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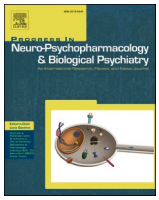

Neurocognitive and clinical profile of male patients with substance use disorder in early remission phase with and without comorbid depression

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ABSTRACT

Substance Use Disorder (SUD) represents one of the most frequent conditions worldwide which commonly coexists with major depressive disorder (MDD). This comorbidity (SUD + MDD) is one of the most prevalent with patients showing certain social and clinical characteristics that could lead to a worsening of their cognitive performance. However, despite these particularities, only a few studies have addressed the possible differences in cognitive performance between patients with SUD + MDD compared with those with SUD-only patients. Therefore, the aim of this study is to examine the clinical and cognitive profile of patients with SUD + MDD *vs.* SUD-only who are in early remission phase. For this purpose, 271 male patients underwent a clinical and neuropsychological assessment (SUD + MDD group: $N = 101$; SUD-only group: $N = 170$). Results indicated that SUD + MDD patients showed worse cognitive performance than SUD in visuospatial reasoning, verbal memory and learning, recognition, and processing speed even after a 3-month period of abstinence. Furthermore, these patients exhibited more self-reported prefrontal symptoms, as well as worse social and clinical conditions. This study indicates that the neurocognitive and clinical profile of patients with SUD + MDD could represent a risk since their characteristics have been associated with poorer recovery and prognosis. Our results could be helpful in clinical practice highlighting the need for cognitive remediation strategies in these populations, providing information that would allow the implementation of more appropriate treatments and preventive strategies.

1. Introduction

Substance use disorder (SUD) affects approximately 39.5 million people worldwide, showing an increase of 45% over the last decade (United Nations Office on Drugs and Crime, 2023). These rates make the different types of SUD a public health issue that comprehensively affects the individual with physical, psychological and social consequences. In patients with SUD, different cognitive domains or functions are frequently affected (Verdejo-García, 2018), with moderate deficits in memory, learning, attention, emotional processing, executive functioning and decision-making (Bruijnen et al., 2019; Verdejo-García et al., 2019) even after a period of abstinence (Almeida et al., 2017; Capella et al., 2015).

The severity of the SUD is determined by a variety of factors, such as the age of substance use onset (Capella et al., 2015) or the presence of dual disorders (DD) (Keen et al., 2022; Marquez-Arrico et al., 2022). A DD is a phenomenon in which SUD coexists with a comorbid mental disorder in the same individual (Adan and Torrens, 2021; Szerman et al., 2022). Patients with DD are characterized by an increased predisposition to clinical and psychosocial complications, as well as poor health-related quality of life and prognosis (Keen et al., 2022; Marquez-Arrico et al., 2019, 2020), among others.

Moreover, the most prevalent mental health disorders coexisting with SUD are the diagnoses of schizophrenia and major depressive disorder (MDD) (Adan et al., 2022). Patients with SUD and comorbid schizophrenia showed a more impaired cognitive performance not only compared to patients with schizophrenia or only SUD (Benaiges et al., 2013; Shah et al., 2021), but also compared to patients with SUD and

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comorbid bipolar disorder or MDD (Marquez-Arrico et al., 2022). In the case of patients with SUD + MDD, there are fewer studies addressing this type of DD despite its high prevalence, which shows values around 40% (Lai et al., 2015). Although these patients have shown normative cognitive functioning in some studies (Hunt et al., 2009, 2015; Marquez-Arrico et al., 2022), a recent review point out that SUD + MDD could enhance cognitive impairment compared to patient with only one diagnosis (Miguel et al., 2023).

Thus, patients with SUD + MDD had lower scores in logical, verbal and visual memory, learning, processing and psychomotor speed, attention, working memory and cognitive flexibility than patients with only MDD (Flores-Medina et al., 2022; Hermens et al., 2013). Furthermore, and compared to DD patients with other comorbid diagnosis, patients with SUD + MDD showed better scores in recognition than patients with schizophrenia and better performance in cognitive flexibility than patients with bipolar disorder (Marquez-Arrico et al., 2022).

Although the results from previous studies demonstrate the existence of certain difficulties in the cognitive performance of patients with SUD + MDD, only a few studies have assessed their differences compared to patients with only SUD. In this regard, in a sample of alcohol consumers, Liu et al. (2010) found that patients with comorbid MDD had lower scores in visual memory and higher impulsivity than patients with only SUD. In the same line, and also from a sample of patients with alcohol consumption, Flores-Medina et al. (2022) showed that patients with SUD + MDD had worse processing speed and cognitive flexibility than patients with only alcohol dependence. However, this study had important limitations such as the small sample size or the lack of an abstinence period prior to assessment, so further studies are needed to corroborate such findings.

For this reason, the aim of this study is to determine, in a large sample of patients, possible differences in cognitive performance between SUD + MDD and SUD patients in early remission phase (abstinence period from 3 to 12 months). We hypothesize that patients with SUD + MDD will show worse cognitive performance than patients from the SUD-only group. Moreover, we look forward to characterize the clinical and social features of the sample, exploring whether any clinical variables related to SUD or to MDD are involved in the performance in the different cognitive domains.

