 Patients with Schizophrenia Showed Worse Cognitive Performance than Bipolar and Major Depressive Disorder in a Sample with Comorbid Substance Use Disorders

Julia E. Marquez-Arrico 1,2, Alvaro Gonzalez-Sanchez 1,2, José Francisco Navarro 3, Rafael Penadés 1,4,5,6 and Ana Adan 1,2,*

1 Department of Clinical Psychology and Psychobiology, School of Psychology, University of Barcelona, Passeig de la Vall d’Hebrón 171, 08035 Barcelona, Spain
2 Institute of Neurosciences, University of Barcelona, 08035 Barcelona, Spain
3 Department of Psychobiology, School of Psychology, University of Málaga, Campus de Teatinos s/n, 29071 Málaga, Spain
4 Barcelona Clinic Schizophrenia Unit (BCSU), Hospital Clinic Barcelona, 08036 Barcelona, Spain
5 Institute of Biomedical Research August Pi i Sunyer (IDIBAPS), 08036 Barcelona, Spain
6 Centro de Investigación Biomédica en Red Salud Mental (CIBERSAM), 28029 Madrid, Spain
* Correspondence: aadan@ub.edu

Abstract: Comorbidity of substance use disorders (SUD) and severe mental illness (SMI) is highly frequent in patients, the most common diagnoses being schizophrenia (SZ), bipolar disorder (BD) and major depressive disorder (MDD). Since comorbidity has its own clinical features, and neurocognitive functioning is not always similar to psychiatric symptoms the present study explores the cognitive performance of patients with dual disorders. A neuropsychological battery of tests was used to assess 120 under treatment male patients, 40 for each group considered (SZ + SUD, BD + SUD and MDD + SUD) who were mainly polyconsumers. Significant differences (with premorbid IQ as a covariate) were found among the groups, with SZ + SUD having a worse performance in attention, verbal learning, short term memory and recognition. The consideration of a global Z score for performance evidenced an impaired neurocognitive pattern for SZ + SUD compared with BD + SUD and MDD + SUD. According to norms, all patients showed difficulties in verbal learning, short-term memory and recognition. Our research indicated that the neurocognitive functioning of dual disorder patients was influenced by the comorbid SMI, with SZ + SUD presenting major difficulties. Future studies should thoroughly explore the role of such difficulties as indicators or endophenotypes for dual schizophrenia disorders, and their usefulness for prevention and treatment.

Keywords: substance use disorders; schizophrenia; bipolar disorders; major depressive disorders; neurocognition; dual disorders

1. Introduction

The coexistence of a psychiatric disorder and a substance use disorder (SUD) is highly prevalent [1,2] and comorbidity rates between the two diagnostic entities are estimated to be between 45–55% [3]. This phenomenon is called dual disorder and entails a more problematic sociodemographic and clinical profile compared to patients who have only a diagnosis of severe mental disorder or SUD [1,4]. Different studies have reported that the most severe and prevalent comorbid diagnoses of SUD in clinical samples are schizophrenia (SZ), bipolar disorder (BD) and major depressive disorder (MDD) [5,6].

The presence of an SUD has been associated in different studies with cognitive deficits in memory, attention, emotional processing, executive functioning and decision-making [7,8]. The study of cognition takes on special relevance in people with dual disorders since their influence on both treatment outcomes for SUD [9,10] and mental disorder has been evidenced [11,12]. In addition, for patients under treatment, knowledge of
their own deficits or areas for improvement is a factor that is largely mediating therapeutic success [13].

Few studies have analysed the influence of dual diagnosis on neurocognition and, although most of the data point to worse performance of dual patients compared to those with only one diagnosis, there are also inconsistent findings. Some studies observe more severe deficits in patients with dual disorders compared to those with only severe mental illness (SMI) [12,14,15], while in other studies no differences were found between them [16,17]. Likewise, other works indicate that patients with dual disorders exhibit better cognitive performance [18,19] with respect to patients with a single diagnosis of SMI. In any case, the existence of possible implications of neurocognitive performance on the status, prognosis and outcomes of dual patients is certainly relevant [20].

The most investigated comorbidity has been the combination of SZ + SUD. Specifically, different studies report more impaired performance in patients with SZ + SUD, compared to SZ patients who are not substance users [21–23]. The functions observed with scores below normative values are premorbid IQ, current IQ, verbal learning, verbal working memory, processing speed and attention [23–25].

In the case of BD, few publications on patients with BD + SUD consistently point to worse performance in these patients compared to patients with BD without SUD in visual and verbal memory, conceptual reasoning, problem-solving skills and executive functioning [15,26,27]. Normalization of cognitive functioning in BD patients is possible, although the coexistence of SUD implies a less favourable recovery with deficits that may persist even when SUD treatment has been completed and the patient is euthymic [28,29].

Existing data on MDD + SUD patients point to the presence of lower scores on tests of verbal memory, immediate memory, processing speed and cognitive flexibility, compared to patients with only a diagnosis of MDD and to healthy controls [30,31]. However, in one study, no differences in cognitive performance were observed between MDD-only and SUD-only patients, who also had a normative performance in priming, short-term memory and verbal fluency [32].

Therefore, this work aims to explore, for the first time, the neurocognitive performance profile of a sample of patients with SUD and the three most prevalent comorbid SMI (SZ, BD and MDD). Our main hypothesis is that patients with dual disorders show similar cognitive functioning regardless of the type of comorbid severe mental disorder.

2. Materials and Methods
2.1. Participants and Procedure

A total sample of 120 male patients with SMI and comorbid SUD were included and considered in three groups, 40 for each psychiatric diagnosis: SZ + SUD, BD + SUD and MDD + SUD. All the participants were under psychiatric and/or psychological treatment, in outpatient or inpatient programs, at different public and private centres in the province of Barcelona (Catalonia) and were referred to our study from their treatment centres.

The inclusion criteria for our study were: (1) male sex (due to the higher prevalence rates of dual disorders for this sex in treatment centres as well as to control the possible SUD/SMI differences related to sex); (2) aged from 18 to 55 years old; (3) SUD diagnosis in initial remission phase (abstinence at least during a 3-month period, up to 12 months and confirmed by urinalysis), according to the Diagnostic and Statistical Manual of Mental Disorders criteria (DSM-5) [33]; (4) having the diagnosis of schizophrenia for the SZ + SUD group, bipolar disorder for the BD + SUD group and major depressive disorder for the MDD + SUD group, according to DSM-5 criteria for all cases; (5) being under treatment and stabilized. Participants were excluded from the study when meeting one of the following criteria: (1) presenting a disorder induced by substance use or medical illness according to DSM-5; (2) meeting DSM-5 criteria for other mental disorders; (3) presenting any physical and/or mental condition that could affect completing tasks. A psychologist from our research team individually administered the assessment protocol and participants were not economically compensated for their participation.
2.2. Instruments

2.2.1. Sociodemographic and Clinical Measures

We designed an ad hoc structured interview to collect sociodemographic and clinical data such as age, marital status, educational level, living arrangements, SUD and psychiatric diagnosis age of onset, SUD relapses and psychopharmacological treatment, among others. In addition, the Structured Clinical Interview (SCID-I) for the DSM-IV-TR [34] was used to confirm SUD, SZ, BD and MDD diagnoses and to complete data collection. We applied the DSM-IV-TR version of the SCID-I because, at the time of assessment, the Spanish version of the DSM-5 was not yet available. Moreover, the Spanish version of the Drug Abuse Screening Test (DAST-20) was used to obtain an indicator of SUD severity following these cut-off points: 0 no addiction, 1–5 mild, 6–10 intermediate, 11–15 high and 16–20 severe [35].

