DUAL DISORDERS (ADDICTIVE AND CONCOMITANT PSYCHIATRIC DISORDERS): MECHANISMS AND TREATMENT

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DUAL DISORDERS (ADDICTIVE AND CONCOMITANT PSYCHIATRIC DISORDERS): MECHANISMS AND TREATMENT

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Editorial: Dual disorders (addictive and concomitant psychiatric disorders): Mechanisms and treatment

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comorbidity, co-occurrence, dual disorders, psychiatry, addiction, pathophysiology, association

Editorial on the Research Topic
Dual disorders (addictive and concomitant psychiatric disorders): Mechanisms and treatment

When we launched this Research Topic dedicated to "*Dual Disorders: Mechanisms and Treatment*" we were highly ambitious. We wanted to offer the opportunity to colleagues all over the world to use it as a window to show their latest research findings. We were especially eager to read and publish new empirical evidence on the nature of the relationship between addiction and other psychiatric disorders as well as new empirical evidence on the treatment of dual disorders.

Indeed, we already know since several decades, that dual disorders, i.e., the comorbidity between addictive and other psychiatric disorders, are the rule rather than the exception. The high prevalence of dual disorders and their association with worse outcomes, not only related to poor compliance, are already well-documented.

The debate on the mechanisms leading to dual disorders as either the result of a self-medication by psychiatric patients, the result of repetitive substance use toxicity on brain functions such as mood dysregulation, or the result of some shared biological (e.g., genetic) or environmental (e.g., childhood adversity) factor, will not be solved by this Research Topic, but the 12 articles published are a good reflection of current researchers' concerns.

Two published articles from this Research Topic are literature reviews. The first one is a general review on how Research Domain Criteria (RDOC) could serve as a basis of dual disorders research (Hakak-Zargar et al. from Canada) taking examples in several specific dual disorders. The second one is dedicated to one dual disorder: the co-occurrence a Post-Traumatic Stress Disorder (PTSD) and one or several addictive

disorders (Renaud et al. from France). The authors have read the literature with a specific focus on the mechanisms linking PTSD symptoms and craving, trying to identify a mechanism behind the worse prognosis of addictions in Substance Use Disorders (SUD) patients *with* compared to SUD patients *without* PTSD.

There are also ten studies with original data published in this Research Topic. Three are cross-sectional studies conducted in the general population, exploring potential mechanisms causing dual disorders. Bourduge et al. from France, explored through questionnaires the association between the first lockdown in French teenagers, coping strategies and substance use, as a model of adaptation disorders. Ágoston et al. in a collaborative work conducted between Hungary and the Netherlands, observed the link between a higher score to a caffeine dependence screening scale and a higher score to adult Attention Deficit/Hyperactivity Disorders (ADHD) screening score, that can serve for a model of the association of stimulant abuse and adult ADHD. Finally, El Archi et al. from France, conducted an internet survey showing the link between a screening questionnaire of gambling disorder and a screening score of adult ADHD, but also depressive symptoms.

The last seven studies, all conducted in patient samples using various methodologies. Three of them were cross-sectional descriptive studies.

Cabé et al. from France, showed a significant association between symptoms of a "high" during cocaine use and the self-report of depression during cocaine "downs." Icick et al. in a collaborative study comparing bipolar patients treated in expert centers in France and Norway, observed statistically different prescribed treatments according to the presence of specific SUDs (cannabis, alcohol, or tobacco use disorder). Lastly, Barrangou-Poueys-Darlas et al. from France, descripted the prevalence of a high score on ADHD screening scales and anxiety disorders in patients in care for Gambling Disorders.

Four prospective experimental studies conducted in patients open an avenue for intervention studies in patients with dual disorders.

Therribout et al. from France, describe their stringent methodology to assess ADHD diagnosis in patients with severe SUD. Cardullo et al. from Italy, conducted a secondary analysis of a prospective r-TMS trial comparing cocaine use disorder patients with and without comorbid ADHD. They did not show a difference in the treatment response between the two groups. Todesco et al. from Canada, studied the predictive power of a decision-making test among treatment seeking dual disorder patients, showing that 4 dimensions of this test predicted drop-out in these patients. Lastly, Fonseca et al. from Spain, prospectively (90 days) studied patients with a major depression with and without cocaine use disorder, assessing cortisol and BDNF levels. Their results suggest that the combination of cortisol and BDNF plasmatic levels could differentiate primary vs. cocaine-induced major depression.

This variety of articles show that dual disorders research is moving forward. On the one hand research involves more and more specific association of pairs of psychiatric and addictive disorders, and on the other hand recent research tries to better understand the mechanisms behind the occurrence or severity of dual disorders. Specific therapeutic studies matching treatments with certain patient characteristics are at reach. We hope that reading those articles will give you plenty of new ideas to move this field forward. Patients suffering from dual disorders are still in great need of effective treatments, and high quality research aiming at changing the poor prognosis of these co-occurring conditions is warranted.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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A Retrospective Comparative Study in Patients With Cocaine Use Disorder Comorbid With Attention Deficit Hyperactivity Disorder Undergoing an rTMS Protocol Treatment

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Background: Adult attention-deficit/hyperactivity disorder (ADHD) is associated with high comorbidity with other psychiatric diseases, including cocaine use disorder (CocUD). Given the common fronto-striatal dysfunction, ADHD patients often use cocaine as self-medication for ameliorating symptoms by increasing striatal dopamine release. Yet, comorbidity with ADHD is related to poor treatment outcomes. CocUD has been treated with transcranial magnetic stimulation (TMS), but no studies investigated the outcomes in patients comorbid with ADHD.

Methods: Twenty-two ADHD/CocUD and 208 CocUD-only participants received a high-frequency (15 Hz) rTMS treatment stimulating the left-DLPFC. We investigated whether both groups of patients shared similar demographic and clinical characteristics at baseline. Then, we monitored the effect of treatment testing for potential differences between groups.

Results: At baseline demographic, toxicology and clinical features were not different between the two groups except for global severity index (GSI from SCL-90): patients of ADHD/CocUD group reported higher general symptomatology compared to the CocUD-only group. Concerning the effect of treatment, both groups significantly improved over time regarding cocaine use, craving, and other negative affect symptoms. No differences were observed between groups.

Conclusions: To our knowledge, this is the first study comparing the demographic characterization and rTMS clinical improvements of patients with a dual diagnosis

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of ADHD and CocUD against CocUD-only patients. Cocaine use and common self-reported withdrawal/abstinence symptoms appear to benefit from rTMS treatment with no differences between groups. Future studies are needed to further investigate these preliminary results.

Keywords: attention deficit hyperactivity disorder, cocaine use disorder, craving, repetitive transcranial magnetic stimulation, dorsolateral prefrontal cortex, dopamine

INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is a neurobehavioral disorder characterized by a persistent pattern of inattention and/or hyperactivity-impulsivity interfering with functioning or development (1). ADHD symptomatology begins in childhood but often persists into adulthood (2), with high comorbidity rates with other mental disorders (3) such as substance use disorders (SUDs). Indeed, the prevalence of ADHD is considerably higher among individuals with SUDs than in the general population (4–14). The co-occurrence of these disorders has relevant prognostic implications, as it is associated with a more severe course of substance use, a higher rate of psychiatric comorbidity, and poorer treatment outcome (4, 5, 7, 15–19). Several studies show similar disruptions of the brain dopamine (DA) fronto-striatal system and executive control impairments in adults with ADHD (20) and in people who chronically use drugs, as cocaine (21, 22). The impairment of dopamine signaling in individuals with ADHD may explain the higher risk of taking addictive drugs, as substances of abuse acutely increase brain DA concentration, and might transitorily improve ADHD symptoms (23). Moreover, these DA dysfunctions have been linked to the initiation and maintenance of addictive behaviors (24), indicating that drug addiction represents a dramatic dysregulation of brain motivational circuits (25). This evidence has led to the development of neurobiology-based interventions to modify functions of the affected neurocircuitry (26). Repetitive transcranial magnetic stimulation (rTMS) appears a novel and promising neuromodulation approach to the treatment of SUDs (27). rTMS influences neural electrical activity at the network level by inducing either short-or long-term effects through the application of magnetic pulses (28). Long-lasting rTMS-induced changes may impact behavioral manifestations of addictive disorders as craving, intake, or relapse (29). Preliminary clinical studies have shown reductions in cocaine craving and intake after rTMS treatments (30–35). In addition, it was reported a positive effect of rTMS on other symptoms connected to substance use and deeply related to the fronto-striatal functioning (36). The modulation of relevant addiction dimensions (e.g., anhedonia) was found to play a key role in modulating the response to the rTMS treatment (37, 38). Considering the evidence of cortical disinhibition across different psychiatric conditions (39), this brain stimulation technique has shown to provide some benefits also in ADHD subjects improving the core symptoms, including attention deficits, hyperactivity/impulsivity, and oppositional defiance (40, 41). Thus, considering that ADHD comorbidity negatively affects conventional treatment results for SUDs as cocaine use disorders (CocUD) (17), the present study aimed to assess the therapeutic response in terms of substance use and accompanying withdrawal symptoms in a sample of CocUD patients with and without ADHD symptoms who underwent a high frequency rTMS stimulation protocol over the left dorsolateral prefrontal cortex (L-DLPFC).

METHODS

Participant Selection

Two-hundred and thirty participants diagnosed as suffering from cocaine use disorder (CocUD) were recruited after they voluntarily referral to a specialty outpatient clinic, Center for Addiction in Padua (Italy). Patients signed informed consent on the day of clinic intake and agreed that their data could be used for research. Patients were informed that the data collected would be processed in accordance with the law on privacy and compliance with Legislative Decree No. 196 of June 30, 2003, "Personal Data Protection Code" ensuring anonymity. The data were extracted from patient clinical records and anonymized for analysis. All subjects gave their informed consent for inclusion before they participated in the study. This is a retrospective chart review of data from 230 patients with CocUD who were treated with an rTMS protocol from 2015 to 2019 in an open-label, no sham control study investigating sleep disturbances. The protocol, limited to the retrospective chart review, was approved by the Ethical Committee for the Psychological Research, Departments of Psychology, University of Padua (Protocol no. 3185, code 82F319362FA08A4C9498620BF072CB72), and the study was conducted in accordance with the Declaration of Helsinki. The current retrospective analysis is listed at ClinicalTrials.gov (identifier: NCT03733821).

Participants were 22 to 59 years old and met diagnostic criteria for CocUD according to the Diagnostic and Statistical Manual of Mental Disorders – 5 (DSM 5) (1), as assessed by a clinical psychiatrist specializing in substance use disorders (SUDs). Exclusion criteria included a prior history of other psychiatric diseases, including major depression, schizophrenia, bipolar disorder or other psychosis, current alcohol and other substance abuse or dependence (excluding nicotine, and caffeine), pregnancy or breastfeeding, personality disorders or sleep disturbances deemed to be the primary disease, current unstable medical illness, substantial neurological illness, and any contraindication for rTMS (including implanted metal and devices in the body, or history of epilepsy). From the entire sample of 230 participants, we identified 22 patients diagnosed as suffering from ADHD as assessed by the structured Diagnostic Interview for ADHD in adults (DIVA 2.0) (42). The clinical

suspicion of adult-ADHD arises from the evidenced role of self-medication in symptom control of cocaine rather than a research of the euphoric properties of the substance. As confirmation of the diagnosis, 19 out of 22 ADHD patients were pharmacologically treated with atomoxetine (mean: 34 mg/die, range: 18–80 mg/die), in addition to the rTMS treatment, with a significant reduction of inattentive and hyperactive symptoms. Thus, we benchmarked the outcomes of the sample of 22 CocUD patients in comorbidity with ADHD against a large cohort of 208 CocUD patients. All participants were required to keep medication use stable throughout the study. During the whole period of observation, cocaine use was assessed either *via* a urine drug test, at each visit, or *via* reports from the patient or significant others. The urine drug screen panel also included the following: morphine, methadone, THC, phencyclidine, amphetamine, and methamphetamine.

Treatment

Each patient underwent rTMS using a medical device (MagPro R30) targeting the L-DLPFC. The stimulation parameters, in accord with international recommendations for patient safety and ethics (43), were: frequency 15 Hz, intensity 100% of the motor threshold, 60 impulses per stimulation train, inter-train interval 15 s, and 40 total trains, for a session duration of 13 min. To best identify the L-DLPFC [Montreal Neurological Institute (MNI) coordinates x: −50, y: 30, z: 36], we used an optical TMS navigator (Localite, St. Augustin, Germany) and a magnetic resonance image (MRI) template. Treatment characteristics are the same described in our previous studies (30, 34): twice-daily rTMS sessions for the first five consecutive days of treatment, followed by twice-daily rTMS sessions once a week over eleven weeks. The time interval between the two sessions within each day was 45–60 min. Then, rTMS was re-administered throughout follow-up on an individualized basis to patients who reported lapses to cocaine use, and to patients whose clinical evaluations showed ongoing cocaine craving, including stress-induced craving. At each session, adverse events, including seizures, syncopes, neurological complications, or subjective complaints about memory, concentration, pain, headache, vertigo, or fatigue were assessed with a self-report questionnaire specifically developed by us for this purpose.

Measures

The primary outcome measure was cocaine use. It was assessed through a combination of urine screening, self-report, and reports by collateral informants (typically family members). Firstly, we considered the lapse to cocaine use. In this analysis, for consistency with our previous works (30, 34), the "zero" day for follow-up monitoring was set at 8 days after the initial 5-day course of rTMS. After that 8-day grace period, any indication of cocaine use was coded as a lapse.

In addition to lapse to cocaine use during follow-up, we evaluated the categorical reduction in cocaine frequency level. We adopted a harm reduction approach already validated for alcohol and cocaine consumption (44, 45). Based on the cocaine use during the 30 days before the assessment, we specified three frequency levels at baseline and day 90: abstinence, low-frequency use (one to 4 days of cocaine use in the past month), and high-frequency use (5 or more days of cocaine use in the past month). We also created a "change" variable to indicate a variation in cocaine frequency level from baseline to day 90: increase one level, no change, decrease one level, decrease two levels.

Secondary outcome measures were craving, perceived sleep quality, depression, anxiety, and other negative affect symptoms, assessed with the following scales: Cocaine Craving Questionnaire (CCQ) (46), Pittsburgh Sleep Quality Index (PSQI) (47), Beck Depression Inventory–II (BDI-II) (48), Self-rating Anxiety Scale (SAS) (49), and Symptoms checklist 90 - Revised (SCL-90-R) (50). Participants were assessed at baseline, immediately after completion of the first week of treatment (Day 5), and 30, 60, and 90 days after the beginning of treatment (Day 30–Day 60–Day 90). The instructions of BDI-II require the participant to consider the last 2 weeks preceding the test; thus, it was not included in the assessment on Day 5. Several participants did not complete every scale at every time point, for the main following reasons: clinical response, missing follow-up visit, missing TMS session, and refusal.

Statistical Analyses

Independent sample *t*-tests and chi-squares were performed to evaluate differences in the demographic and clinical characterization of patients at baseline.

Concerning the treatment primary outcomes, we used Kaplan- Meier survival analysis to calculate the median number of days until the first lapse to cocaine use. Data were coded as right-censored for patients who were still abstinent at the end of monitoring or with whom the clinic lost contact. We also performed chi-squares for assessing differences in Day 90 functioning by cocaine frequency level and frequency changes compared to baseline.

Linear mixed models, with a random intercept for each subject, using the time-point as a 5 levels independent variable ("Baseline," "Day 5," "Day 30," "Day 60," "Day 90,") were computed for each secondary outcome (CCQ, PSQI, BDI-II, SAS, GSI). To estimate the overall effect of treatment, group, and their interaction it was performed a type III analysis of variance with Satterthwaite's method for computing the denominator degrees of freedom of each F-test. We corrected multiple pairwise comparisons between time points using the Bonferroni method.

Thereafter, for examining the best predictor of change in cocaine frequency level we performed an ordinal logistic regression, testing the following predictors: group (ADHD/CocUD vs. CocUD), cocaine frequency level at baseline (abstinence vs. Low use vs. High use), age at the beginning of treatment, age at the first experience with cocaine, age at the time of addiction to cocaine, years of education, and baseline scores at CCQ, PSQI, BDI, SAS and GSI. We did not test for sex differences because most participants were male. To perform this analysis, we removed missing values in any of the predictors: the final sample consisted of 22 patients with ADHD in comorbidity with CocUD, and 156 CocUD patients.

Data were expressed as mean ± standard deviation (SD), unless otherwise specified; alpha was set at < 0.05, two-tailed. All the analyses were performed using RStudio versions 1.2.5001 (51) with R version 3.6.1 (52) and the packages MASS (53), survival (54), lme4 (55), lmerTest (56), and emmeans (57).

RESULTS

Patients Characteristics at Baseline

Demographic and clinical characteristics at baseline of the participants are presented in **Table 1** divided by group. The sample of ADHD/CocUD consisted of 22 patients, 1 female and 21 males, aged between 25 and 53 (37.91 ± 8.71). The sample of CocUD-only consisted of 208 patients, 5 females 203 males, aged between 22 and 59 (37.67 ± 7.05). **Table 1** shows the results of the independent sample *t*-test for assessing differences between groups. ADHD/CocUD patients were not significantly different compared to CocUD-only patients in demographic characteristics such as age, education, age at the first experience with cocaine, and age at the onset of addiction (all $ps \geq 0.37$). Moreover, there were no significantly differences in craving for cocaine (CCQ, $p = 0.82$), self-perceived sleep quality (PSQI, $p = 0.36$), depression (BDI, $p = 0.10$), and anxiety (SAS, $p = 0.06$). However, a broader measure of clinical symptomatology such as the GSI, from SCL-90, revealed higher scores in ADHD/CocUD patients compared to CocUD-only patients (GSI, $p = 0.03$).

Regarding the cocaine use frequency level, most of the patients used 5 or more times in the 30 days before the beginning of treatment (ADHD/CocUD: 86%; CocUD-only: 72%). Only 1% of patients in the CocUD-only group was already abstinent at the beginning of treatment. A chi-square test of independence showed that there was no significant association between group and cocaine frequency level, $\chi^2\ (2) = 2.16$, $p = 0.34$.

TABLE 1 | Demographic and clinical characteristics of participants.

Variables	ADHD/CocUD ($n = 22$)	CocUD-only ($n = 208$)	*t*	dF	*P*
Age (years)	37.91 (8.71)	37.67 (7.05)	0.15	228	0.88
Gender (female/male)	1/21	5/203			
Education (years)	12.59 (3.5)	13 (3.21)	−0.91	228	0.57
Age at first experience (years)	20 (6.09)	21.27 (6.29)	0.23	228	0.37
Age at addiction (years)	29.64 (8.85)	29.83 (8.4)	−0.1	228	0.92
CCQ score at baseline	16.64 (13.11)	16.01 (11.91)	0.23	183	0.82
PSQI score at baseline	9.95 (3.95)	9.1 (4.14)	0.92	194	0.36
BDI-II score at baseline	22.05 (13.55)	17.99 (10.47)	1.66	209	0.10
SAS score at baseline	49.83 (10.19)	45.59 (10.13)	1.86	211	0.06
GSI score at baseline	69.75 (16.62)	62.61 (13.83)	2.24	210	0.03
Cocaine use 30 days before baseline (% frequency level)					
Abstinence	0	1	$\chi^2\ (2) = 2.16$, $p = 0.34$		
Low (1-4 uses)	14	26			
High (5+ uses)	86	72			

Data are presented as mean (standard deviation) unless otherwise specified. ADHD, attention-deficit/hyperactivity disorder; CocUD, cocaine use disorder; CCQ, cocaine craving questionnaire; PSQI, pittsburgh sleep quality index; BDI-II, beck depression inventory-II; SAS, self-rating anxiety scale; GSI, global severity index of the symptoms checklist 90 – Revised; Some percentages add up to slightly <100 due to rounding error.

Primary Outcome: Cocaine Use

The Time to the first lapse is shown in **Figure 1**. The median time to the first use of cocaine use in the ADHD/CocUD group was 58 days (95% confidence interval: 17–267); in the CocUD-only group it was 93 days (95% confidence interval: 63–136). The difference between the two groups was not statistically significant ($p = 0.34$).

At the end of the standard protocol of treatment (Day 90), based on the cocaine use during the 30 days before the assessment, we specified three frequency levels as we did at baseline (**Figure 2A**). The proportion of abstinent patients significantly increased over time in both the ADHD/CocUD group [$\chi^2\ (2) = 24.9$, $p < 0.001$] and the CocUD-only group [$\chi^2\ (2) = 229.33$, $p < 0.001$]: respectively 50 and 63% of patients were abstinent during the 30 days prior to Day 90. There were no differences between groups [$\chi^2\ (2) = 1.69$, $p = 0.42$]. Concerning the variation in cocaine frequency level from baseline to Day 90, 86% of ADHD/CocUD and 82% of CocUD-only patients reported an improvement (decrease one or two levels) (**Figure 2B**). Again, the chi-square test of independence showed that there was no significant association between groups and the variation in cocaine frequency level [$\chi^2\ (3) = 0.91$, $p = 0.82$].

Secondary Outcome: Changes in Craving, Sleep, Depression, and Anxiety

The second goal of our analyses was to investigate changes in clinical outcomes over time and whether there were differences between ADHD/CocUD and CocUD-only patients undergoing rTMS over the L-DLPFC. Using type III analyses of variance, we tested the main effect of *Time* and *Group* and their interaction in each linear mixed model for the different clinical outcomes.

CCQ scores significantly improved at each timepoint after the first week of rTMS treatment [$F_{(4,\ 638)} = 50.35$, $p < 0.001$]. There were no differences between groups and there was not a significant effect of the *Time* × *Group* interaction [$F_{(4,\ 638)} = 0.43$, $p = 0.78$]. Pairwise comparisons showed that CCQ scores at Day 5 were significantly lower than those at baseline in both the ADHD/CocUD group (Day 5: 5.59 ± 7.53; Baseline: 16.64 ± 13.11; $p < 0.001$), and CocUD-only group (Day 5: 3.81 ± 4.95; Baseline: 16.01 ± 11.9; $p < 0.001$). This improvement was maintained through the three subsequence time points in both the groups: ADHD/CocUD Day 30 (6.64 ± 8.17; $p < 0.001$), CocUD-only Day 30 (3.12 ± 5.67; $p < 0.001$), ADHD/CocUD Day 60 (5.55 ± 8.54; $p < 0.001$), CocUD-only Day 60 (3.62 ± 7.25; $p < 0.001$), ADHD/CocUD Day 90 (4.71 ± 5.46; $p < 0.001$), CocUD-only Day 90 (3.19 ± 5.45; $p < 0.001$).

Like craving, we observed a significant reduction over time of sleep disturbances and affective symptoms as reflected by the

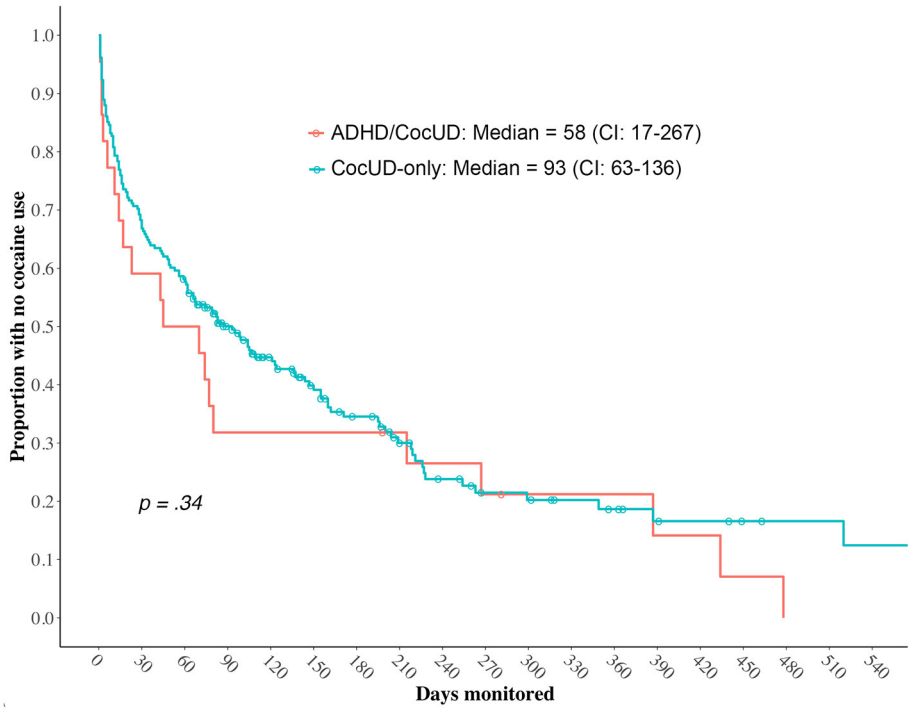

FIGURE 1 | Time to the first resumption of cocaine in ADHD/CocUD and CocUD-only groups. ADHD, attention-deficit/hyperactivity disorder; CocUD, cocaine use disorder.

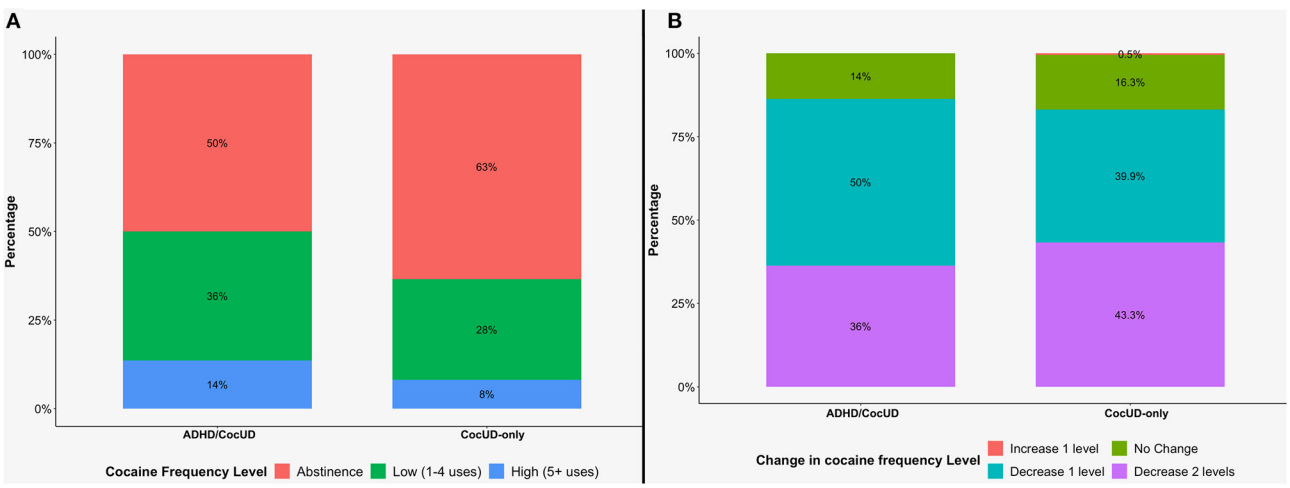

FIGURE 2 | Distribution of patients according to cocaine frequency level at Day 90 **(A)**, and change in cocaine frequency level in comparison to baseline **(B)**. ADHD, attention-deficit/hyperactivity disorder; CocUD, cocaine use disorder.

significant main effect of *Time* in each linear mixed model: PSQI [$F_{(4, 682)} = 28.99$, $p < 0.001$], BDI-II [$F_{(3, 518)} = 101.88$, $p < 0.001$], SAS [$F_{(4, 676)} = 43.87$, $p < 0.001$], and GSI [$F_{(4, 735)} = 92.73$, $p < 0.001$]. Also, for all these measures it was observed a main effect of *Group*: PSQI [$F_{(1, 204)} = 8.01$, $p < 0.01$], BDI-II [$F_{(1, 200)} = 4.48$, $p < 0.05$], SAS [$F_{(1, 217)} = 13.13$, $p < 0.001$], and GSI [$F_{(1, 220)} = 11.26$, $p < 0.001$]. Pairwise comparison allowed to highlight the differences between groups at the different time points. As previously observed, and here confirmed, at baseline groups were significantly different only for GSI scores [$t_{(566)} = 3.03$, *adjusted* $p = 0.01$]. After the first week of treatment both the groups significantly improved in all the scores, and pairwise comparison showed no significant differences for any of the clinical measures, neither at GSI [$t_{(566)} = 2.37$, *adjusted* $p = 0.09$]. At Day 30, pairwise comparison highlighted significant differences between groups for PSQI [$t_{(672)} = 2.99$, adjusted p

$= 0.01$], SAS [$t_{(633)} = 2.77$, *adjusted* $p = 0.02$], and GSI scores [$t_{(709)} = 2.59$, *adjusted* $p = 0.04$]. Other comparison showed that PSQI scores at Day 30 in ADHD/CocUD patient were no longer different from baseline [$t_{(678)} = 2.28$, *adjusted* $p = 0.26$]. However, in all the other cases the scores at Day 30 were still significantly lower than those at baseline in both groups. At Day 60 and Day 90 the differences between groups returned to be not significant for all the clinical measure but SAS [Day 60: $t_{(585)} = 2.93$, *adjusted* $p = 0.02$; Day 90 $t_{(628)} = 3.06$, *adjusted* $p = 0.01$]. Also, PSQI score of ADHD/CocUD patients improved and turned again to be significantly lower than those at baseline [Day 60: $t_{(683)} = 3.74$, *adjusted* $p = 0.002$; Day 90 $t_{(679)} = 3.77$, *adjusted* $p = 0.001$].

For none of the clinical outcomes significant *Time* × *Group* interactions (all *p*s ≥ 0.27) were observed.

Best Predictor of Change in Cocaine Frequency Level

In a separate model, we examined the best predictor of change in cocaine frequency level from baseline to day 90 performing an ordinal logistic regression. The results are summarized in **Table 2**. Above all the predictors, only the cocaine frequency level at baseline and the CCQ score reached the defined alpha level ($\alpha = 0.05$). Higher cocaine frequency level at baseline was associated with higher odds of moving from *no change* to *decrease one level* or *decrease two levels* (OR = 9.76; 95% CI: 4.61–21.77). Also, for a one-unit increase in CCQ score, the odds of moving from *no change* to *decrease one level* or *decrease two levels* were 4% less, given that the other variables in the model are held constant.

TABLE 2 | Coefficient table of the ordinal logistic regression for examining the best predictor of change in cocaine frequency level.

Variables	Value	Std. Error	*t*-value	*P*-value
Group	0.508	0.468	1.085	0.27
Cocaine frequency level at baseline	2.279	0.395	5.774	<0.001**
Age	0.027	0.028	0.973	0.33
Education	−0.038	0.048	−0.798	0.42
Age at first experience	0.003	0.033	0.103	0.91
Age at addiction	0.010	0.027	0.392	0.69
CCQ score at baseline	−0.035	0.015	−2.302	0.02*
PSQI score at baseline	−0.060	0.048	−1.241	0.21
BDI-II score at baseline	0.013	0.025	0.533	0.59
SAS score at baseline	0.002	0.026	0.084	0.93
GSI score at baseline	0.001	0.018	0.033	0.97

*$p < 0.05$; **$p < 0.001$.
CCQ, cocaine craving questionnaire; PSQI, Pittsburgh sleep quality index; BDI-II, beck depression inventory-II; SAS, self-rating anxiety scale; GSI, global severity index of the symptoms checklist 90 – revised.

Safety

None of these 230 patients reported any serious adverse event during the study. There were no seizures, syncopes, neurological complications, or subjective complaints about memory or concentration impairment limiting the treatment and no patient discontinued treatment prematurely due to intolerable stimulation, pain, or other adverse effects such as headache, vertigo, or fatigue.

DISCUSSION

The main aim of the present study was to determine whether attention deficit hyperactivity disorder (ADHD) comorbidity among patients with cocaine addiction is associated with higher clinical symptomatology or less successful results of rTMS treatment.

In our sample the prevalence of ADHD was 9.5%, which is very close to what was found in other populations of cocaine abusers (9), and higher than the one reported in the Italian population (2.8%) (58). In opposite to already published studies and meta-analyses (5, 15, 16), in our cohort cocaine abusers with adult ADHD, compared to those without such comorbidity, were not younger at the clinical admission and did not report an earlier onset of cocaine abuse or a more frequent use in the 30-days before treatment. Moreover, they did not report worse depressive symptomatology, self-perceived quality of sleep, or anxiety as assessed by BDI-II, PSQI, and SAS. At baseline, the only clinical measure which was significantly different between the two groups was the Global Severity Index, indicating a generical status with severe symptoms. The lack of differences between groups may be due to an uncontrolled bias regarding the intrinsic characteristics of the patients who voluntarily refers to the specialty outpatient private clinic in which data were collected. They may have a higher socio-economic status or higher level of education compared to the generic population of cocaine abusers. These elements may flatten the differences found in the already published studies. Further studies are needed to test this hypothesis.

Several studies suggested that psychiatric comorbidity could play a role in determining a worse prognosis (5, 17, 18). Thus, we predicted that co-occurring ADHD would have a negative impact on the outcome of treatment (e.g., cocaine use). In our study, we adopted a harm reduction approach already validated for alcohol and cocaine consumption (44, 45). As reported by other groups, other than abstinence, a reduction in cocaine frequency by the end of treatment might be meaningful for a sustained clinical benefit up to 1 year following treatment (45). Surprisingly, our findings did not replicate the negative prognostic effect: concerning the variation in cocaine frequency level from baseline to Day 90, 86% of ADHD/CocUD and 82% of CocUD-only patients reported an improvement (decrease one or two levels) with no significant differences between groups. Both groups also showed an overall significant improvement of other accompanying symptoms, including depression and perceived sleep quality. On Day 90 there were no differences between groups in none measure, except for SAS scores. Indeed, patients with ADHD comorbidity showed higher anxiety levels compared to CocUD-only patients at Day 60 and Day 90. However, the

mean SAS score in ADHD patients was above the clinical level set to 45, indicating a normal range of anxiety in both groups.

In our sample of ADHD/CocUD patients, 19 out of 22 subjects were pharmacologically treated with atomoxetine, and all received an rTMS treatment in addition to a conventional psychosocial intervention. This integrative multidimensional approach could account for the positive outcome observed in the ADHD/CocUD patient population, that did not differ from the CocUD-only group. However, despite atomoxetine treatment has been associated with clinical improvements in quality of life and executive functions in subjects with ADHD (59), a randomized double-blind placebo-controlled study failed to provide evidence supporting the utility of atomoxetine in treating cocaine dependence (60, 61). Moreover, it has been reported that atomoxetine increases extracellular levels of DA in prefrontal cortex, but not in the striatum and nucleus accumbens (62–65). The rTMS neuromodulatory effect within the reward circuitry may induce significant changes within the dysfunctional dopaminergic signaling underlying ADHD pathophysiology. Functional imaging studies showed a significant reduction dopamine transporter (DAT) and D_2/D_3 receptors within the reward/motivation brain areas in both ADHD and CocUD patients compared to healthy subjects (21, 22, 66, 67). The rTMS protocol over the left DLPFC might restore the aberrant dopaminergic signaling through the dopamine release induced in the caudate nucleus, cingulate cortex, and other regions of the dopamine pathway (68, 69) in both ADHD and addiction conditions. Thus, the modulation of dopamine signaling and the effects on executive functioning due to the rTMS treatment, rather than atomoxetine, may lead to the significant clinical effects we observed indiscriminately in both ADHD/CocUD and CocUD-only patients. This may open a new view in the investigation of the therapeutic effect of high-frequency stimulation on ADHD symptoms. Indeed, conflicting results have been reported regarding the use of rTMS as an effective tool for ADHD treatment (40, 41, 70–72). However, none of these studies stimulated the left DLPFC and further studies are needed to examine his role.

Another aim of our study was to explore the better predictor of treatment outcome. Specifically, we examined the best predictor of change in cocaine frequency level from baseline to day 90 performing an ordinal logistic regression. Above all the predictors, only the cocaine frequency level at baseline and the craving were significant. In previous studies, both of these variables were the most important predictors of successful detoxification from cocaine (73–77). Our results extend these findings to the context of an rTMS treatment. Again, there were no differences between groups: having ADHD in comorbidity is not related to a decreased odd of improvement.

To our knowledge, this is the first study comparing the demographic characterization and rTMS clinical improvements of patients with a dual diagnosis of ADHD and CocUD against CocUD-only patients. Cocaine use and common self-reported withdrawal/abstinence symptoms appear to benefit from rTMS treatment with no differences between groups.

We are aware of the limitations of the naturalistic clinical setting in which our cohort of patients received an rTMS treatment. Considering the absence of a control group or a sham-controlled double-blind design, we cannot rule out a possible placebo effect. Moreover, the unbalanced samples and the lack of a priori power analysis could have influenced the final outcome. Future studies using a more standardized approach are needed to further investigate these preliminary results.

DATA AVAILABILITY STATEMENT

The dataset used in this study is not publicly available due to the sensitive and personal nature of the information included. However, the corresponding author is willing to respond to any reasonable requests for de-identified data.

ETHICS STATEMENT

The protocol, limited to the retrospective chart review, was reviewed and approved by Ethical Committee for the Psychological Research, Departments of Psychology, University of Padua (Protocol no. 3185, code 82F319362FA08A4C9498620BF072CB72). The patients provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SC: data curation, methodology, formal analysis, and writing the original draft. GM and LG: conceptualization, supervision, review and editing original draft. LGP and DC: methodology and data curation. MS, NC, and AT: review and editing the original draft and designed the study. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2021.659527/full#supplementary-material

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Influence of Clinical Markers of Dopaminergic Behaviors on Depressive Symptoms During Withdrawal in Cocaine Users

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Background: During cocaine withdrawal, transient depressive symptoms that do not meet the criteria for depression, but promote relapse, are frequently observed. Their temporality could evoke a role of dopamine, especially since the underlying mechanism of these depressive symptoms is not well understood. We hypothesized that variation in the dopaminergic activity profile, modeled from clinical markers, could be implicated in the development of depressive symptoms during cocaine withdrawal.

Methods: We compared patients reporting depressive symptoms (RDS+) or not (RDS–) during cocaine withdrawal. We evaluated dopaminergic activity through indirect clinical markers based on the known dopaminergic behaviors. A combined criterion was constructed for hyper and hypo dopaminergic models according to the O'Brien method and illustrated by the Hedges' effect-size and forest-plot graph. A multidimensional factorial analysis was carried out to determine which parameters discriminate RDS+/RDS– patients.

Results: 313 patients were included, and 77% reported depressive symptoms during cocaine withdrawal. Hyperdopaminergic variables used to discriminate the two groups had a large overall effect size (−0.669) and included psychotic symptoms (−0.524), hallucinations (−0.548), and delusions (−0.528). The overall effect of the hypodopaminergic component was considerable (−0.604) with a large effect size for the severity of dependence (−0.616), withdrawal symptoms (−0.578), and anhedonia (−0.528). The combined model including hyperdopaminergic and hypodopaminergic components had the largest effect size (−0.785).

Conclusion: The dopaminergic activities profile, assessed by indirect clinical markers, seems to characterize patients with depressive symptoms very well during cocaine withdrawal. RDS+ patients reported moreover higher levels of psychotic symptoms and more severe cocaine use disorder than RDS–.

Keywords: cocaine, withdrawal, dopamine, clinical markers, depressive symptoms

INTRODUCTION

An estimated 20 million individuals worldwide used cocaine according to the world drug report 2021. This global level of cocaine use continues to increase every year (1), and its impact in terms of public health is major, particularly with regard to overdoses (2). The treatment of this addiction is complex, especially when it is associated with a psychiatric disorder, with a high relapse rate and a worse follow-up addiction severity (3, 4). Cocaine, as well as other psychostimulants, can also cause stroke and alterations in mood and cognition (5).

Relapsing patients are more likely to declare serious life-time psychiatric symptoms, including depressive symptoms (6). These patients rated their psychiatric problems as more severe and reported a greater need for treatment for these problems (6). Some studies suggested that depressive symptoms are specifically and significantly associated with an increased risk of relapse after treatment in substance users (7). These mood fluctuations are important because they are a pejorative prognostic factor in cocaine-dependent patients (8) and are associated with increased suicidal risk (9). Furthermore, patients who drop out early have more depressive symptoms than the later dropouts (10). It has been shown that worse depressive symptoms represent a significant predictor of worse medical severity at 12-months follow-up (4). Depressive symptoms seem to play a key role in the process of relapse and so have been chosen in our study as a discriminative factor.

A particular form of transient depressive symptoms is observed during cocaine withdrawal. It is often the subsyndromic form and does not correspond to the well-known timeline of the major depressive disorder. There are several other specificities: (1) these depressive symptoms disappear when taking cocaine, (2) treatment of depression in cocaine users with selective serotonin reuptake inhibitor (SSRI) seems to underperform (11, 12). The mechanism therefore seems different and raises the question of the involvement of dopamine in the emergence of depressive symptoms during cocaine withdrawal. This is especially relevant considering that dopamine plays a central role in the mechanism of cocaine, which works by blocking the dopamine transporter (DAT) and increasing the brain's dopamine level (13). This involvement of dopamine had already been suggested by Dackis and Gold (14).

A potential model of dopaminergic depression can be observed in Parkinson's disease, where symptoms are correlated with dopamine levels (15). In this disease, the hypodopaminergic behaviors results in depression, anxiety, apathy, anhedonia, cognitive dysfunctions, and sleep disorders (15, 16). In the particular case of Parkinson's disease, the hyperdopaminergic behaviors, which is induced by dopaminergic treatments in Parkinson's disease, is characterized by hallucinations, delusions, and compulsive behaviors, such as pathological gambling, hypersexuality, shopping, binge eating, and punding (17, 18). These "dopaminergic behaviors" could be used as indirect clinical markers of dopamine activity. The psychoactive effects of cocaine are fairly well described today (19). Among these symptoms are those that may serve as indirect markers of dopaminergic activity. Cocaine use induces a brief "peak" of pleasure, lasting a few minutes, associated with subjective stimulating effects. Sometimes, there are also psychotic symptoms, especially during high consumption: hallucinations, delusions, or consumption associated behavior (20). This phase then quickly gives way to a withdrawal characterized by contrary symptoms, such as depressive symptoms, anhedonia, and anxiety (21). The intensity of depressive and psychotic symptoms seems to be related to the severity of addiction and the level of use (22).

Based on the Parkinson's disease model and what is clinically observed in cocaine users, we hypothesized that variation in dopamine activity is implicated in the development of depressive symptoms during cocaine withdrawal. Consumers may first experience hyperdopaminergic symptoms upon substance use (psychotic symptoms, or stereotypes), then hypodopaminergic symptoms upon substance withdrawal (depressive symptoms, apathy, and anxiety).

Our objective is to investigate whether patients reporting depressive symptoms during cocaine withdrawal (RDS+) have a different profile of clinical markers of dopaminergic behaviors from those who do not (RDS–).

Abbreviations: RDS+, patients who reported depressive symptoms during withdrawal; RDS–, patients who did not report depressive symptoms during withdrawal; PD, Parkinson's disease; OMT, opioid maintenance treatment.

METHODS

Study Design

This study is an analysis of secondary data from a French multicenter retrospective study called Psychocoke (23). The sample consisted of 313 cocaine users who sought treatment in drug treatment centers in France.

Inclusion criteria were: ≥18 years-old, medical follow-up for a current cocaine use disorder, social security affiliation. Exclusion criteria were be under protective supervision, have blood test contraindication, and not speak or understand French.

Research Instruments

Sociodemographic Data

Sociodemographic and clinical information [e.g., age, gender, marital status, educational and professional level, personal medical history (psychiatric or addictive)] were collected from the staff-administered questionnaires.

Depressive Symptoms

We investigated whether patients subjectively felt the presence of depressive symptoms during cocaine withdrawal. Depressive symptoms in cocaine users are often assessed by self-report measures (22, 24). Some studies found that a significant proportion of patients with depressive symptoms do not meet the criteria for characterized depression during diagnostic evaluation (24). Standardized assessment scales are often not usable in the acute phase of drug use or withdrawal. Therefore, we assessed this aspect by asking them if they had ever experienced depressive symptoms during cocaine withdrawal with the following proposition: "Presence of depressive elements during the descent: No or Yes." The group that reported depressive symptoms was named RDS+ (Reported Depressive Symptoms +), the other group was named RDS–.

Addiction Characteristics

Current and lifetime psychoactive substance use was evaluated in terms of consumption modality, age of onset, frequency, and amount of use for: cocaine, tobacco, opiates, alcohol, sedative drugs, amphetamines, ecstasy/MDMA, hallucinogens, ketamine, poppers, and cannabis.

The severity of cocaine dependence was assessed according to the criteria of DSM-IV (Diagnostical and Statistical Manual) (American Psychiatric Association, n.d.). We also wanted to estimate the severity of dependency with a dimensional approach, as is currently practiced with DSM 5. We therefore added the total number of DSM-IV criteria present for each patient, in order to be as close as possible to the current method of rating a substance use disorder (0 to 7/7 score).

Psychotic Symptoms

Cocaine-induced psychotic symptoms were assessed with the French version of the Scale for the Assessment of Psychotic Symptoms-Cocaine Induced Psychosis (SAPS-CIP) questionnaire (20, 25). This semi directive interview explores different dimensions: hallucinations (auditory hallucinations, visual hallucinations, somesthesic or tactile hallucinations, olfactory hallucinations), delusions (persecutory delusions, delusions of jealousy, delusions of sin or guilt, grandiose delusions, religious delusions, somatic delusions, ideas and delusions of reference, delusions of being controlled, delusions of mind reading), cocaine-associated behavior (aggressive and agitated behavior, repetitive or stereotyped behavior, social and sexual behavior, preparatory behavior) and physical symptoms prior to use (what the subject does to prepare for crack use: place of consumption, type of preparation, rituals, etc.). Each item was scored from 0 to 5, thus leading to a total score from 0 to 15.

Procedures

Data collection was conducted from 2012 to 2016 through interviews performed by a trained psychologist or psychiatrist during a single visit.

Data Analysis

Statistical analyses were performed using Stata software, version 13 (StataCorp, College Station, US) and R software with the ade4 package (http://www.R-project.org). The assumption of normality was checked using normal probability plots and the Shapiro-Wilk's test. The tests were two-sided, with a type I error set at 5%.

First, the comparisons between RDS–/RDS+ concerning categorical data were performed using the Chi-Squared test or Fisher's exact test, whereas the comparisons for quantitative variables among Reported Depressive Symptoms (no/yes) were analyzed using the Student *t* test or the Mann-Whitney test when the conditions of the *t* test were not met. Second, a combined criterion was constructed for hyper and hypo dopaminergic models according to the method developed by O'Brien (26). This framework allows the combination of multiple parameters into a single statistical assessment, without assigning a rank of relative importance.

Then, multidimensional factorial discriminant analysis (FDA) was carried out to uncover the underlying relationships parameters and to determine which parameters discriminated patients with and without RDS.

To illustrate these results and the magnitude of differences, Hedges' effect-size (i.e., difference of means between groups divided by the standard-deviation) and 95% confidence intervals were estimated and represented with a forest-plot graph.

Ethical Aspects

The Research Ethics Committee of Ile de France (Paris area) approved the study protocol under Opinion NCT01569347. Written informed consent was obtained from all the participants.

Results

Among the 313 cocaine-dependent subjects participating in the study, 77% ($N = 241$) showed depressive symptoms during the descent. The data presented in **Table 1** show that there was no significant difference between the two groups for age (38.11 ± 9.28 vs. 38.32 ± 8.80), gender, marital status and school level. In our sample, we found mainly single men with a heterogeneous overall educational level (**Table 1**).

A higher proportion of patients in the RDS+ group (70.12%) reported at least one experience of psychotic symptoms when using cocaine, compared to RDS- patients (45.83%) ($p < 0.001$). With regard to detailed psychotic symptoms, there were significantly more hallucinations ($p < 0.001$), delusions ($p <$

TABLE 1 | Sociodemographic characteristics and psychotic symptoms (assessed by SAPS-CIP) of cocaine users with (RDS+) or without (RDS–) depressive symptoms during cocaine withdrawal.

Variable	Without RDS (RDS–) N = 72 (23%)	With RDS (RDS+) N = 241 (77%)	*p*
Age (years, mean ± SD)	38.11 (± 9.28)	38.32 (± 8.80)	0.87
Gender (Male, %)	77.78	78.84	0.85
Marital status (%)			
Single	84.72	75.52	
Married	6.94	13.69	0.22
Divorced	8.33	10.79	
School level (%)			
Primary	2.78	1.66	
Specialized	11.11	4.15	
Secondary 1st cycle	18.06	16.18	0.20
Secondary 2nd cycle	16.39	31.95	
Superior	41.67	46.06	
Psychotic symptoms (%)	45.83	70.12	**<0.001***
Hallucinations score (mean ± SD)	1.00 (± 1.36)	1.81 (± 1.52)	**<0.001***
Delusions score (mean ± SD)	1.60 (± 1.51)	2.35 (± 1.43)	**<0.001***
Consumption-associated behavior score (mean ± SD)	1.85 (± 1.53)	2.20 (± 1.52)	0.09
Physical symptoms before use score (mean ± SD)	1.01 (± 1.41)	1.65 (± 1.45)	**0.001***

**Significant differences between groups according to independent samples t-tests or χ^2 tests.*

TABLE 2 | Clinical characteristics of cocaine users with (RDS+) or without (RDS–) depressive symptoms during cocaine withdrawal ($N = 313$).

Variable	Without RDS (RDS–)	With RDS (RDS+)	*p*
History of hospitalization for withdrawal (%)	66.67	64.73	0.76
Previous suicide attempt (%)	27.78	38.59	*0.09*
Age at first cocaine use (years, mean ± SD)	22.46 (± 7.06)	23.31 (± 6.78)	0.37
Frequency (Daily, %)	65.28	68.88	0.19
Cocaine use behavior (%)			
Crack	20.83	18.67	
Cocaïne	68.06	71.78	0.83
Crack + Cocaïne	11.11	9.54	
Administration			
Snorted	48.61	63.90	
Smoked	26.39	23.65	**0.04***
Injected	18.06	7.88	
Injected + other way	6.94	4.56	
Poly-drug use in whole lifetime (number of substances, mean ± SD)	7.82 (1.89)	7.50 (1.94)	0.22
Cocaine dependency criteria (DSM IV, %)			
Tolerance	81.94	85.06	0.52
Withdrawal	61.11	84.23	**<0.01***
Loss of control	91.67	90.04	0.82
Persistent desire	59.72	73.03	*0.07*
Excessive time	88.41	95.42	*0.06*
Anhedonia	56.94	79.25	**<0.01***
Continuation despite complications	38.89	46.06	0.47
Total number of dependence criteria	4.75 (± 0.17)	5.53 (± 0.08)	**<0.001***

**Significant differences between groups according to independent samples t-tests or χ^2 tests.*

0.001), and physical symptoms before use ($p < 0.001$) in the RDS+ group (**Table 1**).

All patients selected for the study had a lifetime of cocaine use and were current cocaine users (use within 1 month). The history of addiction hospitalization was similar in both groups and concerned nearly 65% of patients. The average age at which cocaine use began was similar in both groups (22.46 ± 7.06 vs. 23.31 ± 6.78 years), as well as the frequency of use (more than 65% of daily users) and the type of product consumed, mainly cocaine (**Table 2**). A significant difference in consumption patterns ($p = 0.04$) was observed. The nasal route of administration was more frequently found in the group of patients with depressive symptoms (63.90 vs. 48.61%). Injectable or smoked pathways were more frequent in the RDS+ group (26.39 vs. 23.65 % for smoked, 18.06 vs. 7.86 % for injectable). The consumption of other psychoactive substances (Tobacco, Opioid, Alcohol, Sedatives, Amphetamines, Ecstasy/MDMA, Hallucinogens, Ketamine, Poppers, Cannabis) was not significantly different between the two groups. The average number of substances used per patient did not differ.

The study of dependence criteria (DSM IV TR) for cocaine in the two groups showed significantly more withdrawal symptoms in the RDS+ group ($p < 0.01$). In this group (RDS+), there was also significantly more cessation of social or recreational activities that we define as anhedonia ($p < 0.01$). More persistent desire ($p < 0.07$) and excessive time spent around consumption ($p < 0.06$) were not significantly more frequent. Finally, the severity of dependence was significantly higher ($p < 0.001$) (RDS+ vs. RDS–: 5.53 ± 0.08 vs. 4.75 ± 0.17, respectively).

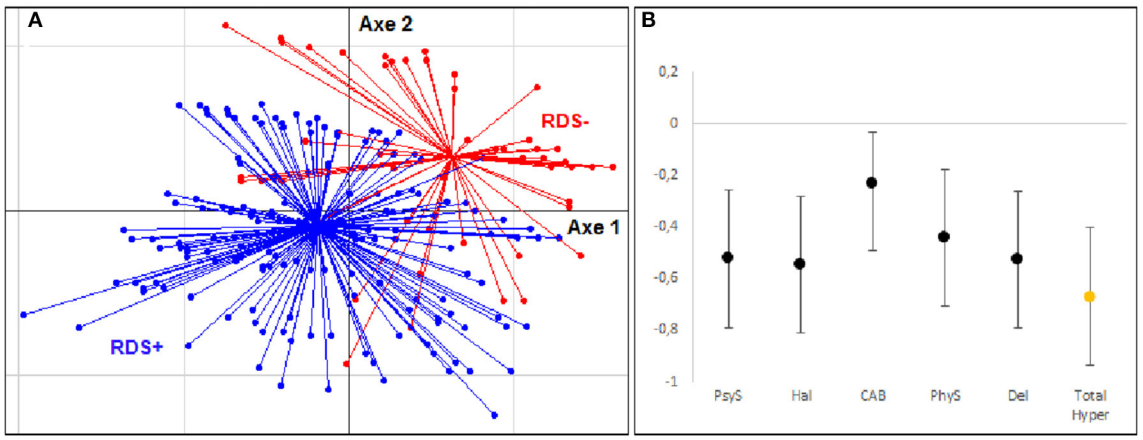

FIGURE 1 | Multidimensional factor analysis and effect size for hyperdopaminergic components. **(A)** Tridimensional representation of the distribution of subjects with and without depressive symptoms during cocaine withdrawal (RDS– group in Red, RDS+ group in Blue) according to clinical variables of hyperdopaminergia: psychotic symptoms (PsyS), hallucinations (Hal), delusions (Del), consumption-associated behavior (CAB), physical symptoms before use (PhyS). **(B)** Hedges' effect-size of each variable for the hyperdopaminergic components.

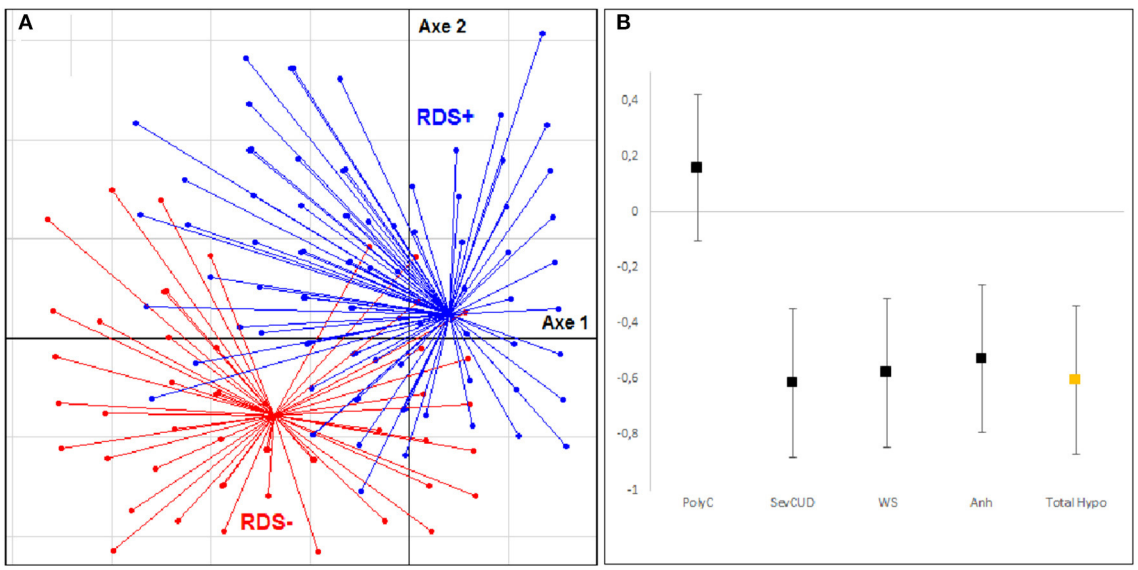

FIGURE 2 | Multidimensional factor analysis and effect size for hypodopaminergic components. **(A)** Tridimensional representation of the distribution of subjects with and without depressive symptoms during cocaine withdrawal (RDS– group in Red, RDS+ group in Blue) according to clinical variables of hypodopaminergia: severity of dependence (SevCUD), withdrawal symptoms (WS), anhedonia (Anh), polyconsumption (PolyC). **(B)** Hedges' effect-size of each variable for the hypodopaminergic components.

