Resting-state EEG, Substance use and Abstinence After Chronic use: A Systematic Review

Liu, Y.; Chen, Y.; Fraga-González, G.; Szpak, V.; Laverman, J.; Wiers, R.W.; Ridderinkhof, K.R.

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Yang Liu[1], Yujie Chen[1], Gorka Fraga-González[2], Veronica Szpak[3], Judith Laverman[3], Reinout W. Wiers[4,*], and K. Richard Ridderinkhof[3,*]

Abstract

Resting-state EEG reflects intrinsic brain activity and its alteration represents changes in cognition that are related to neuropathology. Thereby, it provides a way of revealing the neurocognitive mechanisms underpinning chronic substance use. In addition, it is documented that some neurocognitive functions can recover following sustained abstinence. We present a systematic review to synthesize how chronic substance use is associated with resting-state EEG alterations and whether these spontaneously recover from abstinence. A literature search in Medline, PsycINFO, Embase, CINAHL, Web of Science, and Scopus resulted in 4088 articles, of which 57 were included for evaluation. It covered the substance of alcohol (18), tobacco (14), cannabis (8), cocaine (6), opioids (4), methamphetamine (4), and ecstasy (4). EEG analysis methods included spectral power, functional connectivity, and network analyses. It was found that long-term substance use with or without substance use disorder diagnosis was associated with broad intrinsic neural activity alterations, which were usually expressed as neural hyperactivation and decreased neural communication between brain regions. Some studies found the use of alcohol, tobacco, cocaine, cannabis, and methamphetamine was positively correlated with these changes. These alterations can partly recover from abstinence, which differed between drugs and may reflect their neurotoxic degree. Moderating factors that may explain results inconsistency are discussed. In sum, resting-state EEG may act as a potential biomarker of neurotoxic effects of chronic substance use. Recovery effects awaits replication in larger samples with prolonged abstinence. Balanced sex ratio, enlarged sample size, advanced EEG analysis methods, and transparent reporting are recommended for future studies.

Keywords

EEG, resting-state, substance use, abstinence, recovery

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Introduction

It is well recognized that (chronic) substance use poses threats to one's physical and mental health, with strong associated economic effects.[1] Using behavioral and neurophysiological measurements, chronic substance use has been found to be associated with broad cognitive (see reviews[2,3]) and affective impairments (see review[4]), and there is evidence that at least some of these impairments can partially recover after sustained abstinence.[5] Moreover, in almost all clinical studies, there is no pre-addiction baseline, which makes it difficult to establish whether recovery is partial or full, given that relatively weak scores in many of the same measurements also constitute a risk factor for developing the disorder.[5] Many studies have examined such cognitive and affective effects in relation to brain activity using task-related electroencephalography (EEG). In contrast, chronic substance users' resting-state neural activities is less intensively investigated. Resting-state does not imply inactivity, and its alteration represents changes in cognition that are related to neuropathology and can be used to assess cognitive health.[6] This offers a new way of examining the brain functional alterations related to chronic substance use. Although substance addiction has been studied much more elaborately than behavioral addictions, the latter field has recently been synthesized regarding resting-state

[1]Department of Psychology, School of Education, Shanghai Normal University, Shanghai, China
[2]Department of Child and Adolescent Psychiatry and Psychotherapy, Psychiatric Hospital, University of Zurich, Zurich, Switzerland
[3]Department of Psychology, University of Amsterdam, Amsterdam, Netherlands
[4]Addiction Development and Psychopathology (ADAPT)-Lab, Department of Psychology and Centre for Urban Mental Health, University of Amsterdam, Amsterdam, Netherlands
[*]shared senior authorship.

Corresponding Author:
Yang Liu, Department of Psychology, School of Education, Shanghai Normal University, Shanghai, China.
Email: yliux@outlook.com
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EEG findings (gaming disorder and internet addiction[7]). The present study aims to fill that gap for substance use and discontinuation after chronic use.

Resting-state EEG records brain activity when the participant is awake and not required to engage in a specific task, typically with the eyes closed to prevent the eye movements influencing the EEG signal. A resting-state paradigm is thought to reflect the brain's intrinsic activity.[8,9] A well-established and frequently used method in analyzing EEG signals is spectral power analysis. Traditionally, EEG signals in the frequency domain have been decomposed into the following frequency bands, which have been associated with different cognitive processes: delta (0-3 Hz), theta (4-7 Hz), alpha (8-12 Hz), beta (13-28 Hz), and gamma (>29 Hz). Oscillations in each band are thought to contribute to different functions depending on the location of their sources and parameters like amplitude, frequency, and phase. In general, slower frequencies are believed to represent the coordinated activity of large-scale neuronal networks and higher frequencies may reflect mostly local activity.[10] In addition, functional connectivity analyses (coherence, synchronization likelihood, phase lag index, etc.), and more complex approaches (eg, network analysis, graph theoretical analysis, etc.) have also been utilized in analyzing resting-state EEG data.[11] Functional connectivity refers to the synchronization of EEG rhythms in different areas of the brain, which includes directed and undirected connectivity depending on information communication direction. In graph theoretical analysis, connectivity in the brain is represented as a network composed of nodes (ie, regions) and edges (ie, the connectivity between regions). The derived graph metrics quantify how the connectivity network is organized. For example, they can describe whether most nodes are similarly interconnected or whether there are a small number of nodes that form highly interconnected clusters.[12]

Our aim is to present a systematic review and synthesis of the existing literature. Several previous efforts have proven valuable, but each had some important limitations. To date, at least 9 published studies have summarized resting-state EEG findings in chronic substance users: 6 about alcohol,[13–18] 2 about opioids,[19,20] and 1 about both.[21] For alcohol use, the most dominant finding reported has been that people with alcohol use disorder (AUD) show increased beta band power compared to non-AUD individuals. The prevailing finding of an increased beta band power of AUD implies hyperarousal of the central nervous system.[13] Less significantly, theta and delta bands showed increased power in relation to AUD, while results for the alpha band were inconclusive.[13,16–18] In contrast, one paper concluded that except for the beta band, results for all other frequency bands were ambiguous.[14] In addition, interhemispheric coherence was increased in slower frequencies (eg, delta and fast theta band) and decreased in higher frequencies (fast alpha and fast beta bands) in people with AUD and abstainers compared to controls.[14,15,18] But the evidence on coherence is much more limited than that on spectral power analysis. For opioid use, it is difficult to draw a general conclusion as all three reviews included a limited number of studies that presented conflicting results. For instance, some studies in Ieong and Yuan's[20] review found increased local and remote functional connectivity for beta and alpha bands in opioids abstainers,[22] whereas some others reported decreased remote functional connectivity.[23,24] The spectrum power results in this review were even more mixed. Another review summarized the findings among methadone-substituted opiate users. Some discrepancies notwithstanding, the majority of included studies showed no difference from controls.[19] However, the overarching goal of that study was to examine the pharmacological effect of methadone on resting-state EEG rather than substance use per se. The third review reported increased beta and decreased alpha power for opioids, while the effect was small.[21] The discrepancy between research findings and corresponding review conclusions may arise from variances of sample size, years of opiate use, the stage of addiction (pre vs. post abstinence) and treatment acquisition (eg, methadone maintenance treatment).

Though some work has been done in summarizing the characteristics of resting-state EEG in substance users, a few non-trivial limitations hampered these efforts. First, current alcohol-related surveys were all narrative reviews, without a comprehensive literature search and objective literature selection. This may have led to potential interpretational biases, and explain why the conclusions conflicted with those from a systematic review.[25] A related point is that, without clear inclusion and exclusion criteria, researchers sometimes mixed pure substance use effects with that of comorbid disorders (eg, personality disorder[20]; depression[18]). Similarly, findings from substance users and abstainers (with or without treatment) were sometimes also mixed,[18,20] which is suboptimal as EEG alterations may recover after abstinence.[26] Second, whereas substance use can be treated as a continuous variable, current reviews only compared the two ends of such continuum. Thus, they may overlook potential relationships between resting-state EEG and moderate substance use or different drug dosages. Third, except for alcohol and opioids, resting-state EEG findings of other frequently used substances (eg, tobacco and cannabis) have not been reviewed. Finally, most available reviews focus on EEG power analysis but recent studies are using different approaches like connectivity or network analysis.

To fill the research gap and address some limitations of previous reviews, we present a systematic and up-to-date review. We use clear inclusion and exclusion criteria and exclude studies that did not control for factors that may confound interpretation (like comorbid psychiatric disorders and medical or psychological interventions). Results from active users and abstainers are summarized separately, and there were no restrictions to the substance type, substance use severity, and EEG analysis methods. In sum, the present systematic review aims at examining the evidence on how chronic substance use is associated with (abnormalities in) resting-state EEG, and whether such abnormalities can naturally recover after a period of abstinence.