The assessment of psychiatric symptoms according to the diagnosis was carried out through the Spanish version of the Positive and Negative Syndrome Scale (PANSS) [36] for the SZ + SUD group. The Spanish version of the Young Mania Rating Scale (YMRS) [37] was applied in the BD + SUD group to assess manic symptoms and interpreted as follows: total score ≤ 12 indicates remission; 13–19 minimal symptoms; 20–25 mild mania; 26–37 moderate mania; and 38–60 severe mania. Finally, the Hamilton Depression Rating Scale (HDRS) in its Spanish version with 17 items [38] was used to assess depressive symptoms in the MDD + SUD group with scores from 0 to 7 indicating clinical remission; 8 to 13 mild depression; 4 to 18 moderate depression; 19–22 severe depression; and >23 severe depressive symptoms.

2.2.2. Neurocognitive Performance Assessment Battery

Two subscales of the Wechsler Adult Intelligence Scale-Revised WAIS III [39] were used, the Vocabulary subtest was administered to assess the premorbid verbal IQ while the Digit Span Subtest (direct and indirect) was to assess the attention span [40]. For the correction and interpretation of these two tests, we applied the Spanish normative data available at the time of the assessment [39]. Verbal learning, memory processes, recall and recognition were explored with the Rey Auditory Verbal Learning Test (RAVLT) [41] and interpreted according to normative data [42]. Additionally, two neuropsychological measures were established with the RAVLT. The comparison between trails A5 and A7 was used to see how the participants recover information and the comparison between A7 and RecogA/15 was calculated to establish how the information is codified. Moreover, the Trail Making Test parts A and B (TMT-A and TMT-B) [43] were used and interpreted according to Spanish norms [44]. The TMT-A was administered as a measure of attention and processing speed, while the TMT-B provided a measure of cognitive flexibility and set-shifting.

Two computerized tests were also applied. On the one hand, the Wisconsin Card Sorting Tests (WSCT) [45] was applied as a measure of the ability to shift attention, problem solving, response maintenance, cognitive flexibility and frontal functioning. This test was interpreted according to norms taking into account age and years of education [45]. On the other hand, the Tower of Hanoi [46] in its four disks computerized version served as a measure of planning and problem-solving skills, and working memory was used. For the Tower of Hanoi task, there were no Spanish norms available at the time of the assessment, so their direct results were compared among the groups. All participants completed the full assessment battery.

2.3. Statistical Analysis

Descriptive statistics were calculated for the demographic and clinical variables for the three dual disorder groups, using ANOVA analyses for continuous data and chi-square test for categorical data. Means, standard deviation and percentages were calculated depending on the type of variable. All the results from the neurocognitive tasks (vocabulary, digits, RAVLT, TMT-A and B and WSCT) were transformed from direct to Z scores according to norms (considering sex, age and educational level), with the exception of the Tower of
Hanoi since it has not any norms available for our population. The different cognitive functions considered were attention (Digits form WAIS III and A1 from RAVLT), verbal learning (total words from RAVLT), short-term memory (A6 from RAVLT), recognition (A/15 from RAVLT), processing speed (TMT-A) and cognitive flexibility (Wisconsin Sort Card Test and TMT-B).

The differences in neurocognitive performance among the groups were analysed through ANCOVA or MANCOVA depending on the task; repeated measures MANCOVA analysis were also used for RAVLT. For assessing global performance, following previous works [47–49] the Z scores for the different cognitive functions were all integrated into a global Z score as a measure of general performance. To evaluate the possible influence of sociodemographic variables (e.g., educational level, employment) as well as because it has also shown to be a variable with influence in cognitive performance [9,25], premorbid IQ (Vocabulary from WAIS III) was introduced as a covariable in all the analyses. We also estimated statistic partial eta squared ($\eta^2_p$) to measure the effect size, where a value of 0.01 was low, 0.04 moderate and 0.1 high [50]. All post hoc comparisons were Bonferroni corrected and data were analysed using the Statistical Package for the Social Sciences (SPSS version 25.0, SPSS Inc., Chicago, IL, USA). All the tests were considered bilaterally with a type I error established at 5%.

3. Results

3.1. Sociodemographic Data and Clinical Variables Related to the Comorbid Severe Mental Illness

Analysis of the sociodemographic and clinical data (see Table 1) indicated that the mean age of the total sample of patients included was 37.76 years ($SD = 7.61$), with the age of the SZ + SUD group being lower than that of the MDD + SUD group ($p = 0.012$). Significant differences between groups were found in the variables of family situation, living arrangements and economic situation. In this regard, the SZ + SUD group contributed the highest rates of patients without children ($p = 0.001$), and of sharing a place of residence ($p = 0.001$), while the MDD + SUD group showed the highest number of patients in a situation of unemployment ($p = 0.001$), although with fewer disability pensions ($p = 0.001$).

Table 1. Sociodemographic data for the three groups of patients. Means, standard deviation, percentages and statistical contrasts (ANOVA and chi-square test).

| Sociodemographic Data | SZ + SUD (N = 40) | BD + SUD (N = 40) | MDD + SUD (N = 40) | Contrasts |
|-----------------------|-------------------|-------------------|-------------------|-----------|
| Age (years)           | 34.93 ± 7.71      | 38.55 ± 8.59      | 39.80 ± 5.55      | $F_{(2,119)} = 4.68^*$ |
| Marital status        |                   |                   |                   | $\chi^2{(2)} = 12.59$ |
| Single                | 82.5%             | 55.0%             | 50.0%             |           |
| Married/stable partner| 15.0%             | 42.5%             | 45.0%             |           |
| Separated/divorced    | 2.5%              | 2.5%              | 5.0%              |           |
| Family situation      |                   |                   |                   |           |
| Without children      | 82.5%             | 62.5%             | 50.0%             | $\chi^2{(1)} = 9.45^{**}$ |
| With children         | 17.5%             | 37.5%             | 50.0%             |           |
| Living arrangements   |                   |                   |                   | $\chi^2{(3)} = 21.87^{***}$ |
| Alone                 | 7.5%              | 17.5%             | 5.0%              |           |
| Sharing               | 67.5%             | 62.5%             | 47.5%             |           |
| Therapeutic community | 15.0%             | 20.0%             | 47.5%             |           |
| Supported accommodation| 10.0%            | 0%                | 0%                |           |
| Economic situation    |                   |                   |                   | $\chi^2{(3)} = 35.37^{***}$ |
| Working               | 12.5%             | 10.0%             | 12.5%             |           |
| Unemployed            | 20.0%             | 20.0%             | 57.5%             |           |
| Under sick leave      | 7.5%              | 5.0%              | 17.5%             |           |
| Disability pension    | 60.0%             | 65.0%             | 12.5%             |           |
| Years of schooling    | 9.88 ± 2.43       | 11.25 ± 3.26      | 10.45 ± 2.05      | $F_{(2,119)} = 2.76$ |

BD + SUD: bipolar disorder with comorbid substance use disorder; MDD + SUD: major depressive disorder with comorbid substance use disorder; SZ + SUD: schizophrenia with comorbid substance use disorder. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

Regarding clinical characteristics (see Table 2), the analysis of variables linked to SMI indicated that the mean age at onset was 27.22 years ($SD = 8.72$), with the MDD + SUD
group showing the latest age \((p < 0.001)\). In relation to medication, the SZ + SUD group showed the highest amount of daily medication compared to the MDD + SUD group \((p = 0.021)\), with the prescription of typical \((p = 0.019)\) and atypical antipsychotics \((p < 0.001)\) specific for their SMI. Likewise, the BD + SUD group presented the highest percentage of mood stabilizers prescription \((p < 0.001)\) while the MDD + SUD group stood out for the higher use of antidepressants \((p = 0.017)\). In the case of psychiatric symptoms, the direct PANSS scale scores in the SZ + SUD group were in the following percentiles: 5 for positive symptoms, 15 for negative symptoms, 45 for the composite scale and 10 for general symptomatology. The BD + SUD group showed values on the YMRS and HDRS scales that placed them without significant manic or active depressive symptomatology, while the MDD + SUD group had a higher HDRS score than BD + SUD \((p < 0.001)\), which placed them in the mild depressive symptoms range.

