Cognitive Functioning and Quality of Life in Patients with Dual Diagnosis

Irina Benaiges Fusté

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Dr. Ana Adan

RENDIMIENTO COGNITIVO Y CALIDAD DE VIDA EN PACIENTES CON PATOLOGÍA DUAL

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This thesis is presented by

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A mis padres, Domènec y Maria Cinta.

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Dr Ana Adan, professor at University of Barcelona

CERTIFY that I have supervised and guided the PhD thesis entitled "Cognitive Functioning and Quality of Life in patients with Dual Diagnosis" and I assert that this thesis fulfils the requirements to be defended for the Degree of Doctor of Psychology.

Signature, Barcelona April 2013

This thesis was carried out at the Neuropsychology Group, Department of Psychiatry and Clinical Psychobiology, University of Barcelona.

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La prueba más fuerte contra cualquier teoría,
es su aplicación.

KARL KRAUS (1874-1936)

CONTENIDOS

RESUMEN

Se denomina Patología Dual (PD) a la coocurrencia de un Trastorno Mental Severo (TMS), especialmente de la esfera psicótica y/o afectiva, y un trastorno por uso de sustancias (TUS). Se trata de un trastorno de elevada prevalencia, con una gran repercusión clínica y asistencial debido a las complicaciones asociadas a la comorbilidad entre ambas patologías.

El presente trabajo se propuso dos objetivos, estudiar el rendimiento cognitivo y la calidad de vida Relacionada con la Salud (CVRS) en pacientes con PD. El primero dada la escasez de estudios y la importancia de su evaluación, puesto que el funcionamiento cognitivo se relaciona con el curso clínico de la PD y puede incluso ser un factor predictivo del éxito o fracaso de las intervenciones terapéuticas. Si bien cabrían esperar importantes déficits cognitivos en los pacientes duales, debido a los efectos aditivos del trastorno psiquiátrico y del TUS, una revisión bibliográfica exhaustiva de los principales resultados publicados sugiere que su funcionamiento cognitivo depende, entre otros factores, de la sustancia principal de abuso, del dominio cognitivo evaluado y de la edad de los participantes. Así, nos centramos en evaluar el funcionamiento ejecutivo por una parte y los dominios de atención, memoria y velocidad del procesamiento de la información por otra, en una muestra de pacientes con esquizofrenia y dependencia a la cocaína (SZ+; n=30) comparados con esquizofrénicos sin historia de TUS comórbido (SZ-; n=30) y un grupo con dependencia a la cocaína sin comorbilidad psiquiátrica (COC; n=35).

Aunque en las últimas décadas se ha producido un aumento en el interés de la Calidad de Vida como medida de evaluación y como un indicador de la eficacia de las intervenciones en los TMS y en los TUS, los estudios en la PD son pocos. El segundo objetivo de este trabajo fue evaluar la CVRS en pacientes con PD (n=35), con sólo TMS (n=35) y con sólo TUS (n=35).

Los resultados del rendimiento cognitivo mostraron un patrón de actuación similar en los grupos SZ+ y COC en tareas neuropsicológicas dependientes del funcionamiento ejecutivo, siendo el rendimiento de ambos grupos mejor que el del grupo SZ-. Esto podría sugerir que los pacientes SZ+ poseen mayores habilidades cognitivas que los SZ-, y por tanto, pudiendo ser un subgrupo de SZ con menor vulnerabilidad biológica a desarrollar la enfermedad, presentando mayores habilidades ejecutivas y quizás, un mejor funcionamiento psicosocial premórbido que les haría más hábiles para adquirir las sustancias ilegales. En los dominios de atención, memoria y velocidad del procesamiento de la información, el grupo COC presentó un mejor rendimiento que los grupos SZ+ y SZ-, los cuáles no presentaron diferencias entre ellos. Sin embargo, la edad mostró una asociación negativa con la ejecución cognitiva en el grupo SZ+, los pacientes de mayor edad mostraban peor rendimiento cognitivo. En cambio, el grupo SZ- presentaba un déficit cognitivo estable independiente de la edad. Esto es coherente con la idea de un déficit cognitivo adicional al del trastorno psiquiátrico manifestado en los pacientes duales de mayor edad, debido a la expresión a largo plazo de las consecuencias neurotóxicas del consumo.

En cuanto a la CVRS, todos los grupos aportaron peores puntuaciones de CVRS respecto a los valores normativos españoles. En la mayoría de subescalas y especialmente en el dominio de salud mental, el grupo con PD mostró las peores puntuaciones, el grupo TUS las mejores y el grupo TMS se situó en una posición intermedia. El peor estado en el dominio mental de la CVRS apareció estrechamente relacionado con los intentos de suicidio, el número de medicamentos diarios y el consumo de cafeína en el grupo PD. La evaluación sistemática del estado de la CVRS puede ser útil en la detección de áreas de atención específica para los objetivos del tratamiento, así como medida de la eficacia de las intervenciones aplicadas a la PD.

Nuestros resultados sugieren características de rendimiento neuropsicológico y de CVRS particulares de los pacientes con PD, que los diferencian de aquellos con diagnóstico sólo de TMS o TUS. Ello evidencia el interés de estudiar la población dual como una entidad diagnóstica específica. Sin embargo, se requieren investigaciones futuras que progresen en esta línea de trabajo incorporando además, parámetros neurobiológicos y medidas longitudinales, lo que puede ayudar a mejorar el conocimiento actual de la PD y revertir en beneficios para el manejo clínico de los pacientes.

ABSTRACT

Dual Diagnosis (DD) is the co-occurrence of a Severe Mental Illness (SMI), commonly a major psychotic or affective disorder, and a Substance Use Dependence Disorder (SUD). It is a highly prevalent disorder with a large impact in clinical and health care systems due to the complications arising from the comorbidity between both conditions.

The aim of this work is twofold: the study of the cognitive performance and the Health Related Quality of Life (HRQOL) in patients with DD. The first one, because few studies have examined this question and its assessment is of great interest, since cognitive functioning is related to the clinical course and may even be a predictor of failure or success of the therapeutic interventions. Although major cognitive impairments can be expected in DD due to the additive effects of both psychiatric disorder and SUD, a wide review of published results on the scientific literature suggest that their cognitive functioning depends, among others, on the main substance of choice, the assessed cognitive domain and the age of the participants. Thus, we focus on the assessment of the executive functioning on one hand, and on the domains of attention, memory and speed of processing on the other, in a sample comprised by subjects with schizophrenia and cocaine dependence (SZ+; n = 30) compared to subjects with schizophrenia without SUD history (SZ-; n=30) and to cocaine dependent subjects without psychiatry comorbidity (COC; n=35).

Although in the last decades there has been an increased interest in the Quality of Life as an assessment measure as well as an indicator of the effectiveness of interventions in both SMI and SUD, few studies had focused on DD. For this reason, the second objective of this work was to assess HRQOL in a group with DD (n = 35) and compare it to a group with SMI (n=35) and to another one with SUD (N=35) without comorbidity.

Regarding the cognitive functioning, the results showed a similar pattern of performance in the SZ+ and COC groups in neuropsychological tasks related to executive functions, being their performance better than the SZ- group. This may suggest that patients with SZ+ have higher cognitive skills than the SZ- ones. Therefore, the SZ+ patients may be a subgroup of SZ with lower biological vulnerability to develop the illness and maybe, a better psychosocial premorbid functioning, making them more able to acquire the illegal substance of abuse. In the domains of attention, memory and speed of processing, the COC group performed better than both SZ+ and SZ- groups, without differences between them. However, the age was negative related to the cognitive performance in the SZ+ group. So, the older SZ+ showed worse cognitive functioning. Otherwise, the SZ- patients showed a stable cognitive functioining regardless of the age. This, in agreement with the idea of an additional cognitive impairment to the psychiatric disorder manifested in older SZ+ patients because of the long term expression of the neurotoxic consequences of consumption.

Concerning HRQOL, all the groups showed lower scores compared with the normative Spanish data. The DD group showed the worst scoring in most of assessed scales and in the mental domain, while the SUD group obtained the best, and the SMI obtained intermediate scores. The worse state in the mental domain appeared strongly related to the number of suicide attempts, daily intake of medication and to the caffeine consumption, only in the DD group. The systematic assessment of the HRQOL status could be a useful tool in the detection of specific care areas, helping to improve the treatment goals as well as an assessment measure of the effectiveness of interventions applied to DD patients.

Overall, our results suggest particular characteristics in subjects with DD regarding cognitive performance and HRQOL status, which make them different to the subjects with SMI and SUD. This demonstrates the interest to study DD as a specific diagnostic entity. However, further research in this field, incorporating long term measures and biological parameters, could help to a better understanding of the current knowledge in DD and to increase the benefits in the clinical management of these patients.

GLOSARIO DE ABREVIACIONES (Español)

CI: Coeficiente Intelectual

CIE: Clasificación Internacional de Enfermedades

COC: Dependencia a la cocaina sin comorbilidad psiquiátrica

CPZ: equivalentes de Clorpromazina

CS: Controles Sanos

CV: Calidad de Vida

CVRS: Calidad de Vida Relacionada con la Salud

EEUU: Estados Unidos

HHS: Eje Hipotálamo-Hipófiso-Suprarrenal

ICG: Impresión Clínica Global

LCF: Líquido Cefalorraquídeo

PD: Patología Dual

PEP: Primer Episodio Psicótico

SZ: Esquizofrenia

SZ-: Esquizofrenia sin TUS comórbido

SZ+: Esquizofrenia con TUS comórbido/ dependencia a la cocaína

TB-: Trastorno Bipolar sin TUS comórbido

TB+: Trastorno Bipolar con TUS comórbido

TB-I-: Trastorno Bipolar tipo I sin TUS comórbido

TB-I+: Trastorno Bipolar tipo I con TUS comórbido

TB-II-: Trastorno Bipolar tipo II sin TUS comórbido

TB-II+: Trastorno Bipolar tipo II con TUS comórbido

TMS: Trastorno Mental Severo

TUS: Trastorno por Uso de Sustancias

LIST OF ABBREVIATIONS (English)

APA: American Psychiatric Association

ASI: Addiction Severity Index

AUDADIS: Alcohol Use Disorders and Associated Disabilities Interview Scheduled

CGI: Clinical Global Impression

COC: Cocaine dependence without psychiatric comorbidity

CPZ: Chlopromazine equivalent dosages

DD: Dual Diagnosis

DIS: Diagnostic Interview Schedule

DSM: Diagnostic and Statistic Manual of Mental Disorders

DSM-III: Diagnostic and Statistic Manual of Mental Disorders. Third Edition.

DSM-III-R: Diagnostic and Statistic Manual of Mental Disorders. Third Edition - Revided.

DSM-IV: Diagnostic and Statistic Manual of Mental Disorders. Fourth Edition.

DSM-IV-TR: Diagnostic and Statistic Manual of Mental Disorders. Fourth Edition-Revised.

ECA: Epidemiologic Catchment Area

HIV: Human Inmunodeficiency Virus Infection

HRDS: Hamilton Rating Depression Scale

HRQOL: Health Related Quality of Life

IGT: Iowa Gambling Task

JCR: Journal Citation Reports

LEAD: Longitudinal Expert with All Data

MQOL: McGill Quality of Life Questionnaire

NCS: National Comorbidity Survey

PANSS: Positive and Negative Syndrome Scale

PRISM: Psychiatric Research Interview for Substance and Mental Disorders

PRISM-IV: Psychiatric Research Interview for Substance and Mental Disorders. Fourth Edition

QLS: Quality of Life Scale

QOL: Quality of Life

RAVLT: Rey Auditory Verbal Learning Test

SADS: Schedule for Affective Disorders and Schizophrenia

SCID: Structured Clinical Interview

SCID-I: Structured Clinical Interview- Axis I Disorder

SCID-SAC: SCID for Substance Abuse Comorbidity Version

SF-12: Short-Form 12 Item Health Survey

SF-36: Short-Form 36 Item Health Survey

SJC: SCImago Journal & Country Rank

SMI: Severe Mental Illness

SSAGA: Semi-structured Assesment for the Genetics of Alcoholism

STD: Sexual transmited Diseases

SUD: Substance Use Dependence

SZ: Schizophrenia

SZ-: Schizophrenia without comorbid SUD

SZ+: Schizophrenia with comorbid SUD/cocaine dependence

TMT-A: Trail Making Test part-A

TMT-B: Trail Making Test part-B

WAIS-R: Wechsler Adult Intelligence Scale-Revised

WCST: Wisconsin Card Sorting Test

WHO: World Health Organization

WHOQOL: World Health Organization Quality of Life

WHOQOL-BREF: The World Health Organization Quality of Life Asses

YMRS: Young Mania Rating Scale

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1. INTRODUCCIÓN

1.1 Definición y características generales de la Patología Dual

Se denomina *Patología Dual (PD)* a la concurrencia en el mismo individuo de, por lo menos, un trastorno por abuso o dependencia de sustancias y otro trastorno psiquiátrico grave, especialmente de la esfera psicótica o afectiva (Torrens, 2008). Se trata de un concepto de naturaleza heterogénea, porque puede incluir tanto patología leve como los trastornos de ansiedad, como otros de naturaleza y curso grave como la esquizofrenia y el trastorno bipolar. Asimismo, el concepto incluye tanto los trastornos por abuso como por dependencia de sustancias (Drake & Wallach, 2000). Si bien existe una amplia variedad de combinaciones posibles dada la flexibilidad de esta definición, a lo largo de este trabajo nos referiremos a la PD como la coincidencia de patologías mayores psicóticas y/o afectivas y trastornos relacionados con el alcohol y otras drogas ilegales.

El concepto de PD emergió en la década de los 90 (Stowel, 1991) y se trata de un trastorno con gran repercusión clínica y asistencial (Rodríguez-Jiménez et al., 2008; Torrens, 2008) puesto que ha sido asociado a un aumento en el número de ingresos psiquiátricos (Hunt, Bergen & Bashir, 2002), recaídas e intentos de suicidio (Appleby et al., 1999; Cardoso et al., 2008), comportamiento violento (Soyka, 2000; Swartz et al., 1998) encarcelamiento, problemas familiares, pérdida

de estatus social, detrimento de la calidad de vida (Benaiges, Prat & Adan, 2012), mayor comorbilidad médica e infección por VIH (Dickey, Normand, Weiss, Drake & Azeni, 2002; Drake & Wallach, 2000), así como mayores tasas de desempleo y marginación (Dixon, 1999), incremento del gasto sanitario (Hoff & Rosenheck, 1999; McCrone et al., 2000) pobre adherencia al tratamiento (Kamali et al., 2001; Owen et al., 1996) y fracaso terapéutico en relación tanto al trastorno por uso de sustancias (TUS) como al trastorno mental (Carey, Carey & Simons, 2003; Lambert et al., 2005).

1.2 Prevalencia y especificidades de la Patología Dual

Los principales datos epidemiológicos en PD provienen de dos grandes estudios realizados en población general: el *Epidemiologic Catchment Area* (ECA) (Regier et al., 1990) y el *National Comorbidity Survey* (NCS) *NCS* (Kessler et al., 1994).

El estudio ECA (Regier et al., 1990) encontró que aquellos pacientes que presentaban un trastorno mental, presentaban una elevada prevalencia de abuso y dependencia de alcohol (22%) y de otras drogas ilegales (15%). Por otra parte, el 37% de aquellos con dependencia a alcohol y el 53% de los que abusaban de otras sustancias presentaban un trastorno mental. Es decir, los sujetos dependientes de sustancias presentaban un riesgo 4,5 veces mayor de padecer otro trastorno mental asociado, y las personas con una enfermedad mental tenían 4,5 veces más riesgo de padecer una dependencia. Al considerar las diferentes sustancias, la adicción a la cocaína fue la que más se asoció a los trastornos mentales con una *odds ratio* de 11. Los trastornos psiquiátricos más prevalentes fueron los trastornos de ansiedad, los trastornos afectivos y la esquizofrenia.

El estudio NCS (Kessler et al., 1994) obtuvo resultados similares a los del estudio ECA si bien los valores de comorbilidad fueron aún más elevados en el caso de la Esquizofrenia, mostrando que el 78% de los dependientes a sustancias presentaban un trastorno esquizofrénico comórbido.

Tabla 1. Prevalencia de TUS y esquizofrenia, trastorno bipolar tipo I y tipo II y trastorno depresivo mayor en estudios epidemiológicos en población general.

	Esquizofrenia	Trastorno Bipolar I	Trastorno Bipolar-II	Depresión
ECA	47%	60,7%	48,1%	32%
NCS	78%	60,3%	40,4%	23%

ECA: *Epidemiologic Catchment Area*; NCS: *National Comorbidity Survey*.

Los datos de prevalencia entre estudios varían considerablemente debido a algunos aspectos metodológicos como el tamaño muestral, la selección de los sujetos, los criterios diagnósticos, los instrumentos diagnósticos utilizados y las distintas definiciones existentes sobre la comorbilidad y sobre el trastorno por uso de sustancias (TUS).

El uso de sustancias más frecuentes entre la población dual es, excluyendo la nicotina, el consumo de alcohol y cannabis, seguidos de la cocaína y los estimulantes, aunque lo más frecuente es la existencia de policonsumo (Cardoso et al., 2008; Dixon, 1999). La PD se suele asociar a la predominancia de género masculino y jóvenes, con antecedentes familiares de TUS, bajo nivel social y cultural y mayor ajuste premórbido (Rodríguez-Jiménez et al., 2008; Scheller-Gilkey, Lewine, Caudle & Brown, 1999).

Más específicamente, los pacientes con esquizofrenia que presentan un TUS comórbido se diferencian de aquellos esquizofrénicos no duales en presentar generalmente más síntomas positivos y depresivos y un inicio más temprano de la enfermedad asociado a un peor pronóstico (Potvin, Sepehry & Stip, 2006; Talamo et al., 2006). Suelen recibir prescripciones a dosis más altas de antipsicóticos presentando mayor refractariedad al tratamiento y poca adherencia al mismo (Batel, 2000; Laudet, Magura, Vogel & Knight, 2000). Además, tienden a presentar índices bajos de calidad de vida, mayor comportamiento violento, impulsividad y búsqueda de sensaciones, hostilidad, paranoia y suelen encontrarse en situación de desocupación laboral (Bowie, Serper, Riggio & Harvey, 2005; Dixon, Weiden, Haas, Sweeney & Frances, 1992; Kim, Kim, Park, Lee & Chung, 2007).

En la depresión mayor con TUS comórbido, especialmente en el caso de abuso y/o dependencia de alcohol, se ha descrito un curso más grave de depresión que empeora, a su vez, la severidad del TUS, con la consiguiente multiplicidad de

problemas asociados a cada uno de estos trastornos, incluyendo el incremento del riesgo de suicidio (Sarosi et al., 2008).

De forma similar, en los pacientes bipolares, la manía se complica por la presencia del TUS comórbido, caracterizándose por remisiones menos favorables y mayor severidad de los síntomas psicóticos, incluyendo formas más extremas de labilidad emocional, mayor impulsividad y conducta agresiva. Suelen presentar un curso más crónico y severo de la enfermedad. Los primeros episodios maníacos suelen ocurrir a edades más tempranas, necesitan más tiempo de recuperación entre crisis y presentan mayores tasas de mortalidad comparados con pacientes bipolares no consumidores (Albanese & Pies, 2004; Levy & Weiss, 2009; Salloum, Cornelius, Mezzich & Kirisci, 2002).

1.3 Diagnóstico de la Patología Dual

El diagnóstico de comorbilidad psiquiátrica en sujetos consumidores de sustancias es una tarea ardua para los clínicos debido a que los efectos agudos y crónicos de las drogas simulan muchos síntomas de los trastornos psiquiátricos. Esto hace difícil establecer diferencias entre los síntomas aparecidos debido a los efectos agudos o de abstinencia a una sustancia y los síntomas propios de un trastorno psiquiátrico. Esto se complica aún más por la dificultad diagnóstica inherente a los propios trastornos psiquiátricos. Si bien en las últimas décadas se ha avanzado mucho en el conocimiento de las bases fisiopatológicas de las enfermedades mentales, los trastornos psiquiátricos siguen siendo "síndromes" con patrones de síntomas verificados con algunas pruebas de validez clínica, que no "enfermedades" de fisiopatología conocida con marcadores biológicos sensibles y específicos (Torrens, Mestre & Díaz, 2010). A falta de tales pruebas objetivas de laboratorio, la validez de los diagnósticos psiquiátricos se encuentra bajo el método de la evaluación longitudinal, realizada por un experto que tenga en cuenta todos los datos disponibles, sintetizado bajo las siglas LEAD (*Longitudinal Expert with All Data*) (Kranzler, Tennen, Babor, Kadden & Rounsaville, 1997; Spitzer, 1983).

En respuesta al reconocimiento de la relevancia de la comorbilidad entre las patologías psiquiátricas y el consumo de alcohol y otras sustancias, el DSM-IV (*Manual Diagnóstico y Estadístico de los Trastornos Mentales, 4-rta Edición*) (APA, 1994) y su versión revisada (DSM-IV-TR) (APA, 2000) cambiaron la antigua categoría "orgánico" *vs* "no orgánico" respecto a sus ediciones precedentes del DSM-III (APA, 1980) y DSM-III-R (APA, 1987) por mostrase débilmente fiables y validos en los diagnósticos duales, sustituyéndola según Torrens et al. (2010), por tres categorías:

- Diagnóstico Primario: El trastorno mental no es inducido por sustancias y no se debe a ninguna enfermedad médica. El episodio por tanto, se produce durante un periodo de abstinencia o durante un periodo de consumo ocasional en el cual la cantidad de la sustancia no es suficiente para provocar síndromes de intoxicación y/o abstinencia. Los trastornos mentales primarios se pueden producir en tres circunstancias:

  1) el episodio se produce durante un periodo prolongado de abstinencia o de consumo ocasional de la sustancia.

  2) el episodio comienza por lo menos 2 semanas antes del inicio de un período de consumo excesivo de sustancias

  3) el episodio comienza durante un periodo excesivo de consumo y continua por lo menos 4 semanas o más después que finalice el consumo.

- Efectos esperados: síntomas habituales que aparecen como consecuencia del abuso/ dependencia a las sustancias o a la abstinencia de una sustancia. Tales efectos de intoxicación y/o abstinencia están descritos para cada una de las principales sustancias (alcohol, cocaína, etc.) según criterios DSM-IV-TR.

- Inducido por Sustancias: cuando los síntomas se consideran excesivos en relación con los que suelen aparecer en los síndromes de intoxicación y/o abstinencia a una sustancia. Se diagnostica cuando

  1) Se cumplen todos los criterios para el trastorno según el DSM-IV-TR.

  2) El episodio ocurre por completo durante un periodo de consumo de sustancias excesivo o en las cuatro semanas posteriores a tal consumo.

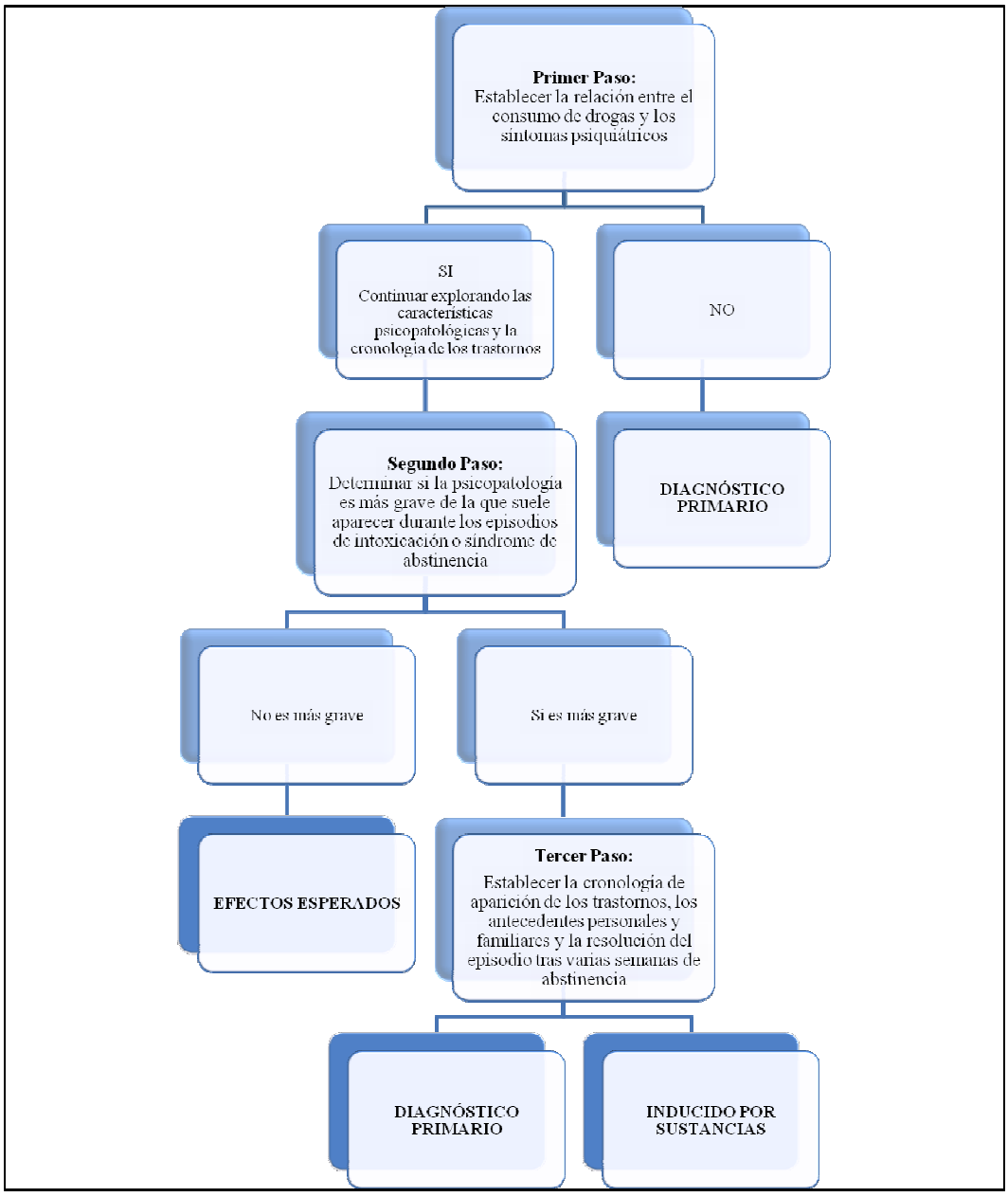
  3) la sustancia consumida es capaz de provocar síntomas idénticos a los del trastorno que se está evaluando.

  4) los síntomas son claramente excesivos respecto a los efectos esperados de intoxicación/abstinencia.

Si bien en la actualidad se disponen de varias entrevistas diagnósticas estructuradas y semi-estructuradas para establecer diagnósticos basados en los criterios DSM-III o DSM-IV para finalidades clínicas y de investigación (Ver tabla 2), las más usadas actualmente en el ámbito de la PD son la *Structured Clinical Interview* (SCID) (First, Spitzer, Gibbon & William, 1998) y la entrevista *Psychiatric Research Interview for Substance and Mental Disorders* (PRISM-IV) (Torrens, Serrano, Astals, Perez-Dominguez & Martin-Santos, 2004). Ambas están basadas en criterios DSM-IV-TR y requieren entrenamiento para su

administración por parte de clínicos expertos. Si bien la SCID es la entrevista más usada en psiquiatría general con índices kappa adecuados para el diagnóstico fiable de los trastornos del eje I y II del DSM-IV, no se dispone de datos actuales que demuestren la fiabilidad de los diagnósticos psiquiátricos comórbidos al uso de sustancias (Torrens et al., 2010). Por otra parte, la PRISM-IV es una entrevista diseñada específicamente para diferenciar los trastornos mentales primarios de los inducidos por sustancias y de los efectos esperados de la intoxicación y de la abstinencia en sujetos consumidores de alcohol y otras sustancias. Esta entrevista ha demostrado fiabilidad y validez en el establecimiento de diagnósticos duales (Torrens et al., 2010; Torrens et al., 2004).

Figura 1. Algoritmo de decisión en el diagnóstico de los trastornos duales basados en criterios DSM-IV-TR.



Nota: Adaptado de San (2004).

Tabla 2. Instrumentos diagnósticos de trastornos psiquiátricos y TUS (Trastorno por Uso de Sustancias) comórbido.

Instrumento	Características	Elementos para el Diagnóstico Diferencial
Programa para el diagnóstico de trastornos afectivos y esquizofrenia (*Schedule for Affective Disorders and Schizophrenia*, SADS; (Endicott & Spitzer, 1978)	•Entrevista semiestructurada •Utilizada en estudios epidemiológicos •Utilizada por entrevistadores expertos •Duración: 1-1,5 horas	•Se considera la distinción entre trastorno inducido y no inducido en función de la edad de aparición del uso de drogas y del otro trastorno.
Programa de entrevista diagnóstica (*Diagnostic Interview Schedule*, DIS; (Regier et al., 1984)	•Entrevista estructurada •Utilizada por entrevistadores poco experimentados •Basada en criterios DSM-III •Duración: 1,15 horas	•Se establece la diferenciación entre trastorno inducido y no inducido según la información del entrevistado y/o el juicio del clínico.
Entrevista clínica estructurada para el DSM-III-R (*Structured Clinic Interview for DSM-III-R*, SCID; (Spitzer, Williams, Gibbon & First, 1992)	•Entrevista semiestructurada •Utilizada por clínicos expertos •Basada en criterios DSM-III-R •Duración: 1-2 horas	•Al final de cada trastorno el clínico establece si el trastorno es debido o no al consumo de sustancias.
Entrevista para trastornos por uso de alcohol y discapacidades asociadas (*Alcohol Use disorders and Associated Disabilities Interview Scheduled*, AUDADIS; (Grant & Hasin, 1992)	•Entrevista estructurada • Utilizada por entrevistadores poco expertos •Limitada al diagnóstico de TUS y depresión mayor •Basada en criterios DSM-IV •Duración: 1-2 horas	•Cataloga depresión primaria cuando aparece antes del TUS, concurrente cuando aparece simultáneamente y secundaria cuando aparece tras el TUS.
Evaluación semiestructurada del la heredabilidad del alcoholismo (*Semi-Strucrured Assesment for the genetics of alcoholism*, SSAGA; (Bucholz et al., 1994)	•Entrevista semiestructurada •Valora la transmisión hereditaria del alcoholismo •Basada en criterios DSM-III-R •Duración: 1,5-2 horas	•Valora la edad de comienzo del TUS y su parición en los descendientes. •Considera trastornos independientes, coexistentes o mixtos.
Versión para trastornos comórbidos con abuso de drogas del SCID (*SCID-Substance Abuse comorbidity versión*, SCID-SAC; (Nunes, Goehl, Seracini, Nunes & Faermer, 1996)	•Especial hincapié en la cronología del uso de drogas y períodos de abstinencia. •Basada en criterios DSM-III-R •Duración: 1,5-2 horas	•Los trastornos se catalogan en primarios cuando aparecen antes del TUS o secundarios cuando aparecen después del TUS y persisten pese a la abstinencia.
Entrevista de investigación	•Entrevista estructurada	•Discrimina trastornos

psiquiátrica para trastornos mentales y TUS (*Psychiatric Research Interview for Substance and Mental Disorders*, PRISM; (Hasin et al., 1996)	•Utilizada por expertos •Basada en criterios DSM-III-R •Duración: 1-2 horas	primarios, y trastornos inducidos por drogas.
Entrevista de investigación psiquiátrica para trastornos mentales y TUS (*Psychiatric Research Interview for Substance and Mental Disorders*, PRISM-IV (Hasin et al., 2006). Versión española: (Torrens et al., 2004)	•Entrevista estructurada •Utilizada por expertos •Basada en criterios DSM-IV •Más criterios y puntos de corte restringidos con mayor fiabilidad en los diagnósticos •Duración: 1-2 horas	•Cataloga los trastornos en primarios, inducidos o efectos esperados por la desintoxicación y/o abstinencia.
Entrevista clínica estructurada para el DSM-IV (*Structured Clinical Interview for DSM-IV*, SCID; (First et al., 1998)	•Entrevista estructurada •Utilizada por clínicos expertos •Basada en criterios DSM-IV •Duración 1-2 horas	•Cataloga los trastornos en primarios, inducidos o efectos esperados por la desintoxicación y/o abstinencia.

Adaptado de San (2004).

1.4 Fundamentos neurobiológicos de la Patología Dual

Si bien empiezan a conocerse los nexos neurobiológicos entre los TUS y el resto de trastornos psiquiátricos, éstos están todavía lejos de ser definitivamente dilucidados. Los datos disponibles hasta la actualidad apuntan a la existencia de una base neurobiológica alterada común entre ambos trastornos constituida por el estrés, una hiperactividad en el eje hipotálamo-hipófiso-suprarrenal (HHS) y la afectación de vías dopaminérgicas que determinan una mayor vulnerabilidad a la PD junto a otros factores genofenotípicos. San (2004) resumen las evidencias en relación a ello como sigue:

- El estrés: diversos modelos experimentales parecen indicar que el estrés incrementa la vulnerabilidad tanto al consumo de drogas como a la patología psiquiátrica. En algunos modelos experimentales de estrés (interacción y aislamiento social, pinzamiento de la cola en el ratón, choques eléctricos, restricción de comida, estrés prenatal) se ha observado un incremento de la autoadministración de psicoestimulantes y opiáceos (Piazza et al., 1991; Piazza & Le Moal, 1998). Diversos estudios en humanos también ponen de manifiesto la relación entre la respuesta biológica al estrés, la poca tolerancia a la frustración y las estrategias de coping no resolutivas con el abuso de drogas y la patología psiquiátrica (Adinoff, Ruether, Krebaum, Iranmanesh & Williams, 2003; Blanchard, Brown, Horan & Sherwood, 2000; Fox & Sinha, 2009). La participación

del estrés en los modelos experimentales de depresión, así como en la fisiopatología clínica de los trastornos ansiosos y depresivos también ha sido demostrada (Fox, Hong, Siedlarz & Sinha, 2008; Hoffmann & Su, 1998; Silberg et al., 1999). Tales resultados sugieren que el estrés es un posible factor subyacente en la etiología de la PD.

- El eje hipotálamo-hipófiso-suprarrenal (HHS): diversos estudios experimentales y clínicos relacionan los corticoesteroides con la vulnerabilidad al abuso de drogas y a los trastornos afectivos. En relación a las conductas adictivas, diversos estudios experimentales encuentra una correlación directa entre las concentraciones de corticosterona y la conducta de autoadministración de anfetaminas, así como correlaciones entre las concentraciones de corticosterona previas a la autoadministración de cocaína y la cantidad de sustancia consumida. Por el contrario, la suprarrenalectomía o la inhibición de la síntesis de corticosteroides con metirapona reducen la autoadministración de cocaína y alcohol (Piazza et al., 1991; Piazza & Le Moal, 1996). Por lo tanto, un incremento en las concentraciones de corticosterona, o una mayor sensibilidad a la misma, aumentaría la vulnerabilidad a las sustancias de abuso. Esta hiperactividad del eje HHS también se ha encontrado en la depresión, manifestada por un incremento de las concentraciones plasmáticas, urinarias y en el líquido cefalorraquídeo (LCF) de cortisol (Dinan, 1994). De modo similar, algunos antidepresivos disminuyen la hiperactividad del eje HHS normalizando las concentraciones elevadas de glucocorticoides (Alamo, López-Muñoz & Cuenca, 1998). Esto apuntaría a la existencia de mecanismos fisiopatológicos comunes en el origen de la PD.

- Circuitos / Vías dopaminérgicos/as mesocortical y mesolímbico: es bien conocida la asociación entre la actividad de las proyecciones dopaminérgicas al núcleo accumbens y la mayor predisposición al consumo de drogas (Koob & Bloom, 1988). La hiperactividad dopaminérgica del núcleo accumbens se asocia también a mayor propensión a la dependencia y a la perpetuación del trastorno a largo plazo (Koob & Le Moal, 2001; 2005). Esto comparte varios nexos neurobiológicos con la hipótesis de la disregulación dopaminérgica en la esquizofrenia, con hipoactividad en la vía mesocortical explicando la sintomatología negativa e hiperactividad en la vía dopaminérgica mesolímbicas, especialmente en el núcleo accumbens, relacionada con la sintomatología positiva (Lusher, Chandler & Ball, 2001). La descripción de tasas elevadas de dopamina en el núcleo accumbens de pacientes esquizofrénicos guarda relación con las

alteraciones de los circuitos de recompensa descritos en los trastornos por uso de sustancias.

- Factores genofenotípicos: Si bien todavía no hay un cuerpo de evidencia concluyente, actualmente proliferan estudios genéticos en humanos con el objetivo de determinar un paralelismo génico que pueda explicar la vulnerabilidad a la adicción y su relación con otros trastornos psiquiátricos. Existe evidencia de que el gen que expresa el receptor dopaminérgico D_4 (DRD4) está asociado con las conductas adictivas y con rasgos de búsqueda de nuevas sensaciones (Lusher et al., 2001). De modo similar se ha encontrado que el gen que expresa el receptor dopaminérgico D_2 (DRD2) está asociado tanto al alcoholismo como a los trastornos de conducta (Lu, Lee, Ko & Lin, 2001). La identificación de polimorfismos genéticos que predisponen a la PD puede facilitar el desarrollo de nuevos agentes terapéuticos, aumentar la capacidad para diagnosticar esta patología y adoptar medidas preventivas y terapéuticas en poblaciones vulnerables a la PD. Si bien el trabajo en este sentido es intenso, en la actualidad los datos recabados no se han podido trasladar a la clínica.

Además de la importancia de estos factores neurobiológicos comunes, no hay que olvidar la importancia de los factores ambientales, que pueden contribuir tanto a la etiopatogenia de la enfermedad como a su tratamiento. Esto se pone de manifiesto en la verificación de los acontecimientos vitales estresantes como desencadenantes de las conductas adictivas y de las patologías psiquiátricas (Back et al., 2000; Blanchard et al., 2000; Hoffmann & Su, 1998), así como en el éxito de muchas terapias coadyuvantes exógenas, de origen psicológico y/o social, en el tratamiento de estas patologías. Recientemente, la American Psychological Association publicó en su web la resolución de la psicoterapia como un tratamiento efectivo y eficiente en términos de coste-beneficio para una gran variedad de trastornos y que es aplicable a todas las poblaciones. En consecuencia, consideran la necesidad de incorporar la psicoterapia en todos los sistemas nacionales de salud como un tratamiento basado en la evidencia (American Psychological Association, 2012).

1.5 Modelos etiopatogénicos de la Patología Dual: Naturaleza de la Asociación

La elevada prevalencia de PD ha dado lugar a abundante investigación con el objetivo de esclarecer las relaciones etiológicas en ambas patologías que den cuenta del fenómeno de la comorbilidad. A continuación se exponen brevemente los cuatro modelos etiopatogénicos principales:

- Modelo de factores comunes: este modelo propone la existencia de factores de vulnerabilidad comunes al desarrollo de ambos trastornos que podrían ser de naturaleza biológica, psicológica y/o social. Si bien la mayoría de estudios se han centrado en factores comunes de origen biológico (estudios genéticos y de heredabilidad), también se han propuesto factores psicológicos (comorbilidad con trastorno antisocial de la personalidad, experiencias traumáticas en la infancia, disfunciones cognitivas compartidas en ambas patologías, etc.) y de origen social (bajo estatus socio-económico y educativo, etc). Cabe mencionar que aunque se han encontrado polimorfismos genéticos como el gen C957T del gen DRD2, que codifica la proteína del receptor dopaminérgico D2 suponiendo un factor de riesgo tanto para la esquizofrenia como para el TUS, ni los estudios de antecedentes psicóticos y antecedentes de TUS en ambos patologías (Gershon et al., 1982; Maier, Lichtermann, Minges, Delmo & Heun, 1995), ni los estudios de heredabilidad en gemelos en ambas patologías (Kendler, 1985), parecen respaldar la hipótesis de la vulnerabilidad genética común. Además, tampoco los estudios acerca de otros factores de vulnerabilidad psicológica y social común, obtienen evidencias que justifiquen por si solas la comorbilidad entre ambos trastornos (Rodríguez-Jímenez, Bagney, Peñas, Gómez & Aragüés, 2010). No obstante, podría ser plausible que el efecto acumulativo de todos estos factores contribuyese a aumentar el riesgo de desarrollar ambos trastornos.

- Modelo del TUS secundario al trastorno psiquiátrico: bajo este modelo subyace la conocida "hipótesis de la automedicación" que, entre otras teorías de corte similar, plantea el uso de tóxicos como un intento de aliviar estados emocionales disfóricos en pacientes psiquiátricos, que a la larga desarrollan el TUS como otra entidad diagnóstica, con sus relativas repercusiones negativas sobre el trastorno primario. De este modo, los pacientes seleccionan una sustancia específica en función de sus efectos concretos como un intento de compensar determinados estados relacionados o producidos por el propio trastorno primario. Si bien esta teoría ha gozado de una gran popularidad entre los clínicos y teóricos que pretendían explicar el fenómeno de la comorbilidad, actualmente se encuentra cuestionada por la falta de hallazgos científicos que relacionen

una sustancia concreta con un síntoma o trastorno específico (Dixon, Haas, Weiden, Sweeney & Frances, 1990; Noordsy et al., 1991), ni relaciones entre la gravedad de la sintomatología y la cantidad del tóxico consumido (Brunette, Mueser, Xie & Drake, 1997; Hamera, Schneider & Deviney, 1995). Parece que los pacientes psiquiátricos suelen consumir sustancias en proporciones similares a la población general, abunda el policonsumo y la elección de la sustancia se relaciona más con la accesibilidad al mercado que con el diagnóstico psiquiátrico (Mueser, Yarnold & Bellack, 1992). Una parte de los pacientes duales refieren el uso de sustancias como un intento de aliviar su sintomatología, por lo que algunos autores plantean que la hipótesis de la automedicación, aunque no generalizable, sí sirve para explicar "*some patients, some substances and some symptoms*" (Goswami, Mattoo, Basu & Singh, 2004).

- Modelo del trastorno psiquiátrico secundario al TUS: dado que las sustancias de abuso actúan sobre los sistemas de neurotransmisión dopaminérgico, glutamatérgico, serotoninérgico, cannabinoide y otros sistemas relacionados con la etiopatogenia de los trastornos psicóticos, se han planteado mecanismos neurobiológicos básicos que explicarían cómo el TUS conduciría al desarrollo de un trastorno psicótico. Si bien la sustancia más estudiada ha sido el cannabis, con una amplia evidencia epidemiológica que señala que su consumo regular predice un riesgo aumentado del desarrollo de esquizofrenia, siendo el riesgo aun mayor según la cantidad consumida y una edad precoz de consumo (Smit, Bolier & Cuijpers, 2004), las relaciones causales entre cannabis y esquizofrenia no se han demostrado. En base a estos resultados, se ha planteado que el cannabis podría ser un factor coadyudante o precipitante en el desarrollo del trastorno en individuos con vulnerabilidad personal y/o familiar (Degenhardt, Hall & Lynskey, 2003). Así, la vulnerabilidad al desarrollo de la esquizofrenia estaría determinada por factores genéticos, ambientales y de interacción entre ambos (van Os, Krabbendam, Myin-Germeys & Delespaul, 2005).

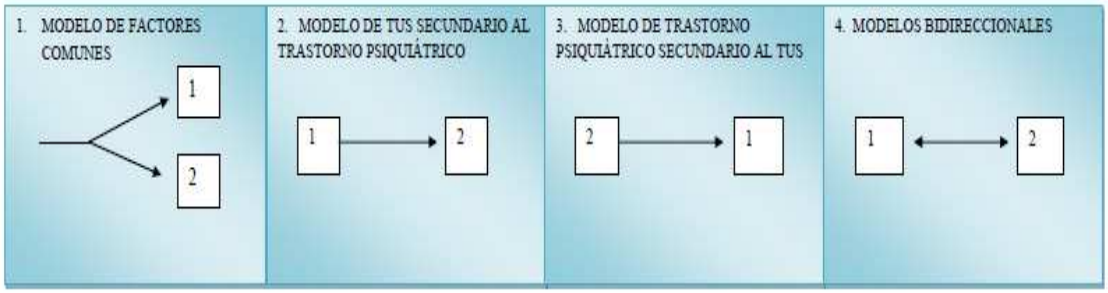
En esta línea, algunos estudios han encontrado un riesgo mayor a experimentar síntomas psicóticos en consumidores de cannabis portadores del alelo 158 valina para el gen de la catecol-orto-metil-transferasa (COMT) en comparación a aquellos portadores del alelo metionina (Caspi et al., 2005; Henquet et al., 2006). Si bien existe menos investigación respecto al alcohol y otras sustancias de abuso como las anfetaminas, la cocaína y los opioides, sí se han establecido relaciones con la aparición de síntomas psicóticos. Pero la investigación actual está lejos de encontrar

relaciones causales entre el uso, abuso y/o dependencia de sustancias y la esquizofrenia (Bernadt & Murray, 1986; Hambrecht & Hafner, 1996).

- Modelos bidireccionales: los modelos bidireccionales nacen como un intento conciliador entre los modelos previos, proponiendo efectos interactivos entre el trastorno psiquiátrico y el TUS. Según estos modelos, ambos trastornos contribuyen a la aparición y mantenimiento del otro. Así, mientras el TUS podría desencadenar el trastorno psiquiátrico en un individuo biológicamente vulnerable, el trastorno psiquiátrico podría a su vez, contribuir al mantenimiento del TUS. Si bien desde un punto de vista clínico es factible pensar que una vez establecida la comorbilidad, ambos trastornos establecerían una relación dinámica que determinará el curso, evolución y pronóstico de ambos trastornos y por tanto, la situación clínica del paciente, desde el punto de vista científico se trata de un modelo altamente teórico y difícilmente contrastable (Mueser, Drake & Wallach, 1998).

Explicar la etiopatogenia de la PD es una tarea ardua, ya que se trata de una situación clínica extremadamente heterogénea dadas las múltiples combinaciones posibles entre trastornos psiquiátrico y TUS. La mayoría de investigaciones se han desarrollado sobre la esquizofrenia, quedando al margen otras patologías como el trastorno bipolar. Por otra parte, el consumo puede ir desde un consumo puntual hasta otras situaciones clínicas como el abuso y la dependencia. El tipo de droga consumida por los pacientes también contribuye a los resultados inconsistentes entre las investigaciones, ya que las diferentes sustancias pueden tener mecanismos etiopatogénicos diversos. Todo ello explicaría el hecho que los modelos planteados hasta hoy se muestren en todos los casos insuficientes y con resultados inconsistentes. Es posible que no exista un único modelo que permita explicar la complejidad clínica de la PD. Por otra parte, los modelos bidireccionales, a pesar de ser altamente inespecíficos desde el punto de vista empírico, pueden ayudar a entender la relación dinámica entre ambas patologías que se retroalimentan entre sí modificando el curso, evolución y pronóstico de los pacientes con PD (Rodríguez-Jímenez et al., 2010).

Figura 2. Modelos etipotogénicos de la Patología Dual.



1: Trastorno psiquiátrico; 2: TUS (Trastorno por Uso de Sustancias).

1.6 Abordajes terapéuticos en Patología Dual

Si bien nos hallamos ante pacientes difíciles puesto que, como se ha mencionado anteriormente, presentan una mayor severidad clínica del trastorno psiquiátrico y un peor pronóstico comparado con los pacientes psiquiátricos no duales, existen contradicciones entre los clínicos acerca de las estrategias de abordaje específicas para los pacientes duales.

Los recursos asistenciales disponibles en la actualidad presentan dificultades en la atención a estos pacientes, ya que sus características mórbidas asociadas y su peor curso clínico y cumplimiento terapéutico, provocan el rechazo de los pacientes duales tanto de las unidades específicas de drogodependientes como de las unidades específicas de psiquiatría. Ello aumenta el sufrimiento de estos pacientes, que sufren el llamado "síndrome de la puerta equivocada", deambulando de un dispositivo a otro sin una respuesta adecuada de tratamiento (San, 2004).

Cabe hacer especial hincapié en que la combinación de psicoterapia y fármacoterapia es más efectiva en el tratamiento de los trastornos psiquiátricos, que cualquiera de ambas intervenciones por separado (Becoña & Cortés, 2008). Así, la Asociación Americana de Psiquiatría, establece los tratamientos psicosociales como elementos esenciales para el abordaje clínico de los trastornos por abuso de sustancias. Esta máxima es extensible al tratamiento de los pacientes duales. Por lo tanto, independientemente del modelo asistencial considerado, la farmacoterapia y la psicoterapia deben coexistir en el tratamiento de la PD.

A continuación se describen los distintos modelos de abordaje terapéutico existente, según Rubio, Torrens, Calatayud & Haro (2010):

- Intervención secuencial. El paciente es tratado primero en uno de los dispositivos específicos asistenciales, ya sea unidad de drogodependencias y/o de salud mental, y posteriormente pasa al otro. Así, el paciente es tratado de forma secuencial e independiente en ambas patologías.

- Intervención en paralelo. El paciente es tratado simultáneamente en ambos dispositivos específicos independientes de forma simultánea.

Estos dos modelos presentan desventajas tanto para el paciente como para los profesionales, puesto que pueden acarrear descoordinación entre ambos dispositivos asistenciales. Es frecuente el solapamiento, duplicación o incluso interferencia de las intervenciones debido a diferencias en los servicios de tratamiento y las políticas propias de cada institución. En ambos casos se perjudica el abordaje integral de los pacientes y no se tienen en cuenta los aspectos de interrelación entre ambos trastornos (Arias, Rubio, López-Muñoz & Ferre, 2001).

- Intervención integral. El paciente recibe un tratamiento global e integrado de las dos patologías que considera la interrelación entre ambas, por un mismo equipo de tratamiento. Estas intervenciones suelen tener lugar en centros específicos de PD con profesionales formados específicamente con las competencias y habilidades necesarias para abordar la PD como una entidad única en lugar de considerar el trastorno psiquiátrico y el TUS por separado.

Si bien este modelo presenta la desventaja de elevadas inversiones asistenciales debido a la creación de unidades específicas de PD, la formación también específica de los profesionales sanitarios, y la obtención de beneficios sólo a medio-largo plazo, supone una ventaja frente a los otros modelos de intervención porque ha demostrado una mayor eficacia de los tratamientos y mayores éxitos terapéuticos (Torrens, Rossi, Martinez-Riera, Martinez-Sanvisens & Bulbena, 2012).

Rubio et al. (2010) describen las siguientes fases en el modelo de intervención integrado:

1) Estabilización de ambos trastornos: con oportunos ingresos en unidades de agudos/desintoxicación hospitalaria en los casos que se estime necesario.

2) Implicación-Enganche: etapa motivacional de vinculación terapéutica y psico-educativa del trastorno.

3) Estabilización prolongada: mantenimiento de la abstinencia, reducción de daños para el trastorno adictivo y estabilización psiquiátrica.

4) Rehabilitación: implicación comunitaria y proceso de reinserción.

Dentro de estas fases se llevan a cabo los siguientes objetivos básicos, siempre adaptados a las características individuales de cada paciente:

1) Establecimiento y mantenimiento de la alianza terapéutica.

2) Vigilancia del estado clínico del paciente.

3) Tratamiento de los estados de intoxicación y abstinencia.

4) Desarrollo y facilitación del cumplimiento de un programa terapéutico individualizado.

5) Prevención de las recaídas.

6) Educación sanitaria individual y familiar.

7) Reducción de la comorbilidad y las secuelas de los trastornos por consumo de sustancias.

8) Integración y coordinación de las intervenciones realizadas.

Mientras en EEUU se están creando unidades especializadas en PD con este enfoque, en Europa siguen siendo objeto de discusión, a pesar de las evidencias científicas que demuestran la eficacia de las intervenciones integrales (Craig et al., 2008; Schulte, Meier & Stirling, 2011). Afortunadamente, en España existen grupos clínicos de reconocido prestigio internacional en el tema y algunas unidades específicas donde se llevan a cabo intervenciones integrales como el programa en el área 11 de salud de la comunidad de Madrid, el programa de PD grave del hospital provincial de Castellón y la unidad de PD del Hospital del Mar de Barcelona, entre otras.

2. NEUROPSICOLOGÍA Y PATOLOGÍA DUAL

2.1 Importancia de la neuropsicología en el ámbito de la Patología Dual

El estudio del funcionamiento neuropsicológico en pacientes con PD merece especial consideración por varias razones. Los déficits cognitivos se relacionan con la vulnerabilidad biológica a la psicosis, considerándose endofenotipos de determinados trastornos mentales como la esquizofrenia y el trastorno bipolar (Levy, Monzani, Stephansky & Weiss, 2008; Snitz, Macdonald & Carter, 2006), y se ha constatado su presencia antes de la aparición del trastorno, en las fases prodrómicas de la enfermedad e incluso en los familiares de primer grado de los pacientes (Schnell, Koethe, Daumann & Gouzoulis-Mayfrank, 2009). Además, éstos han mostrado ser mejores predictores del funcionamiento social y general de los pacientes que la sintomatología positiva y negativa de la enfermedad (Green, 1996; Harvey, Green, Keefe & Velligan, 2004), especialmente en el rendimiento en memoria verbal (Green, 1996; Matza et al., 2006). En este contexto, mayores déficits cognitivos han sido asociados a mayores admisiones psiquiátricas, mayor numero de recaídas, aumento de la duración de los ingresos hospitalarios, falta de adherencia al tratamiento, fracaso terapéutico y peor funcionamiento psicosocial en la comunidad (Jackson, Fein, Essock & Mueser, 2001; Mohamed, Bondi, Kasckow, Golshan & Jeste, 2006). Específicamente, déficits en planificación y

resolución de problemas pueden comprometer seriamente las habilidades de los pacientes para afrontar las exigencias diarias de su vida laboral y familiar (Levy et al., 2008).

Algunos estudios apuntan que la severidad del déficit cognitivo puede incluso predecir la remisión del TUS (Copersino et al., 2004; Goldman, 1990; Martinez-Aran et al., 2002). Así, déficits en el funcionamiento ejecutivo se han mostrado relacionados con los mecanismos básicos de control de los impulsos necesarios para el mantenimiento de la abstinencia, comprometiendo el cambio de foco cognitivo hacia otras conductas alternativas y la focalización hacia nuevas metas incompatibles con la conducta de consumo (Levy & Weiss, 2009; Thoma, Wiebel & Daum, 2007).

De modo similar, ciertos tipos de déficits cognitivos pueden ser predictores de los beneficios de las intervenciones psicoterapéuticas y farmacológicas, o del fracaso de las mismas. Por ejemplo, déficits en memoria y aprendizaje verbal pueden interferir con los abordajes psicológicos ya que requieren la comprensión, codificación y mantenimiento de grandes cantidades de material verbal y capacidad de flexibilidad cognitiva (Bowie et al., 2005).

Por lo tanto, el estudio de los aspectos neuropsicológicos puede contribuir sustancialmente al avance de las aproximaciones teóricas y clínicas en el manejo de los pacientes duales. En un futuro, esto puede ayudar a desarrollar estrategias más efectivas de tratamiento, individualizadas para cada paciente, así como terapias de rehabilitación cognitiva para prevenir y/o compensar los déficits neurocognitivos.

2.2 Rendimiento neurocognitivo en Patología Dual: variables moduladoras

Tradicionalmente, los pacientes duales se excluían de las investigaciones centradas en evaluar el rendimiento cognitivo en trastornos psiquiátricos y en drogodependencias, ya que se consideraban factores de confusión. Sin embargo, en la última década se ha producido un aumento de los trabajos publicados sobre neuropsicología de la PD en asociación con el reconocimiento de la relevancia de su estudio y la constatación de la elevada prevalencia de esta condición psiquiátrica. No obstante, los resultados existentes a día de hoy son heterogéneos y no contamos con un perfil cognitivo consistente en estos pacientes.

La hipótesis subyacente a todos los estudios neuropsicológicos se ha sustentado en los efectos aditivos en el detrimento cognitivo provocados tanto por la patología psiquiátrica como por el TUS, por lo que se esperaba un déficit más

severo en los pacientes que presentaban ambas condiciones. Mientras algunos autores sí han hallado déficits más pronunciado en los pacientes con PD respecto a los pacientes con Trastorno Mental Severo (TMS) no consumidores de sustancias (Allen, Goldstein & Aldarondo, 1999; Bowie et al., 2005; Chang et al., 2012; Levy et al., 2008; Manning et al., 2007; Mohamed et al., 2006; Serper et al., 2000; Serper, Copersino, Richarme, Vadhan & Cancro, 2000; Sevy et al., 2007; Shan et al., 2012; van Gorp, Altshuler, Theberge, Wilkins & Dixon, 1998), otros autores no han encontrado diferencias significativas (Addington & Addington, 1997; Copersino et al., 2004; Mata et al., 2008; Nixon, Hallford & Tivis, 1996; Sanchez-Moreno et al., 2009; Scholes & Martin-Iverson, 2010; van Gorp, Altshuler, Theberge & Mintz, 1999; Wobrock et al., 2007). Sorprendentemente, otros autores han obtenido incluso un mejor estado cognitivo en los pacientes duales en comparación con los TMS (DeRosse, Kaplan, Burdick, Lencz & Malhotra, 2010; Herman, 2004; Jockers-Scherubl et al., 2007; Joyal, Halle, Lapierre & Hodgins, 2003; Potvin et al., 2005; Rodriguez-Sanchez et al., 2010; Schnell et al., 2009; Smelson et al., 2002; Smelson et al., 2003; Thoma et al., 2007; Thoma & Daum, 2008).