We included significant differences or clinically relevant variables in the FDA: the presence of psychotic symptoms, hallucinations, delusions, physical symptoms before use, and consumption-associated behavior (this group was named hyperdopaminergic component), and severity of dependence, presence of withdrawal symptoms, anhedonia and poly-drug use (this group was named hypodopaminergic component).

The analysis (**Figure 1A**) revealed that in the hyperdopaminergic component, our population was well separated into two groups between RDS+ (blue) and RDS– (red) patients.

There were moderate to large effects size (**Figure 1B**) for psychotic symptoms (-0.524 ± 0.266) (PsyS), hallucinations (-0.548 ± 0.267) (Hal), and delusions (-0.528 ± 0.267) (Del).

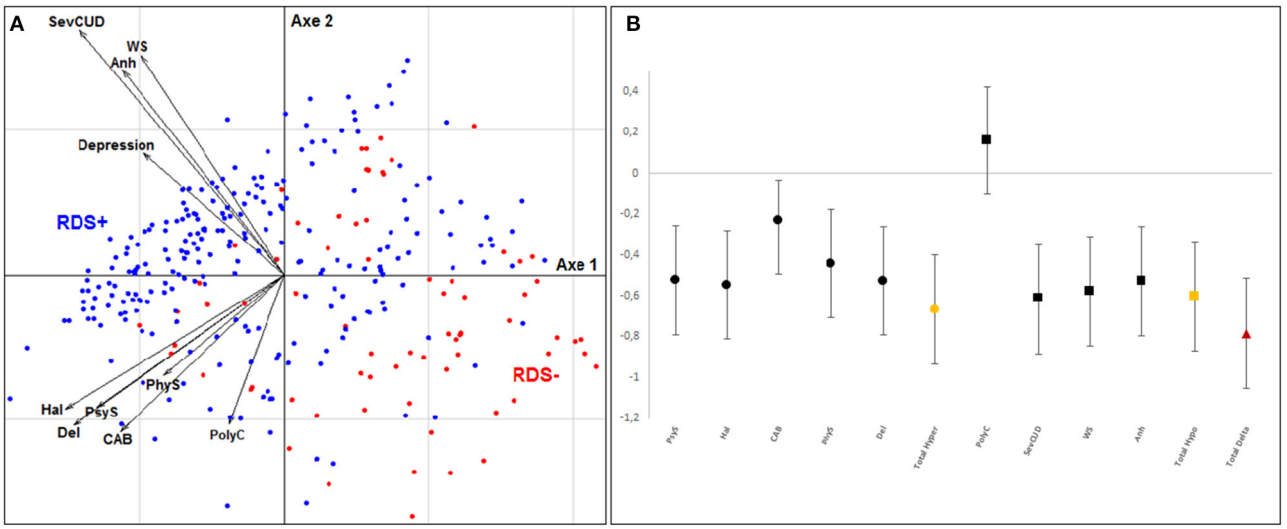

FIGURE 3 | Multidimensional factor analysis and effect size for global model. **(A)** Tridimensional representation of the distribution of subjects with and without depressive symptoms during cocaine withdrawal (RDS– group in Red, RDS+ group in Blue) according to clinical variables of global dopaminergic model: severity of dependence (SevCUD), withdrawal symptoms (WS), anhedonia (Anh), polyconsumption (PolyC), psychotic symptoms (PsyS), hallucinations (Hal), delusions (Del), consumption-associated behavior (CAB), physical symptoms before use (PhyS); and direction of variables. **(B)** Hedges' effect-size of each variable for the global dopaminergic model components.

This effect appeared to be weaker for consumption-associated behavior (-0.231 ± 0.198) (CAB) and physical symptoms before use (−0.443 ± 0.266) (PhyS). The overall effect size of this component was large (−0.669 ± 0.269).

For the hypodopaminergic component (**Figures 2A,B**), the analyses show a good separation of the RDS+ and RDS– groups. The effect sizes found were large for most of the variables: severity of dependence (−0.613 ± 0.264) (SevCUD), withdrawal symptoms (−0.578 ± 0.267) (WS), and anhedonia (−0.528 ± 0.266) (Anh). The effect size of the polyconsumption variable was small (0.158 ± 0.263) (PolyC). The effect size of the overall dimension was large (−0.604 ± 0.267).

To evaluate our dopaminergic model in a global way, we carried out the same analysis by integrating all the variables. **Figure 3A** shows that the RDS + and RDS– subjects are again clearly separated into two groups. **Figure 3A** reveals on the left the existence of a group of subjects belonging to the RDS+ group and sharing very similar characteristics. On the right, the subjects belonging mainly to the other group are more dispersed. The overall effect size of our model was large (−0.785 ± 0.271).

This analysis finally allowed us to position the different variables in this model as vectors. **Figure 3B** shows the two main groups of variables that emerged: the first pointing upwards to the left and grouping variables of hypodopaminergic component, and the second pointing wards to the left and representing variables of hyperdopaminergic dimension. These two axes are well oriented toward the group of patients with depressive symptoms, which indicates that they help to explain this phenomenon.

DISCUSSION

This is one of the first studies to have evaluated mechanisms underlying the onset of depressive symptoms during cocaine withdrawal. The characteristics of our sample corresponded to those of European cocaine users (22, 27). Patients were predominantly single men, with an average age of onset of use of 22 years. They mainly used cocaine by inhalation, then by smoking and finally by injection. Most use was daily, and levels of polydrug use were high.

Our data showed that the RDS+ (Reported Depressive Symptoms +) and RDS– (Not Reported Depressive Symptoms) groups were homogeneous for age, gender, marital status, education, and history of hospitalization for withdrawal. The age of onset, frequency, and type of product most commonly used were also comparable in both groups. Levels of use of other psychoactive substances were identical in both groups, as was the level of polydrug use. These variables did not seem to have an influence on depressive symptoms, as reported by Uslaner et al. (28).

Concerning the modality of use, snorting was found more frequently in the RDS+ group, with depressive symptoms, (63.90 vs. 48.61%). Injectable or smoked pathways were more frequent in the RDS– group (26.39 vs. 23.65% for smoked; 18.06 vs. 7.86 % for injectable). This could be explained by the different pharmacokinetics of cocaine, depending on the form used. Clinical effects appear 3 mins after a cocaine snort and can last up to an hour. For the smoked route, they last only 10–30 mins, but are perceived in 5–10 s. The intravenous route acts in 16–20 s and

has an effect lasting for 10–30 mins. In our depressed patients, snorting may therefore be a way to optimize intake so as to manage depressive symptoms more sustainably. This would be consistent, as the euphoric effects of cocaine are also perceived more intensely in depressed subjects compared to non-depressed subjects (29).

Depressive symptoms are more common among cocaine users than in the general population, with lifetime prevalence ranging from 25 to 61%, depending on the study (30, 31). Our patients have a higher rate of depressive symptoms (77%). Our recruitment sites could explain this phenomenon, as they were centers specialized in the management of opioid users. This corresponds to the data in the literature, which shows that depressive symptoms are found more particularly in patients who have entered the care process, probably because they are more symptomatic, and are associated with a more severe use disorder (31, 32). Our patients were therefore probably at a more severe stage than in other studies with higher recruitment. They had an average of 5.53 DSM IV dependence criteria. Bipolar disorders are also common in this population (33), and some authors confirm a predominance of depression among drug users (34).

The psychotic symptoms associated with cocaine use that we observed were mainly hallucinations, delusions, or stereotypies. They corresponded to those reported in the literature. These psychotic symptoms are found during consumption in 54–80% of patients (35, 36), and during dopaminergic treatments in Parkinson's disease (17, 37–39).

The choice of variables included in our analyses was crucial. We wanted to model the concepts of hyper and hypodopaminergy as well as possible by using indirect clinical markers of dopaminergic behaviors. Severity of dependence ($p < 0.001$), anhedonia ($p < 0.01$), and withdrawal symptoms ($p < 0.01$) were relevant for modeling clinical hypodopaminergic reactions in cocaine users. Psychotic symptoms and particularly hallucinations, delusions, and physical symptoms before use were criteria integrated into our modeling of clinical hyperdopaminergic disease. All of these criteria are consistent with those mentioned in several articles that have tried to clinically characterize these concepts in Parkinson's disease (PD), and define symptoms associated with hyperdopaminergia and hypodopaminergia. During the hyperdopaminergic phases in PD, certain researchers have observed delusions, hallucinations and motor stereotypes (17, 37, 38). More recently, hyperdopaminergia has also been linked to the development of behavioral addictions and still appears to be underestimated. They include compulsive purchases, pathological gambling and sexual behavior disorders (15). Symptoms associated with hypodopaminergia in PD are similar to depressive symptoms (15, 40), anxiety (41) and apathy (42).

Several studies have also investigated the release kinetics of dopamine in the nucleus accumbens during drug intake. In human subjects, a relationship between the subjective effects of cocaine and DA transporter (DAT) occupancy in the striatal areas has been demonstrated (13). Cerebral level curves for cocaine in the striatum are related to the cocaine-induced "high" behavior, with a peak at 10 mins then a progressive decrease of cerebral cocaine level and cocaine effects (13). These observations have also been found in animal models (43, 44). They show that the dopamine peak induced by stimulant intake in mice is almost immediate, followed by a progressive decrease over several tens of minutes or even hours.

Our patients were well discriminated in the analysis of the hyperdopaminergic component, and a large overall effect size of the hyperdopaminergic variables was observed. The most important criteria capable of explaining this difference between the groups were the existence of psychotic symptoms, particularly hallucinations and delirium, which is consistent with the scientific data (35, 36). Associated movements and physical symptoms before use seem to be involved but to a lesser extent. These Cocaine-Related Behavioral (CRB) symptoms are very frequently found in cocaine users, in particular for repetitive/stereotyped behaviors (45). The type of cocaine used does not influence these stereotypes (46), but on the other hand, these symptoms are found more frequently among cocaine injecting users, who were more numerous in the RDS– group. It therefore seems difficult to highlight a difference between our two groups on the basis of the sole criterion of depressive symptom. It would be interesting to study this phenomenon specifically in these injecting vs. non-injecting patients.

Patients were also well separated in the analysis of the hypodopaminergic component and there was a large overall effect size for these variables. Anhedonia, severity of dependence and symptoms appear to be good markers of this dimension. Our polyconsumption criterion, on the other hand, had only a small effect size. This could be explained by the low precision of the data for this variable, which is based on lifetime use of substances and not current or recent use. It might have been interesting to study comorbid opioid use disorder or Opioid Maintenance Treatment (OMT). A previous study using the same sample highlighted the role of OMT on the subjective effects produced by cocaine (23). Patients receiving an OMT at the time of their first cocaine use reported significantly less tachypsychia during this first cocaine intake, suggesting a specific protective effect of OMT on cocaine-induced "high" hyperdomapaminergic effects. Thus, a possible preventive effect on cocaine withdrawal would merit investigation.

These results show the interest of our two dimensions for exploring the phenomenon of depressive symptoms in cocaine users. When we integrated all these variables to perform a global analysis, discriminative capacity was even better, with a large overall effect size. This could indicate that rather than hypo or hyperdopaminergic changes occurring separately, these thymic variations might be explained by the switch from one to the other.

One of the main limitations of this study is that it was based on a cross-sectional study, and therefore causality cannot be established. It would have been interesting to perform a longitudinal evaluation of our two components.

Even so, as we are interested in a short-term phenomenon, namely cocaine "comedown," this cross-sectional analysis appears justified.

We chose to use a subjective assessment of depressive symptoms in cocaine users. This measure is more practical to use in this population, but it would have been appropriate to supplement this self-assessment with a more precise and detailed scale (24). Furthermore, using clinician-rated scales rather than self-reports could be useful if the tool is sufficiently time-sensitive.

Our sample may not perfectly represent the general population of cocaine users, but rather the most severe patients due to selection bias. Indeed, all of our patients were recruited from specialized addiction centers. The small number of subjects in our RDS- group ($N = 72$) is also a limitation.

In our overall model, we highlighted a homogeneous subgroup among RDS+ patients (see **Figure 3A**), but with a few scattered subjects. Other variables not available in our protocol (apathy and anhedonia) might play a role in this model to better condense the group, or to reveal subgroups that were not discriminated by our analyses.

In conclusion, our study was able to better characterize patients presenting depressive symptoms during cocaine withdrawal by comparing them with those who do not, according to their dopaminergic activity profile assessed by indirect clinical markers.

Early identification in the management process of these patients at risk of pejorative evolution or relapse could help to adapt the therapeutic strategy envisaged. The evaluation of depressive disorders in substance abuse patients might be helpful in designing and implementing specialized interventions to reduce the likelihood of relapse (7).

Further studies would be needed to study this phenomenon in more detail, with longitudinal evaluation and more accurate monitoring of symptoms. It would also be interesting to specifically study the very homogeneous group of RDS+ patients highlighted (**Figure 3A**). We could, for example, investigate physiological specificity by analyzing the genetic polymorphisms of the dopaminergic pathway.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Research Ethics Committee of Ile de France (Paris area). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JC: conceptualization, methodology, data curation, writing—original draft preparation, writing—reviewing and editing, and visualization. GB: conceptualization, investigation, supervision, and writing—review and editing. BP: methodology, data curation, and formal analysis. NC and PL: conceptualization and writing—review and editing. EK, E-HZ, RI, and VB: conceptualization. FV: conceptualization, investigation, and writing—review and editing. ID: conceptualization, supervision, methodology, data curation, writing—review and editing, and formal analysis. All authors contributed to the article and approved the submitted version.

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SYSTEMATIC REVIEW
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The Impact of Co-occurring Post-traumatic Stress Disorder and Substance Use Disorders on Craving: A Systematic Review of the Literature

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The frequent co-occurrence of post-traumatic stress disorder (PTSD) and substance use disorders (SUDs) leads to manifestations of both conditions that are more severe and more resistance to treatment than single disorders. One hypothesis to explain this synergy is the impact of intrusive memories on craving which, in turn, increases the risk of relapse among patients with substance use disorders. The aim of this systematic review is to examine this possibility by assessing the impact of PTSD and its symptoms on craving among dual disorder patients. Using PRISMA criteria, four databases were comprehensively searched up to June, 2021, in order to identify all candidate studies based on broad key words. Resulting studies were then selected if they examined the impact of PTSD or PTSD symptoms on craving, and if they used standardized assessments of PTSD, SUD, and craving. Twenty-seven articles matched the selection criteria and were included in this review. PTSD was found to be significantly associated with increased craving levels among patients with alcohol, cannabis, cocaine, tobacco, and other substance use disorders. Exposition to traumatic cues among dual disorder patients was also shown to trigger craving, with an additive effect on craving intensity when exposure to substance-related cues occurred. In addition, certain studies observed a correlation between PTSD symptom severity and craving intensity. Concerning mechanisms underlying these associations, some findings suggest that negative emotional states or emotion dysregulation may play a role in eliciting craving after traumatic exposure. Moreover, these studies suggest that PTSD symptoms may, independently of emotions, act as powerful cues that trigger craving. These findings argue for the need of dual disorder treatment programs that integrate PTSD-focused approaches and emotion regulation strategies, in addition to more traditional interventions for craving management.

Keywords: post-traumatic stress disorder (PSTD), substance use disorder, dual disorder (DD), craving, integrated treatment, systematic (literature) review

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INTRODUCTION

The diagnosis of Post-Traumatic Stress Disorder (PTSD) first appeared in the 3rd edition of the Diagnostic and Statistical Manual of Mental Disorders in 1980 (1), based largely on clinical descriptions of soldiers returning from the Vietnam war (2). Its definition has evolved considerably over recent decades, including its removal from the anxiety disorders in DSM 5 as well as the creation of a distinct diagnostic category for this disorder (3). PTSD is characterized by a variety of symptoms that persist over the months or years following a traumatic event and that notably include intrusive memories, avoidance of cues associated with the event, alterations of cognition and mood, and a state of hyperarousal. Although diverse mental disorders are frequently associated with PTSD, substance use disorders (SUDs) are particularly prevalent (4–6). The principal hypotheses that have been formulated to explain these associations include self-medication (implying that PTSD is the primary condition and that substance use disorders occur later), the notion that addiction to substances may constitute a risk factor for the occurrence of traumatic events (whereby PTSD is a secondary condition), and finally the possibility that both disorders share common vulnerability factors (7). Regardless of which mechanism best explains these forms of dual disorder, the combination of PTSD and addiction leads to poorer prognosis, increases in suicide attempts, greater social disability, poorer treatment adherence, and reduced medication efficacy when compared to patients without comorbidity (8–10). In line with these results, a recent review of clinical investigations also documented a strong relationship between the diagnosis of PTSD and increased substance use and relapse in dual disorder individuals (11), but again the exact mechanisms underlying this association remain unclear.

Craving has been studied extensively over the years and particularly over the past two decades due to acknowledgment of its crucial role in addiction (12, 13). Craving refers to the intense, urgent, and unwanted desire to consume a substance (14) and it is now considered to be a core component of addiction with important diagnostic implications following its inclusion in DSM-5. Based on findings that demonstrate a prospective link between craving episodes and substance use, craving is increasingly viewed as a central construct in the etiology and course of different forms of addiction, and it is a strong predictor of treatment outcome (15–19). Among the diverse factors that may affect craving, a large body of research has highlighted the major role of substance-related cues and stress (20–29). These investigations have shown the ability of substance-related cues and stress exposure to elicit craving among individuals with alcohol, opiate, cocaine, tobacco, and cannabis dependence. Moreover, laboratory studies have also shown that exposure to stress-related events among individuals with alcohol use disorder (AUD) reliably elicits craving in a manner that is as powerful as alcohol-related cues (30, 31). Although similar patterns of reactivity have been shown among individuals with PTSD and alcohol use disorder after exposures to personalized trauma cues *via* "trauma scripts," such scripts were found to provoke greater craving that non-trauma scripts and to be more salient in eliciting alcohol craving (31, 32). These results could suggest that the intrusive memories experienced by persons with PTSD and the significant stress they induce may therefore constitute major triggers of craving as well as explain reductions in treatment efficacy in this population. This pattern of findings is consistent with the findings that patients in SUD treatment who report higher PTSD scores also report higher scores on craving, depression, anxiety and stress (33), with a potential relationship between PTSD severity, SUD severity and craving levels.

One hypothesis to explain the synergy of PTSD and SUDs as a dual disorder is therefore the impact of intrusive memories or trauma-related cues on craving which, in turn, increases the risk of relapse among patients with substance use disorders. Examining this relationship across different forms of substance addiction should help elucidate the mechanisms underlying the general increase in clinical severity in this population, and the literature on this topic is now of sufficient size to permit a reliable summary that should more fully respond to the goals of precision psychiatry and personalized medicine (34). The aim of this systematic review is to address this issue by assessing all published investigations of the impact of PTSD and its symptoms on craving, among dual disorder patients.

METHODS

Research Design

The study involved a systematic review of the literature based on the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines (35).

Information Sources

This review was based on the following databases: PUBMED/MEDLINE, Psychinfo, Cochrane, and Wiley Online Library. The search was performed for all years up to June, 2021.

Search

The following search terms were used:

[(≪ Addiction ≫ or ≪ Substance Use Disorder ≫ or ≪ Substance-related Disorder ≫) and (≪ Post Traumatic Stress Disorder ≫ or ≪ PTSD ≫) and (≪ Craving ≫ or ≪ Urge ≫)].

Eligibility Criteria

The following criteria were used to select investigations for this review:

1. Studies Published in English-Language peer-reviewed journals.
2. Studies concerning patients, with no restrictive criteria regarding age, sex, ethnic origin, or place of residence. Studies had to include participants with PTSD and SUD comorbidity, defined, or explored according to standardized questionnaires.
3. Studies including measures of craving, and assessing the impact of PTSD or PTSD symptoms on craving occurrence or severity. It was not necessary that craving was designated as the primary outcome of the study in order for it to be included in this review.

Studies were excluded if they were based on animal models, or if they were limited to conference abstracts, dissertations, book chapters, or incomplete articles.

Study Selection

Two authors independently examined all titles and abstracts. Relevant articles were obtained in full-text and assessed for inclusion criteria separately by the two reviewers based on the inclusion and exclusion criteria previously mentioned. Disagreements were resolved *via* discussion of each article for which conformity to inclusion and exclusion criteria were uncertain and a consensus was reached. The reference lists of major papers were also manually screened in order to ensure comprehensiveness of the review. All selected studies were read in full to confirm inclusion criteria, study type, and study population.

Quality Assessment

Two reviewers (LJ and MF) assessed the quality of data in the included studies using the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (S2C) from National Institutes of Health (36). This tool is comprised of 14 questions with responses to each being "yes," "no," or "other" (not applicable, NA or nor reported, NR). We rated the overall quality of each included study as "good," "fair," or "poor."

Collecting Data

Sample characteristics (including socio-demographic data, comorbidity, and treatment status), and information on study design and methods of assessment of PTSD, SUD, and craving were extracted. **Table 1** presents these data extracted from the selected studies.

RESULTS

Study Selection

A total of 247 articles were identified through the search of the databases. After review of titles and abstracts, 52 articles were selected for further examination. After reading the full text, 27 met inclusion criteria for this review. This process is described in the PRISMA flowchart (**Figure 1**). The selected articles were published between 2002 and 2021.

Quality Assessment

A summary of risk of bias is presented in **Table 2**. Eleven studies were considered to be of "good" quality, six were "fair" quality and nine of "poor" quality.

Study Results

Study Characteristics

Twenty-seven studies fulfilled criteria for inclusion in this review, of which 12 focused on alcohol, 4 on tobacco, 1 on cannabis, 1 on cocaine, and 9 on various substance use disorders (three studies on AUD and/or Cocaine Use Disorder and six studies on different types of SUD). Among the 27 included studies, 13 were experimental studies, 13 were observational studies and 1 was a randomized controlled trial.

In total, 3580 subjects were enrolled, of which 1960 (54.7%) met criteria for PTSD and SUD, 1206 (33.7%) for SUD only, and 105 for PTSD only. One study (37) did not indicate the prevalence of low vs. high PTSD scores. Participants were most often males (65.6%), with a mean age of 41.3 years. Most participants (n = 3,337; 93.2%) were recruited in care facilities including outpatient (n = 1804; 54%), inpatient (n = 497; 15%), residential (n = 497; 15%) or either inpatient/outpatient (n = 539, 16%) treatment programs. Among the included participants, 61.8% (n = 2212) met criteria for AUD, 10.9% (n = 390) were current smokers, 10.7% (n = 383) met criteria for Cocaine Use Disorder, 9.6% (n = 343) for Cannabis Use Disorder, 6.7% (n = 241) for Opiate Use Disorder, 3.3% (n = 118) for Stimulant Use Disorder, 2.4% (n = 85) for Anxiolytic or Hypnotic Use Disorder, 2.2% (n = 79) for comorbid Cocaine and Alcohol Use Disorder, and 1.2% (n = 45) for Polysubstance Use Disorder.

A detailed description of all studies included and their main results can be found in **Tables 3**, **4**.

Effects of Traumatic Cue- and Stress-Exposure on Craving Across SUD Subgroups

The 13 experimental studies selected for this review consisted, for most part, of exposing participants with comorbid SUD and PTSD to traumatic memories, non-specific stressors, and substance-related cues, and then evaluating their responses across SUD subgroups. Seven experimental studies involved AUD, two involved tobacco use disorder, one involved cocaine use disorder, and three studies included patients suffering from AUD and Cocaine Use Disorder.

Alcohol Use Disorder

The primary finding was that exposure to a traumatic memory (in the form of a script recounting a traumatic life event) generated a significantly greater increase in craving than neutral exposure and similarly to exposure to an alcohol-related cue (31, 38–40). The studies by Coffey et al. (31) and Nosen et al.'s (38) went further, showing that the combination of exposure to a traumatic script followed by an alcohol-related cue generated greater craving than each type of exposure when considered separately. Two studies showed that exposure to a traumatic memory increased craving more than a non-specific stressor (39, 40).

Only one study compared subjects with the comorbidity AUD and PTSD to subjects with AUD alone (41). This study found no significant difference between the two groups in terms of craving intensity after exposure to a non-specific stressor. Ralevski et al. (40) found no correlation between the intensity of craving provoked by the different scripts (traumatic, non-specific stress, and neutral) and the severity of PTSD symptoms, measured by the Clinician Administered PTSD Scale (CAPS). Finally, Schumacher et al. (42) showed that subjects who had suffered early childhood trauma (<13 years of age) presented a more severe AUD, traumatic intrusion symptoms, and post-exposure craving (traumatic script and alcohol-related cues), than subjects who suffered their first trauma later in adolescence (13–18 years of age).

TABLE 1 | Data items extracted from the selected studies.

Evaluation criteria	Variables collected
Study characteristics	Retrospective, prospective or cross-sectional observational studies. (Or) experimental studies: comparative or not, exposure to stimuli (substance-related cues, trauma, and stress) (Or) systematic review or meta-analysis
Sample characteristics	Socio-demographic characteristics (age, sex, employment status, income, and education level), treatment (inpatient, outpatient, no treatment), type of SUD, and comorbidity
Evaluation methods	DSM diagnostic criteria and/or evaluation scales for the different variables of interest: diagnosis and level of severity of SUD and PTSD, craving (frequency and intensity)
Results	Presented according to substance type

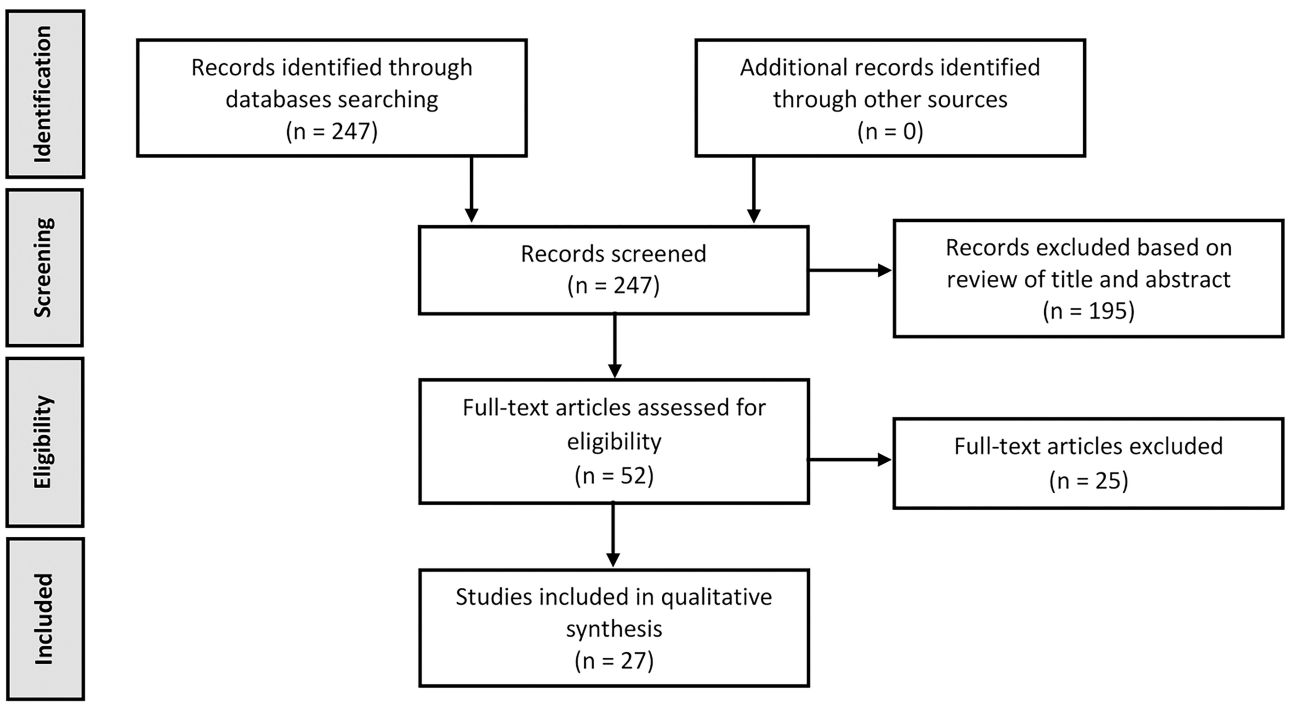

FIGURE 1 | PRISMA flowchart of selected abstracts and articles.

Tobacco Use Disorder

Two experimental studies addressed tobacco use disorder. Beckham et al. (43) showed that the increase in craving, negative affect and traumatic symptoms were stronger after being exposed to traumatic scripts than stressful event scripts and neutral scripts. Subjects with PTSD experienced a more significant increase in craving and negative affect compared to the other group. Cigarette use was associated with a reduction in craving (which was greater in magnitude after a traumatic script), as well as reduction in negative affect, and traumatic symptoms, independently of group type. Dedert et al. (44) found that subjects with PTSD presented more severe withdrawal symptoms and a higher craving level for two dimensions (anticipation of reinforcing effect, anticipation of withdrawal symptoms and negative affect release) during acute withdrawal. Participants with PTSD reported lower craving reductions after smoking.

Cocaine Use Disorder

One experimental study by Tull et al. (45) assessed the effect of exposure to a personalized trauma cue on cocaine craving in patients with cocaine use disorder with or without PTSD. Subjects with PTSD had significantly higher craving for cocaine than other participants after the traumatic script.

Multiple Type of Substance Use Disorder: Alcohol and/or Cocaine Use Disorder

Three experimental studies exposed subjects with alcohol and/or cocaine addiction and a history of traumatic events to combinations of traumatic or neutral scripts and substance-related or neutral cues (32, 46, 47). All studies showed that exposure to traumatic memories and substance-related cues increased craving and negative affect significantly more than neutral exposures. The studies of Saladin et al. (47) and McHugh

TABLE 2 | Overall quality rating of the included studies using the The National Institutes of Health quality assessment tool for observational cohort and cross-sectional studies.

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Quality
Coffey et al. (32)	Y	Y	NR	Y	N	Y	Y	Y	Y	N	Y	N	NA	Y	Good
Saladin et al. (47)	Y	Y	NR	Y	N	Y	Y	Y	Y	N	Y	N	NA	Y	Good
Brady et al. (41)	Y	Y	NR	Y	N	Y	Y	Y	Y	Y	Y	N	Y	Y	Good
Schumacher et al. (42)	Y	Y	NR	N	N	N	Y	N	Y	N	Y	N	N	N	Poor
Coffey et al. (30)	Y	Y	NR	Y	N	Y	Y	Y	Y	Y	Y	N	N	N	Good
Beckham et al. (43)	Y	Y	NR	Y	N	Y	Y	Y	Y	Y	Y	N	N	Y	Good
Driessen et al. (58)	Y	Y	Y	Y	N	NA	N	NA	Y	NA	Y	NA	NA	Y	Fair
Coffey et al. (31)	Y	Y	NR	Y	N	Y	Y	Y	Y	Y	Y	N	NA	Y	Good
Drapkin et al. (51)	Y	Y	NR	Y	N	NA	NA	NA	Y	N	Y	NA	NA	N	Poor
Jayawickreme et al. (50)	Y	Y	NR	Y	N	NA	NA	NA	Y	NA	Y	N	NA	N	Poor
Nosen et al. (38)	Y	Y	NR	Y	N	Y	Y	Y	Y	Y	Y	N	NA	N	Good
Simpson et al. (52)	Y	Y	NR	N	N	Y	Y	NA	Y	Y	Y	NA	Y	N	Fair
Dedert et al. (44)	Y	Y	NR	Y	N	Y	Y	Y	Y	N	Y	N	NA	N	Fair
Boden et al. (56)	Y	Y	NR	Y	N	NA	NA	Y	Y	NA	Y	NA	NA	Y	Fair
Tull et al. (45)	Y	Y	NR	N	N	Y	Y	Y	Y	N	Y	N	NA	Y	Fair
Dedert et al. (54)	Y	Y	NR	Y	N	Y	Y	NA	Y	Y	Y	NA	N	N	Fair
Kwako et al. (39)	Y	Y	NR	Y	N	Y	Y	Y	Y	Y	Y	NA	N	Y	Good
Heinz et al. (49)	Y	Y	NR	Y	N	NA	NA	Y	Y	NA	Y	NA	NA	N	Poor
Kaczkurkin et al. (53)	Y	Y	NR	Y	N	Y	Y	N	Y	Y	Y	Y	N	N	Good
Ralevski et al. (40)	Y	Y	NR	Y	N	Y	Y	Y	Y	Y	Y	NA	NA	N	Good
McHugh et al. (46)	Y	Y	NR	Y	N	Y	Y	N	Y	N	Y	N	NA	N	Poor
Peck et al. (57)	Y	Y	NR	N	N	Y	Y	NA	Y	N	Y	NA	N	N	Poor
Somohano et al. (37)	Y	Y	NR	Y	N	NA	NA	N	Y	NA	Y	N	Y	N	Poor
Lyons et al. (48)	Y	Y	NR	N	N	NA	NA	NA	Y	NA	Y	NA	NA	Y	Poor
Rosenblum et al. (55)	Y	Y	NR	Y	N	NA	NA	NA	Y	NA	Y	N	NA	N	Poor
Vogel et al. (59)	Y	Y	NR	Y	N	Y	Y	N	Y	Y	Y	NA	N	Y	Good

Y, Yes; N, No; NR, Not Reported; NA, Not Applicable.

Q1: Was the research question or objective in this paper clearly stated?; Q2: Was the study population clearly specified and defined?; Q3: Was the participation rate of eligible persons at least 50%?; Q4: Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?; Q5: Was a sample size justification, power description, or variance and effect estimates provided?; Q6: For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?; Q7: Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?; Q8: For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?; Q9: Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?; Q10: Was the exposure(s) assessed more than once over time?; Q11: Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?; Q12: Were the outcome assessors blinded to the exposure status of participants?; Q13:Was loss to follow-up after baseline 20% or less?; Q14: Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?.

TABLE 3 | Details of experimental studies included in the review.

Study	Sample	Method	PTSD evaluation	Craving evaluation	Results
Brady et al. (41) (Alcoholism: Clinical and Experimental Research)	63 adults (35 men, 28 women), with AUD alone ($n = 35$) or associated with PTSD ($n = 28$) according to DSM-IV, recruited *via* advertisements during a 36-month period. Non-inclusion criteria: current mood disorder, major somatic disorder, psychotic disorder, behavioral disorder, bipolar disorder, corticoids, antidepressants, anxiolytics, mood regulators, beta blockers on the last month, opiates agonist or antagonist during last 2 weeks, pregnancy, breast feeding or ineffective contraception, other use disorder (except caffeine, nicotine), according to the Structured Clinical Interview for DSM-IV (SCID-IV). AUD diagnosis with SCID-IV. Alcohol use during 30 days before and after test assessed with the Timeline Follow-back (TLFB), urinary, and breath tests.	Experimental non-randomized study. Exposure to a stressor with craving evaluation, stress level, biological stress response (ACTH and cortisol), right before and after test, and after 5, 30, 60, and 120 min. Evaluation of alcohol use 1 week and 1 month after experimental session.	Current PTSD assessed with the Clinician Administered PTSD Scale (CAPS), according to DSM-IV.	Self-evaluation: Within Session Rating Scale: WSRS (craving analog visual scale).	No significant difference between subjects with AUD with and without PTSD concerning craving and stress level before and after exposition. Among subjects with AUD alone, craving and stress level post-exposition are predictive of alcohol use after 1 week and 1 month. Among subjects with AUD and PTSD, only alcohol use before test was predictive of alcohol use post-exposure. Among subjects with PTSD: no correlation between corticotrope axis response to stress and alcohol use.
Schumacher et al. (42) (The American Journal on Addictions)	42 adults (13 males, 29 females) aged 25–56 years, meeting DSM-IV criteria for AUD and PTSD, with a criterion A traumatic event <18 years. Participants were recruited from two addiction treatment programs in the Northeast USA.	Experimental study. Participants were exposed to traumatic script and alcohol-related cues, then craving was assessed. The authors analyzed the correlations between age of first trauma (before 13 years old vs. 13–18 years old), severity of PTSD and AUD, and post-exposure craving.	PTSD diagnosis with CAPS according to DSM-IV. Presence of A PTSD criterion of DSM-IV with National Women's Study (NWS) PTSD module. PTSD severity assessed with the Impact of Event Scale-Revised (IES-R).	Self-evaluation with analog visual scale (0–10)	86% of participants had their first trauma <13 years old, and 71% had their first episode of drunkenness ≥13 years old. There was no correlation between age of first trauma and first drunkenness. Subjects who had experienced trauma in childhood (<13 years), had more severe AUD, PTSD symptoms (specifically intrusive symptoms), and post-exposure craving than subjects who experienced their first trauma later (13–18 years). However, there was no significant difference regarding alcohol consumption in response to negative emotions.

(Continued)

TABLE 3 | Continued

Study	Sample	Method	PTSD evaluation	Craving evaluation	Results
Coffey et al. (30) (Psychology of Addictive Behavior)	43 subjects (67% women) with comorbidity AUD and PTSD according to DSM-IV who had consumed alcohol in the past 60 days. They were recruited in two outpatient addiction treatment centers in New York. Non-inclusion criteria: psychotic disorder, current manic episode, current severe depressive episode, military trauma, exposure therapy. Participants were not excluded if they met criteria for a SUD other than alcohol.	Randomized experimental study. First lab session: exposure to trauma and neutral scripts alone, then exposure to trauma script followed by neutral or alcohol cues. After each exposure, assessment of craving, emotional distress, and negative emotions. Then randomization in a group of exposure therapy in imagination or a group of therapy based on relaxation (six sessions). Second lab session: identical to the first.	PTSD diagnosis with CAPS according to DSM-IV. Presence of A PTSD criterion of DSM-IV with NWS PTSD module. PTSD severity assessed with the IES-R.	Self-evaluation with analog visual scale (0–10)	No difference in PTSD symptom severity (CAPS or IES-R) between the two groups (expo and relaxation) before randomization. Participants had increased alcohol craving and emotional distress after exposure to trauma script and alcohol cues. The exposure therapy group had a decrease in post-exposition alcohol craving and emotional distress between the two lab sessions (unlike relaxation group). Subjects who had experienced alcohol craving in the first lab session and completed the six therapy sessions had non-significant decrease in PTSD symptoms between the two lab sessions.
Coffey et al. (31) (Experimental and Clinical Psychopharmacology)	40 adults (63% women) with AUD and PTSD according to DSM-IV, who used alcohol in last 60 days. Participants were recruited in a residential care clinic. Non-inclusion criteria: psychotic disorder, current manic episode, benzodiazepine use. Another use disorder was not considered as non-inclusion criterion. Alcohol use disorder screening with the Alcohol Use Disorder Identification Test (AUDIT), and diagnosis with Computerized Diagnostic Interview Schedule. (C-DIS IV). Symptoms and use consequences assessed with Alcohol Dependence Scale (ADS). Objective use measures with urinary and breath tests.	Experimental non-controlled study, non-randomized. Subjects are exposed to four exposition combinations (script related to traumatic events, alcohol cues, neutral cues) Measures after each combination: • Salivary flow • Craving • Emotional distress • Arousal state	PTSD diagnosis with CAPS according to DSM-IV. Presence of A PTSD criterion of DSM-IV with NWS PTSD module. Evaluation of PTSD symptom severity with IES-R.	Self-evaluation with analog visual scale from 0 to 10	Exposure to traumatic script and to alcohol cues led to significantly superior responses (more craving, emotional distress, salivation, and arousal), from neutral expositions. The association between trauma script exposure following with alcohol cue was associated with the more intense craving level.

(Continued)

TABLE 3 | Continued

Study	Sample	Method	PTSD evaluation	Craving evaluation	Results
Nosen et al. (38) (Behavior Modification)	108 adults (58 men and 50 women) with DSM-IV criteria for AUD and PTSD and with at least one day of massive use during last 60 days. Subjects were recruited in a community addiction care center. Non-inclusion criteria: psychotic disorder, current manic episode, benzodiazepine use, or any other medication that could affect craving or salivation. Another use disorder was not considered as non-inclusion criterion. Use measures were identical to Coffey et al study.	Similar method as Coffey et al. with exposition combination, and measures after each combination: • Salivary flow • Craving • Positive and negative affects	Identical measures from Coffey et al.	Self-evaluation with 3 Likert Scales (0–10)	Combination of traumatic script followed by alcohol cue exposure led to more intense craving. Adding alcohol cue to neutral script or traumatic script increased significatively positive and negative affect. In non-traumatic conditions (neutral script), craving level was correlated with negative and positive affect intensity aroused by alcohol cue. In traumatic conditions (traumatic script), only negative affect intensity provoked by alcohol cue was correlated with craving level. Participants classified as ≪ ambivalent ≫ responders to alcohol related cues (high rise of positive and negative affect) reported the most intense craving.
Kwako et al. (39) (Addiction Biology)	52 subjects (55% male) aged 21–50 years, with comorbid AUD and PTSD according to DSM-IV criteria, participating in a study of the efficacy of NK1 antagonists in comorbid subjects. Recruitment was done through a newspaper advertisement. SCID-IV was used for diagnosis of AUD. The severity of addiction was measured by the ADS and alcohol consumption was assessed subjectively (TLFB) and objectively (breath test). Finally, the consequences of alcohol consumption were investigated with the Addiction Severity Score (ASI). Non-inclusion criteria: severe medical problems, inability to participate in all study procedures, inability to provide informed consent.	Experimental study. Comparison of two methods of craving induction by stress (Trier test or traumatic script) or by alcohol-related cues, in subjects with PTSD and AUD. Several measures were performed before and after each test: • Anxiety (SUDS, State Trait Inventory Anxiety: STAI). • Craving (Alcohol Urge Questionnaire: AUQ). • Serum cortisol and ACTH.	Current PTSD diagnosed with the SCID-IV, according to DSM-IV. Severity of PTSD symptoms assessed with the PTSD Symptom Severity Index (PSSI). Childhood Traumatic Event Search with the Childhood Trauma Questionnaire (CTQ).	Self-evaluation with the AUQ.	Both the traumatic and alcohol-related scripts induced significantly higher craving for alcohol than the neutral script. The peak craving induced by exposure to the traumatic script was significantly greater than that induced by the Trier test, which was itself greater than that obtained after exposure to a neutral script. There was no correlation between craving intensity and endocrine response (ACTH and cortisol) after the different tests. Anxiety's level following the Trier Test and the exposure to the traumatic script was significantly higher than the alcohol-related and neutral exposures.

(Continued)

TABLE 3 | Continued

Study	Sample	Method	PTSD evaluation	Craving evaluation	Results
Ralevski et al. (40) (Alcoholism: Clinical and Experimental Research)	25 subjects (92% male) aged 21–65 with comorbid AUD and PTSD according to DSM-IV. Data came from a 12-week double-blind randomized trial comparing Prazosin vs. placebo. Subjects were required to have ≥1 day of heavy drinking (five standard drinks for men, four drinks for women) in the past 14 days. Diagnosis of AUD by SCID, assessment of alcohol consumption over the last 90 days by TLFB. Non-inclusion criteria: pregnant and lactating women, bipolar disorder, schizophrenic disorder, treatment for AUD, suicidal ideation, health problems contraindicating Prazosin. Another use disorder was not considered as non-inclusion criteria.	Experimental study. Exposure to three scripts (traumatic, non-specific stress, and neutral), with several measures taken before and after each exposure: • Craving • Level of anxiety • Negative and positive affect • Heart rate, blood pressure • Salivary cortisol	Diagnosis of current PTSD by the SCID-IV according to DSM-IV. Severity of PTSD assessed by the CAPS	Self-evaluation by the AUQ	Craving, heart rate and blood pressure measured after exposure to the traumatic script were significantly higher than the other two exposures. The level of anxiety and negative affect after exposure to the traumatic and non-specific stress scripts were higher than the neutral script. Craving intensity after exposure to the trauma script only, was correlated with the number of heavy drinking days prior to the study. There was no correlation between the intensity of craving induced by the different scripts and the severity score of traumatic symptoms measured by the CAPS.
Beckham et al. (43) (Addictive Behaviors)	129 smoking adults with ($n = 82$) and without ($n = 47$) PTSD, smoking at least 10 cigarettes a day, recruited by advertisements. Non-inclusion criteria: other use disorder, psychotic disorder, bipolar disorder. Addiction severity assessed with Fagerström questionnaire.	Experimental study. Participants were exposed randomly to one of three types of personalized scripts (traumatic, stressful, neutral), then received randomly two types of cigarettes (with and without nicotine). Several evaluations were repeated at 0, 20, 35, and 50 min: • PTSD symptoms • Negative affect • Craving	PTSD diagnosis with the CAPS according to DSM-IV. PTSD symptoms severity assessed with the Davidson Trauma Scale (DTS).	Self-evaluation with Questionnaire of Smoking Urges (QSU)	Expositions to traumatic scripts and to a lesser extent stressful script led to significant craving, negative affect, and traumatic symptoms severity increase. Effects were more important among smoking patients with PTSD. Smoking, whatever cigarette type, led to craving decrease (significatively more for cigarettes with nicotine), negative affect and traumatic symptoms after exposure to traumatic and stressful scripts, in groups with and without PTSD.

(Continued)

TABLE 3 | Continued

Study	Sample	Method	PTSD evaluation	Craving evaluation	Results
Dedert et al. (44) (Nicotine and Tobacco Research)	47 smokers (68% men) smoking at least 15 cigarettes a day, with expired carbon monoxide: CO ≥ 15 ppm, with ($n = 17$) or without ($n = 30$) associated PTSD, who were not seeking treatment for nicotine dependence. Subjects were recruited *via* flyers and clinician referrals from local outpatient clinics. Non-inclusion criteria: instable somatic disease, acoustical deficit, smoking tobacco in another form than cigarettes, benzodiazepines use, psychotic disorder, manic or depressive current episode, past PTSD, other substance use disorder. Addiction severity was assessed with Fagerström questionnaire.	Experimental study: participants were assigned randomly to one of the three groups (regular cigarette, low nicotine cigarette, no cigarette), then exposed to a neutral script. Subjects fulfilled several evaluations before and after expositions: • Withdrawal symptoms • Craving level • Traumatic symptoms	PTSD Diagnosis with CAPS according to DSM-IV. PTSD symptoms severity assessed with DTS.	Self-evaluation of craving with QSU-Brief. Craving was also assessed with withdrawal symptoms using Shiffman/Jarvik Withdrawal Scale.	PTSD diagnosis or traumatic symptoms severity did not influence initial smoking level. After one night abstinence, subjects with PTSD had more craving and behavioral withdrawal symptoms. They smoked in anticipation of pleasure and of a decrease in negative affect. After smoking, PTSD subjects had less craving release sensation. Among subjects in ≪ non-cigarette ≫ group, those with PTSD reported increase of negative affect between two measures, contrary to subjects without PTSD.
Tull et al. (45) (Journal of Experimental Psychopathology)	60 subjects (55% male) aged 20–58, with cocaine use disorder according to DSM-IV and a history of trauma exposure, admitted for treatment in a residential addiction treatment facility. Subjects were required to have a Mini-Mental State Examination (MMSE) score ≥ 24. Diagnosis of cocaine use disorder made by the SCID-IV, severity of cocaine use over the past year by a Likert scale (0–5). Non-inclusion criteria: current psychotic disorder (determined by SCID-IV).	Experimental study. Participants were exposed to traumatic and neutral scripts with pre- and post-test measures: • Negative affect • Craving	Current PTSD diagnosed with CAPS according to DSM-IV	Self-evaluation with Likert Scale (0–10)	After exposure to the traumatic (but not neutral) script, subjects with PTSD had significantly higher craving for cocaine than other participants. In male subjects only, negative affect (shame, guilt) mediated the relationship between traumatic symptoms and cocaine craving.

(Continued)

TABLE 3 | Continued

Study	Sample	Method	PTSD evaluation	Craving evaluation	Results
Coffey et al. (32) (Drug and Alcohol Dépendance)	75 participants: 30 subjects (87% women) with PTSD + cocaine use disorder according to DSM-IV and 45 subjects (46% women) with PTSD + AUD according to DSM-IV. All had used alcohol and/or cocaine at least once in the last 60 days. Participants were recruited from outpatient or inpatient treatment programs at the Medical University of South Carolina and local treatment facilities in the Charleston area. Non-inclusion criteria: psychotic disorder, current manic or severe depressive episode, current PTSD treatment. Subjects with other SUD were not excluded. Subjects with AUD could also have cocaine use disorder and vice versa.	Experimental study. First session: assessment of PTSD, SUD, consequences of consumption, then creation of trauma script. Second session: assessment of initial craving, then exposure to four combinations (Trauma script + substance cue: TD, Trauma script + wood chips: TN, neutral script + substance cue: ND and neutral script + wood chips: NN). Then assessment of craving and emotions.	PTSD diagnosis with the CAPS and NWS PTSD Module, according to DSM-IV.	Self-evaluation with the Cocaine Craving Questionnaire (CCQ) for cocaine, Alcohol Craving Questionnaire (ACQ) for alcohol and analog visual scale for both.	No difference between alcohol and cocaine use disorder groups regarding PTSD and depressive symptoms. For all participants, initial craving was not correlated with post-exposure craving. Craving, and negative affect after TD and TN exposures was higher than after ND and NN exposures. Post-exposure craving in AUD group was higher than cocaine disorder group.
Saladin et al. (47) (Addictive Behaviors)	124 subjects among which 70 had AUD, 54 crack use disorder according to DSM-IV criteria, who used during last 60 days. Subjects were recruited in addictology service in Medical University of South Carolina or in regional addictology center. Every participant must have suffered from physical and/or sexual violence concordant with DSM-IV A PTSD criterion. 61% of the sample ($n = 76$) met criteria for current PTSD Non-inclusion criteria: psychotic disorder, current manic or depressive episode. Other use disorders were not considered as non-inclusion criteria.	Experimental non-controlled, non-randomized study. Subjects were exposed to traumatic, alcohol, crack, or neutral cues. After each exposition, subjects reported their craving level.	PTSD diagnosis with CAPS according to DSM-IV. 66% subjects with AUD and 56% with crack use disorder had PTSD (61% of total sample). Self-evaluation of traumatic severity symptoms with IES-R.	Self-evaluation with analog visual scale in 21 points	Exposition to traumatic script or substance cue led to craving significatively superior from exposition to neutral scripts and cues. During traumatic script exposition, craving level was positively correlated with PTSD symptom severity, independently from substance exposition. During exposition to substance cue, craving severity was not correlated with traumatic symptoms, only if this exposition was preceded with traumatic script exposition.

(Continued)

TABLE 3 | Continued

Study	Sample	Method	PTSD evaluation	Craving evaluation	Results
McHugh et al. (46) (Comprehensive Psychiatry)	194 adults (50% women) aged 18 to 65, with a history of traumatic exposure according to criterion A PTSD in DSM-IV (27.3% had PTSD), and a current alcohol and/or cocaine use disorder according to DSM-IV. They were recruited in a residential addiction treatment center. 26.3% had cocaine use disorder, 33% had alcohol use disorder and 40.7% had both. Non-inclusion criteria: cognitive impairment (MMSE < 24)/psychotic disorder.	Experimental study. First session: assessment of PTSD (CAPS), SUD (SCID-IV), and anxiety sensitivity (Anxiety Sensitivity Index-3: ASI-3). Second and third sessions: exposure to traumatic and neutral scripts. Measurement of negative affect and craving before and after exposure. Analysis of the correlations between anxiety sensitivity, PTSD severity, negative affect, and craving.	PTSD diagnosis with the CAPS according to DSM-IV	Self-evaluation with a Likert Scale (0–10).	There was a positive correlation between anxiety sensitivity and PTSD severity. Subjects with PTSD had higher anxiety sensitivity. Traumatic exposure resulted in increased craving and negative affect. Anxiety sensitivity was positively correlated with post-traumatic exposure negative affect but not with craving. PTSD severity was positively correlated with post-traumatic exposure negative affect and craving.

et al. (46) showed a positive correlation between the severity of PTSD symptoms and the intensity of craving after traumatic exposure. Finally, McHugh et al. (46) observed a positive correlation between the level of anxiety sensitivity (tendency to react with fear to signs and symptoms of anxiety) and the severity of traumatic symptoms and negative affect, but not craving after the exposures.

Association Between PTSD Symptoms and Craving Across SUD Subgroups

A total of 14 studies investigated the association between PTSD symptoms and craving across SUD subgroups: 12 were observational studies (five for AUD, two for Tobacco Use Disorder, one for Cannabis Use Disorder, and four for different types of Substance Use Disorders), one was an experimental study and one was a Randomized Controlled Trial among AUD individuals.

Alcohol Use Disorder

Five cross-sectional observational studies examined correlations between different variables related to PTSD and AUD. The studies by Lyons et al. (48) and Heinz et al. (49) found a correlation between the intensity of craving for alcohol on the one hand and the severity of PTSD symptoms and consumption on the other, in comorbid subjects. For Lyons et al. (48), traumatic cognitions (self-deprecation, dangerousness of the world) generated negative affect, which in turn triggered craving. Jayawickreme et al. (50) also found a positive correlation between traumatic cognitions about oneself (self-depreciation and tendency to blame oneself), negative beliefs about the world and the intensity of craving, but this relationship was only significant in men. Finally, Drapkin et al. (51) compared the psychosocial functioning of subjects with comorbid PSTD and AUD with those with SUD or PTSD alone. The authors found that social functioning was more impaired (less education, lower income, more unemployment), as well as more severe depressive symptoms and cravings, in the comorbid subjects.

In a 28-day study using a daily monitoring with an Interactive Voice Response (IVR), Simpson et al. (52) found that PTSD severity was positively correlated with craving level on the same day but not the following day. In a more specific way, some traumatic symptoms (startle, irritability), were positively correlated with craving levels on the same day, whereas other symptoms (nightmares, emotional blunt, hypervigilance), predicted craving increases on the following day. On the other hand, craving intensity on a given day was not correlated with PTSD symptom severity on the following day.

Two studies assessed the impact of changes of PTSD symptoms overtime on craving after specific treatment approaches. In a randomized clinical trial conducted by Kaczkurkin et al. (53), 165 comorbid subjects were randomly assigned to four different treatment groups: Naltrexone + exposure therapy, Naltrexone alone, exposure therapy + placebo, and placebo alone. At baseline, participants with greater levels of PTSD symptom severity endorsed a significantly greater percentage of days drinking and alcohol craving. The percentage of days drinking was positively correlated with alcohol craving.

TABLE 4 | Details of observational and interventional studies included in the review.