2. Methods

2.1. Sample recruitment and procedure

A sample of 271 under treatment male patients with SUD were included and divided into two groups according to the presence/absence of a comorbid MDD diagnosis: 170 in the SUD and 101 in the SUD + MDD group. All patients were in treatment with an integrated intervention for SUD and for comorbid MDD, if applicable, by the same team. Integrated intervention includes psychotherapeutic management of patients, both in groups and individually, with motivational therapy, contingency management, cognitive- behavioral therapy, social skills training and relapse prevention.

Participants were recruited following these inclusion criteria: (1) male sex, due to the high prevalence of patients with SUD and with DD in treatment centres and also to control the possible differences associated to biological sex; (2) aged between 18 and 55 years old; (3) having a SUD diagnosis according to The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5; American Psychiatric Association, 2013) and being in early remission with a 3–12 months of abstinence period (confirmed by urinalysis, with the detoxification phase passed); (4) meeting DSM-5 criteria for MDD diagnosis in the case of participants of the SUD + MDD group; (5) giving written informed consent for the participation in the study. On the other hand, the exclusion criteria were: (1) meeting DSM-5 criteria for a substance induced disorder; (2) presenting another mental health disorder according to DSM-5; (3) having any physical and/or mental condition that could affect the performance of the assessment.

All participants completed the assessment battery individually evaluated by a psychologist with a Master's Degree in General Health Psychology. None of the patients were economically compensated for their participation.

2.2. Instruments

To collect sociodemographic and clinical data, an *ad hoc* structured interview was designed including variables such as: age, marital status, educational level, living arrangements, employment status, age of onset of SUD/MDD diagnosis, SUD relapses, and psychopharmacological treatment, among others. Diagnoses of SUD and MDD were confirmed using DSM-5 criteria. Addiction severity was measured through the Spanish version of the Drug Abuse Screening Test (DAST-20; Pérez Gálvez et al., 2010) following these cut-off points: 0 no addiction, 1–5 mild; 6–10 intermediate; 11–15 high; and 16–20 severe. Nicotine dependency was measured by the Fagerström test in its Spanish version, which was applied in smokers and considering dependency scores as it follows: < 4 low; 4–7 moderate, and > 7 high (Becoña and Vázquez, 1998). For the SUD + MDD group, the 17-item Hamilton Depression Rating Scale (HDRS) was used in its Spanish version (Ramos-Brieva and Cordero-Villafafila, 1988) to assess depressive symptoms. The cut-off points considered in this research were: 0–7 clinical remission; 8–13 mild depression; 4–18 moderate depression; 19–22 severe depression; $>$ 23 severe depressive symptoms.

For the cognitive assessment a total of eight tests were applied in all the sample. First, three subscales of the Wechsler Adult Intelligence Scale-Revised WAIS III (Wechsler, 2002) were used: Vocabulary test was administered to assess premorbid verbal IQ; Digit Span Subtest (forward and backward) for attention and working memory; and Block Design to explore visuoperceptual, visuospatial, and visuoconstructive functions. These three subtests of the WAIS were corrected according to the Spanish normative data available at the time of assessment. To measure verbal learning, memory processes, recall, and recognition, the Rey Auditory Verbal Learning Test (RAVLT; Strauss et al., 2006) was applied and interpreted according to normative data (Elst et al., 2005).

Moreover, for evaluating executive functions different tests were used. The Trail Making Test in its parts A and B (TMT-A and TMT-B) (Reed and Reed, 1997) was applied to assess processing speed, cognitive flexibility, and set-shifting. This test was corrected following Spanish norms. Additionally, the Wisconsin Card Sorting Test (WCST; Heaton, 2003) was used to obtain a measure of attentional shifting ability, problem solving, and frontal functioning, among others. Results on the WCST were considered according to norms and taking into account age and years of education (Heaton, 2003). The Tower of Hanoi in its four disks computerized version was used to measure planning, problem-solving skills, and working memory (Humes et al., 1997). For the Tower of Hanoi task, no Spanish norms were available at the time of assessment.

Finally, the 46-item version of the Prefrontal Symptoms Inventory (PSI; Pedrero-Pérez and Ruiz-Sánchez De León, 2013) was applied to obtain a measure of problems in three areas: executive control (divided into three subscales: motivational, executive control, and attention problems), social behaviour, and emotional control. The PSI is answered on a Likert-type scale (0: never or almost never; 1: rarely; 2: sometimes yes and sometimes no; 3: many times; 4: always or almost always), with higher scores corresponding to more symptoms. Scores from our sample were considered according to the available Spanish norms (Pedrero-Pérez and Ruiz-Sánchez De León, 2019).

2.3. Statistical analyses

Sociodemographic and clinical measures were analyzed by descriptive statistics using *t*-tests for continuous data and chi-square tests for contrasts in categorical and ordinal variables. Different calculations

Table 1
Sociodemographic data for the two groups of patients. Means, standard deviation, percentages, and statistical contrasts (*t*-test and Chi Square test).

