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Associations of the P300 Event-Related Potentials and Self-Reported Craving in Substance Use Disorders: A Systematic Review

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Event-related potential · Substance use disorder · Craving · P300 · Attentional bias

Abstract
Introduction: The phenomenon of craving and attention bias towards drug cues is theorized to operate cooperatively, owing to the principles of associative learning. In this context, the conditioned response to drug-related stimuli activates reward mechanisms within the brain, consequently inducing craving and fostering the underlying mechanisms that contribute to relapse in individuals with substance use disorders. Multiple studies have assessed the relationship between attention to substance-related cues and subjective craving through electroencephalography (EEG), but their findings have yet to be synthesized and examined. This review summarizes the association between the amplitude of the P300 event-related potential (ERP) and substance use craving, compares discrepancies in results by type of substance, and discusses gaps in the literature to inform future research. ***Methods:*** A systematic search was conducted on Embase, Web of Science, CINAHL, and PsychINFO databases. Studies were published in English and included peer-reviewed human research investigating the relationship between EEG P300 ERP and self-reported substance use craving. The included study samples comprised of in treatment or non-treatment-seeking participants who use substances. The primary outcomes of interest were those derived from inferential statistics assessing P300 amplitude and substance use craving. ***Results:*** Ten studies were included in the final search and were organized by substance type: three alcohol, three cocaine, two tobacco, one heroin, and one cannabis. Results were mixed for alcohol and cocaine. Studies on tobacco, heroin, and cannabis use were congruent for associations between the P300 amplitude and craving. ***Conclusions:*** Overall findings are mixed between studies addressing the association of the EEG P300 amplitude and craving. These results should be considered in the context of the limited sample size, underpowered analyses, and methodological differences that potentially contribute to discrepancies in outcomes. Further research is required to assess the role of craving assessment, EEG methodology, and substance-related factors on the association between P300 amplitude and self-reported craving.

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Introduction

Drug craving is a pervasive and measurable characteristic of substance use disorders [1] and has remained a fundamental interest in research and treatment [2]. An extensive body of empirical data and anecdotal reports highlight the direct involvement of craving in contributing to SUD maintenance (for a review, see [3]). Craving as a core feature within SUD maintenance is evident by its recent inclusion as a diagnostic criterion for SUDs in the fifth edition Diagnostic and Statistical Manual of Mental Disorders [4]. Craving is primarily associated with the characteristic preoccupation and anticipation behaviours associated with addiction and has been identified to significantly contribute to relapse and overdose [5]. In light of this, there is still uncertainty and debate in the conceptualization and operationalization of drug craving [6–11].

One barrier to understanding craving and its contribution to substance use patterns has been the need for more consensus on its construct and measurement [3]. Although there have been numerous developments in self-reported craving measures, the lack of consensus for a standardized measure and overall understanding of foundational constructs has led to inconsistencies in its conceptualisation (for reviews, see: [6, 7, 12–14]). Some studies restrict the definition of craving to the singular desire for substance use. In contrast, others adopt a broader definition, which includes the anticipation of the drug's effects, the time frame of the craving experience, and whether it is present in the absence of awareness (for a review, see [11]).

One model of addiction has defined craving as patterned attentional responses to drug-related cues [15]. It should be stated that within this systematic review, the authors will be referring to craving hereafter as a "drug acquisitive motivational state," as it has subjective, behavioural, and physiological components [15]. Previous research has demonstrated that with prolonged drug use, a sensitization of drug "wanting" or drug craving leads to the heightened attentional salience of the drug-related cues [16]. During drug abstinence, exposure to drug cues, as opposed to other cues, elicits a greater attention-driven comparison process [17]. There is evidence of attentional biases that increase attention towards drug cues in relation to other naturally rewarding cues in the environment, specifically in those who use alcohol [18], tobacco [19, 20], cannabis [21], cocaine [22], and heroin [17]. The relationship between increased attentional salience to drug-related cues and self-reported craving was initially suggested by Robinson and Berridge [16]. The incentive sensitization theory postulates the underlying mechanism by which substances gain heightened salience and acquire strong motivational properties, thereby eliciting subjective cravings for the substance to emerge [16]. Through classical conditioning, the cue "grabs attention, becomes attractive and 'wanted,' guiding behaviour to the incentive" (20, p. 261). Consequently, the model suggests an underlying process that reflects both subjective craving and attention bias, thus implying a potential correlation between these two constructs.