Methods

Study Identification and Selection

Six databases (Medline, PsycINFO, Embase, CINAHL, Web of Science, and Scopus) were searched until December 3, 2020. Search terms and synonyms indicating substance use (alcohol, amphetamine, cocaine, cannabis, heroin, ketamine, methamphetamine, benzodiazepines) were combined with terms indicative of resting-state EEG (quantitative EEG, spontaneous gamma activity, brain oscillations, etc.). The inclusion criteria were that the studies (a) were presented in English; (b) were conducted on human participants; (c) were empirical and contained primary data; (d) used resting-state quantitative EEG techniques; (e) reported current or past use of at least one kind of substances. We excluded studies (a) that focused on the acute effect of substance use on resting-state EEG; (b) with participants who had already received treatment for addiction by the time resting-state EEG data was collected; (c) in which a pure substance use effect cannot be separated (eg, comorbid disorders such as depression, antisocial personality disorder, neurological diseases); (d) in which family history of substance use was confounded with participants' own substance use in the relationship with resting-state EEG (eg, babies born to substance-abusing mother, fetal alcohol spectrum disorder, etc.); (e) case study; (f) conference paper.

A total of 4088 articles were initially identified after deduplication. Article screening was carried out with Rayyan.[27] Title and abstract screening were performed among YL, YC, GFG, and RR, and full-text screening was performed among YL, YC, JL, and VS, with the rule that each article was blindly screened by at least two authors at each step. Conflicts were first addressed between the two raters, then the whole group for complicated ones. After title and abstract screening, there were 151 articles left, of which another 88 were excluded (see details in Figure 1). In addition, 6 studies did not reply to our query about whether treatment was delivered upon EEG recording and therefore cannot be included (see the list in Supplemental Materials). Finally, 57 articles were included in the present systematic review.

Quality Assessment and Data Extraction

There are three types of studies included: cross-sectional study (n = 48), longitudinal study without a control group (n = 8) and a randomized controlled trial. To assess their qualities, AXIS,[28] NIH for pre-post studies without a control group and NIH for controlled intervention studies[29] were used separately according to Ma et al.[30] These tools evaluate the quality of a study in terms of study aim declaration, appropriateness of study design (intervention study includes randomization and blindness), sample size justification (longitudinal study includes follow-up rate), sufficient results reporting, significance justification, and inference from the results to the conclusions. Items 13, 14, 19 of AXIS and item 12 of NIH (pre-post studies without a control group) were deleted as they were inappropriate for the present aim (items tested were listed in the Supplemental Materials). Each item was rated with "Yes', "No" or "Not Available". The overall quality of a study was represented by the percentage of "Yes' answers in AXIS. For the two NIH-related tools, the evaluators rated "good", "fair" or "poor" based on a general impression. Each study was assessed by two authors independently (YJ, JL, or VS), and the agreement was high (88.9%, 747/870).[31]

Six categories of variables were extracted: 1) aim, 2) demographics, 3) substance use, 4) EEG recording, 5) EEG analysis, and 6) findings. Each paper was blindly coded by two authors (YC, JL, or VS). Given the space limit, we decided to present some key variables in the main text (Table 1) and the remaining in the Supplemental Materials (Table S4).

Results and Discussion

Quality Assessment

The 57 included studies were generally of moderate to high quality (ie, scored no less than 50% in AXIS and "good" to "fair" ratings in NIH-related tools), with only one study scoring lower than 50% (see results in Supplemental Materials). The main limitations were the small sample size, the representative of the sample (eg, some only recruited males), and incomplete reporting of EEG recording and analysis. For a few studies, where the participants were recruited, the blindness of treatment, and limitations were not mentioned.

Main Outcome and Interpretation

Alcohol. There is substantial evidence for abnormalities in alcohol users' resting-state EEG spectral power, covering alcohol dependence, hazardous alcohol consumption, binge drinking, etc. The most predominant finding across these samples is the well-documented increased beta power (Table 2), especially in the frontal and central regions. Increased beta rhythms were deemed to reflect cortical hyperexcitability or disinhibition.[88] Neurophysiological similarities of these groups suggest that binge drinking and hazardous alcohol consumption might be a transition stage into addiction. Though the positive family history of AUD[18] and medicine intake (eg, benzodiazepines)[89] were also related to increased beta rhythms, the screening criteria we used should minimize their influence. As noted in the introduction, the association between these EEG abnormalities and AUD does not necessarily imply that they are caused by excessive alcohol use, they could also be a cause or contributing factor.[5] However, a co-twin study did support alcohol exposure as the preceding cause of this association.[40] Less consistently, some studies found increased theta power, decreased alpha power and reduced alpha mean frequency in alcohol users. Increased theta power may reflect poorer information processing capacity,[13] and decreased alpha power may reflect a high

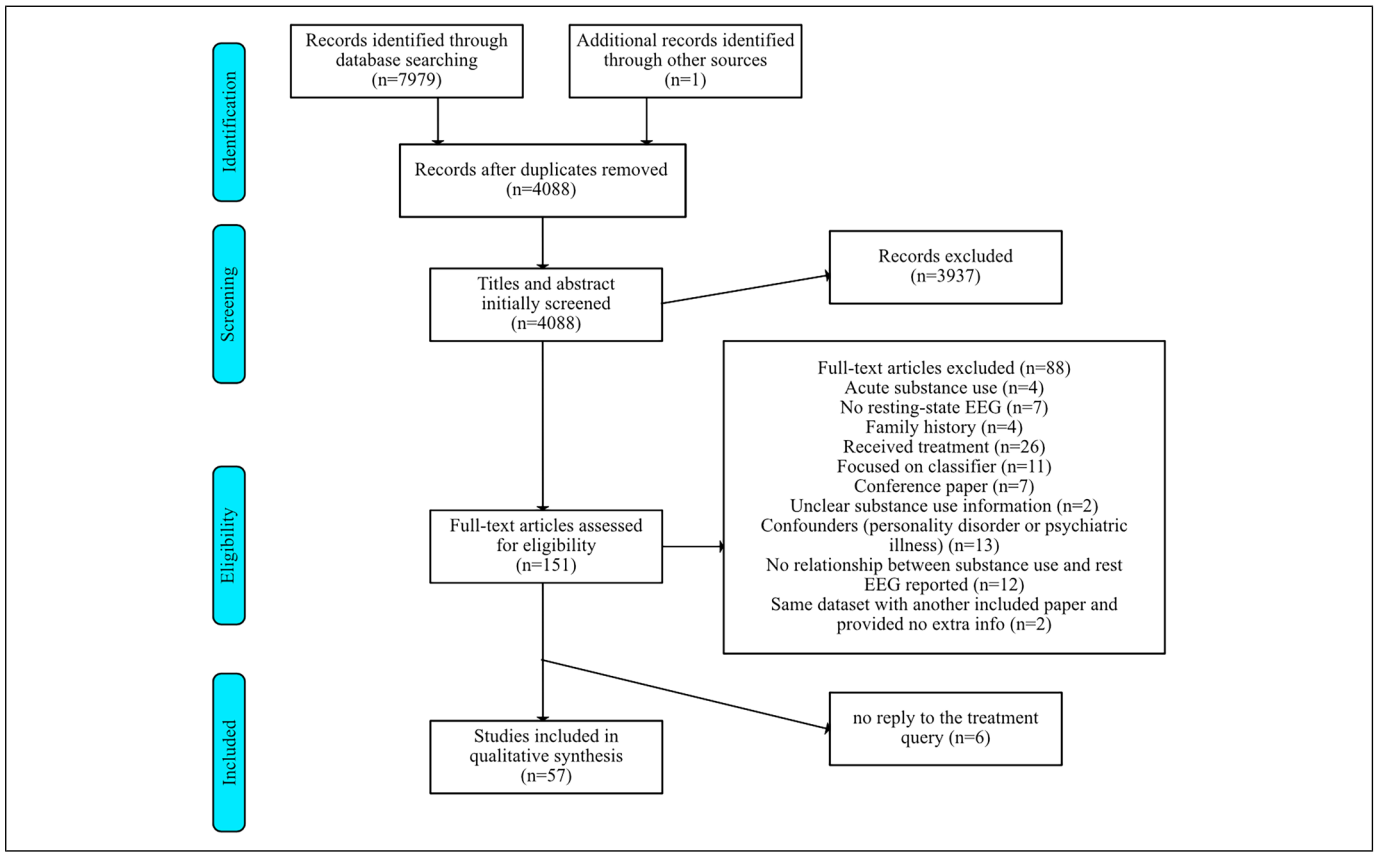

Figure 1. PRISMA flow diagram detailing our paper search and selection decisions.

level of arousal[34] and accompanying deficiency in attention and mental concentration.[90] Furthermore, lower alpha mean frequency may serve as an indicator of basic-level brain dysfunction resulting from the slowing of cortico-thalamic interactions.[91] On the contrary, results for other frequency bands were rather mixed. The onset age of drinking, gender, and addiction severity was claimed to cause such divergent findings.[39] However, we did not observe any simple moderation effect of these factors, nor do we have enough power to examine them quantitatively. Methods examining functional EEG connectivity (eg, coherence, synchronization likelihood) were also used in studies on alcohol users. Increased theta and gamma synchronization in male heavy drinkers reflected changes in the hippocampus, the cortex, and/or hippocampo-neocortical connections that subserve memory formation.[44] Given that optimal brain functioning also requires desynchronization,[92,93] these findings do not necessarily imply better cognitive functioning. When females were also examined, decreased alpha and slow beta synchronization was found, and this was mainly attributed to the left hemisphere activity.[45] These findings all reflected alcohol users' altered coupling between brain regions in the resting state, and factors that influenced spectral power findings (eg, gender, onset age of use) may also play a role here.