En vista de la heterogeneidad de los resultados existentes, llevamos a cabo una revisión bibliográfica sobre la neurocognición en PD con diagnóstico de esquizofrenia y trastorno bipolar, coincidiendo con el primer objetivo de la presente tesis doctoral: comprender el estado actual de la investigación en rendimiento cognitivo en PD y delimitar los posibles factores metodológicos responsables de las diferencias halladas, lo cual ayudaría a trazar las líneas de acción que marcarían nuestros posteriores estudios (Ver estudio 1).

En nuestra revisión evidenciamos, entre otros factores metodológicos, tres ejes principales que podían explicar parte de las diferencias halladas entre los estudios: la edad de los participantes que constituían las muestras, el dominio cognitivo evaluado y el tipo de sustancia principal de abuso.

1) Edad de los pacientes. Los resultados generalmente apuntan a menores déficits cognitivos en los pacientes duales jóvenes comparados con aquellos de su misma edad pero sin TUS comórbido, mientras los duales de mayor edad suelen presentar mayores déficits cognitivos que sus homólogos sin TUS, especialmente en los casos de abuso o dependencia al alcohol. En esta línea, Mohamed et al., (2006) encontraron declive cognitivo en los pacientes esquizofrénicos consumidores de alcohol mayores de 55 años comparados con los de edad entre los 45-55 años y con los esquizofrénicos no duales, en habilidades de aprendizaje y memoria. Bowie et al. (2005) y Manning et al. (2007) también hallaron peores ejecuciones en atención y memoria en duales alcohólicos que se encontraban en la

década de los 40 y 50 años, comparados con sus análogos no consumidores. Asimismo, Allen et al. (1999) observaron una aceleración del déficit cognitivo en pacientes esquizofrénicos consumidores de alcohol a partir de los 40 años. No se dispone de suficientes datos acerca de la influencia de la edad en el trastorno bipolar, debido a que existen muy pocos estudios publicados. Sin embargo, los resultados de Levy et al. (2008) apuntan en la misma dirección que los trabajos con pacientes diagnosticados de esquizofrenia.

Tales resultados sugieren un daño cognitivo adicional en las décadas más tardías, al menos en los pacientes duales consumidores de alcohol, debido posiblemente a las consecuencias neurotóxicas del consumo expresadas a largo plazo, sumándose al déficit cognitivo inherente al del trastorno psiquiátrico. A pesar de ello, no existe consenso en la edad de aparición de este declive neurocognitivo. Por otra parte, en algunos estudios que no encontraron diferencias o encontraron incluso un mejor estado cognitivo en muestras de duales jóvenes, los grupos no duales presentaban edades significativamente mayores a las del grupo dual (Herman, 2004; Thoma et al., 2007; Thoma & Daum, 2008; Wobrock et al., 2007), por lo que los resultados podrían verse contaminados por la influencia de esta variable. Si bien existen pocos estudios que evalúen el efecto de la edad en el funcionamiento neuropsicológico de los pacientes duales, serían de gran interés estudios longitudinales que esclarecieran el grado de déficit asociado a la edad y cuándo es posible que éste aparezca.

2) Dominio cognitivo evaluado. Con frecuencia las funciones que se encuentran más preservadas en los pacientes duales, son la velocidad del procesamiento de la información (Potvin, Joyal, Pelletier & Stip, 2008; Schnell et al., 2009; Smelson et al., 2002; Smelson et al., 2003) y las ejecutivas (Herman, 2004; Joyal et al., 2003; Smelson et al., 2003; Thoma et al., 2007; Thoma & Daum, 2008). En cambio, los resultados de atención y memoria suelen ser más heterogéneos e inconsistentes. Si bien algunos autores no encuentran diferencias entre grupos, otros observan déficits generalizados en memoria verbal tanto en los duales con diagnóstico de esquizofrenia como de trastorno bipolar (Bowie et al., 2005; Levy et al., 2008; Serper et al., 2000; Serper et al., 2000).

Los estudios que encuentran un mejor rendimiento cognitivo en los pacientes duales, especialmente en las funciones ejecutivas, argumentan que ello puede explicarse por un mejor funcionamiento psicosocial premórbido en éstos (Arndt, Tyrrell, Flaum & Andreasen, 1992; Joyal et al., 2003; Potvin et al., 2008; Rabin, Zakzanis & George, 2011; Wobrock et al., 2007). La conducta de búsqueda de drogas requiere un alto nivel de habilidades sociales para establecer los contactos para su adquisición en contextos sociales duros, así como un alto requerimiento de

las funciones ejecutivas, especialmente en el caso de las sustancias de más difícil acceso como la cocaína (Schnell et al., 2009; Silverstein, Mavrolefteros & Close, 2002). La premisa de un mejor funcionamiento psicosocial premórbido junto a mayores habilidades cognitivas en estos pacientes, se encuadra dentro de la hipótesis etiopatogénica de una menor vulnerabilidad genética al trastorno mental en los pacientes duales.

Dado que los déficits cognitivos se consideran endofenotipos de la psicosis, estando ya presentes antes del debut de la enfermedad y también en las fases prodrómicas de la misma, e incluso en familiares de primer grado, un mejor estado cognitivo podría estar reflejando una menor vulnerabilidad biológica al trastorno psiquiátrico (Snitz et al., 2006).

Del mismo modo, también se han evidenciado déficits en el funcionamiento psicosocial antes de la aparición del trastorno, en pacientes con TMS sin TUS comórbido (Silverstein et al., 2002). Por lo tanto, el consumo de sustancias causaría la psicosis debido a disrupciones en el sistema dopaminérgico en pacientes menos vulnerables biológicamente, comparados con aquellos que desarrollan la enfermedad sin ningún desencadenante adicional (Benaiges, Serra-Grabulosa, Prat & Adan, 2013). Esta hipótesis, enmarcada en el modelo etiopatogénico del TUS como desencadenante del trastorno psiquiátrico, pretende explicar el consumo como factor precipitante de la psicosis, en lugar de mejorar la cognición en pacientes psiquiátricos puesto que el déficit cognitivo asociado al consumo ha sido ampliamente evidenciado. El estudio pionero de Potvin, Mancini-Marie, Fahim, Mensour & Stip (2007), utilizando resonancia magnética funcional, obtuvo resultados a favor de un mejor funcionamiento psicosocial en pacientes duales con diagnóstico de esquizofrenia. Los duales mostraron menos déficits que los no duales en el procesamiento de la información socio-emocional, con mayor activación de las áreas implicadas en la cognición social (Ver tabla 5). No obstante, se requiere más investigación en este ámbito de estudio dado que la mayoría de trabajos no incluyen medidas de funcionamiento psicosocial. El desarrollo de más estudios genéticos, también cabe suponer que permitirá dilucidar el peso de la carga genética para desarrollar la enfermedad en pacientes duales *vs* no duales en el futuro.

3) Tipo de sustancia principal de abuso. Los estudios suelen encontrar déficits más pronunciados en los casos de abuso o dependencia al alcohol y a la cocaína (Bowie et al., 2005; Manning et al., 2007; Mohamed et al., 2006; Serper et al., 2000; Serper et al., 2000). Sin embargo, debe tenerse en cuenta que especialmente los estudios de cocaína, han incluido muestras de pacientes con consumo reciente

y/o en fase de abstinencia aguda, con la posibilidad de que ello sea un factor de confusión en los resultados hallados (Serper et al., 2000; Serper et al., 2000).

Por otra parte, el consumo de cannabis aporta en numerosos trabajos un mejor rendimiento cognitivo en pacientes duales (Herman, 2004; Jockers-Scherubl et al., 2007; Potvin et al., 2005; Schnell et al., 2009; Scholes & Martin-Iverson, 2010; Sevy et al., 2007; Stirling, Lewis, Hopkins & White, 2005; Thoma et al., 2007; Thoma & Daum, 2008). Si bien el cannabis se ha asociado a un empeoramiento de la sintomatología psicótica y se considera un factor precipitante de la psicosis (Hambrecht & Hafner, 2000; Henquet et al., 2005), algunos autores defienden, desde un punto de vista especulativo, propiedades neuroprotectoras de los cannabionides, componentes activos de la marihuana, que ayudarían a preservar la cognición en pacientes con esquizofrenia, al menos cuando el consumo no es crónico y se hace a una determinada edad (Coulston, Perdices & Tennant, 2007; Potvin et al., 2008).

No obstante, estudiar los efectos aislados de una sola sustancia es difícil dada la elevada prevalencia de policonsumo en los pacientes duales (Cardoso et al., 2008; Dixon, 1999). Además, el estudio del policonsumo se complica por diferencias entre los patrones de abuso de cada sustancia, en términos de dosis, frecuencia y duración del consumo y tipos de sustancia. A pesar de ello, los estudios con muestras de policonsumidores suelen encontrar también un mejor rendimiento neurocognitivo en los pacientes con PD (Herman, 2004; Potvin et al., 2005; Thoma et al., 2007; Thoma & Daum, 2008). Para explicar estos resultados se han propuesto efectos positivos interactivos entre determinadas sustancias. Es decir, el consumo de algunas sustancias podría enmascarar o incluso proteger de las secuelas neurocognitivas de otras sustancias (Yucel, Lubman, Solowij & Brewer, 2007). Esta hipótesis necesita mayor investigación y en la actualidad carece de estudios que la sustenten.

Potvin, Stavro & Pelletier (2012) en una revisión posterior a la nuestra, además de confirmar los tres ejes propuso efectos de interacción entre ellos. Mientras las muestras de consumidores de cannabis y policonsumidores suelen estar comprendidas por pacientes jóvenes con un mejor funcionamiento ejecutivo, las muestras de consumidores de alcohol suelen comprender pacientes de mayor edad con déficits en memoria verbal. Todo ello, explica la falta de convergencia entre los resultados de los diferentes estudios.

Si bien se han llevado a cabo algunos estudios de neuroimagen estructural en pacientes duales, los hallazgos son tan heterogéneos como los procedentes de trabajos sobre rendimiento neurocognitivo (Ver tabla 5). En los estudios de

esquizofrenia, algunos autores encuentran menor volumen de materia gris y anomalías estructurales en las regiones prefrontales superiores anteriores (Mathalon, Pfefferbaum, Lim, Rosenbloom & Sullivan, 2003), puente cerebral (Sullivan, Rosenbloom, Serventi, Deshmukh & Pfefferbaum, 2003) y mayor dilatación ventricular en los duales comparados con homólogos no consumidores (Rais et al., 2008). Sin embargo, Deshmukh, Rosenbloom, De Rosa, Sullivan & Pfefferbaum (2005) y Sullivan et al. (2003) observaron mayor afectación subcortical en las regiones de putamen, caudado y núcleo acumbens en los esquizofrénicos que tomaban medicación antipsicótica atípica, respecto a los que tomaban antipsicóticos típicos, con independencia de la comorbilidad alcohólica en los participantes de la muestra (Sullivan et al., 2003). Por otra parte, Scheller-Gilkey et al. (1999) y Wobrock et al. (2010) hallaron una tendencia a un menor deterioro estructural en los duales comparados con los TMS.

Aunque los estudios de resonancia magnética con muestras de trastorno bipolar dual son escasos, cabe destacar el de Jarvis et al. (2008) quiénes encontraron alteraciones de naturaleza cortical y subcortical en adolescentes bipolares consumidores de cannabis respecto a los no consumidores. Nery et al. (2011) obtuvieron resultados muy similares en una muestra de pacientes bipolares adultos.

Tal discrepancia de resultados puede explicarse por las mismas variables moduladoras que aportan heterogeneidad a los resultados de los estudios sobre rendimiento cognitivo. Algunos autores ponen de manifiesto que los pacientes duales jóvenes pueden presentar mejor rendimiento cognitivo, debido al uso de áreas cerebrales adicionales que disimulan el déficit a través de mecanismos funcionales compensatorios (Thoma & Daum, 2008). El desarrollo de estudios con parámetros biológicos que incluyan medidas morfométricas cerebrales, determinaciones genéticas, neuroimagen estructural y funcional y potenciales evocados ayudarían a entender la complexidad de la patofisiología de la PD, así como los aspectos subyacentes al rendimiento cognitivo de estos sujetos. Desafortunadamente, todavía hay un largo camino por recorrer en este sentido.

Además, deben tenerse en cuenta otros factores metodológicos que difieren entre los estudios y que es necesario controlar de cara a la investigación futura por sus importantes implicaciones en la cognición.

El diagnóstico psiquiátrico es una variable importante a considerar. La mayoría de estudios se han llevado a cabo en pacientes con esquizofrenia y muy pocos han evaluado la neurocognición en bipolares duales. Además, la mayoría de estudios no especifican el tipo de esquizofrenia o trastorno bipolar que sufren los pacientes de la muestra. La investigación actual propone perfiles cognitivos diferenciales

según el subtipo diagnóstico de esquizofrenia y los resultados revelan un mejor funcionamiento cognitivo en los subtipos paranoide y esquizoafectivo respecto a los subtipos residuales y no especificado (Goldstein, Shemansky & Allen, 2005). Si bien en el trastorno bipolar los resultados son menos consistentes, algunos autores defienden un peor rendimiento cognitivo en los bipolares Tipo I respecto a los Tipo II (Hsiao et al., 2009), mientras otros encuentran un patrón de déficit similar entre ambos tipos (Dittmann et al., 2008). Algunos investigadores incluso consideran subtipos diagnósticos definidos según evaluaciones cognitivas, basados en la premisa que el estado cognitivo es más objetivo que la sintomatología, y está más vinculado a la neurobiología y a la genética de la enfermedad, así como al estado funcional. Así, los métodos de clúster análisis han identificado tres grupos de pacientes caracterizados por déficit moderado, severo y profundo o generalizado (Ammari, Heinrichs & Miles, 2010). Se requieren más trabajos en esta área que puedan ayudar a dilucidar la posibilidad de distintos perfiles neuropsicológicos de la PD según los subtipos diagnósticos.

El hecho que las muestras en los diversos estudios presenten consumo actual o un determinado tiempo de abstinencia, puede determinar en gran parte las diferencias en el rendimiento neuropsicológico. La recuperación de las funciones cognitivas según el tiempo de abstinencia, es un fenómeno poco estudiado en el campo de las drogodependencias y aún menos en PD. El hecho que algunos estudios no describan el tiempo de abstinencia en sus muestras, que el grupo no dual presente historia de consumo remoto, o no se verifique la abstinencia con pruebas objetivas como los controles urinarios, dificulta la interpretación de los resultados existentes. Además, la mayor parte de los estudios no contemplan la duración del TUS, ni tampoco la edad de inicio del consumo en los participantes de sus muestras. Lo que puede ser una importante variable de confusión aportando incongruencias en los resultados. Así, a mayor tiempo de duración del TUS cabría esperar mayor déficit cognitivo. Por otra parte, una edad temprana de inicio del consumo podría empeorar el déficit cognitivo en edades posteriores, si éste ha empezado antes de la completa maduración de los circuitos cerebrales relacionados con la cognición (Ehrenreich et al., 1999; Pope et al., 2003; Wilson et al., 2000). En este contexto, serían de gran interés estudios longitudinales que analicen largos periodos de abstinencia, con la finalidad de determinar la extensión de la recuperación del daño cognitivo, así como la influencia de la edad de inicio del consumo sobre el funcionamiento cognitivo a largo plazo.

Por otra parte, la potencia estadística en los estudios suele verse afectada por el reducido tamaño de las muestras. Si bien es difícil estudiar la PD dadas las complicaciones asociadas a estos pacientes, siendo probable que se nieguen a participar, incumplan con las sesiones o abandonen el estudio, la inclusión de

pocos pacientes en los estudios puede conducir a la ocurrencia de errores tipo II en los resultados. Es frecuente, además, que no se incluyan grupos control, ya sean grupos que presentan TUS sin diagnóstico psiquiátrico, grupos de controles sanos o comparaciones con datos normativos publicados - Este aspecto no permite establecer el grado de déficit neuropsicológico en los pacientes duales.

Además, las muestras suelen estar constituidas principalmente por hombres, debido a la elevada prevalencia masculina en PD. Esto dificulta la generalización de resultados a ambos géneros. Son necesarios estudios que tengan en cuenta la perspectiva de género en la PD, dado que numerosos estudios indican diferencias sexuales en la cognición, en las manifestaciones clínicas de la enfermedad, el pronóstico y la respuesta al tratamiento tanto en la patología psiquiátrica como en el TUS (Gearon & Bellack, 2000; Pellisier & Jones, 2005; Roth, Cosgrove & Carroll, 2004).

El régimen de tratamiento en el que se encuentran los participantes de las muestras también debe tenerse en cuenta como factor de confusión, puesto que los estudios difieren en pacientes evaluados bajo tratamiento ambulatorio y pacientes hospitalizados o en régimen de internamiento. Los pacientes hospitalizados pueden presentar déficits cognitivos más severos debido al florecimiento de la clínica psicótica aguda y el tratamiento farmacológico hipno-sedativo que suelen recibir en condiciones de ingreso psiquiátrico, mientras los pacientes ambulatorios suelen presentar más autonomía y una clínica psicótica estable, sugiriendo un mejor estado cognitivo (Benaiges et al., 2010; Levy et al., 2008).

Parte de las diferencias halladas entre los diversos estudios también puede deberse al empleo de diferentes pruebas neuropsicológicas para evaluar un mismo dominio cognitivo. La estandarización de una batería neuropsicológica que permita una evaluación exhaustiva de todos los dominios cognitivos podría eliminar, al menos en parte, algunas divergencias en los resultados hallados. Además, los estudios también difieren en los instrumentos utilizados para evaluar el TUS. Si bien la mayoría de estudios emplean la escala ASI (*Addiction Severity Index*) como instrumento fiable y válido en la evaluación del TUS (Kosten, Rounsaville & Kleber, 1983; McLelland, Luborsky & Cacciola, 1985) y de uso extendido tanto en la clínica como en la investigación, Carey, Kate, Cocco & Correia (1997) encontraron una pérdida de sus propiedades psicométricas cuando se aplicaba a población psiquiátrica, por lo que su empleo puede no ser apropiado en PD. En este sentido, la entrevista PRISM ha demostrado ser el instrumento de elección en los diagnósticos de comorbilidad de trastornos psiquiátricos con abuso y/o dependencia de sustancias (Hasin et al., 2006; Torrens et al., 2004). No obstante, la larga duración de su aplicación y el alto entrenamiento que requiere

para su uso correcto, hace que esta entrevista diagnóstica no esté incorporada en todos los dispositivos de salud mental. En la actualidad la entrevista SCID es la que se utiliza en la mayoría de redes asistenciales, presentando adecuados índices kappa en la clínica psiquiátrica general (San, 2004).

Debe tenerse en cuenta que entre la población psiquiátrica, especialmente en esquizofrenia y trastorno bipolar, se ha constatado una prevalencia de tabaquismo entre 2 y 3 veces superior a la de la población general (Baker et al., 2007; Ziedonis, Kosten, Glazer & Frances, 1994). Se han descrito prevalencias muy similares de consumo de metilxantinas respecto a la población general, en especial de cafeína, que a su vez se asocia al consumo de nicotina (Gurpegui et al., 2006). El consumo elevado de ambas sustancias, se ha justificado dentro de la hipótesis de la automedicación por varios autores, puesto que sus efectos sobre los receptores dopaminérgicos y colinérgicos contribuyen a mejorar el estado de humor disfórico provocado por la enfermedad, disminuir el estrés y contrarrestar los efectos secundarios del tratamiento psicofarmacológico antagonista dopaminérgico (Goff, Henderson & Amico, 1992; Mobascher & Winterer, 2008). Sin embargo, algunos estudios contradicen esta hipótesis ya que el consumo de estas sustancias estaba ya presente antes del debut de la enfermedad (Barnes et al., 2006). El consumo de nicotina y cafeína se ha asociado a efectos positivos en el rendimiento cognitivo, debido al incremento de la actividad dopaminérgica en las áreas corticales superiores, especialmente las frontales (Kumari & Postma, 2005). La mayoría de estudios publicados sobre rendimiento neuropsicológico en PD no suelen tomar en consideración, como posibles variables moduladoras, ni el consumo de nicotina ni el de cafeína.

Por otra parte, el uso crónico de medicación antipsicótica y anticolinérgica prescrita muy frecuentemente a estos pacientes, junto a otras medicaciones psicofarmacológicas, puede tener también efectos importantes sobre la cognición. Si bien los estudios describen el tratamiento farmacológico en los participantes de las muestras, no suelen evaluar su efecto sobre el rendimiento en las tareas neuropsicológicas.

A pesar de la enorme dificultad que supone controlar estas variables en los trabajos clínicos, se requiere un esfuerzo en esta línea que permita avanzar en el conocimiento de su influencia sobre la neurocognición en pacientes con PD y poderlas distinguir de la afectación cognitiva inherente a la propia patología.

En resumen, la edad de los sujetos que constituyen las muestras, el dominio cognitivo evaluado y la sustancia principal de abuso, son variables que interactúan

entre ellas configurando perfiles cognitivos diferenciales en los pacientes duales. En la actualidad, debe desarrollarse más investigación que tenga en cuenta estas tres variables para focalizar el objetivo de estudio y que controle además la ocurrencia de otras posibles variables moduladoras del rendimiento cognitivo como el diagnóstico psiquiátrico, el consumo de sustancias -tabaco y cafeína- y la medicación psicofarmacológica. Estudios que incorporen muestras amplias, que tengan en cuenta el sexo en el reclutamiento de la muestra, la duración, severidad y edad de inicio del TUS, con controles de abstinencia verificados y que utilicen instrumentos de evaluación válidos y fiables pueden contribuir a encontrar resultados más robustos y consistentes en el rendimiento cognitivo de la PD.

Tabla 3. Resumen de los principales hallazgos de estudios cognitivos en trastorno bipolar dual posteriores a nuestra revisión teórica.

Autores	Muestra	TUS	Resultados	Comentarios
Chang et al. (2012)	•TB-I- (n=22) •TB-II- (n=38) •TB-I+ (n=16) •TB-II+ (n=18) •CS (n= 29)	Abuso/ Dependencia Alcohol	•CS > TB-I-/+ y TB-II-/+ •TB-I+, TB-II+ < TB-I-, TB-II- en memoria, atención, velocidad de procesamiento y funciones ejecutivas.	•Pacientes ambulatorios/ ingresados no disponible. •Evaluación inter-episódica. •Tiempo de abstinencia no disponible.
Shan et al. (2011)	•TB-II- (n=28) •TB-II+ (n=19) •CS (n=22)	Abuso/ Dependencia Alcohol	•CS > TB-II-, TB-II+ •TB-II+ < TB-II- en memoria verbal y visual, atención, velocidad de procesamiento y funciones ejecutivas.	•Pacientes ambulatorios/ ingresados no disponible. •Evaluación inter-episódica. •Tiempo de abstinencia no disponible.

CS: Controles sanos; **TB-I-:** Trastorno bipolar tipo I sin TUS; **TB-II-:** Trastorno Bipolar tipo II sin TUS; **TB-I+:** Trastorno Bipolar tipo I con TUS comórbido; **TB-II+:** Trastorno bipolar tipo II con TUS comórbido.

Tabla 4. Resumen de los principales hallazgos de estudios cognitivos en esquizofrenia dual posteriores a nuestra revisión teórica o no contenidos en el trabajo por no cumplir los criterios de inclusión.

Autores	Muestra	TUS	Resultados	Comentarios
Sevy et al. (2001)	•SZ+ (n=27) •SZ- (n = 91)	Abuso/ Dependencia Cannabis Alcohol Cocaína Alucinógenos opiáceos	•SZ+ > SZ- en funcionamiento cognitivo premórbido, CI general y habilidades verbales. •SZ+ = SZ- en atención, memoria y funcionamiento ejecutivo.	•Pacientes ingresados. •PEP. •Tiempo mínimo de abstinencia de 2 semanas.
Copersino et al. (2004)	•SZ+ (n=23) •SZ- (n=19) •TUS (n=20) •CS (n=20)	Dependencia Cocaína	•CS > TUS > SZ+, SZ- en memoria verbal.	•Pacientes ingresados. •Consumo actual.
De Rosse et al. (2010)	•SZ+ (n=175) •SZ- (n=280)	Abuso/ Dependencia Cannabis	•SZ+ > SZ- en velocidad de procesamiento de la información, fluencia verbal, aprendizaje y memoria verbal. •SZ+ = SZ- en atención y memoria de trabajo.	•Pacientes ingresados y ambulatorios. •Tiempo mínimo de abstinencia de 1 mes.
Jockers-Scherübl et al. (2007)	•SZ+ (n=19) •SZ- (n=20) •TUS (n=21) •CS (n=18)	Abuso Cannabis	•CS y TUS > SZ+, SZ- en CI verbal premórbido, atención, memoria verbal y funciones ejecutivas. •SZ+ > SZ- en velocidad de procesamiento.	•Pacientes ambulatorios. •Tiempo mínimo de abstinencia de28 días.
Mata et al. (2008)	•SZ+ (n=61) •SZ- (n= 71)	Abuso Cannabis Alcohol Cocaína Alucinógenos Opiáceos	•SZ+ < SZ- en CI verbal. •SZ+ < SZ- en toma de decisiones. •SZ+ = SZ- en memoria de trabajo y funciones ejecutivas.	•Pacientes ambulatorios. •PEP. •Tiempo de abstinencia no disponible.
McCleery et al. (2006)	•SZ+TUS moderado (n=57) •SZ+TUS severo (n=91) •SZ- (n=35)	Abuso Cannabis Alcohol Cocaína Alucinógenos opiáceos	•SZ+ TUS moderado y TUS leve > SZ- en factor cognitivo general, atención, memoria verbal y visual, velocidad de procesamiento, habilidad viso-espacial, flexibilidad cognitiva y habilidad cognitiva premórbida. •SZ+TUS moderado = SZ+TUS leve.	•Régimen de tratamiento no disponible. •PEP. •Tiempo de abstinencia no disponible.
Rodríguez-Jiménez et al. (2010)	•SZ+ (n=82) •SZ- (n=121)	Abuso/ Dependencia Cannabis Alcohol	•SZ+ = SZ- en funciones ejecutivas.	•Pacientes ambulatorios. •Tiempo mínimo de abstinencia de 1 mes.

		Cocaína Opiáceos		
Rodríguez-Sánchez et al. (2010)	•SZ+ (n=47) •SZ- (n=57) •CS (n=37)	Abuso Cannabis Alcohol Cocaína Alucinógenos Anfetaminas Opiáceos	•CS > SZ+, SZ- en atención, memoria de trabajo y memoria verbal y visual, funciones ejecutivas y velocidad del procesamiento. •CS = SZ+, SZ- en velocidad y coordinación motora. •SZ+> SZ- en atención y funciones ejecutivas.	•Pacientes ambulatorios. •PEP. •Consumo actual.
Scholes & Martin-Iverson (2010)	•SZ+(n= 22) •SZ- (n=50) •CS (n=38) •TUS (n=36)	Abuso Cannabis	•CS = TUS < SZ+, SZ- en atención, memoria y funciones ejecutivas. •SZ+ = SZ- en atención, memoria de trabajo y funciones ejecutivas.	• Pacientes ingresados y ambulatorios. •Consumo actual.

CI: Coeficiente Intelectual; **CS:** Controles Sanos; **PEP:** Primer Episodio Psicótico; **SZ-:** Esquizofrenia sin TUS comórbido; **SZ+**: Esquizofrenia con TUS comórbido; **TUS:** Trastorno por Uso de Sustancias.

Tabla 5. Resumen de estudios con evaluaciones de Resonancia Magnética estructural y funcional en esquizofrenia y trastorno bipolar dual.

Autores	Muestra	TUS	Resultados	Comentarios
Scheller-Gilkey et al. (1999)	•SZ+ (n=103) •SZ- (n=73)	Abuso/ Dependencia Alcohol Policonsumo	SZ+ = SZ- en anormalidades del volumen cerebral.	•Pacientes ambulatorios/ hospitalizados. •TUS actual.
Mathalon et al. (2003)	•SZ+ (n=35) •SZ- (n=64) •TUS (n=62) •CS (n=62)	Abuso/ dependencia Alcohol	SZ+ < SZ-, TUS < CS volumen de materia gris, y volumen de las regiones prefrontales superiores anteriores.	•Pacientes hospitalizados. •Tiempo mínimo de abstinencia 30 días.
Sullivan et al. (2003)	•SZ+ (n=19) •SZ- (n=27) •TUS (n=25) •CS (n= 51)	Dependencia Alcohol	•CS > TUS, SZ+, SZ-en volumen del puente y el tálamo cerebral. •SZ+ < SZ- en puente cerebral.	•Pacientes hospitalizados. •Muestra total constituida por hombres. •Tiempo de abstinencia no disponible.
Deshmuk (2005)	•SZ+ (n=19) •SZ- (n=27) •TUS (n=25) •CS (n=51)	Abuso/ dependencia Alcohol	•CS > SZ+, SZ-, TUS en volumen de putamen, caudado y núcleo acumbens. •SZ+ = SZ- = TUS en volumen del caudado. •TUS > SZ+, SZ- en volumen putamen y núcleo acumbens.	•Pacientes ambulatorios/ hospitalizados. •Muestra total constituida por hombres. •Tiempo de abstinencia dividido en recientes: < 3 semanas y a largo plazo > 3 semanas.

Potvin et al. (2007)	•SZ+ (n=12) •SZ- (n=11)	Abuso Alcohol Cannabis	SZ+ > SZ- en la activación del córtex prefrontal medial derecho, y giro supramarginal derecho.	•Pacientes ambulatorios/ hospitalizados. •Tiempo de abstinencia no disponible. •Resonancia Magnética funcional.
Jarvis et al. (2008)	•TB+ (n=7) •TB- (n=7)	Abuso/ Dependencia Cannabis Alcohol	•TB+ < TB - volumen de materia gris en regiones corticales frontales y temporales. •TB+ > TB- volumen de materia gris en giro fusiforme derecho y núcleo caudado derecho.	•Pacientes hospitalizados. •Trastorno Bipolar Tipo I. •Estudio longitudinal a 2 años. •TUS actual.
Rais et al. (2008)	•SZ+ (n=19) •SZ- (n=32) •CS (n=31)	Abuso/ Dependencia Cannabis Policonsumo	•SZ+ < SZ- < CS en volumen de materia gris •SZ+ > SZ-, CS en volumen del ventrículo lateral y tercer ventrículo	•Pacientes hospitalizados. •PEP. •Estudio longitudinal a 5 años. •TUS actual.
Wobrock et al. (2010)	•SZ+ (n=20) •SZ- (n=21)	Abuso/ Dependencia Cannabis Policonsumo	•SZ+ = SZ- en volumen de regiones temporo-límbicas (amígdala, hipocampo, giro temporal superior y cingulado.	•Pacientes hospitalizados. PEP. •Tiempo de abstinencia no disponible.
Nery et al. (2011)	•TB+ (n=21) •TB-(n=21) •CS (n=25)	Abuso/ dependencia Alcohol	TB+ < TB-, CS en volumen de materia gris en el giro cingulado anterior y córtex medial frontal.	•Pacientes ambulatorios/ hospitalizados no disponible. •Trastorno Bipolar Tipo I. •Tiempo mínimo de abstinencia 6 meses.

CS: Controles Sanos; **PEP:** Primer Episodio Psicótico; **SZ-:** Esquizofrenia sin TUS comórbido; **SZ+**: Esquizofrenia con TUS comórbido; **TB-:** Trastono Bipolar sin TUS comórbido; **TB+:** Trastorno Bipolar con TUS comórbido; **TUS:** Trastorno por Uso de Sustancias.

2.3 A propósito de la esquizofrenia y la adicción a la cocaína

La relación entre consumo de sustancias psicoestimulantes y esquizofrenia, merece especial consideración dada la proliferación de estudios que evidencian asociaciones entre dicho consumo y la aparición de cuadros psicóticos, en muchos casos persistentes (McKetin, McLaren, Lubman & Hids, 2006).

El consumo de psicoestimulantes entre la población afectada de esquizofrenia se ha estimado que es 4 veces mayor al de la población general (Roncero, 2007), siendo además característica una mayor persistencia del consumo a lo largo del tiempo respecto a los consumidores no esquizofrénicos y una mayor frecuencia de

ingresos hospitalarios por descompensaciones psicóticas, a pesar de que exista una buena adherencia al tratamiento antipsicótico (Brady et al., 1990; Duke, Pantelis, McPhillips & Barnes, 2001; Richard, Liskow & Perry, 1985). Mientras entre las sustancias psicoestimulantes ilegales la más prevalente en cuanto a consumo es la cocaína (Patkar, Alezander, Lundy & Certa, 1999), entre los psicoestimulantes legales destacan las xantinas (cafeína y teofilina) y la nicotina (Casas, Roncero, Castells & Ramos, 2006). Ver tabla 6.

La acción de los psicoestimulantes se caracteriza principalmente por aumentar los niveles de dopamina en las transmisiones sinápticas, aunque con diferentes mecanismos de acción según el tipo de sustancia. Si bien la hipótesis general compartida por muchos autores para explicar la elevada prevalencia de su consumo entre la población psicótica ha sido la hipótesis de la automedicación, sobre todo en los casos de psicosis crónicas (Laudet et al., 2000; North, Pollio, Smith & Spitznagel, 1998; van Harten, van Trier, Horwitz, Matroos & Hoek, 1998), los hallazgos de la investigación no permiten extraer conclusiones acerca de la verificación de esta hipótesis (Carnwath, Garvey & Holland, 2002).

Tabla 6. Prevalencia de consumo de drogas en pacientes con esquizofrenia.

Sustancia	Prevalencia estimada (%)
Cocaína	21-30
Anfetaminas	10-65
Nicotina	90
Cafeína	90
Alcohol	20-60
Cannabis	12-42
Opiáceos	4-12

Tomada de (Roncero, Barral, Grau-López, Esteve, & Casas, 2010)

Entre los pacientes esquizofrénicos es especialmente elevado el consumo de cocaína, con estimaciones que varían entre el 21 y el 30% dependiendo de los estudios (Batel, 2000), aunque hay autores que elevan la prevalencia al 50% debido al aumento de su consumo en los últimos años (WHO, 2004). Esto merece especial atención dado que se han descrito exacerbaciones en el curso de la esquizofrenia debido al consumo de cocaína, provocando en los pacientes estados disfóricos, ansiedad, depresión, insomnio, agitación y aumento de la agresividad (Alterman, Erdlen, Laporte & Erdlen, 1982; Yesavage & Zarcone, 1983). Estos pacientes suelen tener, además, una historia previa de actos violentos a diferencia de los esquizofrénicos consumidores de alcohol y/o cannabis (Miles et al., 2003).

El consumo de psicoestimulantes también parece que crea interferencias con el tratamiento antipsicótico, produciendo peor tolerabilidad a los fármacos y mayor incidencia de efectos adversos extrapiramidales (Potvin, Blanchet & Stip, 2009).

Los estudios del rendimiento neurocognitivo en pacientes esquizofrénicos con consumo de cocaína, aun siendo escasos, apuntan a la presencia de un peor rendimiento en la memoria verbal (Serper et al., 2000; Serper et al., 2000; Sevy, Kay, Opler & van Praag, 1990). Sin embargo, algunos autores no han hallado diferencias en el funcionamiento neuropsicológico de estos pacientes respecto a sus homólogos sin TUS (Cooper et al., 1999; Copersino et al., 2004). Como se ha mencionado anteriormente, diferencias en el tiempo de abstinencia entre los distintos estudios, pueden dar cuenta de la heterogeneidad de resultados puesto que la mayoría evaluaron las muestras tras un consumo reciente de cocaína, con posibles efectos de intoxicación y de abstinencia aguda interfiriendo en el rendimiento cognitivo.

Por otro lado, la premisa de Schnell et al. (2009) de un mejor funcionamiento ejecutivo en los pacientes esquizofrénicos que consiguen sustancias ilegales de difícil acceso como la cocaína, nos abrió a la hipótesis de efectos diferenciales del consumo de cocaína según el dominio cognitivo evaluado. Dada la escasez de estudios focalizados en muestras de esquizofrénicos dependientes a la cocaína y la necesidad de su estudio, debido a la elevada prevalencia de ambas condiciones y a sus complicaciones psiquiátricas derivadas, hemos creído relevante trabajar en esta línea de trabajo, ahondando en el peso del consumo de cocaína sobre el rendimiento cognitivo en pacientes duales con diagnóstico de esquizofrenia, según el dominio cognitivo evaluado. Respaldándonos en los resultados previos publicados, esperábamos un mejor funcionamiento ejecutivo en los pacientes esquizofrénicos consumidores de cocaína, mientras otros dominios cognitivos como el de la memoria verbal, podrían encontrarse comprometidos como consecuencia de su consumo.

Así, reclutamos una muestra de hombres con diagnóstico de esquizofrenia y dependencia a la cocaína como sustancia principal de abuso, según criterios DSM-IV-TR, que debían presentar un tiempo mínimo de abstinencia de 4 meses para evitar efectos de abstinencia aguda, la cual se verificó mediante análisis toxicológicos. Se seleccionó un conjunto de pruebas neuropsicológicas estandarizadas, válidas y fiables para la evaluación de diversas habilidades cognitivas, utilizadas en diversos estudios previos con la finalidad de poder establecer comparaciones de resultados. Se tuvieron en cuenta la edad de los participantes, el consumo de sustancias como la nicotina, la cafeína y la medicación psicofarmacológica, así como la edad de inicio del consumo y la

duración del TUS en los datos de rendimiento cognitivo. Todo ello contribuye a superar algunas de las limitaciones principales existentes en los trabajos precedentes publicados. Del reclutamiento de esta muestra surgieron dos estudios (Ver Estudio 3 y Estudio 4), en los cuales los respectivos apartados de material y método presentan una descripción detallada de las características de la muestra, los criterios de inclusión y exclusión, así como de los materiales y análisis estadísticos utilizados.

3. CALIDAD DE VIDA Y PATOLOGÍA DUAL

3.1 Definición de calidad de vida y calidad de vida relacionada con la salud

La Organización Mundial de la Salud (grupo WHOQOL, 1995) ha definido la Calidad de Vida (CV) como "*individuals perceptions of their position in life in the context of culture and value systems in which they live, and in relation to their goals, expectations, standards and concerns*" (p. 1405). En las últimas dos décadas, se ha producido un aumento en el interés por la CV como medida de evaluación de las intervenciones asistenciales, los efectos adversos del tratamiento y el impacto de la enfermedad a lo largo del tiempo (Zubaran & Foresti, 2009), especialmente en población psiquiátrica (Schaar & Öjehagen, 2009). Muestra de ello es la creación de revistas científicas especializadas, como la *Health and Quality of Life Outcomes* y la *Quality of Life Research,* incorporadas en las principales bases de datos y ocupando posiciones en cuartiles superiores.

Si bien la medición de la CV ha demostrado su utilidad en estudios observacionales, investigaciones epidemiológicas y en la práctica clínica, como indicador de resultados globales terapéuticos (Meijer, Koeter, Sprangers & Schene, 2009; Watson, Swan & Nathan, 2011), la CV depende de los sistemas particulares de valores que se modifican en el tiempo y en el espacio, siendo heterogénea y diversa. Esto contribuye a que exista una falta de consenso en la

definición del constructo CV y que sean pocos los estudios que la incorporen como medida de evaluación en poblaciones especiales de pacientes, como es el caso de la PD.

Un concepto estrechamente relacionado con el de CV es el de Calidad de Vida Relacionada con la Salud (CVRS), como una medida subjetiva del impacto de la enfermedad y su tratamiento en la vida del sujeto. A diferencia de la CV, la CVRS se restringe a un número limitado y bien definido de dimensiones, como el área de la sintomatología, la inhabilidad y al estatus funcional de salud mental y física (Eack & Newhill, 2007). Dichas dimensiones se hallan influenciadas indirectamente por los factores que también afectan a la CV, como la interacción social y el estatus económico, aunque no se contemplen directamente en los instrumentos de medida. La CVRS se refiere pues, a la experiencia subjetiva del impacto de las condiciones de salud y de los síntomas sobre la CV (Eack & Newhill, 2007; Meijer et al., 2009). Si bien la CV y la CVRS son constructos diferentes, con instrumentos de medición específicos y no intercambiables, presentan correlaciones en los dominios de salud mental y funcionamiento físico (Zubaran & Foresti, 2009).

3.2 Aplicabilidad en el ámbito de la Patología Dual

La CVRS es un indicador importante del funcionamiento y de la prognosis del paciente y ha sido ampliamente estudiada en poblaciones generales y específicas (Kilbourne et al., 2009). Los trabajos realizados hasta el momento, observan la afectación tanto de la CV como de la CVRS en trastornos psiquiátricos crónicos como la esquizofrenia y el trastorno bipolar (Brissos, Dias, Carita & Martinez-Aran, 2008; Eack & Newhill, 2007; Kao, Liu, Chou & Cheng, 2011; Meijer et al., 2009; Saarni et al., 2010), así como en los trastornos por dependencia de sustancias (Gonzalez-Saiz, Rojas & Castillo, 2009; Lozano et al., 2008; Pyne et al., 2011).

La evaluación en pacientes con PD tanto de la CV como de la CVRS, puede ayudar a identificar áreas de atención específica y clínicas debido a las características especiales en esta población: recaídas más rápidas (Bebout, Drake, Xie, McHugo & Harris, 1997), mayor número de rehospitalización y encarcelamiento (Drake, Osher & Wallach, 1991), menor participación en los servicios de atención sanitaria, más pérdida del soporte social y de problemas financieros (Drake et al., 1991; Lamb & Lamb, 1990; Watson et al., 2011). Todos estos factores podrían ser indicativos de una menor CV en pacientes afectados de PD, y su detección y atención clínica podrían mejorar la eficacia de las intervenciones. A su vez, la CV y la CVRS también pueden representar una

medida útil para evaluar la eficacia de las intervenciones, especialmente de los tratamientos integrados específicos para PD.

Si bien existen pocos estudios que exploren la CV en PD, la mayoría de los datos publicados hasta el momento muestran peor CV en los pacientes duales. Singh, Mattoo, Sharan & Basu (2005) obtuvieron una peor CV general en pacientes duales con trastorno bipolar comparados con pacientes bipolares sin TUS, con pacientes con TUS sin trastorno psiquiátrico y con un grupo de controles sanos. Kilbourne et al. (2009) encontraron que el uso de drogas ilegales se asociaba con un peor estado en el dominio mental de la CVRS en pacientes con trastorno bipolar, y que este efecto se mantenía al cabo un año, incluso controlando los síntomas maníacos y depresivos de la enfermedad. Kalman et al. (2004), también observaron un peor estado en el dominio mental de la CVRS en una muestra de pacientes duales con diagnósticos psiquiátricos heterogéneos, comparados con sujetos con TMS sin historia de TUS y con un grupo con dependencia al alcohol sin comorbilidad psiquiátrica. Bizzarri et al. (2005) también encontraron una peor puntuación en todos los dominios evaluados de CV en pacientes duales con dependencia al opio, comparados con dependientes sin trastorno mental concomitante, siendo las diferencias más acusadas en los dominios de funcionamiento mental y físico. Y en el estudio de Fassino, Daga, Delsedime, Rogna & Boggio (2004) los pacientes dependientes de heroína con trastorno de personalidad comórbido, presentaban peor CV que aquellos sin trastorno de personalidad comórbido.

Sin embargo, algunos trabajos no obtienen diferencias como el de Astals et al. (2008), que evaluó la CVRS en pacientes con y sin trastorno psiquiátrico concomitante, bajo tratamiento de dependencia a la heroína. En el estudio de Garg, Yates, Jones, Zhou & Williams (1999), los duales presentaron peores puntuaciones en la dimensión de Vitalidad, pero no en los dominios de salud mental y funcionamiento físico. Por último, Wade, Harrigan, McGorry, Burgess & Whelan (2007), en una muestra de pacientes jóvenes con primer episodio psicótico, observaron que la afectación de la CV y el funcionamiento social se relacionaban con el nivel de severidad del consumo de sustancias. Así, la CV en pacientes con consumo moderado no difería de la de no consumidores, siendo ésta peor en los pacientes con consumo elevado.

La disparidad de definiciones sobre CV, la confusión y no diferenciación con el concepto de CVRS, así como las diferencias en la selección y el tamaño de las muestras en el diseño de los estudios y en los procedimientos e instrumentos de evaluación, pueden ser factores explicativos de la disparidad de resultados existentes (Ver Tabla 7).

Sería de gran interés que en el futuro se estudie tanto la CV como la CVRS en la población dual, definiendo ambos constructos adecuadamente. Las muestras deberían incorporar tres grupos experimentales: un grupo con PD, otro grupo con TMS y un tercer grupo con TUS, para observar el peso de cada condición psiquiátrica sobre la afectación de la CV y de la CVRS. Idealmente, también es de interés estudiar un grupo de controles sanos o a falta de éste, establecer comparaciones con datos normativos poblaciones, precisando el grado de deterioro en cada uno de los grupos. Una evaluación clínica detallada que tenga en cuenta también el consumo de otras sustancias como la cafeína y la nicotina, sustancias habituales de consumo en la población psiquiátrica, podría identificar factores asociados al detrimento de la CV y que por tanto, deberán tenerse en cuenta como objetos de intervención en el tratamiento de estos pacientes.

Examinar tanto la CV como la CVRS en PD es importante tanto como complemento al criterio diagnóstico, como a nivel de evaluación y de resultados globales, además de su posible utilidad como pauta adicional para planificar los objetivos de tratamiento, de acuerdo a las necesidades específicas de esta población. La evaluación mediante cuestionarios válidos y fiables, que ofrezcan puntuaciones tanto en los dominios generales como específicos de la CV y CVRS aporta información útil en el establecimiento de las metas terapéuticas, pudiendo ello aumentar la eficacia de las intervenciones. La mejora tanto de la CV como de la CVRS y el manejo terapéutico de los factores asociados a su detrimento en PD, podría beneficiar el funcionamiento y la prognosis de estos pacientes, reduciendo la morbilidad y los costes sociales y sanitarios que supone una entidad diagnóstica de tal envergadura.

Tabla 7. Resumen de los principales hallazgos en los trabajos de Calidad de Vida y Patología Dual.

Autores	Muestra	Instrumento	CV/ CVRS	Resultados	Comentarios
Astals et al. (2008)	•PD (n=83) •TUS (n=106)	SF-12	CVRS	PD = TUS	•Grupo PD diagnósticos psiquiátricos heterogéneos. •Muestra total constituida por dependientes a opiáceos.
Bizarri et al. (2005)	•PD (n=41) •TUS (n=57) •CS (n=45)	WHOQOL-BREF	CV	PD < TUS< CS	•Grupo PD diagnósticos psiquiátricos heterogéneos. •Muestra total constituida por dependientes a opiáceos.
Fassino et al. (2004)	•PD (n=115) •TUS (n=55)	MQOL	CV	PD < TUS	•Grupo PD diagnóstico de Trastornos de la Personalidad. •Muestra total constituida por dependientes de la heroína.
Garg et al. (1999)	•PD (n=45) •TUS (n=58)	SF-36	CVRS	PD = TUS	•El grupo PD solo presentó peores puntuaciones en la dimensión de Vitalidad respecto al grupo TUS.
Kalman et al. (2004)	•PD (n=16) •TUS (n=2) •TMS (n=13) •CS (n=100)	SF-36	CVRS	PD < TMS < TUS < CS	•Grupos PD y TMS diagnósticos psiquiátricos heterogéneos. •Grupo TUS dependencia al alcohol.
Kilbourne et al. (2009)	•PD (n=151) •TMS (n=183)	SF-12	CVRS	PD < TMS	•Muestra total constituida por trastorno bipolar tipo I y tipo II. •Grupo PD policonsumo.
Singh et al. (2005)	•PD (n=40) •TMS (n=40) •TUS (n=40) •CS (n=100)	WHOQOL-BREF	CV	PD < TMS = TUS < CS	•Grupos PD y TMS constituidos por trastorno bipolar. •Grupos PD y TUS policonsumo.
Wade et al. (2007)	•PD con TUS grave (n=21) •PD con TUS moderado (n=27) •TMS (n=44)	QLS	CV	PD con TUS grave < PD con TUS moderado = TMS	•Muestra total constituida por trastorno psicótico.

CS: controles sanos; **MQOL:** *McGill Quality of Life Questionnaire*; **PD:** Patología Dual; **QLS:** *Quality of Life Scale*; **SF-12:** *Short-Form 12 Item Health Survey*; **SF-36:** *Short-Form 36 Item Health survey*; **TMS:** Trastorno Mental Severo; **TUS:** Trastorno por Uso de Sustancias; **WHOQOL-BREF:** *The World Health Organization Quality of Life A*

4. OBJETIVOS DE LA TESIS

El objetivo general de la tesis aquí presentada, es la descripción del estado de la CVRS y del rendimiento neuropsicológico en PD, así como dilucidar posibles factores socio-demográficos y clínicos asociados a los resultados obtenidos, que permitan una caracterización más precisa de esta patología aportando nuevos datos que verifiquen, o por el contrario, refuten las diferentes hipótesis existentes en la actualidad. Con ello, pretendemos contribuir al saber teórico y práctico de la PD, con especial énfasis en la implicación de nuestros resultados en los abordajes terapéuticos destinados a la mejora del funcionamiento psicosocial y la calidad de vida de los pacientes duales.

Para alcanzar el objetivo general, ha sido necesario trazar dos líneas de estudio: una destinada a la evaluación de la CVRS y la otra al rendimiento neuropsicológico, con objetivos específicos y sub-objetivos dentro de cada línea de estudio, que han dado como fruto las diferentes publicaciones que componen esta tesis (Ver Figura 3). Debe tenerse en cuenta que la presentación de los objetivos y los trabajos que de ellos se han derivado, no obedecen a una línea temporal secuencial. El orden de presentación se establece como sigue por mantener una estructura lógica entendible para el lector, más bien que por orden del trabajo realizado y de publicaciones en el tiempo.

4.1 Objetivos específicos del estudio de rendimiento neuropsicológico

1. Llevar a cabo una revisión bibliográfica para comprender el estado actual de la investigación en rendimiento cognitivo en PD y delimitar los posibles factores metodológicos responsables de las diferencias halladas, lo cual sería el punto de partida para sentar las bases de los estudios experimentales posteriores (Ver estudio 1).

2. Evaluar el funcionamiento ejecutivo relacionado con el funcionamiento del córtex frontal (especialmente córtex dosrsolateral y orbitofrontal) en participantes con diagnóstico de esquizofrenia y/o adicción a la cocaína. De este objetivo se desprenden otros sub-objetivos (Ver estudio 2):

    a) Deslindar el posible patrón diferencial en el funcionamiento ejecutivo de pacientes esquizofrénicos con y sin adicción a la cocaína comparado con adictos a la cocaína sin diagnóstico de esquizofrenia.

    b) Ahondar en la hipótesis de una menor vulnerabilidad biológica a la psicosis en los pacientes duales, enmarcada en el modelo etiológico del TUS como desencadenante del trastorno psiquiátrico.

    c) Explorar el efecto diferencial de la edad de inicio de consumo sobre el funcionamiento ejecutivo.

3. Evaluar el rendimiento cognitivo en los dominios de atención, memoria verbal y velocidad del procesamiento de la información en pacientes con diagnóstico de esquizofrenia y/o adicción a la cocaína. De este objetivo se desprenden dos sub-objetivos (Ver estudio 3):

    a) Deslindar el peso de la esquizofrenia y la adicción a la cocaína en el rendimiento cognitivo en función de la presencia o ausencia de comorbilidad diagnóstica en los tres grupos experimentales.

    b) Explorar el efecto de la edad de los pacientes y de la duración del TUS sobre el rendimiento en cada uno de los dominios cognitivos evaluados, según el grupo diagnóstico.

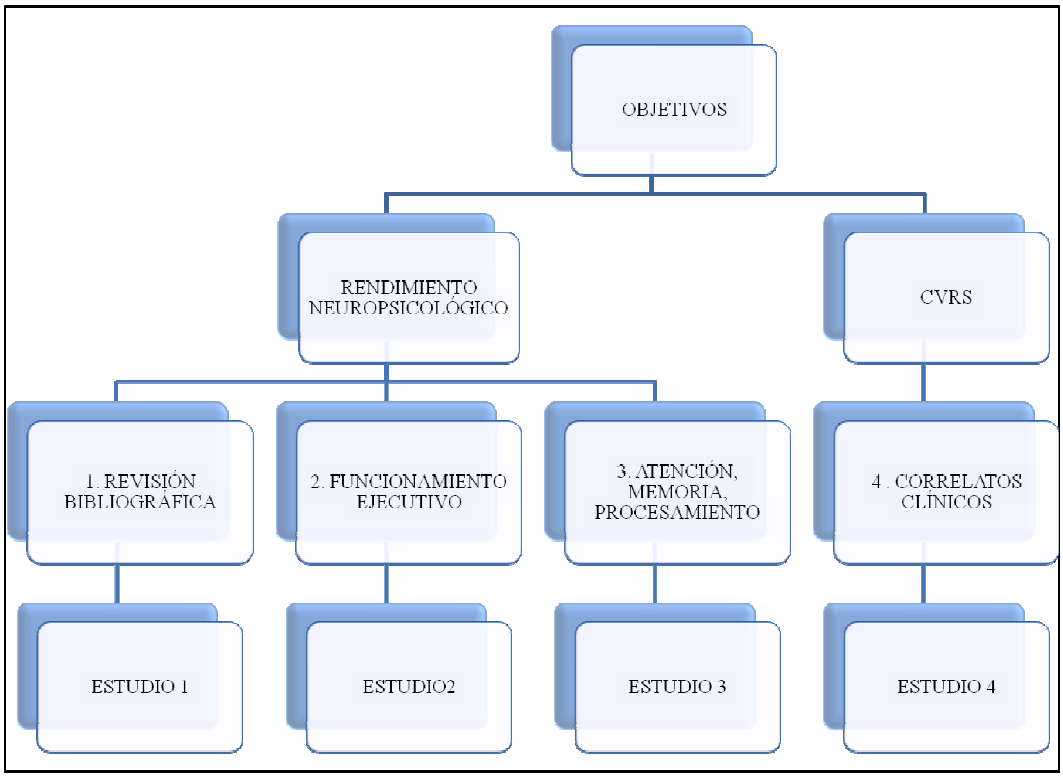
4.2 Objetivos específicos del estudio de CVRS

4. Evaluar el estado de la CVRS en una muestra de pacientes duales y compararlos con dos grupos no duales y con los valores normativos españoles de referencia (Ver estudio 4):

    a) Deslindar el peso del TMS y el TUS en la afectación de todas las dimensiones de la CVRS en función de la presencia o ausencia de comorbilidad diagnóstica en los tres grupos experimentales.

b) Explorar correlatos clínicos asociados al detrimento de la CVRS con especial énfasis en el grupo dual.

Figura 3. Objetivos de la tesis doctoral.



CVRS: Calidad de Vida Relacionada con la Salud.

5. RESULTADOS

5.1 Compendio de artículos

A continuación se describen los resultados obtenidos en esta tesis doctoral, que han dado fruto a la publicación de cuatro artículos, donde se detallan las características de cada publicación (autores, revista, índice de impacto y cuartil) junto a un breve resumen de cada uno, presentados según el objetivo específico de estudio.

Rendimiento neuropsicológico en Patología Dual

- ✓ **Objetivo 1 (Preliminar):**

Estudio 1: *Neuropsychological aspects of Dual Diagnosis*

Autores: Irina Benaiges, Gemma Prat, Ana Adan

Revista: *Current Drug Abuse Reviews* 2010; 3(3): 175-188.

Factor de impacto: 0,905 en el SCImago Journal & Country Rank (SJC 2011, último aparecido)

Posición de la revista:

- Categoría: Psychiatry and Mental Health (70/ 329 revistas). Cuartil 1 (Q1)

Resumen:

Aunque la investigación sobre rendimiento cognitivo en PD ha aumentado considerablemente durante la última década, todavía se sabe poco acerca de su perfil cognitivo ya que los autores encuentran resultados heterogéneos. El conocimiento sobre el tipo y la severidad de potenciales déficits neuropsicológicos en PD, tiene especial relevancia dado que puede ser un factor determinante de la prognosis y del éxito en el tratamiento clínico de esta población.

Material y Método:

Se consultaron las bases de datos científicas más significativas en nuestro campo de estudio (Medline, PsycInfo, ISI Web of Knowledge). Se seleccionaron los artículos publicados durante los últimos 15 años con las siguientes palabras clave en inglés: PD, déficit cognitivo, funciones cognitivas, esquizofrenia, trastorno bipolar, TUS comórbido y Neuropsicología. Los artículos debían comparar grupos con PD con diagnóstico de esquizofrenia y/o trastorno bipolar con sus respectivos homólogos sin TUS comórbido, en diseños experimentales de corte cros-seccional o bien longitudinal. Los estudios debían incluir criterios diagnósticos estandarizados (DSM-IV o CIE) e instrumentos diagnósticos válidos y fiables (SCID-I, PANSS, YMRS o HRDS) y utilizar pruebas de evaluación neuropsicológica de validez y fiabilidad contrastada.