### Table 2. Clinical data for the three groups of patients regarding psychiatric diagnosis. Means, standard deviation, percentages and statistical contrasts (ANOVA and chi-square test).

| Clinical Data                        | SZ + SUD (N = 40) | BD + SUD (N = 40) | MDD + SUD (N = 40) | Contrasts     |
|--------------------------------------|-------------------|-------------------|-------------------|--------------|
| SMI age of onset (years)             | 23.88 ± 7.31      | 25.95 ± 8.82      | 31.83 ± 8.12      | \(F_{(2,119)} = 10.34 \) *** |
| History of suicide attempts          | 45.0%             | 40.0%             | 47.5%             | \(X^2(1) = 0.47\) |
| Pharmacological treatment a          |                   |                   |                   |              |
| Quantity of medications per day      | 3.36 ± 1.56       | 3.12 ± 1.77       | 2.33 ± 1.64       | \(F_{(2,119)} = 4.13\) * |
| Typical antipsychotic                | 28.2%             | 10.0%             | 2.6%              | \(X^2(1) = 15.19\) * |
| Atypical antipsychotic               | 94.6%             | 65.0%             | 22.5%             | \(X^2(1) = 44.89\) *** |
| Mood stabilizers                     | 41.0%             | 67.5%             | 32.4%             | \(X^2(1) = 26.02\) *** |
| Anxiolytics                          | 43.6%             | 35.0%             | 39.8%             | \(X^2(1) = 2.14\) |
| Antidepressants                      | 33.3%             | 46.2%             | 71.8%             | \(X^2(1) = 15.48\) * |
| Anticholinergic                      | 25.6%             | 2.5%              | 0%                | \(X^2(1) = 18.25\) *** |
| Alcohol-aversive-agent               | 25.6%             | 22.5%             | 25.6%             | \(X^2(1) = 0.14\) |
| Other psychotropics                  | 13.2%             | 12.5%             | 17.9%             | \(X^2(1) = 2.24\) |
| Chlorpromazine equivalent dose (mg)  | 422.30 ± 35.22    | 138.81 ± 3.27     | 43.15 ± 34.27     | \(F_{(2,119)} = 31.79\) *** |
| PANSS positive                       | 12.34 ± 6.20      |                   |                   |              |
| PANSS negative                       | 15.07 ± 7.54      |                   |                   |              |
| PANSS composite                      | −2.65 ± 5.83      |                   |                   |              |
| PANSS general                        | 30.71 ± 11.62     |                   |                   |              |
| psychopathology                      |                   |                   |                   |              |
| HDRS total score                     | 7.06 ± 5.17       |                   | 11.10 ± 5.28      | \(F_{(1,79)} = 12.39\) *** |
| YMRS total score                     | 3.16 ± 3.13       |                   |                   |              |

BD + SUD: bipolar disorder with comorbid substance use disorder; HDRS: Hamilton depression rating scale; MDD + SUD: major depressive disorder with comorbid substance use disorder; PANSS: positive and negative syndrome scale; SMI: severe mental illness; SUD: substance use disorder; SZ + SUD: schizophrenia with comorbid substance use disorder; YMRS: Young mania rating scale. a Percentages will not equal 100 as each patient may have taken more than one substance/more than one drug. * \(p < 0.05\); *** \(p < 0.001\).

In reference to the clinical variables related to SUD (see Table 3), the age of onset of the SUD was 18.79 years \((SD = 6.67)\) with no differences between the groups. Polydrug use was the main pattern of substance use in the total sample \((56.7\%)\), with the SZ + SUD group having the highest rate of polydrug patients of the three groups \((p = 0.015)\). The main psychoactive substances consumed were cocaine, alcohol and cannabis, with some significant differences among the groups. The BD + SUD group had the lowest percentage of cocaine use \((p = 0.001)\) while the SZ + SUD group had the highest percentages of cannabis use \((p = 0.004)\), hallucinogens \((p = 0.024)\) and anxiolytic/hypnotic-sedative drugs \((p = 0.017)\). The SZ + SUD and BD + SUD groups had the highest daily cigarette consumption and a higher score on the Fagerström dependence test than the MDD + SUD group \((p ≤ 0.029)\). Significant differences were observed among the groups in severity of addiction \((DAST-20)\); the means of the SZ + SUD and MDD + SUD groups were within the high severity category differing from the BD + SUD group \((p = 0.009)\) with mild severity. The abstinence period of the total sample was 9.69 months on average \((SD = 7.31)\) and the groups did not differ from each other.
Table 3. Clinical data for the three groups of patients regarding substance use and substance use disorder. Means, standard deviation, percentages and statistical contrasts (ANOVA and chi-square test).

| Clinical Data                  | SZ + SUD (N = 40) | BD + SUD (N = 40) | MDD + SUD (N = 40) | Contrasts |
|--------------------------------|-------------------|-------------------|--------------------|-----------|
| SUD age of onset (years)       | 17.50 ± 5.19      | 20.33 ± 7.51      | 18.55 ± 6.94       | $F_{(2,119)} = 3.39$ |
| SUD duration (years)           | 17.49 ± 5.57      | 18.23 ± 9.10      | 21.25 ± 8.59       | $F_{(2,119)} = 2.12$ |
| Quantity of substances used    | 3.74 ± 1.44       | 2.54 ± 1.19       | 2.95 ± 1.41        | $F_{(2,119)} = 7.35$*** |
| Polydrug use                   | 82.5%             | 37.5%             | 50.0%              | $X^2(1) = 38.67$* |
| Type of substance $^a$          |                   |                   |                    |           |
| Cannabis                       | 97.5%             | 65.0%             | 82.5%              | $X^2(1) = 14.14$*** |
| Alcohol                        | 75.0%             | 87.5%             | 90.0%              | $X^2(1) = 3.46$ |
| Cannabis                       | 82.5%             | 47.5%             | 57.5%              | $X^2(1) = 11.09$** |
| Ecstasy                        | 17.5%             | 10.0%             | 5.0%               | $X^2(1) = 3.27$ |
| Hallucinogens                  | 40.0%             | 15.0%             | 20.0%              | $X^2(1) = 7.46$* |
| Opioids                        | 30.0%             | 12.5%             | 25.0%              | $X^2(1) = 3.72$ |
| Anxiolytic/hypnotic-sedative   | 32.5%             | 10.0%             | 12.5%              | $X^2(1) = 8.12$* |
| Daily cigarettes per day       | 21.62 ± 11.29     | 19.35 ± 9.13      | 13.83 ± 7.36       | $F_{(2,119)} = 7.61$*** |
| Fagerström total score         | 6.10 ± 2.60       | 5.03 ± 2.86       | 4.26 ± 2.41        | $F_{(2,119)} = 4.85$** |
| DAST-20 total score            | 12.89 ± 3.03      | 11.17 ± 4.98      | 13.47 ± 4.04       | $F_{(2,119)} = 2.35$ |
| Severity of addiction          |                   |                   |                    | $X^2(3) = 20.47$** |
| Low                            | 3.7%              | 20.8%             | 3.3%               |           |
| Mild                           | 14.8%             | 33.4%             | 16.7%              |           |
| High                           | 70.4%             | 25.0%             | 50.0%              |           |
| Severe                         | 11.1%             | 20.8%             | 30.0%              |           |
| Abstinence period (months)      | 11.13 ± 5.68      | 9.70 ± 6.69       | 8.22 ± 5.72        | $F_{(2,119)} = 0.74$ |
| Quantity of relapses           | 1.60 ± 3.38       | 0.90 ± 1.85       | 0.75 ± 1.30        | $F_{(2,119)} = 1.53$ |

BD + SUD: bipolar disorder with comorbid substance use disorder; DAST-20: drug abuse screening test; MDD + SUD: major depressive disorder with comorbid substance use disorder; SUD: substance use disorder; SZ + SUD: schizophrenia with comorbid substance use disorder. * Percentages will not equal 100 as each patient may have taken more than one substance/more than one drug. ** $p < 0.05$; *** $p < 0.01$; **** $p < 0.001$.