Electroencephalographic (EEG) techniques have been used to assess attentional activity as a function of patterned activation in the human event-related brain potential (ERP; 28). EEG electrodes placed on or near the scalp record ongoing changes in electrical potentials in the brain. When EEG is time-locked to specific events (like the presentation of a cue), the resulting positive and negative voltage changes over time are referred to as ERPs. ERPs are summated post-synaptic potentials of populations of neurons in the brain, reflecting a range of cognitive processes distinguished by their timing, polarity, and response to experimental manipulations [23, 24]. ERP components can be obtained through numerous events, such as the presentation of auditory cues and visual cues. For instance, the "P300," a positive ERP component, peaks between 300 and 800 ms post-stimulus onset [25]. The P300 ERP is postulated to reflect the allocation of cognitive resources in response to the presentation of a visual cue, serving as an index of the cue's incentive salience or motivational significance [26–29]. Specifically, if the cue is not a source of salience, the attentional processes are minimal [30]. If the cue is unexpected, emotionally provocative, or salient, the processing system increases, resulting in an increased allocation of attentional resources to the cue [30]. Additional ERP components representing different cognitive processes can be observed, contingent upon the specific time window captured. A longer ERP component can increase for several seconds following the presentation of a stimulus, reflecting more motivational cognitive functions that contain sustained attention and emotional processes [30]. Theoretically, the differences between P300 and longer ERP components are described as automatic vs. sustained processing, both of which are useful in attention processing and craving within SUDs [30]. Gaining a conceptual understanding of the relationship between attention allocation, as measured by the P300, and craving requires the examination of P300 responses specifically elicited by visual substance-related cues. Thus, a synthesis of studies investigating substance-related cue-evoked P300 and its association with self-reported craving may provide valuable insights into the underlying dynamics within SUDs.

Numerous studies have assessed the association between P300 attentional processing and subjective craving within different SUDs; however, these studies have yet to be synthesized and examined. Thus, this review aims to (1) synthesize the evidence of a relationship between the P300 ERP component and alcohol and drug use craving, (2) compare these relationship patterns across the types of substances where data are sufficiently available, and (3) identify gaps in the literature and future directions.

Methods

Registration and Reporting

This review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [31] and was pre-registered in the International Prospective Register of Systematic Reviews (PROSPERO; CRD42021288810). The review aimed to assess the association between the P300 ERP component and self-reported craving across SUDs. Previous work assessing the relationship between the P300 and craving within Opioid Use Disorders was published by our group and indicated that a more encompassing review of all substances was needed [32].

Databases Utilized and Search Strategy

A systematic search was conducted on Embase, Web of Science, CINAHL, and PsychINFO, based on recommended databases identified by Gusenbauer and Haddaway [33]. Our strategy began with dividing the primary question of whether there is a relationship between the amplitude of the P300 ERP component and subjective reports of craving into the three key concepts: SUD, EEG/P300, and craving. Keywords and controlled vocabulary identified as relevant to each concept were compiled and executed within the databases (online suppl. Table S1; for all online suppl. material, see https://doi.org/10.1159/000533147) without search limiters.

Inclusion and Exclusion Criteria

Inclusion criteria were defined based on the following parameters: (1) published in English; (2) peer-reviewed primary research; (3) P300 ERP component and its relationship with self-reported substance use craving were investigated; (4) focused on recreational and chronic use of drugs, including stimulants, depressants, hallucinogens, inhalants, narcotic analgesics, and cannabis. Those that were excluded were studies that encompassed the following: (1) exclusively tested non-visual stimuli evoking the P300 component, (2) used animal populations, (3) used pediatric populations (under the age of 18), (4) exclusively used electroretinograms, and (5) did not include a positive 300 ms ERP component.

Outcomes Considered

The reported outcomes of interest were those derived from inferential statistics on the relationship between P300 amplitude and subjective substance use craving. In studies where an association between P300 amplitude and subjective craving were reported, the latency of the P300 component, the substance of primary interest, the possible effect at electrode positions, and the visual cue paradigm used were examined.