Resultados:

Se sintetizaron los estudios seleccionados en tablas agrupadas según el diagnóstico de esquizofrenia o trastorno bipolar, con una breve descripción de las características de las muestras, el tipo de TUS comórbido, los resultados neuropsicológicos y otras observaciones de interés de las características de cada estudio.

Se identificaron las variables principales que podían explicar parte de las divergencias en los resultados hallados. La edad de los pacientes que constituían las muestras, el diagnóstico psiquiátrico, el tipo de sustancia principal de abuso, la gravedad del TUS, el tiempo de abstinencia, el dominio cognitivo evaluado y el subtipo diagnóstico de esquizofrenia y /o trastorno bipolar. Del mismo modo, se identificaron otras variables metodológicas que debían tenerse en consideración para interpretar los resultados existentes y para desarrollar futuros estudios: el

tamaño de las muestras, la inclusión de grupos controles o comparaciones con datos normativos poblacionales del rendimiento cognitivo, el género, la incorporación de parámetros neurobiológicos, el régimen de tratamiento bajo el que se encuentran los participantes, la estandarización de una batería neuropsicológica, los instrumentos de medición y el control de la medicación psicofarmacológica sobre los resultados.

Conclusiones:

Explorar la afectación neuropsicológica en PD es de gran interés ya que este conocimiento puede ayudar a prevenir las recaídas, la adherencia al tratamiento, los resultados del tratamiento y el funcionamiento psicosocial en la comunidad. Los resultados sugieren la necesidad de desarrollar futuros estudios que tengan en cuenta los factores metodológicos anteriormente expuestos para mejorar nuestro conocimiento del rendimiento neurocognitivo en PD.

Neuropsychological Aspects of Dual Diagnosis

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Abstract: Dual diagnosis (DD) has been described as the coexistence of a severe mental health condition and a drug abuse and/or dependence disorder. In the last decades, there has been a growing interest in the prevalence and characteristics of dual diagnosis, since it has been argued that DD patients show more clinical treatment difficulties and higher morbidity. Few works have studied the neuropsychological aspects of patients with DD, although neuropsychological deficits have been widely described both in patients showing a severe mental health condition and in those with a drug abuse and/or dependence disorder. Knowledge of the type and severity of potential neuropsychological deficits in patients with DD is of great relevance since it could be an interviewing factor for clinical treatment and prognosis.

The present work aims to review the main data on attention, memory, and executive functions in dual diagnosis patients, from an explanatory point of view. We focus on the diagnoses of Schizophrenia and Bipolar Disorder since these have shown the highest prevalence and severity in DD and have provided a wealth of data. We describe the differences in neuropsychological performance found in these patients and the implications for clinical treatment and psychosocial functioning. Finally, we propose possible working ideas for future studies in order to improve our present knowledge of the neuropsychological aspects of DD.

Keywords: Dual diagnosis, neuropsychology, executive functions, schizophrenia, bipolar disorder.

INTRODUCTION

Dual Diagnosis (DD) has been defined as the concurrence in the same individual of at least one substance abuse or dependence disorder and one severe psychiatric disorder [1-3]. The concept of DD emerged in the decade of the 1980s, when drug addiction began to be considered as a significant clinical entity and some of the research in neuroscience was focused on studying the addiction process and its evolution. It is a pathological condition with great clinical and medical negative consequences [2, 4, 5], since it has been associated to an increase in the number of psychiatric admissions [6], relapses, suicidal attempts [7, 8, 9], violence, imprisonment, family problems, loss of social status, higher medical comorbidity, HIV infection, homelessness and less quality of life [3, 10-15], as well as with higher levels of unemployment and marginality, poor treatment adherence and therapeutic failure [9, 16, 17]. In addition, all these significantly increase treatment costs in DD patients.

The characteristics commonly associated to DD patients are the predominance of males and young adults [18, 19], with an early onset of the disorder and a family history of Substance Use Disorder (SUD) and/or criminal conduct, and frequently with a psychiatric diagnosis of a psychotic or affective disorder [2, 20-23].

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There is consensus on the fact that approximately 50% of the subjects with Schizophrenia (SZ) and Bipolar Disorder (BD) meet criteria for a lifetime Substance Abuse and/or Dependence [24, 25]. These two disorders show the highest prevalence and severity in DD [2], and have been the most studied so far. The estimate on the prevalence of substance abuse among SZ and BD subjects is three times higher compared to the general population [26]. Excluding nicotine, the most consumed substances are alcohol and cannabis, followed by cocaine and stimulants, although what is most frequent is polyconsumption [5, 9, 16, 19].

In the case of SZ patients who meet criteria for SUD, when compared to non-addict SZ patients, the former usually present more positive, extrapyramidal and depressive symptoms, as well as an earlier onset of the disorder [4, 15, 27-30]. They also tend to have less quality of life, more violent behavior, hostility, paranoia, disorganized speech, unemployment and less treatment adherence [31, 32]. Likewise, in BD, mania complicated with SUD is characterized by a less favorable remission and more severe psychotic symptoms, including more extreme forms of emotional lability, impulsive actions and aggressive behavior. Moreover, these patients present a more severe and chronic course of the disorder. The first manic episodes generally occur at an early ages and patients suffer from more lack of social skills, take longer to recover between crises and present higher mortality rates [33-35].

Although the research on neuropsychological performance in DD patients has advanced in the last decade, we still know very little about their cognitive profile [15, 36]. This may be due to the fact that DD subjects are often excluded from the research on both severe mental illness and

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addicted subjects because these may be confounding factors [35, 36]. Cognitive impairment is a central deficit in SZ patients, and research in this area shows deficits which characterize this illness in attentional, memory and executive functions [30, 37, 38]. Generally, studies also find significant cognitive impairment in BD patients, even in the euthymic phases of the illness [39-41]. On the other hand, the effects of drugs on the cognitive functions of the central nervous system are well known. Despite the interest in characterizing the cognitive impact of the coexistence of severe mental illness and SUD, the works published are still limited and unfinished regarding the cognitive functioning of these patients [38, 42-44].

DD AND NEUROPSYCHOLOGICAL FUNCTIONING. RELEVANCE OF ITS STUDY

Research on neuropsychological functioning in DD is of great importance for several reasons. The severity of the cognitive deficit might predict the functional outcome in SZ+ (SZ with comorbid SUD) and BD+ (BD with comorbid SUD) patients. Moreover, some studies suggest that it might also predict the remission of the SUD [35, 45-48]. However, there are few data supporting the relation between cognitive state and remission of the SUD, as well as data on the result of the different treatments applied in DD patients. Thus, further work in this area is needed.

The reduced psychosocial skills of the DD patients may be related to their poor cognitive functioning. Specifically, the deficits in planning and problem solving may seriously compromise these patients' capacity to face life and deal with the demands of work and family [41]. Likewise, severe deficits in executive function have been significantly associated with the increase in psychiatric admissions [49], as well as with the number of relapses and with therapeutic non adherence [50]. For instance, cognitive flexibility assessed with the Wisconsin Card Sorting Test (WCST) has been associated to the length of hospital admissions and with the psychosocial functioning in the community [49]. In fact, the patients' psychosocial functioning shows a higher correlation with neuropsychological measures than with other clinical variables such as the severity of the psychiatric symptoms, both in the cases of BD [41, 51] and in the cases of SZ [32, 52].

There are studies which have also shown that certain specific types of cognitive deficits may be predictors of how the patients may or may not benefit from therapeutic interventions and from adherence to the pharmacological and therapeutic treatments. In particular, deficits in executive function may compromise the mechanisms of impulse control necessary to maintain abstinence, switching the cognitive focus to alternative behaviors and new goals [15, 35, 50].

For all these reasons, the neuropsychological assessment of these patients may contribute to the advancement of both the theoretical development and the clinical management of DD patients [53]. In the future, this should help to design more effective treatment strategies, which in turn would improve these patients' quality of life and reduce the elevated medical and social costs associated.

The aim of this revision is to shed light on the cognitive profile of DD patients with SZ+ or BD+, in order to establish if they present specific neuropsychological characteristics which are different from those of patients with Schizophrenia (SZ-) or Bipolar Disorder (BD-) but without SUD. All this with a special emphasis on the methodological aspects which may be responsible for the heterogeneity of the results obtained so far. Finally, it is suggested that the results found in the neuropsychological literature may have a practical use, in order to contribute to the therapeutic approaches of DD patients.

Several databases were consulted (Medline, PsycInfo, ISI Web of Knowledge) with the purpose of leading an objective and comprehensive revision. The literature search was carried out taking into account the articles published on the topic in the last 15 years, using different keywords such as: Dual Diagnosis, Neurocognitive Impairment, Cognitive Functions, Schizophrenia, Bipolar Disorder, Comorbid Substance Use, and Neuropsychology. The articles were selected if they met the following criteria:

- They were comparative studies between SZ+ and/or BD+ with SZ- and/or BD-
- With cross-sectional or longitudinal designs
- Which included patients aged 18 to 65
- With standardized diagnostic criteria and measures of psychiatric symptomatology to assess psychiatric disorders in the samples such as DSM-IV-R, PANSS, Young Mania Rating Scale or Hamilton Depression Rating Scale
- Which selected measures of cognitive functioning which were standardized, valid, sensitive and reliable, and
- Which included a clear description of the statistical comparative methods used.

DD IN SCHIZOPHRENIC DISORDERS (SZ+)

Main Findings

Some studies find that SZ+ patients show a worse neuropsychological functioning, and this has been attributed to the additional effects of the substance(s) dependence and/or abuse in their cognitive impairment. However, other studies have not found neurocognitive impairment and even others observe better execution. It has been suggested that these may be due to a better premorbid psychosocial functioning in these patients. Table **1** summarizes the main findings of the studies on the neuropsychological functioning of SZ+.

Although there are few studies with young patients, they find variable neuropsychological affectation according to the drug consumed. The work by Nixon *et al.* [38], centered on the dependence to alcohol in SZ+ with an abstinence time of around one month, did not find differences in motor speed, cognitive flexibility and face recognition in comparison to SZ- and alcoholics without a psychiatric disorder. In contrast, the works on cocaine dependence found worse results in verbal declarative memory in SZ+ subjects

Table 1. Summary of the Main Findings from the Neuropsychological Studies of DD with a Diagnosis of SZ

Authors	Population/Age/Gender				SUD	Results	Comments
Addington & Addington, 1996	**• 33 SZ+** 34.3± 7.7 yr 88% M		**• 33 SZ-** 34.6 ± 7.6 yr 88% M		Abuse/ Dependence: Alcohol Cannabis Polysubstances	SZ- = SZ+ on visual-spatial and verbal ability, visual attention, visual and verbal memory, executive and frontal lobe functioning	Outpatients SZ+ current drug abuse The SZ- past substance abuse or past dependence six years ago.
Nixon *et al*., 1996	**•13 SZ –** 35.31± 10.81 yr 88% M	**•13 ALC** 38.00 ± 5.05 yr 88% M	**•13 SZ +** 34.31 ± 6.75 yr 77% M	**•13 HC** 33.85 ± 8.21 yr 54% M	Abuse/ Dependence: Alcohol	HC > ALC = SZ-= SZ+ on motor speed, cognitive flexibility and face recognition	Inpatients ALC group length of abstinence ranged from 21 to 45 days.
Allen *et al*., 1999	**• 217 SZ** 39.16±12.24 yr 100% M	**• 231 ALC** 41.74±13.18 yr	**• 54SZ+** 43.10± 1 3.06 yr	**• 145 OTHERS** 41.99 ± 12.99 yr	Abuse/ Dependence: Alcohol	OTHERS = ALC > SZ- , SZ+ on intelligence and a neuropsychological test battery SZ+ < SZ+ on perceptual disorders and average impairment rating	Inpatients Abstinent for at least two weeks
Allen *et al*., 2000	**• 22 SZ+** 42.0 ± 6.0 yr 100% M		**• 11 SZ-** 36.3 ± 8.5 yr		Abuse/ Dependence: Alcohol	SZ+ < SZ- on cognitive-perceptual factors: memory test, face-hand test, right-left orientation, tap copying, audiovisual integration SZ+ = SZ- on other neurological soft signs	Inpatients Abstinence at least six months
Serper *et al*., 2000a	**• 42 SZ+** 36.6 ± 5.5 yr 80 % M	**• 34 SZ-** 35.8 ± 7.6 yr 82 % M	**• 21 COC** 37.2 ± 7.6 yr 85 % M		Abuse/ Dependence: Cocaine	SZ+ < SZ- = COC on verbal learning and recognition SZ+ = SZ- = COC on semantic categorization, serial clustering, recency, middle or primacy effects and errors of perseveration	Patients from the Psychiatric Emergency Service Recent cocaine abuse within the last 48 h
Serper *et al*., 2000b	**• 21 SZ+** 34.40 ± 6.1 yr 76% M		**• 35 SZ-** 37.62 ± 10.8 yr 83% M		Abuse/ Dependence: Cocaine	SZ+ = SZ- on sustained and selective attention, cognitive flexibility SZ+< SZ- on verbal learning and memory	Inpatients SZ+ tested within 72 h of the last cocaine use
Smelson *et al*., 2002	**•16 SZ+**		**•17 SZ-**		Dependence: Cocaine	SZ+ > SZ- on motor speed and selective executive functioning	Inpatient and outpatient. SZ+ abusing cocaine in the past month and abstinent for at least 72 hours Sample age and gender are not reported

(Table 1) contd…..

Authors	Population/Age/Gender			SUD	Results	Comments
Smelson *et al*., 2003	**•24 SZ+COC** 47.9 ± 6.1 yr	**•23 SZ-** 45.3 ±6.5 yr		Dependence: Cocaine	SZ+ < SZ- on motor skills, attention and concentration SZ+ > SZ- on processing speed	Inpatients Abusing cocaine within the past 45 days Gender is not available
Joyal *et al*., 2003	**• 16 SZ+**	**• 14 SZ-**	**• 30 HC**	Abuse/ Dependence: No specified	HC < SZ-, SZ+ on all cognitive domains except on cognitive flexibility SZ+ > SZ- on verbal fluency, cognitive flexibility and fewer frontal soft signs	Outpatients Sample age and gender not reported.
Herman, 2004	**• 46 SZ+** 30.86 ± 11.1 yr 87% M	**• 43 SZ-** 42.17 ± 11.2 yr 44% M		Abuse/ Dependence: Alcohol Cannabis, Hallucinogens, Stimulants, Narcotics or Polysubstances	SZ+ > SZ- on frontal executive functions: cognitive flexibility, cognitive initiation and sustained attention SZ+ = SZ- premorbid intelligence and memory functions	Inpatients Length of abstinence is not available Abuse or Dependence is not available
Bowie *et al*., 2005	**• 18 SZ+** 52.1 ± 6.7 yr 94% M	**• 17 SZ-** 54.9 ± 10.7 yr 94% M		Abuse/ Dependence: Alcohol	SZ+ < SZ- on attention, verbal learning and memory, verbal working memory	Outpatients Active alcohol abuse
Potvin *et al*., 2005	**• 44 SZ+** 31.4 ± 11 yr 82% M	**• 32 SZ-** 34.3 ± 11.1 yr 84% M		Abuse/ Dependence: Alcohol Cannabis Cocaine Polysubstances	SZ+ > SZ – on explicit memory	Outpatients SZ+ current SUD last 6 months
Mohamed *et al*., 2006	**Age 45 to 54:** **• 35 SZ+** *vs* **•101 SZ -** 49.3 ± 2.8 *vs* 48.8 ± 2.6 yr 89.9 % M *vs* 63.4 % M	**Age 55 over:** **•17 SZ+** *vs* **•119 SZ-** 64.9 ± 7.7 *vs* 64.4 ± 6.9 yr 76.5 % M *vs* 55.4% M		Abuse/ Dependence: Alcohol	SZ+ older < SZ- older SZ+ older < SZ+ younger on global cognitive status, verbal and visual learning and memory abilities SZ+, SZ- older < SZ+ , SZ- younger on visual learning and memory abilities	Outpatients Current Alcohol abuse/ dependence
Manning *et al*., 2007	**• 40 SZ+** 42.4 ± 9.8 yr 67 % M total sample	**• 40 SZ-** 37.5 ± 11.2 yr	**• 40 ALC** 42.2 ± 10.3 yr	Abuse/ Dependence: Alcohol	SZ + < SZ - < ALC on cognitive domains (assessed by MMSE): immediate recall, short-term memory, attention and calculation, ability to follow verbal and written instructions, and constructional ability	Current drug disorder (within the last month)

(Table 1) contd…..

Authors	Population/Age/Gender					SUD	Results	Comments
Sevy *et al.*, 2007	**• 14 SZ +** 30 ± 9.0 yr 63% M		**• 13 SZ-** 30 ± 9.0 yr 63% M		**• 20 HC** 33 ± 10 yr 60% M	Abuse/ Dependence: Cannabis Alcohol Cocaine Polysubstances	HC > SZ+, SZ- on premorbid intelligence, visual attention and working memory, verbal learning and memory, processing speed and executive function HC = SZ+, SZ- on emotion-based decision-making SZ+ > SZ- on auditory attention and verbal working memory	Inpatients and outpatient treatment programs SZ + current SUD (Abstinence for 1 week)
Thoma *et al.*, 2007	**• 23 SZ –** 40.5 ± 10.7 yr 65% M	**• 27 SZ +** 29.8 ± 9.8 yr 81% M	**• 20 ALC** 44.6 ± 10.0 yr 60% M	**• 22 DEP** 43.9 ± 9.4 yr 50% M	**• 22 HC** 40.9 ± 14.0 yr 41% M	Abuse/ Dependence: Alcohol Cannabis or both. Polysubstances	SZ- < SZ+, ALC, DEP, HC on response inhibition and cognitive flexibility and tonic alertness	Inpatient treatment Abuse/ Dependence not reported Length of abstinence at least 1 month for the ALC group and not available for the SZ+
Wobrock *et al.*, 2007	**• 21 SZ+** 22.1 ± 3.9 yr 86% M		**•23 SZ-** 29.0 ± 6.4 yr 48% M			Abuse/ Dependence: Alcohol Cannabis Cocaine Hallucinogens Stimulants	SZ+ = SZ- on visual spatial ability, motor speed, attention, executive function and cognitive flexibility, short-term memory, visual-spatial learning, premorbid intelligence SZ+ < SZ- on verbal fluency	Recent- onset schizophrenia Current substance use
Potvin *et al.*, 2008	**• 30 SZ+** 32.9 ± 10.7 yr 80% M		**• 23 SZ-** 36.4 ± 8.2 yr 74% M			Abuse/ Dependence: Alcohol Cannabis Cocaine Amphetamine Polysubstance	SZ+ = SZ- on psychomotor speed and spatial working memory SZ+ < SZ- strategy on the spatial working memory	Mainly outpatients SZ+ with current SUD in the last 6 months
Thoma & Daum, 2008	See Thoma *et al.*, 2007					Abuse/ Dependence: Alcohol Cannabis Polysubstances	SZ- < SZ+, ALC, DEP,HC on general intelligence, working memory and multitasking	Length of abstinence is not available Abuse/ Dependence is not reported
Schnell *et al.*, 2009	**•35 SZ+** 27.1 yr 69% M		**•34 SZ-** 29.6 yr 82 % M			Abuse/ Dependence: Cannabis	SZ+ < SZ- on academic achievement and vocabulary SZ+ > SZ- on verbal and working memory, visuomotor speed and executive function	Inpatients and outpatients Minimum 3 weeks of abstinence

Abbreviations: **SUD:** Substance Use Dependence. **SZ+:** Schizophrenia with comorbid substance use. **SZ-:** Schizophrenia without comorbid substance use. **ALC:** Alcohol dependence group. **COC:** Cocaine dependence group. **HC:** Healthy controls. **OTHERS:** Other medical and psychiatric conditions. **DEP:** Depression group. **M:** Males. **MMSE:** Mini Mental State Examination.

compared to the SZ-, although they found no differences in tasks of sustained and split attention or in cognitive flexibility [54, 55]. The authors attributed the memory deficit to the effect of the acute cocaine withdrawal, since the subjects' last consumption had been in the 48 hours previous to the record. Schnell *et al.* [56], assessing the influence of cannabis on SZ+ with a minimum period of abstinence of 3 weeks, found an improved performance in verbal and working memory, visuomotor speed and executive function in SZ+. However, these presented lower scores on academic achievement and vocabulary than SZ-.

In contrast, younger SZ+ patients who are polyconsumers show equal or better neuropsychological performance when compared to the SZ- subjects of their same age, especially in executive functions. Thus, Addington & Addington [30] did not find significant differences between the SZ+ and the SZ- of the same age on attentional, verbal and visual memory performance or on executive functioning. In other more recent studies, Sevy *et al.* [57] did not find significant differences in the SZ+ who were polyconsumers with current SUD in premorbid intelligence, visual attention, visual working memory, learning and verbal memory, processing speed, executive functions and decision making. However, the SZ+ group did perform better in attention and verbal working memory in comparison to the SZ- group. In contrast, Wobrock *et al.* [58] and Potvin *et al.* [59] only obtained worse verbal fluency and showed poorer use of strategies in spatial working memory respectively in the SZ+ group, despite the absence of significant differences in the rest of the neuropsychological functions assessed.

In other studies it is observed that young SZ+ patients who are polyconsumers present better neuropsychological functioning and even less signs of frontal damage in comparison to those diagnosed with SZ- who never consumed substances [15, 60-62]. These results were obtained with the application of a set of tests that assessed mainly frontal lobe functions: sustained and split attention, working memory, inhibition, alertness and cognitive flexibility, verbal fluency and processing speed. Herman [61] found that the SZ+ group did not differ from the SZ- regarding IQ or visual and verbal working memory performance, in spite of presenting better executive functioning. However, Potvin *et al.* [44] obtained better results in visuospatial memory for the SZ+ group when compared to the SZ-, using a neuropsychological battery. The study by Sheller-Gilkey *et al.* [63], done with Structural Magnetic Resonance, did not find significant differences in the degree of brain abnormalities between SZ+ and SZ- young patients, independently of the type and number of substances consumed, although the SZ+ presented less abnormalities. These results support the data obtained with the neuropsychological tests.

The authors who find better cognitive functioning in the SZ+ subjects hold the hypothesis that consumption of substances, and even more so of the illegal ones, is related to a large repertoire of social skills and a high demand on their executive functions to obtain the substance [15, 61, 64, 65], which at the same time is possibly related to a premorbid better social functioning. This can contribute to explain the findings about the better cognitive state of the DD patients. The better psychosocial functioning of these patients, despite their psychiatric condition and the problems associated to this and to drug consumption, is what some authors have called "the paradox of dual pathology" [40, 66]. Thus, the motivation and the skills needed to obtain drugs in a social context may be predictive factors of a better prognosis for these patients [30]. The pioneering study by Potvin *et al.* [67] with Functional Magnetic Resonance obtained results that support such a hypothesis. SZ+ patients had fewer deficits than the SZ- in the processing of socio-emotional information, with more active areas involved in social cognition.

Despite the evidence of a better premorbid psychosocial functioning in young SZ+, other possible confounding variables must be studied, such as the subject's personality, the early onset of the illness or the presence of prodromic symptoms [4], among others. All these, added to a good psychosocial functioning, may increase these subjects' exposure to substances and, therefore, to the vulnerability to develop a SUD.

Influence of Age in Neuropsychological Functioning of SZ+

Despite the heterogeneity of findings, it seems that older SZ+ subjects, generally with current alcohol consumption, show a general neuropsychological deficit which is more marked than that of SZ- subjects of the same age.

Works on SZ+ which focus on alcohol consumption mostly find in these patients a degree of neuropsychological impairment larger than that observed in SZ- patients or in those who only have a diagnosis of alcohol dependence and/or abuse, especially when these are older than 40. Thus, Allen *et al.* [42] observed a general cognitive deficit, including worse abstraction skills, social understanding and audio-verbal perception, marked by age in a group of subjects with SZ+, with a significant increase of the deficit in their 40s and 50s. The authors concluded that the chronic neuropathological effects of alcohol begin to appear in the later decades of life, with the expression of a new deficit added to the preexisting one. In the same way, Mohamed *et al.* [50] found that the SZ+ patients who were older than 55, with a history of alcohol abuse or dependence, had a poorer execution on neuropsychological tasks than those SZ- patients without alcohol addiction at the same age. This poorer execution was especially reflected in the score of a dementia scale (Dementia Rating Scale) and on a verbal memory task (CVLT: California Verbal Learning Test). Other studies such as that of Manning *et al.* [26] and Bowie *et al.* [32] also found a poorer execution in neuropsychological tests that assessed several cognitive domains in SZ+ patients who were in their 40s or 50s. These results suggest an acceleration of the cognitive deficit in SZ+ which may be interacting with age. However, it should be highlighted that in all these works the SZ+ patients presented active alcohol abuse or a short abstinence period of at least 2 weeks.

Allen *et al.* [43] also obtained a lower score on the cognitive-perceptual factor in the Neurological Examination Scale (NES) battery in SZ+ with alcohol abuse and/or dependence who had an abstinence period of at least 6 months. Similarly, Mathalon *et al.* [68] found in a SZ+

sample of alcoholic subjects, who were around 40 years old, that they had less grey matter in the prefrontal and anterior parietal cortex than the SZ- subjects. They concluded that this reflected an additional deficit due to the comorbidity or additive effects of the comorbid presence of the consumption and the mental disorder. In their work with patients aged between 40 and 50, Smelson *et al.* [69] observed better processing speed but lower performance in motor skills, attention and concentration tasks in SZ+ dependent on cocaine, in relation to SZ-. The authors suggest this may be due to a larger dysregulation of the dopaminergic system caused by cocaine.

In conclusion, despite the heterogeneity of the neuropsychological profile of the SZ+, substance consumption, especially alcohol, seems to add a deficit on the preexisting one after years of chronic consumption. In contrast, the younger SZ+ show a cognitive performance equal or higher than their SZ- counterparts, especially when there is polyconsumption. The affectation in SZ+ patients with dependence on cocaine must be considered carefully given the short time of abstinence assessed in the existing works.

DD WITH BIPOLAR DISODERS (BD+)

There are very few studies which analyze the neuropsychological performance of BD+ subjects, and the results are also as heterogeneous as with the SZ+ subjects. These results are summarized in Table **2**.

Van Gorp *et al.* [70], in a study with BD+ subjects who were around 50 years old and who presented alcohol dependence, found that these showed more difficulties regarding word recall after an interference list, worse long term memory in a verbal memory task and more deficits in cognitive flexibility than the control subjects. Van Gorp *et al.* [71], in a different study but with a similar sample, found that BD+ subjects with alcohol dependence performed worse in verbal declarative memory tasks but showed no relevant differences in procedural memory compared to BD- subjects. Likewise, Levy *et al.* [41] found that both BD+ subjects with substance abuse in the last 6 months and BD+ subjects with at least a 12-month abstinence period, generally showed a more marked cognitive deficit than the BD- subjects in executive functions, but not in attention or logical memory tasks. Moreover, this study found that the BD+ subjects who were in total remission presented a lower Intelligence Quotient (IQ) than the BD+ subjects with an active substance consumption and these, at the same time, had a lower IQ than the BD- ones. This could support the hypothesis of a neurobiological decline accelerated by age in the DD subjects.

However, and in contrast with the previous results, Sánchez-Moreno *et al.* [72] did not find significant differences between BD+ and BD- using a battery of tasks that assessed performance in attention, working memory, verbal memory, verbal fluency and executive functions.

Finally, the study of Carey *et al.* [40] which included SZ+ and BD+ patients who were polyconsumers found that the DD group performed better in non verbal tasks, including both those patients who met criteria for substance abuse or dependence in the last 6 months and those patients who had remained abstinent for 6 months or longer. However, they did not find significant differences between the SZ+ and BD+ in verbal task performance when compared to SZ- and BD-. Peer *et al.* [73] compared current or remitted dependence cocaine in both SZ+ and AD+ (Affective Disorders) patients. They found a worse performance in immediate and working memory in SZ+, regardless of whether dependence on cocaine was current or had remitted. Moreover, the SZ+ group with current cocaine dependence showed more deficits on flexible problem solving. In contrast, no differences were found between groups in overall intellectual functioning. However, it should be taken into account that this study does not develop the diagnosis for AD+ patients.

There are not enough studies on the neurocognition of BD+ subjects to allow us to establish a possible neuropsychological profile for these patients. Moreover, the BD+ and SZ+ subjects may differ with respect to neurocognition, showing specific and characteristic cognitive profiles depending on their psychiatric diagnosis. This might suggest the existence of cognitive subtypes in DD, depending on the psychiatric disorder they suffered. In fact, Daban *et al.* [74], in a systematic review, found that the BD- subjects usually show fewer cognitive deficiencies than the SZ- group, particularly at the premorbid functioning level and in verbal memory and IQ, the latter being the most discriminating variable between SZ- and BD-. This possibility should be studied in DD patients, since if they were to present differences in their neuropsychological performance according to their clinical diagnosis, this would be of great help in order to establish treatment guidelines and objectives. In this regard, Xie *et al.* [75], in a follow-up study of the results of treatment with DD patients, found that BD+ patients showed a better recovery than the SZ+ group three years later.

CONFOUNDING VARIABLES

The diversity of results in the studies both with SZ+ and BD+ may be due to several factors which should be interpreted as possible confounding variables. These factors must be controlled for in future works with the purpose of studying the neuropsychological functioning of DD patients. Next we review those which seem more relevant.

Dependence and/or Abuse of Substances and Abstinence Time

The possible pharmacological effects and the neurodegenerative risk caused by the different substances of dependence and/or abuse is an essential factor regarding the heterogeneity of the existing results on neurocognition. Thus, some authors state that alcohol and cocaine usually are the substances responsible for a more pronounced deficit in DD patients [32, 41, 44, 70]. Potvin *et al.* [64], in their meta-analysis on the cognitive profile of DD patients, concluded that alcohol was associated to performing worse in working memory tasks and cocaine was associated to poorer results in most of the neuropsychological tests, while cannabis was associated to a better score in the Global Cognitive Index, especially in problem solving tasks and visual memory.

Table 2. Summary of the Main Findings from the Neuropsychological Studies of DD with a Diagnosis of BD

Authors	Population/Age/Gender			SUD	Results	Comments
Van Gorp *et al*., 1998	**•12 BD+** 52.87 ±8.55 yr 100% M	**•13 BD-** 51.84 ±13.36 yr	**•22 HC** 51.73 ± 12.60 yr	Dependence: Alcohol	HC= BD+, BD- on visuospatial, non-verbal memory and psychomotor speed abilities HC > BD+, BD- on verbal memory and executive functions	Outpatients Abstinence for 6 months or longer Type of BD not reported
Van Gorp *et al*., 1999	**• 11 BD+** 52.55 ± 7.61 yr 100% M	**• 20 BD-** 47.95 ± 13.30 yr	**• 18 HC** 54.00 ± 13.50 yr	Dependence: Alcohol	HC > BD- > BD+ on declarative memory HC = BD-, BD+ on procedural memory	Outpatients Abstinence for 6 months or more Type of BD not reported. Assessment in non-acute phase
Levy *et al*., 2008	**• 13 BD+** 35.0 ± 12.9 yr 55% M total sample	**• 9 BD+ FR** 46.8 ± 8.9 yr	**• 41 BD –** 36.1 ± 12.6 yr	Abuse/Dependence: Alcohol but presence of polysubstance abuse in the sample	BD+ , BD+FR < BD- on frontal executive functions BD+ = BD+ FR = BD- on attention and working memory and logical memory BD+ < BD- on verbal and visual memory and perceptual organization BD+ FR < BD + < BD – on intelligence	Inpatients Bipolar Disorder type I BD+ dependence in the past 6 months BD+ FR abstinence in the past 12 months
Sanchez-Moreno *et al*., 2009	**• 30 BD+** 35.8 ± 9.7 yr 53% M	**• 35 BD-** 41.1 ± 8.9 yr 31% M	**• 35 HC** 39.1 ± 12.1 yr 37% M	Abuse/Dependence: Alcohol	HC > BD-, BD + BD- = BD+ on frontal executive functions, attention, working memory, verbal fluency and verbal memory	Outpatients BD I or II but currently euthymic Length of abstinence is not available

Abbreviations: **SUD:** Substance Use Dependence. **BD+:** Bipolar Disorder with comorbid substance use. **BD-:** Bipolar Disorder without comorbid substance use. **BD+ FR:** Bipolar Disorder with comorbid substance use in full remission. **HC:** Healthy controls. **M:** Males.

On the other hand, it has been hypothesized that certain substances may have a beneficial effect on neurocognition. Thus, it has been suggested that cannabis can improve cognitive function in DD patients [36]. A possible explanation for this may be attributed to the neuroprotective effect of cannabinoids, the active components of marihuana [64], specifically -and from a speculative point of view- in people with schizophrenia, at least at a certain age and before consumption becomes chronic [36, 64]. This explanation is in conflict with the evidence that the regular consumption of cannabis can cause deficits in attention and memory, which may persist during periods of abstinence [56]. Ringen *et al*. [76] examined the relation between cannabis use and neurocognition in SZ+ compared with BD+. They observed worse execution in attention, set-shifting and logical learning memory in SZ+, and better semantic and verbal fluency and learning memory in BD+. These findings suggest that cannabis use might improve cognitive functioning in BD+ but worsen it in SZ+. However, such findings must also be considered carefully given the few subjects studied. Moreover, their criterion for substance use was wide (any use in the past six months) with a low median level of cannabis use, without precise information on the amount of smoked cannabis and duration of use, which is of relevance when considering pharmacological factors and possible effects of long-term use.

There is also evidence that cannabis consumption increases moderately the risk of psychotic symptoms, especially in subjects with a tendency to psychosis [77, 78], and it also increases the risk of an earlier onset [77, 79]. Finally, these patients show also a greater risk for a more continuous illness, with more positive symptoms in psychotic patients with cannabis abuse than in those who do not [80].

There are alternative explanations for the association observed between cannabis use and a better neurocognitive functioning in DD patients. The improved premorbid psychosocial functioning may be underlying a better cognitive performance in DD patients, since they require high level skills in a context of drug acquisition. Arndt *et al*. [81] found that dependence on alcohol and cannabis was associated to higher levels of premorbid social functioning, but not dependence on psychostimulants or hallucinogens.

However, alcohol and cannabis are the substances most accessible to the population, and in relation to this Schnell *et al*. [56] suggest that DD patients have less biological vulnerability than those who do not show a comorbid SUD. Thus, less vulnerability may correspond to a higher level of functioning and better cognitive skills. This is in agreement with the idea that cannabis may play an important role in the expression of the disorder.

The high consumption of nicotine in DD patients [5] should also be mentioned. This variable could explain the better performance found in some studies, under the assumption that nicotine improves connectivity in frontal attentional areas [62]. Such a statement is in agreement with the self-medication hypothesis. This hypothesis implies that some adverse cognitive effects of psychosis could be improved thanks to the increase of dopaminergic activity caused by certain substances, decreasing negative symptoms and the executive deficits associated to this mental disorder [82]. However, this association between smoking and cognitive functioning does not allow to make causal attributions. Moreover, most of the studies do not control for the patients' daily consumption of nicotine, and its possible influence in the execution of the neuropsychological tests is never taken into account. A recent study by Yip *et al.* [83] did not find any influence of tobacco consumption in patients with SZ- in cognitive flexibility (WCST) or in decision making assessed with the Iowa Gambling Task in men, although it did find an influence in the women sample. It seems of special importance that future research explores the influence of nicotine and the possible mediating individual differences.

Moreover, there is no consensus in the literature on the differential effect of abuse substances on the cognition of DD patients. To assess this effect is a difficult task given that most of the DD subjects are polyconsumers and there may be great variability in their patterns of abuse in terms of frequency, duration, dose and type of substance. There has been little research on how the consumption of several substances (for example, cannabis and alcohol) may enhance the adverse effects in the long term [84]. While the synergic and additive effects are plausible, most authors who find a better cognitive state in young DD patients study samples where there is polyconsumption. There is some speculation on the hypothesis that consumption of some substances may mask or protect the neurocognitive sequels of other substances [84]. For this reason, we need studies to assess the differences in cognitive profiles depending on the consumption pattern and the type of substances consumed. For all this, the inclusion of substance abuse and dependence disorders in the same category may be potentially influencing the pattern of cognitive deficits observed in individuals with SUD, given that certain factors must be controlled for, such as duration, quantity and time elapsed since last consumption [85].

The fact that DD patients in the sample of the different studies present current substance use or a specific period of abstinence may also be explaining the divergences in the results of their neuropsychological performance. Thus, Pitel *et al*. [86], in a study with alcoholic population without any concomitant psychiatric disorder, concluded that episodic memory and executive functions could return to normal functioning in young people, even in a six-month abstinence period, when the period of alcohol abuse had been short. In older people, the chances of recovery are lower because there is less brain plasticity. This could explain the results in Carey *et al*. [40] and Levy *et al*. [41], since they did not find differences between the former abusers and the current abusers, and in both cases the abstinent subjects were older. Thus, there may be no improvement with abstinence due to the possibility that older age does not allow for the recovery of cognitive functions in a significant way. Peer *et al*. [73] observed only worse flexible problem solving in SZ+ with current cocaine dependence compared to SZ+ with remitted cocaine dependence, proposing two possible interpretations of their results. First, it is possible that the pre-existing cognitive impairment in SZ is so marked that it is minimally impacted by cocaine use. Second, the changes in cognitive functioning in SZ+ do not substantially improve in remission. That is, individuals with DD may accrue significant deficits from cocaine dependence that are not reversible once drug use stops. On the other hand, Serper *et al*. [54, 55] attributed the worse results in SZ+ with cocaine abuse to the neurobiological effect of the withdrawal, this being responsible for the impairment on learning and memory skills.

In order to explain further the contradictory nature of these results, more longitudinal studies are required that analyze long periods of abstinence in order to determine the extension of the recovery of the cognitive deficits, both in prolonged abstinence and in acute withdrawal. Some studies have found some improvement in the functioning of BD+ subjects who had been in SUD remission for at least one year [40, 87]. However, the recovery of cognitive functions in DD patients depending on the time of abstinence is still a poorly-known neuropsychological area due to the lack of pertinent studies. Moreover, the fact that some works do not mention the time of abstinence or the presence of a remote history of consumption in SZ or BD- does not allow us to draw clear or generalized conclusions from the results obtained. The longitudinal studies on substance use and clinical functioning in patients with a DD should also allow in the future to disentangle the effects of selection factors from the impact of substance use on cognitive functioning.

Age of Patients

Age may be an important confounding variable in different studies, as we have already pointed out. In most of the studies which obtain worse neuropsychological performances in DD patients, the sample is made up of DD subjects who are in their 40s or 50s. The data support the hypothesis that an accelerated deficit would interact with the age variable in these patients [42]. Maybe the neuropathological effects of some substances such as alcohol have an effect later in life and add a new deficit to the preexisting one attributed to the psychiatric disorder. This could explain the results that have found a larger neurocognitive deficit in the DD group when compared to the group without a history of substance abuse [26, 32, 50, 70, 71].

Age can also be an explanatory factor in the works that find a better functioning in the DD patients when compared to patients with similar characteristics but without substance

abuse or dependence. In these studies, the DD patients were more than 10 years younger than the non-addiction group [15, 61, 62]. Some authors maintain that the impairment effects on cognition may not have appeared yet in the young DD, especially when referring to their executive functions [15, 58, 61, 88]. This is in agreement with the studies that do not find significant differences in the neuropsychological performance of DD patients when compared to the non-addiction group [30, 38, 57, 58], taking into account that in these studies the patients were of a younger age. Thus, the cognitive damage may appear after some chronic and prolonged period of substance consumption [88], which is easier to find in older patients, in whom the neurotoxic consequences of substance consumption may be more obvious in the long run.

Thus, it is likely that DD patients aged over 40 to 50 present a neurodegenerative deficit, in contrast with those with a psychiatric disorder but without comorbid SUD. In the case of SZ-, no cognitive decline or neurodegeneration associated with age have been found, and the deficit remains stable throughout the years [89], independently of age of onset and duration of illness [90]. We require longitudinal studies to establish how the subjects at high risk of developing DD differ in their premorbid cognitive functions and how their cognitive problems evolve in the course of the disorder. The neuropathology of psychotic and/or AD may have some effect on the neural mechanisms of these same disorders in DD patients [15].

Psychiatric Diagnosis

The diagnosis of DD patients may be another confounding variable in the neuropsychological results currently available. Most of the studies are carried out with SZ+, and there are few studies which assess the neurocognition of BD+. Moreover, most of the studies do not specify the subjects' subtype of SZ or of BD in the sample. Currently, there is a growing number of works on the differential cognitive profiles depending on the clinical subtypes of SZ, and the data point towards a better cognitive functioning in the Paranoid and Schizoaffective subtypes. These types of subjects are almost in the normal cognitive range when compared to the residual or not otherwise specified schizophrenia subjects. However, there is great heterogeneity among the SZ clinical subtypes in relation to their neuropsychological performance [91, 92] and, in addition, some authors suggest that the paranoid subtype is neuropsychologically indistinguishable from the non-paranoid SZ [93]. In the case of BD, the results are also contradictory. Some authors claim that the cognitive deficit is more severe in subjects type I than in type II [94], while others find a similar pattern of deficit in both subtypes of BD [95].

Researchers have also considered subtypes of SZ defined by cognitive tests, based on the premise that the cognitive state is more objective than the symptomatology, with potentially more direct ties to neurobiology and genetics. Moreover, cognitive subtypes may relate more strongly to functional status [96]. Thus, cluster analytic methods have identified a group of patients characterized by moderately, severe and pervasive cognitive impairment [97]. More work is needed to improve our knowledge on the possible cognitive subtypes in both SZ and BD, since this would also shed light on the neuropsychology of DD and help identify the weight of variables that might affect cognitive state, the use of substances and the illness itself. This in turn would allow to improve the clinical management, the cognitive enhancement and the rehabilitation of patients.

Methodological Aspects

The heterogeneity of the results obtained may also be due to different methodological aspects which should be taken into account in the interpretation of the existing results and the planning of further studies which investigate the neuropsychological aspects of DD patients.

Among these factors we should highlight the sample size, since most of the studies have been done with small patient samples, and this could translate into a lack of statistical power which may increase the type II error in the results. Another aspect is the lack of a control group in many studies or the lack of reference to normative data in the population for the execution of neuropsychological tasks, which does not allow to establish the degree of neuropsychological deficit in DD patients.

Most of the investigations do not consider the possibility that gender affects the neuropsychological functioning of DD patients, although there are no doubts that in the general population certain neuropsychological variables, such as manipulative and verbal reasoning, show distinct values for men and women [98]. The fact that the samples are mostly made up of males, although it is consistent with the prevalence of the disorder, does not provide results that can be generalized to both genders. Therefore, gender is a variable that should be better controlled for and could even be incorporated as the objective of study in further research.

There are very few studies analyzing the cognitive functioning of DD patients using neurobiological parameters such as brain volumetric measurements, genetic measurements, structural and/or functional neuroimaging measurements or evoked potentials [58]. Some authors have posed the hypothesis that young DD patients could perform better in neuropsychological tasks due to the possibility that they use additional brain areas that make up for the dysfunction through compensatory mechanisms. Compensatory mechanisms of fronto-cerebral activity have been found in non-psychotic patients addicted to alcohol and cocaine, and this is one reason why functional neuroimaging studies are of vital importance in order to shed light on this topic [62]. Neurofunctional studies of these patients may help to identify the complexity of their pathophysiology and the underlying aspects of the differences in the neurocognitive impact found so far, as well as the possible brain changes in interaction with the concomitant psychiatric diagnosis and the age variable.

On the other hand, the setting of the assessment (inpatient or outpatient) is another factor that has a clear effect on the divergence of the results in these studies. Cognitive deficits in DD patients may be more acute during their admission in psychiatric centers. The temporal proximity of the moment when the crisis appears and the abuse of substances, added to the use of sedative medication during all the time of the hospitalization, may compromise to

a great extent the cognitive states at the moment of discharge [41]. Moreover, ambulatory patients may enjoy more autonomy to deal with the demands of daily life, which suggests a better cognitive state.

The heterogeneity of the neuropsychological results of DD patients in the different studies may also be due to the different instruments used to assess the same cognitive domain. The standardization of an exhaustive neuropsychological battery or the use of an already existing one would allow for an extensive assessment of the main cognitive domains, eliminating at least some of the divergences of the current data.

Moreover, many studies also differ in the instruments used to assess the severity of addiction in DD. Some authors use the Addiction Severity Index (ASI), a reliable and valid instrument in SUD assessment and frequently used both in research and clinical practice [99, 100]. However, Carey *et al*. [101] observed mixed reliability and validity of the ASI in psychiatric population, and so this instrument might not be appropriate in studies with DD patients. In DD patients, the Psychiatric Research Interview for Substance and Mental Disorders (PRISM) may be the instrument of choice to assess the diagnoses of comorbidity in drug abusers according to the DSM-IV, since it has been shown to be more reliable [102]. The proper assessment of the severity of the addiction, the use of the PRISM interview to determine the diagnoses and the appropriate control of abstinence with urine analyses in the studies with DD are aspects that can improve the selection of patients and probably improve the robustness of the results obtained.

Finally, it has been shown that the chronic use of antipsychotics, anticholinergic and benzodiazepine medications may have some effect on the cognitive abilities of attention, vigilance and motor speed. The studies usually describe the patients' medication but do not control for their possible influence on the neuropsychological results. Although it is difficult to assess the impact of this factor, further research should progress on this line of work.

CONCLUSIONS AND PRACTICAL IMPLICATIONS

Further research is needed which takes into account the methodological deficiencies previously cited, and which controls for the possible confounding factors. Thus, more studies should be carried out on the neuropsychological functioning of SZ+ and BD+ patients, including analysis of large samples, which may establish differences or subtypes of DD according to the psychiatric diagnosis or to the type of substance consumed. Longitudinal studies are also highly necessary to help assess empirically the idea of the evolution of the neuropsychological deficit with age. It would be of great interest to explore the relation between cognitive deficit, community adjustment and functional outcome, as well as the response of DD patients to integrative treatments both in mental illness and in SUD. Finally, studies are also needed which include measurements of neurobiological parameters in order to know in depth the neuropsychology of DD patients, aiming to develop effective treatment strategies both for prevention and for intervention.

Although some studies find better cognitive performances especially in the executive functions of DD patients with respect to those who never consumed substances, the former still present worse performance scores when compared to the population normative data or to healthy controls. This suggests that their cognitive abilities are not intact. The deficits in memory and learning have been associated to deficits in adaptive functioning and, moreover, they predict worse therapeutic results [55]. Likewise, executive functions show a correlation with the functioning within the community and with the therapeutic results [49]. Promotion of organization strategies and guidelines in DD patients should be pursued, as well as development of effective learning techniques and cognitive rehabilitation exercises with emphasis on the improvement of the executive functioning. In this way, patients may achieve better treatment adherence and obtain more benefits from pharmacological intervention. In the same way, this could increase the patients' options to benefit from interventions based on psychotherapy, which would in turn facilitate an increase of the clinicians' insights and that they would process the information from their context in a better way to act according to the surrounding needs. Improvement in cognitive functioning can also facilitate the maintenance of abstinence, with a better ability to inhibit automatic responses and shift the focus of attention towards alternative and healthy behaviors.

In order to decide what type of interventions may be the most effective for DD patients, it is essential to assess their cognitive state when they begin treatment. The treatments for SUD that have proven effective are: motivational interview, relapse prevention, social skills training and behavioral, family and couple therapy. However, all these require that patients be able to pay attention to and process the working material when it is presented to them, in order for them to remember and understand the information effectively so that they can apply what they have learned and solve problems [85].

It is very important to explore the neuropsychological affectation of DD patients, since knowledge of it may predict relapses, treatment adherence, outcome of treatment and psychosocial functioning in the community. The results suggest the need to assess this aspect conveniently and to implant cognitive rehabilitation therapies for these patients in order to improve their cognitive functioning, if needed. This may help to improve the course of the disorder, relapse prevention and suicidal attempts, early prevention of a cognitive deficit which may be accelerated in later phases, as well as the psychosocial functioning and quality of life in these patients. This would also decrease the elevated social and medical costs involved.

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Key Learning Objectives:

- To describe the neuropsychological characteristics of dual diagnosis (DD) patients with Schizophrenia or Bipolar Disorder as psychiatric disorder.
- To identify those factors which may be responsible for the heterogeneity of the neuropsychological results in different studies.
- To alert on the need to control several methodological deficiencies in future research.
- To show the importance in DD of the study of the neuropsychological aspects both for assessment and for patient treatment.

Future Research Directions:

- To develop studies which control for the existing methodological deficiencies, detected in this revision, in order to improve our knowledge of the neurocognition of DD patients.
- To develop longitudinal studies which allow us to assess the neurocognitive changes in DD patients according to their psychiatric diagnosis, age, abstinence period and type of substance consumed.
- To incorporate neurobiological brain measures that allow us to improve our knowledge of the neuropsychological aspects of DD patients.

REFERENCES

[1] Drake RE. Dual diagnosis. Psychiatry 2004; 3: 60-3.

[2] Torrens M. Patología dual: situación actual y retos de futuro. Adicciones 2008; 20: 315-20.

[3] Drake RE, Wallach MA. Dual Diagnosis: 15 years of progress. Psychiatr Serv 2000; 51: 1126-9.

[4] Mueser KT, Drake RE, Wallach MA. Dual diagnosis: a review of etiological theories. Addict Behav 1998; 23: 717-34.

[5] Rodríguez-Jiménez R, Aragüés M, Jímenez-Arriero MA, *et al*. Patología dual en pacientes psiquiátricos hospitalizados: prevalencia y características generales. Invest Clin 2008; 49: 195-205.

[6] Hunt GE, Bergen J, Bashir M. Medication compliance and comorbid substance abuse in schizophrenia: impact on community survival 4 years after a relapse. Schizophr Res 2002; 54: 253-64.

[7] Appleby L, Shaw J, Amos T, *et al*. Suicide within 12 months of contact with mental health services: national clinical survey. Br Med J 1999; 318: 1235-9.

[8] Kushner MG, Abrams K, Thyras P, Hanson KL, Brekke M, Sletten S. Follow-up study of anxiety disorders and alcohol dependence in comorbid alcoholism treatment patients. Alcohol Clin Exp Res 2005; 29: 1432-43.

[9] Cardoso BM, Sant'Anna MK, Dias VV, Andreazza AC, Ceresér KM, Kapczinski F. The impact of co-morbid alcohol use disorder in bipolar patients. Alcohol 2008; 42: 451-7.

[10] Swartz MS, Swanson JW, Hiday VA, Borum R, Wagner HR, Burns BJ. Violence and severe mental illness: the effects of substance abuse and non adherence to medication. AM J Psychiatry 1998; 155: 226-31.

[11] Soyka M. Substance misuse, psychiatric disorder and violent and disturbed behaviour. Br J Psychiatry 2000; 176: 345-50.

[12] Hoff RA, Rosenheck RA. The cost of treating substance abuse patients with and without comorbid psychiatric disorders. Psychiatr Serv 1999; 50: 1309-15.

[13] McCrone P, Menezes PR, Johnson S, *et al*. Service use and costs of people with dual diagnosis in South London. Acta Psychiatr Scand 2000; 101: 464-72.

[14] Dickey B, Normand SLT, Weiss RD, Drake RE, Azeni H. Medical morbidity, mental illness, and substance use disorders. Psychiatr Serv 2002; 53: 861-7.

[15] Thoma P, Wiebel B, Daum I. Response inhibition and cognitive flexibility in schizophrenia with and without comorbid substance use disorder. Schizophr Res 2007; 92: 168-80.

[16] Dixon L. Dual diagnosis of substance abuse in schizophrenia: prevalence and impact on outcomes. Schizophr Res 1999; 35: 93-100.

[17] Horsfall J, Cleary M, Hunt GE, Walter G. Psychosocial treatments for people with co-ocurring severe mental illnesses and substance use disorders (dual diagnosis): a review of empirical evidence. Harv Rev Psychiatry 2009; 17: 24-34.

[18] Mueser KT, Yarnold PR, Levinson DF, *et al*. Prevalence of substance abuse in schizophrenia: demographic and clinic correlates. Schizophr Bull 1990; 16: 31-56.

[19] Lammertink M, Löhrer F, Kaiser R, Hambrecht M, Pukrop R. Differences in substance use abuse patterns: multiple drug abuse alone versus schizophrenia with multiple drug abuse. Acta Psychiatr Scand 2001; 104: 361-6.

[20] Comtois KA, Tisdall WA, Holderaft LC, Simpson T. Dual diagnosis: impact of family history. Am J Addict 2005; 14: 291-9.

[21] Merikangas KR, Stolar M, Stevens DE, *et al*. Familial transmission of substance use disorders. Arch Gen Psychiatry 1998; 55: 973-9.

[22] Fenton WS. Comorbid conditions in schizophrenia. Curr Opin Psychiatry 2001; 14: 17-23.

[23] Margalose HC, Malchy L, Negrete JC, Tempier R, Gill K. Drug and alcohol use among patients with schizophrenia and related psychoses: levels and consequences. Schizophr Res 2004; 67: 157-66.

[24] Bradizza CM, Stasiewicz PR, Paas ND. Relapse to alcohol and drug use among individuals diagnosed with co-ocurring mental health and substance use disorders: A review. Clin Psychol Rev 2006; 26: 162-78.

[25] Shuckit MA. Comorbidity between substance use disorders and psychiatric conditions. Addiction 2006; 101: 76-88.

[26] Manning V, Wanigaratne S, Best D, Strathdee G, Schrover I, Gossop M. Screening for cognitive functioning in psychiatric outpatients with schizophrenia, alcohol dependence, and dual diagnosis. Schizophr Res 2007; 91: 151-8.

[27] Talamo A, Centorrino F, Tondo L, Dimitri A, Hennen J, Baldessarini RJ. Comorbid substance-use in schizophrenia: relation to positive and negative symptoms. Schizophr Res 2006; 86: 251-5.

[28] Barnes TR, Mutsatsa SH, Hutton SB, Watt HC, Joyce EM. Comorbid substance use and age at onset of schizophrenia. Br J Psychiatry 2006; 188: 237-42.

[29] Potvin S, Pampoulova T, Mancini-Marie A, Lipp O, Bouchard RH, Stip E. Increased extrapyramidal symptoms in patients with schizophrenia and a comorbid substance use disorders. J Neurol Neurosurg Psichiatry 2006; 77: 796-8.

[30] Addington J, Addington D. Substance abuse and cognitive functioning in schizophrenia. J Psychiatr Neurosci 1996; 22: 99-104.

[31] Dixon L, Weiden PJ, Haas G, Sweeney J, Frances AJ. Increased tardive dyskinesia in alcohol-abusing schizophrenia patients. Compr Psychiat 1992; 33: 121-2.

[32] Bowie C, Serper M, Riggio S, Harvey PD. Neurocognition, symptomatology, and functional skills in older-abusing schizophrenia patients. Schizophr Bull 2005; 31: 175-82.

[33] Salloum IM, Cornelius JR, Mezzich JE, Kirisci L. Impact of concurrent alcohol misuse on symptom presentation of acute mania at initial evaluation. Bipolar Disord 2002; 4: 418-21.

[34] Albanese MJ, Pies R. The bipolar patient with comorbid substance use disorder: recognition and management. CNS Drugs 2004; 18: 585-96.

[35] Levy B, Weiss RD. Cognitive Functioning in bipolar and Co-ocurring Substance Use Disorder: A Missing Piece of the Puzzle. Harv Rev Psychiatry 2009; 17: 226-30.

[36] Coulston C, Perdices M, Tennant CC. The neuropsychology of cannabis and other substance use in schizophrenia: review of the literature and critical evaluation of methodological issues. Aust N Z J Psychiat 2007; 41: 869-84.

[37] Gold JM, Harvey PD. Cognitive deficits in schizophrenia. Schizophrenia 1993; 16: 295-311.

[38] Nixon S, Hallford HG, Tivis RD. Neurocognitive function in alcoholic, schizophrenic, and dually diagnosed patients. Psychiat Res 1996; 64: 35-45.

[39] Martinez-aran A, Vieta E, Colom F, *et al*. Cognitive impairment in euthymic bipolar patients: implications for clinical and functional outcome. Bipolar Disord 2004; 6: 262-70.

[40] Carey KB, Carey MP, Simons JS. Correlates of substance use disorder among psychiatric outpatients: focus on cognition, social

role functioning, and psychiatric status. J Nerv Ment Dis 2003; 191: 300-8.

[41] Levy B, Monzani BA, Stephansky MR, Weiss RD. Neurocognitive impairment in patients with co-ocurring bipolar disorder and alcohol dependence upon discharge from inpatient care. Psychiat Res 2008; 161: 28-35.

[42] Allen DN, Goldstein G, Forman SD, Keshavan MS, Van Kammen DP, Sanders RD. Neurologic examination abnormalities in schizophrenia with and without a history of alcoholism. Neuropsychiatr Neuropsychol Behav Neurol 1999; 13: 184-287.

[43] Allen DN, Goldstein G, Aldarondo F. Neurocognitive dysfunction in patients diagnosed with schizophrenia and alcoholism. Neuropsychol 2000; 13: 62-8.