3.2. Comparisons of Neurocognitive Performance among the Groups and Considering Normative Data

The estimation of the verbal premorbid IQ (vocabulary test) did not provide differences among groups ($F_{(2,119)} = 1.687; p = 0.189; \eta^2 = 0.028$), with Z values in the three cases close to the normative mean: SZ + SUD = −0.27 ± 0.13; BD + SUD = 0.26 ± 0.15, and SUD + MDD = 0.29 ± 0.12. The result in the digit test was similar among the different groups ($F_{(2,119)} = 1.647; p = 0.197; \eta^2 = 0.028$) with group Z-scores and standard error of: SZ + SUD = −0.41 ± 0.14, BD + SUD = −0.28 ± 0.15, and MDD + SUD = −0.05 ± 0.13. As can be seen in Table 4, significant differences were obtained among groups in the performance of the RAVLT and TMT-B tasks. In the RAVLT, SZ + SUD presented the lowest performance in total words compared with BD + SUD and MDD + SUD ($p < 0.01$ in both cases) while these last two groups did not show any significant differences between them ($p = 1.000$). Recognition was worse for SZ + SUD compared to MDD + SUD ($p = 0.002$) while the BD + SUD group was in an intermediate position with no differences compared with SZ + SUD and BD + SUD ($p \geq 0.103$).

On the other hand, the repeated measures analysis of the RAVLT provided significant differences among the groups in the learning curve (see Figure 1). The SZ + SUD group obtained the lowest performance ($F_{(2,119)} = 4.078; p = 0.004; \eta^2 = 0.126$), with respect to both BD + SUD ($p = 0.003$) and MDD + SUD ($p = 0.006$). The learning curve (trials A1 to A5) of the BD + SUD and MDD + SUD groups was similar ($p = 1.000$). Trial A1 of the RAVLT presented differences ($F_{(2,119)} = 3.418; p = 0.036; \eta^2 = 0.056$), with the performance of the SZ + SUD being lower than BD + SUD ($p = 0.034$), while the MDD + SUD group was in an intermediate position. No differences were observed among the groups in trial A2 ($F_{(2,119)} = 2.844; p = 0.062; \eta^2 = 0.040$). On the other hand, trials A3, A4 and A5 showed a worse execution of the task for the SZ + SUD group ($F_{(2,119)} \geq 4.271; p \leq 0.016; \eta^2 \geq 0.070$), their performance was inferior to that of the BD + SUD ($p \leq 0.037$) and MDD + SUD ($p \leq 0.022$) groups. Considering the normative data, all three groups performed below
average on the learning curve (see Figure 1). Moreover, no differences among the groups were observed in the comparison of A5 vs. A7 trials for the delayed recall ($F_{(2,119)} = 1.80$; $p = 0.170$; $\eta^2 = 0.030$) nor for trial A7 vs. Rec A/15 for encoding and recall with cues ($F_{(2,119)} = 0.916; p = 0.403; \eta^2 = 0.016$).

Table 4. Results for the three groups of patients in: RAVLT (Rey Auditory Verbal Learning Test), Trial Making Test (TMT A and B), Wisconsin Card Sorting Tests (WCST) and Tower of Hanoi. Means (in Z scores), standard error and statistical contrasts of the MANCOVA (Multiple Analysis of Covariance).

|                  | SZ + SUD (N = 40) | BD + SUD (N = 40) | MDD + SUD (N = 40) | MANCOVA $F_{(2,119)}$ | $\eta^2_p$ |
|------------------|------------------|------------------|------------------|-------------------------|------------|
| RAVLT            |                  |                  |                  |                         |            |
| Total words      | $-2.00 \pm 0.18$ | $-1.10 \pm 0.19$ | $-1.11 \pm 0.17$ | $7.60 ***$               | 0.119      |
| Recog. list A/15 | $-1.80 \pm 0.24$ | $-0.98 \pm 0.25$ | $-0.60 \pm 0.23$ | $6.25 **$                | 0.097      |
| Trial Making Test|                  |                  |                  |                         |            |
| TMT-A            | $-0.60 \pm 0.19$ | $-0.58 \pm 0.20$ | $-0.22 \pm 0.18$ | $1.58$                  | 0.027      |
| TMT-B            | $-0.70 \pm 0.17$ | $-1.02 \pm 0.18$ | $-0.27 \pm 0.16$ | $4.42 *$                | 0.073      |
| WCST             |                  |                  |                  |                         |            |
| Categories completed | $5.53 \pm 0.21$ | $5.40 \pm 0.19$ | $5.43 \pm 0.20$ | $0.108$                 | 0.002      |
| Total errors     | $19.73 \pm 2.27$ | $20.72 \pm 2.25$ | $20.55 \pm 2.26$ | $0.054$                 | 0.001      |
| Z scores         | $0.76 \pm 0.19$  | $0.50 \pm 0.18$  | $0.45 \pm 0.17$  | $0.786$                 | 0.013      |
| Percentage of errors | $19.25 \pm 1.55$ | $19.10 \pm 1.53$ | $19.90 \pm 1.54$ | $0.076$                 | 0.001      |
| Z scores for percentage | $0.73 \pm 0.20$ | $0.62 \pm 0.18$ | $0.51 \pm 0.17$ | $0.359$                 | 0.006      |
| Perseverative errors | $5.46 \pm 0.98$ | $6.22 \pm 0.97$ | $6.67 \pm 0.96$ | $0.386$                 | 0.007      |
| Z scores         | $2.19 \pm 0.22$  | $1.69 \pm 0.21$  | $1.59 \pm 0.20$  | $2.197$                 | 0.036      |
| Percentage perseverative errors | $4.71 \pm 0.75$ | $5.16 \pm 0.74$ | $5.90 \pm 0.76$ | $0.645$                 | 0.011      |
| Z scores for percentage | $2.45 \pm 0.19$ | $2.10 \pm 0.20$ | $1.95 \pm 0.21$ | $1.584$                 | 0.027      |
| Tower of Hanoi   |                  |                  |                  |                         |            |
| N° of movements  | $25.46 \pm 1.71$ | $25.10 \pm 1.78$ | $29.05 \pm 1.72$ | $1.589$                 | 0.028      |
| Errors           | $1.25 \pm 0.39$  | $1.49 \pm 0.40$  | $1.36 \pm 0.39$  | $0.910$                 | 0.002      |
| Response time    | $211.35 \pm 22.26$ | $202.55 \pm 23.27$ | $246.42 \pm 22.38$ | $1.055$                 | 0.019      |

BD + SUD: bipolar disorder with comorbid substance use disorder; MDD + SUD: major depressive disorder with comorbid substance use disorder; SZ + SUD: schizophrenia with comorbid substance use disorder; $\eta^2_p$: Partial eta squared. * = $p < 0.05$; ** = $p < 0.01$; *** = $p < 0.001$.

Moreover, TMT-A results were not associated with significant differences among groups, although in all three cases processing speed was slower than that of the normal population. In the case of TMT-B, it was the BD + SUD group that presented worse cognitive flexibility with respect to MDD + SUD ($p = 0.011$), with the SZ + SUD group in an intermediate position and with no differences with respect to BD + SUD or MDD + SUD ($p \geq 0.275$).

Performance on the WSCT and Tower of Hanoi tasks (see Table 4) did not provide significant differences among groups. In the case of the WSCT, the performance of the three groups was also within normative values (Z between 1 and −1), with the exception of the number and percentage of perseverative errors where the performance of all three groups was above normative values (Z ≥ 1.5).