Sociodemographic data	SUD + MDD (N = 101)	SUD (N = 170)	Contrasts
Age (years)	41.98 ± 7.11	37.51 ± 8.41	$t = 3.97$***
Marital status			$\chi^2_{(2)} = 8.09$
Single	49.4%	56.5%	
Married/stable partner	17.3%	22.9%	
Separated/divorced	33.3%	20.6%	
Family situation			$\chi^2_{(1)} = 0.494$
Without children	54.5%	58.8%	
With children	45.5%	41.2%	
Living arrangements			$\chi^2_{(1)} = 6.64$*
Alone	18.4%	7.6%	
Sharing	81.6%	92.4%	
Economic situation			$\chi^2_{(3)} = 11.31$*
No incomes	19.4%	13.8%	
Working	8.0%	20.0%	
Unemployed	35.6%	32.4%	
Under sick leave	16.1%	14.1%	
Disability pension	26.4%	14.1%	
Years of schooling	9.36 ± 3.78	10.19 ± 2.64	$t = 1.84$

$p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, SUD + MDD: Substance use disorder with comorbid major depressive disorder, SUD: Substance use disorder.

such as mean, standard deviation, and percentages were estimated depending on the type of variable. For the cognitive assessment results, ANCOVA and MANCOVA main models were performed to explore differences between groups (SUD + MDD and SUD) by introducing the following covariates: age, Vocabulary from WAIS III (as a measure of premorbid IQ), and duration of SUD in years (since this variable presented significant differences between groups). A repeated measures analysis was carried out to explore differences in the learning curve of the groups across tests A1 to A5 from the RAVLT.

Moreover, another set of ANCOVA and MANCOVA analyses were performed to explore the influence of different clinical factors that were introduced as covariates or independent variables. The variables introduced in these variance analyses were the following: period of abstinence (in months); SUD age of onset; presence of polydrug use (yes/no); severity of addiction (DAST-20 score and their cut-off point as categories); and depressive symptoms for the SUD + MDD group (HDRS score and their cut-off point as categories). Finally, following previous works (Benaiges et al., 2013; Marquez-Arrico et al., 2022), in order to have a measure of the overall performance of the groups, the Z scores from the different tasks were considered in cognitive domains and used

Table 2
Clinical data for the two groups of patients. Means, standard deviation, percentages, and statistical contrasts (*t*-test and Chi Square test).

Clinical data	SUD + MDD (*N* = 101)	SUD (*N* = 170)	Contrasts
History of suicide attempts	41.4%	19.4%	$\chi^2_{(1)} = 14.14$***
Pharmachologyical treatment[a]			
Quantity of medications per day	2.57 ± 1.51	0.89 ± 1.32	$t = 2.85$**
Atypical antipsychotics	21.7%	8.4%	$\chi^2_{(1)} = 8.87$*
Mood stabilizers	28.6%	13.2%	$\chi^2_{(1)} = 8.85$**
Anxiolytics	41.7%	9.6%	$\chi^2_{(1)} = 36.19$***
Antidepressants	82.1%	21.6%	$\chi^2_{(1)} = 84.95$***
Other psychotropics	20.7%	10.0%	$\chi^2_{(1)} = 20.82$*
SUD age of onset (years)	20.30 ± 8.45	20.11 ± 7.26	$t = 1.91$
SUD duration (years)	21.15 ± 10.02	16.82 ± 9.21	$t = 3.47$***
Treatment program			$\chi^2_{(1)} = 0.27$
Inpatient	67.8%	68.8%	
Outpatient	32.2%	31.2%	
Quantity substances used	2.78 ± 1.46	2.34 ± 1.22	$t = 2.59$*
Polydrug use	40.2%	38.2%	$\chi^2_{(1)} = 0.09$
Type of substance[a]			
Cocaine	78.2%	85.3%	$\chi^2_{(1)} = 2.06$
Alcohol	85.1%	73.5%	$\chi^2_{(1)} = 4.37$*
Cannabis	42.5%	42.4%	$\chi^2_{(1)} = 0.01$
Hallucinogens	20.7%	12.9%	$\chi^2_{(1)} = 2.63$
Opioids	25.3%	15.3%	$\chi^2_{(1)} = 3.78$
Sedatives/anxiolytics/hypnotics	10.3%	6.5%	$\chi^2_{(1)} = 1.20$
Smokers	91.1%	85.9%	$\chi^2_{(1)} = 1.61$
Cigarettes per day	15.29 ± 8.50	12.89 ± 7.96	$t = 2.23$*
Fagerström total score	4.92 ± 2.52	3.92 ± 2.32	$t = 3.13$**
DAST-20 total score	14.88 ± 3.06	13.60 ± 3.14	$t = 2.79$
Severity of addiction			$\chi^2_{(3)} = 6.98$
Low	1.4%	0.7%	
Mild	5.8%	15.7%	
High	50.7%	56.0%	
Severe	42.0%	27.6%	
Abstinence period (months)	7.09 ± 2.91	6.30 ± 2.93	$t = 2.05$
Quantity of relapses	1.25 ± 1.63	1.15 ± 1.86	$t = 0.45$

[a] Percentages will not equal 100 as each patient may have taken more than one substance, * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, SUD + MDD: Substance use disorder with comorbid major depressive disorder, SUD: Substance use disorder, DAST-20: Drug abuse screening test.