[44] Potvin S, Briand C, Prouteau A, *et al*. CANTAB explicit memory is less impaired in addicted schizophrenia patients. Brain Cogn 2005; 59: 38-42.

[45] Goldman MS. Experience-dependent neuropsychological recovery and the treatment of chronic alcoholism. Neuropsychol Rev 1990; 1: 75-101.

[46] Mur M, Portella MJ, Martinez-Aran A, Pifarre J, Vieta E. Persistent neuropsychological deficit in euthymic bipolar patients: executive function as a core deficit. J Clin Psychiatry 2007; 68: 1078-86.

[47] Martinez- Aran A, Penades R, Vieta E, *et al*. Executive function in patients with remitted bipolar disorder and schizophrenia and its relationship with functional outcome. Psychother Psychosom 2002; 71: 39-46.

[48] Copersino ML, Serper MR, Vadhan N, *et al*. Cocaine craving ans attentional bias in cocaine-dependent schizophrenic patients. Psychiatry Res 2004; 128: 209-18.

[49] Jackson CT, Fein D, Essock SM, Mueser KT. The effects of cognitive impairment and substance abuse on psychiatric hospitalizations. Commun Ment Health J 2001; 37: 303-11.

[50] Mohamed S, Bondi MW, Kasckow JW, Golshan S, Jeste DV. Neurocognitive functioning in dually diagnosed middle aged and elderly patients with alcoholism and schizophrenia. Int J Geriatr Psychiatry 2006; 21: 711-8.

[51] Martínez-Aran A, Vieta E, Torrent C, *et al*. Functional outcome in bipolar disorder: the role of clinical and cognitive factors. Bipolar Disord 2007; 9: 103-13.

[52] Bowie CR, Leung WW, Reichenberg A, *et al*. Predicting schizophrenia patients' real-world behavior with specific neuropsychological and functional capacity measures. Biol Psychiatry 2008; 63: 505-11.

[53] Tracy JI, Josiassen RC, Bellack AS. Neuropsychology of dual diagnosis: understanding the combined effects of schizophrenia and substance use disorders. Clin Psychol Rev 1995; 15: 67-97.

[54] Serper M, Bergman A, Copersino ML, Chou J, Richarme D, Cancro R. Learning and memory impairment in cocaine-dependent and comorbid schizophrenic patients. Psychiat Res 2000; 93: 21-32.

[55] Serper MR, Copersino ML, Richarme D, Vadhan N, Cranco R. Neurocognitive functioning in recently abstinent, cocaine-abusing schizophrenic patients. J Subst Abuse 2000; 11: 205-13.

[56] Schnell T, Koethe D, Daumann J, Gouzoulis-Mayfrank E. The role of cannabis in cognitive functioning of patients with schizophrenia. Psychopharmacol 2009; 205: 45-52.

[57] Sevy S, Burdick KE, Visweswaraiah H, *et al*. Iowa Gambling Task in schizophrenia and co-occurring cannabis use disorders. Schizophr Res 2007; 92: 74-84.

[58] Wobrock T, Sittinger H, Behrendt B, D'Amelio R, Falkai P, Caspari D. Comorbid substance abuse and neurocognitive function in recent-onset schizophrenia. Eur Arch Clin Neurosci 2007; 257: 203-10.

[59] Potvin S, Pampoulova T, Lipp O, Bentaleb LA, Lalonde P, Stip E. Working memory and depressive symptoms in patients with schizophrenia and substance use disorders. Cognitive Neuropsych 2008; 13: 357-66.

[60] Joyal CC, Hallé P, Lapierre D, Hodgins S. Drug abuse and/or dependence and better neuropsychological performance in patients with schizophrenia. Schizophr Res 2003; 63: 297-9.

[61] Herman M. Neurocognitive functioning and quality of life among dually diagnosed and non-substance abusing schizophrenia inpatients. Int J Ment Health Nurs 2004; 13: 282-91.

[62] Thoma P, Daum I. Working memory and multi-tasking in paranoid schizophrenia with and without comorbid substance use disorder. Addiction 2008; 103: 774-86.

[63] Scheller-Gilkey G, Lewine RRJ, Caudle J, Brown FW. Schizophrenia, substance use, and brain morphology. Schizophr Res 1999; 35: 113-20.

[64] Potvin S, Joyal C, Pelletier J, Stip E. Contradictory cognitive capacities among substance-abusing patients with schizophrenia: A meta-analysis. Schizophr Res 2008; 100: 242-51.

[65] Smelson DA, Davis CW, Eisenstein N, *et al*. Cognitive disparity in schizophrenics with and without cocaine dependency. J Subst Abuse Treat 2003; 24: 75-9.

[66] Penk WE, Flannery RB, Irvin E, Geller J, Fisher W, Hanson MA. Characteristics of substance-abusing persons with schizophrenia: the paradox of dually diagnosed. J Addict Dis 2000; 19: 23-30.

[67] Potvin S, Mancini-Marie A, Fahim C, Mensour B, Stip E. Processing of social emotion in patients with schizophrenia and substance use disorder: an fMRI study. Soc Neurosci 2007; 2: 106-16.

[68] Mathalon DH, Pfefferbaum A, Lim KO, Rosenbloom MJ, Sullivan EV. Compounded brain volume deficits in schizophrenia-alcoholism comorbidity. Arch Gen Psychiatry 2003; 60: 245-52.

[69] Smelson DA, Davis CW, Dipano R, Johnson V, Losonczy MF, Ziedonis D. Executive and motor skill functioning among cocaine-dependent schizophrenics and non-drug abusing schizophrenics. J Nerv Men Dis 2002; 190: 200-2.

[70] Van Gorp WG, Altshuler L, Theberge DC, Wilkins J, Dixon W. Cognitive impairment in euthymic bipolar patients with and without prior alcohol dependence: A preliminary study. Arch Gen Psychiatry 1998; 55: 41-6.

[71] Van Gorp W, Altshuler L, Theberge DC, Mintz J. Declarative and procedural memory in bipolar disorder. Biol Psychiatry 1999; 46: 525-31.

[72] Sánchez-Moreno J, Martínez-Aran A, Colom F, *et al*. Neurocognitive dysfunctions in euthymic bipolar patients with and without prior history of alcohol use. J Clin Psychiatry 2009; 70: 1120-7.

[73] Peer J, Benett ME, Bellack AS. Neurocognitive characteristics of individuals with schizophrenia and cocaine dependence: Comparison of currently dependent and remitted groups. J Nerv Ment Dis 2009; 197: 631-4.

[74] Daban C, Martinez-Aran A, Torrent C, *et al*. Specificity of cognitive deficits in bipolar disorder versus schizophrenia. Psychother Psychosom 2006; 75: 72-84.

[75] Xie H, McHugo GJ, Helmstetter BS, Drake RE. Three-year recovery outcomes for long term patients with co-occurring schizophrenic and substance use disorders. Schizophr Res 2005; 75: 337-48.

[76] Ringen PA, Vaskinn A, Sundet K, *et al*. Opposite relationships between cannabis use and neurocognitive functioning in bipolar disorder and schizophrenia. Psychol Med 2010; 40(8): 1337-47.

[77] Hambrecht M, Häfner H. Cannabis, vulnerability, and the onset of schizophrenia: an epidemiological perspective. Aust NZ J Psychiatry 2000; 34: 468-75.

[78] Henquet C, Krabbendam L, Spauwen J, *et al*. Prospective cohort study of cannabis use, predisposition for psychosis, and psychotic symptoms in young people. Brit Med J 2005; 330: 11

[79] Sugranyes G, Flamarique I, Parellada E, *et al*. Cannabis use and age diagnosis of schizophrenia. Eur Psychiatry 2009; 24: 282-6.

[80] Grech A, Van Os J, Jones PB, Lewis SW, Murray RM. Cannabis use and outcome of recent onset psychosis. Eur Psychiatry 2005; 20: 349-53.

[81] Arndt S, Tyrrell G, Flaum M, Andreasen NC. Comorbidity of substance use and schizophrenia: The role of pre-morbid adjustment. Psychol Med 1992; 22: 379-88.

[82] Kumari V, Postma P. Nicotine use in schizophrenia: the self medication hypothesis. Neurosci Biobehav Rev 2005; 29: 1021-34.

[83] Yip SW, Sacco KA, George TP, Potenza MN. Risk/reward decision making in schizophrenia: a preliminary examination of the influence of tobacco smoking and relationship to Wisconsin Card Sorting Task performance. Schizophr Res 2009; 110: 156-64.

[84] Yücel M, Lubman DI, Solowij N, Brewer WJ. Understanding drug addiction: a neuropsychological perspective. Aust N Z J Psychiat 2007; 41: 957-68.

[85] Schrimsher GW, Parker JD, Burke RS. Relation between cognitive testing performance and pattern of substance use in males at treatment entry. Clin Neuropsychol 2006; 21: 489-510.
[86] Pitel AL, Rivier J, Beaunieux H, Vabret F, Desgranges B, Eustache F. Changes in episodic memory and executive functions of abstinent and relapsed alcoholics over a 6-months period. Alcohol Clin Exp Res 2009; 33: 490-8.
[87] Weiss RD, Ostacher MJ, Otto MW, *et al*. Does recovery from substance use disorder matter in patients with bipolar disorder? J Clin Psychiatry 2005; 66: 730-5.
[88] Pencer A, Addington J. Substance use and cognition in early psychosis. J Psychiatry Neurosci 2003; 28: 48-54.
[89] Hyde TM, Nawroz S, Goldberg TE, *et al*. Is there cognitive decline in schizophrenia? A cross-sectional study. Brit J Psychiatry 1994; 164: 494-500.
[90] Heaton R, Paulsen JS, McAdams LA, *et al*. Neuropsychological deficits in schizophrenics: Relationship to age, chronicity, and dementia. Arch Gen Psychiatry 1994; 51: 469-76.
[91] Brazo P, Marié RM, Halbecq I, *et al*. Patrones cognitivos en los subtipos de esquizofrenia. Eur Psychiatry Ed Esp 2002; 9: 449-57.
[92] Goldstein G, Shemansky WJ, Allen DN. Cognitive function in schizoaffective disorder and clinical subtypes of schizophrenia. Arch Clin Neuropsych 2005; 20: 153-9.
[93] Ammari N, Heinrichs WR, Miles AA. An investigation of 3 neurocognitive subtypes in schizophrenia. Schizophr Res 2010; 121: 32-8
[94] Hsiao YL, Wu JY, Hsu MH, *et al*. Neuropsychological functions in patients with bipolar I and bipolar II disorder. Bipolar Disord 2009; 11: 547-54.
[95] Dittman S, Hennig-Fast K, Gerber S, *et al*. Cognitive functioning in euthymic bipolar I and bipolar II patients. Bipolar Disord 2008; 10: 877-87.
[96] Green MF. Cognitive impairment and functional outcome in schizophrenia and bipolar disorder. J Clin Psychiatry 2006; 67: 3-8.
[97] Weickert TW, Goldberg TE, Gold JM, Bigelow LB, Egan MF, Weinberger DR. Cognitive impairments in patients with schizophrenia displaying preserved and compromised intellect. Arch Gen Psychiatry 2000; 57: 907-13.
[98] Kimura D. Sex, sexual orientation and sex hormones influence human cognitive function. Curr Opin Neurobiol 1996; 6: 259-63.
[99] McLelland AT, Luborsky L, Cacciola J, *et al*. New data from the Addiction Severity Index. Reliability and validity in three centers. J Nerv Ment Dis 1985; 173: 412- 23.
[100] Kosten TR, Rounsaville BJ, Kleber HD. Concurrent validity of the Addiction Severity Index. J Nerv Ment Dis 1983; 171: 606-10.
[101] Carey KB, Kate B, Cocco KM, Correia CJ. Reliability and validity of the Addiction Severity Index among outpatients with severe mental illness. Psychol Asses 1997; 9: 422-8.
[102] Torrens M, Martin-Santos R, Samet S. Importance of clinical diagnoses for comorbidity studies in substance use disorders. Neurotox Res 2006; 10: 253-61.

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- ✓ **Objetivo 2: Funcionamiento Ejecutivo**

Estudio 2: *Executive functioning in individuals with schizophrenia and/or cocaine dependence*

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Resumen:

Si bien todavía se conoce poco el rendimiento neuropsicológico en PD, se ha sugerido que los pacientes con esquizofrenia y TUS comórbido, pertenecen a un subgrupo con menor vulnerabilidad genética a desarrollar la psicosis y consiguientemente, presentan un mejor funcionamiento ejecutivo y psicosocial premórbido, haciéndoles más hábiles para adquirir las sustancias ilegales de abuso, especialmente aquellas de más difícil acceso como la cocaína.

Material y método:

Se reunió una muestra de 95 hombres, de edades comprendidas entre los 20 y los 60 años, divididos en tres grupos. Un grupo con esquizofrenia y dependencia a la cocaína (SZ+; n = 30), otro grupo con esquizofrenia sin dependencia a la cocaína (SZ-, n = 30), y un tercer grupo con dependencia a la cocaína sin ningún trastorno psiquiátrico comórbido (COC, n = 35). En los grupos SZ+ y COC se consideraron consumidores tempranos (inicio del consumo a los 16 años o antes) y consumidores tardíos (inicio del consumo a los 17 años o más).

Se recabó información amplia de carácter sociodemográfico y clínico mediante una entrevista semi-estructurada y se evaluó la Impresión Clínica Global (ICG; National Institute of Mental Health, 1976) y la dependencia a la nicotina mediante el test de Fagerström (Heatherton, Kozlowski, Frecker & Fagerstrom, 1991). Para la evaluación neuropsicológica se incluyeron los siguientes test: Dígitos inversos (WAIS-R; Wechsler, 2001), *Trail Making Test* parte B (TMT-B; Reitan & Wolfson, 1985) la versión de 4 discos de la Torre de Hanoi (Lezak, Howieson & Loring, 2004) y la versión computerizada del Wisconsin Card Sorting Test (WCST; Heaton & PAR Staff, 2005) como medidas de memoria de trabajo,

flexibilidad cognitiva, habilidades de planificación y resolución de problemas simples respectivamente, todas ellas dependientes del funcionamiento del córtex dorsolateral. Como medida de funcionamiento del córtex orbito-frontal, se administró el *Iowa Gambling Task* (IGT; Bechara, Damasio, Damasio & Anderson, 1994) para evaluar los procesos de toma de decisiones. El subtest de Vocabulario (WAIS-R; Wechsler, 2001) se utilizó como medida de coeficiente intelectual (CI) verbal premórbido.

Los datos sociodemográficos y clínicos fueron analizados mediante análisis univariantes en el caso de los datos continuos y Chi cuadrado para los datos categoriales. Las diferencias en el rendimiento neuropsicológico entre grupos se analizaron mediante análisis multifactoriales de covarianza, con la introducción de las covariables estado civil, situación económica, ICG, número de medicamentos diarios y consumo de cigarrillos diarios.

Resultados:

Ambos grupos SZ+ y SZ-, presentaron una mayor proporción de solteros y mayor desocupación laboral respecto al grupo COC. También tomaban más medicamentos diarios, especialmente antipsicóticos típicos y atípicos y presentaban una peor ICG que el grupo COC. El grupo SZ+ fumaba más cigarrillos diarios y presentaba puntuaciones más elevadas en dependencia a la nicotina respecto a los otros dos grupos. Los grupos SZ+ y COC no presentaron diferencias en las variables evaluadas del TUS, excepto por un mayor consumo de cannabis en el grupo SZ+.

En cuanto al funcionamiento ejecutivo entre grupos, no se hallaron diferencias en vocabulario, Dígitos inversos ni en el TMT-B. Los grupos SZ+ y COC rindieron mejor que el grupo SZ- en la Torre de Hanoi y el WCST, sin diferencias entre ellos. El grupo COC presentó una mejor toma de decisiones respecto al grupo SZ-, indicada por mejores puntuaciones en el IGT, sin diferencias en el grupo SZ+ respecto a los otros dos.

Respecto a la edad de inicio del consumo se encontraron efectos interactivos en el TMT-B, con una mejor actuación de los consumidores SZ+ tempranos que los tardíos. El grupo COC no mostró diferencias en el rendimiento de los consumidores tempranos respecto los tardíos. A pesar de este efecto en el grupo SZ+, éste presentó peor rendimiento que el grupo COC, independientemente de la edad de inicio de consumo de los participantes.

Conclusiones:

Los grupos SZ+ y COC, mostraron mejor funcionamiento ejecutivo en las tareas dependientes del córtex frontal dorsolateral en comparación con el grupo SZ-, de acuerdo con la hipótesis de un mejor funcionamiento ejecutivo en los duales para adquirir las sustancias ilegales. La explicación más probable es una menor vulnerabilidad a la psicosis en los pacientes duales resultando en mejores habilidades cognitivas, pero que desarrollarían la psicosis por disrupciones en el sistema dopaminérgico ocasionadas por el consumo de sustancias. Mientras el grupo SZ- podría presentar vulnerabilidades neurobiológicas como alteraciones cerebrales sutiles, que darían lugar a déficits cognitivos y desarrollarían la psicosis sin ningún desencadenante adicional. Respecto a la edad de inicio del consumo, nosotros encontramos un efecto diferencial sobre la flexibilidad cognitiva en el grupo SZ+ entre los consumidores tempranos y tardíos. Se requiere mayor investigación para determinar la influencia del consumo de sustancias sobre el cerebro de los SZ+ considerando la edad de inicio de consumo.

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Executive functioning in individuals with schizophrenia and/or cocaine dependence

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Objective Although little is known about neurocognition in Dual Diagnosis, it has been suggested that Schizophrenia (SZ) patients with comorbid substance use belong to a subgroup with lower genetic vulnerability to develop SZ and, consequently, they show better executive and social premorbid functioning. The first aim of this study was to assess the executive functioning, and the second one was to explore the effect of age of onset of substance use in neurocognition in SZ patients with cocaine dependence.
Methods The total sample consisted of 95 male patients, aged 20 to 60 years, divided in three groups: one group with SZ and cocaine dependence (SZ+; $n = 30$), another group with SZ without cocaine dependence (SZ−; $n = 30$), and a control group with cocaine dependence without psychiatric comorbidity (COC; $n = 35$).
Results We found a better executive functioning in both SZ+ and COC than SZ−. We observed a worse performance of SZ+ patients compared with COC in cognitive set-shifting regardless the age of onset of consumption.
Conclusions The results agree with the hypothesis of a lower genetic vulnerability in SZ+ patients to develop psychosis compared with SZ−, who develop it without any additional trigger. However, future research is needed to clarify the current knowledge gaps. Copyright © 2012 John Wiley & Sons, Ltd.

KEY WORDS—executive functioning; schizophrenia; cocaine dependence; age of onset of substance use

INTRODUCTION

Although research has extensively demonstrated frontal dysfunction associated with executive functioning impairment in schizophrenia (SZ) (Toda and Abi-Darghem, 2007; Camchong *et al*., 2006), and in substance use dependence (SUD) (Garavan and Stout, 2005), specially in cocaine dependence (Volkow *et al*., 1992; Block *et al*., 2002; Jovanovski *et al*., 2005), little is known about the combined effects on executive functioning in subjects suffering SZ with comorbid SUD (SZ+) or Dual Diagnosis. The impact of the comorbidity between SZ+ and cocaine dependence on cognition is of great importance because it has been described that 20 to 50% of individuals diagnosed of SZ are cocaine abusers (Regier *et al*., 1990). Given the common involvement of fronto-subcortical dysfunctions in psychotic and cocaine addictive disorders, disproportionately severe cognitive impairment might be expected in patients suffering from both comorbid conditions. However, studies of cognitive function comparing SZ+ (mostly polyconsumers) to subjects with SZ without comorbid SUD (SZ−) have yielded contradictory results.

Regarding executive functioning, some studies have found similar performance when comparing SZ+ versus SZ− (Copersino *et al*., 2004; Addington and Addington, 1997; Cooper *et al*., 1999; Serper *et al*., 2000; Sevy *et al*., 2007; Wobrock *et al*., 2007); others found worse performance in SZ+ patients (Bowie and Serper, 2005), and others even found better executive functioning in SZ+ patients (Carey *et al*., 2003; Joyal *et al*., 2003; Smelson *et al*., 2003; Herman, 2004; Thoma *et al*., 2007; Thoma and Daum, 2008). Methodological differences between these studies may account for conflicting results (see Benaiges *et al*., 2010, for a review).

The authors who find a higher cognitive functioning in SZ+ patients often argue that they present a better premorbid adjustment (Arndt *et al*., 1992), social skills, and prognosis (Dixon *et al*., 1991; Joyal *et al*., 2003). Thus, drug-seeking individuals may possess social skills that allow them to socialize in drug scenes

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facilitating illegal substance acquisition (Joyal *et al*., 2003; Wobrock *et al*., 2007; Potvin *et al*., 2008; Rabin *et al*., 2011). This is associated with better cognitive abilities in subjects with SZ+ (Marshall *et al*., 2002), mainly when the substances are less accessible, as is the case with cocaine (Schnell *et al*., 2009). High levels of executive functions, together with high planning and social skills necessary to keep the SUD, could explain the better cognitive performance of SZ+ compared with SZ− (Dixon *et al*., 1991; Sevy *et al*., 2001; Joyal *et al*., 2003; McCleery *et al*., 2006; Thoma *et al*., 2007; Thoma and Daum, 2008). Although most studies did not evaluate the premorbid social adjustment, those that did found mixed results (Marshall *et al*., 2002; Stirling *et al*., 2005; Ringen *et al*., 2010; Rodríguez-Sánchez *et al*., 2010; Sevy *et al*., 2010). Therefore, the question still remains unclear.

Work focusing on SZ+ with comorbid cannabis use often obtains better general cognitive performance in these patients compared with SZ− (Sevy *et al*., 2001; Loberg *et al*., 2003; Stirling *et al*., 2005; McCleery *et al*., 2006; Jockers-Scherübl *et al*., 2007; Mata *et al*., 2008; Schnell *et al*., 2009; De Rosse *et al*., 2010; Rodríguez-Sánchez *et al*., 2010; Scholes and Martin-Iverson, 2010; Rabin *et al*., 2011; Rentzsch *et al*., 2011). The most common hypothesis in order to explain these results is that of a lower biological vulnerability in SZ+ subjects. It is believed that cognitive deficits are related to neurobiological vulnerability to psychosis, and they are considered endophenotypes of SZ (Snitz *et al*., 2006). Deficits in attention and memory are present in the prodromal state of the illness and even in the relatives of patients (Schnell *et al*., 2009). For this reason, it is possible that a higher cognitive performance reflects their reduced vulnerability compared with patients who develop the disease without any additional trigger (Hall, 1998; Schnell *et al*., 2009). Further support for this hypothesis is (i) an onset of substance abuse preceding the onset of psychiatric illness; (ii) an earlier age of onset of psychiatric illness compared with patients without comorbid SUD; (iii) a better cognitive functioning than schizophrenic nonusers; and (iv) less family psychiatric history of SZ. Although the hypothesis of a lower vulnerability in SZ+ patients has been postulated in schizophrenic cannabis users, it could also be generalized to psychostimulant users because of the common affectation of dopaminergic and catecholaminergic systems in both disorders (Kew and Kemp, 2005; Krystal *et al*., 2005). In this sense, Barnett, *et al*. (2007) found that age of onset of the first psychotic symptoms was positively associated with age at first use of cocaine, ecstasy, amphetamines, and cannabis. In contrast, alcohol and hallucinogens did not show this significance.

The age of onset of substance use may also be influencing the previous heterogeneous results across studies, although it is often not taken into account by most of the preceding works. Some authors found that healthy individuals who initiate cannabis use at an early age (16 years or younger), when the brain is still developing, might be more vulnerable to present lasting neuropsychological effects such as worse visual scanning (Ehrenreich *et al*., 1999), lower verbal IQ (Pope *et al*., 2003), and lower percentage of gray matter relative to whole-brain volume (Wilson *et al*., 2000) than individuals who initiate substance use later (17 years or older). The age group separation was chosen by these authors according to neurodevelopment of the brain, particularly because both cannabinoid and dopaminergic systems reach maturation earlier and largely conclude by the age of 16 years, as opposed to other systems such as the serotonergic system (Lambe *et al*., 2000; Sundram, 2006; Jockers-Scherübl *et al*., 2007). Interestingly, Jockers-Scherübl *et al*. (2007) found that regular cannabis use before the age of 17 years and prior to first psychotic episode improved cognition in some SZ patients. In contrast, neuropsychological performance in healthy controls is worse when regular cannabis use started before the age of 17 years.

The aim of the present study is twofold. Firstly, we evaluate the executive functions related to the functioning of prefrontal cortex (specifically orbitofrontal and dorsolateral prefrontal cortex regions) in patients with SZ+, mainly cocaine dependents. Then, we compare them to SZ− patients and to patients with cocaine dependence without psychiatric comorbidity (COC), through an extensive battery of neuropsychological tests. We expect that the SZ− group will show worse state of executive functioning than the SZ+ and COC groups according to the hypothesis of better executive functioning in these last groups in order to obtain illegal drugs in tough social scenes. A higher performance on frontal related functions in SZ+ than SZ− and very similar to COC patients may represent a coherent picture of substance users as a specific subgroup of SZ patients with better premorbid social adjustment and lower biological vulnerability. Secondly, we explore the differential effect of age of onset of substance use on executive functioning of patients with and without psychiatric comorbidity (SZ+ and COC groups). We consider the earlier consumers (16 years or younger) versus later consumers (17 years or older) as did Jockers-Scherübl *et al*. (2007) in their previous work. According to global literature results, we expect a worse performance in earlier consumers than in later ones.

MATERIAL AND METHODS

Participants

Total sample consisted in 95 males aged 20 to 60 years (37.24 ± 7.62), divided in three groups. Two groups with schizophrenia/schizoaffective disorder with and without cocaine dependence and a third group with COC. Both cocaine dependence groups were abstinent from all type of substances of abuse for at least 4 months prior to testing, controlled by urinalysis. This study was approved by the ethics committees of the University of Barcelona and the Mental Health Division of Althaia, meeting the ethical principles of the Declaration of Helsinki. Written informed consent was obtained from all participants, and the procedures of the study were fully explained to them. They were not compensated for their study participation.

Patients with schizophrenia

Sixty patients were recruited from various outpatient programs at the Mental Health division of the Althaia Foundation in Manresa (Barcelona). Each participant was referred by their treating psychiatrist and had been diagnosed according to the Diagnostic Statistical Manual of Mental Disorders (DSM-IV-R, American Psychiatric Association, 2002) using the Structural Clinical Interview for DSM-IV-R Axis I Disorders (First *et al*., 1998). Inclusion criteria were (i) current diagnosis of schizophrenia or schizoaffective disorder, and (ii) no DSM-IV-R criteria for a current substance-induced psychotic disorder or a psychotic disorder because of a medical condition. The exclusion criteria were unstable or severe medical illness, mental retardation, history of traumatic brain injury or neurological injury, and they had not received electroconvulsive therapy within 12 months prior to their study participation. Twenty seven patients diagnosed of SZ and three patients with schizoaffective disorder without DSM-IV-R diagnosis for substance use or alcohol use disorders were included (SZ−; $n = 30$). Another twenty six patients diagnosed of SZ and four patients diagnosed of schizoaffective disorder and cocaine dependence disorder (SZ+; $n = 30$) were also included with the following additional inclusion criteria: (i) current DSM-IV-R for cocaine dependence in remission for at least 4 months, and (ii) having cocaine as a main drug of choice.

Patients with cocaine dependence without psychiatric comorbidity

Thirty five patients were recruited from various programs at Gressol Catalonia Man Project (Barcelona) (COC; $n = 35$). The inclusion criteria were (i) current DSM-IV-R for cocaine dependence in remission for at least 4 months, and (ii) having cocaine as a main drug of choice. Patients were excluded if they had any history of a psychiatric disorder other than drug dependence.

Clinical measures

Information was collected by means of a *structured interview* of sociodemographic (age, marital status, social class, schooling, and economic status) and clinical variables (diagnosis, psychiatric and substance use family history, age of onset of the disorder and/or consumption, relapses, abstinence periods, type of drug used, suicidal attempts, presence of organic pathology, and type of medication. Chlorpromazine equivalent doses (CPZ) were calculated for antipsychotic medication according to Andreasen *et al*. (2010) and Woods (2003). We also recorded daily consumption of tobacco and caffeine intake. Smokers were administered the *Fagerström* test of nicotine dependence (Heatherton *et al*., 1991). Additionally, the *Clinical Global Impression* questionnaire (CGI; National Institute of Mental Health, 1976) was applied as a subjective measure of the clinical severity of each participant.

Neuropsychological assessment

A neurocognitive battery composed of valid and reliable tests was chosen from those previously used in studies with dual diagnosis patients. The tests included the assessment of intellectual premorbid abilities and main executive functions related to both dorsolateral and orbital prefrontal cortex. To obtain measures of cognitive function related to dorsolateral prefrontal cortex, we selected the *Backward Digits* subtest of the Wechsler Adult Intelligence Scale-Revised (Wechsler, 1981), *Trail Making Test* part B (TMT-B; Reitan and Wolfson, 1985), Tower of Hanoi (four disks version, Lezak *et al*., 2004), the standard computerized version of the *Wisconsin Card Sorting Test* (WCST; Heaton *et al*., 1993; Heaton and Staff, 2005) as measures of working memory, set-shifting, cognitive flexibility, planning abilities, abstract reasoning, and problem solving, respectively. The *Iowa Gambling Task* (IGT; Bechara *et al*., 1994) was administered to measure decision-making capacity, as a measure of orbitofrontal cortex functioning. We used the *Vocabulary* subtest (Wechsler Adult Intelligence Scale-Revised) as a reliable estimate of premorbid verbal IQ (Lezak *et al*., 2004). All subjects completed the full battery.

Statistical analysis

Demographic and clinical data were explored with one-way analysis of variance in the cases of continuous data

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and chi Square test for categorical data. Differences in neuropsychological performance between groups were analyzed with one-way analysis of covariance for Vocabulary, Backward digits subtests, Trail Making Test part B (TMT-B), and multivariate analysis of covariance (MANCOVA) in the case of the Tower of Hanoi, WCST, and IGT with direct scores as dependent variables and diagnostic group (SZ+, SZ− and COC) as between subject factor. Repeated measures MANCOVA was also used in the case of IGT. We carried out the same analyses with both cocaine dependence groups (SZ+, COC) and age at onset of intake drugs (16 years and younger, 17 years and older), considered as between subject factors. The covariates marital status, economic situation, CGI, number of prescribed medication, and consumption of daily cigarettes were introduced in all analyses. We estimated statistic partial squared Eta (η_p^2) to measure the effect size, where a value of 0.01 was low, 0.04 moderate, and 0.1 high. All post-hoc comparisons were Bonferroni corrected. Data were analyzed using the Statistical Package for the Social Sciences (SPSS version 15.0; Chicago, USA). The tests were considered bilaterally with a type I error established at 5%.

RESULTS

Sociodemographic and clinical data

Groups were equivalent in age and years of schooling. Marital status showed a higher proportion of singles in both SZ + and SZ− groups compared with the COC group ($\chi^2 = 12, 61$; $p = 0.002$). The economic situation revealed a higher proportion of active employees with a lower proportion of patients receiving a disability pension from the government in the COC group compared with SZ + and SZ− groups ($\chi^2 = 22, 32$; $p \leq 0.0001$). Table 1.

Table 1. Descriptive statistics (frequencies, mean, and standard error, depending on the case) of sociodemographic data for the three groups of patients

Sociodemographic data	SZ+ ($N = 30$)	SZ− ($N = 35$)	COC ($N = 35$)
Age (years)	36.80 ± 7.47	38.70 ± 8.72	36.37 ± 6.72
Marital status			
Single (%)	83.3	86.7	51. 4
Stable partner (%)	6.7		8.6
Married (%)		3.3	11.4
Separate/Divorced (%)	10.0	10.0	28.5
Years of study	9.14 ± 2.01	9.66 ± 2.44	9.58 ± 2.23
Economic situation			
Active (%)	13.3	16.7	42.9
Disability pension (%)	53. 3	80.0	17.1
Unemployed (%)	16.7		20.0
No income (%)	16.7	3.3	20.0

SZ+, schizophrenia with comorbid cocaine dependence; SZ−, schizophrenia without comorbid cocaine dependence; COC, cocaine dependence without psychiatric comorbidity.

Regarding clinical data, the SZ groups did not differ in the age of psychiatric disorder onset and mean duration of illness. The comparisons between the three groups did not reach significance in psychiatric nor substance use family history, number of suicidal attempts, number of medical comorbidities, and daily intake of caffeine. Otherwise, significant differences were found in number of daily prescribed medications ($F_{(2, 93)} = 41.87$; $p = 0.0001$; $\eta_p^2 = 0.47$). Post-hoc analysis showed that the two SZ groups were taking more daily medications than the COC group ($p \leq 0.0001$), especially both typical and atypical antipsychotics with higher intake of doses of CPZ equivalents ($F_{(2, 93)} = 23.59$; $p = 0.0001$; $\eta_p^2 = 0.33$), without differences between both SZ groups. The SZ + group showed higher daily consumption of cigarettes ($F_{(2, 93)} = 5.30$; $p = 0.007$; $\eta_p^2 = 0.10$) with respect to the SZ− group ($p = 0.002$) and the COC group (0.027), and also higher nicotine dependence on the *Fagerström* test ($\chi^2 = 6.21$; $p = 0.04$) without differences between SZ− and COC groups. The CGI showed main effects ($F_{(2, 93)} = 25.35$; $p = 0.0001$; $\eta_p^2 = 0.35$) being the COC group significantly better compared with SZ− and SZ+ groups ($p = 0.0001$). It is noteworthy that the onset of substance dependence preceded the onset of psychosis in all SZ+ patients (Table 2).

Concerning the data on substance use dependence, SZ+ and COC groups did not differ in the type of consumption, number of substance use, months of abstinence, and number of relapses. Although all patients were dependent on cocaine, most of them were polydrug users. Thus, SZ+ showed a higher frequency of cannabis use than COC group ($\chi^2 = 8.40$; $p = 0.004$), with no differences in the frequency of other substance of abuse. SZ+ group started the consumption at an earlier age than COC group ($F_{(2.63)} = 4.54$; $p = 0.037$; $\eta_p^2 = 0.06$) (Table 3).

Executive functions

The results of the neuropsychological assessment for each group of the sample are shown in Table 4, as well as the results of comparisons between groups. We did not found differences between groups in the direct score of both Vocabulary and Backward digits subtests nor in the TMT-B reaction time.

We found a better performance of the SZ+ and COC group compared with the SZ− on the Tower of Hanoi with fewer errors and shorter reaction time ($p = 0.05$) to complete the task. Despite the good performance of the COC group, they required a higher number of movements to finish the tower compared with the SZ+ group ($p = 0.007$). The SZ+ and COC groups also performed better than the SZ− group in the WCST, with fewer total and non-perseverative errors, more conceptual

Table 2. Descriptive statistics (frequencies, mean, and standard error, depending on the case) of the clinical data for the three groups of patients

Clinical data	SZ+ ($N=30$)	SZ− ($N=30$)	COC ($N=35$)
Psychiatric diagnosis (%=100)			
Schizophrenia	($n=27$) 90.0%	($n=26$) 86.6%	
Schizoaffective	($n=3$) 10.0%	($n=4$) 13.3%	
Age of psychiatric disorder onset (years)	23. 46 ± 6.13	24.24 ± 7.26	
Mean duration of illness (years)	13.42 ± 8.06	14.55 ± 8.75	
Number of relatives with SUD	0.22 ± 0.57	0.07 ± 0.57	0.23 ± 0.59
Number of relatives with psychiatric disorder	0.68 ± 0.90	0.67 ± 0.66	0.49 ± 0.74
Number of suicidal attempts	0.90 ± 1.37	0.40 ± 0.72	0.34 ± 0.87
Number of medical comorbidities	0.57 ± 0.77	0.60 ± 0.77	0.46 ± 0.78
Daily number of medications[a]	3.27 ± 1.53	3.10 ± 1.21	0.69 ± 1.10
Typical antipsychotics (%)	50	23.3	2.9
Atypical antipsychotics (%)	93.3	96.7	5.7
Anticholinergics (%)	26.7	33	
Antidepressants (%)	33. 3	30.0	11.4
Mood stabilizers (%)	23.3	36. 7	11.4
Anxiolytics (%)	36.7	33.3	8.6
Other medication (%)	26.7	16.7	20
CPZ equivalents [b] (mg)	437.31 ± 276.83	499.57 ± 467.24	21.42 ± 71.00
Clinical Global Impression (CGI)	4.80 ± 0.96	4.40 ± 0.72	3.26 ± 1.01
Daily number of cigarettes	21.73 ± 15.94	11.50 ± 12.74	14.74 ± 8.08
Fagerström Score	5.21 ± 2.75	3.23 ± 3.48	3.86 ± 2.48
No dependence (%)	16.7	50.0	17.1
Low dependence (%)	10.0		20.0
Moderate dependence (%)	33.3	26. 7	51.4
High dependence (%)	36.7	23.3	11.4
Daily Number of coffees (cups)	1.83 ± 1.87	1.33 ± 1.49	1.66 ± 1.43
Other daily beverages with caffeine	1.07 ± 1.08	0.80 ± 1.09	0.91 ± 1.26

[a]Percentage will not total to 100 as each participant may be taking more than one medication.
[b]Chlorpromazine equivalents.
SZ+, schizophrenia with comorbid cocaine dependence; SZ−, schizophrenia without comorbid cocaine dependence; COC, cocaine dependence without psychiatric comorbidity.

Table 3. Descriptive statistics (frequencies, mean, and standard error, depending on the case) of substance use for SZ+ (schizophrenic with comorbid cocaine dependence) and COC (cocaine dependence without psychiatric comorbidity) groups

Substance use data	SZ+ ($N=30$)	COC ($N=35$)
Type of intake		
One substance (%)	6.9	20
Two substances (%)	17.2	23.9
Polydrug use (%)	75.9	57.1
Number of substances used	3.62 ± 1.61	3.14 ± 1.53
Substance abuse/dependence [a]		
Cocaine (%)	100	100
Cannabis (%)	86.2	48.6
Alcohol (%)	72.4	68.6
Ecstasy (%)	41.4	25.7
Hallucinogens (%)	27.6	14.3
Opioids (%)	27.6	28.6
Sedatives (%)	10.3	2.9
Months of abstinence	13.42 ± 1.71	9.14 ± 5.07
Number of relapses	1.12 ± 1.30	0.54 ± 1.03
Age of intake onset (years)	16.15 ± 2.31	20.00 ± 8.27
Mean duration of SUD (years)	18.78 ± 8.73	15.60 ± 7.16

[a]Percentages will not total to 100 as each participant may be taking more than one substance of abuse.
SUD, substance use dependence.

level responses and higher number of categories achieved ($p < 0.05$). No more differences between groups were found in other responses of the WCST.

Although the repeated measures MANCOVA analysis for the IGT did not reach significant differences between groups, the MANCOVA analysis showed a better performance of the COC group compared with the SZ− in the last test trial ($p = 0.01$) and in the total score ($p = 0.05$), without difference to the SZ+ group. We did not obtain statistical significance between SZ+ and SZ− groups (Figure 1).

The influence of age of onset of substance use

In order to explore the interacting effects among diagnostic groups and age of onset of substance use, first, we explored the differences in sociodemographic and clinical data between groups (SZ+ vs COC) and age of onset of consumption (16 years or younger vs 17 years or older). Although we did not find differences in these variables regarding age of onset of consumption, the differences between diagnostic groups were maintained for marital status, economic situation, CGI, number of prescribed medications, and cigarette smoking. They were introduced in the following analyses as covariates. All post-hoc comparisons were Bonferroni corrected.

The analyses considering only the differences between diagnostic groups (SZ+ vs COC) showed main effects for the TMT-B test ($F_{(1, 64)} = 5.18$; $p = 0.027$; $\eta_p^2 = 0.08$),

Table 4. Mean scores and standard deviations of the three groups of patients in the neuropsychological tests, together with the results of the MANCOVAs carried out and the significant contrasts among the groups

Test executive functions	Groups			MANCOVA		
	SZ+ ($N=30$)	SZ− ($N=30$)	COC ($N=35$)	F	Effect size	Contrast[a]
Vocabulary (WAIS-III)						
Direct score	40.72 ± 9.05	42.76 ± 6.93	43.02 ± 6.60	0.87	0.02	
Tower of Hanoi						
Number of movements	23.41 ± 8.78	26.63 ± 8.82	29.40 ± 9.38	3.87*	0.08	SZ− = SZ+ < COC
Number of errors	1.00 ± 1.43	1.90 ± 1.95	1.31 ± 1.54	3.22*	0.07	SZ- > SZ + = COC
Reaction Time (seconds)	172.83 ± 118. 73	272.77 ± 183.60	169.94 ± 90.63	5.13**	0.10	SZ+, COC < SZ−
WCST						
Trials administered	96.52 ± 19.05	111.17 ± 19.25	96.60 ± 17.76	4.90*	0.16	SZ+, COC < SZ−
Total correct	75.24 ± 9.39	79.57 ± 9.16	75.83 ± 9.99	1.60	0.03	
Total errors %	20.24 ± 7.53	26.77 ± 8.37	20.11 ± 5.99	6.92**	0.13	SZ+, COC < SZ−
Perseverative errors %	5.79 ± 4.13	9.33 ± 6.50	5.51 ± 4.21	2.49	0.05	
Non-perseverative errors	14.03 ± 5.08	16.63 ± 5.61	13.89 ± 4.98	3.75*	0.08	SZ + = COC < SZ−
Conceptual level responses (%)	73.45 ± 10.76	64.57 ± 12.93	72.63 ± 12.95	5.10**	0.10	SZ+, COC > SZ−
Categories completed	5.62 ± 0.97	4.90 ± 1.47	5.83 ± 0.56	4.20*	0.08	SZ+, COC > SZ−
Trials to first category	15.66 ± 10.12	13.93 ± 5.40	12.97 ± 4.57	0.56	0.03	
Failure to maintain set	1.10 ± 1.37	1.83 ± 2.01	1.03 ± 1.22	1.14	0.01	
Learn to learn	−1.83 ± 5.47	−5.07 ± 8.30	−1.31 ± 2.11	1.45	0.01	
Time reaction (milliseconds)	3843.66 ± 1301.95	4486.43 ± 2091.22	2703.03 ± 732.90	1.74	0.00	
TMT-B						
Time reaction (seconds)	108.79 ± 50.13	107.63 ± 53.16	71.34 ± 30.48	0.45	0.01	
Backward digits (WAIS-III)						
Direct score	4.88 ± 1.94	4.83 ± 1.57	6.03 ± 1.93	1.59	0.03	
IGT						
Trials 1–20	−0.62 ± 3.12	−1.79 ± 3.66	−0.38 ± 5.36	1.08	0.02	
Trials 21–40	−1.10 ± 3.18	−1.03 ± 4.44	0.00 ± 5.37	2.71	0.06	
Trials 41–60	0.45 ± 5.47	1.52 ± 6.12	2.75 ± 7.07	0.67	0.01	
Trials 61–80	0.21 ± 5.16	0.64 ± 6.41	4.19 ± 10.39	1.29	0.03	
Trials 81–100	−1.31 ± 6.87	−0.71 ± 6.64	3.44 ± 7.55	4.55*	0.10	SZ+ = COC > SZ−
Total	1.17 ± 15.14	−1.36 ± 20.66	11.19 ± 27.45	3.14*	0.07	SZ+ = COC > SZ−

[a]Detailed only for the contrasts with Bonferroni corrections that have proved significant.
SZ+, schizophrenia with comorbid cocaine dependence; SZ−, schizophrenia without comorbid cocaine dependence; COC, cocaine dependence without psychiatric comorbidity; WAIS-III, Wechsler Adult Intelligence Scale III; WCST, Wisconsin Card Sorting Test; IGT, Iowa Gambling Task; TMT-B, Trail Making Test part B.
*$p < 0.05$
**$p < 0.01$

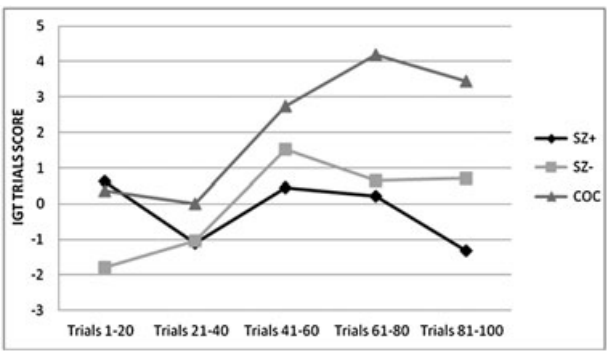

Figure 1. Iowa Gambling Task (IGT) in the three groups of patients through the five blocks of trials. SZ+, schizophrenia with comorbid cocaine dependence; SZ-, schizophrenia without comorbid cocaine dependence; COC, cocaine dependence without psychiatric comorbidity

the last trial ($F_{(1,\ 64)} = 7.26$; $p = 0.009$; $\eta_p^2 = 0.12$), and the total score on the IGT ($F_{(1,\ 64)} = 6.65$; $p = 0.013$ $\eta_p^2 = 0.11$), with a better performance of the COC group. Both groups did not differ in the other measures of executive functions.

The analyses by age of onset of substance use (16 years old vs 17 years old), ignoring the diagnostic group, showed main effects in the TMT-B ($F_{(1,\ 64)} = 12.57$; $p = 0.001$; $\eta_p^2 = 0.09$) and in trials to first category on the WCST ($F_{(1,\ 64)} = 4.08$; $p = 0.048$; $\eta_p^2 = 0.06$). The better execution on both groups was obtained when substance use started before 16 years or earlier. No more main effects in the rest of executive functions were found regarding the age of onset of substance use (Table 5).

There were significant interacting effects between diagnostic groups and age of onset of substance use factors in the TMT-B ($F_{(1,\ 64)} = 8.11$; $p < 0.006$; $\eta_p^2 = 0.12$). Figure 2 illustrates these interacting effects in the reaction time measured by seconds. Lower reaction time to complete the test was observed in both groups when patients began substance use at 16 years or younger. The analysis separated by groups showed that this result was true only for the SZ+ group. The difference in the reaction time on the TMT-B was not significant between those COC patients who started the

Table 5. Mean scores and standard deviations for neuropsychological variables for SZ+ (schizophrenia with comorbid cocaine dependence) and COC (cocaine dependence without psychiatric comorbidity) differentiated by age of onset of substance use

Neuropsychological variables	SZ+		COC	
	16 years and younger ($N = 20$)	17 years and older ($N = 10$)	16 years and younger ($N = 18$)	17 years and older($N = 17$)
Age onset of substance use (years)	15.25 ± 0.91	19.40 ± 3.06	14.61 ± 1.24	25.71 ± 8.74
Vocabulary (WAIS-III)				
Direct score	40.95 ± 9.55	40.50 ± 7.93	42.16 ± 7.20	43.94 ± 5.98
Tower of Hanoi				
Number of movements	23.60 ± 6.60	23.00 ± 12.90	31.67 ± 9.28	27.00 ± 9.15
Number of errors	0.70 ± 0.92	1.67 ± 2.12	1.28 ± 1.52	1.35 ± 1.61
Reaction time/seconds	162.60 ± 98.31	195.56 ± 159.81	185.89 ± 93.92	153.06 ± 86.55
WCST				
Total correct	74.15 ± 9.61	77.67 ± 8.94	76.28 ± 10.71	75.35 ± 9.48
Total errors %	20.20 ± 7.53	20.33 ± 8.01	18.17 ± 5.42	22.18 ± 6.02
Perseverative errors %	5.60 ± 4.38	6.22 ± 3.73	4.78 ± 3.96	6.29 ± 4.45
Non-perseverative errors	14.15 ± 5.24	13.78 ± 4.99	12.28 ± 3.84	15.59 ± 5.58
Conceptual level responses (%)	73.35 ± 10.55	73.67 ± 11.87	73.17 ± 16.15	72.06 ± 8.87
Categories completed	5.70 ± 0.92	5.44 ± 1.13	5.94 ± 0.23	5.71 ± 0.77
Trials to first category	13.65 ± 6.71	20.11 ± 14.80	12.50 ± 4.26	13.47 ± 4.96
Failure to maintain set	0.95 ± 1.39	1.44 ± 1.33	0.94 ± 1.25	1.12 ± 1.21
Learn to learn	−2.50 ± 6.40	0.33 ± 1.93	−1.44 ± 2.06	−1.18 ± 2.21
Time reaction (milliseconds)	3711.45 ± 1198.26	4137.44 ± 1543.32	2786.83 ± 727.06	2614.29 ± 750.67
TMT-B				
Time reaction (seconds)	90.50 ± 21.79	149.44 ± 70.51	67.94 ± 23.18	74.94 ± 37.11
Backward digits (WAIS-III)				
Direct score	5.28 ± 2.02	4.00 ± 1.51	5.72 ± 1.80	6.35 ± 2.06
IGT				
Trials 1–20	−1.00 ± 3.14	0.22 ± 3.07	0.75 ± 4.37	0.00 ± 6.32
Trials 21–40	0.90 ± 2.71	−1.56 ± 4.21	0.63 ± 5.04	0.63 ± 5.78
Trials 41–60	0.45 ± 5.60	2.44 ± 4.87	1.00 ± 7.30	4.50 ± 6.59
Trials 61–80	0.60 ± 5.91	2.00 ± 2.23	2.25 ± 9.03	6.13 ± 11.55
Trials 81–100	0.70 ± 7.54	2.67 ± 5.19	3.50 ± 5.13	3.38 ± 9.57
Total	−1.10 ± 16.29	6.22 ± 11.42	6.75 ± 19.68	15.63 ± 33.58

WAIS-III, Wechsler Adult Intelligence Scale III; WCST, Wisconsin Card Sorting Test; IGT, Iowa Gambling Task; TMT-B, Trail Making Test part B.

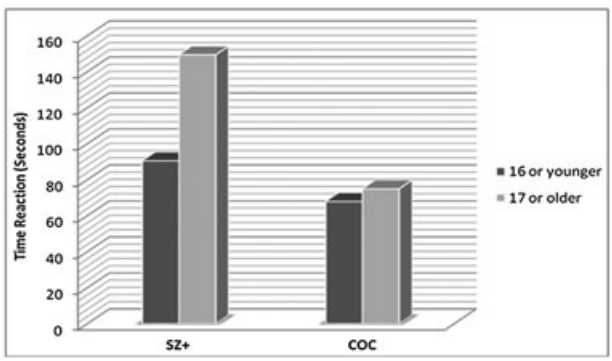

Figure 2. Reaction time (seconds) on Trail Making Test part B (TMT-B) by groups *x* age of onset of substance use (16 years or younger, 17 years or older). Fewer seconds indicate better execution on the task. SZ+, schizophrenia with comorbid cocaine dependence; COC, cocaine dependence without psychiatric comorbidity

consumption before 16 years or at 17 years or older. In contrast, those SZ+ patients who started the consumption before 16 years performed better on this task than those SZ+ patients who started the consumption at age 17 years or later. In spite of this effect, both early and late consumers in the SZ+ group performed worse than the COC group in the TMT-B. No other interacting effects were found.

DISCUSSION

This study intended to clarify the existing literature about neurocognition in patients with SZ+, especially those with cocaine dependence. Although we focused on cocaine dependence, most of our patients were polydrug users, with a high prevalence of cannabis and alcohol, especially in the SZ+ groups. This pattern of consumption is consistent with other research (Rabinowitz *et al*., 1998; Sevy *et al*. 2001). Given the great rates of consumption of both cannabis and alcohol as substances affecting the cognitive state between groups, all the analyses were performed again controlling for these substances. We obtained similar results to the previous ones without appreciable differences. Although we have matched the groups in marital status, economic situation, clinical state, daily prescribed medications, and daily cigarette smoking because significant differences emerged between groups, we must highlight that it was an artificial adjustment that only removed part of the variance on the results. Our study is comprised of non-randomized groups, and the differences between them were meaningful characteristics of each group, and therefore they cannot be successfully controlled.

Moreover, as shown in Table 2, three subjects in the SZ+ group and four subjects in the SZ− group were suffering from schizoaffective disorder. Because schizoaffective patients may have better neuropsychological performance than SZ ones, we excluded these subjects and the analysis were conducted again. The results were very similar to the previous ones. All these considerations are important for interpreting our results.

Executive functioning in SZ+ patients

In order to confirm or refute the vulnerability hypothesis, our first aim was to test higher frontal related functions in both SZ+ and COC groups and also in the SZ− group. As we expected, the SZ+ and COC groups showed better executive functioning sensitive to dorsolateral prefrontal function compared with the SZ− group, with little difference between them. This is in agreement with the hypothesis of a better executive functioning in the SZ+ patients to obtain illegal drugs, especially those difficult to get such as cocaine (Schnell *et al*., 2009).

Regarding the decision-making task linked to orbitofrontal function, the COC group showed a better performance compared with the SZ−, whereas the SZ+ group did not differ from the other two groups. Although Sevy *et al*. (2007) also did not find differences in the IGT between SZ+ and SZ−, our results may be because of the large variance of net scores in the IGT performance.

Even though we measured the premorbid verbal intelligence, this is different to social premorbid functioning. It would be interesting that future studies incorporate measures of premorbid social functioning and its relation to executive functioning in SZ patients.

Our results only partially support the vulnerability hypothesis. Although a higher performance in prefrontal related functions and an onset of substance use preceding the onset of psychosis were found in our sample, we did not find an earlier onset of psychosis in SZ+ compared with SZ− as did Jockers-Scherübl *et al*. (2003), Green, *et al*. (2004), and Arendt, *et al*. (2005). Several other studies also did not find an earlier onset of psychosis in SZ+ patients (Veen *et al*., 2004; Boydell *et al*., 2007; De Rosse *et al*., 2010; Sevy *et al*., 2010). In agreement with Schnell, *et al*. (2009), it is possible that these patients may have noticed the initial symptoms earlier, and they may have developed relatively efficient strategies to deal with their symptoms before being referred to psychiatric services. This is consistent with a better executive functioning in SZ+, which allows them to handle their demands more successfully than SZ−. No difference in family psychiatric history was found between SZ+ and SZ− (Table 2), but the fact that these data were self-reported by patients may account for the lack of differences.

Taken together, our results show higher dorsolateral prefrontal-related functions in SZ+ and COC compared with SZ−, as well as an onset of SUD before the onset of SZ according to the lower biological vulnerability hypothesis. However, these results should be interpreted with caution. The lack of differences in the orbitofrontal functioning, age of psychosis onset, and family psychiatric history between SZ+ and SZ− may be arguments against the vulnerability.

Despite this, the most probable reason for a better executive functioning in SZ+ is that of their lower threshold to develop psychosis resulting in better cognitive abilities, whereas SZ− may have other neurobiological vulnerabilities like subtle brain alterations resulting in cognitive deficits. Thus, substance intake may trigger psychosis by disruptions in the dopaminergic system in patients with lower biological vulnerability to psychosis that had normal cognitive abilities, rather than improve cognition because the adverse effects of substances of abuse in SZ patients have been demonstrated in several studies.

The relatively small sample size, large deviations on IGT net scores, and the use of self-reported information together with the lack of premorbid social functioning measures in our study could be responsible factors of this partially unsupported hypothesis. Future studies should consider these factors incorporating large samples and genetic measures that would allow elucidating the weight of the genetic load in SZ patients with and without comorbid SUD. Measures of orbitofrontal functioning should be added in the cognitive assessments of dual diagnosis patients given their absence in most of the preceding works.

The influence of age of onset of substance use

The second aim was to elucidate the effect of substance use onset on executive functioning in patients with cocaine dependence with and without SZ comorbidity in remission according to earlier consumers (onset at 16 years or before) and later consumers (onset at 17 years or later). The COC group was better at set-shifting and making decisions indicated by a better performance on TMT-B and IGT than the SZ+ group. Surprisingly, when we analyzed the effect of age of substance use, earlier consumers performed better in TMT-B and in trials to first category on the WCST. Similarly, the analyses between groups and age of onset of substance use show interacting effects only in TMT-B, the better performance being in earlier SZ+ consumers than later SZ+ consumers.

Because cocaine dependence mainly affects both dopaminergic and catecholaminergic systems (Block *et al*., 2002; Krystal *et al*., 2005), we expected that

substance use before these systems reach maturation will lead to more deleterious neuropsychological effects than after the age of 17 years, when these systems have already concluded their maturation (Sundram, 2006). We also expected that these effects on earlier consumers would be more obvious on executive functioning because the prefrontal cortex ends their maturation process in late adolescence, after the age of 17 years, through pruning of exuberant synapses and myelination of axons (Woo and Crowell, 2005). However, Jockers-Scherübl *et al.* (2007) obtained similar results in SZ+ and control cannabis users without psychiatric comorbidity. They found that SZ+ performed better on the digit symbol Substitution Test and in the variable "other errors" for the WCST when cannabis use had begun before the age of 17 years, but performed worse when consumption had started at 17 years or later. Otherwise, those controls who had cannabis abuse at 16 years or younger were worse in these tasks than those who had started cannabis abuse at 17 years or later. So, they find a certain preservative effect of cannabis use in those SZ+ patients who started the consumption at an early age. Unlike these authors, we only find a better performance of the earlier consumers in the SZ+ group, but the COC group did not show significant difference between earlier and later consumers in TMT-B. Further, both earlier and later SZ+ consumers performed worse in this task than earlier and later COC consumers (Figure 2). Hence, our results did not show a positive effect of substance use, mainly of cocaine use, in subjects with SZ+ compared with COC. We only found differential effects on SZ+ patients when their started consumption before the age of 16 years than at age of 17 years or later.

