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Insights in addictive disorders: 2022

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ORIGINAL RESEARCH
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Efficacy of the Therapeutic Game "Trisquel" in the Treatment of Patients With Substance-Related Disorders Randomized Clinical Study

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Substance-related disorders (SRD) have been consistently associated with alterations both in cognitive and executive functions, which affect to patients' quality of life. The main objective of this work was to test the beneficial cognitive effects on patients with SRD after the implementation of "Trisquel," an intervention program in board game format. To check the effectiveness of Trisquel program, a group of people diagnosed with SRD was randomly assigned either to the experimental group or to the control group. The experimental group performed Trisquel structured sessions twice a week during 3 months, while the control group performed routinely conventional therapeutic activities with the same frequency and duration. Neuropsychological tests were done to both groups before and after the intervention. After the 3 months of intervention the experimental group showed the following statistically significant improvements for WAIS-III subtests: number key, symbol search, arithmetic, direct digits, inverse digits, total digits, letters-numbers in the processing speed index and in the working memory index. Regarding STROOP tests, statistically significant progress was observed in the phonetic fluency letter P, phonetic fluency letter M, phonetic fluency letter R subtests, word-reading and word-color subtests. The control group only obtained improvements for WAIS-III subtests of arithmetic, letters-numbers and in the working memory index.

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The results of this study confirm that "Trisquel" is an effective intervention program for people diagnosed with SRD, getting improvements in processing speed (psychomotor and reading), attentional subprocesses (focused and sustained) and executive functions (updating and inhibition).

Keywords: substance-related disorders, cognitive impairment, neuropsychological rehabilitation, psychoeducation, Trisquel

INTRODUCTION

The Diagnostic and Statistical Manual of Mental Disorders DSM-5 (1) defines substance-related disorders (SRD) as those health problems caused by acute or chronic use of psychoactive substances. SRD are characterized by the association of cognitive, behavioral and physiological symptoms that lead a person to seek and use a substance despite its negative consequences. To date, SRD remains one of the most prevalent chronic diseases and there is evidence that the cost of treating Drug Use Disorders is much lower than not treating drug dependence. Despite the advancement in the knowledge of SRD and its treatments, relapse and therapeutic failure continue to be frequent problems (2).

Scientific evidence shows that drugs consumption has been consistently associated with the presence of alterations in different neuropsychological processes, such as memory, attention or executive functions (2–4), and these neuropsychological alterations are present even after prolonged periods of abstinence (5).

In Spain, 70% of people with SRD present cognitive impairment (2), which is considered a common feature in this type of patients (6). Literature highlights the relevance of cognitive rehabilitation in SRD and there is a growing number of studies proposing and evaluating different therapeutic interventions aimed at improving the cognitive domains in treatment outcomes (2, 7–9). Experience shows that psychotherapeutic interventions, such as psychotherapy or relapse prevention are failing in the goal of improve cognitive functions in SRD patients (10).

By other hand, an efficacy study of a Mindfulness and Goal Management Program carried out in Spain, has found an improvement in SRD patients regarding executive functioning, processes of reflection and goal achievement in daily activities (11).

Trisquel

Given the clinical and social need to implement, invigorate and improve therapeutic and neurorehabilitative interventions in SRD patients, it was decided to create a new intervention program, called "Trisquel," designed following the reference framework of a "serious game."

"Serious games" do not have entertainment or amusement as their primary goal as are designed to educate, train or change behavior while entertaining players (12). Them have been developed in different formats encompassing both interactive role-playing games and board games (8, 13–18). In just over a decade, there has been an increase in its use as a tool to improve specific skills or competencies in different areas such as outreach, education, training, human resource management and health (12, 19, 20). Different studies on their effectiveness demonstrated that this type of therapeutic games create dynamic and motivating learning environments (13, 14, 19, 21–24). It has been noted that serious games combine three important aspects that contribute to the effectiveness of this approach: repetition, feedback, and motivation (8).

Previous experiences with serious games as "Road to awareness," "The Trivia of Awareness," "Escalation of Awareness," "Trivia Psychotica," "Reaction," and "The Train" (21, 25–27), are clear examples of how a game can be a cognitive stimulation and rehabilitation tool, invigorating interventions, encouraging participation, providing information (psychoeducation) and working on social skills, problem solving, and deficit awareness.

For the design of "Trisquel" (22, 23, 28), the principles of neuropsychological rehabilitation have been taken into account. A neuropsychological assessment was performed, operational objectives were established, tasks were hierarchized and a continuous feedback system was provided. Besides that, different individualized strategies and techniques (restitution and compensation) (29) and others of group character (social skills) were combined and diverse theoretical reference models were taken into account.

The first "Trisquel" version began to be used in March 2008 and was completed in 2009 (Intellectual Property Registry VG 6-09) with a total of 590 theoretical-practical tests. Due to the good reception and evolution of the program, in 2014 a working group was created to carry out an extensive revision of the theoretical-practical contents of the entire program. Redundant, obsolete tests or those that did not provide information were eliminated, and the theoretical-practical contents of the program were expanded (28). To date, Trisquel has been used in over 12 centers in Spain and Portugal.

Although "Trisquel" has been tested in other populations with positive effects, the present work is the first one studying Trisquel effects on cognitive performance in SRD patients.

MATERIALS AND METHODS

Design

Multicenter, longitudinal, prospective, randomized controlled study with pre and post neuropsychological measures.

FIGURE 1 | (A) Trisquel 2014 version, **(B)** box, professional's manual and elements of the Trisquel 2014 game.

Study Population

Participants were selected among those patients under treatment in assistance devices [day unit (UD) and therapeutic community (CT)] of the Galician Network of Care for Drug Addicts (A Coruña, Ferrol and Vigo, Spain) and of the Division for the Intervention of Addictive Behaviors and Dependencies (DICAD) of the Regional Health Administration-North of Portugal (Porto, Portugal). This project was conducted between the years 2018–2020.

Inclusion criteria were: (1) diagnosis of substance-related disorders and other addictions according to DSM-5, (2) having capacity to consent (competence), (3) reading the project information sheet and signing informed consent, (4) being of legal age, (5) being able to read and write.

Exclusion criteria were (1) illiteracy, (2) diagnosis of intellectual disability (IQ $<$ 70), (3) moderate or severe neurological damage, (4) suffering from an acute psychiatric process, (5) inability to be evaluated, (6) having an abstinence of less than 15 days, (7) not having cognitive impairment according, the Montreal Cognitive Assessment (MOCA $\geq$ 26).

A total of 101 people were evaluated, all of them meeting the inclusion criteria and none of them meeting the exclusion criteria. The total 101 were invited to participate, although only 71 patients completed the study. 30 patients (29.70%) dropped out the treatment. From Trisquel group 9 patients (30%) abandoned (3 of them from CT and 6 UD). The reasons for leaving the unit were 17 dropouts, 10 expulsions (due to positive controls and disciplinary reasons) and 3 for health reasons.

Measuring Instruments

A questionnaire to collect sociodemographic data and tables shows a selected battery of neuropsychological tests (**Tables 1**, **2**).

- Montreal Cognitive Assessment, MoCA (30): The Spanish version of the MoCA test (designed by Nasreddine) was used, with a maximum score of 30, being the cut-off points (suggested by the author), 25/26 for mild cognitive impairment and 17/18 for dementia. Normacog scales were applied (31).
- Scale for the Measurement of Adult and Adolescent Intelligence (WAIS III) (32): The number key and symbol search subtests were used to calculate the processing speed index. The letter-number, digit and arithmetic subtests allow to calculate the working memory index. The Spanish adaptation of the WAIS-III was used. Reliability coefficients (two halves) range between 0.77 and 0.96.
- STROOP test (33): It is an instrument that allows a very brief and simple evaluation reading processing speed, the ability to focus and redirect attention and the ability to resist interference. The reliability using the test-retest method is.89 for Stroop-P, 0.84 for Stroop-C and 0.73 for Stroop-PC. Neuronorm scales were used for young adult population in Spain (34).
- TMT Stroop Test (35): The test consists of two parts, A and B. Part A assesses sustained attention, processing speed, motor, and visuospatial visual search skills. Part B assesses alternating attention and cognitive flexibility. Reliability is between 0.86 and 0.94%. Neuronorma scales were used for young adult population in Spain (36).
- Verbal fluency tests (37): Phonemic Fluency test, a task of oral production of words before phonetic instructions, and the Semantic Fluency test (animals), a task of linguistic production that requires the implementation of the mechanisms of access to the lexicon. Neuronorm scales were used for the young adult population in Spain (38).

Procedure

The professionals who participated in the project received specific training on Trisquel's methodology, dynamics and theoretical and practical contents prior to the start of the program. To avoid experimental biases and work overload in the centers, two psychologists were hired for the project to carry out the

TABLE 1 | Tests selected to build a battery of neurological tests and cognitive domains assessed.

Cognitive domain	Test
MOCA	
Screening for mild cognitive impairment.	Montreal Cognitive Assessment (MOCA)
WAIS-III	
Psychomotor processing speed and visual-motor coordination	Number key
Mental arithmetic and working memory	Arithmetic
Focused, sustained attention and working memory	Digits
Visual perception, psychomotor processing speed	Symbol search
Working memory	Letters and numbers
Psychomotor processing speed	Processing speed index
Working memory	Working memory index
Test de STROOP	
Speed of reader processing	Words
Selective attention	Color
Cognitive inhibition	Word-color
Trace test	
Sustained attention, motor, and visuospatial visual search skills	Part A
Alternating attention and cognitive flexibility	Part B
	Verbal fluency test
Functioning of the frontal lobe	Phonemic fluency
Functioning of the temporal lobe	Semantic fluency

TABLE 2 | Descriptive analysis of sociodemographic variables.

	Trisquel group $n = 40$	Control group $n = 31$	p
Age[a]	44.28 ± 9.51	42.81 ± 9.64	0.335[d]
Gender[b]			1.000[c]
Male	33 (82.5%)	25 (80.6%)	
Female	7 (17.5%)	6 (19.4%)	
Cognitive impairment (MOCA)[b]	21.0 ± 3.3	21.3 ± 3.4	0.940[d]
Level of education[b]			[e]
<6 years of education	4 (10%)	2 (6.5%)	
6–9 years of education	28 (70%)	21 (67.7%)	
10–12 years of education	8 (20%)	6 (19.4%)	
>12 years of education	0 (0%)	2 (6.5%)	
Primary drug			[e]
Heroin	12 (30%)	8 (25.8%)	
Cocaine	17 (42.5%)	9 (34.6%)	
Alcohol	9 (22.5%)	11 (35.5%)	
THC	2 (5%)	2 (6.5%)	
Sedatives and hypnotics	0 (0%)	1 (3%)	
Age of drug initiation[a]	20.6 ± 7.7	20.6 ± 10.12	0.702[d]
Personality disorders[b]	10 (62.5%)	6 (37.5%)	0.775[c]
VIH+[b]	6 (15.0%)	0 (0%)	0.032[c]
VHC+[b]	12 (70.6%)	5 (29.4%)	0.268[c]
Unit			
Day unit	23 (57.5%)	14 (45.16%)	0.345[d]
Therapeutic community	17 (42.5%)	17 (54.83%)	

[a] *Values expressed as mean ± standard deviation.*
[b] *Values expressed as frequencies and percentages.*
[c] *Fisher's exact test.*
[d] *T-test for independent samples.*
[e] *Cannot be calculated because there are categories with too few patients.*

pre and post evaluations and the sessions with Trisquel in the respective centers.

All patients from the participating centers were filtered to meet the inclusion and exclusion criteria. On this filtered census, a simple random sampling technique was applied, until the estimated sample size was reached (between 6 and 14 patients per device). The individuals were then assigned to the experimental and control groups using a simple random sampling technique. All participants were provided a sociodemographic data collection questionnaire and a battery of neuropsychological tests before, and 1 week after the last intervention session. All tests were administered in two 30-min evaluation sessions under similar conditions.

Ethical Considerations and Personal Data Protection

This project was approved by the Autonomous Research Ethics Committee of Galicia (Registration Code: 2018/153). All patients were informed about the rehabilitation program before its start. Patients read and signed the informed consent, voluntarily accepted their participation in the study and did not receive any financial or other incentive. The processing, communication and transfer of data was performed in accordance with the provisions of the European Data Protection Regulation (EU Regulation 2016-679 of the European Parliament and of the Council of 27 April 2016).

Cognitive Rehabilitation

The experimental group was treated with Trisquel program and the control group received cognitive rehabilitation in the context of a biopsychosocial treatment, with a holistic and integrative approach, usually in the Treatment Facilities of the Drug Dependence Assistance Network of Galicia (Spain) and DICAD (Portugal). None of the two groups participated in any other rehabilitation program similar to the one proposed in this study. In order to carry out this work in the DICAD (Portugal), Trisquel has been translated and adapted to Portuguese language.

Program Description

Trisquel program combines psychoeducation and cognitive stimulation strategies. Following the theoretical framework of "serious games: the principles of neuropsychological rehabilitation were taken into account and different individual techniques were combined, such as restitution and compensation (29), and others of group character, such as social skills (19, 20). Likewise, different theoretical reference models were taken into account, such as the Therapeutic Milieu, learning from successes, the information processing model of Miller (39), the working memory model of Baddeley and Hitch (40), the model of retrieval processes of information from memory of Moscovitch (41) and the emotional processing model of Ekman (42).

FIGURE 2 | Pictures of Trisquel sessions in different rehabilitation centers.

Trsiquel program consists on a board, cards and thematic blocks of cards with 1,105 theoretical-practical tests. The theoretical-practical questions and cognitive tests are organized in thematic blocks and were elaborated according to the specific intervention needs of the population to be treated (relapse prevention, social skills, HIV prevention, mental health, health interventions, sexually transmitted diseases, etc.) and to the cognitive characteristics of the patients (degree of difficulty, level of cognitive impairment). During the sessions, the difficulty of the tasks is graded by the moderator (member of the therapeutic team) according to the previous results obtained by the participants in the working memory index of the WAIS-III (digits, arithmetic and letters-numbers) and in the MOCA cognitive screening test. Although "Trisquel" includes other additional thematic blocks, for the purpose of this study were used relapse prevention and HIV-AIDS, women, drug addiction, gender violence, social skills (communication pragmatics), executive functions (emotional expression and recognition, planning, inhibition, mention theory), manipulative cognitive tests (psychomotor skills, visoconstructive praxis, instrumental skills) and non-manipulative tests (processing speed, attention, phonemic and semantic fluency, verbal and visual memory, mental arithmetic, topographical orientation), health interventions (sleep hygiene, nutrition), and smoking (information, prevention and treatment) (**Figure 1**).

Dynamics of the game could be compared to that of the popular trivia game. The main differences lie in the figure of the moderator, the graduation and hierarchy of the difficulty of the cognitive tests, the establishment of game rules that encourage participation and the content of the tests themselves (psychoeducational interventions related to the treatment of patients and cognitive stimulation tasks). Trisquel is a competitive game in which, at the end of the session, there is a winning team and the game ends when a test of each colored square (Green, Orange, Blue, Yellow) is correctly performed and the central square (starting place) is reached again. Trisquel sessions involve a maximum of 6 or 7 patients divided into three groups. The cognitive tasks are performed individually and the group tasks can be agreed upon and answered by the members of the group. Each session is structured in terms of working on theoretical and practical aspects. The blocks of cards are ordered numerically (from simple to complex) and by topics to be covered. Most of the program's theoretical-practical tests can be the subject of intervention by the professional, providing clarifications on some theoretical or practical concept, behavioral modifications of the maladaptive behaviors that arise in the role-playing or positive modeling of such behaviors. Since its creation in 2008, Trisquel has gone through several versions and design improvements during previous pilot study processes. For a more detailed description of the program and its characteristics (23, 28).

Trisquel Group

The experimental group consisted on the administration of Trisquel program for 3 months, through 24 sessions of ± 60 min duration, with a frequency of 2 sessions per week, in the context of a usual biopsychosocial treatment in the participating centers. The sessions were carried out in groups of a maximum of 6 or 7 patients (**Figure 2**).

Control Group

This group carried out the routinely conventional therapeutic activities usually scheduled in each Care Center, consisting on Psychosocial Rehabilitation Support Programs (relapse prevention, occupational activities, and cognitive stimulation) implemented by a multidisciplinary team, with the same number of sessions (26), duration (± 60 min) and frequency (2 sessions per week) as the experimental group. The sessions were carried out in groups of a maximum of 6/7 patients. At the end of the study, all subjects in the control group were offered to perform the Trisquel program.

Data Analysis

A descriptive analysis of the data was performed. Frequencies and percentages were calculated for qualitative variables. For quantitative variables, means and deviations were calculated. The normality of the variables in each of the study groups was tested using the Shapiro-Wilks test. To identify differences between the two groups (Experimental and Control), the Mann-Whitney *U*-test or the *t*-test for independent samples were used. For the pre-post intervention comparison, the Wilcoxon test or the *t*-test for related samples were used. Cohen's D was also calculated to quantify the effect size. The programs used were SPSS v.19 and G-power.

RESULTS

Trisquel group consisted of 40 persons with a mean age of 44.28 years, of whom 33 (82.5%) were men and 7 (17.5%) women. Their mean MOCA cognitive impairment was 21.0 ± 3.3. Control group consisted of 31 persons with a mean age of 42.81 years of which 25 (80.6%) were men and 6 (19.4%) women. Their mean MOCA cognitive impairment was 21.3 ± 3.4. The descriptive analysis of the sociodemographic variables of each group is showed in **Table 2**. Statistically significant differences were found between groups in the variable's Cannabis Addiction Diagnosis and HIV-associated organic pathology (**Table 2**).

Intergroup Differences

No statistically significant pre-intervention differences intergroup were found in relation to neuropsychological variables.

Intragroup Differences After the Intervention: Neuropsychological Assessment Module

In the cognitive performance of Trisquel group, statistically significant intragroup differences were found pre-post intervention in the subtests of number key (p = 0.001) with a moderate effect size (d = 0.763), symbol search (p = 0.001) with a moderate effect size (d = 0.598), arithmetic (p = 0.001) with a moderate effect size (d = 0.659), direct digits (p = 0.001) with a moderate effect size (d = 0.653), inverse digits (p = 0.025) with a small effect size (d = 0.385), total digits (p = 0.001) with a moderate effect size (d = 0.657), letters-numbers (p = 0.0001) with a large effect size (d = 0, 803) with WAIS-III, on the processing speed index (p = 0.001) with a moderate effect size (d = 0.598) and on the working memory index (p = 0.001) with a large effect size (d = 0.911) with WAIS-III, on the phonetic fluency subtest letter P (p = 0.001) with a moderate effect size (d = 0.756), phonetic fluency letter M (p = 0.004) with a small effect size (d = 0.488), phonetic fluency letter R (p = 0.002) with a small effect size (d = 0.575), in the word reading subtests (p = 0.007) with a small effect size (d = 0.372) and word-color of the STROOP test (p = 0.001) with a moderate effect size (d = 0.631).

In the cognitive performance of the control group, statistically significant intragroup differences were found pre-post intervention in the arithmetic (p = 0.003) with a small effect size (d = 0.488) and letter-number (p = 0.001) subtests with a moderate effect size (d = 0.652) and in the working memory index with WAIS-III (p = 0.002) with a moderate effect size (d = 0.572). **Table 3** shows the mean scores and standard deviations of each group before and after treatment with respect to cognitive performance (**Table 3**).

DISCUSSION

The aim of this study was to analyze the effect of the board game intervention program "Trisquel" on cognitive performance in people with SRD. The former clinical experience with Trisquel of several professionals in different centers after 13 years of implementation was suggesting that Trisquel helps to reduce therapist-patient distances, facilitates group dynamics, stimulates cognitive functions, is a versatile and adaptable tool to the needs of each patient (level of impairment) and allows the development of motivation on the part of the patients. It was also observed that Trisquel favors the incentive to win, the challenge of reaching a goal and the sense of efficacy, the feedback of progress, the greater adhesion of the members of the same team.

Due to these preliminary observations and the interest aroused by the program in recent years, it was decided to initiate a process of evaluation of the effectiveness of this therapeutic game in different populations (mental health and addictions). This study shows that Trisquel leads to improvements in processing speed, attentional subprocesses and executive functions in patients with SRD diagnosis. Overall, the results of this work are congruent with other studies that support the use of serious games in the clinical approach of patients with different mental disorders and, more specifically, it provides evidence on the usefulness of an intervention program in board game format to induce improvements in cognitive-executive functioning in SRD patients.

TABLE 3 | Intragroup comparison with respect to cognitive performance.

	Trisquel group				Control group			
	Pre	Post	*p*	Cohen d	Pre	Post	*p*	Cohen d
WAIS-III[a]								
Key numbers	34.5 ± 21.2–44.5	41.0 ± 25.5–58.2	*** (0.001)	0.763	39.0 ± 29.7–60.0	42.5 ± 23.5–59.5	0.339	0.121
Arithmetic	7.5 ± 6.7–11.0	9.0 ± 8.0–11.0	*** (0.001)	0.659	8.5 ± 7.0–9.7	10.0 ± 7.2–12.0	0.003	0.488
Direct digits	8.0 ± 6.0–9.0	9.5 ± 7.0–10.2	*** (0.001)	0.653	8.0 ± 6.0–10.0	8.5 ± 7.2–10.0	0.102	0.268
Inverse digits	5.0 ± 3.7–6.0	5.5 ± 4.0–7.2	* (0.025)	0.385	4.0 ± 3.2–5.7	5.0 ± 4.0–6.0	0.444	0.284
Total digits	11.5 ± 10.0–15.0	14.5 ± 11.0–17.2	*** (0.001)	0.657	12.0 ± 10,0–16,0	13,0 ± 11,2–16,0	0.085	0.362
Search symbols	24.0 ± 15.0–30.0	28.0 ± 18.0–34.0	*** (0.001)	0.598	23.5 ± 21.0–29.25	25.5 ± 20.0–30.75	0.079	0.277
Letters and numbers	7.0 ± 6.0–8.0	8.0 ± 7.0–11.0	*** (0.001)	0.803	7.0 ± 5.0–8.0	9.0 ± 7.0–10.0	0.001	0.652
Working memory index	83.5 ± 74.5–94.0	97.0 ± 85.2–106.0	*** (0.001)	0.911	90.0 ± 80.0–96.0	90.0 ± 83.0–102.0	0.002	0.572
Processing speed index	84.0 ± 77.2–92.0	92.0 ± 84.0–101.5	*** (0.001)	0.596	87.0 ± 78.0–98.0	92.0 ± 82.5–99.5	0.085	*** (0.001)
STROOP[a]								
Words	85.5 ± 71.5–96.2	91.0 ± 74.0 102.2	** (0.007)	0.372	89.0 ± 67.0–98.0	90.0 ± 86.0–109.0	0.107	0.322
Colors	57.5 ± 49.2–67.5	63.0 ± 55.0–68.7	0.061	0.239	61.0 ± 55.0–71.0	63.0 ± 60.0–68.0	0.073	0.254
Word-color	33.0 ± 26.2–41.0	39.5 ± 30.2–46.0	* * * (0.001)	0.631	37.0 ± 27.0–44.0	38.0 ± 29.0–44.0	0.559	0.059
TMT[a]								
Part A[b]	36.5 ± 28.7–56.5	35.0 ± 24.5–52.5	0.179	0.201	33.0 ± 22.0–47.0	28.0 ± 22.0–44.5	0.057	0.340
Part B[b]	60.0 ± 47.0–102.5	58.0 ± 46.5–75.0	0.093	0.546	79.0 ± 59.0–97.0	72.0 ± 48.7–86.2	0.064	0.689
Verbal fluency[3]								
Phonemic -P	12.0 ± 8.0–14.0	13.5 ± 11.7–17.2	*** (0.001)	0.756	12.0 ± 9.0–16.0	13.0 ± 10.2–17.5	0.351	0.166
Phonemic –M	11.0 ± 7.7–14.0	12.0 ± 9.0–15.0	** (0.004)	0.488	10.0 ± 8.0–14.7	11.0 ± 8.0–15.0	0.150	0.293
Phonemic -R	9.0 ± 7.0–12.0	10.5 ± 8.0–14.0	** (0.002)	0.575	10.5 ± 7.2–13.7	11.0 ± 7.2–14.0	0.666	0.094
Semantic	17.0 ± 13.0–21.25	18.0 ± 14.0–23.0	0.057	0.289	17.5 ± 14.0–20.0	17.0 ± 11.2–21.0	0.972	0.031

*[a]Values expressed as median ± interquartile range; [b]These scores are inverse, i.e., a higher score implies worse performance; Significance levels: *p < 0,05; **p < 0,01; ***p < 0,001.*

TABLE 4 | Process-based intragroup comparison of cognitive performance.

Cognitive-executive domain		Test	Trisquel group *p*-value	Control group *p*-value
Processing speed	Psychomotor processing speed	WAIS-III Number Key	*** 0.001	0.339
		WAIS-III search symbols	*** 0.001	0.079
		WAIS-III processing speed index	*** 0.001	0.085
	Reader processing speed	STROOP word reading	** 0.007	0.107
	Visuospatial processing speed	TMT part A	0.179	0.057
Attention	Focused and sustained	WAIS-III direct digits	*** 0.001	0.102
	Selective	STROOP colored film	0.061	0.073
Executive functions	Executive update component	WAIS-III inverse digits	* 0.025	0.444
		WAIS-III total digits	*** 0.001	0.085
		WAIS-III arithmetic	*** 0.001	** 0.003
		WAIS-III letters and numbers	*** 0.001	*** 0.001
		WAIS-III working memory index	*** 0.001	** 0.002
		Phonemic fluency letter P	*** 0.001	0.351
		Phonemic fluency letter M	** 0.004	0.150
		Phonemic fluency letter R	** 0.002	0.666
Executive functions	Executive component of inhibition	STROOP color film word-color	*** 0.001	0.559
Executive functions	Executive component of change	TMT Part B	0.093	0.064

*The values expressed in significance levels are: *p ≤ 0.05; **p ≤ 0.01; ***p ≤ 0.001.*

In order to be able to discuss the results, an interpretation of the results was performed following a structure based on a process analysis (processing speed, attentional subprocesses and executive components). To perform this analysis, different theoretical reference models were taken into account such as the factorial structure of attention (43), the clinical model of attention and the factorial model of executive components (44). **Table 4** shows a comparison of the cognitive performance of both

groups, where Trisquel group obtained statistically significant improvements in most of the cognitive-executive processes evaluated in this study.

According factorial structure of attention it is understood that processing speed reflects a basic property of the system where attention is implemented, and considers that it is a modulating factor of attentional performance (43). Trisquel group obtained statistically significant improvements in two of the three types of processing speed tasks evaluated (psychomotor and reading). These results are congruent with those obtained by other rehabilitation programs in which a significant improvement in processing speed is obtained after an intervention program (45, 46). A meta-analysis study on the evaluation of the efficacy of Goal Management Training concludes that intervention programs demonstrated efficacy in different populations by improving functioning in all cognitive-executive domains except processing speed (47, 48).

Regarding the attentional subprocesses performance, following the Clinical Model of Attention (one of the most referenced attention models in the literature), the results of the present study show that in Trisquel group statistically significant improvements were found in the subprocesses of focused and sustained attention, results in line with what has been found with other studies after the completion of a specialized rehabilitation program (45, 49). On the other hand, in control group no statistically significant improvements were found in any of the attentional subprocesses evaluated. These results may be consequence of the specific characteristics of Trisquel program (dynamic and motivating context, 266 cognitive-executive stimulation tasks, continuous reinforcement and feedback by the moderator, group dynamics, social exposure, etc.) or may be the result of the systematic repetition of a series of cognitive stimulation (restoration) exercises over a prolonged period of time. Overall, the results of this work are congruent with other studies that support the use of serious games in the clinical approach of patients with different mental disorders. Also, more specifically, this study provides evidence on the usefulness of an intervention program in board game format to induce improvements in cognitive-executive functioning in patients with SRD (13, 14, 19), in which it is consistently demonstrated that by challenging participants to think, explore and respond, they are motivated to learn new skills, knowledge, attitudes and behaviors, validating serious games as effective treatments of different psychiatric pathologies (21, 23, 24). Regarding executive functioning in the present study, and following one of the most referenced models of executive functioning in the literature (44), it was found that in the executive functioning of Trisquel group, statistically significant differences were found in the executive components of updating (working memory and phonemic fluency) and inhibition (cognitive).

In relation to the improvement of executive component of updating, the results of the present work are consistent with previous studies in which improvements in working memory are reported after the completion of a specialized rehabilitation program (2, 7, 11, 50, 51). Different studies show that the specific work of working memory is a facilitator of cognitive functions such as learning, verbal comprehension, thinking, reasoning or decision-making and a generator of an efficient buffering effect against attentional bias toward salient stimuli related to substance use (52, 53). Similar results to those obtained in the present study have been found in other populations with psychiatric pathologies (54, 55). Specifically, in a recent study assessing the efficacy of Trisquel in patients with a diagnosis of schizophrenia spectrum and other psychotic disorders, improvements in working memory were found after Trisquel program (23). Instead, other studies did not found benefits in specific working memory work, finding no effect on craving, substance use or attention bias (56). On the other hand, control group also obtained a statistically significant improvement in the executive updating component (working memory), indicative that biopsychosocial treatments with a holistic and integrative approach also generate changes in executive functioning, similar to those obtained with cognitive training programs. In this sense, this work may be one of the first studies that evaluates the efficacy of an intervention program in board game format compared to the holistic and integrative treatment model offered to patients with SRD in the care facilities (day unit, therapeutic community) of the Galician and Portuguese network of assistance to drug addicts.

In respect to the results obtained in the executive component of inhibition, Trisquel group obtained statistically significant improvements in the cognitive inhibition task (word-color) of the STROOP test, an executive component that allows us to stop an automated response and enables the inhibition of alternative learned behaviors as in this case represents the reading of words. These results are in line with other studies conducted with SRD patients, after the completion of a rehabilitation program such as Goal Management Training, one of the best validated interventions for executive dysfunction (47). Intervention program that has demonstrated its efficacy alone or in combination with other types of interventions such as mindfulness (11, 50). On the other hand, the control group obtained a worse performance in the cognitive inhibition task of the STROOP test.

Regarding the limitations of the present study, it can be said that the main one was not having studied the reasons for abandoning treatment, nor having correlated the different reasons for abandonment with the level of cognitive-executive deterioration of the patients studied. Another limitation was the absence of follow-up assessments. For this reason, no conclusions can be drawn as to whether the observed cognitive improvement contributed to maintaining abstinence in the following months, a fact found in other studies (57). In other studies it was found that the improvements observed at the end of cognitive training tend to be lost 6 months after the end of the intervention (45), an aspect that has not been assessed in this study either. Future efficacy studies should take these limitations into account.

CONCLUSION

The creation of Trisquel in 2008 was motivated by the clinical need to dynamize the therapeutic interventions offered to patients. In this study, the aims were to dynamize the

psychoeducational group (relapse prevention, social skills, HIV-AIDS) and to include neurorehabilitative interventions. For this reason, a game format was chosen, which allows to generate a therapeutic context that facilitates learning (therapeutic milieu) and allows to work *in vivo* on aspects of group interaction (social skills, emotional expression and recognition).

The present study has important implications for research and clinical practice. It provides explicit information for the planning of future studies (sample selection, assessment protocol, procedure, process-based analysis of results), and evidence of its feasibility. It represents an example of how an intervention program in board game format can generate a motivating therapeutic context that induces improvements in cognitive-executive performance, health perception, perceived symptomatology. It can be considered a versatile and dynamic tool that each professional can adapt to their daily intervention needs. This work shows how an intervention program in board game format integrated in a bio-psycho-social treatment with a holistic and integrative approach, can improve the cognitive-executive performance of patients with cognitive impairment under treatment in care facilities for people with substance-related disorders.

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 the Ethics Committee of Vigo, Pontevedra, and Ourense Registration Code: 2018/153. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AP-B: conceptualization, methodology, writing—reviewing and editing, and supervision. EV-M: methodology and writing—original draft preparation. OG-M: methodology and investigation. PF-P, SR, ML-L, TV, MA, RG-T, AG-L, and VV-D: investigation. D-RA: writing—original draft preparation. ML-M, IV-F, GS-F, JC-M, AF, and SC: project administration. IC-M, FO-L, and JO: project administration, writing—original draft preparation, and supervision. TR-B: data curation and writing—original draft preparation. CS: data curation, supervision, writing–reviewing and editing, and funding acquisition. All authors contributed to the article and approved the submitted version.

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In- and Out-Group Effects on Social Perception and Empathy in Cocaine Use Disorder

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Earlier research revealed that cocaine users display impairments in emotional but not necessarily in cognitive empathy. However, no study to date has tested whether empathy is generally altered or whether impairments are restricted to specific social targets. The current investigation addresses this open question. In addition, we examined whether attributions of warmth and competence as well as personal future expectancies differed between cocaine users and substance-naïve controls. Twenty-two chronic cocaine users and 40 stimulant-naïve controls specified their perceived warmth and competence for four social targets [in-group member, opposite consumption out-group member (cocaine user for controls and non-user for cocaine user), opposite consumption out-group member of opposite gender, and elderly person]. They also specified their cognitive and emotional empathy for these four targets facing eight desirable and eight undesirable events. Finally, they rated the likelihood of these scenarios happening to themselves. Both cocaine users and controls attributed lower warmth to cocaine-using than non-using targets. Comparably, no in-group preference was observed in cocaine user's emotional empathy ratings, and greater denigration of the in-group was associated with higher frequency and doses of cocaine consumption. In addition, cocaine users rated both desirable and undesirable events as more likely to happen to themselves than did controls. Results show that substance-naïve individuals stigmatize cocaine users. They further point to compromised self-esteem in cocaine users resulting from such stigmatization. Interventions should address stigmatization processes to break the vicious circle of mutual social distancing and stronger dedication to the drug.

Keywords: stimulants, cocaine, social cognition, empathy, social perception, optimism bias

"Happiness lies within one's self, and the way to dig it out is cocaine."

— Aleister Crowley, Diary of a Drug Fiend

INTRODUCTION

Recent findings suggest that cocaine users orient toward the drug in order to augment experiences of reward – experiences that they do not (or no longer) obtain from social interactions with others (1, 2). The inability to attain social rewards may be intimately linked with deficient social capacities [e.g., impaired empathic responding; (3, 4)] and diminished sensitivity to social rewards (2, 5, 6). Accordingly, it has been suggested that devotion to cocaine and withdrawal from friends and family mutually influence each other, resulting in a vicious circle (7). Notably, both recreational and dependent cocaine consumers have smaller social networks (8) and display various particularities in social cognition and interactions, including diminished cooperativeness and compliance with social norms (9), lower emotional empathy and disturbed perspective taking (8), a stronger focus on efficiency than fairness in money distribution games (10), and impaired joint attention (5). Consequently, to better understand the involvement of cocaine in social functionality and addiction, investigating social deficits in chronic cocaine use is warranted.

The present investigation focuses on associations between perceptions of warmth and competence in others, and empathic responding, on the one hand, and cocaine use, on the other. Social deficits and conflicts may arise due to altered perceptions of others. For instance, the Stereotype Content Model (11, 12) states that social targets are classified along two orthogonal dimensions: warmth and competence, leading to different affective experiences, attitudes, and behaviors in an observer (11–16). Correspondingly, the current study examined whether cocaine users display particularities in attributions of warmth and competence to different social targets.

Altered processing related person perceptions might also explain the above-reported particularities in empathic responding that accompany cocaine use [cf. Aue et al. (17)]. Contemporary accounts of empathy distinguish between two major concepts, namely cognitive and emotional empathy (18–20). Cognitive empathy requires mentalizing and relates to an individual's capacity to infer other people's mental states, thereby ensuring understanding of other people's feelings. By contrast, emotional empathy describes the appropriation of the affective feeling state of a social target by the perceiver and, hence, involves affective sharing.

Some earlier studies associated cocaine use with impaired cognitive empathy, specifically with reduced emotional intelligence (21) and emotion recognition from faces (22). Another recent comprehensive investigation in a large-scale sample revealed cognitive empathy in cocaine users to be little affected (8, 23), with impairments being limited to auditory stimuli (i.e., recognition of emotions in the voice) or multisensory integration [i.e., regarding (mis)matching information in faces and voices]. There was further evidence that deficient cognitive empathy was restricted to severe cocaine consumption (i.e., addiction) combined with attention-deficit/hyperactivity disorder (ADHD) symptomatology (8, 24), with only long-term users overinterpreting social signs and attributing exaggerated emotions to others. By contrast, in the same large-scale investigation (8, 23), recreational and dependent cocaine users demonstrated marked impairments in both implicit and explicit assessments of emotional empathy, and the degree of impairment was positively correlated with lifetime extent (related to both dose and duration) of cocaine consumption and negatively correlated with social network size. Interestingly, longitudinal data suggest that emotional empathy and prosocial behavior may recover when cocaine use is strongly reduced or quitted (4). In sum, research on empathy related to cocaine use reveals weak links with cognitive empathy deficits, but strong associations with emotional empathy deficits. While suggestive, these observations ask for further refinement. For instance, it is still unclear, whether cocaine users' empathic responses discriminate between different social targets.

Previous studies in the general population have consistently revealed that individuals display greater (mostly emotional) empathy for in-group (i.e., people they identify with) compared with out-group members (25–28). Moreover, people's empathic responding clearly differentiates between different kinds of social out-groups (17). Because chronic cocaine use has been linked to social isolation and diminished sensitivity to social rewards, it is possible that users perceive the in-group and out-groups differently than do non-users, which then feeds back to their empathic responses. Accordingly, in the current study, we examined differences between cocaine users and non-using controls regarding (a) perceptions of warmth, (b) perceptions of competence, (c) cognitive empathy, and (d) emotional empathy displayed for/toward an in-group member and three different kinds of out-group members (specified below).

Furthermore, apart from showing altered processing of social stimuli, cocaine users reveal particularities in processes that relate to the self. Among others, acute effects of cocaine have been reported to subsume euphoria, augmented ego distinctiveness, exaggerated self-confidence, as well as an excessive sense of mastery over fate (29) – with regulation problems related to ego functions and reality testing arising as negative aftereffects once the acute effects of the drug have faded out (also known as "crash"). Moreover, chronic use of cocaine has been reported to go along with feelings of depression or emotional blunting (30–32). Together, therefore, these observations point to deviated future outlooks in cocaine users. Accordingly, we broach the idea that cocaine use relates to future expectancies. The majority of people in our population expects their personal future to more likely provide positive rather than negative outcomes (33, 34). What is more, they also believe that desirable (undesirable) events are more (less) likely to happen to themselves than to a comparison person of same age and gender (35). Cocaine use may particularly predispose to such thinking, with the negative postacute effects of the drug possibly shifting the bias into the opposite direction (i.e., into a pessimism bias with an overestimation of undesirable over desirable future outcomes).

Importantly, there are other facts that made us hypothesize that cocaine use and optimistically biased expectancies cohere. Reward impulsivity and wanting (36) have been put forth as key factors in research on cocaine use (10, 37), and these same factors are considered essential in theories on optimism bias [see Kress and Aue (34)]. Furthermore, structural and metabolic aspects of some important brain regions (e.g., inferior frontal gyrus, medial prefrontal cortex, anterior cingulate cortex, and striatum) involved in optimism and optimism bias (33, 34) have been shown to be affected by cocaine use (37–41). Consequently, we tested whether cocaine users are characterized by peculiarities in optimistic outlooks.

In the current investigation, chronic cocaine users as well as stimulant-naïve healthy control participants imagined different desirable and undesirable scenarios and specified their cognitive and emotional empathy toward four different social targets experiencing those scenarios: one in-group member (cocaine user of same gender for cocaine using participants; non-cocaine user of same gender for control participants) and three different out-group members (for cocaine users: an elderly person of same gender, a same-aged non-cocaine using target of same gender, and a same-aged non-cocaine using target of the opposite gender; for control participants: an elderly person of same gender, a same-aged cocaine-dependent target of same gender, and a same-aged cocaine-dependent target of the opposite gender). They further designated their level of identification with each social target (manipulation check to verify that greatest identification arose with respect to the presumed in-group) and how warm and competent they perceived these targets. Our participants also specified their personal likelihood of experiencing any of the scenarios involved in the social task (assessment of self-related expectancies, targeting optimism bias). Based on the literature reviewed, we tested the following hypotheses (summarized in **Table 1**):

Perception of the Social Targets

Earlier research [e.g., Aue et al. (17), Dricu et al. (42, 43), Moser et al. (44)] has shown that substance-naïve participants stigmatize substance users in that they attribute low warmth and low competence to them. By contrast, the same individuals perceive in-group members as both warm and competent and elderly persons as warm but little competent. Accordingly, we predicted controls to rate the in-group and the elderly out-group as warmer than both cocaine-dependent social targets (H1a). In addition, cocaine targets were expected to be rated as less competent than the remaining social targets by the control participants, with the elderly population lying in between the cocaine targets and the in-group target (H1b). Because of the reported link between cocaine use and social isolation, we further predicted that cocaine users would see others in less bright colors, thereby attributing lower warmth to the different social targets than controls (the difference being particularly pronounced for the in-group target; H1c). The same hypothesis was tested for the competence ratings (H1d). Finally, due to greater social distancing from others, cocaine users were hypothesized to demonstrate comparably small differences in their warmth and competence ratings for the different social targets (H1e and H1f).

Cognitive Empathy

Consistent with earlier observations (17), we predicted controls to display greater cognitive empathy for the elderly and in-group targets than the cocaine-using targets – but solely for positive scenarios (no difference for negative scenarios because of society's conviction that everybody has the right to feel bad; H2a). Based on the finding that cognitive empathy is virtually unaffected by cocaine use (8, 23), we expected controls and cocaine users to display comparable overall levels of cognitive empathy (H2b). Yet, we predicted our cocaine-using participants to display less differentiation between the different social targets (H2c).

Emotional Empathy

In line with previous findings (17), we expected control participants to state the highest emotional empathy for the elderly target, the lowest for the cocaine-using targets, and the in-group placed in between (H3a). Based on the demonstrated impairments in emotional empathy in cocaine use (8, 23), we further predicted cocaine users to display overall lower levels of emotional empathy than control participants (H3b). Finally, cocaine users were hypothesized to reveal reduced differentiation between the social targets (H3c).

Self-Related Future Expectancies

Control participants were predicted to display an optimism bias (33), with higher likelihood ratings for positive compared with negative events anticipated for their personal future (H4a). This bias was hypothesized to be altered in cocaine users (H4b; no directed hypothesis).

MATERIALS AND METHODS

Participants

The present sample is a subsample of a previously published study (32). Whereas all $n = 40$ stimulant-naïve healthy control participants had completed the tasks of interest for the current investigation, time limitations resulted in only $n = 22$ (out of 59) cocaine users doing so. Cocaine users were included in the study if cocaine was the primary illegal drug they used, if a lifetime cumulative consumption of at least 100 g of cocaine was estimated by self-report, and if their current abstinence duration was <6 months. General exclusion criteria comprised a family history of genetically mediated psychiatric disorders ($h^2 > 0.5$, e.g., autism, schizophrenia, and bipolar disorder), any severe neurological disorder or brain injury, intake of medication with potential action at the central nervous system during the last 7 days, and participation in a large previous study from our lab, the Zurich Cocaine Cognition Study (8).

Controls were excluded if they had Axis I adult psychiatric disorders according to the Diagnostic and Statistical Manual of Mental Disorders-IV – Text Revision [DSM-IV-R; (45)] or recurrent illegal substance use (>15 occasions lifetime, with the exception of cannabis for reasons of participant matching). We excluded cocaine users with regular use of illegal substances

TABLE 1 | List of hypotheses.

Index	Dependent variable	Hypothesis	Specification of results/additional comments
H1a	**Perceived warmth** Controls	Cocaine-using targets are rated as less warm than in-group and elderly out-group[a]	Higher warmth attributions in females compared with males
H1b	**Perceived competence** Controls	Highest competence attributed to in-group, then elderly, then cocaine-using targets[b]	
H1c	**Perceived warmth** Comparison cocaine users vs. controls	Lower ratings of warmth in cocaine users than controls (esp. for in-group)[b]	Cocaine-consuming social targets are perceived as colder than non-cocaine-consuming targets by both cocaine users and controls: lower warmth ratings for in-group in cocaine users than controls; cocaine users rate non-consuming targets as warmer than controls rate cocaine-consuming targets
H1d	**Perceived competence** Comparison cocaine users vs. controls	Lower ratings of competence in cocaine users than controls (esp. for in-group)[b]	
H1e	**Perceived warmth** Cocaine users	Little or no differentiation between the different social targets[b]	Higher warmth attributions in females compared with males
H1f	**Perceived competence** Cocaine users	Little or no differentiation between the different social targets[a]	
H2a	**Cognitive empathy** Controls	Positive scenarios: greater cognitive empathy for elderly and in-group targets than for cocaine-using targets[a/b]; Negative scenarios: no difference between the social targets[a]	Positive scenarios: greater cognitive empathy expressed for elderly than cocaine-using targets; no difference of either with respect to in-group character
H2b	**Cognitive empathy** Comparison cocaine users vs. controls	Comparable overall levels of cognitive empathy in cocaine users and controls[a]	
H2c	**Cognitive empathy** Cocaine users	Little or no differentiation between the different social targets[b]	No reduced differentiation compared with controls, but no differentiation between positive and negative scenarios; attribution of stronger feelings to the three out-group characters compared with the in-group character; greater cognitive empathy in female than male cocaine users
H3a	**Emotional empathy** Controls	Highest emotional empathy expressed for elderly, then in-group, then cocaine-using targets[a]	Difference between elderly and in-group is not statistically significant
H3b	**Emotional empathy** Comparison cocaine users vs. controls	Lower ratings of emotional empathy in cocaine users than controls[b]	
H3c	**Emotional empathy** Cocaine users	Little or no differentiation between the different social targets[a]	
H4a	**Self-related future expectancies** Controls	Higher likelihood ratings for positive compared with negative scenarios (optimism bias)[a]	
H4b	**Self-related future expectancies** Comparison cocaine users vs. controls	Altered optimism bias in cocaine users (no directed hypothesis)[b]	Cocaine users attribute greater likelihood to both positive and negative scenarios than do controls

[a] *Study data are supportive of hypothesis.*
[b] *Study data are not supportive of hypothesis.*

other than cocaine, such as heroin or other opioids (with the exception of cannabis), a polysubstance use pattern, and an Axis I adult psychiatric disorder diagnosis (e.g., schizophrenia, bipolar disorder, current major depressive episode, eating disorders, and current anxiety disorder) according to DSM-IV, with exception for cocaine, cannabis, and alcohol abuse/dependence, previous depressive episodes, and ADHD.

Experimental protocols, methods of data collection, data handling, and data analysis were approved by the Ethics Committee of the Canton Zurich (BASEC ID 2016-00278) and are fully in accord with the Declaration of Helsinki (46).

Experimental Tasks

Included tasks were programmed with E-Prime 2.0 Professional (version 2.0.10.356; Psychology Software Tools, Pittsburgh, PA, United States). All but one task (self-related expectancies) comprised four social targets, displayed as still animations of an in-group member and three out-group members (**Figure 1**). Specifically, for cocaine participants/non-cocaine participants, the included characters were as follows (a) a cocaine user/non-cocaine user of same gender as the participant (in-group; IG), (b) a non-cocaine user/cocaine user of same gender (out-group use; OG_u), (c) a non-cocaine user/cocaine user of different gender (i.e., double out-group termed out-group use + gender; OG_{ug}), and (d) an elderly person of same gender (out-group age; OG_a). Social targets (and backgrounds of the different scenarios, relevant for the empathy ratings only) were created with *The Sims 4* (Electronic Arts, CA, United States). All stimuli were controlled in brightness and contrast using MATLAB R2017a (The Math Works, Inc., MA, United States).

FIGURE 1 | Social targets included in the current study. From top to bottom: non-cocaine user, cocaine user, elderly person. Left, male; right, female.

Level of Identification With the Different Social Targets (Manipulation Check)

Our participants rated their similarity with each of the four social targets on the Inclusion of Other in the Self [IOS; (47)] scale (**Supplementary Figure 1**). The IOS scale consists of seven pairs of circles that vary in their degree of overlap, describing the perceived similarity of a social target with the self. Possible scores ranged from 1 (very dissimilar, almost no overlap) to 7 (very similar, almost complete overlap).

Perceived Warmth and Perceived Competence of the Different Social Targets

Participants stated the perceived warmth for each of the four social targets on a continuous visual analog scale with the endpoints "not at all warm" (yielding a stored value of 0) and "very warm" (resulting in a stored value of 100; **Supplementary Figure 2**). In addition, they rated each social target's perceived level of competence on a scale with the endpoints "not at all competent" (yielding a stored value of 0) and "very competent" (resulting in a stored value of 100).

Cognitive and Emotional Empathy for the Different Social Targets

Cognitive empathy relates to metacognitive abilities and was assessed *via* the question: "In your opinion, how good/bad does the depicted character feel in this specific situation?" Emotional empathy refers to affective sharing and was assessed *via* the question: "How good/bad do you feel when you see the depicted character in this specific situation?" Cognitive and emotional empathy ratings for the four social targets were given on continuous visual analog scales that ranged from −50 (feeling "very bad") to 50 (feeling "very good"; **Supplementary Figure 3**). For each social target, participants rated eight positive and eight negative scenarios [matched with respect to event frequency and controllability as assessed in an earlier study (42); refer to **Supplementary Material** for the exhaustive list of events]. Thus, participants specified each their cognitive and their emotional empathy for 64 scenario × target combinations.

Self-Related Future Expectancies (Optimism Bias)

Our participants rated their personal likelihood (scale range: 0–100%; corresponding to "not at all" to "absolutely certain") of encountering each of eight negative and eight positive future scenarios (identical to the scenarios included in the empathy task) on a continuous visual analog scale.

Clinical and Substance-Related Assessment

The psychopathological assessment was carried out with the Structured Clinical Interview I [SCID-I; (48)] according to DSM-IV-R (45) to determine the presence of DSM-IV Axis I psychiatric disorders. The Structured Clinical Interview for DSM-IV Axis II

Disorders questionnaire [SCID-II; (49)] was used to assess cluster B personality disorder symptoms. The German vocabulary test Mehrfachwahl-Wortschatz-Intelligenztest [MWT-B; (50)] was applied to estimate premorbid verbal intelligence. ADHD symptoms were collected with the ADHD self-rating scale [ADHD-SR; (51)]. Depressive symptomatology was measured with the German version of the Beck Depression Inventory (52). For the determination of the social network size, an adapted version of the Social Network Questionnaire [SNQ; (8, 53)] was administered. Self-reported drug use was assessed with the structured and standardized Interview for Psychotropic Drug Consumption (54).

Urine and Hair Toxicological Analysis

For the drug urine screening a semi-quantitative enzyme multiplied immunoassay method was used (Dimension RXL Max, Siemens, Erlangen, Germany). In addition, quantitative analysis of hair samples using liquid chromatography tandem mass spectrometry (LC-MS/MS) was applied to investigate substance use over the last 4 months as represented in the proximal 4 cm-segment of the hair samples. In total 88 compounds were assessed [for details see Scholz et al. (55)].

Procedure

Upon their arrival at the laboratory, participants signed an informed consent form. Subsequently, they underwent a sequence of tasks, interviews, sampling of urine and hair, and psychometric instruments [see Kluwe-Schiavon et al. (32)], of which only the relevant ones are outlined here. Specifically, participants rated in a fixed sequence (1) their personal likelihood of encountering different positive and negative future events; (2) their cognitive and emotional empathy for four different social targets experiencing the same set of events; (3) how warm and competent they perceived the four different targets to be; and (4) how similar they felt to the social targets. After the completion of the tasks, participants were debriefed.

Data Preparation and Analysis

Level of Identification With (Manipulation Check), Perceived Warmth of and Perceived Competence of the Different Social Targets

For each dependent variable, we conducted a repeated-measures analysis of variance (ANOVA) with the between-participants factors *Group* (cocaine and control) and *Gender* (male and female) and the within-participants factor *Target Character* (IG, OG_u, OG_{ug}, and OG_a).

Cognitive and Emotional Empathy for the Different Social Targets

Because our data should reflect the appropriateness of attributed (cognitive empathy) or experienced (emotional empathy) affective states, we reversed the scores given for the undesirable scenarios, so that higher scores represent greater (assigned) suffering. For the desirable scenarios, such recoding was not indicated (higher scores already reflect more positive affect). For each participant, an average cognitive empathy score and an average emotional empathy score were calculated for each combination of *Scenario Valence* (negative and positive) and *Target Character* (IG, OG_u, OG_{ug}, and OG_a). Two repeated-measures ANOVAs with the between-participants factors *Group* (cocaine and control) and *Gender* (male and female) and the within-participants factors *Scenario Valence* (negative and positive) and *Target Character* (IG, OG_u, OG_{ug}, and OG_a) were calculated – one for the participants' cognitive, and another for the participants' emotional empathy ratings.

Self-Related Future Expectancies

Rating scores were averaged for each level of scenario valence in every participant. A repeated-measures ANOVA with the between-participants factors *Group* (cocaine and control) and *Gender* (male and female) and the within-participants factor *Scenario Valence* (negative and positive) was calculated on the averaged likelihood ratings.

All Dependent Variables

Because we only had six female cocaine-consuming participants, we did not include any term relating to the interaction between the factors *Group* and *Gender* in our ANOVAs.

RESULTS

Pearson product moment correlation coefficients for the association between the different social constructs are displayed in **Supplementary Material**. To enable better comprehension of the results presented, only significant and meaningful non-significant effects are described. A complete overview of effects can be found in **Supplementary Material**.

Characterization of the Study Sample

The final sample included in our analyses consisted of 62 participants, 22 chronic cocaine users (16 male) and 40 controls (24 male). Age ranged between 21 and 51 years (M = 30.4 years, SD = 6.57 years). **Table 2** summarizes the participants' age, verbal intelligence, and characteristics assessed *via* clinical scales. It also displays substance use features. Cocaine users were characterized by lower verbal intelligence, higher depression and antisociality scores, as well as higher scores on the ADHD-SR than were controls. Compared with controls, cocaine users also reported greater weekly alcohol use. Finally, self-reported substance use and hair toxicological results of cocaine users showed a clear preference for cocaine over other substances.

Level of Identification With the Different Social Targets (Manipulation Check)

A repeated-measures ANOVA with the between-participants factors *Group* (cocaine and control) and *Gender* (male and female), and the within-participants factor *Target Character* (IG, OG_u, OG_{ug}, and OG_a) was calculated on the similarity ratings. The main effect of *Target Character* achieved significance, $F(3,177) = 17.74$, $p < 0.001$, $\eta_p^2 = 0.23$ (cf. **Figure 2**). As

TABLE 2 | Overview of participants' age, verbal intelligence, scores on clinical scales, and consumption features.