To examine resting-state EEG changes after abstinence, we can do either within-study comparisons (ie, baseline vs. follow-up) or between-study comparisons (ie, whether predominant findings in active chronic heavy drinkers were absent in studies with abstainers). The current evidence indicates some spontaneous recovery effects, such that alpha activity increased from baseline to follow-up, and that the commonly seen increased theta and beta power in active chronic heavy drinkers were not found in abstainers. Interestingly, these findings also suggest that resting-state activities may not continue to ameliorate but instead stabilize at a certain level after some abstinence.[48] Furthermore, the recovery effect is more likely to appear in those severely impaired.[47]

Tobacco. Tobacco differs from other substances in its short inter-dose interval. This makes the chronic tobacco use effects on EEG confounded with subacute and withdrawal effects (depending on the timing, when EEG is recorded shortly after smoking or when it disrupts the typical smoking behavior, respectively). The second issue is that it is unclear when withdrawal symptoms disappear, and a recovery effect can be examined subsequently. The majority of studies included in this review focused on short-term tobacco deprivation, with a minor emphasis on the chronic effect and relatively

Table 1. Summary of Included Studies.

			Characteristics of the substance use group			EEG recording	EEG analysis		
Study	Aim of study	Sample size (gender, age: mean ± sd)	Duration of use	Criteria for the heavy/problematic substance use group	Abstinence duration	EC/EO	EEG analysis methods	Frequency Bαnd αnαlyzed	Main results[a] (SUG vs CON)
Alcohol									
Fein et al. (2005)[32]	To examine: 1) EEG power in treatment-naive, actively drinking alcoholics compared with age- and sex-matched controls; 2) within alcoholics, how EEG spectra is associated with age and drinking variables	51SUG (31 M, 33 ± 8.4; 20F, 30.3 ± 7); 51CON (31 M, 33.4 ± 8.5; 20F, 30.4 ± 7.1)	SUG (M: 16.75 ± 8.59; F: 14.63 ± 7.3), CON (M: 12.86 ± 8.82; F: 10.83 ± 8.3) in yrs.	1) met lifetime DSM-IV-R criteria for alcohol dependence; 2) were currently drinking; 3) never sought treatment for alcoholism	24 h	EC	AP	θ, α1 (7.5-10 Hz), α2 (10-12 Hz), β1 (12-16 Hz), β2 (16-20 Hz), β3 (20-28 Hz)	θ↑, α↑, β↑
Ehlers et al. (2010)[33] (alcohol part)	To examine the heritability of bipolar EEG spectral phenotypes and to determine their associations with marijuana (MD) and alcohol dependence (AD)	369AD (169 M, 30.96 ± 0.57), 257CON (90 M, 29.98 ± 0.87)	NA	DSM-III-R and SSAGA for alcohol use disorder	≥24 h	EC	AP	δ, θ, α, β1 (12-20 Hz), β2/γ (20-50 Hz)	β↑, γ↑
Jones et al. (1976)[34]	Whether alcoholics produce lower levels of α than nonalcoholic	20SUG (M, 44.5), 20CON (M, 45.5)	NA	most had long-term alcohol abuse history	1 week	EC	AP	α	α↓
Kumar et al. (2015)[35]	To examine resting-state EEG changes in alcoholics	20SUG, 20CON, all are males aged between 32 to 38	> 10 yrs.	clinically confirmed for chronic alcoholism	on the day before the EEG test no alcohol	NA	AP, RP & peak power frequency	δ, θ, α, β1(12-16 Hz), β2(16-30 Hz)	RP: δ↓, α↓, θ↑, β↑
Mumtaz et al. (2016)[36]	To propose a machine learning method to classify alcoholics, alcohol abusers and healthy controls	12SUG abusers (X; 56.70 ± 15.33), 18SUG alcoholics (X; 46.80 ± 9.29), 15CON (X;42.67 ± 15.90)	NA	AUDIT > 7, and a further categorization into alcoholics and alcohol abusers were performed based on MINI	NA	EC & EO	AP & RP	δ, θ, α, β1 (12-25 Hz), β2 (25-30 Hz), γ1 (30-40 Hz), γ2 (40-50 Hz)	AP: θ↓, α↓, γ↓, δ↑; RP: δ↑, α↑, β↑, θ↓

(continued)

Table 1. (continued)

Study	Aim of study	Sample size (gender, age: mean ± sd)	Characteristics of the substance use group			EEG recording	EEG analysis		Main results[a] (SUG vs CON)
			Duration of use	Criteria for the heavy/problematic substance use group	Abstinence duration	EC/EO	EEG analysis methods	Frequency Bαnd αnαlyzed	
Friese et al. (2016)[37]	To investigate how individual differences in neural baseline activation in the lateral PFC moderate the association between implicit alcohol attitudes and drinking behavior	89 participants (35 M; 23.6 ± 2.8)	NA	AUDIT: 7.04 ± 5.05 (range 0-22), last week alcohol consumption was tested by TLFB	NA	EC & EO	AP and sLORETA	δ, θ, α1(8.5-10 Hz), α2(10.5-12 Hz), β1(12.5-18 Hz), β2(18.5-21 Hz), β3(21.5-30 Hz)	α1 activity was positively correlated with last week alcohol intake
Núñez-Jaramillo et al. (2015)[38]	To determine the neurophysiological correlates of hazardous alcohol consumption	17SUG (12 M, 19.39 ± 0.19); 25CON (12 M, 19.26 ± 0.21)	NA	met DSM-IV criteria for hazardous drinking	NA	EC & EO	AP, RP & MF	θ, β	AP: β↑
Herrera-Morales et al. (2019)[39]	To determine whether Hazardous alcohol consumption (HAC) and risk of alcohol dependence (DEP) present different neurophysiological correlates compared to controls	45HAC (17F, 19.11 ± 0.21; 28 M, 19.3 ± 0.19), 21DEP (16F, 19.05 ± 0.23; 5 M, 18.9 ± 0.18), 48CON (26F, 19.15 ± 0.21; 22 M, 19.08 ± 0.13)	NA	HAC: AUDIT-total≥2, item 2 & item 3 ≥1, and items 4, 5 and 6 = 0; DEP: AUDIT-total≥3, and items 4, 5, 6 >0	NA	EC	AP, RP & MF	δ, θ, α, β	HAC and higher AP & RP of β, EDP had lower AP of δ
Burwell et al. (2017)[40]	Use co-twin control analyses to investigate the possible causal nature of drinking on resting-state EEG	481 (199 M, 24.5 ± 0.7), 208 complete twin pairs	NA	a single cumulative drinking measure was calculated when participants were 11, 14, 17 years old, and at the current assessment	no alcohol on the day of the test	EO	AP	δ, θ, α, β, γ1(30-58 Hz), γ2(62-98 Hz), γ3(102-127.5 Hz)	β↑
	To assess resting	32HBD(16 M,	32HBD(16 M,	HBD: ≥10 drinks	≥ 48 h	EO	AP	δ, θ, α, β1, β2, γ	

(continued)

Table 1. (continued)