We were not sure about the explanation for the differential effects among earlier and later substance use in SZ+ patients. Development of higher-order association cortices including parietal, superior temporal, and prefrontal regions underlying maturation of executive functions among other cognitive functions (Casey *et al*., 2000; Sowell *et al*., 2001) occurs during late adolescence. Therefore, these higher-order functions are expected to be more impacted by earlier use of drugs. Despite, we used the Bonferroni correction method in order to avoid the occurrence of type I error, that is, detecting an effect when there is none, our results are clearly counterintuitive. The little sample size in the analyses carried out by groups and age of onset of substance use could be inducing the occurrence of this type of error. It should be noted that our aim to explore the effect of substance use onset on neurocognition has an exploratory character. Further, the participants of our sample were mostly polyconsumers, and we were not able to study the specific impact of each substance of use because of the small sample size.

Future research is needed to determine the influence of substance use in the brain of the SZ+ patients depending on the age of onset of intake. This knowledge could have many implications for the prevention of substance use in patients at risk of developing SZ in later ages.

Despite this, our results do not seem affected by the residual effects of substance use because of the extensive abstinence time. The fact that our sample is comprised only of males eliminates the influence of gender-related variables. The inclusion of two SZ groups, with and without cocaine dependence, and a group with cocaine dependence without SZ, allows for a more comprehensive understanding of the effects of substance use on SZ+ versus non-SZ patients. All these are lacking factors in many of the preceding works. Nevertheless, our study is not free of some limitations.

One of the most important limitations in our study is the fact that we did not perform a standardized assessment of SZ symptoms. The difference in neurocognitive functioning between SZ patients with and without cocaine dependence may be linked to differences in general psychopathology, mainly to differences in positive and negative symptoms in these two groups. Although we assessed the clinical state by the CGI, unfortunately it is not sufficient as a measure of the clinical severity of the symptomatology.

The fact that both SZ groups were taking more daily medication than COC group, as well as a greater amount of CPZ equivalents, may have a direct influence on neuropsychological functioning. This could explain some of the differences found between both SZ groups and the COC group. Although we introduced the medication as a covariate in the analyses, it should be noted that we are not able to control their effect over neuropsychological performance because it is a clinical idiosyncratic characteristic of each group, as we mentioned earlier. Other limitations such as a relatively small sample size, the retrospective characterization of lifetime drug use obtained by self-reporting, and the naturalistic design of the study may have influenced our results. However, we obtained a suitable effect size in the analysis, and our results agree with most of the preceding works. Prospective studies, as well as future works incorporating genetic and neuroimaging measures in addition to cognitive assessments would help to clarify the current knowledge gaps about neurocognition of dual diagnosis.

CONCLUSIONS

This study shows a very similar pattern of executive functioning in SZ+ and COC groups. Both groups performed better on dorsolateral prefrontal related tasks than SZ−. These results agree with the current assumption of an SZ+ belonging to a subgroup with a lower genetic vulnerability; and as a consequence, they exhibit higher cognitive abilities, making them better able to obtain drugs of abuse. Concerning the influence of age of onset of substance use in cognition, we only found differences on set-shifting between earlier and later consumers in SZ+ patients, without differences between earlier and later consumers in the COC group. Despite this, the SZ+ group showed more deleterious effects than the COC group on set-shifting regardless of the age of onset of intake.

CONFLICT OF INTEREST

The authors have declared that there is no conflict of interest.

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CONTRIBUTORS

Ana Adan conceived the original idea for the study, sought funding, wrote the protocol and managed the day to day running of the study. Irina Benaiges collected the data of the sample and carried out all data analyses. The manuscript was written by Irina Benaiges and Ana Adan with input from Josep Maria Serra-Grabulosa and Gemma Prat. All authors have approved the final manuscript.

REFERENCES

Addington J, Addington D. 1997. Substance abuse and cognitive functioning in schizophrenia. *J Psychiatry Neurosci* **22**(2): 99–104.

American Psychiatric Association. 2000. *Diagnostic and statistical manual of mental disorders*, 4th *ed., text revised*. American Psychiatric Association: Washington, DC.

Andreasen NC, Pressler M, Nopoulos P, Miller D, Ho B-C. 2010. Antipsychotic dose equivalents and dose-years: a standardized method for comparing exposure to different drugs. *Biol Psychiatry* **67**: 255–262.

Arendt M, Rosenberg R, Foldager L, Perto G, Munk-Jorgensen P. 2005. Cannabis-induced psychosis and subsequent schizophrenia-spectrum disorders: follow-up study of 535 incident cases. *Brit J psychiatry* **187**: 510–515.

Arndt S, Tyrrell G, Flaum M, Andreasen NC. 1992. Comorbidity of substance abuse and schizophrenia: the role of pre-morbid adjustment. *Psychol Med* **22**(2): 379–388.

Barnett JH, Werners U, Secher SM, *et al*. 2007. Substance use in a population-based clinic sample of people with first-episode psychosis. *Brit J Psychiatry* **190**: 515–520.

Bechara A, Damasio AR, Damasio H, Anderson SW. 1994. Insensitivity to future consequences following damage to human prefrontal cortex. *Cognition* **50**: 7–15.

Benaiges I, Prat G, Adan A. 2010. Neuropsychological aspects of dual diagnosis. *Curr Drug Abuse Rev* **3**(3): 175–188.

Block RI, Erwin WJ, Ghoneim MM. 2002. Chronic drug use and cognitive impairments. *Pharmacol Biochem Behav* **73**: 491–495.

Bowie C, Serper M, Riggio S. Harvey PD. 2005. Neurocognition, symptomatology, and functional skills in older-abusing schizophrenic patients. *Schizophr Bull* **31**(1): 175–182.

Boydell J, Dean K, Dutta R, Giouroukou E, Fearon P, Murray R. 2007. A comparison of symptoms and family history in schizophrenia with and without prior cannabis use: implications for the concept of cannabis psychosis. *Schizophr Res* **93**: 203–210.

Camchong J, Dyckman KA, Chapman CE, Yanasak NE, McDowell JE. 2006. Basal ganglia – thalamocortical circuitry disruptions in schizophrenia during delayed response task. *Biol Psychiatry* **60**(3): 235–241.

Carey KB, Carey MP, Simons JS. 2003. Correlates of substance use disorder among psychiatric outpatients: focus on cognition, social role functioning, and psychiatric status. *J Nerv Ment Dis* **191**(5): 300–308.

Casey BJ, Giedd JN, Thomas KM. 2000. Structural and functional brain development and its relation to cognitive development. *Biol Psychiatry* **54**: 241–257.

Cooper L, Liberman D, Tucker D, Nuechterlein KH, Tsuang J, Barnett HL. 1999. Neurocognitive deficits in the dually diagnosed with schizophrenia and cocaine abuse. *Psychiatry Rehab Skills* **3**(2): 231–245.

Copersino ML, Serper MR, Vadhan N, *et al*. 2004. Cocaine craving and attentional bias in cocaine-dependent schizophrenic patients. *Psychiatry Res* **128**(3): 209–218.

De Rosse P, Kaplan A, Burdick KE, Lencz T, Malhotra AK. 2010. Cannabis use disorders in schizophrenia: effects on cognition and symptoms. *Schizophr Res* **120**: 95–100.

Dixon L, Haas G, Weiden PJ, Sweeney J, Frances AJ. 1991. Drug abuse in schizophrenic patients. Clinical correlates and reasons for use. *Am J Psychiatry* **148**(2): 224–230.

Ehrenreich H, Rinn T, Kunert HJ, *et al*. 1999. Specific attentional dysfunction in adults following early start of cannabis use. *Psychopharmacology* **142**(3): 295–301.

First MB, Spitzer RL, Gibbon M, William JBW.1998. *Structural Clinical Interview for Axis-I DSM-IV Disorders*, patients' edition. Biometric Research Department, New York State Psychiatric Institute: New York, NY.

Garavan H, Stout JC. 2005. Neurocognitive insights into substance abuse. *Trends Cogn Sci* **9**(4): 195–201.

Green AI, Tohen MF, Hamer RM, *et al*. 2004. First episode schizophrenia-related psychosis and substance use disorders: acute response to olanzapine and haloperidol. *Schizophr Res* **66**: 125–135.

Hall W 1998. Cannabis use and psychosis. *Drug Alcohol Rev* **17**(4): 433–444.

Heatherton TF, Kozlowski LT, Frecker RC, Fagerström KO. 1991.The Fagerström test for nicotine dependence: a revision of the Fagerström tolerance questionnaire. *Brit J Addiction* **86**: 1119–1127.

Heaton RK, Chelune GJ, Talley JL.1993. *Wisconsin Card Sorting Test Manual-Revised and Expanded*. Psychological Assessment Resources: Odessa, FL.

Heaton RK, PAR Staff. 2005. *WCST: Computer Version 4*. Research Ed. Psychological Assessment Resources: Lutz, FL.

Herman M 2004. Neurocognitive functioning and quality of life among dually diagnosed patients and non substance abusing schizophrenia inpatients. *Int J Ment Health Nurs* **13**: 282–291.

Jockers-Scherübl MC, Matthies U, Danker-Hopfe, H, Lang UE, Mahlberg R, Hellweg R. 2003. Chronic cannabis abuse raises nerve growth factor serum concentrations in drug-naïve schizophrenic patients. *J Psychopharmacol* **17**(4): 439–445.

Jockers-Scherübl MC, Wolf T, Radzei N, *et al*. 2007. Cannabis induces different cognitive changes in schizophrenic patients and in healthy controls. *Prog Neuro-psychopharmacol Biol Psychiatry* **31**: 1054–1063.

Jovanovski D, Erb S, Zakzanis KK. 2005. Neurocognitive deficits in cocaine users: a quantitative review of the evidence. *J Clin Exp Neuropsychol* **27**(2): 189–204.

Joyal CC, Hallé P, Lapierre D, Hodgins S. 2003. Drug abuse and/or dependence and better neuropsychological performance in patients with schizophrenia. *Schizophr Res* **63**: 297–299.

Kew JN, Kemp JA. 2005. Ionotropic and metabotropic glutamate receptor structure and pharmacology. *Psychopharmacology* **179**(1): 4–29.

Krystal JH, Perry EB, Gueorguieva R, *et al*. 2005. Comparative and interactive human psychopharmacologic effects of ketamine and amphetamine: implications for glutamatergic and dopaminergic model psychosis and cognitive function. *Arch Gen Psychiatry* **62**(9): 985–994.

Lambe E, Krimer L, Goldman-Rakic PS. 2000. Differential postnatal development of catecholamine and serotonin inputs to identified neurons in prefrontal cortex of rhesus monkeys. *J Neurosci* **20**: 8780–8787.

Lezak MD, Howieson DB, Loring DW. 2004. *Neuropsychological Assessment*. 4th *edition*. Oxford University Press: Oxford.

Loberg EM, Jorgensen HA, Hugdahl K. 2003. The effects of previous drug abuse on neurocognition in schizophrenia. Abstract. *J Int Neuropsychol Soc* **9**: 172.

Marshall L, Silverstein ML, Mavrolefteros G, Close D. 2002. Premorbid adjustment and neuropsychological performance in schizophrenia. *Schizophr Bull* **28**(1): 157–165.

Mata I, Rodríguez-Sánchez, JM, Pelayo-Terán JM, *et al*. 2008. Cannabis abuse is associated with decision-making impairment among first-episode patients with schizophrenia-spectrum psychosis. *Psychol Med* **38** (9): 1257–1266.

McCleery A, Addington J, Addington, D. 2006. Substance misuse and cognitive functioning in early psychosis: a two year follow-up. *Schizophr Res* **88**: 187–191.

National Institute of Mental Health. 1976. CGI. Clinical global impressions. In: *Manual for the EDCEU Assessment Battery.2*. rev. ed. Guy W, Bonato RR (eds). Chevy Chase: Maryland.

Pope HG, Gruber AJ, Hudson JI, Cohane G, Huestis MA, Yurgelun-Todd D. 2003. Early onset cannabis use and cognitive deficits: what is the nature of the association? *Drug Alcohol Depen* **69**(3): 303–310.

Potvin S, Joyal CC, Pelletier J, Stip E. 2008. Contradictory cognitive capacities among substance-abusing patients with schizophrenia: a meta-analysis. *Schizophr Res* **100**: 242–251.

Rabin RA, Zakzanis KK, George TP. 2011. The effects of cannabis on neurocognition in schizophrenia: a meta-analysis. *Schizophr Res* **128**: 111–116.

Rabinowitz J, Bromet EJ, Lavelle J, Carlson G, Kovasznay B, Schwartz JE. 1998. Prevalence and severity of substance use disorders and onset of psychosis in first-administration psychotic patients. *Psychol Med* **28**(6): 1411–1419.

Regier DA, Farmer ME, Rae DS, *et al*. 1990. Comorbidity of mental disorders with alcohol and other drug abuse. Results from the epidemiologic catchment area (ECA) study. *JAMA-J Am Med Assoc* **264** (19): 2511–2518.

Reitan RM, Wolfson D. 1985. *The Halstead – Reitan Neuropsychological Test Battery*. Neuropsychological Press: Tucson.

Rentzsch J, Buntebart E, Stadelmeier A, Gallinat J, Jockers-Scherübl MC. 2011. Differential effects of chronic cannabis use on preattentional cognitive functioning in abstinent schizophrenic patients and healthy subjects. *Schizophr Res* **130**: 222–227.

Ringen PA, Vaskinn A, Sundet K, *et al*. 2010. Opposite relationships between cannabis use and neurocognitive functioning in bipolar disorder and schizophrenia. *Psychol Med* **40**(8): 1337–1347.

Rodríguez-Sánchez JM, Ayesa-Arriola R, Mata I, *et al*. 2010. Cannabis use and cognitive functioning in first-episode schizophrenia patients. *Schizophr Res* **124**: 142–151.

Schnell T, Koethe D, Daumann J, Gouzoulis-Mayfrank E. 2009. The role of cannabis in cognitive functioning of patients with schizophrenia. *Psychopharmacology* **205**(1): 45–52.

Scholes KE, Martin-Iverson MT. 2010. Cannabis use and neuropsychological performance in healthy individuals and patients with schizophrenia. *Psychol Med* **40**(10): 1635–1464.

Serper MR, Copersino ML, Richarme D, Vandham N, Cranco R. 2000. Neurocognitive functioning in recently abstinent, cocaine-abusing schizophrenic patients. *J Subst Abus* **11**(2): 205–213.

Sevy S, Burdick KE, Visweswaraiah H, *et al*. 2007. Iowa Gambling Task in schizophrenia and co-occurring cannabis use disorders. *Schizophr Res* **92**: 74–84.

Sevy S, Robinson DG, Napolitano B, *et al*. 2010. Are cannabis use disorders associated with an earlier age at onset of psychosis? A study in first episode schizophrenia. *Schizophr Res* **120**: 101–107.

Sevy S, Robinson DG, Solloway S, *et al*. 2001. Correlates of substance misuse in patients with first episode schizophrenia and schizoaffective disorders. *Acta Psychiatr Scand* **104**(5): 367–374.

Smelson DA, Davis CW, Einstein N, *et al*. 2003. Cognitive disparity in schizophrenics with and without cocaine dependency. *J Subst Abuse Treat* **24**(1): 75–79.

Snitz BE, McDonald AW, Carter CS. 2006. Cognitive deficits in unaffected first- degree relatives of schizophrenia patients: a meta-analytic review of putative endophenotypes. *Schizophr Bull* **32**(1): 179–194.

Sowell ER, Delis D, Stiles J, Jerningan TL. 2001. Improved memory functioning and frontal lobe maturation between childhood and adolescence: a structural MRI study. *J Int Neuropsychol Soc* **7**(3): 312–322.

Stirling J, Lewis S, Hopkins R, White C. 2005. Cannabis use prior to first onset psychosis predicts spared neurocognition at 10-year follow-up. *Schizophr Res* **75**: 135–137.

Sundram S. 2006. Cannabis and neurodevelopment: implications for psychiatric disorders. *Hum Psychopharmacol Clin Exp* **21**: 245–254.

Thoma P, Daum I. 2008. Working memory and multi-tasking in paranoid schizophrenia with and without comorbid substance use disorder. *Addiction* **103** (5): 774–786.

Thoma P, Wiebel B, Daum I. 2007. Response inhibition and cognitive flexibility in schizophrenia with and without comorbid substance use disorder. *Schizophr Res* **92**: 168–180.

Toda M, Abi-Darghem A. 2007. Dopamine hypothesis of schizophrenia: making sense of it all. *Curr Psychiatry Rep* **9**(4): 329–336.

Veen ND, Selten JP, Van d TI, Feller WG, Hoek HW, Kahn RS. 2004. Cannabis use and age at onset of schizophrenia. *Am J Psychiatry* **161**(3): 501–506.

Volkow N, Hitzemann R, Wang GJ, *et al*. 1992. Long-term frontal brain metabolic changes in cocaine users. *Synapse* **11**(3): 184–190.

Wechsler D 1981.*Wechsler Adult Intelligence Scale-Revised*. The Psychological Corporation: New York.

Wilson W, Mathew R, Turkington T, Hawk T, Coleman RE, Provenzale J. 2000. Brain morphological changes and early marijuana use: a magnetic resonance and positron emission tomography study. *J Addict Dis* **19**(1): 1–22.

Wobrock T, Sittinger H, Behrendt B, D'Amelio R, Falkai P, Caspari D. 2007. Comorbid substance abuse and neurocognitive function in recent-onset schizophrenia. *Eur Arch Psychiatry Clin Neurosci* **257**(4): 203–210.

Woo TUW, Crowell AL. 2005. Targeting synapses and myelin in the prevention of schizophrenia. *Schizophr Res* **73**: 193–207.

Woods SW. 2003. Chlorpromazine equivalent doses for the newer atypical antipsychotics. *J Clin Psychiatry* **64**(6): 663–667.

- ✓ **Objetivo 3: Atención, memoria verbal y velocidad de procesamiento**

Estudio 3: *Neuropsychological functioning and age-related changes in schizophrenia and/or cocaine dependence*

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Resumen:

Todavía lejos de dilucidar el perfil neurocognitivo de los pacientes duales, la investigación actual sugiere que el rendimiento cognitivo en PD depende del dominio cognitivo evaluado, la edad de los sujetos y de la sustancia principal de abuso. Mientras el funcionamiento ejecutivo de los duales suele estar mejor conservado, las funciones de memoria y atención verbal suelen hallarse más comprometidas. La edad juega un papel importante dado que los pacientes de mayor edad suelen presentar un déficit cognitivo adicional al del trastorno psiquiátrico, debido a la probable expresión de las consecuencias neurotóxicas del TUS a largo plazo, especialmente en los consumidores de alcohol y cocaína. Sin embargo, los pacientes duales jóvenes muestran un rendimiento cognitivo igual o superior a sus homólogos sin TUS, principalmente en los casos de consumo de cannabis o policonsumo.

Material y método:

Se reunió una muestra de 95 hombres, de edades comprendidas entre los 20 y los 60 años, divididos en tres grupos. Un grupo con esquizofrenia y dependencia a la cocaína (SZ+; n = 30), otro grupo con esquizofrenia sin dependencia a la cocaína (SZ-, n = 30), y un tercer grupo con dependencia a la cocaína sin ningún trastorno psiquiátrico comórbido (COC, n = 35).

Se recabó información amplia de carácter sociodemográfico y clínico mediante una entrevista semi-estructurada y se evaluó la *Impresión Clínica Global* (ICG; National Institute of Mental Health, 1976) y la dependencia a la nicotina mediante el test de *Fagerström* (Heatherton et al., 1991). Para la evaluación

neuropsicológica se incluyeron los siguientes test: Subtests de *Vocabulario* y *Cubos* (WAIS-R; Wechsler, 2001) como medida del coeficiente intelectual verbal y no verbal premórbido. El span atencional se evaluó mediante el subtest de *Dígitos* (WAIS-R; Wechsler, 2001) y la memoria verbal mediante el *Rey Auditory Verbal Learning Test* (RAVLT; Schmidt, 2011) que ofrece puntuaciones en la curva de aprendizaje, la memoria verbal a corto y a largo plazo, y en el reconocimiento. Por último, el *Trail Making Test parte A* (TMT-A; Reitan & Wolfson, 1985) se administró como medida de la velocidad del procesamiento de la información. Las puntuaciones directas de cada subtest fueron transformadas en puntuaciones Z (media = 0 y desviación típica =1) y se generó un componente cognitivo global.

Los datos sociodemográficos y clínicos fueron analizados mediante análisis univariantes en el caso de los datos continuos y Chi cuadrado para los datos categoriales. Las diferencias en el rendimiento neuropsicológico entre grupos, se efectuaron con las puntuaciones Z mediante análisis unifactoriales, multifactoriales y análisis de medidas repetidas de la covarianza con la puntuación Z del subtest de cubos y la puntuación directa del test de Fagerström como covariables. Para explorar el efecto de la edad y la duración del TUS sobre el rendimiento cognitivo se efectuaron correlaciones y posteriormente análisis de regresión lineal.

Resultados:

Ambos grupos SZ+ y SZ-, presentaron una mayor proporción de solteros y mayor desocupación laboral respecto al grupo COC. También tomaban más medicamentos diarios, especialmente antipsicóticos típicos y atípicos y presentaban una peor ICG que el grupo COC. El grupo SZ+ fumaba más cigarrillos diarios y presentaba puntuaciones más elevadas en dependencia a la nicotina respecto a los otros dos grupos. Los grupos SZ+ y COC, no presentaron diferencias en las variables evaluadas del TUS, excepto por un mayor consumo de cannabis en el grupo SZ+.

Respecto al rendimiento neuropsicológico, los grupos no difirieron en los subtest de Vocabulario y Dígitos. El grupo COC presentó mejores puntuaciones en el subtest de Cubos respecto al grupo SZ-, sin diferencias respecto al grupo SZ+. El grupo COC también presentó mejores puntuaciones en el RAVLT que ambos grupos SZ, tanto en la capacidad de aprendizaje como en la memoria a corto y a largo plazo, así como en la velocidad del procesamiento de la información y en el componente cognitivo global, sin diferencias entre SZ+ y SZ-. En cuanto a la influencia de la edad, el grupo SZ+ presentó correlaciones negativas entre la edad, la memoria verbal y el componente cognitivo global. Los

otros dos grupos no mostraron una influencia negativa de la edad sobre el rendimiento cognitivo. El análisis de regresión lineal mostró la edad, pero no la duración del TUS, como variable explicativa del rendimiento cognitivo global en el grupo SZ+.

Conclusiones:

El grupo COC mostró un mejor rendimiento cognitivo respecto a los otros dos grupos, sin diferencias entre SZ+ y SZ-. Sin embargo, la edad reveló un efecto de detrimento en la memoria verbal y en el rendimiento cognitivo general en el grupo SZ+, mientras los otros dos grupos no mostraron déficits cognitivos relacionados con la edad. Este resultado apoya la idea de un declive cognitivo que interactúa con la edad en los pacientes duales, resultando en un daño cerebral adicional al del trastorno psiquiátrico debido a la expresión neurotóxica de las sustancias de abuso a largo plazo. La evaluación neuropsicológica en los pacientes duales mayores es necesaria para desarrollar estrategias terapéuticas apropiadas y desarrollar terapias de rehabilitación cognitiva. La prevención temprana de estos déficits en la población dual puede ayudar a mejorar su funcionamiento general a largo plazo.

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Neuropsychological functioning and age-related changes in schizophrenia and/or cocaine dependence

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ABSTRACT

Although little is known about the combined effects of Schizophrenia (SZ) and Substance Use Dependence (SUD) in neurocognitive functioning, the current literature points out that performance depends on the specific cognitive domains, the age of individuals and the type of substance of abuse. Our aim is to elucidate, in a sample with SZ and/or cocaine dependent individuals in remission for more than 4 months, their performance in attention, verbal memory and speed of processing, taking into account the possible effect of both age and duration of SUD. The total sample consisted of 95 male patients, aged 20 to 60 years, divided in three groups: one group with SZ and cocaine dependence (SZ+), another group with SZ without cocaine dependence (SZ−) and a third group with cocaine dependence without psychiatric comorbidity (COC). Our results show that those SZ+ who were abstinent for more than four months did not differ from their SZ− counterparts in the neuropsychological functioning. Both SZ groups performed significantly worse than the COC group. A negative impact of age on the neuropsychological performance was found in the SZ+ group, suggesting additive later cognitive deficits in SZ+ patients due to the long-term brain damage of SUD.

1. Introduction

Lifetime rates of comorbid substance use have been established for approximately 50% in patients with schizophrenia (SZ) (Kavanagh et al., 2002; Regier et al., 1990). Although it is well-known that substance use has a worse impact on the clinical course of SZ, its effects on cognition are less understood (Mueser and McGurk, 2012). The study of cognitive functioning in patients with SZ with comorbid substance dependence (SZ+) deserves a great consideration since cognitive deficits are better predictors of social and functional outcomes than positive and negative symptoms (Green, 1996; Harvey et al., 2004), especially verbal memory (Green, 1996; Matza et al., 2006). However, after over 20 years of research on the impact of substance use on cognition in patients with SZ, the studies show inconsistent findings. Whereas some authors reported worse cognitive functioning in SZ+, others reported no differences and still others reported a better cognitive functioning than schizophrenic patients without substance use (SZ−). In view of these paradoxical findings some reviews and meta-analytic studies have recently appeared in order to delineate potential explanatory factors that may account for these mixed results across studies (Benaiges et al., 2010; Coulston et al., 2007; Potvin et al., 2008, 2012). Among other methodological factors, the authors of these reviews agree with three important factors which were highlighted and summarized in the review by Potvin et al. (2012); (i) the age of the individuals, (ii) the cognitive domain assessed, and (iii) the type of preferred substance of abuse.

Generally, younger SZ+ have fewer cognitive deficits compared to SZ− patients, while older SZ+ have increased cognitive deficits than SZ− individuals of the same age, mainly those abusing alcohol. Thus, Mohamed et al. (2006) found a cognitive decline in SZ+ patients aged over 55 years with current alcohol abuse/dependence compared to those aged 45 to 55 years, and also compared to SZ− patients in learning and memory abilities. Similarly, Bowie et al. (2005) and Manning et al. (2007) also found a poorer execution on attention and memory functioning on SZ+ with alcohol users who were in their 40s and 50s compared to their SZ− counterparts. In this line, Allen et al. (2000) found an acceleration of the cognitive deficit in SZ+ alcohol users from the age of 40 years. Therefore, it appears that older SZ+ would present an additional cognitive damage because the neurotoxic consequences of substance consumption become more obvious in a long term. In spite of this, the authors do

Abbreviations: CGI, Clinical Global Impression; COC, Cocaine dependence without psychiatric comorbidity; CPZ, Chlorpromazine equivalents; DSM-IV-R, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition Text Revised; RAVLT, Rey Auditory Verbal Learning Test; SCID-I, Structured Clinical Interview for Axis-I Disorders; SUD, Substance use dependence; SZ−, Schizophrenia without comorbid cocaine dependence; SZ+, Schizophrenia with comorbid cocaine dependence; TMT-A, Trail Making Test part A; WAIS-R, Wechsler Adult Intelligence Scale-Revised.

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not agree on at what age this cognitive decline starts to appear in SZ+ subjects. Whereas some authors suggest that the onset of cognitive decline begins between 40 and 50 years old (Allen et al., 2000; Mohamed et al., 2006), the meta-analysis by Potvin et al. (2008) found that the patients older than 30 years started to show increased cognitive deficits.

Regarding the specific cognitive domains, it seems that speed of processing (Potvin et al., 2008; Schnell et al., 2009; Smelson et al., 2002, 2003) and executive functioning are relatively better in SZ+ subjects (Herman, 2004; Joyal et al., 2003; Smelson et al., 2003; Thoma and Daum, 2008; Thoma et al., 2007). In contrast, attentional and memory functions are less understood due to a wide variety of results across studies.

The type of substance consumed also explains part of the heterogeneity of the results. While studies with SZ+ cannabis and/or polysubstance users often obtain better cognitive functioning than SZ− patients (Herman, 2004; Jockers-Scherübl; Potvin et al., 2005; Schnell et al., 2009; Scholes and Martin-Iverson, 2010; Sevy et al., 2007; Stirling et al., 2005; Thoma and Daum, 2008; Thoma et al., 2007), the studies focused on alcohol show a worse performance of the SZ+ groups (Allen et al., 2000; Bowie et al., 2005; Manning et al., 2007; Mohamed et al., 2006). Although few studies examine the impact of cocaine, those that do generally obtain impaired verbal memory (Serge et al., 1990; Serper et al., 2000a, 2000b), while others fail to obtain differences respect to SZ− patients (Cooper et al., 1999; Copersino et al., 2004). Differences in the length of abstinence across studies that focused on SZ+ cocaine users may account for this disparity of findings. On the other hand, despite the high consumption of cigarette smoking in the schizophrenic samples, authors often do not asses its use and therefore do not control its effect on neurocognition. This is relevant since cigarette smoking has been shown to have beneficial effects on cognitive functions enhancing dopaminergic activity in frontal attentional networks (Kumari and Postma, 2005).

It should be noted that an interaction may exist between the age of patients, the type of substance intake and the assessed cognitive domain. Whereas the samples of SZ+ cannabis and polysubstance users usually comprised young subjects showing a better executive functioning, those samples with SZ+ alcohol users often comprised older patients with severe impairments in verbal memory. Although cognitive functioning seems to remain stable over time in SZ−, verbal memory has shown inconclusive results (Bozikas and Andreou, 2011). It is unknown how verbal memory and other cognitive domains are affected in SZ+ patients by age, especially when they are cocaine users, due to the lack of studies examining this question.

Taking all these into consideration, our aim in this study is twofold. Firstly, to evaluate attention, verbal memory and processing speed in SZ+ patients who are mainly cocaine dependent and to compare them to SZ− patients and to patients with cocaine dependence without any comorbid psychiatric disorder (COC), controlling for the effect of tobacco consumption. Both SZ+ and COC groups have an extensive length of abstinence in order to avoid residual effects of substance consumption on cognition. Cognitive deficits have been shown to improve within the first months of abstinence (Drake et al., 1994; Tönne et al., 1995) and the cognitive recovery correlates with the increasing time of abstinence in samples with mainly cocaine dependence (O'Malley et al., 1992). Secondly, we explore the effect of patients' age and the length of SUD in the assessed cognitive domains in each group. Taking into account the results of the literature, we expect a better performance of the COC group compared to both SZ groups. In contrast, more harmful effects can be expected on the neuropsychological functioning in the SZ+ group compared to SZ− , especially in those of an older age and greater duration of SUD, due to their additive negative impact on neurocognition. This result would represent a proof of cognitive decline in older SZ+ due to the additive effects of the psychiatric diagnosis and substance use interacting with age.

2. Material and methods

2.1. Participants

In a cross-sectional study design, we enrolled 95 male patients, aged between 18 and 60 years, divided in three groups. Two groups with schizophrenia/schizoaffective disorder with cocaine dependence (SZ+; n = 30) or without any comorbid substance use (SZ−; n = 30), admitted to "The social club program" at the Mental Health Division of the Althaia Foundation in Manresa (Barcelona). The third group comprised patients with cocaine dependence without any comorbid psychiatric disorder (COC; n = 35) under treatment in the therapeutic community of the Gressol Catalonia Man Project (Barcelona). Both cocaine dependent groups were abstinent for at least 4 months, controlled by urinalysis. Data were collected between January 2010 and December 2011.

Each participant was consecutively referred by their treating psychiatrist, who was blind to the aims of the study. The patients had been diagnosed according to the DSM-IV-R (2000), using the Structural Clinical Interview for DSM-IV-R Axis I Disorders (SCID-I; First et al., 1998). The inclusion criteria were: (1) current diagnosis of schizophrenia/schizoaffective disorder and/or current diagnosis of cocaine dependence in remission for at least 4 months; (2) male gender; and (3) age between 18 and 60 years. Both cocaine dependent groups (SZ+ and COC) had the following additional criteria: (4) having cocaine as a main drug of choice; and (5) absence of relapses at least one month before their participation in the study. It should be noted that poly-substance users were not excluded. The exclusion criteria were: no DSM-IV-R criteria for a current substance induced-psychiatric disorder or psychiatric disorder due to a medical condition, unstable or severe medical illness, mental retardation, history of traumatic brain injury or neurological injury, and they had not received electroconvulsive therapy within 12 months prior to their study participation. Patients in the COC group were also excluded if they had any history of psychiatric disorder other than drug dependence.

This study was approved by the ethics committees of the University of Barcelona and the Mental Health division of Althaia, meeting the ethical principles of the declaration of Helsinki. All participants provided written informed consent after the study procedure was fully explained to them. They were not compensated for their participation in the study.

2.2. Clinical measures

Information was collected by means of a *structured interview* of sociodemographic (age, marital status, schooling and economic status) and clinical variables (diagnosis, psychiatric and substance use family history, age of onset of the disorder and/or onset of consumption, relapses, abstinence periods, type of drugs used, lifetime use, suicidal attempts, presence of organic pathology and medication). We confirmed the self-reported data by patients with the medical history of the database of the hospital and with their treating psychiatrist. Chlorpromazine equivalent doses (CPZ) were calculated for antipsychotic medication according to Andreasen et al. (2010) and Woods (2003). We also recorded daily consumption of cigarettes and cups of coffee as well as other intake of beverage with caffeine, such as tea or cola. Smokers were administered the *Fagerström* test of nicotine dependence (Heatherton et al., 1991). Additionally, the *Clinical Global Impression* questionnaire (CGI; National Institute of Mental Health, 1976) was applied as a subjective measure of the clinical severity of each participant.

2.3. Neuropsychological assessment

Cognitive functioning was assessed by a battery of cognitive measures routinely used in studies with individuals with schizophrenia.

The Vocabulary and Block Design subtests of the Wechsler Adult Intelligence Scale-Revised (WAIS-R) were administered to assess their premorbid Verbal and Non Verbal IQ, respectively (Lezak et al., 2004).

Attention Span was assessed with the Digit Span Subtest (WAIS-R). Verbal learning and memory variables were assessed with the Rey Auditory Verbal Learning Test (RAVLT; Schmidt, 2011). The RAVLT involves the repeated administration of a 15 word list (List A) presented in a fixed order and a total sum of total learned words over the five trials (A1–A5) as a measure of learning. A second interference word list (List B) is then presented for one trial and the subject is asked to recall the items from that list. Immediately following List B, a short delay free recall of List A is conducted as a measure of short term memory (A6). Free recall of the list is asked again after a 20 minute delay (A7) as a measure of delayed recall. Recognition of List A (A/15) is measured immediately following the long delay recall using a yes or no recognition format in a list with 35 distractor words. We counted the amount of well-recognized words from the target list relative to the distractor words. Finally, the Trail Making Test part A (TMT-A; Reitan and Wolfson, 1985) was administered as a measure of processing speed.

The evaluations were performed in a fixed order. First, the RAVLT trials 1–5, list B and immediate recall were administered, followed by the Vocabulary, Block Design, Digits WAIS subtests, and TMT. After approximately 20 min, the RAVLT delayed recall and recognition were administered.

Raw scores on the neurocognitive tests were transformed to Z scores (mean = 0; SD = 1), based on the normative data for the RAVLT measures (Schmidt, 2011), the WAIS-R subtests (Wechsler, 2001) and TMT-A (Spreen and Strauss, 1998). Averaging the Z scores of eight neurocognitive measures (total learned words, short term memory, delay memory, recognition, Vocabulary, Block Design, attention span, and processing speed) generated a neurocognitive composite Z score.

2.4. Statistical analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS; version 15.0). Group differences in demographic and clinical data were explored with one-way analysis of variance (ANOVA) for continuous data. Categorical data were examined by non parametric Chi Square test (marital status, economic situation, living situation, type of medical comorbidities, and type of psychotropic medication, type of psychiatric diagnosis, type of intake, type of substance/dependence and degree of nicotine dependency). Differences in neuropsychological performance were explored with one-way analyses of covariance (ANCOVA's) in the case of Vocabulary, Block Design and Digits subtest,

Table 1
Sociodemographic and clinical data for the three groups of patients and the statistical contrasts carried out.

Sociodemographic data	SZ+ (N = 30)	SZ− (N = 35)	COC (N = 35)	Statistical contrasts
Age (yr)	36.80 ± 7.47	38.70 ± 8.72	36.37 ± 6.72	F = 0.50
Marital status				$\chi^2 = 12.61^{**}$
Single	83.3%	86.7%	51.4%	
Stable partner	6.7%		8.6%	
Married		3.3%	11.4%	
Separate/divorced	10.0%	10.0%	28.5%	
Years of schooling	9.14 ± 2.01	9.66 ± 2.44	9.58 ± 2.23	F = 0.92
Economic situation				$\chi^2 = 22.32^{***}$
Active	13.3%	16.7%	42.9%	
Disability pension	53. 3%	80.0%	17.1%	
Unemployed	16.7%		20.0%	
No income	16.7%	3.3%	20.0%	
Clinical data				
Psychiatric diagnosis				$\chi^2 = 0.30$
Schizophrenia	90.1%	86.8%		
Schizoaffective	9.9%	13.2%		
Age of psychiatric disorder onset	23. 46 ± 6.13 yr	24.24 ± 7.26 yr		F = 0.19
Mean duration of illness (yr)	13.42 ± 8.06 yr	14.55 ± 8.75 yr		F = 0.21
Number of relatives with SUD	0.22 ± 0.57	0.07 ± 0.57	0.23 ± 0.59	F = 1.00
Number of relatives with psychiatric disorder	0.68 ± 0.90	0.67 ± 0.66	0.49 ± 0.74	F = 0.64
Number of suicidal attempts	0.90 ± 1.37	0.40 ± 0.72	0.34 ± 0.87	F = 2.80
Number of medical comorbidities	0.57 ± 0.77	0.60 ± 0.77	0.46 ± 0.78	F = 0.30
Daily number of medications [a]	3.41 ± 1.45	3.10 ± 1.21	0.69 ± 1.10	$F = 46.48^{***}$
Typical antipsychotics	36.7%	20.0%	2.9%	$\chi^2 = 19.58^{***}$
Atypical antipsychotics	70.0%	70.0%	5.7%	$\chi^2 = 66.66^{***}$
Antidepressants	23. 3%	30.0%	11.4%	$\chi^2 = 5.37$
Mood stabilizers	23.3%	33. 3%	8.6%	$\chi^2 = 7.56^{*}$
Anxiolytics	33.3%	26.7%	8.6%	$\chi^2 = 6.07^{*}$
Other medication	20.0%	30.0%	20%	$\chi^2 = 0.91$
CPZ equivalents	437.31 ± 276.83	499.57 ± 467.24	21.42 ± 71.00	$F = 23.59^{***}$
Clinical global impression (CGI)	4.80 ± 0.96	4.40 ± 0.72	3.26 ± 1.01	$F = 25.35^{***}$
Daily number of cigarettes	21.73 ± 15.94	11.50 ± 12.74	14.74 ± 8.08	$F = 5.30^{*}$
Fagerström score	5.21 ± 2.75	3.23 ± 3.48	3.86 ± 2.48	$F = 3.59^{*}$
No dependence	16.7%	50.0%	17.1%	
Low dependence	10.0%		20.0%	
Moderate dependence	33.3%	26.7%	51.4%	
High dependence	36.7%	23.3%	11.4%	$\chi^2 = 6.21^{*}$
Daily number of coffees (cups)	1.83 ± 1.87	1.33 ± 1.49	1.66 ± 1.43	F = 0.75
Other daily beverages with caffeine	1.07 ± 1.08	0.80 ± 1.09	0.91 ± 1.26	F = 0.40

[a]Percentages will not equal 100 as each participant may take more than one medication.
SZ+: Schizophrenia with comorbid cocaine dependence; SZ−: Schizophrenia without substance dependence; COC: Cocaine dependence.
* $p<0.05$.
** $p<0.01$.
*** $p<0.001$.

Table 2
Descriptive statistics (frequencies, mean and standard error, depending on the case) for substance use data.

Substance use data	SZ+ (N=30)	COC (N=35)	Statistical contrasts
Type of intake			$\chi^2=0.17$
One substance	6.9%	20%	
Two substances	17.2%	23.9%	
Polydrug use	75.9%	57.1%	
Number of substances used	3.62±1.61	3.14±1.53	F=0.97
Substance abuse/dependence[a]			
Cocaine	100%	100%	
Cannabis	86.2%	48.6%	$\chi^2=8.40^{**}$
Alcohol	72.4%	68.6%	$\chi^2=0.17$
Ecstasy	41.4%	25.7%	$\chi^2=1.48$
Hallucinogens	27.6%	14.3%	$\chi^2=1.52$
Opioids	27.6%	28.6%	$\chi^2=0.02$
Sedatives	10.3%	2.9%	$\chi^2=1.40$
Months of abstinence	13.42±1.71	9.14±5.07	F=2.41
Number of relapses	1.12±1.30	0.54±1.03	F=3.20
Age of intake onset (yr)	16.15±2.31	20.00±8.27	$F=4.54^{*}$
Mean duration of SUD (yr)	18.78±8.73	15.60±7.16	F=2.65

[a]Percentages will not equal 100 as each participant may take more than one substance of abuse.
$^{*}p<0.05$.; $^{**}p<0.01$.; $^{***}p<0.001$.
SZ+: Schizophrenia with comorbid cocaine dependence; SZ−: Schizophrenia without substance dependence; COC: Cocaine dependence.

as well as in the TMT-A and in the neurocognitive Z score. Multivariate analysis of covariance was applied in the RAVLT test. A repeated measures multivariate analysis of covariance (RM MANCOVA) was conducted to examine the extent of learning over the five trials of RAVLT List A (A1–A5). In all cases, we introduced the Z score of the Block Design subtest and the scores of the Fagerström test as covariates. In order to explore the effect of age on the cognitive performance in each group, as well as the effect of the years of duration of SUD on SZ+ and COC groups, we carried out a bivariate correlational analysis between the Z scores of the cognitive performance and age of patients and duration of SUD. Then, we introduced the age of independent variables and duration of SUD in a lineal regression analysis with the neurocognitive composite Z score as the dependent variable.

All the analyses of variance were performed with age-corrected Z scores and were Bonferroni corrected. In all cases we estimated the power sample considering suitable values from 0.70, as well as the statistic partial squared Eta (ηp^2) to measure the effect size, where a value of 0.01 was low, 0.04 moderate and 0.1 high. The tests were considered bilaterally with a type I error established at 5%.

3. Results

3.1. Sociodemographic and clinical data

Regarding the sociodemographic variables, our groups were equivalent in age and years of schooling. Marital status shows higher rates of singles in both SZ groups compared to higher rates of married patients in the COC group ($p=0.002$) as well as higher rates of SZ patients receiving disability pension from the government compared to higher active workers in the COC group ($p<0.0001$).

Analyses of the clinical variables indicated a group difference in number of medications, where both SZ groups were taking more daily psychotropic medications than the COC group ($p<0.0001$), with higher intake of CPZ equivalents in both SZ groups compared to the COC group ($p\leq0.0001$). The SZ+ groups show higher cigarette consumption per day than the other two groups ($p\leq0.027$) without differences between SZ− and COC groups. Similarly, the *Fagerström* test indicated higher scores in the SZ+ group compared to the SZ− ($p=0.011$), without differences with the COC group. The qualitative analysis of level of dependency also showed higher nicotine dependence in the SZ+ group ($p=0.045$) compared to the SZ− and COC groups. The CGI indicated a better clinical state in the COC group compared to both SZ groups ($p=0.0001$). No group difference emerged in number of relatives with psychiatric disorder or substance use dependence, suicide attempts, medical comorbidities, daily number of cups of caffeine per day or other intake of beverages containing caffeine. Both SZ groups did not show differences in type of psychiatric

Table 3
Mean scores and standard deviations [M (SD)] of the three groups of patients in the neuropsychological tests, together with the results of the analyses carried out and the significant contrasts among the groups.

Neuropsychological tasks	Groups			ANCOVA/MANCOVA[a]			
	SZ+ (N=30)	SZ− (N=30)	COC (N=35)	F	Effect size	Power sample	Contrast
Premorbid IQ							
Vocabulary (WAIS-III). Direct score	40.71±9.22	42.76±6.93	43.02±6.60	1.69	0.03	0.34	
Block design (WAIS-III) Direct score	39.32±11.44	34.93±11.10	43.02±6.60	6.72^{*}	0.13	0.90	SZ−<COC=SZ+
Attentional span							
Digits (WAIS-III). Direct score	13.23±3.79	12.20±2.75	14.29±2.88	2.27	0.10	0.05	
Verbal memory							
AVLT (number of recorded words)				12.13^{b***}	0.21	0.99	COC>SZ+, SZ−
A1	4.48±1.09	4.63±1.42	5.60±1.35	5.37^{**}	0.11	0.83	SZ+<COC=SZ−
A2	6.45±2.01	6.33±1.64	8.34±1.62	11.03^{***}	0.20	0.99	COC>SZ+, SZ−
A3	7.72±2.10	7.73±2.24	10.11±1.90	11.09^{***}	0.20	0.99	COC>SZ+, SZ−
A4	8.97±2.50	8.97±2.17	11.17±1.96	8.89^{**}	0.17	0.96	COC>SZ+, SZ−
A5	10.03±2.33	9.77±2.54	12.20±2.05	8.01^{**}	0.15	0.95	COC>SZ+, SZ−
Total words	37.79±8.87	37.43±8.52	47.43±6.85	11.76^{***}	0.27	0.99	COC>SZ+, SZ−
B1 (interference list)	4.45±1.76	4.13±1.97	4.91±1.50	0.58	0.01	0.17	
A6	7.34±2.27	7.63±2.59	9.63±2.71	5.28^{**}	0.10	0.82	COC>SZ+, SZ
A7	7.34±2.75	6.67±3.10	9.40±2.61	6.49^{**}	0.13	0.89	COC>SZ+, SZ
REC A/15	12.35±1.92	12.27±2.73	13.48±1.50	2.20	0.04	0.43	
Processing speed							
TMT-A (seconds)	43.93±18.32	44.73±18.04	22.97±6.20	25.15^{***}	0.36	1.00	COC<SZ+, SZ−
Global component Z Score	−0.89±0.55	−0.98±0.65	−0.20±0.49	12.29^{***}	0.22	0.99	COC<SZ+, SZ−

[a]The analyses were carried out with Z scores.
[b]Results of the RM MANCOVA for the five trials.
SZ+: Schizophrenia with comorbid cocaine dependence; SZ−: Schizophrenia without substance dependence; COC: Cocaine dependence.
* $p<0.05$.
** $p<0.01$.
*** $p<0.001$.

diagnosis (schizophrenia and schizoaffective disorder), age of onset and mean duration of psychiatric disorder (see Table 1).

Concerning data on substance abuse, the SZ+ showed an earlier age of onset of substance intake than the COC patients ($p=0.012$), as well as higher rates of cannabis use ($p=0.004$), without differences in the use of other substances. No other differences between these groups were obtained (see Table 2).

3.2. Neuropsychological functioning

3.2.1. Differences in neuropsychological functioning between groups

First, we only considered the differences in neuropsychological performance between subject groups (SZ+, SZ− and COC), which are summarized in Table 3. Although no differences emerged between groups in the Vocabulary subtest, the SZ− group performed significantly worse in the non-verbal IQ than the COC group ($p=0.001$), without differences to the SZ+ group. Thus, the Z score for the Block Design subtest was introduced as a covariate in the subsequent analysis of variance. No differences were found regarding Digit attentional span subtest.

The RM MANCOVA analyses for the RAVLT reached a significant difference, being the COC group better on the learning capacity across the five trials (A1–A5) than the SZ+ and SZ− groups ($p=0.0001$), without differences between both SZ groups. The MANCOVA's analyses also showed main effects in these five trials ($p\leq0.006$) with a better execution of the COC group compared to both SZ groups, without differences between them. The COC group also recorded more total words across the five trials than both SZ groups ($p\leq0.001$), without differences between SZ− and SZ+ (see Fig. 1).

Both SZ groups showed a worse short memory (A6) ($p\leq0.003$) and a worse delay memory (A7) ($p\leq0.002$), indicated by fewer recorded words in both trials when compared to the COC group. The SZ− and SZ+ did not differ between them. No differences were obtained in memory recognition (A/15) and in interference list (B1).

The COC group also showed a better processing speed ($p\leq0.0001$) and a better global cognitive component than the two SZ groups ($p\leq0.0001$), without differences between the SZ+ and SZ− groups (see Fig. 2).

3.2.2. The influence of patient's age and length of SUD in the neuropsychological functioning

In order to explore the effect of patients' age and the length of SUD in the assessed cognitive domains, bivariate correlational analyses were performed.

While the analyses with the whole sample showed significant correlations between patient's age and the Z scores of the trials A2 ($p=0.048$), A3 ($p=0.029$) and B1 ($p=0.041$) of the RAVL tests, the correlational analyses separated by groups did not provide any significance for the SZ−. However, the SZ+ group showed negative age correlations with verbal memory, specifically for the five trials (A1–A5) ($p\leq0.039$), total learning words ($p=0.005$), short memory (A6) ($p=0.018$) and delay memory (A7) ($p=0.006$), as well as with the global cognitive component ($p=0.007$). In contrast, the COC group showed a positive age correlation with processing speed ($p=0.047$) (see Table 4).

Then, we performed bivariate correlational analyses for SZ+ and COC groups regarding the length of SUD and cognitive performance. No significant correlations appeared in any group.

Finally, we performed a lineal regression analysis with the global cognitive component as the dependent variable and both patients' age and the length of SUD as independent variables in each group of our sample. The general model was significant only for the SZ+ group ($F_{(33,2)}=5.20$; $p=0.013$), explaining 24.0% of the variance in the global cognitive component, where the only significant variable was age (see Table 5).

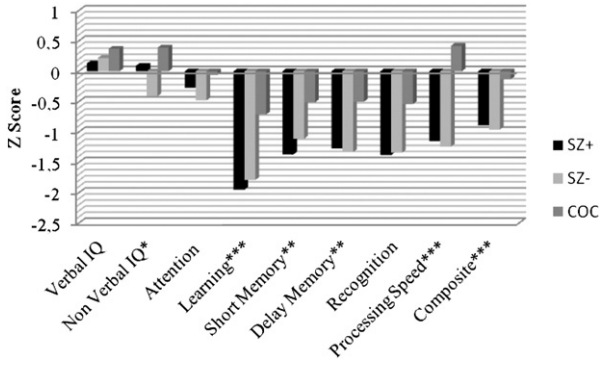

Fig. 2. Z scores on the assessed cognitive domains by groups. *p<0.05; **p<0.01; ***p<0.001. SZ+: Schizophrenia with cocaine dependence; SZ-: Schizophrenia without cocaine dependence; COC: Cocaine dependence. Note: Verbal IQ: Vocabulary (WAIS-III); Non Verbal IQ: Block Design (WAIS-III); Attentional Span: Digits (WAIS-III); Learning: Total words (RAVLT); Short Memory: Trial A6 (RAVLT); Recognition: A/15 (RAVLT); Processing Speed: TMT-A.

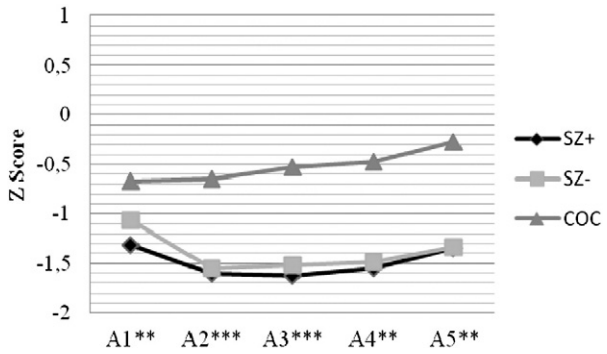

Fig. 1. Z scores on the RAVLT learning trials by groups. SZ+: Schizophrenia with cocaine dependence; SZ-: Schizophrenia without cocaine dependence; COC: Cocaine dependence. *$p<0.05$; **$p<0.01$; ***p<0.001.

Table 4
Correlations between Z scores on the neuropsychological tasks and age of patients for the total sample, and for SZ+, SZ− and COC groups.

	Age of patients			
Z scores	TS	SZ+	SZ−	COC
Premorbid IQ				
Vocabulary (WAIS-III)	−0.157	−0.018	0.297	0.271
Block design (WAIS-III)	−0.108	−0.230	0.121	−0.126
Attentional span				
Digits (WAIS-III).	−0.076	−0.217	0.195	0.250
Verbal memory				
AVLT (number of recorded words)				
A1	−0.009	−0.403*	0.071	0.288
A2	−0.203*	−0.483**	0.095	−0.184
A3	−0.224*	−0.596**	−0.050	−0.032
A4	−0.148	−0.394*	0.105	−0.096
A5	−0.131	−0.379*	0.080	−0.062
Total words	−0.060	−0.495**	0.272	0.138
B1 (interference list)	−0.211*	−0.179	−0.224	−0.168
A6	−0.079	−0.428*	0.185	−0.029
A7	−0.195	−0.489**	0.043	−0.148
REC A/15	−0.097	−0.279	−0.110	0.192
Processing speed				
TMT-A (Seconds)	−0.048	−0.077	−0.117	−0.338*
GLOBAL COMPONENT				
Z Score	−0.116	−0.509**	0.052	0.174

SZ+: Schizophrenia with comorbid cocaine dependence; SZ−: Schizophrenia without substance dependence; COC: Cocaine dependence; TS: Total sample. * p<0.05; ** p<0.01; *** p<0.001.

Table 5
Lineal regression for the global cognitive component for the three groups of patients.

Global cognitive component						
	Adjusted R	IV	Standardized β	*p* values	Tolerance	VIF
SZ+	0.24	Age	−0.56	0.004	0.94	1.06
		SUD duration	0.24	0.23	0.94	1.06
SZ−	−0.03	Age	0.05	0.78	1.00	1.00
COC	−0.02	Age	0.20	0.27	0.92	1.08
		SUD duration	−0.09	0.58	0.92	1.08

IV: Independent Variables; SZ+: Schizophrenia with comorbid cocaine dependence; SZ−: Schizophrenia without substance dependence; COC: Cocaine dependence; VIF: Variance inflation factor; SUD: Substance use dependence.

4. Discussion

This study intended to clarify the existing literature about neurocognition in SZ+ as well as to analyze the effect of age in SZ+ individuals in remission, regarding attention, memory functioning and processing speed, and controlling for non-verbal premorbid intelligence and tobacco consumption. Even though we followed the prevailing objectives of the research in this field (see Mueser and McGurk, 2012), some factors should be taken into consideration when interpreting our results: (i) Although we focused on cocaine as a main drug of choice by the subjects enrolled in our sample, they were mostly polydrug users, with a high intake of alcohol and cannabis. In order to control the potential confounding effects of these substances, we performed again the analyses with consumption of both alcohol and cannabis as covariates. We obtained similar results to the previous ones. (ii) Groups in our sample did differ in some demographic and clinical characteristics such as marital status, economic situation, clinical state, psychotropic medication and CPZ equivalents, which may have contributed somehow to the cognitive profiles among subject groups, explaining part of the intergroup differences. (iii) Three subjects in the SZ+ group and four subjects in the SZ− group were suffering from schizoaffective disorder (Table 1). Since the schizoaffective patients may have better neuropsychological performance than the SZ ones, we conducted analyses excluding these subjects, obtaining very similar results to the whole SZ groups. Therefore, we decided to keep them in the study.

4.1. Neuropsychological performance in schizophrenia and/or cocaine dependence

We conducted all the analyses of variance with Z scores enabling comparisons with normative data. This also eliminated age-related variance in cognitive performance. Further, we obtained Z scores ranging between −1 and −2 in both SZ groups, in agreement with the literature (Sakyn et al., 1994; Wolwer et al., 2008).

As we expected, the COC group performed better than both SZ groups in verbal memory, specifically in learning over the five trials, in the total learned words, in short memory, delayed memory, processing speed and in the global cognitive component. Groups did not differ in their premorbid verbal IQ, attentional span, and recognition memory. Despite the worse execution of both SZ groups in verbal memory, whether learning over the five trials, short or delayed memory, it should be noted that there were no differences between groups regarding recognition. This result seems to indicate that deficits in both SZ groups are related to retrieval of verbal information stored in memory, rather than deficits in encoding of information.

Except for a worse premorbid non-verbal IQ in the SZ− compared to the COC group, we did not find differences between SZ+ and SZ− in any cognitive measure, as other works have observed (Cooper et al., 1999; Copersino et al., 2004). Unfortunately, most studies with SZ+ patients fail to incorporate the COC group but those that do observe a worse performance of the SZ+ on verbal memory (Serper et al., 2000a, 2000b; Sevy et al., 1990). In all these studies, the SZ+ group was tested in acute cocaine cessation (last use within 72 h) and the authors attribute this worse performance on verbal learning to dopaminergic and serotoninergic depletion following binge use of cocaine (Parsons et al., 1995; Serper et al., 2000a,b; Volkow et al., 1997). Since in our sample the patients were abstinent for more than 4 months, somehow recovery on cognitive functioning may be plausible, explaining the lack of differences between SZ+ and SZ− groups. However, a long-term disturbance on the dopaminergic system affecting cognitive functioning due to SZ plus cocaine addiction could appear in those patients of an older age, as we explain below.