Table 3
Results for the two groups of patients in Block Design, Digits, RAVLT (Rey Auditory Verbal Learning Test) and Trial Making Test (TMT A and B). Means in direct scores, standard error, and statistical contrasts.

	SUD + MDD (N = 101)	SUD (N = 170)	ANCOVA / MANCOVA[a]		
			$F_{(1,270)}$	ηp^2	1-β
Vocabulary	40.87 ± 0.86	42.01 ± 0.65	1.15	0.004	0.188
Block design	36.84 ± 1.17	42.13 ± 0.91	14.07***	0.054	0.962
Digits					
Direct	8.31 ± 0.18	8.28 ± 0.14	0.28	0.001	0.053
Indirect	5.87 ± 0.19	5.70 ± 0.16	0.47	0.002	0.105
Total	14.18 ± 0.32	13.97 ± 0.25	0.25	0.001	0.079
RAVLT					
A1	4.87 ± 0.15	5.45 ± 0.11	9.50**	0.034	0.867
A2	7.14 ± 0.19	8.03 ± 0.14	13.88***	0.050	0.960
A3	9.05 ± 0.22	9.79 ± 0.17	7.03**	0.026	0.752
A4	9.78 ± 0.23	10.64 ± 0.17	8.85**	0.032	0.842
A5	10.87 ± 0.22	11.52 ± 0.16	5.53*	0.020	0.649
Total words	41.70 ± 0.83	45.42 ± 0.63	12.44***	0.045	0.940
B1	4.83 ± 0.18	4.91 ± 0.14	0.10	0.001	0.062
A6	8.91 ± 0.28	9.37 ± 0.21	1.67	0.006	0.251
A7	8.33 ± 0.29	9.07 ± 0.23	3.60	0.013	0.472
Recognition list A/15	12.74 ± 0.20	13.33 ± 0.15	5.34*	0.020	0.634
Recognition list B/15	12.46 ± 0.27	13.14 ± 0.21	3.91*	0.014	0.504
Recognition 35	30.36 ± 0.41	31.90 ± 0.31	8.69**	0.032	0.836
Trial Making Test					
TMT-A	37.60 ± 3.35	28.53 ± 2.56	4.48*	0.017	0.560
TMT-B	79.43 ± 3.47	72.25 ± 2.65	2.62	0.010	0.365
TMT B – A	50.33 ± 4.05	44.61 ± 3.09	1.23	0.005	0.197

[a] All the ANCOVA and MANCOVA considered age, Vocabulary test, and duration of the SUD (in years) as covariates with the exception of the results in Vocabulary with only age as a covariate, * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, SUD + MDD: Substance use disorder with comorbid major depressive disorder, SUD: Substance use disorder, ηp^2: Partial eta squared, 1-β: statistical power.

to compose a global Z score.

All statistical contrasts were considered bilaterally with a type-I error established at 5% and all *post hoc* comparisons were Bonferroni corrected. Two statistics were also calculated to estimate possible errors and the effect size of each contrast. Partial eta squared (η_p^2) was calculated to measure the effect size, where a value of 0.01 was low, 0.04 moderate, and 0.1 high (Richardson, 2011); statistical power (*1-β*) was also calculated to ascertain the degree of possible type-II error. All data were analyzed using the Statistical Package for the Social Sciences (SPSS version 25.0, SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Sociodemographic and clinical characteristics of the sample

Sociodemographic variables depending on group (SUD + MDD or SUD) are shown in Table 1. The mean age of the total sample was 39.01 years (*SD* = 8.30) and patients with SUD + MDD were older than those with SUD ($p < 0.001$). The groups did not differ in terms of marital status, family situation, or years of schooling. Most patients were single, childless and cohabitating with other people, but SUD + MDD patients presented higher rates of living alone ($p = 0.032$). Although most

Table 4
Results for the two groups of patients in WSCT (Wisconsin Card Sorting Test) and Tower of Hanoi, means of direct scores and standard error.[a]