Comparison of	**Cocaine users**	**Controls**			
Measure	***M* (SD)**	***M* (SD)**	**Test statistic**	**df**	***p***
Age, years	32.3 (6.0)	29.3 (6.7)	$t = 1.75$[a]	60	0.086
Gender (m/f)[f]	16/6 (73/27)	24/16 (60/40)	$\chi^2 = 1.00$[b]	1	0.316
Verbal IQ	95.9 (7.0)	102.2 (8.6)	$t = -2.93$[a]	60	0.005
ADHD-SR, score	16.4 (11.0)	9.7 (9.7)	$t = 2.46$[a]	60	0.017
BDI, score	7.5 (6.7)	3.5 (5.2)	$t = 2.57$[a]	57[e]	0.013
SCID-II histrionic, score	1.9 (1.4)	1.6 (1.4)	$t = 0.65$[a]	60	0.517
SCID-II narcissistic, score	3.9 (2.8)	2.8 (2.5)	$t = 1.62$[a]	60	0.111
SCID-II borderline, score	4.6 (3.2)	2.8 (2.9)	$t = 2.30$[a]	60	0.025
SCID-II antisocial, score	5.9 (23.1)	2.7 (2.4)	$t = 4.28$[a]	60	<0.001
SNQ (network size), score	12.7 (8.8)	18.8 (14.9)	$t = 1.74$[a]	60	0.087
Substance use features					
Nicotine					
Smoker[f,h]	20 (91)	34 (85)	$\chi^2 = 0.54$[b]	1	0.462
Cigarettes per week[g,i,j]	78.8 (10.00–245.00)	70.0 (7.0–175.0)	$U = 278.00$[c]		0.264
Alcohol					
Pure alcohol, grams per week[g,j]	145.5 (35.5–1,415.1)	75.1 (0.2–375.7)	$U = 268.50$[c]		0.012
Cannabis					
Years of use	10.8 (8.8)	6.3 (6.2)	$t = 2.12$[d]	32.7	0.042
Times per week[g,j]	0.0 (0.0–3.0)	0.0 (0.0–2.0)	$U = 359.50$[c]		0.191
Grams per week[g,j]	0.0 (0.0–0.5)	0.0 (0.0–1.2)	$U = 349.50$[c]		0.152
Cumulative lifetime grams[g]	692 (0.0–25,719)	3.6 (0.0–2,630)	$U = 232.50$[c]		0.002
Urine toxicology (pos)[f]	4 (18)	2 (5)	$\chi^2 = 2.82$[b]	1	0.093
Cocaine					
Times per week[j]	2.3 (2.4)				
Grams per week[j]	4.0 (7.4)				
Abstinence (days)	19.0 (32.7)				
Cumulative lifetime grams	1,552.0 (1,485.0)				
$Cocaine_{total}$, pg/mg in hair[k]	31,240 (51,230)				
Cocaine, pg/mg in hair	21,469 (38,557)				
Benzoylecgonine, pg/mg in hair	9,239 (14,302)				
Norcocaine, pg/mg in hair	533 (800)				
Cocaethylene, pg/mg in hair	697 (1,130)				
Urine toxicology (pos)[f]	6 (27)	0 (0)	$\chi^2 = 12.10$[b]	1	<0.001
DSM-IV cocaine dependency (lifetime)[f]	19 (86)	0 (0)	n/a	n/a	n/a
DSM-IV cocaine abuse (lifetime)[f]	21 (96)	0 (0)	n/a	n/a	n/a

[a] *Independent t-test.*
[b] χ^2 *test for frequency data.*
[c] *Mann–Whitney U test.*
[d] *Welch's t-test.*
[e] *Due to missing scores from 3 control participants.*
[f] *n (%) is reported.*
[g] *Median (range) is reported.*
[h] *Individuals were considered smokers if they smoked ≥7 cigarettes/week.*
[i] *Only for smokers.*
[j] *Average use during the last 6 months.*
[k] $Cocaine_{total}$ *(= cocaine + benzoylecgonine + norcocaine) as a more robust parameter (74).*
Verbal IQ, verbal intelligence quotient estimated with the German vocabulary test (MWT-B); ADHD-SR, ADHD self rating scale; BDI, Beck Depression Inventory; SCID-II, Structured Clinical Interview for DSM-IV Axis II Disorders questionnaire; SNQ, Social Network Questionnaire.

intended, our participants identified more strongly with their pre-determined in-group (M = 4.1, LCI = 3.7, UCI = 4.5) compared with the three out-groups (OG_u: M = 2.7, LCI = 2.3, UCI = 3.1; OG_{ug}: M = 2.1, LCI = 1.7, UCI = 2.5; OG_a: M = 2.5, LCI = 2.1, UCI = 3.0; pairwise Tukey HSD comparisons with the IG: all p-values < 0.001; remaining p-values > 0.169). In addition, there was a significant main effect of *Gender*, $F(1,59) = 6.47$, $p = 0.014$, $\eta_p^2 = 0.10$, with males more strongly identifying with the targets than females (Ms = 3.0 and 2.4, respectively).

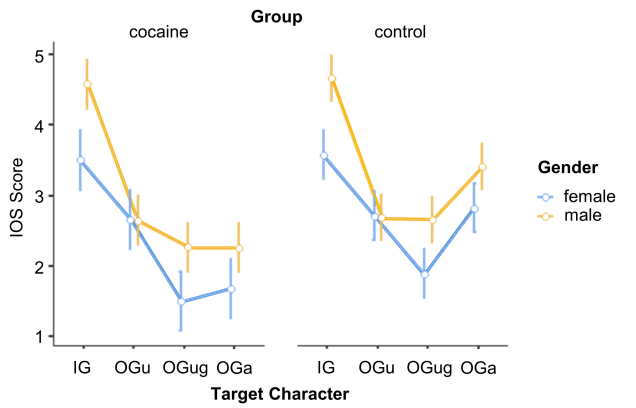

FIGURE 2 | Identification with the social targets. IOS, Inclusion of Other in the Self Scale; IG, in-group; OG_u, out-group use; OG_{ug}, out-group use + gender; OG_a, out-group age. Error bars, standard errors.

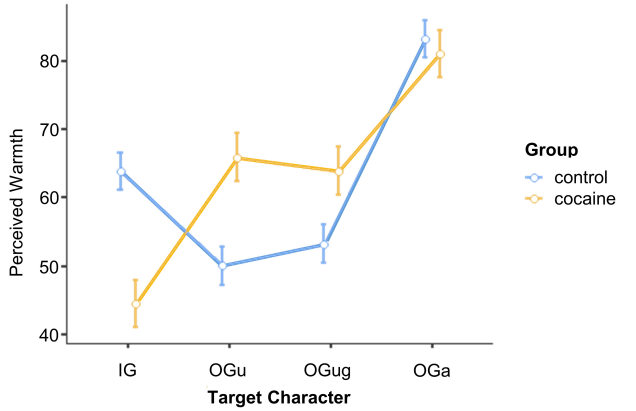

FIGURE 3 | Perceived warmth of the different social targets. IG, in-group; OG_u, out-group use; OG_{ug}, out-group use + gender; OG_a, out-group age. Error bars, standard errors.

Perceived Warmth of the Different Social Targets

A repeated-measures ANOVA with the between-participants factors *Group* (cocaine and control) and *Gender* (male and female) and the within-participants factor *Target Character* (IG, OG_u, OG_{ug}, and OG_a) was run on our participants' warmth ratings. Not supportive of our H1c, the main effect of *Group* was not significant, $F(1,59) = 0.29$, $p = 0.590$, $\eta_p^2 = 0.01$, suggesting that the two groups did not differ in the overall amount of warmth attributed to the social targets.

By contrast, the ANOVA revealed a significant main effect of *Target Character*, $F(3,177) = 31.76$, $p < 0.001$, $\eta_p^2 = 0.35$, that was qualified by the significant interaction *Group* × *Target Character*, $F(3,177) = 13.17$, $p < 0.001$, $\eta_p^2 = 0.18$ (**Figure 3**). Both groups attributed the greatest warmth to the elderly out-group (OG_a) characters [p-values < 0.004, for all (except two) pairwise comparisons (Tukey HSD) including the elderly character; $p = 0.063$ for comparison of OG_a vs. OG_u ratings in cocaine users; $p = 0.997$ for comparison of OG_a ratings for controls vs. cocaine users]. However, while the cocaine group rated the OG_u and OG_{ug} as warmer than their in-group (p-values ≤ 0.004), the control group showed, consistent with H1a, the opposite pattern ($p = 0.005$ for the comparison of IG and OG_u; $p = 0.079$ for the comparison of IG and OG_{ug}). Moreover, cocaine users evaluated the IG target as significantly colder than did the control group ($p < 0.001$), and their warmth ratings for both OG_u, and OG_{ug} were higher than were the ratings for OG_u in the control group (p-values < 0.045). Neither group differentiated between OG_u and OG_{ug} (p-values > 0.987). In sum, therefore, leaving the elderly out-group aside, cocaine-consuming social targets were perceived as colder than non-cocaine consuming targets by both groups of participants. Moreover, inconsistent with our H1e, the data do not support the idea of cocaine users being characterized by limited variance in warmth attributions to different social targets. Finally, there was a significant main effect of *Gender*, $F(1,59) = 10.74$, $p = 0.002$, $\eta_p^2 = 0.15$, because females ($M = 67.0$, LCI = 63.8, UCI = 70.2) rated the social targets as warmer than did males ($M = 59.5$, LCI = 56.3, UCI = 62.6).

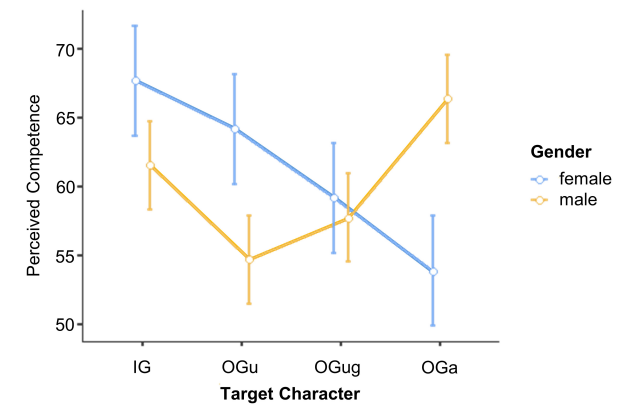

FIGURE 4 | Perceived competence of the different social targets. IG, in-group; OG_u, out-group use; OG_{ug}, out-group use + gender; OG_a, out-group age. Error bars, standard errors.

Perceived Competence of the Different Social Targets

The repeated-measures ANOVA with the between-participants factors *Group* (cocaine and control) and *Gender* (male and female) and the within-participants factor *Target Character* (IG, OG_u, OG_{ug}, and OG_a) yielded a significant interaction *Gender* × *Target Character*, $F(3,177) = 4.01$, $p = 0.007$, $\eta_p^2 = 0.06$ (cf. **Figure 4**). All *post hoc* pairwise comparisons (Tukey HSD) for this interaction failed to reach significance, and there was only a trend in male participants to attribute higher competence to the OG_a target than to the OG_u target ($p = 0.090$, p-values for the remaining pairwise comparisons >0.200). In sum, thus, the participants' competence ratings are not in line with our hypotheses H1b, H1d, and H1e.

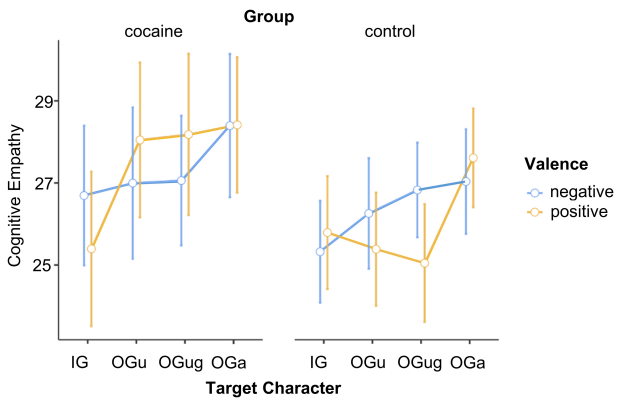

FIGURE 5 | Cognitive empathy expressed for the different social targets. IG, in-group; OG_u, out-group use; OG_{ug}, out-group use + gender; OG_a, out-group age. Error bars, standard errors.

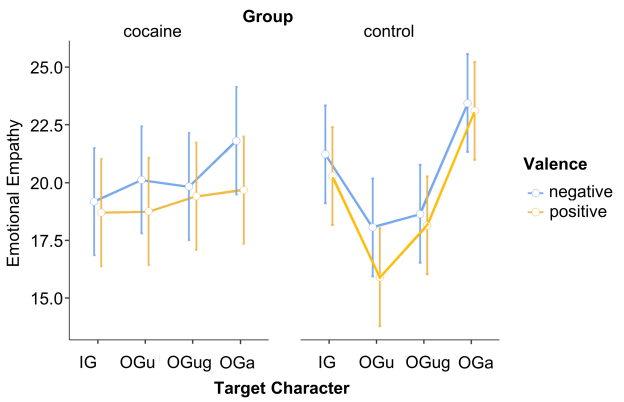

FIGURE 6 | Emotional empathy expressed for the different social targets. IG, in-group; OG_u, out-group use; OG_{ug}, out-group use + gender; OG_a, out-group age. Error bars, standard errors.

Cognitive Empathy for the Different Social Targets

A repeated-measures ANOVA with the between-participant factors *Group* (cocaine and control) and *Gender* (male and female) and the within-participants factors *Scenario Valence* (negative and positive) and *Target Character* (IG, OG_u, OG_{ug}, and OG_a) was calculated on the participants' cognitive empathy ratings. In line with our H2b, cocaine users and control participants did not differ in overall level of cognitive empathy, indexed by the non-significant main effect of *Group*, $F(1,58) = 0.43$, $p = 0.517$, $\eta_p^2 = 0.01$. The ANOVA showed a main effect of *Target Character*, $F(3,174) = 6.11$, $p < 0.001$, $\eta_p^2 = 0.10$, that was qualified by the interaction *Group* × *Scenario Valence* × *Target Character*, $F(3,174) = 2.78$, $p = 0.043$, $\eta_p^2 = 0.05$ (**Figure 5**).

To resolve this three-way interaction, we calculated separate ANOVAs (with the factors *Scenario Valence* and *Target Character*) for each level of *Group*. The ANOVA for control participants revealed a significant main effect of *Target Character*, $F(3,111) = 3.23$, $p = 0.025$, $\eta_p^2 = 0.08$, that was qualified by the interaction *Scenario Valence* × *Target Character*, $F(3,111) = 3.59$, $p = 0.016$, $\eta_p^2 = 0.09$. *Post hoc* Tukey tests revealed no significant differences between the target characters in the negative scenarios, which is consistent with H2a. By contrast, in the positive scenarios both same and other gender cocaine users (OG_u and OG_{ug}) obtained (marginally) lower cognitive empathy ratings than did the OG_a (p-values = 0.067 and 0.012, respectively; p-values for the remaining *post hoc* Tukey tests related to this interaction >0.275). Overall, this result is consistent with our H2a. However, the fact that the in-group character differed neither from the cocaine-using targets nor from the elderly target is not in line with our assumption that the in-group character should evoke greater cognitive empathy than the cocaine-using targets. Hence, H2a is only partially supported by our data.

The ANOVA for cocaine users yielded a significant main effect of *Target Character*, $F(3,60) = 6.14$, $p = 0.001$, $\eta_p^2 = 0.24$. This effect arose because cocaine users attributed stronger feelings to the three out-group characters compared with the in-group character (p-values < 0.043), with no difference between the former (p-values > 0.446). There was further a main effect of *Gender*, $F(1,20) = 7.93$, $p = 0.011$, $\eta_p^2 = 0.28$, because female cocaine users displayed greater cognitive empathy ($M = 30.7$, LCI = 26.8, UCI = 34.6) than did male cocaine users ($M = 22.9$, LCI = 19.0, UCI = 26.8). Overall, cocaine users' ratings (compared with control participants' ratings) for cognitive empathy were not characterized by reduced differentiation between the social targets, thereby conflicting with our H2c. Yet, while control participants made a clear distinction between positive and negative scenarios, this was not the case in cocaine users.

Emotional Empathy for the Different Social Targets

A repeated-measures ANOVA with the between-participants factors *Group* (cocaine and control) and *Gender* (male and female) and the within-participants factors *Scenario Valence* (negative and positive) and *Target Character* (IG, OG_u, OG_{ug}, and OG_a) was calculated on the participants' emotional empathy ratings. Inconsistent with H3b, cocaine users and control participants did not differ in overall level of emotional empathy displayed, shown by the non-significant main effect of *Group*, $F(1,58) = 0.00$, $p = 0.950$, $\eta_p^2 = 0.00$. The four-factorial ANOVA yielded a main effect of *Target Character*, $F(3,174) = 5.07$, $p = 0.002$, $\eta_p^2 = 0.08$, that was qualified by the interaction *Group* × *Target Character*, $F(3,174) = 2.92$, $p = 0.036$, $\eta_p^2 = 0.05$ (cf. **Figure 6**).

Post hoc Tukey tests for this interaction revealed greater emotional empathy attributed to the IG character than the OG_u character in the control participants ($p = 0.037$; consistent with H3a). Furthermore, the control participants rated their emotional empathy as higher for OG_a than for both OG_u and OG_{ug} (p-values ≤ 0.002; consistent with H3a). The remaining pairwise comparisons for this interaction did not reach significance (p-values > 0.407). Thus, while control participants more strongly

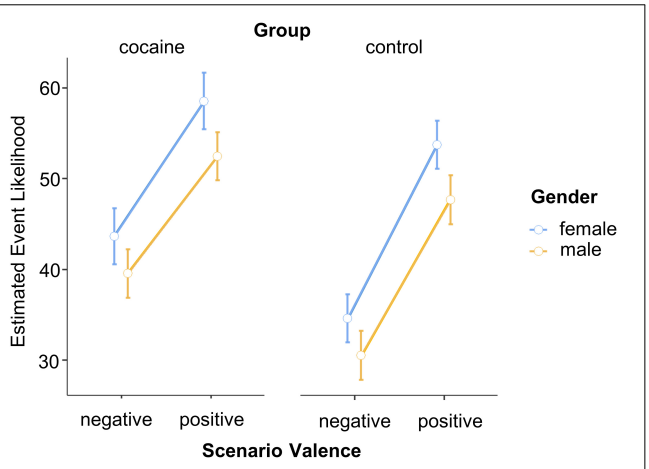

FIGURE 7 | Self-related future expectancies. Error bars, standard errors.

emotionally empathized with IG and OG_a than with OG_u and OG_{ug}, our cocaine users did not show any distinction between the social targets, which is supportive of H3c. Notably, this lack of differentiation was particularly strong in the cocaine users who were characterized by more enhanced consumption. Specifically, the lower the empathy score for IG – OG_u, the higher were (a) frequency [cocaine use in times per week: Spearman's rho (22) = −0.440, p = 0.040] and (b) doses [cocaine use in g per week: Spearman's rho (22) = −0.469, p = 0.028] of cocaine consume. None of the effects involving *Scenario Valence* turned out significant. Hence, emotional empathy did not differ between negative and positive scenarios.

Self-Related Future Expectancies

The ANOVA with the between-participants factors *Group* (cocaine and control) and *Gender* (male and female) and the within-participants factor *Scenario Valence* (negative and positive) revealed a significant main effect of *Scenario Valence*, $F(1,59) = 66.10$, $p < 0.001$, $\eta_p^2 = 0.53$. As expected, participants displayed a strong optimism bias in that they attributed a greater likelihood to the occurrence of positive (M = 52.9%, LCI = 49.7%, UCI = 56.2%) rather than negative (M = 37.0%, LCI = 33.8%, UCI = 40.2%) scenarios (**Figure 7**). Notably, this effect was observed in both groups: absence of an interaction between *Group* and *Scenario Valence*, $F(1,59) = 1.37$, $p = 0.247$, $\eta_p^2 = 0.02$. Together, these observations are in line with H4a (existence of optimism bias in controls), but not with H4b (no altered optimism bias in cocaine users). Yet, *post hoc* Spearman correlations with consumption parameters in cocaine users revealed a positive correlation between the extent of optimism bias displayed and cocaine use in g per week, Spearman's rho (22) = 0.543, p = 0.009. Additionally, we observed a significant main effect of *Group*, $F(1,59) = 6.92$, $p = 0.011$, $\eta_p^2 = 0.11$, relating to the fact that cocaine users (M = 48.6%, LCI = 44.8%, UCI = 52.3%) attributed overall greater likelihood to the occurrence of (both negative and positive) future events than did control participants (M = 41.4%, LCI = 37.6%, UCI = 45.1%).

DISCUSSION

The current study investigated whether person perception, cognitive and emotional empathy, as well as future expectancies are altered in cocaine users.

Level of Identification (Manipulation Check)

As intended, our participants identified strongest with their respective in-group. Moreover, cocaine users and controls did not statistically differ in their overall level of identification with the target characters. Compared with controls, cocaine users also did not display reduced identification strength with the in-group, in particular. Consequently, the below findings cannot be explained by divergent levels of identification with the target characters in the current study.

Perceived Warmth

Consistent with our H1a, controls attributed greater warmth to their in-group and the elderly targets than to the cocaine-using targets, displaying their stigmatization and discrimination of substance users (56). Such stigmatization may be problematic because it can feed back to the stigmatized group's mental and physical health (57). By contrast, our H1c, specifying our expectation that cocaine users (compared with controls) would, overall, display lower ratings of warmth for the social targets did not reach support by the data at hand. The same was true for our H1e, which predicted little or no differentiation in warmth ratings between the social targets in cocaine users.

Cocaine users attributed lower warmth to the cocaine-using target (their in-group) than to the three non-cocaine-using targets. On the one hand, this result may speak to self-stigmatization of cocaine users [possibly resulting from their own public stigmatization; (56)]. Indeed, recent research [e.g., Crapanzano et al. (58)] has demonstrated that substance use disorder goes along with severe self-stigmatization processes, whose levels even surpass those revealed by individuals suffering from other mental illnesses [e.g., schizophrenia; (59)]. On the other hand, prior research has demonstrated reduced emotional empathy (8), lowered prosociality (10), and increased Utilitarian and Machiavellian tendencies (9) in cocaine use – wherefore our findings for warmth may alternatively or additionally map realistic person appraisals in both cocaine users and controls. If the latter were true, our results would hence speak to ego-syntonicity in cocaine users. In sum, therefore, both groups of participants rated the elderly target as warmest and the cocaine-consuming target(s) as colder than the non-cocaine-consuming targets. In addition, we observed higher warmth attributions in females than males, which may relate to females' increased communal responsiveness (60).

Perceived Competence

The first two hypotheses for competence (H1b: differing competence ratings for the four social targets in control participants, H1d: lower competence ratings in cocaine users than controls) were not supported by the existing data. By

contrast, findings for our H1f were fully in line with our expectations in that cocaine users' competence ratings did not distinguish between the different social targets. This could indeed speak to a tendency in cocaine users to reflect less about person characteristics in others. Yet, because control participants behaved in the same way, this result should not be over-interpreted. Unexpectedly, we observed a significant interaction *Target Character* × *Gender*, related to the trend in male participants to attribute particularly high competence to the elderly target. However, all *post hoc* tests failed to achieve significance, wherefore this effect clearly needs replication.

That we found only small effects in competence compared with warmth attributions is consistent with Abele and Wojciszke (61)'s theory regarding the impact of perspective taking on the ponderation of person characteristics. It may be assumed that participants in the current study adopted a so-called observer perspective and therefore weighted the targets' competence less than their warmth (because another person's warmth will serve the achievement of their own goals best). It will be interesting to study whether the opposite pattern will be observed when participants in an experiment adopt an actor perspective.

Cognitive Empathy

Our cognitive empathy data suggest that potential discrimination and stigmatization of cocaine users by control participants in the current study may be limited to positive scenarios. Consistent with our H2a, for positive scenarios, controls expressed greatest cognitive empathy for the elderly target and lowest for cocaine-using targets. The in-group target was located in between. No such differentiation between the social targets was observed when negative scenarios were considered. This finding aligns with our earlier observation of reduced variation in cognitive empathy ratings for different social targets facing negative scenarios (17). The current data hence strengthen our earlier interpretation that people think that everybody has the right to feel bad and suffer. Such a point of view may have arisen from societal norms that rule how to empathize with others after those have experienced detrimental influences.

In line with our H2b, we found comparable overall levels of cognitive empathy in cocaine users and controls, suggesting that cocaine users are not characterized by generally impaired cognitive empathy. This observation harmonies with earlier findings revealing that cognitive empathy is not *per se* deviant in cocaine users (7, 8). Instead, there may exist specific impairments, expressed in reduced emotion recognition from prosody or integration of multiple emotional information sources (23).

Finally, the data at hand conflict with our H2c. Compared with the control participants' cognitive empathy ratings, there was no indication of reduced variance in the cocaine users' cognitive empathy ratings for the different social targets. Yet, the pattern of response in the two groups was different: cocaine users attributed weaker feelings to their in-group compared with all no substance using out-groups. This result possibly relates to blunted social reward processing in cocaine users (5). Whereas the general population tends to treat warm fellows (including their in-group) favorably across various domains (17, 42), this was not the case in our cocaine-using participants. Moreover, in the current study such unfavorable treatment of the in-group was observed across both types of scenarios, positive and negative. Contrary to the control group, the cocaine users therefore did not consider everybody to have the same right to feel bad.

Emotional Empathy

In accordance with our H3a, control participants expressed the highest emotional empathy for the elderly and were least emotionally involved with the cocaine-using targets. Our results thus align with earlier findings in the area (17) and point once more to the stigmatization of substance users (56). Of note, our participants were not informed by personal characteristics or traits of any of the social targets under investigation. The sole mention of group membership was sufficient to provoke markedly different affective responses toward the social targets. Hence, our findings demonstrate the powerful influence of social classification, an influence that may turn out beneficial for members of some social groups (e.g., the elderly) but potentially damaging for members of other social groups [e.g., substance users such as cocaine users or alcoholics; (57)].

H3b, by contrast, was not supported by the data, because we did not find different overall levels of emotional empathy in cocaine users vs. controls. Hence, we did not replicate an earlier finding that revealed lowered emotional empathy in cocaine users (8). Yet, it has to be taken into consideration that the current task differed importantly from the Multifaceted Empathy Task [MET; (62)], which was employed in the earlier investigation. Whereas the MET involves emotionally-laden pictures that are presented to provoke emotional contagion, emotional perspective taking in the present task was more abstract, less automatic, and possibly characterized by higher cognitive and less emotional load.

Importantly, while the two groups of participants demonstrated a comparable level of overall emotional empathy, unlike the controls, cocaine users were characterized by a reduced differentiation between the social targets, which is consistent with H3c. A likely interpretation of this finding is that cocaine users are somewhat insensible or inattentive to social signals in their environment [including social stereotypes; see (5) for supportive evidence]. Of interest, our correlation analyses performed on the cocaine users' empathy scores revealed that the favorability of the IG over OG_u varied as a negative function of the extent of their use of the drug. These data hence suggest that the degree of indifference reflected in emotional empathy directly relates to individual consumption patterns.

Self-Related Expectancies

In line with our predictions (H4a), control participants displayed an optimism bias in that they imagined their future to be more positive than negative. Importantly, the included events had been judged for their likelihood of appearance in the general population in a previous study [see Dricu et al. (42), for details] and the average likelihood did not differ between positive and negative events. Therefore, our results cannot be explained by different base rates for positive vs. negative events in the general population.

We had further hypothesized that the size of the optimism bias would be altered in cocaine users (H4b). Yet, contrary to our expectations, the size of optimistic bias was comparable in cocaine users and controls. Notably, whereas there was no group

difference revealed, our subsequently performed correlation analyses uncovered that optimism bias in cocaine users varied as a positive extent of dose levels. Thus, it is possible that participants with high doses more strongly benefited from enhancing effects of the drug. Interestingly, cocaine users rated the likelihood of both desirable and undesirable events higher than did controls, suggesting altered likelihood estimation *per se*. This observation may explain why cocaine users are bad decision makers also often taking higher risks [see (10, 32)] and possibly relates to lowered cortical thickness in the frontal cortex [(63), (64), see also (65), (66) for the frontal cortex' involvement in cognitive estimation, prediction errors, and regulative actions].

LIMITATIONS

We may be criticized because our study included a lower number of cocaine users than controls and an unequal distribution of males and females in the two groups of participants. We nonetheless believe that our results are valid because the prevalence of cocaine use is generally lower among females than males as revealed by the European Drug Report.[1] Yet, because the overall sample size was comparably small for a cognitive study with chronic cocaine users, replication of the results is desired.

Furthermore, **Table 2** revealed significant differences between cocaine users and controls on several clinical scales. ADHD-SR, BDI, and the SCID-II -borderline and antisocial personality disorder have been linked with cocaine use disorder before (4, 32, 67). It hence is possible that high scores on those scales are partially caused by using cocaine (or that these characteristics, in turn, influence the use of cocaine). Ideally, one would want to filter out the influences of such potentially confounding variables, i.e., by performing an analysis of covariance (ANCOVA). For two reasons, we decided not to conduct ANCOVAs with the relevant questionnaire scores as covariates. First, considering the low number of participants, the inclusion of any covariate would have reduced statistical power. Second, interpretation of ANVOCA results may be seriously compromised if the covariate and group membership are correlated [e.g., (68)]. The question of whether the personality characteristics influence drug consumption or vice versa cannot be addressed by the current study and requires future investigations. It thus remains to be determined whether the effects observed in the present research can be attributed to the consumption of the drug or to specific personality patterns prevailing in the cocaine users. Only a longitudinal study can address this question.

FUTURE DIRECTIONS

The social phenomena investigated in cocaine use may be extended to the study of social optimism bias (42, 69–71). Because social expectancies are important for social interaction, it may pay off to identify critical social expectancies that should be corrected. Such an approach might permit cocaine users a more successful communication with others and support prevention of social isolation. In this context it will also be worthwhile to test for functional and structural particularities (43, 44, 72) that are likely associated with altered social expectancies in substance use disorders. Furthermore, substance-naïve individuals have been demonstrated to hold rather pessimistic future expectancies for substance users (42, 71, 72). Such overpessimistic expectancies may require modification to reduce stigmatization and discrimination of cocaine users by the general population (56).

Finally, our data compared with earlier findings suggest that the revelation of emotional empathy impairments in cocaine use is somewhat dependent on the task. In future examinations, the same sample of participants (users and controls) should therefore undergo different experimental paradigms (e.g., MET and the current paradigm) to permit better identification of the specific facets of emotional empathy that are impaired.

SUMMARY AND CONCLUSION

We did not find differences in social identification (manipulation check) between cocaine users and controls, suggesting that such automatic and basic social processing is not flawed in cocaine users. However, we observed that cocaine users (compared with substance-naïve individuals) attribute lower warmth to people they feel alike. Moreover, they see non-consuming individuals as warmer and more likeable than they see people, who are like themselves. That the in-group is suchlike debased is rather uncommon and may point to massively compromised self-value and self-esteem resulting from (self-)stigmatization. Comparably, we observed no in-group preference in the cocaine users' emotional empathy ratings. An in-group that is evaluated as more unlikeable than diverse out-groups may not trigger enhanced affective sharing, which is typically elicited once we see similar others in emotional situations. Our data further suggest that such deviance might be a direct consequence of a user's consumption pattern – or vice versa. Together, our findings point to multiple interdependencies between (a) personal factors (e.g., cocaine users' perception of the self and others), (b) the external environment (social distancing from and stigmatization of cocaine users by substance-naïve individuals), and (c) substance-related behavior (cocaine intake), which is fully in line with recently suggested reciprocal determinism and metacontingencies in addiction (73). Future interventions should hence address critical (self-)stigmatization processes to break the vicious circle of mutual social distancing and increased dedication to the drug. Finally, self-related future expectancies are not *per se* more negative or positive in cocaine users compared with controls. Yet, it remains to be determined whether there are peculiarities when it comes to social future expectancies.

DATA AVAILABILITY STATEMENT

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

[1] https://www.emcdda.europa.eu/publications/edr/trends-developments/2021_en

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of the Canton Zürich. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

TA, LS, and BQ developed the study concept and design. A-KK and BK-S conducted the assessments. SB and BK-S programmed the experiment. A-KK curated the data and wrote sections of the manuscript. TA performed the statistical analysis and wrote the first draft of the manuscript. MB conducted hair analyses and supported data interpretation. LS supported data interpretation. 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.2022.879016/full#supplementary-material

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Knowledge atlas of the involvement of glutamate and GABA in alcohol use disorder: A bibliometric and scientometric analysis

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Introduction: Abnormal neurotransmission of glutamate and γ-aminobutyric acid (GABA) is a key characteristic of alcohol-related disorders. To track research output, we conducted a bibliometric analysis to explore the current status and trends in this field over the past decades.

Methods: Studies related to neurotransmitters and alcohol use disorder published in English from 2005–2021 were retrieved from the Web of Science Core Collection and Scopus databases. The R–*bibliometrix* package was used for a descriptive analysis of the publications. Citespace, WOSviewer, and R–*bibliometrix* were used to construct networks of countries/institutions/authors based on co-authorship, co-citation analysis of cited references and co-occurrence as well as burst detection of keywords.

Results: A total of 4,250 unique articles and reviews were included in the final analysis. The annual growth rate of publications was 5.4%. The USA was the most productive country in this field, contributing nearly half of the total documents. The top ten most productive institutions were all located in the USA. The most frequent worldwide collaboration was between the USA and Italy. The most productive and influential institution was the University of California. The author contributing the most productions to this field was Marisa Roberto from the Scripps Research Institute. The top co-cited reference was a review titled "Neurocircuitry of addiction." The top journal in terms of the number of records and citations was *Alcoholism: Clinical and Experimental Research*. Comprehensive analyses have been conducted over past decades based on co-cited reference analysis, including modulators, transporters, receptor subtypes, and animal models. In recent years, the research frontiers have been shifting to the identification of risk factors/biomarkers, drug development for alcohol use disorder, and mechanisms related to alcoholic and non-alcoholic fatty liver.

Conclusion: Our bibliometric analysis shows that glutamate and GABA continue to be of interest in alcohol use disorder. The focus has evolved from mechanisms and medications related to glutamate and GABA in

alcohol use disorder, to novel drug development, risk factor/biomarker identification targeting neurotransmitters, and the mechanisms of related diseases.

KEYWORDS

glutamate, GABA, alcohol use disorder, bibliometrics, scientometrics, visualization

Introduction

Alcohol is the oldest and most extensively used addictive substance. Acute and chronic consumption of alcohol may lead to alcohol dependence, alcohol withdrawal syndrome and other alcohol-related disorders. Meanwhile, alcohol intake is a risk factor for a variety of diseases such as hypertension, diabetes, and liver cirrhosis. The harmful use of alcohol has become a severe global threat, leading to more than 3.3 million deaths every year (1). In some countries, the all-cause mortality rate of alcohol is as high as 10% (1). Alcohol use disorder is a complex dynamic process, involving adaptive changes related to the neuroendocrine system, neurotransmitters [γ-aminobutyric acid (GABA), glutamate, monoamines], neuropeptides [corticotropin releasing factor (CRF), neuropeptide Y (NPY)] and ion channels (voltage-gated ion channels, small-conductance Ca^{2+}-activated K^{+} channel, big potassium ion channel). The disruption of neurochemical homeostasis not only facilitates symptoms of alcohol-related disease, but also augments the sensitivity to harmful drinking behavior.

Glutamate is the major neurotransmitter for excitatory synaptic signaling in the brain. Numerous studies in recent years have suggested a complex influence of alcohol on glutamate receptors, glutamate transporters, and synaptic glutamate homeostasis in different brain regions and neurocircuitries, as well as corresponding behavioral changes. Glutamate receptors are categorized into metabotropic glutamate receptors (mGluRs) and ionotropic glutamate receptors (iGluRs), regulating slow and rapid glutamatergic neurotransmissions, respectively. Acute exposure and chronic exposure to alcohol have opposite effects on N-methyl-D-aspartate receptor (NMDAR)-mediated synaptic plasticity and glutamatergic synaptic transmission (2). Chronic exposure enhances the NMDAR-mediated synaptic plasticity and glutamatergic synaptic transmission, while acute alcohol exposure exerts an inhibitory effect. Alcohol also increases subunits [GluA1, GluA2, and GluA3 (3)] of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) expression and its synaptic localization. In general, acute alcohol exposure inhibits neuronal excitability, while chronic alcohol exposure increases the functioning of iGluRs. By contrast to iGluRs, alcohol exposure has a modest effect on mGluRs. Expression of group I mGluRs (mGluR1 and mGluR5), predominantly localized in the post-synaptic neurons regulating slow excitatory neurotransmission, is upregulated by alcohol. Meanwhile, expression of mGluR2/3, which plays a critical role in reducing the release of glutamate from pre-synaptic glutamatergic neurons, is downregulated. Agonism of group I mGluRs and/or antagonism of group II mGluRs by alcohol restores glutamate homeostasis in the brain. Accumulating evidence indicates that alcohol exposure alters the expression and functions of the glutamate transporters. Excitatory amino acid transporters (EAAT1-5) are region- and cell subtype-specific, and are responsible for removing glutamate from the synapse into the glial cells to maintain glutamate homeostasis. The EAAT1 (GLAST) and EAAT4 are mainly expressed in the cerebellum. The EAAT2 (GLT-1) is largely located in the forebrain. The EAAT3 is primarily expressed in neurons more homogeneously, and the EAAT5 is limited to ocular cells. The cystine–glutamate antiporter (xCT) is also important in extra-synaptic glutamate homeostasis, by exchanging extracellular cystine for intracellular glutamate in astrocytes. The expression of GLT-1 and xCT is downregulated by chronic alcohol exposure (3), leading to a significant increase in extracellular glutamate levels. Given that the major glutamate transporters GLAST, GLT-1, and xCT are predominantly expressed in astrocytes, astrocytes are inevitably important for glutamate homeostasis in the brain. Alcohol exposure dysregulates glutamatergic neurotransmission *via* glutamate receptors and transporters in the mesocorticolimbic brain regions, and modulations to these targets attenuate alcohol-seeking behavior [for a review, see (3)].

GABA is the major inhibitory neurotransmitter in the brain, underlying many alcoholic behavioral changes including anxiolytic, anticonvulsant, sedative-hypnotic, cognitive-impairing, and motor-incoordinating actions (4). Alcohol exerts direct and indirect effects on GABA receptors and GABA release. There are two classes of GABA receptors: $GABA_A$ (ligand-gated ion channels) and $GABA_B$ (G-protein-coupled receptors). $GABA_A$Rs are postsynaptic pentameric complexes assembled with various subunits. The functions of $GABA_A$R subtypes are mainly defined by the specific α subunit: α1, α2, and α4 subunits are the most relevant subunits in alcohol dependence (4). Low-dose alcohol enhances the tonic inhibition mediated *via* multiple subunits such as α4/6βδ- and α1δ-$GABA_A$ (5), which may be involved in the maintenance of ethanol self-administration. Alcohol also mediates post-translational

modification of $GABA_A$ receptors, including phosphorylation of $GABA_A$ receptor subunits by protein kinase C (PKC) (6), and alters $GABA_A$ expression by protein kinase A (PKA). The cAMP-PKA signaling pathway also plays an important role in the neurobiological responses and behavioral actions induced by alcohol. Apart from direct modulation of $GABA_A$Rs, alcohol may influence functions of $GABA_A$Rs in an indirect way *via* neurosteroids (7). Accumulating evidence also shows that alcohol increases GABAergic synaptic transmission by increasing presynaptic GABA release from vesicles, especially in the central amygdala (CeA) (8). The utility of alcohol in facilitating GABA transmission may be limited by GABA feedback onto presynaptic $GABA_B$. GABA transporters (GAT1-3) are responsible for removing GABA from the synaptic cleft. GAT-1 is predominantly found in axon terminals and glial cells, and GAT-3 is exclusively located on glial cells (9). Recently, Augier et al. (10) found that GAT-3 expression was selectively decreased in the CeA of alcohol-choosing rats and alcohol-dependent people. The impaired GABA clearance within the CeA contributes to alcohol addiction, and may be a target for new pharmacotherapies.

Glutamate and GABA exert interacting effects, including not only inverse synaptic signaling but also bioconversion in the brain. Endogenous brain GABA influences the glutamate–glutamine cycling flux. In astrocytes, glutamate and GABA are converted to glutamine through the glutamine synthetase pathway. After being transferred back to neurons, glutamine is converted to glutamate by glutaminase. Meanwhile, glutamate is the precursor to GABA and is back-converted to GABA *via* glutamic acid decarboxylase. Glutamate and GABA are important therapeutic targets in alcohol use disorder. Several glutamate system modulators (acamprosate, gabapentin, and topiramate) and GABA system modulators (benzodiazepines, baclofen, and sodium oxybate) have been recommended as pharmacotherapy for patients with alcohol use disorder (11, 12). Considering the prominent and interacting effects of glutamate and GABA in alcohol use disorder, there is a need to summarize and review the current research status in this domain.

The number of publications in journals is expanding exponentially over time. It is becoming more and more difficult to identify the research frontier and extract the key knowledge nodes of a certain subject or domain. Over the past two decades, bibliometric analysis has become an emerging statistical and visualization tool. It focuses on the impacts of publications, the contributions of individuals, institutes and countries, as well as research frontiers and hotspots in the field (13). Citespace and WOSviewer are two of the most popular bibliometric software packages. CiteSpace is a free Java-based bibliometric software package developed by Dr. Chaomei Chen (14). It provides multiple functions for bibliometric studies including collaboration network analysis, co-citation analysis, and co-occurrence analysis (15). A series of knowledge maps generated by Citespace helps one to explore the research frontiers and evolution of a scientific domain, and reveals the collaboration characteristics of institutions and authors in research fields (16). WOSviewer, created by Leiden University's Center for Science and Technology Studies, is another popular and freely available software package for science mapping (17). It enables network layout and network clustering, and provides integrated visualization of scientific maps. A new open-source tool, *bibliometrix*, developed by Dr. Massimo Aria and Dr. Corrado Cuccurullo (18), is programmed in R and can be integrated with other statistical R-packages. *Bibliometrix* provides a set of tools for quantitative analyses and visualization in bibliometrics and scientometrics.

Considering that studies on the involvement of glutamate and GABA in alcohol use disorder have developed rapidly over the past two decades, it is necessary to summarize the literature characteristics and research direction as a whole, to explore how the research has changed over time, and to predict future trends in this domain. However, there is no bibliometric analysis of the literature in this field. Accordingly, we conducted a bibliometric analysis of publications since 2005 to provide an overview of documents and explore the hot topics and emerging trends in this field.

Materials and methods

Data sources and search strategy

Data were retrieved from two large, multidisciplinary citation databases, Scopus and the Web of Science Core Collection (WoSCC). The search phrases associated with the neurotransmitters glutamic acid and GABA included gamma-aminobutyric acid, GABA, glutamate, glutamine, and glutamic acid, and the phrases associated with alcohol use disorder included alcohol use disorder, alcohol abuse, alcohol dependence, alcoholi*, and alcohol addiction. The WoSCC includes cited references from 2005. Thus, the search time span was set as the years 2005–2021. Only two types of document, articles and reviews, were included to better represent the research field. The publication language was restricted to English. The same search strategy was applied to both databases. Raw data including full records and cited references were downloaded from Scopus and WOSCC as ris or txt file required for further processing in CiteSpace.

Data analysis

The data were obtained on April 22nd, 2022 from different databases. Data cleaning was conducted using CiteSpace software in combination with manual searching.

In this study, R–*bibliometrix* was used to perform descriptive analysis of the leading research authors,

countries, and journals, identify core journals, and produce a country/region collaboration map. Bradford's law (19, 20) was used as an objective measurement for core journals. In the collaboration map within countries/regions, the darkness of color represents the number of publications from different countries/regions, and the thickness of lines between two countries/regions suggests the intensity of collaborations between individual countries/regions.

CiteSpace 6.1.R1 was employed to detect the collaboration characteristics of institutions and authors, the reference co-citation network and keywords citation bursts. The parameters of CiteSpace were set as follows: time-slicing was performed from January 2005 to December 2021 (1–2 years per slice); the strength of links was calculated based on the Cosine algorithm; the selection was based on a modified g-index with a scale factor k = 25 for collaboration detection, and the top 50 items were selected for keyword analysis and reference co-citation analysis; a pruning with minimum spanning tree was used for concurrence analysis. Nodes and links were used to generate visualization knowledge maps. The size of nodes represents the number of citations. The color of rings indicates citation years: the transition from cool to warm represents early to recent publications. A link between two nodes suggests a co-occurrence or co-citation relationship. Line thickness represents the strength and the color corresponds to the first co-occurrence or co-citation time. In addition to the number of publications and citations, "centrality" was used as a measurement of significance. "Centrality" detects the interactions of a node with other nodes. Nodes with high centrality are considered as an important "bridge" between different groups and represent turning points or pivotal points in this field. Nodes with centrality > 0.1 were surrounded by a purple ring. Co-occurrence analysis of keywords was conducted using WOSviewer 1.6.18. Keywords occurring more than ten times were presented in three visualizations (network, overlay, and density visualization) to identify important terms.

Results

General characteristics of publication outputs and sources

The total numbers of documents in the Scopus and WoSCC databases were 3,524 and 2,315. Duplicated records were identified and removed. A total of 4,250 unique records from Scopus and WoSCC, including 3,817 primary research articles and 433 reviews, were used for further analysis (Figure 1). The total number of cited references was 222,734. The life span of these documents was 2005–2021. Publication outputs showed a fluctuating growth trend, with an annual growth rate of 5.4% from 2005 to 2021 (Figure 2).

The total number of citations has increased in the past 17 years. Seventeen articles were qualified as "citation classics" in this area, i.e., having 400 or more citations (21). The most frequently cited document was The International Classification of Headache Disorders by Olesen et al. (22), and the most co-cited document was Neurocircuitry of Addiction by Koob et al. (23). These findings indicate a sustained interest in the involvement of glutamic acid and GABA in alcohol use disorder.

The literature was published in 1,248 sources. The journal with the highest number of publications was *Alcoholism: Clinical and Experimental Research* (260 publications, IF_{2020} = 3.455). After Bradford's law was applied, the core distribution comprised 22 journals (Table 1). Most of the top journals were specialized neuroscience or substance abuse journals. The top journals belong to the substance abuse category. These journals are mostly located in the United States (USA) and the United Kingdom (UK). The impact factor of *Biological Psychiatry* (36 publications, IF_{2020} = 13.382) and *Proceedings of the National Academy of Sciences of the United States of America* (27 publications, IF_{2020} = 11.205) exceeds 10.

Active countries/regions, institutions, and researchers

Eighty-one countries or regions have contributed to publications in the field of research on the involvement of glutamate and GABA in alcohol use disorder. The data extracted from Scopus and WoSCC indicated that the USA was the most productive country (52%), followed by the People's Republic of China (6%), Germany (4%), Italy (4%), and Australia (3%). The centralities of the USA (1.03), Italy (0.15), France (0.13), Canada (0.13), Ukraine (0.12), and the Russian Federation (0.12) are > 0.1, indicating that these countries might deeply cooperate with other countries and act as important intermediaries in this field. Figure 3 displays the numbers of documents and the cooperation networks of the active countries/regions. There were 279 collaborating countries/regions worldwide, of which the top three were USA–Italy, followed by USA–China and USA–Australia.

From 2005 to 2021 3,626 institutions in this field published papers. Table 2 lists the top 10 institutions based on publications and centrality. Figure 4 exhibits the major productive co-institutions in this field. The University of California is the most influential institute in this field, with a total number of 238 publications and centrality of 0.16, followed by the Medical University of South Carolina and Yale University. The top ten productive institutions in this research field are all located in the USA.

A total of 18,145 authors contributed relevant publications. Figure 5 shows the co-authorship network map. Marisa Roberto from the Scripps Research Institute was the most prolific author (57 documents), with the highest centrality of 0.06. The other productive researchers were Giancarlo

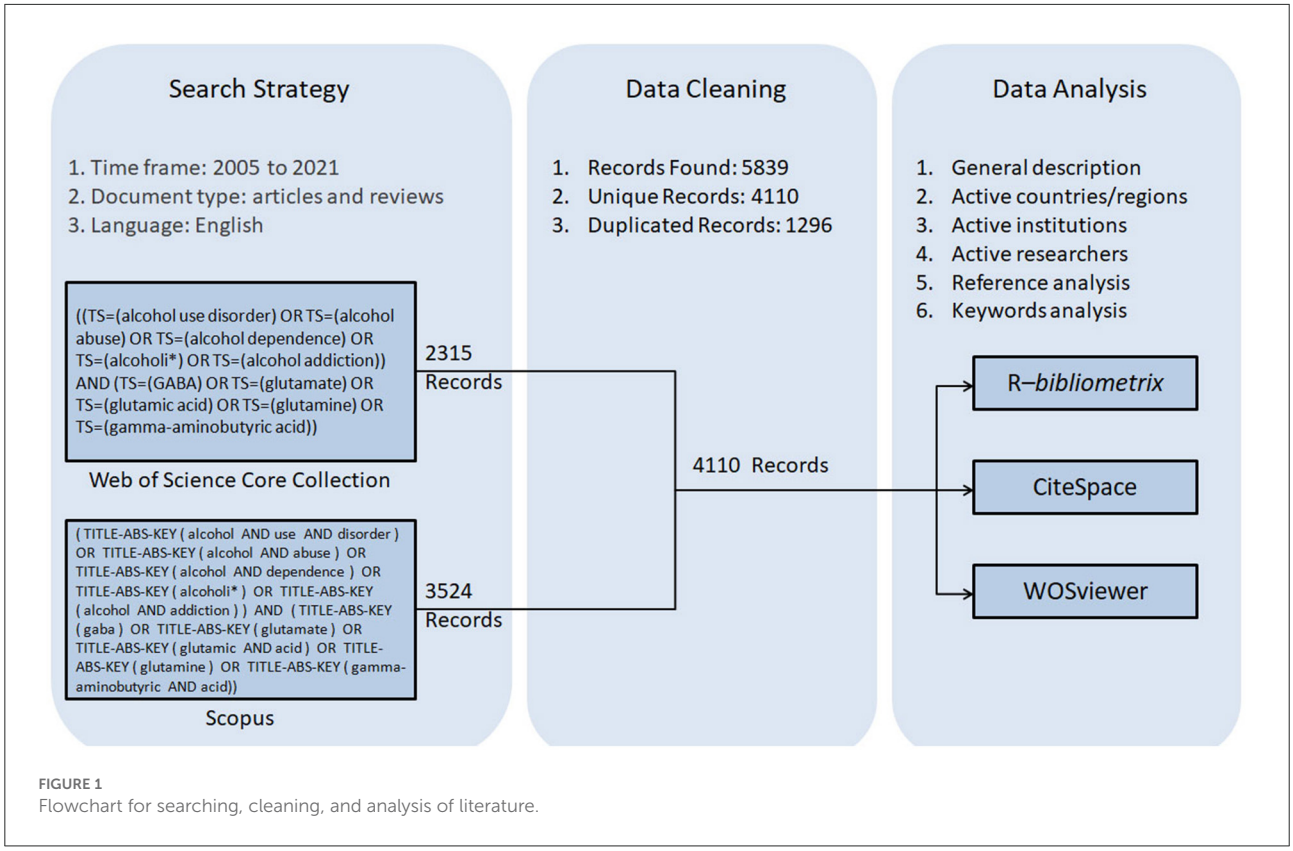

FIGURE 1
Flowchart for searching, cleaning, and analysis of literature.

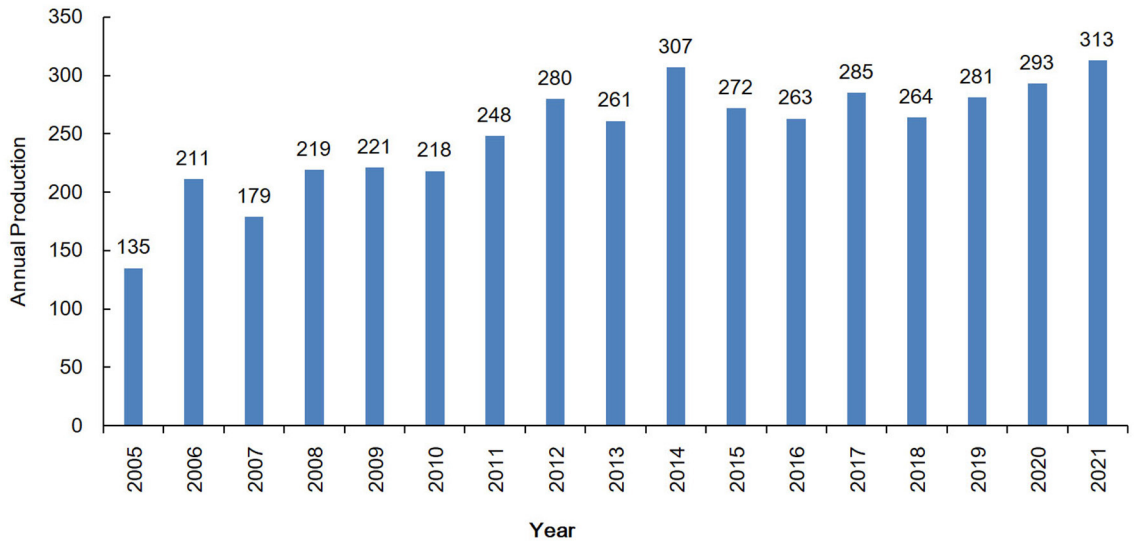

FIGURE 2
Annual production with regard to the involvement of glutamic acid and GABA in alcohol use disorder.

Colombo (National Research Council, Italy) and Youssef Sari (University of Toledo, USA). Table 3 lists the top 10 productive authors in this research field, their affiliations and centralities.

Analysis of co-cited references

The top co-cited references with the most citation counts and highest centralities are shown in Table 4. According to the

TABLE 1 Core journals of glutamate and GABA involved in alcohol use disorder.

Rank	Journal	Publications	Citations[a]	Country/region	IF^{b}_{2020}	Category and JCI quartile
1	Alcoholism: Clinical and Experimental Research	260	10468	USA	3.455	Substance Abuse, Q2
2	Addiction Biology	125	1999	England	4.28	Biochemistry & Molecular Biology, Q1; Substance Abuse, Q1
3	Alcohol	100	2572	USA	2.405	Pharmacology & Pharmacy, Q2; Substance Abuse, Q3; Toxicology, Q2
4	Neuropharmacology	99	2858	England	5.251	Neurosciences, Q1; Pharmacology & Pharmacy, Q1
5	Neuropsychopharmacology	99	4144	England	7.855	Neurosciences, Q1; Pharmacology & Pharmacy, Q1; Psychiatry, Q1
6	Psychopharmacology	99	5324	Germany	4.53	Neurosciences, Q2; Pharmacology & Pharmacy, Q1; Psychiatry, Q1
7	Alcohol and Alcoholism	62	2025	England	2.826	Substance Abuse, Q3
8	Pharmacology Biochemistry and Behavior	62	2596	England	3.533	Behavioral Sciences, Q2; Neurosciences, Q2; Pharmacology & Pharmacy, Q2
9	Journal of Neuroscience	55	7248	USA	6.167	Neurosciences, Q1
10	Plos One	52	1494	USA	3.24	Multidisciplinary Sciences, Q1
11	Behavioral Brain Research	42	1136	Netherlands	3.332	Behavioral Sciences, Q2; Neurosciences, Q2
12	Frontiers in Psychiatry	39	299	Switzerland	4.157	Psychiatry, Q2
13	Neuroscience	38	2203	England	3.59	Neurosciences, Q2
14	Drug and Alcohol Dependence	37	1704	Switzerland	4.492	Psychiatry, Q1; Substance Abuse, Q1
15	Biological Psychiatry	36	2863	USA	13.382	Neurosciences, Q1; Psychiatry, Q1
16	Brain Research	33	2674	Netherlands	3.252	Neurosciences, Q3
17	Current Pharmaceutical Design	32	203	U Arab Emirates	3.116	Pharmacology & Pharmacy, Q3
18	Neuroscience Letters	31	1103	Netherlands	3.046	Neurosciences, Q3
19	Journal of Psychopharmacology	27	394	England	4.153	Clinical Neurology, Q2; Neurosciences, Q2; Pharmacology & Pharmacy, Q2; Psychiatry, Q2
20	Neuroscience and Biobehavioral Reviews	27	748	England	8.989	Behavioral Sciences, Q1; Neurosciences, Q1
21	Proceedings of the National Academy of Sciences of the United States of America	27	3064	USA	11.205	Multidisciplinary Sciences, Q1
22	Frontiers in Neuroscience	26	284	Switzerland	4.677	Neurosciences, Q2

[a]cited by reference.
[b]impact factor in category according to Journal Citation Reports (2020) by Clarivate.

ranking of frequency and centrality in the co-cited references, half were review papers, and a few were original research papers. The first ranked citation in terms of frequency was the review published in *Neuropsychopharmacology* titled "Neurocircuitry of addiction" (23). In this review, Koob et al. conceptualized drug addiction as an addiction cycle composed of three stages: "binge/intoxication," "withdrawal/negative affect," and "preoccupation/anticipation" (craving). He described discrete circuits involved in these three stages, and that neuroplasticity in these structures contributed to the transition to addiction. The co-cited reference with the highest centrality was an article published in *Neuroscience* by Sari et al. (24). In this article, the authors found that neuroimmunophilin GPI-1046 attenuates ethanol intake in part through the upregulation of GLT1 in the pre-frontal cortex (PFC) and nucleus accumbens core (NAc) of alcohol-preferring rats.