Taken together, these results seem to point to a similar execution on the assessed cognitive domains, mainly attention, verbal memory, processing speed and the global cognitive performance in both SZ groups.

4.2. The influence of patients' age and length of SUD in the neuropsychological functioning

While the correlational analyses for the total sample show negative correlations with trials A2, A3 and B1 on the RAVL test, the analyses separated by groups only show a negative effect of the patients' age for the SZ+ group regarding verbal memory and the global cognitive component. Thus, verbal memory and global cognitive functioning are worse in those SZ+ subjects with an older age. Whereas SZ− did not show any age related-change on cognitive performance, the COC group showed a better execution on speed of processing in the older subjects. Moreover, the regression analyses show that age was the variable explaining a worse cognitive functioning in older SZ+ subjects. Unexpectedly, the length of SUD did not appear significantly correlated to cognitive functioning in both SZ+ and COC groups. This result agrees with the idea of a cognitive decline interacting with age in the SZ+ patients as a result of an additive damage in the brain. This may be due to the long term expression of the neurotoxic consequences of substance use, as proposed by other authors (Allen et al., 2000; Bowie et al., 2005; Mohamed et al., 2006). Thus, the contradictory results in the current literature about neurocognition in SZ+ and SZ− may be influenced by different age samples.

Surprisingly, we also observed a tendency to a better speed of processing in the older COC. Although no effects were observed regarding the length of SUD, differences in both frequency and quantity of use of cocaine and intake of other substances could explain these results of a better processing speed. Similarly, it could also be affecting the results in the SZ+, resulting in dose-dependent effects which covary with the age of the subjects resulting in a drug x age phenomenon. We are not able to disentangle these possible effects since no measures of these variables were performed. Future studies are needed examining these possible effects.

However, our study is not free of some limitations. Although we assessed the clinical state with the CGI, we did not perform a standardized assessment of SZ symptoms. The differences found in our study regarding the age of individuals might be influenced by differences in psychopathology between the SZ+ and SZ− groups. In spite of this, some longitudinal findings indicate that neurocognitive deficits are relatively stable in SZ− individuals and not tightly linked to symptom severity or to other clinical variables such as chronicity or severity of illness (Asarnow and McCrimmon, 1978; Lewandowski et al., 2011), but there are no similar data for SZ+ individuals. Moreover, the fact that both SZ groups were taking more daily medication and CPZ equivalents than the COC group may have a direct influence on neuropsychological functioning. Although significant cognitive improvements are reported in first-episode psychosis under antipsychotic treatment (Keefe et al., 2006, 2007; Kopala et al., 2006), some studies have highlighted differences between typical and atypical agents (Crespo-Facorro et al., 2009; Purdon et al., 2000) and those studies comparing SZ medicated *vs* non-medicated did not report any advantage of medicated groups on cognitive functioning (Hill et al., 2004;

Rundt et al., 2007). Further research is needed about specific medication effects on cognition in chronic SZ+.

Noteworthy, our cross-sectional nature design does not allow us to determine the manner in which substance use and SZ interact over time. Longitudinal studies are required to determine the age-related changes in the SZ+ subjects in terms of neuropsychological functioning and functional outcome. Other limitations such as a relatively small sample size and the retrospective characterization of life-time drug use obtained by self reporting data may have influenced our results.

However, our results do not seem affected by residual effects of substance use due to the extensive abstinence time. The fact that our sample comprised only males eliminated the influence of gender-related variables, and the conversion of raw scores to Z scores eliminates the influence of age-related variables also enabling the comparisons with normative data. The inclusion of two SZ groups, with and without cocaine dependence, and one COC group, allows for a more comprehensive understanding of the effects of substance use on SZ+ *vs* non SZ patients. All these are lacking factors in many of the preceding works.

Our results have clinical implications. Deficits in verbal memory and learning in SZ patients have been associated to deficits in adaptive functioning and they predict worse therapeutic results (Green, 1996; Serper et al., 2000a, 2000b), since they are not able to obtain benefits from psychotherapeutic approaches which require storage of large amounts of information and mental flexibility (Bowie et al., 2005). Thus, treatment programs may prove ineffectively in older SZ+ patients. The assessment of neurocognitive deficits in SZ+ patients, especially in older ones, is necessary by the clinicians in order to know the more appropriate therapeutic treatments and develop cognitive enhancement therapies. The early prevention of a cognitive deficit which may be accelerated in older ages may help to improve the functional outcome of these patients in a long term.

5. Conclusions

This study obtains a better performance of the COC group in verbal memory, processing speed and global cognitive performance compared to both SZ groups, while the SZ+ patients who are abstinent for more than four months do not differ from the SZ− patients in their cognitive functioning. However, the neuropsychological impairment in SZ+ individuals is negative related to age. This is in agreement with the idea of an additional cognitive deficit in older SZ+ patients due to the long-term neurotoxic brain damage of substance intake, while the cognitive performance of the SZ− does not seem related to the age. Although we did not find that the duration of SUD is related to cognitive performance, future research is needed to clarify the current knowledge gaps.

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Contributors

Ana Adan conceived the original idea for the study, sought funding, wrote the protocol and managed the day to day running of the study. Irina Benaiges collected the data of the sample and carried out all data analyses. The manuscript was written by Irina

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References

Allen DN, Goldstein G, Aldarondo F. Neurocognitive dysfunction in patients diagnosed of schizophrenia and alcoholism. Neuropsychology 2000;13:62–8.
Andreasen NC, Pressler M, Nopoulos P, Miller D, Ho B-Ch. Antipsychotic dose equivalents and dose-years: a standardized method for comparing exposure to different drugs. Biol Psychiatry 2010;67:255–62.
Asarnow RF, McCrimmon DJ. Residual performance deficit in clinically remitted schizophrenics. A marker of schizophrenia? J Abnorm Psychol 1978;87(6):597–608.
Benaiges I, Prat G, Adan A. Neuropsychological aspects of dual diagnosis. Curr Drug Abuse Rev 2010;3:175–88.
Bowie CR, Serper MR, Riggio S, Harvey PD. Neurocognition, symptomatology, and functional skills in older alcohol-abusing schizophrenia patients. Schizophr Bull 2005;31(1):175–82.
Bozikas VP, Andreou C. Longitudinal studies of cognition in first episode psychosis: a systematic review of the literature. Aust N Z J Psychiatry 2011;45:93-108.
Cooper L, Liberman D, Tucker D, Nuechtertlein KH, Tsuang S, Barnett HL. Neurocognitive deficits in the dually diagnosed with schizophrenia and cocaine abuse. Psychiatr Rehabil Skills 1999;3(2):231–45.
Copersino ML, Serper MR, Vedhan N, Goldberg BR, Richarme D, Chou JC-Y, et al. Cocaine craving and attentional bias in cocaine dependent schizoprhrenic patients. Psychiatry Res 2004;128(3):209–18.
Coulston CM, Perdices M, Tennant CC. The neuropsychology of cannabis and other substance use in schizophrenia: a review of the literature and critical evaluation of methodological issues. Aust N Z J Psychiatry 2007;41:869–84.
Crespo-Facorro B, Rodríguez-Sanchez JM, Perez-Iglesias M, Mata I, Ayesa R, Ramirez-Bonilla M, et al. Neurocognitive effectiveness of haloperidol, risperidone and olanzapine in first-episode psychosis: a randomized controlled 1-year follw-up comparison. J Clin Psychiatry 2009;70:717–29.
Drake Al, Butters N, Shear PK, Smith TL, Bondi M, Irwin M, et al. Cognitive recovery with abstinence and its relationship to family history for alcoholism. J Stud Alcohol 1994:104–9.
First MB, Spitzer RL, Gibbon M, William JBW. Structural Clinical Interview for Axis-I DSM-IV Disorders, Patient's edition. New York, NY: Biometric Research Department, New York state Psychiatric Institute; 1998.
Green MF. What are the functional consequences of neurocognitive deficits in schizophrenia? Am J Psychiatry 1996;153:321–30.
Harvey PD, Green MF, Keefe RS, Velligan DI. Cognitive functioning in schizophrenia: a consensus statement on its role in the definition and evaluation of effective treatments for the illness. J Clin Psychiatry 2004;65:361–72.
Heatherton TF, Kozlowski LT, Frecker RC, Fagerström KO. The Fagerström test for nicotine dependence: a revision of the Fagerström tolerance questionnaire. Br J Addict 1991;86:1119–27.
Herman M. Neurocognitive functioning and quality of life among dually diagnosed patients and non substance-abusing schizophrenia inpatients. Int J Ment Health Nurs 2004;13:282–91.
Hill SK, Schuepbach D, Herbener ES, Keshavan MS, Sweeney JA. Pretreatment and longitudinal studies of neuropsychological deficits of antipsychotics-naïve patients with schizophrenia. Schizophr Res 2004;68:49–63.
Joyal CC, Hallé P, Lapierre D, Hodgins S. Drug abuse and/or dependence and better neuropsychological performance in patients with schizophrenia. Schizophr Res 2003;63:297–9.
Kavanagh DJ, McGrath J, Saunders JB, Dore G, Clark D. Substance misuse in patients with schizophrenia: epidemiology and management. Drugs 2002;62(5):743–55.
Keefe RS, Seidman LJ, Christensen BK, Sharma T, Sitskoorn MM, Rock SL, et al. Long-term neurocognitive effects of olanzapine or low-dose haloperidol in first episode psychosis. Biol Psychiatry 2006;59:97-105.
Keefe RS, Sweeney JA, Gu H, Hamer RM, Perkins DO, McEvoy JP, et al. Effects of olanzapine, quetiapine and risperidone on neurocognitive function in early psychosis: a randomized double-blind 52 week comparisons. Am J Psychiatry 2007;164:1061–71.
Kopala LC, Good KP, Milliken H, Buiteman C, Woodley H, Rui Q, et al. Treatment of a first episode psychotic illness with quetiapine: An analysis of 2 years outcome. Schizophr Res 2006;81:29–39.
Kumari V, Postma P. Nicotine use in schizophrenia: the self-medication hypotheses. Neurosci Biobehav Rev 2005;29:1021–34.
Lewandowski KE, Cohen BM, Öngur D. Evolution of neuropsychological dysfunction during the course of schizophrenia and bipolar disorder. Psychol Med 2011;41:225–41.
Lezak MD, Howieson DB, Loring DW. Neuropsychological assessment. 4th edition. Oxford: Oxford University Press; 2004.
Manning V, Wanigaratne S, Best D, Strathdee G, Schrover I, Gossop M. Screening for cognitive functioning in psychiatric outpatients with schizophrenia, alcohol dependence and dual diagnosis. Schizophr Res 2007;91:151–8.
Matza LS, Buchanan R, Purdon S, Brewster-Jordan J, Zhao Y, Revicki DA. Measuring changes in functional status among patients with schizophrenia: the link with cognitive impairment. Schizophr Bull 2006;32(4):666–78.
Mohamed S, Bondi MW, Kasckow JW, Golshan S, Jeste DV. Neurocognitive functioning in dually diagnosed middle aged and elderly patients with alcoholism and schizophrenia. Int J Geriatr Psychiatry 2006;21:711–8.
Mueser KT, McGurk SR. Cognitive functioning in schizophrenia and co-ocurring substance use disorders: where do we go from here? J Dual Diagn 2012;8(1):48–9.
National Institute of Mental Health. CGI. Clinical global impression. In: Guy W, Bonato RR, editors. Manual for the EDCEU Assessment Battery. 2. rev. ed. Maryland: Chevy Chase; 1976.
O'Malley S, Adamse M, Heaton RK, Gawin FH. Neuropsychological impairment in chronic cocaine abusers. Am J Drug Alcohol Abuse 1992;18(2):131–44.

Parsons LH, Koob GF, Weiss F. Serotonin dysfunction in the nucleus accumbens of rats during withdrawal after unlimited access to intravenous cocaine. J Pharmacol Exp Ther 1995;274:1182–92.
Potvin S, Briand C, Prouteau A, Bouchard RH, Lipp O, Lalonde P, et al. CANTAB explicit memory is less impaired in addicted schizophrenia patients. Brain Cogn 2005;59(1):38–42.
Potvin S, Joyal CC, Pelletier J, Stip E. Contradictory cognitive capacities among substance-abusing patients with schizophrenia: a meta-analysis. Schizophr Res 2008;100:242–51.
Potvin S, Stavro K, Pelletier J. Paradoxical cognitive capacities in dual diagnosis schizophrenia: the quest of explanatory factors. J Dual Diagn 2012;81(1):35–47.
Purdon SE, Jones BD, Stip E, Labelle A, Addington D, David SR, et al. Neuropsychological changes in early phases schizophrenia during 12 months of treatment with olanzapine, risperidone or haloperidol. The Canadian collaborative group for research in schizophrenia. Arch Gen Psychiatry 2000;57:249–58.
Regier DA, Farmer ME, Rae DS, Locke BZ, Keith SJ, Judd LL, et al. Comorbidity of mental disorders with alcohol and other drug abuse: results from the epidemiological catchment area (ECA) study. JAMA- J Am Med Assoc 1990;264:2511–8.
Reitan RM, Wolfson D. The Healsted—Reitan neuropsychological test battery. Tucson: Neuropsychological Press; 1985.
Rundt BR, Melle I, Friis S, Johannessen JO, Larsen TK, Midboe LJ, et al. The course of neurocognitive functioning in first episode psychosis and its relation to premorbid adjustment, duration of untreated psychosis, and relapse. Schizophr Res 2007;91:132–40.
Serge S, Stanley RK, Lewis AO, Herman M. Significance of cocaine history in schizophrenia. J Nerv Ment Dis 1990;178(10):642–8.
Sakyn AJ, Shtasel DL, Gur RE, Kester B, Mozley LH, Stafiniak P, et al. Neuropsychological deficits in neuroleptic naïve patients with first-episode schizophrenia. Arch Gen Psychiatry 1994;51:124–31.
Schmidt M. Rey auditory Verbal Learning Test: A Handbook. Lutz, FL: Psychological Assessment Resources; 2011.
Schnell T, Koethe D, Daumann J, Gouzoulis-Mayfrank E. The role of cannabis in cognitive functioning of patients with schizophrenia. Psychopharmacology 2009;205(1):45–52.
Scholes KE, Martin-Iverson MT. Cannabis use and neuropsychological performance in healthy individuals and patients with schizophrenia. Psychol Med 2010;40(10):1635–46.
Serper MR, Bergman A, Copersino ML, Chou J, Richarme D, Cancro Ra. Learning and memory impairment in cocaine-dependent and comorbid schizophrenic patients. Psychiatry Res 2000a;93:21–32.
Serper MR, Copersino ML, Richarme D, Vandham N, Cranco R. b. Neurocognitive functioning in recently abstinent, cocaine-abusing schizophrenic patients. J Subst Abuse 2000b;11(2):205–13.
Sevy S, Kay SR, Opler L, Van Praag HM. Significance of cocaine history in schizophrenia. J Nerv Ment Dis 1990;178(10):642–8.
Sevy S, Burdick KE, Visweswaraiah H, Abdelmessih S, Lukin M, Yechiam E, et al. Iowa Gambling task in schizophrenia and co-occurring cannabis use disorders. Schizophr Res 2007;92:74–84.
Smelson DA, Davis CW, Dipano R, Johnson V, Losonczy MF, Ziedonis D. Executive and motor skill functioning among cocaine dependent schizophrenics and non-drug abusing schizophrenics. J Nerv Ment Dis 2002;190:200–2.
Smelson DA, Davis CW, Einstein N, Engelhart C, Williams J, Losonczy M, et al. Cognitive disparity in schizophrenics with and without cocaine dependence. J Subst Abuse Treat 2003;24(1):75–9.
Spreen O, Strauss E. A Compendium of Neuropsychological tests. Administration, Norms and Commentary. New York: Oxford University Press; 1998.
Stirling J, Lewis S, Hopkins R, White C. Cannabis use prior to first onset psychosis predicts spared neurocognition at 10 year follow-up. Schizophr Res 2005;75:135–7.
Thoma P, Daum I. Working memory and multi-tasking in paranoid schizophrenia with and without comorbid substance use disorders. Addiction 2008;103(5):774–86.
Thoma P, Wiebel B, Daum I. Response inhibition and cognitive flexibility in schizophrenia with and without comorbid substance use disorder. Schizophr Res 2007;92:168–80.
Tönne U, Hiltunen AJ, Vikander B, Engelbrektsson K, Bergman H, Bergman I, et al. Neuropsychological changes during steady-state drug use withdrawal and abstinence in primary benzodiazepine-dependent patients. Acta Psychiatr Scand 1995;91:299–304.
Volkow ND, Wang GJ, Fowler JS, Logan J, Gatley SJ, Hitzemann R, et al. Decreased striatal dopaminergic responsiveness in detoxified cocaine-dependent subjects. Nature 1997;386:830–3.
Wechsler D. Wechsler Adult Intelligence Scale—revised. Madrid: TEA ediciones; 2001 [Spanish Version].
Wolwer W, Brinkmeyer J, Riesbeck M, Freimüller L, Klimke A, Wagner M, et al. Neuropsychological impairments predict the clinical course of schizophrenia. Eur Arch Clin Neurosci 2008;258(5):28–34.
Woods SW. Chlorpromazine equivalent doses for the newer atypical antipsychotics. J Clin Psychiatry 2003;64(6):663–7.

- ✓ **Objetivo 4: CVRS y correlatos clínicos**

Estudio 4: *Health-related Quality of Life in patients with Dual Diagnosis: Clinical correlates.*

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Resumen:

Si bien en las últimas dos décadas se ha producido un aumento en el interés de la CV y de la CVRS como medidas de evaluación de las intervenciones, los efectos adversos de los tratamientos y del impacto de la enfermedad a lo largo del tiempo, especialmente en población psiquiátrica, son escasos los estudios que incorporan su evaluación en el ámbito de la PD. El estudio de la CV/ CVRS en pacientes duales y las variables clínicas asociadas a su estado, puede aportar información útil tanto desde el punto de vista diagnóstico como para mejorar la calidad de las intervenciones terapéuticas.

Material y Método:

Se llevó a cabo un estudio cros-seccional basado en la comparación de tres grupos experimentales. Un grupo con Patología Dual (PD, n = 35) y un grupo con Trastorno Mental Severo (TMS, n=35), ambos con diagnóstico psiquiátrico de Esquizofrenia, Trastorno Bipolar y Depresión y un tercer grupo con Trastorno por Uso de Sustancias (TUS, n=35) sin comorbilidad psiquiátrica.

Se recabó información amplia de carácter sociodemográfico y clínico mediante una entrevista semi-estructurada y se evaluó la Impresión Clínica Global (ICG; National Institute of Mental Health, 1976), la dependencia a la nicotina mediante el test de Fagerström (Heatherton et al., 1991) y el consumo de cafeína diaria. Para la evaluación de la CVRS se administró el cuestionario *Short-Form 36 Item Health Survey, SF-36* (Ware & Sherbourne, 1992).

Los datos sociodemográficos y clínicos fueron analizados mediante análisis univariantes en el caso de los datos continuos y Chi cuadrado para los datos categoriales. Las diferencias intergrupales en CVRS se examinaron mediante análisis de la multivarianza con el número de medicamentos diarios, intentos de suicidio y cigarrillos diarios, introducidos posteriormente como covariables. Para la identificación de factores clínicos asociados a la CVRS, se efectuaron análisis de correlación y regresión lineal.

Resultados:

Ambos grupos PD y TMS, presentaron una mayor proporción de solteros y mayor desocupación laboral respecto al grupo TUS. Respecto a las variables clínicas, PD y TUS tomaban mas medicación antipsicótica, estabilizadores del estado del ánimo y ansiolíticos, así como una peor ICG que el grupo TUS. El grupo PD presentaba más intentos de suicidio que los otros dos grupos. Ambos grupos PD y TUS, presentaban mayor consumo de cigarrillos diarios y mayor dependencia a la nicotina que el grupo TMS. No se encontraron más diferencias entre grupos en el resto de variables clínicas.

En cuanto a la CVRS, el grupo PD presentó peores puntuaciones en la mayoría de subescalas del cuestionario y en la escala compuesta de salud mental respecto a los grupos TMS y TUS, sin apenas diferencias entre ellos. La introducción de las covariables, generalmente mantuvo el peor estado del grupo PD respecto a los otros grupos, excepto en la escala compuesta de salud mental. Las comparaciones con datos normativos españoles confirmaron un estado pésimo de la CVRS en el grupo PD. El análisis correlacional reveló correlaciones negativas entre el dominio de salud mental de la CVRS y el número de cafés diarios en el grupo PD. Posteriormente, el análisis de regresión lineal confirmó que el número de cafés diarios explicaba el 14,2% de la varianza en la escala compuesta de salud mental. Este efecto no se halló en los grupos TMS y TUS.

Conclusiones:

En términos generales, el grupo con PD presentó un peor estado de la CVRS, especialmente en el dominio de salud mental. Las mejores puntuaciones las aportó el grupo TUS, mientras el grupo TMS ocupó una posición intermedia entre los otros dos grupos. El consumo de cafeína se mostró negativamente asociado al dominio de salud mental en el grupo PD. Desde un punto de vista especulativo, puede que la cafeína se asocie a otros factores de riesgo como el consumo de nicotina, ambas sustancias asociadas a su vez a mayores intentos de suicidio y a menor eficacia del tratamiento farmacológico. Todos estos factores han demostrado afectar directa o indirectamente la CVRS.

La evaluación sistemática de la CVRS en pacientes con PD, permitirá mejorar nuestro conocimiento acerca de los factores clínicos asociados a ella, siendo una herramienta útil en la detección de áreas específicas de atención, así como en la planificación de los objetivos del tratamiento y en la evaluación de las intervenciones.

HEALTH AND QUALITY OF LIFE OUTCOMES

RESEARCH Open Access

Health-related quality of life in patients with dual diagnosis: clinical correlates

Irina Benaiges[1], Gemma Prat[1] and Ana Adan[1,2*]

Abstract

Background: Although the studies published so far have found an affectation in the Health Related Quality of Life (HRQOL) in both psychiatric and substance use dependence disorders, very few studies have applied HRQOL as an assessment measure in patients suffering both comorbid conditions, or Dual Diagnosis. The aim of the current study was to assess HRQOL in a group of patients with Dual Diagnosis compared to two other non-comorbid groups and to determine what clinical factors are related to HRQOL.

Methods: Cross-sectional assessment of three experimental groups was made through the Short Form – 36 Item Health Survey (SF-36). The sample consisted of a group with Dual Diagnosis (DD; N = 35), one with Severe Mental Illness alone (SMI; N = 35) and another one with Substance Use Dependence alone (SUD; N = 35). The sample was composed only by males. To assess the clinical correlates of SF-36 HRQOL, lineal regression analyses were carried out.

Results: The DD group showed lower scores in most of the subscales, and in the mental health domain. The group with SUD showed in general a better state in the HRQOL while the group with SMI held an intermediate position with respect to the other two groups. Daily medication, suicidal attempts and daily number of coffees were significantly associated to HRQOL, especially in the DD group.

Conclusions: The DD group showed lower self-reported mental health quality of life. Assessment of HRQOL in dual patients allows to identify specific needs in this population, and may help to establish therapeutic goals to improve interventions.

Keywords: Quality of life, Health-related quality of life, Dual diagnosis, Substance use, Severe mental illness

Background

In the last two decades there has been an increasing interest in Quality of Life (QOL) and Health related Quality of life (HRQOL) as an assessment measure in care interventions, adverse effects of treatment and the impact of the illness through time [1], especially in psychiatric population [2]. Different studies have found an affectation both in the QOL and in the HRQOL in psychiatric disorders such as schizophrenia and bipolar disorder [3-7], as well as in substance dependence disorders [8-10].

Assessment of both QOL and HRQOL in Dual Diagnosis (DD) patients may help to identify areas of specific and clinical attention, given the special characteristics of this population: faster relapses [11], higher rates of rehospitalization and imprisonment [12], lower participation in the health services, more loss of social support and financial problems [12-14]. All these factors may be indicative of a lesser QOL in patients with DD, and its detection and clinical assistance could improve the efficacy of the interventions. Both QOL and HRQOL may represent useful measurements to assess the efficacy of such interventions.

Although there are few studies on the QOL in DD, most of the data published up to now show a worse QOL in these patients. Singh et al. [15] obtained a worse general QOL in DD patients with bipolar disorder compared with bipolar patients without comorbid Substance Use Dependence (SUD), with patients with SUD alone and with a normal control group. Kilbourne et al. [16] found that illicit drug use was associated with a decreased

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mental HRQOL in patients with bipolar disorder, and this effect continued one year later, even after controlling for the maniac and depressive symptoms of the disorder. Kalman et al. [17] obtained a lower mental HRQOL in a sample of dual patients with heterogeneous psychiatric disorders, compared with subjects with Severe Mental Illness (SMI) alone and with alcohol dependence alone. Bizarri et al. [18] also found a worse score in all the assessed domains of QOL in DD patients with opium dependence compared to patients without a concomitant mental disorder, and the differences were more marked in the domains of mental and physical functioning. In the study by Fassino et al. [19], the heroin dependent patients with comorbid personality disorder presented a worse QOL than those heroin dependent without the comorbidity.

However, some works do not obtain such differences, as for example in Astals et al. [20], which assessed the HRQOL in patients with and without a concomitant psychiatric disorder under treatment for heroin dependence. In the study by Garg et al. [21], the DD had worse scores in the dimension of Vitality but not in mental and physical health domains. Finally, Wade et al. [22], in a sample of young patients with a first psychotic episode, observed that the affectation in both QOL and social functioning were related to the level of severity in substance use. Thus, the QOL in patients with mild consumption did not differ from that of non-consumers, while it was worse in patients with heavy consumption. The variety of definitions on QOL, sample characteristics, design of the studies and different instruments and procedures applied can be explanatory factors of the heterogeneity of results.

The aim of our study was to assess HRQOL through SF–36 in a group of patients with DD, and compare it to the group with SMI and to the third group with SUD as well as to establish comparisons to published values for the normal Spanish population according to the mean age of our sample and male gender norms [23]. To our knowledge, no other previous research has worked with this design, including these three experimental groups and their comparisons to normative data. We expected higher scoring in the SUD group, indicative of a better HRQOL state, while the SMI group would be in the medium scoring range and DD would present the worse HRQOL scores, especially in the mental health domain. In an exploratory way, we further sought to determine which clinical factors would be related to HRQOL, with special interest in the DD group.

Material and methods

Sample and procedure

This study is part of a larger study on health related quality of life, neurocognitive functioning and personality traits in patients with DD. In the present paper, we only present the data concerning health-related quality of life.

In a prospective cross-sectional design we enrolled 125 male patients aged 18 to 60 years, divided in three groups. Two groups with a severe mental illness (schizophrenia, bipolar disorder, or major depressive disorder) with comorbid SUD (DD) and without comorbid SUD (SMI), and they were consecutively admitted to "social club program" at the Mental Health Division of the Althaia Foundation in Manresa (Barcelona, Spain). A third group of patients with SUD without psychiatric comorbidity (SUD) was under treatment on the therapeutic community of the Gressol Catalonia Man Project (Barcelona), between January 2010 and June 2011. Each participant was consecutively referred by their treating psychiatrist, who was blind to the aims of the study, and had been diagnosed using the Structural Clinical Interview for DSM-IV-R [24] Axis I Disorders (SCID-I) [25]. The inclusion criteria were: (1) Current diagnosis of schizophrenia, bipolar disorder or major depression; or current diagnosis of substance use dependence in remission for at least four months and absence of relapses at least one month before the study participation; (2) male gender; (3) age between 18–60 years. The SUD group has the additional criterion of no other current DSM-IV-R criteria for any Axis I or II disorders. The exclusion criteria were: no DSM-IV-R criteria for a current substance-induced psychiatric disorder or psychiatric disorder due to a medical condition, unstable or severe medical illness, mental retardation, history of traumatic brain injury or neurological injury, violent behavior and having received electroconvulsive therapy within 12 months prior to their study participation.

The procedure of the study was divided into 4 one hour long sessions. The data presented in this study was collected in the first session by a doctoral level psychologist, and written informed consent was obtained from all participants after the procedures of the study were fully explained to them. In the following sessions we carried out neurocognitive and personality assessments. A urine drug screen was performed between the first and the second session of the study. After this initial assessment and during the course of the study, 20 patients were excluded. The analyses were performed with a total sample of 105, divided into 35 subjects in each group (see Figure 1).

This study was approved by the ethics committees of the University of Barcelona and the Mental Health Division of Althaia, meeting the ethical principles of the Declaration of Helsinki.

Instruments

Clinical measures

Information was collected by means of a *structured interview* of sociodemographic (age, marital status, social

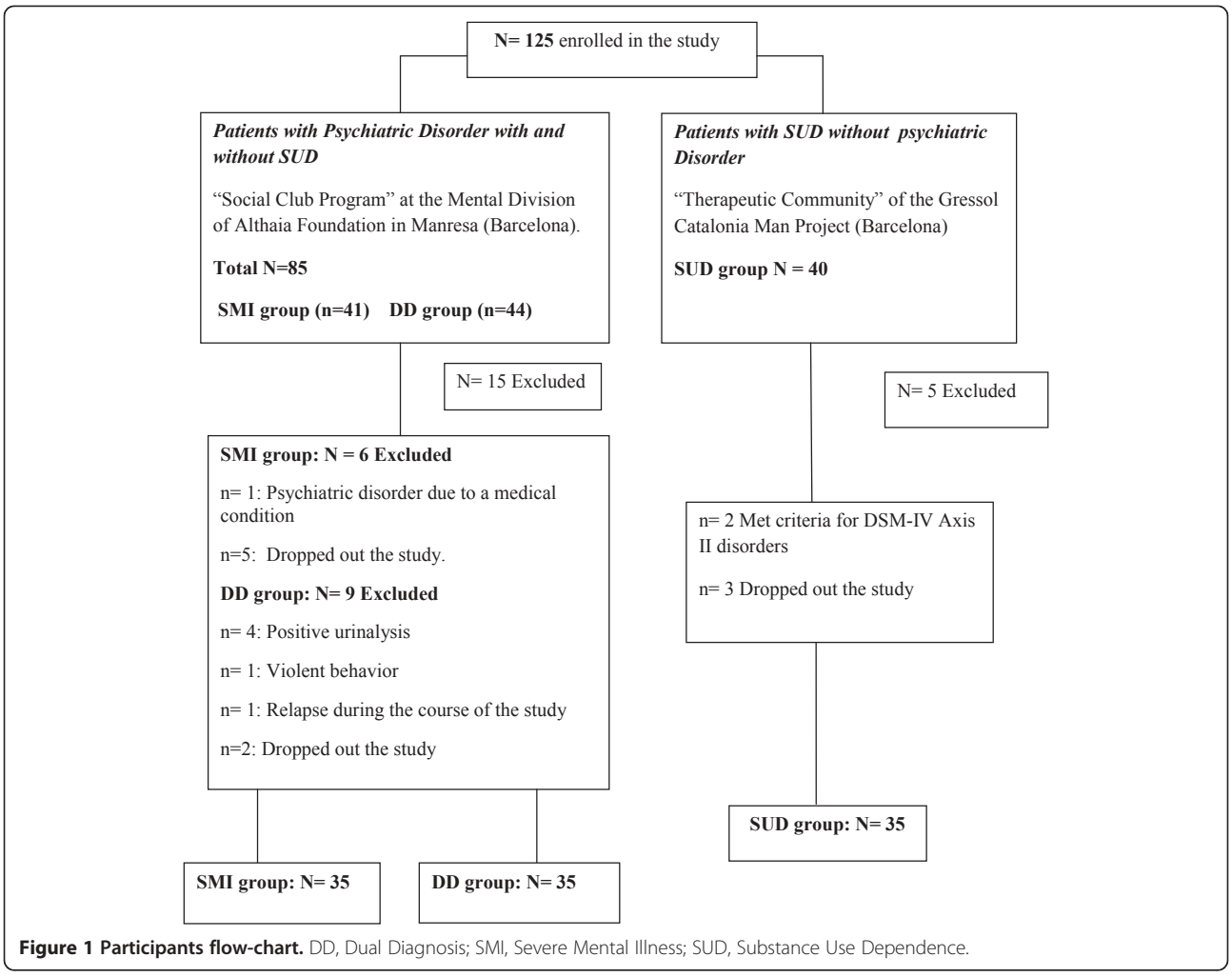

Figure 1 Participants flow-chart. DD, Dual Diagnosis; SMI, Severe Mental Illness; SUD, Substance Use Dependence.

class, schooling and economic status) and clinical variables (diagnosis, psychiatric and substance use family history, age of onset of the disorder and/or consumption, relapses, abstinence periods, type of drug used, suicidal attempts, presence of organic pathology and medication). We reviewed the medical records of the patients, contrasting the self-reported data with the medical history on the database of the hospital and with their treating psychiatrist. Daily consumption of cigarettes and cups of coffee as well as other intakes of beverage with caffeine, such as tea or cola, were recorded. Smokers were administered the *Fagerström* test [26] of nicotine dependence. Additionally, the *Clinical Global Impression* [27] was applied as a subjective measure of the clinical severity of each participant.

Health- related quality of life

To assess the HRQOL we selected the SF-36 questionnaire [28] (Short Form –36 Item Health Survey), one of the most used and adequate generic instruments in psychiatric [29,30] and drug addicted population [31]. The Spanish version has good psychometric properties and reference population values [23]. The SF-36 provides scores in 8 dimensions: Physical Functioning, Role - Physical, Role - Emotional, Social Functioning, Mental Health, General Health, Bodily Pain, and Vitality, with scores ranging from 0 to 100, where a higher score indicates a better functioning in the scale. It also has an additional item measuring the Health Changes perceived by the subject in comparison to the previous year (Health Transition item). The questionnaire provides two composite standardized scales in T scores with mean 50 and standard deviation 10: the Physical health Component Summary (PCS) and the Mental health Component Summary (MCS). These two scales explain 80 to 85% of the variance in the 8 original dimensions and have shown greater reliability [32].

Statistical analysis

We calculated the descriptive statistics for all the variables. The possible intergroup differences (DD, SMI and SUD) in the sociodemographic and clinical variables

were explored using univariate (ANOVA) and multivariate analyses (MANOVA) for the continuous data. Categorical data were examined with Chi Square tests in the case of variables with nominal scales (marital status, economic situation, living situation, type of medical comorbidities, and type of psychotropic medication, psychiatric diagnosis, type of intake of substance/dependence and degree of dependency on the Fagerström tests).

The intergroup differences in the HRQOL were examined by MANOVAs and later introduced covariates in analysis (MANCOVA) to explore the variance of its effect on the HRQOL. In all cases, we estimated the power sample so that the statistical test would not reject the null hypothesis wrongly by not detecting an effect if there were one. We considered values from 0.70 as suitable. The statistic partial squared Eta (η_p^2) was also estimated to measure the effect size, that is, the degree to which each factor is affecting the dependent variable, where a value of 0.01 was low, 0.04 moderate and 0.1 high [33]. Both statistics are used to avoid the occurrence of type II error. All analyses were Bonferroni corrected due to the multiple comparisons carried out in order to control the possibility that the statistical tests would find an effect where there was not one. Thus, this correction method prevents from the occurrence of Type I error.

Finally, in an exploratory way, we carried out a bivariate correlational analysis between the demographic and clinical variables with the summatory scores of the PCS and the MCS. We intended to identify the variables of interest to be introduced in the following lineal regression analysis, trying to find clinical correlates of the HRQOL. The analyses were done with the statistical package SPSS (version 15.0) and the tests were considered bilaterally with a type I error established at 5%.

Results

Sociodemographic and clinical variables

Table 1 and Table 2 summarize the sociodemographic and clinical data of the sample. Groups were equivalent in age, number of children, years of schooling and type of cohabitation. There were intergroup differences in marital status ($\chi^2 = 9.891$; $p = 0.007$), with a higher percentage of singles in the SMI than in both DD and SUD groups, and in the economic status ($\chi^2 = 26.651$; $p < 0.0001$), with a higher percentage of subjects receiving a disability pension in both DD and SMI groups compared to a higher percentage of active workers in SUD group (See Table 1).

With respect to the clinical variables (Table 2), we obtained main effects in number of daily medications ($F_{(2,102)} = 47.162$; $p = 0.0001$; $\eta_p^2 = 0.048$). The DD group was taking more daily medications than the SMI group ($p = 0.016$) and the latter more than the SUD group ($p = 0.0001$). Considering the type of psychotropic medication, both DD and SMI groups were taking more typical and atypical antipsychotics, mood stabilizers, anxiolytics and than the SUD group ($\chi^2 \geq 8.864$; $p \geq 0.012$).

Table 1 Sociodemographic data for the three groups of patients

Sociodemographics	DD (N = 35)	SMI (N = 35)	SUD (N = 35)
Age	37.91 ± 8.34 yr	38.63 ± 8.73 yr	36.37 ± 6.72 yr
Marital status			
Single	60.0%	85.7%	51.4%
Stable partner	11.4%	0%	8.6%
Married	2.9%	5.7%	11.4%
Separate/Divorced	11.5%	8.6%	28.5%
Widower	2.9%		
Number of children	0.49 ± 1.09	0.17 ± 0.51	0.51 ± 0.78
Living			
Alone	20.0%	8.6%	2.9%
Accompanied	77.1%	91.4%	88.6%
Years of study	9.14 ± 2.01	9.66 ± 2.44	9.58 ± 2.23
Economic situation			
Active	8.6%	14.3%	42.9%
Disability pension	65.7%	74.3%	17.1%
Unemployed	11.4%		20.0%
No income	8.6%	11.4%	20.0%

DD, Dual Diagnosis; *SMI*, Severe Mental Illness; *SUD*, Substance Use Dependence.

The DD group also had more suicidal attempts ($F_{(2,102)} = 4.630$; $p = 0.010$; $\eta_p^2 = 0.083$) than the SMI and SUD ($p = 0.010$) groups, without difference between the latter two groups.

A higher score in the Fagerström test was found in the DD and SUD groups ($F_{(2,102)} = 5.453$; $p = 0.006$; $\eta_p^2 = 0.097$) with higher daily consumption of cigarettes ($F_{(2,102)} = 4.405$; $p = 0.015$; $\eta_p^2 = 0.080$). Although the groups did not differ in number of medical comorbidities, the analysis by type of medical illness showed a higher prevalence of HIV infection in the SUD group ($\chi^2 = 5.816$; $p = 0.050$) and an increased incidence of triglycerides and cholesterol in the SMI group compared with the other two ($\chi^2 = 7.467$; $p = 0.024$). The CGI showed a worse clinical state in both DD and SMI groups ($F_{(2,102)} = 25.097$; $p = 0.0001$; $\eta_p^2 = 0.033$) compared to the SUD group ($p = 0.0001$). We did not find any differences in family psychiatric history, family SUD history and daily number of coffees or other beverages containing caffeine. No differences emerged between the DD and SMI groups in type of psychiatric diagnosis, age of onset of mental illness and years of illness duration.

Table 3 summarizes the data on substance consumption for both DD and SUD groups. They did not differ

Table 2 Clinical data for the three groups of patients

Clinical data	DD (N = 35)	SMI (N = 35)	SUD (N = 35)
Psychiatric Diagnosis (% = 100)			
Schizophrenia	45.7%	80%	
Bipolar Disorder	28.6%	14.3%	
Major Depression Disorder	25.7%	5.7%	
Age of psychiatric disorder onset	24.82 ± 7.47 yr	25.67 ± 8.07 yr	
Mean duration of illness (yr)	12.27 ± 7.81 yr	14.09 ± 8.66 yr	
Number of relatives with SUD	0.35 ± 0.69	0.06 ± 0.23	0.23 ± 0.59
Number of relatives with psychiatric disorder	0.65 ± 1.01	0.86 ± 0.87	0.49 ± 0.74
Number of suicidal attempts	1.60 ± 3.2	0.34 ± 0.68	0.34 ± 0.87
Number of medical comorbidities [a]	0.66 ± 1.05	0.57 ± 0.73	0.46 ± 0.78
Asthma/Allergy	11.4%	8.6%	2.9%
Triglycerides/Cholesterol	11.4%	25.7%	2.9%
Diabetes	2.9%	2.9%	2.9%
Obesity		2.9%	
Hypertension	2.9%	8.6%	2.9%
HIV	5.7%		14.3%
Hepatitis B or C	5.7%	2.9%	5.7%
Others	14.3%	2.9%	5.7%
Daily number of medications[a]	3.86 ± 1.83	3.03 ± 1.20	0.69 ± 1.10
Typical antipsychotics	20.0%	17.1%	2.9%
Atypical antipsychotics	57.0%%	60.0%	5.7%
Antidepressants	28.6%	25.7%	11.4%
Mood stabilizers	25.0%	31.4%	8.6%
Anxiolytics	40%	22.9%	8.6%
Other medication	31.4%	25.7%	20%
Clinical Global Impression (CGI)	4.69 ± 0.96	4.50 ± 0.74	3.26 ± 1.01
Daily number of cigarettes	18.34 ± 12.41	10.43 ± 12.44	14.74 ± 8.08
Fagerström score	5.11 ± 2.52	2.89 ± 3.38	3.86 ± 2.48
No dependence	14.3%	54.3%	17.1%
Low dependence	8.6%		20.0%
Moderate dependence	45.7%	25.7%	51.4%
High dependence	31.4%	20%	11.4%
Daily Number of coffees (cups)	1.77 ± 1.73	1.17 ± 1.44	1.66 ± 1.43
Other daily beverages with caffeine	0.86 ± 1.00	0.71 ± 1.04	0.91 ± 1.26

DD, Dual Diagnosis; *SMI*, Severe Mental Illness; *SUD*, Substance Use Dependence.
[a] Percentage will not equal 100 as each participant may suffer from more than one medical illness or take more than one medication.

in number or type of intake, number of substances used, type of substances used, months of abstinence, number of relapses, age of onset of substance use or duration of SUD disorder.

HRQOL comparisons

The results obtained in the 8 subscales and the two composite scales of the SF-36 are shown in Table 4, as well as the contrasts among groups. The analyses provided main significant differences in most of the subscales, except for Bodily Pain. The Health Transition item and the composite scale MCS have also proved significant.

The post-hoc analysis revealed a worse score for the DD group in most of the subscales except in Role-Physical and Role-Emotional compared to the SUD group. The DD also obtained worse scoring in the Health Transition item and in the MCS scale compared

Table 3 Substance Use data in Dual Diagnosis (DD) and Substance Use Dependence (SUD) patients

Substance use data	DD (N = 35)	SUD (N = 35)
Type of intake		
One substance	25.7%	20%
Two substances	25.9%	22.9%
Polydrug use	48.4%	57.1%
Number of substances used	2.80 ± 1.79	3.14 ± 1.53
Substance Abuse/Dependence [a]		
Cocaine	100%	100%
Cannabis	54.3%	48.6%
Alcohol	71.4%	68.6%
Ecstasy	28.6%	25.7%
Hallucinogens	17.1%	14.3%
Opioids	22.9%	28.6%
Sedatives	5.7%	2.9%
Months of abstinence	13.41 ± 14.31	9.14 ± 5.07
Number of relapses	1.35 ± 2.52	0.54 ± 1.03
Age of intake onset (yr)	19.82 ± 7.32	20.00 ± 8.27
Mean duration of SUD (yr)	16.85 ± 7.32	15.60 ± 7.16

[a] Percentages will not equal 100 as each participant may take more than one substance of abuse.

to the SUD group. The DD group also scored lower than the SMI group in most of the HRQOL domains except for General Health and the Health Transition item. The SUD and SMI groups only differed in Vitality, General Health and in the Health Transition item, without differences in the rest of the scales (see Table 4).

In view of significant group differences on certain clinical variables, especially relevant in the DD group, we carried out the analyses again introducing number of daily medication, suicidal attempts and number of daily cigarettes as covariates. The significance was maintained for the scales of Physical Functioning ($F_{(2,102)} = 4.924$; $p = 0.009$; $\eta^2_p = 0.082$), Role - Emotional ($F_{(2,102)} = 4.592$; $p = 0.012$; $\eta^2_p = 0.088$), Social Functioning ($F_{(2,102)} = 3.012$; $p = 0.050$; $\eta^2_p = 0.060$), Vitality ($F_{(2,102)} = 9.818$; $p = 0.0001$; $\eta^2_p = 0.171$) and the Health Transition item ($F_{(2,102)} = 8.556$; $p = 0.0001$; $\eta^2_p = 0.153$) with power sample values of ≥ 0.760 in all cases. There were again no differences in the subscale of Bodily Pain and the PCS scale. Previous main differences in Role - Physical, Mental Health, General Health subscales and in the MCS disappeared when the covariates were introduced.

The contrast *a posteriori* only maintained the differences between the DD and SUD groups in Physical Functioning ($p = 0.031$), Vitality ($p = 0.0001$) and in the Health Transition item ($p = 0.004$), with a better score in the SUD group. This group also presented a better score in Vitality ($p = 0.008$) and in the Health Transition item ($p = 0.0001$) with respect to the SMI group. The differences between the DD and SMI groups were maintained for Physical Functioning ($p = 0.015$), Role - Emotional ($p = 0.016$) and Social Functioning ($p = 0.050$), with lower scores in the DD group.

The comparison of the group means with the Spanish normative data [23] showed that, although all the groups

Table 4 Mean and standard deviation in the SF-36 and results of the MANOVAs

				MANOVA			
SF-36	DD (N = 35)	SMI (N = 35)	SUD (N = 35)	F	Effect size	Power sample	Contrasts [a]
Subscales							
Physical Functioning	86.40 ± 14.32	93.67 ± 9.23	96.00 ± 8. 20	7.06**	0.12	0.92	DD < SMI, SUD
Role- Physical	70.31 ± 39.36	92.64 ± 24.25	76.71 ± 40.58	3.50*	0.06	0.64	DD < SMI/DD = SUD
Role-Emotional	46.87 ± 44.69	83.32 ± 34.09	68.55 ± 39.57	7.04**	0.12	0.92	DD < SMI/DD = SUD
Social Functioning	60.56 ± 28.77	82.05 ± 26.98	80.71 ± 24.87	6.58**	0.11	0.90	DD < SMI, SUD
Mental Health	50.12 ± 19.27	62.47 ± 18.89	65.60 ± 17.22	6.47**	0.11	0.89	DD < SMI, SUD
General Health	50.46 ± 20.69	57.47 ± 21.07	73.74 ± 14.18	13.60**	0.21	0.99	DD, SMI < SUD
Bodily Pain	67.65 ± 25.24	77.32 ± 27.35	72.34 ± 25.95	1.12	0.02	0.24	
Vitality	42.19 ± 16.36	51.91 ± 20.59	68.00 ± 16.54	17.76**	0.26	1.00	DD, SMI < SUD
Health Transition Item	63.28 ± 31.09	63.97 ± 24.76	92.14 ± 20.80	14.03**	0.22	0.99	DD, SMI < SUD
Composite Scales							
PCS	50.31 ± 9.18	52.82 ±7.11	53.66 ± 7.80	1.54	0.03	0.32	
MCS	34.61 ± 13.02	44.03 ± 12.49	45.42 ± 10.63	7.82**	0.13	0.94	DD < SMI, SUD

DD, Dual Diagnosis; *MCS*, Mental health Component Summary; *PCS*, Physical health Component Summary; *SMI*, Several Mental Illness; *SUD*, Substance Use Dependence.
[a] We detail only the significant contrasts.
* $p < 0.05$; ** $p < 0.001$.

generally presented lower scores, this was more marked in the DD group. The DD scores in the scales of Social Functioning, Role - Emotional, Mental Health, General Health and Vitality were below the norm. The SMI group presented one standard deviation below the norm only in the Vitality scale and the SUD group did not present scores below the norm in any scale (see Figure 2). Regarding the composite scales, the DD group was the only one that was one standard deviation below the norm in the MCS scale (see Figure 3).

Factors contributing to HRQOL

The correlational analysis in the whole sample did not provide any significant association between the score in the PCS scales and the sociodemographic and clinical variables. In contrast, the score in the MCS scale showed negative associations with the number of suicidal attempts ($r = -0.268$; $p = 0.007$), medication ($r = -0.303$; $p = 0.002$) and daily number of coffees ($r = -0.209$; $p = 0.036$). The correlational analysis taking into account each group of patients only provided a significant association in the DD group between the MCS scale and the daily number of coffees ($r = -0.497$; $p = 0.004$). The suicidal attempts and the medication did not reach significance in any group.

These three variables were later introduced as independent variables in a lineal regression analysis with the whole sample and the MCS scale as a dependent variable. The analysis of the general model was significant ($F = {}_{(3,102)} = 6.536$; $p = 0.0001$), explaining 14.2% of the variance in the MCS scale. The results showed that daily number of medications was related to the mental health component of the HRQOL (see Table 5). When the same analysis was done for each group, the general model only maintained the significance in the DD group ($F_{(3,32)} = 4.224$; $p = 0.010$), explaining 21.8% of the variance, where the only significant variable was daily consumption of coffee (see Table 5).

Discussion

As we expected, the DD group presented worse HRQOL scores in most of the scales compared to the other two groups, especially in the mental health domain assessed by the MCS scale. In contrast, the groups did not differ in the scale of Bodily Pain or in Physical functioning (PCS). In general, the SUD group had better scores in most of the scales of the SF-36, with marked differences with respect to the DD group, while the SMI group obtained intermediate scores.

The introduction of the covariates suicidal attempts, medication and daily consumption of cigarettes as variables that may be potentially associated to the HRQOL and QOL [34-36] kept the worst HRQOL scores in the DD group except for Mental Health, General Health and MCS, where the three groups had similar scores. After the adjustment, the SUD group showed a better feeling of vitality and energy, and a better perception of the evolution of the health state with respect to the previous year (Health Transition item), compared to the SMI and DD groups. The SUD group also showed a better perception of the physical health state compared to the DD, while there were no differences in the rest of the scales. These data suggest that the SUD group shows a lower functional disability, and this could be related to a better community functioning, as suggested by the fact that in this group there is a higher percentage of subjects who are active workers.

Thus, suicide attempts, number of daily medication and daily cigarette consumption appear to modulate the differences between the DD and SUD groups regarding HRQOL expression. These variables should be taken into account in further research, since they may be

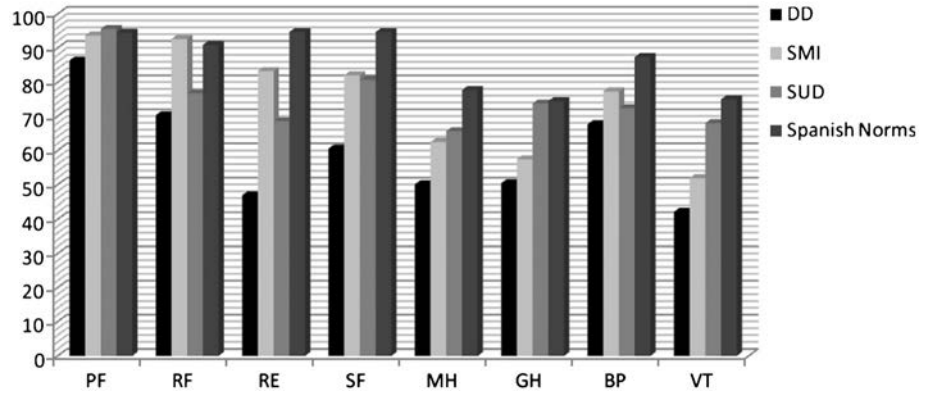

Figure 2 Mean scores for the three groups of patients and the Spanish norms in the 8 scales of the SF-36. PF, Physical Functioning; RF, Role – Physical; RE, Role – Emotional; SF, Social Functioning; MH, Mental Health; GH, General Health, BP, Bodily Pain; VT, Vitality.DD, Dual Diagnosis; SMI, Severe Mental illness, SUD, Substance Use Dependence.

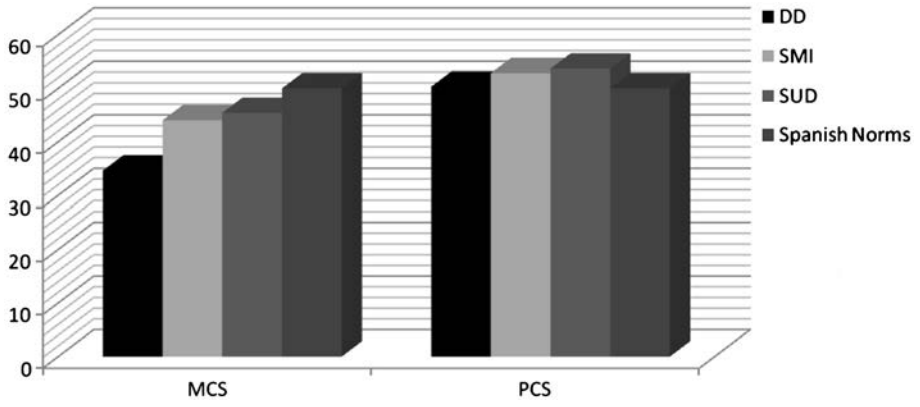

Figure 3 Mean scores for the three groups of patients and the Spanish norms in the MCS and the PCS. MCS, Mental Health Component Summary; PCS, Physical Component Summary. DD, Dual Diagnosis; SMI, Severe Mental Illness, SUD, Substance Use Dependence.

determinant in DD scores on scales assessing the mental domain of HRQOL. However, after the adjustment on these clinical variables, the DD group continued showing a lower degree of physical and emotional health, with higher perceptions of limitations in daily social and occupational life, as well as a higher feeling of tiredness and exhaustion compared with the SMI group. This result, in agreement with the work by Kalman et al. [17], may highlight the moderating negative effect of substance use on the relationship between psychiatric disorder and mental HRQOL in patients with DD.

This is also in line with the work by Kilbourne et al. [16], who observed a negative association between substance consumption and the mental domain of the HRQOL in bipolar patients, even after controlling for the depressive and manic symptoms of the disorder. Our results suggest a major detrimental effect on HRQOL in people with a psychiatric disorder with comorbid SUD than in those without comorbid SUD or other psychiatric disorders, despite clinical severity and other variables related to substance use, such as type of substance used or time of abstinence. Although our results agree with several previous studies [15-19], most of them only compared DD and SUD patients, and they were lacking the specific impact of the mental disorder related to HRQOL in DD patients.

Regarding factors associated to HRQOL, the MCS scale was negatively related with the number of suicidal attempts, daily number of medication and daily number of coffees. When there were more suicidal attempts, more daily medication intake and/or a higher daily number of coffees, the score in the MCS scale was lower. These variables were related to a worse state in the mental domain of the HRQOL. However, the separate analysis by groups showed that the model was met only in the case of DD patients, and that caffeine consumption was the best predictive variable. Although this result indicated that in DD patients the high number of coffees taken is related to a higher affectation in the mental domain of the HRQOL, coffee consumption in this group was not higher than in the SMI or SUD groups.

Caffeine consumption, as well as other methylxanthines, has long been associated with psychiatric illness, possibly due to its beneficial impact on extrapyramidal side effects of antipsychotic medication through dopaminergic agonism in the nigrostratial pathways [37]. However, caffeine consumption may have detrimental effects on DD patients through dopaminergic agonists in other brain pathways

Table 5 Lineal regression for the MCS for the total sample and for the Dual Diagnosis group

MCS	Adjusted R^2	IV	ß standardized	p values	Tolerance	VIF
TS (N =105)	0.142	Coffee[a]	−0.179	0.059	0.975	1.025
		Medication [b]	−0.265	0.006	0.960	1.042
		Suicidal Attempts	−0.188	0.052	0.937	1.067
DD (N = 35)	0.218	Coffee[a]	−0.468	0.007	0.975	1.026
		Medication [b]	−0.171	0.290	0.997	1.003
		Suicidal Attempts	−0.134	0.413	0.997	1.023

DD, Dual Diagnosis; *IV*, Independent Variables; *MCS*, Mental Health Component Summary; *TS*, Total sample; *VIF*, Variance Inflation Factor.
[a] Daily number of coffees.
[b] Daily number of medications.

such as the mesolimbic and the mesocortical, resulting in an increase of psychotic symptomatology. Since intraindividual variations have been described in the psychoactive effects of caffeine in the general population [38], our results point to the possibility that the DD population is the most sensitive one to the effects of caffeine, even under moderate doses compared to the other two groups.

Different hypotheses could explain this result. One explanation could be that the DD group may present different genetic polymorphisms from the general population, both in metabolic enzymes and in brain receptors to the effects of caffeine. A more plausible explanation may be that caffeine covaries with other risk factors associated with the DD group: more suicidal attempts, higher daily medication intake, and higher cigarette consumption. Thus, caffeine intake has been associated with higher cigarette consumption [39], and the consumption of both substances has been in turn associated with a higher risk of suicidal attempts in the psychiatric population [40,41] and to a lower efficacy of the pharmacological treatment [39,40]. All these factors, at the same time, have been directly or indirectly associated with a worse QOL and HRQOL [34-36,42,43].