	SUD + MDD	SUD	MANCOVA		
	(N = 101)	(N = 170)	$F_{(1, 270)}$	ηp^2	1-β
WSCT					
N° of trials	96.30 ± 2.18	97.97 ± 1.61	0.37	0.001	0.093
Total correct	73.31 ± 1.19	74.33 ± 0.88	0.50	0.002	0.103
Total errors	22.18 ± 1.63	23.98 ± 1.20	0.38	0.003	0.140
Percentage	20.69 ± 1.09	21.85 ± 0.80	0.72	0.003	0.134
Perseverative errors	6.95 ± 0.90	8.15 ± 0.67	1.12	0.004	0.184
Percentage	6.01 ± 0.69	6.83 ± 0.51	0.69	0.003	0.131
Nonperseverative errors	15.36 ± 0.89	15.28 ± 0.66	0.01	0.001	0.051
Percentage	16.13 ± 1.03	14.91 ± 0.76	0.89	0.004	0.156
Conceptual level responses	68.85 ± 1.19	67.48 ± 0.88	0.84	0.003	0.150
Percentage	73.17 ± 1.62	71.34 ± 1.20	0.81	0.003	0.146
Categories completed	5.58 ± 0.12	5.48 ± 0.09	0.55	0.002	0.115
Trials to complete 1st category	16.29 ± 1.23	15.72 ± 0.91	0.14	0.001	0.065
Failure to maintain set	1.14 ± 0.15	1.06 ± 0.11	0.19	0.001	0.072
Learning to learn	−1.04 ± 0.54	−1.74 ± 0.40	1.05	0.004	0.175
Response time (ms)	3365.00 ± 136.28	2875.30 ± 100.65	8.13**	0.032	0.811
Tower of Hanoi					
N° of moves	28.48 ± 1.13	26.94 ± 0.86	1.14	0.004	0.186
Errors	1.40 ± 0.46	1.92 ± 0.35	0.81	0.003	0.146
Response time	217.55 ± 11.51	179.68 ± 8.79	6.63*	0.024	0.728

[a] All the MANCOVA considered age, Vocabulary test, and duration of the SUD (in years) as covariates, * $p < 0.05$, ** $p < 0.01$, SUD + MDD: Substance use disorder with comorbid major depressive disorder with, SUD: Substance use disorder, N°: Number, ηp^2: Partial eta squared, 1-β: statistical power.

Table 5
Results for the two groups of patients in PSI (Prefrontal Symptoms Inventory), means (direct scores and percentages) and standard error.[a]

	SUD + MDD	SUD	MANCOVA		
	(N = 101)	(N = 170)	$F_{(1, 270)}$	ηp^2	*1-β*
PSI					
Motivational problems	10.43 ± 0.83	7.30 ± 0.51	10.12**	0.066	0.885
Executive control problems	19.71 ± 1.37	14.55 ± 0.84	10.14**	0.066	0.886
Attention problems	11.66 ± 0.94	9.51 ± 0.58	3.76	0.026	0.486
Total executive problems	41.80 ± 2.78	31.37 ± 1.70	10.07**	0.067	0.883
Social behaviour problems	10.43 ± 1.12	9.73 ± 0.69	0.280	0.002	0.082
Emotional control problems	10.69 ± 0.94	9.25 ± 0.58	1.67	0.012	0.250
Total score	63.94 ± 4.13	50.36 ± 2.53	6.60*	0.044	0.723

[a] MANCOVA considered age, Vocabulary test, and duration of the SUD (in years) as covariates, * $p < 0.05$, ** $p < 0.01$, SUD + MDD: Major depressive disorder with comorbid substance use disorder, SUD: Substance use disorder, ηp^2: Partial eta squared, 1-β: statistical power.

patients were not working, the SUD + MDD group was significantly characterized by no income and no disability pension ($p = 0.026$).

Regarding clinical variables (see Table 2) the groups differed in the history of suicide attempts (self-reported) ($p < 0.001$), psychopharmacological treatment ($p < 0.031$), SUD duration ($p < 0.001$), rate of alcohol use ($p = 0.043$), and smoking habits ($p < 0.022$). In this sense, the SUD + MDD group presented characteristics related to a worse clinical situation. The mean age of MDD onset for the SUD + MDD group was 30.85 years old (*SD* = 11.32), 42.6% of them had a history of suicide attempts, and the majority were taking antidepressants and anxiolytics. The mean total score of the HDRS in the SUD + MDD group was 10.01 (*SD* = 5.30), indicating mild depressive symptoms for these patients. In reference to variables related to SUD, 39.1% of patients from the total sample had a pattern of polydrug use without significant differences between groups; cocaine and alcohol were the substances most commonly used with alcohol being significantly more prevalent for SUD + MDD. Besides, SUD + MDD had a longer duration of the SUD and more types of substances used. Almost all patients in the sample (91.9%) were smokers with SUD + MDD who showed a greater number of cigarettes consumed per day as well as a higher nicotine dependency.

3.2. Cognitive performance in SUD + MDD and SUD patients

The ANCOVAs and MANCOVAs analyses (Tables 3, 4 and 5) indicated that there were not any significant differences between groups in the estimation of the verbal premorbid IQ (Vocabulary test; $p = 0.285$) nor in the Digits task ($p \geq 0.619$), with *Z* values from −0.5 to 1.0 in all cases. The Block Design test showed differences between the groups, with patients from the SUD + MDD groups presenting worse performance ($p < 0.001$; $Z = -1.30$) than SUD patients ($Z = -0.70$). Regarding results in the RAVLT, the SUD + MDD group presented worse verbal memory performance than SUD patients. Differences were found in trials A1 to A5 ($p \leq 0.019$), total words ($p < 0.001$; SUD + MDD $Z = -1.1$; SUD $Z = -0.6$), and in the recognition lists A/15 ($p = 0.022$; SUD + MDD $Z = -0.9$; SUD $Z = -0.5$), B/15 ($p = 0.049$) and recognition 35 ($p = 0.003$). There were no significant differences between groups in the learning curve of the RAVLT ($F_{(1,270)} = 0.522$; $\eta_p^2 = 0.005$; *1-β* = 0.110; $p = 0.472$), with the two groups exhibiting a similar learning trend throughout the trials.