			Characteristics of the substance use group			EEG recording	EEG analysis		
Study	Aim of study	Sample size (gender, age: mean ± sd)	Duration of use	Criteria for the heavy/problematic substance use group	Abstinence duration	EC/EO	EEG analysis methods	Frequency Bαnd αnαlyzed	Main results[a] (SUG vs CON)
Courtney et al. (2010)[41]	EEG in young adult high-binge drinkers(HBD), low-binge drinkers (LBD) and controls	20.81 ± 1.97; 16F, 19.94 ± 1.12), 32LBD(16 M, 20.50 ± 0.97; 16F, 20.38 ± 1.15), 32CON(16 M, 21.81 ± 1.68; 16F, 20.38 ± 1.26)	3.06 ± 1.24; 16F, 3.13 ± 1.54), 32LBD(16 M, 2.69 ± 1.59; 16F, 2.88 ± 1.50), 32CON(16 M, 3.69 ± 2.55; 16F, 1.91 ± 0.97) in yrs.	(LBD: 5/4-7/6 drinks) within 2 hrs. ≥ once for the past 6 months					HBD>LBD: δ; HBD> CON: β
López-Caneda et al. (2017)[42]	To assess the pattern of resting-state EEG oscillations in college-aged binge drinkers (BDs)	40SUG (20 M; 18.10 ± 0.30); 40CON (20 M; 18.13 ± 0.33)	the onset age of regular drinking: 14.7 ± 1.15	binge drink ≥ once/ month for the past 6 months & AUDIT≤20	24 h	EC & EO	AP and eLORETA	δ, θ, α, β	β↑, θ↑
Affan et al. (2018)[43]	To examine rest EEG as a function of young adults' alcohol use quantity, frequency, and pattern of use	30 Binge drinker/ BD (15 M, 23.41 ± 3.45), 31 light drinker/LD (15 M, 23.32 ± 3.4)	the onset age of drinking: 15.9 ± 1.5, LD: 18.6 ± 2.0	in the past 6 months, ≥5 binge episodes	≥48 h	EC & EO	AP & APF	θ, α, β	BD versus LD: ↑θ, β↑
de Bruin et al. (2004)[44]	Whether heavy drinking students show differences in functional connectivity compared to light drinking controls	11SUG (M, 24.1 ± 1.63); 11CON (M, 241 ± 1.78)	SUG: 9.9 ± 2.59 yrs., CON: 10.3 ± 2.15 yrs.	>30 drinks per week	24 h	EC	FC/SL	δ, θ, α, β1 (12-20 Hz), β2 (20-30 Hz), γ	synchronization↑ in θ and γ
de Bruin et al. (2006)[45]	To investigate whether EEG synchronization differs between light, moderate, and heavy drinkers	29light drinkers: 13 M(46.4 ± 9.6), 15F(49.5 ± 7.8); 33moderate drinkers: 17 M(49.3 ± 8.5), 16F(50.8 ± 7.6); 34heavy drinkers:	Light: M(29.9 ± 8.3), F(32.1 ± 8.1); Moderate: M(32.8 ± 7.7), F(33.5 ± 7.2); Heavy: M(35.8 ± 7.4), F(31.2 ± 6.6) in yrs.	light (0.5-6 drinks/ week), moderate (7-20 drinks/week), heavy (21-60 drinks/week)	NA, but have to pass breath test for alcohol	EC	FC/SL	δ, θ, α, β1(8-12 Hz), β2(12-20 Hz), γ	heavy drinkers displayed a loss of lateralization in α and β1 synchronization

(continued)

Table 1. (continued)

Study	Aim of study	Sample size (gender, age: mean ± sd)	Characteristics of the substance use group			EEG recording	EEG analysis		Main results[a] (SUG vs CON)
			Duration of use	Criteria for the heavy/problematic substance use group	Abstinence duration	EC/EO	EEG analysis methods	Frequency Bαnd αnαlyzed	
		19 M(51.9 ± 80), 15F(48.1 ± 5.5)							
Mumtaz et al. (2017)[46]	To propose a machine learning method to classify AUD patients from healthy controls by rest-EEG	30SUG (55.4 ± 12.87), 15CON (42.67 ± 15.90), gender: NA	NA	met AUDIT criteria for alcohol use disorder and AUDIT score≥7	NA	EC & EO	AP, RP & coherence	δ, θ, α, β1(12-25 Hz), β2(25-30 Hz), γ1(30-40 Hz), γ2(40-50 Hz)	θ↑, γ2↑
Zilm et al. (1980)[47]	In a longitudinal study, examine changes in EEG among alcoholics	14SUG (M, mean age:45, range 28-60) 8 CON (NA)	22 yrs. (range: 13-35)	10 yrs. heavy drinking history and ≥80 g ethanol/day	session 1: within 16 days (range: 7-37 days), session 2 &3, during the 6 to 10 weeks" abstinence and with 2 to 3 weeks interval	EC	RP	α, 20 to 30 Hz	The impaired group at baseline showed increased 20 to 30 Hz power after 4 to 6 weeks, no change for the unimpaired group
Andrew et al. (2010)[48]	Resting-state EEG differences between long-term abstinent alcoholics and nonalcoholic controls	SUG and CON each consisted of 48 participants: 23F and 25 M, aged 35 to 58 (46.3 ± 6.8)	NA	DSM-IV criteria for alcohol dependence	≥6 months	EO	AP	θ	NS
Son et al. (2015)[49]	To investigate resting-state QEEG differences between internet gaming disorder(IGD), alcohol use disorder(AUD), and controls	17AUD (M, 29.71 ± 4.88); 25CON (M, 23.88 ± 4.66)	NA	1) met DSM-5 criteria for AUD; 2) AUDIT score: 25.71 ± 5.37; 3) drinks/day: 10.35 ± 2.89	≥2 weeks	EC & EO	AP & RP	δ, θ, α, β	AP: δ↑
Tobacco									
Rass et al. (2016)[50]	To measure the resting EEG profile of chronic smokers in a non-deprived, non-peak state	22 daily smokers/DS (13 M, 27.2 ± 5.3), 31 nondaily smokers/NDS (12 M, 23.9 ± 4.4), 30 Non-smokers/	DS: 9.4 ± 6.4 yrs.; NDS: 5.6 ± 4.4 yrs.	DS: smoked daily ≥12 months and FTCD ≥4; NDS: 1) smoked for ≥3 yrs.; 2) smoked <27 days per month for	No	EC & EO	AP	δ, θ, α, β, γ	EC: α↓, EO: δ↓

(continued)

Table 1. (continued)

Study	Aim of study	Sample size (gender, age: mean ± sd)	Characteristics of the substance use group			EEG recording	EEG analysis		Main results[a] (SUG vs CON)
			Duration of use	Criteria for the heavy/problematic substance use group	Abstinence duration	EC/EO	EEG analysis methods	Frequency Bαnd αnαlyzed	
		NS (14 M, 25.2 ± 4.3)		the past 6 months; and (3) in the preceding 90 days, smoked on ≥10 days or smoked ≥20 cigarettes; NS: lifetime cigarettes <10 and did not smoke last month					
Su et al. (2017)[51]	To examine differences in global network efficiency between young smokers and nonsmokers	20SUG (M; 20.95 ± 1.2), 20CON (M; 20.29 ± 1.1)	SUG: 4.24 ± 1.8 yrs.	DSM-IV criteria for nicotine dependence	60 min	EO	FC/PLI and network/MST	δ, θ, α, β	FC↓
Knott et al. (1977)[52]	to examine the hypothesis that deprived smokers are characterized by a state of cortical hypo-excitation	17 Deprived smoker/DS (M, 22.3), 13 Non-deprived smoker/NDS (M, 21.1), 10 Non-smokers/NS (M, 19.3)	≥1 yr.	DS & NDS: ≥10 cigarettes/day for ≥1 yr.	DS: 13 to 15 h	EC	AP and MF	α	DS versus NDS/ NS: slower α frequencies
Knott et al. (1996)[53 b]	To determine whether a long-term smoking history alters the aging brain	10 young SUG (6 M; 25.4 ± 6.9), 10 elderly SUG (5 M; 69.3 ± 5.6), 10 young CON (4 M; 24.3 ± 2.4), 10 elderly CON (5 M; 70 ± 3.7)	young SUG: 9.3 ± 5.0 yrs.; elderly SUG: 52 ± 5.3 yrs.	≥15 cigarettes/day for the past 5 yrs.	overnight beginning at 12:00am (the acute smoking condition was not considered)	EC	AP, RP and MF	δ, θ, α1(7.5-10 Hz), α2(10-12.5 Hz), β	faster mean β frequency
Knott et al. (1997a)[54 b]	To examine EEG coherence concerning smoker status (ie, nonsmoker vs smoker) and the aging process(ie,	10 young SUG (6 M; 25.4 ± 6.9), 10 elderly SUG (5 M; 69.3 ± 5.6), 10 young CON (4 M; 24.3 ± 2.4),	young SUG: 9.3 ± 5.0 yrs.; elderly SUG: 52 ± 5.3 yrs.	≥15 cigarettes/day for the past 5 yrs.	overnight beginning at 12:00am (the acute smoking condition was not considered)	EC	coherence	δ, θ, α1(7.5-10 Hz), α2(10-12.5 Hz), β	interhemispheric α coherence↑

(continued)

Table 1. (continued)