Study	Sample	Method	PTSD evaluation	Craving evaluation	Results
Drapkin et al. (51) (Journal of Substance Abuse Treatment)	512 subjects aged 19–81 years: 167 subjects seeking care for comorbid AUD and PTSD; 105 subjects seeking care for PTSD alone; and 240 subjects seeking care for AUD alone. The three groups came from three randomized controlled trials. Recruitment was made in general population through advertisements in local newspapers. Non-inclusion criteria: bipolar or psychotic disorder. Participants in AUD group could not have PTSD diagnosis, participants in PTSD group could not have AUD, contraindication to sertraline or previous failure to Sertraline. Subjects with AUD could not have Naltrexone contraindication or other SUD diagnosis.	Cross-sectional study. Comparison of psychosocial variables between subjects with comorbid AUD and PTSD, and subjects with PTSD or AUD alone.	PTSD diagnosis with the PSS-I and the Structured Interview For PTSD (SIP) according to DSM-IV.	Self-evaluation with the Penn Alcohol Craving Scale (PACS).	Comorbid subjects had less employment, less college education, and lived alone more often than PTSD or AUD group and had lower income than PTSD group. Comorbid subjects were not different in terms of alcohol consumption compared to subjects with AUD alone, but experienced more craving. Comorbid subjects had more depressive symptoms than subjects with PTSD alone.
Jayawickreme et al. (50) (Psychology of Addictive Behavior)	167 subjects (34% female) seeking care for comorbid PTSD and AUD according to DSM-IV criteria. Participants were recruited through advertisements in the University of Pennsylvania's Center for the Treatment and Study of Anxiety. Non-inclusion criteria: SUD other than alcohol, tobacco, cannabis, bipolar and psychotic disorders, opiate use in past month, somatic problems that may interfere with addiction treatment, pregnancy or risk of pregnancy.	Cross-sectional study. Analysis of correlations between sex, traumatic cognitions, craving, and addiction consequences.	PTSD diagnosis with the PSS-I. Posttraumatic cognitions assessed with the Posttraumatic Cognitions Inventory (PTCI).	Self-evaluation with the PACS.	In men only, traumatic cognitions (specifically self-depreciation) were correlated with craving. Traumatic cognitions (self-deprecation and guilt) were correlated with negative consequences related to addiction.

(Continued)

TABLE 4 | Continued

Study	Sample	Method	PTSD evaluation	Craving evaluation	Results
Simpson et al. (52) (Psychology of Addictive Behaviors)	29 subjects (93% men) with AUD according to DSM-IV criteria, who used alcohol during last 30 days. 89, 7% of participants had PTSD. Subjects were recruited in a veteran medical center ($n = 24$) or in an urban addiction center in Seattle ($n = 5$). Another use disorder was not considered as non-inclusion criteria. Use severity was assessed with the AUDIT.	Evaluation of interactions between traumatic symptoms and craving. Observational study in everyday life during 28 days. Subjects reported everyday PTSD symptoms severity and their craving level using Interactive Voice Response (IVR).	PTSD diagnosed with the PTSD Check List (PCL-C) according to DSM-IV.	Self-evaluation with the PACS.	Initial PTSD severity was correlated with craving and alcohol use. Traumatic symptom severity (irritability and outbursts) was correlated with craving levels on the same day. Traumatic nightmares, affective blunting and hypervigilance symptoms were correlated with craving levels the next day. However, there was no correlation between craving level sand traumatic symptom severity the next day.
Heinz et al. (49) (Military Medicine)	68 military veterans (90% male) with AUD according to DSM-IV, wanting to stop or reduce their alcohol consumption and having been exposed to a traumatic event during their life. The participants came from a randomized controlled trial concerning Topiramate. They were recruited from the San Francisco Veterans Affairs Medical Center. Diagnosis of AUD with SCID-IV. Alcohol use in the past 90 days was assessed with the TLFB. Non-inclusion criteria: unstable psychiatric or somatic disorder, suicidal ideation or suicide attempt in the last 6 months.	Cross-sectional observational study. Assessment of cognitive functions (processing speed, executive functions, risk-taking/impulsivity, verbal learning, and memory), and analysis of correlations with different variables (alcohol consumption, craving, and severity of PTSD symptoms).	PTSD diagnosed with the PCL-C according to DSM-IV.	Self-evaluation with the Obsessive Compulsive Drinking Scale (OCDS).	Severity of PTSD symptoms was positively correlated with craving and alcohol consumption in the past 3 months. Craving intensity was also correlated with the frequency and quantity of alcohol consumption. Lower verbal learning and memory were correlated with more intense alcohol consumption. Higher level of impulsivity was correlated with stronger craving.

(Continued)

TABLE 4 | Continued

Study	Sample	Method	PTSD evaluation	Craving evaluation	Results
Kaczkurkin et al. (2016) (Behavior Research and Therapy)	165 subjects (65.5% male) seeking care for comorbid PTSD and AUD according to DSM-IV-TR. Recruitment at the University of Pennsylvania's Center for the treatment and Anxiety Studies and the Philadelphia Veteran's Affairs Hospital. Inclusion criteria: current diagnoses of PTSD and AUD according to DSM-IV-TR criteria, PSS-I score $\geq$ 15, consumption $>$ 12 drinks/week in the past month, with 1 day with $\geq$ 4 drinks consumed. Non-inclusion criteria: SUD other than alcohol, tobacco, or cannabis, current psychotic disorder; suicidal ideation or, opioid use during the last month, diseases that may interfere with treatment, pregnancy, or nursing.	Randomized controlled trial. The participants were randomized to four treatment groups (Naltrexone + Prolonged exposure, Naltrexone alone, placebo + Prolonged exposure, placebo alone). Different measures were collected every four weeks, before, during and after the treatment (PTSD symptoms, percentage days drinking, craving).	Current PTSD diagnosis with PSS-I according to DSM-IV.	Self-evaluation with the PACS.	**Baseline measures:** PTSD severity was positively correlated with the percentage of drinking days and craving. The % of drinking days was positively correlated with alcohol craving. **Evolution with treatment:** The Naltrexone + prolonged exposure group had significantly greater reduction in craving than the Naltrexone alone group. There was no difference in terms of reduction in % drinking days between groups. Subjects with higher initial PSS-I score had a more rapid decrease in craving over time. Craving at a given time was correlated with measures of % drinking days and severity of traumatic symptoms at previous time.
Lyons et al. (48) (Journal of Dual Diagnosis)	136 veterans (90% male), with full or subthreshold (one missing symptom) PTSD, and alcohol abuse or dependence, seeking treatment, enrolled in a randomized controlled trial. The participants had at least 20 days of massive use (four drinks for females and five drinks for males) over the past 90 days. Alcohol consumption over the past 90 days was assessed by the TLFB.	Cross-sectional observational study, using data collected from a randomized controlled trial. The study assessed the relationship between PTSD negative cognitions, negative affect, and alcohol craving.	PTSD diagnosis with the CAPS according to DSM-5.	Self-evaluation with PACS.	Alcohol craving was positively correlated with the number of massive drinking days, severity of PTSD symptoms, negative affect, and trauma-related cognitions. Negative emotions mediated relationship between trauma-related cognitions and alcohol craving.

(Continued)

TABLE 4 | Continued

Study	Sample	Method	PTSD evaluation	Craving evaluation	Results
Dedert et al. (44) (Nicotine and Tobacco Research)	52 adult smokers (18–65 year olds) with PTSD who smoked at least 10 cigarettes a day. Recruitment took place in the general population or in a veteran medical care center using flyers or brochure from previous study. Non-inclusion criteria: nicotine use in another form than cigarettes, instable major somatic disease, use of bupropion or benzodiazepines. Another use disorder was not considered as non-inclusion criteria. Addiction severity was assessed using Fagerström questionnaire.	Observational everyday life study using EMA method. Subjects were followed over 2 weeks (1 week smoking freely then 1 week after stopping smoking). Participants had to fulfill evaluations randomly during the day (every 2–3 h first week, then 1–2 h second week). Those evaluations included: • PTSD symptoms • Negative affect • Craving	PTSD diagnosis using CAPS according to DSM-IV PTSD symptoms severity assessed with DTS	Self-evaluation of craving with a scale (1–5)	Compared to free use period, abstinence period was marked by decrease of PTSD and mean craving levels, but not negative affect. Variability of traumatic symptoms from one measure to another and negative affect decreased during abstinence period. Avoidance symptoms, hypervigilance and negative affect during EMA evaluation were correlated with craving level during next EMA evaluation, but not the reverse.
Rosenblum et al. (55) (Journal of Dual Diagnosis)	162 US Army veterans (6.4% female) aged 18–65 years, smoking at least 10 cigarettes a day, with expired CO $\geq$ 8 ppm, with or without PTSD or current depressive episode. Subjects were recruited by flyers from a veterans affairs hospital in Wisconsin. Addiction severity assessed with Fagerstrom and motivation to smoke with the Brief Wisconsin Inventory For Smocking Dépendance Motives (WISDM). Non-inclusion criteria: other psychiatric disorders, use of Varenicline or Bupropion.	Cross-sectional observational study assessing motivational processes influencing tobacco addiction in smokers with PTSD or depressive episode.	Current PTSD diagnosis using CAPS according to DSM-IV.	Self-evaluation with the Brief WISDM.	Subjects with PTSD had higher mean Fagerstrom scores than other participants. Subjects with PTSD or depressive episode had greater craving than the control group. No significant difference in craving was found between subjects with PTSD and depressive episode.

(Continued)

TABLE 4 | Continued

Study	Sample	Method	PTSD evaluation	Craving evaluation	Results
Boden et al. (56) (The American Journal on Addictions)	94 US military veterans (94% men), with cannabis use disorder according to DSM-IV-TR (with DSM 5 withdrawal criteria), asking for care. Subjects were recruited using advertisements in an outpatient PTSD clinic among veterans during previous study. Non-inclusion criteria: intellectual deficit, already have decreased daily cannabis use from at least 25% during last month, pregnancy, breast feeding, suicidal thoughts. Another use disorder was not considered as non-inclusion criterion. Tobacco, alcohol, and cannabis use were measured using TLFB, cannabis use motives with the Marijuana Motives Measure (MMM), use consequences with the Marijuana Problems Scale (MPS), and cannabis withdrawal symptoms with the Marijuana Withdrawal Checklist (MWC).	Cross-sectional observational study comparing subjects with cannabis use disorder with and without PTSD on their cannabis use and its consequences.	PTSD diagnosis using CAPS according to DSM-IV, Self-evaluation of traumatic symptoms severity with PCL-M	Self-evaluation with the Marijuana Craving Questionnaire (MCQ)	Subjects with PTSD used more often cannabis as coping strategy. Subjects with PTSD experienced a higher craving level during compulsive, emotional and anticipatory use. Traumatic symptom severity was positively correlated with withdrawal symptom intensity and emotional component of craving.
Driessen et al. (58) (Alcoholism: Clinical and Experimental Research)	459 subjects aged 15–60 years, treated in addictology in Germany (73% inpatients, 10% followed in a day clinic, 17% outpatients) for a SUD (alcohol: 66% and/or other substance 60%). Participants had to be abstinent from all psychoactive substances for at least 2 weeks. Diagnosis of SUD with International Diagnostic Checklist (IDCL) according to DSM-IV, assessment of addiction severity with the ASI, objective measurement of substance use with urine and breath tests.	Cross-sectional observational study. Analysis of the relationship between PTSD diagnosis, type of addiction (alcohol or other substances), addiction severity, and craving intensity. Participants were classified by addiction type: • Group A (AUD alone; $n = 182$) • Group D (SUD other than alcohol; $n = 154$) • Group AD (AUD + SUD; $n = 123$) And by PTSD status: • PTSD group (score positive on the IDCL and PDS) • Subthreshold PTSD group (score positive on the IDCL or PDS) • Subjects who have been exposed to a traumatic event without PTSD • Subjects who have never been exposed to a traumatic event.	Diagnosis of current PTSD according to DSM-IV by IDCL and Posttraumatic Diagnostic Scale (PDS).	Assessed with ASI	Prevalence of PTSD in groups AD and D was significantly higher than group A. Subjects with PTSD had a higher addiction severity score on ASI, a greater number of inpatient admissions to addiction care, a shorter mean time of abstinence between relapses, and experienced more frequent craving than other participants. Addiction severity was higher in subjects with a SUD other than alcohol.

(Continued)

TABLE 4 | Continued

Study	Sample	Method	PTSD evaluation	Craving evaluation	Results
Wieferink et al. (33) (Addictive Behaviors)	297 Dutch subjects, aged 17–73 years (72% male) followed between 2012 and 2014 for SUD according to DSM-IV criteria. Assessment of past 30 days and lifetime substance use by the MATE substance use Inventory. Non-inclusion criteria: severe psychiatric or somatic disorder.	Prospective study, assessing efficacy of standard, non-integrated SUD treatment in subjects with higher or lower PTSD symptoms.	Diagnosis of current PTSD by SRIP according to DSM-IV.	Self-evaluation with the OCDS.	**Baseline assessment:** Subjects with high severity of PTSD symptoms had significantly higher levels of craving and anxiety-depressive symptoms than other participants. However, there was no significant difference in the number of days of use. **Measures at 3 and 6 months of treatment:** Subjects had a significant decrease in days of use regardless of PTSD symptom severity. Subjects with high severity of traumatic symptoms had a significantly greater decrease in craving.
Peck et al. (57) (Journal of Anxiety Disorders)	72 military veterans (71 men and 1 woman) with PTSD and SUD according to DSM-IV-TR, in treatment in veterans medical center of South-East USA. Subjects were recruited during inscription to cognitive processing therapy program of 6 weeks proposed by the medical center. Use frequency was assessed with the Brief Addiction Monitor (BAM).	Prospective study. Subjects participated in PTSD-specific treatment (cognitive processing therapy) during 6 weeks. Evaluations were performed before and after treatment: • PTSD symptoms • Craving • Traumatic cognitions • Depressive symptoms	PTSD diagnosis with the MINI according to DSM-IV-TR. Self-evaluation of PTSD symptoms with PCL-S. Evaluation of erroneous cognitions linked to PTSD with the PTCI.	Self-evaluation with the Craving Questionnaire—Short Form Revised (CQSFR)	Traumatic initial dysfunctional cognitions were correlated with initial craving level. There was no correlation between PTSD symptoms severity and craving. The therapy allowed a significant decrease of craving, PTSD symptoms, depressive symptoms and erroneous traumatic cognitions. Improve of dysfunctional traumatic cognitions with the cognitive processing therapy did not explain craving decrease following the therapy.
Somohano et al. (37) (Journal of Dual Diagnosis)	257 adults with SUD who were abstinent after outpatient or inpatient treatment, waiting for rehabilitation care as part of a randomized controlled trial from 2014. Recruitment was performed with advertisements in addictology treatment centers. Non-inclusion criteria: dementia syndrome, psychotic disorder, suicidal thoughts, subjects who already benefited mindfulness therapy. Use disorder severity was assessed with the Severity of Dependence Scale (SDS).	Cross-sectional observational study, using from data collected previously in a randomized controlled trial during rehab treatment. Evaluation of relationship between PTSD symptoms and craving according to the substance (alcohol, psycho stimulants, opiates, cannabis).	Diagnosis with the PCL-C according to the DSM-IV-TR.	Self-evaluation with PACS adapted for other substances.	For alcohol ($n = 131$), craving was correlated with global PTSD severity, more specifically with hypervigilance symptoms. Concerning psychostimulants ($n = 66$), craving was correlated with global PTSD severity, more specifically with avoidance syndrome. Concerning opiates ($n = 36$): craving was correlated with global PTSD severity, but not with specific PTSD symptoms. Concerning cannabis ($n = 24$), there was no correlation between craving and PTSD.

(Continued)

TABLE 4 | Continued

Study	Sample	Method	PTSD evaluation	Craving evaluation	Results
Vogel et al. (59) (Drug and Alcohol Dependence)	108 adults (25% female) with SUD and comorbid PTSD, beginning inpatient detoxification. Non-inclusion criteria: severe cognitive deficit, symptoms of psychotic disorder.	Observational study, Evaluation of correlation between PTSD symptoms and craving level.	PTSD assessed with the PCL-5 according to the DSM-5. Screening for life trauma event with the Life Events Checklist (LEC-5).	Self-evaluation with the Mannheimer Craving Scale (MaCs)	PTSD symptoms were positively associated with craving level but were not predictors of craving level the following day.

Participants in the Naltrexone + exposure therapy group had a greater decrease in craving than in the Naltrexone alone group. Subjects with higher initial PTSD severity had a more rapid decrease in craving intensity over time. Finally, the percentage of drinking days and the severity of traumatic symptoms at time t predicted the intensity of craving at time $t + 1$, with alcohol craving being dependent on the amount of PTSD symptoms and alcohol use reported at the previous time point. Coffey et al. (30) compared the effectiveness of exposure therapy and relaxation-based therapy in 43 subjects with comorbid AUD and PTSD using a laboratory-based experiment. A first session conducted before the beginning of treatment showed an increase in craving and emotional distress of the participants after exposure to a traumatic script and alcohol-related cues. Follow-up analyses after six sessions of group exposure therapy found a reduction of both PTSD symptoms and alcohol craving overtime.

Tobacco Use Disorder

In 2014, Dedert et al. (54) used Ecological Momentary Assessment (EMA) to follow smokers with PTSD in daily life over 14 days. Participants were allowed to smoke freely during the first week, then had to begin withdrawal without any substitute or pharmacological treatment in the second week. Compared with the pre-withdrawal phase, abstinence was associated with reductions in PTSD symptoms and craving, but not negative affect. During withdrawal period, an increase in traumatic symptom intensity predicted an increase in craving at next EMA evaluation, but the reverse association was not observed.

Rosenblum et al. (55) compared three groups composed by 162 US Army veteran daily smokers: a PTSD group (52 subjects with PTSD alone or with a comorbid depressive episode); a depressive episode group (52 subjects with depressive episode without comorbidity); and a control group (58 subjects with no psychiatric disorder). The PTSD group (with or without depression) described higher craving than the control group without any psychiatric disorder.

Cannabis Use Disorder

Boden et al. (56) explored the links between PTSD and different characteristics associated with cannabis use (motivation, relational problems, withdrawal symptoms, and craving) in veterans with cannabis use disorder with and without PTSD. Patients with PTSD used cannabis more frequently as a coping strategy and reported a significatively higher level of craving in several components (compulsive, anticipating release of emotional distress, and use planification). Traumatic symptom severity was positively correlated with the emotional component of craving (release of emotional distress).

Multiple Type of Substance Use Disorder

Two studies assessed the course of craving during SUD treatment according to PTSD symptoms severity at baseline. Wieferink et al. (33) assessed outcomes of standard, non-integrated SUD

treatment among 297 SUD outpatients (AUD, or Cannabis or Cocaine Use Disorder) with higher (≥48) or lower (<48) PTSD symptom severity based on the Self-Reported Inventory for PTSD (SRIP). At baseline, there was no difference in the number of days of use between subjects, however, subjects with more severe PTSD symptoms had significantly higher levels of craving and anxiety-depressive symptoms. After 3 and 6 months of treatment, there was a decrease in the number of days of use for all subjects, a significantly greater decrease in craving for subjects with more severe traumatic symptoms, and a significant decrease in anxiety-depressive symptoms for subjects with severe traumatic symptoms only. However, patients with higher levels of PTSD symptoms still reported significantly higher scores on depression, anxiety and stress after 6 months of SUD treatment. Peck et al. (57) assessed the impact of a 6 weeks therapeutical program including cognitive processing therapy, Alcoholics Anonymous (AA) meetings, and group discussion with 72 American veterans suffering from PTSD and a substance use disorder (AUD, Cannabis Use Disorder, Cocaine Use Disorder, Opiate Use Disorder, Amphetamine Use Disorder, or Anxiolytic Use Disorder). Baseline dysfunctional cognitions associated with the trauma were positively correlated with PTSD and craving severity. However, PTSD severity was not correlated with craving levels. Cognitive processing therapy was associated with significant improvements in erroneous cognitions, trauma-cued substance craving, and depressive or trauma-related symptoms. Reduction in depressive or trauma-related symptoms was partly explained by the therapy's impact on erroneous cognitions, contrary to craving.

In a cross-sectional study, Driessen et al. (58) focused on the relationship between the type of addiction (alcohol or drug addiction or both), the severity of the addiction and of craving, and the presence or not of comorbid PTSD. Participants with PTSD had a higher addiction severity score, were more often hospitalized, had a shorter abstinence time between relapses and experienced craving more frequently than other participants. Somohano et al. (37) assessed the correlation between severity of different symptoms of PTSD and craving according to four classes of substances: alcohol, psychostimulants (cocaine, amphetamines), opiates and cannabis. Concerning subjects with alcohol use disorder ($n = 131$), global PTSD severity and hypervigilance levels were associated with craving intensity. For participants with psychostimulant use disorder ($n = 66$), craving levels were correlated with global PTSD severity and more precisely with avoidance syndrome intensity. Among subjects with opiate use disorder ($n = 36$), global PTSD severity was correlated with craving levels, but with no association to specific symptoms. Finally, for subjects with cannabis use disorder, no variable was associated with craving. An observational study led by Vogel et al. (59), highlighted a positive correlation between craving levels and PTSD symptoms over 6 days following admission for detoxification among comorbid patients (PTSD with alcohol, cannabis, sedatives or mixed use disorder). However, no correlation was found concerning PTSD symptoms at Day 1 and craving the following day.

Association of Negative Affect With Trauma Exposure and Craving

Alcohol Use Disorder

Several studies focused on the role played by negative affect during different forms of exposures (31, 38, 40). The results were similar to those obtained for craving and showed that exposure to a traumatic script and an alcohol-related cue generated a more intense level of negative affect than during a neutral exposure. Nosen et al. (38) reported that in a traumatic context (exposure to a traumatic script), the intensity of craving was correlated with the severity of negative affect. The study of Coffey et al. (30), through a laboratory-based experiment, found a decrease of both craving and emotional distress after trauma-focused imaginal exposure, suggesting that negative emotions should constitute a mechanism of alcohol craving induced by trauma exposure. Lyons et al. (48) examined more specifically the mediation role of negative affect on the association between PTSD cognitions and craving among 136 treatment-seeking veterans with PTSD and AUD. Mediation models demonstrated that negative affect mediated the association between specific posttraumatic cognitions related to the self, the world, the self-blame, and craving controlling for PTSD/AUD symptom severity and gender. Posttraumatic cognitions were associated with increased negative affect, which in turn was related to increased craving. Finally, one observational study (50) examined sex differences in trauma cognitions and their relationship to symptoms of AUD including craving. Specifically, negative cognitions about the self were associated with increased craving in men, but not in women, a finding that could be related to greater subjective negative emotions related to traumatic experiences in men. In this perspective, higher craving levels could be explained as a result of maladaptive coping of trauma-related negative emotions.

Tobacco Use Disorder

The study of Dedert et al. (54) investigated whether craving for cigarettes was driven by PTSD symptoms and negative affect among smokers with PTSD attending to quit, using an EMA procedure. Negative emotions were identified as predictors of craving during the withdrawal period (54). Increased PTSD symptoms and negative affect predicted an increase in craving at the next EMA evaluation, even on days with low levels of craving, but the reverse association was not observed.

Cocaine Use Disorder

In the experimental study of Tull et al. (45), in male subjects only, the experience of negative emotions (shame, guilt) in response to the traumatic script mediated the relationship between traumatic symptoms and craving for cocaine. The experience of self-conscious negative affect in response to the trauma script accounted for the relation between PTSD diagnosis and cocaine craving following trauma script exposure.

DISCUSSION

Twenty-seven studies fulfilled criteria for inclusion in this review, of which 12 focused on alcohol, 4 on tobacco, 1 on cannabis, 1

on cocaine and 9 on various substance use disorders. The results showed that regardless of substance type, PTSD and SUD dual disorder was associated with more intense craving levels and was characterized by a prospective link between PTSD symptom severity and craving episodes. Exposure to traumatic memories in experimental studies was associated with emotional distress whose severity was correlated with craving intensity (31, 38).

Whatever for alcohol (31, 38), tobacco (43), or cocaine (47), experimental results showed that exposure to traumatic cues among subjects with PTSD and substance use disorder comorbidity triggered craving in the same way as exposition to substance cues. There also was an additive effect of the association of both forms of exposure on craving, a finding that is consistent with literature showing an association between exposure to stress and craving among patients with substance use disorder (26, 60). However, beyond stress exposure, there appears to be a specific effect of traumatic memories on craving. According to the study by Beckham et al. (43), exposition to traumatic cues triggered significatively greater craving compared with exposure to non-traumatic stress cues. This result could explain the lack of difference in craving levels between subjects with and without PTSD, after exposition to a cold pressor task (neutral stress) in the investigation by Brady et al. (41). In this way, persons with these comorbidities are repeatedly exposed to traumatic memories and therefore to more intense craving, which could increase the risk of relapse. Moreover, the study by Boden et al. (56) lends support to this interpretation by highlighting the correlation between traumatic symptom severity and craving intensity. Finally, studies using EMA observed a prospective link in the association between PTSD symptoms and craving, showing notably that craving daily variation was a reaction to traumatic symptoms intensity. Such results are generally supportive of self-medication theory, as aggravation of PTSD symptoms would then trigger greater craving and lead to substance use as a means of assuaging traumatic symptoms.

In line with this interpretation, some studies in this review also highlighted the role of negative affect associated with traumatic exposure in the risk of relapse and thereby indicating that substance use may constitute a coping strategy to deal with negative affect. Experimental studies among subjects with alcohol and tobacco use disorder (31, 38, 43) showed a correlation in evolution of negative affect and craving after exposition to a traumatic factor. Moreover, negative emotions were identified as predictors of craving after exposition to traumatic cues as well as in daily follow-ups during withdrawal (54). This literature has also demonstrated a salient association between PTSD, addiction and negative emotions, and points specifically to the mediation role of negative emotions and the relationship between traumatic symptoms and alcohol use (61). According to Zvolensky et al. (62), smokers experience greater negative affect if they have comorbid PTSD. Individuals with comorbidity would also use emotions to assuage emotional distress, in accordance with the principle of negative reinforcement. This dysphoric state could be explained by a decrease in dopaminergic D2 receptor density in the reward network (ventral striatum) among persons with substance use disorders (63) and a higher number of DAT dopamine transporters in persons with PTSD (64) that are correlated with craving intensity. Perturbations of the stress axis could also be implicated in these dual disorders, as anomalies of the stress response among subjects with substance use disorders is associated with the activation of extra hypothalamic corticotropin-releasing factor (CRF) synthesis, excessively activating the amygdala (the brain structure implicated in emotional reactions such as fear) (65, 66). Such hyperactivity has also been observed among individuals with PTSD (67) and it is associated with the presence of enduring negative emotional states (anxiety, irritability, dysthymia). While the prefrontal cortex has a major impact on emotional regulation by the inhibition of the amygdala (68), SUD and PTSD are both associated with a hypoactivation of this area (69, 70) that could explain the major emotional dysregulation among these cases of dual disorder (71, 72). Thus, a negative emotional state or emotional dysregulation characterized by significant fluctuations in daily life could constitute a clinical feature of these dual disorders leading to greater craving frequency and/or intensity, although this hypothesis requires further investigation.

Another important observation of this review that could further understanding for mechanisms underlying PTSD and craving is the impact of early trauma. Schumacher and colleagues (42) demonstrated that patients with dual disorders and early trauma (<13 y.o.) experienced more severe PTSD symptoms, more craving after exposure, and more severe AUD. This is consistent with previous studies highlighting a link between age that the trauma was experienced and PTSD severity (73). The link with craving intensity could be partly explained by the fact that early trauma leads to deficit in inhibitory control during stress exposure, which might facilitate the use of substances as coping strategy (74). Indeed, deficits in inhibition capacities during adolescence is known to be associated with a greater risk of both substance experimentation and the development of substance use disorders (75).

Several limitations of this systematic review should be considered in interpreting its findings. A first concern is the heterogenous nature of the selected studies. Based on the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (S2C), most studies included in this review could be qualified as being of "Good" or "Fair" quality ($n = 17$ or 65%). However, nine studies (35%) were classified as "Poor" quality, and this may partly explain the considerable variation observed in study methods. The majority of investigations classified as "Poor" quality were observational studies while most of the "Good" quality studies were cross-sectional in nature. Moreover, the studies used a large variety of questionnaires to assess SUD, PTSD, and craving. Substance use was mainly reported using self-report questionnaires and only six studies used objective methods of assessment (urine or breath tests). Nevertheless, the majority of experimental studies on cue-reactivity administered single-item instruments, mainly visual analog scale which are considered as an acceptable and valid tool in experimental paradigms, while observational studies used different multi-items questionnaires. The heterogeneity of self-report measures of craving and research design in observational studies could explain some variability in the findings. Finally, few studies addressed sex differences in the analysis, although

some results indicated specific relationships between trauma-related cognitions and emotions (self-depreciation and self-blame) and craving among males. More comprehensive analyses are needed to examine the impact of sex (and gender) on the underlying relationship between PTSD and SUD across different SUD subgroups. Despite these limitations, the results strongly underscore the strong relationship between PTSD and substance craving and the necessity to concomitantly treat SUD and PTSD as dual disorder.

Concerning treatment approaches, recent studies assessed several classes of pharmacological agents in the treatment of this dual disorder based on neurobiological mechanisms implicated in both disorders when considered individually (76). Moreover, the positive effect on alcohol use and traumatic symptoms was demonstrated with the association of Disulfiram and Naltrexone in a randomized trial (77), and the use of Desipramine led to an improvement of alcohol use and PTSD symptoms (78). Promising results have also been found with treatments using noradrenergic (Prazosine, Propranolol), GABA and glutamatergic system (Memantine, N-Acetyl-Cysteine, and Topiramate). The results of this review also suggest the importance of improving regulation of negative emotions associated with traumatic memories, and treatments of erroneous or dysfunctional cognitions linked with the traumatism. Furthermore, the potential mediation role of post-traumatic cognitions on negative affect and craving raises the issue to consider posttraumatic cognitions and negative emotions as a salient target for craving reduction. On this issue, several therapies targeting emotion regulation and dysfunctional cognitions linked with traumatism such as Prolonged Exposure and Cognitive Processing Therapy were found to be efficacious for substance use, craving and PTSD symptoms (53, 57, 79). The study of Coffey et al. (30) using trauma-focused exposure therapy led to reductions in negative affect and craving, although the potential link between negative post-traumatic cognitions, negative affect and craving was not specifically assessed. Integrated treatment combining prolonged exposure and naltrexone among individuals with comorbid PTSD and AUD demonstrated better outcomes in terms of alcohol craving compared to exposure alone or naltrexone alone. The necessity of global treatment approaches for comorbid patients, including pharmacological treatment, psychotherapies, and psycho-social treatment has also emphasized (80), but further studies are needed in other SUD populations to generalize these findings and examine the temporal changes of emotion dysregulation, trauma-related emotions such as guilt and shame, on subsequent craving and substance use.

CONCLUSIONS

Findings from the current study further inform our understanding of the synergetic relationship between PTSD and SUDs that lead to craving that is greater than that observed with either disorder alone. PTSD symptoms can act as powerful craving cues with an additive effect when combined with exposure to substance-related cues, thereby constituting a salient risk factor for relapse. The craving elicited by PTSD may differ according to specific PTSD symptoms and the effects of specific forms of substance use, although this possibility requires further investigation. Daily life studies using Ecological Momentary Assessment appear to be particularly adapted to investigating the temporal relationship between different PTSD symptoms, emotional states and the clinical expression of addiction, and hold considerable promise for the development of more personalized interventions in dually-diagnosed individuals. Since the majority of the studies included in our review concern alcohol and tobacco, it would be also interesting to expand this research to other substances as well as to behavioral addictions. Specifically, no studies examined the association between craving and MDMA or psychedelic drugs, that is a major issue in view of novel treatment approaches of PTSD.

Our data therefore challenge our current clinical practice in the treatment of patients suffering from dual diagnosis, and argue for the integration of an additional trauma-focused strategies into addiction facilities, notably including cognitive-behavioral therapies based on prolonged exposure. While all individuals suffering from SUD should be systematically assessed for trauma history and PTSD, the present data suggest that PTSD treatment should not be delayed until abstinence has been achieved. The direct relationship between PTSD symptoms and craving argues for the need of these integrated therapies in the goal of providing the most comprehensive and efficacious treatment possible.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

FR, LJ, JS, and MF designed the review, wrote, and reviewed the manuscript. FR and LJ reviewed the abstracts and the papers. FR, LJ, and MF obtained the data from the selected articles. All authors approved the final version.

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BRIEF RESEARCH REPORT
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Lockdown Impact on Stress, Coping Strategies, and Substance Use in Teenagers

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Background: In response to the COVID-19 pandemic, the French government took many measures, the most notable of which was a national lockdown on 17 March 2020. Its effects have been widely studied, but to our knowledge, no study has sought to determine how adolescents have adapted to cope with this situation. The present study set out to explore teenagers' stress levels, coping strategies, and substance use during this period.

Methods: This paper is a cross-sectional study that rides on an existing prevention program interviewed 348 French middle school students (209 girls and 139 boys) in grade 8 (M_{age} = 13.45; SDage = 0.54) using an online questionnaire between March 17 and May 11, 2020 (COVID-19 lockdown). The study examined the teenagers' perceived stress, coping strategies they had used, including recent use of tobacco, alcohol and cannabis, during COVID-19 lockdown.

Results: Teenagers reported lower perceived stress during lockdown than usually, with a significant decrease for girls. Those who perceived the least social support reported the highest levels of stress. The strategies of planning, behavioral disengagement, self-distraction, positive reframing, acceptance, and religion were used more than usual, while active coping and self-blame were used less. Acceptance was the most often used strategy and a source of decreased stress during lockdown. A significant decrease in recent tobacco, alcohol and cannabis use was also observed.

Conclusion: Changes in the use of coping strategies, withdrawal from the stressful school environment, and greater exposure to parents than to peers caused adolescents to be less stressed and to decrease their substance use during the lockdown.

Keywords: COVID-19, lockdown, teenagers, stress level, coping strategies, substance use

INTRODUCTION

The COVID-19 pandemic began in China, in the Wuhan region, in December 2019, and later spread to Europe. The first cases reached France in late January 2020. The French government then implemented many measures, the most notable of which was a national lockdown on March 17, 2020, for a period of 2 months. Among children and adolescents, the prolonged closure of schools, involving disruption of educational, sports and social activities, coupled with home lockdown, may have had negative effects on their physical and psychological health (1). However, to our knowledge, no studies have investigated how adolescents adapted to cope with this novel situation. The present study examined the stress levels, coping strategies, and substance use of teenagers in this context.

Hawryluck et al. (2) previously highlighted that quarantine beyond 10 days in a pandemic setting increased stress. In addition, the fear of being infected or of infecting others, isolation (3), intolerance to uncertainty (4), cessation of work activities (5), or exposure to conflicting information from the media (6) are also important factors in increasing stress. This increase in stress was indeed found in adults (1, 5, 7), in children and in teenagers (3, 8, 9) during the COVID-19 pandemic lockdown. This stressful situation is a factor that could influence the mental health of adolescent (10, 11), because they are more vulnerable than adults to mental health problems, in particular during a lockdown (12). However, the literature shows that social support is a factor in decreasing symptoms in the face of stressful events (13–15). A study showed that prisoners in solitary lockdown had more depressive and anxious symptoms than those in non-solitary lockdown (16). During lockdown, those most stressed were those who received the least social support (7).

In this stressful context of lockdown, the coping strategies mobilized by each person may explain the inter-individual differences observed during this period. Coping is defined as "the cognitive and behavioral efforts made to master, tolerate, or reduce external and internal demands and conflicts among them" [(17), p. 223]. Coping is evolutionary: it adapts to each stressful event to reduce the effect of stress on well-being (18). Coping therefore depends on people's ability to develop new strategies and to abandon those that have become ineffective (19–21). This adaptive capacity appears as early as mid-childhood, with the development of metacognitive abilities that allow better adjustment of coping efforts to the stressor through an increase in the diversity and flexibility of available coping responses (20). During the first half of adolescence (grades 6–8), planning, positive reframing and acceptance strategies tend to be emphasized (22). Strategies related to emotional and instrumental support begin to be used in the second half of adolescence (grade 9–12). The most functional strategies, i.e., those that act most effectively on the stressor, are active coping, planning, positive reframing and acceptance. By contrast, denial, behavioral disengagement, and substance use are dysfunctional (23–26).

During lockdown, studies have still found increased tobacco and alcohol use in the general population (27–29). However, teenagers use these substances differently from adults: it is during adolescence that substance use behaviors begin, become established and cause developmental and mental health disorders (30). At this age, alcohol is the most often consumed product, followed by tobacco, and finally various other drugs (31). Two psychosocial factors come into play as a "pattern" of vulnerability to substance use: parental and peer influence (32). For Windle (33), parents are an important protective factor against substance use. However, after the age of 12, parental influence decreases, while peer influence increases (34). It is peers who encourage experimentation (35): they provide direct access to substances and socially reinforce their use (36). Hence in adolescence, substance use takes place within the peer group, not in the family sphere (29). However, during lockdown, teenagers remained in the family home, limiting exchanges with peers to virtual contact, and so likely reducing their influence on substance use behavior.

In the context of the first COVID-19 pandemic lockdown, the present study examined the stress level, coping strategies and substance use of teenagers. In the light of recent studies, we hypothesized an increase in stress levels. This variation would be sensitive to differences in perceived social support, classically observed in the literature. We also expected a modification in the coping strategies mobilized during lockdown, along with a change in their effectiveness on stress. Finally, we expected that teenagers would decrease their use of tobacco, alcohol and cannabis.

METHODS

Participants

Three hundred and forty-eight middle school students [209 (60.06%) girls and 139 (39.94%) boys] in grade 8 (M_{age} = 13.45, SD_{age} = 0.54) from 12 schools in the Auvergne-Rhône-Alpes region of France took part in the study. Initially, these participants were part of a voluntary sample (741 middle-school students, see **Figure 1**) to test an addiction prevention program within their school during the school year (37), based on self-concept theory (Bourduge et al., in prep). Schools have voluntarily chosen to participate in the prevention program. Students were only able to participate with parental consent. This study was conducted in accordance with ethical standards and has the approval of local ethics comities (INSERM agreement reference: 19||134-00, ANSM registration number: 2019-A03131-56).

Materials and Procedure

The prevention program consisted of 13 1-h interactive sessions and was based on Social Influence approach and addresses social and personal skills, knowledge, and normative beliefs. In order to evaluate this program, a paper questionnaire of the recent tobacco, alcohol and cannabis use (use of the product at least once during the 30 days preceding the survey) was completed at the beginning of the school year (October 2019) (see **Figure 1**).

Then, an online questionnaire was sent by the schools to the students during the lockdown (between March 17, 2020, and May 11, 2020) using a link generated by the Qualtrics XM online questionnaire creation software. Three hundred and forty-eight participants (see **Figure 1**) then answered questions about

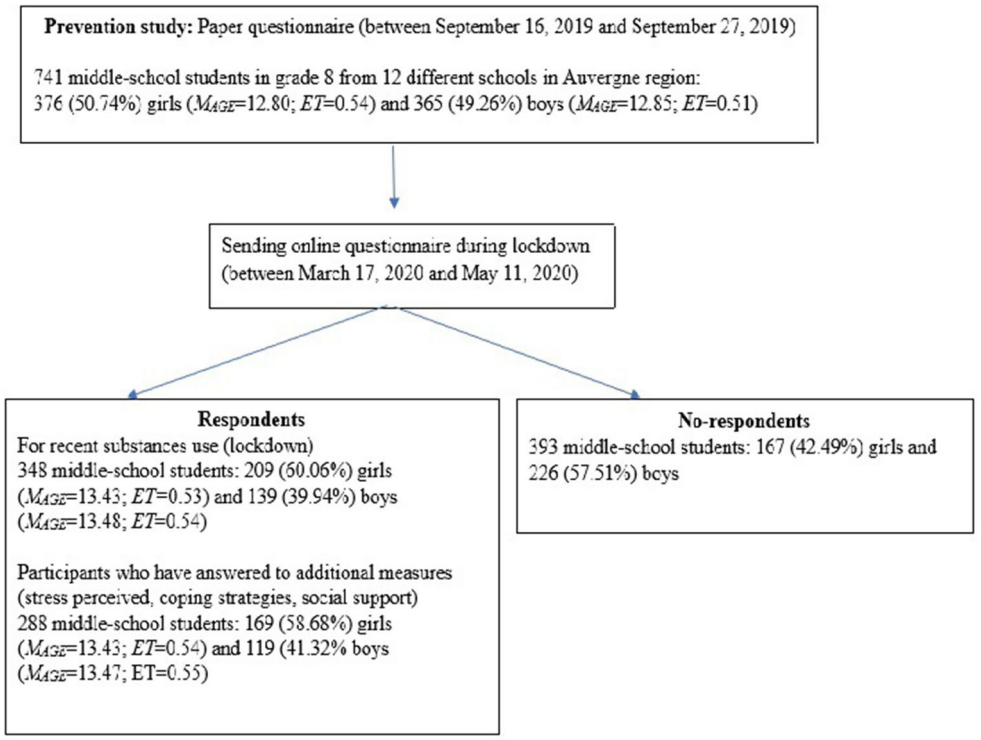

FIGURE 1 | Flowchart of the inclusion procedure.

recent tobacco, alcohol and cannabis use. Additional measures were added to assess the impact of lockdown. The perceived stress level was measured usually and during lockdown. Only one question measured, from 1 ("Not stressed at all") to 10 (Extremely stressed"), the stress level usually ("Are you usually a stressed person?") and during lockdown ("How were you stressed during lockdown?"). A high score indicates a high level of stress. Coping strategies used were measured with the French version (23) of the Brief-COPE (38). The Brief COPE contains 28 items assessing the following coping dimensions: active coping, planning, use of instrumental support, use of emotional support, venting, behavioral disengagement, self-distraction, self-blame, positive reframing, humor, denial, acceptance, religion and substance use. Each of the 14 dimensions was measured with the sum of 2 items, scored with a 4 point-scale ranging from 1 ("Not at all") to 4 ("always"). A high score indicates a strategy estimated to be used a lot. We used the scale in the dispositional format to assesses how teenagers cope usually (active coping $\alpha = 0.34$, planning $\alpha = 0.58$, use of instrumental support $\alpha = 0.78$, use of emotional support $\alpha = 0.77$, venting 0.55, behavioral disengagement $\alpha = 0.59$, self-distraction $\alpha = 0.30$, self-blame $\alpha = 0.68$, positive reframing $\alpha = 0.69$, humor $\alpha = 0.70$, denial $\alpha = 0.58$, acceptance $\alpha = 0.70$, religion $\alpha = 0.74$, and substance use $\alpha = 0.53$) and the situational format to assesses how teenagers cope during lockdown (active coping $\alpha = 0.41$, planning $\alpha = 0.63$, use of instrumental support $\alpha = 0.77$, use of emotional support $\alpha = 0.78$, venting 0.62, behavioral disengagement $\alpha = 0.58$, self-distraction $\alpha = 0.37$, self-blame $\alpha = 0.51$, positive reframing $\alpha = 0.71$, humor $\alpha = 0.71$, denial $\alpha = 0.58$, acceptance $\alpha = 0.70$, religion $\alpha = 0.71$, and substance use $\alpha = 0.71$). Perceived social support was measured through 3 elements. Staying in contact with their friends and how much they missed them was measured with only one question each, on a 10 point-scale from 1 ("Not at all") to 10 ("A lot"). A high score indicates that they stayed a lot in contact with their friends or that they missed their friends a lot. How many hours they spent online per day with their friends was measured with a slider from 0 to 24 h. The higher the number, the more time the participants spent online each day with their friends (see **Supplementary Material** for details). However, owing to the time required and the large number of scales, only 288 participants completed the additional measures (see **Figure 1**).

Statistical Analyses

The analyses of this study were performed using SPSS 25 software. We have ensured the normality of our data. The effect of lockdown (IV) (difference between "usually" and "during lockdown") and gender (IV) on stress level (DV) (see **Figure 2**) was measured using a repeated measures ANOVA test. The impact of perceived social support (IVs) (staying in contact, missing, and time online) on stress level (DV) was measured using multiple linear regressions.

The impact of lockdown (IV) and gender (IV) on the estimated use of coping strategies (DV) was measured using a repeated measures ANOVA test (see **Table 1**). The effect of

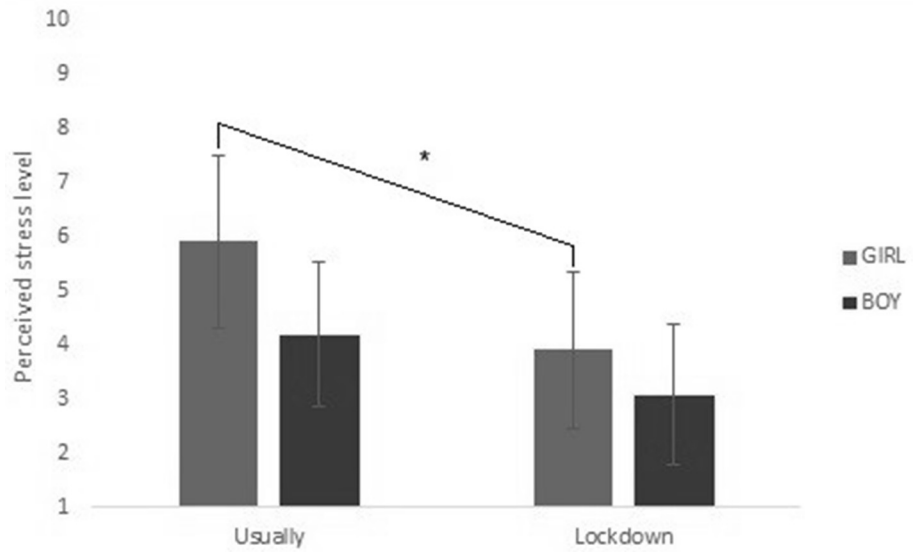

FIGURE 2 | Interaction effect between lockdown and gender in stress. *The significative effect described in the section results, in stress paragraph.

TABLE 1 | Estimate of coping strategies used usually and during lockdown, by gender.

Brief-COPE	Usually			Lockdown			Lockdown effect *p*	Gender effect *p*	Lockdown × gender *p*
	Total *M* (SD)	Girls *M* (SD)	Boys *M* (SD)	Total *M* (SD)	Girls *M* (SD)	Boys *M* (SD)			
Active coping	4.45 (1.43)	4.42 (1.39)	4.50 (1.48)	4.28 (1.49)	4.21 (1.44)	4.38 (1.55)	<0.05*	>0.05	>0.05
Planning	4.19 (1.56)	4.27 (1.55)	4.08 (1.57)	4.34 (1.76)	4.40 (1.81)	4.26 (1.69)	<0.05*	>0.05	>0.05
Using instrumental support	4.20 (1.66)	4.40 (1.69)	3.91 (1.57)	4.08 (1.75)	4.20 (1.81)	3.90 (1.61)	>0.05	<0.05*	>0.05
Using emotional support	3.86 (1.65)	4.05 (1.77)	3.58 (1.43)	3.88 (1.80)	4.04 (1.88)	3.67 (1.67)	>0.05	<0.05*	>0.05
Venting	3.86 (1.61)	3.97 (1.65)	3.72 (1.54)	3.85 (1.70)	3.93 (1.77)	3.74 (1.61)	>0.05	>0.05	>0.05
Behavioral disengagement	3.17 (1.39)	3.13 (1.43)	3.23 (1.35)	3.38 (1.49)	3.45 (1.54)	3.30 (1.40)	<0.01**	>0.05	>0.05
Self-distraction	5.07 (1.45)	5.22 (1.34)	4.86 (1.58)	5.37 (1.57)	5.51 (1.43)	5.18 (1.74)	<0.001***	<0.05*	>0.05
Self-blame	4.16 (1.74)	4.49 (1.79)	3.70 (1.56)	3.95 (1.65)	4.21 (1.64)	3.58 (1.51)	<0.01**	<0.001***	>0.05
Positive reframing	4.74 (1.72)	4.87 (1.75)	4.56 (1.67)	4.87 (1.83)	4.99 (1.88)	4.70 (1.74)	<0.05*	>0.05	>0.05
Humor	4.15 (1.73)	4.05 (1.73)	4.27 (1.73)	4.07 (1.83)	3.98 (1.90)	4.20 (1.73)	>0.05	>0.05	>0.05
Denial	3.10 (1.42)	3.27 (1.54)	2.86 (1.20)	3.09 (1.42)	3.16 (1.49)	3.02 (1.30)	>0.05	>0.05	<0.05*
Acceptance	5.74 (1.72)	5.65 (1.73)	5.85 (1.72)	5.91 (1.74)	5.88 (1.70)	5.96 (1.79)	<0.01**	>0.05	>0.05
Religion	2.44 (1.06)	2.46 (1.06)	2.40 (1.06)	2.50 (1.17)	2.53 (1.18)	2.46 (1.16)	<0.05*	>0.05	>0.05
Substance use	2.10 (0.50)	2.09 (0.42)	2.11 (0.54)	2.10 (0.48)	2.07 (0.34)	2.13 (0.62)	>0.05	>0.05	>0.05

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

coping strategies (IV) on stress levels (DV) was measured using multiple linear regressions.

The numbers of tobacco, alcohol and cannabis use at baseline and during lockdown were compared with the French Drug Observatory (OFDT) data (31) (see **Figure 3**). The OFDT is a French organization which collects national substance use data every 4 years. This comparison was made using a confidence interval calculated on our data: we looked to see whether the OFDT data fell within this interval. No other factors could be taken into account because of the small number of consumers.

RESULTS

Stress

Our participants mostly felt less stressed [$F_{(1, 286)} = 70.01$, $p < 0.001$, $\eta_p^2 = 0.197$] during the lockdown ($M = 3.57$, SD = 2.82) than they usually do ($M = 5.21$, SD = 3.10). 56.90% felt less stress, 22.90% felt the same stress, and 20.10% felt more stress during lockdown.

We also observed a main effect of gender [$F_{(1, 286)} = 19.168$, $p < 0.001$, $\eta_p^2 = 0.063$], with higher perceived stress in girls than in boys. In addition, the interaction effect between lockdown

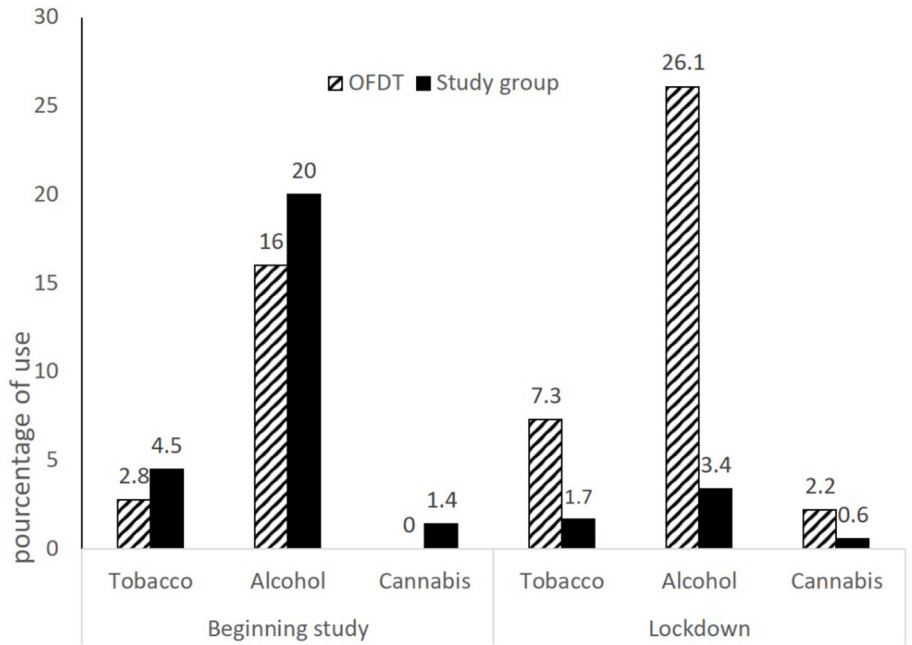

FIGURE 3 | Recent tobacco, alcohol and cannabis use at the beginning of the school year and during lockdown, compared with data collected by OFDT.

and gender [$F_{(1, 286)} = 5.661$, $p < 0.05$, $\eta_p^2 = 0.019$] revealed a greater decrease in stress for girls than for boys during lockdown (see **Figure 2**).

We could also see that during lockdown, the more they missed their friends [$B = 0.369$, $t_{(145)} = 4.095$, $p < 0.01$], the higher was their stress level. And the more they stayed in contact with them [$B = -0.210$, $t_{(145)} = -2.240$, $p < 0.05$], the lower was their stress level. Nevertheless, the time spent per day online with their friends did not influence their stress level [$B = -0.044$, $t_{(145)} = -0.539$, $p > 0.05$] [$R^2 = 0.108$, $F_{(3, 145)} = 5.831$; $p < 0.01$].

Coping Strategies

Coping data are reported in **Table 1**. Usually and during lockdown, acceptance, self-distraction and positive reframing strategies are estimated to be the most often used during stressful situations. Conversely, religion and substance use are estimated to be the least often used. During lockdown, our participants estimated they had significantly increased the use of planning [$F_{(1, 279)} = 4.134$, $p < 0.05$, $\eta_p^2 = 0.015$], behavioral disengagement [$F_{(1, 279)} = 8.552$, $p < 0.01$, $\eta_p^2 = 0.030$], self-distraction [$F_{(1, 279)} = 18.275$, $p < 0.001$, $\eta_p^2 = 0.061$], positive reframing [$F_{(1, 279)} = 4.427$, $p < 0.05$, $\eta_p^2 = 0.016$], acceptance [$F_{(1, 279)} = 7.341$, $p < 0.01$, $\eta_p^2 = 0.026$] and religion [$F_{(1, 279)} = 5.806$, $p < 0.05$, $\eta_p^2 = 0.020$]. On the contrary, active coping [$F_{(1,279)} = 5.449$, $p < 0.05$, $\eta_p^2 = 0.019$] and self-blame [$F_{(1, 279)} = 10.326$, $p = 0.001$, $\eta_p^2 = 0.036$] were estimated to be less often used.

Girls estimated using instrumental [$F_{(1, 279)} = 3.979$, $p < 0.05$, $\eta_p^2 = 0.014$] and emotional [$F_{(1, 279)} = 4.566$, $p < 0.05$, $\eta_p^2 = 0.016$] support, self-distraction [$F_{(1, 279)} = 4.118$, $p < 0.05$, $\eta_p^2 = 0.015$] and self-blame [$F_{(1, 279)} = 13.652$, $p < 0.001$, $\eta_p^2 = 0.047$] more than boys. Finally, we found an interaction effect between lockdown and gender for denial [$F_{(1, 279)} = 4.499$, $p < 0.05$, $\eta_p^2 = 0.016$]. Girls felt they used this strategy less during lockdown than usually, but boys felt they used it more.

Coping Strategies and Stress

Usually, the estimate of self-blame use [$B = 0.270$, $t_{(266)} = 4.262$, $p < 0.01$] predicted increased stress. Estimating the use of active coping [$B = -0.129$; $t_{(266)} = -2.041$, $p < 0.05$], acceptance [$B = -0.180$, $t_{(266)} = -2.681$, $p < 0.01$] and substance use [$B = -0.151$, $t_{(266)} = -2.630$, $p < 0.01$] predicted decreased stress [$R^2 = 0.236$, $F_{(14, 266)} = 5.885$; $p < 0.001$].

During lockdown, the estimated use of emotional support [$B = 0.367$, $t_{(266)} = 4.951$, $p < 0.01$] and self-blame [$B = 0.123$, $t_{(266)} = 2.091$, $p < 0.05$] predicted increased stress. Estimated use of acceptance [$B = -0.134$, $t_{(266)} = -2.064$, $p < 0.05$] predicted decreased stress [$R^2 = 0.311$, $F_{(14, 266)} = 8.559$; $p < 0.001$].

