UNIVERSITAT DE BARCELONA

Factores de riesgo, neurocognición y respuesta al tratamiento en los trastornos del espectro impulsivo-compulsivo

Bernat Mora Maltas

FACTORES DE RIESGO, NEUROCOGNICIÓN Y RESPUESTA AL TRATAMIENTO EN LOS TRASTORNOS DEL ESPECTRO IMPULSIVO-COMPULSIVO

Memoria de la tesis doctoral presentada por

Bernat Mora Maltas

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Dirigida por:

Susana Jiménez Murcia[1,2,3,4]

Fernando Fernández Aranda[1,2,3,4]

[1]Servicio de Psicología Clínica, Hospital Universitario de Bellvitge, L'Hospitalet de Llobregat

[2]Grupo de Investigación Psiconeurobiología de los Trastornos de la Conducta Alimentaria y Conductas Adictivas, Programa en Neurociencias, Instituto de Investigación Biomédica de Bellvitge – IDIBELL, L'Hospitalet de Llobregat

[3]Departamento de Ciencias Clínicas, Facultad de Medicina y Ciencias de la Salud, Universidad de Barcelona, Barcelona

[4]CIBER Fisiopatología de la Obesidad y la Nutrición (CIBERobn), Instituto de Salud Carlos III, Madrid

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GLOSARIO DE ACRÓNIMOS

AN	Anorexia Nerviosa
AN-R	Anorexia Nerviosa Restrictiva
APA	Asociación Americana de Psiquiatría
ATC	Antidepresivo Tricíclico
BN	Bulimia Nerviosa
CC	Compra Compulsiva
CCK	Colecistoquinina
CPFDL	Corteza Prefrontal Dorsolateral
DM2	Diabetes Mellitus tipo 2
DSM	*Diagnostic and Statistical Manual of Mental Disorders* (Manual Diagnóstico y Estadístico de los Trastornos Mentales)
FFEE	Funciones Ejecutivas
GLP-1:	*Glucagon-like peptide 1* (péptido similar al glucagón tipo 1)
GWAS	*Genome-Wide Association Studies* (Estudios de Asociación del Genoma Completo)
HUB	Hospital Universitario de Bellvitge
IMC	Índice de Masa Corporal
ISRS	Inhibidor Selectivo de la Recaptación de Serotonina
LEAP-2	*Liver-Expressed Antimicrobial Peptide* 2 (Péptido antimicrobiano expresado en el hígado 2)
NIMH	*National Institute of Mental Health* (Instituto Nacional de Salud Mental)
OSFED	*Other Specified Feeding or Eating Disorder* (Otro Trastorno de la Conducta Alimentaria o de la Ingesta de Alimentos Especificados)
PYY	Péptido YY
RDoC	*Research Domain Criteria* (Criterios de Dominio de Investigación)

TA	Trastorno por Atracón
TCA	Trastornos de la Conducta Alimentaria
TCANE	Trastorno de la Conducta Alimentaria o de la ingesta de alimentos No Especificados
TCC	Terapia Cognitivo-Conductual
TDAH	Trastorno por Déficit de Atención e Hiperactividad
TDM	Trastorno Depresivo Mayor
TEA	Trastorno del Espectro Autista
TEPT	Trastorno de Estrés Postraumático
TJ	Trastorno de Juego
TLP	Trastorno Límite de la Personalidad
TOC	Trastorno Obsesivo Compulsivo
TUS	Trastorno por Uso de Sustancias
WCST	Test de Clasificación de Tarjetas de Wisconsin

ENUMERACIÓN DE ARTÍCULOS QUE COMPONEN LA TESIS

Tesis en formato de compendio de artículos.

La tesis consta de tres objetivos generales y cinco artículos. Todos los artículos se han realizado en las siguientes unidades: Unidad de Trastornos de la Conducta Alimentaria y Unidad de Trastorno de Juego y otras Adicciones Conductuales, del Departamento de Psicología Clínica del Hospital Universitario de Bellvitge (HUB).