The network map of the co-cited references is displayed in Figure 6. The reference co-citation network was divided into 17 co-citation clusters. The clusters are labeled by keywords of the cited articles using the LLR (log-likelihood ratio) algorithm as

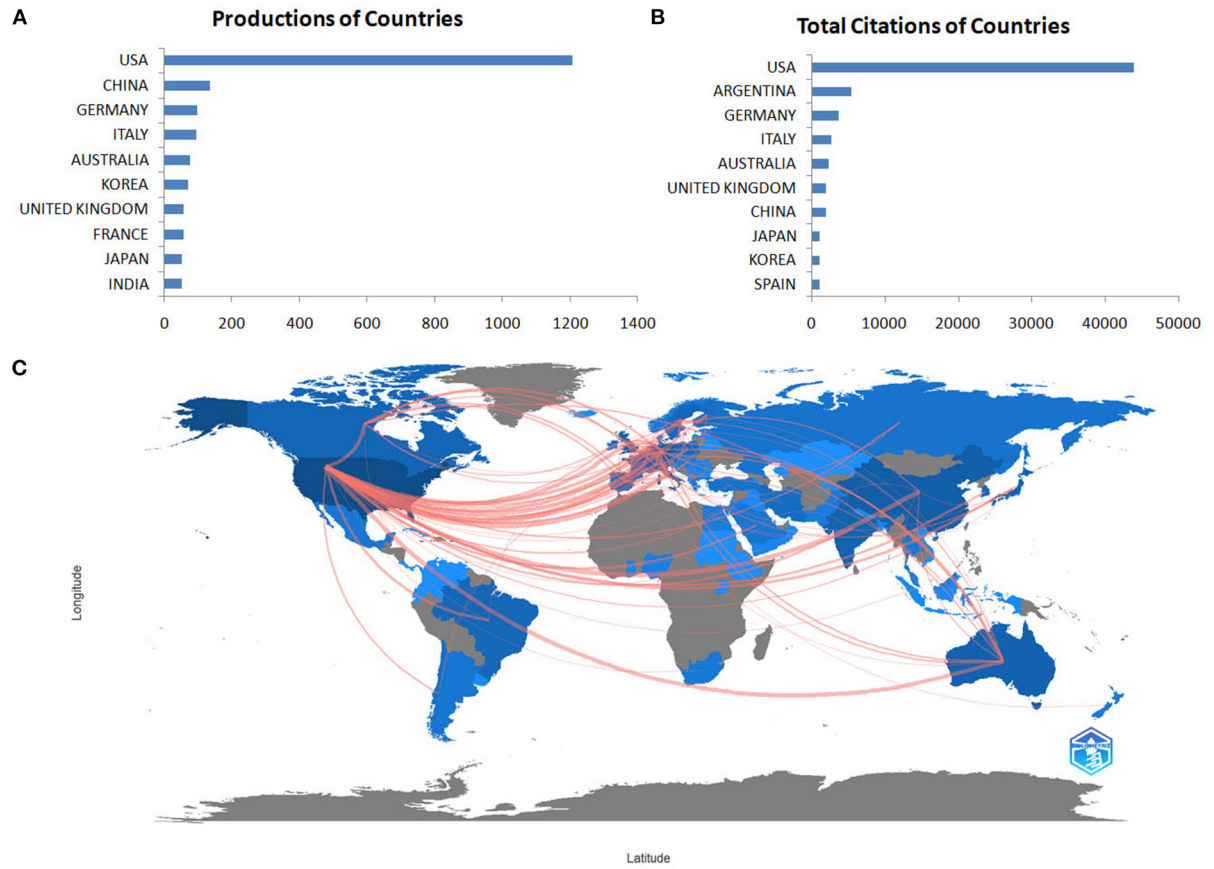

FIGURE 3
The number of documents **(A)**, citations **(B)** and cooperation networks **(C)** of the active countries/regions.

TABLE 2 The top ten institutions related to glutamate and GABA in alcohol use disorder.

Rank	Institution	Number of publications	Centrality	Country/region
1	Univ Calif	238	0.16	USA
2	Med Univ S Carolina	163	0.07	USA
3	Yale Univ	155	0.08	USA
4	Scripps Res Inst	152	0.06	USA
5	Univ N Carolina	238	0.04	USA
6	NIAAA	80	0.04	USA
7	Oregon Hlth & Sci Univ	121	0.03	USA
8	Indiana Univ	170	0.04	USA
9	Univ Texas	117	0.04	USA
10	Univ Connecticut	67	0.03	USA

the extraction method. In the study period, the labels of the top ten clusters were: #0 NPY, #1 GLT-1, #2 acamprosate, #3 $GABA_A$ receptor subtypes, #4 EAAT2, #5 baclofen, #7 corticotropin releasing hormone receptor 1 (CRHR1), #8 alcohol use disorder, #9 C57BL/6, #10 COR659 (a $GABA_B$ positive allosteric modulator). In the research period, a comprehensive analysis referring to multiple studies mainly focused on the following: (1) mechanism, including modulators, transporters, receptor subtypes, and the development of animal models; (2) drug development targeting glutamate and the GABA system for

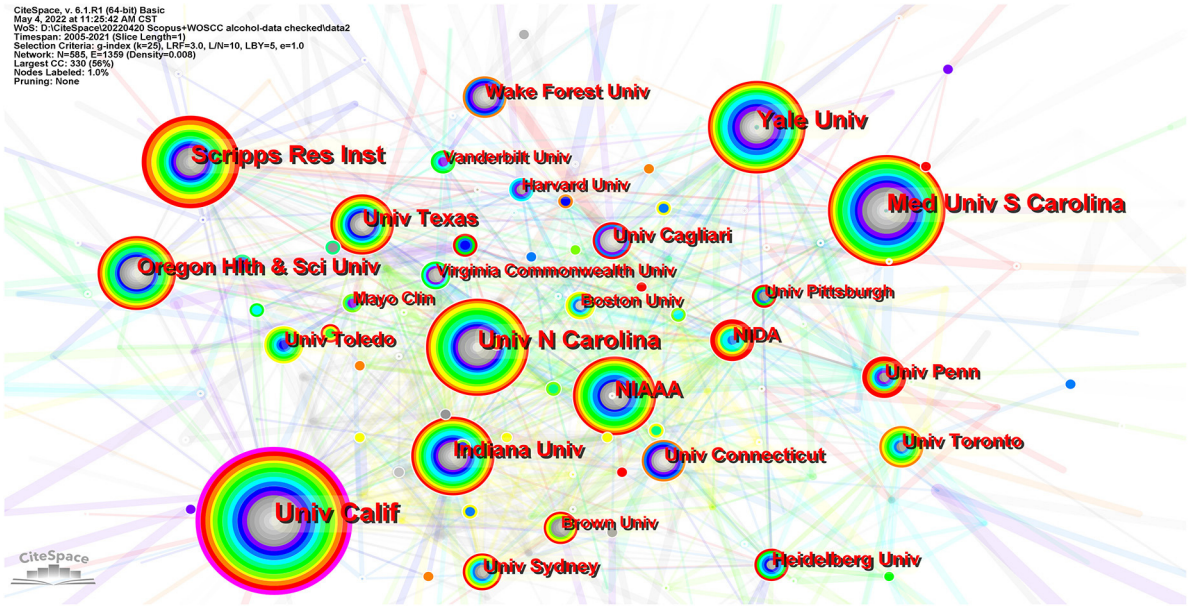

FIGURE 4
The major productive co-institutions in this field. Each node represents one institute. The size of a node represents the number of citations, and the color indicates citation years, from cool to warm representing early to recent. The links suggest collaborative relationships between institutions. Significant nodes are surrounded by a purple ring.

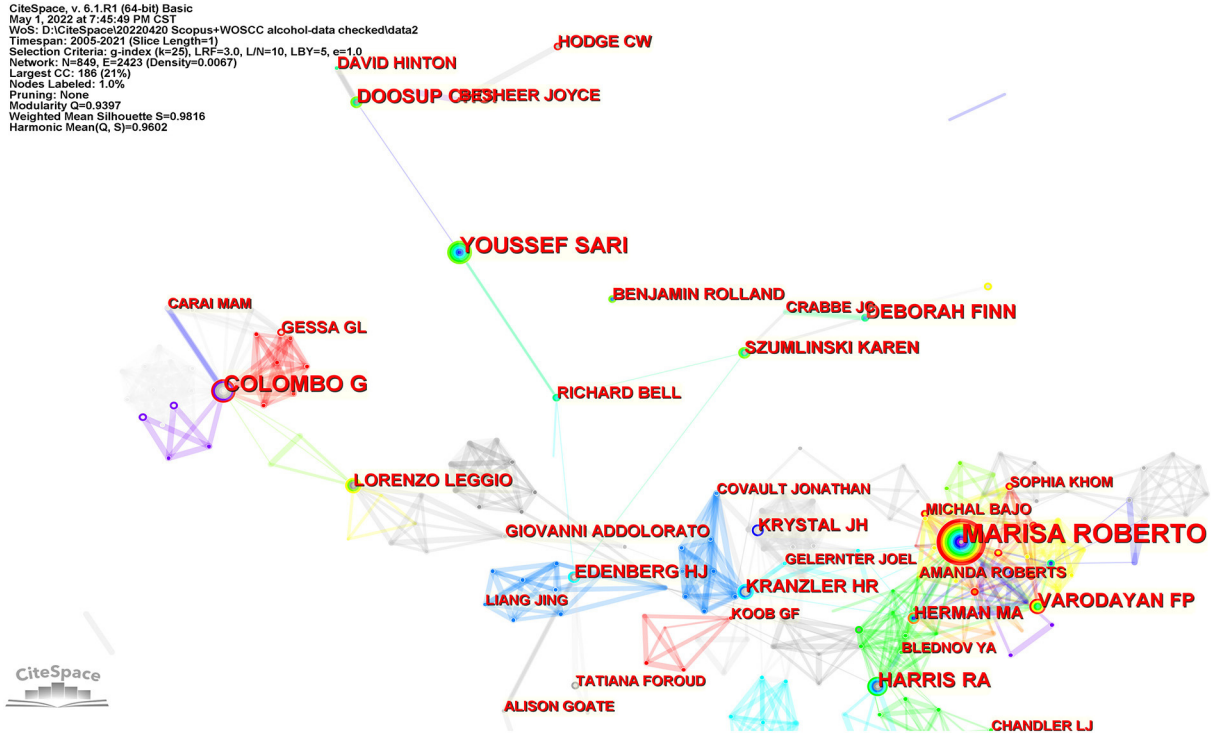

FIGURE 5
The major productive authors in this field. Each node represents one author. The size of a node represents the number of citations, and the color indicates citation years, from cool to warm representing early to recent. The links suggest collaboration relationships between authors.

TABLE 3 The top ten authors related to glutamate and GABA in alcohol use disorder.

Rank	Author	Number of publications	Centrality	Institution
1	Roberto M	57	0.06	Scripps Res Inst
2	Colombo G	36	0.02	National Research Council
3	Sari Y	32	0.01	University of Toledo
4	Harris R	27	0.01	University of Texas
5	Choi D	21	0.01	Mayo Clinic
6	Varodayan F	21	0.00	Scripps Research Institute
7	Finn D	23	0.01	Oregon Health & Science University
8	Kranzler H	29	0.04	University of Pennsylvania
9	Edenberg H	22	0.01	Indiana University
10	Szumlinski K	27	0.01	University of California

the treatment of alcohol use disorder, including acamprosate, baclofen and COR659.

Analysis of keywords

A keyword co-occurrence knowledge map was generated by WOSviewer (Figure 7). The font size of the keywords represents their frequencies in records. The highest landmark nodes, such as human, non-human, clinical trial, controlled study, and animal experiment, represented the objects and methods of research. The keywords that occurred more than ten times were organized into three clusters (Figure 7). The three most frequently used keywords were "human," "alcohol," and "nonhuman." In cluster 1, "alcoholism" is the largest node, and includes review, baclofen, drug efficacy, benzodiazepine, naltrexone, placebo, acamprosate, clinical trial, diazepam, dose response, treatment outcome, drug safety, benzodiazepine derivative, gabapentin, and topiramate. Cluster 1 focuses on clinical studies intended to investigate therapeutic medications for alcohol use disorder. In cluster 2, "alcohol" is the largest node. The other main node includes non-human, glutamic acid, GABA, GABA receptor, addiction, brain, dopamine, NAc, cocaine, NMDA receptor, PFC, hippocampus, and ventral tegmental area. Cluster 2 focuses on neurotransmitter transmission in different brain regions and explores relevant mechanisms for alcohol use disorder. In cluster 3, "human" is the largest node and includes controlled study, metabolism, unclassified drug, genetics, protein expression, oxidative stress, middle-aged, gene expression, signal transduction and non-alcoholic fatty liver. Cluster 3 represents the current research hotspot related to risk factor/biomarker identification and drug development for alcohol use disorder and mechanisms related to alcoholic fatty liver.

A map based on the top 20 keywords with the strongest citation bursts was generated by Citespace (Figure 7). The noticeable keywords in the early stage (2005–2012) included clinical trial, drug mechanism, diazepam, acamprosate, placebo, glutamate receptor, naltrexone, and dose response. In recent years (2013–2021), genetics, non-alcoholic fatty liver, physiology, metabolism, pathology, alcohol use disorder, major clinical study, amino acid, and blood were the main research frontiers. The early stage of research mainly focused on drug development for alcohol-related disorders and mechanisms underlying the involvement of glutamic acid and GABA in alcohol use disorder. The research frontiers are shifting to risk factor/biomarker identification, drug development and the pathology of alcohol use disorder, and the genetics, physiology, pathology and amino acid metabolism of related liver disease.

Discussion

General trends

In this study, bibliometric analyses and network visualizations were conducted to characterize the knowledge domains of glutamate and GABA related to alcohol use disorder. The contributions of countries, institutions, journals, and authors to this field were analyzed. Research frontiers and hot topics in the coming years were also identified. Since 2005, the annual publication number in the field has increased steadily.

The USA has the largest number of publications and citations, the strongest collaborations worldwide, and the highest centrality among countries/regions. The following countries, China, Germany, Italy, Australia, and Korea, accounted for 20% of all studies included, whilst Argentina, Germany, Italy, Australia and the UK constituted 22% of total citations. China ranked second in the total number of publications, but ranked seventh in the total number of citations and ninth in collaboration with other countries/regions, reflecting China's lack of international cooperation in research. The top ten most productive institutions are located in the USA.

TABLE 4 The top ten co-cited references.

Rank	Local citations	Representative author	Publication year	Journal	DOI	Title
1	160	Koob G	2010	Neuropsychopharmacol	10.1038/NPP.2009.110	Neurocircuitry of addiction
2	135	Edenberg H	2004	Am J Hum Genet	10.1086/383283	Variations in GABRA2, encoding the alpha 2 subunit of the GABA(A) receptor, are associated with alcohol dependence and with brain oscillations
3	117	Gass J	2008	Biochem Pharmacol	10.1016/J.BCP.2007.06.039	Glutamatergic substrates of drug addiction and alcoholism
4	115	Lovinger D	1989	Science	10.1126/SCIENCE.2467382	Ethanol inhibits NMDA-activated ion current in hippocampal neurons
5	110	Kumar S	2009	Psychopharmacology	10.1007/S00213-009-1562-Z	The role of GABAA receptors in the acute and chronic effects of ethanol: a decade of progress
6	107	Grobin A	1998	Psychopharmacology	10.1007/S002130050685	The role of GABAA receptors in the acute and chronic effects of ethanol
7	106	Addolorato G	2002	Alcohol Alcoholism	10.1093/ALCALC/37.5.504	Baclofen efficacy in reducing alcohol craving and intake: a preliminary double-blind randomized controlled study
8	106	Kalivas P	2009	Nat Rev Neurosci	10.1038/NRN2515	The glutamate homeostasis hypothesis of addiction
9	102	Roberto M	2004	J Neurosci	10.1523/JNEUROSCI.3004-04.2004	Cellular/molecular increased GABA release in the central amygdala of ethanol-dependent rats
10	99	Roberto M	2003	P Natl Acad Sci USA	10.1073/PNAS.0437926100	Ethanol increases GABAergic transmission at both pre- and postsynaptic sites in rat central amygdala neurons

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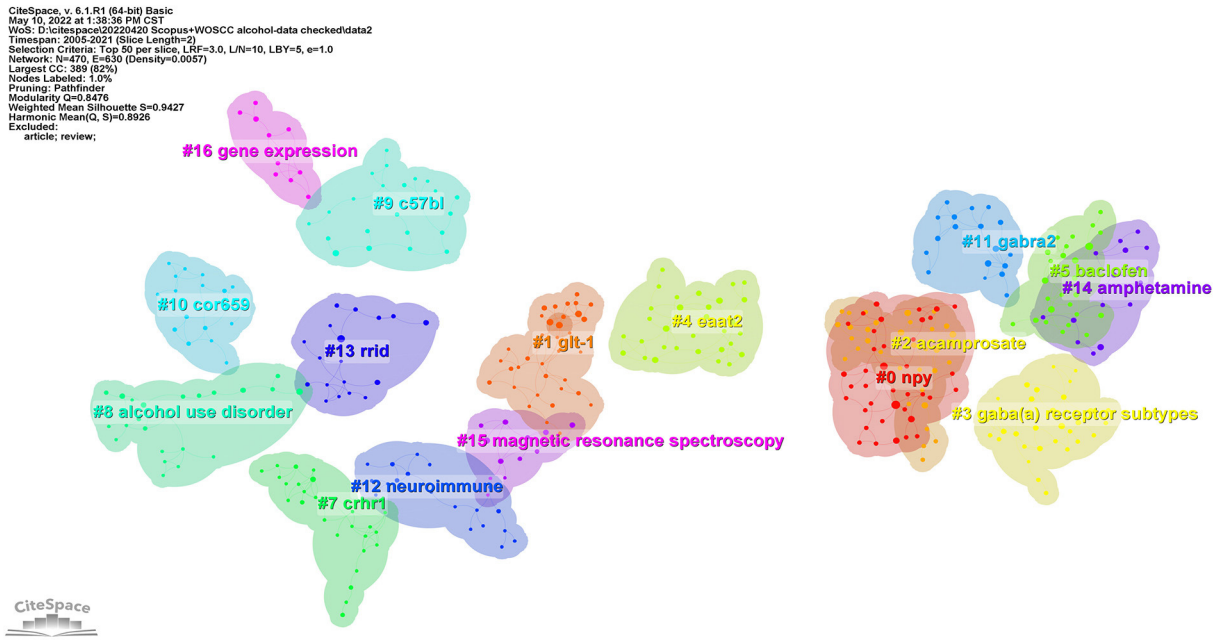

FIGURE 6
The network map of the cited references.

Therefore, the USA is currently the world leader in this research domain, and has a significant impact on the direction of research in this field.

Influential authors and affiliations

Three of the most prolific authors were Marisa Roberto (Scripps Research Institute, USA), Giancarlo Colombo (National Research Council, Italy), and Youssef Sari (University of Toledo, USA). Each of them was in discrete collaborative relationships. Marisa Roberto, Florence P. Varodayan, Amanda Roberts, Sophia Khom, and Michal Bajo, from the Scripps Research Institute, formed a close collaborative relationship, in which Melissa Herman from the University of North Carolina, R. Adron Harris, and Blednov Y.A. from the University of Texas participated. With the largest number of documents and the highest number of citations, Dr. Marisa Roberto is the most important researcher in this collaboration. Marisa Roberto identified the key role of the CeA in alcohol use disorder and that aberrant amygdala GABA transmission was associated with alcohol use disorder (25). Her most cited article was about the key role of CRF-induced amygdala GABA release in alcohol dependence (26). She has recently focused on the impact of interleukin (IL) on CeA transmission (27, 28) and the sex difference (29) associated with alcohol use disorder.

Giancarlo Colombo, Gian Luigi Gessa, and Mauro A. M. Carai, affiliated to the National Research Council of Italy, form a close collaborative relationship. Dr. Giancarlo Colombo is the most important researcher in this collaboration. He mainly focuses on the role of positive allosteric modulators targeting the $GABA_B$ receptor in drinking behavior. His most co-cited document was about baclofen-induced reduction of alcohol reinforcement in alcohol-preferring rats (30). Recently, he has focused on preclinical investigations of novel positive allosteric modulators of the $GABA_B$ receptor as treatments for alcohol use disorder (31, 32).

Youssef Sari (University of Toledo), Karen Szumlinski (University of California), Deborah Finn (Oregon Health &Science University), Howard J. Edenberg (Indiana University), Richard L. Bell (Indiana University), and Liang Jing (University of Southern California) are in a loose collaborative relationship, in which Youssef Sari is the most important researcher. Dr. Youssef Sariis concerned with the association between brain glutamate homeostasis and substance abuse, and evaluates medications such as antibiotics targeting glutamate transporters to reduce ethanol consumption. His most co-cited document was about the use of ceftriaxone, a beta-lactam antibiotic, as a potential drug to reduce ethanol consumption in alcohol-preferring rats (33). He has recently investigated how antibiotics influence xCT and GLT-1 modulation of glutamate (2, 34).

In addition, Henry R Kranzler (University of Pennsylvania), John Krystal (Yale University), Jonathan M. Covault (UConn John Dempsey Hospital) and Joel Gelernter (Yale University), were in a collaborative relationship. Although the University of California is the most prolific institution, collaboration was not detected among its researchers.

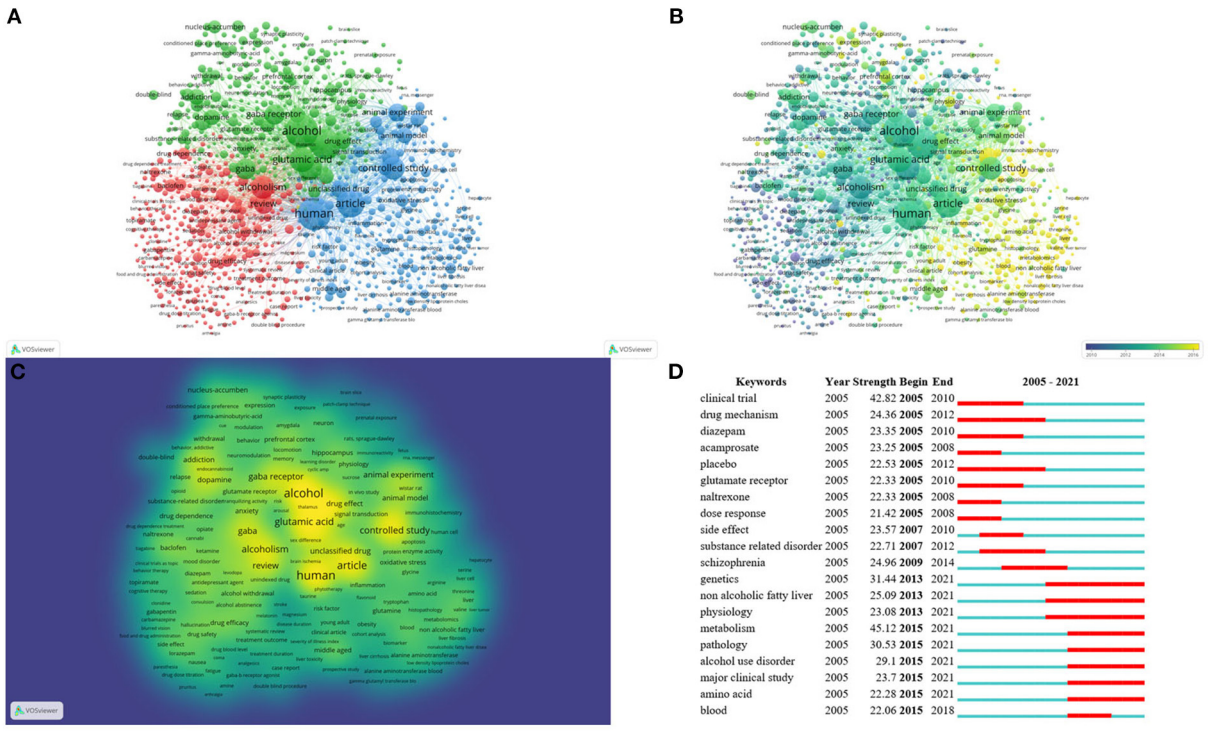

FIGURE 7
Keyword analysis. Co-occurrence analysis of keywords by WOSviewer, including **(A)** cluster visualization for keywords of studies, **(B)** time trend visualization of keywords (average publication year from blue to yellow indicating from earlier to later), and **(C)** density visualization of keywords (keywords in yellow represent the highest frequency). Also shown are the top 20 keywords with the strongest citation bursts according to Citespace **(D)**, in which the blue part indicates the time interval, and the red part indicates the duration of the citation burst.

Dr. George F. Koob, director of the National Institute on Alcohol Abuse and Alcoholism (NIAAA) at the National Institutes of Health, is an expert on substance addition not restricted to alcohol abuse. He conceptualized the substance addiction process into three stages (binge/intoxication, withdrawal/negative affect, and preoccupation/anticipation) and three domains of dysfunction (incentive salience/pathologic habits, negative emotional states, and executive function, respectively) *via* changes in the basal ganglia, extended amygdala/habenula, and frontal cortex (23). Koob et al. proposed the term "hyperkatifeia", defined as a greater intensity of negative emotional/motivational signs and symptoms during withdrawal from drugs of abuse in the withdrawal/negative affect stage of the addiction cycle, providing an additional source of motivation for compulsive drug seeking via negative reinforcement in his latest review (35).

Outlook

Our co-occurrence network maps, clustered by keywords and co-cited references, indicate that the current hot topics and future directions in the association of glutamate and GABA with alcohol use disorder may be divided into several branches: clinical study and novel drug development; biomarker identification; neuropathology; risk factors. A short synopsis of the main trend topics is shown in Table 5.

TABLE 5 The synopsis of the main trend topics.

(1) Major clinical studies show baclofen as a treatment for alcohol dependence is still premature.
(2) Biomarkers such as gut microbial fingerprint, DNA methylation in GABA receptor genes, and blood metabolites have been identified for alcohol use disorder.
(3) Abnormal glial cell functions are promising neuropathology for alcohol use disorder.
(4) Females are more likely to develop alcohol use disorder.

Major clinical studies

Recently, multiple clinical studies have been conducted in different countries to evaluate the efficacy of baclofen in

the treatment of alcohol dependence. However, the efficacy of baclofen was questioned. Baclofen did not show superiority over placebo in the maintenance of abstinence, while causing a reduction in alcohol consumption and craving, as observed in the ALPADIR study (36). The efficacy and safety of high doses of baclofen for the treatment of alcohol dependence were also examined in a multicenter, double-blinded, and placebo-controlled trial. The results indicated that large-scale prescription of baclofen for the treatment of alcohol dependence seems premature and should be reconsidered (37). Another multisite, double blind, placebo-controlled, randomized clinical trial indicated that baclofen may be an effective treatment option for patients with alcoholic liver disease (38). However, baclofen is not as good as chlordiazepoxide in the treatment of uncomplicated alcohol withdrawal syndrome (39). Several systematic meta-analyses have been conducted to investigate baclofen as a treatment for alcohol use disorders. Baclofen was associated with higher rates of abstinence than placebo, but showed no superiority in increasing the number of abstinent days, or decreasing heavy drinking, craving, anxiety, or depression (40). The long-term utility of baclofen at both normal and high doses in the treatment of alcohol use disorder was also questioned (41). Therefore, the use of baclofen as a treatment for alcohol dependence is premature and needs to be confirmed in large-scale clinical trials.

Biomarkers

Several potential blood biomarkers for alcohol use disorder have been found. Liu et al. (42) conducted an epigenome-wide association study of the methylation of cytosine-phosphate-guanine dinucleotide sites in 13 population-based cohorts and identified an alcohol-related DNA methylation signature. Differential methylation in two GABA receptor genes ($GABA_A\delta$ and $GABA_B$ subunit 1) was found. Analysis of DNA methylation may be a promising diagnostic test for heavy drinking. Harada et al. (43) identified nineteen metabolites associated with alcohol intake, and three biomarker candidates (threonine, guanidinosuccinate, and glutamine) for alcohol-induced liver injury by using metabolomics, indicating that the glutamate/glutamine ratio might be a good biomarker for alcohol-induced liver injury. Hyperhomocysteinemia is associated with liver and metabolic diseases. Small heterodimer partner (SHP) inhibits the transcriptional activation of betaine-homocysteine S-methyltransferase and cystathionine γ-lyase by FOXA1. Disruption of SHP in mice alters the timing of expression of genes that regulate homocysteine metabolism and the liver responses to ethanol and homocysteine (44).

Patients with alcohol use disorder present some types of specific gut microbial fingerprint. Alcohol induces gut dysbiosis in human patients and rodent models with alcohol use disorder. Changes in the gut flora were correlated with increased impulsivity, vulnerability, and striatal dopamine 1 receptor expression as well as decreased striatal dopamine receptor 2 expression (45). Moreover, the gut microbiota play a critical role in the progression of alcohol-related liver damage, and interactions between the gut microbiome and liver diseases have been found. Addolorato et al. (46) characterized the gut microbial composition and function in patients with alcohol-associated liver disease (AALD). The alcohol use disorder-associated gut microbiota showed an increased expression of GABA metabolic pathways and energy metabolism. In patients with alcohol use disorder, increased endotoxaemia, systemic inflammatory status, and functional alterations may be involved in the progression of AALD and in the pathogenesis of alcohol use disorder. However, the altered microbial communities vary in different studies, probably owing to differences in alcohol administration regimen and concomitant liver disease (47), so the findings need to be verified.

Neuropathology

Research on neuropathology associated with alcohol is increasing recently. Astrocytes are critical constitutions of the brain glutamate–glutamine cycle and play an important role in synaptic glutamate homeostasis. The expression of glial fibrillary acidic protein, a biomarker of astrocyte function, alters following short-term and long-term exposure to alcohol (48). Various glutamate transporters (i.e., GLAST/EAAT1, GLT-1/EAAT2 and xCT) expressed on astrocytes are dynamically regulated by acute and chronic alcohol exposure. Adermark et al. (49) reviewed prominent features displayed by astrocytes and how these properties are influenced by acute and long-term alcohol exposure. Microglia is regarded as "cleaner" of the central nervous system. Alcohol activated the microglia and increased expression of multiple pro-inflammatory cytokines such as tumor necrosis factor α and IL-1β, which may enhance alcohol consumption and contribute to the development of alcoholism. IL-1β mediated ethanol-induced neuroinflammation and interacted with ethanol's effects on CeA GABAergic signaling (50). The innate immune system may also be activated when exposed to excessive ethanol. Toll-like receptor 4 and CD14 signaling are important in the effects of acute ethanol exposure on GABAergic transmission in the CeA (51). In summary, glial cells might be an important target for the development of next-generation treatments for alcoholism.

Risk factors

Peltier et al. (52) discussed the critical structures and neurotransmitters underlining sex differences in stress-related alcohol use, the involvement of sex and stress in alcohol-induced

neurodegeneration, and the role of ovarian hormones in stress-related drinking in a review. Women are generally more likely to drink to regulate negative affect and stress reactivity. Sex differences in the onset and maintenance of alcohol use begin to develop during adolescence, continue to affect alcohol use into adulthood, and may contribute to chronic and problematic alcohol use.

Limitations

To the best of our knowledge, this is the first bibliometric analysis to investigate the current status and research trend for glutamate and GABA in alcohol use disorder. However, our analyses have some limitations. First, because the publication language was restricted to English, potential studies in other languages were omitted. Second, the analyses might have been affected by the presupposed criteria of selection. Taking keywords analysis for example, the threshold of keyword occurrence was ten and keywords with occurrence smaller than ten were not included in subsequent analysis. Therefore, latest research trends with related keywords were omitted. Third, the analyses were conducted based on the number of publications and citations as well as centralities to date. For some recently published important studies with low citation frequency, their contributions may have been underestimated.

Conclusion

Our bibliometric analysis showed that glutamate and GABA continue to be of interest in alcohol use disorder. The USA is a major contributor to knowledge in this field, with the highest number of top institutions and collaborations. Marisa Roberto of the Scripps Research Institute is the most productive author from the largest collaborative relationship. George F. Koob of NIAAA is an expert who has made a significant contribution in substance addiction. The keywords indicate that the focus has evolved from mechanisms and medications targeting glutamate and GABA in alcohol use disorder, to novel drug development, risk factor/biomarker identification in alcohol use disorder, and mechanisms of liver diseases. Our study provides valuable information on potential collaborators and institutions in this field and provides an insight into the developing trends, which may guide new directions for further study.

Data availability statement

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

Author contributions

ZW and XN designed the study and retrieved the data. ZW performed the statistical analysis and wrote the first draft. XZ made further modifications. DS and YW supervised the whole process and provided modification advice. All authors contributed to the article and approved the submitted version.

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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.

Publisher's note

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Role of maintenance treatment on long-term efficacy of bilateral iTBS of the prefrontal cortex in treatment-seeking cocaine addicts: A retrospective analysis

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CUD, like other addictions, is a chronic disease characterized by a high rate of relapse and drop-out (DO) from medical and behavioral treatment programs, which is positively correlated with relapse. Repetitive transcranial Magnetic Stimulation (rTMS) protocols have shown therapeutic potential in addiction in the short term, but only a few studies have explored their long-term efficacy, so far. This study explores the long-term outcome of bilateral intermittent theta-burst stimulation (iTBS) of the prefrontal cortex (PFC) in cocaine use disorder (CUD) and the possible influence of maintenance treatment in improving abstinence and decreasing DO rates. Eighty-nine treatment-seeking CUD patients were exposed to 20 sessions of iTBS. At the end of the treatment 61 (81%) abstinent patients underwent a 12 months follow-up. Among these, 27 patients chose to follow a maintenance treatment (M), whereas 34 patients chose not to adhere to a maintenance treatment (NM). Overall, among patients reaching the 12 months follow-up endpoint, 69.7% were still abstinent and 30.3% relapsed. In NM-patients the DO rate was significantly higher than in M-ones (58.82 vs. 29.63%). The present observations show the long-term therapeutic effect of bilateral PFC iTBS to decrease cocaine consumption. Moreover, they underline the importance to perform a maintenance protocol to consolidate abstinence and decrease DO rates over time.

KEYWORDS

cocaine use disorder, intermittent theta burst stimulation (iTBS), addiction, follow up, drop out, repetitive Transcranial Magnetic Stimulation (rTMS)

Introduction

Cocaine use disorder (CUD) is a chronic, relapsing brain disease, causing health and social problems; cocaine, after cannabis, represents the second most widely used illegal substance in Europe (1, 2). As with other addictions, CUD patients show a high rate of relapse, up to 74% within the first 3 months (3, 4). Vulnerability to drug relapse depends on several factors (4, 5), among which a long-lasting reduced release of dopamine is thought to play a pivotal role (6–9). Many pharmacological and behavioral approaches have been conducted to treat CUD but the results are far from encouraging showing high dropout rates and poor medication adherence (10). Psychosocial approaches such as cognitive-behavioral therapy (CBT) and contingency management (CM) display good efficacy after short and long-term treatment in psychostimulant addiction either alone or in combination, but they are time-consuming, expensive, and often display high drop-out rates (11–14). Among the non-pharmacological strategies, repetitive Transcranial Magnetic Stimulation (rTMS) has shown therapeutic potential in treating substance and behavioral addictions targeting focal or wide bilateral areas of the brain (15). The ability of rTMS to induce long-lasting therapeutic effects relies on several mechanisms such as neurotransmitter release, modulation of synaptic activity, and expression of neurotrophic factors at the site of stimulation and in distant connected areas, thus modulating Hebbian plasticity of entire brain networks (15–17). According to the so-called "addiction cycle" described by Koob and Le Moal (18), addiction is characterized by an altered functionality of the prefrontal cortex and basal ganglia, resulting in impairment in decision making and reduced sensitivity to natural rewards; furthermore, an increase in stress-conditioned responses, modulated by the limbic system, occurs. Indeed, TMS strategies in CUD are either directed to enhance the reduced functionality of the prefrontal areas with excitatory protocols or to decrease the excessive functionality of the limbic system with inhibitory ones (19). Both approaches have shown ability in reducing cocaine intake and craving (20–24) and in modulating cue-induced responses (25), but the heterogeneity of protocols among different studies has hindered a standardization of protocols thus lowering the level of evidence for the therapeutic use of rTMS in CUD and other addictions (15). Theta-burst stimulation (TBS) protocols that mimic hippocampal endogenous theta rhythms can induce synaptic long-term potentiation (LTP) and depression (LTD), in their intermittent and continuous patterns, respectively (26, 27). TBS protocols were thought to induce longer-lasting effects on brain plasticity than conventional protocols, but a large-scale study on depression has shown a similar short- and long-term efficacy of intermittent TBS (iTBS) compared to conventional protocols in reducing depressive symptoms (28). The main advantage of this protocol is its short duration leading to more tolerability and time saving than other rTMS protocols. Indeed, iTBS has shown therapeutic potential in CUD and other forms of addiction when applied to prefrontal areas with similar efficacy as high-frequency conventional stimulation (23, 24). Nevertheless, although TBS and other rTMS protocols have shown promising results in the short term, only a few studies have studied long-term outcome and the role of maintenance treatment for consolidating long-term abstinence, with conflicting results (29–31).

Based on this evidence, the aim of this study was to retrospectively explore the long-term efficacy of bilateral prefrontal cortex (PFC) iTBS in CUD and the effect of a maintenance iTBS treatment on long-term abstinence and follow-up adherence.

Methods

Experimental design

This is a retrospective analysis of data from clinical records of 89 CUD patients referring to an outpatient clinic from 2018 to 2021. Patients provided written informed consent to disclose their clinical data for research, anonymously. The consent form included all information regarding the nature of the TMS treatment and possible side effects. The Chief Medical Officer of the outpatient clinic approved the study and gave permission to access patients' clinical records for research scopes following Italian Legislative Decree No. 196 of June 30, 2003, "Personal Data Protection Code." The study endorsed the Principles of Human Rights, as adopted by the World Medical Association (18th WMA General Assembly) in 1964 in Helsinki (Finland) and then amended by the 64th WMA General Assembly in 2013 in Fortaleza (Brazil). As described in Figure 1, 89 CUD patients were included in the study. Patients were treated with iTBS applied bilaterally to PFC for 20 sessions. Follow-up was performed in patients that resulted stably drug-free at the end of the treatment. Among these, 27 patients underwent maintenance sessions of iTBS (one treatment a week for 1 month followed by one treatment every 2 weeks for 2 months) while 34 drug-free patients chose not to perform a maintenance treatment. Patients and their relatives/caregivers were asked to perform urine tests at the clinic or at home once a week. Data were collected at 3, 6, and 12 months.

Patients

Eighty-nine treatment-seeking outpatients, diagnosed according to DSM-V criteria (32) were enrolled in the study. Inclusion criteria were: age between 18 and 65 years, current CUD (i.e., have a positive urine drug screen for cocaine), motivation to stop intake, and ability to understand and sign the informed consent. Exclusion criteria were: medical

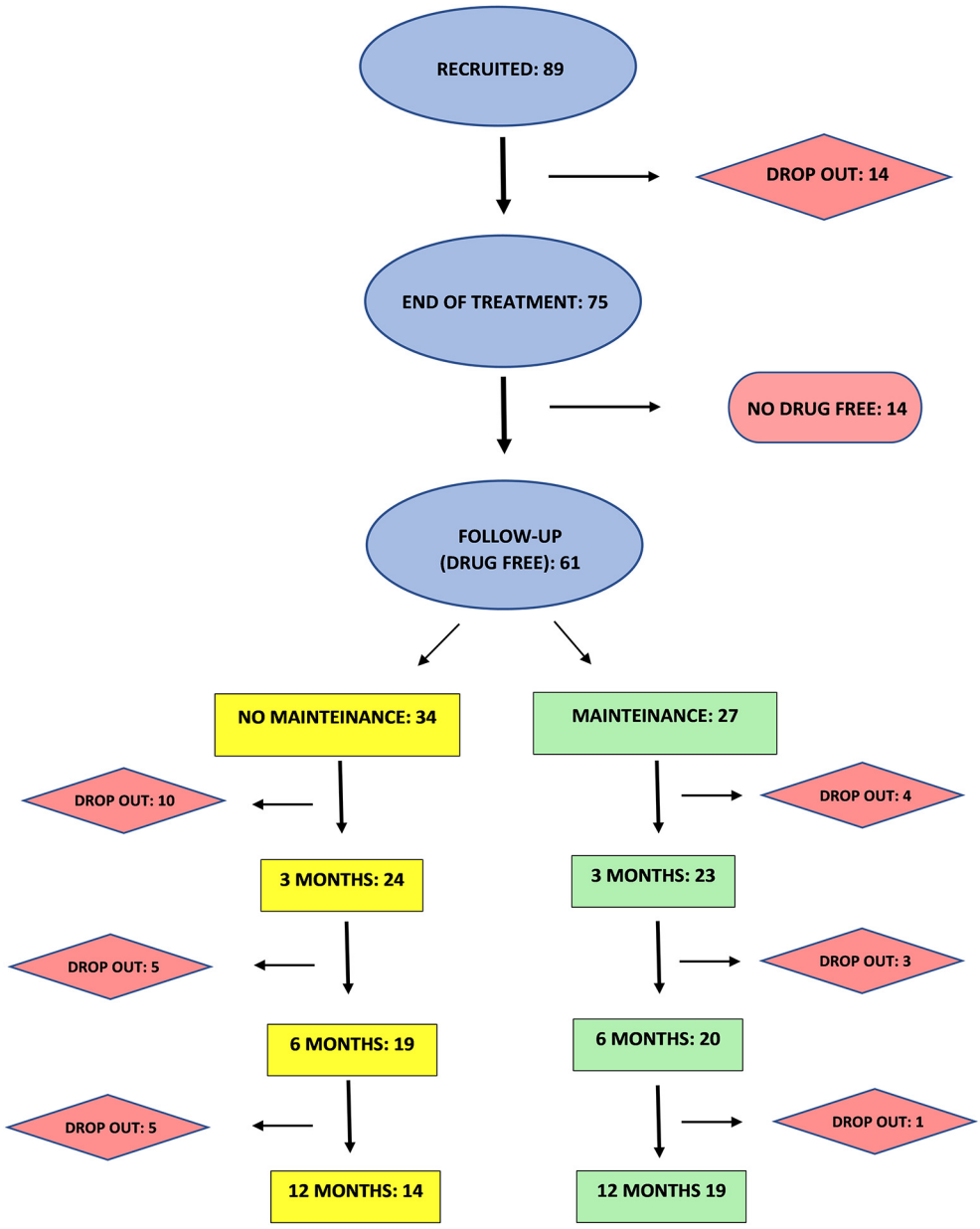

FIGURE 1
Experimental procedure flow-chart.

devices (pacemaker, metal implants, devices for inflating), epilepsy, and pregnancy (33). The screening included medical history, physical and in-depth neurological examinations. Patients were asked about the weekly amount of cocaine consumed at baseline, at the end of rTMS treatment, and throughout follow-up; cocaine consumption was evaluated twice a week through a commercially available urine drug screen test (Home Health Ltd., Hertfordshire, United Kingdom).

Intermittent theta burst stimulation

Magstim Rapid stimulator (Magstim Company, Whitland, Wales, UK) was used along with H4-Coil (Brainsway Ltd., Jerusalem, Israel) specifically designed to stimulate bilateral PFC and insula symmetrically (34, 35). Subjects received 20 stimulations over 4 weeks as previously described (23). ITBS protocol consisted of bursts containing 3 pulses at 50 Hz repeated at 200-ms intervals for 2 s (i.e., at 5 Hz). A 2-s train of

iTBS was repeated every 10 s for 190 s and 600 pulses (26). The intensity was set at 100% of the visual resting motor threshold (RMT). For maintenance treatment 1 weekly session of iTBS was administered for 2 months.

Statistical analysis

GraphPad Prism 8.01 software (San Diego, CA, USA) was used. To compare demographic features, multiple independent samples Student's *t*-test and Chi-Squared test were performed for normally distributed variables and categorical variables, respectively.

Results

Table 1 shows the demographic and clinical features of patients involved in the study and the rate of side effects induced by iTBS. Treatment was well tolerated and side effects were mild and transient, when observed.

TABLE 1 Baseline socio- demographic and clinical characteristics of the sample. Data are expressed as mean and (standard deviation) or (percentage).

Patients		***n* = 89**
Gender (F/M)	F	8
	M	81
Age (yr)		36.7 (9.1)
Duration of cocaine use (years)		13.2 (7.4)
Weekly cocaine amount (g)		8.7 (7.6)
Route of administration	Inhalation	65
	Smoke	17
	Injective	7
Psychiatric comorbidities		28 (31%)
	Mood disorder	8
	Personality disorder	6
	Anxiety	14
Psychoactive prescription drugs		36 (40%)
	Mood stabilizers	9
	Benzodiazepines	11
	Antidepressants	9
	Antipsychotics	7
Other actual addictions		61 (69%)
	Nicotine	61
	Alcohol	33
	Gap	12
	Heroin	6
	Cannabis	18
rTMS side effects		28 (31%)
	Headache	10
	Dizziness	2
	Sleepiness	16
	Insomnia	9

Effect of 20 sessions of ITBS on cocaine consumption

Eighty-nine patients were recruited, among which 14 did not complete the treatment. As shown in Figure 1, 61 (81%) of patients completing the 20 sessions treatment were found stably negative in at least three consecutive urine tests at the end of the treatment, while 14 (19 %) were still positive.

Long-term follow-up on drug-free patients

The 61 patients resulting drug-free after 20 iTBS sessions were included in the follow-up. Segregating by maintenance treatment, as shown in Table 2, both M and NM patients display a similar rate of abstinence at 3, 6, and 12 months respectively, with no significant differences between groups for positive and negative rates at every time point.

Drop-out rates

Figure 2 depicts the drop-out (DO) rates at different time points in M and NM patients. A significantly higher rate of total DO in the NM group was found, reaching 58.82 % of enrolled patients vs. 29.63 % in the M group (Fisher exact test $p = 0.04$). Moreover, DO rates in the NM group show a tendency to be higher at every time point of follow-up, (as compared to the M group) reaching a statistically significant difference at 12 months (Fisher exact test $p = 0.04$; NM= 26.3%, M = 5.0 %).

Discussion

Our data confirm our previous observation on the efficacy of bilateral iTBS in the treatment of CUD, as previously shown in a pilot study performed in a smaller sample (23). Importantly, the present data also shows that a 20-session protocol of iTBS may promote long-term abstinence in CUD patients and it suggests that a maintenance iTBS treatment increases follow-up adherence and decreases drop-out rates.

The main therapeutic issue in addiction is the long-term efficacy of pharmacological and non-pharmacological treatments; indeed, addiction is considered a chronic disease with a high relapse rate after different therapeutic approaches

TABLE 2 Cocaine positive and negative patients at 3, 6 and 12 months of follow up in maintenance and no-maintenance group. Data are expressed as raw data and percentages.

Time		Maintenance				No maintenance			
		Negative	Positive	Drop out	Total	Negative	Positive	Drop out	Total
3 months	N	17	6	4	27	18	6	10	34
	%	63.0	22.2	14.8	100.0	52.9	17.7	29.4	100.0
6 months	N	14	6	3	23	15	4	5	24
	%	60.9	26.1	13.0	100.0	62.5	16.7	20.8	100.0
12 months	N	13	6	1	20	10	4	5	19
	%	65.0	30.0	5.0	100.0	52.6	21.1	26.3	100.0

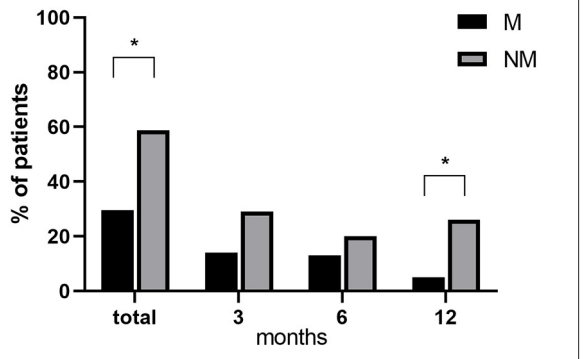

FIGURE 2
Differences in drop-out rates between M and NM at different time points. $^{*}p < 0.05$ M vs. NM.

even in treatment-seeking patients (36–38). rTMS protocols targeting prefrontal areas have shown therapeutic efficacy in several types of addiction, including CUD, due to their ability not only in reducing drug consumption but also in ameliorating the psychological burden related to addiction (15, 22). Despite a proven short-term efficacy of rTMS treatments in CUD and other addictions, only a few studies have explored the long-term efficacy of neuromodulation: a recent metanalysis (31) shows that rTMS can reduce craving and promote abstinence from different drugs (and overeating) in short, mid and long-term. Indeed, previous studies have shown a long-term efficacy of an acute rTMS treatment in different SUDs (29, 39); on the other hand, a recent randomized, double-blind, sham-controlled multi-center study on 42 treatment-seeking CUD patients, showed no difference between real and sham stimulation in reducing cocaine craving and consumption in short and mid-term, but a marked reduction in depressive symptoms only in the real TMS patients undergoing a maintenance treatment (40). Maintenance sessions are currently proposed for different chronic disorders such as depression, but the length and frequency of sessions vary widely among different studies. Madeo et al. (30) showed that a maintenance treatment improves the efficacy of rTMS in CUD, which outlasts the reduction of treatment frequency throughout follow-up; conversely, a previous study on nicotine addiction (41) showed that rTMS can reduce cigarette smoking only in an acute setting, while the effect tends to dissipate when the sessions are less frequent.

It is well known that the heterogeneity of different studies is due to different factors, among which target area and parameters of stimulation may play an important role (8, 23, 29). Indeed, we used an iTBS protocol which is able to induce long-lasting effects on brain plasticity modulating different cellular mechanisms and whose parameters are less prone to be changed (27, 42). When considering addiction as a "*whole brain*" disease, the use of H-coil, which delivers a simultaneous stimulation of both prefrontal cortices (43), may, in theory, boost higher levels of dopamine and influence plasticity of several areas of both hemispheres which, in turn, may modulate different behavioral and cognitive processes involved in addiction neural underpinnings (8, 44). Accordingly, our data show the efficacy of bilateral iTBS of the prefrontal cortex in reducing cocaine consumption and promoting abstinence in the short and long term; moreover, they show that maintenance treatment is associated with a significantly lower percentage of drop-out rates, suggesting a better efficacy in the long term.

Drop-out is one of the main problems interfering with addiction therapies outcome (45); it has been shown that a high drop-out rate in psychosocial and pharmacological treatments is a relapse predictor (37, 45) depending on several factors, among which duration of treatment is positively associated with a better outcome (45). This is not surprising, since CUD, and SUD in general, are by definition chronic relapsing diseases and vulnerability to relapse remains high even after detoxification programs and correlates with a persistent blunted dopamine transmission and impaired executive functions (46, 47). Thus, it becomes of primary importance to keep patients' motivation and adherence to treatment to limit the relapse rate as shown in psychosocial interventions such as contingency management and cognitive-behavioral therapies (13, 48). Present data show that CUD patients undergoing a maintenance treatment display a significantly higher adherence to follow-up compared to

those who did not, which display 59% of drop-out rates. Thus, based on the above-mentioned evidence, although we measured similar abstinence rates between groups, it can be inferred that the percentage of relapse to cocaine use might be higher in the NM group due to the high percentage of drop-out rates.

Limitations

This paper has several limitations that we must recognize. First of all, this study lacks a control group since data originate from observations in treatment-seeking patients who voluntarily underwent rTMS; indeed, previous studies on SUD have shown no differences between sham and real stimulation in reducing drug intake in the short term, while significant differences emerged in the follow up (29, 49); we may speculate that is probably due to a *placebo* effect of the treatment which tend to vanish overtime. Another limit concerns the follow-up data that are mostly obtained from telephone interviews with patients and/or caregivers doing at-home urine tests. Further, in our sample the percentage of female patients is very low, which is a common problem in rTMS addiction studies (15); however, a recent paper on women with methamphetamine use disorder showed the same responsiveness to rTMS, as compared with men (50). Indeed gender differences should be better explored taking into account hormonal, psychological and cognitive indicators (51). Lastly, we did not perform any psychometric measure which might be helpful to investigate whether abstinence is accompanied by a change in mood parameters or executive functions, as already described by other authors for rTMS and other SUD treatments (5, 22, 40, 52).

Conclusions

In conclusion, despite these limits, this paper confirms the effectiveness of iTBS in treating CUD in the short term and extends these observations to the long term. It shows that maintenance treatments may promote a better adherence to follow-up suggesting an improvement in long-term abstinence, thereby preventing relapse.

Data availability statement

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

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study.

Author contributions

AS, PB, GC, and MD conceived the study and designed the experiments. MD supervised the research. AS, VB, MCDV, GS, and LM performed the study. AS and VB analyzed the data. AS, PB, VB, and MD discussed the data and prepared the manuscript. All authors read and approved the final manuscript.

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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.

Publisher's note

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The impacts of academic stress on college students' problematic smartphone use and Internet gaming disorder under the background of neijuan: Hierarchical regressions with mediational analysis on escape and coping motives

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With sluggish economic growth in the post-pandemic era, the phenomenon "neijuan" becomes increasingly severe in many Asian countries like China. Neijuan refers to a hypercompetitive social environment wherein individuals involuntarily get involved in inhumane work or study hours, resulting in a considerable amount of tension and stress. Previous pathology research has shown that stress can trigger the overuse of Internet-based devices and services, which can subsequently lead to problematic smartphone use (PSU) and Internet gaming disorder (IGD). Provided college students are generally deemed one of the groups most susceptible to neijuan, limited attention has been given to the stimuli and the resultant psychological and behavioral ill-beings. Our study examined the impacts of academic stress on Chinese college students' PSU and IGD problems, with the inclusion of escape and coping motives as mediators. Based upon the results of hierarchical regressions and path analysis, we found that whereas academic stress increased IGD tendency mediated through escape and coping motives, excessive use of smartphone might have developed into a habitual behavior rather than effective escape and coping instruments. Demographic and academic characteristics, such as gender and whether studying at a prestigious institution, also exerted influences on college students' IGD intensity.

KEYWORDS

academic stress, problematic smartphone use, Internet gaming disorder, neijuan, escape, coping, China's education problems, behavioral addictions

1. Introduction

In addition to COVID-induced depression (1, 2), college students have to cope with substantial academic stress in the post-pandemic era, especially in Asian countries like China. As of 2022, there are 44.3 million students attending colleges and universities in China, not only making it home to the largest higher education system in the world (3) but also producing over 10 million graduates poised to enter the workforce (4). In view of this trend, academic performance deserves elevated importance mainly for two reasons. First and foremost, the pessimistic prospects about economic growth and grossly exacerbated difficulties in job search and employment have cultivated a prevailing fear of "neijuan," which refers to a hypercompetitive social environment wherein individuals are forced to get involved in inhumane work or study hours, rather than creativity and innovation, as the sole means of maintaining and/or increasing their socioeconomic status (5). The phenomenon of neijuan highly resembles the "prisoner's dilemma" (6) in game theory, meaning someone's improvement in wellbeing occurs at the expense of others as opposed to additionally created wealth of the whole society. Notably, neijuan is most commonly observed among college students and high-tech employees in China (7). For many college students, graduate programs can be regarded as a temporary shelter, where they are allowed to wait for the economy to recover whilst gaining relevant skills and knowledge. In the face of relatively scarce opportunities of graduate admission, which are earned primarily by participating in a national test called *kaoyan*, today's Chinese college students have to put forth disproportionate effort to compete for the entry tickets, which can potentially intensify their susceptibility to academic stress. Second, on top of the rampant neijuan phenomenon, multiple incidents of academic plagiarism scandals in China's higher education institutions over the recent years have urged the administers to enact much more strict rules and policies on thesis and dissertation defenses (8), ending up with an enlarged number of student complaints about the increasingly demanding graduation requirements.

Previous pathology research has found that stress can readily trigger overuse of Internet-based devices and services (9–11). For example, although playing online games can be conducive to relieving stress, socializing, and enabling escapism from daily routines (12–14), uncontrolled and excessive engagement in Internet gaming tends to be closely aligned with maladaptive psychological and behavioral responses (15). In the education psychology literature, there is a growing body of research that reports a positive association between academic stress and Internet addiction, with particular interest in problematic smartphone use [PSU; (16–18)] and Internet gaming disorder [IGD; (19–21)]. Specifically, bearing striking resemblance to substance abuse, PSU entails withdrawal symptoms if unable to use the phone (22, 23), conflicts with family members or friends (24, 25), and relapses to addictive behaviors following a period of abstinence (26, 27). Aside from "problematic," other terms such as "addictive," "excessive," "compulsive," and "compensatory" have been used to portray PSU symptoms (28). On the other hand, while psychological and clinical studies had started to investigate IGD before smartphones became prevalent, PSU and IGD, having many similar negative outcomes such as those mentioned above, are increasingly examined and discussed in juxtaposition (29–32) considering smartphones' flexibility, portability, and accessibility, which greatly facilitate mobile play (28). Referred to as a "persistent and recurrent use of the Internet to engage in games, often with other players, leading to clinically significant impairment of distress" (p. 795), IGD was identified as a potential psychiatric disorder by the American Psychiatric Association (APA) and included in the third section of the fifth revision of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) (33). Moreover, in light of the growing social concerns surrounding pathological gaming, the World Health Organization (WHO) also incorporated "gaming disorder" in the *International Classification of Disorders*, 11th edition (ICD-11).

