to alcohol compared to non-alcohol stimuli.	Active-three stimulus-visual oddball
Petit, 2012	Al	Ab: 18(12 male, current, M age: 21.28);CO: 18 (8 male, M age : 21.94)	P100 , P3b , N2b	P100 (A): In alcoholics, the P100 elicited by the alcohol-related stimuli were significantly larger than those elicited by the non-alcohol stimuli.N2b: No significant effect.P3b (A): In both user and control groups, negative stimuli elicited significantly larger P3b compared to neutral.	Greater number of doses consumed per week correlated with the larger P100 amplitude to Alcohol-related cues. RT: All participants had significantly faster responses to alcohol-related stimuli compared to non-alcohol related ones.	Active-three stimulus -visual oddball

Fleming, 2014	Al	Ab: 85 (54% women, current, 51% LS , M age: 19.5);CO: -	N2, P3	N2 (A): LS subjects showed significantly larger N2 to alcohol-cued trials in low probability No-Go trial relative to high probability ones. Hs group had a predictable increase in N2 when no-go probability was low relative to high. P3 (A): LS individuals compared to their HS peers showed an enhancedP3 in response to low-probability inhibition trials cued by alcohol but not those cued by non-alcohol and not when inhibition was a high-probability event.	RT: LS participants were faster to respond to alcohol-cued targets compared to non-alcohol-cued targets, but HS subjects did not show any RT bias. Craving: The increased duration and intensity of exercise result in decreased craving.	Cued Go/No-Go (a cue preceded the target)
Petit, 2014	Al	Ab: 27 (7 females, abstinent, M age: 45);CO: 27 (7 females, M age: 45)	N2, P3 ,P3d	P3 (A): Equal go P3 between groups but significantly enhanced No-Go P3 amplitudes in patients P3d (A): Statistically different P3d between patient and controls. P3d was significantly larger in relapsers compared to non-relapsers. This variable predicted the chance of relapse. N2 (A): had not any significant effects.	Omission error rates: Patients made more omission errors than controls Commission error rates: Patients made more commission errors than controls RTs: No significant effect was observed for RTs.	Go/No-Go
Korucuoglu , 2014	Al	Ab: 87 (33 males, current, M age:17.6);CO: -	N2, ERN	N2(A): No-Go N2 for the alcohol cues was larger than the neutral cues in both placebo and alcohol conditions and acute alcohol decreased NoGo N2 amplitude only to alcohol cues. ERN (A): It was significantly smaller in the alcohol than the placebo condition. Negative correlation between change in AUDIT and the ERN contrast in the alcohol cues.	Error rate: It was lower for neutral than beverage images. RT: It was shorter in the placebo condition for trials with commission errors and correct Go responses.	Go/No-Go

Ceballos, 2012	Al	Ab: 75 (38 male, current, M age: 23.5);CO: -	P3,N2	N2 (A): Stress enhanced N2 amplitudes to drug related and nonrelated stimuli regardless of their target status. 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 by stress beyond practice effects.	RT: It decreased following the stress manipulation. RTs of the alcohol targets were shorter relative to neutral target.	Active-three stimulus-visual oddball
Matheus-Roth, 2016	Al	Ab: 30 (5 female, M age : 44.3, abstinent);CO: 31 (6 female, M age: 43.3, abstinent)	P100, N170	P100 & N170(latency): No significant results for both ERP . No-Go P100 and G0-P100 of patients showed longer latencies when depression acted as covariate. N170 (A): Larger occipital No-Go N170 in response to the alcohol- related stimulus was associated with relapse in 3 months following detoxification.	No main results	Go (ignoring response to frequent non-addiction target) ; NoGo(ignoring response to infrequent addiction target)
Stein, 2018	Al	Ab: 15(abstinent, M age: 46.2);CO: 15 (M age: 43.4)	P3,N2	P3: amplitude of P3 was reduced in subjects with AUD. N2: NoGo-N2 amplitude in patients was trendily lower than controls. In subjects with strong craving, the conflict reflected in the NoGo-N2 was enhanced in the alcohol-related context	RT: It was significantly slower on alcohol related compared with neutral Go trials in AUD group.	Go/No-Go