In the case of TMT, significant differences were observed in TMT-A, with patients in the SUD + MDD group showing a worse performance ($p = 0.035$; $Z = -1.4$) than SUD ($Z = 0.1$), while no differences were found for TMT-B and TMT B-A ($p \geq 0.107$). The execution for the WCST in all its indexes ($p \geq 0.290$) and in Hanoi Tower (number of movements $p = 0.288$; errors $p = 0.370$) did not show any differences between groups, with the exception of the response time in both tasks. The SUD + MDD group was slower than SUD in the WCST ($p = 0.005$) and in Hanoi Tower ($p = 0.011$).

In relation to the PSI, the higher scores for the SUD + MDD group indicated more prefrontal symptoms according to the results in motivational ($p = 0.002$; SUD + MDD $Z = 0.5$; SUD $Z = 0.0$), executive control ($p = 0.002$; SUD + MDD $Z = 1.4$; SUD $Z = 0.7$) and total executive problems ($p = 0.002$; no normative data available), as well as for the total score ($p = 0.011$; SUD + MDD $Z = 1.2$; SUD $Z = 0.6$). For the rest, no significant differences were found between groups in attention, social behaviour, or emotional control problems.

On the other hand, the continuous and categorical clinical variables included as covariates or independent variables did not contribute to

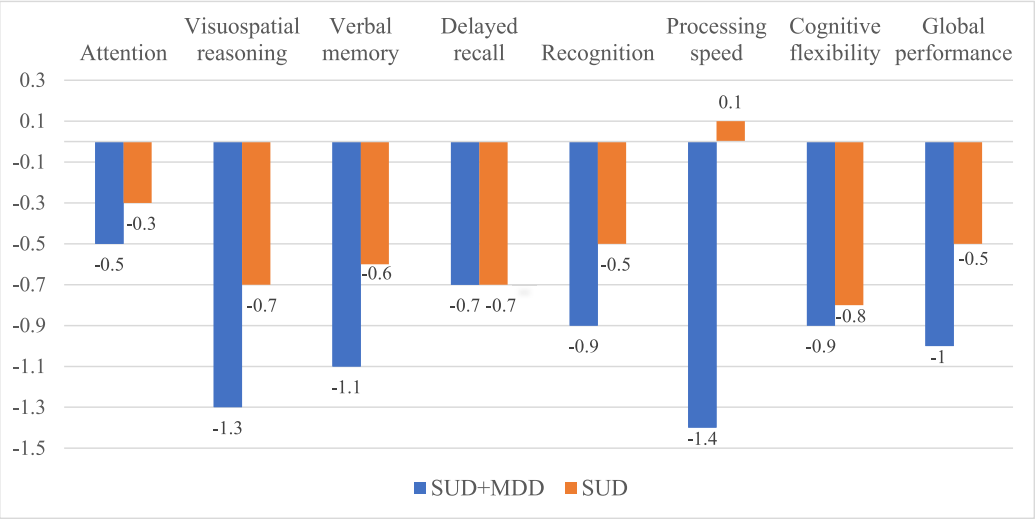

Fig. 1. Z scores on the assessed cognitive domains for each group.

any substantial differences with respect to the first analyses. Neither the period of abstinence, nor SUD age of onset, nor the presence of polydrug use nor the severity of addiction -despite the different distribution in the categories- seem to explain the differences found between groups. The consideration of the severity of depressive symptoms (HDRS score and categories) in SUD + MDD patients also showed no significant effect on their cognitive performance and self-reported prefrontal symptoms. Thus, the differences observed in the main analyses (Tables 3, 4 and 5) did not change, with the SUD + MDD group showing worse performance than SUD patients (Fig. 1).

SUD + MDD: Substance use disorder with comorbid Major Depressive Disorder, SUD: Substance use disorder, Attention: Digits (WAIS III), Visuospatial reasoning: Block Design Tests (WAIS III), Verbal Memory: Total words Rey Auditory Verbal Learning Test (RAVLT), Delayed Recall: Trial A7 RAVLT, Recognition: A/15 (RAVLT), Processing Speed: Trial Making Test A, Cognitive Flexibility: Trial Making Test B, Global performance: mean scores from all the domains assessed.

4. Discussion

As far as we know, this is the first study carried out in a large sample that evaluates differences in several cognitive domains between male patients with SUD + MDD and SUD in early remission phase and considering the influence of clinical variables. According to expectations, our data show that patients with SUD + MDD had poorer cognitive performance in some domains than SUD patients without comorbidity. Our results are in line with previous studies that have explored differences between these two groups, although in smaller samples with alcohol-only users and without specific data on abstinence periods (Flores-Medina et al., 2022; Liu et al., 2010). Thus, patients with SUD + MDD presented worse performance in visuospatial and visuoconstructive reasoning, memory and verbal learning, recognition, and processing speed, as well as more motivational and executive self-reported problems even when they were in the early remission phase of their SUD. Moreover, even though the performance of both groups was within the considered normative values (Z from −1.5 to 1.5) in all the assessed domains and in the overall performance, all the zeta values were negative with the exception of processing speed for SUD patients.