Substance Use

The OFDT data (end of grade 7) for tobacco (2.80%), alcohol (16.00%) and cannabis (0.00%) were below the confidence intervals [$CI_{tobacco}$ (3.21; 6.28), $CI_{alcohol}$ (17.21; 23.11), $CI_{cannabis}$ (0.76; 2.56)] of our data (beginning of grade 8). During lockdown, this observation was reversed: the OFDT data (end of grade 8) for tobacco (7.30%), alcohol (26.1%) and cannabis (2.20%) were found to be higher than our confidence intervals [$CI_{tobacco}$ (0.79; 3.71), $CI_{alcohol}$ (1.98; 5.93), $CI_{cannabis}$ (0.16; 2.07)] (end of grade 8). This means that our figures were significantly lower than the ODFT data during lockdown, whereas at the beginning of

the year they were significantly higher than the OFDT data (see **Figure 3**).

DISCUSSION

First, during lockdown, we observed a decrease in perceived stress. We also noted an evolution in the estimation of the use of coping strategies during lockdown, with in particular, a strong decrease in recent tobacco, alcohol and cannabis use.

Recently, studies have highlighted the deleterious impact of lockdown on stress in adults 1,2,4,5,7. For teenagers, on the contrary, we found a decrease in perceived stress during the COVID-19 pandemic lockdown. This decrease appears to be essentially explained by the fact that teenagers were less exposed to school pressures during this period through home-based learning. School, with teachers and pears pressure, marks or bullying, has been shown to be a stressful environment for teenagers (39, 40). This decrease was greater for girls than for boys, although they maintained higher levels of stress than boys. Girls tend to feel more affected and stressed by the school setting (40–43) and by teacher pressure (44) than boys. The fact that they are more stressed by the school setting explains why being removed from it had a greater impact on their stress level than on that of the boys. Finally, we found that 10.80% of the observed variance in stress could be explained by perceived social support. Consistent with the literature, those who perceived the least social support (7, 45, 46) had the highest levels of stress.

On the other hand, more than 30% of the differences in stress was also due to the coping strategies used by the teenagers. We noted that the use of acceptance and positive reframing strategies was favored, as classically observed during the first half of adolescence (22). We also found a gender difference, with greater use of instrumental support, emotional support and self-blame in girls than in boys (23). In addition, our participants altered their use of certain strategies to cope with lockdown (17–21). They increased their use of planning, behavioral disengagement, self-distraction, positive reframing, acceptance, and religion strategies during lockdown compared to usual, and decreased their use of active coping and self-blame. Finally, active coping and acceptance did explain a decrease in usual stress in our study, as noted in the literature in adults (23). However, during the lockdown situation, only acceptance explained the decrease in stress. In summary, during lockdown, a modification of the strategies mobilized could be observed. Acceptance was the most often used strategy and was a source of stress reduction. These findings could therefore also explain part of the decrease in stress observed in the teenagers during this period.

Among the coping strategies, substance use was estimated to be the least often used by teenagers, and we found no change in its use during lockdown. However, our results showed a decrease in recent tobacco, alcohol and cannabis use during lockdown, whereas at this age, use increases (31). We can hypothesize that during lockdown, teenagers remained in contact with their parents, who are generally considered a protective factor against substance use (33). By contrast, they had little exposure to the influence of their peers, with whom use at this age takes place (29), together with the first experimentation (35). We consider that this change in exposure to parents and peers would explain this decrease.

We identified several limitations to our study. First of all, the use of an online questionnaire, with self-reported measures, didn't let us control the conditions under which the questionnaire was administered, nor the influence of parents on the answers given. We cannot ensure that the questionnaire was administered in a calm environment, without distraction, and that the teenagers' attention was focused on it. In addition, single-item measures we used for stress level or social support, perceived less precision than a validated multi-item scale. Concerning changes in the use of coping strategies, although significant increases and decreases were observed, it should be noted that the effects size are small. Moreover, it is important to note the low reliability of the items measuring the strategies of active coping, venting, denial, self-distraction and behavioral disengagement. Another limitation is that our sample was located in the Auvergne-Rhône-Alpes region, which has a low urban density. This means that our sample had more access to the outdoors and the countryside, which are a source of more well-being (47, 48). Thus, our results could only be generalized to adolescents who spent the confinement in rural areas. A final important consideration is participation in the prevention program, which is a significant confounding variable. The program is based on the acquisition of psychosocial skills. These skills allow to acquire the necessary competencies to face situations. It is therefore also possible that some of the observed results may be due to participation in this program.

To conclude, the shift in the use of coping strategies enabled teenagers to be less stressed and decreased their substance use during the lockdown situation. However, this decrease in stress, also due to removal from the stressful environment of school, made it a source of distress for adolescents to return to school (49, 50). We think that extending the implementation of school-based prevention program based on the development of psychosocial skills could help adolescents to face the return to school.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding authors.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by ANSM Registration Number: 2019-A03131-56. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

FM, GB, and FT contributed to conception and design of the study. CB organized the database, performed the statistical

analysis, and wrote the first draft of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2021.790704/full#supplementary-material

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Changes in Loss Sensitivity During Treatment in Concurrent Disorders Inpatients: A Computational Model Approach to Assessing Risky Decision-Making

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Background: Recent studies have employed computational modeling to characterize deficits in aspects of decision-making not otherwise detected using traditional behavioral task outcomes. While prospect utility-based modeling has shown to differentiate decision-making patterns between users of different drugs, its relevance in the context of treatment has yet to be examined. This study investigated model-based decision-making as it relates to treatment outcome in inpatients with co-occurring mental health and substance use disorders.

Methods: 50 patients (*M*age = 38.5, *SD* = 11.4; 16F) completed the Cambridge Gambling Task (CGT) within 2 weeks of admission (baseline) and 6 months into treatment (follow-up), and 50 controls (*M*age = 31.9, *SD* = 10.0; 25F) completed CGT under a single outpatient session. We evaluated 4 traditional CGT outputs and 5 decisional processes derived from the Cumulative Model. Psychiatric diagnoses and discharge data were retrieved from patient health records.

Results: Groups were similar in age, sex, and premorbid IQ. Differences in years of education were included as covariates across all group comparisons. All patients had ≥1 mental health diagnosis, with 80% having >1 substance use disorder. On the CGT, patients showed greater Deliberation Time and Delay Aversion than controls. Estimated model parameters revealed higher Delayed Reward Discounting, and lower Probability Distortion and Loss Sensitivity in patients relative to controls. From baseline to follow-up, patients ($n = 24$) showed a decrease in model-derived Loss Sensitivity and Color Choice Bias. Lastly, poorer Quality of Decision-Making and Choice Consistency, and greater Color Choice Bias independently predicted higher likelihood of treatment dropout, while none were significant in relation to treatment length of stay.

Conclusion: This is the first study to assess a computational model of decision-making in the context of treatment for concurrent disorders. Patients were more impulsive and slower to deliberate choice than controls. While both traditional and computational outcomes predicted treatment adherence in patients, findings suggest

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computational methods are able to capture treatment-sensitive aspects of decision-making not accessible via traditional methods. Further research is needed to confirm findings as well as investigate the relationship between model-based decision-making and post-treatment outcomes.

Keywords: impulsivity, decision-making, drug use, mental health, concurrent disorders, treatment outcome

INTRODUCTION

Psychiatric comorbidities are prevalent among substance users (1, 2), and their co-occurrence (or concurrent disorders) contribute substantially to the global disease burden (3). Individuals with concurrent disorders pose greater challenges to public healthcare systems than any psychiatric disorder alone, such as with more emergency service utilization and higher rates of psychiatric hospitalization (4). Moreover, treatment services are often ill-equipped to effectively manage the issues of mental health and substance use concurrently (1, 5, 6), and this could in part be attributed to the relatively few data representative of concurrent disorders patients as a coherent group in treatment (5). Research has historically focused on individual psychiatric disorders studied separately from one another (7), and drug use has frequently been treated as a criterion for participant exclusion from clinical study (5, 8). Given the heterogeneity of clinical characteristics with concurrent disorders that can vary vastly from persons to persons (9), multidisciplinary approaches aimed at addressing common underlying issues in the treatment are needed (10). While mental healthcare settings are increasingly adopting integrated care and showing it benefits to improved outcomes (11, 12), limited evidence supports the clinical management guidelines that have been mostly derived through studies of individual psychiatric disorders (5, 12). Thus, research representative of concurrent disorders patients, collectively as a single clinical group, are needed to better inform the development of interventions for broader spectrum problems and risks underlying poor treatment outcomes.

Suboptimal decision-making under conditions of risk or uncertainty [or risky decision-making; (13)] has been reported in individuals with schizophrenia (14), bipolar disorder (15), depression (16), anxiety (17), and various substances of use (18). Decision-making is often assessed using task-based measures of impulsivity. High levels of impulsivity and risk-taking are implicated in the development, maintenance, and severity of substance dependence (19, 20) and mental health disorders (21) and are associated with negative treatment outcomes, including poorer treatment adherence, higher rates of rehospitalization, morbidity, and mortality (22). Where problems in decision-making have been implicated in mental health disorders (23–25) and substance use disorders (19), impulsivity and risk-taking are also key risks where both psychiatric disorders co-occur (26–29). Recent evidence suggests individuals with co-occurring mental health and substance use disorders exhibit greater impulsivity than those with a single disorder (30). Studies have employed behavioral models, such as the Cambridge Gambling Task [CGT; (31)], to examine decision-making involving risk and reward. While robust evidence shows that deficits in CGT performance (19, 32, 33) predict adverse drug use outcomes (e.g., quality of decision-making, risk-taking), no studies to date have investigated its relevance in the context of treatment for concurrent disorders.

Recent advances with computational modeling have yielded techniques that can assess more nuanced aspects of decision-making that traditional outcomes have not been sensitive or capable of capturing (34). These model-based analyses can characterize subtle variation in cognitive processes underlying risk behavior, amending a significant limitation of traditional approaches in identifying underlying sources of behavioral task deficits (34). By more directly assessing cognitive processes underlying choice behavior, as opposed to overt task performance as a proxy for cognitive functioning, modeling may reduce interpretative bias and increase reproducibility of behavioral data, systematizing our understanding of cognition that underlies decision-making (35, 36). Moreover, the advantages to model-based approaches include their potential to detect aspects of cognition relevant to psychiatric diagnoses (37, 38). For example, the Prospect-Utility function has been applied to generate quantifiable parameters reflecting cognitive-motivational processes (e.g., reward valuation), based on an individual's choice patterns. Studies utilizing this approach with substance-using [e.g., (39, 40)], and other psychiatric populations (41) have identified distinct cognitive impairments underpinning choice behavior, as compared to controls (39) and between users of different drugs (42). While these computational methods show advantages over traditional methods in identifying specific cognitive indices of decision-making, they have yet to be studied in concurrent disorders and the clinical relevance of these computational data have yet to be explored (34, 37).

This study investigated risky decision-making in patients with concurrent disorders and assessed the utility of decision-making outcomes derived from computational modeling in predicting treatment outcomes. First, we hypothesized that patients would show worse decision-making performance than controls. Second, in patients, decision-making would predict treatment outcome. Third, the patterns of relationship between treatment outcome and decision-making would differ between indices of task performance collected through traditional techniques vs. those derived from computational modeling.

METHODS

Participants

An initial 56 inpatient and 50 control males and females were recruited for a broader study investigating cognitive functioning and stress. Data from this broader study were not reported here,

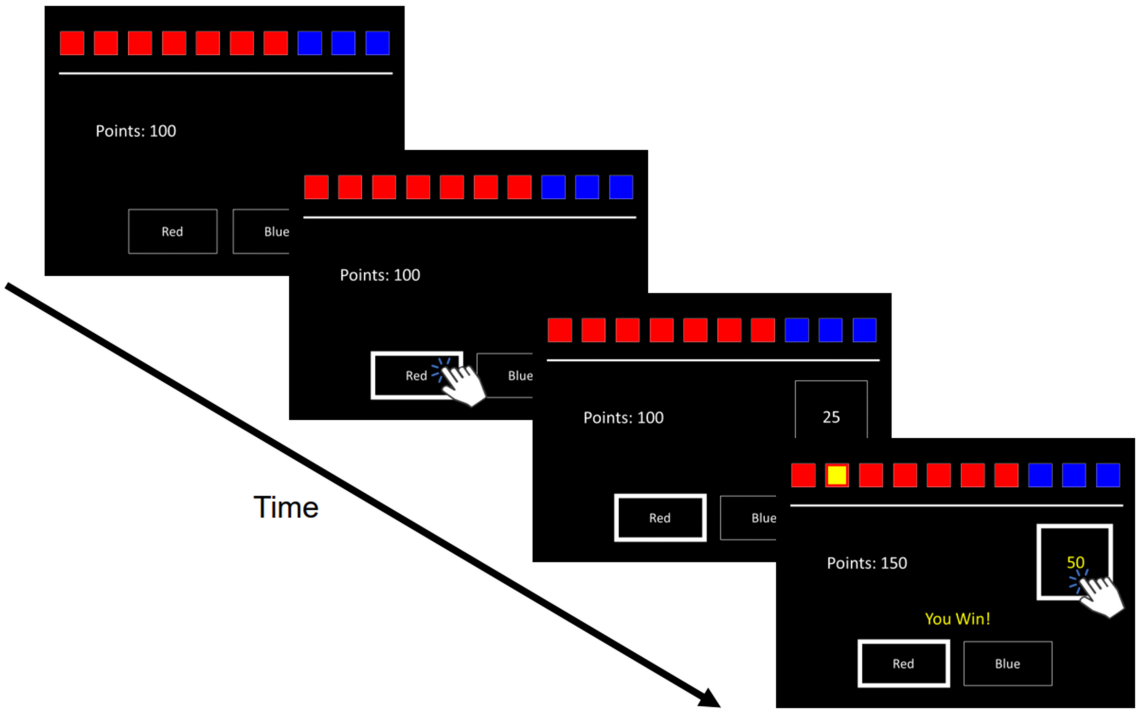

FIGURE 1 | Trial Schematic of the Cambridge Gambling Task. Ten boxes are displayed varying in proportions of red to blue. Respondents guess which color hides a yellow token. Participants are then prompted to select a bet, with bet amounts appearing in either ascending or descending order. If respondents guess correctly or incorrectly, the selected bet amount is either added or subtracted to their total points.

given they addressed a separate set of hypotheses. Participants had to be 19 years or older and fluent in English. They were excluded if they self-reported a history of neurologic disorder, or if they had uncorrected visual or auditory deficits.

Patients were recruited from the Burnaby Centre for Mental Health and Addictions, a 100-bed tertiary care facility. As required for treatment admission, all patients had to have co-occurring mental health and substance use disorders confirmed at intake by a licensed medical or mental health professional. Standard care included medications, individual and group psychotherapy (emphasizing harm reduction leading to abstinence), stepped care, and case management for up to 9 months [see (43)]. All patient participants were cleared by the unit psychiatrist, where patients had to be stable on medications and not exhibiting signs of withdrawal. Psychiatric diagnoses and discharge information (treatment length of stay, and reasons for discharge) were retrieved from patient medical records and reviewed by a PhD clinician.

Controls were volunteers recruited via community flyers and online advertisements. Self-reports and structured interviews probing medical history, mental health status, and drug use were administered by trained research staff. Controls could not have any current or chronic mental health disorder and/or a current or past substance use disorder.

Informed consent was obtained in accordance with procedures approved by the University of British Columbia Behavioral Research Ethics Board.

Experimental Protocol

All eligible patients were invited to undergo two separate testing sessions, within the first two weeks of admission (baseline) and again 6 months into treatment (follow-up). Controls completed the same baseline assessments in a single outpatient session hosted at the university. Demographics, drug use [Addiction Severity Index–Lite, D1-D13; (44)], and premorbid IQ [NART; (45)] were assessed at baseline. At each session, participants were administered the Cambridge Gambling Task (CGT) followed by a package of self-report questionnaires. These self-reports were administered as part of the broader investigation and are not discussed here. Upon completion of each visit, patients were compensated a $10 Starbucks gift card and controls received $10 cash.

Measures

Cambridge Gambling Task

The CGT is a standardized cognitive test used to assess decisions made under risk. On the screen are 10 boxes colored either red or blue (**Figure 1**). The ratio of red-to-blue boxes varied across trials. On each trial, participants had to guess whether a yellow token was hidden behind a red or blue box. With an initial endowment of 100 points, participants wagered points fixed to 5, 25, 50, 75, or 95% of their total standing points on having made the correct guess (blue or red box). Two within-subject task conditions presented betting options in either ascending (5, 25...95%) or descending (95,

75...5%) order. Because betting options were displayed one at a time with brief inter-interval delays, participants had to wait for their desired percentage bet to appear to place their bet. Instructions were to accumulate as many points as possible. Four traditional CGT outcomes were assessed: Quality of Decision-Making (QDM) is the proportion of trials participants chose the more likely color; Deliberation Time (DT) reflected the mean latency from the presentation of colored boxes to participants making a bet choice; Delay Aversion (DA) measures the difference in betting ratios across ascending and descending conditions, where large differences would indicate more impulsive betting; and, Risk-Taking (RT) reflected the mean proportion of accumulated points participants wagered on trials they chose the more likely color (i.e., the color with the highest proportion of boxes).

Computational Model

Computational modeling of trial-by-trial choice data followed Romeu et al. "Cumulative Model" [CM; (46)] and was executed in R using the hBayesDM package (47). Compared to other models, the CM has been shown to produce the best fit for the data and yield high predictive and convergent validity with standard CGT outcomes (46). While a brief overview of the CM is provided, we refer to Romeu et al. (46) for comprehensive mathematical specifications.

The CM assumes each box color and bet option has an expected utility (EU; or a "perceived advantage") relative to all other options. The probability that a particular option will be chosen is derived from its EU; hence, the CM constructs per-trial probability estimates for all possible color and bet options. For instance, an option with the highest EU is one which is perceived to provide the largest reward and lowest risk of loss; thus, the CM would assign this option with the highest probability of being chosen.

The CM generates parameter estimates from choice data to capture four latent aspects of decision-making: Probability Distortion (α), Loss Sensitivity (ρ), Delayed Reward Discounting (β), and Choice Consistency (γ). Estimates for all parameters are computed per participant/group. To control for individual preference for red or blue boxes, Color Choice Bias ($0 \leq c \leq 1$) is included as an additional fifth parameter, with values closer to 1 indicating red bias and values closer to 0 indicating blue bias.

Probability Distortion ($0 \leq \alpha \leq 5$) is posited as the underlying mechanism driving Quality of Decision-Making. It describes the frequency at which individual's color choice aligns with the proportion of red-to-blue boxes displayed ("objective odds"). Objective probability weighting is captured by $\alpha = 1$, with higher α values indicating more optimal choices.

Loss Sensitivity ($0 \leq \rho \leq +\infty$) captures individual variation in sensitivity to loss vs. gain. A $\rho < 1$ suggests decreased Loss Sensitivity (greater Risk-Taking), $\rho > 1$ suggests increased Loss Sensitivity (greater Loss Aversion), and $\rho = 1$ suggests there is no difference in sensitivity to loss vs. gain. Delayed Reward Discounting (where $0 \leq \beta \leq +\infty$), is the propensity for individuals to perceive rewards as less valuable the longer it takes to receive them. The CM assumes that the EU of a given bet option diminishes linearly with the passage of time, and β is the slope of this decline. Higher values for β suggests greater impulsivity and more rapid discounting over time (i.e., steeper slope). Choice Consistency ($0 \leq \gamma \leq +\infty$) reflects the degree of randomness present in an individual's choices as compared to the model's predictions, where larger values indicate greater consistency and predictability of choice patterns.

Statistical Analyses

Due to incomplete data and data loss, 4 controls did not have baseline computational outcomes, 2 patients were missing computational data for follow-up, and 1 was missing traditional data for follow-up. From the initial sample, data from 50 patients and 50 controls were included for final analyses.

Because the Hierarchical Bayesian Analysis (HBA) is not well adapted for within-group comparisons (48–50), a frequentist approach was employed for primary within- and between-group analyses. We report HBA posterior estimates of group-level means and difference distributions in our **Supplementary Materials**.

Demographics were compared between patients and controls using Chi-square and independent samples *t*-tests. All subsequent analyses controlled for demographics where group differences were indicated. Because outputs derived from the CM are assumed to be not normally distributed (46), rank analysis of covariance [ANCOVA; (51)] was used to identify group effects on CGT outcomes [e.g., (52)]. In patients, related-samples Wilcoxon Signed Rank test was performed on non-normal CGT outcomes data to test within-subject changes from baseline to 6-month follow-up. For treatment outcomes, discharge status was coded as a binary outcome variable (discharge against medical advice vs. planned treatment termination/completion). Logistic regressions were conducted on discharge status and linear regressions were performed on treatment length of stay, both with CGT outcomes as predictor variables.

To probe for potential sampling bias, Mann-Whitney U tests were performed to assess differences in baseline CGT outcomes between patients who did vs. did not complete the follow-up session. Moreover, Spearman's Rank order correlations were used to test potential influence of psychiatric diagnoses (mental health disorders, substance use disorders) on obtained results. Significant correlations were followed up with rank repeated-measures ANCOVA to reassess outcomes with diagnosis included as a covariate (53). Original results (without diagnosis) were reported if there were no differences in outcome between controlling vs. not controlling for diagnoses.

For parametric tests (regressions), isolated univariate outliers with z-scores > 3.29 were truncated to one increment higher or lower than the closest non-outlier value within that group (54). We reported results from original data if there were no difference in outcome from truncated data. Data for non-parametric tests were not treated for potential outliers, given rank-based tests are robust to outliers. All analyses were computed using SPSS version 27.0 (IBM, Armonk, NY).

TABLE 1 | Demographic characteristics.

	Patients	Controls
N	50 (16*F*)	50 (25*F*)
Age	38.5 ± 11.4	31.9 ± 10.0
Education (years)	10.8 ± 2.8*	16.5 ± 2.9
Estimated premorbid IQ	103.2 ± 7.3	107.8 ± 9.5
Race/Ethnicity	***N* (%)**	***N* (%)**
White	35 (70)	20 (40)
Indigenous	10 (20)	1 (2)
Black	1 (2)	1 (2)
Asian	1 (2)	25 (50)
Latinx	1 (2)	2 (4)

*Data presented as means ± SD, except where otherwise specified. *p < 0.05.*

TABLE 2 | Patient diagnoses.

	Patients *N* (%)
N	50
Substance use disorders	
>1 disorder	40 (80)
Alcohol only	5 (10)
Methamphetamine only	1 (2)
Subthreshold	4 (8)
Mental health disorders	
Psychotic disorders	23 (46)
Schizophrenia/schizoaffective/unspecified	12/3/8
Mood disorders	23 (46)
Bipolar/depressive/unspecified	8/8/7
Anxiety disorders	13 (26)
Social/generalized/unspecified	5/2/1
PTSD	5 (10)
ADHD	4 (8)

ADHD, attention-deficit/hyperactivity disorder; PTSD, posttraumatic stress disorder.

TABLE 3 | Substance use in patients.

Patient		Patient *(cont'd)*	
Polydrug		**Methamphetamine**	
Lifetime any use (*n*)	42	Lifetime any use (*n*)	28
age onset[a,b]	16.0 ± 5.7	age onset[a,b]	24.0 ± 10.6
years used[b]	15.8 ± 12.1	years used[b]	7.4 ± 7.3
Past 30-day user (*n*)	31	Past 30-day user (*n*)	10
days used[c]	14.8 ± 11.4	days used[c]	12.9 ± 9.7
Alcohol		**Heroin**	
Lifetime any use (*n*)	44	Lifetime any use (*n*)	30
age onset[a,b]	11.9 ± 3.5	age onset[a,b]	27.0 ± 10.0
years used[b]	19.8 ± 12.8	years used[b]	7.5 ± 10.5
Past 30-day user (*n*)	27 (57.0)	Past 30-day user (n)	11
days used[c]	19.8 ± 12.8	days used[c]	8.3 ± 9.7
Cigarettes		**Other opioids**	
Lifetime any use (*n*)	36	Lifetime any use (*n*)	22
age onset[a,b]	14.1 ± 6.4	age onset[a,b]	23.1 ± 9.6
years used[b]	22.9 ± 11.8	years used[b]	8.7 ± 11.0
Past 30-day user (n)	23	Past 30-day user (n)	12
less than 10/day[d]	65%	days used[c]	14.0 ± 12.8
11-20/day[d]	22%	**Sedatives/tranquilizers**	
21+/day[d]	13%	Lifetime any use (*n*)	21
Cannabis		age onset[a,b]	19.4 ± 5.7
Lifetime any use (*n*)	43	years used[b]	7.7 ± 7.5
age onset[a,b]	13.2 ± 3.0	Past 30-day user (*n*)	12
years used[b]	18.0 ± 13.7	days used[c]	19.5 ± 10.2
Past 30-day user (*n*)	25		
days used[c]	14.7 ± 11.3		
Cocaine			
Lifetime intranasal/ smoked/both (*n*)	3/10/30		
age onset[a,b]	21.6 ± 7.7		
years used[b]	11.5 ± 10.0		
Past 30-day user (*n*)	23		
days used[c]	12.7 ± 10.7		

Data presented are means ± SD, except otherwise specified. Number of days used in past 30 days underestimate average use per month due to overlap with days in treatment. [a]Polydrug: n = 31, alcohol: n = 38, cigarettes: n = 35, cannabis: n = 35, cocaine n = 34, methamphetamine: n = 28, heroin: n = 23; sedatives/tranquilizers: n = 14, due to missing data. [b]Data from patients who reported lifetime ≥1x use of the substance. [c]Data from patients who reported past 30 days ≥1x use of the substance. [d]Data based on responses on Fagerstrom Test for Nicotine Dependence [n = 23; (55)].

RESULTS

Participants

Demographic characteristics are depicted on **Table 1**. Patients had fewer years of education whereas similar estimated premorbid IQ and age relative to controls. Because of group differences on education, years of education was included as a covariate for all subsequent group comparisons. There were no differences by age or group composition of males vs. females.

In patients, rate of disorders by diagnostic categories were 46% psychotic, 46% mood, 26% anxiety and stress-related, and 8% attention-deficit/hyperactivity disorder (**Table 2**), and 80% of all patients had >1 substance use disorder. Self-reported lifetime illicit drug use of highest prevalence in patients were cocaine (60%), heroin (60%), and methamphetamine (56%), with use averaging 11.5, 7.5, and 7.4 years, respectively (**Table 3**). The three most common drugs recently used were cocaine (46%), opioids (24%), and sedatives/tranquilizers (24%). In controls, 2% reported cocaine, 2% polydrug, and 4% non-prescription amphetamine use in the past 30-days.

Group Differences on CGT Measures

On traditional CGT outcomes, patients exhibited higher Delay Aversion ($F_{(1,98)} = 12.96$, $p = 0.017$) and Deliberation Time ($F_{(1,98)} = 22.01$, $p = 0.012$) than controls (**Figure 2**). There were no group differences on Risk Taking or Quality of Decision-Making. For CGT model-based outcomes, patients exhibited

lower Probability Distortion ($F_{(1,94)} = 20.54$, $p = 0.025$), lower Loss Sensitivity ($F_{(1,94)} = 29.43$, $p = 0.007$), and higher Delayed Reward Discounting ($F_{(1,94)} = 22.55$, $p = 0.013$) relative to controls (**Figure 2**), with no group differences for Choice Consistency (γ) or Color Choice Bias (c).

In patients ($n = 24$), there was a decrease in Loss Sensitivity ($d = 0.36$, $p = 0.039$) and Color Choice Bias ($d = 0.01$, $p = 0.003$) from baseline to 6-month follow-up (**Figure 3**). No other changes in CGT outcomes across time were statistically significant. Comparisons between patient follow-up completers and non-completers revealed higher baseline Delayed Reward Discounting in non-completers (Mann-Whitney Uc = 200.0; $p = 0.031$), with no other differences in baseline CGT outcomes. There were no significant correlations between psychiatric diagnoses and CGT outcomes on CGT differences scores (follow-up minus baseline) to warrant follow-up with diagnoses included as a covariate in the statistical model.

CGT Performance and Treatment Outcome in Patients

There was a significant relationship between baseline CGT performance and treatment outcome, such that higher Quality of Decision-Making (OR = 168.17, $p = 0.032$) and Choice Consistency (OR = 1.08, $p = 0.045$) and lower Color Choice Bias (or greater blue bias; OR = 0.00, $p = 0.027$) predicted greater likelihood of adherence to treatment (**Table 4**). No other traditional or computational CGT outcomes were associated with reason for discharge, and there was no relationship between CGT outcomes and treatment length of stay.

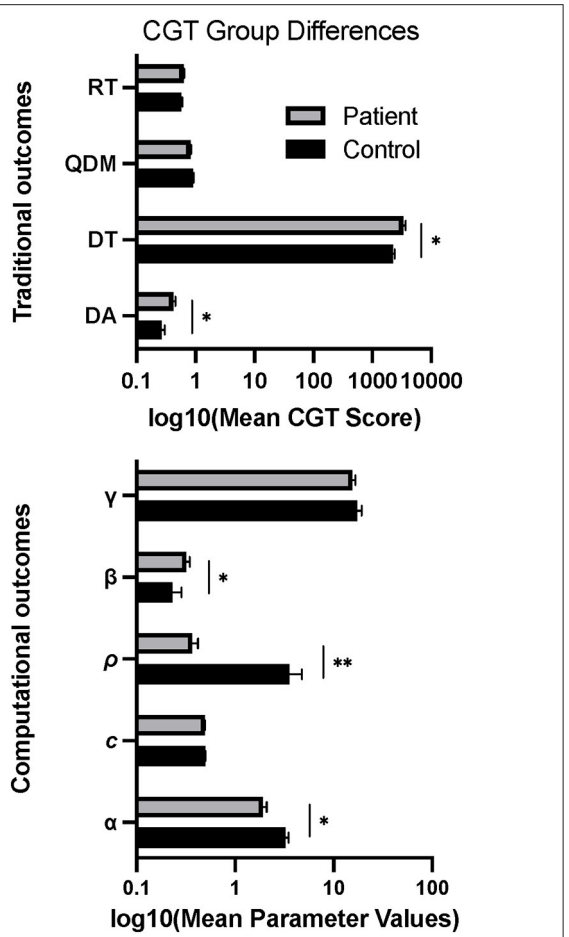

FIGURE 2 | Group differences in mean scores on behavioral and computational CGT measures. Error bars show standard error. *$p < 0.05$, **$p < 0.01$.

DISCUSSION

Our study extends findings of computational modeling of decision-making under risk to concurrent disorder in-patients and is the first to characterize the relationship between treatment outcome and decisional processes in this population. On traditional CGT measures, patients had longer deliberation times and greater delay aversion at baseline than controls. With model-based CGT outcomes, patients showed lower loss sensitivity and probability distortion, and higher delayed reward discounting relative to controls. In patients, while aspects of decision-making elucidated using model parameters showed decreases in (red) color choice bias and loss sensitivity from baseline to 6 months into treatment, no changes were indicated for measurements of traditional indices of CGT performance. Moreover, some behavioral aspects of decision-making, as assessed via both traditional and computational methods, were found to predict treatment outcome. Higher choice consistency and quality of decision-making, and lower (red) color choice bias at baseline was associated with greater likelihood of treatment adherence, with no observed relationship between decision-making and treatment length of stay.

In line with prior research, patients performed worse on CGT task outcomes, as measured by traditional and computational methods, with the model-based approach revealing group-differences undetected by traditional measures of behavioral performance. Data showing greater baseline deliberation time and delay aversion in patients are consistent with previous reports of psychomotor slowing and slower choice processing (56, 57), and aversion to delays (58) among patients with substance use disorders. Moreover, between-group patterns for model parameters were consistent with those reported in Romeu et al. (46), with substance use disorder patients exhibiting similarly low loss sensitivity and probability distortion, and high delayed reward discounting estimates relative to healthy controls.

Lower loss sensitivity, as conceptualized by Romeu et al. (46), is indicative of riskier behavior. However, decrease in loss sensitivity as it relates to treatment in our study is not well understood. Further research is needed to elucidate the functional and clinical significance of cognitive processes that are malleable with treatment, including their relation to post-treatment outcomes (e.g., mortality, relapse, symptom reduction, drug use). Nonetheless, these findings demonstrate the clinical relevance of this aspect of decision-making and support further investigation of decisional processes as they relate to post-treatment outcomes.

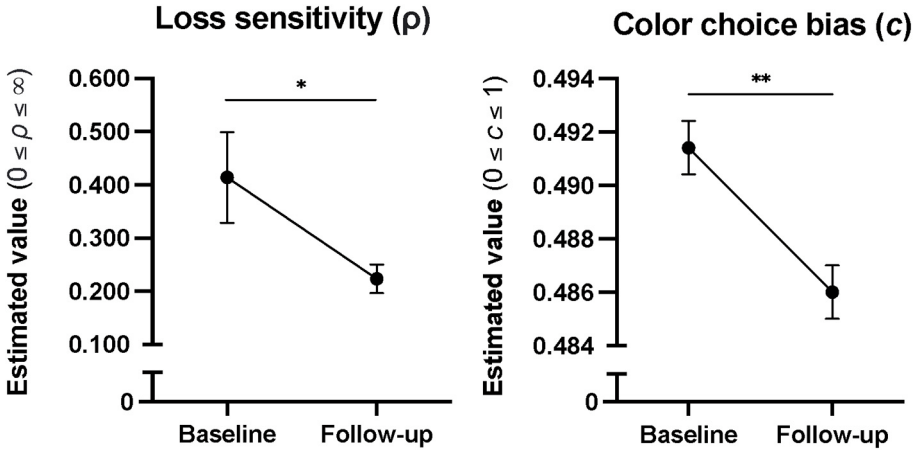

FIGURE 3 | Cumulative model parameter estimates in patients from baseline to 6 months into treatment, showing decreases in Color Choice Bias and Loss Sensitivity over time. Error bars represent standard error. *$p < 0.05$, and **$p < 0.01$.

Comparisons between patients who completed follow-up vs. those who did not complete follow-up revealed greater baseline delayed reward discounting among non-completers, with no other differences. Delayed reward discounting is a well-established risk for poor treatment outcomes among substance users, including treatment adherence [for review, see (59)]. Hence, non-completers may have been more likely to have prematurely terminated their treatment, however, our examination of the patient data did not reveal this to be the case. Given there were no other differences between patient completers and non-completers, results for decreased loss sensitivity and color choice bias across time in treatment were unlikely to have been influenced by sample bias.

Lower quality of decision-making and choice consistency, and higher values for color choice bias at baseline were identified as predictors for greater likelihood of unplanned treatment termination (against medical advice). These findings are consistent with prior research reporting the negative influence of inconsistent choice bias (60) and suboptimal quality of decision-making [i.e., rational choice passed on probability; (32)] in lowering the rate of treatment retention among substance use disorder patients. Color choice bias emerged as findings consistent with those reported in the prior study (46). Although originally formulated as a control for noise in CM, some evidence suggests a blue color choice bias may be associated with drug-related dopaminergic activity (61–63) and drug use status (63). Future investigations may further examine for a possible link between perceptual color bias and drug use, and their influence on choice patterns in mental health and substance-using populations. Likewise, the absence of change in behavioral indices of decision-making performance, specifically those that predicted poorer treatment outcomes, also highlight potential areas to examine novel targeted interventions.

While the heterogeneity of individuals and patient samples with concurrent disorders can be vast (9), computational approaches offer an opportunity to further advance our understanding of the potential common denominators (e.g., constituent processes in decision-making) leading to poor treatment outcomes in the broader clinical groups as a whole. Model-based assays for cognitive factors underpinning symptoms and disorders may yield insights into concurrent disorders and potential treatments, especially since psychopathology beyond symptom count have been understudied in this population (12).

It is increasingly clear that transdiagnostic risk factors contribute to mental disorders, be they substance induced or not. In order to better understand and treat multimorbidity such as concurrent disorders further development of computational models are needed.

This study includes notable limitations. First, attention deficit hyperactivity disorder (ADHD) was not excluded in the sample. Because individuals with ADHD receive treatment in psychiatric care settings, and they tend to have high rates

TABLE 4 | Logistic regression predicting treatment outcome (unplanned vs. planned).

						95% CI for OR	
Variable	**B**	**SE**	**Wald**	**df**	**OR**	**Lower**	**Upper**
DT	0.00	0.00	1.63	1	1.00	0.99	1.00
DA	0.28	1.34	0.04	1	1.32	0.10	18.05
QDM*	5.13	2.39	4.59	1	168.17	1.55	18295.14
RT	3.35	2.56	1.71	1	28.41	0.19	4302.72
α	0.37	0.24	2.49	1	1.45	0.91	2.30
ρ	−0.94	0.81	1.33	1	0.39	0.08	1.93
β	0.55	1.43	0.15	1	1.73	0.11	28.44
γ^*	0.08	0.04	4.00	1	1.08	1.00	1.16
c^*	−205.89	93.31	4.87	1	0.00	0.00	0.00

*α, Probability Distortion; c, Color Choice Bias; ρ, Loss Sensitivity; β, Delayed Reward Discounting, γ, Choice Consistency; CI, confidence interval; DA, Delay Aversion; DT, Deliberation Time; OR, odds ratio; RT, Risk Taking; SE, standard error; QDM, Quality of Decision-Making. *$p < 0.05$.*

of comorbidity with co-occurring mental health conditions (64), the inclusion of this disorder was consistent with the study's main objectives in assessing a representative sample of patients with concurrent disorders as a group. Second, patients had a low rate of attendance for testing at 6-month follow-up. Non-completers may have been overall more severe patients, as this was supported by worse delayed discounting at baseline relative to completers. Because we found no differential baseline performances on measures that changed during treatment, it is unlikely longitudinal findings were due to sample bias. Third, findings cannot speak to sex differences. Our sample did not comprise enough females to perform subgroup comparisons. Future assessment of sex and gender differences is warranted. Fourth, given the cross-sectional, non-experimental design, the etiology of differences in decision-making cannot be determined. However, with evidence to demonstrate alteration in aspects of decision-making in response to treatment. Regardless of causality, the clinical implications are important and need to be further explored, including broader longitudinal follow-ups investigating their relevance in relation to outcomes post-treatment (e.g., relapse, overdose, rehospitalization). Fifth, given the heterogeneity of the concurrent disorder population, factors such as psychiatric disorders and their related clinical characteristics may have driven some results more than others, including those derived through modeling. However, statistical controls for diagnoses were carefully tested to confirm this to be unlikely. Further, there is currently little evidence to suggest there are substance-specific effects on decision-making, and part of the reason is precisely because of the complication of overlapping drug use across many types of different drugs (65). Alternatively, distinguishing outcomes by diagnoses was beyond the scope of the study. Lastly, a primary limitation of computational models is that they do not have explanatory power of the cognitive phenomena underlying behavior but rather, form quantitative predictions of how behavior is generated (34, 66). More research is needed to establish generalizability of parameter interpretations and to incorporate other factors that may be of importance to choice processes, such as affective state and environmental factors (34, 67). The purpose was to study concurrent disorders patients as a single coherent group and to examine the clinical utility of computationally modeled decision-making behaviors.

Limitations notwithstanding, this is the first study to demonstrate clinical utility of decision-making in concurrent disorders populations. Our results underscore the advantages of computational models in assessing functional impairment in psychiatric disorders, as compared to traditional approaches. Findings support further investigation of model-based assessments of decision-making behaviors as they relate to mental health and substance use outcomes.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Files**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by University of British Columbia Behavioral Research Ethics Board. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

ST conducted data analyses and drafted the introduction, results, discussion, and figures. LS computed all data used in the computational analyses. LS and KT wrote the methods section, drafted the tables, and contributed to revising the overall manuscript. TC and CS supervised ST in the data analytic plan, drafting of the manuscript, and revised the manuscript for important intellectual content. All authors contributed to the article and approved the submitted version.

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Self-Medication of ADHD Symptoms: Does Caffeine Have a Role?

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Objective: Stimulants are the most effective treatment for Attention Deficit/ Hyperactivity disorder (ADHD). In addition, studies have shown that nicotine dependence in patients with ADHD is probably best explained by self-medication. The question is whether this is also true for caffeine use and caffeine dependence. The aim of our study was, therefore, to examine the relationship of ADHD symptoms, caffeine consumption, caffeine use disorder (CUD) and well-being. We hypothesized that those who have more ADHD symptoms and regularly consume caffeine have higher psychological well-being than those who have more ADHD symptoms, but do not consume caffeine.

Methods: A general population sample ($N = 2,259$, 70.5% male, mean age 34.0) filled out the 10-item Caffeine Use Disorder Questionnaire (CUDQ), the Adult ADHD Self-report Scale (ASRS) and the WHO-5 Well-Being Index (WHO-5) and were asked about their caffeine consumption habits in an online survey.

Results: There were no associations between ADHD and coffee, tea, energy drink or cola consumption or daily caffeine consumption. However, the results of the path analysis showed that the level of ADHD symptoms was positively associated with the level of CUD ($\beta = 0.350$) and negatively with the WHO-5 ($\beta = -0.259$).

Conclusions: Caffeine consumption was not associated with ADHD symptom severity and thus not likely to represent self-medication. On the contrary, caffeine use disorder severity is associated with more ADHD symptoms and both caffeine use disorder and ADHD are associated with lower well-being.

Keywords: caffeine, caffeine use disorder, ADHD, well-being, self-medication

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INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) can be characterized by a pattern of attention deficit, hyperactivity and/or impulsivity, which interferes with development or daily functioning (1). The prevalence of ADHD in the general population is worldwide about 6% in childhood/adolescence and about 2.5–7.2% in adulthood (2–5). Children and adults with ADHD have lower quality of life and lower subjective well-being compared with children and adults without ADHD (6, 7).

Stimulant medication (e.g., dextroamphetamine, methylphenidate) is an evidence based and accepted treatment option for ADHD (8, 9). Therefore, the question arises whether other–relatively mild–stimulants, such as nicotine and caffeine could also alleviate ADHD symptoms, and thus be used as some kind of self-medication (9–11). Indeed, a recent review concluded that nicotine dependence in patients with ADHD is probably best explained by self-medication (12). The question is whether this is also true for caffeine use and caffeine dependence.

The effects of caffeine on ADHD symptoms have been studied in several animal studies, comparing spontaneous hypertensive (SHR) rats with Wistar (WIS) rats (13, 14) or Wistar Kyoto (WKY) rats (15), or using 6-OHDA lesioned rats (16). According to Prediger et al. (13), 1 to 10 mg/kg pre-training administration of caffeine improved the spatial learning deficit in SHR rats, but did not alter the performance of WIS rats. Pires et al. (14) found that both long-term caffeine (3 mg/kg) and methylphenidate treatment (2 mg/kg) in prepubertal age improved the deficits in object-recognition in SHR rats (however, both treatment deteriorated object-recognition in WIS rats). In the experiment of Pandolfo et al. (15), chronic caffeine treatment (2 mg/kg) did not affect the performance of WKY rats while it improved memory deficits as well as inattention in SHR rats. Caballero et al. (16) found that long-term caffeine treatment in prepubertal age did not alter motor activity in either 6-OHDA lesioned rats or saline-treated rats, but it improved the attention deficit of the 6-OHDA lesioned rats. Overall, animal experiments suggest that certain symptoms of ADHD (spatial learning deficits, memory problems, attention deficit) are improved by caffeine, whereas caffeine has generally no effect on non-ADHD like rats.

A review of studies from the 1970–80s (17) found that only a relatively small number of studies examined the effectiveness of caffeine in the treatment of ADHD (or minimal brain dysfunction) and these studies usually had small sample sizes or weak protocols. Most of these studies have found that caffeine is less effective than methylphenidate and d-amphetamine, but it was beneficial for some participants. Stein et al. (18) conducted a meta-analysis of 21 studies examining the effects of theophylline and caffeine on children's cognition and found that both methylxanthines slightly reduced children's externalizing behavior (e.g., hyperactivity, problematic or aggressive behavior) based on parents' evaluation. Another review (19) focused especially on those studies, which examined caffeine's effects on the cognitive, psychomotor or affective functioning of children with ADHD. This review concluded that caffeine was more effective than no treatment or placebo for ADHD severity, executive functions, hyperactivity, impulsivity and aggression according to parents and teachers. However, methylphenidate and amphetamines were more effective than caffeine for these indicators. The combination of caffeine and other stimulants (if they eventuate a moderate increase in arousal) may lead to better results than the separate use of each compound (19). Although these results were applied only to children, Liu et al. (9) argue that it would be worth examining the efficacy of tea consumption for the treatment of adult ADHD because it is likely to be a suitable form of treatment for those who are difficult to involve in other medication treatments. Ioannidis, Chamberlain and Müller (20) chronologically reviewed those studies related to ADHD and caffeine and pointed out that caffeine may be mistakenly excluded from the repertoire of ADHD medications and it could be especially useful for the treatment of mild/moderate adult ADHD. According to Ross and Ross (1982, cited by (21)) the ideal therapeutic dose of caffeine would be 100–150 mg for children (which is equivalent to about 1–2 cups of coffee), but adults may need higher doses. It is also important to consider the possible consequences of long-term caffeine treatment such as tolerance (20). Drawing the right conclusions may be hampered by the methodological differences of the studies. Therefore, Grimes et al. (22) examined the methodological background of 16 experiments that focused on the effects of caffeine on ADHD and found that the experiments showed a high degree of variability in sampling, the dose of caffeine used in the experiment, the duration of treatment, the design of the experiment, and the dependent variables (e. g. physiological measures, performance tests, etc.). The possible benefits of using caffeine compared to other stimulants in the treatment of ADHD would be that it is easily available and has low addictive potential (15, 17) and its use is less stigmatized compared to other substances (20).

General caffeine consumption patterns and ADHD have been investigated in cross-sectional studies with adults (mainly students) and children. Martin et al. (23) found that in adolescents high caffeine consumption is associated with a variety of externalizing behaviors (e.g., aggressive behavior, ADHD). Caffeine consumption among smokers is associated with a higher number of ADHD symptoms, depression and anxiety among young adults (24). Kelly and Prichard (25) have studied risk behavior, sleep patterns and mental disorders among university students, comparing frequent energy drink consumers (3 or more cans/month) and frequent coffee consumers (16 or more coffee/month) with those who consume less energy drinks/coffee. They found that frequent energy drinkers reported more risk behavior (e.g., increased alcohol and drug use) and sleep problems and more often had a mental disorder (including ADHD) compared to those who consumed less energy drinks, while there were no differences between more frequent and less frequent coffee consumers. According to Walker et al. (26), adolescents with ADHD diagnosis are twice as likely to consume caffeinated drinks (coffee and/or other caffeinated drinks) than those without ADHD. Cipollone et al. (27) found similar patterns among soldiers: those with ADHD diagnosis tended to consume more caffeinated products and also had a higher prevalence of SUD than those without an ADHD diagnosis. However, not only the consumption of traditional caffeinated drinks (e. g. coffee, soft drinks, energy drinks) has been associated with ADHD. The results of Van Eck, Markle and Flory (28) suggest that ADHD symptoms also predict the consumption of caffeine-containing over-the-counter medications. Although caffeine consumption has been associated with several positive health effects (29), regular consumers can develop a problematic pattern of caffeine use. Caffeine withdrawal has been included in DSM-5, while caffeine use disorder (CUD) has been listed as a "condition for further study" (1).

In general, these results suggest that habitual caffeine consumption has a positive correlation with the presence of

ADHD symptoms/diagnosis. It is important to note that research in this field is extremely heterogeneous regarding the age of participants as well as the measurement of ADHD and caffeine consumption. The majority of studies did not separate the consumption of various caffeinated products and there were also differences in the main focus of the studies: some of them focused mainly on caffeine consumption, and ADHD was a more peripheral topic [e.g., 25], while in other studies ADHD was the main focus instead of caffeine consumption [e.g., 28]. It is also important to note that, due to its effects on different neurotransmitter systems, caffeine can have both beneficial and detrimental effects not only on ADHD, but on several other mental disorders as well, such as mood disorders, anxiety disorders and schizophrenia, and besides the possible self-medication motives, some patients may consume it to counteract the side effects of their medication (17). The frequent comorbidity of mental disorders (30, 31) also challenges a better understanding of the effects of caffeine. Although measurement tools developed to screen for adult ADHD–such as the ADHD Self-Report Scale-V1.1 (ASRS-V1.1), which was used in the current study–are reliable and have good convergent and divergent validity (32, 33), the identification of adult ADHD is not always straightforward: some symptoms may be obscured by the consequences of a chronic illness, such as substance use disorders, and some symptoms may overlap with those of affective disorders (34). Therefore, the results of studies using a cross-sectional design and screening tools to establish the presence of probable disorders should be interpreted from a transnosographic or transdiagnostic perspective.

The possibility that caffeine is used by people with ADHD– or ADHD-like symptoms–as a kind of self-medication strategy has been raised by several authors (17, 19, 20), but so far the complex relationship between ADHD symptoms, the consumption of different caffeinated beverages, caffeine use disorder (CUD), and psychological well-being has not been studied. Including CUD symptoms and psychological well-being, as variables, allows us to explore the mediating effect of caffeine consumption between ADHD symptoms and well-being: can people successfully compensate the symptoms of ADHD by using caffeine or do they rather experience the negative consequences of caffeine consumption? Therefore, we hypothesize that those who have more ADHD symptoms and regularly consume caffeine have higher psychological well-being than those who have more ADHD symptoms but do not consume caffeine.

MATERIALS AND METHODS

Sample and Procedures

A sample from the adult general population (N = 2,259) was asked about its caffeine consumption habits, ADHD symptoms and well-being in a cross-sectional online survey using convenience sampling. The questionnaire was presented on one of the biggest and most visited news website of Hungary (www.444.hu) and adults (above 18 years) who consume caffeine at least weekly were invited to participate.

The study was approved by the Research Ethics Committee of ELTE Faculty of Education and Psychology. The number of the ethical approval is 2015/254. Participants could read the informed consent after they clicked on the hyperlink of the questionnaire and they could carry on with the questionnaire only if they marked in a check box that they read the consent.

Measures

Caffeine Consumption

Participants reported the frequency and quantity of coffee, instant coffee, tea (black and green), energy drink, cola and caffeine pill consumption on an eight-point scale (0 = never, 1 = weekly or less, 2 = several times a week, 3 = one portion per day, 4 = two portions per day, 5 = three portions per day, 6 = four portions per day, 7 = five or more portions per day). Total daily caffeine consumption was computed from the daily use of different caffeinated beverages. The consumption of coffee, tea, energy drink and cola was dichotomized (consumes it daily or not). The method of calculation of caffeine content was published elsewhere (35).

Caffeine Use Disorder Symptoms

Participants filled out the 10-item Caffeine Use Disorder Questionnaire (CUDQ), which aims to assess the presence of caffeine use disorder symptoms during the last 12 months. The answers are scored on a four-point Likert scale (1 = never, 2= sometimes, 3 = often, 4 = very often), but the items were transformed into binary answers by combing the last three answering options into one "yes" answer. The discriminative value and severity of the various items of CUDQ were reported in another article (36). Internal consistency of the CUDQ total score was acceptable in the current study ($\alpha = 0.71$).

ADHD Symptoms

We used the Adult ADHD Self-Report Scale-V1.1 (ASRS-V1.1) Part A (37) for the assessment of ADHD symptoms. The questionnaire consists of six items which target certain symptoms associated with attention deficit and hyperactivity in the last 6 months. Participants could respond on a five-point Likert-scale and could receive a score of 0–4 for each item. The scale can be used as a continuous variable (Cronbach's alpha = 0.63–0.72) and people can be classified in four groups based on the total score: low negative (0–9 points), high negative (10–13 points), low positive (14–17 points) and high positive (18–24 points) (38). The low negative and high negative groups are more likely to be non-ADHD participants, while the low positive and high positive groups are considered to have ADHD, based on clinical interviews, but there are some differences between the two "negative" and two "positive" categories as well (38, 39). Participants were asked about the age of onset of the symptoms as well. The ASRS-V1.1 had acceptable internal consistency in a previous study with Hungarian adults ($\alpha = 0.72$) (40) and in the current study ($\alpha = 0.75$).

Well-Being

The five-item WHO Well-Being Index (WHO-5) was used for the evaluation of psychological well-being. The one-factor WHO-5 had excellent internal consistency in a previous study on a

representative sample in Hungary (α = 0.85) (41) and in the current study (α = 0.80).

Statistical Analysis

ADHD symptoms were used as an independent categorical variable in the Chi-square tests and ANOVAs. The ADHD categories were based on the recommendations of Kessler et al. (38) (see in the Section Measures).

The probability of the consumption of each caffeinated beverage (coffee/tea/energy drink/cola) in the four ADHD groups was compared by using Chi-square tests. We also compared the four ADHD groups regarding the magnitude of daily caffeine consumption and caffeine use disorder symptoms by using ANOVAs with Games-Howell *post hoc* tests. The bivariate associations of the variables were examined by Pearson correlations.

Two path models with observed variables were used to explore the relationship between self-reported ADHD symptoms, caffeine consumption, caffeine use disorder symptoms and psychological well-being. We used the total score on the ASRS-V1.1 as a continuous independent variable, the score on WHO-5 as a continuous dependent variable and the CUDQ total score as a continuous mediator variable in both models. We used the total daily caffeine consumption as a continuous mediator variable in the first model and coffee, tea, cola and energy drink consumption as dichotomous mediator variables (consumes it daily/does not consume it daily) in the second model. In the first model, we used the maximum likelihood estimation method (ML) because all variables were continuous. In the second path model we used probit regression with WLSMV estimation and delta parameterization because of the dichotomous mediator variables. We used the STDYX output of Mplus to determine the standardized regression coefficients (β) and the indirect effects.

Model fit was investigated by examining χ^2-test statistic, the Comparative Fit Index (CFI) (acceptable above 0.90, excellent above 0.95) (42–44), the Tucker–Lewis Index (TLI) (acceptable above 0.90, excellent above 0.95) (43–45), the Root Mean Square Error of Approximation (RMSEA) (acceptable below 0.08, excellent below 0.05) (43, 44, 46) and the 90% confidence interval of RMSEA (47).

The two path analyses were performed with MPLUS 6.0 (48) and the descriptive statistics, Cronbach's alphas, Chi-square tests, Pearson correlations and ANOVAs were performed with SPSS 22 (49).

RESULTS

Sample Characteristics

Most participants (70.5%) were male, and the mean age was 34.0 years (SD = 9.3 years). This is a generally well-educated group with 73.5% having a college degree or higher, 24.9% with a high school diploma, and only 1.6% with elementary school or vocational school as the highest educational attainment. Most of the participants were employed with 77.5% having a full-time job, 10.2% having less than full-time job and "only" 12.3% being unemployed. The sample was mainly urban with 63.1% of the participants living in Budapest, 31.1% living in other cities, and only 5.8% living in a town or village.

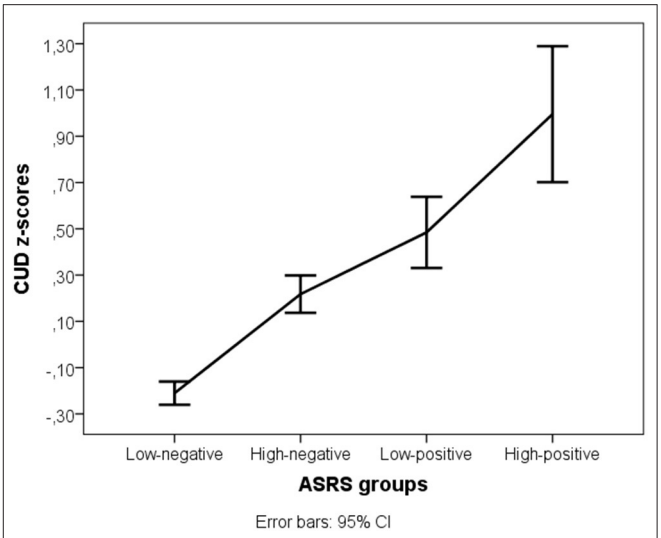

FIGURE 1 | Caffeine use disorder symptom z-scores in the four ADHD groups. ASRS, Attention-deficit/hyperactivity disorder symptoms; CUD, Caffeine Use Disorder symptoms.