Data Extraction and Synthesis

References extracted from the initial search across databases were deduplicated using the Mendeley (mendeley.com, London, United Kingdom) reference manager, then uploaded onto Covidence (covidence.org, Melbourne, Australia) for the subsequent title and abstract screening, full-text review, and article extraction. All titles, abstract reviews, and full-text reviews were performed independently by trained research staff (C.L., B.H.Z., L.F., A.L.). Sorting conflicts and disagreements were reviewed and resolved by graduate-level research trainees (T.E., A.S.). All stages of the review procedures were overseen by a postdoctoral researcher (T.C.). A meta-analysis was not performed due to high variability in the methodologies across studies.

Risk of Bias Assessment

The risk of bias in the included studies was assessed by two reviewers (A.S. and T.E.) using the Risk of Bias Assessment tool for Nonrandomized Studies (RoBANS) for nonrandomized controlled trials [34]. The utilization of the RoBANS is imperative in research designs that are particularly prone to bias and confounding variables, as these methodological factors have the potential to undermine the validity and reliability of study outcomes [34]. The tool focuses on six potential sources of bias: participant selection (evaluates the potential bias in the selection and recruitment of study participants, such as the inclusion and exclusion criteria, representativeness of the sample, and comparability of the groups), extraneous confounds (assesses the potential influence of confounding factors and whether the study design and statistical analysis adequately controls for these factors), performance bias (evaluates the exposure to the intervention or treatment of interest, including the reliability and validity of the measurement tools, and the possibility of differential misclassification), blinding of the outcome (reports whether the outcome assessors were blinded to the intervention status of the participants, as the lack of blinding can introduce measurement bias), completeness of data (evaluates the potential bias related to missing

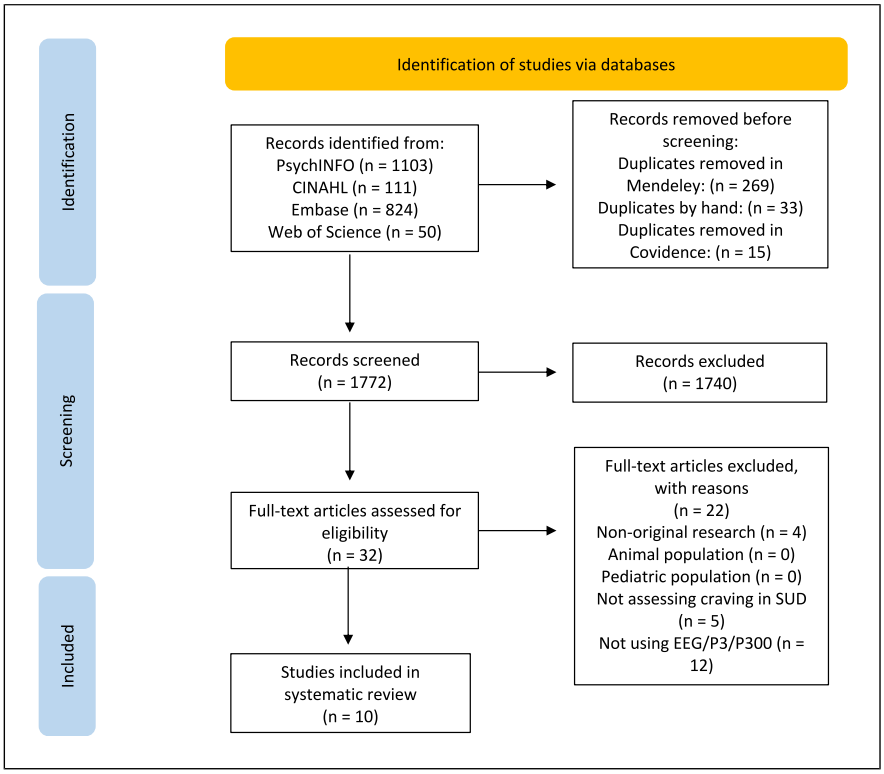

Fig. 1. PRISMA flow chart of study selection.

outcome data, such as attrition, loss to follow-up, or exclusion of participants from the analysis), and selective outcome (assesses the selective reporting of outcomes, which might occur if the study authors only report favourable results or modify the pre-specified outcomes to suit their findings). In addition, the sources are graded low, medium, and high risk of bias.

Results

Summary of Search Results

The initial search yielded 2,088 references across the four databases. A total of 1,772 references remained following the removal of duplicates. A further 1,740 references were excluded from the title and abstract screening. Full-text articles were retrieved and reviewed for the remaining 32 references, yielding the final ten articles identified for this review, as described in Figure 1.