Study	Aim of study	Sample size (gender, age: mean ± sd)	Characteristics of the substance use group			EEG recording	EEG analysis		Main results[a] (SUG vs CON)
			Duration of use	Criteria for the heavy/problematic substance use group	Abstinence duration	EC/EO	EEG analysis methods	Frequency Bαnd αnαlyzed	
	young vs elderly adults)	10 elderly CON (5 M; 70 ± 3.7)							
Knott et al. (1997b)[55 b]	To examine the influence of smoking status (non-smoker vs smoker) in the comparison of EEG asymmetry between young and elderly adults	10 young SUG (6 M; 25.4 ± 6.9), 10 elderly SUG (5 M; 69.3 ± 5.6), 10 young CON (4 M; 24.3 ± 2.4), 10 elderly CON (5 M; 70 ± 3.7)	young SUG: 9.3 ± 5.0 yrs.; elderly SUG: 52 ± 5.3 yrs.	≥15 cigarettes/day for the past 5 yrs.	overnight beginning at 12:00am (the acute smoking condition was not considered)	EC	asymmetry	δ, θ, α1(7.5-10 Hz), α2(10-12.5 Hz), β	NS
Xu et al. (2000)[56]	The effect of tobacco use and deprivation on the brain electrical activity	7SUG (3 M), 7CON (3 M), all aged between 20 to 40	NA	20 to 40 cigarettes/day	12 hrs. (the acute smoking condition was not considered)	EC	AP	δ, θ, α1(7.75-10 Hz), α2(10.25-12.5 Hz), β1(12.75-20 Hz), β2(20.25-30 Hz)	NS
Gilbert (1988)[57]	To examine EEG differences between smokers and non-smokers	22SUG M, 22CON M, age range: 25 to 35	≥ 1 yr.	≥ 10 cigarettes/day (average: 22.6 ± 8.05) for ≥1 yr.	no tobacco and other drug use on the morning of the experiment	EC	AP & RP	θ, α, β1(13.2-19.0 Hz), β2(19.1-28.1 Hz)	θ magnitude↓, β1 magnitude↑
Ulett et al. (1969)[58]	To examine smoking deprivation on EEG change	8 M, age range: 16 to 21	NA	≥20 cigarettes/day	24 h	EO	MF, APF	3 to 33 Hz: θ, α, β, slow γ	APF↓
Herning et al. (1983)[59]	To examine effects of repeated doses of smoked tobacco and placebo cigarettes on rest EEG	study 1: 11SUG (6 M); study 2: 7SUG(5 M); age range: 35.9 ± 11.5	NA	≥30 cigarettes/day	overnight	EO	AP, APF, MF	δ, θ, α, β	θ↑, α↑ after deprivation
Brown (1968)[60]	EEG activity differences between smokers and non-smokers	13 heavy smokers/HS (5 M), 8 average smokers/AS (4 M), and 6 former heavy smokers/FHS (5 M), 15	HS: ≥ 2 yrs.	HS: 50 to 100 cigarettes/day for ≥ 2 yrs.; AS: 10 to 20 cigarettes/day	9 HS were deprived for 12 hrs., but did not differ from the non-deprived ones, so combine the results; FHS: 3 to 12 yrs.	EC & EO	Frequency Analysis	α, β	HS versus NS: less α and more β activities; faster α frequency

(continued)

Table 1. (continued)

Study	Aim of study	Sample size (gender, age: mean ± sd)	Characteristics of the substance use group: Duration of use	Characteristics of the substance use group: Criteria for the heavy/problematic substance use group	Characteristics of the substance use group: Abstinence duration	EEG recording: EC/EO	EEG analysis: EEG analysis methods	EEG analysis: Frequency Bαnd αnαlyzed	Main results[a] (SUG vs CON)
		non-smokers/NS (10 M), all aged between 25 and 45							
Teneggi et al. (2004)[61]	To examine resting EEG during free smoking and smoking abstinence by testing two to three times a day	12 M smokers: 28.9 ± 6.7, age range: 20 to 41, no CON	≥ 1 yr.	≥15 cigarettes/day in the last year, 9≥ FTQ ≥7	34 h	EC	AP, RP & MF	δ, θ, α, β	abstinence led to δ↑, θ↑, α↑
Gilbert et al. (1999)[62]	To characterize EEG of nicotine abstinence across 31 days	20 quit (M; 28.1 ± 6.3), 20 continue to smoke (M, 26 ± 6.3), all younger than 40	NA	≥15 cigarettes/day for at least the past 2 yrs.	2 tests before quitting, and 3, 10, 17, 31 days since abstinence	EC & EO	AP, asymmetry & MF	δ, θ1(4.0-6.0 Hz), θ2(6.0-7.5 Hz), α1(7.5-10.0 Hz), α2(10.0-12.5 Hz), β1(12.5-20.0 Hz), β2(20.0-30.0 Hz)	abstinence led to δ↑, θ↑, α1↑
Pickworth et al. (1989)[63]	To assess the tobacco deprivation-induced EEG change	7 male smokers (mean age: 31.7, range: 23-42), no CON	mean: 16 yrs., range: 8 to 27	1)≥20 cigarettes/day for ≥5 yrs.; 2) all are heavy smokers with FTND average score of 7.7 (range: 5-10)	EEG was tested at 5, 29, 96, 168, and 216 h. since abstinence.	EC & EO	AP & peak frequency	δ, θ, α, β	abstinence led to α↓, β↓, θ↑
Cannabis									
Struve et al. (1998)[64]	To examine quantitative EEG alterations in long-term daily marihuana users	15SUG-heavy (X, 35.1 ± 4.8), 11SUG-moderate (X, 25.2 ± 3.8), 22Control-1 (X, 27.3 ± 5.8), 35Control-2 (X, 25.1)	SUG-heavy: Mean = 19.6 yrs., SUG-moderate: mean = 4.1 yrs.	SUG-heavy: daily use continuously for 15 to 24 yrs., SUG-moderate: daily use continuously for 3 to 6 yrs.	NA	EC	AP, RP, asymmetry & coherence	δ, θ, α, β	AP: θ↑, α↑, RP: α↑, coherence: θ↑, α↑
Ehlers et al. (2010)[33] (cannabis part)	To examine the heritability of bipolar EEG spectral phenotypes and to determine	207MD (113 M, 28 ± 0.6), 419CON (146 M, 31 ± 0.6)	NA	DSM-III-R for marijuana use disorder	≥24 h	EC	AP	δ, θ, α, β1 (12-20 Hz), β2/γ (20-50 Hz)	δ↑

(continued)

Table 1. (continued)

Study	Aim of study	Sample size (gender, age: mean ± sd)	Characteristics of the substance use group			EEG recording	EEG analysis		Main results[a] (SUG vs CON)
			Duration of use	Criteria for the heavy/problematic substance use group	Abstinence duration	EC/EO	EEG analysis methods	Frequency Bαnd αnαlyzed	
	their associations with marijuana (MD) and alcohol dependence (AD)								
Prashad et al. (2018)[65]	To characterize resting-state EEG (spectral power, connectivity) in cannabis users	17SUG (11 M, 30.9 ± 7.4), 21CON (12 M, 33.1 ± 11.6)	NA	last month cannabis use ≥7 days, 8 were cannabis abuse, 4 were cannabis dependence	36.8 ± 12.1 h	EC	RP, coherence & FC	δ, θ, α, β, γ	θ↑, β↑, γ↑, δ↓; coherence↑, FC↓
Imperatori et al. (2020)[66]	To examine the association between problematic cannabis use and triple network EEG functional connectivity	12SUG (7 M, 23.33 ± 3.47), 24CON (9 M, 21.21 ± 2.70), all between 18 to 30 yrs.	NA	CAST≥7 and last year cannabis use ≥20 times	NA for cannabis; 4 h before: no alcohol, caffeine, and cigarettes; two weeks before: no other illicit drug.	EC	FC/LPS	δ, θ, α, β, γ	δ connectivity↑
Struve et al. (1999)[67]	To examine the influence of marijuana use on EEG	18SUG: 27.8, 35CON: 25.1, all between 18 to 40; gender: NA	10.3 yrs.	history of daily THC exposure ≥3 yrs.	24 h	EC	AP, RP, Asymmetry & coherence	δ, θ, α, β	AP: all↑; RP: α↑, δ↓, β↓; coherence: α↑, θ↑, δ↑
Allsop et al. (2016)[26]	Uses EEG to explore moderators of recovery during cannabis abstinence	10SUG (6 M; 28.8 ± 5.39), no CON	12.6 ± 4.06 yrs.	DSM-IV criteria for cannabis dependent	EEG was tested before and after 2 weeks of abstinence	EC	AP	θ, α, β	group level: NS, abstinence only led to β↑ in later onset users
Herning et al. (2003)[68]	To understand marijuana abusers" abnormal EEG patterns during abstinence	29SUG (23 M, 32.6 ± 9.1), 21CON (11 M, 23.0 ± 5.1)	6.6 ± 3.8 yrs.	DSM III-R criteria for marijuana dependence or abuse	SUG was tested twice, first: within 3 days of admission; second: 28 to 30 days of monitored abstinence	EC	AP	δ, θ, α1(8-10 Hz), α2(10-13 Hz), β1(13-25 Hz), β2(25 – 50 Hz)	baseline & follow-up: α1↓, θ↓
Herning et al. (2008)[69]	To assess to what extent marijuana abuse-associated neurological	56SUG-short (38 M, 21.4 ± 3.4), 19SUG-long (11 M, 24.3 ± 4.1);	SUG-short: 4.4 ± 1.5 yrs., SUG-long: 9.6 ± 1.8 yrs.	SUG-short: <8 yrs.; SUG-long: ≥8 yrs.	SUG was tested twice, first: within 3 days of admission; second: 28 to 30	EC	AP, RP & APF	δ, θ, α1(8.0-9.9 Hz), α2(10.0-13.9 Hz),	baseline & follow-up: α2↓, β2↓