Almost all participants (92.1%) were daily caffeine users. The average daily caffeine consumption was 255.40 mg (SD = 145.36) for males (which is the equivalent to about 2.5 cups of coffee) and 223.35 mg (SD = 125.61) for females (which is the equivalent to about 2.3 cups of coffee), which is higher than the average consumption: 121.70 mg/day for males (1.2 cups/day) and 123.1 mg/day for females (1.2 cups/day) in Hungary in 2009 (50). Participants reported a mean of 3.11 (SD = 2.04) CUD symptoms in the last year.

The mean score for the WHO-5 was 8.46 (SD = 2.86) and for the ASRS-V1.1. 8.21 (SD = 4.48). The average age of ADHD symptom detection was 16.8 years (SD = 10.4). Of all 2,259 participants, 59.8% (n = 1,351) belonged to the low negative category, 25.8% (n = 583) to the high negative category, 9.3% (n = 210) to the low positive category, and 2.3% (n = 52) to the high positive category (missing data: 2.8%, n = 63).

ADHD, Caffeine Consumption and CUD

There were no significant differences between the four ADHD groups in daily coffee consumption [$\chi^2_{(3)} = 0.722$, $p = 0.868$], tea consumption [$\chi^2_{(3)} = 6.674$, $p = 0.083$], cola consumption [$\chi^2_{(3)} = 1.989$, $p = 0.575$] and energy drink consumption [$\chi^2_{(3)} = 0.942$, $p = 0.815$].

Daily caffeine consumption and the CUDQ score were normally distributed, however the requirement of homogeneity of variances was fulfilled only for daily caffeine consumption [$F_{(3,2,191)} = 0.276$, $p = 0.843$] but not for CUDQ scores [$F_{(3,2,092)} = 4.765$, $p = 0.003$]. There was no difference between the four ADHD groups in daily caffeine consumption [$F_{(3)} = 0.823$, $p = 0.481$], but the groups had significantly different CUDQ scores

[Welch $F_{(3,202.001)} = 59.207$, $p < 0.001$, $r = 0.29$]. The *post-hoc* test showed that each group significantly differed from the others: the low negative ADHD group had the lowest CUDQ score compared to the other three ADHD groups ($p < 0.001$), the high negative ADHD group significantly differed from the low positive ($p = 0.014$) and high positive ADHD groups ($p < 0.001$), and the low positive ADHD group also differed from the high positive ADHD group ($p = 0.015$) (**Figure 1**).

Correlations Between ADHD Symptoms, Caffeine Consumption Variables, CUD Symptoms, and Well-Being

The correlations of the variables are presented in **Table 1**. The number of ADHD symptoms was negatively associated with well-being and positively associated with the number of CUD symptoms, while well-being had a moderate negative correlation with CUD symptoms. Neither total daily caffeine consumption, nor the daily consumption of each caffeinated beverage was associated with ADHD symptoms. Interestingly, well-being had small, negative correlations with daily cola and energy drink use and a small positive correlation with daily tea consumption.

Path Models

The first path analysis, which included ADHD symptoms, total caffeine consumption, and caffeine use disorder symptoms resulted in a saturated model. The unstandardized and standardized regression coefficients of the first path analysis are depicted on **Figure 2**. ADHD symptoms and caffeine consumption were positively associated with CUD symptoms, while ADHD symptoms and CUD symptoms were negatively associated with well-being. Caffeine consumption was neither associated with ADHD symptoms, nor with well-being directly. We found two significant indirect paths in the first path analysis: (1) *ADHD* → *CUD* → *well-being* (B = −0.027, S.E. = 0.005, $p < 0.001$, β = −0.042, S.E. = 0.008, $p < 0.001$, total indirect effect from ADHD to well-being: B = −0.026, S.E. = 0.005, $p < 0.001$, β = −0.041, S.E. = 0.008, $p < 0.001$), where more ADHD symptoms predict more CUD symptoms and more CUD symptoms predict lower well-being, and (2) *total caffeine consumption* → *CUD* → *well-being* ($B = -0.001$, S.E. = 0.000, $p < 0.001$, β = −0.026, S.E. = 0.006, $p < 0.001$), where higher total daily caffeine consumption predicts more CUD symptoms and more CUD symptoms predict lower well-being.

The second path analysis, which included ADHD symptoms, coffee, tea, cola and energy drink consumption, CUD symptoms and well-being had poor fit indices [$\chi^2 = 122.246$, df = 6, $p < 0.001$; CFI = 0.854; TLI = 0.488; RMSEA = 0.094 (CI: 0.080–0.109)]. Based on the examination of the modification indices, the covariances between the four caffeinated beverages were introduced to the model. This modified path analysis was a saturated model. The unstandardized and standardized regression coefficients of the second path analysis are depicted on **Figure 3**. Importantly, none of the caffeinated beverages was associated with ADHD symptoms and only tea consumption was associated with well-being. Coffee and energy drink consumption was associated with more CUD symptoms. For the second path analysis, we found three significant indirect paths: (1) *ADHD* → *CUD* → *well-being* ($B = -0.017$, S.E. = 0.009, $p = 0.046$, β = −0.027, total indirect effect from ADHD to well-being: $B = -0.022$, S.E. = 0.008, $p = 0.004$, β = −0.034), which also appeared in the first path model, (2) *coffee* → *CUD* → *well-being* ($B = -0.107$, S.E. = 0.054, $p = 0.048$, β = −0.037), where coffee consumption was associated with more CUD symptoms and more CUD symptoms with lower well-being, and (3) *energy drink* → *CUD* → *well-being* ($B = -0.098$, S.E. = 0.049, $p = 0.046$, β = −0.034), where energy drink consumption was associated with more CUD symptoms and more CUD symptoms predicted lower well-being.

DISCUSSION

Our analyses, which focused on the relationship of self-reported ADHD symptoms and caffeine consumption showed some unexpected results. Caffeine consumption– whether treated as a continuous or a dichotomous variable, taking into account the type of the caffeinated beverage–did not correlate with the number of ADHD symptoms and was not different in the four ADHD groups. At the same time, ADHD symptoms showed a moderate positive association with the number of caffeine use disorder symptoms in the ANOVA and in both path models. Overall, these results suggest that it is not caffeine consumption *per se*, but rather the problematic use of caffeine that is related to self-reported ADHD symptoms. Looking at the differences between the four ADHD groups, the relationship seems to be linear: an increased probability of ADHD is associated with an increased number of caffeine use disorder symptoms. Caffeine consumption did not mediate the relationship between ADHD symptoms and well-being, but caffeine use disorder symptoms were a significant mediator in both path analyses with reduced well-being in participant with more caffeine use disorder symptoms. Together, these findings suggest that the hypothesis of (successful) self-medication does not apply to ADHD symptoms and caffeine consumption, but it seems that those who have more ADHD symptoms may be more prone to develop caffeine use disorder regardless of the magnitude of caffeine consumption. This result is partly contradicting and partly in line with the findings of Cipollone et al. (27): they found that caffeine consumption among soldiers with ADHD had a low, negative correlation with some of the ADHD symptoms, indicating successful self-medication attempts. On the other hand, they found a higher prevalence of SUD among soldiers with ADHD, which means that they probably have a higher vulnerability regarding the negative consequences of the use of certain substances. In the current study, lower well-being–which is associated with ADHD symptoms–is partly explained by the appearance of caffeine use disorder symptoms. It is possible that the relationship between the two disorders–ADHD and CUD–represents a common psychopathological factor (51) based on common environmental factors or a common genetic vulnerability [e.g., (52)]. It is also worth considering the type of caffeinated beverage: according to our results, tea consumption-although it is not associated with ADHD symptoms-has a

TABLE 1 | Correlation matrix of the variables in the present study.

	ADHD	well-being	total caffeine	coffee	tea	energy drink	cola
well-being	**−0.301**						
total caffeine	0.038	**−**0.029					
coffee[a]	0.041	0.015	**0.574**				
tea[a]	**−**0.036	**0.073**	**0.104**	**−0.104**			
energy drink[a]	0.015	**−0.079**	**0.116**	**−0.113**	**−**0.005		
cola[a]	**−**0.015	**−0.049**	**0.066**	**−0.100**	**−**0.033	**−0.189**	
CUD	**0.357**	**−0.207**	**0.233**	**0.209**	**−0.63**	**0.132**	**0.045**

N = 2169–1994. Significant correlations (p < 0.05) are boldfaced. ADHD, Attention-deficit/hyperactivity disorder symptoms; CUD, Caffeine Use Disorder symptoms.
[a]Coded as: 0 = Absence of daily consumption, 1 = Presence of daily consumption.

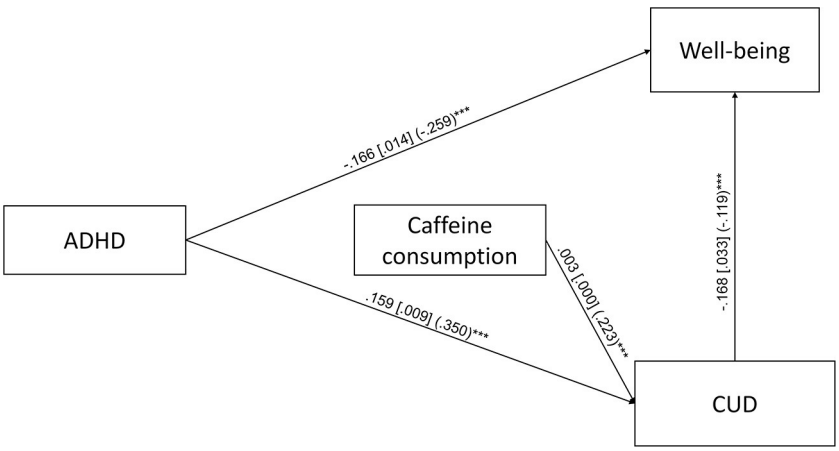

FIGURE 2 | Path analysis for the association of ADHD symptoms, caffeine consumption, caffeine use disorder symptoms (CUD) and well-being ($N = 2{,}196$). Unstandardized regression coefficients, their standard errors (in brackets) and standardized coefficients (in parentheses) are presented in the figure. Only the significant ($p < 0.05$) direct paths are presented ***$p < 0.001$.

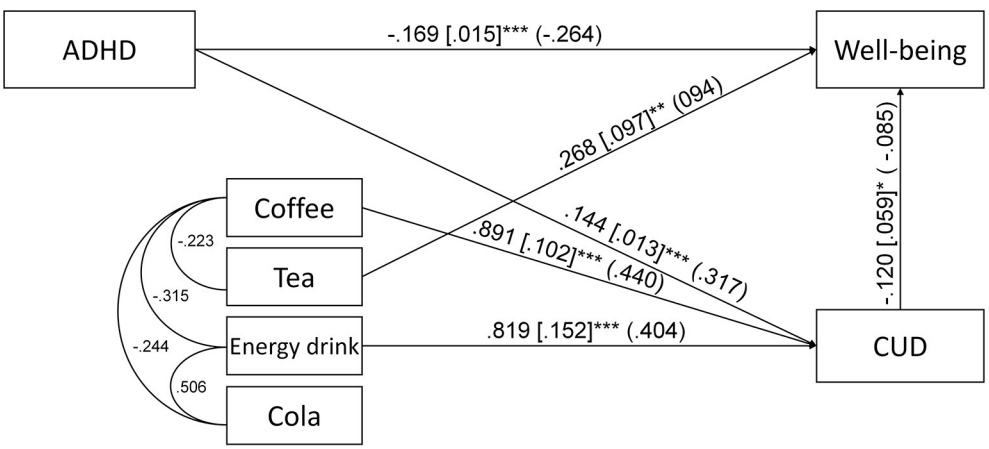

FIGURE 3 | Path analysis for the association of ADHD symptoms, coffee, tea, energy drink and cola consumption, caffeine use disorder symptoms (CUD) and well-being. Unstandardized regression coefficients, their standard errors (in brackets) and standardized coefficients (in parentheses) are presented in the figure. Only the significant ($p < 0.05$) direct paths and error covariances are presented *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

positive association with perceived psychological well-being, which may confirm the recommendation of Liu et al. (9) that tea can be an appropriate agent for the treatment of adults with ADHD. Since coffee and tea are absorbed similarly leading to similar plasma-caffeine concentrations after either tea or coffee consumption [(53), cited by (54)], the difference in their

psychological effects is probably not due to pharmacokinetics, but it rather originates from the different chemical composition or the different expectations associated with the two beverages. It is also possible that people who drink tea and those who drink coffee differ in certain physical and psychological characteristics (55, 56).

The consumption of coffee and energy drinks indirectly-through caffeine use disorder symptoms-and negatively contributed to psychological well-being. This is in line with our the previous results (36) indicating that a caffeine use disorder can indeed influence quality of life. Since lower well-being is probably influenced by factors other than ADHD and CUD as well (for example various physical illnesses, mental disorders), it is important to consider several other-potential confounding-variables in future studies.

Although we assumed certain relationships between ADHD symptoms, caffeine consumption, caffeine use disorder symptom and well-being, we could not present causal relationships because of the cross-sectional nature of the research. It is, therefore, possible that there is reverse or bidirectional causality between some of the variables. In addition, the sample was not representative of the Hungarian population: men, people with higher educational attainment and employment were overrepresented, which could affect caffeine consumption habits as well as ADHD symptoms since higher intellect can be a protective factor against the development and the negative consequences of ADHD (57). This divergence in demographics probably reflects the composition of the readership of the news website used for recruitment. Despite this distortion, we have achieved to reach a wide range of the population, as 444.hu is among the 25 most visited websites in Hungary. A further limit of the study is that we did not ask participants whether they have an ADHD diagnosis and a treatment history of ADHD, so the analysis was based only on the currently experienced ADHD symptoms. It is important to note that at least some of the symptoms should have occurred before the age of 12 for an ADHD diagnosis. However, in the current study 65.6% of the participants dated the first appearance of the ADHD symptoms at age of 13 or older, which may arise from the difficulty of recalling childhood memories, or suggest that the symptoms are not the signs of ADHD, but some other disorder (e.g., bipolar disorder, cluster B personality disorder). It is also possible, that several participants had late-onset ADHD symptoms, which may begin in adolescence or early adulthood (58) and which-according to some authors-can occur independently from childhood-onset ADHD (59). Including other relevant-potential confounding-variables, such as substance use other than caffeine, should be considered in future studies since they may affect the observed associations.

An important strength of the current study is that we included and examined ADHD symptoms, caffeine consumption, caffeine use disorder symptoms, and psychological well-being in a coherent and complex model, and also reflected on the differences between certain caffeinated products.

CONCLUSION

The study found moderate associations between ADHD symptom severity, caffeine use disorder symptoms and psychological well-being: people with more ADHD symptoms had lower well-being, and caffeine use disorder symptoms partly mediated this relationship. Although the results indicate that people with more ADHD symptoms do not consume more caffeine in any form, but they are probably more sensitive for the reinforcing effects of caffeine, which lead to more CUD symptoms. Therefore, caffeine does not seem to be a compound for successful self-medication.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Research Ethics Committee of ELTE Faculty of Education and Psychology. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

CÁ: conceptualization, investigation, data curation, formal analysis, methodology, visualization, funding acquisition, writing–original draft, and writing–review and editing. RU and ZH: formal analysis and methodology. WB: writing–review and editing. ZD: conceptualization, investigation, methodology, funding acquisition, supervision, and writing–review and editing. All authors contributed to the article and approved the submitted version.

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MINI REVIEW
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The Utility of Research Domain Criteria in Diagnosis and Management of Dual Disorders: A Mini-Review

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The Research Domain Criteria (RDoC) initiative has been considered a comprehensive alternative classification framework for understanding neuropsychiatric ailments, as opposed to the longstanding, traditional DSM framework. Where the DSM categorizes neuropsychiatric disorders as each being distinct and diagnostically defined by the presence of specified symptoms, RDoC provides a multidimensional conceptualization of psychiatric disorders with neurobiological roots. By taking a multidimensional approach, RDoC overcomes two major constraints of the DSM framework: that is, that the DSM is categorical in its approach to psychiatric disorders to the point of understating the intersectionality between concomitant disorders, and that the DSM focuses mainly on clinical features. RDoC seems to better account for the intersection between dual disorders and considers a range of factors, from the more microscopic (e.g., genetics or molecular functions) to the more macroscopic (e.g., environmental influences). The multidimensional approach of RDoC is particularly appealing in the context of dual disorders. Dual disorders refers to a concurrent psychiatric disorder with an addiction disorder. RDoC accounts for the fact that there is often overlap in symptoms across and bidirectional influence between various disorders. However, to date, there is limited research into the clinical utility of RDoC, and less so in the context of the clinical management of dual disorders. In this Mini-Review, we discuss how RDoC differs from the DSM, what outcomes have been reported in utilizing RDoC clinically, the utility of RDoC for the diagnosis, management, and monitoring of psychopathology, and the limitations of RDoC as well as avenues for future research.

Keywords: Research Domain Criteria (RDoC), concurrent disorders, substance use disorder, dual disorders, psychiatric management models

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INTRODUCTION

There are several approaches developed by various organizations to classify mental health disorders. The American Psychiatric Association published its 5th edition of the Diagnostic and Statistical Manual of Mental Disorder (DSM-5) in 2013, while the U.S. National Institute of Mental Health produced its Research Domain Criteria (RDoC) in 2009. While there are clear overlaps in the approaches taken by these organizations, there are some key distinctions that make each method more suitable for a different purpose (1). The DSM-5 is designed purely as a diagnostic tool and views disorders as distinctly separate. The classification of mental disorders into distinct categories follows the traditional clinical approach of identifying disorders as distinct categorical entities.

Its findings are primarily based on self-reported information from patients who often have varying levels of understanding regarding these phenomenology-based psychological symptoms, which could lead to contradictory diagnoses. The RDoC, however, has a very different approach, primarily focusing on linking neuroscience research findings to clinical phenomena and ultimately diagnoses. RDoc is an alternative approach to the DSM-5 series and is not intended to be a direct replacement (2). While the current RDoC framework shows noteworthy promise, there are challenges and concerns that need to be addressed to reach its potential for use in clinical settings (3).

Dual disorders, also known as concurrent disorders, are one of the most challenging psychiatric problems of our time. Most commonly, the term "dual disorders" is applied to indicate the diagnosis of a co-existing psychiatric disorder and substance use disorder (SUD). Dual disorders imply that patients have multiple needs, necessitating that multiple sectors within health care services are involved in providing care for dual disorder patients. However, many if not most patients with a dual disorder are not identified by health services and do not receive adequate treatment. In addition, these services are not sufficiently linked to one another in providing care, leading to fragmentation and lack of continuity of care. The risk exists that patients are shunted between services and that they eventually drop out of care. Research confirms this concern by explaining that dual disorder patients might not always meet the criteria for treatment within a specific service (mental health or substance use), and they might be referred back and forth between these services without a specific service taking responsibility for their care (4). Other studies add that even when dual diagnosis patients have access to treatment, this treatment might not be tailored to their specific needs. This raises concerns, as dual disorders are associated with a poor prognosis, complex needs, increased severity of symptoms, poor treatment adherence, and increased contact with the criminal justice system. The complexity and the increased prevalence of dual disorders necessitate the need for a comprehensive and standardized neurodiagnostic assessment.

Despite the application of RDoC in research and in the classification of mental health disorders, there is limited knowledge regarding its utility for SUD, and consequently dual disorders. We conducted a comprehensive review of the literature focusing on the published literature to the utility of RDoC in the management and diagnosis of dual disorders across clinical settings. This mini-review will provide a narrative summary of the literature, gaps, and the future direction for this emerging tool.

RDOC VS. DSM-5

The RDoC project was initiated in 2009 by the NIMH as a response to an increased understanding of the importance of factors that were not accounted for in existing diagnostic systems (such as neurobiological systems) in understanding psychopathology (1, 5). The main goal of this new system was to incorporate research findings from various fields to create a research system that looks at multiple levels of human functioning impacted by a given pathology instead of conducting research based on the limited symptom-based diagnoses used in the DSM-5 (6–8).

An experimental approach to the new research framework was deemed necessary, given the budding state of the science of mental disorder and the constraints of research based on current classification systems. It was apparent that if developments in basic and translational science were to be applied to the science of mental disorder, a long-term approach would be needed. Such an approach would need to examine psychopathology with reference to behavioral and brain mechanisms rather than in terms of existing disorder categories (1, 2, 8). RDoC is not intended to replace the existing diagnostic systems that guided research, but rather to supplement it and to encourage research into the wider range of mechanisms that are disrupted in mental and SUD (2, 9, 10). RDoC was developed to respond to the existing reliance on the DSM-5 and ICD diagnostic categories, with the intention of guiding research and the limitations placed on research by their structures (1). The fact that new research has failed to support existing diagnostic systems in their ability to capture the full range of factors impacting psychopathology supports the use of RDoC in tandem with the DSM-5 and ICD (1, 8, 10).

RDOC DIFFERS FROM THE DSM-5 IN A FEW IMPORTANT WAYS

First, it is based upon a fundamentally different approach to dimensionality, one more in line with DSM-5's Alternative Models for Personality Disorders than current diagnostic procedures are (1). RDoC considers six "domains" of human functioning and behavior (negative and positive valences, cognitive systems, systems for social processes, arousal/regulatory systems, and sensorimotor systems) that can be impacted by a particular condition. These six domains provide categories into which a variety of more specific factors, or "constructs," can be divided. These constructs, and the domains into which they fall, can be each analyzed across a number of specific units of analysis, such as genes, molecules, cells, circuits, physiology, behavior, and self-reports (6–8). This design encourages the analysis of different facets of pathology on multiple levels, thus allowing for a better understanding

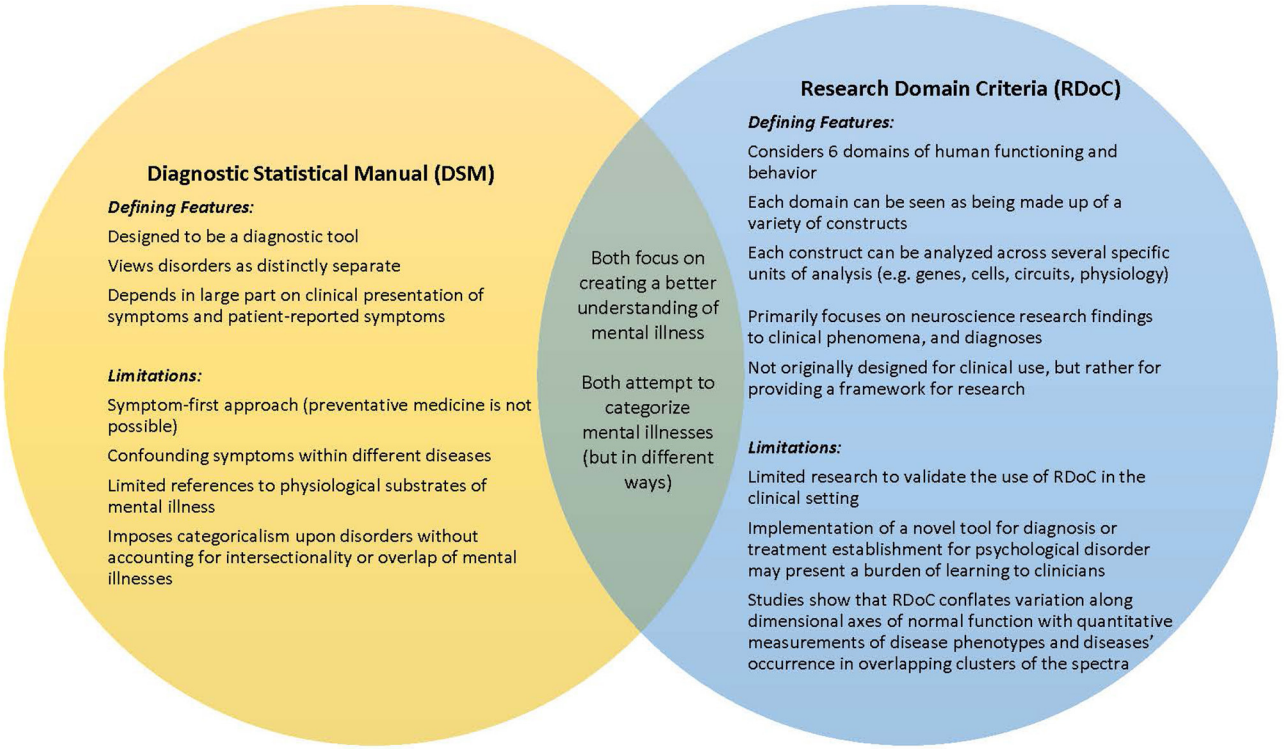

FIGURE 1 | Comparison between the diagnostic statistical manual and the research domain criteria approaches to dual disorders.

of the many factors at play which might not be considered in the DSM-5. Neurobiology, in particular, is one factor that was given limited consideration in the DSM-5, but would be analyzed in the RDoC approach (1, 2). Critically, the goal with RDoC is not to explain current syndromes in terms of these dimensions; rather, it is to characterize the negative effects that result from an abnormality in a given dimension or interacting set of dimensions (1).

Second, the RDoC project was not intended for practical clinical use in the near future. Rather, it provides a framework for research. It does not formally incorporate any current ICD or DSM disorders; in fact, it does not define mental disorder or any specific disorders at all (1, 2). It is simply a research tool to facilitate more in-depth research into psychopathology, and in doing so, it avoids taking a "symptom-first" approach to psychopathology. This allows for the possibility of it being used for preventative medicine, as opposed to the curative nature of current diagnostic systems (11).

Given those primary differences, in our review we will be taking a look at these two different systems in order to understand the utility of RDoC in the clinic setting. A summary of these differences have been provided in **Figure 1**.

CLINICAL USE OF RDOC

RDoC attempts to approach psychopathology with reference to neurobehavioral mechanisms rather than classify them into pre-existing categories. In principle, RDoC takes patients' cognitive, emotional, social, and behavioral experiences, or in other words, subjective experiences, into account as an equal counterpart to the brain or other biological processes (3, 12).

The primary argument being put forth here is that there is evidence of neurobiological factors at play for psychopathology, which suggests not only a means for increased understanding of mental illness, but also an avenue for management and monitoring of these illnesses by tracking and perhaps even directly addressing these same neurobiological parameters. There are a number of examples of psychopathologies that have been associated with specific neurobiological markers; four of these examples have been summarized in brief here.

As a first example, SUD, which are in part characterized by compulsivity and impulsivity, are linked to a reduction of arousal and termination of behaviors, cognitions, and affect, observable as a shift over time from ventral to dorsal striatum activation (6). Studies into genetic factors that may predispose individuals to SUD link impulsivity behaviors related to addiction with genes encoding cannabinoid brain receptor type 1 and mu-opioid receptor type 1, which both play a role in the corticolimbic reward pathway (6). Structural variation in large-scale brain systems related to motor inhibitory control, including the cortico-thalamic-striatal-cortical circuitry, may mediate a component of the genetic risk for compulsivity (6). Furthermore, there is compelling evidence that specific mutations in glutamatergic striatal kainate receptor genes are linked to perseverative and repetitive behaviors common to compulsivity and may well be a candidate biomarker for therapeutic monitoring (6).

Alcohol use disorder (AUD), a specific type of substance use disorder, has likewise been found to have a number of specific genetic neurobiological factors which contribute to the likelihood of its development (13). Broadly speaking, the likelihood of AUD developing seems to relate to an individual's subjective response to alcohol: a reduced response to the sedative and unpleasant effects increases risk of AUD, while, independently, a higher sensitivity to the stimulant and pleasant effects of alcohol likewise increases risk of AUD (13). How this subjective response manifests, both in pleasant and unpleasant ways, is highly multifactorial, influenced by both genetics/neurobiology and lifetime experiences (13, 14). Several genes have been found to play a role, including genes influencing alcohol metabolism, as well as opioidergic, dopaminergic, GABAergic, serotonergic, and neurosteroidergic genes (13, 15). Some specific examples include the ALDH2 gene, which plays a role in alcohol metabolism and has been linked to AUD, and similarly the ADH1B gene, which is involved again in alcohol metabolism and is associated with decreased sensitivity to the pleasant effects of alcohol (13). Some gene variants affecting alcohol dehydrogenase (a key enzyme in alcohol metabolism) lead to highly unpleasant effects from alcohol, such as flushing, headaches, tachycardia, and nausea (13). Genes affecting the $GABA_A$ receptor, as well as genetic variation in nicotinic acetylcholine receptors and polymorphism in serotonin transporter gene SLC6A4, have been associated with attenuation of the aversive/sedative subjective responses to alcohol (13, 15). A single nucleotide polymorphism (SNP) in the mu opioid receptor gene (OPRM1), specifically the Asn40Asp SNP, seems to be a key facilitator of the stimulant and pleasant subject responses to alcohol (15). Litten et al. (14) suggest that the DSM-5 be utilized to diagnose AUD, but, given the immense variability in the presentation of this disorder and our increasing understanding of the diverse neurobiological factors at play, they suggest that an Alcohol Addiction RDoC, or AARDoC, be used subsequent to diagnosis to personalize treatment to the individual.

Another example can be seen with internet gaming disorder (IGD). This condition has been associated with higher activity in the superior medial frontal gyrus, right anterior cingulate cortex (ACC), right superior and middle frontal gyrus, the left inferior parietal lobule, the left precentral gyrus, and the left precuneus and cuneus, suggesting worse response-inhibition and impaired prefrontal cortex functioning, alongside decreased activity in the bilateral middle and inferior temporal gyri, and the right superior parietal lobule, suggesting decreased visual and auditory functioning. In the context of IGD, decreased white matter density has been demonstrated in the inferior frontal gyrus, insula, amygdala, and anterior cingulate, indicating reduced capacities for decision-making, behavioral inhibition, and emotional regulation. Studies have also found increased volume in the right caudate and nucleus accumbens (pleasure centers of the human brain) and decreased resting-state functional connectivity in the prefrontal cortex (suggesting decreased cognitive control), similar to that which is seen in SUD (8). As with SUD, IGD is associated with greater impulsivity, which has been suggested to be related to abnormalities in gray matter in areas related to executive control (e.g., decreased gray matter density in dorsomedial prefrontal cortex, the orbitofrontal cortex, bilateral insula, amygdala, and fusiform) (8). These changes relate to impaired behavior inhibition, attention, and emotional regulation, which may contribute to impulse control problems (8). It was found that brain dopamine D2 (D2)/serotonin 2A (5-HT2A) receptor function and glucose metabolism is altered in those with IGD, suggesting that individuals with IGD have significantly decreased glucose metabolism in the prefrontal, temporal, and limbic systems. It has been proposed that D2/5-HT2A receptor-mediated dysregulation of the orbitofrontal cortex in particular underlies a mechanism for loss of control and compulsive behavior in individuals with IGB (8).

For a fourth example, gambling disorder (GD) has some overlap neurobiologically with IGD, including impaired activity in the prefrontal cortex leading to reduced cognitive control (10). Diminished volume in the left hippocampus and right amygdala is also associated with GD, which in turn are associated with higher scores on the behavioral inhibition system scale (i.e., decreased tendency to avoid punishment). Reduced striatal activation is seen in GD during reward anticipation and reward outcomes, thought to be correlated with lower dopamine receptor availability in the striatum. This correlates with mood-related impulsivity and behavioral disinhibition (10). Although there are overlaps between the neurobiological markers of SUD, IGD, and GD, it is notable that diffusional kurtosis imaging has found significant differences in the microstructures of the brain associated with each of these conditions (8). Notably, these conditions are commonly comorbid with mood disorders, thus becoming dual disorders. Where the DSM-5, based upon the symptoms of the patient, may miss the presence of the comorbid condition, RDoC offers a more comprehensive diagnostic and management approach across its domains and units of analysis, so that underlying factors (such as the presence of comorbid conditions) as well as symptoms are addressed.

Crucially, it has been seen in genome-wide association studies (GWAS) that psychiatric disorders are both phenotypically and genetically highly heterogeneous, not to mention polygenic and pleiotropic (16, 17). Furthermore, not only do we see that there is overlap between disorders in their symptoms, but there is also overlap in the genetic associations seen in various disorders (17). For example, in a GWAS of cannabis dependence, it was found that there was consistent overlap in genetic patterns associated with higher risk for major depressive disorder and schizophrenia; likewise, there is overlap in the genetic risk factors for obsessive compulsive disorder and schizophrenia, and overlap between genetic risk factors for generalized anxiety disorder, bipolar disorder, and schizophrenia (17). Therefore, as we continue to increase our understanding of these neurobiological markers in the above mental health disorders as well as others, the RDoC matrix and dimensions may become all the more useful in researching and, crucially, treating and monitoring not merely the symptomatic and behavioral aspects of these disorders, but the underlying neurobiological and genetic contributors, while taking into account that each psychiatric disorder may not be completely phenotypically or genetically distinct. That said, even though RDoC in theory offers a less restrictive approach and opens doors to a more well-rounded classification

system, its clinical utility requires greater research. Work is currently being done in this area; below, we discuss three specific psychopathologies that have been studied for diagnosis using RDoC.

Firstly, RDoC's clinical utility in the use of antidepressants has been studied, and is supported, but the evidence casts a question of discriminant validity between some of the constructs in the classification system. To put it more specifically, potential threat and loss are separated as two distinct constructs, but there is no evidence that they should not be combined into one (7). In the domain of cognitive systems, RDoC may provide a broader and transdiagnostic approach to understanding suicidal behavior, which may lead to better suicide prevention and treatment models (5).

As a second example, in a study examining temper loss in children, RDoc was found to perform better than DSM-5 criteria in predicting the development of mood or disruptive disorders (18). Notably, using the RDoC framework, the risk of developing a disorder was found to be significantly elevated, as much as 67%, at levels of temper loss that are considered normative by current criteria (18). These findings highlight the advantages of using a truly dimensional framework, like RDoC, as opposed to the more traditional categorical approach.

As a third example, a study identified three neurobiologically unique psychosis subtypes which do not follow traditional diagnostic boundaries (19). Even though these subtypes have unique underlying structures, there was a significant overlap in the behavioral symptoms displayed by each subtype, indicating that behavior can have multiple biological causes. In this reality, using a biologically driven nosology such as RDoC has the potential to drastically increase not only the reliability but the validity of the clinical diagnosis.

While these studies prove promising, their impact is not likely to be felt by practicing clinicians for some time. A more immediate issue of adopting a new nosology system facing clinical researchers is the compatibility between old and new diagnostic systems. If the two nosologies are too discrepant, clinicians and clinical researchers would have to learn an entirely new vocabulary to discuss cases.

Through all the domains that have been examined, there is unity in suggesting that more research is needed to increase RDoC's utility in having a more comprehensive assessment of psychopathology (5).

LIMITATIONS OF RDOC

Research indicates that the RDoC paradigm may be valuable for understanding normal human psychology with conditions interpreted as extremes of normal variation. Further, studies show that RDoC conflates variation along dimensional axes of normal function with quantitative measurements of disease phenotypes and diseases' occurrence in overlapping clusters of the spectra. This moves away from the medical model of mental illnesses. RDoC contrasts with our current classification systems, the DSM-5, which defines psychiatric disorders based on clusters of symptoms instead of constructs derived from neurobiological mechanisms. In addition, RDoC aims to eliminate the normal to abnormal dimensions of these so-called fundamental behavioral concepts, which then can overlap and interact to constitute, perhaps, new clusters of symptomatology. Cuthbert and Insel (20) pointed out that taking a dimensional approach also allows for non-linear patterns to emerge. Limitations to further study of RDoC will be to design valid measures capable of capturing the full range of these dimensions, with appropriate sensitivity to transitional junctions along these dimensions associated with impaired functioning. However, in its current form, the RDoC may be a limited theoretical model intended to provide a complete understanding of why mental illness develops, how it progresses, and how different treatments might control it. Previous studies raise the question of whether a more comprehensive version of the RDoC or a different paradigm altogether by incorporating diagnostic assessments, the DSM-5 and RDoC, will be needed to guide clinical research and clinical practice in psychiatry.

DISCUSSION/CONCLUSION

Dual disorders refers to a concurrent psychiatric disorder (e.g., depression, anxiety, schizophrenia) with an addiction disorder. RDoC allows a more intersectional approach to concurrent diagnoses, while the DSM is argued by some to be the stronger framework in a clinical setting, where the distinction between disorders enables a more clear-cut diagnosis. That said, the fact is that there is considerable overlap in symptoms across various disorders, and in the event of dual disorders, bidirectional influence between the disorders can usually be expected. Moreover, our understanding of the neurobiological markers for psychopathologies is continuing to grow, providing an opportunity for disease management that must not be neglected. In that light, a better understanding of transdiagnostic concepts is desirable. To that end, we explored through a mini-review how RDoC provides a greater multidimensional and transdiagnostic understanding of dual disorders, and how RDoC has already shown promise in clinical use. That being said, the overall utilization and study of RDoC in dual disorder is still in its early stages and more research in the field is warranted. Basic research is still needed to better understand the interconnection between the neurobiology of psychological disorders (including dual disorders) and their forms, onset, course, and sociocultural processes; this will then support ongoing research into the integration of RDoC into clinical practice. Alongside this, extensive research will be needed to establish the validity of clinical use of RDoC for each disorder. This will likely demand novel research strategies to better analyze how multiple factors simultaneously and interactively impact psychopathology (1). Ideally, future studies will not only incorporate a multidimensional view of the various factors that intersect in psychopathology, but will also take a transdiagnostic approach, taking into consideration how dual (or multiple) disorders interact, overlap, and, crucially, may be treated intersectionally.

AUTHOR CONTRIBUTIONS

BH-Z supervised the project, conducted the literature review, and drafted and edited the manuscript. AT and JM conceptualized the research topic, conducted the literature review, and drafted the manuscript. TV drafted and edited the manuscript and conducted the revisions. AS drafted the manuscript. CS supervised the project and reviewed and edited the manuscript. All authors contributed to the article and approved the submitted version.

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BDNF and Cortisol in the Diagnosis of Cocaine-Induced Depression

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Background: Major depressive disorder (MDD) and cocaine use disorder (CUD) are related with disability and high mortality rates. The assessment and treatment of psychiatric comorbidity is challenging due to its high prevalence and its clinical severity, mostly due to suicide rates and the presence of medical comorbidities. The aim of this study is to investigate differences in brain derived neurotrophic factor (BDNF) and cortisol plasmatic levels in patients diagnosed with CUD-primary-MDD and CUD-induced-MDD and also to compare them to a sample of MDD patients (without cocaine use), a sample of CUD (without MDD), and a group of healthy controls (HC) after a stress challenge.

Methods: A total of 46 subjects were included: MDD ($n = 6$), CUD ($n = 15$), CUD-primary-MDD ($n = 16$), CUD-induced-MDD ($n = 9$), and 21 HC. Psychiatric comorbidity was assessed with the Spanish version of the Psychiatric Research Interview for Substance and Mental Disorders IV (PRISM-IV), and depression severity was measured with the Hamilton Depression Rating Scale (HDRS). Patients were administered the Trier Social Stress Test (TSST) before and after the biological measures, including BDNF, and cortisol levels were obtained.

Results: After the TSST, Cohen's *d* values between CUD-primary-MDD and CUD-induced-MDD increased in each assessment from 0.19 post-TSST to 2.04 post-90-TSST. Pairwise differences among CUD-induced-MDD and both MDD and HC groups had also a large effect size value in post-30-TSST and post-90-TSST. In the case of the BDNF concentrations, CUD-primary-MDD and CUD-induced-MDD in post-90-TSST (12,627.27 ± 5488.09 vs.17,144.84 ± 6581.06, respectively) had a large effect size (0.77).

Conclusion: Results suggest a different pathogenesis for CUD-induced-MDD with higher levels of cortisol and BDNF compared with CUD-primary-MDD. Such variations should imply different approaches in treatment.

Keywords: depression, cocaine use disorder, cortisol, dual diagnosis, brain derived neurotrophic factor (BDNF)

INTRODUCTION

Mental and substance use disorders (SUD) are related with 7% of the global burden of disease as measured in disability-adjusted life years (DALYs) and increasing significant mortality rates (1). In women, DALYs are generally associated with major depression disorder (MDD) while, in men, addictive disorders are more prevalent (1).

The assessment and treatment of psychiatric comorbidity is challenging because of its high prevalence (2, 3) and clinical severity, mostly due to suicide rates and the presence of medical comorbidities (4–6). Moreover, it is essential to distinguish between primary and induced MDD as they vary with respect to prognosis, relapse risk (7), and response to antidepressants (8). Traditionally, the implications of induced depression have been minimized. Some clinicians believe that it involved a mild syndrome that could revert with substance abstinence. As a consequence, induced MDD was not treated unless symptoms persisted (9). Subsequent research, however, demonstrates that relapse risk is even greater in the case of induced MDD than primary (7). Moreover, some longitudinal studies demonstrate that patients with an initial diagnosis of induced MDD after some years developed a primary one (10). With respect to antidepressants, a number of studies and reviews indicate differences in response depending on the type of depression with worse response to serotonin selective reuptake inhibitors (SSRI) for induced MDD (11, 12).

At the international level, cocaine is one of the most widely used illicit drugs. The 2021 United Nations Office on Drugs and Crime World Report estimated that around 20 million individuals aged 15–64 years (0.4%) had consumed cocaine during 2019 (13). Its use is associated with medical and psychopathological comorbidities, for example, increased risk of blood-borne infections (such as HIV and hepatitis C); elevated rates of mortality; and increased prevalence of mental health disorders, mainly depression, psychotic episodes, and suicide attempts (14). There are no approved pharmacological treatments for cocaine use disorder (CUD), and only some weak effects from psychotherapy are described (14, 15).

Individuals taking cocaine are reported to present a high risk of depression (16). The euphoria induced by acute cocaine use can induce a cycle of self-treatment of depressive symptoms, leading to a severe presentation of both CUD and MDD.

Due to the reasons mentioned above, clinicians are faced with having to distinguish between CUD-primary-MDD and CUD-induced-MDD in cocaine consumers. In a similar manner to psychiatric disorders, there are, however, no valid biomarkers for their correct identification. The diagnosis of MDD (induced/primary) is based on the subjective identification of clinical symptoms, and there are no clear standards for differential diagnosis. A recent study comparing DSM-5 criteria only found that "changes in weight or appetite" had a differing prevalence among the two disorders (17). The identification of biological markers in depressive disorders and SUD could help in the process of accurate diagnosis. MDD and CUD share some neurobiological pathways (18), for example, brain derived neurotrophic factor (BDNF) and cortisol levels. They are described as being able to assist in the diagnosis and identification of outcome predictors in MDD not associated with substance use (19).

The hypothalamic-pituitary-adrenal (HPA) axis is involved in the pathogenesis of MDD (20). Traditional studies observed a blunted stress response in MDD following a stress challenge, such as the Trier Social Stress Test (TSST) (21). Other studies, however, found a hyper-response but only in patients with severe depression (22). The HPA axis could also play a role in both CUD and MDD. In a study performed in cocaine-dependent patients, an infusion of intravenous cocaine was associated with adrenocorticotropic hormone (ACTH) and cortisol levels and depressive symptoms measured with the Hamilton Depression Rating Scale (HDRS) (23).

The BDNF belongs to the peptide family involved in neural plasticity, neurogenesis, and neural survival (24). It also has a key role in acute and chronic responses to substances of abuse. For instance, in a prospective study, BDNF plasma concentrations were associated in cocaine addiction with relapse risk in early recovery (25). Another study demonstrated that plasma concentrations of BDNF during early cocaine abstinence correlated with withdrawal syndrome and craving (26). Moreover, BDNF is associated with a number of psychiatric syndromes, including depression (27). The neurotrophic hypothesis of depression postulates that low levels of BDNF could induce atrophy at limbic structures and prefrontal cortex (28), whereas antidepressant treatment increases BDNF levels in depressed patients (29). With respect to dual diagnosis patients, BDNF levels are shown to present differences in samples from cocaine addicts with and without depression. Those with a comorbid diagnosis of cocaine addiction and depression, irrespective of being primary or induced, show lower BDNF levels (30).

Both MDD and SUD are complex diseases that result from changes in differing physiological systems. Thus, to better understand their pathophysiologies, the combined study of different systems and networks is required. In this regard, a recent paper by Chen et al. finds that combining the results of serum BDNF, cortisol, and interferon-gamma could help in making an accurate diagnosis of MDD (31).

At present, it is crucial to perform accurate diagnoses of CUD-primary-MDD and CUD-induced-MDD. As the monoamine hypothesis of depression is proven insufficient to explain differences between both types of MDD (32), it is essential to investigate the involvement of different systems in dual depression. We, therefore, carried out this study aimed at investigating differences in BDNF and cortisol plasmatic levels in patients diagnosed with CUD-primary-MDD and CUD-induced-MDD and also to compare them with a sample of MDD patients (without cocaine use), a sample of CUD (without MDD), and a group of healthy controls (HC) before and after a stress challenge.

METHODS

Subjects and Study Design

In this cohort study, the sample included subjects with (i) MDD ($n = 6$), (ii) CUD ($n = 15$), (iii) CUD and primary MDD ($n = 16$), and (iv) CUD and induced MDD ($n = 9$). All

patients were recruited at the addiction treatment facilities of the Parc Salut Mar Institute of Neuropsychiatry and Addiction in Barcelona, Spain.

Inclusion criteria were aged >18 years, Caucasian origin, body mass index 19–29 Kg/m^2, and the absence of any other psychiatric disorder and/or SUD other than MDD and/or CUD. In patients with primary/induced MDD the most recent episode had to be in remission, and the 17-item HDRS (33, 34) score <6. In the CUD groups, subjects had to have maintained at least 4 weeks of substance abstinence prior to the trial as confirmed by random urine controls. Cognitive or language limitations that precluded assessments, pregnancy or breast-feeding, use of anti-inflammatory drugs or monoamine oxidase inhibitors, and any medical problem that might interfere in the study procedures were considered exclusion criteria.

HCs ($n = 21$) were included from a database of subjects willing to participate in medical research projects at the Pharmacology Unit of the Hospital del Mar Institute of Medical Research (IMIM), Barcelona, Spain. In the HC group, the exclusion criteria were any Axis I psychiatric disorder, family history of depression, and any SUD except nicotine.

After basal clinical and psychiatric assessment, both patients and HCs participated in the stress experimental sessions with the TSST.

Subjects were admitted to the IMIM Clinical Research Unit facilities at 08.00. Those presenting nicotine addiction were treated during the experimental session with patches according to their nicotine daily dose. A urine sample was collected for drug testing (Instant-View®, Multipanel 10 Test Drug Screen, Alfa Scientific Designs Inc., Poway, CA, USA). Participants were required to be drug-free before the experimental session. The subjects remained sitting/lying in a calm laboratory environment during the session with restricted social interactions. The TSST was performed at 13.00 hours. This was carried out to (i) assure a similar waking time for all participants the day of the test, (ii) control activities that could affect HPA axis functioning, (iii) avoid heterogeneity of the cortisol response, and (iv) assure a period of rest before the protocol was administered (35, 36).

Clinical and Psychiatric Assessments

At baseline assessment, a closed-ended questionnaire was used to record participants' sociodemographic characteristics, family history, medical assessment, history of substance use, and previous psychiatric treatment. Psychiatric diagnoses were performed according to DSM-IV-TR criteria with the Spanish version of the Psychiatric Research Interview for Substance and Mental Disorders IV (PRISM-IV) (37). PRISM was specifically designed to deal with the issues of psychiatric diagnosis in SUD patients. It helps differentiate primary disorders, SUD, and the expected effects of intoxication and withdrawal. Diagnoses obtained through the PRISM interview are demonstrated to have good-to-excellent validity and test–retest reliability for primary-MDD and substance-induced MDD (38). In the MDD patients, depression severity was evaluated with the Spanish version of the HDRS (34).

TSST

The TSST is an acute stress test that consists of two tasks: public speaking and a mathematical task (39). Participants were asked to deliver a speech about their holidays or favorite book/film to a group of experts in nonverbal communication. After 5 min, three individuals (the audience) unfamiliar to the participant entered the room. The participant was instructed by one audience member (the spokesperson) to begin his/her prepared speech (without notes) for 5 min. If the individual paused, he/she was instructed by the spokesperson to continue. At the end of the speaking task, the individual was instructed to serially subtract 17 from 3,164 or 2,043 (randomly) as quickly and accurately as possible. The mental mathematic recitation continued for 5 min, at the end of which the spokesperson instructed the individual to stop, and the audience left the procedure room. Both tests were videorecorded. The experimental assessment was conducted before the test (pre-TSST); immediately after (post-TSST); and after 30 (post30-TSST), 60 (post60-TSST), and 90 min (post90-TSST). At the same time points, physiological and biochemical data were obtained. The TSST is proven useful in inducing acute stress response even in patients with CUD (40).

Biological Measurements

Heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), respiratory rate (RR), and temperature were monitored by Dash 3,000 monitor (GE, Wisconsin, USA) at different times: before the test (pre-TSST); immediately after (post-TSST); and after 30 (post30-TSST), 60 (post60-TSST), and 90 min (post90-TSST). At the same time points, blood samples were collected from the subjects.

Cortisol

To assess cortisol levels, 5 ml of peripheral blood sample was centrifuged at 4,000 rpm for 10 min. The serum obtained was frozen at −20°C until analysis was conducted by electrochemiluminescence, using an Immulite-2000 XPi analyzer (Siemens).

BDNF

BDNF was obtained before (pre-TSST), immediately after (post-TSST), and at 90 min (post90-TSST). Five milliliters of peripheral blood sample was centrifuged at 4,000 rpm for 10 min. The serum obtained was frozen at −20°C until analysis, which was performed with 500 microliters of serum by ELISA and the kit Human BDNF Quantikine ELISA Kit of R&D-Vitro SA and polyclonal antibodies.

Statistical Analysis

A descriptive analysis of all variables of interest was carried out separately in each of the study groups. For this purpose, the mean, median, standard deviation, and range were calculated. Repeated-measure ANOVA models were used to analyze the intragroup and intergroup changes of both the cortisol and BDNF concentrations. The models included group condition as a main factor in addition to all two- and three-way interactions. The computation of simultaneous confidence intervals and adjusted p-values to guarantee a family-wise error rate of 0.05

TABLE 1 | Sociodemographic and clinical characteristics of the sample at baseline ($n = 67$).

	HC ($N = 21$)	MDD ($N = 6$)	CUD-induced-MDD ($N = 9$)	CUD-primary-MDD ($N = 16$)	CUD ($N = 15$)
Sex (Male) N (%)	14 (66.7)	5 (83.3)	7 (77.8)	13 (81.3)	12 (80)
Age (Mean ± SD)	32.6 ± 4.8	45.7 ± 13.2	37.7 ± 11.4	44.8 ± 7.8	38.0 ± 9.5
Civil status (% Single)	10 (47.6)	2 (33.3)	6 (66.7)	6 (37.5)	10 (66.7)
Work status (% Employed)	10 (47.6)	2 (33.3)	3 (33.3)	7 (43.8)	4 (26.7)
Depression (MDD)					
HDRS (Mean ± SD)	0.57 ± 1.21	1.17 ± 1.83	0.56 ± 0.73	1.38 ± 1.09	0.73 ± 1.33
Age of onset first induced-MDD (Mean ± SD)	-	-	33.3 ± 11.8		-
Age of onset first primary-MDD (Mean ± SD)	-	36.2 ± 10.9	-	37.5 ± 6.4	-
Number of episodes (Mean ± SD)	-	1.8 ± 1.0	3.2 ± 2.1	2.5 ± 1.9	-
Family history of depression (%)	-	5 (83.3)	4 (44.4)	11 (68.8)	5 (33.3)
Current antidepressant treatment (%)	-	5 (83.3)	4 (44.4)	10 (62.5)	2 (13.3)
Age of cocaine problematic use	-	-	26.3 ± 9.0	29.3 ± 6.8	26.3 ± 7.1
Nicotine use disorder (%)	-	-	7 (77.8)	12 (75)	11 (73.3)

HC, healthy controls; MDD, major depression disorder; CUD, cocaine use disorder; SD, standard deviation.

was based on the multivariate t distribution of the vector of test statistics.

Next, one-way ANOVA models were fitted to compare the study groups with the mean of the variables. The model assumptions (homoscedasticity and normally distributed residuals) were checked with residual plots and the Levene (homoscedasticity) and Kolmogorov-Smirnov tests, respectively. If assumptions held and group differences were statistically significant, the Bonferroni test was applied for the *post hoc* pairwise comparisons. Cohen's d was used to quantify the effect size of the pairwise differences among study groups (small: $d \leq 0.20$; medium: $d \geq 0.50$; large: $d \geq 0.80$; very large: $d \geq 1.30$). Cohen's d is a standardized score, analogous to a z score. Following Cohen's effect size conventions, only differences higher than a medium effect size ($d \geq 0.50$) were considered of relevance.

All data were analyzed using the IBM Corp. Released 2013 IBM SPSS Statistics for Windows, Version 22.0 (Armonk, NY: IBM Corp.). In the case of the group comparisons, statistical significance was set at 0.05 (to protect against type I errors), and for model assumption tests at 0.1 (to protect against type II errors).

Ethics Statement

The clinical protocol was approved by the local Research Ethical Committee CEIC-Parc de Salut Mar, Barcelona, Spain (2009/3494/I and 2012/4751/I), and the study was conducted in accordance with the Declaration of Helsinki and Spanish laws concerning clinical research. Volunteers were financially compensated. All subjects gave written informed consent prior to their participation in the study.

RESULTS

Demographic and Clinical Characteristics

A total of 67 subjects were included in the study to assess possible differences in BDNF and cortisol levels during the TSST. The main sociodemographic and clinical characteristics of the sample are described in **Table 1**. The final groups were 21 HC, 6 MDD, 9 CUD-induced-MDD, 16 CUD-primary-MDD, and 15 CUD.

More than 76% of the total sample were single men aged >32 years. All groups had low HDRS scores, and the depressed groups had more than one MDD episode with a similar age of onset. Family history of depression and current treatment with antidepressants were also more prevalent in these groups. In the CUD groups, the age of onset of problematic cocaine use was very similar, and current nicotine use was >73%.

Five out of six subjects in the MDD group were on varying types of antidepressants. In the CUD-induced and primary-MDD groups, the majority of patients were also on antidepressant treatment. The CUD-primary-MDD patients were treated with SSRIs although in the induced-MDD group other types of antidepressants were prescribed. Types of antidepressants in the study groups are described in (**Supplementary Table S1**).

Trier Social Stress Test (TSST)

Biological Measures

Changes in HR, SBP, DBP, and RR before and after the TSST are depicted in **Supplementary Table S2**. CUD and HC presented significant changes over time in HR and DBP without differences in the rest of the groups.

Cortisol

All groups showed a similar response pattern during the TSST follow-ups with the CUD-induced-MDD presenting the highest cortisol concentrations in post-60 TSST and the CUD-primary-MDD the lowest cortisol concentrations in post-90 TSST (**Figure 1**).

One-way ANOVA tests yielded p-values >0.117 when comparing groups in each assessment (**Table 2**). A paired T-test showed significant within-group changes in cortisol concentrations over time except in the MDD group with the lowest range of change [9.48 ± 2.7–12.7 ± 3.47].