The compensatory Internet use (CIU) theory proposed by Kardefelt-Winther, (34, 35) conceptualizes addiction to the Internet as a means of compensating unsatisfied needs originated from the offline setting, which can help individuals cope with depression, anxiety, and stress. Researchers adopting the CIU model to analyze Internet addiction argue that it is warranted to better disentangle the mechanisms mediating the relationship between risk factors (e.g., stress) and pathological use of the Internet (36–38). The relevant literature has extensively explored smartphone and video game users' motivations. Pertaining to stress reduction and relaxation, escape and coping are believed to be important driving forces of prolonged time spent on smartphone usage (39–41) and Internet gaming (13, 14, 42, 43). Specifically, whereas escapism refers to "unidirectional and potentially permanent movement from the physical to the more favorably perceived gaming environment" [(44), p. 3], coping motives reflect "persistently changing cognitive and behavioral efforts in order to manage specific external and/or internal demands that are seen as taxing or exceeding the resources of the person" [(45), p. 3], Prior inquiries into the relationship between academic stress and PSU and IGD were often focused on young adolescents (17–19, 46–48). Provided sluggish economic growth in the post-pandemic era, college students, who have to confront increased difficulties in job search and employment, have become one of the most vulnerable groups to academic stress caused by neijuan. However, little is known about the maladaptive psychological and behavioral effects of neijuan on college students. With this in mind, the present paper aimed to examine how neijuan-related academic stress impacts Chinese college students' PSU and IGD

problems, using escape and coping motives as the mediators. Accordingly, we propose the following hypotheses:

H1a. *Escape motive will mediate the relationship between academic stress and PSU.*
H1b. *Escape motive will mediate the relationship between academic stress and IGD.*
H2a. *Coping motive will mediate the relationship between academic stress and PSU.*
H2b. *Coping motive will mediate the relationship between academic stress and IGD.*

2. Methods

2.1. Participants

We capitalized on WeChat, one of the most widely used instant messaging and social media apps in China, to recruit participants and collected survey responses using the Tencent Questionnaire (https://wj.qq.com/). Specifically, 54 volunteers were recruited from a university in East China to participate in a prior pilot study, and after no major concerns arose, they helped send the survey link *via* personal WeChat account to their acquaintances (e.g., former high school classmates) who were enrolled in college as well. While 602 responses were initially received, 22 of them (3.65%) were dropped because of invalid answers (e.g., "1" or "male" for age; $N = 7$) or the participants not playing any video games at all ($N = 15$). Therefore, 580 valid responses were finally used for analysis. Among the respondents, 259 (45%) were male and 321 (55%) were female, and their ages ranged from 17 to 25 years, with a mean of 19.77 (SD = 1.30). In particular, 12% of the respondents were studying at higher education institutions listed in the so-called "985 and 211 project," which are typically considered prestigious institutions in China [see (49)]. Descriptive statistics of more detailed academic information, including which year of college they were and their GPA rankings, appear in Table 1. We compared both the demographic and academic characteristics between male and female participants and found no significant gender differences in those characteristics. Our study was approved by the Institutional Review Board (IRB) of the university, and voluntary informed consent was obtained from the respondents, who were guaranteed anonymity and confidentiality.

2.2. Measurement

2.2.1. Awareness of neijuan

We used two items to measure the participants' awareness of neijuan. For perceived severity, the respondents were asked to rate the item "Neijuan is common and severe in today's society" on a 5-point Likert scale (1 = *Strongly disagree*, 5 = *Strongly agree*). For concerns, the respondents scored the item "I am concerned about neijuan" also on a 5-point Likert scale (1 = *Strongly disagree*, 5 = *Strongly agree*).

2.2.2. Academic stress

Items for measuring academic stress were adopted from Kohn and Frazer's (50) Academic Stress Scale (ASS), which has already been validated among Chinese college students (51). While the original ASS scale consisted of 35 items, the participants of the pilot study suggested that certain items might be less appropriate or relevant in the contemporary higher education environment of China. For example, students can use their laptops, tablets, or even smartphones to take notes if they do not have pencil/pen with them in class (i.e., the "forgetting pencil/pen" item). In light of this, we conducted exploratory factor analysis (EFA) to determine which items of the original ASS scale can be dropped so as to make a concise survey. Firstly, principal components analysis (PCA) was implemented to extract 35 factors. Second, eight components that have eigenvalues >1 were selected (52). Next, with factor loadings obtained from rerunning PCA using the eight components, we adopted a cutoff value of 0.4 (53) to decide which items to retain. Finally, out of the 35 items of the original ASS scale, 15 were eliminated and 20 were kept. The survey respondents were asked to evaluate the level of stress for academic stressors such as "Final grades," "Excessive homework," and "Class speaking" on a 5-point Likert scale (1 = *Not stressful*, 5 = *Extremely stressful*). Provided the removal of those items, the Cronbach's α still achieved 0.93, which suggested excellent internal consistency.

2.2.3. Escape and coping motives

To evaluate college students' escape and coping motives, we used two subscales (four items for escape and four for coping) extracted from the Motives for online Gaming Questionnaire (MOGQ) developed by Demetrovics et al. (54). The Chinese version of the MOGQ scale, validated by Wu et al. (55), was applied in our study. The scale was slightly modified by incorporating "smartphone" into the descriptions. Sample items included "playing smartphone games helps me to forget about daily hassles" (escape) and "playing smartphone games helps me get into a better mood" (coping), with a 5-point Likert scale ranging from 1 (*Almost never*) to 5 (*Almost always*). As the Cronbach's αs for escape and coping motives were both 0.92, the items can be considered internally consistent.

2.2.4. PSU

The respondents' PSU tendency was assessed with the Problematic Use of Mobile Phones (PUMP) scale developed by Merlo et al. (56). The scale contains 22 items with a 5-Likert scale (1 = *Strongly disagree*, 5 = *Strongly agree*). Sample items were "When I decrease the amount of time spent using my cell phone,

TABLE 1 Demographic and academic characteristics grouped by gender.

Variable	Male ($N = 259$)		Female ($N = 321$)		
	Mean or N	SD or %	Mean or *N*	SD or %	*t* or χ^2
Age	19.78	1.15	19.63	1.23	1.59
985 and 211 project	33	12.74%	37	11.53%	0.44
Grade[a]					2.25
Freshman	44	16.99%	53	16.51%	
Sophomore	123	47.49%	184	57.32%	
Junior	59	22.78%	64	19.94%	
Senior	33	12.74%	20	6.23%	
GPA ranking[a]					1.07
Top 25%	77	29.73%	117	36.45%	
25–50%	105	40.54%	125	38.94%	
50–75%	56	21.62%	54	16.82%	
75–100%	21	8.11%	25	7.79%	

$N = 580$. [a]Fisher's exact tests, all $p > 0.05$.

I feel less satisfied" and "When I stop using my cell phone, I get moody and irritable." The Cronbach's α being 0.95 indicated that the scale was internally consistent.

2.2.5. IGD

In accordance with the DSM-5's essential criteria for IGD, Pontes and Griffiths (57) developed and validated a 9-item unidimensional scale, termed as IGDS9-SF, for evaluating and diagnosing IGD-related symptoms. The respondents scored their Internet gaming behavior based on a 5-point Likert scale ranging from 1 (*Never*) to 5 (*Very often*) for items such as "Do you feel more irritability, anxiety or even sadness when you try to either reduce or stop your gaming activity" and "Do you systematically fail when trying to control or cease your gaming activity." Our study employed the simplified Chinese version of IGDS9-SF (58). The Cronbach's α was 0.96, meaning that the scale was internally consistent.

2.3. Statistical analysis

Prior to conducting regression analysis, we first computed the descriptive statistics for all measures. In particular, *t* or *F* tests were implemented to check for any significant differences in the variables of interest depending on the demographic and academic characteristics of the respondents. Then, two sets of hierarchical multiple regressions were conducted while designating psychological motivations (i.e., escape and coping) and behavioral outcomes (i.e., PSU and IGD) as the dependent variable, respectively. At Step 1, demographic and academic variables, including age, gender, 985 and 211 project, and GPA ranking, were used in the model specification. At Step 2, we took into account the respondents' awareness of neijuan, including their perceived severity of and concern for the increasingly competitive atmosphere. At Step 3, we then incorporated academic stress as well as escape and coping motives, if necessary, to estimate their impacts on the dependent variable under consideration. Based upon the results derived from the above steps, structural equation modeling (SEM) was utilized to conduct path analysis with the package lavaan (59) developed specifically for latent variable analysis in the software R. To evaluate model fitness, we adopted three indices, namely comparative fit index (CFI), incremental fit index (IFI), and root-mean squared error of approximation (RMSEA). With regard to the cut-offs of the fit indices, we considered values larger than 0.95 for CFI (60) and IFI (61) and values <0.05 for RMSEA (62) as signs of good model fit. Lastly, the significances of the direct and indirect effects were examined by constructing bias-corrected bootstrap confidence intervals based on 5,000 bootstrapped samples.

3. Results

3.1. Preliminary analysis

Table 2 displays the means and standard deviations of the variables analyzed in this study. Particularly, *t* or *F* statistic was provided to see if there existed any significant differences in the psychological and behavioral measures of interest, grouped by different demographic and academic conditions. According to the results of preliminary analysis, male college students tended to have higher scores on escape and coping motives than their

TABLE 2 Descriptive statistics of psychological and behavioral variables analyzed in this study.

Variable	Escape motive		Coping motive		PSU		IGD	
	Mean (SD)	*t*/*F*	Mean (SD)	*t*/*F*	Mean (SD)	*t*/*F*	Mean (SD)	*t*/*F*
Gender		3.24**		4.05***		−0.09		3.23**
Male	2.36 (1.09)		2.83 (1.12)		2.92 (0.87)		2.04 (1.05)	
Female	2.06 (1.12)		2.44 (1.21)		2.92 (0.80)		1.77 (0.96)	
985 and 211 project		3.49***		4.90***		0.63		3.04**
Yes	1.77 (1.07)		2.01 (1.10)		2.85 (0.94)		1.56 (0.98)	
No	2.25 (1.11)		2.70 (1.17)		2.93 (0.81)		1.94 (1.00)	
Grade		0.49		0.28		0.31		0.13
Freshman	2.22 (1.06)		2.62 (1.06)		2.95 (0.96)		2.02 (1.00)	
Sophomore	2.14 (1.09)		2.59 (1.19)		2.90 (0.79)		1.83 (1.00)	
Junior	2.36 (1.19)		2.71 (1.23)		2.99 (0.80)		1.97 (1.08)	
Senior	1.83 (1.03)		2.22 (1.17)		2.83 (0.93)		1.70 (0.85)	
GPA ranking		2.14		0.71		1.55		0.79
Top 25%	2.23 (1.08)		2.62 (1.16)		3.06 (0.74)		1.81 (0.95)	
25–50%	2.19 (1.14)		2.62 (1.19)		2.94 (0.89)		1.92 (0.98)	
50–75%	2.35 (1.16)		2.76 (1.21)		2.89 (0.79)		2.04 (1.12)	
75–100%	1.68 (0.94)		2.20 (1.11)		3.13 (0.95)		1.75 (1.08)	

$N = 580$. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.

female counterparts ($t = 3.24$, $p < 0.01$; $t = 4.05$, $p < 0.001$). Whereas the two genders barely differed in PSU ($t = -0.09$, $p > 0.05$), male participants were found to be more susceptible to IGD problems than females ($t = 3.23$, $p < 0.01$), which is consistent with previous findings in the literature (63–65). Interestingly, college students who were studying at prestigious institutions (i.e., 985 and 211 project) showed lower scores on escape and coping motives than those who were not ($t = 3.49$, $p < 0.001$; $t = 4.90$, $p < 0.001$). They were also less prone to IGD problems ($t = 3.04$, $p < 0.01$), though they did not display much difference in PSU tendency ($t = 0.63$, $p > 0.05$). Moreover, it is worth noting that the respondents' evaluations were not sensitive to which year they were studying in college and their GPA rankings ($p > 0.05$). Considering college year should be positively related with the respondent's age, it will not be included as a control variable in the following analysis. Table 3 reports the correlation matrix of the variables analyzed in this study.

3.2. Examining contributory factors to escape and coping motives

Tables 4, 5 present the results of hierarchical regression analysis on the factors contributing to escape and coping motives, respectively. To be precise, at Step 1 (i.e., Model 1) demographic and academic characteristics accounted for 4% of the variance of escape motive. At Step 2 (i.e., Model 2), the inclusion of neijuan-related factors, namely perceived severity and concerns, resulted in the model explaining 23% of the variance of escape motive. At the final step (i.e., Model 3), with the incorporation of academic stress, the specified model further explained 38% of the variance in escape motive. Age and GPA ranking were not significant predictors throughout the models. Based on the results of the full model (i.e., Model 3), it can be seen that female participants, compared to males, had a lower escape motive ($B = -0.26$, $p < 0.01$, $\beta = -0.12$). In addition, college students enrolled at 985 and 211 project institutions reported lower scores on escape motive than those who were not ($B = -0.28$, $p < 0.05$, $\beta = -0.08$). In terms of neijuan-related factors, whereas awareness about the severity of neijuan was negatively associated with escape motive ($B = -0.19$, $p < 0.001$, $\beta = -0.16$), concerns for neijuan significantly increased this motive ($B = 0.43$, $p < 0.001$, $\beta = 0.45$). Finally, academic stress was detected to positively predict the participants' propensity to escape from daily routines ($B = 0.34$, $p < 0.001$, $\beta = 0.24$).

Regarding coping motive, demographic and academic characteristics (Mode 1) explained 6% of its variance. In Model 2, the integration of perceived severity of and concerns for neijuan collectively contributed to the model accounting for 21% of the variance. In Model 3, by incorporating academic

TABLE 3 The correlation matrix of the variables analyzed in this study.

Variable	1	2	3	4	5	6	7	8	9	10	11
1. Age	1										
2. Gender	−0.07	1									
3. 985 and 211 project	0.10*	−0.02	1								
4. GPA ranking	0.06	−0.05	−0.02	1							
5. Severity of neijuan	−0.01	0.11**	−0.05	0.07	1						
6. Concerns for neijuan	0.04	−0.01	−0.12**	0.02	0.45***	1					
7. Academic stress	0.00	0.01	−0.07	0.11**	0.33***	0.26***	1				
8. Escape motives	0.03	−0.13**	−0.14***	−0.06	0.11**	0.45***	0.30***	1			
9. Coping motives	0.00	−0.16***	−0.19***	−0.04	0.09*	0.41***	0.27***	0.77***	1		
10. PSU	−0.03	0.00	−0.03	0.02	0.23***	0.28***	0.50***	0.06	0.04	1	
11. IGD	0.03	−0.13**	−0.12**	0.04	0.05	0.32***	0.33***	0.73***	0.58***	0.34***	1

$N = 580$. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.

TABLE 4 Hierarchical regression analysis on escape motives.

Independent variables	Model 1			Model 2			Model 3		
	B	SE	*β*	*B*	SE	*β*	*B*	SE	*β*
Step 1									
Age	0.03	0.04	0.04	0.01	0.03	0.01	0.01	0.03	0.01
Gender	−0.31***	0.09	−0.14***	−0.27**	0.08	−0.12**	−0.26**	0.08	−0.12**
211&985 project	−0.51***	0.14	−0.15***	−0.31*	0.13	−0.09*	−0.28*	0.12	−0.08*
GPA ranking	−0.09	0.05	−0.07	−0.09	0.04	−0.07	−0.11	0.06	−0.09
Step 2									
Severity of nejiuan				−0.11*	0.05	−0.10*	−0.19***	0.05	−0.16***
Concerns for neijuan				0.46***	0.04	0.48***	0.43***	0.04	0.45***
Step 3									
Academic stress							0.34***	0.05	0.24***
Adjusted R^2	0.04			0.23			0.38		
F (4, 575)	6.68***			30.38***			33.35***		

$N = 580$. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.

stress, the model rationalized 32% of the variance in coping motive. Similar to the case of escapism, age and GPA ranking were not significant predictors for coping motive throughout the models. According to the results of the full model (Model 3), female participants tended to score lower on coping motive than their male counterparts ($B = -0.36$, $p < 0.001$, $\beta = -0.15$). Also, 985 and 211 project college students were found to have a lower coping motive than those from non-prestigious schools ($B = -0.49$, $p < 0.001$, $\beta = -0.14$). For neijuan-related factors, perceived severity of neijuan attenuated coping motive ($B = -0.19$, $p < 0.001$, $\beta = -0.15$) while concerns about neijuan intensified this motive ($B = 0.41$, $p < 0.001$, $\beta = 0.40$). Lastly, academic stress generated a significantly positive effect on the participants' inclination to cope with unintended emotions ($B = 0.33$, $p < 0.001$, $\beta = 0.22$).

3.3. Examining contributory factors to PSU and IGD

Tables 6, 7 present the results of hierarchical regression analysis on the variables causing PSU and IGD symptoms, respectively. For PSU, the respondents' demographic and academic characteristics explained only 1% of the variance in Model 1. The inclusion of neijuan-related factors led to a model

TABLE 5 Hierarchical regression analysis on coping motives.

Independent variables	Model 1			Model 2			Model 3		
	B	SE	*β*	*B*	SE	*β*	*B*	SE	*β*
Step 1									
Age	0.01	0.04	0.01	−0.01	0.04	−0.01	−0.01	0.04	−0.01
Gender	−0.40***	0.10	−0.17***	−0.37***	0.09	−0.16***	−0.36***	0.09	−0.15***
211&985 project	−0.71***	0.15	−0.20***	−0.52***	0.14	−0.14***	−0.49***	0.13	−0.14***
GPA ranking	−0.06	0.05	−0.05	−0.06	0.05	−0.05	−0.09	0.05	−0.07
Step 2									
Severity of nejiuan				−0.12***	0.05	−0.09***	−0.19***	0.05	−0.15***
Concerns for neijuan				0.43***	0.04	0.43***	0.41***	0.04	0.40***
Step 3									
Academic stress							0.33***	0.06	0.22***
Adjusted R^2	0.06			0.21			0.32		
$F(4, 575)$	10.32***			27.20***			29.08***		

$N = 580$. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.

TABLE 6 Hierarchical regression analysis on problematic smartphone use.

Independent variables	Model 1			Model 2			Model 3		
	B	SE	*β*	*B*	SE	*β*	*B*	SE	*β*
Step 1									
Age	−0.02	0.03	−0.03	−0.03	0.03	−0.05	−0.03	0.02	−0.05
Gender	0.01	0.07	0.01	−0.01	0.07	−0.01	0.06	0.06	0.04
211&985 project	−0.06	0.11	−0.02	0.03	0.10	0.01	0.13	0.09	0.05
GPA ranking	0.11	0.09	0.12	0.10	0.08	0.11	0.09	0.08	0.09
Step 2									
Severity of nejiuan				0.11**	0.04	0.12**	0.04	0.04	0.05
Concerns for neijuan				0.16***	0.04	0.22***	0.03	0.03	0.04
Step 3									
Academic stress							0.41***	0.04	0.39***
Escape motives							0.19***	0.04	0.26***
Coping motives							0.12***	0.02	0.14***
Adjusted R^2	0.01			0.10			0.32		
F (4, 575)	5.85***			11.23***			31.81***		

$N = 580$. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.

(Model 2) explaining 10% of the variance of PSU problems. In Model 3, the addition of academic stress as well as escape and coping motives accounted for 32% of the variance. Interestingly, in the full model (Model 3), all of the demographic and academic characteristics as well as neijuan-related factors were not significant predictors. However, academic stress significantly increased the respondents' PSU propensity ($B = 0.41$, $p < 0.001$, $\beta = 0.39$) and so did escape and coping motives ($B = 0.19$, $p < 0.001$, $\beta = 0.26$; $B = 0.12$, $p < 0.001$, $\beta = 0.14$).

For IGD, the respondents' demographic and academic characteristics explained 3% of the variance (Model 1). The inclusion of neijuan-related factors contributed to a model

TABLE 7 Hierarchical regression analysis on Internet gaming disorder.

Independent variables	Model 1			Model 2			Model 3		
	B	SE	*β*	*B*	SE	*β*	*B*	SE	*β*
Step 1									
Age	0.02	0.03	0.03	0.01	0.03	0.01	0.03	0.02	0.04
Gender	−0.27**	0.08	−0.13**	−0.24**	0.08	−0.12**	−0.18**	0.06	−0.16**
211&985 project	−0.40**	0.13	−0.13**	−0.27*	0.12	−0.09*	−0.06	0.09	−0.02
GPA ranking	0.03	0.05	0.03	0.03	0.04	0.03	0.06	0.07	0.06
Step 2									
Severity of nejiuan				−0.11	0.09	−0.10	−0.07	0.08	−0.07
Concerns for neijuan				0.30***	0.04	0.35***	0.24***	0.03	0.16***
Step 3									
Academic stress							0.18***	0.04	0.13***
Escape motives							0.62***	0.04	0.68***
Coping motives							0.22***	0.03	0.26***
Adjusted R^2	0.03			0.13			0.55		
F (4, 575)	5.26***			14.89***			80.19***		

$N = 580$. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

(Model 2) explaining 13% of the variance. By incorporating academic stress and escape and coping motives, the model (Model 3) finally accounted for 55% of the variance in IGD scores. According to the results of the full model (Model 3), whereas age and 985 and 211 project did not serve as significant predictors for IGD problems, female college students tended to be less susceptible to online gaming addiction ($B = -0.18$, $p < 0.01$, $\beta = -0.16$). Furthermore, although the respondents seemed not to be sensitive to the perceived severity of neijuan ($B = -0.07$, $p > 0.05$, $\beta = -0.07$), their concerns for neijuan significantly increased their IGD tendency ($B = 0.24$, $p < 0.001$, $\beta = 0.16$). Last but not least, academic stress was found to be an important external stimulus of IGD symptoms ($B = 0.18$, $p < 0.001$, $\beta = 0.13$), while both escape and coping motives functioned psychologically in increasing IGD tendency ($B = 0.62$, $p < 0.001$, $\beta = 0.68$; $B = 0.22$, $p < 0.001$, $\beta = 0.26$).

3.4. Mediational analyses

The results of mediational analyses are provided in Table 8 and Figure 1, with factors including gender, 985 and 211 project, perceived severity of neijuan, and concerns for neijuan being controlled for. Our findings revealed that, while academic stress had a direct positive effect on PSU (c1: $B = 0.71$, $p < 0.001$, $\beta = 0.44$), its indirect effects mediated *via* escape and coping motives were not significant (a1b11: $B = -0.09$, $p > 0.05$ $\beta = -0.04$; a1b12: $B = -0.02$, $p > 0.05$, $\beta = -0.01$). Nevertheless, the total effect of academic stress on PSU was still significant ($B = 0.61$, $p < 0.001$, $\beta = 0.45$). With regard to path analysis on IGD symptoms, in addition to a significantly positive direct effect (c2: $B = 0.28$, $p < 0.001$, $\beta = 0.12$), academic stress exerted indirect impacts on the respondents IGD tendency through escape and coping motives (a2b21: $B = 0.57$, $p < 0.001$, $\beta = 0.25$; a2b22: $B = 0.15$, $p < 0.01$, $\beta = 0.10$). The model fit indices were CFI = 0.98, TLI = 0.96, RMSEA = 0.04, pointing to good model fitness (66). In summary, the results of mediational analyses supported H1b and H2b but rejected H1a and H2a.

4. Discussion

Provided the growing awareness of and concerns for neijuan, especially in Asian countries like China, Japan, and South Korea, only limited academic attention has been given to this topic [e.g., (67, 68)]. The current study empirically examined the impacts of academic stress on Chinese college students, a group particularly susceptible to neijuan, with the focus on their escape and coping motives as well as their likelihood to suffer from PSU and IGD problems. The results in our study indicated that high academic stress was positively correlated with college students' motives to seek escapism from daily routines and adopt coping methods for alleviating negative status, which resonated with the broader discussions surrounding stress reduction (69–71). Academic stress was also closely aligned with college students' susceptibilities to PSU and IGD, which helped confirm those of previous research reporting positive associations between stress and PSU and IGD among college students (18, 72–74).

TABLE 8 Results of mediational analysis.

Paths	*B*	SE	*β*	95% CI for *B*	Hypothesis
Academic stress -> escape motives (a1)	0.78***	0.13	0.32	[0.53, 1.02]	
Academic stress -> coping motives (a2)	0.72***	0.14	0.30	[0.44, 1.01]	
Escape motives -> PSU (b11)	−0.12	0.07	−0.13	[−0.26, 0.03]	
Coping motives -> PSU (b12)	−0.02	0.06	−0.04	[−0.14, 0.10]	
Escape motives -> IGD (b21)	0.79***	0.08	0.83	[0.64, 0.95]	
Coping motives -> IGD (b22)	0.20***	0.06	0.30	[0.08, 0.32]	
Direct effect					
Academic stress -> PSU (c1)	0.71***	0.11	0.44	[0.49, 0.94]	
Academic stress -> IGD (c2)	0.28**	0.10	0.12	[0.06, 0.48]	
Indirect effect					
Academic stress -> escape motives -> PSU (a1*b11)	−0.09	0.07	−0.04	[−0.22, 0.06]	H1a
Academic stress -> coping motives -> PSU (a1*b12)	−0.02	0.05	−0.01	[−0.12, 0.08]	H1b
Academic stress -> escape motives -> IGD (a2*b21)	0.57***	0.14	0.25	[0.30, 0.85]	H2a
Academic stress -> coping motives -> IGD (a2*b22)	0.15**	0.05	0.10	[0.05, 0.25]	H2b
Total effect					
PSU (c1+a1*b11+a1*b12)	0.61***	0.10	0.45	[0.42, 0.81]	
IGD (c2+a2*b21+a2*b22)	0.99***	0.14	0.65	[0.70, 1.26]	

$N = 580$. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.

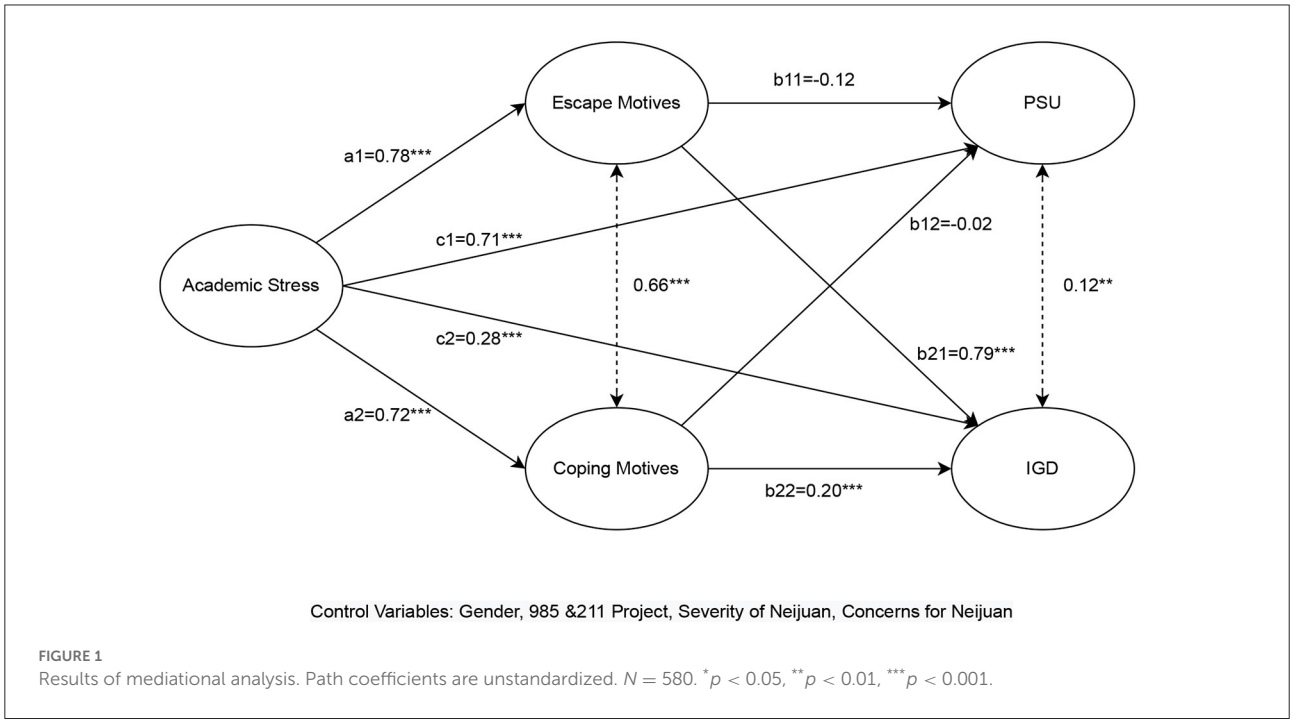

FIGURE 1
Results of mediational analysis. Path coefficients are unstandardized. $N = 580$. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.

Furthermore, escape and coping motives were found to serve as important underlying mediators that can help interpret the relation between academic stress and IGD tendency. It has been well established in the literature that the need to find an outlet for escape from reality and maladaptive coping styles can positively predict Internet addiction (75, 76), which is especially the case for playing video games as well as watching video game-themed contents (77–79). Radically different from IGD, there

was no significant indirect association between college students' academic stress and PSU tendency through such a mediating mechanism. This finding implied that smartphone use might have already developed into a habitual behavior instead of effective escape and coping instruments.

Some other interesting findings were also obtained in our study. For example, the participants who expressed greater concerns for neijuan were inclined to have higher escape and coping motives as well as stronger PSU and IGD tendencies. In contrast, those who were fully conscious of neijuan did not give high scores on the above measures, implying they might have taken neijuan for granted. This can also be justified by Antonovsky's (80) sense of coherence, referring to comprehensibility as the extent to which people might cognitively perceive both internal and external stimuli as being understandable in some kinds of rational way. Notably, female participants in our study had significantly lower scores on escape and coping motives than their male counterparts, which is vastly different from prior investigations on substance and behavioral addictions (78, 81). In addition, whereas GPA ranking was not effective in predicting the participants' PSU and IGD motivations and behaviors, college students studying at prestigious higher education institutions tended to have lower escape and coping motives and were less prone to IGD problems than those who were not. Therefore, this finding suggested an inter-institutional, rather than intra-institutional, difference in the related risk factors among college students.

Our study had several limitations. First, other variables pertaining to the theory of behaviors in question were not examined. For example, previous research has found that poor interpersonal relationships can impose emotional stress on college students (82). Accordingly, it follows that social exclusion within the campus context may influence college students' PSU and IGD propensities. Second, the cross-sectional nature of the data in our study can only unveil the relationships between the variables of interest but does not necessarily ensure causal inferences. Therefore, future research might consider adopting longitudinal or experimental designs to infer causal relationships. Third, our sample was restricted to college students in China, which may compromise the generalizability of the findings due to underlying cultural differences.

5. Conclusion

Our study found that neijuan-related academic stress tremendously impacted college students' PSU and IGD motivations and symptoms. The findings suggested that, whereas academic stress increased IGD tendency mediated *via* escape and coping motives, overuse of smartphone might have developed into a habitual behavior as opposed to effective escape and coping tools. Moreover, demographic and academic characteristics, such as gender and whether studying at a prestigious institution, also exerted influences on college students' IGD problems.

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 Institutional Review Board, School of Cultural Creativity and Management, Communication University of Zhejiang. The patients/participants provided their written informed consent to participate in this study.

Author contributions

XG and EM contributed to conception and design of the study. EM organized the database, performed the statistical analysis, and wrote sections of the manuscript. XG wrote the first draft of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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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.

Publisher's note

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Compulsory care of individuals with severe substance use disorders and alcohol- and drug-related mortality: A Swedish registry study

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Aim: This study used 17 year of Swedish registry data (2003–2019) for 25,125 adults assessed for their severity of substance use to identify the baseline factors predicting the risk of being court-ordered into compulsory care and examine the association between admission to compulsory care and mortality risks due to alcohol- or drug-related causes.

Methods and materials: Addiction Severity Index (ASI) assessment data were linked to register data on demographic characteristics, compulsory care, and alcohol- and drug-related mortality. Cox regression models were used to identify baseline factors predictive of post-assessment admission to compulsory care in the 5 years post-substance use assessment. Discrete-time random-effect logistic regression models were used to examine the association between compulsory care duration and alcohol or drug-related mortality risks. Propensity score matching was used for validation.

Results: The first models identified that younger age, female gender, and ASI composite scores for drug use, mental health and employment were significantly associated with the risk of placement in compulsory care for drugs other than alcohol. Female gender and ASI composite scores for alcohol, drug use and employment were significantly associated with compulsory care treatment for alcohol use. The second models showed that older individuals and men were more likely to die due to alcohol-related causes, while younger individuals and men were more likely to die due to drug-related causes. Length of stay in compulsory care institutions significantly increased the likelihood of dying due to substance use-related causes. Propensity scores analyses confirmed the results.

Conclusion: In Sweden, a significant concern is the higher likelihood of women and young individuals to be court-ordered to compulsory care. Although compulsory care is often advocated as a life-saving intervention, our findings do not provide strong support for this claim. On the contrary, our findings show that admission to compulsory care is associated with a higher risk of substance use-related mortality.

Factors such as compulsory care often not including any medical or psychological therapy, together with relapse and overdose after discharge, may be possible contributing factors to these findings.

KEYWORDS

compulsory care, addiction treatment, alcohol-related mortality, drugs other than alcohol-related mortality, addiction severity index (ASI)

1. Introduction

There is a strong association between having a severe substance use disorder and a range of problems in other life domains, such as physical or mental health issues, impairment in social relations, risk of engaging in criminal behavior, housing instability, employment, and financial problems (1). This substance use-related biopsychosocial vulnerability may in worst case lead to premature death. Many studies have in fact identified a relationship between severe substance use disorders and increased mortality risk (2–7). A way to mitigate this vulnerability, and therefore reduce the risk of premature death, is to offer substance use disorder treatment (5). In many countries, when individuals with substance use severe enough to put themselves or others in danger refuse to undergo voluntary treatment, they can be mandated to compulsory care, usually through a court order (8).

Sweden is one of the countries where courts can order compulsory care for individuals with severe alcohol and or drug use disorders. Compulsory care for severe substance use is relatively common in Sweden and about 1,000 people per year are court-ordered to the treatment (8–13). Individuals who are admitted to compulsory care for severe substance use tend to have more severe alcohol and drug use disorders as well as to be younger and more socially disadvantaged compared with those engaging in voluntary treatment options (14, 15). Moreover, individuals self-reporting a history of compulsory care treatment for severe substance use are more likely to have greater treatment needs, more substance use related-problems and experience more social exclusion (e.g., from social relationships, or related to unstable housing and employment, or due to various forms of discrimination), compared with those with only a history of voluntary treatment (14–17).

Previous studies have focused on the association between compulsory care for severe substance use and mortality (18, 19). These studies compared the mortality risks of patients who have been discharged from compulsory care for severe substance use and the general population or focused on within-group differences among those with a history of compulsory care. Their findings showed higher mortality risks for those who were required to undergo compulsory care for severe substance use, compared to the Swedish population as a whole. For example, the study by Hall et al. (18) found that between 2001 and 2009 compulsory care patients had a death rate between 8 and 10 times higher than the general population. Ledberg and Reitan (19) showed that those discharged from compulsory care for severe substance use, and young patients in particular, faced the greatest mortality risk within 2 weeks after the end of the treatment.

Yet, no previous study has investigated whether individuals with severe substance use disorders who have been mandated to compulsory care are more or less likely to die due to alcohol- or drug-related causes compared to those with similar substance use profiles who were not mandated to participate in treatment. To address this knowledge gap, this study: (1) Identified risk-factors associated with placement in compulsory care for risky substance use; and (2) examined whether placement in compulsory care was associated with either reduced or increased risk of substance use-related mortality after discharge. Addiction Severity Index (ASI) assessment data and register data on demographic characteristics, compulsory care admission and alcohol- and drug-related mortality were linked and analyzed to address these research questions.

2. Materials and methods

2.1. Study setting

In Sweden, individuals with substance use problems so severe to constitute a danger for themselves or others, and for whom voluntary treatment is deemed to be inadequate, can be legally mandated to compulsory care for substance use disorder. Sweden's Care of Abusers (Special Provisions) Act (*Lag om vård av missbrukare i vissa fall*, or LVM) is founded on the framework of civil law, and not on a criminal justice framework (10). In comparison with the United States or other Nordic countries, where compulsory care for severe substance use typically takes place within the criminal justice system or within the psychiatric care system (10), Swedish compulsory care for substance use disorder is overseen and implemented by the Swedish National Board of Institutional Care (*Statens institutionsstyrelse*, or SiS). The National Board of Institutional Care is an independent Swedish government agency that has the legal right and responsibility to provide compulsory care in locked facilities to individuals who are deemed to require such treatment. It is possible to remain in compulsory care for up to 6 months, usually without participating in any medical or psychological therapy for substance use disorder. This means that it is virtually possible to stay in compulsory care without receiving any treatment for substance use problems. Patients are only required to remain abstinent from alcohol and drug use during this period. The decision to terminate the treatment is taken jointly by the compulsory care institution and the municipal social service board that required the treatment. Municipal social service boards are legally responsible for all decisions related to compulsory care admissions. This means that they are legally obliged to justify the need for treatment by determining that a person is at risk to oneself or others due to their substance use problems and is also unwilling to undergo voluntary treatment. Admission decisions are taken by the municipal social service boards but need to be submitted to regional administrative courts. Regional administrative courts take the final decision regarding compulsory care admissions. A policy concern in

Sweden, but also in other countries with similar addiction treatment systems, is to assess whether mandatory treatment reduces mortality risks among individuals with risky and severe substance use.

2.2. Research questions

This study addressed two questions: (1) What baseline factors predicted the risk of being court-ordered into compulsory care within 5 years after being assessed for substance use severity? (2) Was admission to court-ordered compulsory care post-assessment of substance use severity associated with a reduced risk to die of alcohol or drug-related causes, compared to individuals assessed for substance use severity who were not admitted to compulsory care? Each of the questions was addressed using different survival analysis modeling approaches and different samples from the same data sources.

2.3. Data sources

This study uses ASI assessment data from 144 Swedish municipalities over the period 1999–2019. The individuals in the database represent approximately 40 percent of individuals who completed an ASI baseline interview in Sweden during the study period. The database is representative of the urban adult population with ASI-assessed problems, with an underrepresentation of smaller and rural municipalities. The use of the ASI as an assessment tool for substance use disorders and associated problems is common in Sweden. About 93 percent of the Swedish population live in municipalities where social workers use the ASI tool. Social workers' training to use the ASI tool is supervised at the national level by the Swedish National Board of Health and Welfare (NBHW, or Socialstyrelsen), which provided us with the original data. Patients are often self-referred to ASI-assessments, but they can also be referred by primary and secondary health-care services, police and court officials, or through family members and other venues.

The baseline ASI survey was linked to three other databases using pseudonymized individual identifiers: (1) Data on adults court-mandated to compulsory care for their substance use problems, which come from the registers of the Swedish National Board of Institutional Care (SiS, or *Statens institutionsstyrelse*); (2) data from the Swedish Causes of Death Register, maintained by the NBHW; (3) data from Swedish population registers containing demographic information on age, gender, country of birth and date of emigration, maintained by Statistics Sweden.

The NBHW, the Regional Ethical Review Board at Umeå University (DNR: 2016/504-31; amendment 2020-06233) and Institutional Review Board (IRB) of the University of Denver reviewed and approved the study protocol. All study data were de-identified and the study met criteria for IRB exemption.

2.4. Study design and population

We use two different samples from the same data sources for our study. The first sample was created to address our first research question (i.e., what baseline factors predicted the risk to be court-ordered into compulsory care). From the ASI-database, we selected all adults (18 years of age and older) with complete demographic data (N = 14,395) who were assessed for substance abuse disorders between 1999 and 2014 and did not have a history of emigration or die in the 5 years following the assessment. We linked these data to register data for compulsory care entries in the 5 years post-assessment to identify the background factors associated with the likelihood of admission to treatment.

To address the second research question (i.e., whether entry into court-mandated compulsory care is associated with mortality due to alcohol or drug-related causes), we created a larger sample including all adult individuals who completed an ASI-assessment between 1999 and 2019 (N = 25,125), excluding those who emigrated during the study period. We linked these data to the nationwide register data for compulsory care and to the causes of death register to assess the association between admission to compulsory care and alcohol- and drug-related mortality.

2.5. Outcome variables

The dependent variable for the two models addressing the first research question was entry into court-mandated compulsory care. We distinguished two types of compulsory care, based on the type of substance use disorder being treated: Compulsory care for alcohol-use disorder and compulsory care for drug-use disorder. The two outcomes were categorized as a yes/no dichotomous variable and were not mutually exclusive. In fact, about one fifth of compulsory care patients in our sample (192 cases out of N = 931 cases) received treatments for both alcohol and drug problems and were thus included in both categories.

The two dependent variables for the models addressing the second research question were alcohol-related mortality and drugs other than alcohol, related mortality. Alcohol-related mortality and drugs other than alcohol related mortality were categorized as yes/no dichotomous variables, derived from the NBHW Causes of Death Register. Causes of deaths were determined by the NBHW based on ICD-10 codes. Alcohol-related death was defined as having either an underlying or contributing cause of death related to alcohol, such as, for example, alcoholism, toxic effect of alcohol or mental and behavioral disorders due to the use of alcohol. A death is considered drug-related if a drug played a role in the death, either directly or indirectly (20). The two outcomes were not mutually exclusive because 6.6 percent of the individuals with substance-related death died from both alcohol- and drug-related causes (92 cases out of N = 1,390 cases).

2.6. Covariates

Control variables were based on answers reported at the ASI baseline assessment or on the other register databases used in the study. The variable *Age* was recoded into a categorical variable with 7-year age bands up to age 24, then three 10-year age bands (25–34, 35–44, and 45–54), with a last age band for all those 55 and older. Prior studies based on Swedish data found that the profiles of substance use disorders differ by age group, with alcohol use disorders being more common among older individuals (21) and drug use problems more common among younger cohorts (22).

The *Gender* variable was a dichotomous variable, with male as the reference category, and female assuming a value of one. This

variable refers to biological sex and one limitation of our study is that we are unable to identify individuals who identify themselves as non-binary or transgender.

Immigrant background was a five-category variable considering country of origin and distinguishing first- and second-generation immigrants: Individual and their parents all born in Sweden (the reference group); individual born in Norway, Finland, or Denmark (first-generation immigrant); individual born outside of Sweden, Norway, Finland, or Denmark (first-generation immigrant); individual born in Sweden with at least one parent born in Norway, Finland, or Denmark and no parent outside of Nordic countries (second generation immigrant); and individual born in Sweden with at least one parent born outside Nordic countries (second-generation immigrant). In Sweden, about every fifth person is a first- or second-generation immigrant. Unlike other countries, Swedish public authorities are not allowed to collect data on race or ethnicity, and they are only allowed to collect data on country of birth. Prior studies have identified significant differences by immigration status in alcohol or drugs other than alcohol related mortality, with individuals from non-Nordic countries being significantly less likely to die of such causes (7).

The ASI composite scores for severity of alcohol, drug, mental health, health, family and social relationships, employment, and legal problems were numeric variables with higher values indicating more problems/needs in the specific area (23, 24). Each ASI CS is an index computed from answers to questions related to an ASI problem area. As recommended by the developers of the ASI CSs (24), equal weighting is given to all questions/items within an ASI CS and each score is adjusted for the answer range of each item and the total number of items in the composite. The answer to each question is then divided by the highest possible response, and by the total number of questions in the ASI CS. The reliability of ASI CSs has been rigorously explored and tested by many studies carried out in different countries (25, 26). For example, recent studies based on Swedish ASI-data indicated that the ASI CS for mental health was a significant predictor of future inpatient hospitalization for mental health disorder (27) and the ASI CS for legal problems was a significant predictor for future imprisonment (28).

The main explanatory variable for the models addressing the second research question was days in compulsory care per year, recoded into hundreds of days. The variable is derived from the SiS register database and spells occurring over multiple calendar years were split to assign days to their corresponding calendar year.

2.7. Statistical analysis

As a first step, we examined descriptive statistics of the study sample. We stratified individuals by whether they were admitted to compulsory care at least once during the course of the study period, after ASI-assessment, and addressed differences in the control variables between those who were admitted to compulsory care and those who were not. Mean and percentages were analyzed for significance using student *t*-test or chi-square test, as appropriate.

In the second step, two Cox proportional hazards models were fit to identify the baseline factors differentiating those who were court-ordered into compulsory care from those who were not. The first model included admission into compulsory care for alcohol-use disorder as a dependent variable, while the dependent variable in the second model was admission into compulsory care for drug-use disorder. Based on a subset of individuals (N = 14,395) who were ASI-assessed between 1999 and 2014, we considered the first admission to either type of compulsory care within the 5 years post-ASI assessment (i.e., we did not consider entries after the first one or entries occurring after the time-range examined here). We excluded individuals who emigrated or died within the 5 years post-ASI-assessment. Since individuals could be assessed and court-ordered into compulsory care multiple times during the study period we adjusted standard errors to account for clustering of repeated observations within individuals using the *vce(cluster id)* option within the *stcox* command in Stata. We tested proportional hazards by testing for the independence between the scaled Schoenfeld residuals and the time-at-risk. The tests showed that only one variable violated the proportional hazard assumption, i.e., the ASI CS for drug in the model for entry into compulsory care for alcohol-use disorder. Therefore, this variable was included in the Cox model for entry intro alcohol-related compulsory care as a time-varying covariate interacted with time.

In the third step, our aim was to analyze the association between compulsory care and substance use-related mortality. We used all observations in the ASI-database (from 1999 to 2019) and individuals were followed until date of mortality or, for those surviving, through the end of the study period (i.e., 31 December 2019), at which point their event history was right-censored. Individuals who emigrated from Sweden during the study period were excluded from the analyses, resulting in N = 25,125 individuals. Our main independent variable, i.e., time in compulsory care, is time varying and indicates the cumulative number of days of treatment for that year since entry into the study (i.e., the first ASI-assessment). We applied discrete-time event history analysis with logistic estimation, because this a form of event history analysis that is appropriate for the investigation of the probability of the occurrence of our event of interest (substance-use related mortality), conditional on both time-varying and time- constant variables which may influence the probability of the specified event occurring (29). An advantage with discrete-time even history analysis is that we can treat compulsory care as an intermediate event, between ASI-assessment and survival or death, by defining it as a time-varying covariate. Two separate models were specified: the first model examines the association between the yearly cumulative duration of compulsory care spells and alcohol-related mortality while the second model examines the association between the yearly cumulative duration of compulsory care spells and drugs other than alcohol related mortality. In both models, duration of compulsory care is measured in days. We arranged our dataset in person-year format, with individuals contributing as many observations as the number of years they have been at risk of experiencing the risk in question, i.e., from the year of the first ASI assessment through to the year of last observation (or death). Therefore, after ASI assessment, individuals were prospectively followed-up for a mean (SD) of 7.2 (4.2) years and, for each year, it was reported the cumulative number of days in compulsory care (rescaled in hundreds). After the exclusion of missing data, our analytical sample contained 181,455 person-year observations for N = 25,125 individuals. For each individual, and in each year, we defined two dichotomous dependent variables, measured yearly, for the two types of substance-related death, with categories "death" and "survival" corresponding to the two possible outcomes each year. We defined the unit of analysis as a year because life duration is typically generally rounded to the last birthday, rather than reported as an exact age (e.g., in months or days). We believe that this time unit provide sufficient detail to analyze

TABLE 1 Descriptive statistics in relation to admission to compulsory care.

Variable	With at least a compulsory care spell post-ASI assessment (*N* = 1,496), % or mean (±SD)	Without any compulsory care spell post-ASI assessment (*N* = 23,629), % or mean (± SD)	Total (*N* = 25,125), % or mean (± SD)
*Status at the end of the study period****			
Still living	86.5	94.6	94.1
Deceased due to alcohol-related causes	5.3	2.7	2.9
Deceased due to drug-related causes	7.2	2.4	2.7
Deceased due to alcohol- and drug-related causes	1.0	0.3	0.4
*Age at ASI assessment****	39.3 (13.8)	33.8 (12.8)	39.0 (13.8)
*Age group****			
18–24	33.6	17.9	18.9
25–34	27.3	25.1	25.2
35–44	15.6	19.6	19.3
45–54	14.9	20.7	20.4
+55	8.6	16.7	16.2
*Gender****			
Male	64.2	70.7	70.3
Female	35.8	29.3	29.7
Immigrant background			
Individual and their parents born in Sweden	72.5	69.5	69.7
Individual born in either Norway, Denmark, or Finland	3.4	3.7	3.7
Individual born outside of Sweden, Norway, Denmark, and Finland	6.7	10.7	10.5
Individual born in Sweden and at least one parent born in Norway, Denmark or Finland (no other country outside Sweden)	9.8	8.0	8.1
Individual born in Sweden and at least one parent born outside Sweden, Norway, Denmark, and Finland	7.6	8.0	8.0
ASI composite scores at the assessment			
Health	0.38 (0.34)	0.36 (0.34)	0.36 (0.34)
Employment***	0.87 (0.23)	0.77 (0.29)	0.77 (0.29)
Alcohol**	0.29 (0.29)	0.32 (0.29)	0.32 (0.30)
Drug***	0.16 (0.15)	0.11 (0.13)	0.11 (0.13)
Legal***	0.17 (0.23)	0.13 (0.21)	0.13 (0.21)
Mental health*	0.36 (0.24)	0.34 (0.24)	0.34 (0.24)
Family and social relations**	0.29 (0.23)	0.27 (0.22)	0.27 (0.22)
*Days in compulsory care until the end of the study period****	219.2 (175.8)	0.0 (0.0)	13.1 (67.3)

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

the effect of compulsory care on substance-use related mortality. A finer time unit (e.g., months) would not add substantively to our analyses and would make our sample computationally unfeasible. Year was recoded as an ordinal variable (with the assessment year = 1) and both models control for year of observation. Another advantage with discrete-time logistic models is that they can include a random effect term for individuals to account for individual-specific, time invariant unobservable characteristics (30). The presence of unobserved heterogeneity at the individual level is assessed by performing a likelihood ratio test for the intraclass correlation (rho).

TABLE 2 Multivariate Cox regression models for entry into compulsory care for alcohol-use or drug-use disorders.

Independent variables	Model 1: Compulsory care for alcohol-use disorder	Model 2: Compulsory care for drug-use disorder
Age group		
18–24	1 (Reference)	1 (Reference)
25–34	0.86 (0.63–1.19)	0.63 (0.51–0.77)***
35–44	0.81 (0.59–1.12)	0.31 (0.23–0.41)***
45–54	0.90 (0.67–1.23)	0.23 (0.16–0.33)***
>55	0.80 (0.55–1.17)	0.10 (0.04–0.21)***
Gender		
Male	1 (Reference)	1 (Reference)
Female	1.37 (1.11–1.71)**	1.39 (1.15–1.69)***
Immigrant background		
Individual and their parents born in Sweden	1 (Reference)	1 (Reference)
Individual born in either Norway, Denmark or Finland	1.03 (0.66–1.60)	0.30 (0.10–0.94)*
Individual born outside of Sweden, Norway, Denmark, and Finland	0.56 (0.35–0.87)*	0.63 (0.45–0.87)**
Individual born in Sweden and at least one parent born in Norway, Denmark or Finland (no other country outside Sweden)	1.34 (0.99–1.81)	1.14 (0.86–1.51)
Individual born in Sweden and at least one parent born outside Sweden, Norway, Denmark, and Finland	0.78 (0.50–1.22)	0.88 (0.65–1.18)
ASI-composite scores		
Mental health	0.67 (0.42–1.07)	1.56 (1.02–2.40)*
Family and social relations	0.93 (0.56–1.53)	0.95 (0.59–1.51)
Employment	2.86 (1.87–4.39)***	5.45 (3.27–9.08)***
Alcohol	3.93 (2.85–5.44)***	0.52 (0.36–0.76)***
Drug use	0.00 (0.00–0.00)***	48.20 (24.13–96.28)***
Drug use X time (days)	1.00 (1.00–1.01)***	–
Health	1.26 (0.93–1.70)	1.27 (0.97–1.67)
Legal	0.65 (0.38–1.12)	0.82 (0.57–1.18)
Cases	14,395	14,395
Failures	413	518
Log-likelihood	−3476.23	−4118.65
pseudo-R2	0.02	0.07

Hazard ratios (with 95% confidence intervals). *$p < 0.05$, **$p < 0.01$, and ***$p < 0.001$.

The test is significant in both models, implying that subject-level random effects explain part of the variance between individuals (i.e., we can reject the null hypothesis of rho = 0). We used a random effect specification instead of a fixed effect model because most of our variables are time-invariant, whose effect cannot be estimated by fixed effect models. Fixed effect models would only use data on individuals whose values on the outcome variables change over time (i.e., individuals who died due to alcohol- or drug-related causes during the study period), hence ignoring most of the data. Estimates based on this highly selected subset of individuals could not be generalized to the rest of the sample. Therefore, we use random-effect models also because these models do not imply a selection based on the outcome variables but make use of the entire sample.

As mentioned before (section 2.4. Study design and population), the outcomes for the models for both research questions are not mutually exclusive and this prevented us from adopting a competitive risks framework in our survival analyses.

As a sensitivity analysis, we created two propensity-score matched samples to balance baseline characteristics between individuals with and without post-assessment compulsory care during the study period. The variables for the propensity score matching were selected based on the results of the Cox regression models for entry into the two types of compulsory care. Different iterations of the propensity models were run using different model specifications and different nearest neighbor ratios by executing the Stata command *psmatch2* (31). We chose a 10-nearest neighbor matching because this matching algorithm ensured sufficiently large validation datasets for precise estimates, while still keeping bias (i.e., the difference in the mean of covariates between the groups with and without compulsory care) as low as possible. Next, as a robustness check, we created person-year datasets selecting the propensity score matched cases and re-run the discrete-time random-effect logistic models for these subsamples (10,310 individuals for the model for alcohol-related mortality and 10,032 individuals for the model for drug-related mortality). Our results were robust to the choice of different nearest neighbor matching algorithms (results available on request).

TABLE 3 Discrete-time random-effect (RE) logistic models for dying of substance use disorder-related causes, 1999–2019.

Independent variables	Model 1: Alcohol-related mortality	Model 2: Drugs-related mortality
Age group		
18–24	1 (Reference)	1 (Reference)
25–34	1.34 (0.51–3.52)	0.96 (0.74–1.26)
35–44	4.86 (1.94–12.15)***	1.03 (0.78–1.36)
45–54	16.12 (6.58–39.48)***	0.64 (0.48–0.86)**
>55	32.99 (13.41–81.16)***	0.34 (0.25–0.47)***
Gender		
Male	1 (Reference)	1 (Reference)
Female	0.72 (0.60–0.86)***	0.43 (0.35–0.52)***
Immigrant background		
Individual and their parents born in Sweden	1 (Reference)	1 (Reference)
Individual born in either Norway. Denmark or Finland	0.92 (0.68–1.25)	0.96 (0.62–1.50)
Individual born outside of Sweden. Norway. Denmark and Finland	0.61 (0.43–0.87)**	0.54 (0.40–0.72)***
Individual born in Sweden and at least one parent born in Norway, Denmark or Finland (no other country outside Sweden)	0.87 (0.65–1.18)	1.06 (0.82–1.37)
Individual born in Sweden and at least one parent born outside Sweden, Norway, Denmark, and Finland	0.51 (0.39–0.83)**	0.87 (0.65–1.14)
Days in compulsory care (in hundreds)	1.48 (1.34–1.62)***	1.48 (1.29–1.53)***
Constant	0.00 (0.00–0.00)***	0.00 (0.00–0.01)***
Observations	181,455	181,455
Individuals	25,125	25,125
Log-likelihood	−4776.31	−4814.75
Wald Chi^2	349.76***	201.19***
BIC	9697.93	21277.96
Random parameter σ_u	1.29 (0.92–1.81)	1.11 (0.68–1.83)
Rho	0.33 (0.20–0.50)	0.27 (0.12–0.50)
LR test of rho	7.22**	3.05*

Reference category: Still alive. Odds ratios (with 95% confidence intervals). *$p < 0.05$, **$p < 0.01$, and ***$p < 0.001$. Both models control for year of observation.

Stata version 17 was used for all calculations (StataCorp, College Station, TX, USA). Minimum statistical significance was set at p-value < 0.05 for all statistical analyses.

3. Results

Descriptive statistics are displayed in Table 1. We show only the descriptive statistics for the larger sample because percentages and means were essentially equivalent for the two samples. The proportion of individuals who died due to either cause was higher among those who entered compulsory care (13.5 percent) than among those who did not (5.4 percent), and the difference between the two groups was significant ($p < 0.001$). About 70 percent of the sample was men but the proportion of women was significantly higher (35.8 percent) in the compulsory care group ($p < 0.001$). Age also differed significantly between the two groups, measured either as categorical or continuous measure ($p < 0.001$). Those who were admitted to compulsory care were a younger population than their counterparts, with those in the age group 18–24 comprising 33.6 percent among those entering compulsory care after ASI-assessment, while they accounted for 18.9 percent of the total sample. Native-born individuals were slightly overrepresented and non-Nordic immigrants were underrepresented among those admitted to compulsory care. When looking at the ASI composite scores those admitted to compulsory care report more severe problems for all domains, except for alcohol. Finally, the average cumulative duration of treatments, until the end of the observation period, was 219.2 days for those admitted to compulsory care (albeit with a high SD: 175.8 days).

Table 2 shows the results of Cox regression models for the likelihood of entering compulsory care for either alcohol-use or drug-use disorders for individuals assessed for addiction severity between 1999 and 2014, within 5-years after their ASI-assessment. Results are presented as hazard ratios with 95 percent confidence intervals, indicating a change in the outcome variable (i.e., in the risk of entering compulsory care) given a change in the covariate. Depending on the type of the covariate (i.e., categorical or continuous), hazard ratios either compare the risk of one group to another group or compare the risk after a change in the continuous covariate to the risk at its original value. The *Age group* variable is significant only in the

TABLE 4 Balance of the matching variables in relation to alcohol-related compulsory care.