Seven of the included articles investigated the P300 and subjective craving as the primary outcome and the remaining three as secondary findings. The country with the highest prevalence of relevant articles was the Netherlands (n = 4), followed by the USA (n = 3). The study samples comprised inpatients (n = 8) and college students and staff (n = 2). The most common substances investigated were alcohol (n = 3) and cocaine (n = 3), followed by tobacco (n = 2), heroin (n = 1), and cannabis (n = 1). The measures for cue-reactivity included visual cue presentations (n = 7), tasks of impulsiveness (n = 1), and tasks for attentiveness (n = 2).

All studies included in this review introduced cue-induced craving via the presentation of positive, negative, or neutral photos and substance-related images. The P300 amplitude assessed varied across studies by the interval time after following exposures to substance cues (ranging 150–2000 ms; Table 1).

Risk of Bias Assessment

The studies overall demonstrated a low risk of biases in selecting participants, confounding variables, blinding of the outcome, selective outcome, and mostly incomplete outcome data. Unclear sections existed in the measures of exposure. Each study reported craving outcomes using self-reported craving measures. Self-report measures, predominantly self-reported craving questionnaires and surveys, are at high risk for bias. One study reported unclear confounding variables and incomplete reporting of data [35]. The overview assessment grades can be found in online supplementary Table S2.

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Table 1. Summary of sample demographics and findings for included studies

Substance	Author and location	Recruitment	Sample size	Substance users		Controls, age	P300 ERP component, ms	Cue reactivity paradigm	Channel(s) used to quantify P300	Images used	Craving measure	Presence of relationship between P300 and subjective craving
				age	abstinence period before testing and use status							
Alcohol	Batschelet et al. [41] 2021, Switzerland	Inpatients and community volunteers	59 AUD (36% F) 20 HCs (35% F)	43.4±10.1	Alcohol use: ≥1 week abstinent	44.7±11.2	150–1,500	Go/NoGo	Whole scalp (64 channels)	Alcohol and neutral	OCDS	No; craving was not correlated with P300 amplitude for alcohol cues[e]
	Brown et al. [43] 2020, USA	Community volunteers	68 AUD[c] (47% F)	52.2±13.6	Alcohol use: ≥30 days abstinent	*N/R*	300–2,000	Passive viewing	POz/Pz	Alcohol, neutral, and negative	VAS	Yes; correlations between changes in craving and P300 amplitude for alcohol cues ($\beta = -0.28$)
	Namkoong et al. [42] 2004, Korea	Inpatients and community volunteers	16 AUD (13% F) 12 HC (17%F)	37.5±6.4	Alcohol use: ≥2 weeks abstinent	35.4±5.6	250–500	Passive viewing	F4, C3, Cz, C4, P3	Smoking, neutral, and positive	VAS	Yes; correlations between changes in craving and P300 amplitude for alcohol cues (F4 ($r = 0.506$), C3 ($r = 0.403$), Cz ($r = 0.409$), C4 ($r = 0.414$), P3 ($r = 0.406$), and P4 ($r = 0.398$))
Tobacco	Littel et al. [45] 2007, Netherlands	College students and staff	21 individuals who currently smoke[a]	Currently smoking 21.6±2.5	Currently smoke: ≥10x/day	19.6±1.2	300–400	Passive viewing	Oz, Pz, Cz, and Fz	Smoking and neutral	QSU	Yes; correlation between craving and P300 amplitude to smoking cues relative to neutral cues ($r = 0.32$)
			18 individuals who smoke formally smoked[a]	Formerly smoking 23.1±4.1	Formerly smoked: ≥6 months							
			24 individuals who have never smoked[a]									
	Mashhoon et al. [44] 2018, USA	Local advertisements	8 early-onset[b] smoking (50% F)	Early-onset smoking 35.0±2.5	Cigarette use: 10–20x daily)	31.1±3.9	250–500	Passive viewing	Fz, Cz, and Pz	Alcohol and neutral	QSU	Yes; correlation between craving and P300 amplitude for smoking cues ($r = 0.50$)
			10 late-onset[b] smoking (50% F)	Late-onset smoking 31.2±4.8	≥12 h abstinence required before testing							
			10 non-smoking (50% F)									

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Table 1 (continued)