(continued)

Table 1. (continued)

Study	Aim of study	Sample size (gender, age: mean ± sd)	Characteristics of the substance use group			EEG recording	EEG analysis		Main results[a] (SUG vs CON)
			Duration of use	Criteria for the heavy/problematic substance use group	Abstinence duration	EC/EO	EEG analysis methods	Frequency Bαnd αnαlyzed	
	changes are indicative of cerebral perfusion deficits	33CON (15 M, 22.8 ± 5.3)			days of monitored abstinence			β1(14.0-24.9 Hz), β2(25.0-40.0 Hz)	
Cocaine									
Copersino et al. (2009)[70]	To identify the relationship between EEG and intensity of cocaine use	99SUG (76 M, 34.3 ± 5.2), 42CON (22 M, 28.2 ± 8.1)	8.6 ± 5.0 yrs.	no specific, but used cocaine for 17.8 ± 7.7 days in the last month	Days since admission in the ward: 1.9 ± 2.3(range: 1-8), may start abstinence before this	EC	AP	δ, θ, α, β1, β2	θ↓, β↓
King et al. (2000)[71]	To examine whether cocaine-abusing females differ from male counterparts in resting-state EEG	SUG: 20F(33.8 ± 4.8), 20 M(32.6 ± 4.6); Con: 12F(31.4 ± 9.3), 20 M(30.5 ± 7.7).	F(7.6 ± 4.6), M(8.2 ± 4.8) yrs.	DSM-III-R criteria for cocaine dependence	F: 4.8 ± 4.7 days, M: 6.3 ± 4.4 days	EC	AP	δ, θ, α, β	SUG males versus other three groups: β↑, α↓
Herning et al. (1997)[72]	To determine whether a central nervous system marker of cocaine dependence might exist	33cocaine dependent/CD: (M, 32.0 ± 5.4), 20drug control/ DUC: (M, 31.8 ± 6.1), 10nondrug control/NDC: (M, 32.7 ± 7.1)	CD: 119.3 ± 83.2 months, DUC: 98.9 ± 70 months	CD: DSM-III-R criteria for cocaine dependence and use cocaine 2.9 ± 2.7 g/week; DUC: no cocaine dependence and use cocaine 1.4 ± 2.7 g/week	cocaine-dependent group: 10.3 ± 3.7 days; DUC: 5 to 10 days	EC	RP	δ, θ, α, β	CD versus DUC&CON: β↑, θ↓
Roemer et al. (1995)[73]	To examine QEEG in subjects of polysubstance dependence (cocaine as the main drug of use)	N = 90 (33Black Female: 38.7 ± 6.1; 41Black Male: 36.5 ± 6.9; 2White Female: 31.0 ± 2.8; 14White Male: 36.2 ± 11.4)	the median age of cocaine use onset age: 24	all met DSM-III-R criteria for cocaine dependence	3 to 1830 days (median = 90)	EC	AP, RP, asymmetry & coherence	δ, θ, α, β	Increased cocaine exposure is related with AP: δ↓, β↓, coherence: δ↓, interhemispheric asymmetry: α↑, β↑
Levin et al. (2007)[74]	To examine the effects of cocaine withdrawal on EEG	20SUG (16 M, 34.8 ± 4.1),	9 ± 5.4 yrs.	1)DSM-V Criteria for cocaine abuse or dependence; 2)	EEG was tested three times: 1, 9, and 13 weeks since	EC	AP	δ, θ, α1(8-9.9 Hz), α2(10-13.9 Hz),	β1↑, δ↑

(continued)

Table 1. (continued)

Study	Aim of study	Sample size (gender, age: mean ± sd)	Characteristics of the substance use group			EEG recording	EEG analysis		Main results[a] (SUG vs CON)
			Duration of use	Criteria for the heavy/problematic substance use group	Abstinence duration	EC/EO	EEG analysis methods	Frequency Bαnd αnαlyzed	
	during 3 months of abstinence	8CON (NA, with matched age)		cocaine use averaging 2 g/ month for the 3 months before screening, and 3) ≥5 days of use in the 2 weeks before admission	admission to the ward			β1(14-24.9 Hz), β2(25-40 Hz)	
Noldy et al. (1994)[75]	To describe the post-acute effect of chronic cocaine use on resting-state EEG	36SUG (25 M, 27.3 ± 6.82), no CON	4.7 ± 4.2 yrs., 28 use cocaine orally and 8 intravenously	cocaine as the primary drug of use ≥1 yr., and cocaine use interferes with occupational and social functioning	EEG-1: day2 (36.2 ± 13.1 h), EEG-2: day6, EEG-3: 4 weeks (only 9 participants left)	EC	AP, RP, APF & coherence	δ, θ, α, β1 (12-18 Hz), β2(18-26 Hz)	abstinence led to β2↓ in AP & RP
Opioids									
Wang et al. (2015)[76 c]	To investigate changes in resting EEG following methadone treatment in opiate addicts	17SUG (11 M, 37.38 ± 7.44); 25CON (14 M, 36.12 ± 6.61) (methadone group was not listed)	≥1 yr.; Mean: 11.41 ± 8.6 yrs.	≥1 yr.; Mean: 11.41 ± 8.6 yrs.	No	EC & EO	AP	δ, θ, α, β1 (14.5-20 Hz), β2 (20-25 Hz), β3 (25-30 Hz)	β↑, α↑, θ↑
Wang et al. (2016)[77 c]	To investigate differences in resting γ power between controls, current opiate users, and those undergoing methadone maintenance treatment	17SUG (11 M, 37.38 ± 7.44), 25CON (14 M, 36.12 ± 6.61) (methadone group was not listed)	≥1 yr.; Mean: 11.41 ± 8.6 yrs.	≥1 yr.; Mean: 11.41 ± 8.6 yrs.	No	EC & EO	AP & sLORETA	γ	γ↑
Motlagh et al. (2017)[78]	To introduce a new approach to evaluate brain electrophysiological properties among addicts	19 SUG(M; M = 39.3 ± 7.7); 19 Con(M; M = 34.3 ± 7.5)	17.7 ± 7.1 yrs.	DSM-IV for heroin dependency, ≥1 yr. of documented heroin addiction, and/or a minimum 6 yrs. of drug abuse.	≥6 h	EC	AP	δ, θ, α, β	δ↓, θ↓, α↓, β↑
Hu et al. (2017)[79]	To identify the abnormality of resting-state heroin	15SUG (M, 31.2 ± 6.2), 14CON (M, 30.9 ± 7.9)	≥2 yrs.	DSM-V Criteria for opioid dependence	NA (have abstained, not sure how long)	EC	effective connectivity &	δ, θ2, α, β1(13-18 Hz), β2(18-30 Hz), γ	abnormal FC

(continued)

Table 1. (continued)