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RESUMEN

Introducción

La neurocognición es uno de los procesos neurobiológicos que permite conceptualizar la impulsividad y la compulsividad. Desde un enfoque transdiagnóstico, es clínicamente útil enfocarse en los procesos neuropsicológicos alterados, ya que estos pueden representar un mecanismo fisiopatológico común en varios trastornos. Los trastornos del espectro impulsivo-compulsivo, donde se incluyen los trastornos de la conducta alimentaria (TCA), la obesidad, y el trastorno de juego (TJ), se caracteriza por déficits en las funciones ejecutivas (FFEE). Las FFEE son aquellos procesos cognitivos superiores que asocian ideas, movimientos y acciones y los orientan a la resolución de problemas.

Los TCA se caracterizan por alteraciones en la ingesta de alimentos y en la autoimagen corporal, los cuales conllevan una serie de problemas físicos y afectan considerablemente el funcionamiento psicosocial del individuo. Los déficits neuropsicológicos relacionados con la impulsividad y la compulsividad, como la toma de decisiones o la flexibilidad cognitiva, se asocian a los síntomas observados en estos pacientes. Asimismo, estas alteraciones cognitivas también se relacionan con la gravedad del trastorno y a una peor respuesta al tratamiento. En la obesidad, perfiles cognitivos deficitarios se han asociado al inicio y progresión de la enfermedad.

El TJ se caracteriza por una conducta de juego desadaptativa, persistente y recurrente que causa una afectación significativa en el funcionamiento psicosocial del individuo. Una de las clasificaciones más comunes divide a los pacientes con TJ según el papel del azar de su modalidad de juego, dando lugar a los jugadores estratégicos y los jugadores no estratégicos. A nivel neuropsicológico, la mayoría de los estudios han identificado deficiencias neuropsicológicas en las FFEE, como la toma de decisiones, la flexibilidad cognitiva, el control inhibitorio o la memoria de trabajo. Estas dificultades cognitivas, asociadas a los circuitos motivacionales y de autorregulación, aumentan la probabilidad de iniciar o mantener comportamientos adictivos. Asimismo, alteraciones cognitivas también se han relacionado con la gravedad del TJ y con mediadores importantes en la conducta de juego como las distorsiones cognitivas o la impulsividad.

Hipótesis y Objetivos

Se preveía que los pacientes con TCA y obesidad presentarían un peor rendimiento cognitivo y que estas dificultades estarían asociadas a una mayor gravedad de los síntomas y/o a mayor duración del trastorno. También se hipotetizó que aquellos pacientes que presentaban comorbilidad con otro trastorno del espectro impulsivo-compulsivo, como la compra compulsiva (CC), mostrarían un peor rendimiento cognitivo y una peor respuesta al tratamiento.

En el TJ, se hipotetizó que el rendimiento cognitivo estaría afectado y podría estar vinculado a distorsiones cognitivas específicas y a una mayor impulsividad, así como a un perfil neuroendocrino determinado. Se preveía que el rendimiento cognitivo tendría un impacto distinto en la gravedad del trastorno en función de las preferencias del tipo de juego (estratégico / no estratégico).

De esta manera, la presente tesis tuvo como objetivo comparar el rendimiento neuropsicológico en pacientes del espectro impulsivo-compulsivo y personas sanas, así como analizar la asociación entre la gravedad clínica y psicopatológica y el rendimiento neuropsicológico en estos pacientes. Por último, se propuso comparar el funcionamiento cognitivo y la respuesta a tratamiento en personas con TCA, con y sin adicción conductual comórbida.

Métodos

La tesis se compuso por un total de cinco estudios llevados a cabo en las Unidades de TCA y de Adicciones conductuales del Hospital Universitario de Bellvitge. Los diagnósticos de TCA y de TJ se realizaron en base al DSM-5. Para lograr los objetivos, se realizaron evaluaciones para recopilar datos que incluían variables neuropsicológicas, clínicas y neuroendocrinas.