The results in Z scores according to the cognitive functions assessed (see Figure 2) indicated differences among groups for attention ($F_{(2,119)} = 3.933; p = 0.037; \eta^2 = 0.051$), verbal learning ($F_{(2,119)} = 7.087; p = 0.001; \eta^2 = 0.115$), short-term memory ($F_{(2,119)} = 6.653; p = 0.002; \eta^2 = 0.109$) and recognition ($F_{(2,119)} = 6.252; p = 0.003; \eta^2 = 0.103$), as well as in global performance ($F_{(2,119)} = 7.332; p = 0.001; \eta^2 = 0.19$). In all cases, the SZ + SUD group presented the worst performance and altered values (Z ≤ −1.5) in verbal learning, short-term memory and recognition. In contrast, no differences were found in the domains of processing speed ($F_{(2,119)} = 1.198; p = 0.306; \eta^2 = 0.022$) and cognitive flexibility ($F_{(2,119)} = 2.100; p = 0.127 \eta^2 = 0.037$).
indicated differences among groups for attention (\( \eta^2 = 0.022 \)) and cognitive flexibility (\( \eta^2 = 0.016 \)). In the case of the WSCT, the performance of the A5 vs. A7 trials was lower than that of the normal \( p < 0.05 \) and \( p < 0.01 \), respectively. Considering the normative data, all three groups performed below average in an intermediate position. No differences were observed among the groups in trial A2 \( F(2,119) = 1.198; p = 0.306 \) for encoding and recall with cues, although in all three cases processing speed was slower than that of the normal group \( F(2,119) = 7.087; p = 0.001; \eta^2 = 0.19 \). In all cases, the SZ + SUD group presented the worst performance and altered values (Z = 0.403; \( p < 0.05 \)).

The neurocognitive performance findings are consistent with previous studies \([15,16,26,30]\) since a performance below normative means was observed in our sample of alcohol, cocaine and cannabis use, as well as the type of patients receiving SUD treatment. *Moreover, TMT-A results were not associated with significant differences among groups, although in all three cases processing speed was slower than that of the normal group. *In all cases, the SZ + SUD group presented a worse social and clinical situation. Such characteristics are relevant since in previous studies they have been related to poorer adherence to the treatment \([53]\), clinical course \([55,57]\), and comorbid substance use disorder. *Figure 1. Learning curve in Z scores for the Rey Auditory Verbal Learning Test trials by groups. SZ + SUD: schizophrenia with comorbid substance use disorder; BD + SUD: bipolar disorder with comorbid substance use disorder; MDD + SUD: major depressive disorder and comorbid substance use disorder. *\( p < 0.05 \); **\( p < 0.01 \).

The results in Z scores according to the cognitive functions assessed (see Figure 2) are as follows:

- **Attention**
- **Verbal Learning**
- **Short Term Memory**
- **Recognition**
- **Processing Speed**
- **Cognitive Flexibility**
- **Global Performance**

**Note:** Attention is composed by digits (WAIS III) and A1 (RAVLT). Verbal learning refers to total words (RAVLT). Short term memory is composed by A6 (RAVLT). Recognition refers to Recog. list A/15 (RAVLT). Processing speed is TMT-A. Cognitive flexibility was calculated from Wisconsin Sort Card Test and TMT-B. SZ + SUD: schizophrenia with comorbid substance use disorder; BD + SUD: bipolar disorder with comorbid substance use disorder; MDD + SUD: major depressive disorder and comorbid substance use disorder. *\( p < 0.05 \); **\( p < 0.01 \); ***\( p \leq 0.001 \).

**Figure 2.** Z scores on the assessed cognitive domains for each of the groups. **Note:** Attention is composed by digits (WAIS III) and A1 (RAVLT). Verbal learning refers to total words (RAVLT). Short term memory is composed by A6 (RAVLT). Recognition refers to Recog. list A/15 (RAVLT). Processing speed is TMT-A. Cognitive flexibility was calculated from Wisconsin Sort Card Test and TMT-B. SZ + SUD: schizophrenia with comorbid substance use disorder; BD + SUD: bipolar disorder with comorbid substance use disorder; MDD + SUD: major depressive disorder and comorbid substance use disorder. *\( p < 0.05 \); **\( p < 0.01 \); ***\( p \leq 0.001 \).
4. Discussion

Contrary to our expectations, dual disorders showed different cognitive profiles in patients with comorbid SZ, BD and MDD. Thus, the neurocognitive functioning of dual disorders was influenced by the comorbid SMI, with the SZ + SUD group showing higher impairments. To the best of our knowledge, this study provides the first data on the possible differences in cognitive performance for patients with dual disorders according to their diagnosis of SMI. The sociodemographic and clinical characteristics of the patients in our sample are in line with previous studies [51,52] with the SZ + SUD group showing a worse social and clinical situation. Such characteristics are relevant since in previous studies they have been related to poorer adherence to the treatment [53], clinical course and prognosis [54]. The results for the type of drug used in the total sample and for each group reflect the current state of SUDs in our population [55,56] with a high prevalence of alcohol, cocaine and cannabis use, as well as the type of patients receiving SUD treatment [55,57]. The neurocognitive performance findings are consistent with previous studies [15,16,26,30] since a performance below normative means was observed in our sample regardless of the comorbidity combination. It should be specified, however, that patients with SZ + SUD are those who presented the worst performance in functions such as attention, learning ability and memory. Our results on the performance of each group extend previous findings [22,24,25] to patients in the early remission phase of SUD and to those with an SZ + SUD diagnosis with stabilized psychotic symptomatology.

Through the analysis of the learning curve, it has been shown that patients with SZ + SUD perform worse as the test progresses without the beneficial effect of repetition or verbal learning, and this performance pattern is not found in patients with BD + SUD or MDD + SUD (Figure 1). All this supports the evidence that verbal declarative memory is one of the most altered functions in patients with SZ + SUD and could be considered an indicator or endophenotype of schizophrenia spectrum disorders [23,58].

Regarding the results in executive functions measured by the TMT-B and WSCT, the performance of the groups was similar to previously published data [47,59] as well as to normative values. Performance on the TMT-B test was worse in BD + SUD patients, which has also been observed in BD patients without substance use [60]; in the future, this finding should be explored as a possible trait or cognitive correlate differentiating BD + SUD patients from those with MDD + SUD.

On the other hand, performance on the WSCT was similar among the different groups and with respect to normative data. This is not consistent with previous studies that found a worse performance on executive functions for patients with SUD [61] and/or SZ [17], BD [27] or MDD [30]. However, the study by Verdejo-García and Pérez-García (2007) which suggested that WSCT would not be an adequate test to discriminate performance between patients with SUD and healthy controls, should be considered. Our data are in this line and extend such observations to dual patients regardless of the comorbid SMI considered. A possible explanation for this normative executive performance in our patients may be that they are in the early remission phase of SUD, being well known for the benefit of the months of abstinence for the recovery of executive functions [62,63].

A noteworthy finding was the better performance of the groups in the number and percentage of perseverative WSCT errors compared to the general population. This better performance was not reflected in the number of categories completed, attempts to complete the first category or in the learning to learn score. Perseverative errors occur when the subject gives a response adjusted to the previously learned strategy [45]. Thus, the lower number with respect to the normal population would indicate a quick change in criterion or an unreflective way of responding to the test. This result could also be valued as an indicator of functional impulsivity, related to the rapid generation of ideas and decision-making [64].

At the global performance level, the score that includes all the evaluated domains shows differences among groups, being the patients with SZ + SUD those who presented the worst performance compared with BD + SUD and MDD + SUD patients. Although all three groups obtained scores below the normative mean, it is the score of the SZ + SUD...
group that can be considered altered in neuropsychological terms. Considering the presence of the two diagnoses in the patients studied, an important alteration in their cognitive performance could be expected, which does not occur in the BD + SUD and MDD + SUD groups. A possible explanation is found in the theoretical framework that points out a lower biological vulnerability in dual disorders with respect to SMI without comorbidity [19,47]. Patients with dual disorders would start from a better premorbid functioning that would have allowed them a level of social functioning to acquire illegal substances of abuse [65] and have ended up developing the SMI possibly as a result of drug abuse.