Substance	Author and location	Recruitment	Sample size	Substance users		Controls, age	P300 ERP component, ms	Cue reactivity paradigm	Channel(s) used to quantify P300	Images used	Craving measure	Presence of relationship between P300 and subjective craving
				age	abstinence period before testing and use status							
Cannabis	Henry et al. [46] 2014, USA	University students	97 frequent users of cannabis (51% F) 137 infrequent users of cannabis (50% F) 119 never used (51% F)	Frequent users of cannabis 18.4±0.5 Infrequent users of cannabis 18.4±0.4	Frequent: cannabis use 5 days/week in the past year Infrequent: cannabis use ≤4x/month	18.3±0.5	270–400	Oddball	Pz	Cannabis, exercise, and neutral	AUQ[d]	Yes; correlation between craving and P300 amplitude to cannabis relative to exercise cues (r = 0.16)
Cocaine	Franken et al. [48] 2004, Netherlands	Inpatients	10 CUD with high level craving[a] 11 CUD with low level craving[a]	High craving 31.6±10.7 Low craving 27.1±7.2	Cocaine use: ≥1 week abstinent	*N/R*	300–400	Passive viewing	Fz, Cz, and Pz	Cocaine, pleasant, unpleasant, and neutral	DDQ	No; craving was not correlated with P300 amplitude of any cue category (F(3,57) = 2.39)
	Franken et al. [47] 2008, Netherlands	Inpatients and community volunteers	23 CUD (0% F) 16 HC (0% F)	37.2±8.9	Cocaine use: ≥1 week abstinent	33.1±13.0	250–750	Passive viewing	Collapsed anterior (AF7/8, AF3/4, F7/8, F5/6, F3/4, Fp1/2), central (FT7/8, FC5/6, FC3/4, T7/8 C5/6, C3/4, TP7/8, CP5/6, CP3/4), and posterior (P7/8, P5/6, P3/4, PO7/8, PO3/4, O1/2)	Cocaine and neutral	OCDS	Yes; correlation between craving and P300 amplitude for cocaine relative to neutral cues (F8 (r = 0.70) and C4 (r = 0.52))
	Van de Laar et al. [40] 2014, Netherlands	Inpatients and treatment centre staff	26 CUD (0% F) 20 HC (0% F)	35.4±7.6	Cocaine use: ≥1 month abstinent	40.6±9.9	300–400	Passive viewing	F8, F7, F4, F3, P4, P3, Fz, Cz, and Pz	Cocaine and neutral	OCDS and DDQ	No; craving was not correlated with P300 for any cues[e]
Heroin	Lubman et al. [49] 2008, Australia	Outpatients	20 heroin users (0% F) 13 HC (0% F)	33.3±5.5	Heroin use: ≥2 weeks abstinent	31.8±5.4	250–550	Passive viewing	Fz, Cz, Pz	Opioid, neutral, and positive	VAS	Yes; baseline craving predicted P300 amplitude for opioid cues (FCz (β = 0.54), Cz (β = 0.72), and Pz (β = 0.51))

AUD, alcohol use disorder; CUD, cocaine use disorder; HC, healthy controls; N/R, not recorded; OCDS, Obsessive-Compulsive Drinking Scale; VAS, Visual Analog Scale; QSU, Questionnaire on Smoking Urges; AUQ, Alcohol Urge Questionnaire; DDQ, Desire for Drugs Questionnaire. [a]Percentage female not reported by study. [b]Early onset described as initiating smoking before 16 years old, late onset described as initiating smoking after 16 years old. [c]Included participants with lifetime diagnosis of SUD. [d]Modified version [e]Magnitude of effect size not reported.

Self-Report Craving and the P300 in Different Drug Types

Alcohol

Three studies focused on alcohol cues: two comprised both inpatients and community volunteers (those without a SUD who are willing to participate, recruited through local advertisements) [36, 37], and one strictly recruited community volunteers [38]. Batschelet et al. [36] had a sample size of 59 inpatients (36% female; 43.4 years ± 10.1) and 20 controls (35% female; 44.7 years ± 11.2), all of whom were abstinent from alcohol use for at least 1 week prior to the study. Brown et al. [38] had a sample of 68 adults with alcohol use disorder (47% female; 52.2 years ±13.6), all of whom were at least 1 month abstinent from alcohol use. Namkoong et al. [37] had a sample size of 28 participants, 16 of whom had alcohol use disorder (13% female; 37.5 years ±6.4) and 12 controls (17% female; 35.4 years ±5.6), all of whom were at least 2 weeks abstinent from alcohol use. Two articles found that the baseline craving rated on a visual analogue scale (VAS) score correlated with P300 amplitude in response to drug-related cues [37, 38]. Namkoong et al. [37] found channel-specific correlations at the F4 ($r = 0.506$), C3 ($r = 0.403$), Cz ($r = 0.409$), C4 ($r = 0.414$), P3 ($r = 0.406$), and P4 ($r = 0.398$) electrodes. Brown et al. [38] did not report a channel-specific effect but found an overall main effect of craving ($\beta = -0.28$) and ERP amplitude for alcohol cues ($\beta = -0.28$) over time. Batschelet et al. [36] found no correlation between the Obsessive-Compulsive Drinking Scale (OCDS) craving score and the P300 (effect size not reported).