Resultados

Las FFEE asociadas a la impulsividad y a la compulsividad resultaron alteradas en los trastornos estudiados. Los pacientes con diagnóstico de trastorno del espectro bulímico con y sin CC comórbida, anorexia nerviosa restrictiva (AN-R), obesidad con y sin diabetes (DM2) y TJ mostraron mayores dificultades en la toma de decisiones y/o en la flexibilidad cognitiva en comparación con los individuos sanos. En el TJ, la conducta

compulsiva de abstinencia fue el criterio del DSM-5 de mayor relevancia. En el grupo de obesidad con DM2, se hallaron mayores niveles de impulsividad cognitiva, mientras que en el grupo de obesidad sin DM2, se encontraron mayores niveles de compulsividad cognitiva.

Respecto a la asociación entre el rendimiento neuropsicológico y la gravedad de los trastornos, en los TCA, los déficits en la flexibilidad cognitiva se asociaron a pacientes con AN y con trastorno del espectro bulímico que presentaban una mayor duración de la enfermedad, mientras que los criterios de gravedad del DSM-5 y la obsesión por la delgadez no lograron discriminar las dificultades cognitivas. El grupo de pacientes con trastorno del espectro bulímico y CC comórbida eran los que presentaban una peor flexibilidad cognitiva y toma de decisiones, así como un perfil de mayor gravedad en comparación con el grupo control y los pacientes con trastornos del espectro bulímico sin comorbilidad. En el TJ, los déficits en la toma de decisiones, flexibilidad cognitiva, memoria de trabajo y control inhibitorio se asociaron a la gravedad del TJ debido a su asociación con la impulsividad rasgo y las distorsiones cognitivas. Sin embargo, un mejor rendimiento cognitivo se asoció de forma directa con una mayor gravedad del TJ. En los individuos con preferencia por el juego no estratégico, los déficits en la memoria de trabajo se asociaron a distorsiones cognitivas de expectativa y de control predictivo, mientras que quienes presentaban una preferencia por el juego estratégico, las dificultades en la flexibilidad cognitiva se asociaron a distorsiones de ilusión de control, control predictivo e incapacidad para parar de jugar. Aunque el rendimiento cognitivo no mostró asociaciones con las variables neuroendocrinas estudiadas, bajos niveles de adiponectina se relacionaban con la gravedad del TJ.

Conclusiones

A través del estudio del endofenotipo cognitivo de los TCA, la obesidad y el TJ, se aportan nuevas evidencias para estudiar la impulsividad y la compulsividad desde una perspectiva neurobiológica. Aquellas personas que presenten dificultades en las FFEE puede que no se beneficien de los tratamientos tradicionales, precisamente debido a sus características neuropsicológicas. Por lo tanto, el desarrollo de intervenciones terapéuticas centradas en la mejora de las funciones cognitivas, podrían ser eficaces para abordar estos aspectos que forman parte de la sintomatología de estos trastornos, y garantizar un adecuado enfoque terapéutico para estas personas.

1. INTRODUCCIÓN

1.1. MODELOS EXPLICATIVOS EN PSICOPATOLOGÍA

Las aproximaciones actuales para el abordaje clínico de los trastornos mentales, en gran medida, no logran integrar la complejidad y heterogeneidad de los síntomas que pueden ocurrir en un trastorno particular (1). A pesar de que el Manual Diagnóstico y Estadístico de los Trastornos Mentales (*Diagnostic and Statistical Manual of Mental Disorders* [DSM]) de la Asociación Americana de Psiquiatría (APA) es un instrumento útil de investigación y que aporta una ayuda clínica incalculable, su criterio se basa en un modelo categorial. Las diferentes categorías diagnósticas se generan a partir de varios síntomas observables o autorreportados, en lugar de fundamentarse en una base biológica sólida (2,3). Este hecho conlleva que los pacientes presenten diversas comorbilidades con otros trastornos psiquiátricos debido al solapamiento de algunos de los síntomas, que pueden estar presentes en numerosos diagnósticos (2).