The present study has strengths and limitations. One of its strengths is that it represents a first approximation of the cognitive performance profile of patients with dual disorders according to their diagnosis of SMI, exploring their cognitive functions with a wide battery of tests. Likewise, having considered Z scores according to scales has allowed comparison with normative data, and controlling for the effect of age on performance. However, the study has limitations such as having a sample with a majority pattern of polydrug use that does not allow discriminating of the possible differential effect of the psychoactive substance and not controlling the possible effect of medication among groups. The differences among the groups in the type of medication are according to the expected (since it is related to the type of SMI) but it might influence their cognitive performance. Oncoming studies should consider the type and dose of pharmacological treatment and their possible influence on patients with SMI and SUD. Moreover, we did not include women to assess the different profiles according to sex or longitudinal measures that allow analysing of the evolution of cognitive functions as the treatment received by the patient progresses. In this sense, including both inpatients and outpatients in or sample might be considered a limitation of this work. Some evidence shows that inpatients have worse cognitive performance than outpatients [66] while other data indicate that such differences are not significant or observed [67]. Future studies should include larger sample sizes that allow analyses to explore the differences associated with the type of treatment beyond the SMI. Our data emphasize that the pattern of cognitive performance observed in SZ + SUD patients is more similar to the deficits found in SZ than in SUD, pointing to the need to assess neurocognition in these dual patients. This may help to incorporate rehabilitation strategies during treatment, which seems to be of particular relevance in the SZ + SUD group, as is the case with SZ diagnosis alone [68]. Likewise, the impairment of memory functions for SZ + SUD should be considered in the design of treatment programs as it implies a limitation in the ability to learn and recognize information that may negatively affect treatment adherence [69].

5. Conclusions

This study explored the neurocognitive profiles in the three most severe and prevalent psychiatric diagnoses in patients with dual disorders. The SZ + SUD group presented an altered performance in memory, short-term memory, verbal learning and global performance, supporting previous studies that point to alterations in declarative memory as putative indicators or endophenotypes of SZ spectrum disorders. The neurocognitive performance profile in patients with SZ + SUD points to a greater vulnerability, emphasizing the need for its evaluation and consideration for incorporating cognitive rehabilitation strategies that may be essential for the success of the therapeutic approach with these patients.

Author Contributions: Conceptualisation, A.A.; methodology, A.A., A.G.-S. and J.E.M.-A.; validation, A.A., A.G.-S. and J.E.M.-A.; formal analysis, A.A., A.G.-S. and J.E.M.-A.; investigation, A.G.-S. and J.E.M.-A.; resources, A.A.; data curation, A.A.; writing—original draft preparation, A.A., A.G.-S. and J.E.M.-A.; writing—review and editing, A.A., A.G.-S., J.E.M.-A., J.F.N. and R.P.; visualisation, A.A., A.G.-S., J.E.M.-A., J.F.N. and R.P.; supervision, A.A.; project administration, A.A.; funding acquisition, A.A. All authors have read and agreed to the published version of the manuscript.
**Funding:** This research was funded by the grant PID2020-117767GB-I00 of Spanish Ministry of Science and Innovation (MCIN/AEI/10.13039/501100011033) and the Generalitat de Catalunya (2017SGR-748).

**Institutional Review Board Statement:** The study was conducted in accordance with the Declaration of Helsinki and approved by the Research Committee of the University of Barcelona (protocol code IRB00003099).

**Informed Consent Statement:** Informed consent was obtained from all subjects involved in the study.

**Data Availability Statement:** The data presented in this study are available on request from the corresponding author.

**Acknowledgments:** We thank Projecte Home Catalunya, ATRA Association, Mental Health of Althaia Foundation, and Dianova International Association for providing the sample of the study.

**Conflicts of Interest:** The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

**References**

1. Keen, C.; Kinner, S.A.; Young, J.T.; Jang, K.; Gan, W.; Samji, H.; Zhao, B.; Krausz, M.; Slaunwhite, A. Prevalence of co-occurring mental illness and substance use disorder and association with overdose: A linked data cohort study among residents of British Columbia, Canada. *Addiction* **2022**, *117*, 129–140. [CrossRef] [PubMed]

2. Zubiri, A.; Waqas, A.; Naveed, S.; Hossain, M.M.; Rahman, A.; Saeed, K.; Fuhr, D.C. Prevalence of mental disorders in the WHO eastern mediterranean region: A systematic review and meta-analysis. *Front. Psychiatry* **2021**, *12*, 1035. [CrossRef] [PubMed]

3. Hunt, G.E.; Malhi, G.S.; Lai, H.M.X.; Cleary, M. Prevalence of comorbid substance use in major depressive disorder in community and clinical settings, 1990–2019: Systematic review and meta-analysis. *J. Affect. Disord.* **2020**, *266*, 288–304. [CrossRef] [PubMed]

4. Arnau, F.; Benito, A.; Villar, M.; Ortega, M.E.; López-Peláez, L.; Haro, G. Addressing dual disorders in a medium-term admission unit. *Brain Sci.* **2022**, *12*, 24. [CrossRef]

5. Hunt, G.E.; Large, M.M.; Cleary, M.; Lai, H.M.X.; Saunders, J.B. Prevalence of comorbid substance use in schizophrenia spectrum disorders in community and clinical settings, 1990–2017: Systematic review and meta-analysis. *Drug Alcohol Depend.* **2019**, *191*, 234–258. [CrossRef]

6. Lai, H.M.X.; Cleary, M.; Sitharthan, T.; Hunt, G.E. Prevalence of comorbid substance use, anxiety and mood disorders in epidemiological surveys, 1990–2014: A systematic review and meta-analysis. *Drug Alcohol Depend.* **2015**, *154*, 1–13. [CrossRef]

7. Almeida, P.P.; de Araújo Filho, G.M.; Malta, S.M.; Laranjeira, R.R.; Marques, A.C.R.P.; Bressan, R.A.; Lacerda, A.L.T. Attention and memory deficits in crack-cocaine users persist over four weeks of abstinence. *J. Subst. Abuse Treat.* **2017**, *81*, 73–78. [CrossRef]

8. Verdejo-Garcia, A.; Garcia-Fernandez, G.; Dom, G. Cognition and addiction. *Dialogues Clin. Neurosci.* **2019**, *21*, 281–290. [CrossRef]

9. Capella, M.D.M.; Benaiiges, I.; Adan, A. Neuropsychological performance in polyconsumer men under treatment. Influence of age of onset of substance use. *Sci. Rep.* **2015**, *5*, 12038. [CrossRef]

10. Scott, J.C.; Lynch, K.G.; Cenkner, D.P.; Kehle-Forbes, S.M.; Polusny, M.A.; Gur, R.C.; Chen, S.; Foa, E.B.; Oslin, D.W. Neurocognitive predictors of treatment outcomes in psychotherapy for comorbid PTSD and substance use disorders. *J. Consult. Clin. Psychol.* **2021**, *89*, 937–946. [CrossRef]

11. Rezapour, T.; DeVito, E.E.; Sofuoglu, M.; Ekhtiari, H. Perspectives on neurocognitive rehabilitation as an adjunct treatment for addictive disorders: From cognitive improvement to relapse prevention. In *Progress in Brain Research*; Ekhtiari, H., Paulus, M.P., Eds.; Elsevier: Cham, Switzerland, 2016; Volume 224, pp. 345–369.