	Propensity-score-matched sample n. 1, % or mean (± SD)	
Matching covariates	With at least a compulsory care spell post-ASI assessment (N = 1,402)	Without any compulsory care spell post-ASI assessment (N = 8,908)
*Age at ASI assessment****	33.8 (12.9)	36.0 (13.2)
Gender		
Male	64.2	66.1
Female	35.8	33.9
*Immigrant background**		
Individual and their parents born in Sweden	72.8	69.4
Individual born in either Norway, Denmark, or Finland	3.4	3.5
Individual born outside of Sweden, Norway, Denmark, and Finland	6.3	8.7
Individual born in Sweden and at least one parent born in Norway, Denmark or Finland (no other country outside Sweden)	10.1	10.1
Individual born in Sweden and at least one parent born outside Sweden, Norway, Denmark, and Finland	7.6	8.3
*ASI composite score for alcohol***	0.29 (0.29)	0.32 (0.29)

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

TABLE 5 Balance of the matching covariates in relation to drug-related compulsory care.

	Propensity-score-matched sample n. 2, % or mean (± SD)	
Matching covariates	With at least a compulsory care spell post-ASI assessment (N = 1,451)	Without any compulsory care spell post-ASI assessment (N = 8,581)
Age at ASI assessment	33.8 (12.8)	34.5 (12.6)
*Gender***		
Male	64.4	64.5
Female	35.6	35.5
*Immigrant background****		
Individual and their parents born in Sweden	72.6	67.4
Individual born in either Norway, Denmark, or Finland	3.3	4.9
Individual born outside of Sweden, Norway, Denmark, and Finland	6.4	8.7
Individual born in Sweden and at least one parent born in Norway, Denmark or Finland (no other country outside Sweden)	10.1	11.0
Individual born in Sweden and at least one parent born outside Sweden, Norway, Denmark, and Finland	7.6	7.9
ASI composite score for drug	0.16 (0.15)	0.16 (0.14)

**$p < 0.01$ and ***$p < 0.001$.

model for compulsory care for drug-use disorder and indicates that the risk decreases with age. In fact, all age groups have a lower risk to end up in compulsory care for drug-use disorder than do those aged 18–24, and the risk is extremely low for those over 55 years of age (HR = 0.10; 95% CI = 0.04–0.21). Hence, in Sweden drug-related compulsory care seems to be a coercive measure targeted especially at young people, whereas age is not significant when looking at the risk of entering compulsory care for alcohol use disorder. Regarding the *Gender* variable, women were more likely to be court-ordered to compulsory care than men, regardless of the substance use disorder to be treated. Compared to men, women had 37 percent increase on the risk of entering alcohol-related compulsory care (HR = 1.37; 95% CI = 1.11–1.71) and 39 percent increase on the risk of ending up in drug-related compulsory care (HR = 1.39; 95% CI = 1.15–1.69). Looking at the *Immigrant background*, first-generation immigrants from countries other than Northern Europe had a 44 percent lower risk to enter compulsory care for alcohol-related problems (HR = 0.56; 95% CI = 0.35–0.87) and a 37 percent lower risk of compulsory care for drug-related problems (HR = 0.63; 95% CI = 0.45–0.87), compared to the Swedish-born reference group. Immigrants from other Northern European countries had a 70 percent lower risk to enter drug-related compulsory care compared to Swedish-born (HR = 0.30; 95% CI = 0.09–0.94). The *ASI CSs* for employment, alcohol- and drug-use were significant in the model for entry into compulsory care for alcohol use disorder. Unsurprisingly, the ASI CS for alcohol was the strongest positive predictor in the model (HR = 3.93; 95% CI = 2.85–5.44), followed by the ASI CS for employment (HR = 2.86; 95% CI = 1.87–4.39). The hazard-ratio for the time-dependent variable for the ASI CS for drug is statistically significant and higher than one, indicating that the hazard for entry into alcohol-related compulsory care tends to increase over time, from the ASI-assessment, for those with a high score for drug use. This can be interpreted as a higher risk of alcohol-related compulsory care for individuals with an alcohol use disorder as main diagnosis upon assessment but who also are polysubstance users. In the model for drug-related compulsory care, the hazard ratios for the ASI CSs for drug use, employment, mental health, and alcohol are significant. As expected, the strongest positive predictor for the model was the ASI CS for drug use disorder (HR = 48.20; 95% CI = 24.13–96.28). Individuals with high scores for alcohol use disorder are less likely to be court-ordered into this type of compulsory care because they are more likely to end up in the other type of compulsory treatment for alcohol-related problems. Patients in compulsory care for drug use disorders are also more likely to have mental health problems (HR = 1.56; 95% CI = 1.02–2.40).

The results of the discrete-time event-history random effect logistic models are shown in Table 3. The first model shows the association between days in compulsory care and alcohol related mortality, while the second model shows the association between

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TABLE 6 Discrete-time random-effect (RE) logistic models for dying of substance use disorder-related causes, 1999–2019 (with propensity score adjustment).

Independent variables	Model 1: Alcohol-related mortality	Model 2: Drugs-related mortality
Age group		
18–24	1 (Reference)	1 (Reference)
25–34	1.42 (0.40–5.04)	0.95 (0.68–1.33)
35–44	6.25 (1.85–21.12)**	1.13 (0.78–1.65)
45–54	20.11 (6.06–66.77)***	0.63 (0.42–0.97)*
>55	40.82 (12.06–138.16)***	0.42 (0.25–0.68)***
Gender		
Male	1 (Reference)	1 (Reference)
Female	0.70 (0.510.97)*	0.37 (0.28–0.49)***
Immigrant background		
Individual and their parents born in Sweden	1 (Reference)	1 (Reference)
Individual born in either Norway. Denmark or Finland	0.90 (0.52–1.55)	0.68 (0.35–1.33)
Individual born outside of Sweden. Norway. Denmark and Finland	0.41 (0.19–0.87)*	0.49 (0.30–0.79)**
Individual born in Sweden and at least one parent born in Norway, Denmark or Finland (no other country outside Sweden)	0.68 (0.40–1.16)	0.93 (0.66–1.32)
Individual born in Sweden and at least one parent born outside Sweden, Norway, Denmark, and Finland	0.32 (0.12–0.87)*	0.75 (0.49–1.16)
Days in compulsory care (in hundreds)	1.53 (1.36–1.72)***	1.41 (1.28–1.55)***
Constant	0.00 (0.00–0.01)***	0.00 (0.00–0.01)***
Observations	75,88	72,456
Individuals	10,310	10,032
Log-likelihood	−1719.83	−2365.68
Wald Chi^2	142.30***	104.95***
BIC	3574.50	4865.66
Random parameter σ_u	1.75 (1.27–2.44)	1.38 (0.90–2.12)
Rho	0.48 (0.33–0.64)	0.37 (0.20–0.58)
LR test of rho	9.47**	4.50*

Reference category: Still alive. Odds ratios (with 95% confidence intervals). With propensity score adjustment for alcohol-related compulsory care (Model 1) and drug-related compulsory care (Model 2). *$p < 0.05$, **$p < 0.01$, and ***$p < 0.001$. Both models control for year of observation.

days in compulsory care and drugs other than alcohol-related death. Both models control for demographic characteristics. The findings show that admission to compulsory care is significantly associated with higher odds ratios of substance use-related mortality. In fact, 100 days in compulsory care increased the odds ratio of dying due to alcohol by 48 percent (*OR* = 1.48; 95% *CI* = 1.34, 1.62) and the odds of dying due to drugs other than alcohol by 41 percent (*OR* = 1.41; 95% *CI* = 1.29–1.53). Based on these results, we can exclude that admission to compulsory care decreases the substance-related mortality risk of individuals who received an assessment for substance use severity.

With respect to the other covariates, we find that the likelihood of dying due to alcohol-related causes increased with age, keeping other things constant, and this variable is the strongest predictor of alcohol-related mortality. On the other hand, individuals in the two oldest age groups were less likely to die due to drugs other than alcohol than those in the youngest age group (44–55 years old: *OR* = 0.64; 95% *CI* = 0.48–0.86; >55 years old: *OR* = 0.34; 95% *CI* = 0.25–0.47). Taken together this suggests that the age profiles of those dying of drug-related causes are congruent with the age profiles of those who are also more likely to be admitted into compulsory care for drug addiction. The *Gender* variable was also a significant predictive factor for both types of mortality. Women were 28 percent less likely to die of alcohol-related cause (*OR* = 0.72; 95% *CI* = 0.60–0.86) and 57 percent less likely to die of drugs other than alcohol-related causes (*OR* = 0.43; 95% *CI* = 0.35–0.52) than men were. Hence, women were more likely to end up in both types of compulsory care but at the same time they were less likely to die either of due to alcohol- or drug-related reasons. This finding is in line with prior evidence from studies on gender differences in substance-related mortality conducted in Sweden and in other countries (32–34). With respect to *Immigrant background*, first-generation immigrants from outside Northern Europe (*OR* = 0.61; *CI* = 0.43–0.87) and second-generation immigrants with at least one parent born outside Northern Europe (*OR* = 0.51; *CI* = 0.31–0.83) had a lower risk of dying from alcohol-related causes, compared with the native-born. Individuals born outside the Nordic countries had also a lower likelihood of dying of drugs other than alcohol-related causes compared with individuals

born in Sweden to parents born in Sweden (OR: 0.54; CI: 0.40–0.72). These findings confirm earlier research on the association between immigrant-background and substance use-related mortality in Sweden (7).

In order to account for potential selection bias due to the non-randomized nature of our data, we performed two propensity score matching analyses. The analyses were done to create treatment and control groups that were more similar in their baseline characteristics, allowing a more accurate assessment of the association between compulsory care duration and substance use-related mortality. Matching was done using logit propensity score nearest neighbor matching procedures. Selection of covariates was informed by the results obtained from the Cox models presented in Table 2. Both samples were thus matched on *Age*, *Gender*, and *Immigration Status*. The *ASI CS for alcohol* was entered in the propensity-score model for alcohol-related compulsory care, while the *ASI CS for drug* was entered in the propensity score model for drug-related compulsory care. Tables 4, 5 present the balance of the matching covariates according to treatment status (i.e., whether they received compulsory care or not) for two propensity-score-matched samples. After propensity matching, differences in covariates were substantially reduced between groups, compared to the original sample. Next, discrete-time event-history random effect logistic models were run on the matched samples to corroborate our findings. Table 6 shows that propensity score adjusted results were similar to the unadjusted analysis. The associations between compulsory care duration and alcohol-related mortality (*OR* = 1.53; 95% *CI* = 1.36, 1.72) and between compulsory care duration and drug-related mortality (*OR* = 1.41; 95% *CI* = 1.28, 1.55) were confirmed by the propensity score adjusted estimates.

4. Discussion

Our study identified two key findings. First, among adults assessed for substance use severity, there were significant differences between those who were court-ordered into compulsory care and those who were not required to participate in compulsory care. Those who were court-ordered to compulsory care for use of drugs other than alcohol were likely to be younger, have higher ASI CS for drug use and score higher on ASI CS for mental health and employment, while scoring lower on ASI CS for alcohol. Those who were court-ordered to compulsory care for alcohol were instead more likely to have higher ASI CS for alcohol compared to their counterparts, together with a high score for ASI CS for employment. ASI CS for drug also had a positive small effect for each year following assessment. For both types of compulsory care, women were more likely than men to end up in compulsory care. The second key finding of this study is that court-ordered admissions to compulsory care were significantly associated with higher odds of substance use-related mortality. This is a concerning finding for both scholars and practitioners since, in Sweden as in other countries with similar addiction-treatment systems, compulsory care for severe substance use is designed to reduce the risk of endangering oneself, after discharge, due substance use problems.

Other important findings are related to the higher likelihood of young adults and women among individuals placed in compulsory care for substance use severity. We can suggest some hypotheses to explain the overrepresentation of these groups. With respect to young adults, this finding may be due to a lower willingness to seek voluntary treatment, compared to older age groups. A first possible explanation for the overrepresentation of women could be that mothers tend not to seek voluntary treatment for addiction at an early stage of their substance use disorder, possibly due to concerns related to the risk of losing their children to the child welfare system. A second tentative explanation is that women are more likely to end up in compulsory care because their substance use problems tend to be evaluated as more severe than those of men by social workers. A third possibility is that women are given priority to this treatment, compared to men, due to the limited availability of other types of long-term care in Sweden. However, these hypotheses require further investigation in future studies.

5. Conclusion

Swedish compulsory care for severe substance use does not seem to be associated with a lower risk of substance use related mortality among individuals with risky substance use or substance use disorders. In fact, our study results point to the opposite. One possible reason for this is that, for many individuals placed in compulsory care for substance abuse treatment, the time in treatment corresponds to an imprisonment period in a locked care facility without any medical or psychological therapy. Accordingly, our findings support the recommendation that when compulsory care is deemed necessary, this type of care should include the highest quality of evidence-based care and supportive services to prevent a worsening of substance use problems after discharge. A second recommendation is the importance of providing access to both addiction treatment and psychiatric treatment during compulsory care, particularly for individuals placed in care due to drug other than alcohol use disorders. Previous studies have in fact found that this is a particularly vulnerable group and that worse mental health conditions at assessment were significantly associated with higher rates of mortality from suicide or where drug overdose was the primary or secondary cause of death (35).

5 1. Limitations

One limitation of this study is that substance use severity was only measured by the ASI CSs for alcohol and drug use and we are unaware of the representativeness of our sample of individuals with ASI-assessed problems to all individuals with substance use problems in Sweden. Another limitation is that we do not have information on whether (and how) ASI CSs are used in decision making regarding being mandated to compulsory care and, by and large, about the possible long-term interactions between the assessment and the compulsory care systems. However, the ASI-interview is the most used assessment tool by Swedish social workers in order to assess substance use (and related) problems and plan interventions responding appropriately to the nature of these problems. Moreover, ASI composite scores have been rigorously tested for reliability and validity in many settings over the years and the results presented here corroborate previous findings about factors associated with higher odds of substance use-related mortality in Sweden (7, 25, 36, 28).

Data availability statement

The register data used in this study cannot be made publicly available under Swedish privacy laws. Data for this research project are from the National Board of Health and Welfare and Statistics Sweden, which do not permit data-sharing according to the Swedish Secrecy Act. Investigators may apply to access the study data by contacting the Swedish National Board of Health and Welfare (registerservice@socialstyrelsen.se) and Statistics Sweden (mikrodata.individ@scb.se).

Ethics statement

The NBHW, the Regional Ethical Review Board at Umeå University (DNR: 2016/504-31; amendment 2020-06233) and Institutional Review Board (IRB) of the University of Denver reviewed and approved the study protocol. Written informed consent from the patients was not required to participate in this study in accordance with the national legislation and the institutional requirements.

Author contributions

SS: conceptualization, data curation, formal analysis, methodology, and writing—original draft preparation. RG: conceptualization and writing—original draft preparation. LL: conceptualization, funding acquisition, project administration, supervision, validation, and writing—review and editing. All authors contributed to the article and approved the submitted version.

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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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Problematic Social Networking Site use-effects on mental health and the brain

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The association between excessive use of Social Networking Sites (SNS) and mental health is raising serious concern among health and education professionals. Problematic SNS use has been associated with an increased rate of depression, anxiety, stress, obsessive-compulsive disorder (OCD), attention-deficit/hyperactivity disorder (ADHD), and propensity to excessive alcohol use. It may also lead to vulnerability to aggression, cyberbullying and fear of missing out (FOMO). There is little evidence for cognitive impairments, but there is some preliminary event-related potentials (ERPs) evidence for inefficiency in allocating and monitoring resources and inhibitory control. Problematic SNS has been associated with the personality traits of conscientiousness agreeableness and neuroticism, and with narcissism. There is evidence for reduced sleep quality and quantity, longer sleeping latency and more sleep disturbance. The few brain imaging studies show some similarity between problematic SNS use and other addictions related to inhibitory-control mechanism, reduced gray matter volumes in the nucleus accumbens, amygdala, and the insula, suggesting rewarding effects of SNS use on the brain. Finally, there is preliminary evidence that treatment with Cognitive Behavior Therapy (CBT) can assist in short-term abstinence intervention to treat problematic SNS use. We conclude that problematic SNS use may have deleterious effects on emotional and social relationships, and more research is required on its effects on cognitive and brain function.

KEYWORDS

problematic Social Network Site use, social media addiction, social media, fear of missing out, social networks

Introduction

Over the past decade there has been a growing interest in the problematic use of social networking sites (SNSs) or Social media activity. The purpose of this narrative review is to summarize studies on problematic SNS use and Social media addiction from 2010 until now. Keywords were entered in a PubMed and Scopus search using "Problematic Social Networking Site use" and "Social media addiction" as search words and publications were limited from 2010 to October 2022. The search has yielded 797 records. These were screened for suitability by using inclusion criteria of English language, published in peer-reviewed journals, measure brain imaging in human subjects. Exclusion criteria were abstracts, dissertations, methodological papers and conference papers. Based on title and abstract, following these criteria, 699 records were excluded, and 98 records were included in this narrative review.

The magnitude and definition of Problematic Social Networking Site use

There is a significant increase in the use of social networking sites (SNSs) or Social media activity. In 2021, over 4.26 billion people were using social media worldwide, a number projected to increase to almost six billion in 2027. Social media is an integral part of daily Internet use. On average, Internet users spend 144 minutes per day on social media and messaging applications, an increase of more than half an hour since 2015 (1). Facebook who leads the market, was the first to have over 1 billion accounts and it currently has more than 2.89 billion monthly users. The company also owns four companies Facebook, WhatsApp, Facebook Messenger, and Instagram with over 1 billion users each, and in 2021, Facebook reported over 3.58 billion monthly users (1). Given the extensive use of SNS, it is important to understand the potential risks involved in problematic SNS use. The World Health Organization (2) has raised Public health concerns over the similarity between signs and symptoms of Internet Gaming Disorder (IGD) including problematic SNS use, gambling disorder and substance use disorders.

Problematic SNS use has been defined by Andreassen and Pallesen (3) as "being highly concerned about SNSs, driven by a strong motivation to use SNSs, and to devote a lot of time and effort to SNSs that it impairs other social activities, education and or occupation, interpersonal relationships, and or psychological health and wellbeing." There are different terms describing problematic SNS use, these include Social Media Use Disorder, or Social Media Disorder, and Networks Use Disorder, and the taxonomy of problems in the study of Internet use disorder is being discussed by Montag (4). The prevalence of problematic SNS varies among populations ranging from 1.6% in Nigeria (5), 4.5% in Hungary (6), 8.6% in Peru (7), and 12% in China (8), 8.9% among Italian adolescents (9). A meta-analysis has analyzed 63 independent samples of around 35,000 respondents from 32 nations has shown that prevalence rates varied among studies and the prevalence estimate was 5% for studies who used strict classifications (10).

Comorbidity with other disorders

A recent review by Hussain and Griffiths (11) has shown a relationship between problematic SNS and depression, anxiety, stress, ADHD and OCD. Studies have shown a positive correlation between Problematic SNS use and depression (12–18) anxiety (12, 14, 16–19), ADHD and OCD (12) and stress (14, 19). Since then, new studies have found an association with depression (20–22) ADHD (23) and Social anxiety (24). Patients with major depressive disorder (MDD) were more addicted to SNS and "relapse" to problematic SNS use predicted depressive symptoms in these patients (25). A recent study has shown an association between problematic SNS use and eating disorder that was mediated by muscle dysmorphia (26). Problematic SNS use symptoms correlated with anxiety and narcissism (27, 28). Finally, problematic SNS use may place individuals at risk for potentially problematic drinking (29). Adolescents (age 11–13) in Italy, showed that problematic SNS use was linked with the propensity for substance use (30).

In summary, problematic SNS use is associated with mental health problems that are similar to those of an IGD, such as depression, anxiety (including social anxiety), OCD and ADHD and risk for problematic drinking.

Emotional and social factors associated with problematic SNS use

Low self-esteem and social anxiety

Low self-efficacy, positive outcome expectancies, and impulsivity have been identified in excessive SNS users (8). Among 8,912 college students across seven countries (U.S., Canada, Spain, England, Argentina, Uruguay, and South Africa) high ruminating thoughts have accounted for major depressive and social anxiety symptoms (31). Several studies have shown an association between low self-esteem (32, 33) and fear of negative self-evaluation (34) anxiety (35) and problematic SNS use.

Cyberbullying, emotional abuse and distress

Problematic SNS use was linked with cyberbullying and cyber victimization of university students (36, 37). Students who reported that their upbringing style as inconsistent and unbalanced and those who showed an aggressive trait had higher scores of problematic SNS use (38). Child emotional abuse, indicated by deficient self-other differentiation and impaired reflective function was also associated with problematic SNS use (39). Stress, impulsiveness and reduced inhibitory control contributed to problematic SNS among lower socio-economic families in China (40). Finally, lower emotional intelligence predicted perceived stress, which contributed to depressive symptoms and problematic SNS use (41).

Social comparison and "peer phubbing"

Problematic SNS use was also associated with social comparison which is linked with stress and impaired wellbeing) (42). "Peer phubbing" (the act of ignoring other people in the context of social contact by paying attention to his/her phone instead of focusing on the person directly in his/her company)

correlated with problematic SNS use (43). Furthermore, social anxiety mediated the association between "peer phubbing" and problematic SNS use, particularly among undergraduates with family financial difficulties (43). Finally, "peer phubbing" was associated with loneliness and problematic SNS use (44).

Emotion recognition and meta cognition deficits

Emotion recognition deficits among individuals with problematic SNS use were demonstrated on the Reading the Mind in the Eyes Test (RMET) (45). A following study has shown that faulty meta-cognitions (like worry, superstition, punishment, beliefs about responsibility, and cognitive monitoring) but not emotion recognition predicted problematic SNS use in adolescents (46).

Body shame and body image

Female adolescents reported higher scores of body shame, social physique anxiety and problematic SNS use (47). Awareness and internalization mediated the association between body dissatisfaction and problematic SNS use (48). Depression and anxiety mediated the relationship between perceived stress and problematic SNS use and this relationship was moderated by psychological resilience, but not by social support (49). Negative body image correlated with frequency of SNS use and it was enhanced by exposure to appearance-related content on the Internet. Furthermore, negative body image or body shame was indirectly associated with adolescents' problematic SNS use (50). Finally, high levels of self-reflection was a protective factor against problematic SNS use among adolescents. Adolescents with problematic SNS use tend to have low exploration of self-identity and in crisis they consider alternative commitments instead (51).

Depression

A meta-analysis has reported that depressive symptoms weakly correlated with time spent using SNS and intensity of SNS use (52). However, depressive symptoms moderately correlated with problematic SNS use, and it was not moderated by other factors like age or gender.

External motivations of social reward

The urge to use SNS was associated with handling boredom rather than increase positive emotions or reduce negative emotions (53). Others stress the importance of social rewards like "likes," social comparisons and connection with other people rather than motivations based on enjoyment and negative power (54). There is supporting evidence that young people tend to use SNSs to enhance their external expectations of having a large network size rather than internal expectations for subjective wellbeing (55). Finally, young adults who used social media for 2 h or more daily, increased perceived social isolation compared with those who use it for <30 min each day (56). Similar associations were reported in middle-aged and older adults (57). It has been suggested that people who have reduced off-line social experiences and are highly influenced by social media tend to have unrealistic self-perceptions.

In summary, problematic SNS use has been associated with internal emotional factors like depression and anxiety, aggression and negative body image and external social motivations.

Impaired cognitive and executive function

Emotional states and stress mediated the association between executive function, and problematic SNS use among Chinese female college students (58). There were no differences between problematic and non-problematic SNS use groups in cognitive flexibility and inhibitory control aspects of Executive Function measured by performance on the Wisconsin Card Sorting Test (WCST) (20). Categories achieved and number of perseverative errors correlated with scores Social Media Addiction (20). Finally, a study of inhibitory control mechanisms together with event-related potentials (ERPs) using an SNS Go-No Go task showed no performance differences between problematic and non-problematic users (59). However, there was an indication of larger N1 amplitude following SNS images than control images and a larger N2 amplitude and smaller NoGo-P3 amplitude in excessive users. These findings may suggest inefficient allocation and monitoring of resources and problems inhibitory control mechanisms (59). In summary, there is little evidence that problematic SNS use may lead to impaired flexibility of inhibitory control mechanisms, though there may be ERP evidence for late inhibitory control (unsupported by behavioral data).

Social needs and "fear of missing out"

It has been suggested that problematic social media use has been associated with FoMO in order to serve and compensate for individuals' social needs (60). FoMO mediated the relationship between the fear of a negative and positive evaluation and social use of the smartphone (60). FoMO and withdrawal ratings were higher among participants with 72 h of restricted access to smartphones compared with those

without access to smartphones (61). FOMO also predicted excessive smartphone use by female WhatsApp users (62) and it was associated with the use of smartphones by American undergraduate students for social purposes (63). FoMO mediated the relationship between depression and anxiety and the severity of problematic smartphone use. This finding suggests that individuals experiencing social anxiety who desire social contact are likely to use the smartphone as an avoidance mechanism (63).

A survey of college students has found that greater social activity is a positive predictor of addiction to the social media application Snapchat (64). Among young adults who use Facebook, FoMO, dysfunctional cognitions, and distress predicted problematic SNS use (65). FoMO and rumination mediated the connection between social anxiety and problematic Facebook use (66). FoMO also played an important role in increased sensitivity to stress which is associated with neglect and problematic SNS use, and these in turn were associated with negative emotions (67). Finally, FoMO mediated the association between mental health and symptoms of Internet Use Disorder (IUD) (68).

Attachment

The evidence on the relationship between attachment and problematic SNS use is scarce. The association between anxious attachment and problematic SNS use was mediated by FoMO and online social support, and online social support negatively mediated the association between avoidant attachment and problematic SNS use (69). A recent review has suggested that problematic SNS use negatively correlated with secure attachment and positively correlated with anxious attachment, but there was no clear association with avoidant attachment. Furthermore, the associations between problematic SNS use and attachment were mediated by individual and interpersonal variables (70).

Personality

Only few studies that have investigated the relationships between personality and problematic SNS use. Emotional stability, extraversion, and conscientiousness predicted Problematic Facebook use, among adolescents (71). Among the big 5 personality factors, agreeableness, conscientiousness, and self-liking negatively correlated with Instagram addiction (72). Furthermore, self-liking partially mediated the association between Instagram addiction with agreeableness and fully mediated the relationship between Instagram addiction with conscientiousness (72). Conscientiousness, Extraversion, Neuroticism, and Loneliness were predictors of Facebook Addiction. Neuroticism but not extroversion, had a positive correlation with problematic SNS use (73). Furthermore, frequency of status updates mediated the association between each personality trait and problematic SNS use. "Likes" mediated the association between extraversion and problematic SNS use and there was no effect for neuroticism (74). Finally, problematic SNS use correlated with the dark triad traits psychopathy, narcissism and Machiavellianism, and emotion dysregulation (75). Furthermore, emotion regulation played an important role mediating the association between dark triad traits and problematic SNS use (75). Specifically to narcissism, vulnerable narcissists reported a stronger preference for online social interactions and higher overall levels of problematic use of SNSs than grandiose narcissists (76). In summary, problematic SNS use has been associated with FoMO, attachment difficulties and certain personality characteristics like conscientiousness, agreeableness and neuroticism. There is contradictory evidence regarding extraversion and some evidence for an association with narcissism.

Effects of health including sleep

Few studies have explored the effects of problematic SNS use on sleep quality and duration in adolescents and young adults. A negative correlation was reported between time spent on screen-based devices and sleep quality and quantity (77). Furthermore, higher rates of insomnia, reduced sleep duration, later sleep onset and problems in sleep efficiency and evening screen time were reported among students who also showed similar patterns of sleep problems together with poorer academic achievements, reduced life satisfaction and depression (78). Among young adults in Italy, problematic SNS use was not directly associated with poor sleep quality and it was mediated by depression and stress (79). A majority of Czech adolescents use SNS before bedtime, 20% eat dinner while using SNS, about a third use SNS continuously, SNS use is associated with alcohol use and parental restriction can reduce problematic SNS use (80). Self-reported screen time and symptoms of withdrawal correlated with problematic SNS use, stressing the addictive properties of SNS use among adolescents (81). Finally, problematic SNS use was linked with male and female sexual difficulties (82). In summary, there is evidence that problematic SNS use is associated with reduced sleep quality and quantity, longer sleeping latency and more sleep disturbance and some evidence for sexual problems.

COVID-19 effects on problematic SNS use and longitudinal studies

During COVID-19 social distancing in a period when there were hardly any in-person interactions, problematic SNS use correlated positively with frustration over the need to relate to others as well as depressive symptoms and loneliness (83)

and negatively with engagement and wellbeing (84). Problematic SNS use was shown as a predictor of emotional distress during covid-19 (85). Several reviews have outlined the problems of social network use during COVID-19. During lockdown prevalence of problematic social media use in young adults was higher compared to non-lockdown periods (86). Although problematic Internet use is associated with health problems in a minority of young people, the COVID-19 pandemic may have enhanced such use and consequently increased health problems (87). Social distancing and lockdowns have increased negative emotions like stress, anxiety, and depression but it had also been associated with positive aspects like enhanced social connections and the use of entertainment. Although most users of Internet technology made an adaptive use of this technology, vulnerable individuals were at risk of developing problematic use of the Internet and require support and guidance (88).

Recently, there is an increasing number of longitudinal studies on problematic social media use, some of them during COVID-19 pandemic with some conflicting results. A reciprocal relationship was reported between the level of problematic SNS use and anxiety over 9 months among Hong Kong and Taiwanese students (89). Increased insomnia and problematic SNS use was reported after 3 month follow-up among Iranian adolescents (90). During three waves of COVID-19 over 6 months in China, problematic social media use was associated with problematic smartphone use, and problematic social media use was associated with an increase in depression and anxiety (91). Although higher levels of problematic smartphone use were not related to greater psychological distress before the COVID-19 outbreak, this prospective relationship became significant during the COVID-19 outbreak in school children in China (92). Chinese schoolchildren spent more time on the smartphone and social media, but not gaming during the school suspension compared to before the outbreak of COVID-19 and those who were highly engaged with Internet-related activities showed an increased level of psychological distress especially during school suspension (93). During COVID-19, problematic use of Internet-related activities in Chinese school children were increased among low and moderate users of the Internet, but it has surprisingly declined among participants with high usage of the Internet (94). A 6-month longitudinal study of Taiwanese students has surprisingly shown that problematic social media use correlated with higher physical activity (95). Finally, a 3-month longitudinal study among Hong Kong students has expectedly shown that social media use negatively correlated with physical activity and sleep quality (96).

Brain imaging

The go/no-go paradigm was used in 20 Facebook users who responded to Facebook and traffic sign control stimuli in functional MRI (97). There was a positive correlation between Facebook go trials and addiction scores but there was no association between inhibitory mechanisms and addiction scores. These findings have indicated that Facebook addiction shares some neural features with substance and gambling addictions, related to inhibitory-control brain mechanisms (97). Problematic SNS use was associated with reduced gray matter volumes in the amygdala but not in the nucleus accumbens in twenty social network site (SNS) users (98). The authors have argued that these alterations indicate impulsivity thus resemble other addictions. Furthermore, they have found a normal gray matter volume in the Anterior Cingulate Cortex (ACC) which suggests unimpaired inhibition mechanisms (98). Montag (99) have recorded actual Facebook use of 62 participants on their smartphones over the course of 5 weeks and they have reported that higher daily frequency of checking Facebook on the smartphone correlated with smaller gray matter volumes of the nucleus accumbens, suggesting that Facebook use has rewarding effects on the brain. An MRI study of social media users showed a negative correlation between gray matter volume of the insula with problematic SNS use symptoms that was mediated by delay discounting, an indicator of impulsivity (100). Symptom severity of problematic SNS use correlated with attentional impulsivity but not with executive function or inhibitory control of SNS-related cues (101). Finally, a study has investigated social anxiety-related inhibitory control comparing individuals who are addicted to gaming, problematic SNS users, and control participants. They have used a Go/no Go task with emotional words and the Emotional Stroop Task in fMRI (102). IGD participants showed impulsivity, social anxiety and impaired emotional competence, however there were no between group differences in performance of both tasks. During interference of socially anxious words there was decreased middle and superior temporal gyrus activity in gaming addicted participants compared with problematic SNS users (102). In summary, there is evidence that problematic SNS use is associated with impaired inhibitory mechanisms and reduced gray matter in several brain structures such as the amygdala, nucleus accumbens and the Insula. There is some evidence for impulsivity in these users but it is based on correlation and not on group differences.

Intervention

A short-term abstinence intervention program based on Cognitive Behavior Therapy (CBT), has treated 65 clients with problematic SNS use. They had sessions of over 2 h breaks from social media for 2 weeks, compared with a control group that has used social media as usual. Intervention had a positive effect on emotional wellbeing, behavioral and cognitive function during abstinence and afterwards. These findings suggest that CBT-based short-term abstinence intervention can be useful to improve problematic SNS use (103). There is also preliminary evidence that "Social Media Detoxification" among university

students can increase positive mood, reduce anxiety and improve sleep during and immediately after detoxification (104).

Discussion

Problematic SNS use is associated with potentially harmful behaviors such as loss of control over daily life activities, low self-esteem, anxiety, loneliness and depression. The studies reviewed so far have consistently shown evidence of comorbidity with psychiatric disorders such as depression, anxiety, OCD, stress and ADHD resembling what was reported by Weinstein and colleagues in adolescents and young adults diagnosed with Internet and Gaming Disorder and with excessive smartphone use (105, 106). Other emotional factors included ruminating thoughts, aggression and problems in emotion regulation. This similarity is not surprising, given the strong correlation between measures of Internet addiction and problematic SNS use that was found through these studies. Both conditions are characterized by the loss of cognitive and emotional control, which is associated with impairment in family function and in relationships with friends and low self-esteem. Both conditions also share increased levels of depression, anxiety, and stress and socializing is an important motivation in video game play (14). There are differences between problematic SNS use and Internet addiction. The motivation to use social media can be in order to obtain external social rewards such as "likes," to make social comparisons and to have connection with a large group of other people rather than enjoyment or subjective wellbeing (54, 55). IGD is closely associated with sensation and novelty seeking (105), impulsivity, enhanced sensitivity to reward and impaired cognitive control (107). There is little evidence for impaired cognitive control and impulsivity in problematic SNS use. Furthermore, there is some evidence that problematic SNS use is characterized by deficits in emotion regulation, for example, reduced striatal activation during self-reflection compared to during ideal reflection while performing on a self-retrieval task in fMRI (108). This is compatible with recent evidence for low self-reflection among problematic SNS users (51).

There is little research on problematic SNS use and personality factors, several studies have found a connection with neuroticism agreeableness and conscientiousness and there are conflicting results regarding the association with extraversion. There is little evidence for impairment in executive cognitive function such as mental flexibility and inhibitory control. There is some ERP evidence of inefficiency in resource allocation and inhibitory control. Due to the lack of difference in behavioral performance this evidence should be interpreted with caution. Also, very few health problems have been reported in problematic SNS use, mainly related to sleep quality and duration. There are few studies on sex differences in problematic SNS use. Turel (109) have shown that the negative association between SNS addiction symptoms and wellbeing is enhanced by neuroticism, and that this enhancement is stronger for women than for men.

There are very few studies investigating whether problematic SNS use meets the main components of "behavioral addiction," namely; salience, mood modification, tolerance, withdrawal, conflict and relapse (110). Two experiments have used a cue-reactivity paradigm to investigate craving in problematic SNSs use (111). They have found that SNS-related word clues induced craving and excitability in problematic SNS users. Furthermore, craving induced by an image clue was significantly higher than the craving induced by a word clue (111). A recent study has shown that Facebook-related cues elicited larger ERP positivity than other stimuli in Facebook users and that craving correlated with lower later positivity to pleasant and unpleasant cues (112). These findings indicate that Facebook-related cues and craving are given attention priority over other emotions (112). Cue-elicited urges to use SNS correlated with excessive and problematic SNS use (113). Desires and urges to use SNSs (wanting) were dissociated from enjoyment and pleasure (liking) related to SNSs, suggesting that similarly to drug addiction, wanting was more predictive than liking to the intensity and problematic SNS use (113).

There is further evidence for selective attention to SNS cues and deficient decision-making in problematic SNS users. Problematic SNS users who performed on a visual dot probe task, showed attentional bias for SNS-related images, a mechanism that is common to addictive disorders (114). Problematic SNS users also show disadvantageous decision making which was indicated by high self-disclosure posting in SNS sites while neglecting long-term risks (115). There was also evidence that problematic SNS use was associated with impaired decision–making indicated by taking more risk-taking decisions on the Iowa gambling task similarly to individuals with behavior or substance use disorder (116). However, the study reported a negative correlation between Facebook addiction scores and performance on the IGT over the last block of 20 trials but not in earlier blocks of trials. This is weak evidence of impulsivity since it is based on correlation and not on significant group differences in risky decision-making. These studies support the argument that problematic SNS use, similarly to IGD and other behavioral addictions, has the components of craving, selective attention to salient stimuli and impaired decision making. However, they fall short of a full validity of problematic SNS use as a distinct behavioral addiction. Finally, ADHD symptoms have led to increased stress and decreased self-esteem and it has been suggested that together with ADHD, they facilitated cravings to use social network while driving (117).

Few brain imaging studies have investigated the neural correlations of problematic SNS use. There is some evidence for reduced gray matter volume in the amygdala, but not in the ACC and there are conflicting results about gray matter volume in the nucleus accumbens. Several studies have suggested that similar to drug and other behavioral addictions, impulsivity and

impaired inhibitory control mechanisms relate to problematic SNS use, but the evidence is mainly based on correlations than actual group differences. There is also little evidence that suggests that brain mechanisms in response to emotional stimuli are different between IGD participants who are addicted to games compared with problematic SNS users. Finally, very few studies on treatment and abstinence, have suggested that CBT based treatment can ameliorate problematic SNS use.

There are several ways of handling the emotional and social problems associated with problematic social media use. First, parents can restrict the use of social media to several hours a day, in particular during bedtime, meals and sports. Especially bedtime is important since social media use has negative effects on sleep quality and quantity. Secondly, alternative activities like indoor and outdoor sport activity and social activity with family should be encouraged. Educational programs at school should be encouraged especially about the negative emotional effects of social media use like loneliness in order to increase awareness to the problem. Educational efforts should be made to deal with the emotional problems associated with excessive social media use. Adolescents should be encouraged not to use social media when they feel "down" or depressed since it can exacerbate their emotional state and also to avoid social comparisons since social medial does not often reflect real life and how to deal with FoMO that is known to exacerbate loneliness and negative emotions.

Finally, problematic social networking use may be associated with self-stigma. Recent studies assessing the problematic social networking use and self-stigma among people with mental illness have shown an association between problematic social networking use and self-stigma. For example, people with substance use disorders were found that their problematic use may lead to their self-stigma (118, 119). It is useful to investigate further this important association.

Limitations

One of the major limitations in studies of problematic SNS use, similar to Internet and Gaming Disorder and excessive smartphone use is that they are mainly cross-sectional studies without baseline measures and they rely on relationship between structural and functional changes in the brain and subjective measures. These relationships do not provide any proof that problematic SNS use affects the development of the adolescent or adult brain. Factors that mediate such associations tend to be educational, cognitive, emotional, and social in nature. Methodological considerations also include age (e.g., use by adolescents and students), and lack of comparison with substance use disorder. Finally, very few studies have considered sex differences in cognitive and brain function in problematic SNS users.

Summary

Easy access to the smartphone enables users to connect to social media and social networks. Unfortunately, in some users this can lead to excessive use and may have negative effects on mental health, especially social anxiety and depression. Problematic SNS use affects sleep quality and quantity as well as altered emotional communication patterns, and FOMO. These characteristics should send an alarm signal to clinicians and educators to investigate problematic SNS use particularly in children and adolescents. Gaps in our knowledge- more research is necessary on the cognitive and brain changes associated with problematic SNS use, on personality and sex-differences and treatment. Finally, problematic SNS use correlates strongly with Internet addiction; hence, the similarity in cognitive, emotional, and social consequences. The evidence so far does not support the inclusion of problematic SNS use as a clinical diagnosis as a behavioral addiction but rather as a type of Internet and Gaming Disorder.

Author contributions

The author confirms being the sole contributor of this work and has approved it for publication.

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Conflict of interest

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

Publisher's note

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Alpha peak activity in resting-state EEG is associated with depressive score

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Introduction: Depression is a serious psychiatric disorder characterized by prolonged sadness, loss of interest or pleasure. The dominant alpha peak activity in resting-state EEG is suggested to be an intrinsic neural marker for diagnosis of mental disorders.

Methods: To investigate an association between alpha peak activity and depression severity, the present study recorded resting-state EEG (EGI 128 channels, off-line average reference, source reconstruction by a distributed inverse method with the sLORETA normalization, parcellation of 68 Desikan–Killiany regions) from 155 patients with depression (42 males, mean age 35 years) and acquired patients' scores of Self-Rating Depression Scales. We measured both the alpha peak amplitude that is more related to synchronous neural discharging and the alpha peak frequency that is more associated with brain metabolism.

Results: The results showed that over widely distributed brain regions, individual patients' alpha peak amplitudes were negatively correlated with their depressive scores, and individual patients' alpha peak frequencies were positively correlated with their depressive scores.

Discussion: These results reveal that alpha peak amplitude and frequency are associated with self-rating depressive score in different manners, and the finding suggests the potential of alpha peak activity in resting-state EEG acting as an important neural factor in evaluation of depression severity in supplement to diagnosis.

KEYWORDS

alpha peak activity, depression, frequency spectrum, resting-state EEG, correlation analysis

1. Introduction

Depression is characterized by prolonged sadness, loss of interest, difficulty to experience pleasure, and possibly leads to suicide in extreme cases (Friedrich, 2017). Globally, over 300 million people are suffering from this serious neurological disorder (World Health Organization, 2017). In clinical practice, the diagnosis of depression faces difficulties. The first is the complex symptoms of depression, particularly the combined symptoms with other disorders such as addictive disorders and anxiety disorders (for reviews, see Tiller, 2013; Emery and Akil, 2020). A categorical distinction between depression and other psychological disorders remains ambiguous and antidepressant drugs are sometimes effective for unrelated disorders (Kalat, 2015). In this regard, measurement scales such as the Self-Rating Depression Scales (SDS) are valuable to help clinicians further evaluate symptoms and better identify, diagnose, and treat depression in practice (Gelenberg, 2010). Second, the depression diagnosis lacks quantitative measures that are required to further evaluate the severity of patients, and the SDS is such a test that provides an evaluation of the severity of depressive symptom. Regarding this, in supplement to a diagnosis of patients vs. healthy controls, the SDS measure allows further quantitative assessment of the severity of depressive symptoms of patients.

The human electroencephalogram (EEG) measures oscillating brain activity in a broad frequency range typically including the delta (1–3 Hz), theta (4–6 Hz), alpha (7–13 Hz), beta (14–30 Hz), and gamma (30–100 Hz) bands, and alpha activity is the most prominent rhythmic activity and is manifested by a peak (∼10 Hz) in the frequency spectrum (Klimesch, 1999). Deferent measurements have been adopted to quantify the characteristics of activities in the alpha range (Klimesch, 1999; Pfurtscheller and da Silva, 1999; Angelakis et al., 2004). In terms of dividing the alpha spectrum into sub-bands, low (8–9 Hz) and high (11–12 Hz) alpha bands that are below and above the peak frequency of alpha activity have been suggested and are assumed to be generated by different pacemakers with different cortical/thalamic origins. Besides the best-known alpha rhythm that is widely distributed with larger amplitudes over posterior regions, the rolandic mu (mu stands for motor) rhythm manifests over the motor cortex and the auditory tau (tau stands for temporal) rhythm is best seen over the auditory cortex. The alpha activity investigated in the present study referred to the classic alpha activity. An alternative way to observe alpha activity is regarding individual alpha peaks, i.e., focusing on analyzing the characteristics of alpha peak activity. After identifying individual alpha peaks, two measures of alpha peak activity are typically investigated. Alpha peak amplitude assesses amplitude of activity around alpha peak. While alpha band amplitude and alpha peak amplitude both measure amplitude of alpha activity, the former is applied for a defined alpha frequency range and the latter emphasizes spectrum characteristics around individual alpha peaks. Alpha peak amplitude is suggested to reflect synchronous neural discharging and enhanced alpha peak amplitude is considered as an indicator of cortical hypoactivity (Klimesch, 1999). Another major measure of alpha peak activity is alpha peak frequency, which is the frequency at which the strongest spectrum activity appears. It has been observed that alpha peak frequency is associated with cerebral blood flow and oxygenation. For example, alpha peak frequency positively correlated with cerebral blood flow (Jann et al., 2010) and decreased after hypoxia with hemoglobin oxygen (Van der Worp et al., 1991). Alpha peak frequency is assumed to be related to brain metabolism and is considered as an indicator of cognitive preparedness that reflects the brain's capacity for optimal cognitive performance (Angelakis et al., 2004). The amplitude and frequency of alpha peak activity vary across individuals and have been shown to be associated with a broad range of cognitive functions and states (Angelakis et al., 2004; Cecere et al., 2015; Ronconi and Melcher, 2017). Individual alpha peak amplitudes and frequencies of the same subjects were also found to be reliable across examination sessions on separate days using intraclass correlation coefficient (Katyal et al., 2019). The dominant alpha peak activity in resting-state EEG has been suggested to be a potential intrinsic neuromarker of diagnosis of mental disorders (Klimesch, 1999; Lefebvre et al., 2018; Newson and Thiagarajan, 2019).

A large body of depression research has investigated EEG band amplitudes in different frequency ranges. The results generally found elevated amplitude of patients compared to normal controls in the theta, alpha, and gamma bands, though some did not observe the increased amplitude or found decreased amplitude in patients (for reviews, see de Aguiar Neto and Rosa, 2019; Fernández-Palleiro et al., 2019; Schiller, 2019). Among the frequency ranges, alpha peak activity is of particular interest, partly due to the early proposal of its relation with affective processing "The ability to produce "good" alpha waves seems to be a neurophysiological characteristic which is related in some way to the affective capacity of the individual" (Lemere, 1936). Increased amplitude in the alpha frequency range (∼7–13 Hz) has been generally found in depression patients compared to healthy controls (for review, see Olbrich and Arns, 2013). Moreover, the alpha amplitude of patients vs. healthy controls has been found to exhibit hemispheric asymmetries, generally with relatively stronger alpha amplitude over left then right frontal regions, as well as relatively stronger right parietotemporal alpha amplitude (for reviews, see Bruder et al., 2017; Van der Vinne et al., 2017; Kaiser et al., 2018). Despite the extensive investigation of comparing alpha band amplitudes between patients and normal controls, the research that further evaluates severity of depression patients by investigating the relationship between individual alpha peak activities and depression severities is sparse and existing understanding is largely ambiguous. A related clue was from a recent non-clinical study that used resting-state EEG with 19 electrodes and investigated correlations between alpha peak activities and self-report depressive scores of non-clinical subjects (Tement et al., 2016). The results did not show a significant correlation between alpha peak amplitudes and depressive scores, although for females there was a non-significant trend of a negative correlation. For alpha peak frequency, a significant correlation was also lacking for the overall subjects, despite that the results suggested a modulation by gender that there was a significant positive correlation for males and a significant negative correlation for females.

Therefore, the present study aimed to examine the association between individual depressive patients' alpha peak activities

and the severities of their depressive symptoms. We recruited 155 depressive patients and recorded their 5-min resting-state EEG. Correlation analysis was performed between the alpha peak measures including alpha peak amplitude and alpha peak frequency and the patients' SDS scores. As introduced above, assessment of the SDS score allowed further evaluation of individual patients' depression severities. Accordingly, analysis of alpha peak activity focused on individual characteristics of alpha activity, and the measures of alpha peak amplitude and alpha peak frequency provided examination in terms of different physiological mechanisms. Moreover, the EEG source reconstruction research has recently made considerable progresses in localizing cortical sources of resting-state scalp EEG signals and overcoming the issue of correlated signals from scalp electrodes (Schoffelen and Gross, 2009; Niso et al., 2019), which would be of particular importance when the accuracy and efficiency of a neuromarker are under concern in clinical applications. The EEG data in the present study were thus analyzed on the cortical source level.

Together, given the role of alpha peak activity in diagnosing mental disorders, we hypothesize that alpha peak activity is an important factor for evaluation of depression severity in supplement to diagnosis and predict that individual patients' alpha peak measures in resting-state EEG would correlate with their depressive scores.

2. Materials and methods

2.1. Participants

Totally 155 patients with depression (42 males; mean age 35.14 years, *SD* = 11.98) were recruited from Guangdong Provincial Hospital of Chinese Medicine, China. The patients were diagnosed depressive episodes according to the International Classification of Diseases 10th Edition (ICD-10, F32) by professional psychiatrists. [Note that major depressive disorder is the diagnosis according to the Diagnostic and Statistical Manual of Mental Disorders 5th Edition (DSM-5)]. The patients were recruited with the following criteria. Inclusion criteria: (1) Aged between 18 and 65 years; (2) Diagnosed with a first appearance depressive disorder; (3) Have not received medications for depression within 12 weeks prior to enrollment in the study. Exclusion criteria: (1) Have a tendency to commit suicide (be evaluated by psychiatric specialists); (2) Have participated in other clinical trials within 4 weeks before the start of the study; (3) A history of severe cardiac, pulmonary, hepatic, and renal disease requiring treatment; (4) The patient was a pregnant or lactating woman; (5) Who install a pacemaker or an artificial joint; (6) Addiction to drugs or alcohol; (7) Taking antidepressants or the pharmacological effects of such anti-depressants had not been washed out. The SDS scores (Zung, 1965) were obtained for 154 among the 155 patients.

The research protocols in this study followed the tenets of the Declaration of Helsinki and were approved by the Ethics Committee of Guangdong Provincial Hospital of Chinese Medicine (YF-2020-198-01) and the Institutional Review Board of Psychology Department of Sun Yat-sen University. All participants provided written informed consent before their participation.

2.2. Data acquisition and analysis

The participants were asked to sit and relax for 5 min with their eyes closed during the EEG recording. An EGI (Electrical Geodesic Inc., OR, USA) system with a 128 electrode Hydro Cel Geodesic Sensor Net was used to record the EEG. The EEG was digitized at 1,000 Hz and filtered with a 0.05–100 Hz band-pass filter. The electrodes were referenced to CZ. Electrodes impedances were kept below 50 kΩ .

A prior power analysis was performed using G*Power 3 (Faul et al., 2007). The analysis was in accordance to the effects reported in a previous study (Tement et al., 2016). The mean effect size for electrodes showing significant correlation between alpha peak frequency and depressive score was 0.32 for males and −0.31 for females. Based on the smaller effect size of −0.31, the alpha level of $p < 0.05$ (two tailed), and the power of 0.80, 79 subjects were required.

The EEG data were analyzed by a customized processing routine involving the usage of MATLAB (The Mathworks, Natick,MA, USA), EEGLAB (for artifact removal with Independent Component Analysis),[1] Brainstorm (for source reconstruction),[2] and mfeeg (for basic EEG signal processing).[3] The EEG was down-sampled to 100 Hz and 0.5–45 Hz band-pass filtered. Bad electrodes were determined by a Clean Rawdata procedure in EEGLAB (rejecting flat channels, channels with a large amount of noise based on their standard deviation, and channels poorly correlated with other channels) and then interpolated with data from neighboring electrodes. The Infomax Independent Components Analysis (ICA) module in EEGLAB was used to decompose the EEG and artifact components (including ocular and muscle artifact) were removed (Delorme et al., 2007; Pion-Tonachini et al., 2019). Data quality was further examined *via* a manual checking procedure, in which data from one patient were excluded due to large signal noise. Finally, EEG and clinical data of 153 among the 155 recruited patients were subjected into the following analyses. The EEG was then re-referenced to the common average reference. Source reconstruction was conducted using the forward and inverse models implemented in Brainstorm (Tadel et al., 2011). The strength of the source transformed signal was under the sLORETA normalized unit. The cortical surface was parcellated into 68 brain regions with the Desikan-Killiany atlas (Desikan et al., 2006), and source time series of the brain regions were extracted by averaging vertex time series in each region. The frequency spectra of the time series (68 time series for 68 source regions) were computed by the Fast Fourier transform (FFT). The amplitude was transformed to a $\log_{10}$ scale and the spectrum was smoothed with a 0.17 Hz moving-average window. For each participant, we obtained the alpha peak frequency with maximum amplitude between 7 and 13 Hz *via* a customized automatic procedure utilizing MATLAB function findpeaks, and calculated the alpha peak amplitude as the average amplitude within ±1 Hz around the alpha peak frequency (Klimesch, 1999; Tement et al., 2016). BrainNet Viewer was used to present the locations of source regions on a brain template (Xia et al., 2013).

1 https://sccn.ucsd.edu/eeglab
2 https://neuroimage.usc.edu/brainstorm
3 http://sourceforge.net/p/mfeeg

An evaluation procedure was conducted to identify the source regions that showed valid alpha peak activity. For each of the source regions, a *t*-test was performed on alpha peak amplitude relative to the average amplitude of one neighboring frequencies on either side (Norcia et al., 2015), and a valid alpha peak was indicated by alpha peak amplitude being significantly larger than the amplitudes of surrounding frequencies ($p < 0.01$).

The correlation analyses were conducted using the parametric Pearson or non-parametric Spearman correlation method depending on the normality of data. Confounding effects of age and gender were controlled for by partial correlation (the present study focused on a direct correlation between EEG and depressive measures, see the **Supplementary material** for further analyses of effects of gender and age. In brief, for gender, the results showed a negative correlation between alpha peak amplitude and depressive score in females; for age, a negative correlation was observed between alpha peak amplitude and age and between alpha peak frequency and age). False discovery rate corrections (Storey, 2002) were applied to the results and corrected *p*-values < 0.05 were considered significant.

3. Results

3.1. Self-rating depression scales score

The SDS scores of the patients ranged from 22 to 74. The histogram distribution of individual scores is illustrated in **Figure 1** and the Kolmogorov–Smimov (K-S) test indicated that the data satisfied the normality assumption (K-S $p > 0.05$).

3.2. Alpha peak activity

For alpha peak activity, we first carried out an evaluation procedure to identify the source regions that showed significantly larger amplitude of alpha peak activity relative to the amplitudes of surrounding frequencies. Valid alpha peak activity was found in 63 source regions (**Figure 2A**). Only the source regions that showed valid alpha peaks entered into the following correlation analyses.

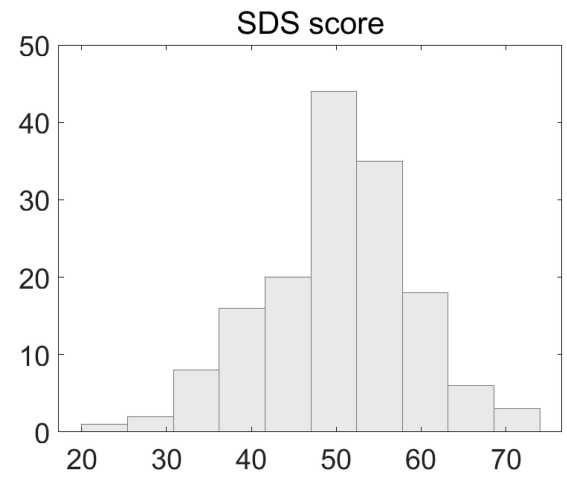

FIGURE 1
Illustration of scores of Self-Rating Depression Scales. Shown is the histogram distribution of individual patients' SDS scores.

3.3. Correlation between EEG and clinical measures

We then performed correlation analyses between the EEG measures and clinical scores. Because the data of alpha peak amplitude were not always normally distributed [the amplitude data satisfied the normality assumption (K-S $p > 0.05$) in 48 among the 68 regions], we conducted the correlation analyses using the Spearman correlation method. The Pearson correlation method was used for alpha peak frequency [the frequency data satisfied the normality assumption (K-S $p > 0.05$) in all the 68 regions].

Both alpha peak amplitude and alpha peak frequency were found to be significantly correlated with the SDS score, and the results further revealed different correlation patterns for alpha peak amplitude and frequency. For alpha peak amplitude, significant negative correlations were found at 16 source regions ($p_{corrected} < 0.05$), including the bilateral fusiform, right lateral occipital, bilateral lateral orbitofrontal, left medial orbitofrontal, right middle temporal, right parahippocampal, right pars opercularis, left pars orbitalis, right precentral, bilateral rostral anterior cingulate, right temporal pole, right superior temporal and right transverse temporal areas (**Figure 3** and **Table 1**). Moreover, for each region that showed significant correlation on either hemisphere, **Table 2** lists a right/left asymmetry ratio that represent the ratio between correlation *r*-values of the right and left hemispheres (Bouchard et al., 1990).

For alpha peak frequency, the results showed significant positive correlations at 8 source regions ($p_{corrected} < 0.05$) including the left bankssts, bilateral medial orbitofrontal, right paracentral, right precuneus, left superior frontal, right superior temporal and right supramarginal areas (**Figure 4** and **Table 3**). **Table 4** further lists the right/left asymmetry ratio for each region that showed significant correlation on either hemisphere.

4. Discussion

The present study examined the association between alpha peak activity of resting-state EEG and depressive scores of patients with depression. Over widely distributed brain regions, a significant negative correlation was found between individual patients' alpha peak amplitudes and SDS scores and a significant positive correlation was found between individual patients' alpha peak frequencies and SDS scores.