Tobacco

Two studies examined responses to cigarette cues by local volunteers [39] and college students and staff [40]. Littel and Franken [40] had a sample of 21 individuals who smoke (% female not reported; 21.6 years ± 2.5), 18 individuals who had previously smoked (% female not reported; 23.1 years ± 4.1), and 24 adults who had no history of smoking (% female not reported; 19.6 years ± 1.2). Individuals who did smoke were required to abstain from cigarette smoking for at least 10 days, while those who formerly smoked were required to be at least 6 months abstinent from cigarette smoking [40]. Mashhoon et al. [39] had a sample of eight who began smoking before 16 years of age (50% female; 25.0 years ± 2.5), ten who began smoking after 16 years of age (50% female; 31.2 years ± 4.8), and ten individuals who did not smoke (50% female; 31.1 years ± 3.9), all of whom were at least 12 h abstinent from cigarette smoking prior to testing. There were positive correlations between P300 amplitude and craving, as measured by the Questionnaire on Smoking Urges – Brief (QSU – Brief) found in both studies [39, 40]. Specifically, Mashhoon et al. [39] found that the evoked signal at electrode Cz correlated with the statement, "*Nothing would be better than smoking right now,*" on the QSU-Brief ($r = 0.50$). In contrast, Little and Franken [40] found that the evoked signal at electrode Fz correlated with the first subscale of the QSU-brief, "desire and intention to smoke," in those who smoke versus those who had never smoked ($r = 0.32$).

Cannabis

Henry et al. [41] investigated craving correlation and response to cannabis cues in a sample of college students consisting of 97 frequent cannabis users (51% female; 18.4 years ± 0.5), 137 infrequent users (50% female; 18.4 years ± 0.4) and 119 who had never used (51% female; 18.3 years ± 0.5). Those who used cannabis at least 4 days per week in the last year were categorized as frequent users, while those who used cannabis less than 4 times a month were identified as infrequent users. Participants who were frequent users used cannabis an average of 26 days out of the past 30 days prior to assessment, and infrequent users averaged 1.68 days involving cannabis use over the last 30 days. Henry et al. [41] found a correlation between cannabis craving and P300 amplitude using a modified version of the Alcohol Urge Questionnaire (AUQ; $r = 0.16$). Specifically, associations between greater cannabis craving and P300 amplitude were found following cue exposure, but the relevant electrode positions were not reported [41].

Cocaine

Responses to cocaine cues were investigated in three studies. All samples involved inpatients. One recruited community volunteers [42] and another involved treatment centre staff [35]. Franken et al. [43] had a sample of 21 patients (% female not reported) with cocaine use disorder. A high craving ($n = 10$; 31.6 years ±10.7) and a low craving group ($n = 11$; 27.1 years ±7.2) were identified using a median split on self-reported craving. All participants were abstinent from cocaine use for at least 1 week. Franken et al. [42] compared 16 male controls (33.1 years ±13.0) to 23 male patients with cocaine use disorder (37.2 years ±8.9) who abstained from cocaine use for at least 1 week. Van de Laar [35] assessed 20 male controls (40.6 years ±9.9) relative to 26 male patients with cocaine use disorder (35.4 years ±7.6) all of whom were abstinent from cocaine use for at least 1 month. Franken et al. [42] found a positive correlation between cocaine craving levels as measured by the Obsessive-Compulsive

Drug Use Scale (OCDUS) and the ERP amplitude for cocaine cues at electrode F8 (r = 0.70) as well as at electrode C4 (r = 0.52). Conversely, an earlier study by Franken et al. [43] found no correlation between the measure of craving and P300 amplitude for cocaine cues (F[3, 57] = 2.39). These studies measured craving using different scales – the Desire for Drugs Questionnaire (DDQ; [50]) and OCDUS [42]. Similarly, Van de Laar and colleagues [35] found no correlation between P300 amplitude and cocaine craving, as measured by the OCDUS (effect size not reported).