Study	Aim of study	Sample size (gender, age: mean ± sd)	Characteristics of the substance use group: Duration of use	Characteristics of the substance use group: Criteria for the heavy/problematic substance use group	Characteristics of the substance use group: Abstinence duration	EEG recording: EC/EO	EEG analysis: EEG analysis methods	EEG analysis: Frequency Bαnd αnαlyzed	Main results[a] (SUG vs CON)
	abstinent brain functional system						brain source decomposition		
Methamphetamine									
Newton et al. (2003)[80]	qEEG differences between recently abstinent methamphetamine dependents and controls	11SUG (8 M, 32.7 ± 7.5); 11CON (8 M, 36.5 ± 7.3)	11.0 ± 3.5 yrs.	DSM-IV criteria for methamphetamine dependence and methamphetamine use ≥0.5 g/week for the past 6 months.	4 days	EC	AP	δ, θ, α, β	δ↑, θ↑
Yun et al. (2012)[81]	To investigate if methamphetamine (MA) abusers exhibit alterations resting-state EEG	48SUG (M, 37.0 ± 5.0), 20CON (M, 34.5 ± 7.7)	11.8 ± 6.5 yrs.	1)met DSM-IV criteria for MA abuse or dependence; 2)use MA intravenously ≥ 2 yrs.	days: 30.5 ± 27.2 (range: 6-90)	EC	RP & ApEn	δ, θ, α, β	SUG versus CON: δ↓, ApEn↓; abstinence effect: NS
Ahmadlou et al. (2013)[82]	To determine effects of chronic methamphetamine (MA) abuse on brain network	36SUG (M, 31.68 ± 8.76); 36CON (M, 32.68 ± 6.77)	≥2 yrs., Mean: 6.42 ± 3.13 yrs.	DSM-IV criteria for MA dependence	1 to 3 weeks	EC	small-worldness by linear (coherence) and non-linear (visibility graph similarity) synchronization methods	δ, θ, α, β, γ	altered FC
Khajehpour et al. (2019)[83]	To examine chronic methamphetamine use related brain network alterations by using resting-state EEG	36SUG (M, 30.55 ± 6.43); 24CON (M, 30.75 ± 4.63)	8.35 ± 4.07 yrs.	NA	1 to 6 months	EO	AP & Graph theoretical analysis	δ, θ, α, β, γ	AP: NS; FC: abnormal
XTC/MDMA									
Dafters et al. (1999)[84]	To examine whether there is a correlation between quantitative EEG	23(X, Mean = 24, range 18-42), no CON	NA	no specific, MDMA use was treated as a continuous variable	7 days, except for alcohol and tobacco	EC	AP, RP & coherence	α, β, δ, θ	AP & RP: α↑, β↑

(continued)

Table 1. (continued)

Study	Aim of study	Sample size (gender, age: mean ± sd)	Characteristics of the substance use group			EEG recording	EEG analysis		Main results[a] (SUG vs CON)
			Duration of use	Criteria for the heavy/problematic substance use group	Abstinence duration	EC/EO	EEG analysis methods	Frequency Bαnd αnαlyzed	
	and level of prior use of MDMA								
Gamma et al. (2000)[85]	To examine whether chronic exposure to MDMA is associated with altered resting-state EEG	15SUG (8 M; 22.5 ± 2.7), 14CON (8 M, 26 ± 2.7)	NA	lifetime XTC tablets use: 222 ± 358.4, only two participants<100 tablets	1 week except for alcohol and tobacco	EC & EO	AP & LORETA	δ, θ, α1(8.5 ± 10 Hz), α2(10.5 ± 12 Hz), β1(12.5 ± 18 Hz), β2(18.5 ± 21 Hz), β3(21.5 ± 30 Hz)	θ↑, α↑, β↑
Herning et al. (2005)[86]	To examine the effect of long-term MDMA use on EEG	8MDMA (3 M, 22.4 ± 1.3), 15marijuana (12 M, 21.1 ± 1.0), 8MDMA + marijuana (4 M, 23.7 ± 1.3), 17CON (9 M, 23.7 ± 5.5)	MDMA use: MDMA group (2.4 ± 1.3) yrs., MDMA + marijuana group (1.6 ± 1.3) yrs.; Marijuana use: MDMA group (3.5 ± 1.1)yrs., marijuana group (6.4 ± 0.8)yrs.; MDMA + marijuana group (5.9 ± 2.2)yrs.	NA	1 to 7 days	EC	AP	δ, θ, α1(8.0-9.9 Hz), α2(10.0-13.9 Hz), β1(14.0-24.9 Hz), β2(25.0-40.0 Hz)	MDMA group versus other three groups: δ↑, α2↑
Adamaszek et al. (2010)[87]	To examine specific neurotoxicity of ecstasy use by resting-state EEG	101 poly-drug users with former ecstasy use, 41 poly-drug users without ecstasy use, and 11	≥12 months	ecstasy group was subdivided into light(1-99), moderate (100-499), and high (500 or more)	Mean: 5 months (range: 3 days to 8 yrs.)	NA	AP & APF	δ, θ1(3.5-5.0 Hz), θ2(5.0-7.5 Hz), α1(7.5-9.0 Hz), α2(9-11 Hz), β1(13.5-20 Hz),	moderate and high ecstasy users AP: β↑, α1↑, θ↑

(continued)

Table 1. (continued)

Study	Aim of study	Characteristics of the substance use group				EEG recording	EEG analysis		
		Sample size (gender, age: mean ± sd)	Duration of use	Criteria for the heavy/problematic substance use group	Abstinence duration	EC/EO	EEG analysis methods	Frequency Bαnd αnαlyzed	Main results[a] (SUG vs CON)
		drug-naive controls, in total: 153 (X, 22 ± 3.70)		group by accumulated tablets				β2(20-22 Hz), β3(22-30 Hz)	

Note. Gender: M: all are males, F: all are females, X: mixed (the specific number for males and females is coded if it was reported, eg, 17 M); SUG: substance use group (the meaning of other abbreviations assigned to this group can be read from the study aim). CON: control group; THC: Tetrahydrocannabinol; DSM: Diagnostic and Statistical Manual of Mental Disorders; AUDIT: Alcohol use Disorder Identification Test; TLFB: Timeline Follow-Back; FTQ: Fagerstrom Nicotine Tolerance Questionnaire; FTND: Fagerstrom Test For Nicotine Dependence; CAST: Cannabis Abuse Screening Test; EC: Eyes-closed, EO: Eyes-open; AP: absolute power; RP: relative power; APF: alpha peak frequency; MF: mean frequency; FC: functional connectivity; PLI: Phase Lag Index; SL: Synchronization Likelihood; LPS: Lagged Phase Synchronization; ApEn: Approximate Entropy; LORETA: Low-resolution electromagnetic tomography analysis; MST: Minimum Spanning Tree; NA: not available; NS: no significant difference.

[a]a detailed version of the results was in the Supplemental Materials.

[b]the same database.

[c]the same database.

long abstinence effect. It was found that smokers had decreased delta and theta power,[50] and an altered global brain network (ie, less integrated and decreased global efficiency)[51] compared with non-smokers. These alterations may reflect the upregulated nicotine cholinergic receptors caused by chronic smoking.[94] On the other hand, tobacco deprivation (a couple of hours to 31 days) consistently produced an increase in theta power and decreased dominant alpha frequency, which usually peaked within the first day and could last for 31 days.[62,63] This pattern of alteration in EEG power was interpreted to reflect neural hypoactivation. This interpretation is compatible with the depression and anxiety mood experienced after tobacco deprivation.[95] Furthermore, tobacco exposure is associated with larger abstinence-related EEG slowing during the early phase (within the first three days), while trait depression in the whole process.[62] Only one study recruited ex-smokers who abstained from tobacco for 3 to 12 years and found a greater median alpha frequency than non-smokers.[60] More studies are needed before a solid recovery effect is confirmed.

Cannabis. Though it was well documented that chronic cannabis use is associated with resting-state EEG alteration, there was no converging pattern of frequency bands or brain regions in which such changes appeared. For instance, Struve and colleagues found a positive relationship between cannabis exposure duration and resting-state EEG change through a series of experiments. Specifically, casual cannabis users did not differ from controls, and long-term daily users (≥ 15 years) showed increased fontal-central theta power[64] in addition to the alpha hyperfrontality (ie, increased absolute power, relative power, and coherence of alpha over the bilateral frontal cortex) found in short-term daily users (≥ 3 years).[67] Increased theta can be interpreted as a sign of slowed cognitive processing,[64] and hyperfrontality alpha may indicate early withdrawal effects.[26] Others also found increased delta power in cannabis-dependent participants[33], which may reflect cognitive impairment and memory decline.[96] These inconsistent results may derive from variance in gender, bipolar or monopolar recording of EEG, the severity of cannabis use, etc.[33] In addition, cannabis users presented less efficient communication between cortical regions than controls, which may underlie cognitive impairments.[65] Furthermore, cannabis users may have a particular focus on reward-based decision making, as was reflected by the increased functional connectivity between the central executive network and the salience network.[66] Concerning the abstinence effect, Herning et al.[68,69] failed to find neurocognitive rehabilitation from cannabis use over a month of abstinence in two experiments. As these findings conflicted with the improved cognitive performance in behavior after abstinence reported by others,[97] Allsop et al.[26] explored possible moderators. Only in later onset cannabis users, a recovery effect was confirmed, which coincide with the opinion that adolescence is a vulnerable stage for substance use as it is difficult for the neural pruning to be reversed.[98] It is notable that, the

Table 2. Summary of Absolute Spectral Power Findings in Active Drinkers.