The sociodemographic characteristics showed that the SUD + MDD group was composed by older patients, with a small proportion of them being married or with a stable partner, and also by more patients living alone. Previous data suggest that SUD + MDD patients have more severe problems related to social isolation since Birtel et al. (2017) found that perceived social support was negatively associated with depressive symptoms in patients with SUD. Therefore, it is possible to expect that patients with SUD + MDD tend to use social support less as a coping strategy than SUD patients without comorbidity (Adan et al., 2017). Furthermore, as observed in previous works (Adan et al., 2017; Marquez-Arrico et al., 2019) SUD + MDD comorbidity was associated to higher percentages of patients who were not working. These results could highlight the special social and economic vulnerability of SUD + MDD even when compared with patients with a SUD-only diagnosis.

Regarding SUD characteristics, patients with SUD + MDD had more severe conditions, since they had a longer SUD duration, used more substances, and had higher nicotine dependence. Additionally, the SUD + MDD group presented more patients who were alcohol users. MDD and alcohol use frequently co-occur (Ehlers et al., 2019; Karpyak et al., 2019) and some studies have suggested that the addictive disorder could be influencing the development of the MDD, which could explain the greater SUD severity of the SUD + MDD group (Boden and Fergusson, 2011; Ibáñez et al., 2020; Marquez-Arrico et al., 2020).

The results in cognitive performance pointed out that the comorbidity of SUD + MDD was linked to a worse neuropsychological profile with visuospatial and visuoconstructive reasoning, verbal memory, and processing speed being the domains with the worst performances. Difficulties in visuospatial and visuoconstructive reasoning were related to severe alcohol consumption (Bates et al., 2002) and the SUD + MDD group presented a higher prevalence of alcohol use than the SUD group. Regarding verbal memory and learning, two factors (among others) could be contributing to the observed results. Firstly, it is well established that patients with MDD have difficulties in verbal memory and verbal learning (Knight and Baune, 2018), even in the remitted state of depression (Kriesche et al., 2022) probably as a result of the consequences of acute depressive episodes (McIntyre et al., 2013). Secondly, alcohol was used by 85.1% of patients within the SUD + MDD group and similar impairments have been found in alcohol use disorder patients with an abstinence period of 2 to 12 months (Stavro et al., 2013). Thereby, our data indicate that patients with a diagnosis of MDD and alcohol use could present a risk profile in terms of verbal learning and memory performance. Future studies should explore whether impairments in verbal memory could operate as a marker or endophenotype for SUD + MDD in the same way as they do for the MDD diagnosis (Goldstein and Klein, 2014; Hasler et al., 2004).

Moreover, in line with Flores-Medina et al. (2022) and Hermens et al. (2013), a relevant finding from our study was that the different tasks showed a slower processing speed for SUD + MDD compared to SUD. It is noteworthy that, while the scores for the SUD group in this domain were the only ones with values not below the normative mean, for the SUD + MDD group it was the most affected function. In fact, some studies have found a worse processing speed for SUD + MDD (Marquez-Arrico et al., 2022) compared to MDD or SUD-only patients (Hermens et al., 2013; Liu et al., 2010). Our findings on processing speed showing that patients with SUD + MDD were slower in all the time measures registered extend previous observations and give support to the idea that this function is considered a potential irreversible marker for depression (Halvorsen et al., 2012; Lam et al., 2014). We may suggest that, given the fact that patients with only MDD have shown a slower psychomotor speed (Nuño et al., 2021; Pan et al., 2019) the comorbidity of SUD + MDD may accentuate this deficit.

Based on normative data, and in line with previous studies carried out with DD and SUD-only patients, the results of both groups in the neuropsychological tasks were below the means in all domains (except for processing speed in the SUD group). Nevertheless, the results for SUD + MDD in visuospatial and visuoconstructive reasoning, verbal memory and learning, processing speed, and in overall performance should be considered, as they indicate borderline performances in all cases ($Z \leq -1$). Longitudinal studies should be cautious when exploring the evolution of these variables for patients with SUD in sustained remission. In this regard, given the cross-sectional nature of our data, it is difficult to determine whether the cognitive functioning of these patients predisposed to or was a consequence of drug use, just as it is not possible to establish if the cessation of use has led to changes in cognitive performance. Despite this fact, it should be noted that the sample was composed by patients under treatment in early remission. Cognitive training has shown promising results in patients with SUD (Hendershot et al., 2018; Verdejo-Garcia, 2016), so achieving abstinence and receiving comprehensive treatment may have a positive influence on cognitive performance, which should be extended and even more necessary for patients with SUD + MDD.