Further research is needed in this area, exploring the HRQOL state in the DD population, taking into account the consumption of nicotine and caffeine in order to explore their impact on HRQOL and with which risk factors their effects may be associated. Likewise, studying the QOL/HRQOL in DD women is of great interest, since there is evidence of a worse state in the mental domain in female substance users [21,44]. Thus, given the differences in HRQOL state between sexes, it should be noted that our results may be representative only of male DD patients.

Strengths and limitations of the study

In our study, we bring improvements over previous research on this topic. The group comparisons to the Spanish normative data have provided evidence of the degree of impairment in the assessed domains of HRQOL. We also bring new data on the major factors associated with DD and lower mental HRQOL such as suicidal attempts, cigarette smoking, daily caffeine intake and number of prescribed medications. All these clinical factors are rarely taken into account in previous studies. Likewise, the control of abstinence time by urinalysis and the calculations of power sample in all analyses are important methodological factors preventing the influence of possible intermediate variables and their control has provided strength to our results.

However, the limitations of the study should also be noted. Although the cross-sectional study design allowed us to ascertain the weight of each psychiatric condition in HRQOL of DD, it did not allow us to investigate causal relationships between substance disorders, psychiatric comorbidities and HRQOL. We failed to analyze the independent effects of different types of substances on HRQOL because a vast percentage of subjects in our sample were polyconsumers. Another important limitation is that the study was based on clinically acquired and partially retrospective self-reported data that may have been subject to recall bias, including information about suicidal acts and substance intake. The heterogeneity of the psychiatric disorders included and the relatively small sample size might have affected the representativeness of the sample. Further, the inclusion of only males makes difficult to interpret our findings as specific characteristics of the subjects suffering from DD since the results cannot be extrapolated to female gender. Noteworthy, we did not include the information of the subjects who dropped out the study or were excluded, so it is unknown whether the results are subject to bias due to the exclusion of these subjects. Finally, all subjects in our sample were contemplating treatment maybe affecting the generalisability of the results to those subjects who were not considering treatment.

Conclusions

Overall, our findings show a worse state in the mental domain of the HRQOL in the DD patients with respect to the other two groups without comorbidity and to the general population. Suicidal attempts, a higher intake of daily medication and caffeine consumption appear as factors associated to the impairment in the mental domain of the HRQOL, especially in the DD group. The systematic assessment of the HRQOL in DD patients should allow us to improve our knowledge of its associated factors. It may also be a useful tool in the detection of areas of specific assistance to the goals of treatment planning, thereby improving the effectiveness of the intervention and the assessment of the results.

Abbreviations

BP: Bodily Pain; CGI: Clinical Global Impression; DD: Dual Diagnosis; GH: General Health; HT item: Health Transition on Time item; MCS: Mental health Component Summary; MH: Mental health; PCS: Physical Health Component Summary; PF: Physical Functioning; RE: Role-Emotional; RF: Role-Physical; SF: Social Functioning; SF-36: Short-Form 36 Item Health Survey; SMI: Severe Mental Illness; SUD: Substance Use Dependence; VT: Vitality.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

AA conceived the original idea for the study, sought funding, wrote the protocol and managed the day to day running of the study. IB collected the data of the sample and carried out all data analyses. The manuscript was written by IB and AA with input from GP. All authors have approved the final manuscript.

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References

1. Zubaran C, Foresti K: **Quality of life and substance use: concepts and recent tendencies.** *Curr Opin Psychiatr* 2009, **22:**281–286.
2. Schaar I, Öjehagen A: **Predictors of improvement in quality of life of severe mentally ill substance abusers during 18 months of co-operation between psychiatric and social services.** *Soc Psych Psych Epid* 2009, **38:**83–87.
3. Meijer CJ, Koeter MWJ, Sprangers MAG, Schene AH: **Predictors of general quality of life and the mediating role of health related quality of life in patients with schizophrenia.** *Soc Psych Psych Epid* 2009, **44:**361–368.
4. Eack SM, Newhill CE: **Psychiatric symptoms and quality of life in schizophrenia: a meta-analysis.** *Schizophrenia Bull* 2007, **33:**1225–1237.
5. Brissos S, Videira-Dias V, Carita AI, Martínez A: **Quality of life in bipolar type I disorder and schizophrenia in remission: clinical and neurocognitive correlates.** *Psychiat Res* 2008, **160:**55–62.
6. Kao YC, Liu YP, Chou MK, Cheng TH: **Subjective quality of life in patients with chronic schizophrenia: relationships between psychosocial and clinical characteristics.** *Compr Psychiat* 2011, **52:**171–180.
7. Samuli I, Saarni SI, Viertiö S, Perälä J, Koskinen S, Lönnqvist J: **Quality of life of people with schizophrenia, bipolar disorder and other psychotic disorders.** *Brit J Psychiat.* 2010, **197:**386–394.
8. Lozano OM, Domingo-Salvany A, Martínez-Alonso M, *et al*: **Health-related quality of life in young cocaine users and associated factors.** *Qual Life Res* 2008, **17:**977–985.
9. González-Saiz F, Lozano O, Iraurgi I: **Measuring the impact of psychoactive substance on health-related quality of life: an update.** *Curr Drug Abuse Rev* 2009, **2:**5–10.
10. Pyne JM, Tripathi S, French M, McCollister K, Rapp RC, Booth BM: **Longitudinal association of preference-weighted health-related quality of life measures and substance use disorder outcomes.** *Addiction* 2011, **106:**507–515.
11. Bebout RR, Drake RE, Xie H, McHugo GJ, Harris M: **Housing status among formerly homeless dually diagnosed adults.** *Psychiat Serv* 1997, **48:**936–941.
12. Drake RE, Osher FC, Wallach MA: **Homelessness and dual diagnosis.** *Am Psychol* 1991, **46:**1149–1158.
13. Rudolf H, Watts J: **Quality of life in substance abuse and dependency.** *Int Rev Psychiatry* 2002, **14:**190–197.
14. Lamb HR, Lamb DM: **Factors contributing to homelessness among the chronically and severely mental ill.** *Hosp Community Psychiatry* 1990, **41:**301–305.
15. Singh J, Mattoo SK, Sharan P, Basu D: **Quality of life and its correlates in patients with dual diagnosis of bipolar affective disorder and substance dependence.** *Bipolar Disord* 2005, **7:**187–191.
16. Kilbourne AM, Perron BM, Mezuk B, Welsh D, Ilgen M, Bayer MS: **Co-occurring conditions and health-related quality of life in patients with bipolar disorder.** *Psychosom Med* 2009, **71:**894–900.
17. Kalman D, Lee A, Chan E, *et al*: **Alcohol dependence, other psychiatric disorders, and health related quality of life: a replication study in a large random sample of enrollees in the veterans health administration.** *Am J Drug Alcohol Abuse* 2004, **30:**473–487.
18. Bizzarri J, Rucci P, Vallotta A, *et al*: **Dual diagnosis and quality of life in patients in treatment for opioid dependence.** *Subst Use Misuse* 2005, **40:**1765–1776.
19. Fassino S, Abbate-Daga G, Delsedime N, Rogna L, Boggio S: **Quality of life and personality disorders in heroin abusers.** *Drug Alcohol Depen* 2004, **76:**73–80.
20. Astals M, Domingo-Salvany A, Castillo-Buenaventura C, *et al*: **Impact of substance dependence and dual diagnosis on the quality of life of heroin users seeking treatment.** *Subst Use Misuse* 2008, **43:**612–632.
21. Garg N, Yates WR, Jones R, Zhou M, Williams S: **Effects of gender, treatment site and psychiatric comorbidity on quality of life outcome in substance dependence.** *Am J Addict* 1999, **8:**44–54.
22. Wade D, Harrigan S, McGorry PD, Burgess PM, Whealan G: **Impact of severity of substance use disorder on symptomatic and functional outcome in young individuals with first-episode psychosis.** *J Clin Psychiat* 2007, **68:**767–774.
23. Alonso J, Regidor E, Barrio G, Prieto L, Rodríguez C, de la Fuente L: **Valores poblacionales de referencia de la versión española del cuestionario de salud SF-36.** *Med Clin* 1998, **111:**410–416.
24. American Psychiatric Association: *Diagnostic and statistical manual of mental disorders*. 4th edition. Washington, DC: American Psychiatric Association; 2002.
25. First MB: *Entrevista Clínica Estructurada para los trastornos del eje I del DSM-IV-SCID-I*. Barcelona: Masson; 1999.
26. Heatherton TF, Kozlowski LT, Frecker RC, Fagerström KO: **The Fagerström test for nicotine dependence: a revision of the Fagerström tolerance questionnaire.** *Brit J Addiction* 1991, **86:**1119–1127.
27. National Institute of Mental Health: **CGI Clinical Global Impression**. In *Assessment manual for psychopharmacology*. Edited by Guy W, Bonato RR. Rockville: 1976:217–222.
28. Ware JE, Sherbourne CD: **The MOS 36-item short-form health survey (SF-36). I. conceptual framework and item selection.** *Med Care* 1992, **30:**473–483.
29. Leese M, Schene A, Koeter M, *et al*: **SF-36 scales, and simple sums scales, were reliable quality of life summaries for patients with schizophrenia.** *J Clin Epidemiol* 2008, **61:**588–596.
30. Newnham EA, Harwood KE, Page AC: **Evaluating the clinical significance of responses by psychiatric inpatients to the mental health subscales of the SF-36.** *J Affect Disorders* 2007, **98:**91–97.
31. Morales-Manrique CC, Castellano-Gómez M, Valderrama-Zurián JC, Aleixandre-Benavent RA: **Medición de la calidad de vida e importancia de la atención a las necesidades autopercibidas en pacientes drogodependientes.** *Trastornos Adictivos* 2006, **8:**212–221.
32. Vilagut G, Valderas JM, Ferrer M, Garin O, López-García E, Alonso J: **Interpretación de los cuestionarios de salud SF-36 y SF-12 en España: componentes físico y mental.** *Med Clin* 2008, **130:**726–735.
33. Huberty CJ: **A history of effect sizes indices.** *Educ Psychol Meas* 2002, **62:**227–240.
34. Bebbington PE, Angermeyer M, Azorin JM, Marwaha S, Marteau F, Tourni M: **Side-effects of antipsychotic medication and health-related quality of life in schizophrenia.** *Acta Psychiat Scand* 2009, **119:**22–28.
35. Laaksnonen M, Rahkonen O, Martikainen P, Karvonen S, Lahelma E: **Smoking and SF-36 health functioning.** *Prev Med* 2006, **42:**206–209.
36. Ponizovsky AM, Grinshpoon A, Levav I, Ritsner MS: **Life satisfaction and suicidal attempts among persons with schizophrenia.** *Compr Psychiat* 2003, **44:**442–447.
37. Casas M, Torrens M, Duro P, Pinet C, Alvarez E, Udina C: **Utilisation des méthylxanthines, caffeine et théophylline dans le traitement des troubles extrapyramidaux secondaires aux traitements par les neuroleptiques. Déroulement d'une hyphotèse thérapeutique.** *L'encephale* 1989, **15:**177–180.
38. Paton C, Beer D: **Caffeine: the forgotten variable.** *Int J Psychiat Clin* 2001, **5:**231–236.
39. Lara D: **Caffeine, mental health, and psychiatric disorders.** *J Alz Dis* 2010, **20:**239–248.
40. Baethge C, Tondo L, Lepri B, Baldessarini RJ: **Coffee and cigarette use: association with suicidal acts in 352 Sardinian bipolar disorder patients.** *Bipolar Disord* 2009, **11:**494–503.
41. Keizer I, Gex-Fabry M, Eytan A, Bertschy G: **Smoking in psychiatric inpatients: association with working status, diagnosis, comorbid substance use and history of suicide attempts.** *Addict Behav* 2009, **34:**815–820.
42. Alonso J, Croudace T, Brown J, *et al*: **Health-related quality of life (HRQL) and continuous antipsychotic treatment: 3-year results from the Schizophrenia Health Outcomes (SOHO) Study.** *Value Health* 2009, **12:**536–543.

43. Kasckow J, Montross L, Golshan S, *et al*: **Suicidality in middle aged and older patients with schizophrenia and depressive symptoms: Relationship to functioning and quality of life.** *Int J Geriatr Psych* 2007, **22:**1223–1228.
44. Lev-Ran S, Imtiaz S, Taylor BJ, Shield KD, Rehm J, Le Foll B: **Gender difference in health-related quality of life among cannabis users: results from the national epidemiologic survey on alcohol related condictions.** *Drug Alcohol Depen* 2012, **123:**190–200.

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6. DISCUSSION

6.1 Reviewing the neuropsychological aspects of Dual Diagnosis: Needs of future research

After an extensive bibliographic review that arose to our first study, we summarized three important factors, among other methodological considerations, that may account for the mixed findings across the studies: the patients' age, the cognitive domain assessed and the type of substance of abuse. Thus, older patients show a trend toward a worse cognitive impairment than younger ones, possibly due to the long-term cognitive damage of substance use, with a pronounced deficit in memory an attention. Executive functioning and speed of processing are often well preserved in younger schizophrenic users in order to obtain illegal substance of abuse. Alcohol and cocaine are associated to a worse cognitive performance than the use of cannabis and polysubstance, mainly affecting declarative memory. Potvin et al. (2012) highlighted these three factors in a later review about neurocognition and dual diagnosis, proposing interacting effects among these factors. Therefore, younger patients usually intake more than one substance and they are often cannabis users, while the older ones are alcohol users and have more cognitive deficits due to the influence of age and alcohol use, especially in memory functioning. This consideration is of great importance and must be taken

into account in the selection of the samples in future works aiming the neurocognition in Dual Diagnosis (DD).

Other methodological considerations that should be taken into account in the selection of the samples are the psychiatric diagnosis and, whenever possible, the diagnostic subtype, as well as the sample size and gender. Regarding substance use disorder (SUD) it is necessary to take into consideration if they are abusers or dependents, the main substance of choice, the time of abstinence in terms of current or former users, verified with valid procedures such urinalysis; as well as both duration and severity of the disorder. The age of onset of consumption is important in order to determine differential effects on cognition, when the substance intake starts before certain brain regions reach the whole maturation. The standardization of an exhaustive neuropsychological battery for an extensive assessment of main cognitive domains, would eliminate part of the divergences on the current data due to different instruments of choice. Similarly, a suitable clinical assessment considering the psychopharmacologic medication and the intake of both caffeine and nicotine as substances affecting the cognitive performance, could improve the methodological deficiencies providing major strenghts on the results.

Further research is required, which needs to take into account the methodological considerations previously mentioned and controlling the confounding factors on cognitive performance in subjects suffering DD. More studies should be developed in schizophrenia and even more in bipolar disorder, including large samples and clarifying possible subtypes of dual diagnosis, according to the psychiatric disorder and type of substance consumed. Longitudinal studies are needed to explore both evolution of cognitive deficits interacting with age and the extent of cognitive recovery interacting with abstinence time. Future studies including neurobiological parameters such as structural and functional magnetic resonances and/or evoked potentials, as well as genetic studies, may help to a better understanding of the neuropsychology of these patients and their biological ties into developing this disorder.

It is known that cognitive deficit is related to biological vulnerability of schizophrenia and bipolar disorder, being a better predictive factor of the functional outcome than positive and negative symptomatology. It is also related to both psychiatric and substance relapses, the treatment adherence and its results. So, the study of cognitive functioning becomes of great interest in the DD field. All together suggest the need of the neuropsychological assessment as a measure of severity and prognoses of the disorder that may, in turn, predict the treatment outcomes contributing to the development of new therapeutic targets. Cognitive

rehabilitation therapies, in those cases that may be necessary, could help to improve the course of the disorder and prevent the relapses and suicidal attempts. Similarly, the early prevention of major cognitive deficits accelerated in later ages, would improve the psychosocial functioning and quality of life of these patients decreasing the high morbidity and social costs involved in the treatment of DD.

6.2 Executive functioning in schizophrenia and/or cocaine dependence

6.2.1 Testing the vulnerability hypothesis

Since our review points out the differential impact on cognitive domains depending on the main substance of abuse, in studies carried out with mainly schizophrenic subjects, we decided to conduct a study focused on executive functioning in schizophrenic individuals, mainly cocaine dependents, due to the lack of studies focused in this subject. The impact of comorbidity between SZ and cocaine deserve greater attention since it there had been described rates of comorbidity ranging between 20 to 50% (Regier et al., 1990).

Although more executive impairment might be expected in subjects suffering both conditions given the common front-subcortical dysfunction caused by both disorders, some authors find better executive functioning in SZ+ compared to SZ- (Carey et al., 2003; Herman, 2004; Joyal et al., 2003; Smelson et al., 2003; Thoma et al., 2007; Thoma & Daum, 2008). The authors who find a higher cognitive functioning in SZ+, often defend a better premorbid adjustment compared to SZ-. Thus, higher premorbid executive functioning together with higher social skills, are necessary to keep the SUD and facilitate the acquisition of illegal substance, even more those less accessible in the immediate environment such as cocaine (Schnell et al., 2009). The current scientific literature shows that cognitive deficits are endophenotypes of SZ (Snitz et al., 2006) and are related to psychotic biological vulnerability. Therefore, a higher cognitive performance on the SZ+ suggests less biological vulnerability compared to those SZ-, who develop the disorder without any additional trigger (Hall, 1998). This is in the line of a less biological vulnerability in dual diagnosis patients, as it is stated by one of the most important ethiological models. Further support for this hypothesis is: (i) an onset of substance use preceding the onset of SZ (ii) an earlier age of onset of SZ (iii) a better cognitive functioning (iv) fewer first-degree relatives suffering a psychiatric disorder compared to SZ-.

In order to test the vulnerability hypothesis, we evaluate the executive functions linked to both dorsolateral and orbitofrontal prefrontal cortex, in

patients with SZ who were depending from cocaine. They were compared with SZ- and COC groups. A higher performance on frontal related functions in SZ+ than SZ-, being very similar to the COC group, may represent a coherent picture of substance users as a specific subgroup of SZ, with better premorbid adjustment and less biological vulnerability. After the groups were matched on marital status, economic situation, clinical severity, number of prescribed medication and nicotine consumption, the results were close to those expected.

As we expected, the SZ+ and the COC group, showed better executive functioning sensitive to dorsolateral prefrontal function compared with the SZ-, with little difference between them. This is in agreement with the idea of a better executive functioning in SZ+ patients to obtain illegal drugs, especially those more difficult to get, such as cocaine (Schnell et al., 2009). Regarding decision making linked to orbitofrontal functioning, the results are less clear. While the COC group shows a better performance than the SZ- group, the SZ+ did not differ from the other two groups. However, a qualitative appraisal on the performance of the three groups reveals a worse execution in the SZ+. Although the quantitative analysis did not reveal a worse execution of SZ+ patients compared to the other two, the large variance of net scores obtained in the IGT could had eliminated the statistical difference between groups. This qualitative appraisal could suggest, at least under a speculative point of view, that a worse decision making may be related to a predisposition to substance use in SZ+ individuals.

It should be noted that our results only partially support the vulnerability hypothesis. Although we found a higher performance on the executive functions related to dorsolateral prefrontal functioning, and an onset of substance use preceding the onset of SZ in all SZ+ individuals, other premises in order to confirm the hypothesis were not supported by our results. Unexpectedly, the SZ+ neither presented an earlier onset of the disease nor more family psychiatric history compared to the SZ- group.

However, several other studies could not find an earlier onset of the disorder in the SZ+ individuals (Boydell et al., 2007; DeRosse et al., 2010; Sevy et al., 2010; Veen et al., 2004). In agreement with Schnell et al. (2009) it is possible that the SZ+ have earlier noticed their symptoms, but they may have developed relatively efficient strategies to deal with their symptoms before being referred to psychiatric services for the first time. This is in the line of the assumption of a better executive functioning in SZ+ individuals in order to handle their demands more successfully than SZ-. In the other hand, the lack of difference in family psychiatric history in SZ- compared to SZ+, could be explained by patient's self-reported data as a weak source of information.

Taken together, our results show higher dorsolateral prefrontal related functions in the SZ+ and COC groups than in the SZ- group, as well as an onset of SUD before the onset of SZ according to the lower biological vulnerability hypothesis. However, the lack of differences in the orbitofrontal functioning, age of psychosis onset and family psychiatric history between SZ+ and SZ-, could work as arguments against the hypothesis.

Despite this, the most probable reason of a better executive functioning in SZ+ is that their lower threshold to develop psychosis resulting in better cognitive abilities, whereas the SZ- subjects may have other neurobiological vulnerabilities like subtle brain alterations, resulting in cognitive deficits. It is important to highlight that substance intake may trigger psychosis through disruptions in the dopaminergic system in patients with lower biological vulnerability to develop the disorder and therefore, with higher cognitive abilities, rather than improve the cognition since the detrimental effects of substance use on cognition have been demonstrated in several studies. The development of future genetic studies may help to understand the biological vulnerability to psychosis in schizophrenic patients with and without comorbid SUD.

6.2.2 The influence of the age onset of consumption on executive functioning

Regarding the influence of age of onset of consumption on executive functioning in individuals with cocaine dependence in remission, with and without comorbid SZ, it should be noted that our study is one of the first studies exploring this effect, except for the work of Jockers-Scherubl et al. (2007) that did so in SZ+ individuals abusing cannabis. As those authors did, we considered earlier consumers (onset of consumption 16 years old or younger) and later consumers (onset of consumption 17 years old or older). Given that cocaine dependence mainly affects both catecholaminergic and dopaminergic systems (Block, Erwin & Ghoneim, 2002; Krystal et al., 2005), we expected that substance use before these systems reach maturation, will lead to more deleterious cognitive deficits than consumers who started after the age of 17, when these systems have already concluded their maturation (Lambe, Krimer & Goldman-Rakic, 2000; Sundram, 2006). We also expected that these effects on earlier consumers would be more obvious on executive functioning, because the prefrontal cortex, underlying the maturation of higher-order cognitive functions, ends their maturation process in late adolescence, after the age of 17, through pruning of exuberant synapses and myelination of axons (Casey, Giedd & Thomas, 2000; Sowell, Delis, Stiles & Jernigan, 2001; Woo & Crowell, 2005). Therefore, these higher order cognitive functions are expected to have a greater impact by earlier

use of drugs. In this line, previous studies with samples comprised by individuals with cannabis use without psychiatric comorbidity, found lasting neuropsychological effects on visual scanning (Ehrenreich et al., 1999), lower verbal IQ (Pope et al., 2003) and less grey matter relative to whole brain (Wilson et al., 2000) in earlier consumers (16 years old or younger), than those who have initiated the consumption after the age of 17. However, when we analyzed the effect of age of onset of substance use, contrary to our initial expectations, earlier SZ+ consumers, performed better in TMT-B and in trials to first category in WCST. Similarly, the analysis between groups and age of onset of substance use show interacting effects only in TMT-B with a better performance in earlier consumers than in later ones.

Although we were not sure about the reasons why a better cognitive set-shifting occurs in earlier SZ+ consumers than in later ones, there could be some plausible explanations.

Even though development of higher-order association cortices including parietal, superior temporal and prefrontal regions, strongly related to maturation of cognitive functions (Casey et al., 2000; Sowell et al., 2001), occurs during late adolescence, the preadolescent brain may have greater resiliency capacity during this remodeling brain period, enabling a more complete recovery (Schweinsburg, Brown & Tapert, 2008), at least before the SZ onset. Only studies that include structural and functional neuroimaging measures, could clarify the question of a grater neuroplasticity in younger SZ+ patients. Another explanation would be the differential impact of certain drugs in specific regions of the brain, given that most of the subjects in our sample were polyconsumers. Unfortunately, we were not able to study the specific impact of each substance, due to the small sample size. Nevertheless, it should be noted that the SZ+ group showed more prevalence of cannabis use than the COC group. Jockers-Scherubl et al. (2007) found a certain preservative effect of cannabis use in those SZ+ patients who started the consumption before the age of 16. In this line, some authors speculate that cannabis may restore frontal dysfunctions in SZ patients (Pomarol-Clotet et al., 2008). These effects could take place over a certain stage of development in which the brain has greater plasticity to model the effects of drug use. However, this explanation is in conflict with well-established findings of a negative impact of cannabis use in SZ (D'Souza et al., 2005; D'Souza, Sewell & Ranganathan, 2009). Hence, it does not seem to explain our results given that we performed again the analyses controlling the influence of cannabis use, without getting appreciable differences to the previous results.

Despite the use of the Bonferroni correction method in statistical analysis, in order to avoid the occurrence of Type I error, the little sample size when exploring the effect of age of substance use, could induce this type of error, explaining so the counterintuitive nature of this result. However, it should be noted that this aim had an exploratory character in our study.

Future studies should be conducted to determine the influence of substance use in the brain of SZ+ patients, depending on the age of onset of intake. This knowledge could have many implications for the prevention of substance use in patients at risk of developing SZ in later ages.

6.3 Age-related changes in neuropsychological performance in schizophrenia and/or cocaine dependence

6.3.1 Differences in attention, verbal memory and speed of processing

The first aim in the third study was to evaluate differences regarding attention, verbal memory and processing speed performance across the three experimental groups. We transformed the raw scores on Z scores enabling comparisons with normative data and eliminating the age-related variance in cognitive performance. In all the analysis, the non verbal premorbid IQ and the level of nicotine dependence were introduced as covariates, since differences emerged among the groups and cigarette consumption can improve neuropsychological performance through enhancing dopaminergic activity in frontal attentional networks.

As we expected, the COC group performed better than both SZ groups in verbal memory, specifically in learning over the five trials, the total learned words, short memory, delayed memory, processing speed and in the global cognitive component. There were no differences between groups in recognition memory. This result suggests that memory deficits in both SZ groups are related to retrieval of verbal information stored in memory, rather than deficits in encoding information. No other difference appears in premorbid verbal IQ, attentional span, and recognition.

Both SZ+ and SZ- groups had a similar execution on the neuropsychological tasks in contrast to other authors who found a worse performance in the SZ+ group (Cooper et al., 1999). However, some studies failed to incorporate the COC group, but those ones who did, found a worse performance on verbal memory in the SZ+ group (Serper et al., 2000; Serper et al., 2000; Sevy et al., 1990). It should be noted that in all of these studies, the SZ+ group was tested in acute cocaine cessation, affecting verbal learning through dopaminergic and

serotoninergic depletion following binge use of cocaine (Parsons, Koob & Weiss, 1995; Volkow et al., 1997). Our results did not seem affected by this effect since SZ+ and COC groups were abstinent for a period of 4 months or even longer. So, somehow recovery in cognitive function with long abstinence time could be plausible, explaining the lack of differences between SZ+ and SZ- groups. However, a long term-disturbance on the dopaminergic system affecting cognitive functioning, could appear in those SZ+ patients of an older age.

Taking together, these results seem to point out a similar execution on attention, verbal memory and speed of processing as well as in global cognitive performance in both SZ groups.

6.3.2 Age-related changes in neuropsychological performance

In order to elucidate the effect of both age and duration of SUD in individuals with schizophrenia and/or cocaine dependence, and taking into account that current gaps of knowledge exists in this area, we conducted other analyses in the third study, exploring the influence of those variables in attention, verbal memory and speed of processing.

The correlational analyses only revealed an effect of age in the SZ+ group on verbal memory and in the global cognitive component. Thus, verbal memory and general neuropsychological functioning are worse in the SZ+ individuals of an older age. Otherwise, the SZ- group did not show any age-related change in their cognitive performance, in agreement with the idea of a stable cognitive deficit in these patients regardless of chronicity and the severity of illness (Asarnow & MacCrimmon, 1978; Lewandowski, Cohen & Ongur, 2011). This result agrees with the idea of a cognitive decline interacting with age in the SZ+ individuals as a result of an additive brain damage, possibly due to the long-term expression of neurotoxic consequences of SUD, as other authors stated before (Allen et al., 1999; Bowie et al., 2005; Mohamed et al., 2006). Therefore, the inclusion of different age samples, could be an important factor explaining the contradictory results of neurocognition in studies comparing SZ- and SZ+ groups. To our surprise, the COC group showed a better processing speed in the older subjects. Nevertheless, no more significant correlations were found between age and cognitive performance in this group.

Unexpectedly, the length of SUD did not appear correlated to cognitive performance in both SZ+ and COC groups. Furthermore, the regression analysis showed the age of the SZ+ individuals as the only variable explaining the 24% of the variance in the global cognitive component, without any significance of the length of SUD. In spite of this result, differences in both frequency and quantity use of cocaine may be more strongly related to general cognitive performance

than the length of SUD measured by years of duration of the disorder. This could explain the better processing speed in older COC subjects, as well as the results obtained in the SZ+ group, leading to dose-dependent effects which covary with the age of subjects resulting in a drug per age interaction phenomenon. Unfortunately, we were not able to disentangle these possible effects since no measures of these variables were performed. Future studies are needed examining this question.

Our results have important clinical implications. Deficits in verbal memory are shown to be associated to adaptive functioning and they predict worse therapeutic results (Green, 1996; Serper et al., 2000; Serper et al., 2000), because psychotherapeutic approaches requires storage of large amounts of information and mental flexibility (Bowie et al., 2005). Therefore, treatment programs may prove ineffectively for older SZ+ patients. The assessment of neurocognitve deficits in SZ+ patients, especially in the older ones, is necessary in order to know the more appropriate interventions and to develop cognitive enhancement therapies. The early prevention of a cognitive deficit, which may be accelerated in older ages, may help to improve the functional outcome of these patients in the future.

6.4 Health related quality of life in Dual Diagnosis: clinical correlates

The work of Health-related Quality of Life (HRQOL) is carried out with a different sample than the other ones. With the proposal of asses the HRQOL in patients with Dual Diagnosis, namely, people suffering from both comorbid conditions, compared with people suffering only one of them, we enrolled a sample of 95 participants, only males, divided in three groups. Seventy patients with current diagnosis of schizophrenia, bipolar disorder and major depression, with (DD, n=35) and without (SMI, n=35) comorbid substance use dependence were included. In addition, another group with only Substance Use Dependence (SUD, n= 35) was recruited. Both DD and SUD groups were in remission of substance use at least for four months. In an exploratory way, we also sought to determine which clinical factors would be related to HRQOL, with special interest in the DD group.

As we expected, the DD group showed a major detrimental on most of all the subscales assessing HRQOL, being especially relevant the affectation on mental health domain rather than physical health domain, without differences between groups in bodily pain and physical functioning. In general terms, the SUD group obtained better scores in the SF-36 with marked differences when compared to

DD group, while the SMI group showed intermediate scores between the other two.

The introduction of the covariates suicidal attempts, medication and daily consumption of cigarettes, as clinical variables probably affecting HRQOL (Bebbington et al., 2009; Laaksonen, Rahkonen, Martikainen, Karvonen & Lahelma, 2006; Ponizovsky, Grinshpoon, Levav & Ritsner, 2003) which in turn, showed significant differences in DD compared to the other groups, kept the worst HRQOL in DD group, but made disappeared the previous differences in Mental Health, General Health and MCS. After this adjustment, the SUD group showed a better feeling of vitality and energy as well as an improvement of their health state, compared to the previous year of both SMI and DD groups. These data suggest that SUD patients had lower functional disability, possibly related to their better community functioning, since they were often active workers.

The fact that those clinical variables made disappear the worse scoring of the DD group respect both SMI and SUD groups, in the scales mainly related to mental health, suggest that suicidal attempts, cigarette consumption and intake of medication, modulates the mental HRQOL expression in DD patients. So, these variables should be taken into account in further research since they seem to be involved in mental HRQOL. However, after the adjustment, the DD group continued showing a lower degree of physical and emotional health, with higher perceptions of limitations in their social and occupational life, as well as higher feelings of tiredness compared to the SMI group. This result, in agreement with Kalman et al. (2004), may highlight the negative effect of the comorbid substance use in mental HRQOL in patients with SMI. This is also in line with the work of Kilbourne et al. (2009) who observed a negative impact of comorbid substance use in patients with bipolar disorder, even after controlling the depressive and maniac symptoms of the disorder.

Our results suggest a major detrimental effect in mental HRQOL domain in patients with DD compared to SMI and SUD groups, despite the fact that they were abstinent for a long time. Although our results agree with several previous studies (Bizzarri et al., 2005; Kalman et al., 2004; Kilbourne et al., 2009; Singh et al., 2005), most of them were lacking the inclusion of SMI group. This fact, does not allow to elucidate the harmfull effects of the psychiatric disorder on HRQOL.

The correlation analysis considering the clinical data collected showed that the MCS scale was associated to number of suicidal attempts, daily amount of medication and the number of coffees consumed per day. Thus, when there were more suicidal attempts and more intakes of both medication and coffee, the score in the MCS scale was lower. The analysis separated by groups showed that these

associations were true only for the DD group. Similarly, the regression analysis confirmed that the model was only met by the DD group, and the caffeine intake was the only predictive variable explaining the 21.8% of the variance. Although this result indicates that a higher intake of caffeine consumption in DD patients is related to a higher affectation in the mental HRQOL, they did not ingest more coffees a day than SMI and SUD groups.

Caffeine consumption, as well as other methylxanthines, has long been associated with psychiatric illness, possibly due to its beneficial impact on extrapyramidal side effects of antipsychotic medication, thorough dopaminergic agonists in the nigrostratial pathways (Casas et al., 1989). This is in agreement with the self-medication hypothesis. However, caffeine consumption may have detrimental effects in DD patients through dopaminergic agonists in other brain pathways such as mesolimbic and mesocortical, as well as causing interference to antipsychotic treatment offsetting the effects of medication. All together, may increase the psychotic symptomatology.

Since intraindividual variations have been described in the psychoactive effects of caffeine in the general population (Paton & Beer, 2001), our results could be explained, at least in part, by the possibility that DD would be the most sensitive one to the effects of caffeine, even under moderate doses, compared to the other two groups. In other words, the DD group may present different genetic polymorphisms from the general population, both in metabolic enzymes and in brain receptors, to the effects of caffeine. A more plausible explanation is that caffeine covaries with other risk factors associated to DD group such as: more suicidal attempts, a higher daily medication intake and higher cigarette consumption (Lara, 2010). The consumption of nicotine and caffeine, has been associated with higher risk of suicide attempts in the psychiatric population (Baethge, Tondo, Lepri & Baldessarini, 2009; Keizer, Gex-Fabry, Eytan & Bertschy, 2009), as well as with a lower efficacy of antipsychotic medication (Lara, 2010; Baethge 2009). It must be highlighted that all this factors have been related, directly or indirectly, with worse QOL and HRQOL (Alonso et al., 2009; Bebbington et al., 2009; Kasckow et al., 2007; Laaksonen et al., 2006; Ponizovsky et al., 2003).

Our results are encouraging further research in this area, exploring the HRQOL state in this population, taking into account the consumption of nicotine and caffeine in order to explore their impact on HRQOL and with which factors their effects may be associated. Likewise, studying the QOL/HRQOL in DD women is of great interest, since there is evidence of a worse state in the mental domain in female substance users (Garg et al., 1999; Lev-Ran et al., 2012). Thus, given the

differences in the HRQOL state between sexes, it should be noted that our results may be representative only on male patients.

The systematic assessment of HRQOL in DD patients, should allow us to improve our knowledge about the impact of the illness in the patients' life as well as the associated factors on HRQOL detriment. It may also be a useful tool in the detection of specific attention areas, contributing to a better direction of the intervention targets in treatment planning, and thereby, improving the intervention's effectiveness and the assessment of their results.

7. STRENGHTS, LIMITATIONS AND FUTURE RESEARCH

Our work provides improvements over previous research on neuropsychology and QOL topics. The groups' comparisons to normative Spanish data have shown evidence about the impairment's degree of the three experimental groups in the HRQOL. Similarly, the conversion of the raw scores into Z standardized scores made in the third study, enables comparisons of neuropsychological performances in the three groups to the normative data, and eliminates the normal age-related variations, in order to establish deep impairments than those considered as normal cognitive changes associated to age. The control of abstinence time and its verification by urinalysis seems have eliminated, at least in part, acute effects of substance use in cognitive performance and in HRQOL scores, providing a major robustness in the results. The inclusion of the three experimental groups (the comorbid group with DD compared with the two non comorbid groups) allow us to elucidate the impact of each condition on the independent variables assessed in each study of this thesis, being a lacking factor in most of the preceding works.

Nevertheless, this brought to our work the inherent limitations of naturalistic coss-sectional designs. The fact that we included only male patients is a strenght in our reserach due to specific characteristics tightly linked to gender in the DD pathology, which affects both neurocognitive performance and QOL. This

eliminates the interfering effects of gender in the results. However, this can be seen as a limitation in the generalization of our results, since they cannot be extrapolated to female gender. Recent evidences point out differences in DD according to gender. The usual good prognosis in SZ women disappears in dual disorders (Miquel, Roncero, López-Ortiz & Casas, 2011). Dual SZ women have a greater facility to become intoxicated and develop substance dependence than men (Schuckit, Anthenelli, Bucholz, Hesselbrock & Tipp, 1995). Positive symptoms appear more quickly (Gearon & Bellack, 2000) and they have higher risk of suffering sexually transmited diseases (STD), as Human Immunodeficiency Virus infection (HIV), compared with their male counterparts (Krakow, Galanter, Dermatis & Westreich, 1998).

The wide sociodemographic and clinical data recorded, have allowed us to understand some of their associations to both cognitive and QOL assessments. This sociodemographic and clinical variables were rarely taken into account by the previous studies. Regarding studies about neurocognitive functioining, we followed the prevailing objectives of the current research in the DD field (Mueser & McGurk, 2012), as follows: the focus of cocaine as a main substance of choice, the sample comprised by SZ patients with a long time of abstinence, the control of influence of both SUD duration and nicotine consumption in the cognitive performance, the assessment of individual cognitive domains, the fact of having considered the psychotropic medication and other specific clinical variables often associated to DD on the cognitive results, the study of both age of patients and substance intake age onset as intermediate variables possibly affecting neuropsychological performance. Finally, the calculations of effect sizes and the use of Bonferroni method in all the analysis prevent the occurrence of type I and type II errors in our results providing strengths to our work.

However, some aspects must be taken into consideration when interpreting our results (i) although we focused on cocaine as a main drug of choice in participants enrolled in our sample, they were mostly polydrug users with a high intake of alcohol and cannabis. We performed the analysis again controlling the effect of both substances obtaining similar results to the previous ones. (ii) The groups in our sample did differ in some demographic variables like marital status and economic situation, as well as in clinical variables like clinical state, medication, CPZ equivalents and cigarettes consumption. Although in the study of executive functioning (Study 2) these variables were introduced as covariates in the analyses, we were aware that this was an artificial adjustment. Our sample is constituted by non randomized groups and although their control has a perfect sense in a statistical point of view, these differences across groups are in fact, meaningful characteristics of each group that cannot be successfully controlled in

the real life. For these reason, we decided not to covary their effect on the following study (Study 3), where we only introduced as covariates the differences in non-verbal premorbid IQ and nicotine consumption given their potential effect on the cognitive results. In spite of this, it cannot be underestimated that sociodemographic and clinical differences across the three experimental groups may have contributed somehow to the cognitive profiles among subject groups in the study 3. (iii) Three subjects in the SZ+ group and four subjects in the SZ- group were suffering from schizoaffective disorder. Since the schizoaffective patients may have better neuropsychological performance than the SZ ones, we conducted the analysis again excluding these subjects. We obtained very similar results to the whole SZ groups. Therefore, we decided to keep them in the study .(iv) In the HRQOL study, we did not include the information about subjects who dropped-out of the study or that were excluded, so it is unknown whether the results are subject to bias due to the exclusion of these subjects. (v) All subjects included in the studies were undergoing treatment, maybe affecting the extrapolation of our results to those who are not considering treatment. Furthermore, the DD/ SZ+ and SMI/ SZ- groups were recruited from different healthcare systems and with different planning treatments than COC/SUD group. COC/ SUD groups were recruited from the therapeutic community of Gressol Catalonia Man Project, where the treatment means more control, more compliance, and discipline from the users than the other two groups arising from the Mental Health Division of the Althaia Foundation in Manresa, where the treatment does not require much involvement. This variable could be affecting somehow our results.

The main limitations of our work also must be mentioned. Although we assessed the clinical state with the CGI, we did not perform a standardized assessment of SZ symptoms. Therefore, all of our results might be influenced by differences in the psychopathology between SZ+ and SZ- or between DD and SMI groups. The fact that the psychiatric diagnostic groups in our samples were taking higher amount of medication, especially antipsychotics with more CPZ equivalent dosages than COC/SUD groups, may have a direct influence on the neurocognitive and HRQOL scoring among subject groups. Although significant cognitive improvements are reported in first-episode psychosis under antipsychotic treatment (Keefe et al., 2006; Keefe et al., 2007; Kopala et al., 2006) some studies have highlighted differences between typical and atypical agents (Crespo-Facorro et al., 2009; Purdon et al., 2000), while other authors did not report any advantage of medicated groups *vs* those non-medicated (Hill, Schuepbach, Herbener, Keshavan & Sweeney, 2004; Rund et al., 2007). So, it is unknown how antipsychotic agents are affecting the results of our work. Our cross-sectional nature design does allow us to determine only correlate factors

rather than casual relationships between the independent and dependent variables of our studies.

Another important limitation is that the study was based on clinical acquired and partially retrospective self-reported data. Although we reviewed the medical records of the patients, contrasting the self-reported data with the medical history on hospital's database and with their treating psychiatrist, the information may have been subject to recall bias, including the information about suicidal attempts and substance use. Finally, the relativly small sample and the heterogeneity of psychiatric diagnostics included in the study of HRQOL might have affected the representativeness of the participants included.

Further research is needed to overcome the previous limitations. Thus, longitudinal studies including large samples are warranted to determine the age-related changes in SZ+ as well as, the extent of cognitive recovery interacting with abstinence time and the impact of the age of onset of consumption in a long term, establishing dose-dependent effects and relations to the functional outcome. Future studies must take into consideration the effect of antipsychotic agents and other substances such as caffeine and nicotine on neurocognition. Studies including neurobiological parameters (such as structural and functional magnetic resonance, evoked potentials and genetic studies) could elucidate the genetic load to develop the disorder helping to a better understanding of cognitive mechanisms in DD. Further studies exploring the affectation of both QOL/HRQOL are also needed in order to develop more effective interventions and to reduce the impact of the illness on the patient's nature context. Finally, studies in DD women, from the gender perspective, are of great interest in order to establish new and specific therapeutic targets for them. Overall, this may help to clarify the current knowledge gaps in the DD field.

8. CONCLUSIONS

The accurate review of the current scientific literature about cognitive functioning in patients with DD, points out that there is an interaction between the main drug of choice, the assessed cognitive domain and the age of patients. Our results show a similar pattern of the dorsolateral executive functioning in SZ+ and COC groups compared to SZ-. This is in agreement with the assumption of SZ+ as individuals belonging to a subgroup with SZ with a lower genetic vulnerability, and as a consequence, they exhibit higher cognitive abilities, making them more able to obtain illegal drugs of abuse. Concerning the influence of age of onset of substance use in cognition, we only found differences on set-shifting between earlier and later SZ+ consumers, while this effect was not found in the COC group. Despite this, the SZ+ group showed more deleterious effects than the COC group on set-shifting, regardless of the age of onset of consumption.

However, the SZ+ group shows a similar pattern of execution in verbal memory, processing speed and in global cognitive performance as the SZ- group, both of them being more deficient than the COC group. The difference between SZ- and SZ+ is that deficits in SZ+ group are negative related to age, while the SZ- are not. This is in agreement with the idea of an additional cognitive damage in the brain of the SZ+ individuals, due to the possible long-term expression of neurotoxic consequences of substance use. Although we did not found the

duration of SUD related to cognitive performance, future research is needed in order to confirm or refute our results.

Regarding HRQOL, our results showed a worse state in the mental domain of the HRQOL in the DD patients respect to the other two non-comorbid groups and to the general population. Suicide attempts, higher intake of daily medication and caffeine consumption appear as associated factors to the impairment in the mental domain of HRQOL, especially in the DD group. The systematic assessment of the HRQOL in DD patients, should allow us to improve our knowledge of its associated factors. It may also be a useful tool in the detection of areas of specific assistance to the goals of treatment planning as well as an assessment measure of the effectiveness of interventions.

Further research is needed to develop studies which control the methodological deficiencies of the previous work. Longitudinal studies and those incorporating neurobiological parameters, addressed to clarify the current knowledge gaps about the neurocognition of DD, are required.

REFERENCES

Addington, J. & Addington, D. (1997). Substance abuse and cognitive functioning in schizophrenia. *Journal of Psychiatry & Neuroscience, 22*(2), 99-104.

Adinoff, B., Ruether, K., Krebaum, S., Iranmanesh, A. & Williams, M. J. (2003). Increased salivary cortisol concentrations during chronic alcohol intoxication in a naturalistic clinical sample of men. *Alcoholism, Clinical and Experimental Research, 27*(9), 1420-1427.

Alamo, C., López-Muñoz, F. & Cuenca, E. (1998). Contribución de los antidepresivos y reguladores del humor al conocimiento de las bases neurobiológicas de los trastornos afectivos. *Psiquiatría.com, 2*(3).

Albanese, M. J. & Pies, R. (2004). The bipolar patient with comorbid substance use disorder: recognition and management. *CNS Drugs, 18*(9), 585-596.

Allen, D. N., Goldstein, G. & Aldarondo, F. (1999). Neurocognitive dysfunction in patients diagnosed with schizophrenia and alcoholism. *Neuropsychology, 13*(1), 62-68.

Alonso, J., Croudace, T., Brown, J., Gasquet, I., Knapp, M. R., Suarez, D. & Novick, D. (2009). Health-related quality of life (HRQL) and continuous antipsychotic treatment: 3-year results from the schizophrenia health outcomes (SOHO) study. *Value in Health, 12*(4), 536-543.

Alterman, A. I., Erdlen, D. L., Laporte, D. J. & Erdlen, F. R. (1982). Effects of illicit drug use in an inpatient psychiatric population. *Addictive Behaviors, 7*(3), 231-242.

American Psychological Association. (2012). *Recognition of psychotherapy effectiveness*. Retrieved August http://www.apa.org/about/policy/resolution-psychotherapy.aspx

Ammari, N., Heinrichs, R. W. & Miles, A. A. (2010). An investigation of 3 neurocognitive subtypes in schizophrenia. *Schizophrenia Research, 121*(1-3).

APA. (1980). In American Psychiatric Association (Ed.). *Diagnostic and statistical manual of mental disorders* (3rd ed.). Washington, DC: American Psychiatric Press.

APA. (1987). In American Psychiatric Association (Ed.). *Diagnostic and statistic manual of mental disorders.* (3 rev ed.). Washington, DC: American Psychiatric Press.

APA. (1994). In American Psychiatric Association (Ed.). *Diagnostic and statistic manual of mental disorders.* (4th ed.). Washington, DC: American Psychiatric Press.

APA. (2000). In American Psychiatric Association (Ed.). *Diagnostic and statistic manual of mental disorders.* (4 rev ed.). Washington, DC: American Psychiatric Press.

Appleby, L., Shaw, J., Amos, T., McDonnell, R., Harris, C., McCann, K. & Parsons, R. (1999). Suicide within 12 months of contact with mental health services: national clinical survey. *BMJ (Clinical Research Ed.), 318*(7193), 1235-1239.

Arias, F., Rubio, G., López-Muñoz, F. & Ferre, F. (2001). Introducción al tratamiento de la patología dual: aspectos asistenciales y terapéuticos. In Rubio, G., et al. (Ed.), *Trastornos psiquiátricos y abuso de sustancias* (pp. 257-272). Madrid: Panamericana.

Arndt, S., Tyrrell, G., Flaum, M. & Andreasen, N. C. (1992). Comorbidity of substance abuse and schizophrenia: the role of pre-morbid adjustment. *Psychological Medicine, 22*(2), 379-388.

Asarnow, R. F. & MacCrimmon, D. J. (1978). Residual performance deficit in clinically remitted schizophrenics: a marker of schizophrenia? *Journal of Abnormal Psychology, 87*(6), 597-608.

Astals, M., Domingo-Salvany, A., Buenaventura, C. C., Tato, J., Vazquez, J. M., Martin-Santos, R. & Torrens, M. (2008). Impact of substance dependence and dual diagnosis on the quality of life of heroin users seeking treatment. *Substance use & Misuse, 43*(5), 612-632.

Back, S., Dansky, B. S., Coffey, S. F., Saladin, M. E., Sonne, S. & Brady, K. T. (2000). Cocaine dependence with and without post-traumatic stress disorder: a comparison of substance use, trauma history and psychiatric comorbidity. *The American Journal on Addictions, 9*(1), 51-62.

Baethge, C., Tondo, L., Lepri, B. & Baldessarini, R. J. (2009). Coffee and cigarette use: association with suicidal acts in 352 Sardinian bipolar disorder patients. *Bipolar Disorders, 11*(5), 494-503.

Baker, A., Richmond, R., Haile, M., Lewin, T. J., Carr, V. J., Taylor, R. L. & Moeller-Saxone, K. (2007). Characteristics of smokers with a psychotic disorder and implications for smoking interventions. *Psychiatry Research, 150*(2), 141-152.

Barnes, M., Lawford, B. R., Burton, S. C., Heslop, K. R., Noble, E. P., Hausdorf, K. & Young, R. M. (2006). Smoking and schizophrenia: is symptom profile related to smoking and which antipsychotic medication is of benefit in reducing cigarette use? *The Australian and New Zealand Journal of Psychiatry, 40*(6-7), 575-580.

Batel, P. (2000). Addiction and schizophrenia. *European Psychiatry, 15*(2), 115-122.

Bebbington, P. E., Angermeyer, M., Azorin, J. M., Marwaha, S., Marteau, F. & Toumi, M. (2009). Side-effects of antipsychotic medication and health-related quality of life in schizophrenia. *Acta Psychiatrica Scandinavica.Supplementum, (438):22-8.*

Bebout, R. R., Drake, R. E., Xie, H., McHugo, G. J. & Harris, M. (1997). Housing status among formerly homeless dually diagnosed adults. *Psychiatric Services, 48*(7), 936-941.

Bechara, A., Damasio, A. R., Damasio, H. & Anderson, S. W. (1994). Insensitivity to future consequences following damage to human prefrontal cortex. *Cognition, 50*(1-3), 7-15.

Becoña, E. & Cortés, M. (2008). *Guía clínica de intervención psicológica en adicciones*. Socidrogalcohol.

Benaiges, I., Prat, G. & Adan, A. (2012). Health-related quality of life in patients with dual diagnosis: clinical correlates. *Health and Quality of Life Outcomes, 10*, 106.

Benaiges, I., Prat, G. & Adan, A. (2010). Neuropsychological aspects of dual diagnosis. *Current Drug Abuse Reviews, 3*(3), 175-188.

Benaiges, I., Serra-Grabulosa, J. M., Prat, G. & Adan, A. (2013). Executive functioning in individuals with schizophrenia and/or cocaine dependence. *Human Psychopharmacology, 28*(1), 29-39.

Bernadt, M. W. & Murray, R. M. (1986). Psychiatric disorder, drinking and alcoholism: what are the links? *The British Journal of Psychiatry, 148*, 393-400.

Bizzarri, J., Rucci, P., Vallotta, A., Girelli, M., Scandolari, A., Zerbetto, E. & Dellantonio, E. (2005). Dual diagnosis and quality of life in patients in treatment for opioid dependence. *Substance use & Misuse, 40*(12), 1765-1776.

Blanchard, J. J., Brown, S. A., Horan, W. P. & Sherwood, A. R. (2000). Substance use disorders in schizophrenia: review, integration, and a proposed model. *Clinical Psychology Review, 20*(2), 207-234.

Block, R. I., Erwin, W. J. & Ghoneim, M. M. (2002). Chronic drug use and cognitive impairments. *Pharmacology, Biochemistry and Behavior, 73*(3), 491-504.

Bowie, C. R., Serper, M. R., Riggio, S & Harvey, P. D. (2005). Neurocognition, symptomatology, and functional skills in older alcohol-abusing schizophrenia patients. *Schizophrenia Bulletin, 31*(1), 175-182.

Boydell, J., Dean, K., Dutta, R., Giouroukou, E., Fearon, P. & Murray, R. (2007). A comparison of symptoms and family history in schizophrenia with and without prior cannabis use: implications for the concept of cannabis psychosis. *Schizophrenia Research, 93*(1-3), 203-210.

Brady, K., Anton, R., Ballenger, J. C., Lydiard, R. B., Adinoff, B. & Selander, J. (1990). Cocaine abuse among schizophrenic patients. *The American Journal of Psychiatry, 147*(9), 1164-1167.

Brissos, S., Dias, V. V., Carita, A. I. & Martinez-Aran, A. (2008). Quality of life in bipolar type I disorder and schizophrenia in remission: clinical and neurocognitive correlates. *Psychiatry Research, 160*(1), 55-62.

Brunette, M. F., Mueser, K. T., Xie, H. & Drake, R. E. (1997). Relationships between symptoms of schizophrenia and substance abuse. *The Journal of Nervous and Mental Disease, 185*(1), 13-20.

Bucholz, K. K., Cadoret, R., Cloninger, C. R., Dinwiddie, S. H., Hesselbrock, V. M., Nurnberger, J. I. & Schuckit, M. A. (1994). A new, semi-structured psychiatric interview for use in genetic linkage studies: a report on the reliability of the SSAGA. *Journal of Studies on Alcohol, 55*(2), 149-158.

Cardoso, B. M., Kauer Sant'Anna, M., Dias, V. V., Andreazza, A. C., Cereser, K. M. & Kapczinski, F. (2008). The impact of co-morbid alcohol use disorder in bipolar patients. *Alcohol, 42*(6), 451-457.

Carey, K. B., Kate, B., Cocco, K. M. & Correia, C. J. (1997). Reliability and validity of the addiction severity index among outpatients with severe mental illness. *Psychological Assesment, 9*, 422-428.

Carey, K. B., Carey, M. P. & Simons, J. S. (2003). Correlates of substance use disorder among psychiatric outpatients: focus on cognition, social role functioning, and psychiatric status. *The Journal of Nervous and Mental Disease, 191*(5), 300-308.

Carnwath, T., Garvey, T. & Holland, M. (2002). The prescription of dexamphetamine to patients with schizophrenia and amphetamine dependence. *Journal of Psychopharmacology, 16*(4), 373-377.

Casas, M., Roncero, C., Castells, X. & Ramos, J. (2006). In Cervera G., Valderrama J. C., Pérez de los Cobos, J., Rubio G. & San L. (Eds.). *Tratado SET de trastornos adictivos.* Madrid: Panamericana.

Casas, M., Torrens, M., Duro, P., Pinet, C., Alvarez, F. & Udina, C. (1989). Utilisation des méthhylxantines, caffeine et téophylline dans le traitements des troubles extrapyramidaux secondaires aux traitements par les neuroleptiques: déroulement d'une hyphotèse thérapeutique. *L'Encephale, 15*, 177-180.

Casey, B. J., Giedd, J. N. & Thomas, K. M. (2000). Structural and functional brain development and its relation to cognitive development. *Biological Psychology, 54*(1-3), 241-257.

Caspi, A., Moffitt, T. E., Cannon, M., McClay, J., Murray, R., Harrington, H. & Craig, I. W. (2005). Moderation of the effect of adolescent-onset cannabis use on adult psychosis by a functional polymorphism in the catechol-O-methyltransferase gene: longitudinal evidence of a gene X environment interaction. *Biological Psychiatry, 57*(10), 1117-1127.

Chang, Y. H., Chen, S. L., Lee, S. Y., Hsu, Y. W., Wu, J. Y., Chen, S. H. & Lu, R. B. (2012). Neuropsychological functions in bipolar disorders I and II with and without comorbid alcohol dependence. *Progress in Neuro-Psychopharmacology & Biological Psychiatry, 37*(2), 211-216.

Cooper, L., Liberman, D., Tucker, D., Nuechtertlein, K. H., Tsuang, S. & Barnett, H. L. (1999). Neurocognitive deficits in the dually diagnosed with schizophrenia and cocaine abuse. *Psychiatric Rehabilitation Skills, 3*(2), 231-245.

Copersino, M. L., Serper, M. R., Vadhan, N., Goldberg, B. R., Richarme, D., Chou, J. C. & Cancro, R. (2004). Cocaine craving and attentional bias in cocaine-dependent schizophrenic patients. *Psychiatry Research, 128*(3), 209-218.

Coulston, C. M., Perdices, M. & Tennant, C. C. (2007). The neuropsychology of cannabis and other substance use in schizophrenia: review of the literature and critical evaluation of methodological issues. *The Australian and New Zealand Journal of Psychiatry, 41*(11), 869-884.

Craig, T. K., Johnson, S., McCrone, P., Afuwape, S., Hughes, E., Gournay, K. & Thornicroft, G. (2008). Integrated care for co-occurring disorders: psychiatric

symptoms, social functioning, and service costs at 18 months. *Psychiatric Services, 59*(3), 276-282.

Crespo-Facorro, B., Rodriguez-Sanchez, J. M., Perez-Iglesias, R., Mata, I., Ayesa, R., Ramirez-Bonilla, M. & Vazquez-Barquero, J. L. (2009). Neurocognitive effectiveness of haloperidol, risperidone, and olanzapine in first-episode psychosis: a randomized, controlled 1-year follow-up comparison. *The Journal of Clinical Psychiatry, 70*(5), 717-729.

Degenhardt, L., Hall, W. & Lynskey, M. (2003). Testing hypotheses about the relationship between cannabis use and psychosis. *Drug and Alcohol Dependence, 71*(1), 37-48.