Alpha peak amplitude and frequency have been commonly reported to correlate with a behavioral measure in distinct manners and are considered to have different psychophysiological significances (Klimesch, 1999; Tement et al., 2016; Katyal et al., 2019). For example, in a visual perceptual task, alpha peak frequency but not alpha peak amplitude showed a significant correlation with perceptual performance (Katyal et al., 2019). For depression related research, as described in the Introduction, Tement et al. (2016) found that alpha peak amplitude and

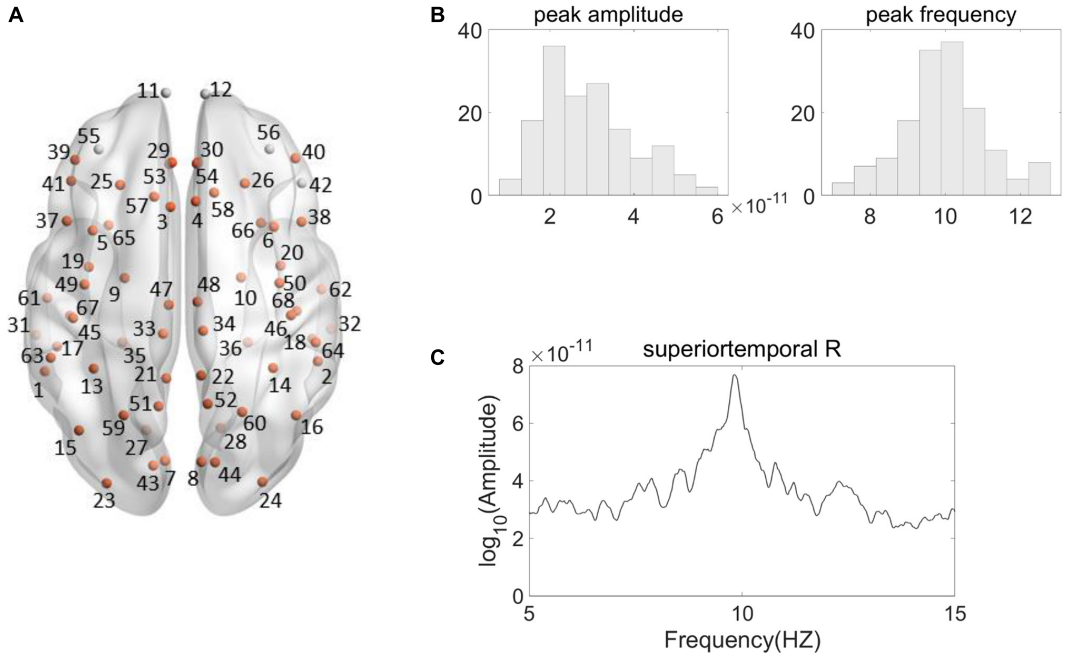

FIGURE 2
Illustration of Alpha peak activity in the frequency spectrum. **(A)** Shown are the 68 Desikan–Killiany regions from a top view, among which the source regions showing valid alpha peak activity are indicated by the orange color. (The name and the number of the regions are according to the standard Desikan–Killiany atlas, see **Supplementary Table 1** for further details). **(B)** Shown are the histogram distributions of individual alpha peak amplitudes (left) and frequencies (right) from a representative region (right superior temporal). **(C)** The spectrum of the representative region from a representative participant is shown. The source signal strength was under the sLORETA normalized unit.

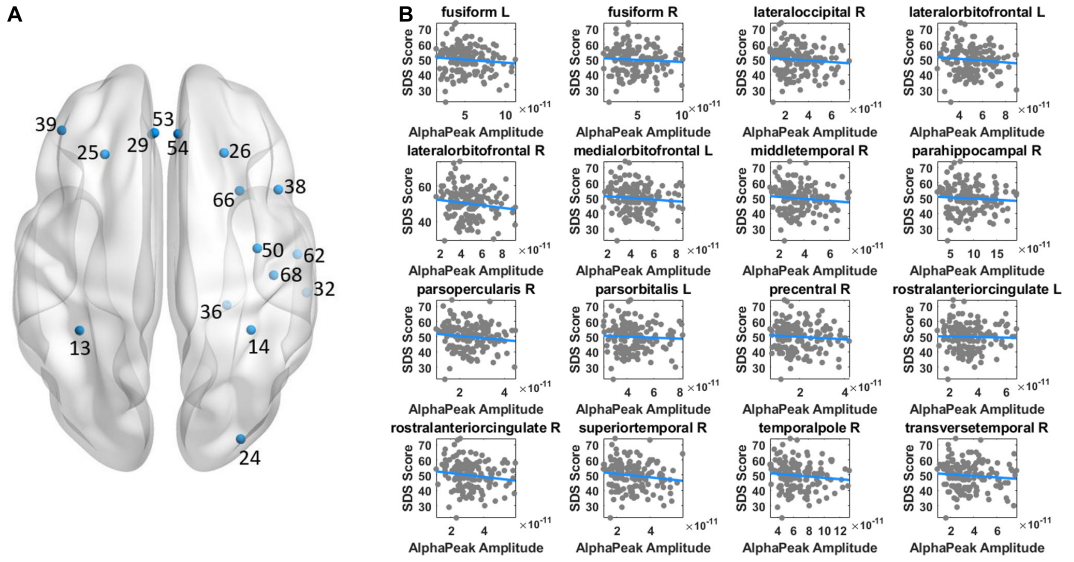

FIGURE 3
Illustration of correlation results between alpha peak amplitude and depressive score. **(A)** The source regions that showed significant correlations are indicated by colored points. Positive or negative correlations are indicated by the red or blue color, respectively. **(B)** Shown are the scatter plots of significant correlations at individual regions. The color of the fitted line indicates positive (red) or negative (blue) correlation. The results revealed a negative correlation between alpha peak amplitude and depressive score. Other conventions are as in **Figure 2**.

frequency correlated with depressive scores in different manners although the effects were largely related to a gender modulation. It appeared that a negative correlation between alpha peak amplitude and depressive score was observed in both the results of Tement et al. (2016) and the present results. Note that the two studies have differences in many aspects. For instance, Tement et al. (2016) involved non-clinical students and the present study investigated depressive patients. The depression scales in the study of Tement et al. (2016) is the Center for Epidemiologic Studies Depression Scale (CES–D) (Radloff, 1977). Both of the CES-D and the SDS

were commonly used depression scales. While the CES–D depicts symptoms that are associated with depression, the measure of the SDS reflects common symptoms of depression (Umegaki and Todo, 2017) and was preferred in our clinical practice. It would be also emphasized that the present study focused on a direct association between alpha peak activity and depressive score, with the possible effects of age and gender being controlled for. Therefore, while the two studies are supplementary and indicative to each other in improving our understanding of the relationship between alpha peak activity and depression, direct comparison between the two studies might be inappropriate.

For the psychophysiological backgrounds and significances of alpha peak amplitude and frequency, alpha peak amplitude is suggested to be more associated with synchronous neural discharging (Klimesch, 1999) and alpha peak frequency is considered to be more related to brain metabolism (Klimesch, 1999; Angelakis et al., 2004). Angelakis et al. (2004) suggests that alpha peak frequency should not be compared to alpha peak amplitude. In other words, for the prominent alpha peak activity in the human EEG, alpha peak amplitude and frequency provide measures based on different physiological mechanisms. Therefore, the observed differences in the correlation patterns between alpha peak amplitude and frequency reflect different physiological substrates (which should not be interpreted with regard to incompatible/compatible results). Specifically, for the clinical application of identifying a potential neuromarker for the severity of depression patients, alpha peak amplitude and frequency would provide valuable contributions in terms of different physiological mechanisms. One concern could be whether the different correlation patterns between alpha peak amplitude and frequency may result from a negative relation between the amplitude and frequency themselves. There was a significant negative correlation between alpha peak amplitude and frequency (see **Supplementary Table 5**). However, it is worth noting that in statistics, correlations between data A and C and between data B and C do not necessarily result from a correlation between data A and B. Accordingly in the current empirical data, the 16 regions showing significant negative correlation for alpha peak amplitude and the eight regions showing significant positive correlation for alpha peak frequency only overlapped in two regions. In other words, if a significant negative correlation between amplitude and frequency at a region could result in a significant negative correlation between the amplitude and clinical score and a significant positive correlation between the frequency and clinical score at that region, it explained data of only two regions. Therefore, the correlation between alpha peak amplitude and frequency was unlikely a major factor for the present observation. As discussed above, instead of direct comparison between the two measures, alpha amplitude and frequency are suggested to be investigated with respect to their different physiological significances (Angelakis et al., 2004).

We adopted the source reconstruction approach with a particular interest to identify cortical locus of alpha peak activity that would be associated with depression severity. This could have significant implications for clinical applications, such as when more precise cortical localization is under consideration in diagnosis of depression. The present results indicated the involvement of a wide brain network including the frontal, parietal, temporal, as well as occipital regions in depression, which is consistent

TABLE 1 Significant correlation *r*-values between alpha peak amplitude and depressive score.

Region name	*r*-value	Region name	*r*-value
Fusiform L	−0.19	Pars opercularis R	−0.20
Fusiform R	−0.23	Pars orbitalis L	−0.18
Lateral occipital R	−0.20	Precentral R	−0.21
Lateral orbitofrontal L	−0.21	Rostral anterior cingulate L	−0.20
Lateral orbitofrontal R	−0.24	Rostral anterior cingulate R	−0.28
Medial orbitofrontal L	−0.26	Superior temporal R	−0.27
Middle temporal R	−0.27	Temporal pole R	−0.25
Parahippocampal R	−0.21	Transverse temporal R	−0.20

TABLE 2 *R*-values of the left and right hemispheres and the right/left asymmetry ratio for each region showing significant correlation between alpha peak amplitude and depressive score on either hemisphere.

Region name	Left	Right	Right/left ratio
Fusiform	−0.19	−0.23	1.21
Lateral occipital	−0.04	−0.20	5.00
Lateral orbitofrontal	−0.21	−0.24	1.14
Medial orbitofrontal	−0.26	−0.15	0.58
Middle temporal	−0.09	−0.27	3.00
Parahippocampal	−0.14	−0.21	1.50
Pars opercularis	−0.11	−0.20	1.82
Pars orbitalis	−0.18	−0.13	0.72
Precentral	0.00	−0.21	397.03
Rostral anterior cingulate	−0.20	−0.28	1.40
Superior temporal	−0.06	−0.27	4.50
Temporal pole	−0.11	−0.25	2.27
Transverse temporal	−0.06	−0.20	3.33

A right/left ratio larger than one indicates greater correlation on the right hemisphere and a right/left ratio smaller than one indicates greater correlation on the left hemisphere. (That for the precentral region, the extremely large right/left ratio was due to the fact that the *r*-value of the left hemisphere was nearly zero).

with the reported engagement of widely distributed brain areas in depression research using resting-state functional Magnetic Resonance Imaging (fMRI) approach (Wu et al., 2011; Pizzagalli, 2014; Gong and He, 2015; Cheng et al., 2018; Malhi and Mann, 2018; Shi et al., 2020; Wang et al., 2020). Despite different physiological sources of fMRI and EEG signals (indirect measure of neuronal activity for fMRI; direct measure of electrophysiological activity for EEG which allows investigation of frequency-specific oscillatory activity), analysis and comparison of cortical regions and networks of fMRI and EEG activities (for EEG, indicated by source reconstruction) would be indicative (Hipp et al., 2012). Future research of alpha peak activity is recommended to adopt the source reconstruction approach, particularly when clinical applications are involved. Moreover, previous studies comparing alpha band amplitude between patients and normal controls have shown relatively stronger left frontal and right parietotemporal alpha amplitude in patients (see Bruder et al., 2017; Van der Vinne et al., 2017; Kaiser et al., 2018). The present patients' correlation results between the alpha peak amplitude and SDS score appeared to show

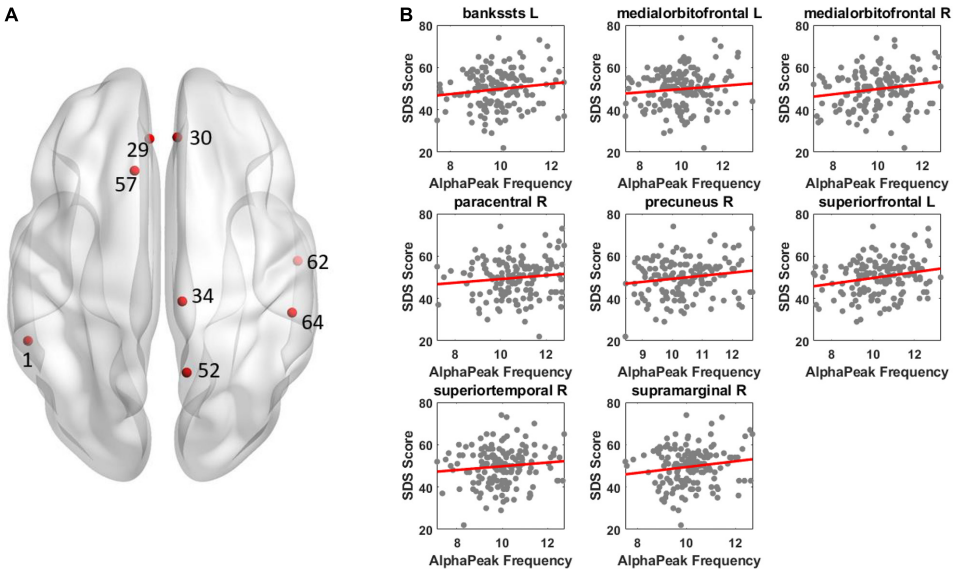

FIGURE 4
Illustration of correlation results between alpha peak frequency and depressive score. The results revealed a positive correlation between alpha peak frequency and depressive score. Other conventions are as in Figure 3.

TABLE 3 Significant correlation *r*-values between alpha peak frequency and depressive score.

Region name	*r*-value	Region name	*r*-value
Van kssts L	0.25	Precuneus R	0.19
Medial orbitofrontal L	0.18	Superior frontal L	0.29
Medial orbitofrontal R	0.23	Superior temporal R	0.21
Paracentral R	0.19	Supramarginal R	0.19

TABLE 4 *R*-values of the left and right hemispheres and the right/left asymmetry ratio for each region showing significant correlation between alpha peak frequency and depressive score on either hemisphere.

Region name	Left	Right	Right/left ratio
Ban kssts	0.25	0.11	0.44
Medial orbitofrontal	0.18	0.23	1.28
Paracentral	0.12	0.19	1.58
Precuneus	0.04	0.19	4.75
Superior frontal	0.29	0.17	0.59
Superior temporal	0.16	0.21	1.31
Supramarginal	0.13	0.19	1.46

Conventions are as in Table 2.

similar asymmetry patterns, through mainly for parietotemporal areas (Figure 3 and Table 2): the right/left ratio was smaller than 1 at 2 left frontal regions and was larger than 1 at 6 right parietotemporal regions; whereas was larger than 1 at 3 right frontal regions and was smaller than 1 at 0 left parietotemporal region. In addition, similar patterns were also observed for the correlation of alpha peak frequency (Figure 4 and Table 4), the right/left ratio was smaller than 1 at 1 left frontal region and was larger than 1 at 3 right parietotemporal regions; whereas was larger than 1 at 2 right frontal regions and was smaller than 1 at 1 left parietotemporal region.

Either the eye-closed condition or the eye-open condition has been adopted in resting-state EEG depression studies investigating alpha activity (Van der Vinne et al., 2017; Newson and Thiagarajan, 2019). EEG alpha activity is highest in the eyes-closed condition and is reduced when eyes open or engaged in attention-demanding tasks. Relative to the resting-state alpha activity with eyes closed that indicates a baseline state of the brain unbiased by any task, the reduction of alpha activity reflects higher levels of attention or arousal states (Klimesch, 1999; Fingelkurts and Fingelkurts, 2015; Katyal et al., 2019). In previous resting-state EEG depression studies, the increased alpha amplitude in depression patients compared to healthy controls and the alpha asymmetry have been observed in both the eye-closed and eye-open conditions (Van der Vinne et al., 2017). A resting-state EEG study investigating correlations between alpha peak activities and depressive scores of non-clinical subjects also used the eye-closed condition (Tement et al., 2016). Moreover, considering the long-time 5 min EEG recoding of our clinical patients, the more relaxed eye-closed condition would help avoid extra burden and fatigue and prevent potential large EEG signal noise (Fingelkurts and Fingelkurts, 2015; Barry and De Blasio, 2017). Therefore, the eye-closed condition was adopted in the current study.

The present study has the following limitations. The first is the lack of a group of healthy control subjects that matched in gender and sex and had a comparable sample size, and the current study did not carry out a replication analysis for the prior finding of greater alpha amplitude for patients vs. normal controls. Second, the present study conducted diagnosis of depression. Disorders that have combined symptoms with depression, such as anxiety disorders, were not separately diagnosed. The present results would be to some extent associated with the symptoms of disorders related to depression. Accordingly, it is worth noting that the previous finding of greater alpha amplitude for patients vs.

healthy controls and the present result of the negative relationship between alpha amplitude and the SDS score were supplementary, rather than conflicting, to each other. As have been discussed, the depression diagnosis involves considerations of combined symptoms and the SDS score is a further evaluation of depressive symptoms supplementary to the diagnosis. Particularly, it has been hypothesized that anxious arousal in patients is associated with right parietotemporal hyperactivation and studies have found that depression patients having a comorbid anxiety disorder showed less alpha amplitude over the right than left parietal sites (for review, see Bruder et al., 2017). Future research is required to further explore the relationship between depression and related disorders, and studies should relate alpha activity to not only depression but also severity of anxiety or other symptoms. Meantime, further attempts are also required to adopt or formulate distinct behavior and neural measures, for an improved understanding of the neural substrates of patients' depressive symptoms.

Conclusion

In conclusion, the present results showed an association between alpha peak activity in resting-state EEG and the severity of depressive symptom. These findings indicate a potential role of alpha peak activity in evaluation of depression severity in supplement to diagnosis.

Data availability statement

The data generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of Guangdong Provincial Hospital of Chinese Medicine (YF-2020-198-01) and the Institutional Review Board of Psychology Department of Sun Yat-sen University. The patients/participants provided their written informed consent to participate in this study.

Author contributions

XW conceived the research. QW, LZ, WF, and XW designed the research. QW, ZG, LZ, CW, DL, SW, QY, JL, FZ, LL, and PZ collected the data. LZ, CW, QW, ZG, DL, SW, QY, JL, FZ, and LL analyzed the data. PZ was involved in the discussion of the data. PZ, WF, and XW were responsible for project supervision and funding acquisition. QW, LZ, CW, and XW wrote the manuscript. All authors commented on and edited the manuscript and approved the final version of the manuscript.

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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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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnins.2023.1057908/full#supplementary-material

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Chronic alcohol consumption shifts learning strategies and synaptic plasticity from hippocampus to striatum-dependent pathways

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Introduction: The hippocampus and striatum have dissociable roles in memory and are necessary for spatial and procedural/cued learning, respectively. Emotionally charged, stressful events promote the use of striatal- over hippocampus-dependent learning through the activation of the amygdala. An emerging hypothesis suggests that chronic consumption of addictive drugs similarly disrupt spatial/declarative memory while facilitating striatum-dependent associative learning. This cognitive imbalance could contribute to maintain addictive behaviors and increase the risk of relapse.

Methods: We first examined, in C57BL/6J male mice, whether chronic alcohol consumption (CAC) and alcohol withdrawal (AW) might modulate the respective use of spatial vs. single cue-based learning strategies, using a competition protocol in the Barnes maze task. We then performed *in vivo* electrophysiological studies in freely moving mice to assess learning-induced synaptic plasticity in both the basolateral amygdala (BLA) to dorsal hippocampus (dCA1) and BLA to dorsolateral striatum (DLS) pathways.

Results: We found that both CAC and early AW promote the use of cue-dependent learning strategies, and potentiate plasticity in the BLA→DLS pathway while reducing the use of spatial memory and depressing BLA→dCA1 neurotransmission.

Discussion: These results support the view that CAC disrupt normal hippocampo-striatal interactions, and suggest that targeting this cognitive imbalance through spatial/declarative task training could be of great help to maintain protracted abstinence in alcoholic patients.

KEYWORDS

alcohol, learning strategies, memory systems, hippocampus (CA1), dorsal striatum, synaptic plasticity, addiction, amygdala

1. Introduction

Worldwide, 3 million deaths every year result from harmful use of alcohol, this represent 5.3% of all deaths, and more than 200 diseases and injury conditions are alcohol-attributable (1). Beyond health consequences, alcohol use disorders bring significant social and economic losses to individuals and society at large. Although treatments currently available help in maintaining protracted abstinence, they have limited impact to improve the high relapse rate observed in alcoholic patients (80%) defined as the inability to abstain from alcohol consumption despite health and social negative consequences (2). The consequences of excessive alcohol use

on cognitive functions have been extensively investigated using both human and animal models (3). Studies in alcoholic patients and animal models have generally provided converging evidence to support the idea that long-term alcohol exposure has deleterious effects on cognition. However, this may depend on the type of cognitive processes involved, and critical factors such as time between consumption and test or duration of withdrawal are often unknown (3, 4). Furthermore, the contribution of cognitive effects of alcohol to the development and maintenance of alcohol use disorders (AUDs) remains poorly understood.

In both humans and animals, distinct neural systems underlie different learning and memory processes (5, 6). Cognitive forms of memory such as declarative memory, which encodes life events in a specific space–time framework and in an explicit and conscious way and spatial memory or relational memory which are based on stimulus–stimulus associations, rely on the hippocampus, especially but not exclusively the dorsal CA1 (5, 7–9). In contrast, procedural memory which lead to unconscious habits require stimulus–response (S-R) associative processing supported by the dorsal striatum (10–12). Yet, these memory systems interact during learning either cooperatively or competitively (6, 12–16). For instance, spatial learning with reference to an array of distal cues can be subject to competition with striatal-dependent response learning, and dorsolateral striatal lesions facilitate spatial learning (17). It was proposed that a persistent cognitive imbalance could maintain addictive behaviors and increase the risk of relapse by disrupting spatial/declarative memory while facilitating cue-dependent learning (18–22). These qualitative changes in memory formation are also induced by stress, which promotes a shift from spatial/declarative memory to cued/procedural memory systems in both rodents and humans (15, 23–26). Emotional modulations of hippocampal and dorsal striatum memory systems are thought to be critically mediated by the basolateral amygdala (BLA) which encodes stimulus-reinforcement associations (27–29).

Strikingly, despite the large number of studies looking at the consequences of alcohol use on cognition in humans and animals (3, 30), the impact of chronic alcohol consumption (CAC) and/or alcohol withdrawal (AW) on dynamic interactions between memory systems has not been extensively investigated. A long-lasting impairment in working memory associated with frontal but not hippocampal alterations was reported following AW (31). Yet, it remains of critical importance to determine whether CAC have differential effects on hippocampus vs. striatum dependent memory. Evidence supporting the cognitive imbalance hypothesis between spatial and cue dependent memory in CAC and/or AW animals would provide essential information about cognitive behavioral therapies that could be used to maintain protracted abstinence.

Here, we investigated the effects of CAC and AW on the selection of navigational learning strategies, as well as learning-induced synaptic plasticity within the hippocampus and dorsal striatum in awaked, freely moving mice. As previously demonstrated, it is possible to model flexibility properties and temporo-contextual indexation of the human declarative memory through the study of spatial memory in rodents via navigational tasks (32–34). We assessed spatial and cued [i.e., beacon (35, 36)] learning strategies in mice after 5 month-CAC, or after a 1-week AW using a dual-solution task in a Barnes maze (24, 37). The latter is an adaptation of previously published procedures to assess competition between hippocampus-dependent spatial learning and striatum-dependent cued learning in the water maze (21, 38–42). As compared to the Morris water-maze, the Barnes maze minimizes the test-induced stress (43) and allows *in vivo* electrophysiological studies in freely moving mice. Therefore, we analyzed in freely moving mice how CAC and AW alter learning-induced changes in synaptic plasticity in the dorsal CA1 of the hippocampus (spatial learning-related), and in the dorsolateral striatum (beacon cue-based learning).

2. Materials and methods

2.1. Animals

All surgical and experimental procedures were conducted in accordance with the European Community, reviewed and approved by The Ethics Committee of the University of Bordeaux (CEE50, approval #12283). The study was conducted on 60 male C57BL6/J mice obtained from Janvier Labs (France). Mice of 10 weeks old at arrival were housed by groups of 10 in collective cages (425 × 276 × 153 mm; 820 cm^2) and maintained at 22°C ± 1°C, under a 12:12 light–dark cycle (lights on at 7:00 a.m.). They were provided with food and water *ad libitum*. At the age of 4 months, 40 of them were submitted to a 5 months-CAC as described below. The C57BL6/J strain has a natural appetence for alcohol, and therefore exhibit spontaneous oral consumption of significant amounts (44, 45). C57BL6/J mice perform well in different spatial memory tasks including the Barnes maze (46, 47). Mice were kept in social housing for 4 months of the CAC, then housed individually following surgery and for all the following procedures (last month of CAC, AW, and subsequent Barnes maze and electrophysiological experiments). Mice were aged 9 months for intracranial electrodes implantation and 9–10 months at the beginning of the behavioral and electrophysiological experiments. To reduce fear reactivity to the experimenter and non-specific experimental stress, mice were handled 3–5 min/day (48). All experimental procedures were performed between 8:00 a.m. and 6:00 p.m.

2.2. Experimental design

Twenty mice collectively housed were provided with water *ad libitum*, and 40 other mice collectively housed were provided with alcohol 12% *ad libitum* as the only drink for 18 weeks (chronic alcohol consumption protocol, CAC; Figure 1A, blue). Stereotaxic surgeries were then performed on these 60 mice for implanting two intracranial electrodes allowing future repeated electrophysiological recordings of the amygdalo-hippocampal (BLA → dCA1) or amygdalo-striatal (BLA → DLS) transmission (Figure 1A, red and Figure 1B). Following surgery, all 60 mice were kept single-housed. After 10 days of recovery, 22 of the mice that underwent the CAC procedure were submitted to a progressive alcohol withdrawal (AW mice), while the 18 others remained under alcohol 12% diet (CAC mice; Figure 1A, blue). The 20 mice under water regimen still only had access to water (Ctrl mice).

In order to investigate whether CAC and AW induced synaptic plasticity modifications in BLA → dCA1 and BLA → DLS pathways, we used an *in vivo* electrophysiological approach in freely moving mice. Using the previously implanted intracranial electrodes (Figure 1B), we recorded evoked field potentials (EFPs) in the dCA1 and the DLS after stimulating the BLA with various intensities. Thirty

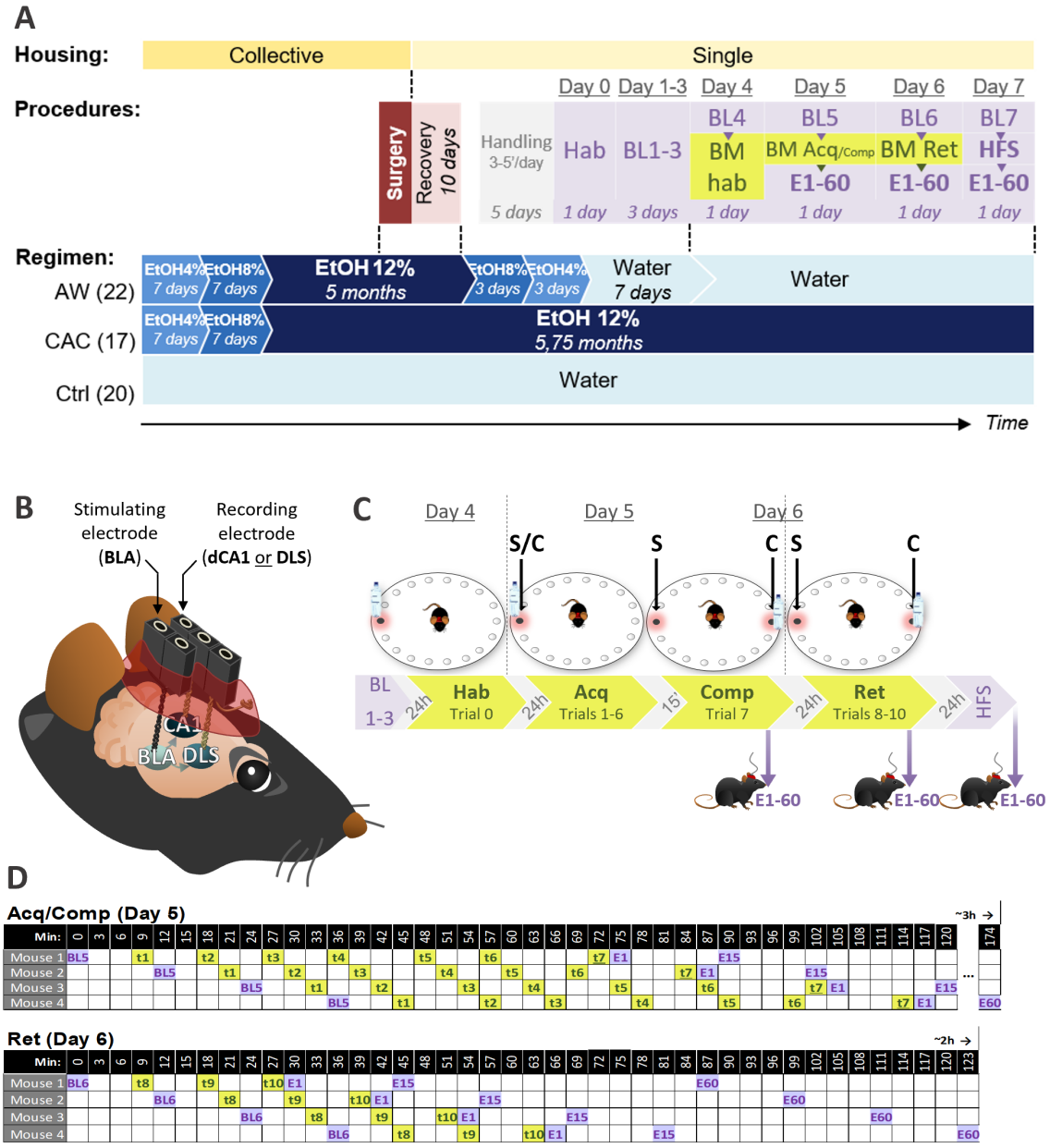

FIGURE 1
Experimental procedures. **(A)** Timeline describing the mice housing conditions (yellow), the drinking regimen (blue), and the temporal arrangement of experimental procedures including stereotaxic surgery (red), handling (gray), Barnes Maze task (green), and concurrent *in vivo* electrophysiological recordings (purple). Three mice groups were established based on their drinking regimen: AW (Alcohol Withdrawn, *n*=22), CAC (Chronic Alcohol Consumption, *n*=17), and Ctrl (Controls, *n*=20). **(B)** Intracranial electrodes implanted by stereotaxic surgery for *in vivo* electrophysiology in freely moving mice. All mice received a stimulating electrode in the basolateral nucleus of the amygdala (BLA), and a recording electrode either in the dorsal CA1 of the hippocampus (dCA1) or in the dorsolateral striatum (DLS), to record evoked field potentials (EFPs) either in the BLA→dCA1 or BLA→DLS pathway. **(C)** Barnes Maze protocol used to assess spatial vs. non-spatial learning strategies. One of the 18 holes, called escape hole (red frame), led to a shelter under the board allowing to escape from the exposed area of the BM. After habituation (Hab, Trial 0, Day 4), mice were trained through 6 acquisition trials to enter the escape hole (Acq, Trials 1–6, Day 5). Remaining at the same location during trials 0–6, and signaled by a proximal cue (bottle), the escape hole could be found through Random, Serial, Spatial or Cued strategy. To dissociate the use of Spatial vs. Cued-strategy (S/C), a competition trial (Comp, Trial 7) was performed with two escape holes: the one at the same location that during Acq (S) and the one at the opposite where the proximal cue was relocated. **(C)** Three retention trials were performed on Day 6 (Ret, Trials 8–10). **(D)** Timeline of EFPs recordings (BL, E1, E15, E60; purple) and BM trials (t1–7; green) in a 4-mice cohort during Day 5 and 6. Mice were tested by cohort of maximum 4 individuals following the order of passage and inter-trial intervals depicted in top (Acq/Comp, Day 5) and bottom (Ret, Day 6) tables. A maximum of 4 cohorts (16 mice) were tested per day. Acq, acquisition; BL, Baseline recordings of EFPs in the BLA → dCA1 or DLS pathway; BM, Barnes Maze; E, Evoked field potentials in the BLA → dCA1 or DLS pathway from1 to 60′ after BM or HFS; Hab, habituation; Ret: retention; t, trial.

mice were used to study the BLA → dCA1 pathway (11 AW, 9 CAC, and 10 ctrl mice), while the 30 others were used to study the BLA → DLS pathway (11 AW, 9 CAC, and 10 ctrl mice). After a habituation session (transport to the experimental room, electrodes connection-disconnection; *Day 0*, *Hab*, Figure 1A, purple), an input–output curve was established to determine the optimal stimulation

intensity of the BLA (BL1, Day 1). Mice were then recorded once a day for 3 days and the collected data were used as baseline (BL2-4, Day 2–4; Figure 1A, purple) for the following electrophysiological measures.

To study the impact of CAC and AW on spatial and non-spatial learning strategies, the 60 mice were then tested in the Barnes maze task (*BM*; Figure 1A, green). The BM was a circular, exposed and brightly lit area with 18 holes along its circumference (Figure 1C). One of the 18 holes, called escape hole (red frame on Figure 1C), led to a shelter under the maze allowing to escape from the exposed area of the BM. After habituation (*Trial 0, Hab, Day 4*; Figure 1C), mice were trained through six acquisition trials to locate and enter in the escape hole that remained at the same location and was also signaled by a proximal cue which can be used as a beacon to reach the goal (*Trials 1–6, Acq, Day 5*; Figure 1C). This design allowed the use of four search strategies: spatial, cued, serial, and random (Figure 2). To dissociate the use of Spatial vs. Cued strategy (S/C), a Competition trial (*Trial 7, Comp*; Figure 1C) was performed with two escape holes: the one at the same location that during Acquisition (S) and the one at the opposite where the beacon cue was relocated (C). Three retention trials were performed on Day 6 (*Trials 8–10, Ret*; Figure 1C).

With the aim of investigating whether CAC and AW procedures impact the learning-induced BLA → dCA1 and BLA → DLS transmission, EFPs were recorded before (BL5 and 6) and after (1, 15 and 60 min: E1, E15, E60) Acquisition/Competition (Day 5) and Retention (Day 6; Figures 1A,C, purple). On Day 7, we finally investigated the learning-induced metaplasticity in the BLA → dCA1 and BLA → DLS pathways. To this aim, a high-frequency stimulation (HFS) was applied in the BLA and responses were recorded (either in dCA1 or DLS) 1, 15, 45, and 60 min post HFS (Figures 1A,C, purple).

To perform electrophysiological recordings at specific delays, mice were tested in the BM task by cohort of maximum four individuals (with at least one representative mouse of each group), following the timeline described in Figure 1D. To test one cohort, it took 3 h for Acquisition-related measures (Day 5; BL5 + trials 1–6 + E1-60), and 2 h for Retention-related measures (Day 6; BL6 + trials 8–10 + E1-60). Per day, a maximum of 4 cohorts were tested (two cohorts in the morning and one or two cohort(s) in the afternoon, a maximum of 16 mice/day). It took a total of 7 days for the whole BM experiment with the associated electrophysiological recordings. The entire experiment has been repeated 4 times on distinct dates to achieve a total number of 60 mice. Days 5 and 6 required two experimenters (one performing behavioral assessment and another one concurrently performing electrophysiological recordings).

At the end of the study, one CAC mice was excluded from BM analysis due to the apparition of postural symptoms (rotation). Five mice (3 AW and 2 Ctrl) were excluded from electrophysiological analysis due to: electrode misplacement (DLS: 1 AW; BLA: 1 Ctrl), or to signal loss (dysfunctional or displaced electrode; dCA1: 1 AW, DLS: 1 AW, 1 Ctrl).

2.3. Chronic alcohol consumption and alcohol withdrawal procedures

At the age of 4 months, 40 mice (AW and CAC groups) were given alcohol as unique source of drink, in concentrated solutions as follows: 4% the first week, 8% the second week and 12% for five consecutive months (Figure 1A, blue). Previous studies in mice or rats demonstrated that repeated exposure up to 4 weeks did not result in spatial deficits (49–52), whereas long-term drinking (about 3 months) produced more consistent evidence of a spatial memory deficit (4, 53–55). Alcohol drinking solutions were prepared from ethanol 96% (VWR Chemicals BDH®), diluted with tap water at either 4%, 8%, or 12% final concentration. The mean daily alcohol intake was 3.57 ± 0.6 mL/mouse, namely 15.34 ± 4.3 g/kg/day of alcohol. The average blood alcohol level achieved during CAC was 0.57 ± 0.23 g/L [commercial ELISA kit according to the procedure previously described (31)]. After 5 months of CAC, a part of alcohol-treated mice was progressively withdrawn from alcohol as follows: 8% for 3 days, then 4% for 3 days and finally water (AW group; Figure 1A, blue). Mice of CAC group remained under the 12% (v/v) alcohol diet. We previously showed that (i) pair-fed animals receiving, during the same duration of alcohol exposure, an isocaloric solution of dextromaltose did not exhibit any sign of neurobiological disorders; (ii) alcohol ingestion represented less than 20 percent of the total caloric intake; and (iii) the alcohol group consumed a higher daily amount of solution than water controls (56). Therefore, mice of the CAC group were neither malnourished nor dehydrated during the alcohol treatment.

2.4. Stereotaxic surgery

All mice received two intracranial electrodes (Figure 1B) by stereotaxic surgery: a stimulating electrode in the basolateral nucleus of the amygdala (BLA, in mm from Bregma: −1.6 AP, +3.0 L, −4.5 DV), and a recording electrode either in the dorsal CA1 of the hippocampus (dCA1, in mm from Bregma: −2.0 AP, +1.3 L, −1.15 DV) or in the dorsolateral striatum (DLS, in mm from Bregma: +0.5 mm AP, +2.1 L, −2.0 DV). Each electrode was composed of two twisted tungsten wire of 80 µm in diameter, soldered to connectors. Under general anesthesia (10% Ketamine +4% Xylazine, 0.1 mL/10 g, i.p injection), mice were mounted on a stereotaxic frame and HCL Lidocaine (Xylocaine®, 5%) was locally applied. Once the scalp was incised and retracted, electrode positions were identified from Bregma and according to stereotaxic coordinates indicated above. Stimulating and recording electrodes were both implanted in the right cerebral hemisphere, and were fixed in place with dental cement (Palavit G, Promodentaire) and two screws (inox; screw thread: Ø = 0.5 mm; length = 1 mm; FOM 2000) inserted in the skull. Mice were allowed to recover from surgery for at least 10 days before beginning of the AW procedure, while their weight and general state of health were controlled daily.

2.5. Assessing spatial vs. non-spatial learning strategies in the Barnes maze

2.5.1. Apparatus

The Barnes Maze (BM) was a white circular board (110 cm Ø), elevated and pierced with 18 regularly spaced holes on its circumference (Figure 1C). The underside of the maze enabled to fix, under the desired hole(s), a small shelter cavity with black hard plastic base covered by litter. The holes leading to a shelter (escape holes) were indicated by a red frame in the Figure 1C. As in Schwabe et al. (24), a transparent 0.5 L plastic bottle filled with water was used as

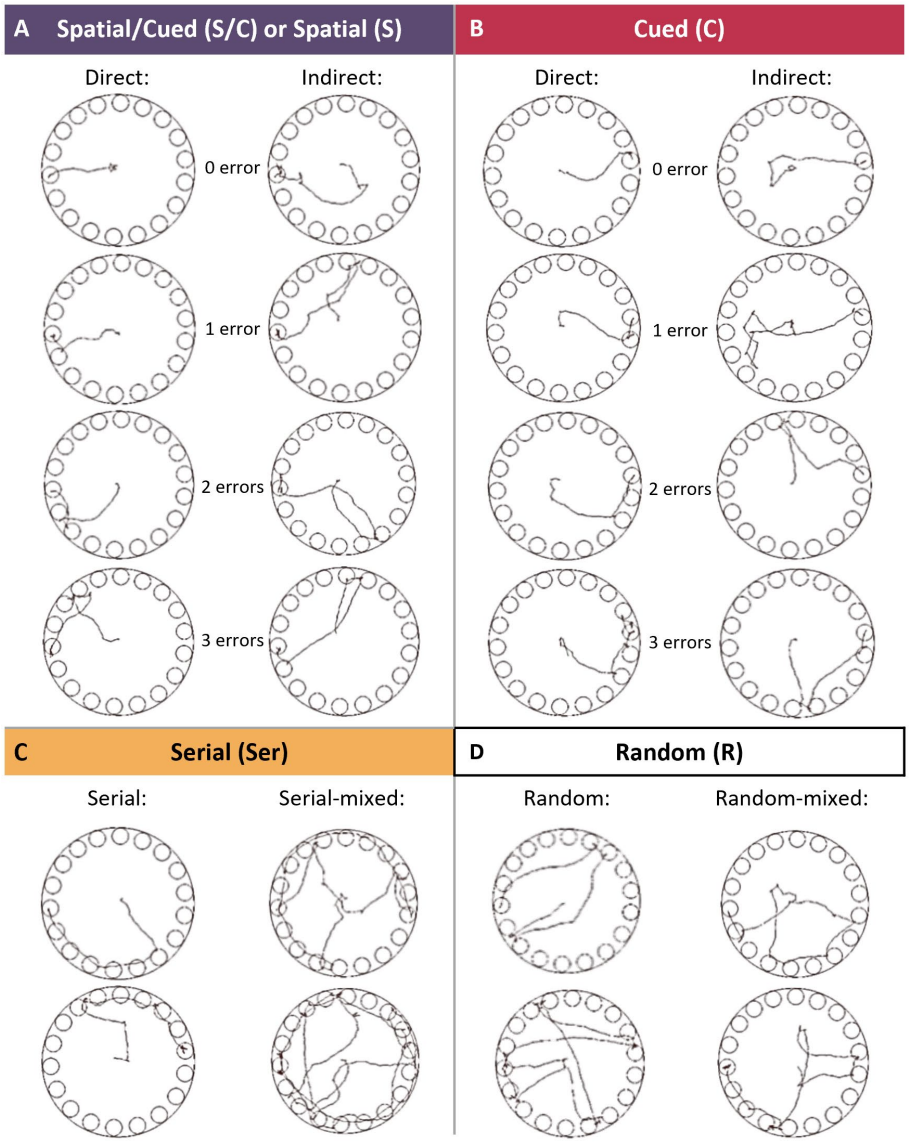

FIGURE 2
Search strategies in the Barnes maze task. **(A)** The Spatial/Cued strategy was defined as moving directly to the S/C hole (0 error) or to less than 3 holes before entering in the S/C hole (≤3 errors), during Habituation and Acquisition sessions. The Spatial strategy was defined as moving directly to the S hole (0 error) or to less than 3 holes before entering in the S hole (≤ 3 errors), during Competition and Retention sessions. Errors were made on holes either adjacent (direct), or non-adjacent (indirect) to the escape one. **(B)** The Cued strategy was defined as moving directly to the C hole (0 error) or to less than 3 holes before entering in the C hole (≤3 errors), during Competition and Retention sessions. Errors were made on holes either adjacent (direct), or non-adjacent (indirect) to the escape one. **(C)** The Serial strategy was allocated when the entry into the escape hole was preceded by visiting at least 4 adjacent holes in serial manner (clockwise or counter-clockwise direction). **(D)** The Random strategy was defined as hole searches separated by crossing through the center of the maze.

beacon cue to signal the desired escape holes. Extra-maze visual cues (e.g., wall decoration, furniture in the room) provided mice with spatial references. The experimenter remained out of the BM room so as not to become a spatial cue for the animal and was able to see trials directly through video monitoring. The course of each animal was recorded and analyzed with an automated tracking system (VideoTrack®, Champagne au Mont d'Or, France). A bright lightening (200 lux) and a fan generating an airflow of 3 m/s motivated animals to leave the exposed area by entering in the escape hole. Prior every BM session, mice had a 30 min-period of acclimation to the experimental room during which drinking bottles were removed from the home cages.

2.5.2. Habituation (trial 0, day 4)

At the beginning of each trial, mice were placed in a cylinder (25 cm high, 10 cm in diameter) located at the center of the maze. After 5 s, the cylinder was lifted and mice could explore the board during 3 min and exit through the unique hole offering a shelter (Figure 1C, *Hab*). At the end of that period of 180 s, if necessary, the mouse was gently guided and confined in front of the escape hole

through a turned transparent cage. Once in the shelter, the mouse was left 30 s and then replaced in its home cage.

2.5.3. Acquisition (trials 1–6, day 5), competition (trial 7, day 5), and retention (trials 8–10, day 6)

On Day 5 (24 h after habituation), mice were trained during six consecutive trials to locate and enter in the escape hole in less than 180 s. Learning in the BM was assessed by the escape latency (time to enter into the escape hole), total number of errors committed before entering the escape hole, and path length (total distance) required to enter the escape hole. There was a unique escape hole that remained at the same position over the six-acquisition trials and was signaled by the cue (bottle; Figure 1C, *Acq*). This design allowed the use of three search strategies: (1) the employment of the extra-maze distal cues and/or the intra-maze beacon cue (Spatial/Cued); (2) the sequential verification of holes (Serial strategy); and (3) the unorganized search (Random strategy). Detailed definitions of the search strategies are provided in Figure 2. The relatively low number of trials was chosen to avoid training to asymptotic performance which would promote the exclusive use of a Cued strategy (24, 57). At the beginning of each trial, the cylinder was left in such way that the head of the mouse was randomly oriented. If a mouse did not enter the shelter within 180 s, the experimenter guided it as during habituation. After each trial, the board was wiped with 12% ethanol solution to spread odor cues and litter in the cavity was changed. The inter-trial interval (ITI) was from 6 to 9 min.

Fifteen minutes after the last (6th) trial of the Acquisition, mice were submitted to a Competition trial (*Trial 7, Comp*; Figure 1C) in order to dissociate the use of Spatial vs. Cued strategy (S/C). In this trial 7, the bottle was relocated to the hole symmetrically opposite to its position during the trials 0–6, and two escape holes were available: the one at the same location that during acquisition (S) and the one at the opposite where the beacon cue (bottle) was relocated (C). In this trial, moving directly to the S hole (0 error) or to less than 3 holes before entering in the S hole ($\leq$ 3 errors) was classified as spatial strategy (S). Moving directly to the C hole (0 error) or to less than three holes before entering in the C hole ($\leq$3 errors) was classified as Cued strategy (C) (See Figure 2). Three retention trials, identical to trial 7, were performed 24 h later on Day 6 (*Trials 8–10, Ret*; Figure 1C).

2.6. *In vivo* electrophysiology in freely moving mice

2.6.1. Induction and recording of evoked field potentials (days 0–6)

As measures were performed on awaked animals, mice were previously habituated to the transport to the experimental room and to electrodes connection-disconnection (*Hab, Day 0*; Figure 1C, purple). Habituation was followed by 4 days (Days 1–4) of basal electrophysiological responses recording (BL1-4, one session per day; Figure 1C, purple). Field potentials were evoked in the dCA1 or DLS by ipsilateral stimulation of the BLA (100 µs rectangular biphasic pulses). Stimulating electrode was connected to operational amplifiers with JFET input (Junctions in Field Effect Transistors) placed on the mouse head. Evoked field potentials (EFPs) were amplified (×1,000), filtered by bandwidths (1–1,000 Hz; A-M systems), and recorded with a microcomputer (1401 CED interface) for ulterior analysis (Signal3 software). Six responses, at 0.1 Hz frequency, were recorded per session. The amplitude of the dCA1 responses were measured from the top peak (black asterisk; Figure 3E, *dCA1*) to the bottom of the sink of the negative wave N1 (Figure 3E, *dCA1*) and the amplitude of the DLS responses were measured from the bottom of the small sink right after the stimulation artifact (black asterisk; Figure 3E, *DLS*) to the top of the positive wave P1 (Figure 3E, *DLS*). Baseline (BL) responses were established by means of stimulation intensity sufficient to elicit a response representing 50%–70% of the maximal amplitude of the evoked field potentials (EFPs). To determine the optimal stimulation intensity for each mouse, an input–output curve was established at various stimulus intensities (0.05, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, and 0.7 mA) on Day 1 (BL1). This determined optimal stimulation intensity was then used to evoke all the field potentials recorded before and after the BM task (Days 2–6; Figure 1A, purple). On Day 4, EFPs in the BLA → dCA1 or BLA → DLS pathway were recorded 6 min before the trial 0 of BM Habituation (*BL4*). On Day 5, EFPs were recorded 6 min before the trial 1 of BM Acquisition (*BL5*) and 1, 15, and 60 min after the trial 7 of BM Competition (*E1, 15, 60*). On Day 6, EFPs were recorded 6 min before the trial 8 of BM Retention (*BL6*) and 1, 15, and 60 min after the trial 10 of BM Retention (*E1, 15, 60*). Learning-induced changes were expressed as the mean percentage (±SEM) of the individual basal values (BL2-4) of animals for each group.

2.6.2. High-frequency stimulation protocol (day 7)

On Day 7, EFPs in the BLA → dCA1 or BLA → DLS pathway were recorded and compared with baseline established on Day 2–4 (BL2-4), and stimulating intensity were adjusted (decreased or increased) to reach this basal level. A High-Frequency Stimulation protocol (HFS: 5 trains of 5 pulses at 100 Hz) designed to induce a Long-Term Potentiation (LTP) was applied in the BLA immediately after the record of a new basal line. Ten responses at 0.1 Hz were recorded (either in CA1 or DLS) 1, 15, 45, and 60 min post HFS. HFS-induced changes were expressed as the mean percentage (±SEM) of the individual basal values.

2.7. Statistical analysis

The performance variables in the BM (escape latency, number of errors, and path length) were analyzed using one-way and two-way analyses variance (ANOVAs), with one between-subject factor "Group" (CAC, AW, Ctrl) and the within-subject factor with repeated measures "Trial." *Post-hoc* Bonferroni/Dunnett's multiple comparisons analysis were performed when adequate. Concerning the strategies, an overall frequency was calculated for each type of search strategy (Random, Serial, Spatial/Cued, Cued, and Spatial) for each mouse, and these rates were averaged to obtain a group mean for each strategy for a session (Habituation, Acquisition, Competition, or Retention). For each search strategy, differences among groups were determined by one-way and two-way ANOVAs with the between-subject factor "Group" (AW, CAC, Ctrl) and the within-subject factor with repeated measures "Session" (Habituation, Acquisition, Competition, and Retention). The paired *t*-test was used to determine whether within the same group the frequency of use of a strategy differed significantly from a session to another one. For electrophysiological data, the

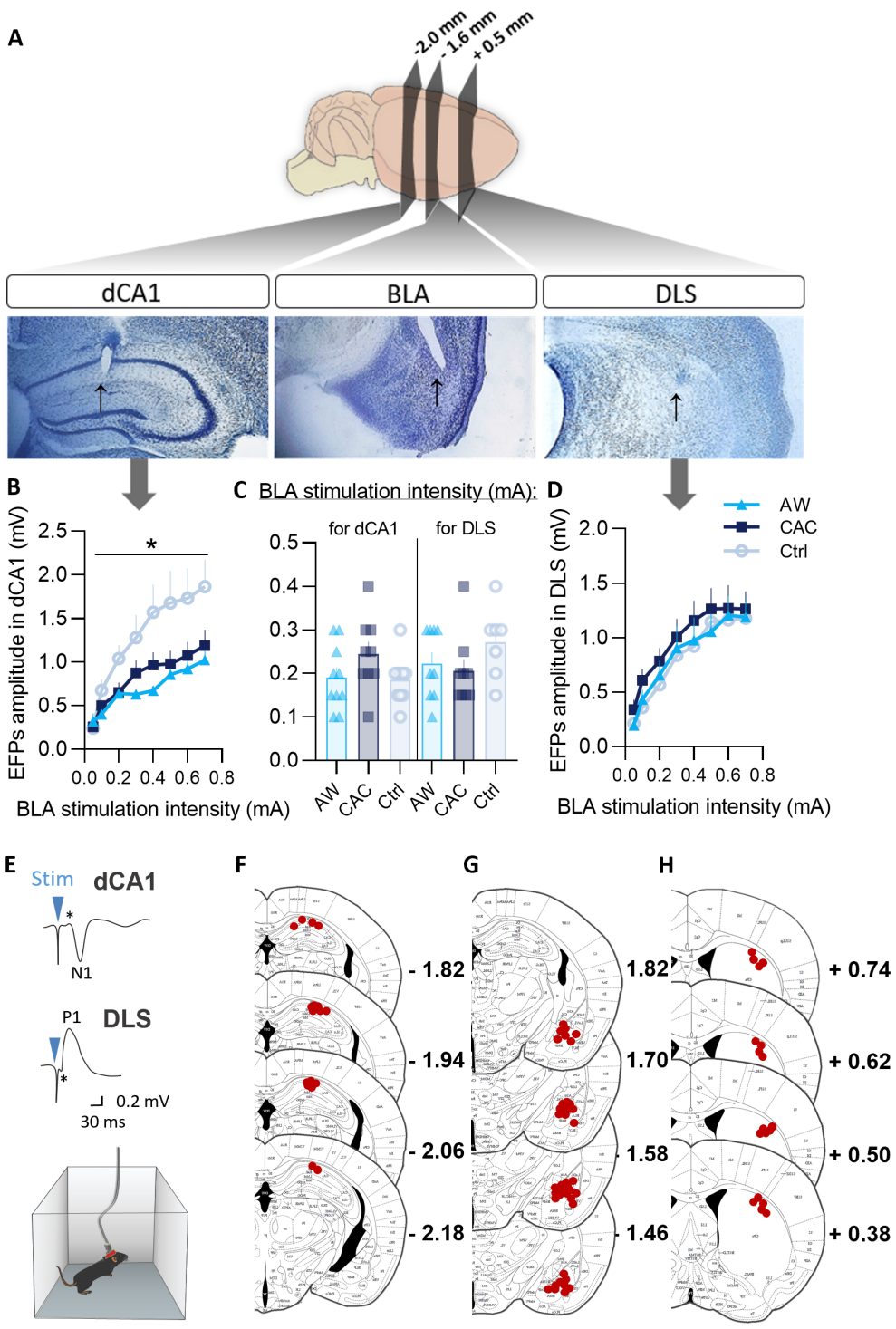

FIGURE 3
Effects of CAC and AW procedures on BLA→dCA1 and BLA→DLS neurotransmission. **(A)** Microphotographs of thionine-stained 50μm-thick brain slices showing (black arrows) the localization of the recording electrode tip in the dCA1 (left) and the DLS (right); and of the stimulating electrode tip in the BLA (center). **(B–D)** I/O curves showing the variation of EFPs amplitudes as a function of various BLA stimulation intensities (0–0.7mA; curves) and the BLA stimulation intensities used to evoked FPs representing 50%–70% of the maximal amplitude of the EFPs **(C)** in the dCA1 **(B)**, or in the DLS **(D)**. *$p<0.05$: group effect. **(E)** Representative trace of BLA stimulation-EFPs *in vivo* recordings in dCA1 and DLS. **(F–H)** detailed locations of the recording electrode tip in the dCA1 **(F)** and the DLS **(H)**; and of the stimulating electrode tip in the BLA **(G)**.

paired *t*-test was used to determine whether EFPs differed significantly from baseline. Then, differences among groups were determined by ANOVAs with the between-subject factor "Group" (AW, CAC, Ctrl) and the within-subject factor with repeated measures "Delay" (3 or 4 delays: 1, 15, 60 min post-Acquisition or post-Retention; and 1, 15, 45, and 60 min post-HFS). These analyses were conducted using

GraphPad Prism and Statview. For all tests, $p < 0.05$ was considered statistically significant.

3. Results

3.1. Effects of CAC and AW on spatial vs. non spatial learning strategies

Mice were first trained during one habituation trial (*Trial 0, Hab, Day 4*) and six consecutive acquisition trials (*Trials 1–6, Acq, Day 5*) to escape from the exposed area of the Barnes maze by entering the escape hole in less than 180 s (*red frame,* Figure 1C). As shown in Figures 4A–C, all groups learned the BM task as indicated by the decreases in escape latencies, errors, and path lengths across trials. Repeated-measures group x trials ANOVAs including data from trial 0 to 6 revealed a significant effect of trial for each of these performance variables [Escape Latency: $F(6,336) = 14.91$, $p < 0.0001$; Errors: $F(6,336) = 4.97$, $p < 0.0001$; Path Length: $F(6,336) = 7.45$, $p < 0.0001$; *t0-6, Hab-Acq,* Figures 4A–C]. However, there was no effect of group or group x trial interactions for these measures, suggesting that both CAC and AW mice learned the BM task with similar performance accuracy relative to controls.