Regarding prefrontal symptoms, compared with the SUD group and normative data, patients with SUD + MDD showed more self-reported problems in daily activities that may be related to prefrontal dysfunctions. To our knowledge, this is the first study to assess self-reported prefrontal symptoms in a sample with SUD + MDD and it extends previous findings about more prefrontal symptoms in SUD than in healthy controls (Khemiri et al., 2022; Terán-Mendoza et al., 2016). In more detail, our patients showed differences in motivational, executive control, and total executive problems, with SUD + MDD patients presenting more symptoms. With respect to motivational problems, these could be due to the presence of depressive symptomatology, such as anhedonia, which could lead to self-perceived motivational problems. Besides, we suggest that these differences could be related to the cognitive slowing

exhibited by the SUD + MDD group, which could interfere with the performance of many daily activities that patients deal with. Nevertheless, no objective correlations were found with scores on standardized tasks of other executive functions, indicating that it is likely that these SUD + MDD patients perceive a greater impairment in their actual performance. These data are of interest in clinical practice, as they suggest that these subjective complaints should preferably be treated through psychotherapeutic approaches such as cognitive restructuring.

Overall, the worst cognitive performance observed for the SUD + MDD group may arise from compromised functional networks that mainly encompass verbal memory, processing speed, and some executive components which are shared across various diagnoses. Therefore, our findings could be seen as a support to the common pathway disorder hypothesis since the continued impairment following early remission indicates the presence of enduring neurocognitive limitations rather than attributing these difficulties to a temporary or transient state (Allott et al., 2016; Nigg, 2023). In this sense it points to the fact that neither the presence of depressive symptomatology nor other clinical features are sufficient reasons for to explain the worse functioning of SUD + MDD patients To gain a deeper insight into this hypothesis is imperative to conduct longitudinal studies that investigate neurocognitive functioning both prior and subsequent to the onset of full-threshold MDD, with a particular focus on monitoring changes throughout recurrent episodes and/or drug use. Moreover, some approaches may be included during treatment interventions with SUD + MDD patients, such as implementing memory support strategies which have been seen as promising for enhancing coping skills and adherence to treatment, as well as patient outcomes (Dong et al., 2017; Sarfan et al., 2023).

Some limitations of this study require comment. The samples from both groups were composed by men, as they are the majority of the patients receiving SUD treatment. Moreover, male patients are also the majority of patients with SUD + MDD receiving treatment in the healthcare system (Hunt et al., 2020; National Institute on Drug Abuse, 2022). Therefore, our findings are not covering cognitive functioning in women and cannot be extended to them. Furthermore, although all patients were under treatment, including both inpatients and outpatients in the sample could be considered as a limitation since the type of treatment and its different needs may be associated to the cognitive performance profile (Brewer et al., 2005). However, it is noteworthy that we did not find any effect nor an interaction between the type of treatment and the performance in the cognitive assessed domains. Approximately 40% of patients in each group had a pattern of polydrug use and, although the groups did not differ in the percentage of patients using different drugs (except for alcohol, with a higher percentage in SUD + MDD group), future studies should investigate the possible differential effect of each drug in similar samples. Finally, we have not analyzed the effect of pharmacological treatment that could influence cognitive performance; although the SUD-MDD group took more medications per day (antidepressants, anxiolitics and mood stabilizers), the heterogeneity of mechanisms of action of the active ingredients, combination and doses made an adequate categorisation difficult and we considered that it would not be very useful or reliable to explore the effect of mere quantification. Nevertheless, despite these limitations, this cross-sectional study has strengths, such as the large patient sample, the control of abstinence periods through urinalysis, and the comprehensive neuropsychological assessment, including different cognitive domains.

5. Conclusions

Our findings pointed out that the SUD + MDD comorbidity implies a worse cognitive performance as well as worse social and clinical conditions than the SUD-only diagnosis. The performance of our sample was below norms, especially for the SUD + MDD group, which showed a poorer performance in visuospatial and visuoconstructive reasoning, verbal memory, and processing speed, and more motivational and executive self-reported problems. Thus, some of the cognitive limitations observed for patients with MDD could get accentuated due to the presence of the SUD. Overall, MDD comorbidity in SUD patients could be understood as an added risk, showing a greater vulnerability to poorer cognitive performance and more difficulties to face treatment and recovery even during the early remission phase. This work provides useful data for the elaboration of high-risk profiles in SUD, as well as for the implementation of preventive and cognitive rehabilitation treatment strategies.

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Ethical statement

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (approved by the Research Committee of the University of Barcelona protocol code IRB00003099) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all patients for being included in the study.

CRediT authorship contribution statement

Julia E. Marquez-Arrico: Writing – review & editing, Writing – original draft, Investigation, Formal analysis. **Judit Catalán-Aguilar:** Writing – review & editing, Writing – original draft, Investigation, Formal analysis. **José Francisco Navarro:** Writing – review & editing, Methodology, Conceptualization. **Ana Adan:** Writing – review & editing, Writing – original draft, Supervision, Resources, Methodology, Investigation, Formal analysis, Conceptualization.

Declaration of competing interest

The authors have no conflicts of interest relevant to this article to disclose.

Data availability

The datasets used and/or analyzed during the study will be available from the corresponding author on reasonable request.

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