Para ayudar a abordar estas limitaciones, el Instituto Nacional de Planes Estratégicos en Salud Mental (NIMH, por sus siglas en inglés "*National Institute of Mental Health*") de los Estados Unidos desarrolló la iniciativa *Research Domain Criteria* (RDoC) como una herramienta para incentivar a los investigadores nuevas formas de clasificar los trastornos mentales, más allá de las nosologías tradicionales. Este enfoque pretende clasificar la psicopatología mediante un modelo dimensional basado en el comportamiento observable y con medidas neurobiológicas (4,5). Su objetivo es determinar constructos que ayuden a la comprensión y clasificación de los trastornos mentales (6) y convertirse en una herramienta transdiagnóstico (7). Varios modelos dimensionales han sido propuestos. Por ejemplo, el espectro internalizante-externalizante (p.ej., depresión - abuso de sustancias) (8) o el espectro del humor (depresión - manía) (9). El espectro en el que se contextualizan los estudios incluidos en esta tesis es el conocido como espectro impulsivo-compulsivo. En él se incluyen trastornos de la conducta alimentaria (TCA) y adicciones comportamentales, entre otros (10), tal como se muestra en la Figura 1.

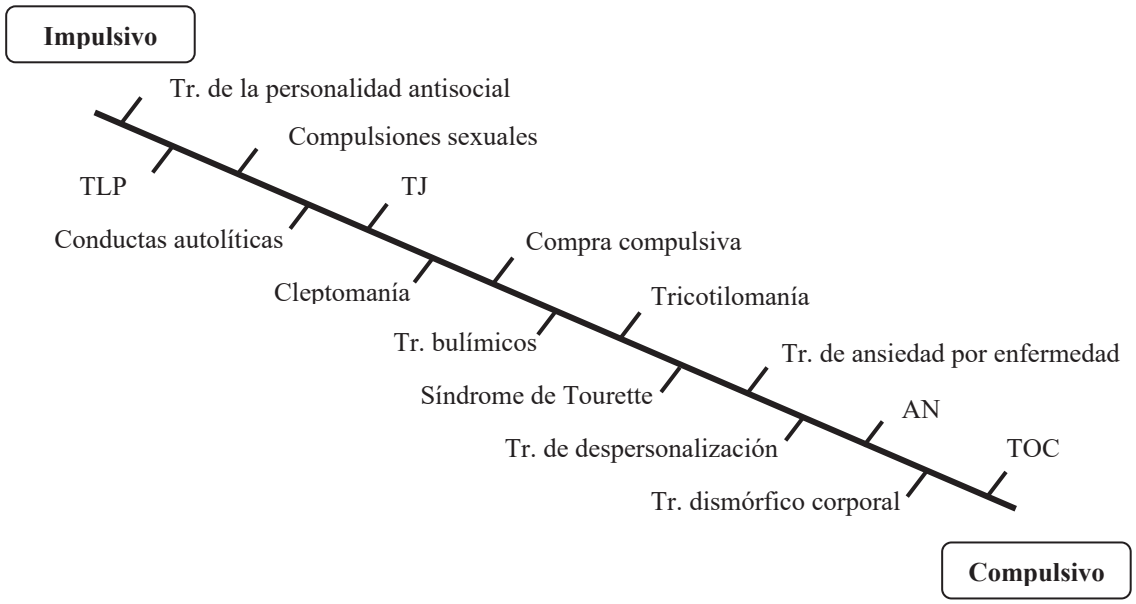

Figura 1. Espectro impulsivo – compulsivo.