Jiang, 2015	MA	Ab: 26 (14 male, abstinent, M age: 31.7);CO:29 (15 male, M age: 29.4)	P3	P3 (A): MA-dependent patients displayed significantly larger P3 than the healthy controls. The relationship between the changes of VAS scores for MA craving and the changes of P3 elicited by MA-related word within the first 3 months was significant.	RT & error rate: There were no significant differences between two groups in the RT or the error rate at baseline and 6 months after detoxification.	Active -word color matching-Stroop
Wang, 2016	MA	Ab: 92 (14 females age:49.7,current) ;Co:-	N2		Go-RT/ NoGo -RT: Moderate intensity exercisers showed shorter RT to MA stimuli than light/high/ control exercisers. The high group was speeder than light and control groups. Craving: The increased duration and intensity of exercise result in decreased craving.	Go/No-Go
				Go-N2 / Nogo-N2 (A): Moderate -intensity exercisers had larger amplitudes than light/high/control exercisers.		
				Go-N2/ Nogo-N2 (latency): Moderate exercisers had shorter latency than light/high/control exercisers.		
Wang, 2015	MA	Ab: 24(M age:31.46, 20 male, current);CO:-	N2, P3	N2 (latency): No significant exercise effect. N(A): Only for MA –related task, Nogo-N2 were significantly larger than Go-N2 . Go/NoGo N2 for exercisers were significantly larger than controls . P3: No alterations in the P3 amplitude or latency following acute exercise.	Go-RT: Exercisers showed partially shorter RT than controls to MA-cue.	Go/No-Go (a standard & a MA-related)
					Go-accuracy: exercisers had partially improved accuracy than controls. Craving: MA craving was significantly attenuated during and following the cessation of aerobic exercise.	

Morie, 2014	Co	Ab: 23(7 males, M age:44, 24 h abstinent);CO:27(7 mal3, M age:41)	ERN , Pe , N2 ,P3		N2 amplitude was associated with duration of drug use. Inhibitory control and anhedonia were correlated, but only in controls. Commission error rates: Cocaine users made significantly more errors. RT: cocaine users were generally slower.	Go/No-Go
				N2,P3,ERN and Pe amplitudes were smaller in addicts than in controls		
Moeller, 2013	Co	Ab: 73(63 males, abstinent; DAT1 10R/10R Allele: M age=44.2, CUD+=18, CUD-=28; DAT1 9R Allele: M age=44.3, CUD+=17, CUD-=10);CO: 47(41 males age: 40.85, CUD+=24, CUD-=23)	LPP	10R allele group: Cocaine-mines-pleasant LPPs of CUD+ was larger than healthy controls.	A greater response to cocaine cues correlated with greater cocaine craving and fewer days of current cocaine abstinent.	Passive-four stimulus -picture viewing
				9R allele group: Cocaine-mines-pleasant LPPs of CUD+ was larger than CUD-.		
				10R/10R vs 9R allele: Cocaine-mines-pleasant LPPs of 10R/10R CUD+ were larger than 9R allele CUD-.		
				In both CUD groups, Cocaine-cue LPPs was larger than pleasant-cue LPPs.		

Henry, 2014	Ca	234 (137 infrequent users , M age: 18.38 , 50.4% female, ,current; 97 frequent users ,current, 50.5% female, Mage: 18.35);Co:119 (51.3% female age: 18.31)	P3	P3(A): P3 to cannabis cues among frequent cannabis users (not infrequent users) was larger than never users. Cannabis use was associated with greater P3 reactivity to cannabis images. Infrequent cannabis and exercise images each elicited larger P3s than the more frequently presented neutral images. Both auditory irrelevant and relevant oddball tones elicited larger P3 relative to standard tones.	Cannabis cue reactivity was significantly related to self-reported cannabis craving.	Active-visual oddball ; Active-auditory oddball
Asmaro, 2014	Ca	Ab: 12 (all males, 24 h abstinent, M age: 22.23);CO: 14(all males, M age: 20.27)	P3b , LPP, EAP	EAP (A): It increased to drug stimuli compared to emotionally negative stimuli between cannabis users.	Accuracy: Cannabis users committed more errors while responding to	Picture based - Stroop
				P3 & LPP (A): P3 and LPP enhancements to drug stimuli were not greater in cannabis users relative to non-users.	Stimuli in the Drug blocks than non-users did.	
					RT: It was slower for emotional than neutral Stimuli.	

DS=Daily Smokers; - = Not Recruited; OS= Occasionally Smokers; ms= millisecond; M age= Mean age; RT=Reaction Time; Current= Current substance users at the time of testing; h= hour; abstinent=participants were abstinent at the time of testing; CUD+= Cocaine Use Disorder with urine positive; CUD-= Cocaine Use Disorder with urine negative; MA=methamphetamine; LS= Low Sensitive; HS= High Sensitive; GWLs=Graphic Warning Labels; ER=Emotional Reaction ; CPD= Cigarette Per Day; omission-error rates =no response in go trials; commission-error rates =key press in no-go trials; VAS = Visual Analogue Scale; AUDIT= Alcohol Use Disorder Identification Test ; Active= The subject is required to respond physically or mentally to the target; Passive= The subject is not required to respond physically or mentally to the target; SU= Substance abused ; MA= Methamphetamine ; Ni=nicotine; Al= Alcohol; Co=Cocaine ;Ca=Cannabis; Controls are healthy volunteers; The location of electrodes are based on International 10–20 system. All Go/NoGo tasks are active.

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, indicting 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.

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