Heroin

One article investigated heroin-related cue response in 20 male outpatients (33.3 years ±5.5) relative to 13 male treatment staff (31.8 years ±5.4;51). Patients abstained from heroin use for at least 2 weeks prior to testing. The results indicated that baseline craving predicted larger P300 amplitudes at individual electrodes, FCz (β = 0.54), Cz (β = 0.72), and Pz (β = 0.51) for opioid-related stimuli [44].

Discussion

Studies have assessed the association between P300 attentional processing and subjective craving within different SUDs; however, these studies had not previously been synthesized and examined. The primary aims of this systematic review were to synthesize the evidence of a relationship between the P300 ERP component and alcohol and drug use craving, compare these relationship patterns across the types of substances where data were sufficiently available, and identify gaps in the literature and future directions. Ten studies were identified that analysed the relationship between self-reported craving and amplitude of the P300 ERP component in alcohol [36–38], cocaine [35, 42, 43], tobacco [39, 40], heroin [44], and cannabis [41]. While studies that assessed the relationship between craving and the P300 are limited, the results from this systematic review are mixed. Nevertheless, this systematic review highlights the methodological differences and concerns across the included studies, thereby offering valuable insights for informing future research in this field.

Of the substances included in this systematic review, tobacco exhibited the most substantial support for the link between P300 amplitude and self-reported craving based on converging evidence. Both studies utilizing tobacco found correlations between P300 amplitude and craving [39, 40]. Moreover, these studies used similar methodologies, including the same craving measure (the QSU-Brief), similar cigarette-use status, and comparable recruitment populations [39, 40]. Nevertheless, variations in topographic effects were found; specifically, Mashhoon et al. [41] found maximal differences at electrode Cz, whereas Littel and Franken [42] found a maximal effect at electrode Fz. These discrepancies contribute to the methodological and analytical differences between the studies. Whether they relate to the association between craving and attention bias is inconclusive.

The majority of the research in this systematic review focused on alcohol or cocaine, presenting mixed results on the relationship between the P300 and craving. Of the studies focusing on alcohol, two analysed the P300 component and yielded conflicting results [36, 37]. Although both studies had similar recruited samples (inpatients and community volunteers), mixed findings may be a consequence of differences in craving measurements and abstinence periods [36, 37]. Brown and colleagues [38] assessed alcohol craving using an ERP component comprising the 300 ms time frame, which was extended to 2,000 ms. Brown and colleagues [38] found a main effect of craving and ERP component over time, suggesting that the recorded component of the positive amplitude may differ according to the relationship between attentional processes and craving. As such, this implies that the craving for substances may result from sustained motivational processes rather than intrinsic attentional processes of the P300 component.

Similarly, mixed findings were found in studies that used cocaine as the primary drug of interest. For instance, two cocaine-related studies found no relationship between P300 amplitude and self-reported craving [35, 43]. These studies utilized the same measure of craving (DDS), suggesting that cocaine may not share the same attentional and craving processes that exist within tobacco and alcohol [35, 43]. The third study examined the ERP component between 250 and 750 ms [42]. Franken et al. [42] found a positive correlation between craving levels and ERP component in individuals with cocaine use disorder.

Finally, correlations between P300 amplitude and craving measure were found in studies assessing craving in heroin [44] and cannabis [41]. Due to the dearth of studies assessing these substances and the differences in methodology, it is difficult to conclude whether a drug-specific effect for heroin and cannabis exists in the relationship between the P300 and craving.

The mixed results from this review are likely due to the limited availability of studies, the underpowered analyses within the studies, and the heterogeneity in study methodology. These limitations are outlined to guide future research in this field. The heterogeneity in study methodologies across and within substance categories includes the following: craving measures, cue-reactivity paradigms, cue types, time windows for capturing the ERP component, age of participants, recruited samples, and length of abstinence across participants (as highlighted in Table 1). For instance, the vast array of craving measurements varies from generalizable to all substance classes (VAS and OCDS) to specific to a particular substance class (QSU-Brief and AUQ). Although these measures independently may yield some advantages, it remains uncertain whether craving exhibits distinct characteristic and conceptual variations across all substance types or whether its manifestation is relative to specific classes of substances. For example, studies using state (vs. trait-like) measures of craving, such as VAS and AUQ, were more likely to find significant associations between P300 and craving. The finding suggesting considerable support for the link between P300 and craving in the context of tobacco may be as a result of these studies using state versus trait-like measures of craving. The measurement of craving within and between substance classes has been an ongoing debate [45]. This review highlights the discrepancies within studies and emphasizes the necessity for a standard measure of craving within the field.