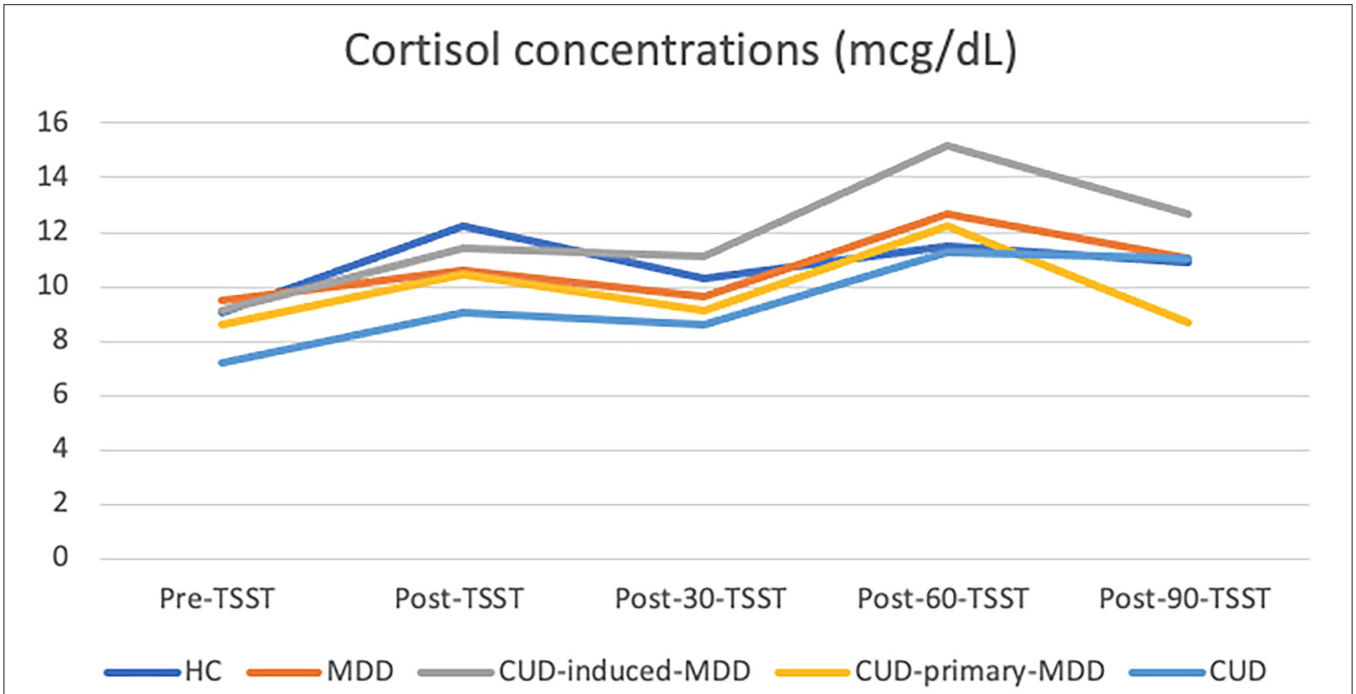

FIGURE 1 | Mean cortisol concentrations during Trier social stress test (TSST). HC, healthy control ($n = 21$); MDD, major depression disorder ($n = 6$); CUD, cocaine use disorder ($n = 15$), CUD-primary-MDD, ($n = 16$), CUD-induced-MDD ($n = 9$).

TABLE 2 | Mean cortisol concentrations during Trier social stress test (TSST).

Cortisol mcg/dL	Pre-TSST Mean ± SD	Post-TSST Mean ± SD	Post-30-TSST Mean ± SD	Post-60-TSST Mean ± SD	Post-90-TSST Mean ± SD
HC ($N = 21$)	9.06 ± 3.67	12.24 ± 4.52*	10.27 ± 3.95*	11.45 ± 3.36	10.87 ± 3.72*
MDD ($N = 6$)	9.48 ± 2.7	10.62 ± 1.35	9.63 ± 3.55	12.7 ± 3.47	11.05 ± 2.55
CUD-induced-MDD ($N = 9$)	9.09 ± 5	11.4 ± 6.95*	11.1 ± 5.15*	15.18 ± 2.17*	12.64 ± 1.55
CUD-primary-MDD ($N = 16$)	8.63 ± 2.17	10.48 ± 3.09	9.11 ± 2.6*	12.25 ± 4.3	8.69 ± 2.11*
CUD ($N = 15$)	7.16 ± 3.03	9.03 ± 3.06*	8.6 ± 2.99	11.27 ± 4.25*	11.01 ± 6.12
One-way ANOVA	$p = 0.453$	$p = 0.253$	$p = 0.461$	$p = 0.117$	$p = 0.160$

**Paired T-Test <0.05.*
TSST, Trier social stress test; HC, healthy controls; MDD, major depression disorder; CUD, cocaine use disorder; SD, standard deviation.

After the TSST, Cohen's *d* values between CUD-primary-MDD and CUD-induced-MDD increased in each assessment from 0.19 post-TSST to 2.04 post-90-TSST. Pairwise differences among CUD-induced-MDD and both MDD and HC groups had also a large effect size value post-30-TSST and post-90-TSST (**Table 3**).

BDNF

All groups showed a similar decreasing pattern in BDNF concentrations during TSST follow-ups. The CUD-induced-MDD group had the highest BDNF concentrations in each assessment (**Figure 2**).

One-way ANOVA demonstrated statistical differences post-90-TSST ($p = 0.032$); no differences, however, were reported when performing Bonferroni's *post-hoc* comparisons (**Table 4**). A paired *T*-test showed significant within-group changes in BDNF concentrations over time except in the MDD group.

Table 5 depicts the pairwise differences among the CUD-induced-MDD and HC groups that had the largest effect size value in the three assessments with values >0.94. The difference in BDNF concentrations between CUD-primary-MDD and CUD-induced-MDD post-90-TSST (12,627.27 ± 5488.09 vs.17,144.84 ± 6581.06, respectively) also had a large effect size (0.77).

DISCUSSION

The most important finding of this study is the different response observed after a stress challenge (TSST) in the levels of cortisol and BDNF in primary and induced depression.

As the diagnosis of depression is based on clinical criteria, sometimes with suboptimal rates of validity and accuracy, the detection of measurable biomarkers has implications in the study of the pathophysiology of depression and the introduction of effective treatments.

TABLE 3 | Effect size coefficient (Cohen's d) pairwise comparisons of cortisol concentrations in each assessment.

		MDD	CUD-induced -MDD	CUD-primary -MDD	CUD (*N* = 15)
Pre-TSST	HC (*N* = 21)	0.12	0.01	0.14	0.56
	MDD (*N* = 6)		0.09	0.37	0.79
	CUD-induced-MDD (*N* = 9)			0.13	0.50
	CUD-primary-MDD (*N* = 16)				0.56
Post-TSST	HC	0.40	0.16	0.44	0.81
	MDD		0.14	0.05	0.59
	CUD induced MDD			0.19	0.49
	CUD primary MDD				0.47
Post-30-TSST	HC	0.17	0.19	0.34	0.47
	MDD		0.32	0.18	0.33
	CUD induced MDD			0.54	0.64
	CUD primary MDD				0.18
Post-60-TSST	HC	0.37	1.22	0.21	0.05
	MDD		0.90	0.11	0.35
	CUD induced MDD			0.79	1.08
	CUD primary MDD				0.23
Post-90-TSST	HC	0.05	0.54	0.70	0.03
	MDD		0.80	1.06	0.01
	CUD induced MDD			2.04	0.33
	CUD primary MDD				0.51

Cohen's effect size: small (d > 0.20), medium (d > 0.50), large (d > 0.80), and very large (d > 1.30). HC, healthy controls; MDD, major depression disorder; CUD, cocaine use disorder; TSST, Trier social stress test.

As previously reported, the monoamine theory of depression cannot completely explain the pathogenesis of induced depressions (32), and other physiological systems should be studied. Stress is related to both MDD (41, 42) and SUD (43, 44), and in turn, cortisol is associated with stress. In our study, patients diagnosed with CUD-induced-MDD showed higher levels of cortisol after an acute stress challenge compared with CUD-primary-MDD ones. Such differences could indicate that varying mechanisms are involved in these two types of depression.

Moreover, when analyzing BDNF plasma levels, we observed similar differences with higher concentrations of BDNF at 90 min after the TSST in the CUD-induced-MDD compared with the CUD-primary-MDD and MDD without cocaine use. Traditional research describes lower levels of BDNF in depressive patients (28). In our sample, higher levels of BDNF at 90 min were observed in the CUD and the CUD-induced-MDD groups; surprisingly, the HC group showed the lowest BDNF concentrations. Varying concentrations and level changes depending on the type of depression could explain differences in therapeutical response to treatment between induced and primary depressive disorders and the lack of response of some of them.

The use of cortisol and BDNF levels as markers to differentiate cocaine-induced and primary depressions could help in the design of personalized treatments. They would permit the correct selection of antidepressant, thus avoiding prolonged periods before patient response to treatment (45). Nevertheless, reviews and meta-analysis have not clearly defined whether there are differences in BDNF level increases depending on the antidepressant evaluated (29). With respect to BDNF levels in

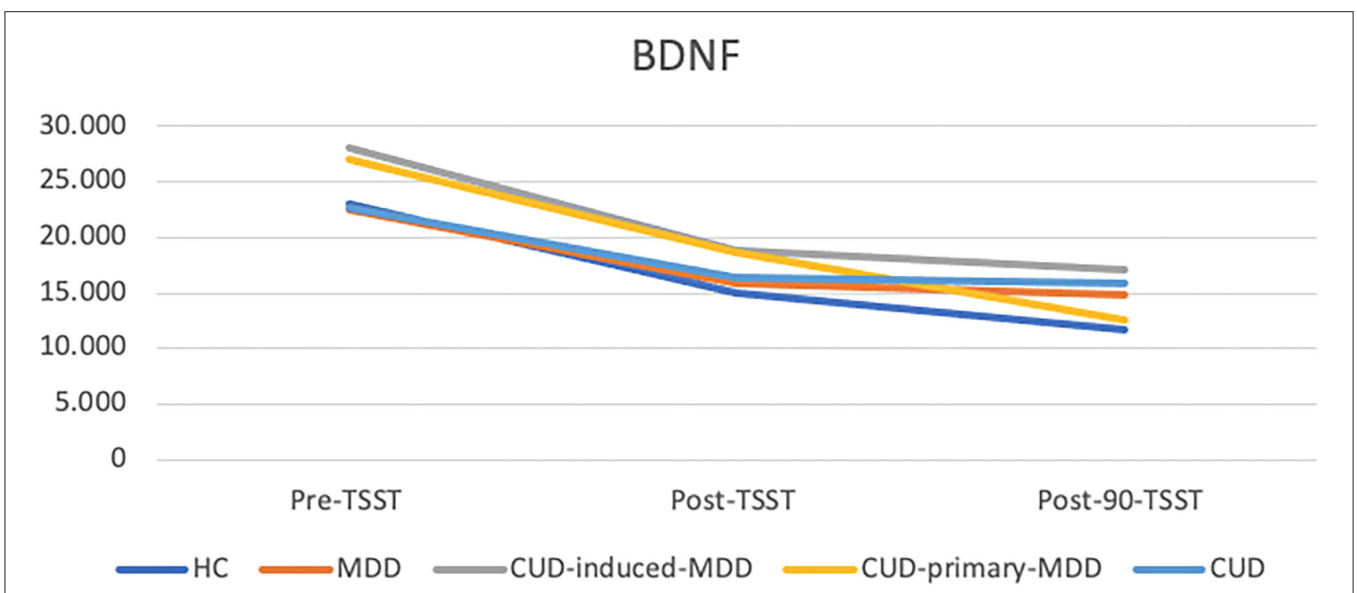

FIGURE 2 | Mean BDNF concentrations during Trier social stress test (TSST). HC, healthy control (*n* = 21); MDD, major depression disorder (*n* = 6); CUD, cocaine use disorder (*n* = 15), CUD-primary-MDD, (*n* = 16), CUD-induced-MDD (*n* = 9).

TABLE 4 | Mean BDNF concentrations during Trier social stress test (TSST).

BDNF	Pre-TSST	Post-TSST	Post-90-TSST
HC ($N = 21$)	23,053.15 ± 4,818.28	14,993.06 ± 3,882.56*	11,782.55 ± 4,138.4*
MDD ($N = 6$)	22,510.41 ± 5619.91	15,912.88 ± 3,456.21	14,872.87 ± 2,471.91
CUD-induced-MDD ($N = 9$)	28,040.91 ± 5,287.74	18,854.29 ± 4,662.07*	17,144.84 ± 6,581.06*
CUD-primary-MDD ($N = 16$)	27,076.84 ± 8,457.33	18,735.27 ± 6,045*	12,627.27 ± 5,488.09*
CUD ($N = 15$)	22,739.07 ± 5,673.17	16,423.37 ± 4,950.92*	15,888.35 ± 5,050.1*
One-way ANOVA	$p = 0.082$	$p = 0.125$	$p = 0.032$

**Paired T-Test <0.05.*
HC, healthy controls; MDD, major depression disorder; CUD, cocaine use disorder; TSST, Trier social stress test.

TABLE 5 | Effect size coefficient (Cohen's d) pairwise comparisons of BDNF concentrations in each assessment.

	BDNF	MDD	CUD-induced -MDD	CUD-primary -MDD	CUD ($N = 15$)
Pre-TSST	HC ($N = 21$)	0.11	1.01	0.61	0.06
	MDD ($N = 6$)		1.02	0.58	0.04
	CUD-induced-MDD ($N = 9$)			0.13	0.96
	CUD-primary-MDD ($N = 16$)				0.60
Post-TSST	HC	0.24	0.94	0.76	0.33
	MDD		0.69	0.51	0.11
	CUD-induced-MDD			0.02	0.50
	CUD-primary-MDD				0.42
Post-90-TSST	HC	0.80	1.08	0.18	0.91
	MDD		0.42	0.46	0.22
	CUD-induced-MDD			0.77	0.22
	CUD-primary-MDD				0.62

Cohen's effect size: small (d > 0.20), medium (d > 0.50), large (d > 0.80), and very large (d > 1.30). HC, healthy controls; MDD, major depression disorder; CUD, cocaine use disorder; TSST, Trier social stress test.

CUD, one study evaluated changes in plasma concentrations during detoxification. It was observed that chronic cocaine use was associated with lower levels of BDNF, and during detoxification, the levels increased, correlating with cocaine craving (26). In our sample, at baseline, subjects with higher concentrations of BDNF were those with CUD and MDD, either primary or induced, although findings were nonsignificant. In addition, after the stress challenge, BDNF levels decreased in all groups although maintaining the higher levels those of the CUD-induced-MDD group.

Our findings do not signify a causal model, and it was not possible to clarify whether the differences in cortisol and BDNF levels were primary or secondary to induced/primary depression. Could a previously disrupted HPA axis be a marker of depression risk? Another study reported that patients with CUD presented a previous childhood history (parent neglect), higher scores in depression severity (measured by the SCL-90), and greater levels of ACTH and cortisol in plasma than HCs. The authors concluded that early life events (neglect and poor attachment to parents) influenced HPA axis function, and additionally, such individuals presented increased vulnerability to depression and substance use (46). In this regard, another study evaluated salivary cortisol and hemodynamic data (BP and HR) response to the TSST in subjects prenatally exposed to cocaine. When comparing these subjects to nonexposed ones, it was observed that the former presented higher rates of cortisol levels before and after the TSST, a finding that suggests an impaired response to stress in subjects prenatally exposed to cocaine (47). Another explanation could be the presence of untreated depression as a risk factor for CUD. In a study evaluating an animal model, depressed rats administered more cocaine than nondepressed ones showed higher concentrations of BDNF at the prelimbic cortex (48). In this regard, it should be noted that our participants were either abstinent or in remission from the last depressive episode. Previous research has not described differences depending on the time patients were abstinent from psychostimulant drugs and TSST response (40). For instance, the fact that patients did not present depressive symptoms (HDRS < 6) hindered results being presented as a state marker although they could be interpreted as a trait maker. In other words, CUD-induced and CUD-primary-MDD should have different stress responses, and levels of BDNF and cortisol correlate with impaired stress responsiveness in these types of patients. The TSST has been useful in other kinds of research to discriminate different stress responses, for example, in young people exposed to prenatal cocaine (47).

More comprehensive knowledge regarding dual depression biomarkers and the differences between primary and induced depression are essential to introduce effective treatment, particularly as the improvement of depressive symptoms requires at least 4 weeks after commencement of antidepressant therapy. Moreover, previous research, in accordance with the present results, demonstrates differential neurobiological processes underlying induced and primary MDD (32, 49) suggesting poor outcomes with SSRI antidepressants (8, 12). For instance, in the case of depression with lower levels of BDNF, the first line treatment should be those antidepressants that are shown to raise BDNF levels, such as agomelatine (50). Martinotti reports that, in patients with MDD, a correlation between depressive symptom improvement and BDNF serum concentrations was observed after 2 weeks of agomelatine treatment. A recent review also (29) focused on the effects of antidepressants in BDNF levels and found that, in general, antidepressants increased the levels of BDNF. It was not possible, however, to identify the

differential effects by type of antidepressant; a better description of depression phenotypes is probably called for.

There are several limitations to this study. First, the sample size was small for all groups. Indeed, the strict inclusion criteria made it difficult to find pure cocaine/depressed-only patients. For this reason, although our results suggest biochemical differences between CUD-primary-MDD and CUD-induced-MDD, such findings should be confirmed by the analysis of a larger set of samples. A second limitation is that the MDD patients were under remission, and differences could, therefore, be underestimated. The decision to include patients in remission was made due to ethical reasons in order not to expose individuals with depression to a stress situation (even in a controlled environment). This means that the differences observed should be considered as trait markers or risk factors to develop depression and not clinical depression itself. In previous research, the TSST is useful to discriminate risk factors in stress response for healthy controls (51), the general population (52), and patients with active depression (53). In addition, most of the depressed group participants were under antidepressant treatment, which could influence BDNF levels as previously described (29). Finally, the small sample size also hindered a proper evaluation of the effect of gender on the results. Previous authors observe differences in the cortisol response to acute stress between genders after an acute stress challenge (54, 55). Studies evaluating the results between men and women are therefore essential to adapt interventions.

Reliable biomarkers are needed to detect and diagnose depression subtypes. One strength of the study is that these molecules could be analyzed routinely. Future studies investigating their involvement in the outcome and response to treatment are warranted.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and the clinical protocol was approved by the local Research Ethical Committee CEIC-Parc de Salut Mar, Barcelona, Spain (2009/3494/I and 2012/4751/I) and the study was conducted in accordance with the Declaration of Helsinki and Spanish laws concerning clinical research. Volunteers were financially compensated. All subjects gave written informed consent prior to their participation in the study. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MT was the principal investigator of the grants supporting the research. MT and MF were responsible for the study concept and design. MT, MF, JM-P, and FF designed the protocol. FF, RR-M, CP-M, and EP selected the participants. JM-P, CP-M, EP, and MF conducted the TSS test sessions. JM-P and KL performed the statistical analysis and FF, JM-P, MF, and MT interpreted findings. FF, JM-P, and MB wrote the initial draft of the manuscript. MT and MF provided critical revision of the manuscript for key intellectual content. All authors have read and agreed to the published version of the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2022.836771/full#supplementary-material

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Co-occurrence of Adult ADHD Symptoms and Problematic Internet Use and Its Links With Impulsivity, Emotion Regulation, Anxiety, and Depression

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The co-occurrence of attention-deficit/hyperactivity disorder (ADHD) and problematic Internet use (PIU) is associated with increased severity of PIU and poorer treatment outcomes. The main objective of this study was to examine the association between PIU and adult ADHD symptoms and determine whether adult ADHD symptoms were a predictor of PIU in the general adult population. We also examined the potential mediating role of the dimensional psychopathological factors, including anxiety, depression, impulsivity, and emotion regulation, in this relationship. To achieve these aims, we recruited 532 regular Internet users online from the general adult population. The participants completed an online questionnaire assessing PIU (Internet Addiction Test), anxiety and depression symptoms (Hospital Anxiety and Depression Scale), adult ADHD symptoms (Adult ADHD Self-Report Scale-V1.1), emotion regulation (Emotion Regulation Questionnaire), and impulsivity (UPPS-P Impulsive Behavior Scale). We conducted a multiple regression analysis to determine the predictors of PIU and mediation analyses to identify the psychopathological mediators of the association between adult ADHD symptoms and PIU. PIU was observed in 17.9% of our sample. A significantly higher proportion of respondents with PIU screened positive for adult ADHD symptoms compared to respondents without PIU (50.5 vs. 21.7%; $p < 0.001$). Individuals with PIU reported significantly higher scores than those without PIU for anxiety and depressive symptoms, impulsivity, and the emotion regulation strategy of expressive suppression. Additionally, they had significantly lower scores than those without PIU on cognitive reappraisal than non-problematic Internet users. In addition to adult ADHD symptoms, the multiple regression analysis revealed that PIU was also positively predicted by depressive symptoms, positive urgency, lack of perseverance, and expressive suppression, and is negatively predicted by cognitive reappraisal and negative urgency. The mediation analysis showed that lack of perseverance, positive urgency, and depressive and anxiety symptoms were partial mediators of the relationship between

adult ADHD symptoms and PIU. Our results highlight the significant co-occurrence of PIU and adult ADHD symptoms. This study also provides support for a theoretical model in which impulsivity dimensions, emotion regulation strategies, as well as the tendency to anxiety and depressive symptoms, may play a mediating role in this co-occurrence. In summary, the findings emphasize the need to assess these psychological characteristics in problematic Internet users, as they can be a factor of clinical complexity, as well as the importance of targeting them as part of integrated interventions for both adult ADHD symptoms and PIU.

Keywords: Internet Addiction, ADHD, impulsivity, anxiety disorders, depressive disorders, dual diagnosis

INTRODUCTION

Problematic Internet use (PIU) is a highly prevalent problematic behavior, especially among young people. It was first described by Young (1, 2), who defined it as an impulse-control disorder that does not involve an intoxicant. According to Spada (3), the two main features of PIU are (1) preoccupation with a loss of control over Internet use, and (2) negative consequences. A meta-analysis based on 133 surveys across 31 countries conducted between 2003 and 2018 reported PIU prevalence rates ranging from 0.5 to 40.0%, with a pooled prevalence of 8.9% in eastern countries and 4.6% in western countries (4). As with other problematic behaviors (such as sexual or food addictions), PIU is not recognized as an addictive disorder by international diagnostic classifications [Diagnostic and Statistical Manual of Mental Disorders 5th edition, DSM-5 (5); International classification of diseases 11th revision, ICD-11 (6)]. Therefore, in order to further our understanding of PIU, it may be beneficial to draw inspiration from other problematic behaviors that are included in international classifications, such as problem gambling. We thus based the rationale for our study on the seminal work of Blaszczynski and Nower (7), which proposed a three-pathway model of problem gambling. Firstly, this model includes a behaviorally conditioned pathway, referring to the effects of conditioning, distorted cognitions and poor decision-making. Secondly, the emotionally vulnerable pathway refers to individuals with premorbid anxiety or depression, and a history of poor coping skills. Finally, the antisocial-impulsivity pathway includes individuals with characteristics of impulsivity, antisocial personality disorder, and attention deficit.

In terms of the comorbidities associated with PIU, previous investigations have yielded divergent results for some PIU comorbidities. However, a meta-analysis conducted in 2014 reported a low level of between-study heterogeneity regarding the comorbidity of ADHD and PIU (8). ADHD is a neurodevelopmental disorder characterized by inattention and hyperactivity-impulsivity (5). ADHD affect 5.0–7.0% of children (9, 10) before the age of 12 and persist in adulthood in ∼65% of cases (11). Other ADHD symptoms include high reward sensitivity, high sensation seeking, impaired cognitive control, and urgency, which may also be involved in the onset or maintenance of problematic behaviors. Specifically, Yoo et al. (12) found a significant link between PIU and ADHD in children and showed that ADHD was an important risk factor for PIU. Similar results have also been found with adults (13). Furthermore, results of a meta-analysis conducted in 2017 indicated that individuals with PIU are two and a half times more likely to be diagnosed with ADHD (prevalence ranging from 19.5 to 42.5%) compared with individuals without PIU (prevalence ranging from 4.6 to 15.2%) (14). Finally, both inattention and hyperactivity-impulsivity are more severe in individuals with PIU than healthy controls (14). Taken together, these results support the hypothesis of a positive association between PIU and ADHD.

The psychopathological mechanisms underlying the co-occurrence of problematic behaviors and ADHD are still unclear. However, identifying the psychological characteristics involved in this comorbidity may be useful for developing targeted interventions to improve treatment outcomes and prevent problematic behaviors in individuals with ADHD. Based on the three-pathway model proposed by Blaszczynski and Nower (7), we hypothesized that certain psychopathological factors lead ADHD individuals to engage in problematic behaviors, such as PIU. For example, the antisocial-impulsivity and emotionally vulnerable pathways show shared psychological factors between ADHD and problematic behaviors. Therefore, impulsivity, the use of maladaptive emotion regulation strategies, and anxiety and depressive symptoms could be interesting candidates as mediators of the association between ADHD and PIU.

In terms of anxiety and depression symptoms, a short-term longitudinal study found that anxiety and depressive symptoms positively predicted PIU in 12- to 18-year-old adolescents (15). According to LaRose et al. (16), Internet use may be a way for individuals with low levels of stimulation, such as those with depressive disorders, to alleviate their dysphoria. Therefore, depression associated with impaired self-regulation may lead to difficulties with controlling Internet use, thus causing PIU. Emotion regulation refers to "the processes by which individuals influence which emotions they have, when they have them, and how they experience and express these emotions" (17). Emotion dysregulation is prevalent in individuals with ADHD (18), and these difficulties with emotion regulation may lead to the use of maladaptive strategies, such as emotion suppression, and ultimately to PIU. Similarly, previous studies have suggested that emotion dysregulation may contribute to problematic behaviors, such as addictive disorders (19–22).

Impulsive actions may provide immediate rewards and alleviate negative emotions (23), which are a significant feature of ADHD. Moreover, previous studies have suggested that the association between ADHD and problematic behaviors may be mediated by impulsivity (24) or anxiety and depressive symptoms (25). Taken together, the previous research is in line with the hypotheses that negative affectivity (i.e., anxiety and depressive symptoms), the use of maladaptive emotion regulation strategies, and impulsivity are psychological features that may partially explain the association between ADHD and PIU. However, there is a lack of studies investigating these hypotheses together in the specific population of individuals with PIU.

In this study, we aimed to investigate the prevalence of the co-occurrence of PIU and adult ADHD symptoms and the independent and mediation effects of psychological factors on the relationship between these two conditions, especially in terms of negative affectivity (anxiety and depressive symptoms), emotion regulation, and impulsivity. We hypothesized that respondents with PIU may have a higher level of impulsivity (especially in terms of urgency) and negative affectivity (anxiety and depressive symptoms) and may tend to use maladaptive emotion regulation strategies. We expected that these dimensional variables predict PIU severity, and may mediate this association between adult ADHD symptoms and PIU severity.

MATERIALS AND METHODS

The research was conducted in accordance with the Helsinki Declaration, as revised in 1989. Prior to inclusion in the study, all participants provided written informed consent once the procedure had been fully explained to them. The protocol was approved by the Institutional Review Board (France) in April 2019 (IRB number: 2019-03-01).

Population and Procedure

This cross-sectional study was conducted online. The participants were recruited over ∼1 year via the social media of three psychology students and two researchers (i.e., Facebook, Twitter, blogs, and forums) of the University of Tours (France). The participants were self-selected, and their participation was voluntary. They were considered eligible for inclusion if they were at least 18 years old, used the Internet at least once a week, gave their informed and signed consent, and completed the questionnaire in its entirety.

The participants were provided with a brief text giving them information about the study, including the aims and methods, the inclusion criteria (as defined above), and the confidential and anonymized nature of the data. The eligible participants were assessed using self-administered questionnaires, which were designed and completed online using LimeSurvey software. In total, 544 participants completed the questionnaire. Twelve participants were excluded overall because of being aged under 18 years old ($N = 1$) and having missing data ($N = 11$). Therefore, our final sample comprised 532 Internet users.

TABLE 1 | Socio-demographic data and independent variables: comparison of PIU and non-PIU individuals.

	PIU ($N = 95$) [% or mean (SD)]	Non-PIU ($N = 437$) [% or mean (SD)]	Statistics	
			(χ^2 or U)	*p*
Gender (% women)	66.0	74.8	1.159	0.282
Age	26.9 (11.2)	27.3 (10.0)	18695.5	0.128
Marital status			10.159	0.006*
Married/partnered	31.6	48.1		
Single	62.1	49.2		
Divorced/separated	6.3	2.7		
Occupation			21.205	<0.001*
Employed	24.2	42.6		
Unemployed	6.3	4.3		
Students	60.0	51.0		
Other situations	9.5	2.1		
Problematic internet use (IAT)	57.8 (6.6)	34.8 (7.8)	41515.0	<0.001*
Anxiety and depression (HADS total)	12.4 (5.0)	9.5 (4.8)	13438.5	<0.001*
Anxiety symptoms	7.7 (3.2)	6.5 (3.2)	15755.0	<0.001*
Depression symptoms	4.6 (2.8)	3.1 (2.5)	13475.5	<0.001*
Impulsivity (UPPS-P total)	48.9 (7.8)	45.0 (7.5)	14436.5	<0.001*
Negative urgency	10.9 (2.9)	10.5 (3.1)	19476.0	0.343
Positive urgency	10.8 (2.6)	10.1 (2.7)	17546.0	0.017*
Lack of premeditation	8.2 (2.4)	7.3 (2.3)	15637.5	<0.001*
Sensation seeking	10.2 (3.0)	10.3 (2.9)	20323.0	0.748
Lack of perseverance	8.7 (3.0)	6.8 (2.4)	12936.5	<0.001*
Adult ADHD symptoms (ASRS)	3.4 (1.5)	2.4 (1.4)	12662.0	<0.001*
Expressive suppression (ERQ)	17.4 (5.5)	14.9 (5.2)	14423.0	<0.001*
Cognitive reappraisal (ERQ)	23.6 (9.0)	27.6 (6.9)	15120.0	<0.001*

$p \leq 0.05$; χ^2 = chi-squared test; U, Mann–Whitney coefficient; PIU, problematic internet use assessed by the Internet Addiction Test; IAT, Internet Addiction Test; HADS, Hospital Anxiety and Depression Scale; ASRS, Adult ADHD Self-report Scale; ERQ, Emotion Regulation Questionnaire.

Measures

Socio-Demographic and Internet Activity Data

We collected socio-demographic data, including age, gender, marital status, and employment status. The participants were asked to report their marital status (among the proposals specified in **Table 1**) and their employment status: "employed" (including full-time employment, part-time employment and irregular work), "unemployed" (including unemployed and retired), "students" and "other situations" (included disabled and others situations). The participants were also asked to report their favorite Internet activity: e-mail-related activity, social media use (i.e., Facebook, Twitter, Instagram), taking or looking at photographs, watching videos, playing games, using search engines, reading news, downloading, online purchasing, watching pornography online, online gambling, and using online dating sites. There were two questions regarding Internet activities. The first one was: "Was are the activities you practice online?" and the second: "Please report your three favorites online activities (the ones you spend the most time on, or your favorite if you spend the same amount of time on several

activities), and classify them from 1 (first favorite) to 3 (third favorite)." For each question, participants had the choice in the list of activities mentioned above.

Problematic Internet Use

We assessed PIU using the Internet Addiction Test [IAT; (2), French version by (26)], which is a 20-item self-report scale for identifying individuals who exhibit addictive-like behavior in their Internet use. This scale is based on the Diagnostic and Statistical Manual of Mental Disorders Text Revision Fourth Edition [DSM-IV-TR; (27)] criteria for pathological gambling: loss of control over Internet use, significant impact of Internet use in different areas of life, and tolerance and dependence symptoms. Each item is rated on a 5-point Likert scale, ranging from "rarely" to "always," and the total score is obtained by summing the scores of all the items. A score over 50 suggests that the individual experiences problems with Internet usage (26). In this study, we used a cut-off score of 50 to differentiate between individuals with and without self-reported PIU. The IAT has excellent internal consistency ($\alpha = 0.86$, in the current study) and is the most widely used self-administered questionnaire for evaluating PIU.

Adult ADHD Symptoms

Adult ADHD symptoms was screened using the self-reported Adult ADHD Self-Report Scale-V1.1 (ASRS-V1.1), which is a 6-item self-administered questionnaire designed with the support of the World Health Organization to screen for adult ADHD symptoms in both community surveys and clinical settings based on criteria of the DSM-IV-TR (28). The items are rated on a 5-point Likert scale, with a cut-off score for each item. The ASRS is an effective tool for screening adults for ADHD symptoms, with a Cronbach's α ranging from 0.63 to 0.72 in the overall population (29) and good internal consistency ($\alpha = 0.84$) and construct validity in adult patients with addictive disorders (30). The current study internal consistency was 0.69. The presence of at least four significant items (i.e., above the defined cut-off scores) suggests a high risk of adult ADHD symptoms (28). Therefore, we used this criterion to differentiate between participants with and without adult ADHD symptoms.

Anxiety and Depressive Symptoms

To assess anxiety and depressive symptoms, we used the Hospital Anxiety and Depression Scale [HADS; (31); French version by (32)]; this is a 14-item self-report scale that screens for both anxiety (7 items) and depression (7 items). It has good psychometric properties (31, 33), is quick to administer, and is, thus, suitable for field research. Scores of 0–7 indicate no disorder, 8–10 indicate doubtful cases, and 11 and over indicate definite cases (31). In this study, we used a cut-off score of 8 [possible disorder; (33)]. The HADS has been widely used in research and has good psychometric qualities (34). The current study internal consistency was 0.69 for anxiety and 0.47 for depression.

Emotion Regulation

We used the Emotion Regulation Questionnaire (ERQ) to assess emotion regulation [(35); French version by (36)]. This 10-item scale is a self-report measure of two distinct emotion regulation strategies: cognitive reappraisal (CR; transforming the way a situation is perceived in order to change its meaning and emotional impact) and expressive suppression (ES; inhibiting or reducing facial expression of emotions). Both the original version and the French version have good psychometric properties (35, 36), indicating that the ERQ is a reliable tool for assessing these strategies. Factorial and confirmatory analyses revealed a two-factor structure of the scale: 6 items assess cognitive reappraisal, and 4 items assess expressive suppression. The current study internal consistency was 0.76 for both CR and ES.

Impulsivity

Impulsivity was assessed using the UPPS Impulsive Behavior Scale, short version (UPPS-P) [(37), French version by (38)]. This is a 20-item self-administered questionnaire based on the UPPS model (37, 39), with one additional measure of positive urgency (23). The scale assesses five facets of impulsivity: negative urgency, positive urgency, lack of premeditation, lack of perseverance, and sensation seeking (40). The UPPS-P provides a sub-score for each facet, and higher scores indicate higher intensity of impulsivity. In the current study, the UPPS-P showed acceptable to good psychometric properties, as the Cronbach's α values were 0.83 for negative urgency, 0.77 for positive urgency, 0.78 for lack of premeditation, 0.84 for lack of perseverance, and 0.66 for sensation seeking.

Statistical Analyses

Analyses were conducted using SPSS® version 22 (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0, IBM Corporation, Armonk, NY, USA). Analyses were two-tailed and p-values ≤ 0.05 were considered statistically significant. Descriptive statistics were presented using percentages for ordinal variables and the means and standard deviations for continuous variables. Percentage values were analyzed using the Chi-Square test, and quantitative data (scale scores) were analyzed using the Mann–Whitney U test [the threshold of significant was adjusted for multiple comparisons ($\alpha' = \alpha$/number of subdimensions of the scale)].

We conducted a multiple regression analysis to determine whether the quantitative variables (adult ADHD symptoms, anxiety, depression, five impulsivity sub-dimensions, and two emotion regulation sub-dimensions) were predictors of PIU (IAT score as the dimension). As there were no latent variables in the proposed models, mediation analyses with a regression-based approach were performed using the PROCESS macro (version 3.5.3) for IMB SPSS Statistics 22 (41) rather than structural equation modeling. The regression assumptions were confirmed, outliers were removed, and normal distribution and homoscedasticity were ensured through the square root transformation of the dependent variables. Bootstrap sampling was conducted using 5,000 resamples. We assessed collinearity between variables by making sure that variance inflation factor (VIF) was under 5 as recommended (42).

The following procedure was utilized to assess the mediation effects of anxiety and depressive symptoms, emotion regulation, and impulsivity in the association between self- adult ADHD symptoms and PIU. Gender and age were adopted as covariables. In the mediation model of the effect of X on Y through M, X was adult ADHD symptoms (ASRS score), Y was PIU (IAT score as a dimension), and M was the mediator variable. We conducted 3 multiple mediations to examine the independent mediation effects of the two HADS scores, the two ERQ scores, and the five UPPS-P scores (M variables) in the association between adult ADHD symptoms (ASRS score) and PIU (IAT score). Unstandardized regression coefficients were identified: *path a* (the effect of adult ADHD symptoms on M), *path b* (the effect of M on PIU), *path c* (the total effect of adult ADHD symptoms on PIU), and *path c*' (the direct effect of adult ADHD symptoms on PIU). Overall, the indirect effect of adult ADHD symptoms on PIU was the product of *path a* and *path b*.

RESULTS

Socio-Demographic Data, PIU, and Internet Activities

In our sample, the proportion of respondents with PIU was 17.9% ($N = 95$). The mean age of participants was 27.23 (SD = 10.18), and 73.9% of the sample were women. No differences in respondent with PIU were identified for age and gender (age: $U = 18695.5$; $p = 0.13$; gender: $\chi^2 = 1.159$; $p = 0.28$). However, there were significant differences between individuals with and without PIU in terms of their marital status and occupation, as individuals with PIU were more likely to be single (details are presented in **Table 1**). There were no differences ($\chi^2 = 19.749$; $p = 0.14$) in preferred online activity between the PIU and non-PIU groups. Overall, the most prevalent activities included the use of social media (42.9%), e-mails (20.1%), information searches (12.6%), and gaming (12.2%).

Prevalence of Adult ADHD Symptoms

The proportion of respondents who screened positive for adult ADHD symptoms in individuals with PIU (50.5%, $N = 48$) was significantly higher than in individuals without PIU (21.7%, $N = 95$; $\chi^2 = 32.9$, $p < 0.001$).

Comparison of Internet Users With and Without PIU

Table 1 presents the variable scale scores for both PIU and non-PIU individuals. Those with PIU scored significantly higher than those without PIU on every variable, except cognitive reappraisal, which was significantly higher among individuals without PIU. Only the impulsivity sub-dimensions of lack of perseverance and lack of premeditation were significantly higher for individuals with PIU than those without PIU.

Multiple Regression Model

The multiple regression model explained 20.0% of the variance of IAT scores [$F_{(10,531)} = 14.55$; $R^2 = 0.22$; *Adjusted* $R^2 = 0.20$; $p < 0.001$]. As shown in **Table 2**, IAT scores were significantly predicted by HAD-depression symptoms, UPPS-positive urgency, UPPS-lack of perseverance, ASRS, and ERQ-expressive suppression scores. Additionally, UPPS-negative urgency and ERQ-cognitive reappraisal scores were a negative predictor of IAT. Details are presented in **Table 2**.

TABLE 2 | Multiple regression model explaining IAT scores.

	β	Err-type	b	Err-type	$t_{(530)}$	*p*
OrdOrig.			5.34	0.28	19.09	<0.001*
Anxiety symptoms	0.07	0.04	0.02	0.01	1.56	0.12
Depression symptoms	0.12	0.05	0.04	0.02	2.62	0.009*
Negative urgency	−0.09	0.04	−0.03	0.01	−1.96	0.05*
Positive urgency	0.17	0.04	0.06	0.02	3.85	<0.001*
Lack of premeditation	−0.043	0.04	−0.02	0.02	−0.96	0.34
Lack of perseverance	0.11	0.05	0.04	0.02	2.27	0.02*
Sensation seeking	−0.05	0.04	−0.02	0.01	−1.31	0.19
Adult ADHD symptoms	0.23	0.04	0.15	0.03	5.15	<0.001*
Cognitive reappraisal	−0.13	0.04	−0.02	0.01	−3.22	0.001*
Expressive suppression	0.12	0.04	0.02	0.01	3.01	0.003*

$p \leq 0.05$; β, standardized coefficient; b, unstandardized coefficient; IAT, Internet Addiction Test.

TABLE 3 | Multiple regression model explaining IAT score with stepwise method.

	B	Err-type	*β*	$t_{(530)}$	*p*
OrdOrig.	5.24	0.25		20.863	<0.001*
Adult ADHD symptoms	0.151	0.03	0.24	5.342	<0.001*
Depression symptoms	0.05	0.02	0.15	3.460	<0.001*
Cognitive reappraisal	−0.02	0.01	−0.13	−3.364	<0.001*
Positive urgency	0.06	0.01	0.16	3.879	<0.001*
Expressive suppression	0.02	0.01	0.12	2.952	0.003*
Negative urgency	−0.03	0.01	−0.09	−2.139	0.033*
Lack of perseverance	0.03	0.02	0.09	2.002	0.046*

$p < 0.05$; β, standardized coefficient; B, unstandardized coefficient; IAT, Internet Addiction Test.

The multiple regression model conducted with the stepwise method explained 20.0% of the variance of IAT scores [$F_{(7,531)} = 20.012$; $R^2 = 0.21$; *Adjusted* $R^2 = 0.20$; $p < 0.001$]. As shown in **Table 3**, IAT scores were significantly positively predicted by ASRS scores, HAD-depression symptoms, UPPS-positive urgency, UPPS-lack of perseverance, and ERQ-expressive suppression scores. ERQ-cognitive reappraisal and UPPS-negative urgency scores were negative predictors of IAT scores. Details are presented in **Table 3**.

Mediation Analysis

The total effect of ASRS on IAT was 0.21 [model: $R^2 = 0.11$; $F_{(1,531)} = 62.81$; $p < 0.001$]. **Table 4** demonstrates the mediating role of UPPS-P, ERQ, and HADS scores on the relationship between ASRS and IAT.

ASRS and UPPS-P sub-scores significantly predicted IAT scores [$F_{(8,523)} = 12.19$, $p < 0.001$; $R^2 = 0.16$]. The direct effect of ASRS on IAT (c'-path) was significant (0.17,

TABLE 4 | Mediation models of the association between adult ADHD symptoms and PIU.

Model	Mediators		a[1]	b[1]	Indirect effect, a × b (95% CI)[1]
1	UPPS-NU	Negative urgency	0.05***	−0.14	−0.007 (−0.017, 0.001)
	UPPS-LPr	Lack of premeditation	0.08***	−0.07	−0.005 (−0.021, 0.010)
	UPPS-LPe	Lack of perseverance	0.14***	0.30**	0.041 (0.015, 0.069)
	UPPS-PU	Positive urgency	0.03*	0.39***	0.011 (0.00, 0.025)
	UPPS-SS	Sensation seeking	0.02	−0.13	−0.003 (−0.009, 0.002)
2	ERQ-CR	Cognitive reappraisal	0.02	−0.22***	−0.004 (−0.015, 0.008)
	ERQ-ES	Expressive suppression	0.02	0.15**	0.003 (−0.004, 0.012)
3	HADS-A	Anxiety symptoms	0.12***	0.12*	0.015 (0.000, 0.032)
	HADS-D	Depression symptoms	0.17***	0.21***	0.036 (0.017, 0.056)

[1] *Unstandardized coefficients.*

*Bias-corrected bootstrap results for the indirect effect, number of resamples 5,000; a: "path a" effect; b: "path b" effect; *p ≤ 0.05, **p ≤ 0.01, ***p < 0.001.*

$p < 0.001$). Therefore, the results suggested that UPPS-positive urgency and UPPS-lack of perseverance scores were partial mediators of the association between ASRS and IAT [indirect effect of positive urgency: 0.011, 95% CI (0.000, 0.025); indirect effect of lack of perseverance: 0.041, 95% CI (0.015, 0.069)]. Details are presented in **Table 4** and **Figure 1**.

ASRS and ERQ sub-scores significantly predicted IAT scores [$F_{(5,526)} = 19.32$, $p < 0.001$; $R^2 = 0.16$]. The direct effect of ASRS on IAT (c'-path) was significant (0.20, $p < 0.001$). ERQ sub-scores significantly predicted IAT (b-path) but were not predicted by ASRS (a-path). Therefore, emotion regulation sub-scores did not mediate the association between ASRS and IAT. Details are presented in **Table 4** and **Figure 1**.

ASRS and HADS sub-scores significantly predicted IAT scores [$F_{(5,526)} = 19.32$, $p < 0.001$; $R^2 = 0.16$]. The direct effect of ASRS on IAT (c'-path) was significant (0.15, $p < 0.001$). HADS sub-scores significantly predicted IAT (b-path) and were predicted by ASRS (a-path). Therefore, the results suggested that HADS-anxiety and HADS-depression scores were partial mediators of the association between ASRS and IAT [indirect effect of anxiety: 0.015, 95% CI (0.000, 0.032); indirect effect of depression: 0.036, 95% CI (0.012, 0.056)]. Details are presented in **Table 4** and **Figure 1**.

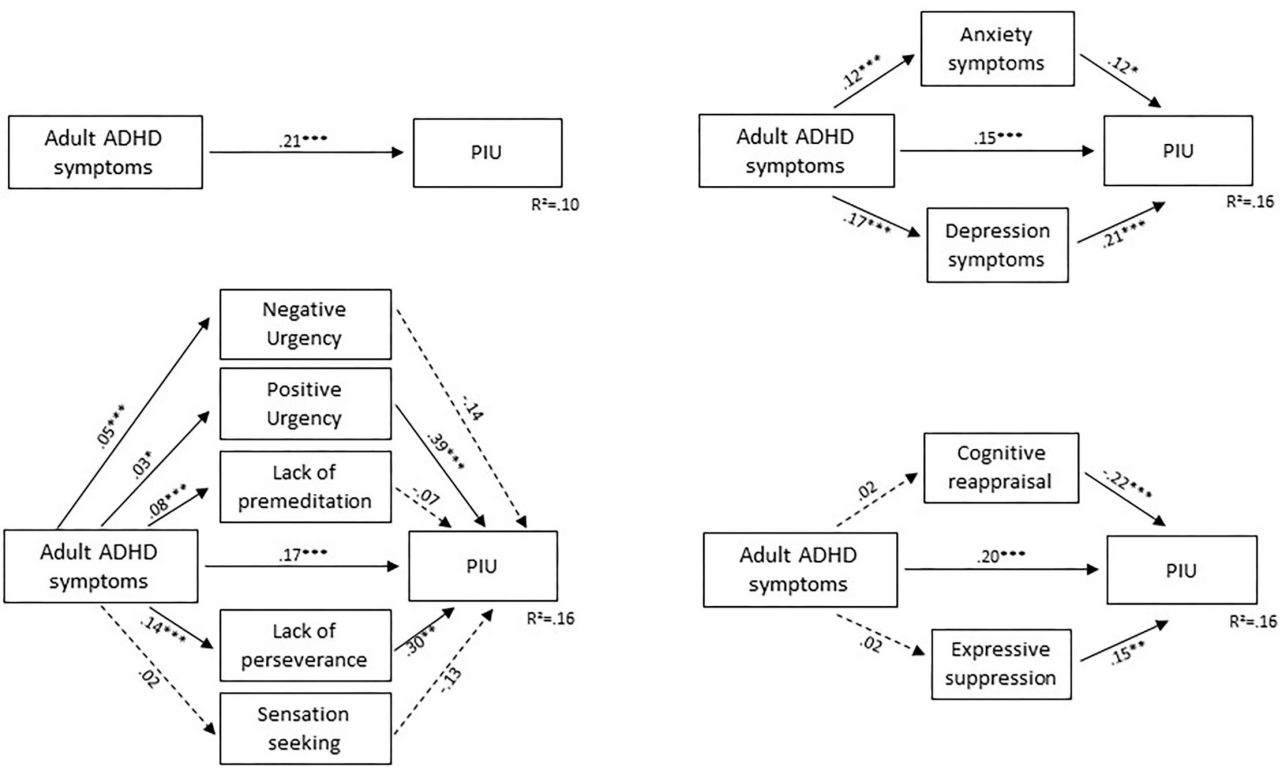

FIGURE 1 | Mediation models of the association between adult ADHD symptoms and PIU. Unstandardized coefficient; *$p < 0.05$, **$p < 0.1$, ***$p < 0.001$; PIU, problematic internet use assessed by the Internet Addiction Test; Non-continuous arrow, non-significant effect; continuous arrow, significant effect.

DISCUSSION

The purpose of this study was, firstly, to investigate the risk of adult ADHD symptoms in individuals with PIU. Secondly, we investigated how individuals with PIU differed from those without PIU in terms of several psychological factors such as anxiety, depression, impulsivity, emotion regulation and adult ADHD symptoms. Additionally, we investigated the predictive role of these factors (especially adult ADHD symptoms) in PIU severity. Finally, our study aimed to examine the possible mediating role of anxiety, depression, impulsivity and emotion regulation on the relationship between adult ADHD symptoms and PIU. The results of this study showed that the proportion of respondent who screened positive for adult ADHD symptoms was higher for individuals with PIU. Moreover, they had higher scores for anxiety and depressive symptoms, impulsivity (especially lack of perseverance, and premeditation), and expressive suppression and lower scores for cognitive reappraisal, than those without PIU. PIU severity was positively predicted by adult ADHD symptoms, depressive symptoms, positive urgency, lack of perseverance, and expressive suppression, and was negatively predicted by cognitive reappraisal and negative urgency. Finally, anxiety and depressive symptoms, positive urgency, and lack of perseverance were partial mediating factors of the association between adult ADHD symptoms and PIU severity.

Firstly, the results of this research confirm the significantly higher proportion of individuals with PIU who screened positive for adult ADHD symptoms, than those without PIU. These findings are in line with those of previous studies investigating ADHD-PIU comorbidity (8, 43–45). Therefore, it appears that individuals with PIU compared to those without are more likely to present with comorbid adult ADHD symptoms. Moreover, the mean age of our sample was young. And, the risk of engagement in problematic behaviors is higher in adolescents and young adults (46), especially if ADHD symptoms co-occurred (47). These results question the causal relationship between PIU and adult ADHD symptoms. Are PIU and adult ADHD independently caused by similar risk factors or does one cause the other?

Comparative analyses highlighted the clinical features of individuals with PIU, thus providing a better understanding of their function in terms of impulsivity, emotion regulation, and anxiety-depressive symptoms. Based on the results of this study, these individuals showed greater impulsivity, with significantly higher scores on lack of premeditation, and lack of perseverance, than those without PIU. Taken together, individuals with PIU therefore generally showed more marked impulsivity than those without PIU. These results are in line with a study conducted by de Vries et al. (44), which found that individuals with PIU had higher scores on the Barratt Impulsiveness Scale than those without PIU. In addition, the analyses of emotion regulation in this study indicated that expressive suppression was significantly higher, whereas cognitive reappraisal was significantly lower in people with PIU than individuals without PIU. The results of the linear multiple regression analysis showed that certain factors may explain the severity of PIU. Indeed, adult ADHD symptoms, depression symptoms, positive urgency, and expressive suppression were all predictors of the severity of PIU. Additionally, the results suggested that cognitive reappraisal can protect against the development of PIU, and negative urgency negatively predicts the disorder's severity. According to Gross and John (35), expressive suppression is associated with rumination about events that make the individual feel bad, high levels of negative emotions and depressive symptoms. These results highlight the greater vulnerability of individuals with PIU, as they tend to use ineffective emotion regulation strategies and to be more impulsive than those without PIU. The hypothesis that individuals with PIU have greater difficulty regulating their emotions has also been suggested by Koronczai et al. (48) and Przepiorka et al. (49). These results are in line with previous publication which highlighted the predictive role of emotion dysregulation on addictive behaviors (50). Engagement in addictive behaviors may be a way to avoid or regulate negative emotions, and "prolong or extend positive emotional states, if they demonstrate poor regulation over their emotions or lack alternative ways of responding" Estévez et al. (50). Depression may be a mediator between emotional stability and PIU (48), thus may explaining the significantly higher anxiety and depression scores of our participants with PIU.

It is highly likely that individuals with adult ADHD symptoms have important emotional dysregulation difficulties (18) and are at significant risk of using inappropriate strategies to cope with life events. Emotional impulsivity (18), anxiety and mood disorders (51, 52) are frequently observed in individuals with ADHD. "One important consideration is the possibility of depressive symptoms manifesting as a result of coping with lower hedonic tone in ADHD rather than being representative of a depressive disorder separate from ADHD" (53). Previous publications have suggested that impulsivity in ADHD may stimulate addictive behavior (54). Based on research with gambling disorders, three profiles of problem behaviors can be identified: behaviorally conditioned, emotional vulnerability, and anti-social impulsivity (7). The emotionally vulnerable and the anti-social impulsivity profiles may partly apply to individuals with adult ADHD symptoms, thus explaining their high risk of problematic behavior, especially in terms of PIU. Di Nicola et al. (52) suggest individuals with mood disorders and comorbid ADHD has a higher risk of suicide attempts, and lifetime substance use disorder, than individuals without comorbid ADHD. Additionally, individuals with problematic behaviors who report ADHD symptoms have higher levels of impulsivity, anxiety disorders, negative emotionality, and lower positive emotionality than individuals without ADHD (55). Individuals with PIU are at higher risk of having comorbid adult ADHD symptoms than those without PIU, which may be expressed through more marked impulsivity and emotion regulation difficulties (18). These results suggest either these two disorders have similar dysfunction-related underpinnings (features such as poor emotion regulation strategies, impulsivity and negative affectivity), one disorder represents an unsuccessful attempt to regulate the other or that the causality is bi-directional.

Finally, the mediation analyses provided a better understanding of the possible mediating effects of variables

including impulsivity, emotion regulation, and anxiety-depressive symptoms on the co-occurrence of adult ADHD symptoms and PIU. The results demonstrated a mediating role of impulsivity through two of its sub-dimensions (positive urgency and lack of perseverance), as well as of anxiety and depressive symptoms. Conversely, emotion regulation, through expressive suppression and cognitive reappraisal, did not have a mediating effect on the comorbidity of these two disorders. It would be interesting to look at that issue in more depth. Further studies should use the Difficulty in Emotion Regulation Scale [DERS; (56)], which identifies 6 sub-dimensions of emotion dysregulation: non-acceptance, goals, impulse, strategies, awareness, and clarity. Indeed, the use of this multidimensional model and its corresponding questionnaire could reveal difficulties in emotion regulation in individuals with comorbid adult ADHD-PIU, which could then provide a useful basis for therapeutic interventions. Kalbag and Levin (57) suggested cognitive-behavioral therapy to manage both ADHD and problematic behavior such as substance abuse. They reported the importance of managing poor coping skills and strategies, control of emotional reactions, feelings of being overwhelmed by negative life events, and negative emotions, which in turn will reduce substance reliance. In line with the literature, we hypothesize impulsivity, mood, and anxiety disorders may further increase the risk of problematic behaviors such as PIU, even more for individuals who screen positive for adult ADHD symptomatology. The current results agree the hypothesis that the use of the Internet may be a way of coping with the difficulties arising from having comorbid adult ADHD symptoms. Therapeutic and preventive interventions targeting emotional impulsivity and anxiety-depressive symptoms may be contemplated to prevent and manage comorbid PIU and adult ADHD symptoms.

This study has some limitations. The cross-sectional design and the lack of investigation of the comorbid addictive behaviors prevent any conclusions about causality. Future studies should opt for a longitudinal design and plan investigation of comorbid addictive disorders to ensure that the differences between groups are associated with PIU, not other addictive behavior. Future investigations should also screen for comorbid psychiatric disorders. The study was carried out with a sample of non-clinical adults, and it would be beneficial to conduct further investigations with a clinical population of adults with diagnosed ADHD or PIU, who have more marked psychopathological features. Additionally, all data was collected online, and the participants were recruited on the social media. We did not have access to the number and the characteristics of the total potential participants, for which the questionnaire was visible. This questions the representativeness of the sample. We also used self-administered questionnaires. For example, the ASRS has limitations in terms of screen for adult ADHD symptoms. Using a semi-structured diagnostic interview for adult ADHD, such as the Diagnostisch Interview Voor ADHD bij volwassenen (DIVA), which assesses the occurrence of DSM-5 ADHD criteria (inattention, hyperactivity, and impulsivity) across both childhood and adulthood, may strengthen the results presented in the current paper. We also did not consider the effect of different Internet activities on PIU. Therefore, PIU may vary and possibly involve different psychopathological mechanisms depending on the type of Internet activity. For example, previous investigations have found that PIU in adolescents with ADHD is specifically associated with online gaming, emailing, and social networking (58). Their results emphasize that PIU is associated with specific online activities, which warrants further in-depth investigation.