12. Scott, T.M.; Arnsen, J.; Olsen, J.P.; Arias, F.; Cunningham, C.O.; Rivera Mindt, M. Neuropsychiatric, psychiatric, and substance use characteristics in a diverse sample of persons with OUD who are starting methadone or buprenorphine/naloxone in opioid treatment programs. *Addict. Sci. Clin. Pract.* **2021**, *16*, 64. [CrossRef] [PubMed]

13. Castine, B.R.; Albein-Urios, N.; Lozano-Rojas, O.; Martinez-Gonzalez, J.M.; Hohwy, J.; Verdejo-Garcia, A. Self-awareness deficits associated with lower treatment motivation in cocaine addiction. *Am. J. Drug Alcohol Abuse* **2019**, *45*, 108–114. [CrossRef] [PubMed]

14. Adan, A.; Arredondo, A.Y.; Capella, M.D.M.; Prat, G.; Forero, D.A.; Navarro, J.F. Neurobiological underpinnings and modulating factors in schizophrenia spectrum disorders with a comorbid substance use disorder: A systematic review. *Neurosci. Biobehav. Rev.* **2017**, *75*, 361–377. [CrossRef] [PubMed]

15. Balanza-Martinez, V.; Crespo-Facorro, B.; Gonzalez-Pinto, A.; Vieta, E. Bipolar disorder comorbid with alcohol use disorder: Focus on neurocognitive correlates. *Front. Physiol.* **2015**, *6*, 108. [CrossRef]

16. Hunt, S.A.; Kay-Lambkin, F.J.; Baker, A.L.; Michie, P.T. Systematic review of neurocognition in people with co-occurring alcohol misuse and depression. *J. Affect. Disord.* **2015**, *179*, 51–64. [CrossRef] [PubMed]

17. Scholes, K.E.; Martin-Iverson, M.T. Cannabis use and neuropsychological performance in healthy individuals and patients with schizophrenia. *Psychol. Med.* **2010**, *40*, 1635–1646. [CrossRef]

Acknowledgments: We thank Projecte Home Catalunya, ATRA Association, Mental Health of Althaia Foundation, and Dianova International Association for providing the sample of the study.

Conflicts of Interest: The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.
18. Schnakenberg Martin, A.M.; Bonfils, K.A.; Davis, B.J.; Smith, E.A.; Schuder, K.; Lysaker, P.H. Compared to high and low cannabis use, moderate use is associated with fewer cognitive deficits in psychosis. *Schizophr. Res. Cogn.* 2016, 6, 15–21. [CrossRef]

19. Schnell, T.; Koethe, D.; Daumann, J.; Gouzoulis-Mayfrank, E. The role of cannabis in cognitive functioning of patients with schizophrenia. *Psychopharmacology* 2009, 205, 45–52. [CrossRef]

20. Lepage, M.; Bodnar, M.; Bowie, C.R. Neurocognition: Clinical and functional outcomes in schizophrenia. *Can. J. Psychiatry* 2014, 59, 5–12. [CrossRef]

21. Epstein, K.A.; Kumra, S. Executive attention impairment in adolescents with schizophrenia who have used cannabis. *Schizophr. Res.* 2014, 157, 48–54. [CrossRef]

22. Shah, R.; Ghosh, A.; Avasthi, A.; Nehra, R.; Ahuja, C.K.; Khandelwal, N. Do neurocognitive functions in cannabis induced psychosis groups differ from schizophrenia with cannabis use? A controlled cross-sectional study. *Int. J. Psychiatry Clin. Pract.* 2021, 25, 283–291. [CrossRef]

23. Benaiges, I.; Serra-Grabulosa, J.M.; Adan, A. Neuropsychological functioning and age-related changes in schizophrenia and/or cocaine dependence. *Prog. Neuro-Psychopharmacol. Biol. Psychiatry* 2013, 40, 298–305. [CrossRef] [PubMed]

24. Bogaty, S.E.R.; Lee, R.S.C.; Hickie, I.B.; Hermens, D.F. Meta-analysis of neurocognition in young psychosis patients with current cannabis use. *J. Psychiatr. Res.* 2018, 99, 22–32. [CrossRef] [PubMed]

25. Smith, M.J.; Cobia, D.J.; Wang, L.; Alpert, K.I.; Cronenwett, W.J.; Goldman, M.B.; Manah, D.; Barch, D.M.; Breiter, H.C.; Csernansky, J.G. Cannabis-related working memory deficits and associated subcortical morphological differences in healthy individuals and schizophrenia subjects. *Schizophr. Bull.* 2014, 40, 287–299. [CrossRef] [PubMed]

26. Li, C.; Palka, J.M.; Brown, E.S. Cognitive impairment in individuals with bipolar disorder with and without comorbid alcohol and/or cannabis use disorders. *J. Affect. Disord.* 2020, 272, 355–362. [CrossRef]

27. Marshall, D.F.; Walker, S.J.; Ryan, K.A.; Kamali, M.; Saunders, E.F.H.; Weldon, A.L.; Adams, K.M.; McInnis, M.G.; Langenecker, S.A. Greater executive and visual memory dysfunction in comorbid bipolar disorder and substance use disorder. *Psychojtry Res.* 2012, 200, 252–257. [CrossRef]

28. Levy, B.; Manove, E.; Weiss, R.D. Recovery of cognitive functioning in patients with co-occurring bipolar disorder and alcohol dependence during early remission from an acute mood episode. *Ann. Clin. Psychiatry* 2012, 24, 143–154. [CrossRef]

29. Prisciandaro, J.J.; Mellick, W.; Mitaro, E.; Tolliver, B.K. An evaluation of the impact of co-occurring anxiety and substance use disorder on bipolar disorder illness outcomes in STEP-BD. *J. Affect. Disord.* 2019, 246, 794–799. [CrossRef]

30. Hermens, D.F.; Lee, R.S.C.; De Regt, T.; Lagopoulos, J.; Naismith, S.L.; Scott, E.M.; Hickie, I.B. Neuropsychological functioning is compromised in binge drinking young adults with depression. *Psychojtry Res.* 2013, 210, 256–262. [CrossRef]

31. Liu, I.C.; Chiu, C.H.; Yang, T.T. The effects of gender and a co-occurring depressive disorder on neurocognitive functioning in patients with alcohol dependence. *Alcohol Alcohol.* 2010, 45, 231–236. [CrossRef]

32. Uekermann, J.; Daum, I.; Schlebusch, P.; Wiebel, B.; Trenchmann, U. Depression and cognitive functioning in alcoholism. *Addiction* 2003, 98, 1521–1529. [CrossRef] [PubMed]

33. American Psychiatric Association DSM-5. *Diagnostic and Statistical Manual of Mental Disorders*: APA; Washington, DC, USA, 2013.

34. First, M.B.; Spitzer, R.L.; Gibbon, M.; Williams, J.B.W. *Diagnostic and Statistical Manual of Mental Disorders*, Versión Clínica. Masson: Barcelona, Spain, 1999.

35. Gálvez, B.P.; Fernández, L.G. Validación española del Drug Abuse Screening Test (DAST-20 y DAST-10). *Health Addict.* 2010, 10, 35–50.

36. Peraltá, V.; Cuesta, M.J. Validación de la escala de los síndromes positivo y negativo (PANSS) en una muestra de esquizofrénicos españoles. *Actas Luso-Esp. Neurol. Psiquiatr. Cienc. Afines* 1994, 22, 171–177.

37. Colom, F.; Vieta, E.; Martinez-Arán, A.; García-García, M.; Reinares, M.; Torrent, C.; Goikolea, J.; Banús, S.; Salamero, M. Versión española de una escala de evaluación de la manía: Validez y fiabilidad de la escala de Young. *Med. Clin.* 2002, 119, 366–371. [CrossRef]

38. Bobes, J.; Bulbena, A.; Luque, A.; Dal-Re, R.; Ballesteros, J.; Ibarra, N. Evaluación psicométrica comparativa de las versiones en español de 6, 17 y 21 ítems de la Escala de Valoración de Hamilton para la evaluación de la depresión. *Med. Clin.* 2003, 120, 693–700. [CrossRef]

39. Wechsler, D. *WAIS-III: Test de Inteligencia Para Adultos de Wechsler*; Paidós: Buenos Aires, Argentina, 2002.

40. Boone, D.E. WAIS-R scatter with psychiatric inpatients: I Intrastest scatter. *Psychol. Rep.* 1992, 71, 483–487.

41. Schmidt, L.M.; Hesse, M.; Lykke, J. The impact of substance use disorders on the course of schizophrenia—A 15-year follow-up study. *Schizophr. Res.* 2011, 130, 228–233. [CrossRef]

42. Van der Elst, W.; van Boxtel, M.P.J.; van Breukelen, G.J.P.; Jolles, J. Rey’s verbal learning test: Normative data for 1855 healthy adults. *J. Int. Neuropsychol. Soc.* 2005, 11, 290–302. [CrossRef]

43. Reed, J.C.; Reed, H.B.C. The Halstead—Reitan Neuropsychological Battery. In *Contemporary Approaches to Neuropsychological Assessment. Critical Issues in Neuropsychological Assessment*. Goldstein, G., Incagnoli, T.M., Eds.; Springer: Boston, MA, USA, 1997; pp. 93–129.