Furthermore, given the discrepancies in findings between the P300 and the longer ERP components, it is of interest to further elucidate whether craving is primarily characterized by attentional, motivational, or both processes by identifying differences in the time window used to characterize the P300. The cognitive functions that underlie different ERP components have been largely identified in previous research and have emphasized the particular time windows reflecting these functions. Table 1 outlines the disparities in the reported ERP time window (150–2,000 ms). Thus, the results outlined in this review may signify different cognitive processes that occur following stimulus presentation. In addition to differences in ERP time windows, the cue-reactivity paradigms used significantly differ across studies, with the majority using passive viewing paradigms and a few using Go/NoGo or Oddball. These paradigm discrepancies may, moreover, contribute to different cognitive functions that are represented in the ERPs obtained, resulting in differences in the speculative conclusions across studies. Within the task paradigms used, it should be also noted that the temporal proximity between the assessments of P300 amplitude and subjective craving impact the association. For instance, assessments done closer in time show larger associations compared to those done further apart. Temporal proximity may drive integration through a memory tagging and allocation mechanism, where neurons and synapses recruited to represent a recent episode are more readily engaged [46]. The studies included in this review show differing temporal proximities of ERP and craving assessments, which may explain why some studies found significant associations, but others did not. In addition to heterogeneity in task paradigms, the cues used within these tasks differ substantially. While many of these studies compare drug cues to neutral, pleasant, or unpleasant, this is not consistent across studies, moreover, contributing to the inclusivity of the results.

Apart from task-related differences, while the populations seem mostly comparable across studies, there is variability in the ages of participants (which may be related to length of drug use, impacting attention bias as well as EEG output differences in general), whether the participants were in a treatment program or facility (impacting their craving and attention bias), length of required abstinence from the substance (which may contribute to discrepancies in aspects of attentional processes; [47]), and whether they looked at just individuals substance use disorders and no control (which may artificially restrict the range of both the P300 amplitudes and craving score and thus limiting their ability to detect significant associations). While these factors may contribute to the limitations of this systematic review, they also provide directions for future research in understanding the relationship between the P300 and self-reported craving.

Future studies elucidating the relationship between the P300 ERP component and self-reported craving within different substance types are warranted, particularly in understanding and identifying the following:

- Differences in the quantification of attentional or motivational processes with the visual analogue scale or drug-specific craving measures.
- Differences in cue-reactivity paradigms, cue types, and ERP component windows and their effect on attention bias and craving
- Sample differences that may impact craving and attention bias including length of abstinence, length of drug use (years participating in drug use), and treatment effects.

Conclusion

This systematic review identified ten studies that evaluated the relationship between self-reported craving and the P300 amplitude in alcohol, cocaine, tobacco, Heroin, and cannabis. Within these studies, there is significant variability in their methodologies. While research in this field is limited, the results from this systematic review are mixed for the relationship between the P300 ERP component and craving. Future research that elucidates this relationship and addresses the role of craving measures, ERP components, and abstinence periods is warranted.

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Statement of Ethics

An ethics statement is not applicable because this study is based exclusively on published literature.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

The authors confirm contribution to the paper as follows: study conception and design: Tanisse Epp, Asal Skrenes, Thomas Chao, Olav Krigolson, and Christian Schütz; data collection: Tanisse Epp, Asal Skrenes, and Thomas Chao; analysis and interpretation of results: Tanisse Epp, Asal Skrenes, Thomas Chao, Olav Krigolson, and Christian Schütz; and draft manuscript preparation: Tanisse Epp, Asal Skrenes, Thomas Chao, Olav Krigolson, and Christian Schütz. All authors reviewed the results and approved the final version of the manuscript.

Data Availability Statement

This study is based exclusively on published literature; data can be found within each article or their corresponding authors. Further enquiries can be directed to the corresponding author.

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