Analysis of the search strategy indicated that the groups did not differ also in their way of solving the task (Figures 4D,E). Indeed, during training (trials 0–6), the escape hole was signaled by a proximal beacon cue (bottle) and was always located in the same position relative to distal extra-maze cues in the room. In this configuration, the strategy used to locate the escape hole was classified as Spatial/Cued, Serial or Random (Figure 2). During the first trial, all groups exhibited similar strategy patterns with a strong preference for a Random strategy (mean use of 76.3% ± 4.2%) over Serial and Spatial/Cued searches (*t0, Hab,* Figure 4D). Twenty-four hours later, all groups decreased their use of the Random strategy (from mean use of 76.3 ± 4.2% to 33.6 ± 2.3%), and conversely increased their use of the Spatial/Cued strategy which became predominant (from mean use of 6.8 ± 3.3 to 43.8 ± 2.5%; *t1–6, Acq,* Figure 4E). In line with these findings, ANOVAs confirmed the main effect of session for the use of these strategies (Random: $F(1,56)=39.56$, $p < 0.0001$; Spatial/Cued: $F(1,56)=80.14$, $p < 0.0001$) but no effect of group nor group x session interaction (Figure 4E).

To better understand the dynamics of these strategy patterns, we examine the efficiency of each search strategy. To this aim, escape latencies and errors of all acquisition trials were pooled per strategy regardless of the group (t1–6; *Acq*, Figures 4H,I). One-way ANOVAs indicated a main effect of strategy for the two variables [escape latency: $F(2,140) = 36.25$, $p < 0.0001$; and error: $F(2,140) = 80.98$, $p < 0.0001$]. The Random strategy was significantly slower than the Serial strategy (Bonferroni *post-hoc* analysis, $p = 0.0088$), which, in turn, was significantly slower than the Spatial/Cued strategy (Bonferroni *post-hoc* analysis, $p < 0.0001$; Figure 4H). Both Random and Serial strategies led to significantly more errors than the Spatial/Cued strategy (Bonferroni *post-hoc* analysis, respectively: $p < 0.0001$ and $p < 0.0001$; Figure 4I). Again, no effect of group nor interaction group x strategy were found. Thus, the escape was optimized by the use of proximal and/or numerous distal cues (i.e., Spatial/Cue strategy) in all groups.

To dissociate the use of Spatial vs. Cued strategy (S/C), the 7th trial was performed in a competition configuration, i.e., with two escape holes: the spatial one at the same location that during acquisition (same position relative to distal extra-maze cues in the room; S) and the cued one at the opposite where the beacon cue was relocated (C; *Trial 7, Comp, Day 5*; Figure 1C). As in the previous trials, there was no effect of group on escape latencies, errors, and path lengths during trial 7 (*t7, Comp*; Figures 4A–C). This competition trial revealed that all groups favored the Spatial strategy over a Cued strategy (respectively, 40.9 ± 2.5% vs. 27.3 ± 2.0% for AW; 70.6 ± 2.2% vs. 11.8 ± 1.1% for CAC; and 50.0 ± 2.6% vs. 15.0 ± 1.3% for Ctrl; Figure 4F). However, AW mice tended to have lower use of the Spatial strategy and conversely higher use of the Cued strategy as compared to CAC and Ctrl mice.

When tested 24 h later in the same competition design (*Trials 8–10, Ret*; Figure 1C), the three groups differed both in terms of performance and strategy patterns. A main effect of group was found for escape latencies [$F(2,56) = 3.36$, $p = 0.041$] and errors [$F(2,56) = 4.01$, $p = 0.023$], but not for path lengths (*t8–9, Ret*; Figures 4A–C). AW mice exhibited longer escape latencies than the Ctrl group (Bonferroni/Dunnett's *post-hoc* AW vs. Ctrl: $p = 0.014$), and also committed significantly more errors ($p = 0.0070$). Furthermore, while Ctrl mice mostly favored the Spatial strategy (66.7% ± 11.7%) over non-spatial strategies, AW group did not have predominant search strategy during Retention (use of each of the four strategies closed to 25%; Figure 4G). Interestingly, the CAC group showed an intermediate profile: half of their searches based on a Spatial strategy (49.0% ± 8.5%) and the other half distributed equitably between the three non-spatial strategies. In accordance with these observations, the frequency of use of a Spatial strategy was significantly reduced in the AW group compared to Ctrl group [group effect: $F(2,56)=6.08$, $p = 0.0041$; Bonferroni/Dunnett's *post-hoc* AW vs. Ctrl: $p = 0.0010$]. Conversely, the frequency of use of a Cued strategy was increased in the AW compared to Ctrl group (19.7% ± 10.0% vs. 5.0% ± 1.5%; $p = 0.060$).

In contrast to Ctrl group, AW group did not display a preference for the Spatial strategy over the Cued strategy during Retention (Figure 4L). Accordingly, there was a main effect of group for the Spatial over Cued preference score [$F(2,57) = 5,88$, $p = 0,0047$; AW vs. Ctrl: $p = 0,0035$; Figure 4L]. Analysis of the strategy efficiency (Figures 4J,K), indicated that the Cued strategy took as long and leads to the same number of errors as the Spatial strategy. Thus, the increased use of the Cued strategy observed in AW mice (and at a lesser extend in CAC mice) may compensate a lower ability to use the Spatial strategy. However, despite this switch, AW mice exhibited lower performances than CAC and Ctrl mice during trials 8 to 10. This was likely due to their lower prevalence of the use of cue-based strategies (Cued and Spatial) vs. non-cue responses (Random and Serial), respectively: 53% vs. 47%, compared to 72% vs. 28% in Ctrl and 63% vs. 37% in CAC mice. Indeed, as illustrated in Figures 4J,K, the two non-cue responses (Random and Serial) were less efficient that the cue-based strategies (Cued and Spatial). Thus, leading to an effect of search strategy for escape latencies and errors [latencies: $F(3,113) = 14,86$, $p < 0,0001$; R vs. S: $p < 0,0001$; R vs. C: $p < 0,0001$; errors: $F(3,113) = 35,76$, $p < 0,0001$; R vs. C: $p < 0.0001$; R vs. S: $p < 0.0001$; Ser vs. C: $p = 0.0003$; Ser vs. S: $p < 0.0001$].

Mice were tested in the BM experiment between 9 a.m. and 4:30 p.m., and all three groups were homogenously spread across

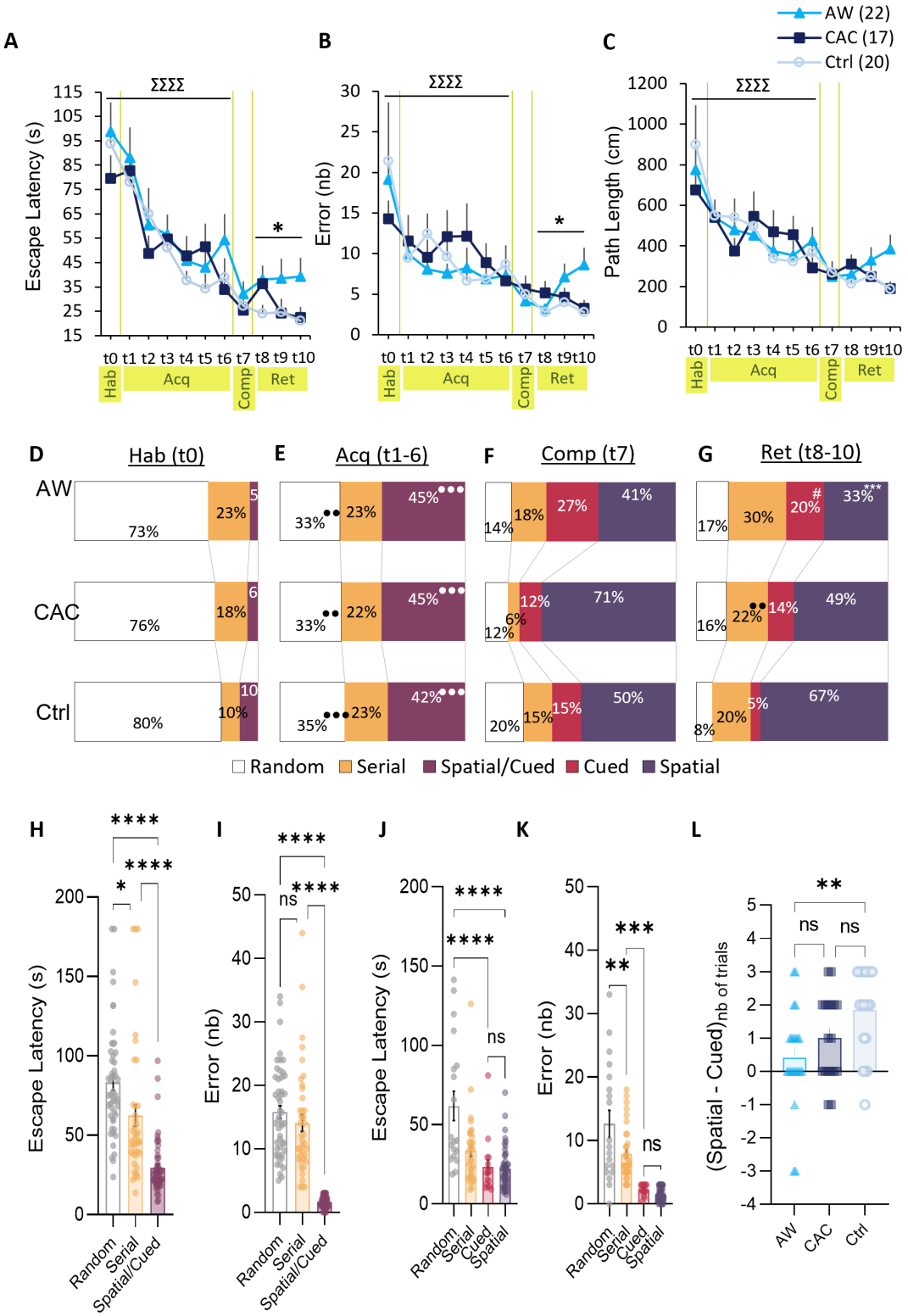

FIGURE 4
Effects of CAC and AW on Spatial vs. non-Spatial learning strategies in the Barnes maze task. **(A–C)** Escape latencies **(A)**, errors **(B)**, and path lengths **(C)** over the course of the habituation trial (*t0, Hab*), the six acquisition trials (*t1–6, Acq*), the competition trial (*t7, Comp*), and the 3 retention trials (*t8–10, Ret*). Data are represented as mean±SEM. ∑∑∑∑p<0.0001: trial effect; *p<0.05: group effect. **(D–G)** Relative use of each search strategy in AW, CAC and Ctrl group (from top to bottom) during: habituation **(D)**, acquisition **(E)**, competition **(F),** or retention **(G)**. ***p<0.05: comparison with Ctrl group; ●●●p<0.001: comparison with previous session. #p=0.060: vs. Ctrl group, close to significance. **(H,I)** Escape latency **(H)** and errors **(I)** for all acquisition trials, pooled per search strategy. **(J,K)** Escape latency **(J)** and errors **(K)** for all retention trials, pooled per search strategy. *p<0.05, ***p<0.001, ****p<0.0001: pairwise strategy comparison. **(L)** Score of preference for the Spatial strategy over the Cued strategy during retention trials 8 to 10. The score was calculated as followed: number of trials solved with a Spatial strategy, minus the number of trials solved with a Cued strategy.

mornings and afternoons. Still, we controlled for the influence of test time, and found no effect of this parameter for the frequency of use of each search strategy (Supplementary Figure 1), as it was previously reported that rodents will change their learning behavior from spatial to procedural depending on the light–dark cycle (58). Moreover, changes observed in alcohol-treated groups cannot be attributed to alterations of locomotor activity, as there was no group difference in velocity: neither during the very first trial (mean speed in m/s: 7.7 ± 3.1, 8.1 ± 2.1, and 9.0 ± 4.0 for AW, CAC, and Ctrl group, respectively; t0, hab, Day 4); nor throughout the whole BM experiment (8.4 ± 3.0, 8.9 ± 4.0 and 9.3 ± 3.4; t0-t10, Day 4–6).

3.2. Effects of CAC and AW on BLA→dCA1 and BLA→DLS neurotransmission

We then investigated whether CAC and AW induced functional modifications in the BLA → dCA1 and BLA → DLS transmission, using *in vivo* electrophysiology in freely moving mice. We examined field potentials evoked (EFPs) in the dCA1 and the DLS by stimulation of the BLA. Three mice were excluded from the study due to signal loss (dysfunctional or displaced electrode; dCA1: 1 AW, DLS: 1 AW, 1 Ctrl). Based on histological analysis, two supplemental mice were excluded due to electrode misplacement (DLS: 1 AW; BLA: 1 Ctrl). All other selected animals on the basis of electrophysiological criteria (i.e., quality and stability of basal recordings: $n = 55$) showed a correct positioning of the stimulating and recording electrodes, respectively, in the BLA and dCA1/DLS. Examples of correct locations are provided in Figure 3A and detailed locations are provided in Figures 3F–H.

The input–output curves established the optimal stimulation intensities (Figure 3C) and showed that both CAC and AW treatments reduced basal excitability in the BLA → dCA1 but not the BLA → DLS pathway (Figures 3B vs. 3D). In support, repeated-measures group x intensities ANOVAs indicated a main effect of group [$F(2,25) = 5.17$, $p = 0.013$; Bonferroni/Dunn *post-hoc*, AW vs. Ctrl: $p = 0.0051$], and a significant intensity x group interaction [$F(14,175) = 3.77$, $p < 0.0001$], for the EFP measures in dCA1 (Figure 3B).

3.3. Effects of CAC and AW on learning-induced BLA→dCA1 and BLA→DLS transmission

3.3.1. BLA→dCA1 pathway

With the aim of investigating whether CAC and AW impact the learning-induced changes in BLA → dCA1 transmission, we analyzed EFPs recorded at different time points before and after the BM task (Figure 5A). We first observed that AW mice exhibited a transient decrease in BLA → dCA1 signal amplitude relative to baseline level, 1 and 15 min after BM Acquisition/Competition [post-Acq/Comp vs. BL: $t(29)=2.58$, $p = 0.015$; 1′ vs. BL: $t(9)=5.58$, $p = 0.0003$; 15′ vs. BL: $t(9)=2.024$, $p = 0.073$ ns; *Post-Acq/Comp,* Figure 5A]. No significant change was observed in CAC and Ctrl groups [post-Acq/Comp vs. BL, in CAC: $t(26)=1.01$, $p = 0.32$ ns; in Ctrl: $t(29)=1.88$, $p = 0.069$ ns]. Changes observed in AW mice 1 min after completion of the BM Acq/Comp were significantly different from Ctrl mice [$F(1,18) = 8.03$, $p = 0.011$; *1′ post-Acq/Comp,* Figure 5A].

Post retention recordings revealed an opposite pattern of changes in BLA → dCA1 transmission in both alcohol-exposed groups as compared to controls (*Post-Ret*, Figure 5A). Ctrl mice exhibited a significant increase in amplitude relative to BL, 1 to 60 min after BM Retention [$t(29)=2.97$, $p = 0.0059$]. In contrast, CAC and AW mice displayed a decrease which was significant only for AW mice at 1 and 15 min post-Ret [$t(29)=4.84$, $p < 0.0001$; at 1′: $t(9)=2.95$, $p = 0.016$; at 15′: $t(9)=3.28$, $p = 0.0095$]. Repeated-measures group x delays ANOVA that included recordings from 1 to 60 min post-Ret revealed a significant effect of group [$F(2,26) = 5.52$, $p = 0.010$] and delay [$F(2,52) = 7.78$, $p = 0.0011$], but no group x delay interaction [$F(4,52)=1.85$, $p = 0.13$ ns]. Changes observed in AW mice were significantly different from Ctrl mice from 1 to 60 min after BM Ret [1′: $F(1,18) = 7.08$, $p = 0.015$; 15′: $F(1,18) = 6.38$, $p = 0.021$; 60′: $F(1,18) = 0.0029$]. Changes observed in CAC mice were significantly different from Ctrl mice only 1 min after BM Ret [$F(1,17) = 4.29$, $p = 0.050$].

BM-induced modifications in BLA → dCA1 synaptic plasticity did not persist, as evoked responses amplitude always returned to pre-test values 24 h later (*24 h post-Hab, 24 h post-Acq/Comp* and *24 h post-Ret*, Figure 5A). No group effect was observed at any of these 24 h delays.

3.3.2. BLA→DLS pathway

We found that learning-induced modifications in the BLA → DLS transmission were completely inverted as compared to those observed in the BLA → dCA1 pathway (see Figures 5A vs. 5B). AW and CAC mice displayed a significant increase in DLS EFPs amplitude following BM Acquisition/Competition [post-Acq/Comp vs. BL, in AW: $t(26) = 4.303$, $p = 0.0002$; in CAC group: $t(26) = 2.42$, $p = 0.022$; *Post-Acq/Comp,* Figure 5B]. Ctrl mice exhibited instead a significant decrease relative to baseline at the first delay [1′ post-Acq/Comp vs. BL: $t(7) = 3.16$, $p = 0.015$]. The amplitude of DLS-EFPs in AW mice was significantly higher than Ctrl mice, regardless of the delay [Group effect: $F(1,15) = 8.32$, $p = 0.011$; Delay effect: $F(2,30) = 1.92$, $p = 0.16$ ns; Group × Delay interaction: $F(2,30) = 0.23$, $p = 0.79$ ns].

Changes in BLA → DLS synaptic transmission following the BM Retention were similar to those observed after the training (*Post-Ret*, Figure 5B). All alcohol-exposed, but mainly AW mice displayed a significant increase in BLA → DLS transmission [Post-Ret vs. BL, in AW mice: $t(26) = 4.87$, $p < 0.0001$; in CAC group: $t(26) = 2.48$, $p = 0.019$]. In sharp contrast, Ctrl mice displayed a significant short-term decrease [15′ post-Ret vs. BL: $t(7) = 4.69$, $p = 0.0022$]. Repeated-measures group x delays ANOVA that included recordings from 1 to 60 min post-Ret thus yielded a main effect of group [$F(2,23) = 3.52$; $p = 0.046$] and a significant effect of delay [$F(2,46) = 4.46$; $p = 0.017$]; but no group × delay interaction [$F(4,46) = 1.25$, $p = 0.30$ ns].

As in the dCA1, BM-induced modifications in BLA → DLS synaptic plasticity did not persist, as evoked responses amplitude recorded 24 h later were not significantly different from pre-BM values (*24 h post-Hab, 24 h post-Acq/Comp* and *24 h post-Ret*; Figure 5B). No group effect was observed at any of these 24 h delays.

3.3.3. Learning-induced metaplasticity: effects of high-frequency stimulation

In control mice, high-frequency stimulation (HFS) induced a strong LTP in dCA1 [post-HFS vs. BL: $t(39) = 4.46$, $p < 0.0001$; Figure 5C], but elicited a significant post-tetanic depression (−40%) in the DLS [post-HFS vs. BL: $t(31) = 2.82$, $p = 0.0083$; Figure 5D] with a return to BL within 15 min. In contrast, HFS induced a steady LTP in the DLS of AW mice [post-HFS vs. BL: $t(35) = 3.83$, $p = 0.0005$; Figure 5D], and no significant modification in the CAC group. No significant changes were observed in dCA1 for these two groups after

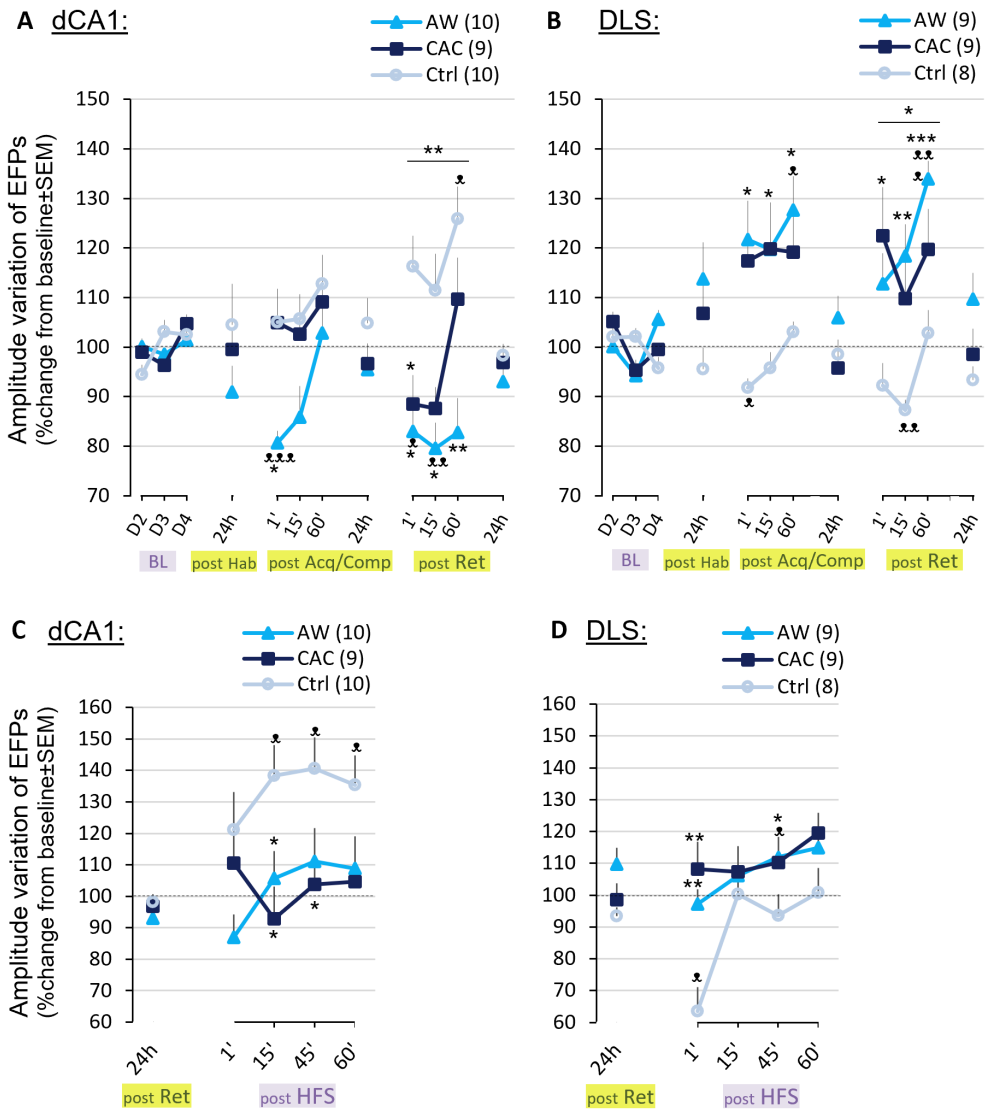

FIGURE 5
Effects of CAC and AW procedures on the learning-induced BLA→dCA1 and BLA→DLS neurotransmission. **(A,B)** Changes in BLA→dCA1 **(A)** or BLA→DLS (**B**) amplitude (EFPs, in % change from baseline ± SEM) at different time points before and after the BM task. **(C,D)** Amplitude variation of signals (in % change from baseline ± SEM) 1, 15, 45, and 60min after BLA HFS, recorded in the dCA1 **(C)** or DLS **(D)**. •p<0.05, ••p<0.01, •••p<0.001: comparison with BL; *p<0.05, **p<0.01, ***p<0.001: comparison with Ctrl group.

HFS. Repeated-measures group x delays ANOVA that included DLS recordings from 1 to 60 min post-HFS, revealed a main effect of group [$F(2,23) = 3.31$, $p = 0.050$], a significant effect of delay [$F(3,69) = 12.47$, $p < 0.0001$] and a significant Group × Delay interaction [$F(6,69) = 2.91$, $p = 0.013$].

4. Discussion

In the present study, we investigated spatial and cued (i.e., beacon) learning abilities in chronically alcoholized (CAC), alcohol withdrawn (AW), and control (Ctrl) mice, using a competitive version of the Barnes maze task and *in vivo* electrophysiological recordings of neurotransmission in dorsal CA1 and dorsolateral striatum. We first observed that learning performances were very similar in alcohol exposed and non-alcohol exposed mice, suggesting that neither CAC nor AW induced apparent deficits as assessed by escape latencies, errors, and path lengths. Furthermore, all groups similarly learnt to favor the cue-guided strategies, which were more efficient than serial or random searches to solve the task. Among these cue-based strategies, both alcohol exposed and non-alcohol exposed groups favored the Spatial strategy over the Cued one, as revealed by the competition trial performed at the end of the training session. These results are in line with previous studies demonstrating that mice use spatial cues preferentially when both spatial and beacon cues are available (59). However, this preference was less marked in AW mice, which tended to show a lower use of a Spatial strategy and conversely higher use of a Cued strategy as compared to CAC and Ctrl mice. More importantly, evaluation of the performances 24 h after training, revealed an impairment in hippocampus-dependent learning and memory processing in alcohol exposed mice. Indeed, while Ctrl mice increased their use of Spatial over non-spatial strategies and kept

improving their escape performances between acquisition and retention trials, the use of the Spatial strategy decreased in both alcohol exposed groups. In particular, AW mice significantly differed both quantitatively and qualitatively from Ctrl group. The lower use of the Spatial strategy observed in AW mice was compensated by a higher use of the Cued strategy. The availability of salient intra-maze cues is known to prevent the impairment of spatial memory (24, 26, 60), which fits well with the conceptual frame of dynamic interactions between memory systems (6, 14, 38). Accordingly, we found that the Cued strategy was as performant as the Spatial one. Nevertheless, the Spatial-to-Cued switch observed in AW mice did not appear sufficient to solve the task optimally in a retention situation, as they displayed lower escape performances than Ctrl mice. Currently, it is thought that, in dual-solution navigational tasks, the spatial memory system is the first recruited and that with task repetitiveness, the striatal system takes over and starts to guide behavior (57, 61, 62). In the present study, we chose a limited number of training trials to avoid the exclusive use of a striatal Cue-based strategy (38). Thus, whether an increased number of trials could help AW mice to eventually perform to the level of Ctrl is an open question that need to be further investigated. Still, AW mice did not exhibit apparent learning deficits during acquisition, suggesting that, when available, the DLS-dependent strategy may also be recruited from the initial stages of learning a navigational task. Indeed, we previously highlighted that the hippocampus is not always the first to provide a solution (38). Accordingly, a more recent study showed that in a dual double-H maze task, rats first approach the task on the basis of response learning (i.e., Cued strategy) and construct a cognitive map later on (16).

Since the CAC group showed an intermediate profile between the AW and Ctrl groups, it is likely that long-term alcohol exposure is responsible for the spatial deficit observed during Retention, which appear to be precipitated during AW (3). Importantly, the Spatial-to-Cued switch was a complementary yet different mechanism from the well-known habit-forming action of addictive drugs and specific S-R associations which play a critical role in cue-induced relapse (63–65). Instead, as previously described for opiates (18, 21), we suggest that CAC could maintain the DLS memory circuit in a hyperactive mode, thus disrupting flexible interactions between memory systems that normally occur during learning. This view fits well with the general frame of dual-process models dissociating the role of impulsive automatic/reflexive vs. goal-directed, reflective, and controlled behaviors in alcohol and drug addiction (66, 67).

We then carried out a series of electrophysiological recordings in freely moving mice to determine whether modifications in synaptic plasticity could be related to CAC and AW-induced changes in cognitive strategies used to solve the task. Modulation of the connection strength between neurons is considered as one of the mechanisms by which memory traces are encoded and stored in the brain. The selection of the most adapted memory system is based on synaptic rearrangements through LTP or LTD. Previous studies have reported post-training increases in synaptic plasticity markers such as phosphorylation of CREB in the dorsal hippocampus after spatial learning and in the dorsal striatum after cued learning, respectively (68, 69). We first observed that, as expected, accurate spatial reference memory was associated with a potentiation in the dCA1 following acquisition of the Barnes maze task in Ctrl mice. Interestingly, we found a concurrent depression of synaptic transmission in the DLS. Strikingly, this pattern of synaptic plasticity was completely inverted in alcohol-exposed mice (CAC and AW groups), which displayed a strong LTD in the dCA1 but a potentiation in the DLS. These findings are consistent with the view that, like other addictive drugs, alcohol use disrupts normal synaptic dCA1 transmission (70) and hippocampal-striatal interactions, as previously reported in mice with a history of opiate self-administration (18, 19, 21). In non-alcohol exposed mice, the use of spatial strategy relied on an enhanced BLA → dCA1 transmission and a reduced BLA → DLS transmission. A completely opposite pattern was observed in both CAC and AW mouse which used the Cued strategy more frequently, displayed a reduced BLA → dCA1 transmission and an enhanced BLA → DLS transmission.

In physiological conditions, metaplasticity is adjusted so that neuronal networks are prepared for specific information encoding, thereby ensuring long-term memory storage. Yet the ability to generate LTP is impaired in the dCA1 of CAC and AW mice, and conversely enhanced in the DLS of AW mice. Impaired LTP in BLA → dCA1 pathway and enhanced synaptic transmission in BLA → DLS pathway in AW and mice still under alcohol provides a neuronal basis for the preferential use of Cue learning as revealed by the Barnes maze task. This view is in good agreement with the previous observation of a preferential use of habitual over spatial strategies, combined with an increased dendritic complexity in the DLS of chronically stressed rats (71). It should be noted that BLA → DLS transmission increased more moderately in mice still under alcohol, and that BLA → dCA1 transmission declined more moderately than in withdrawn mice. Consistently, memory performance also appeared intermediate between those of control and withdrawn mice. Our results thus suggest that withdrawal could aggravate the cognitive and neural alterations which progressively develop over CAC. These findings raise fundamental issues concerning the emergence of withdrawal-induced cognitive deficits, and the therapeutic intervention that must be taken to limit them. Indeed, there is ample evidence that memory deficits are either aggravated or progressively developed after alcohol withdrawal (31, 72). In its early phase, withdrawal induces an acute stress state with high anxiety and corticoid levels that will have direct deleterious effects on cognitive performance, as for other forms of acute stress (26, 73). However, in the present study, cognitive tasks were realized after a progressive withdrawal procedure lasting 2 weeks so that, at the time of testing, mice show moderate or no signs of anxiety as assessed across different tasks (74).

We previously reported a persistent impairment of working memory in withdrawn mice, which could be related to long-lasting increases in corticosterone in the prefrontal cortex (31). Interestingly, the neuronal loss in the dCA1 of CAC-treated rats is estimated to 18%, but the neuronal loss is further increased to 15% in 1-month withdrawn rats relative to non-withdrawn animals (72). Withdrawal-induced activation of HPA axis could reveal/aggravate glutamatergic hyperactivity, GABA receptor deregulation and related neuronal loss or loss of neurogenesis, thereby contributing to the alteration of cognitive processes that were not apparent during CAC (3). Accordingly, the administration of baclofen (an agonist of GABAB receptors) during withdrawal reversed the stress-induced reinstatement of alcohol-seeking behavior and HPA axis dysfunction in withdrawn animals (74). Together, these data support the view that alcohol-induced memory deficits could be initially caused by chronic alcohol consumption, but that underlying cellular and synaptic

plasticity changes would be unraveled or precipitated during early withdrawal. To identify the neural bases of these persistent deleterious effects that could be targeted during withdrawal is a remaining, critical challenge.

Intracerebral electrode insertion is associated with a cascade of inflammatory responses, such as astrogliosis and recruitment of brain-resident microglia to the insertion site which may affect not only the electrodes' ability to stimulate and record effectively, but also neuronal activity (75, 76). Therefore, it is possible that the development of glial encapsulation on the electrodes (77–79) have led to the deterioration/loss of signal, as reported in the three mice excluded from this study. However, this process did not seem specific of a particular group or structure since this loss of signal affected mice from Ctrl and AW groups, or dCA1 and DLS structures. Still, glial encapsulation on the dCA1 recording electrode could have contributed to the changes in input/output curves observed in AW and CAC mice. Reactive gliosis may also influence the excitability of individual local neurons, the synaptic transmission of signals between them, and the broader population activity detected and stimulated by electrodes implanted in the brain (80, 81). Major glial-induced modifications of the neuronal activity begin within the first hours, but peak around day 2–7 post-implantation (82–85). After a traumatic brain injury, microglia rapidly decline to control levels approximately 21 days after the lesion, while astrocytes exhibit a long-lasting proliferative response, at least 28 days after (85). Similarly, a longitudinal study combining analysis of abiotic and biotic metrics related to tungsten electrode implantation in a large cohort of rats, showed that the first period of 14–21 days is the most dynamic in the lifetime of a chronic electrode implant (83). We started baseline recordings around 23–27 days after implantation of both stimulating and recording tungsten electrodes. Therefore, it is likely that the recovery time used in the present study allowed for sufficient restoration of astrogliosis.

Independently from electrodes implantation, alcohol itself is a potent neurotoxic substance triggering neuroinflammatory responses and oxidative stress. In particular, chronic alcohol consumption is associated with excessive oxidative damage and reduced levels of endogenous antioxidants, leading to excessive reactive oxygen species (ROS) production (86, 87), which ultimately impacts neuronal cell viability (88). Accumulating evidence from preclinical and clinical studies supports the view that activation of microglia and astroglia contributes to the chronic alcohol-induced oxidative stress and associated neurodegeneration (89–91). Moreover, the glial response to alcohol could depend on the brain region (92, 93). As a result, the chronic alcohol consumption could elicit differential neuroimmune responses, oxidative damage or synaptic remodeling within discrete brain regions. The hippocampus seems to be one of the main targets of alcohol toxicity in the brain (94–97). However, alcohol-elicited reactive gliosis and oxidative damage are not well characterized in the dorsolateral striatum, and mechanisms that drive regional selectivity in glial activation are currently unknown. Nevertheless, differential alcohol-induced cellular changes may be involved in the hippocampus-to-striatum shift reported in the present study. Also, alterations in the oxidative and neuroinflammation status have been linked to the early withdrawal phase (98), during which they may be even more intense than during previous ethanol exposure (99). This may account for the higher deficits observed in AW mice compared to CAC mice.

In conclusion, a prime cognitive signature of chronic alcohol-exposure/early alcohol withdrawal could be the switch in learning strategies as revealed by an increased use of cue-guided memory to compensate for spatial memory deficits. Change in learning behavior was associated with a reduced amygdala-hippocampal transmission and, conversely, an enhancement of synaptic plasticity within the amygdalo-striatal pathway. This mechanism underlies a persistent neurocognitive imbalance which could account for the extreme difficulty in extinguishing alcohol drinking / seeking behavior, and fits well with dual process models of addiction. Any treatment, whether pharmacologic or psychotherapeutic, contributing to restore hippocampal function and balanced interactions between striatum- and hippocampus-dependent learning circuits could promote the recovery of behavioral flexibility, and therefore could be of great help to AUD patients.

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 animal study was reviewed and approved by the Ethics Committee of the University of Bordeaux (CEE50, approval #12283).

Author contributions

LT carried out all experiments and wrote the first draft of the paper. R-MV contributed to *in vivo* electrophysiological experiments and edited the paper. MC and NH contributed to the Barnes maze experiments and edited the paper. DB provided advice for the CAC and AW protocols and edited the paper. J-LG contributed to the Barnes maze experiments and edited the paper. VD designed the research, funded the research, contributed to the Barnes maze experiments, and edited the paper. All authors contributed to the article and approved the submitted version.

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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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Supplementary material

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How, when, and to what degree do people with alcohol dependence recover their psychological wellbeing and quality of life? The Madrid Recovery Project

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Introduction: The consensus on recovery from alcohol use disorder (AUD) has shifted toward encompassing psychological wellbeing and quality of life dimensions. However, few studies have explored the long-term recovery process and its dimensions, timing, styles, and modes. The aim of this study was to investigate the extent, timing, and process of psychological wellbeing and quality of life recovery in alcohol use disorder (AUD) patients, as well as the relationship with classic dimensions of AUD recovery.

Method: A cross-sectional study has been carried out with 348 participants with AUD, in different abstinence periods (1month–28years), and 171 control subjects. Participants underwent a psychological evaluation, which included self-informed measures of psychological wellbeing, quality of life, negative emotionality, and coping strategies related to alcohol consumption avoidance. Statistical analysis included linear and non-linear regression models between psychological dimensions and maintenance of abstinence, as well as matching the scores of the sample with AUD to those of controls. Scatter plots were used to explore inflection points. In addition, mean comparison tests were performed between participants with AUD and controls and by gender.

Results: In general, according to the regression models, there were pronounced increases in indices of wellbeing and coping strategies (and pronounced decreases in negative emotionality) during the first 5years of abstinence, followed by less pronounced improvements. The matching of AUD subjects in wellbeing and negative emotionality indices with controls occurs at different times: (a) 1year or less: physical health; (b) 1–4years: psychological health; (c) 4–10 years: social relationships, wellbeing, and negative emotionality; and (d) more than 10 years: autonomy and self-acceptance. There are statistically significant differences by gender for the negative emotionality and physical health variables.

Conclusion: Recovery from AUD is a long process that involves improvements in wellbeing and quality of life. Four stages can be described in this process, with the most pronounced changes occurring during the first 5years of abstinence. However, AUD patients take more time to obtain similar scores to controls in several psychological dimensions.

KEYWORDS

alcohol use disorder, quality of life, psychological wellbeing, recovery stages, negative emotionality, coping strategy, Madrid Recovery Project

1. Introduction

The term "recovery" has been broadly studied and associated with alcohol and other substance use disorder processes (1). Nevertheless, at the present time, we still lack a solid consensus on the meaning of recovery and how it should be measured (1–5). For decades, a large part of treatment perspectives has focused on abstinence maintenance and attendance to self-help groups, such as 12-step programs, as measures of recovery. This vision might have led to a reductionist view of recovery. Nonetheless, the biopsychosocial models propose a more comprehensive view of recovery, which includes the management of different resources and abstinence maintenance strategies aimed to improve personal and familial assets, together with psychological and relational health improvements (6).

Among the newer and broader definitions of recovery, SAMHSA's (7) one stands out, describing the recovery process as the change that allows individuals to improve their health and wellbeing, to drive their own life, and to boost their potential. A more current definition is offered by Witkiewitz et al. (5), which is based on previous definitions and a recent empirical study. The authors propose that recovery is a process of behavioral change characterized by improvements in biopsychosocial functioning and life purpose (5). People in recovery usually experience relevant increases in physical, emotional, and relational health. Moreover, evidence of these improvements is shown in studies from several countries, such as Canada (8, 9), the United States (10), the United Kingdom (11), and Australia (12, 13). Recovery aspects seem to be related to factors such as lifestyle changes, wellbeing, and available resources or assets (as understood within the recovery capital framework) (3, 6, 14–19).

The ecological framework of recovery capital (RC) considers the various interrelated factors that promote recovery. Thus, RC refers to the total sum of the own resources that one can use to initiate and maintain recovery from alcohol and other drug dependence (20). From Granfield and Cloud's (20) proposal, resources are distinguished at the individual and societal levels. We have focused on individual resources. Hennessy's (21) systematic review of RC sets out that individual resources include those as follows: (I) physical capital (tangible capital, e.g., material resources such as money or the availability of a public treatment center); (II) human capital (personal characteristics to achieve goals: e.g., knowledge, interpersonal skills, emotional stability, or mental health); (III) growth capital it is based on a person's innate desire to grow and develop in a positive direction. It refers to the external and internal resources that support this growth. The recovery process attempts to remove obstacles to further growth so that it initiates and continually supports further growth toward recovery progress [see Hennessy's review (21)]. Additionally, recovery capital models include a dimension that refers to personal recovery. This dimension combines physical capital and human capital. The biaxial recovery model of Kelly and Hoeppner (3) proposes that recovery is constituted in two axes: (I) one related to the substance, which they call 'remission' and refers to withdrawal or abstinence time and (II) another that alludes to recovery capital from the framework of Cloud and Granfield (20). According to this biaxial recovery model (3), the relationship between remission and recovery capital must be reciprocal. Therefore, more time in remission will increase the positive consequences that flow from it. At the same time, increasing these positive consequences, i.e., possessing greater recovery capital, will increase the likelihood of long-term remission. Thus, it appears that recovery capital is a framework that is gaining momentum in the study of recovery and has gained interest in the treatment field and in addiction recovery research, by providing a broad perspective on the process (21). For example, the UK government's addiction agenda has shifted from a focus on harm management and a primarily disease-based view of addiction, to a focus on building recovery capital and fostering the role of patient activation and self-management to enhance recovery (22).

Despite the increasing need to expand and detail the dimensions of recovery, most studies published until now show a series of methodological limitations that make it difficult to obtain broader a vision of the recovery process. There is abundant literature on the first step of recovery and on factors that predict the acquisition of abstinence, whereas quantitative studies on long-term recovery characteristics are quite scarce (6, 15, 17).

A small number of studies have addressed recovery considering long-term changes in psychological processes and a perspective that goes beyond the reduction of symptoms. Among them, we can outline the study of Kelly et al. (16), which includes participants from community samples, or the study of Witbrodt et al. (23) in clinical samples. Moreover, studies usually include a small sample size. A recent systematic review (1) showed that from the 36 studies reviewed, only 11 included samples superior to 100 participants.

In relation to studies aimed at recovery in terms of wellbeing and quality of life, the results from community samples by Kelly et al. (16) show an improvement in quality of life and psychological wellbeing, as the abstinence period increases, especially in the first 5 years. The review by Donovan et al. (24) reports that alcohol-dependent people experience improvements in their quality of life throughout treatment and with abstinence, both in the short and long term. This review notes that "despite these improvements, many individuals' QoL is unlikely to equal or exceed that of normative groups" (24).

Regarding the temporal sequence of psychological dimensions, changes, and quality of life improvement in recovery, the evidence published to date indicates that most variables improve during the 1st month/year after ceasing alcohol consumption (25–27). For instance, Laudet et al. (25), in a cross-sectional study, observed that distress ameliorated rapidly during the 1st year and continued to improve at a slower pace until the 3rd year. Dennis et al. (26), in a prospective study, observed that quality of life variables improved over time; however, at the 3rd year, an exacerbation of the psychological distress was found. In addition, our research group found in a 6-year follow-up study of outpatients with alcohol dependence that negative emotionality variables diminished during the first 3 years and then stabilized, while meaning in life kept improving until the end of the follow-up period (27, 28).

These findings have led us to propose a sequence in psychological recovery that would initiate with lifestyle behavioral changes, such as developing avoidance strategies against alcohol use, followed by improvements in clinical dimensions such as anxiety, sadness, and impulsivity and an overlapped increase in meaning in life (28). Nonetheless, a more detailed characterization of AUD recovery and information on how individuals with AUD recover psychological wellbeing is required. Moreover, the extent of improvement in wellbeing, quality of life, depression, or anxiety during the recovery process is still to be determined, and the equation of these dimensions to normative groups is yet to be explored. As Kelly et al. (16) pointed out, regarding long-term recovery, the question is more about the process, how and to what extent people with AUD experience improvement in wellbeing, and it is less about whether it takes place or not.

Learning about the elements of recovery could serve to identify the milestones or the turning points that might indicate the periods of increased vulnerability, resilience, or personal growth during the adaptation period. The competence in this field should include the understanding of the nature, level, the changing periods of different indexes that reflect wellbeing and functioning of the individuals. At the same time, this can provide information on the services needed to maintain the long-term recovery in several junctures and periods and personalized attention for the patient.

To achieve a deeper knowledge on the recovery course and the different psychological dimensions and quality of life in patients with severe AUD, research in a metropolitan area of Madrid was carried out, at the Public Alcohol Dependence Treatment Program of 12 de Octubre Hospital. The aim of this study was to examine the complexity of the recovery process in a clinical sample by analyzing various dimensions. The study examined the involvement of abstinence time understood as the "remission" axis proposed by Kelly and Hoeppner (3) in the Recovery Capital axis (3) and other clinical variables (negative emotionality and impulsivity). This provides a clinical perspective on the different temporal moments of the recovery process in patients with AUD in abstinence.

Abstinence time was utilized as a follow-up measure for recovery, given its relevance in cognitive-behavioral treatment that patients attended and previous literature supporting its role as a factor of recovery (15). In contrast to other studies, this research measured clinical manifestation variables, including negative emotionality and symptoms such as anxiety, depression, experiential avoidance, and impulsivity, as well as quality of life and psychological wellbeing. Additionally, recovery capital and coping strategies in relation to alcohol use and dependence were assessed. Furthermore, the possibility to evaluate patients at different stages of the recovery process would allow to observe the evolution of changes in the studied variables, having a control group of healthy participants would also enable a better view of patients' recovery.

2. Materials and methods

2.1. Experimental design

A cross-sectional study of a control and case study was carried out. On the one hand, 348 abstinent individuals with alcohol use disorder (AUD), that attended outpatient programs, either at the Psychiatry Service of 12 de Octubre Hospital, or self-help groups of the Community of Madrid, were included in the study. On the other hand, 171 healthy controls took part in the study, and they were matched in age, gender, and educational level.

All procedures were approved by the 12 de Octubre Ethics Committee.

2.2. Participants

With respect to participants with AUD, the sample consisted of 348 participants in a situation of complete abstinence (abstinence time range: 1 month–28 years). All participants were attending treatment aimed at abstinence, either at the public program of the Hospital 12 de Octubre or in mutual help groups. Participants with less than 2 years of abstinence attended the therapeutic program of the Psychiatry Service of the Hospital 12 de Octubre on an outpatient basis. Details regarding the therapeutic program can be read in Rubio et al. (27). This is a public treatment program (financed and managed by the public health system, so it is free of charge) with a duration of 2 years. This program sequentially addresses different aspects of abstinence-directed recovery: detoxification and motivation for abstinence; relapse prevention, social skills, consolidation of healthy habits and lifestyle, and preparation for discharge. Subsequently, it can be continued by participation in mutual help groups. Participants proceeding from 12 de Octubre Hospital were recruited in the treatment context. Senior adjunct psychiatrists, head of the program, asked them to join the study. They emphasized that participation was voluntary, and, under no circumstances, it would affect their treatment. Those who accepted to carry out the study were individually evaluated in the hospital's facilities.

To complete the sample of patients with more than 2 years of abstinence, those attending mutual help groups were invited to participate. Specifically, three associations of the Federation of Alcoholics of the Community of Madrid (FACOMA) and three of Alcoholics Anonymous (AA) participated in the study. In this case, the recruitment was done by the psychologist in charge of the therapeutic groups and the psychological assistance in FACOMA's locations. Recruitment conditions were similar to the previous one: They had explicit indications regarding voluntary participation, without treatment repercussions. Individuals were assessed at each location of the FACOMA. For individuals coming from AA groups, recruiting was carried out through a representative that was responsible for the invitation to the study. Once they manifested interest in the study, a senior psychiatrist from 12 de Octubre Hospital contacted them to assess them inside the hospital's facilities.

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TABLE 1 Clinical and sociodemographic description.

Sociodemographic data		AUD group			Control group		
		N/Frequency	Mean (SD)/ Frequency (%)	Min/Max	N/Frequency	Mean (SD)/ Frequency (%)	Min/ Max
Age		348	52.71 (9.01)	27–75	171	51.92 (8.71)	29–75
Gender	Men	234	67.24%		120	70.18%	
	Women	114	32.76%		51	29.82%	
Educational level	Compulsory education	135	38.79%		43	25.15%	
	High school education / Vocational training	94	27.01%		63	36.84%	
	Superior training	119	34.20%		65	38.01%	
Work situation	Active worker	138	39.66%		141	82.46%	
	Unemployed	73	20.98%		18	10.53%	
	Sick leave	41	11.78%		4	2.34%	
	Student	3	0.86%		0	0.00%	
	Retired	92	26.44%		8	4.68%	
Marital status	Single	75	21.55%		19	11.11%	
	Married	158	45.40%		122	71.35%	
	Divorced	58	16.67%		15	8.77%	
	Separated	13	3.74%		0	0.00%	
	In a relationship	39	11.21%		15	8.77%	
	Widower/Widow	5	1.44%		0	0.00%	

Clinical data							
		AUD group			Control group		
		N/Frequency	Mean (SD)/ Frequency (%)	Min/Max	*N*/Frequency	Mean (SD)/ Frequency (%)	Min/Max
Alcohol intake (yes/no)	Yes	0	0%		117	75.48%	
Abstinence time (in years)		348	3.84 (4.44)	0.8–28	–	–	
Age of initial consumption		348	14.55 (4.07)	4–47	171	16.36 (2.73)	9–72
Age of onset of daily consumption		348	27.89 (10.90)	12–65			
Age of dependence onset		348	29.95 (11.23)	12–65			
Amount of years of dependence		348	22.54 (11.51)	1–52			
Tobacco use	No	173	49.71%		135	78.95%	
	Yes	172	49.43%		36	21.05%	
Other substance use (In the past)	No	206	59.20%		–	–	
	Yes	142	40.80%		–	–	

Clinical and demographic means, standard deviations (SD), and frequency values (expressed in %) for participants with alcohol use disorder (AUD) and control groups.

The sample with AUD was composed of 114 women and 234 men, aged between 27 and 75 years old ($X = 52.71$; $SD = 9.01$). Patients had mostly compulsory education (38.79%) or higher education (34.20%). Nearly 39.66% of participants with AUD were active workers (See Table 1).

Regarding clinical variables (Table 1), the sample was composed of abstinent individuals that had ceased drinking from 1 month to 28 years ($X = 3.84$ years) (see distribution in Figure 1). On average, patients started drinking alcohol during their adolescence ($X = 14.55$; SD = 4.07) and the mean age onset of dependence was approximately

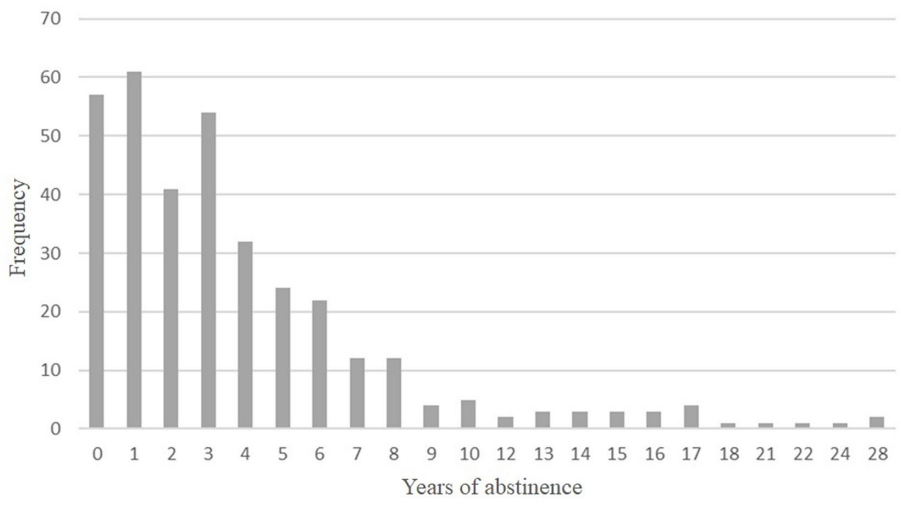

FIGURE 1
Patients with AUD frequency (expressed in percentages %) distribution according to abstinence time (in years).

30 years ($X = 29.95$; SD = 11.23). A total of 71.8% of the clinical sample had previous unsuccessful attempts to maintain alcohol abstinence. The number of previous abstinence attempts ranged from 0 to 15, with a mean of 2.11 (SD = 2.71). Most patients had received previous treatments (68.6%). Moreover, 68.6% of the sample showed a family history of substance dependence in first-degree relatives.

All patients were at least 1 month abstinent and had no active consumption of other substances (except for coffee and/or tobacco). Participants diagnosed with any psychiatric or neurological condition were excluded, due to their possible interfering role in the assessments.

With respect to the control group, the sample was composed of 171 participants (120 men and 51 women) with a mean age of 52 years. Nearly 38% of the participants had superior studies (See Table 1). The control group was recruited through a convenience sampling method in the waiting room of several health centers in the local area. Once they manifested interest in the study, the assessor from the 12 de Octubre Psychiatry Service established contact with them and carried out the MINI clinical interview (29) to exclude psychopathologies. All assessments were carried out in the healthcare center's facilities. Inclusion criteria were also determined by sociodemographic characteristics in an attempt to match control subjects and the AUD group in gender, age, and educational level. Exclusion criteria implied participants diagnosed with substance use disorders or any psychiatric [tested by the international neuropsychiatric interview; MINI (29)] or neurological condition.

2.3. Instruments

All scales were administered in their Spanish version.

2.3.1. Psychological scales applied to AUD and control groups

- *Quality of Life Scale (WHOQOL-BREF).* WHOQOL-BREF is a shortened version (27 items) of the original WHOQOL-100 (30). It includes four domains: physical health, psychological health, social relations, and environment, that show an alfa internal consistency of 0.82, 0.81, 0.68, and 0.80, respectively (31). The Spanish version of WHOQOL-BREF shows an internal consistency that ranges between 0.69 and 0.77 (32).
- *Psychological Wellbeing Scale (PWBS).* This scale is based on Ryff's multidimensional model of psychological wellbeing (33, 34). A version of 54 items (nine by each domain, with six answer options) was applied in the study (35). It comprises six dimensions: self-acceptance, autonomy, environmental mastery, purpose in life, personal growth, and social relations, that show internal consistencies of 0.83, 0.78, 0.77, 0.73, 0.65, and 0.80, respectively (35). The Spanish version, validated in the elderly population (36), has an internal consistency that varies between 0.58 and 0.71.
- *Satisfaction with Life Scale (SWLS).* Satisfaction with life refers to the global assessment that individuals make of their life, by comparing their own circumstances with the vision of what is considered as generally adequate by standard norms (37). The original version shows an internal consistency of 0.87 (37, 38). The Spanish version of SWLS shows an internal consistency of 0.88 (39).
- *Hamilton Anxiety Rating Scale (HAM-A).* A self-informed measure that assesses the severity or intensity of anxiety-like symptoms. It consists of 14 elements defined by symptoms for both psychological and somatic symptoms. Its internal consistency values range between 0.79 and 0.86 (40). It has been translated into Cantonese, French, and Spanish (41). It is the Spanish version of Lobo et al. (42).
- *Hamilton Depression Rating Scale (HAM-D).* A self-informed measure that measures the symptomatic profile and severity of depression. The version used has 21 items with five answer options. Internal consistency values vary between 0.76 and 0.92 (43). The Spanish version of HAM-D shows an internal consistency of 0.78 (44).
- *Barratt Impulsivity Scale (BIS-11).* It evaluates trait impulsivity and behavior through three subscales: motor, cognitive, and non-planned impulsivity. It shows internal consistency values between 0.69 and 0.83 (45). The Spanish version showed adequate linguistic equivalence, conceptual equivalence, and scale equivalence with the original version (46).

- *Acceptance and Action Questionnaire (AAQ-II).* It assesses experiential avoidance and psychological inflexibility. In this study, a Spanish version of 10 items with 7 Likert options was employed. The original scale presents an internal consistency of 0.87 (47).

2.3.2. Psychological scales applied to the AUD group

- *Litman's Coping Behaviors Inventory (CBI).* It identifies coping strategies employed in order to avoid consumption when experiencing drinking desire or risk-related situations. It distinguishes between four factors or strategies: (A) positive thinking, (B) negative thinking, (C) distraction, and (D) avoiding. These explain 54% of the variance, with coefficients of 0.91, 0.81, 0.65, and 0.75, respectively (48). Studies in Spanish samples show internal consistencies of 0.90 in alcohol-dependent individuals (49).
- *Recovery Capital Assessment (VCR).* It evaluates 10 elements involved in recovery: abstinence/use of substances, global psychological health, global physical health, community involvement, social support, leisure activities, family environment, risk taking, life functioning, and recovery experience. The original one-dimensional scale shows intraclass correlations between 0.50 and 0.73 (50), and the Spanish adaptation shows an internal consistency of 0.90 (51).

2.3.3. Psychological scales applied to the control group

- *Mini-International Neuropsychiatric Interview (MINI).* The MINI is a short-structured diagnostic interview compatible with DSM-III-R/IV and ICD-10 criteria (52). The instrument included a series of questions about the following symptoms: sleep, feeding, depression, panic attacks, generalized anxiety disorder, obsessive–compulsive disorder, post-traumatic stress disorder (PTSD), suicidal risk, substance abuse disorder (SAD), and cognitive complaints. This study used the Spanish version of the interview validated by Ferrando (29).
- *Alcohol Use Disorders Inventory Test (AUDIT):* It is a 10-item self-administered questionnaire which covers the domains of alcohol consumption, drinking behavior, and alcohol-related problems. Responses to each question are scored from 0 to 4, giving a maximum possible score of 40 (53). It is recommended by the WHO (World Health Organization) as a screening test (53). It is one of the most widely used worldwide, both in healthcare and non-healthcare settings. Internal consistency (Cronbach α) values are 0.80 for the controls and 0.80 for the alcohol-dependent individuals (54). It has a Spanish validation carried out by Rubio et al. (55).