	Decrease		Increase	
Frequency band	Study	Count	Study	Count
delta	Herrera-Morales et al.[39]	1	Fein et al.[32], Mumtaz et al.[36]	2
theta	Mumtaz et al.[36]	1	Affan et al.[43], Fein et al.[32], López-Caneda et al.[42], Mumtaz et al.[46]	4
alpha	Jone et al.[34], Mumtaz et al.[36]	2	Fein et al.[32], Friese et al.[37]	2
Beta	—	0	Affan et al.[43], Ehlers et al.[33], Fein et al.[32], Herrera-Morales et al.[39], López-Caneda et al.[42], Núñez-Jaramillo et al.[38]	6
gamma	Mumtaz et al.[36]	1	Ehlers et al.[33], Fein et al.[32], Mumtaz et al.[46]	3

Note. eyes-closed condition was not differentiated from eyes-open condition.

Table 3. Main Findings of Resting-State EEG in Active and Abstinent Substance Users.

Relatively consistent findings	Corresponding substances
Chronic use	
Abnormal rhythms of different frequency bands	
θ↑	alcohol, MDMA
α↑	MDMA
β↑	alcohol, opioids, MDMA
α↓	alcohol, tobacco
alpha mean frequency↓	alcohol
Altered functional connectivity	alcohol, tobacco, cannabis, opioids
Abstinence	
Recovery	
yes	alcohol
unclear	tobacco, cannabis, cocaine, methamphetamine, MDMA
Preventers of recovery	
the early onset age of use	cannabis
Abnormal rhythms of different frequency bands	
δ↑	tobacco
θ↑	tobacco, methamphetamine
β↑	cocaine*
dominant alpha frequency↓	tobacco
Altered functional connectivity	methamphetamine
Vulnerability factors of the above changes	
male (vs female)	cocaine
intravenous users (vs smokers)	cocaine

Note. *This also included results from short-term cocaine abstainers, where subacute and chronic substance use effects cannot be excluded.

above findings may partially represent the subacute effect of cannabis use as all of the studies used an abstinence duration shorter than 1 month when the subacute effect did not diminish yet.[5]

Cocaine. The cocaine-related studies generally found increased power in higher frequencies (eg, beta) and decreased power in lower frequencies (eg, delta) during cocaine abstinence. The increased beta power may be due to the neural loss (eg, cortical atrophy) caused by the reduced cerebral blood flow (eg, vertebrobasilar artery insufficiency) that is associated with chronic cocaine use.[72] Alternatively, it was explained as a premorbid characteristic of cocaine abusers as positive family history of alcoholism and antisocial personality disorder were also associated with increased beta power.[77] This argument is less plausible here as the influence of those factors should be minimized for the studies included. A third explanation is the withdrawal-induced sleep disturbance that is associated with the increased beta power,[71] which can be validated by examining other withdrawal symptoms (eg, craving) in the future. As to the decreased delta power, it may reflect the upregulation of some neurotransmitters (eg, dopamine, norepinephrine) after abstinence. Albeit the greater abundance of higher frequencies reported, the inconsistency between research findings should be realized. Two moderators identified were gender and cocaine administration approach, with males (vs. females)[71] and intravenous users (vs. smokers)[75] being more vulnerable to these neurophysiological alternations. Other mediators include EEG recording length, abstinence duration, and other substance use.[74]

Other Substances. Heroin and opiate users differed from controls in theta, alpha, beta (frontal and central regions)[78], and gamma (widespread)[77] bands power. These alternations signal potential cognitive function deficits. Specifically, heroin addicts' long-term memory, working/short-term memory, problem-solving abilities, and psychomotor speed performance were believed to be associated with delta, theta, alpha, and beta band properties respectively.[99] In addition, abnormally weaker and stronger functional connectivity were found in the parietal and the left occipital regions respectively. More evidence was needed for both spectral power and functional connectivity analyses.

Chronic methamphetamine use has been associated with long-lasting deficits on the dopaminergic and serotonergic system.[100] These deficits may explain some of the EEG alterations found in the reviewed studies, such as increased lower

frequency band (eg, delta, theta) power,[80] global hypersynchronization in the gamma band,[82] and reduced neural network integration[81] after short methamphetamine abstinence (mean ≤1 month). Using a longer abstinence duration (1-6 months), researchers found altered functional connectivity networks in former methamphetamine users, especially for the gamma and delta bands.[83] These alternations may implicate cognitive deficits (eg, incentive salience and attentional bias to drug-related stimuli). The assumption that the findings after short and long abstinence duration reflected withdrawal and chronic methamphetamine exposure effect respectively need further validation. However, the reversibility of these changes still needs to be examined with longer abstinence durations as there is evidence of recovery after 1.5 years of withdrawal in an animal study.[101]

Ecstasy and its frequent compound MDMA use were found generally associated with increased high-frequency band (eg, theta, alpha, and beta) power. These findings are in accord with the assumption that ecstasy is neurotoxic specifically to the serotonergic neurotransmission systems.[102] Furthermore, these alternations may reflect memory and attention deficits that are related to chronic ecstasy use.[87] The subtle inconsistency between research findings may be due to the use of other substances, abstinence duration, etc.

General Discussion

This is the first systematic review that summarized resting-state EEG of chronic substance users comprehensively. In sum, we found that chronic substance use (with or without the diagnosis of substance use disorder) was associated with altered resting-state EEG, manifested mainly as the abnormal rhythm of different frequency bands, and altered functional connectivity (Table 3). Some similarities were shared by certain drugs (eg, increased beta power for alcohol, opioids, and MDMA use). In addition, chronic substance use is generally associated with neural hyperactivation (ie, increased power for high-frequency bands). Whereas abstinence is usually associated with neural hypoactivation (ie, increased power for low-frequency bands), which may partially be due to the drowsiness caused by withdrawal. A recovery effect seems to be found more often for some substances (eg, alcohol) but not others (eg, cannabis), which may reflect differences in degrees of neurotoxicity. Next, we discuss some limitations and future directions.

There are several limitations of the current review worth consideration. First, poly-substance use is prevalent in the studies included. Though the practice of attributing the results to the main drug of use is not optimal, it is difficult to test additive and interactive effects of different substances in a single study (but this can be done in a meta-analysis using individual participant data, cf,[103]). Second, we did not set a lower bound to the sample size. Therefore, some studies may be underpowered to detect a group effect. Third, for studies that did not report information on comorbid disorders such as antisocial personality disorder and depression, there is no clue about how much group differences of EEG can be attributed to these factors. Fourth, with the data at hand, we cannot assess how demographics, substance use and EEG recording parameters may contribute to the inconsistency of findings quantitatively. Fifth, EEG recorded during abstinence may be confounded with the subacute and withdrawal effect, therefore, an abstinence duration should be established in the future. Sixth, some old studies included are of suboptimal quality, which may be constrained by the recording and analyzing facilities available at that time and the reporting standard generally accepted by then. However, it is not easy to confine the publication year of included studies as there is no rule to follow and it is usually an arbitrary range (eg, from the year of 2000 till now).

In the future, more longitudinal studies are needed to clarify the causal relationship between substance use and altered resting-state EEG. For clinical purposes, future studies should evaluate the different qEEG dimensions (spectral power analysis, functional connectivity analysis, network analysis, and graph theoretical analysis), and possibly also evoked potentials, not only vis-à-vis clinically relevant cognitive dysfunction but also vis-à-vis clinically relevant neural dysfunction or deterioration, since the latter may have additional implications for individual neuropsychological diagnosis and treatment. Most importantly, studies using larger sample sizes, increased reporting transparency, and extended abstinence duration (when the abstinence effect is of focus) in examining substance use and resting-state EEG are highly recommended.

Conclusion

The current systematic review included 57 empirical studies on chronic substance use and resting-state EEG. The main finding is that long-term substances use, including alcohol, tobacco, cannabis, cocaine, opioids, heroin, methamphetamine, and XTC are associated with broad resting-state EEG abnormalities, the majority of which cannot be automatically recovered from short abstinence. Similarities and discrepancies of findings for different drugs may reflect their common and distinct effect on the neurotransmitters and corresponding brain regions. These findings await confirmation from studies with larger sample sizes and adopting longer abstinence durations. More transparent reporting of substance use and completeness in reporting EEG recording procedures are highly suggested.

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Author Contribution

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Ethical Approval

Not applicable, because this article does not contain any studies with human or animal subjects.

ORCID iDs

Yang Liu https://orcid.org/0000-0001-8344-6478
Veronica Szpak https://orcid.org/0000-0002-7215-1778

Supplemental material

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