DeRosse, P., Kaplan, A., Burdick, K. E., Lencz, T. & Malhotra, A. K. (2010). Cannabis use disorders in schizophrenia: effects on cognition and symptoms. *Schizophrenia Research, 120*(1-3), 95-100.

Deshmukh, A., Rosenbloom, M. J., De Rosa, E., Sullivan, E. V. & Pfefferbaum, A. (2005). Regional striatal volume abnormalities in schizophrenia: effects of comorbidity for alcoholism, recency of alcoholic drinking, and antipsychotic medication type. *Schizophrenia Research, 79*(2-3), 189-200.

Dickey, B., Normand, S. L., Weiss, R. D., Drake, R. E. & Azeni, H. (2002). Medical morbidity, mental illness, and substance use disorders. *Psychiatric Services, 53*(7), 861-867.

Dinan, T. G. (1994). Glucocorticoids and the genesis of depressive illness. A psychobiological model. *The British Journal of Psychiatry, 164*(3), 365-371.

Dittmann, S., Hennig-Fast, K., Gerber, S., Seemuller, F., Riedel, M., Emanuel Severus, W. & Grunze, H. C. (2008). Cognitive functioning in euthymic bipolar I and bipolar II patients. *Bipolar Disorders, 10*(8), 877-887.

Dixon, L. (1999). Dual diagnosis of substance abuse in schizophrenia: prevalence and impact on outcomes. *Schizophrenia Research, 35*, 93-100.

Dixon, L., Haas, G., Weiden, P., Sweeney, J. & Frances, A. (1990). Acute effects of drug abuse in schizophrenic patients: clinical observations and patients' self-reports. *Schizophrenia Bulletin, 16*(1), 69-79.

Dixon, L., Weiden, P. J., Haas, G., Sweeney, J. & Frances, A. J. (1992). Increased tardive dyskinesia in alcohol-abusing schizophrenic patients. *Comprehensive Psychiatry, 33*(2), 121-122.

Drake, R. E., Osher, F. C. & Wallach, M. A. (1991). Homelessness and dual diagnosis. *The American Psychologist, 46*(11), 1149-1158.

Drake, R. E. & Wallach, M. A. (2000). Dual diagnosis: 15 years of progress. *Psychiatric Services, 51*(9), 1126-1129.

D'Souza, D. C., Abi-Saab, W. M., Madonick, S., Forselius-Bielen, K., Doersch, A., Braley, G. & Krystal, J. H. (2005). Delta-9-tetrahydrocannabinol effects in schizophrenia: implications for cognition, psychosis, and addiction. *Biological Psychiatry, 57*(6), 594-608.

D'Souza, D. C., Sewell, R. A. & Ranganathan, M. (2009). Cannabis and psychosis/schizophrenia: human studies. *European Archives of Psychiatry and Clinical Neuroscience, 259*(7), 413-431.

Duke, P. J., Pantelis, C., McPhillips, M. A. & Barnes, T. R. (2001). Comorbid non-alcohol substance misuse among people with schizophrenia: epidemiological study in central London. *The British Journal of Psychiatry, 179*, 509-513.

Eack, S. M. & Newhill, C. E. (2007). Psychiatric symptoms and quality of life in schizophrenia: a meta-analysis. *Schizophrenia Bulletin, 33*(5), 1225-1237.

Ehrenreich, H., Rinn, T., Kunert, H. J., Moeller, M. R., Poser, W., Schilling, L. & Hoehe, M. R. (1999). Specific attentional dysfunction in adults following early start of cannabis use. *Psychopharmacology, 142*(3), 295-301.

Endicott, J. & Spitzer, R. L. (1978). A diagnostic interview: the schedule for affective disorders and schizophrenia. *Archives of General Psychiatry, 35*(7), 837-844.

Fassino, S., Daga, G. A., Delsedime, N., Rogna, L. & Boggio, S. (2004). Quality of life and personality disorders in heroin abusers. *Drug and Alcohol Dependence, 76*(1), 73-80.

First, M. B., Spitzer, R. L., Gibbon, M. & William, J. B. W. (1998). *Structural clinical interview for axis-I DSM-IV disorders, patient's edition.* New York: Biometric Research Department, New York State Psychiatric Institute.

Fox, H. C., Hong, K. I., Siedlarz, K. & Sinha, R. (2008). Enhanced sensitivity to stress and drug/alcohol craving in abstinent cocaine-dependent individuals compared to social drinkers. *Neuropsychopharmacology, 33*(4), 796-805.

Fox, H. C. & Sinha, R. (2009). Sex differences in drug-related stress-system changes: implications for treatment in substance-abusing women. *Harvard Review of Psychiatry, 17*(2), 103-119.

Garg, N., Yates, W. R., Jones, R., Zhou, M. & Williams, S. (1999). Effect of gender, treatment site and psychiatric comorbidity on quality of life outcome in substance dependence. *The American Journal on Addictions, 8*(1), 44-54.

Gearon, J. S. & Bellack, A. S. (2000). Sex differences in illness presentation, course, and level of functioning in substance-abusing schizophrenia patients. *Schizophrenia Research, 43*(1), 65-70.

Gershon, E. S., Hamovit, J., Guroff, J. J., Dibble, E., Leckman, J. F., Sceery, W. & Bunney, W. E. (1982). A family study of schizoaffective, bipolar I, bipolar II, unipolar, and normal control probands. *Archives of General Psychiatry, 39*(10), 1157-1167.

Goff, D. C., Henderson, D. C. & Amico, E. (1992). Cigarette smoking in schizophrenia: relationship to psychopathology and medication side effects. *The American Journal of Psychiatry, 149*(9), 1189-1194.

Goldman, M. S. (1990). Experience-dependent neuropsychological recovery and the treatment of chronic alcoholism. *Neuropsychology Review, 1*(1), 75-101.

Goldstein, G., Shemansky, W. J. & Allen, D. N. (2005). Cognitive function in schizoaffective disorder and clinical subtypes of schizophrenia. *Archives of Clinical Neuropsychology, 20*(2), 153-159.

Gonzalez-Saiz, F., Rojas, O. L. & Castillo, I. I. (2009). Measuring the impact of psychoactive substance on health-related quality of life: an update. *Current Drug Abuse Reviews, 2*(1), 5-10.

Goswami, S., Mattoo, S. K., Basu, D. & Singh, G. (2004). Substance-abusing schizophrenics: do they self-medicate? *The American Journal on Addictions, 13*(2), 139-150.

Grant, B. F. & Hasin, D. S. (1992). *The alcohol use disorders and associated disabilities interview schedule.* Rockville, MD: National Institute on Alcohol and Alcoholism.

Green, M. F. (1996). What are the functional consequences of neurocognitive deficits in schizophrenia? *The American Journal of Psychiatry, 153*(3), 321-330.

Gurpegui, M., Aguilar, M. C., Martinez-Ortega, J. M., Jurado, D., Diaz, F. J., Quintana, H. M. & de Leon, J. (2006). Fewer but heavier caffeine consumers in schizophrenia: a case-control study. *Schizophrenia Research, 86*(1-3), 276-283.

Hall, W. (1998). Cannabis use and psychosis. *Drug and Alcohol Review, 17*(4), 433-444.

Hambrecht, M. & Hafner, H. (1996). Substance abuse and the onset of schizophrenia. *Biological Psychiatry, 40*(11), 1155-1163.

Hambrecht, M. & Hafner, H. (2000). Cannabis, vulnerability, and the onset of schizophrenia: an epidemiological perspective. *The Australian and New Zealand Journal of Psychiatry, 34*(3), 468-475.

Hamera, E., Schneider, J. K. & Deviney, S. (1995). Alcohol, cannabis, nicotine, and caffeine use and symptom distress in schizophrenia. *The Journal of Nervous and Mental Disease, 183*(9), 559-565.

Harvey, P. D., Green, M. F., Keefe, R. S. & Velligan, D. I. (2004). Cognitive functioning in schizophrenia: a consensus statement on its role in the definition and evaluation of effective treatments for the illness. *The Journal of Clinical Psychiatry, 65*(3), 361-372.

Hasin, D. S., Trautman, K., Miele, G. M., Samet, S., Smith, M. & Endicott, J. (1996). Psychiatric research interview for substance and mental disorders (PRISM): reliability for substance abusers. *American Journal of Psychiatry, 153*, 1195-1201.

Hasin, D., Samet, S., Nunes, E., Meydan, J., Matseoane, K. & Waxman, R. (2006). Diagnosis of comorbid psychiatric disorders in substance users assessed with the psychiatric research interview for substance and mental disorders for DSM-IV. *The American Journal of Psychiatry, 163*(4), 689-696.

Heatherton, T. F., Kozlowski, L. T., Frecker, R. C. & Fagerstrom, K. O. (1991). The fagerstrom test for nicotine dependence: a revision of the fagerstrom tolerance questionnaire. *British Journal of Addiction, 86*(9), 1119-1127.

Heaton, P. K. & PAR Staff. (2005). *WCST: Computer version 4* (Research Edition ed.). Lutz, FL: Psychological Assesment Resources.

Henquet, C., Krabbendam, L., Spauwen, J., Kaplan, C., Lieb, R., Wittchen, H. U. & van Os, J. (2005). Prospective cohort study of cannabis use, predisposition for psychosis, and psychotic symptoms in young people. *BMJ (Clinical Research Ed.), 330*(7481), 11.

Henquet, C., Rosa, A., Krabbendam, L., Papiol, S., Fananas, L., Drukker, M. & van Os, J. (2006). An experimental study of catechol-o-methyltransferase Val158Met moderation of delta-9-tetrahydrocannabinol-induced effects on psychosis and cognition. *Neuropsychopharmacology, 31*(12), 2748-2757.

Herman, M. (2004). Neurocognitive functioning and quality of life among dually diagnosed and non-substance abusing schizophrenia inpatients. *International Journal of Mental Health Nursing, 13*(4), 282-291.

Hill, S. K., Schuepbach, D., Herbener, E. S., Keshavan, M. S. & Sweeney, J. A. (2004). Pretreatment and longitudinal studies of neuropsychological deficits in antipsychotic-naive patients with schizophrenia. *Schizophrenia Research, 68*(1), 49-63.

Hoff, R. A. & Rosenheck, R. A. (1999). The cost of treating substance abuse patients with and without comorbid psychiatric disorders. *Psychiatric Services, 50*(10), 1309-1315.

Hoffmann, J. P. & Su, S. S. (1998). Stressful life events and adolescent substance use and depression: conditional and gender differentiated effects. *Substance use & Misuse, 33*(11), 2219-2262.

Hsiao, Y. L., Wu, Y. S., Wu, J. Y., Hsu, M. H., Chen, H. C., Lee, S. Y. & Lu, R. B. (2009). Neuropsychological functions in patients with bipolar I and bipolar II disorder. *Bipolar Disorders, 11*(5), 547-554.

Hunt, G. E., Bergen, J. & Bashir, M. (2002). Medication compliance and comorbid substance abuse in schizophrenia: impact on community survival 4 years after a relapse. *Schizophrenia Research, 54*(3), 253-264.

Jackson, C. T., Fein, D., Essock, S. M. & Mueser, K. T. (2001). The effects of cognitive impairment and substance abuse on psychiatric hospitalizations. *Community Mental Health Journal, 37*(4), 303-312.

Jarvis, K., DelBello, M. P., Mills, N., Elman, I., Strakowski, S. M. & Adler, C. M. (2008). Neuroanatomic comparison of bipolar adolescents with and without cannabis use disorders. *Journal of Child and Adolescent Psychopharmacology, 18*(6), 557-563.

Jockers-Scherubl, M. C., Wolf, T., Radzei, N., Schlattmann, P., Rentzsch, J., Gomez-Carrillo de Castro, A. & Kuhl, K. P. (2007). Cannabis induces different cognitive changes in schizophrenic patients and in healthy controls. *Progress in Neuro-Psychopharmacology & Biological Psychiatry, 31*(5), 1054-1063.

Joyal, C. C., Halle, P., Lapierre, D. & Hodgins, S. (2003). Drug abuse and/or dependence and better neuropsychological performance in patients with schizophrenia. *Schizophrenia Research, 63*(3), 297-299.

Kalman, D., Lee, A., Chan, E., Miller, D. R., Spiro, A.,3rd, Ren, X. S. & Kazis, L. E. (2004). Alcohol dependence, other psychiatric disorders, and health-

related quality of life: a replication study in a large random sample of enrollees in the veterans health administration. *The American Journal of Drug and Alcohol Abuse, 30*(2), 473-487.

Kao, Y. C., Liu, Y. P., Chou, M. K. & Cheng, T. H. (2011). Subjective quality of life in patients with chronic schizophrenia: relationships between psychosocial and clinical characteristics. *Comprehensive Psychiatry, 52*(2), 171-180.

Kasckow, J., Montross, L., Golshan, S., Mohamed, S., Patterson, T., Sollanzano, E. & Zisook, S. (2007). Suicidality in middle aged and older patients with schizophrenia and depressive symptoms: relationship to functioning and quality of life. *International Journal of Geriatric Psychiatry, 22*(12), 1223-1228.

Keefe, R. S., Seidman, L. J., Christensen, B. K., Hamer, R. M., Sharma, T., Sitskoorn, M. M. & HGDH Research Group. (2006). Long-term neurocognitive effects of olanzapine or low-dose haloperidol in first-episode psychosis. *Biological Psychiatry, 59*(2), 97-105.

Keefe, R. S., Sweeney, J. A., Gu, H., Hamer, R. M., Perkins, D. O., McEvoy, J. P., & Lieberman, J. A. (2007). Effects of olanzapine, quetiapine, and risperidone on neurocognitive function in early psychosis: A randomized, double-blind 52-week comparison. *The American Journal of Psychiatry, 164*(7), 1061-1071. doi: 10.1176/appi.ajp.164.7.1061

Keizer, I., Gex-Fabry, M., Eytan, A. & Bertschy, G. (2009). Smoking in psychiatric inpatients: association with working status, diagnosis, comorbid substance abuse and history of suicide attempts. *Addictive Behaviors, 34*(10), 815-820.

Kendler, K. S. (1985). A twin study of individuals with both schizophrenia and alcoholism. *The British Journal of Psychiatry, 147*, 48-53.

Kessler, R. C., McGonagle, K. A., Zhao, S., Nelson, C. B., Hughes, M., Eshleman, S. & Kendler, K. S. (1994). Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Results from the national comorbidity survey. *Archives of General Psychiatry, 51*(1), 8-19.

Kilbourne, A. M., Perron, B. E., Mezuk, B., Welsh, D., Ilgen, M. & Bauer, M. S. (2009). Co-occurring conditions and health-related quality of life in patients with bipolar disorder. *Psychosomatic Medicine, 71*(8), 894-900.

Kim, J. H., Kim, D., Park, S. H., Lee, H. B. & Chung, E. K. (2007). Novelty-seeking among schizophrenia patients with comorbid alcohol abuse. *The Journal of Nervous and Mental Disease, 195*(7), 622-624.

Koob, G. F. & Bloom, F. E. (1988). Cellular and molecular mechanisms of drug dependence. *Science, 242*(4879), 715-723.

Koob, G. F. & Le Moal, M. (2001). Drug addiction, dysregulation of reward, and allostasis. *Neuropsychopharmacology, 24*(2), 97-129.

Koob, G. F. & Le Moal, M. (2005). Plasticity of reward neurocircuitry and the 'dark side' of drug addiction. *Nature Neuroscience, 8*(11), 1442-1444.

Kopala, L. C., Good, K. P., Milliken, H., Buiteman, C., Woodley, H., Rui, Q. & Honer, W. G. (2006). Treatment of a first episode of psychotic illness with quetiapine: an analysis of 2 year outcomes. *Schizophrenia Research, 81*(1), 29-39.

Kosten, T. R., Rounsaville, B. J. & Kleber, H. D. (1983). Concurrent validity of the addiction severity index. *The Journal of Nervous and Mental Disease, 171*(10), 606-610.

Krakow, D. S., Galanter, M., Dermatis, H. & Westreich, L. M. (1998). HIV risk factors in dually diagnosed patients. *The American Journal on Addictions, 7*(1), 74-80.

Kranzler, H. R., Tennen, H., Babor, T. F., Kadden, R. M. & Rounsaville, B. J. (1997). Validity of the longitudinal, expert, all data procedure for psychiatric diagnosis in patients with psychoactive substance use disorders. *Drug and Alcohol Dependence, 45*(1-2), 93-104.

Krystal, J. H., Perry, E. B., Gueorguieva, R., Belger, A., Madonick, S. H., Abi-Dargham, A. & D'Souza, D. C. (2005). Comparative and interactive human psychopharmacologic effects of ketamine and amphetamine: implications for glutamatergic and dopaminergic model psychoses and cognitive function. *Archives of General Psychiatry, 62*(9), 985-994.

Kumari, V. & Postma, P. (2005). Nicotine use in schizophrenia: the self medication hypotheses. *Neuroscience and Biobehavioral Reviews, 29*(6), 1021-1034.

Laaksonen, M., Rahkonen, O., Martikainen, P., Karvonen, S. & Lahelma, E. (2006). Smoking and SF-36 health functioning. *Preventive Medicine, 42*(3), 206-209.

Lamb, H. R. & Lamb, D. M. (1990). Factors contributing to homelessness among the chronically and severely mentally ill. *Hospital & Community Psychiatry, 41*(3), 301-305.

Lambe, E. K., Krimer, L. S. & Goldman-Rakic, P. S. (2000). Differential postnatal development of catecholamine and serotonin inputs to identified neurons in prefrontal cortex of rhesus monkey. *The Journal of Neuroscience, 20*(23), 8780-8787.

Lambert, M., Conus, P., Lubman, D. I., Wade, D., Yuen, H., Moritz, S. & Schimmelmann, B. G. (2005). The impact of substance use disorders on clinical outcome in 643 patients with first-episode psychosis. *Acta Psychiatrica Scandinavica, 112*(2), 141-148.

Lara, D. R. (2010). Caffeine, mental health, and psychiatric disorders. *Journal of Alzheimer's Disease, 20*(1), 239-248.

Laudet, A. B., Magura, S., Vogel, H. S. & Knight, E. (2000). Recovery challenges among dually diagnosed individuals. *Journal of Substance Abuse Treatment, 18*(4), 321-329.

Lev-Ran, S., Imtiaz, S., Taylor, B. J., Shield, K. D., Rehm, J. & Le Foll, B. (2012). Gender differences in health-related quality of life among cannabis users: results from the national epidemiologic survey on alcohol and related conditions. *Drug and Alcohol Dependence, 123*(1-3), 190-200.

Levy, B., Monzani, B. A., Stephansky, M. R. & Weiss, R. D. (2008). Neurocognitive impairment in patients with co-occurring bipolar disorder and alcohol dependence upon discharge from inpatient care. *Psychiatry Research, 161*(1), 28-35.

Levy, B. & Weiss, R. D. (2009). Cognitive functioning in bipolar and co-occurring substance use disorders: a missing piece of the puzzle. *Harvard Review of Psychiatry, 17*(3), 226-230.

Lewandowski, K. E., Cohen, B. M. & Ongur, D. (2011). Evolution of neuropsychological dysfunction during the course of schizophrenia and bipolar disorder. *Psychological Medicine, 41*(2), 225-241.

Lezak, M. D., Howieson, D. B. & Loring, D. W. (2004). *Neuropsychological assesment.* (4th ed.). Oxford: Oxford University Press.

Lozano, O. M., Domingo-Salvany, A., Martinez-Alonso, M., Brugal, M. T., Alonso, J., de la Fuente, L. & ITINERE Investigators. (2008). Health-related quality of life in young cocaine users and associated factors. *Quality of Life Research, 17*(7), 977-985.

Lu, R. B., Lee, J. F., Ko, H. C. & Lin, W. W. (2001). Dopamine D2 receptor gene (DRD2) is associated with alcoholism with conduct disorder. *Alcoholism, Clinical and Experimental Research, 25*(2), 177-184.

Lusher, J. M., Chandler, C. & Ball, D. (2001). Dopamine D4 receptor gene (DRD4) is associated with novelty seeking (NS) and substance abuse: the saga continues. *Molecular Psychiatry, 6*(5), 497-499.

Maier, W., Lichtermann, D., Minges, J., Delmo, C. & Heun, R. (1995). The relationship between bipolar disorder and alcoholism: a controlled family study. *Psychological Medicine, 25*(4), 787-796.

Manning, V., Wanigaratne, S., Best, D., Strathdee, G., Schrover, I. & Gossop, M. (2007). Screening for cognitive functioning in psychiatric outpatients with schizophrenia, alcohol dependence, and dual diagnosis. *Schizophrenia Research, 91*(1-3), 151-158.

Martinez-Aran, A., Penades, R., Vieta, E., Colom, F., Reinares, M., Benabarre, A. & Gasto, C. (2002). Executive function in patients with remitted bipolar disorder and schizophrenia and its relationship with functional outcome. *Psychotherapy and Psychosomatics, 71*(1), 39-46.

Mata, I., Rodriguez-Sanchez, J. M., Pelayo-Teran, J. M., Perez-Iglesias, R., Gonzalez-Blanch, C., Ramirez-Bonilla, M. & Crespo-Facorro, B. (2008). Cannabis abuse is associated with decision-making impairment among first-episode patients with schizophrenia-spectrum psychosis. *Psychological Medicine, 38*(9), 1257-1266.

Mathalon, D. H., Pfefferbaum, A., Lim, K. O., Rosenbloom, M. J. & Sullivan, E. V. (2003). Compounded brain volume deficits in schizophrenia-alcoholism comorbidity. *Archives of General Psychiatry, 60*(3), 245-252.

Matza, L. S., Buchanan, R., Purdon, S., Brewster-Jordan, J., Zhao, Y. & Revicki, D. A. (2006). Measuring changes in functional status among patients with schizophrenia: the link with cognitive impairment. *Schizophrenia Bulletin, 32*(4), 666-678.

McCrone, P., Menezes, P. R., Johnson, S., Scott, H., Thornicroft, G., Marshall, J. & Kuipers, E. (2000). Service use and costs of people with dual diagnosis in south london. *Acta Psychiatrica Scandinavica, 101*(6), 464-472.

McKetin, R., McLaren, J., Lubman, D. I. & Hids, L. (2006). The prevalence of psychotic pymptoms among methamphetamine users. *Addiction, 101*, 1473-1478.

McLelland, A. T., Luborsky, L. & Cacciola, J. (1985). New data from de addiction severity index. Reliability and validity in three centers. *Journal of Nervous and Mental Disease, 173*, 412-423.

Meijer, C. J., Koeter, M. W., Sprangers, M. A. & Schene, A. H. (2009). Predictors of general quality of life and the mediating role of health related quality of life in patients with schizophrenia. *Social Psychiatry and Psychiatric Epidemiology, 44*(5), 361-368.

Miles, H., Johnson, S., Amponsah-Afuwape, S., Finch, E., Leese, M. & Thornicroft, G. (2003). Characteristics of subgroups of individuals with psychotic illness and a comorbid substance use disorder. *Psychiatric Services, 54*(4), 554-561.

Miquel, L., Roncero, C., López-Ortiz, L. & Casas, M. (2011). Diferencias de género, epidemiológicas y diagnósticas según eje I en pacienets con patología dual. *Adicciones, 23*, 165-172.

Mobascher, A. & Winterer, G. (2008). The molecular and cellular neurobiology of nicotine abuse in schizophrenia. *Pharmacopsychiatry, 41*(1), 51-59.

Mohamed, S., Bondi, M. W., Kasckow, J. W., Golshan, S. & Jeste, D. V. (2006). Neurocognitive functioning in dually diagnosed middle aged and elderly patients with alcoholism and schizophrenia. *International Journal of Geriatric Psychiatry, 21*(8), 711-718.

Mueser, K. T. & McGurk, S. R. (2012). Cognitive functioning in schizophrenia and co-ocurring substance use disorders: where do we go from here? *Journal of Dual Diagnosis, 8*(1), 48-49.

Mueser, K. T., Drake, R. E. & Wallach, M. A. (1998). Dual diagnosis: a review of etiological theories. *Addictive Behaviors, 23*(6), 717-734.

Mueser, K. T., Yarnold, P. R., & Bellack, A. S. (1992). Diagnostic and demographic correlates of substance abuse in schizophrenia and major affective disorder. *Acta Psychiatrica Scandinavica, 85*(1), 48-55.

National Institute of Mental Health. (1976). In Guy W. & Bonato R. R. (Eds.), *CGI. clinical global impression* (2nd ed.). Maryland: Chevy Chase.

Nery, F. G., Matsuo, K., Nicoletti, M. A., Monkul, E. S., Zunta-Soares, G. B., Hatch, J. P. & Soares, J. C. (2011). Association between prior alcohol use disorders and decreased prefrontal gray matter volumes in bipolar I disorder patients. *Neuroscience Letters, 503*(2), 136-140.

Nixon, S. J., Hallford, H. G. & Tivis, R. D. (1996). Neurocognitive function in alcoholic, schizophrenic, and dually diagnosed patients. *Psychiatry Research, 64*(1), 35-45.

Noordsy, D. L., Drake, R. E., Teague, G. B., Osher, F. C., Hurlbut, S. C., Beaudett, M. S. & Paskus, T. S. (1991). Subjective experiences related to alcohol use among schizophrenics. *The Journal of Nervous and Mental Disease, 179*(7), 410-414.

North, C. S., Pollio, D. E., Smith, E. M. & Spitznagel, E. L. (1998). Correlates of early onset and chronicity of homelessness in a large urban homeless population. *The Journal of Nervous and Mental Disease, 186*(7), 393-400.

Nunes, E. V., Goehl, I., Seracini, A., Nunes, Y. & Faermer, J. (1996). Evaluation of depression and panic disorder in methadone patients using a modification of the structural clinical interview for DSM-III-R: test-retest reliability. *American Journal on Addictions, 5*, 241-248.

Parsons, L. H., Koob, G. F. & Weiss, F. (1995). Serotonin dysfunction in the nucleus accumbens of rats during withdrawal after unlimited access to intravenous cocaine. *The Journal of Pharmacology and Experimental Therapeutics, 274*(3), 1182-1191.

Patkar, A. A., Alezander, R. C., Lundy, A. & Certa, K. M. (1999). Changing patterns of illicit substance abuse among schizophrenia patients: 1984-1996. *American Journal on Addictions, 8*(1), 65-71.

Pelissier, B. & Jones, N. (2005). A review of gender differences among substance abusers. *Crime Delinquency, 51,* 343-372.

Piazza, P. V. & Le Moal, M. (1998). The role of stress in drug self-administration. *Trends in Pharmacological Sciences, 19*(2), 67-74.

Piazza, P. V. & Le Moal, M. L. (1996). Pathophysiological basis of vulnerability to drug abuse: role of an interaction between stress, glucocorticoids, and dopaminergic neurons. *Annual Review of Pharmacology and Toxicology, 36*, 359-378.

Piazza, P. V., Maccari, S., Deminiere, J. M., Le Moal, M., Mormede, P. & Simon, H. (1991). Corticosterone levels determine individual vulnerability to amphetamine self-administration. *Proceedings of the National Academy of Sciences of the United States of America, 88*(6), 2088-2092.

Pomarol-Clotet, E., Salvador, R., Sarro, S., Gomar, J., Vila, F., Martinez, A. & McKenna, P. J. (2008). Failure to deactivate in the prefrontal cortex in schizophrenia: dysfunction of the default mode network? *Psychological Medicine, 38*(8), 1185-1193.

Ponizovsky, A. M., Grinshpoon, A., Levav, I. & Ritsner, M. S. (2003). Life satisfaction and suicidal attempts among persons with schizophrenia. *Comprehensive Psychiatry, 44*(6), 442-447.

Pope, H. G., Gruber, A. J., Hudson, J. I., Cohane, G., Huestis, M. A. & Yurgelun-Todd, D. (2003). Early-onset cannabis use and cognitive deficits: what is the nature of the association? *Drug and Alcohol Dependence, 69*(3), 303-310.

Potvin, S., Blanchet, P. & Stip, E. (2009). Substance abuse is associated with increased extrapyramidal symptoms in schizophrenia: a meta-analysis. *Schizophrenia Research, 113*(2-3), 181-188.

Potvin, S., Briand, C., Prouteau, A., Bouchard, R. H., Lipp, O., Lalonde, P. & Stip, E. (2005). CANTAB explicit memory is less impaired in addicted schizophrenia patients. *Brain and Cognition, 59*(1), 38-42.

Potvin, S., Joyal, C. C., Pelletier, J. & Stip, E. (2008). Contradictory cognitive capacities among substance-abusing patients with schizophrenia: a meta-analysis. *Schizophrenia Research, 100*(1-3), 242-251.

Potvin, S., Mancini-Marie, A., Fahim, C., Mensour, B. & Stip, E. (2007). Processing of social emotion in patients with schizophrenia and substance use disorder: An fMRI study. *Social Neuroscience, 2*(2), 106-116.

Potvin, S., Sepehry, A. A. & Stip, E. (2006). A meta-analysis of negative symptoms in dual diagnosis schizophrenia. *Psychological Medicine, 36*(4), 431-440.

Potvin, S., Stavro, K. & Pelletier, J. (2012). Paradoxical cognitive capacities in dual diagnosis schizophrenia: the quest of explanatory factors. *Journal of Dual Diagnosis, 81*(1), 35-47.

Purdon, S. E., Jones, B. D., Stip, E., Labelle, A., Addington, D., David, S. R. & Tollefson, G. D. (2000). Neuropsychological change in early phase schizophrenia during 12 months of treatment with olanzapine, risperidone, or haloperidol. The canadian collaborative group for research in schizophrenia. *Archives of General Psychiatry, 57*(3), 249-258.

Pyne, J. M., Tripathi, S., French, M., McCollister, K., Rapp, R. C. & Booth, B. M. (2011). Longitudinal association of preference-weighted health-related quality of life measures and substance use disorder outcomes. *Addiction, 106*(3), 507-515.

Rabin, R. A., Zakzanis, K. K. & George, T. P. (2011). The effects of cannabis use on neurocognition in schizophrenia: a meta-analysis. *Schizophrenia Research, 128*(1-3), 111-116.

Rais, M., Cahn, W., Van Haren, N., Schnack, H., Caspers, E., Hulshoff Pol, H. & Kahn, R. (2008). Excessive brain volume loss over time in cannabis-using first-episode schizophrenia patients. *The American Journal of Psychiatry, 165*(4), 490-496.

Regier, D. A., Farmer, M. E., Rae, D. S., Locke, B. Z., Keith, S. J., Judd, L. L. & Goodwin, F. K. (1990). Comorbidity of mental disorders with alcohol and other drug abuse. Results from the epidemiologic catchment area (ECA) study. *The Journal of the American Medical Association, 264*(19), 2511-2518.

Regier, D. A., Myers, J. K., Kramer, M., Robins, L. N., Blazer, D. G., Hough, R. L. & Locke, B. Z. (1984). The NIMH epidemiologic catchment area program. Historical context, major objectives, and study population characteristics. *Archives of General Psychiatry, 41*(10), 934-941.

Reitan, R. M. & Wolfson, D. (1985). *The healsted-reitan neuropsychological test battery.* Tucson: Neuropsychological Press.

Richard, M. L., Liskow, B. I. & Perry, P. J. (1985). Recent psychostimulant use in hospitalized schizophrenics. *The Journal of Clinical Psychiatry, 46*(3), 79-83.

Rodríguez-Jiménez, R., Aragüés, M., Jiménez-Arriero, M. A., Ponce, G., Muñoz, A., Bagney, A. & Palomo, T. (2008). Patología dual en pacientes psiquiátricos hospitalizados: prevalencia y características generales. *Investigación Clínica, 49*(2), 195-205.

Rodríguez-Jímenez, R., Bagney, A., Peñas, J. M., Gómez, N. & Aragüés, M. (2010). Modelos etiopatogénicos de la patología dual. In Haro, G., Bobes, J., Casas, M., Didia, J. & Rubio, G. (Eds.), *Tratado sobre patología dual: Reintegrando la salud mental.* (pp. 187-207). Barcelona: MRA médica, S.L.

Rodriguez-Sanchez, J. M., Ayesa-Arriola, R., Mata, I., Moreno-Calle, T., Perez-Iglesias, R., Gonzalez-Blanch, C. & Crespo-Facorro, B. (2010). Cannabis use and cognitive functioning in first-episode schizophrenia patients. *Schizophrenia Research, 124*(1-3), 142-151.

Roncero, C., Barral, C., Grau-López, L., Esteve, O. & Casas, M. (2010). *Patología dual. Protocolos de intervención. Esquizofrenia.* Edikamed, S.L.

Rubio, G., Torrens, M., Calatayud, M. & Haro, G. (2010). Modelos asistenciales en patología dual. In Haro G., Bobes, J., Casas, M., Didia, J. & Rubio, G. (Eds.), *Tratado sobre patología dual: Reintegrando la salud mental.* (pp. 745-761). Barcelona: MRA médica, S.L.

Rund, B. R., Melle, I., Friis, S., Johannessen, J. O., Larsen, T. K., Midboe, L. J. & McGlashan, T. (2007). The course of neurocognitive functioning in first-episode psychosis and its relation to premorbid adjustment, duration of untreated psychosis, and relapse. *Schizophrenia Research, 91*(1-3), 132-140.

Saarni, S. I., Viertio, S., Perala, J., Koskinen, S., Lonnqvist, J., & Suvisaari, J. (2010). Quality of life of people with schizophrenia, bipolar disorder and other psychotic disorders. *The British Journal of Psychiatry, 197*(5), 386-394.

Salloum, I. M., Cornelius, J. R., Mezzich, J. E. & Kirisci, L. (2002). Impact of concurrent alcohol misuse on symptom presentation of acute mania at initial evaluation. *Bipolar Disorders, 4*(6), 418-421.

San, L. (2004). Estrategias diagnósticas en patología dual. In *Consenso del SEP sobre patología dual* (Psiquiatría Editores). (pp. 39-51). Barcelona: Arsmedica, S.L.

Sanchez-Moreno, J., Martinez-Aran, A., Colom, F., Scott, J., Tabares-Seisdedos, R., Sugranyes, G. & Vieta, E. (2009). Neurocognitive dysfunctions in euthymic bipolar patients with and without prior history of alcohol use. *The Journal of Clinical Psychiatry, 70*(8), 1120-1127.

Sarosi, A., Gonda, X., Balogh, G., Domotor, E., Szekely, A., Hejjas, K., Sasvari-Szekely, M. & Faludi, G. (2008). Association of the STin2 polymorphism of the serotonin transporter gene with a neurocognitive endophenotype in a major depressive disorder. *Progress in Neuropsychopharmacology & Biological Psychiatry, 32* (7); 1667- 1672.

Schaar, I. & Öjehagen, A. (2009). Predictors of improvement in quality of life of severe mentally ill substance abusers during 18 months of co-operation between psychiatric and social services. *Social Psychiatry and Psychiatric Epidemiology, 38*, 83-87.

Schan, C. Lee, S.Y., Chang,Y.H., Wu, J.Y., Chen, S.L., Chen, S.H., Hsiao,Y.L., Yang, H.F., Lee, I.H., Chen, P.S., Yeh, T.L., Yang,Y.K. & Lu,R. B. (2011).Neuropsychological functions in Han Chinese patients in Taiwan with bipolar II disorder comorbid and not comorbid with alcohol abuse/alcohol dependence disorder. *Progress in Neuropsychopharmacology & Biological Psychiatry, 35* (1); 131- 136.

Scheller-Gilkey, G., Lewine, R. R., Caudle, J. & Brown, F. W. (1999). Schizophrenia, substance use, and brain morphology. *Schizophrenia Research, 35*(2), 113-120.

Schmidt, M. (2011). *Rey auditory verbal learning test: A handbook.* Lutz FL: Psychological Assessment Resources.

Schnell, T., Koethe, D., Daumann, J. & Gouzoulis-Mayfrank, E. (2009). The role of cannabis in cognitive functioning of patients with schizophrenia. *Psychopharmacology, 205*(1), 45-52.

Scholes, K. E. & Martin-Iverson, M. T. (2010). Cannabis use and neuropsychological performance in healthy individuals and patients with schizophrenia. *Psychological Medicine, 40*(10), 1635-1646.

Schuckit, M. A., Anthenelli, R. M., Bucholz, K. K., Hesselbrock, V. M. & Tipp, J. (1995). The time course of development of alcohol-related problems in men and women. *Journal of Studies on Alcohol, 56*(2), 218-225.

Schulte, S. J., Meier, P. S. & Stirling, J. (2011). Dual diagnosis clients' treatment satisfaction - a systematic review. *BMC Psychiatry, 11*, 11-64.

Schweinsburg, A. D., Brown, S. A. & Tapert, S. F. (2008). The influence of marijuana use on neurocognitive functioning in adolescents. *Current Drug Abuse Reviews, 1*, 99-111.

Serper, M. R., Bergman, A., Copersino, M. L., Chou, J. C., Richarme, D. & Cancro, R. (2000). Learning and memory impairment in cocaine-dependent and comorbid schizophrenic patients. *Psychiatry Research, 93*(1), 21-32.

Serper, M. R., Copersino, M. L., Richarme, D., Vadhan, N. & Cancro, R. (2000). Neurocognitive functioning in recently abstinent, cocaine-abusing schizophrenic patients. *Journal of Substance Abuse, 11*(2), 205-213.

Sevy, S., Burdick, K. E., Visweswaraiah, H., Abdelmessih, S., Lukin, M., Yechiam, E. & Bechara, A. (2007). Iowa gambling task in schizophrenia: a review and new data in patients with schizophrenia and co-occurring cannabis use disorders. *Schizophrenia Research, 92*(1-3), 74-84.

Sevy, S., Kay, S. R., Opler, L. A. & van Praag, H. M. (1990). Significance of cocaine history in schizophrenia. *The Journal of Nervous and Mental Disease, 178*(10), 642-648.

Sevy, S., Robinson, D. G., Napolitano, B., Patel, R. C., Gunduz-Bruce, H., Miller, R. & Kane, J. (2010). Are cannabis use disorders associated with an earlier age at onset of psychosis? A study in first episode schizophrenia. *Schizophrenia Research, 120*(1-3), 101-107.

Silberg, J., Pickles, A., Rutter, M., Hewitt, J., Simonoff, E., Maes, H. & Eaves, L. (1999). The influence of genetic factors and life stress on depression among adolescent girls. *Archives of General Psychiatry, 56*(3), 225-232.

Silverstein, M. L., Mavrolefteros, G. & Close, D. (2002). Premorbid adjustment and neuropsychological performance in schizophrenia. *Schizophrenia Bulletin, 28*(1), 157-165.

Singh, J., Mattoo, S. K., Sharan, P. & Basu, D. (2005). Quality of life and its correlates in patients with dual diagnosis of bipolar affective disorder and substance dependence. *Bipolar Disorders, 7*(2), 187-191.

Smelson, D. A., Davis, C. W., Di Pano, R., Johnson, V., Losonczy, M. F. & Ziedonis, D. (2002). Executive and motor skill functioning among cocaine-dependent schizophrenics and non-drug-abusing schizophrenics. *The Journal of Nervous and Mental Disease, 190*(3), 200-202.

Smelson, D. A., Davis, C. W., Eisenstein, N., Engelhart, C., Williams, J., Losonczy, M. F. & Ziedonis, D. (2003). Cognitive disparity in schizophrenics with and without cocaine dependency. *Journal of Substance Abuse Treatment, 24*(1), 75-79.

Smit, F., Bolier, L. & Cuijpers, P. (2004). Cannabis use and the risk of later schizophrenia: a review. *Addiction, 99*(4), 425-430.

Snitz, B. E., Macdonald, A. W. & Carter, C. S. (2006). Cognitive deficits in unaffected first-degree relatives of schizophrenia patients: a meta-analytic review of putative endophenotypes. *Schizophrenia Bulletin, 32*(1), 179-194.

Sowell, E. R., Delis, D., Stiles, J. & Jernigan, T. L. (2001). Improved memory functioning and frontal lobe maturation between childhood and adolescence: a structural MRI study. *Journal of the International Neuropsychological Society, 7*(3), 312-322.

Soyka, M. (2000). Substance misuse, psychiatric disorder and violent and disturbed behaviour. *The British Journal of Psychiatry, 176*, 345-350.

Spitzer, R. L. (1983). Psychiatric diagnosis: are clinicians still necessary? *Comprehensive Psychiatry, 24*(5), 399-411.

Spitzer, R. L., Williams, J. B., Gibbon, M. & First, M. B. (1992). The structured clinical interview for DSM-III-R (SCID- I): history, rationale, and description. *Archives of General Psychiatry, 49*(8), 624-629.

Stirling, J., Lewis, S., Hopkins, R. & White, C. (2005). Cannabis use prior to first onset psychosis predicts spared neurocognition at 10-year follow-up. *Schizophrenia Research, 75*(1), 135-137.

Stowel, R. (1991). Dual diagnosis issues. *Psychiatric Annuals, 21*, 98-104.

Sullivan, E. V., Rosenbloom, M. J., Serventi, K. L., Deshmukh, A. & Pfefferbaum, A. (2003). Effects of alcohol dependence comorbidity and antipsychotic medication on volumes of the thalamus and pons in schizophrenia. *The American Journal of Psychiatry, 160*(6), 1110-1116.

Sundram, S. (2006). Cannabis and neurodevelopment: implications for psychiatric disorders. *Human Psychopharmacology, 21*(4), 245-254.

Swartz, M. S., Swanson, J. W., Hiday, V. A., Borum, R., Wagner, H. R. & Burns, B. J. (1998). Violence and severe mental illness: the effects of substance abuse and nonadherence to medication. *The American Journal of Psychiatry, 155*(2), 226-231.

Talamo, A., Centorrino, F., Tondo, L., Dimitri, A., Hennen, J. & Baldessarini, R. J. (2006). Comorbid substance-use in schizophrenia: relation to positive and negative symptoms. *Schizophrenia Research, 86*(1-3), 251-255.

Thoma, P. & Daum, I. (2008). Working memory and multi-tasking in paranoid schizophrenia with and without comorbid substance use disorder. *Addiction, 103*(5), 774-786.

Thoma, P., Wiebel, B. & Daum, I. (2007). Response inhibition and cognitive flexibility in schizophrenia with and without comorbid substance use disorder. *Schizophrenia Research, 92*(1-3), 168-180.

Torrens, M., Mestre, J. & Díaz, L. (2010). Instrumentos diagnósticos en patología dual. In Haro, G., Bobes, J., Casas, M., Didia, J. & Rubio, G. (Eds.), *Tratado sobre patología dual: Reintegrando la salud mental.* (pp. 655-671). Barcelona: MRA médica, S.L.

Torrens, M. (2008). Patología dual: Situación actual y retos de futuro. *Adicciones, 20, 315-320.*

Torrens, M., Rossi, P. C., Martinez-Riera, R., Martinez-Sanvisens, D. & Bulbena, A. (2012). Psychiatric co-morbidity and substance use disorders: treatment in parallel systems or in one integrated system? *Substance use & Misuse, 47*(8-9), 1005-1014.

Torrens, M., Serrano, D., Astals, M., Perez-Dominguez, G. & Martin-Santos, R. (2004). Diagnosing comorbid psychiatric disorders in substance abusers: validity of the Spanish versions of the psychiatric research interview for substance and mental disorders and the structured clinical interview for DSM-IV. *The American Journal of Psychiatry, 161*(7), 1231-1237.

van Gorp, W. G., Altshuler, L., Theberge, D. C. & Mintz, J. (1999). Declarative and procedural memory in bipolar disorder. *Biological Psychiatry, 46*(4), 525-531.

van Gorp, W. G., Altshuler, L., Theberge, D. C., Wilkins, J. & Dixon, W. (1998). Cognitive impairment in euthymic bipolar patients with and without prior alcohol dependence. A preliminary study. *Archives of General Psychiatry, 55*(1), 41-46.

van Harten, P. N., van Trier, J. C., Horwitz, E. H., Matroos, G. E. & Hoek, H. W. (1998). Cocaine as a risk factor for neuroleptic-induced acute dystonia. *The Journal of Clinical Psychiatry, 59*(3), 128-130.

van Os, J., Krabbendam, L., Myin-Germeys, I. & Delespaul, P. (2005). The schizophrenia enviroment. *Current Opinion in Psychiatry, 18*(2), 141-145.

Veen, N. D., Selten, J. P., van der Tweel, I., Feller, W. G., Hoek, H. W. & Kahn, R. S. (2004). Cannabis use and age at onset of schizophrenia. *The American Journal of Psychiatry, 161*(3), 501-506.

Volkow, N. D., Wang, G. J., Fowler, J. S., Logan, J., Gatley, S. J., Hitzemann, R. & Pappas, N. (1997). Decreased striatal dopaminergic responsiveness in detoxified cocaine-dependent subjects. *Nature, 386*(6627), 830-833.

Wade, D., Harrigan, S., McGorry, P. D., Burgess, P. M. & Whelan, G. (2007). Impact of severity of substance use disorder on symptomatic and functional outcome in young individuals with first-episode psychosis. *The Journal of Clinical Psychiatry, 68*(5), 767-774.

Ware, J. E. & Sherbourne, C. D. (1992). The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Medical Care, 30*(6), 473-483.

Watson, H. J., Swan, A. & Nathan, P. R. (2011). Psychiatric diagnosis and quality of life: the additional burden of psychiatric comorbidity. *Comprehensive Psychiatry, 52*(3), 265-272.

Wechsler, D. (2001). *Wechsler adult intelligence scale-revised.* (Spanish Version ed.). Madrid: TEA ediciones.

Wilson, W., Mathew, R., Turkington, T., Hawk, T., Coleman, R. E. & Provenzale, J. (2000). Brain morphological changes and early marijuana use: a magnetic resonance and positron emission tomography study. *Journal of Addictive Diseases, 19*(1), 1-22.

Wobrock, T., Hasan, A., Malchow, B., Wolff-Menzler, C., Guse, B., Lang, N. & Falkai, P. (2010). Increased cortical inhibition deficits in first-episode schizophrenia with comorbid cannabis abuse. *Psychopharmacology, 208*(3), 353-363.

Wobrock, T., Sittinger, H., Behrendt, B., D'Amelio, R., Falkai, P. & Caspari, D. (2007). Comorbid substance abuse and neurocognitive function in recent-onset schizophrenia. *European Archives of Psychiatry and Clinical Neuroscience, 257*(4), 203-210.

Woo, T. U. & Crowell, A. L. (2005). Targeting synapses and myelin in the prevention of schizophrenia. *Schizophrenia Research, 73*(2-3), 193-207.

Yesavage, J. A. & Zarcone, V. (1983). History of drug abuse and dangerous behavior in inpatient schizophrenics. *The Journal of Clinical Psychiatry, 44*(7), 259-261.

Yucel, M., Lubman, D. I., Solowij, N. & Brewer, W. J. (2007). Understanding drug addiction: a neuropsychological perspective. *The Australian and New Zealand Journal of Psychiatry, 41*(12), 957-968.

Ziedonis, D. M., Kosten, T. R., Glazer, W. M. & Frances, R. J. (1994). Nicotine dependence and schizophrenia. *Hospital & Community Psychiatry, 45*(3), 204-206.

Zubaran, C. & Foresti, K. (2009). Quality of life and substance use: concepts and recent tendencies. *Current Opinion in Psychiatry, 22*(3), 281-286.

ANEXOS

ANEXO 1. HISTORIA CLÍNICA

"Características rítmicas, de personalidad y rendimiento neuropsicológico en pacientes con patología dual"

1. DATOS SOCIODEMOGRÁFICOS

Nombre: _____
Fecha de nacimiento: _____Sexo:_____

Estado civil:
Soltero ☐ Casado ☐ Divorciado ☐ Separado ☐ Viudo ☐
Hijos: _____ Pareja estable: Si ____ No___

Convivencia: Sólo ☐ Acompañado ☐ ¿Con quién?_____

Genograma:

Dominancia manual: Diestro ☐ Zurdo ☐

Clase socioeconómica:

☐ Clase I Alta:

☐ Clase II Media-Alta:

☐ Clase III Media:

☐ Clase IV Media-Baja:

☐ Clase V Baja:

Condición académica:

☐ No escolarizado

☐ Estudios primarios incompletos

☐ Estudios primarios completos

☐ Estudios secundarios incompletos

☐ Estudios secundarios completos

☐ Estudios universitarios

Situación laboral:
Activo: _____Profesión: _____
Inactivo: ___Parado ☐ Pensionista ☐ ILT ☐

2. ANTECEDENTES PSIQUIATRICOS FAMILIARES Y PERSONALES

2.1 Concomitancia de patología orgánica en la familia (diabetes, hipertensión, enfermedad cardiovascular, alteración respiratoria, etc.): Si ____ No _____
¿Cuál?

_____

_____

Presencia de trastorno psiquiátrico en algún familiar de primer grado: Si ___No____
Especificar: _____

2.2 Concomitancia de patología orgánica en el paciente (diabetes, hipertensión, enfermedad cardiovascular, alteración respiratoria, etc.): Si ____ No _____
¿Cuál?

_____

_____

Antecedentes psiquiátricos personales:

Tipo de trastornos	Si	No
Psicóticos	__	__
Trast. Est. Animo	__	__
Trast. Ansiedad	__	__
De inicio en la infancia	__	__

Otros trastornos (especificar) _____

Intentos previos de suicidio: Si ___No ___ Número de intentos: _____

3. CARACTERÍSTICAS DEL DIAGNÓSTICO

3.1. DIAGNÓSTICO PSIQUIÁTRICO (DSM/ICE). *(No relacionado con sustancias)*

Diagnóstico actual:_____
Inicio del trastorno:_____

Tratamiento actual

Farmacológico

Nombre: _____Cantidad:_____ Duración:_____
Nombre: _____Cantidad:_____ Duración:_____
Nombre: _____Cantidad:_____ Duración:_____
Otros fármacos: _____

Tratamiento actual

Psicológico

Tipo de terapia psicológica:

_____

Intervenciones anteriores

Farmacológico

Nombre: _____Cantidades:_____ Duración:_____

Nombre: _____Cantidades:_____ Duración:_____

Nombre: _____Cantidades:_____ Duración:_____

Otros fármacos:_____

Psicológico

Tipo de terapia psicológica:

_____

3.2 DIAGNÓSTICO RELACIONADO CON SUSTANCIAS (DSM/ICE).

Diagnóstico de patología dual: Si ___No _____ ¿Cuál? _____

Inicio del trastorno dual: _____

Diagnóstico Trastorno por Consumo de Sustancias: Abuso ☐ Dependencia ☐

Sustancia principal: _____

Otras sustancias: _____

Tiempo de abstinencia: _____

Recaídas: _____

Problemas legales Si __ No__ Tipo: _____

Problemas familiares Si___No__ Tipo: _____

Problemas laborales Si__ No__ Tipo: _____

Tratamiento actual

Farmacológico

Nombre: _____Cantidades:_____ Duración:_____

Nombre: _____Cantidades:_____ Duración:_____

Nombre: _____Cantidades:_____ Duración:_____

Otros fármacos:_____

Tratamiento actual

Psicológico

Tipo de terapia psicológica:

_____

Intervenciones anteriores

Farmacológico

Nombre: _____Cantidades:_____ Duración:
Nombre: _____Cantidades:_____ Duración:
Nombre: _____Cantidades:_____ Duración:
Nombre: _____Cantidades:_____ Duración:_____
Otros fármacos:_____

4. HÁBITOS

4.1. CICLO SUEÑO-VIGILIA

Hora de levantarse:_____Hora de acostarse:_____
Siesta: Si_____ No_____ Tiempo aprox.: _____
¿Cuántas horas aprox. duerme al día?

4.2 CONSUMO DE OTRAS SUSTANCIAS

¿Consumo de nicotina? Si_____No____Cantidad de cigarros/día:_____
Tiempo que hace que es fumador_____

¿Consumo de café? Si ____No ____ Cantidad de cafés/día:_____
¿Consumo de te? Si ____No ____ Cantidad de te/día: _____
¿Consumo de cafeína? Si____No_____ Cantidad de coca-cola/día:_____
¿Consumo de alguna otra sustancia?_____

5. IMPRESIÓN CLÍNICA GLOBAL (ICG).

Gravedad de la enfermedad en la actualidad
0. No evaluado____
1. Normal, ningún trastorno____
2. Al límite de la enfermedad____
3. Levemente enfermo____
4. Moderadamente enfermo____
5. Marcadamente enfermo____
6. Gravemente enfermo____
7. Extremadamente enfermo____

Proyecto de investigación: "Ritmicidad circadiana, rendimiento cognitivo y personalidad en pacientes con patología dual"

Apreciado Sr/Sra.

Solicitamos su colaboración para participar en el proyecto de investigación "Ritmicidad circadiana, rendimiento cognitivo y personalidad en pacientes con patología dual", perteneciente al Departamento de Psiquiatría y Psicobiología Clínica de la Facultad de Psicología, Universidad de Barcelona. Para considerar su participación es necesario que lea atentamente la siguiente información y nos plantee todas las cuestiones que crea necesarias.

Justificación/Objetivo

El objetivo de este estudio es el de profundizar en el conocimiento de las posibles características de funcionamiento rítmico, de rendimiento neuropsicológico y de rasgos de personalidad que se hallan presenten en los pacientes con patología dual. Los resultados podrán utilizarse para mejorar los abordajes tanto de prevención como de tratamiento de dichos pacientes.

¿En qué consiste su participación en el estudio?

En el transcurso del tratamiento o de la asistencia que recibe, se incluirán 3 o 4 días de exploración por parte de un profesional de la salud mental. En estas sesiones se le pasarán 8 cuestionarios que consisten en que le hagan algunas preguntas sobre su forma de pensar o actuar, así como el estado actual en que se encuentra.

También deberá realizar 9 tareas de rendimiento, algunas de ellas presentadas en el ordenador y otras que se las pasará el profesional. El tercer día de exploración se le colocará una muñequera que lleva incorporado un aparato de registro de la temperatura corporal periférica y que llevará durante dos días sin que ello le impida realizar todas sus actividades habituales (para ducharse puede colocar una bolsa de plástico por encima) y que devolverá el último día de exploración.

Se prevé que las sesiones de exploración duren entre 2,5h. y 3h., dependiendo de la rapidez con la que se responda o ejecuten las tareas. Por último, se le recogerá una muestra de saliva de primera hora de la mañana para efectuar una determinación endocrina (melatonina) coincidiendo con una de las visitas programadas en su Centro de Salud Mental o unidad de referencia para el estudio. Las muestras de saliva sólo se

utilizarán para la medición de sus niveles de melatonina.

Beneficios

El hecho de participar en el estudio no implica ningún beneficio directo o inmediato para Ud., pero permitirá mejorar su evaluación e incorporar mejoras en la atención no solo a su persona sino a todas las personas afectadas por esta patología.

Compromiso de confidencialidad.

Toda la información sobre usted y su enfermedad será tratada de forma confidencial y solo podrán tener acceso a ella los profesionales responsables de su atención relacionadas con el presente estudio.

De conformidad con lo que establece la ***L.O. 15/1999, de 13 Diciembre y de Protección de Datos de Carácter Personal (artículo 3, punto 6 del Real Decreto 223/2004***), declaro haber sido informado:

1. De la existencia de un fichero o tratamiento de datos de carácter personal, de la finalidad de la recogida de éstos y de los destinatarios de la información.
2. De la identidad y dirección del responsable del fichero de datos.
3. De la disponibilidad de ejercitar los derechos de acceso, rectificación y oposición dirigiéndome por escrito al titular del fichero de datos.

Voluntariedad

La participación en este estudio es totalmente voluntaria y se puede retirar de él en cualquier momento sin que deba dar explicaciones a nadie.

Más información.

Si desea más información sobre este proyecto puede solicitarla a los profesionales de este estudio.

Consentimiento Informado del paciente para participar en el estudio "Ritmicidad circadiana, rendimiento cognitivo y personalidad en pacientes con patología dual"

El Sr./Sra. (nombre y apellidos) .....accedo a participar en la investigación "Ritmicidad circadiana, rendimiento cognitivo y personalidad en pacientes con patología dual" y declaro que:

1. He recibido y comprendido la información sobre el estudio en el que me proponen participar.
2. He recibido una hoja informativa que explica las características del estudio.
3. He sido informado de los riesgos y beneficios derivados de la participación.
4. Soy consciente de que la participación es voluntaria y que puedo retirarme cuando lo desee sin tener que dar explicaciones y sin que esto repercuta en mis cuidados médicos.

De conformidad con lo que establece la L.O. 15/1999, de 13 Diciembre y de Protección de Datos de Carácter Personal (artículo 3, punto 6 del Real Decreto 223/2004), declaro haber sido informado:

1. De la existencia de un fichero o tratamiento de datos de carácter personal, de la finalidad de la recogida de éstos y de los destinatarios de la información.
2. De la identidad y dirección del responsable del fichero de datos.
3. De la disponibilidad de ejercitar los derechos de acceso, rectificación y oposición dirigiéndome por escrito al titular del fichero de datos.

Y consiento que los datos clínicos referentes a mi enfermedad sean almacenados en un fichero automatizado, cuya información podrá ser manejada exclusivamente para fines científicos y referentes a este estudio.

Y he expresado estar de acuerdo en participar en el estudio.

(Firma del paciente) (Firma del investigador)

En,_____, _____de_____20