2.4. Statistical analysis

An exploratory analysis was carried out to evaluate sociodemographic, clinical, and psychological dimensions. AUD and control groups were analyzed in descriptive terms (mean and standard deviations) for continuous variables and by frequencies for categorical ones.

Continuous variables were submitted through normality tests by the Kolmogorov–Smirnov index. Intergroup comparisons were performed for AUD versus control groups and according to gender by parametrical Student *t*-tests if they followed a normal distribution or the Mann–Whitney–Wilcoxon test if not. Adjusted value of *p*s for multiple comparisons were realized using the Benjamini and Hochberg (56) method. Categorical data were compared through the chi-square test (χ^2). The significance level was set at a value of p of <0.05.

Psychological dimensions were evaluated as a function of abstinence time, through regression model analyses. Before this step, psychological test scores were normalized to Z scores. All models were evaluated by the need to adjust to the non-linear presence of years of abstinence, as well as its squared and cubic values, in addition to the linear component of years of abstinence. The starting point was the saturated model with non-transformed years of abstinence and the quadratic and cubic transformations, included as variables in the same model, in addition to the variables age and gender. The selection of the best model was carried out using the Akaike information criterion (AIC). Regardless of statistical significance, age and gender were incorporated into the model as covariates. For each explanatory model, the estimated value for an individual can be estimated by substituting the subject values into the equation: $\beta0 + \beta1$*age $+ \beta2$* gender $+\beta3$*(years abstinent) $+ \beta4$*(years abstinent)2 $+ \beta5$*(years abstinent)3. $\beta0$ indicates the starting level of the dependent variable for a person at abstinence time 0, aged 52.71 years and male. The value of the dependent variable will change $\beta1$ times for every unit change in the person's age relative to the mean age of 52.71 years, a quantity of $\beta2$ as a function of being a female relative to being a male, and $\beta3$ times in combination with $\beta4$ and $\beta5$ for every unit increase in the abstinence time variable. It should be noted that in some models, quadratic or cubic years of abstinence were discarded. In those cases, where the AIC discarded the non-transformed abstinence time variable because it was not statistically significant, the regression model graphs were built with the average of the following variables: gender, age, and $\beta0$.

Scatter plots were used to explore inflection points and scores matching between the AUD group and the control group. Regression plots show the intersection between point estimations of the AUD equation line and the average scores for control subjects.

All data were inserted and analyzed by SPSS v.22 (57) and SAS v.9.4 (58).

3. Results

3.1. Intergroup comparison of psychological dimensions (*t*-test AUD group vs. control group)

Table 2 includes the descriptive data for the different psychological scales applied to AUD and control subjects. It also includes the mean comparisons of the scores of different scales between the AUD and control groups, using Student's *t*-test. The *t*-test shows that there are statistically significant differences ($p < 0.05$) between control and AUD

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TABLE 2 Psychological measures description and Student T intergroup comparisons.

	AUD group			Control group			Student *T* comparisons		
Variables	Mean (SD)	Min.	Max.	Mean (SD)	Min.	Max.	*t*	df	*p*
Quality of Life (WHOQOL-BREF)									
Physical health	13.67 (1.88)	8.00	17.71	13.50 (1.45)	9.71	18.29	1.097	424.291	0.273
Psychological health	14.04 (2.25)	6.67	18.00	14.20 (1.63)	9.33	17.33	−0.928	445.762	0.354
Social relations	13.56 (3.01)	5.00	20.00	14.48 (3.00)	6.67	20.00	−3.283	513	0.001
Environment	15.40 (2.08)	9.00	20.00	15.09 (1.92)	10.50	20.00	1.627	513	0.104
Psychological Wellbeing (PWBS) and Satisfaction with Life (SWLS)									
Autonomy	37.60 (6.68)	17.00	51.00	39.76 (6.30)	23.00	54.00	−3.526	517	<0.001
Relations with others	39.87 (7.73)	20.00	54.00	41.78 (6.19)	25.00	54.00	−3.030	411.539	0.003
Self-Acceptance	35.61 (8.29)	10.00	53.00	40.57 (6.35)	23.00	53.00	−7.510	427.544	<0.001
Environmental Mastery	38.70 (8.22)	16.00	54.00	41.20 (6.44)	18.00	53.00	−3.760	421.686	<0.001
Purpose in Life	37.05 (7.52)	13.00	54.00	39.56 (5.58)	27.00	51.00	−3.858	509	<0.001
Personal Growth	37.66 (7.96)	15.00	53.00	37.94 (6.98)	26.00	52.00	−0.394	506	0.694
Satisfaction With Life	21.33 (6.47)	5.00	35.00	24.14 (3.52)	17.00	33.00	−6.397	508.667	<0.001
Negative emotionality									
Depression (HAM-D)	11.76 (8.15)	1.00	47.00	5.40 (5.42)	0.00	28.00	10.566	472.176	<0.001
Anxiety (HAM-A)	9.03 (6.85)	1.00	42.00	3.44 (4.80)	0.00	36.00	10.757	456.168	<0.001
Impulsivity. Total Score (BIS-11)	45.41 (14.75)	8.00	84.00	36.88 (11.02)	11.00	73.00	7.349	436.765	<0.001
Experiential avoidance and psychological inflexibility (AAQ-II)	32.37 (11.14)	11.00	64.00	24.54 (8.26)	10.00	45.00	9.006	438.443	<0.001
Coping strategies (CBI)									
Positive thinking	28.90 (4.53)	10.00	37.00	–	–	–	–	–	–
Negative thinking	17.34 (5.39)	0.00	24.00	–	–	–	–	–	–
Distraction	16.89 (6.66)	0.00	30.00	–	–	–	–	–	–
Avoidance	9.03 (3.06)	0.00	15.00	–	–	–	–	–	–
Other measures									
Recovery Capital	43.55 (6.68)	8.00	50.00	–	–		–	–	–
AUDIT	–	–	–	3.13 (2.83)	0.00	11.00	–	–	–

Psychological measures descriptions in terms of means, standard deviations (SD), and minimum (Min.) and maximum (Max.) scores for participants with alcohol use disorder (AUD) and control subjects. Student T comparisons are also presented, through t-index, degree of freedom (df), and value of *p*s.

groups for the following scales and subscales: social relations (WHOQOL); all the PWBS subscales (except for personal growth); satisfaction with life (SWLS); depression (HAM-D); anxiety (HAM-A); impulsivity total score (BIS-11); and experiential avoidance and psychological inflexibility (AAQ-II).

3.2. Gender differences in the AUD group

Compared to men with AUD, women obtained significantly lower scores in WHOQOL-BREF's physical health subscale ($t = -2.46$; $p = 0.014$). On the counterpart, they showed significantly higher scores than men in Hamilton's depression ($t = 2.64$; $p = 0.009$), anxiety scales ($t = 4.30$; $p = 0.000$), and experiential avoidance one ($t = 3.20$; $p = 0.002$). Women also had significantly higher scores in motor impulsivity measured by BIS-11 ($t = 2.16$; $p = 0.032$).

3.3. Psychological dimensions as a function of abstinence time

3.3.1. Quality of life (WHOQOL-BREF) and recovery capital

Scatter plots in Figure 2 show the regression models for standardized scores in quality of life, in relation to abstinence time (transformed to quadratic values for physical health, psychological health, and relations). Regarding quality-of-life dimensions, physical health seems to improve faster, followed by psychological health and social relations, with negligible changes in the environment.

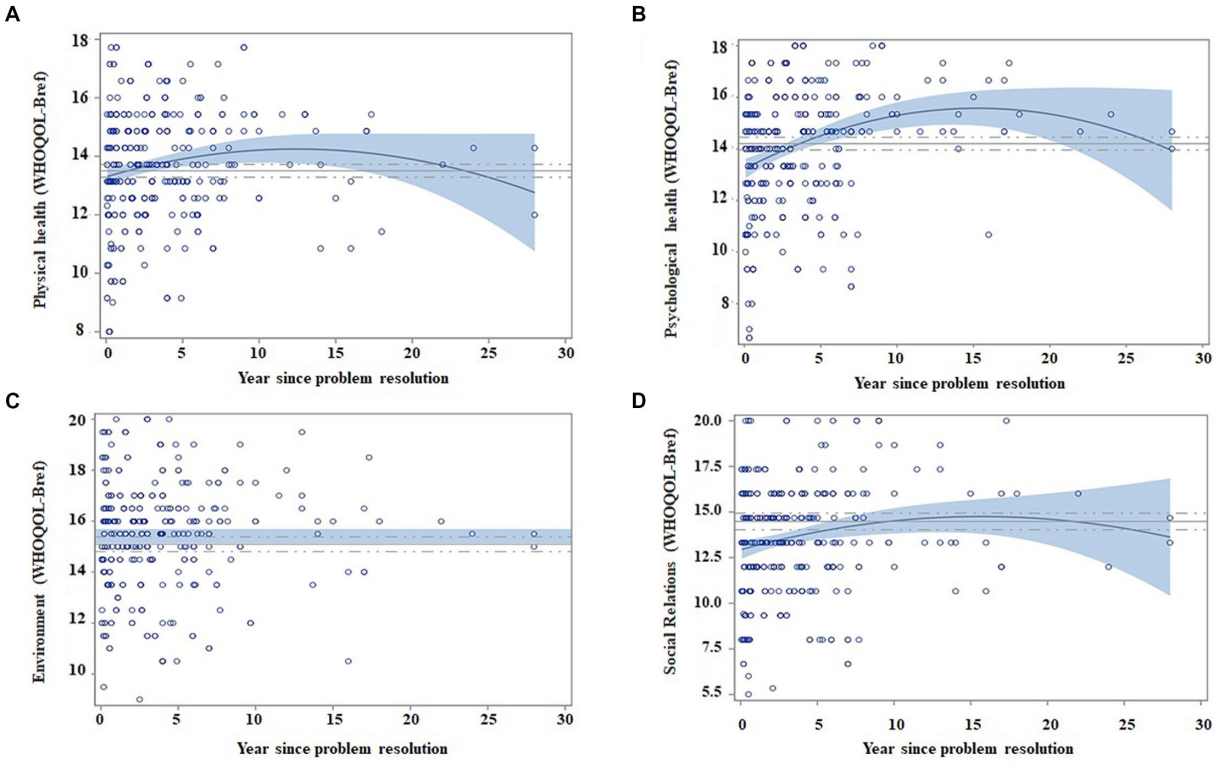

FIGURE 2
Regression models of quality of life as a function of abstinence time, adjusted by age and gender. Matching AUD with controls. Scatter plots indicate the recovery indexes (standardized) during the first 28 years after ceasing alcohol consumption. For each explicative model, the estimated value for an individual can be estimated by displacing the subject's values in the following equation: $\beta 0+\beta 1 * \text{age}+\beta 2 * \text{gender} + \beta 3 * (\text{years of abstinence})+\beta 4 * (\text{years of abstinence})^2$. The continuous blue line indicates the regression equation between abstinence time and the scores obtained from the questionnaires. The blue shading represents the confidence interval (95%) for the regression equation in the AUD group. The continuous gray line indicates the mean score obtained on each questionnaire by the control subjects, and the dashed gray line indicates the confidence interval (95%). The figure depicts the following: **(A)** Patients improve their scores in physical health over time (Year since problem resolution), and they match control scores at 1 year of abstinence; **(B)** patients improve in psychological health over time and match control values at the 4th year of abstinence; **(C)** the environment dimension does not show changes, and it seems to be similar between patients and controls; and **(D)** social relations increase after ceasing alcohol consumption and equate control scores at 10 years of abstinence.

The regression model did not identify abstinence time as a variable that would contribute to WHOQOL-BREF environment variability (see Table 3). The remaining WHOQOL-BREF's dimensions (physical, psychological health, and social relations) improve with abstinence time, regardless of the age and gender of subjects, except for physical health scores, that were higher for male subjects (see Table 3).

When matching AUD participants and control subjects, we observed that patients reached similar scores (with an interval confidence of 95%) in the 1st year of abstinence for physical health, the 4th year for psychological health, and the 10th year for relations with others (Figure 2). Despite the fact that environment does not vary with abstinence time, its scores were similar between patients and control subjects ($p = 0.104$), as observed in the *t*-test AUD group versus control group section.

With respect to recovery capital, AIC selected the quadratic model. The plateau of the regression curve began at the 10th year of abstinence (see Table 3).

3.3.2. Psychological wellbeing and satisfaction with life

Scatter plots in Figures 3, 4 show regression models for PWBS and SWLS standardized scores in relation to abstinence time. The fastest changes (in the first 4–5 years) occur in environmental mastery, personal growth, purpose in life, and satisfaction with life, whereas the slowest ones take place for self-acceptance and autonomy. Additionally, no clear changes were appreciated for positive relations.

As Table 4 shows, Psychological Wellbeing and Life Satisfaction scores increase as abstinence is maintained for both men and women. However, the regression model did not find abstinence time as a variable with an effect on positive relations (patients and control subjects showed significantly different scores, $p = 0.005$, see section *t*-test AUD group vs. control group). Additionally, age was a factor that increased PWBS and SWLS scores, except for the purpose in life and personal growing PWBS subscales.

Figures 3, 4 show that patients match controls in environmental mastery at 7 years of abstinence, in purpose in life, personal growth and satisfaction with life at 10 years, in autonomy at 15 years, and for self-acceptance at 22 years. AUD participants did not match control scores for positive relations at any measured abstinence period.

3.3.3. Affective and impulsivity manifestations

Scores in anxiety, depression, and experiential avoidance progressively declined across the first 5–7 years, and then, they slowly

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TABLE 3 Regression model for quality of life and recovery capital as a function of abstinence time, adjusted by age and gender in the AUD group.

Model	Beta	SE	*t*	Value of *p*
Quality of Life (WHOQOL-BREF)				
WHOQOL-Physical Health				
intercept	13.511	0.184	73.500	<0.0001
Age	0.017	0.012	1.430	0.152
Gender	−0.447	0.216	−2.060	0.040
Years	0.134	0.055	2.430	0.016
Years (quadratic)	−0.006	0.003	−2.270	0.024
WHOQOL-psychological health				
intercept	13.179	0.216	61.150	<0.0001
Age	0.014	0.014	1.010	0.313
Gender	0.201	0.254	0.790	0.430
Years	0.301	0.065	4.640	<0.0001
Years (quadratic)	−0.010	0.003	−3.170	0.002
WHOQOL-social relations				
intercept	13.071	0.296	44.120	<0.0001
Age	0.026	0.019	1.390	0.165
Gender	−0.190	0.349	−0.540	0.586
Years	0.210	0.089	2.360	0.019
Years (quadratic)	−0.007	0.004	−1.680	0.093
WHOQOL-environment				
intercept	15.382	0.137	112.300	<0.0001
Age	0.028	0.013	2.230	0.026
Gender	0.064	0.242	0.260	0.793
VCR-recovery capital				
intercept	41.200	0.642	64.20	<0.0001
Age	0.079	0.042	1.90	0.059
Gender	1.223	0.763	1.60	0.110
Years	0.694	0.192	3.61	0.0004
Years (quadratic)	−0.021	0.009	−2.27	0.024

Table expresses regression models for quality of life (WHOQOL-BREF) and recovery capital (VCR) as a function of abstinence time, adjusted by age and gender. Beta, *SE* (standard error), *t*, and value of *ps* are indicated for each type of variable. For each model, the estimated value for an individual can be computed by replacing his values from the equation: $\beta0 + \beta1*\text{age} + \beta2*\text{gender} + \beta3*(\text{years of abstinence}) + \beta4*(\text{years of abstinence})^2$. All models were evaluated and adjusted for the non-linear presence of years of abstinence as a raw value, quadratic or cubic estimate, as well as for the linear component of abstinence. Generally, β0 indicates the starting point for quality of life or recovery capital for an individual at time of abstinence of value 0, for a male, of 52.71 years old.

diminished (non-linear regression model representation can be seen in Figure 5, and its data can be checked in Table 5). The regression model did not identify abstinence time as a variable that would contribute to impulsivity variability (Table 5).

Regression models from Table 5 indicate that all negative emotionality dimensions diminished with abstinence maintenance, regardless of age, whereas being a woman was associated with higher scores in anxiety and experiential avoidance.

Figure 5 shows that patients reached similar scores to control subjects after 7 years of abstinence for depression and at 10 years of abstinence for anxiety and experiential avoidance. AUD patients did not match control scores for impulsivity (as seen in the *t*-test AUD group vs. control group, there are statistically significant differences; $p = 0.001$).

3.3.4. Coping strategies against alcohol use (CBI)

Coping strategies differed in their evolution throughout the abstinence maintenance. Figure 6 graphs show an improvement in all subscales in the first 5 years and posterior stabilization.

Regarding CBI, subscale changes across abstinence periods, positive and negative thinking, and distraction adjusted to a non-linear model, while avoidance had a quadratic model (Table 6). Negative thinking scores decreased along the abstinence, whereas the rest of coping strategies increased. Specifically, avoidance strategies increased during the 1st year and then had light stabilization and a posterior decrease. Changes occurred irrespectively of age, except for positive thinking.

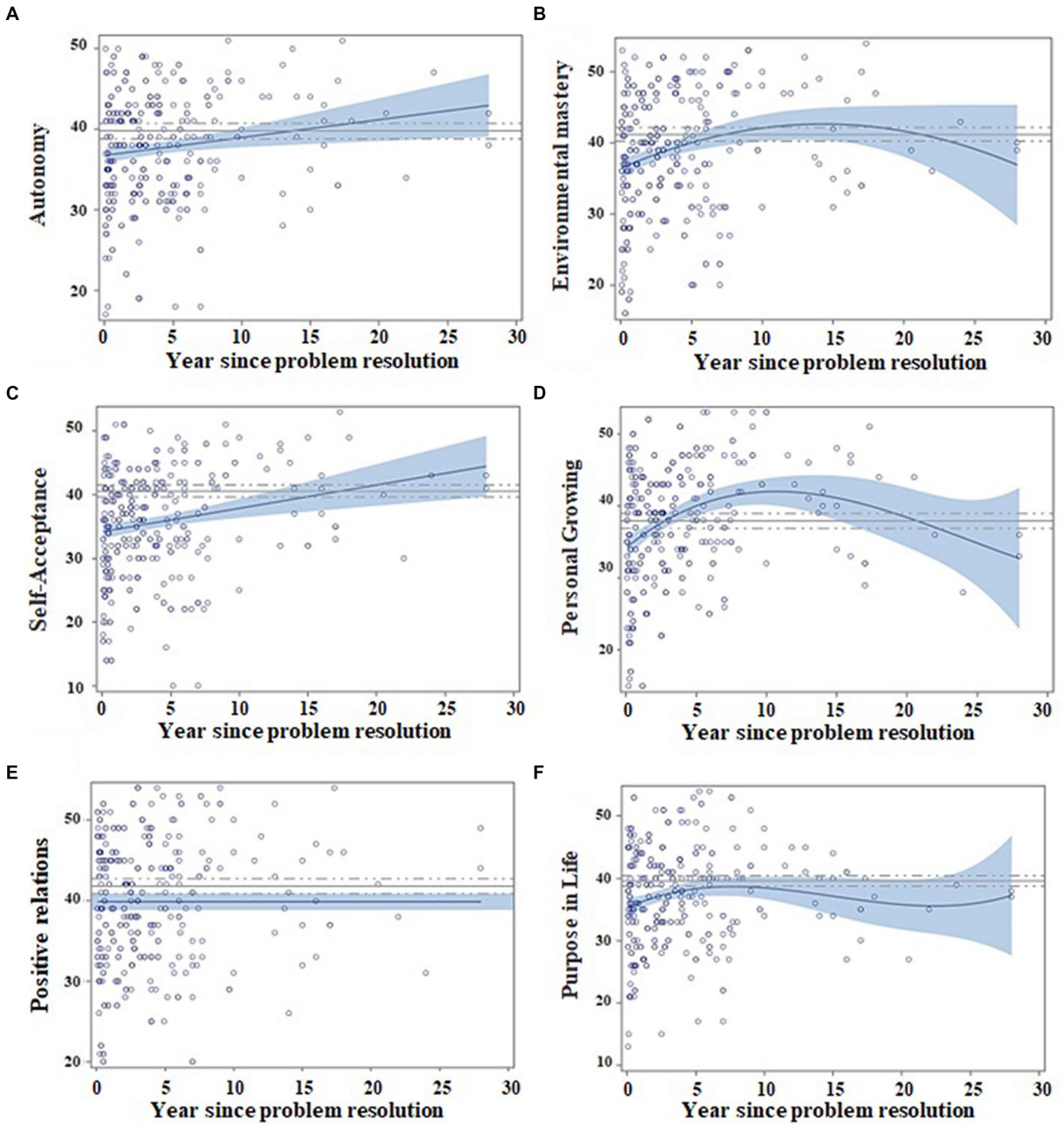

FIGURE 3
Regression models for psychological wellbeing as a function of abstinence time, adjusted by age and gender. Matching AUD with controls. Scatter plots indicate the recovery indexes (standardized) during the first 28 years after ceasing alcohol consumption. For each explicative model, the estimated value for an individual can be estimated by displacing the subject's values in the following equation: $\beta 0+\beta 1 *$ age $+\beta 2 *$ gender $+ \beta 3 *$ (years of abstinence) $+\beta 4 *$ (years of abstinence)$^2+\beta 5 *$ (years of abstinence)^3. The continuous blue line indicates the regression equation between abstinence time and the scores obtained from the questionnaires. The blue shading represents the confidence interval (95%) for the regression equation in the AUD group. The continuous gray line indicates the mean score obtained on each questionnaire by the control subjects, and the dashed gray line indicates the confidence interval (95%). The figure depicts the following: **(A)** Patients improve their scores in autonomy over time (year since problem resolution), and they match control scores at 15 years of abstinence; **(B)** patients improve in environmental mastery over time and match control values at the 7th year of abstinence; **(C)** the self-acceptance dimension is better in time and AUD patients match control scores at 22 years of abstinence; **(D)** personal growing AUD scores overcome controls and reach a maximum at 10 years, showing a decrease afterward; **(E)** relations with others do not show changes over time; and **(F)** purpose in life grows over time and matches control values at 10 years of abstinence.

4. Discussion

The aim of this study was to examine how, when, and to what extent persons with alcohol use disorder (AUD) recover their psychological wellbeing and quality of life. Most studies regarding AUD recovery had been carried out with samples that had rather short periods of abstinence, impeding the analysis of long-term recovery, changing patterns, or the improvement on several psychological dimensions over time, in comparison with healthy participants (16). This is the first study carried out in a Spanish clinical sample of

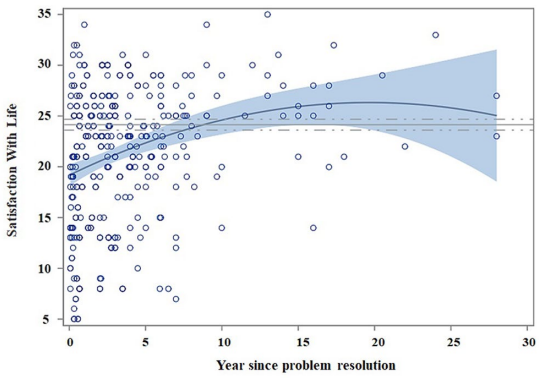

FIGURE 4
Regression model for satisfaction with life as a function of abstinence time. Matching AUD with controls. Scatter plots indicate the recovery indexes (standardized) during the first 28 years after ceasing alcohol consumption. For each explicative model, the estimated value for an individual can be estimated by displacing the subject's values in the following equation: $\beta 0+\beta 1 * \text{age}+\beta 2 * \text{gender} + \beta 3 * (\text{years of abstinence})+\beta 4 * (\text{years of abstinence})^2$. The continuous blue line indicates the regression equation between abstinence time and the scores obtained from the questionnaires. The blue shading represents the confidence interval (95%) for the regression equation in the AUD group. The continuous gray line indicates the mean score obtained on each questionnaire by the control subjects, and the dashed gray line indicates the confidence interval (95%). The scatter plot indicates the improvement in satisfaction with life over time (year since problem resolution) and the equation with control subjects at 10 years of abstinence.

alcohol-dependent individuals with different abstinence periods and a healthy control group.

The main findings of this study were as follows: (A) Recovery is a long process that may involve a relation between abstinence length and improvements in psychological wellbeing, quality of life, and recovery capital; (B) changes in negative emotionality could also associated to abstinence duration; (C) during the 1st year of abstinence, the prevailing coping strategies were avoidance and distraction, while with further abstinence, positive thinking strategies seemed to increase while avoidance became a less used strategy; (D) the most pronounced changes occurred during the first 5 years in all the psychological dimensions studied; (E) recovery in women with AUD differed from the one developed in men; and (F) patient seemed to reach similar scores to control subjects, according to different abstinence periods: first, in physical health (the 1st year); second, in psychological health (4th year) and the following subscales at longer periods of abstinence, with the exception of two dimensions that remained different from healthy participants: impulsivity and positive relations.

4.1. How do psychological dimensions of wellbeing, quality of life, negative emotionality, and coping strategies recover depending on abstinence?

Recovery is a slow process, where long-term abstinence maintenance relates to improvements in quality of life and wellbeing. Abstinence duration is also linked to other dimensions associated with recovery, such as negative emotionality (depression and anxiety symptoms and experiential avoidance) and coping strategies to avoid consumption. The results exhibit more pronounced changes in psychological recovery dimensions during the first 5 years, after ceasing alcohol consumption. Specifically, our findings indicate marked improvements in quality-of-life subscales during the first 4 years of abstinence, with the following sequence relation: physical–psychological–social relations. Two reviews pointed out the decline in quality of life in AUD and its improvement after treatment (24, 59) although most studies were carried out within short or medium abstinence periods (1–18 months). Of note is the study by Frischknecht et al. (60). This study found positive correlations between quality-of-life scores and maintenance of abstinence in alcohol-dependent patients, 7 years after treatment ($r = 0.316$; $p < 0.01$). People who remained abstinent showed better scores than those who kept consuming alcohol (60).

Abstinence periods also relate to enhancements in recovery capital, as well as psychological wellbeing and satisfaction with life. The latter rapidly improved during the first 4–5 years and then attenuated their increase. Furthermore, negative emotionality scores rapidly decreased during the first 5–7 years and attenuated their course over longer periods of abstinence. These results support the biaxial model of recovery of Kelly and Hoeppner (3), which proposes that greater availability and accumulation of recovery capital would favor the resilience and coping strategies and help reduce and buffer the stress, subsequently sustaining continuous remission (3, 61). In this line, psychological wellbeing has been proposed as a protective factor for stress and anger (62), which may reflect a similar mechanism to the one proposed by Kelly and Hoeppner (3). Carlon et al. (63) proposed a similar mechanism for improvements in quality of life. This study suggests that positive and negative affect, as well as decreased stress experiences, help explain why QOL increases significantly for individuals following treatment for AUD (10 weeks, 36 weeks, and 52 weeks following treatment) (63). This suggests that improvements in some areas favor amelioration in others, thus constituting elements of recovery beyond abstinence.

Regarding the coping strategies, to the best of our knowledge, this is the first time they have been evaluated in the context of long-term recovery. Our findings evidence that persons with AUD that follow treatment show a fast enhancement in their coping strategies repertoire, which has the aim to prevent a new consumption (especially during the first 5 years). This would support the proposal of Laudet (64), which presents coping strategies management as one of the pillars of recovery. These results indicate that strategies such as distraction and avoidance are employed more promptly than other cognitive strategies. However, while the use of avoidance is reduced with prolonged abstinence (after 7 years), the use of positive thinking and distraction is maintained through time. Unlike the rest of the strategies, negative thinking diminishes over abstinence time, meaning that reflecting more about the negative consequences of consumption when risky situations take place might not be the most used strategy in order to remain abstinent, whereas reflecting on the benefits of non-consumption, by using distraction strategies and avoiding risky situations are more used through time and might be more beneficial. These precise results regarding strategies that consolidate during the first abstinence periods coincide with our previous studies (27, 28), where

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TABLE 4 Regression model for psychological wellbeing and satisfaction with life as a function of abstinence time, adjusted by age and gender in the AUD group.

Model	Beta	SE	*t*	Value of *p*
Psychological wellbeing (PWBS)				
PWBS-autonomy				
Intercept	36.885	0.552	66.870	<0.0001
Age	0.111	0.041	2.680	0.008
Gender	0.301	0.766	0.390	0.695
Years	0.161	0.083	1.930	0.055
PWBS-positive relations				
Intercept	39.472	0.503	78.450	<0.0001
Age	0.131	0.046	2.820	0.005
Gender	1.218	0.889	1.370	0.171
PWBS-self-acceptance				
Intercept	34.807	0.679	51.280	<0.0001
Age	0.141	0.052	2.730	0.007
Gender	−0.832	0.946	−0.880	0.380
Years	0.272	0.103	2.650	0.009
PWBS-environmental mastery				
Intercept	36.496	0.802	45.480	<0.0001
Age	0.149	0.051	2.900	0.004
Gender	0.758	0.943	0.800	0.422
Years	0.774	0.240	3.220	0.001
Years (quadratic)	−0.029	0.012	−2.520	0.012
PWBS-purpose in life				
Intercept	35.092	0.852	41.160	<0.0001
Age	−0.072	0.048	−1.500	0.134
Gender	−0.231	0.885	−0.260	0.794
Years	1.115	0.416	2.680	0.008
Years (quadratic)	−0.096	0.048	−2.020	0.044
Years (cubic)	0.002	0.001	1.600	0.111
PWBS-personal growth				
Intercept	35.092	0.852	41.160	<0.0001
Age	−0.072	0.048	−1.500	0.134
Gender	−0.231	0.885	−0.260	0.794
Years	1.115	0.416	2.680	0.008
Years (quadratic)	−0.096	0.048	−2.020	0.044
Years (cubic)	0.002	0.001	1.600	0.111
SWLS-satisfaction with life				
Intercept	19.174	0.612	31.340	<0.0001
Age	0.091	0.039	2.340	0.020
Gender	0.582	0.721	0.810	0.421
Years	0.671	0.183	3.660	<0.0001
Years (quadratic)	−0.018	0.009	−1.990	0.047

Table expresses regression models for psychological wellbeing (PWBS) and satisfaction with life (SWLS) as a function of abstinence time, adjusted by age and gender. Beta, *SE* (standard error), *t*, and value of *p*s are indicated for each type of variable. For each model, the estimated value for an individual can be computed by replacing his values from the equation: $\beta0 + \beta1*\text{age} + \beta2*\text{gender} + \beta3*(\text{years of abstinence}) + \beta4*(\text{years of abstinence})^2 + \beta5*(\text{years of abstinence})^3$. All models were evaluated and adjusted for the non-linear presence of years of abstinence as a raw value, quadratic or cubic estimate, as well as for the linear component of abstinence. Generally, β0 indicates the starting point for psychological wellbeing and satisfaction with life for an individual at time of abstinence of value 0, for a male, of 52.71 years old.

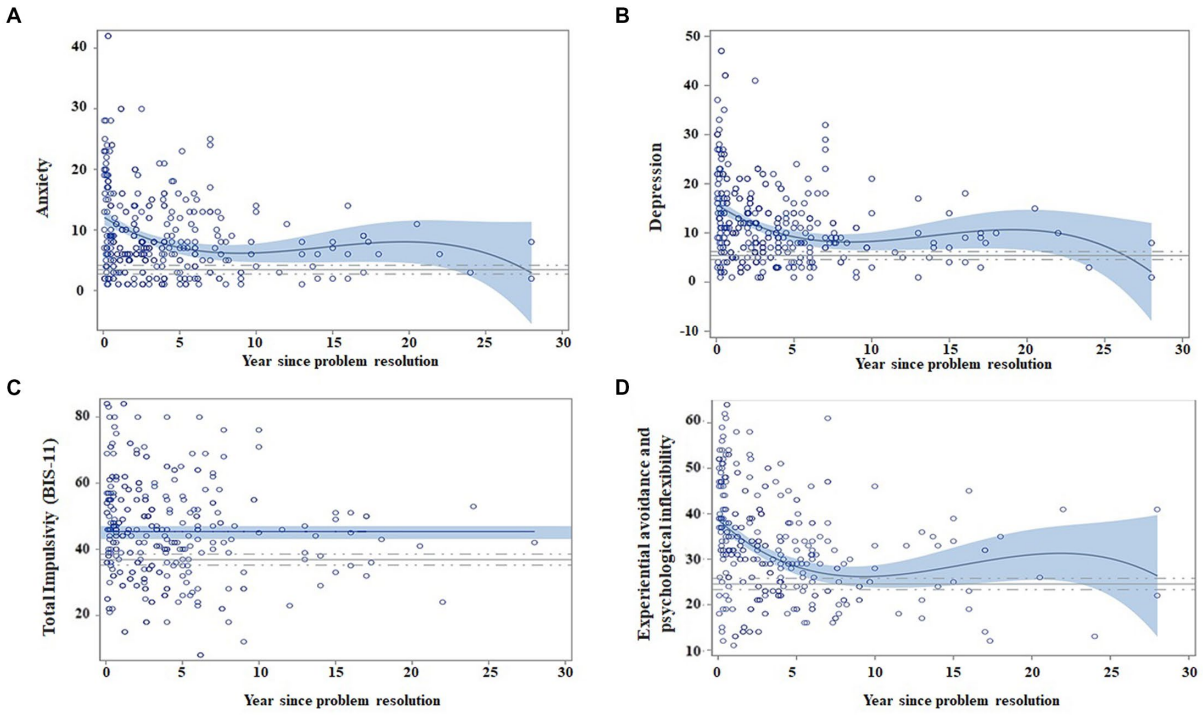

FIGURE 5
Regression models for negative emotionality and impulsivity dimensions, as a function of abstinence time, adjusted by age and gender. Matching AUD with controls. Scatter plots indicate the recovery indexes (standardized) during the first 28 years after ceasing alcohol consumption. For each explicative model, the estimated value for an individual can be estimated by displacing the subject's values in the following equation: $\beta0+\beta1 * age+\beta2 * gender + \beta3 * (years\ of\ abstinence)+\beta4 * (years\ of\ abstinence)^2+\beta5 * (years\ of\ abstinence)^3$. The continuous blue line indicates the regression equation between abstinence time and the scores obtained from the questionnaires. The blue shading represents the confidence interval (95%) for the regression equation in the AUD group. The continuous gray line indicates the mean score obtained on each questionnaire by the control subjects, and the dashed gray line indicates the confidence interval (95%). The figure depicts the following: **(A)** Patients have less anxiety over time (year since problem resolution), and they match control scores at 10 years of abstinence (fluctuations are due to the small sample size); **(B)** depression also diminishes over time over time and match control values at the 7th year of abstinence; **(C)** total impulsivity does not show changes over time; and **(D)** experiential avoidance and psychological inflexibility decrease over time and match control values at 10 years of abstinence.

avoidance was established as the most solid strategy used to maintain abstinence after a 6-year follow-up. In the same way, the gradual use of positive thinking would be in agreement with Litman's study that proposes a transition from behavioral to cognitive coping strategies along the maintained abstinence (65). Additionally, the slow yet sustained increase in positive thinking could relate to the changes in wellbeing, as Laudet et al. (64) proposed having something to lose if the consumption is resumed would be one of the strongest individual predictors associated with remission; and the possible losses might occur in the areas of satisfaction with life, health, acquaintances, and family members.

With respect to gender differences, the results indicate that women show more difficulties to recover in physical health and negative emotionality dimensions. These differences have also been pointed out in other studies (16, 66) that indicate that women tend to experience more psychological distress than men. As Kelly et al. (16) proposed, recovery for women could suppose a greater challenge when dealing with psychological stress and lower satisfaction with quality-of-life aspects. In this way, interventional-recovery programs should offer emotional control improvement strategies for women. Nonetheless, general population (non-clinical) results show higher self-perceived health in women compared to men (67–69). Overall, a special consideration toward gender should be implemented in the study of recovery, as other health contexts already attempt.

4.2. Matching psychological dimensions with healthy participants: to what extent can patients improve?

Matching psychological dimension scores of AUD participants with the control group happened at different time periods of abstinence. AUD individuals seem to match healthy controls in quality of life in the first 4 years (with the exception of social relations, that happened over 10 years of abstinence) and in psychological wellbeing after more than 10 years of abstinence. This might imply a long course of the recovery process. Additionally, in our samples, some variables never seem to equal the control group, such as positive relations.

Based on quality of life, psychological wellbeing, and coping strategies scores, our results allow to draw a possible staging of the following recovery phases in AUD persons that follow treatment or attend self-help associations (see Table 7). *First Stage/Early Sobriety (0–1 years)*: improvement of physical quality of life, reaching values similar to healthy subjects; great improvement in anxiety; and use of behavioral strategies (such as distraction and avoidance). *Second*

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TABLE 5 Regression model for negative emotionality and impulsivity as a function of abstinence time, adjusted by age and gender.

Model	Beta	SE	*t*	*p*-value
Hamilton anxiety (*)				
Intercept	11.040	0.730	15.13	<0.0001
Age	−0.012	0.041	−0.30	0.764
Gender	2.905	0.753	3.86	0.0001
Years	−1.542	0.354	−4.35	<0.0001
Years (quadratic)	0.129	0.041	3.17	0.002
Years (cubic)	−0.003	0.001	−2.57	0.011
Hamilton depression				
Intercept	14.873	0.866	17.18	<0.0001
Age	−0.115	0.049	−2.37	0.018
Gender	1.633	0.894	1.83	0.069
Years	−1.938	0.420	−4.61	<0.0001
Years (quadratic)	0.168	0.048	3.47	0.001
Years (cubic)	−0.004	0.001	−2.89	0.004
BIS-11-Total. Impulsivity				
Intercept	44.986	0.957	47.01	<0.0001
Age	−0.348	0.088	−3.93	0.0001
Gender	1.173	1.694	0.69	0.489
AAQ-II. Experiential avoidance and psychological inflexibility				
intercept	37.030	1.157	32.01	<0.0001
Age	−0.182	0.065	−2.81	0.005
Gender	2.838	1.194	2.38	0.018
Years	−2.854	0.561	−5.08	<0.0001
Years (quadratic)	0.223	0.065	3.45	0.001
Years (cubic)	−0.005	0.002	−2.51	0.012

Table expresses regression models for Hamilton Anxiety and Depression variables as well as Impulsivity (BIS-11) and experiential avoidance and psychological inflexibility (AAQ-II), as a function of abstinence time, adjusted by age and gender. Beta, *SE* (standard error), *t*, and *p*-values are indicated for each type of variable. For each model, the estimated value for an individual can be computed by replacing his values from the equation: $\beta0 + \beta1*age + \beta2*gender + \beta3*(years\ of\ abstinence) + \beta4*(years\ of\ abstinence)^2 + \beta5*(years\ of\ abstinence)^3$. All models were evaluated and adjusted for the non-linear presence of years of abstinence as a raw value, quadratic or cubic estimate, as well as for the linear component of abstinence. Generally, β0 indicates the starting point for affective symptoms (anxiety and/or depression) or experiential avoidance for an individual at time of abstinence of value 0, for a male, of 52.71 years old. Abstinence time does not influence BIS-11 values since it is does not appear in the equation.

Stage/Sustained Sobriety (1–4 years): enhancement in psychological quality of life, reaching values similar to controls; distinct improvement in affective dimensions such as sadness and experiential avoidance; and the incorporation of positive thinking to the repertoire of cognitive strategies and the decrease of negative thinking. *Third Stage/Long-term Sobriety (4–10 years)*: stabilization of negative emotions; a progressive increase of psychological wellbeing and satisfaction with life, matching control subjects' scores; and decrease of avoidance strategies use. *Fourth Stage/Very long-term recovery (>10 years)*: predominance of satisfaction with life and psychological wellbeing; autonomy and self-acceptance reach matching values to control subjects; and prevailing of distraction and positive thinking coping strategies. These stages can be comparable to the ones described by the Betty Ford Institute panel (70), which are mainly based on the common experiences of persons in recovery. Considering the diffuse literature consensus on this topic, they carried out a first effort to describe the duration and sobriety stability in the following phases. *Early Sobriety:* a sobriety period of at least 1 month and less than 1 year; *Sustained Sobriety:* that lasts at least 1 year but less than 5 years; and *Stable Sobriety:* over a 5-year period.

On another note, the significant differences in quality of life and psychological dimensions found between patients and controls can bring more light upon the relation of these variables with abstinence but also their slow progress over time. In other words, people with AUD need long periods of abstinence for their quality of life and wellbeing to change significantly. This might be in line with other findings (16, 25, 61). In the same way, our results are similar to those observed by Kelly et al. (16), obtained from a community sample. Authors indicated that the quality of life continuously improved over the first 11 years after ceasing consumption, and it was similar to the control population after 15 years of abstinence. They first reached similar scores to controls in physical health, followed by psychological health and social relations at 10 years of abstinence. In this way, our results, in a similar manner to other research (71), support the consideration of recovery as a slow process and are in line with the recommendations of the Betty Ford Institute (70) and SHAMSA (7) to include quality of life and wellbeing indicators for recovery.

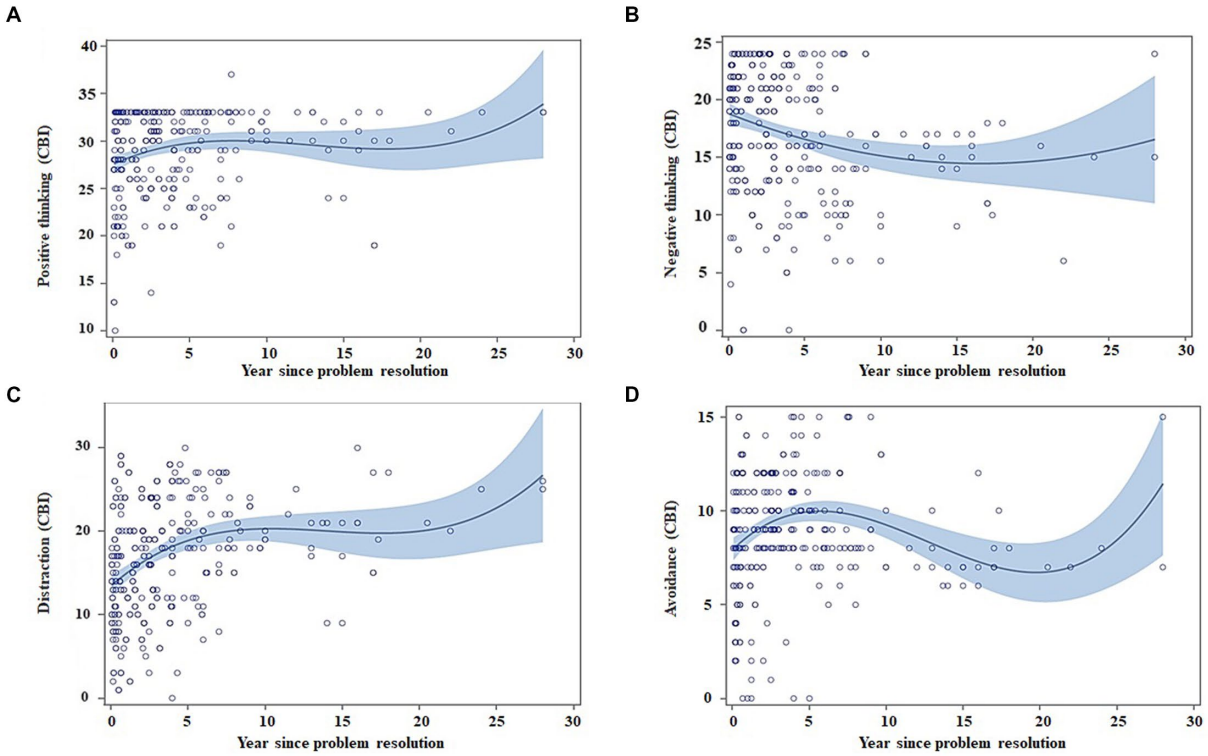

FIGURE 6
Regression models for coping strategies (CBI) as a function of abstinence time, adjusted by age and gender. Scatter plots indicate the recovery indexes (standardized) during the first 28 years after ceasing alcohol consumption. For each explicative model, the estimated value for an individual can be estimated by displacing the subject's values in the following equation: $\beta 0+\beta 1 * \text{age}+\beta 2 * \text{gender}+\beta 3 * (\text{years of abstinence})+\beta 4 * (\text{years of abstinence})^2+\beta 5 * (\text{years of abstinence})^3$. The blue shading represents the confidence interval (95%) for the regression equation in the AUD group. **(A)** Patients show an increase in the use of the positive thinking throughout the time of abstinence **(B)** the use of the negative thinking strategy decreases throughout the time of abstinence; **(C)** the use of the distraction strategy increases throughout the time of abstinence; and **(D)** the use of the avoidance strategy increases in the first years of abstinence and subsequently decreases.

In regard to psychological wellbeing and its improvement with abstinence, our results concur with other findings (27, 28, 72–75). However, in our study, recovery dimensions seem to be slower, especially for autonomy and self-acceptance, that also match control sample values with recovery periods over 10 years.

With respect to negative emotionality, our findings concur with our previous study. The fact that stabilization of recovery does not happen until patients reach abstinence periods superior to 5 years and those patients do not match control subject scores until 7–10 years of sobriety, along with the relevance of emotional states in relapses (27, 76), makes us think that services should provide for strategies to regulate them at the long-term course of recovery.

Finally, despite the maintenance of abstinence, statistically significant differences have been found between the group with AUD and the control group in impulsivity scores (BIS-11) and positive relationships (PWBS). Impulsivity is a heterogeneous personality and behavioral construct, consistently identified as a trait in substance use disorders, including AUD. Moreover, impulsivity characteristics frequently overlap with various alcohol dependence symptoms, such as unplanned and uncontrolled drinking, despite the negative consequences. The impulsivity role in the initiation and progress of addictive behaviors has been previously highlighted by the literature (77, 78). Our group previously explored the impulsivity role in recovery, and, contrary to other findings showing a decrease in impulsivity after several months of abstinence (28), we found that AUD patients have significantly higher impulsivity scores compared to controls, even after 4 years of abstinence maintenance (28). This might be due to impulsivity characteristics as stable traits (as measured by BIS-11). Despite the possible reductions in impulsive behaviors over time and along the recovery period, trait impulsivity might remain as a personality factor. Additionally, possible inconsistencies across studies regarding impulsivity changes across time could also be related to the clinical characteristics of the samples and the heterogeneous distribution of impulsivity across the population. Regarding the social domain, it is noticeable that AUD patients show similar scores to controls after 4 years of abstinence in social relations measured by the Quality of Life Questionnaire (WHOQOL-BREF), whereas positive relations evaluated by PWBS do not show any relation with abstinence time. Moreover, AUD and control groups maintain statistical differences over time in positive relations. This particular result might indicate difficulties in managing particular characteristics of social relations in AUD patients during the recovery process. One possible explanation for the discrepancy with the WHOQOL-BREF social relationships may be related to its different conceptual features. WHOQOL-BREF provides an overview of general satisfaction with personal relationships, social support, and sexual activity, whereas PWBS's positive relations attempt to capture specific aspects of social interactions, such as reliance, stability of the

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TABLE 6 Regression model for coping strategies as a function of abstinence time, adjusted by age and gender.

Model	Beta	SE	*t*	*p*-value
Positive thinking				
Intercept	27.362	0.509	53.78	<0.0001
Age	0.069	0.029	2.43	0.016
Gender	1.197	0.543	2.21	0.028
Years	0.645	0.250	2.58	0.010
Years (quadratic)	−0.060	0.028	−2.10	0.036
Years (cubic)	0.002	0.001	1.93	0.055
Negative thinking				
Intercept	18.775	0.530	35.41	<0.0001
Age	−0.005	0.034	−0.14	0.891
Gender	0.075	0.645	0.12	0.908
Years	−0.522	0.160	−3.25	0.001
Years (quadratic)	0.016	0.008	2.04	0.043
Distraction				
intercept	12.987	0.721	18.00	<0.0001
Age	0.037	0.040	0.91	0.363
Gender	1.631	0.767	2.13	0.034
Years	1.586	0.355	4.46	<0.0001
Years (quadratic)	−0.119	0.040	−2.96	0.003
Years (cubic)	0.003	0.001	2.48	0.014
Avoidance				
intercept	7.809	0.342	22.82	<0.0001
Age	−0.025	0.019	−1.32	0.189
Gender	0.024	0.363	0.07	0.947
Years	0.839	0.168	4.98	<0.0001
Years (quadratic)	−0.093	0.019	−4.86	<0.0001
Years (cubic)	0.002	0.001	4.49	<0.0001

Table expresses regression models for coping strategies against alcohol consumption variables, as a function of abstinence time, adjusted by age and gender. Beta, *SE* (standard error), *t*, and *p*-values are indicated for each type of variable. For each model, the estimated value for an individual can be computed by replacing his values from the equation: $\beta 0 + \beta 1 * \text{age} + \beta 2 * \text{gender} + \beta 3 * (\text{years of abstinence}) + \beta 4 * (\text{years of abstinence})^2 + \beta 5 * (\text{years of abstinence})^3$. All models were evaluated and adjusted for the non-linear presence of years of abstinence as a raw value, quadratic or cubic estimate, as well as for the linear component of abstinence. Generally, β0 indicates the starting point for coping strategies for an individual at time of abstinence of value 0, for a male, of 52.71 years old.

TABLE 7 Recovery enhancement in AUD and achieving values similar to a control sample proposed stages of recovery and the corresponding components of wellbeing.

	Early recovery (0–1 years)	Sustained recovery (1–4 years)	Long-term recovery (4–10 years)	Very long-term recovery (>10 years)
Quality of life	Physical quality of life	Psychological quality of life	Social relations quality of life	
Psychological wellbeing	Marked improvement in personal growth	Increase in personal growth and purpose in life	Enhancement of environmental mastery and satisfaction with life	Achieving autonomy and self-acceptance
Negative emotionality	Relevant improvement in anxiety symptoms	Relevant improvement in depression symptoms and experiential avoidance Anxiety improvement stagnates	Negative emotions stabilization	
Coping strategy	Use of distraction and avoidance	Increase in distraction, avoidance, and positive thinking use Decrease in negative thinking	Decrease of avoidance use	Distraction and positive thinking use stabilize

social relation, and feeling understood by others. Thus, PWBS's positive relations might reflect specific characteristics of social interactions where AUD patients might encounter more difficulties and possible challenges. Nonetheless, the particular and detailed aspects of social interactions, benefits, and other characteristics should be further analyzed and differentiated in future studies along several stages of the recovery process.

In summary, the results indicate that the most pronounced changes happen during the first 5 years of abstinence. However, the time needed to reach standardized scores (similar or equal to healthy individuals) in quality of life, wellbeing, and negative emotionality can be fairly more extended since, in our data, individuals with AUD seem to take more than 10 years to match similar values in these dimensions, compared to a control sample. Taking into consideration the relevance of recovery programs based on values [12-steps and Help-yourself, Help-us initiatives (28, 72)] for the self-help group consolidations and their extended time periods, recovery comprehension could benefit from a broadening of the therapeutic stages. At least this could be the case for patients with more severe AUD, beyond the 5-year period of abstinence conceptualized as stable recovery, as proposed by the Betty Ford Institute Panel (70). It should be noted that this stage is not empirically established, and it could derive from the available literature and the common experiences of individuals in recovery.

5. Key implications for research, politics, and practice

In consonance with the growing acknowledgment of addiction as a public health matter, a series of key political changes have been made to support the expansion of addiction services. In our opinion, there is a growing need for increasing efforts directed to change the addiction paradigm in the public politics field. The focus should be directed toward a more generalized use of what is known as Recovery Oriented Attention Systems (ROSC), characterized by the use of continuous multi-systemic attention and centered on the person. Hereby, the input of the present study to a multidimensional measure of recovery represents a significant opportunity to eliminate an impediment to progress in this field and could, ultimately, serve as a relevant contribution to guide research, public policies, and future practice. In a similar manner to other disorders, substance consumption and recovery are related to sanitary costs and quality of life. By deepening studies, on recovery, we could obtain a more efficient use of the resources.

Moreover, this study could support therapists and other service providers in the clinical field. The sequence of recovery in different psychological dimensions related to the quality of life provides a model for the orientation of healthcare resources and therapeutic strategies toward recovery times: Initially, it requires a focus on the more medical aspects of recovery (detoxification, physical problems related to alcohol consumption), and it should not ignore that life quality dimensions do not stabilize until several years of abstinence have passed; quality of life needs have to be thoroughly considered during the 1st year of recovery by service providers. These 1st years of recovery have a relevant role in alcohol addiction and in self-help association framework since formal treatments have a shorter duration and these associations can accompany the patients during the whole process, while they are still recovering. Moreover, other considerable dimensions, such as the fight against stigmatization, become relevant, knowing that quality of life improvement in interpersonal relations takes a significantly long time to happen.

6. Conclusion

The recovery concept implies improvements in quality of life and wellbeing, which are associated with abstinence maintenance. In this way, recovery is presented as a long and slow process, where the most pronounced changes occur during the first 5 years of abstinence. However, indexes of wellbeing and clinical manifestations (such as anxiety, depression, and experiential avoidance) do not seem to reach values similar to healthy subjects until at least 10 years of abstinence.

Moreover, the results point to a differential progress of the contemplated variables. While the physical quality of life seems to evolve rapidly, reaching similar values to controls after 1 year of abstinence (a stage traditionally named as early sobriety), psychological quality of life perception takes a longer time to improve until equaling control subjects' values, at the 4th year of abstinence. Furthermore, in negative emotionality, wellbeing and relations require more time, with patients reaching similar values to controls at 10 years of abstinence (after the lifestyle changes possibly involved). Regarding coping strategies, recovery also involves greater use of strategies to impede consumption. It seems like, in the 1st year of abstinence, distraction and avoidance strategies show a fast rise, while positive thinking displays a slower but constant increase, that occur beyond 10 years of abstinence.

7. Limitations and future perspectives

Among the limitations of this study, the most prominent one is related to its design since it is a cross-sectional study, and this might limit the causal inferences and increase measure errors. One of the inherent limitations of this design is the lack of temporality regarding the association exposition effect, hampering the possibility to know whether abstinence favors the improvement in different psychological dimensions or whether the enhancements in these dimensions facilitate the maintenance of abstinence. It may involve, as Kelly and Hoeppner (3) indicate, a reciprocal relationship.

Additionally, the sample was obtained by recruiting patients that collaborated voluntarily and was not randomized, which might have a possible bias effect. Another limitation can be sample characteristic variability, and though we paired them in gender, age, and educational level, we could not cover other sociodemographic variables. In addition, the number of control subjects was inferior to patients, which limits the statistical power to detect significant differences between groups.

Lastly, different variables have been studied by intragroup comparisons, which allowed us to know more about dimensions evolutions; however, this strategy might implicate limitations when comparing dimensions and their changes. In this way, it would be of interest to know the relation between the different dimensions along the recovery process. Exploring this interaction might help to understand how they might modulate one another or how the change

in one of them can facilitate the change in others. All this could allow for an integral perspective that goes beyond the abstinence relevance, and it would contribute to recommendations for the general practice. It would also be relevant to investigate what other factors are affecting the course and slowing down the process, such as stigmatization.

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.

Ethics Statement

The studies involving human participants were reviewed and approved by 12 de Octubre Ethics Committee (19/086). The patients/participants provided their written informed consent to participate in this study.

Author contributions

GR, LE, RJ-B, and AS contributed to conception, design, and implementation of the study. LE, MB, AZ-B, MC-M, AM-M, DP-S, ER-E, JR-D, and MM contributed to the recruitment of the sample. DL, GR, LE, FA, AS, and RJ-B performed the statistical analysis. GR, LE, AS, and RJ-B wrote sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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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.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2023.1130078/full#supplementary-material

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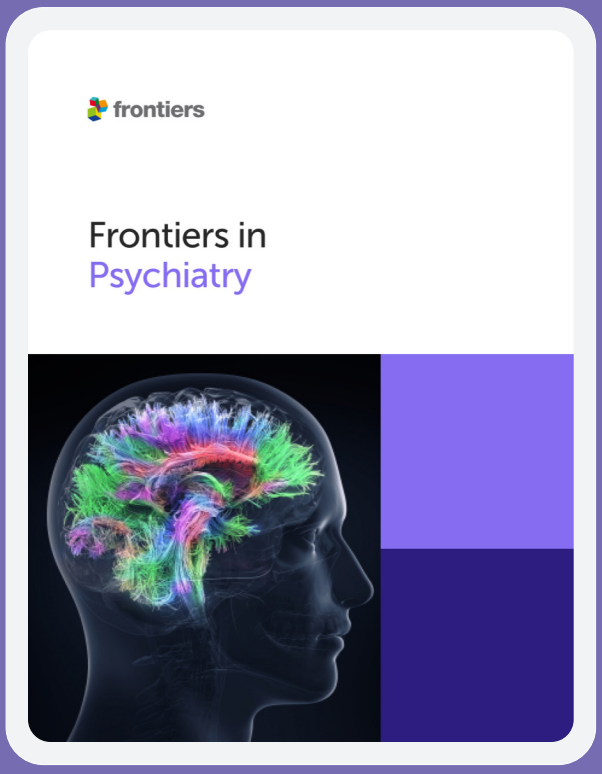

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