In conclusion, the results of this research confirmed the high levels of comorbidity between adult ADHD symptoms and PIU in the general population. The current study also highlighted the need for further investigation of PIU in individuals with adult ADHD symptoms and of adult ADHD symptoms in individuals with PIU in order to reduce the co-occurrence of these two disorders, which may lead to negative outcomes. Individuals with PIU presented characteristics similar to those observed in individuals with adult ADHD symptoms, including in terms of high levels of impulsivity and its sub-dimensions, difficulties with emotion regulation, and anxiety and depression. The results of the impulsivity sub-dimensions and anxiety-depressive symptoms were in line with a mediating effect in the relationship between the two disorders. Therefore, future studies should investigate clinical interventions targeting both adult ADHD and PIU by focusing on impulsivity, emotion dysregulation, and comorbid psychiatric disorders such as anxiety and depression. This study conducted in non-clinical population identified psychopathological risk factors of PIU and enable the identification of vulnerable individuals who prevention interventions may target. Adolescents and young adults are especially at risk for problematic behaviors, mood and anxiety disorders. Therefore, further investigations in this specific population are needed.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by IRB 2019-03-01. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SB: data collection. SB, AR, and SE: writing—original draft preparation and writing—review and editing. IV, PB, and SB: study design, concept, and supervision. All authors have read and approved the published version of the manuscript.

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Preventive Medication Patterns in Bipolar Disorder and Their Relationship With Comorbid Substance Use Disorders in a Cross-National Observational Study

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Objective: The potential role of sub-optimal pharmacological treatment in the poorer outcomes observed in bipolar disorder (BD) with vs. without comorbid substance use disorders (SUDs) is not known. Thus, we investigated whether patients with BD and comorbid SUD had different medication regimens than those with BD alone, in samples from France and Norway, focusing on compliance to international guidelines.

Methods: Seven hundred and seventy patients from France and Norway with reliably ascertained BD I or II (68% BD-I) were included. Medication information was obtained from patients and hospital records, and preventive treatment was categorized according to compliance to guidelines. We used Bayesian and regression analyses to investigate associations between SUD comorbidity and medication. In the Norwegian subsample, we also investigated association with lack of medication.

Results: Comorbid SUDs were as follows: current tobacco smoking, 26%, alcohol use disorder (AUD), 16%; cannabis use disorder (CUD), 10%; other SUDs, 5%. Compliance to guidelines for preventive medication was lacking in 8%, partial in 44%, and complete in 48% of the sample. Compliance to guidelines was not different in BD with and without SUD comorbidity, as was supported by Bayesian analyses (highest Bayes Factor = 0.16). Cross national differences in treatment regimens led us to conduct country-specific adjusted regression analyses, showing that (1) CUD was associated with increased antipsychotics use in France (OR = 2.4, 95% CI = 1.4–3.9, $p = 0.001$), (2) current tobacco smoking was associated with increased anti-epileptics use in Norway

(OR = 4.4, 95% CI = 1.9–11, $p < 0.001$), and (3) AUD was associated with decreased likelihood of being medicated in Norway (OR = 1.2, 95% CI = 1.04–1.3, $p = 0.038$).

Conclusion: SUD comorbidity in BD was overall not associated with different pharmacological treatment in our sample, and not related to the level of compliance to guidelines. We found country-specific associations between comorbid SUDs and specific medications that warrant further studies.

Keywords: bipolar disorder, substance use disorder, treatment guidelines, tobacco smoking, comorbidity

INTRODUCTION

Bipolar disorder (BD) is a chronic and relapsing condition associated with a high burden for individuals, caregivers, and societies (1). This burden is strongly associated with the high level of comorbidity in BD (2, 3). Comorbid substance use disorders (SUDs, including nicotine dependence/tobacco smoking) are found in up to 50–60% individuals with BD (4–6). Compared to BD alone, the presence of comorbid SUD (BD + SUD) has been associated with poorer outcomes, including premature mortality (7), higher rates of suicide attempts (8), and suicide mortality (9), as well as delayed remission from acute mood episodes (10). The presence of comorbid SUDs may complicate the pharmaceutical management of BD (11); e.g., tobacco use disorders have been associated both with a more severe psychopathology, as shown by our group (8) and others (12), and complicated pharmaceutical management (13). Beyond age and gender, additional dimensions related to abnormal self-awareness might contribute to increased SUD risk in BD, namely sensation seeking (14) and anxiety (15). These may co-exist in individuals with particularly complex BD course in case of, e.g., comorbid borderline personality disorders (16), further increasing the likelihood of complicated pharmaceutical management.

To date, there is no specific guideline for the pharmaceutical treatment of BD + SUD (17). Indeed, guidelines are often limited by the fact that they are typically based on the results of randomized controlled double-blind trials, which include selected BD patients. Consequently, patients with psychiatric comorbidities such as SUDs are often excluded. Moreover, a substantial proportion of BD patients show inadequate response to medication (18). Medication patterns in community BD samples and naturalistic settings often diverge from guidelines, increasing the risk of poor clinical outcome (19). This includes scarce lithium use (20), polypharmacy (21), frequent antidepressant (22), and benzodiazepine use (23) despite lack of evidence for their efficacy in BD and additional risk of addiction for the latter (24).

Comorbid SUDs are may play a role in both the lack of treatment response and the use of non-recommended medication regimens in BD for several reasons. Firstly, psychoactive substances can elicit a wide range of BD symptoms [e.g., psychotic and manic symptoms with cannabis (25)], which may increase the need for symptomatic treatment. Secondly, substance use also alters the pharmacodynamics [e.g., amphetamines (26)] and the pharmacokinetics [e.g., tobacco and P450 enzymes (13)] of medications for BD. Thirdly, BD + SUD has been associated with reduced treatment adherence compared to BD alone (27) – although this may be accounted for by impulsiveness (28). Fourthly, both clinicians' and patients' perceptions might influence prescription attitudes and modify the pharmaceutical treatment of BD in case of comorbid SUD. This might be due to lower psychoeducation level, increased stigma, or lack of confidence in treatment efficacy (29, 30). With that regards, one study reported no difference of medication profiles in BD + SUD vs. BD inpatients at discharge (31). Two other studies, although not specifically aimed at comparing BD with vs. without SUDs, reported discrepant results. One study conducted among homeless persons with BD showed that comorbid SUDs were significantly associated with inappropriate prescription regimens (32), while a nationwide French cohort study (independent from the sample analyzed in the current study) did not observe any difference in preventive BD medication in outpatients with vs. without SUDs (33). Given the paucity of available literature, knowledge about the sources of variability (34) and non-compliance to guidelines of pharmacological treatment in BD + SUD remains limited. Furthermore, the clinical management of BD patients can be affected by local customs, expert opinions, and differences in treatment availability. Likewise, the epidemiology of SUD also shows major cross-national differences. This warrants cross-national comparisons to disentangle the effects of SUDs from national trends in SUD and medication usage.

To investigate this issue, we used data from a large, well-characterized sample of patients with BD from France and Norway. Our objective was to investigate whether the presence of SUDs would be associated with different preventive medication regimens, including more frequent deviations from European guidelines, differences in the use of individual medication classes, and different likelihood of receiving current preventive medication. We further aimed to clarify whether putative relationships between medication regimens and SUDs are independent from clinical and demographic variables, especially country of inclusion.

MATERIALS AND METHODS

This was a *post hoc* study of a sample of patients with ascertained BD recruited in France (2000–2012) and Norway (2003–2020). Both original studies aimed to extensively characterize BD in order to inform future prevention and treatment strategies, using similar assessment protocols.

Participants

Inclusion criteria for France were: (1) age ≥18 years; (2) meeting criteria for a diagnosis of BD-I or BD-II disorder according to the Diagnostic and Statistical Manual for Mental Disorders, 4th edition, text revised (DSM-IV-TR) (35); and (3) willingness and ability to provide written informed consent. In France, participants also had to (1) be under preventive medication and be euthymic at inclusion, as defined by a Montgomery-Asberg Depression Rating Scale (MADRS) score ≤8 (36) and a Young Mania Rating Scale (YMRS) score of ≤5 (37); (2) master the French language. Moreover, in France, ability to provide written informed consent also required the absence of clinically significant cognitive impairment, which was assessed using clinical judgment. In Norway, although euthymia was not a formal inclusion criterion, participants had to be clinically stable and to master a Scandinavian language. Also, specific effort was made to include cases early in their first treatment for BD. Additional exclusion criteria in Norway were: (1) history of severe head trauma and (2) intellectual disability. For Norwegian cases, who participated in a neurocognitive assessment we used an estimated IQ based on two subtests of the WAIS with a good concordance with total IQ. For a small subset of participants who did not attend the neurocognitive assessment, we undertook a comprehensive review of educational attainment, school grades, and general interview performance to rule out the presence of intellectual disability (which is defined as an IQ < 70).

Written informed consent was obtained from all participating patients in both countries. In France, The Research Ethics Board of Pitié-Salpêtrière Hospital reviewed and approved this study. In Norway, the project was approved by the Regional Committee for Medical Research Ethics and the Norwegian Data Inspectorate. This involved being registered in the database and having one's data analyzed for research purposes.

Study Sample

A total of 770 patients with BD-I (n = 526) or BD-II (n = 244) and reliable medication status were included. Recruitment was consecutive in both countries. Patients who sought treatment for BD in psychiatric units were evaluated for eligibility for study participation by their treating clinician. We do not know how many who refused to participate, but of those referred, the refusal rate was <5%. Due to ethical regulation, data about patients, who refused to enter the study could not be analyzed. The study of treatment compliance to guidelines and individual medication classes was performed in 670 medicated cases from France and Norway. All French cases received some medication at the time of inclusion in line with inclusion criteria. They were therefore excluded from the medicated vs. unmedicated analysis. Thus, the comparison of medicated vs. unmedicated status was performed in 525 cases from Norway only (**Figure 1**).

Clinical Assessment

Trained psychiatrists, medical doctors, and clinical psychologists carried out clinical assessments aimed at providing reliable lifetime DSM-IV BD and SUD diagnoses in both samples. Investigators used the Diagnostic Interview for Genetic Studies [DIGS (38)] in France and the Structured Clinical Interview for DSM-IV axis-I disorders [SCID-I (39)] in Norway. The course of BD was also extensively characterized.

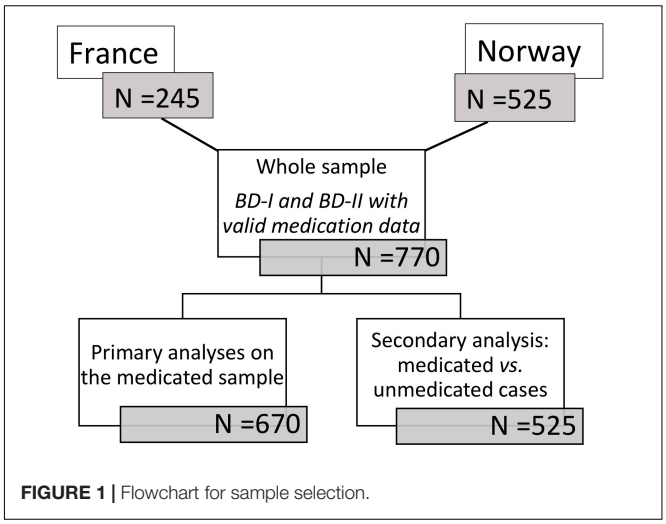

FIGURE 1 | Flowchart for sample selection.

Substance Use Assessments

Tobacco smoking was defined as smoking on a daily basis – a reliable proxy of DSM-IV nicotine dependence (40). In the French subsample, lifetime tobacco smoking (former + current) was assessed, while in the Norwegian subsample, only current tobacco smoking was considered. As such, tobacco smokers in the French subsample (N = 160) were both current (N = 99) and former smokers (N = 61), whereas those from the Norwegian subsample were current smokers only (N = 261). Diagnoses of abuse or dependence to other substances were combined to obtain single binary variables of "use disorder" for alcohol and cannabis use disorders (hereafter termed AUD and CUD, respectively), yielding the following categories: current tobacco smoking, lifetime AUD, lifetime CUD, and lifetime SUDs not related to tobacco nor alcohol nor cannabis, hereafter termed "other SUDs." Additionally, we kept the possibility of analyzing all SUDs that were not AUD, i.e., CUD + "other SUDs," in case the subgroups would be deemed too small and/or yielded borderline associations.

Medication Regimens

In both countries, current medications were recorded and categorized by the investigator into: lithium, anti-epileptics (valproate derivatives including valpromide, carbamazepine, lamotrigine), antipsychotics, antidepressants, and benzodiazepines. The sample can be considered as naturalistic with regards to medications since participants were recruited with their treatment as prescribed by the clinician in charge, which was thus unrelated to the current study (although being medicated was an inclusion criterion in the French sample).

Treatment Compliance to Guidelines

Firstly, we categorized the sample in relation to level of compliance to recommendations for preventive

treatment of international guidelines [e.g., NICE (41), CANMAT/ISBD (42)], where lithium, several antiepileptics (valproate/valpromide/carbamazepine/lamotrigine) and antipsychotics are considered first-line mood-stabilizers. Antiepileptics and antipsychotics with primary indication in BD were identified from the Norwegian and French national recommendations. Compliance to those guidelines was deemed absent when the participant was using antidepressant or benzodiazepine without mood-stabilizer, partial if any antidepressant or benzodiazepine was used together with mood-stabilizer and complete when no antidepressant or benzodiazepines and any mood-stabilizer was used. Importantly, we focused on preventive treatment, since the samples are euthymic or next-to-euthymic and the range of episode-specific treatments was deemed too large. Regardless of underlying mood-stabilizing treatment, we considered that antidepressants and benzodiazepines remained not fully compliant in the maintenance phase of BD. Such medications are often used at some point in the course of BD, whether during the initial – often undiagnosed – phase where unspecific depressive and anxiety can prevail (43), to alleviate symptoms of comorbid anxiety disorders (3), or for the acute treatment of depressive episodes. Benzodiazepines and/or antidepressants are not easily discontinued. This may be due to prevasive residual symptoms (44) and/or clinicians' beliefs and patients' anticipatory anxiety regarding medication cessation (28). However, they have been associated with a wide range of adverse features in BD, including manic symptoms and rapid cycling for antidepressants (45) and cognitive impairment and addictive disorders for benzodiazepines (23). Additionally, both the possible causes and consequences of prescribing antidepressants and/or benzodiazepines in BD have been associated with SUD comorbidity in BD (46, 47), further warranting the focus on these medication classes as proposed in the current study.

Individual Medical Classes

Secondly, we analyzed each individual medication class and their relationship to SUD and key sociodemographic and clinical variables, by country.

Medicated vs. Unmedicated

Thirdly, in the Norwegian subsample we were also able to compare SUD rates in those not using any psychotropic treatment ("unmedicated") vs. those receiving psychotropic medication ("medicated"). Here, we excluded cases in their first treatment episode for (hypo)mania (n = 195), as preventive treatment may not yet have been initiated in these cases. We analyzed the "medicated" status separately because we anticipated that this would be associated with different patient histories and clinical correlates as compared to guidelines compliance and medication regimens. In order to explore these results further, we also present data from a subsample of 161 cases, who filled in both the *Medication Adherence Rating Scale* (MARS) (48) to measure adherence, and the *Beliefs about Medicines Questionnaire* (BMQ) (49) to measure the general attitude toward medicine and medication and to estimate how much the patients' concerns overcome his/her perceived needs for medication, using the general and the specific subscales. Of note, these secondary analyses are provided for discussion purposes only.

Statistics

Data are described as means (standard deviation, SD), medians (interquartile range, IQR) or counts (frequency). Bivariate tests were performed for SUDs only and medication-related variables, namely: in the sample as a whole and – if any of these variables exhibited cross-national differences – in each country, separately for compliance to guidelines and individual medication classes (lithium, anti-epileptics, antipsychotics, antidepressants, and benzodiazepines) and in the Norwegian subsample for the status "being medicated." We used trend tests for variables with >2 groups and Chi-squared or Fisher's exact tests for the others, based on a threshold for statistical significance at $p < 0.05$ (two-tailed tests). In order to verify the null hypothesis when a lack of difference in the medication pattern according to the SUD status will be observed, we computed Bayes factors (BF) with the R package *BayesFactor*. A BF can take any decimal value above zero. A value of 1 indicates equal evidence for both the H_1 and H_0 hypotheses. The more the value closes to zero, the stronger evidence for an absence of difference. To interpret BFs, we used the recommended thresholds (50) (**Supplementary Table 1**).

Each medication pattern variable (compliance to guidelines, specific medication classes and being medicated vs. unmedicated) significantly associated with one of the SUD variables was used as the dependent variable into regression models to ascertain the independence of associations from potential confounders. These confounders were chosen when they were associated with a given medication variable, at $p < 0.05$, two-tailed bivariate tests. In the case of a lack of association between and SUDs and our main medication-related variables – namely: compliance to guidelines and the status of "being medicated," an exploratory regression model was still performed in order to fully test our main hypotheses. All analyses were conducted with R version 4.0.2 (51) through R studio version 1.3.1093 for Mac OS® X.14.6. A summary of the packages that were used is available as a **Supplementary Methods**.

RESULTS

Description of Medication and Substance Use Disorder in the Whole Sample (n = 670)

Compliance with international guidelines was distributed as follows: absent in 53 (8%) cases, partial in 296 (44%) cases, and complete in the remaining 321 (48%) cases. A majority of patients (55%) reported polypharmacy. Current smoking was reported by 174 participants (26%). AUD was diagnosed in 104 (16%), CUD in 66 (10%), and other SUDs in 28 (5%) patients (**Table 1**).

Compliance to Guidelines Across Substance Use Disorders

We found no difference in terms of compliance to guidelines regarding comorbid SUDs (**Table 2**); fully consistent with Bayes

TABLE 1 | Description of the medicated sample, as a whole, and by country.

	Whole medicated sample	*N*	Norway	France	Test value	*p*-Value Norway vs. France
	***N* = 670**		***N* = 425**	***N* = 245**		
Gender (women vs. men)	402 (60%)	670				
Age***	36 (27–47)	670				
Site (Norway vs. France)	425 (63%)	670				
BD-II subtype (vs. BD-I)	190 (28%)	670				
AAO of BD*	21.0 (17–28)	528				
BD duration***	13.0 (7–23)	528				
Rate of MDE/year of BD***	0.3 (0.1–0.8)	480				
Rate of (hypo)manic episodes/year of BD*	0.4 (0.1–1.4)	363				
History of psychosis	394 (60%)	669				
Lifetime SA**	205 (39%)	525				
Current tobacco smoking***	174 (26%)	670				
Lifetime AUD*	104 (16%)	662				
Lifetime CUD	66 (10%)	664				
Other SUD lifetime*	28 (5%)	523				
Compliance to treatment guidelines						
Complete	321 (48%)	670	221 (52%)	100 (41%)		0.006
Partial	296 (44%)		168 (40%)	128 (52%)	10.2	
Absent	53 (8%)		36 (9%)	17 (7%)		
Current lithium treatment***	196 (30%)	661	99 (42%)	97 (23%)	25.7	<0.001
Current anti-epileptic treatment***	256 (38%)	670	97 (23%)	99 (42%)	14.3	<0.001
Current antipsychotics treatment***	329 (49%)	669	139 (33%)	117 (48%)	51.1	<0.001
Current antidepressant treatment***	289 (43%)	669	254 (60%)	75 (31%)	0.0215	0.883
Current benzodiazepine treatment***	124 (19%)	790	185 (44%)	104 (43%)	60.3	<0.001

*Data are given as N (%) or median (IQR). Significant association with compliance to treatment guidelines in the whole sample are marked as *p < 0.05, **p < 0.01, ***p < 0.001. Tests and p-values are from Chi-squared, Fisher's, or Mann–Whitney tests for differences between Norway and France, uncorrected.*
BD, bipolar disorder; AAO, age at onset; MDE, major depressive episode; SA, suicide attempt; AUD, alcohol use disorder; CUD, cannabis use disorder; SUD, substance use disorder.

TABLE 2 | Variables associated with compliance to treatment guidelines in the whole medicated sample (*N* = 670).

Compliance with international guidelines	Complete	Partial	Absent	Test value	*p*-Value	*N*
	***N* = 321**	***N* = 296**	***N* = 53**			
Gender (women vs. men)*	176 (55%)	189 (64%)	37 (70%)	7.53	0.023	670
Age*	34 (26–45)	39 (28–48)	33 (28–49)	6.51	0.039	670
Site (Norway vs. France)**	221 (69%)	168 (57%)	36 (68%)	10.2	0.006	670
BD-II subtype (vs. BD-I)***	59 (18%)	103 (35%)	28 (53%)	37.4	<0.001	670
AAO of BD	22 (18–30)	20 (17–28)	20 (15–27)	2.666	0.264	528
BD duration	11 (6–22)	14 (8–23)	13 (6–28)	4.851	0.088	528
Rate of MDE/year of BD**	0 (0–1)	0 (0–1)	0 (0–1)	11.751	0.003	479
Rate of (hypo)manic episodes/year of BD	0 (0–1)	0 (0–2)	0 (0–2)	5.6811	0.125	363
History of psychosis***	218 (69%)	154 (53%)	22 (42%)	22.9	<0.001	660
Lifetime SA**	72 (30%)	118 (47%)	15 (41%)	14.2	0.001	525
Current tobacco smoking	78 (24%)	86 (29%)	10 (19%)	3.32	0.19	670
Lifetime AUD	46 (14%)	50 (17%)	8 (15%)	0.93	0.628	662
Lifetime CUD	28 (9%)	31 (11%)	7 (13%)	1.3	0.521	664
Other SUD lifetime*	10 (4%)	17 (7%)	1 (3%)	NA[a]	0.456	523

*Data are given as N (%) or median (IQR). *p < 0.05, **p < 0.01, ***p < 0.001. Tests and p-values are from Chi-squared, Fisher's, or Kruskal–Wallis tests.*
BD, bipolar disorder; AAO, age at onset; MDE, major depressive episode; SA, suicide attempt; AUD, alcohol use disorder; CUD, cannabis use disorder; SUD, substance use disorder. Other SUDs refer to SUDs not related to alcohol, nor cannabis.
[a]*Fisher's exact test.*

Factors (**Supplementary Figure 1**), which indicated strong evidence for a lack of difference. In ordinal logistic regression, neither current smoking, AUD or CUD were associated with non-guideline compliant treatment (lowest *p*-value = 0.21 for CUD). However, in this model, female gender (OR = 1.6, $p = 0.014$) and BD-II subtype (OR = 2.6, $p < 0.001$) remained independently associated with lower compliance to guidelines (data not shown).

Individual Medication Classes Across Substance Use Disorders

There was no significant difference in individual medication classes as a function of SUDs (**Supplementary Table 2**), which was supported by Bayes Factors as well (**Supplementary Figure 1**). The complete medication patterns as a function of SUD comorbidity is shown in **Supplementary Figure 2**. Since there were significant differences in the proportion of French vs. Norwegian cases regarding compliance to guidelines (**Table 1**) and every individual medication classes but antidepressants (highest $p = 0.006$), we further characterized country effects and country-specific medication regimens.

Norwegian cases were more likely than the French to receive compliant treatment (52 vs. 41%, overall $p = 0.006$), probably due to the higher proportion of French cases receiving treatment with partial compliance to guidelines (40 vs. 52%). This was likely driven by large differences in benzodiazepine use (10 vs. 34%). Additionally, the absence of compliance to guidelines seemed more frequent in Norway compared to France (9 vs. 7%), which further legitimated country-specific follow-up analyses of the relationship between (1) SUDs and compliance to guidelines and (2) SUDs and individual medication classes, as shown below.

Country-Specific Associations Between Substance Use Disorders and Compliance to Guidelines

Both BFs (**Supplementary Figure 2**) and exploratory ordinal regressions (data not shown) supported an absence of country effect in the compliance to guidelines (lowest *p*-values = 0.21 for AUD in France and 0.45 for CUD in Norway, respectively).

Country-Specific Associations Between Substance Use Disorders and Individual Medication Classes

In Norway (**Supplementary Table 3**), antiepileptics use was more frequent in current compared to former + never smokers ($p = 0.001$). Follow-up binary regressions showed that tobacco smoking remained significantly associated with increased antiepileptics use (OR = 2.4, 95% CI = 1.4–3.9, $p = 0.001$) after controlling for the effects of BD subtype (BD-II vs. BD-I, OR = 1.7, 95% CI = 1.1–2.6, $p = 0.019$) (**Figure 2A**). The AUC of the model was 0.68, based on 239 cases. There was no other association between individual SUD and individual medication classes in the Norwegian subsample.

In France (**Supplementary Table 4**), antipsychotics use was more frequent in case of lifetime CUD ($p < 0.001$). This was confirmed by binary regression, where CUD remained significantly associated with antipsychotics use (OR = 4.4, 95% CI = 1.9–11, $p < 0.001$) after controlling for the effect of BD subtype ($p = 0.8$), and history of psychosis (OR = 2.2, 95% CI = 1.1–5.6, $p = 0.03$) (**Figure 2B**). The AUC of the model was 0.77 based on 191 cases. There was no other association between individual SUDs and individual medication classes in the French subsample.

Substance Use Disorder and Medicated vs. Unmedicated Cases

The Norwegian subsample comprised 274 (83%) medicated and 56 (17%) unmedicated cases after exclusion of first-treatment cases ($n = 195$). Being medicated vs. unmedicated had no significant association with any SUD (**Table 3**).

When including current smoking and both lifetime AUD and CUD in a binary regression analysis (**Figure 3**), we uncovered an independent association between being unmedicated and AUD (OR = 1.2, 95% CI = 1.04–1.3, $p = 0.038$). Being currently unmedicated was also independently associated with a higher number of (hypo)manic episodes (OR = 1, 95% CI = 1.02–1.07, $p < 0.001$) and a lower probability of lifetime suicide attempt (OR = 0.88, 95% CI = 0.79–0.97, $p = 0.014$). AUC of this model was 0.78, based on 195 cases. Of note, we entered AAO of BD and the absolute number of (hypo)manic episodes together instead of the rate of (hypo)manic episodes in order to avoid multicollinearity and to be able to dissect the effects from both AAO and the number of episodes.

Finally, there was no indication that BD cases with comorbid SUD had higher resistance (lowest *p*-values = 0.499 for the BMQ-general and 0.374 for the BMQ-specific) or lower adherence (*p*-value = 0.39 for MARS) regarding their medication, as compared to BD cases without any SUD. Interestingly though, the BMQ necessity subscore was higher in the BD+AUD than in the BD alone group, $p = 0.037$.

DISCUSSION

In this study of a large sample of patients from France and Norway, who were extensively characterized for both BD and SUD history, we found no significant association between the compliance to pharmacological treatment guidelines and comorbid SUDs. Thus, our results suggest that it is feasible to follow existing guidelines to treat BD, also for patients with comorbid SUD. In line with this, no SUD was associated with individual medication classes in the sample as a whole. However, country-specific analyses identified independent associations between current tobacco smoking and anti-epileptics use and between AUD and being unmedicated in the Norwegian subsample; as well as between CUD and antipsychotics use in France. To the best of our knowledge, this study reports among the most detailed characterization of the links between comorbid SUD and preventive medication in BD, with a focus on both medication patterns and level of medication compliance to guidelines. Our main finding, which is negative, was ascertained with the computation of Bayes factors, meaning that we had adequate statistical power and that this finding can be considered as reliable. Importantly as regards generalizability, the medication

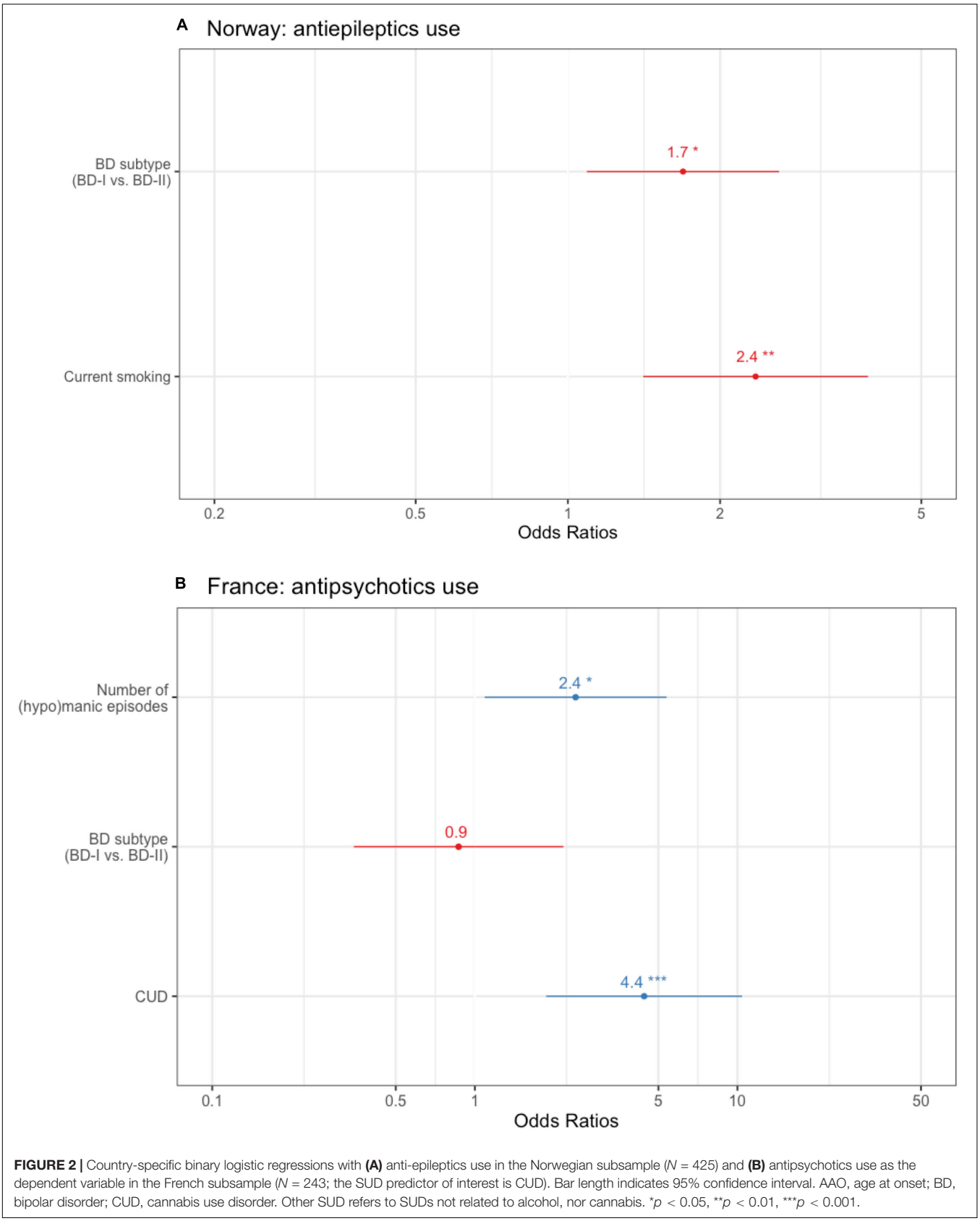

FIGURE 2 | Country-specific binary logistic regressions with **(A)** anti-epileptics use in the Norwegian subsample (N = 425) and **(B)** antipsychotics use as the dependent variable in the French subsample (N = 243; the SUD predictor of interest is CUD). Bar length indicates 95% confidence interval. AAO, age at onset; BD, bipolar disorder; CUD, cannabis use disorder. Other SUD refers to SUDs not related to alcohol, nor cannabis. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

TABLE 3 | Variables associated with the current medicated status in the Norwegian subsample, who was not in their first mood episode.

	Unmedicated	Medicated	Test value	*p*-Value	Effect size (95% CI)	*N*
	N = 56	*N* = 274				
Gender (women vs. men)	33 (59%)	166 (61%)	0.0065	0.936	1.1 (0.6, 1.9)	330
Age	34 (24–46)	36 (27, 46)	6973	0.282	−0.13 (−0.45, 0.17)	330
BD-II subtype (vs. BD-I)**	33 (59%)	97 (35%)	9.82	0.002	2.6 (1.5, 4.7)	330
AAO of BD*	18 (14–22)	20 (16.8–27)	2778	0.016	−0.43 (−0.81, −0.09)	237
BD duration	15 (8–26)	12.0 (7–20)	4277	0.132	0.28 (−0.09, 0.66)	237
Lifetime SA	6 (17%)	66 (33%)	3.11	0.078	2.4 (1.0–6.8)	236
History of psychosis	26 (46%)	154 (57%)	1.78	0.182	1.5 (0.9–2.8)	325
Rate of MDE/year of BD	0.4 (0.1–1)	0.4 (0.2–0.9)	2878	0.895	0.09 (−0.32, 0.49)	219
Rate of (hypo)manic episodes/year of BD**	1 (0.2–3)	0.4 (0.2–1)	4816	0.004	0.4 (0.07–0.75)	237
Current tobacco smoking	4 (7%)	50 (18%)	3.42	0.065	2.8 (1.1–9.8)	330
Lifetime AUD	11 (20%)	33 (12%)	1.71	0.191	0.6 (0.3–1.2)	330
Lifetime CUD	8 (14%)	20 (7%)	NA[a]	0.111	0.5 (0.2–1.2)	330
Other SUDs	4 (11%)	13 (6%)	NA[a]	0.308	0.6 (0.2–2.1)	240

*Data are given as N (%) or median (IQR). *p < 0.05, **p < 0.01. Tests and p-values are from Chi-squared, Fisher's, or Mann–Whitney tests. Effect size expressed as univariate odds ratio for categorical variable and Cohen's d for continuous variables. Medicated status represents the reference group.*
BD, bipolar disorder; AAO, age at onset; MDE, major depressive episode; SA, suicide attempt; AUD, alcohol use disorder; CUD, cannabis use disorder; SUD, substance use disorder. Other SUDs refer to SUDs not related to alcohol, nor cannabis.
[a]*Fisher's exact test.*

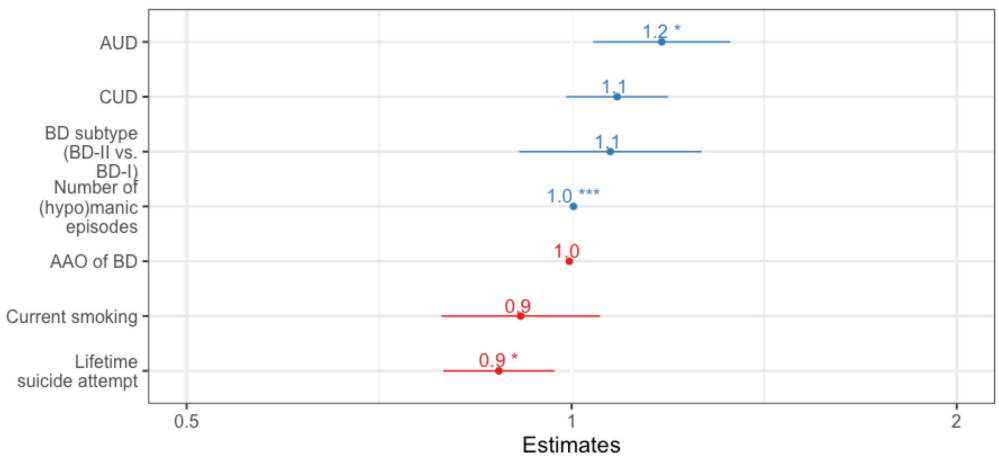

FIGURE 3 | Forest plot for binary logistic regression in Norway, with "being unmedicated vs. medicated" as the dependent variable. *N* = 195 after exclusion of first-episode cases. Bar length indicates 95% confidence interval. AAO, age at onset; BD, bipolar disorder; AUD, alcohol use disorder; CUD, cannabis use disorder. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

regimens of our samples were similar to previous studies. For instance, in 7,406 individuals with BD-I, II and NOS diagnoses from the United States community (52), 18% would have been categorized as having non-compliant preventive treatment, 51% received polypharmacy, 24% benzodiazepines, and 71% antidepressants (the only category that seemed to differ from our sample). As for the prevalence of SUD, our sample remains within the range of tertiary care samples for BD (53, 54), which often show relatively low rates of SUDs compared to other clinical samples (5).

Available literature examining the possibility that comorbid SUD would be associated with non-evidence based treatment in BD reported either less specific or borderline findings, as compared to ours. One study found that BD-SUD inpatients showed less use of mood-stabilizers at discharge, as compared to BD only patients (31). The second study reported the absence of association between SUD and a reduced adherence to BD medication guidelines, but with $p = 0.06$ (55). This may be due to the smaller size of these samples. In a larger registry study (52), BD subjects with AUD or other SUDs showed a decrease in mood-stabilizers use during follow-up, as measured by medication possession ratio. Although this was primarily interpreted as lower adherence to treatment, the authors acknowledged that their measurement captured all kinds of treatment interruption. Thus, this finding was in line with that of Norwegian cases having less likelihood of proper preventive

treatment for BD in case of comorbid AUD. Interesting as well in this study was that bipolar illness complexity was also associated with reduced mood-stabilizer use. More precisely, we replicated an association between reduced compliance to guidelines and BD-II vs. BD-I subtype (55), and evidenced an independent association between female gender and lack of compliance to guidelines, which had not been specifically reported previously (55). This finding was not due to common characteristics of BD associated with female gender (56, 57), most of which were controlled for in our study. However, this could have been due to other factors associated with antidepressant prescription, which was significantly higher in women vs. men (**Supplementary Table 2**) and likely drove the association between gender and compliance to guidelines in our study. This includes anxiety/anxiety disorders (58) and fear of weight gain (59). We suggest that the fear of weight gain could be much higher for mood-stabilizers and antipyschotics than for antidepressants, thereby increasing the likelihood for prescribing antidepressants as opposed to mood-stabilizers in women. In line with this, we found previous associations between female gender and complex polypharmacy in BD (60). Overall, these data highlight the need for further research regarding gender issues in patients' and prescribers' adherence to guidelines.

We investigated the correlates of being unmedicated in the Norwegian subsample. The regression analysis showed that comorbid AUD was associated with current lack of pharmacological treatment. AUD may increase the likelihood of delayed diagnosis/underdiagnosis of BD in these patients, especially if AUD preceded BD (61). Conversely, cocaine use disorders have been associated with a risk of overdiagnosing and/or precipitating BD (62, 63). Compared to BD without AUD, comorbid AUD in BD is rather associated with depressive symptoms in BD, including a positive correlation between depressive symptoms and alcohol craving (64), and – possibly – a more frequent depressive predominant polarity (65, 66). This may hamper identification of the BD and thus delay treatment. However, studies reporting associations between AUD and bipolar depression have often yielded discrepant results (67, 68), noting that merely all SUDs may predict longer time to recovery from bipolar depression (10, 67). In line with underdiagnosis, our results also raise the possibility that clinicians are less inclined to initiate mood-stabilizers in cases with continuous alcohol use, even in the presence of mood episodes. Thus, until the years 2010s, it was usually recommended to start such treatment after alcohol detoxification or – at least – after a large reduction in alcohol use (61). In line with this general hypothesis of difficult diagnosis/treatment choice in BD with vs. without AUD, we found no evidence of decreased adherence or increased concern/necessity ratio across AUD groups. This suggests that non-prescription may have prevailed over non-adherence regarding the unmedicated status associated with AUD in our sample. One of the key issues might be the consideration of current vs. past AUD (10) and of moderate vs. heavy alcohol drinking (69), the latter being more strongly associated with incident bipolar depression than the former (70).

In the Norwegian subsample, we also found an independent association between current smoking vs. past- and never-smoking and increased anti-epileptics use. We can hardly think of the rationale for this association. Anti-epileptics were also more commonly prescribed to BD-II cases, but this did not alter the association with current tobacco smoking. Other possible reasons due to gender differences (valproate being avoided in women of childbearing age) or to the clinical expression of BD were ruled out, yet, there may be some bias due to the fact that "non-current smokers" were a mixed group of never + former smokers. We did not retrieve previous evidence of such association in the literature, so that a pilot, prospective study on this specific issue with detailed data regarding the reasons for prescribing/choosing to take anti-epileptics seems warranted.

Cannabis use disorder has overall been associated with a heavy burden in BD (71, 72). In the French subsample, it was associated with increased use of antipsychotics, suggesting that clinicians may have needed to maintain these medications to manage persistent mood instability and/or psychotic symptoms.

Limitations

The study was cross-sectional and medication data were collected by self-report, thus sensitive to recall bias and making us less able to disentangle non-prescription from patients' non-adherence. We did not collect individual treatment names or dosages to assess fine-grained compliance to guidelines and polypharmacy. No correction was applied for multiple testing, however, we believe that using Bayes and regression analyses reduced the risk of both false positives and false negatives. We did not assess further comorbidity such as anxiety, personality and attention deficit/hyperactivity (ADHD) disorders, which have been associated with BD+SUD comorbidity (3) and could lead to altered medication regimens. We relied on lifetime SUD diagnoses, although the amount and recency of exposure to addictive substances may have played an additional role in prescription patterns, especially by encouraging clinicians to wait for abstinence before prescribing proper BD medication. Importantly, the associations evidenced here are likely bi-directional, without any possible conclusion about causal inference.

CONCLUSION

Overall, SUDs were not associated with lack of compliance toward guidelines for preventive BD treatment in a large, cross-national sample. However, individuals with comorbid AUD were significantly less likely to be medicated in the Norwegian sample. Specific guidelines are lacking for the subgroup of BD+SUD cases, and treating clinicians in our study seem to have remained compliant to general guidelines for BD despite the presence of comorbid SUD. In the absence of specific treatment, available evidence thus suggests that intensive and early mood-stabilizing therapy can be used for BD+SUD. With that regards, more specific psychosocial treatments showed promise for BD+SUD cases (73, 74). We believe our study also highlights the fact that, in general, it is necessary to examine SUD comorbidity by individualizing tobacco, alcohol, cannabis, and other substances of abuse given that each of these categories

showed relevant associations that would not have been uncovered if we had regrouped them. Moreover, our findings contribute to a better knowledge for both patients and clinicians. In dually diagnosed BD patients, integrated care and improved diagnostic and therapeutic strategies are urgently required. Some of these strategies have already shown promising results (46, 73, 75–77) and should be implemented in both psychiatric and addiction care settings.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Comité de Protection des Personnes, Hôpital Pitié-Salpêtrière, and Regional Committee for Medical Research Ethics and Norwegian Data Inspectorate. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

RI, TL, and IM wrote the first draft of the manuscript. BE, MH, SG, SA, ML, OA, RB, CH, TB, J-PK, NS, and FB designed the initial study and recruited the sample. All authors have contributed to and critically reviewed the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2022.813256/full#supplementary-material

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Feasibility of an Extensive Strategy for Adult Diagnosis of Attention Deficit Hyperactivity Disorder Among Patients Suffering From Substance Use Disorders

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Introduction: Attention Deficit Hyperactivity Disorder (ADHD) is found in up to 20% adults with Substance Use Disorder (SUD). ADHD + SUD is associated with a more complex clinical presentation and poorer outcomes than each disorder alone. In the presence of SUD, adult ADHD is particularly difficult to diagnose as both disorders can mimic or hide the symptoms of each other. Our university hospital in Paris recently started an extensive outpatient diagnostic procedure for adult patients with SUD to ascertain or refute ADHD diagnosis and to provide therapeutic guidance. Here, we report the acceptability of the assessment procedure for patients and the preliminary description of the current and lifetime clinical profiles as a function of the final diagnosis "ADHD vs. no ADHD."

Method: Adult SUD patients with suspected ADHD were included in the current pilot study after stating they had no objection that their de-identified data were used for research purposes, according to French ethical procedures. Patients were evaluated for ADHD, comorbid mental disorders, cognitive state and dimensional psychological variables. They were assessed by trained psychologists and psychiatrists using standardized tools over a day. ADHD diagnosis was mainly based on the Diagnostisch Interview Voor ADHD for DSM-5 (DIVA-5).

Results: Out of 18 eligible patients, 17 were included in the cohort (1 excluded) and none was opposed to using their data. Thirteen (76%) participants were diagnosed with ADHD. All patients appointed for the ADHD diagnostic procedure came, respected schedules and finished the evaluation. All patients were impaired on cognitive functioning and were highly comorbid, but ADHD patients seems to suffer even more from those conditions, especially for cannabis and stimulant use disorders.

Discussion: Preliminary results show high acceptability of the procedure by ADHD-SUD patients. This result could be explained by all the organization adapted to

the psychopathology. Patients' baseline motivation to participate also represents an uncontrolled variable that could promote the ability to follow the procedure. Acceptance results of the protocol are promising and represent a starting point to identify the best procedures to design patient-centered pharmacological and non-pharmacological therapies.

Keywords: diagnosis, acceptability, stimulant, cognitive, cocaine, attention deficit-hyperactivity disorder (ADHD), dual disorder (DD), substance use disorder (SUD)

INTRODUCTION

Attention Deficit Hyperactivity Disorder (ADHD) is a pervasive neurodevelopmental disorder that is likely to persist into adulthood (1). In the general population, ADHD is found in 2.6% adults. This prevalence raises up to 6.8% when the presence of ADHD during childhood—a prerequisite for adult diagnosis according to several classification systems—is not considered (2). One of the most burdensome comorbidity of ADHD is substance use disorder (SUD), which often develops when ADHD persists throughout adolescence, so that up to 20% patients seeking treatment for SUD suffer from comorbid ADHD (3). Prevalence of ADHD in SUD adults varies across culture, substance and methodologies, from 2% in Islandic adolescents (4) to 83% in Japanese stimulant abusers (5). Standardized clinical interview in methodology instead of questionnaires resulted in a prevalence variability reduction at 5.4–34.3% (6), emphasizing the need of clinical interview, especially to take into account socio-cultural aspects (7).

Comorbid ADHD is associated with more severe patterns of SUD (8), including higher rate of poly-dependence, earlier onset (9), and cocaine-induced psychotic symptoms (10). Consequently, diagnosing ADHD in people with SUDs is of utmost importance.

The overlapping symptoms between ADHD and SUD represent a challenge for ADHD diagnosis procedure and treatment (11). Both disorders seem to have a bi-directional causal relationship with common symptoms contributing to maintain both disorders (12). Several instruments allow for screening and diagnosing ADHD in adult populations, however, they present limitations when used in SUD population, especially if used in an isolated manner. Regarding screening tools, the six-item World Health Organization's Adult ADHD Self-Report Scale (ASRS-6) has been validated in SUD populations (13), however, the ASRS still yields high rate of false negatives in SUD population (14). This has also been observed with the Conner's ADHD Adult Rating Scale (CAARS). The Wender Utah Rating Scale (WURS) may be a relevant complementary strategy to increase the screening accuracy of ADHD in this population (15, 16).

As for diagnostic tools, the Conner's ADHD Adult Diagnostic Interview for DSM-IV (CAADID) is often considered as the golden standard to diagnose ADHD, including in SUD adult population. Unfortunately, it remains only available in English and Dutch and, while providing in-depth investigations such as age at onset of each ADHD symptom, it remains mostly based on DSM-IV classification and its length can be a downside in SUD populations. When compared with the CAADID, the ADHD section of the Psychiatric Research interview for Substance and Mental Disorders (PRISM) showed good psychometric properties to detect ADHD in SUD population (17), yet again being based on DSM-IV criteria. The ADHD module of the Mini International Neuropsychiatric Interview (MINI) showed promising criterion validity in treatment-seeking SUD patients (18). Finally, the *Diagnostisch Interview Voor ADHD* (DIVA-5) has recently been translated in French and allows for both child and adult ADHD diagnosis while assessing functional impairment. The first validation study of the DIVA-5 concluded that it seemed to be a reliable tool in a Korean population (19). Overall, several screening and diagnostic instruments for ADHD have been developed, but most of them remain only available for specific languages and/or former DSM versions.

In this context of unmet diagnostic needs for ADHD, neurocognitive measures may hold promises in the ADHD diagnosis procedure, particularly regarding processing speed and working memory (20). However, the cognitive profile is easily affected by the presence of comorbidities such as depressive disorder (21) and should only be considered as a support for the diagnostic procedure (22, 23).

Available evidence highlighted that assessing ADHD among SUD population is profitable to both the diseases (24, 25). The international consensus on screening, diagnosis and treatment of SUD with comorbid ADHD (26) thus recommends a systematic screening of ADHD in SUD populations and *vice-versa*.

In order to address the major issue of diagnosing ADHD in SUD individuals, we developed an extensive assessment procedure that occurs over a day in our public academic hospital. Our main research aims are to validate the French versions of several diagnostic instruments in their DSM-5 versions and to detect potential neurocognitive profiles of ADHD in this population. For the current report, we chose to provide the preliminary descriptive and comparative statistics of the first case series of included patients. We focused on participants' ability to undergo the full procedure and on the SUD and main cognitive characteristics of those eventually diagnosed with ADHD vs. those who were not. Our hypotheses were that at least 5% participants would have serious difficulties in fulfilling all assessments and that ADHD would show clinical profiles suggestive of increased severity.

FIGURE 1 | Evaluation procedure. WAIS-IV, Wechsler Adult Intelligence Scale fourth edition; BEARNI, Brief Evaluation of Alcohol-Related Neuropsychological Impairment; FAB, Frontal Assessment Battery; MINI-S, Mini International Neuropsychiatric Interview DSM-5 edition; DDSI, Dual Diagnosis Screening Instrument; DIGS, Diagnostic Interview for Genetic Studies, suicide module; DIVA-5, Diagnostic Interview for ADHD DSM-5 edition.

MATERIALS AND METHODS

Participants

Participants were unpaid adult French-speaking outpatients receiving medical or psychological care for SUD. Fifty three percent presented a severe SUD pattern and 24% were in early remission. Recorded by the Weiss Functional Impairment Rating Scale self-report (WFIRS), the largest functional impairment is reported in self-concept, followed by school field and life skills. Inclusion criteria for the current study were the same as the expert assessment that is conducted at our day hospital for addiction medicine. Patients were referred from primary or tertiary addiction care settings by word-of-mouth to ascertain or refute adult ADHD diagnosis. They underwent a full diagnostic procedure, whichever their comorbidities, provided that they fulfilled a set of screening questionnaires, including: a free text form summarizing the referral's motives for assessment and participants' current treatment and medical history; Adult ADHD Self-Report Scale 6 items version for DSM-IV (ASRS-6, the DSM-5 version being unavailable at the time of the current study); the Wender Utah Rating Scale, 25-items (WURS-25), the Alcohol Use Disorder Identification Test (AUDIT); the Cannabis Use Disorder Identification Test (CUDIT) and the Fagerström Test for Nicotine Dependence (FTND).

There was no additional inclusion criteria for the current study. Additional exclusion criteria were: unable to complete assessments due to unstable medical condition (including acute intoxication), compulsory admission, or current guardianship. According to the French ethical bylaws, patients could be included without signing written informed consent, if they did not express their opposition to participate and that their data were pseudonymized. The study was conducted according to the tenets of the Declaration of Helsinki (Declaration of Helsinki, 2013) and of Paris-Nanterre University ethics committee rules (CPP sud-est IV, on February 22, 2021).

Assessments

Before assessments, all participants were contacted by phone to properly describe the whole assessment procedure and to arrange an appointment, which was further confirmed by phone text-message. Once they arrived on site, they were also accompanied by a nurse to carry out administrative procedures and to collect vital signs (heart rate, blood pressure, weight, urine drug screening, and alcohol breath-testing). This moment also allowed flexibility for late arrivals.

All assessments were conducted face-to-face with trained psychiatrists and psychologists, who were assigned different questionnaires between participants. A typical assessment day includes (**Figure 1**):

- An anamnestic interview for the main clinical and socio-demographic background, including the number of DSM-5 criteria for the main current substance use;
- We assessed a range of cognitive functions in two steps, using:
  - three subtests of the Wechsler Adult Intelligence Scale (WAIS-IV) encompassing Processing Speed and Working Memory (Symbols, Code, and Number Memory subtests). The WAIS (27) is the most commonly used battery to assess intellectual functioning (28), and impairments in both processing speed and working memory have been identified in adults with ADHD (20);
  - a screening of cognitive dysfunction with the Brief Evaluation for Alcohol Related Neuropsychological Impairment (BEARNI) and the Frontal Assessment Battery (FAB).
- Psychiatric and addictive comorbidities were then ascertained using the Mini International Neuropsychiatric Interview Simplified for DSM-5 (MINI-S). The MINI-S provides categorical diagnoses for 13 psychiatric disorders, including SUDs, and their current remission status. To date, the Mini-S had been validated for the depressive symptoms (29). However, the MINI-Plus based on DSM-IV criteria has shown acceptable validity for the screening of adult ADHD in SUD samples (18). Participants also underwent Dual Disorder Screening Instrument (DDSI), as part of the primary cohort objective of French validation (30).
- Lifetime history of suicidal attempt was collected using the "suicide" section of the Diagnostic Interview for Genetic Studies, v 4.0 (DIGS 4.0) (31). The first questions on the presence (and number) of lifetime suicide attempts were followed by an assessment of the self-reported worst attempt (method, intention to die).
- Participants were then offered lunch onsite for 60 min. Afterwards, they were asked to complete four self-rating scales aimed to estimate (i) the functional impact of their symptoms using the Behavior Rating Inventory of Executive Function Adult version – BRIEF-A (32) and the Weiss Functional Impairment Rating Scale self-report – WFIRS) (33), (ii) anxiety and depression levels (Hospital Anxiety and Depression scale – HAD) (34, 35) and (iii) trait-impulsiveness (Urgency, Premeditation, Perseverance, Sensation Seeking, Positive Urgency, Impulsive Behavior Scale – UPPS-P) (36).
- Finally, all participants underwent the Diagnostic Interview for ADHD in adults (DIVA-5) to investigate ADHD symptoms

during childhood and adulthood and ascertain the diagnosis, regardless from the results on ADHD screening scales. Importantly, this questionnaire allows collecting hetero-anamnestic data from child health record, parents' testimony, teachers' evaluations and comments on academic transcripts to reinforce diagnostic reliability. The DIVA is one of the structured interviews recommended in adults with SUDs, for whom ADHD is suspected by clinicians, whether the screening was positive or not (26).

The time allowed for each assessment (indicated in brackets on **Figure 1**) was higher than the time typically required to permit regular breaks during the day and increase the overall flexibility of the assessment procedure. We identified a high heterogeneity in assessments durations, particularly for semi-directive diagnostic interviews. We explain longer evaluations in two ways: patients' difficulties to focus on the one hand, and the presence of psychiatric comorbidities, requiring specific symptoms investigations on the other hand. Overall, patients stayed at the unit form 8:30 a.m. to 4:30 p.m. The range of the tools assessing each domain of interest remained relatively restricted. This was deemed *a priori* in order to maintain a good balance between collecting data relevant for the clinics and research and yielding a feasible assessment procedure.

A second appointment was proposed to each participant for a debriefing session during which the final diagnosis and therapeutic guidance were discussed, along with basic psychoeducation regarding ADHD and/or comorbid disorders.

Statistical Analyses

For the current descriptive study, we report the preliminary results from anamnestic self-reports regarding sociodemographic data and current substance use, the DIVA-5, the MINI-S, the BEARNI and the FAB. First, descriptive statistics were calculated to examine characteristics of the total sample. Second, these clinical and sociodemographic variables were described as a function of the presence/absence of current ADHD according to the DIVA-5. Data were roughly classified into sociodemographics, SUD, mental disorders other than SUDs and ADHD, and ADHD data—if applicable. Third, we selected the most salient descriptive results to plot relevant data, according to these categories. We used R and Rstudio on Mac OS X.12.3.