44. Tamayo, F.; Casals-Coll, M.; Sánchez-Benavides, G.; Quintana, M.; Manero, R.M.; Rognoni, T.; Calvo, L.; Palomo, R.; Aranciva, F.; Peña-Casanova, J. Estudios normativos españoles en población adulta joven (Proyecto NEURONORMA jóvenes): Normas para las pruebas span verbal, span visuospatial, letter-number sequencing, Trail Making Test y symbol digit modalities Test. *Neurología* 2012, 27, 319–329. [CrossRef]
45. Heaton, R. WCST-CV4. Wisconsin Card Sorting Test®: Computer Version 4–Research Edition; Psychological Assessment Resources: Lutz, FL, USA, 2003.

46. Humes, G.E.; Welsh, M.C.; Retzlaff, P.; Cookson, N. Towers of hanoi and london: Reliability and validity of two executive function tasks. Assessment 1997, 4, 249–257. [CrossRef]

47. Benaihgs, I.; Serra-Grabulosa, J.M.; Prat, G.; Adan, A. Executive functioning in individuals with schizophrenia and/or cocaine dependence. Hum. Psychopharmacol. 2013, 28, 29–39. [CrossRef] [PubMed]

48. Horelyck, L.D.; Obenhansen, K.; Jansari, A.; Ullum, H.; Miskowiak, K.W. Virtual reality assessment of daily life executive functions in mood disorders: Associations with neuropsychological and functional measures. J. Affect. Disord. 2021, 280, 478–487. [CrossRef] [PubMed]

49. Miskowiak, K.W.; Petersen, J.Z.; Ott, C.V.; Knorr, U.; Kessing, L.V.; Gallagher, P.; Robinson, L. Predictors of the discrepancy between objective and subjective cognition in bipolar disorder: A novel methodology. Acta Psychiatr. Scand. 2016, 134, 511–521. [CrossRef] [PubMed]

50. Richardson, J.T.E. Eta squared and partial eta squared as measures of effect size in educational research. Educ. Res. Rev. 2011, 6, 135–147. [CrossRef]

51. Serrano-Serrano, A.B.; Marquez-Arrico, J.E.; Navarro, J.F.; Martinez-Nicolas, A.; Adan, A. Circadian characteristics in patients under treatment for substance use disorders and severe mental illness (schizophrenia, major depression and bipolar disorder). J. Clin. Med. 2021, 10, 4388. [CrossRef]

52. Marquez-Arrico, J.E.; Rio-Martinez, L.; Navarro, J.F.; Prat, G.; Adan, A. Personality profile and clinical correlates of patients with substance use disorder with and without comorbid depression under treatment. Front. Psychiatry 2019, 10, 764. [CrossRef]

53. Lynn Starr, H.; Bermak, J.; Mao, L.; Rodriguez, S.; Alphs, L. Comparison of long-acting and oral antipsychotic treatment effects in patients with schizophrenia, comorbid substance abuse, and a history of recent incarceration: An exploratory analysis of the PRIDE study. Schizophr. Res. 2018, 194, 39–46. [CrossRef]

54. Abdel-Baki, A.; Ouellet-Plamondon, C.; Salvat, E.; Grar, K.; Potvin, S. Symptomatic and functional outcomes of substance use disorder persistence 2 years after admission to a first-episode psychosis program. Psychiatry Res. 2017, 247, 113–119. [CrossRef]

55. Llanes-Alvarez, C.; Andrés-de Llano, J.M.; Alvarez-Navares, A.I.; Pastor-Hidalgo, M.T.; Roncero, C.; Franco-Martin, M.A. Trends in psychiatric hospitalization for alcohol and drugs in Castilla y León between 2005 and 2015. Adicciones 2022, 34, 189–196. [CrossRef]

56. Sánchez-Niubò, A.; Sordo, L.; Barrio, G.; Indave, B.; Domingo-Salvany, A. Onset and progression of drug use in the general population of Catalonia, Spain. Adicciones 2020, 32, 32–39.

57. European Monitoring Centre for Drug and Addiction (EMCDDA). European Drug Report 2022: Trends and Developments; Publications Office of the European Union: Luxembourg, 2022; ISBN 978-92-9497-742-7.

58. Donati, F.L.; D’Agostino, A.; Ferrarelli, F. Neurocognitive and neurophysiological endophenotypes in schizophrenia: An overview. Biomark. Neuropsychiatry 2020, 3, 100017. [CrossRef]

59. Helldin, L.; Kane, J.M.; Kariampi, U.; Norlander, T.; Archer, T. Remission and cognitive ability in a cohort of patients with schizophrenia spectrum disorders with comorbid substance use disorder. J. Psychiatr. Res. 2018, 103, 39–46. [CrossRef] [PubMed]

60. O’Donnell, L.A.; Deldin, P.J.; Pester, B.; McNinis, M.G.; Langenecker, S.A.; Ryan, K.A. Cognitive flexibility: A trait of bipolar disorder that worsens with length of illness. J. Clin. Exp. Neuropsychol. 2017, 39, 979–987. [CrossRef]

61. Hagen, E.; Erga, A.H.; Hagen, K.P.; Nesvåg, S.M.; McKay, J.R.; Lundervold, A.J.; Walderhaug, E. Assessment of executive function in patients with substance use disorder: A comparison of inventory and performance-based assessment. J. Subst. Abuse Treat. 2016, 66, 1–8. [CrossRef] [PubMed]

62. Verdejo-Garcia, A.; Pérez-Garcia, M. Ecological assessment of executive functions in substance dependent individuals. Drug Alcohol Depend. 2007, 90, 48–55. [CrossRef]

63. Schulte, M.H.J.; Cousijn, J.; Den Uyl, T.E.; Goudriaan, A.E.; Van Den Brink, W.; Veltman, D.J.; Schilt, T.; Wiers, R.W. Recovery of neurocognitive functions following sustained abstinence after substance dependence and implications for treatment. Clin. Psychol. Rev. 2014, 34, 531–550. [CrossRef]

64. Richard, Y.; Moustafa, A. Impulsive behavior in drug addiction: Clinical, cognitive, and neural correlates. In Cognitive, Clinical, and Neural Aspects of Drug Mixture; Moustafa, A.A., Ed.; Academic Press: London, UK, 2021; pp. 1–20.

65. Prat, G.; Marquez-Arrico, J.E.; Rio-Martinez, L.; Navarro, J.F.; Adan, A. Premorbid functioning in schizophrenia spectrum disorders with comorbid substance use: A systematic review. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 2021, 110, 110310. [CrossRef]

66. Brewer, W.J.; Francey, S.M.; Wood, S.J.; Jackson, H.J.; Pantelis, C.; Phillips, L.J.; Young, A.R.; Anderson, V.A.; McGorry, P.P. Memory impairments identified in people at ultra-high risk for psychosis who later develop first-episode psychosis. Am. J. Psychiatry 2005, 162, 71–78. [CrossRef]

67. Okasha, T.A.; Hussein, H.; Shorub, E.; Nagi, H.; Moustafa, A.A.; El-Serafi, D. Cognitive dysfunction among inpatients and outpatients with schizophrenia: Relationship to positive and negative symptoms. Middle East Curr. Psychiatry 2020, 27, 58. [CrossRef]

68. Fitapelli, B.; Lindenmayer, J.P. Advances in cognitive remediation training in schizophrenia: A review. Brain Sci. 2022, 12, 129. [CrossRef]

69. Mogami, T. Cognitive remediation for schizophrenia with focus on NEAR. Front. Psychiatry 2018, 8, 304. [CrossRef] [PubMed]