RESULTS

Preliminary Data About Feasibility

All participants ($n = 18$) attended, respected their schedule and attended the entire evaluation procedure. One participant showed external signs of discomfort and irritability. The others reported good subjective tolerance to the procedure. They pointed out to the protocol length and reported subjective tiredness but found it bearable due to previous notice regarding the evaluation procedure and internal motivation to investigate their symptomatology. One of these, however, was excluded of the protocol because of unstable medical condition, leaving a study sample of 17 participants.

TABLE 1 | Sample description.

	***N* = 17**
Age	37 (29–41)
Gender	
Women	7 (41%)
Men	10 (59%)
BMI	24 (22–24)
High school degree or more	7 (41%)
Unemployed	10 (59%)
Single	14 (82%)
Adult ADHD	13 (76%)
Combined	10 (83%)
Hyperactive/impulsive	1 (8%)
Inattentive	1 (8%)
Main SUD at referral	
Alcool	6 (35%)
Cannabis	4 (24%)
Cocaine	3 (18%)
Cathinones	2 (12%)
Benzodiazepines	1 (6%)
Psychiatric comorbidity	
Any mood disorder	7 (41%)
Any anxiety disorder	8 (47%)
Number of DSM5 disorders	4 (3–5)
Lifetime suicide attempt	8 (62%)

Data are presented as median (interquartile range) or n (%). BMI, body mass index; ADHD, attention deficit hyperactivity disorder; SUD, substance use disorder.

Total Sample

Sample characteristics are described in **Table 1**. Participants were 37 years old (interquartile range, IQR = 29–41), 10 (59%) were men, three (18%) were in a relationship, thirteen (76%) participants had a high school degree or higher and ten (59%) were currently unemployed (including one retired person and one on disability leave). Current substance use was as follows: ten (59%) tobacco smokers, fifteen (88%) alcohol users, eight (47%) cannabis smokers, five (29%) cocaine users, and two (12%) opioid users. Main SUD diagnosis according to both patients and their referring clinician are listed in **Table 1**. No significant difference in participants' characteristics were observed between those with vs. without adult ADHD (**Table 2**), except for the number of ADHD criteria during childhood, which was higher among ADHD participants (Mann Whitney test, $p = 0.02$).

Thirteen (76%) participants were diagnosed with ADHD according to the DIVA-5. Seven patients (41%) presented with any comorbid mood disorder and eight (47%) with any comorbid anxiety disorder.

ADHD ($n = 13$) vs. Non-ADHD ($n = 4$) Cases

Sociodemographic Data

ADHD cases seemed older and better-educated than non-ADHD cases, with a possibly higher proportion of women (46 vs. 25%). The distribution of marital and employment status seemed similar in both groups (**Table 2**).

TABLE 2 | Clinical and sociodemographic variables as a function of adult ADHD.

	No adult ADHD *N* = 4 (24%)	Adult ADHD *N* = 13 (76%)	*N*
Age	33 (29–39)	38 (36–41)	17
Gender			17
Women	1 (25%)	6 (46%)	
Men	3 (75%)	7 (54%)	
BMI	24 (22–24)	24 (22–24)	17
High school degree or more	1 (25%)	6 (46%)	17
WURS25 total score	54 (46–66)	64 (54–72)	15
ADHD criteria during childhood	5 (2–9)	8 (5–12)	17
ASRS-6 above cut off	3 (100%)	10 (83%)	
Unemployed	2 (50%)	8 (62%)	17
Single	4 (100%)	10 (77%)	17
Current substance use			
Current tobacco smoking	2 (50%)	8 (62%)	17
Current alcohol use	4 (100%)	11 (85%)	17
Current cannabis use	1 (25%)	7 (54%)	17
Current opioid use	1 (25%)	1 (8%)	17
Current cocaine use	0 (0%)	5 (38%)	16
SUD diagnoses			
Nicotine dependence	0 (0%)	5 (42%)	15
Any AUD	1 (25%)	5 (42%)	16
Any CUD	1 (25%)	8 (62%)	17
Any OUD	1 (25%)	2 (15%)	17
Any sedative use disorder	1 (25%)	2 (15%)	17
Any stimulant use disorder	0 (0%)	6 (46%)	17
Severity of DSM5 AUD			6
Early remission	0 (0%)	1 (20%)	
Severe	1 (100%)	4 (80%)	
Severity of DSM5 SUD			13
Mild to moderate	2 (100%)	5 (45%)	
Severe	0 (0%)	6 (55%)	
Psychiatric comorbidity			
Any mood disorder	2 (50%)	5 (38%)	17
Any anxiety disorder	2 (50%)	6 (46%)	17
Post-traumatic stress disorder	0 (0%)	3 (23%)	17
Total number of DSM5 diagnosis	3 (3–4)	5 (3–5)	17
Lifetime suicide attempt	2 (67%)	6 (60%)	13

Data are presented as median (interquartile range) or n (%). SUDs measured by MINI DSM5, except for nicotine dependence, defined as FTND > 5. BMI, body mass index; ADHD, attention deficit hyperactivity disorder; WURS, Wender Utah Rating Scale 25 items; ASRS, Adult Self-Report Scale 6 items; AUD, alcohol use disorder; CUD, cannabis use disorder; OUD, opioid use disorder, SUD, substance use disorder; FTND, Fagerström Test for Nicotine Dependence.

Several interesting patterns appeared between ADHD and non-ADHD patients in **Table 2**. As regards sociodemographic data, gender ratio seem more balanced in the ADHD (46% women) vs. the non-ADHD group (25% women). ADHD cases seem younger that non-ADHD cases (33 vs. 38 years old) with higher level of education. As regards childhood ADHD symptoms, even non-ADHD participants had relatively high levels of WURS-25 and DIVA-5 scores, suggesting that they might have been diagnosed with ADHD if the assessments would have been conducted back then, but with probable remission in early adulthood. Most participants screened positive on the ASRS-6, including 100% no-ADHD cases. Conversely, two ADHD cases screened negative on the ASRS-6. When referring to the results of the DIVA-5 as a gold standard for ADHD diagnosis, the ASRS-6 showed 83% sensibility—same as for the WURS-25. Both screeners specificity were low (50% and lower), however they were deemed not interpretable due to the small sample size. As a whole, screening tools seemed to have a low diagnosis accuracy in the study sample, conversely to a previous study (37). Finally, as regards psychiatric comorbidity, the proportions of mood and anxiety disorders and lifetime suicide attempts were similar in both groups, noticing that all three PTSD cases also had ADHD.

Substance Use and SUDs

Both cocaine (38 vs. 0%) and cannabis use (54 vs. 25%) and their related disorders (46 vs. 0% and 62 vs. 25%, respectively) seemed more frequent in ADHD vs. non-ADHD participants (**Table 2**). Tobacco smoking was similar in both groups, however, 42% ADHD cases showed nicotine dependence compared to none in the non-ADHD group. Tobacco smoking was recorded by patients' response to the following question: "Do you currently smoke tobacco?," and all current tobacco smokers fulfilled the Fagerström test for nicotine dependence (FTND).

Although current cocaine use and lifetime Stimulant Use Disorder seemed strongly overrepresented in ADHD vs. non-ADHD cases, those differences were not significant. Thus, we further explored ADHD symptoms load as a function of these cocaine use patterns. By doing so, we evidenced that cocaine use was associated with increased ADHD symptoms, but only seen in adulthood, for inattention criteria (Mann whitney tests, $p = 0.037$, Cohen's $d = 1.06$ for cocaine use) (**Figure 2**).

Neurocognitive Measures

The BEARNI showed among the whole population a mean total score of 15.4 ($SD = 3.8$), which corresponded to moderate/severe impairment. ADHD participants (mean = 14.5; $SD = 3.4$) appeared significantly more altered than non-ADHD (18.6; $SD = 3.8$) on total score (Mann whitney test, $p = 0.03$; Cohen's $d = 1.2$) (**Table 3**). The FAB total score for the whole sample was 16 ($SD = 2$) which seems normal compared to the test norms and no significant difference was observed between the two groups. However, ADHD patients had lower scores on the Go-No Go subscale (mean = 2.2; $SD = 0.9$), compared to non-ADHD participants (mean = 3; $SD = 0$) but after the Holm's correction the difference was not significant (Mann whitney, uncorrected $p = 0.025$) (**Figure 3**). The WAIS-IV scores did not significantly differ from the norms and did not differ as a function of ADHD diagnosis.

DISCUSSION

In this first case series of a sample of treatment-seeking SUD outpatients, who was thoroughly assessed for adult ADHD using a wide range of clinical and neurocognitive measures, participants did not report difficulties to attend and undergo all

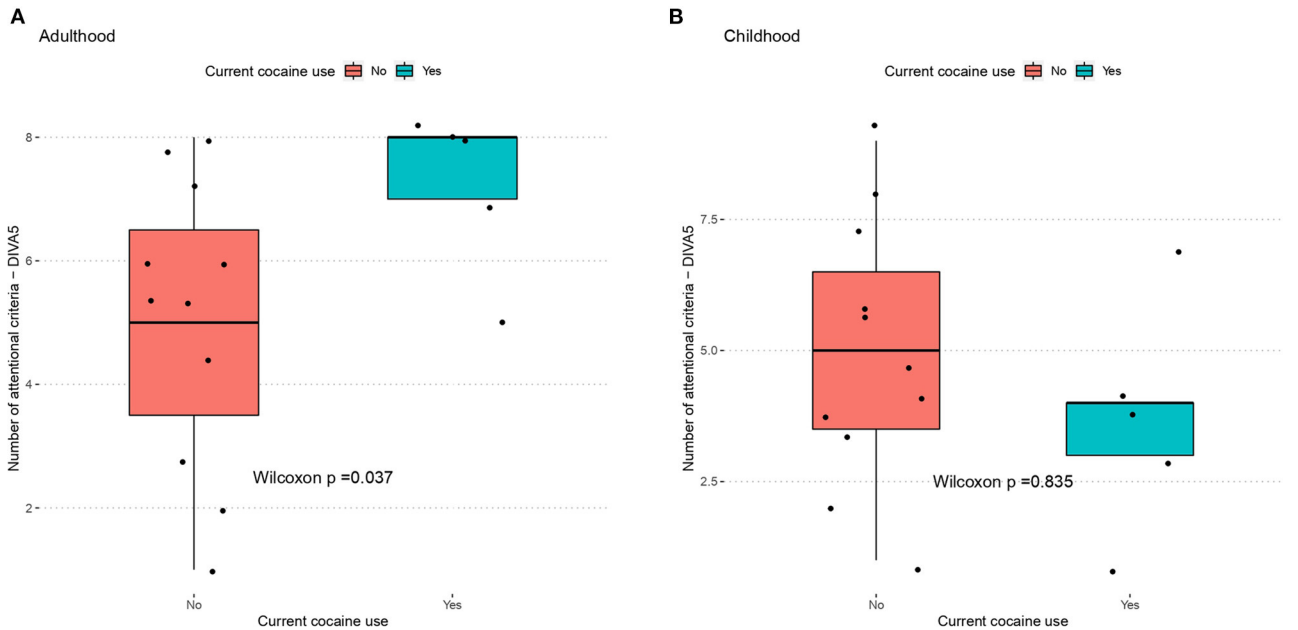

FIGURE 2 | Cocaine use as a function of inattentive symptoms during **(A)** adulthood and **(B)** childhood. ADHD measured by the DIVA-5, cocaine use measured by anamnestic interview. BEARNI, Brief Evaluation for Alcohol Related Neuropsychological Impairment; FAB, Frontal Assessment Battery; DIVA, Diagnostic Interview for ADHD in Adult.

evaluations. Using exploratory analyses, we identified possible cognitive impairment associated with ADHD and relevant relationships between child vs. adult ADHD symptoms load and cocaine use—both warranting further exploration. We relied on a selected set of validated tools chosen to cover a wide range of symptoms and functioning domains.

Feasibility

The extensive diagnosis strategy applied to SUD patients for diagnosing ADHD seemed extremely feasible. First, all patients attended and respected their schedule. This was not straightforward given the well-documented difficulty to plan and remind appointments for ADHD (38) and SUD people (39). In fact, both experiment executive difficulties with daily organization consequences, such as appointment attendance (40, 41). This was possibly supported by the text message and phone calls they received on the day before and by motivational bias, because of the entry procedure requiring the completion of several questionnaires before getting an appointment. Second, all participants finished the assessments. This finding was somehow unexpected because of the discomfort during lengthy activities of people with SUD, especially in case of comorbid ADHD. There are several suggestion to explain patients acceptance: (1) the procedure was presented in detail to participants beforehand; (2) they were helped for administrative formalities; (3) they benefited breaks between assessments and could ask for breaks at any time during the assessments; (4) evaluations were conducted by different clinicians; (5) lunch occurred onsite; (6) environment was convivial (coffee, healthcare staff availability); (7) patients had the same consultation room throughout the day (healthcare staff moved). Importantly as regards our global research aims, the DIVA-5 seemed to be well-accepted by participants, although it was the last evaluation of the day.

TABLE 3 | Neurocognitive measures as a function of adult ADHD.

	No Adult ADHD *N* = 4 (24%)	Adult ADHD *N* = 13 (76%)	*N*
BEARNI_TOTAL	20 (18–21)	14 (12–16)	17
FAB_TOTAL	18 (17–18)	17 (15–17)	17

Data are presented as median (interquartile range). BEARNI, Brief Evaluation of Alcohol Related Neuropsychological Impairment; FAB, Frontal Assessment Battery.

ADHD diagnosis among SUD adults already has been reported as feasible using the Conners' Adult ADHD Diagnostic Interview for DSM-IV (42), a thorough and demanding assessment. In line with this, our first case series also suggests the good feasibility of an even more extensive strategy to diagnose ADHD in this population. The large majority of participants tolerated the long and *a priori* tiring evaluation procedure well. During the final feedback interview, ADHD and non-ADHD patients reported moderate tiredness and argued that internal motivation to explore ADHD symptomatology helped them to support the procedure. We plan to incorporate proper satisfaction and feasibility measures in our assessments for the near future to assess theses subjective data using a more empirical method.

This preliminary study supports the feasibility of using the DIVA-5 as the core diagnostic instrument for ADHD among a

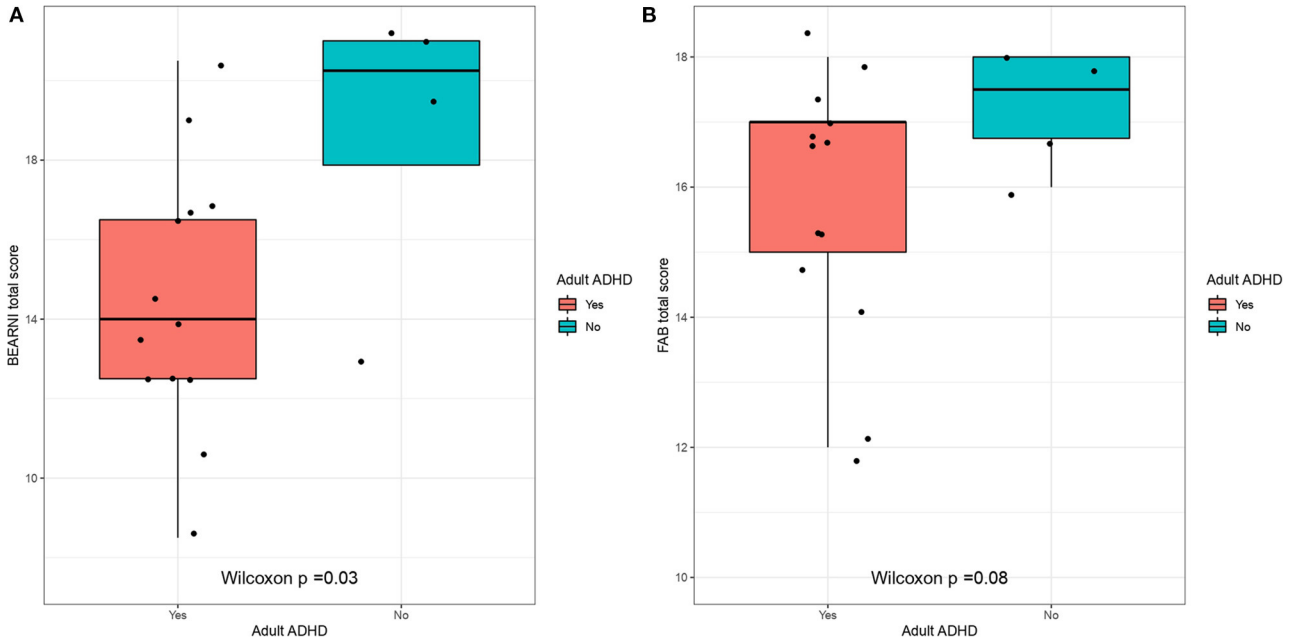

FIGURE 3 | Neurocognitive scores as a function of ADHD. ADHD measured by the DIVA-5, neurocognitive profiles measured by **(A)** BEARNI and **(B)** FAB. BEARNI, Brief Evaluation for Alcohol Related Neuropsychological Impairment; FAB, Frontal Assessment Battery; DIVA, Diagnostic Interview for ADHD in Adults.

full set of evaluations. However, a larger sample will be required in order to formally investigate its psychometric properties. Nonetheless, extensive strategy to diagnose ADHD in adults suffering from SUD seems relevant. A similarly extensive strategy has been used by Swedish researchers to diagnose participants in an interventional study (43), with no report of major refusal or attrition rates. However, this study did not precise if all assessments were done on a single day and its population strongly differed from ours regarding sociodemographic characteristics.

Gender Balance

In our case series, the males:females ratio for ADHD was ∼1 (46% women), thus possibly differing from the 1.5:1 usually reported (44). This may be explained by interactions between SUD, ADHD and gender, hypothesizing that, in SUD samples, gender balance would be reduced given that ADHD is a strong risk factor for SUD. SUDs are much more frequent for men (7.5%) compared to women (2.0%) (45) in the general population.

Cocaine and Cannabis Use Patterns

ADHD participants were more likely to use cannabis and to suffer from cannabis use disorder than non-ADHD patients, and the same patterns were observed for cocaine. This may be due to the high score of sensation seeking (46) often reported in ADHD. This temperamental profile has been associated with multiple substance use experiments. These associations could also be related to the hypothesis of ADHD as a causal factor for lifetime cannabis use (47). Mirroring this, cannabis use could help ADHD patients to regulate their symptoms (as impulsivity, hyperactivity, anxiety, irritability), which is supported by patient's subjective motivation to use cannabis for its expected beneficial effects on ADHD symptoms (48). As regards cocaine, the self-medication hypothesis could be "classically" considered as an explanation. However, given the fact that the ADHD-cocaine association was only found for adult ADHD symptoms, but not for child, this finding may reflect the pharmacological effects of cocaine on individuals, who presented some childhood ADHD symptoms that increased after protracted cocaine use throughout their adulthood. This hypothesis of ADHD syndromes secondary to cocaine use—as is plausible for other mental disorders such as e.g., bipolar disorder (49)—has been suggested by our group, based on screening tools (50). It warrants further discussion and validation using structured interviews such as those conducted in the current study.

Cognitive Profiles

On the whole sample, BEARNI total scores corresponded to moderate/severe impairments (<16), according to the test validation (51), with ADHD patients significantly more impaired than non-ADHD patients on the BEARNI total score. A recent study also found prominent neuropsychological impairments on executive functions in psychiatric adult outpatients seeking clinical evaluation of ADHD (52). There have been a large number of reports for cognitive function in ADHD. However, those reports are discrepant (53), owing to the various nature of the samples included in terms of sociodemographic and clinical profiles (54).

Clinical Relevance of Assessment Procedures on ADHD Diagnosis and Treatment

The aim of this study was to describe patients' ability to undergo the full procedure and describe preliminary results on cognitive characteristics. Since both screening questionnaires and diagnostic interviews were used, we are able to report their initial diagnostic accuracy. ASRS-6 and WURS-25 sensibility was good when the scales were used separately or combined, however, they showed a non-acceptable false positive rate. The ASRS psychometric properties in SUD population have already been described, but remain inconsistent across studies. The false-positive rate appeared very high in one study (55), and acceptable but lower than sensitivity in others (13, 56). However, van de Glind et al. (13) identified a better specificity in participants for whom alcohol was the primary substance of abuse, compared to other substances (76 vs. 56%). This suggests an effect of substance type on ASRS specificity and could explain the poor ASRS specificity in our sample, where alcohol is the primary substance of abuse for only 35% patients. Other reasons might be at play, however, since other studies reported a higher specificity than sensitivity for the ASRS (86 vs. 61%) in adults seeking treatment for cannabis (57) or cocaine use disorders (16). Interestingly enough, in both studies the WURS specificity was lower than its sensitivity. Our sample size is too small yet to identify an effect of substance type on the psychometric qualities of screening assessments. Overall, it seems that the recommended ADHD screeners show inconstant, thus unsatisfactory properties, so that clinicians are encouraged to complete their evaluations when they strongly suspect ADHD, even when standardized screening was negative. Moreover, screening tools are especially expected to show very high sensitivity, at the possible cost of specificity. With that regards, the hyperactivity/ADHD subscale of the Strengths and Difficulties Questionnaire (SQQ) was recently validated in young adults and could represent an alternative to both the ASRS and the WURS (58). Thus, the authors found a high validity for the SQQ to distinguish ADHD and non-ADHD patients. However, further research is needed to explore its validity in SUD populations, especially with various primary substance of abuse.

Given the likely effect of substance type on the validity of screening questionnaires, one should bear in mind the crucial role of clinical interview and follow-up to diagnose adult ADHD in SUD populations. However, such a relatively unstructured approach seems more efficient when it is combined with standardized instruments. This may be explained by the fact that the clinical expression and impact of ADHD changes substantially over the lifespan. Thus, compared to childhood, adult ADHD is strongly represented by internalizing symptoms, impaired functioning and much higher comorbidity rates (59, 60). If screening questionnaires seem to not represent a sufficiently precise method, the DIVA-5 could be helpful, as it drives the clinician to investigate each DSM-5 ADHD criterion with additional clinical appreciation based on day life symptoms impact. The DIVA strongly highlights the needs to consider differential diagnosis and give the clinician a large freedom to do so. However, as regards our study, we deemed relevant to further use structured instruments to ascertain such diagnoses, for both clinical and research purposes. In this study we decided to use structured interviews to help the differential diagnosis process, but the interpretation of these interview results as a differential diagnosis or a comorbidity requested a clinical judgment. Globally, the DIVA-5 can be recommended as a useful help to diagnose ADHD among adults (with or without SUD) through the main steps of a diagnosis procedure (61), while leaving room for clinical investigations.

Finally, neuropsychological assessments are also often used to support the diagnosis procedure, as significant differences were identified between ADHD and non-ADHD on processing speed and work memory (20, 62). However, no significant difference was observed in our sample regarding processing speed and working memory between ADHD and non-ADHD. A more recent study also concluded to a limited utility of processing speed and working memory measures as indicators of the severity of ADHD (63). In fact, significant differences seem to disappear when IQ and depressive symptoms are included as covariate (21). Single neuropsychological measures seem to perform poorly in identifying ADHD, so that an extensive test battery may be necessary to control for the effects of comorbidity when searching for markers of ADHD diagnosis (64). These results could explain the non-significant difference observed in our study on WAIS-IV subtests, as it constitutes a single test measure performed with a highly comorbid sample.

One of the main aims of the evaluation procedure presented in the current manuscript was to provide therapeutic guidance to the clinician and explain it to the patient. This guidance included both pharmacological and non-pharmacological strategies, and the "hows and whens" of each proposed strategy. Although available evidence remains scarce, we relied on ADHD type (levels of inattention and hyperactivity), comorbidity profiles and functioning (both cognitive and daily life) to propose a personalized care plan to each participant, following the general recommendation for adult ADHD (26).

- As for stimulant medication, we recommended long-acting methylphenidate for five ADHD participants with strong functional impairment (combined and inattentive types) and atomoxetine in three participants. Atomoxetine was suggested because of age-associated risk factors of methylphenidate, potential comorbidity with bipolar disorder and current injection of psychostimulants (65, 66). For these participants, a delay before introducing methylphenidate was recommended (one after treating severe depressive symptoms, one after treating impulsiveness using valproic acid).
- Specific Cognitive and Behavioral Therapy (CBT) was systematically recommended in addition to pharmacological treatment in ADHD participants (26).
- The full procedure allowed to diagnose previously unidentified psychiatric comorbidities such as anxiety or mood disorders—especially PTSD and bipolar disorder; and cognitive impairment. Thus, in addition to recommendations on ADHD care and because of overlap between ADHD and comorbidities, we also suggested some interventions about these comorbidities. For instance, specific CBT for anxiety disorder was recommended for two ADHD participants and

a specific exploration of bipolar disorder was suggested for one participant.
- Complete neurocognitive evaluation was recommended for two ADHD participants because of low scores in neurocognitive assessments (BEARNI, FAB, WAIS-IV subtests) and/or recent exacerbation of neurocognitive symptoms. Also, neurocognitive assessments led to recommend cognitive remediation for ADHD participants with strong executive difficulties.
- Finally, for non-ADHD participants, specific intervention targeting anxiety and mood disorders could be recommended.

The whole evaluation procedure resulted in personalized proposals for ADHD treatment, taking comorbidities into consideration as well as cognitive and emotional difficulties. Relevant psychological dimensions could also be identified in some cases, further increasing the personalization of both pharmacological or psychotherapeutic interventions. Also, the number of assessments facilitated the differential diagnosis to avoid false positive for ADHD. A major goal for treating burdensome mental conditions is functional recovery. We expect the personalized interventions proposed through our procedure to eventually lead to significant improvement of functional impairment, as was evidenced in the French expert centers for bipolar disorder, which use similarly thorough assessments as ours (67).

Generalizability

We found a prevalence of ADHD of 76% among SUD outpatients. This frequency is considerably higher than others studies among SUD patients where ADHD is found for 15–25% of SUD patients (3, 8). It is difficult to date to compare these findings, noticing that our prevalence stands for people who were suspected for ADHD. Moreover, the study sample size was very small. For those reasons, the ADHD prevalence is not generalizable of all SUD patients.

Limitations

The study has several limitations. First, the sample was very small, thereby reducing statistical power and results interpretation: a dimensional approach to describe ADHD symptoms intensity and evolution across a developmental spectrum would be interesting. Second, there might be a selection bias because of the entry procedure requirements. Patients had to complete several questionnaires to be evaluated and their clinicians had to complete a referral letter. As a result, maybe this procedure included only patients who did not had difficulties in assessments completion. Third, the procedure is fairly demanding in terms of resources. Moreover, there was no control group and no formal assessment of the tests scoring fidelity. Finally, we did not record age of onset of ADHD and SUD nor patients' background or developmental history which could have been helpful for a more comprehensive assessment of ADHD and SUD.

CONCLUSION

We report here a detailed methodology for a reliable assessment of complex dual diagnoses such as ADHD, paving the way for a future validation study of major tools in the field. With a larger sample, we will be able to precisely describe the clinical and neurocognitive correlates of adult ADHD in severe SUD. Additionally, we will strive to identify the minimum set of assessments required for a reliable ADHD diagnosis in SUD populations, since not all clinicians or care settings will gather enough resources for using as many evaluations as we did.

These assessments are useful to refer patients to specific care settings for ADHD and SUD patients, that remain to be further developed, as specific Cognitive Behavioral Therapy for ADHD-SUD and specific neurocognitive interventions.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The study was conducted according to the tenets of the Declaration of Helsinki (Declaration of Helsinki, 2013) and of Paris-Nanterre University ethics committee rules. It was formally approved by the relevant Ethics Committee (CPP sud-est IV, on February 22, 2021).

AUTHOR CONTRIBUTIONS

NT: conceptualization, methodology, investigation, formal analysis, and writing—original draft. LR: methodology, validation, writing—review and editing, and supervision. AM: investigation. AD: methodology, investigation, and resources. FV: resources and validation. EK: methodology, investigation, and writing—review and editing. RI: methodology, investigation, formal analysis, writing—review and editing, validation, and supervision. All authors contributed to the article and approved the submitted version.

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Gaming Disorder Seen Through the Prism of Dual Diagnosis: Prevalence and Associated Factors

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Introduction: Dual diagnosis (DD) is defined as the co-occurrence of at least a psychiatric disorder and at least an addictive disorder. Most studies about DD considered substance use disorders. In 2018, gaming disorder (GD) was recognized as a formal disorder and integrated into the category of addictive disorders in the 11th version of the International Classification of Diseases. Our objectives were to measure DD prevalence among GD patients and to assess factors associated with the presence of DD.

Methods: As part of the EVALuation of behavioral ADDictions (EVALADD) cohort, 92 patients with GD were included in the present study. Psychiatric disorders, including anxiety, mood, and psychotic disorders, were explored with the Mini International Neuropsychiatric Interview (MINI 5.0.0). Probable adult attention-deficit/hyperactivity disorder (ADHD) was screened with the Wender Utah Rating Scale (WURS) in childhood and with the ADHD Self-Report Scale-V1.1 (ASRS) in adulthood. Finally, personality was assessed using the 125-item version of the Temperament and Character Inventory (TCI-125), motives for gaming with the Videogame Motives Questionnaire (VMQ) and attachment styles with the Relationship Scales Questionnaire (RSQ). To measure the prevalence of DD among GD patients, we considered the occurrence of current GD with current anxiety, mood, or psychotic disorders, or with probable current ADHD. We also performed a multivariate analysis to identify independent factors associated with DD.

Results: More than half (55.4%) of GD patients suffered from DD. We found a high prevalence of probable ADHD (38%) and anxiety disorders (29% suffering from generalized anxiety disorder, social, agoraphobia or panic disorder). Four variables were significantly associated with DD: suicidal thoughts [odds ratio (OR) = 6.83, 95% confidence interval (95%CI) (1.66–28.09)], VMQ "coping" scores [OR = 1.18, 95%CI (1.01–1.38)], TCI-125 "harm avoidance" scores [OR = 1.04, 95%CI (1.01–1.07)] and "novelty seeking" scores [OR = 1.03, 95%CI (1.00–1.06)].

Discussion: The prevalence of certain psychiatric disorders among GD patients far exceeded that observed in the general population. Both ADHD and suicidal ideations should particularly be screened among GD patients. Specific interventions targeting personality dimensions associated with DD but also on the management of negative affect should represent new treatment opportunities.

Keywords: dual diagnosis, gaming disorder, addiction, associated factors, risk of suicide

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INTRODUCTION

Since 1983, some authors have noticed "obsessive" behaviors among video game players (1). Thirty years later, "Internet Gaming Disorder" first appeared in section III of the Diagnostic and Statistical Manual fifth edition (DSM-5) (2). Finally, in May 2018, after many debates, the World Health Organization (WHO) recognized gaming disorder (GD) as a formal addictive disorder in the 11th International Classification of Diseases (ICD-11), given the common characteristics with the other addictive disorders already included (3). According to the ICD-11, the three core symptoms considered for a diagnosis of GD are impaired control over gaming, increasing priority to gaming over other activities and continuation of gaming despite negative consequences. These symptoms must occur for at least 12 months and result in a significant impairment in important areas of functioning.

Multiple mechanisms are involved in the initiation and persistence of GD, such as motivations to play and escapism (4–6), attachment style (7, 8) and certain psychopathological traits, such as impulsivity and poor emotion regulation (9). Numerous studies have reported links between GD and comorbid psychiatric disorders including anxiety disorders, depressive disorders, attention-deficit/hyperactivity disorder (ADHD), conduct disorder, substance use disorders (SUDs) and pathological personality traits (10–14). Associated disorders can be a cause or consequence of GD, but the association can also form a complex clinical entity.

The term "dual diagnosis" (DD) describes the co-occurrence of a SUD and a psychiatric disorder (15) while the term "dual disorder" illustrates a new disorder including an addictive disorder and another psychiatric disorder. This combination creates a new pathology that is more complex than the simple summation of the two disorders. Studying the links between addictive and other psychiatric disorders is of growing interest due to the prevalence and gravity of these situations. DD patients have less favorable prognoses with more severe symptoms for each of the disorders and greater chronicity (15–17). DDs are mostly studied *via* specific associations such as cannabis consumption and psychosis or alcohol consumption and mood disorders, but the mechanisms shared by all types of DD remain incompletely understood. Previous studies found that patients with DD were more likely to be men, be young, and have a history of aggression (18). A recent comprehensive review and meta-analysis comparing personality traits between patients suffering from psychotic disorders with and without comorbid SUDs found impulsive and externalizing trait personality domains unique to the DD group (19).

Although DD has mostly been studied through its association with a SUD, studying the applicability of DD to all addictive disorders, including behavioral addictions, would allow a better understanding of behavioral addictions. The existence of many different combinations of addictive and psychiatric disorders support this hypothesis (20). In particular, due to the recent inclusion of GD in the framework of disorders due to substance use or addictive behaviors, it seems relevant to study whether specific psychopathological or clinical features, known to be associated with GD, might also be differentially associated with DDs involving GD.

We made the assumption that patients suffering from GD have frequent co-occurrent psychiatric disorders, and that they do not constitute a homogeneous clinical group. It would be important to differentiate the management of those suffering from an isolated GD from those suffering from a DD. Thus, our main objective was to determine the prevalence of DD among GD patients at the beginning of treatment. We also aimed to identify characteristics associated with DD among GD patients.

MATERIALS AND METHODS

Procedure

Data for this study were extracted from the EVALuation of behavioral ADDictions (EVALADD) cohort (NCT01248767). The EVALADD cohort involves a prospective follow-up of outpatients over 15.25 years old (the threshold that separates pediatric and adult care in our hospital) from the initiation of specific care for a behavioral addiction at Nantes University Hospital, France. Only patients who provided their written informed consent (including consent from parents or guardians for participants under age 18) were included in the EVALADD cohort, and patients with cognitive impairment or difficulties reading or writing French were not included. The EVALADD procedure includes several repeated assessments conducted at the initiation of addiction treatment, after 6 months, after 1 year and then after each subsequent year as long as the patient agrees to complete the follow-up. The assessments are based on a multiaxial psychological assessment performed through a face-to-face structured interview and self-administered questionnaires. The structured interviews were conducted by trained and qualified research staff with experience with behavioral addictions.

Participants

For the present study, we selected only 130 outpatients (the sample is composed of an adolescent and adult population) who were referred for excessive video game use (according to the patient himself or herself or according to his or her relatives) from August 2012 to August 2020. After exclusion of those who did not match the GD ICD-11 criteria or those for whom data were incomplete, 92 patients were included in the analysis (**Figure 1**). We used only data collected at the initiation of addiction treatment.

Measures

Gaming

As the ICD-11 criteria had not yet been published at the time of the study, a thorough investigation of the medical records of the 130 identified patients allowed us to search retrospectively for the presence or absence of the three ICD-11 criteria during the 12 months preceding inclusion, and for evidence of functional impairment. Inclusion in the study required satisfying the 3 criteria and having a functional impairment that led to confirmation of the diagnosis of GD. All patients' medical records

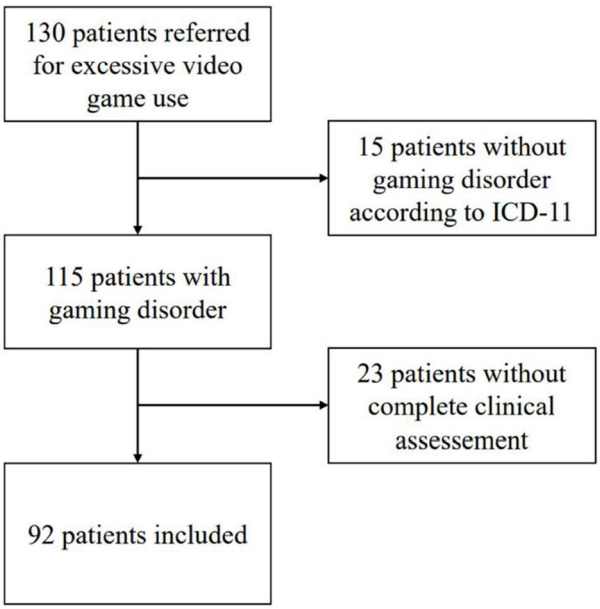

FIGURE 1 | Flow chart of patients participating in the study from August 2012 to August 2020.

were analyzed by a researcher and the referred psychiatrist in a double-blind manner.

We used the Videogame Motives Questionnaire (VMQ), derived from the Gambling Motives Questionnaire (GMQ) (21), to evaluate patients' motives for gaming. The only adaptation was to switch "gambling" to "gaming". This questionnaire assesses three dimensions: coping, enhancement, and social motivation. Higher scores for a particular type of motivation corresponds to higher levels of motivation in that dimension. It should be noted that there are no cut-off scores and that this questionnaire results in a profile of the motivations for playing.

Other Psychiatric Disorders

DD status in our study was defined as the association of GD and at least one current psychiatric disorder at inclusion.

We used the Mini International Neuropsychiatric Interview version 5.0.0 (MINI) (22) to diagnose the following current psychiatric disorders: depressive episodes, dysthymia, manic or hypomanic episodes, panic disorder, agoraphobia, social phobia, obsessive-compulsive disorder, post-traumatic stress disorder, psychotic disorders and generalized anxiety. Furthermore, current SUDs were assessed, even if they were not considered for the definition of DD.

The EVALADD cohort did not include a formal ADHD diagnosis but probable ADHD was explored through two screening questionnaires. Probable ADHD symptoms in childhood were explored by the Wender Utah Rating Scale-Child (WURS-C) (23), and symptoms in adulthood were explored by the Adult Attention Deficit Hyperactivity Disorder Self-Report Scale Screener v1.1 (ASRS-1.1) (24, 25). Based on the results of these questionnaires, it was possible to screen for the presence of current probable ADHD among minor patients (WURS-C score $\geq$ 46/100) and among adult patients (WURS-C score $\geq$ 46/100 and a positive screening with the ASRS Screener v1.1).

Furthermore, suicidal ideation was assessed by a specific section of the MINI.

Psychopathology

The Relationship Scales Questionnaire (RSQ) (26) is one of the most commonly used questionnaires for assessing different attachment styles. We calculated the weighted average of the scores for each attachment dimension and thus determined the patient's predominant attachment style.

The Temperament and Character Inventory—125 items (TCI-125) (27, 28) is a self-administered questionnaire providing a personality profile. It measures seven dimensions including four temperaments ("novelty seeking," "harm avoidance," "reward dependence," and "persistence") and three character traits ("self-directedness," "self-cooperation," and "self-transcendence"). All items are coded as true or false, with the attribution of 0 or 1 point based on the item. For each dimension, the score is calculated by the following formula to obtain a standardized mean: sum of the score of the items*100/number of items of the dimension. Scores for each dimension could range from 0 to 100.

Statistical Analysis

Statistical analyses were performed using STATA 11® v 11.2 (Statistical Data Analysis/TX/USA) software.

First, a descriptive analysis of the characteristics of our population was carried out, and DD prevalence among the GD patients was calculated. These data are presented as means for continuous variables and percentages for categorical variables. We tested the equality of variances and the normality of the distributions in the comparative analyses.

Then, univariate analyses were conducted comparing results between the patients suffering from isolated GD and those suffering from DD. For categorical variables, a Chi^2-test was used when possible or Fisher's exact-test if not. For continuous variables, we used Welch's parametric t-test (if variance equality was rejected) or the non-parametric Mann-Whitney test, with a p-value ≤ 0.05 defining a significant difference between the two groups.

Thereafter, a multivariate logistic regression analysis was performed using an iterative selection procedure to select the variables that were significantly associated with "DD" status, as assessed by likelihood ratio tests. Variable candidates for the model were those associated with "DD" in the univariate analyses with a p-value < 0.20 (29). Then, backward selection was applied using the p-value < 0.05 criterion. The corresponding odds ratio (OR) and associated 95% confidence interval (95% CI) were estimated. The ability of the final model to discriminate between the presence or absence of a DD was assessed using the area under the receiver operating characteristic (ROC) curve, and the goodness-of-fit of the model was assessed using the Hosmer-Lemeshow test.

Ethics

The EVALADD cohort study was conducted in accordance with the Good Clinical Practice Guidelines and the Declaration of Helsinki, with approval from the local ethics committee (Groupe Nantais d'Ethique dans le Domaine de la Santé, GNEDS, Nantes) on September 6, 2012 and amended by the Research Ethics Committee (CPP Ile de France VI) on August 3, 2018.

RESULTS

Description of the Sample

The results are shown in **Table 1**. A large majority of our patients were young men, single, unemployed, with a family history of addictive disorders. Ages ranged from 15 to 72 years, with a median age of 22. Suicidal ideation was reported by 28% of the sample.

Moreover, current SUDs were diagnosed, with 30 patients (32.6%) for tobacco, 10 patients (10.9%) for alcohol, 9 patients (9.8%) for cannabinoids, and 0 patient for other illicit substances. Finally, four patients (4.3%) also suffered from current gambling disorder.

Prevalence of Dual Diagnosis

Out of 92 patients, 51 (55%) suffered from DD: 22 DD were characterized by multiple current psychiatric disorders and 29 by a single psychiatric disorder. Of the 29 patients with a single current comorbid psychiatric disorder, 18 suffered from probable ADHD, 9 from an anxiety disorder (generalized anxiety disorder, social phobia, agoraphobia, or panic disorder) and 2 from a mood disorder (major depressive episode, manic episode, or dysthymia). The description of associated disorders is available in **Table 2**.

Factors Associated With Dual Diagnosis

The results of the comparison between "Isolated GD" and "DD" are provided in **Table 1**. Among the 17 variables of interest, 12 were associated with DD at a 0.20 level of significance: the presence of professional activity, presence of family history of addictive disorder, recent suicidal thoughts, the three VMQ dimensions (Coping, Enhancement and Social), RSQ predominant insecure attachment style, and five TCI-125 dimensions (harm avoidance, novelty seeking, self-cooperation, self-directedness, and self-transcendence). These variables were then entered as candidates in the multivariate regression, from which four variables were found to be independently associated with DD in the final model (**Table 3**). Recent suicidal thoughts [OR = 6. 83, 95% CI (1.66–28.09), $p = 0.008$], TCI-125 "novelty seeking" scores [OR = 1.03, 95% CI (1.00–1.06), $p = 0.029$], TCI-125 "harm avoidance" scores [OR = 1.04, 95% CI (1.01–1.07), $p = 0.002$] and VMQ "coping" scores [OR = 1.18, 95% CI (1.01–1.38), $p = 0.042$] were factors associated with the presence of a DD. The Hosmer-Lemeshow goodness-of-fit test showed that the final model was well calibrated, with $p = 0.87$ (p-value > 0.05 indicates good model fit), and the area under the ROC curve was 0.84 (0.76–0.92) (**Figure 2**), showing that the model discriminated well between patients with "Isolated GD" and patients with "DD".

DISCUSSION

Main Results

Our observational study of GD patients seeking treatment aimed to determine DD prevalence and to identify characteristics associated with DD. More than half of the sample had GD associated with at least another current psychiatric disorder.

TABLE 1 | Sample description and univariate analyses by the presence or absence of dual diagnosis among gaming disorder patients ($N = 92$).

	Variable [mean (SD) or *n* (%)]	Total ($n = 92$)	Isolated GD ($n = 41$)	DD ($n = 51$)	*p*-value
Sample characteristics	Age	24.6 (±9.67)	24.7 (±11.0)	24.5 (±8.59)	0.93
	Male	84 (91%)	38 (93%)	46 (90%)	0.73
	Single	78 (85%)	34 (83%)	44 (86%)	0.66
	Professional activity*	16 (17%)	12 (29%)	4 (7.8%)	0.01
	Family history of addictive disorder*	56 (61%)	19 (46%)	37 (73%)	0.01
	Recent suicidal ideation*	25 (27%)	4 (9.8%)	21 (41%)	0.001
VMQ	Coping*	15.3 (±3.54)	13.8 (±3.64)	16.5 (±3.01)	0.01
	Enhancement*	15.0 (±3.11)	14.2 (±3.05)	15.6 (±3.06)	0.07
	Social*	8.87 (±2.94)	8.10 (±2.29)	9.49 (±3.27)	0.01
RSQ	Predominantly insecure attachment style*	72 (78%)	28 (68%)	44 (86%)	0.04
TCI-125	Temperament harm avoidance*	57.3 (±24.6)	47.1 (±22.9)	65.6 (±22.8)	0.01
	Temperament novelty seeking*	54.2 (±21.6)	50.9 (±19.4)	57.0 (±23.1)	0.17
	Temperament persistence	33.0 (±28.8)	33.7 (±28.1)	32.5 (±29.7)	0.85
	Temperament reward dependence	51.2 (±18.2)	50.7 (±19.1)	51.6 (±17.6)	0.70
	Character self-cooperation*	68.9 (±19.0)	71.8 (±18.7)	66.5 (±19.1)	0.15
	Character self-directedness*	45.4 (±18.4)	52.6 (±17.2)	39.6 (±17.4)	0.01
	Character self-transcendence*	30.4 (±22.7)	26.5 (±19.8)	33.6 (±24.4)	0.13

DD, dual diagnosis; GD, gaming disorder; RSQ, Relationship Scales Questionnaire; TCI-125, Temperament and Character Inventory−125; SD, standard deviation; VMQ, Videogame Motives Questionnaire (from Gambling Motives Questionnaire).

**Variables included in the initial multivariate model (p-value < 0.20).*

TABLE 2 | Prevalence of associated disorders ($N = 92$).

	n (%)
Dual diagnosis	51 (55%)
Probable ADHD	35 (38%)
Generalized anxiety disorder	14 (15%)
Social phobia	12 (13%)
Major depressive episode	12 (13%)
Agoraphobia	10 (11%)
Post-traumatic stress disorder	3 (3%)
Obsessive compulsive disorder	2 (2%)
Manic episode	2 (2%)
Panic disorder	2 (2%)
Psychotic disorders	1 (1%)
Dysthymia	0 (0%)

ADHD, attention-deficit/hyperactivity disorder.

TABLE 3 | Multivariate analysis of factors associated with dual diagnosis among gaming disorder patients ($N = 92$).

Variable	Odds ratio	95% Confidence interval	*P*-value
TCI-125 novelty seeking	1.03	(1.00–1.06)	0.029
TCI-125 harm avoidance	1.04	(1.01–1.07)	0.002
VMQ coping	1.18	(1.01–1.38)	0.042
Recent suicidal ideation	6.83	(1.66–28.09)	0.008

TCI-125, Temperament and Character Inventory−125; VMQ, Videogame Motives Questionnaire.
Global fitness was assessed using the Hosmer-Lemeshow goodness-of-fit test, with a p-value > 0.05 (0.87), indicating that the model was well calibrated.

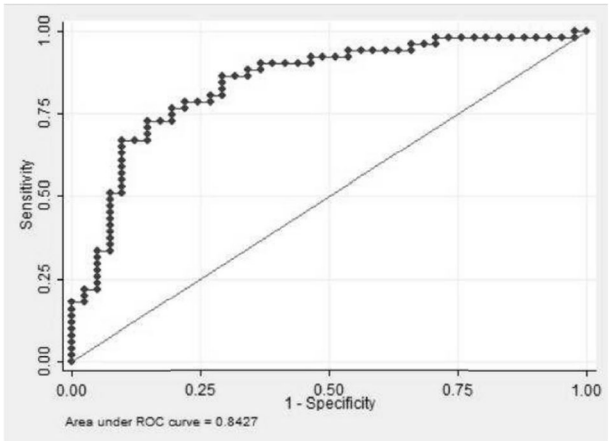

FIGURE 2 | Receiver operating characteristic curve of the final model.

Compared to those found in studies on other behavioral addictions, especially gambling disorder, this rate might seem low. For example, in a previous publication, we reported that 75% of our sample of pathological gamblers seeking treatment suffered from at least one psychiatric comorbidity (30). However, we must keep in mind that we only considered current psychiatric disorders in the present study, rather than lifetime disorders, as is the case in many studies. In addition, patients with GD are relatively young, as confirmed in our study, which may limit the possibility to observe the occurrence of a psychiatric disorder. We showed that GD patients were more frequently affected by psychiatric disorders than the general population (31) and that the proportion of DD was quite similar when considering GD (55% in our study) or SUDs, with almost 1 out of 2 patients (32). The main comorbid disorders were essentially anxiety disorders and probable ADHD, with a prevalence of ADHD symptoms almost 10 times higher than that observed in the general population (33). This result is consistent with the literature (11, 14, 34). The high proportion of probable ADHD found in our population may also be explained by certain common characteristics found with patients suffering from gaming disorder such as high impulsivity. Patients with ADHD may find a form of self-medication in playing certain types of video games as a coping mechanism (35). This hypothesis could open up new therapeutic options. ADHD is already known to be highly comorbid with SUDs, and additional comorbid disorders are more frequent among SUDs patients with ADHD than those without ADHD (36). Validating the close links between probable current ADHD and addictive disorders, in this case GD, reinforces the hypothesis of the applicability of the DD concept to addictions in general and to GD more specifically. Regarding comorbid anxiety disorders, several studies have described not only associations between anxiety disorders and GD but also predictive relationships between gaming and depression, anxiety and social phobia with increased levels of these disorders among GD patients and lower levels among patients who ceased gaming (9, 37). Studies have suggested that depressive and anxiety symptoms before the COVID-19 pandemic positively predicted videogame use and problematic gaming during the COVID-19 pandemic (38). On the one hand, anxiety symptoms may facilitate the emergence of GD, and on the other hand, gaming can be used to cope with stressful events and negative emotions. This close and dynamic interrelationship can result in the modification of the features of both GD and associated anxiety disorders, potentially resulting in a DD.

We highlighted that some psychopathological and clinical characteristics of GD patients were associated with DD. First, 41% of patients in the DD group reported suicidal ideation in the month preceding the evaluation and/or a history of suicide attempts. In contrast, a French epidemiological study found that 4.7% of 18–75-year-olds reported having thought about suicide in the previous 12 months and that 7.2% had attempted suicide in their life (39). Suicidal risk should be assessed systematically in patients with DD, particularly in the context of GD. Independent of GD, an association between DD and suicidal ideation has been previously reported in the literature (40). DD patients with one disorder attempting to regulate another disorder may more frequently feel desperate as coping mechanisms fail, which may lead to accumulating negative consequences or the two disorders potentiating each other (e.g., withdrawal in depression and GD); these situations could favor the emergence of suicidal ideation. Finally, since there are multiple pathways to care, promoting

liaison care between health services is essential, as suicidal ideation may be a trigger for initiating treatment for GD.

Second, "novelty seeking" and "harm avoidance" dimensions were associated with DD. A recent publication described different personality profiles among GD patients based on the number of comorbid disorders (41). As developed by Cloninger, "novelty seeking" corresponds to behavioral activation to rewarding stimuli and signals, whereas "harm avoidance" reflects a behavioral inhibition to signals recognized as punitive or frustrating (27). One might think that such opposite temperaments linked to the same "DD" entity could reflect diversity among this entity. GD patients with a high "novelty seeking" temperament could develop a different type of DD than "harm avoidance" GD patients given the core difference defining these gamers personalities. Thus, different gamer profiles with different personality traits could favor the emergence of particular comorbid psychiatric disorders and thus favor very different DDs. Recently, a study about ADHD symptoms and video game addiction stated that impulsivity appears to be the ADHD symptom most strongly correlated with video game addiction (42). Therefore, both psychiatric disorders and GD reinforce each other depending on the specific patient temperament. A similar idea of subgroups based on different patient characteristics had previously been identified for gambling disorder. According to Blaszczynski and Nower, three main profiles could be distinguished: behaviorally conditioned problem gamblers, emotionally vulnerable problem gamblers associated with premorbid anxiety and depressive disorders, and antisocial impulsive problem gamblers (43). A recent neuroimaging study attempted to distinguish distinct pathways to explain the development of internet gaming disorder (IGD), according to history of childhood ADHD. IGD participants without childhood ADHD exhibited abnormal hyperconnectivity within the default mode network compared with controls, while IGD participants with childhood ADHD showed expanded functional connectivity between the posterior cingulate cortex and cerebellum, a region involved in executive control, suggesting that altered neural system for executive control in ADHD may predispose to the development of IGD (44).

However, further studies are necessary to consolidate an etiological model of GD based on neurobiology and neuroscience.

Third, we highlighted that gaming to reduce or avoid negative emotions, as measured by the VMQ "coping" dimension, was associated with DD. This specific motivation supports the main concept underlying DD, i.e., gaming is used to alter symptoms of an underlying mental disorder that generates negative emotions. Confronted with mental disorders and negative emotions, one could easily engage in specific activities to regulate these emotions. Escapism through video games as a coping mechanism is a known predictive factor of GD (4, 5); however, in contrast to passive escapism where individuals are merely observers, "active escapism" (45) provides the additional opportunity to interact with the environment, which can facilitate affirmation and empowerment. Using video games as a tool to facilitate the regulation of negative emotions can open new therapeutic perspectives with virtual environments. Thus, gaming motives should be considered not only as a vulnerability factor for the development of DD under certain circumstances but also as a way to discover new treatments for such DD.

Strengths and Limitations

Our study included patient data only at the initiation of addiction treatment for GD in a cross-sectional manner, without taking into consideration the temporal changes in psychopathology. Longitudinal studies could help understand the onset sequence of disorders and could explore causal links in the emergence of DD. In addition, we used screening and not diagnostic tools in the assessment of ADHD. However, we have sought to limit the risk of over-screening by combining two screening tools. Finally, due to the differences in assessment tools (in particular, no use of semi-structured clinical interviews in other studies) and in the evaluation period (in particular, we focused on current disorders in our study), we were unable to compare our results with previous literature regarding clinical and non-clinical populations.

Nevertheless, we were able to collect a large sample of patients with a homogeneous distribution between the "Isolated GD" and "DD" groups. Our clinical sample is typical of patients suffering from GD, namely, outpatients that include a majority of single young men (46). The exhaustive assessment of a large spectrum of psychiatric disorders, the use of recognized and standardized questionnaires and diagnosis interviews, and the use of the new ICD-11 GD criteria are strengths of our study.

Orientation and Management

Screening patients for the presence of suicidal ideations is a key point, as they represent one aspect of the urgency and gravity of DD and are highly prevalent among GD patients. Probable ADHD, being the most prevalent comorbid disorder identified in our study, must also be systematically screened for and treated if confirmed.

Assessing patients' personality traits, among other personal characteristics, could help manage GD, as these characteristics could be central within a DD, and certain traits might even lead to specific form of a DD. Integrating therapeutic education sessions about the recognition and prevention of psychiatric disorders into the treatment of those with GD would make it possible to prevent the occurrence of these disorders among the most at-risk patients. Implementing prevention efforts and the early recognition of the function of video games as a potentially harmful coping mechanism would be beneficial among patients suffering from mental disorders. Considering GD through the prism of DD helps us understand the mechanisms involved not only in the emergence of GD but also in the development of DD in general. Future prospective studies focused more on the sequence of onset and development of these disorders would be of

great help in understanding the more common forms of DD involving GD.

Integrated health care is now recognized by the Substance Abuse and Mental Health Services Administration (SAMHSA) as the reference for treating DD (47) and we should think about implementing these principles in the treatment of GD.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because the raw anonymized data will be made available only if the purpose is consistent with the consent given by participants and in accordance with the legislation in force in France. Requests to access the datasets should be directed to MG-B, marie.bronnec@chu-nantes.fr.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Groupe Nantais d'Ethique dans le Domaine de la Santé, GNEDS, Nantes Research Ethics Committee, Comités de protection des personnes (CPP) Ile de France VI. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

MB-P-D, CC, JL, MG-B, and GC-B performed survey and data collection. MG-B, MB-P-D, CC, and GC-B carried out materials and methods and manuscript writing. MB-P-D and VG carried out statistical analysis. MG-B, GC-B, MB-P-D, CC, VG, JL, and BR designed the research and project. All authors contributed to the article and approved the submitted version.

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