Nota. Tr.: trastorno; TLP: trastorno límite de la personalidad; TJ: trastorno de juego; AN: anorexia nerviosa; TOC: trastorno obsesivo-compulsivo. Adaptada de Holander y Rosen (10)

1.2. ESPECTRO IMPULSIVO-COMPULSIVO

El espectro impulsivo-compulsivo, descrito en la Figura 1, se presentó como un modelo dimensional prometedor en la búsqueda de marcadores en los trastornos psiquiátricos y a nivel clínico (11). El constructo *impulsividad* se refiere a conductas o acciones que son inapropiadas, prematuras, indebidamente pensadas y arriesgadas que conducen a resultados adversos (12–14), mientras que la *compulsividad* se refiere a una tendencia hacia acciones repetitivas a pesar de sus consecuencias desfavorables y que tienen como objetivo aliviar el malestar (1). Clásicamente, se ha sugerido que ambos conceptos podrían constituir extremos opuestos de un espectro (15,16). Sin embargo, varios estudios coinciden en el solapamiento de estos dos constructos en términos neurobiológicos (17–19), y por tanto, síntomas impulsivos y compulsivos pueden coexistir en un mismo individuo (20). Asimismo, existe un alto nivel de comorbilidad entre los trastornos impulsivos y compulsivos y, cuando estos trastornos ocurren juntos, tienden a ser más graves (21).

1.3. ENDOFENOTIPO NEUROCOGNITIVO

Uno de los procesos neurobiológicos comunes donde es posible conceptualizar la impulsividad y la compulsividad es el de las medidas neurocognitivas. Desde un punto de vista transdiagnóstico, se destaca la utilidad clínica de centrarse en los procesos neuropsicológicos alterados, de manera que pueden trascender los límites de diagnóstico tradicionales y constituir un mecanismo fisiopatológico central común (1,22,23) o endofenotipo (Figura 2).

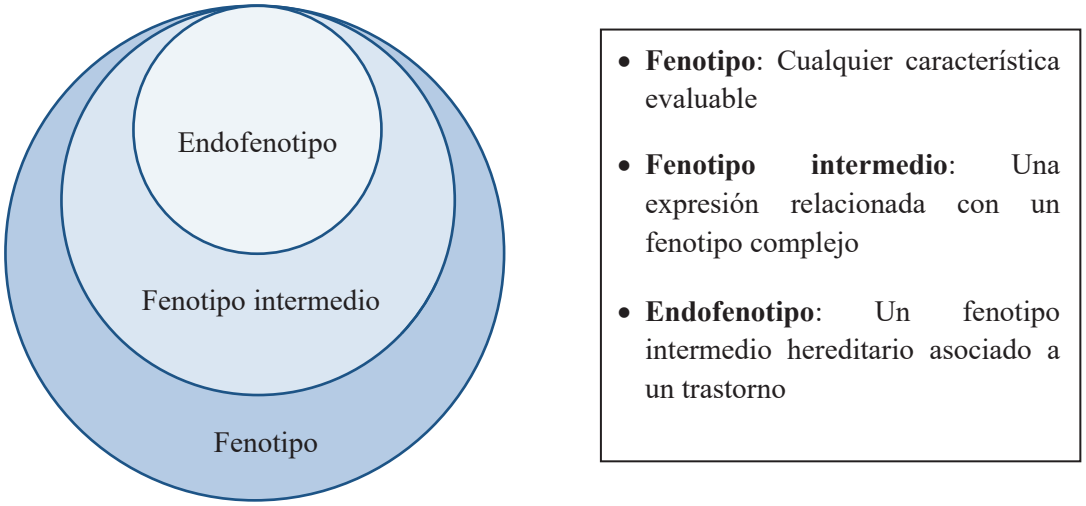

Figura 2. Fenotipos y endofenotipos. Adaptada de Goldman (24)

El término *endofenotipo* pretende mejorar la definición de los procesos conductuales y cognitivos asociados a déficits en los sistemas neurales, proporcionando medidas más cuantitativas y descripciones más precisas de los posibles déficits, evitando utilizar únicamente puntuaciones de cuestionarios clínicos (1). Un ejemplo de esta metodología es el consenso entre los expertos del RDoC, que describe un marco neuropsicológico transdiagnóstico en la adicción, evidenciando la existencia de un grupo de funciones neuropsicológicas comunes relacionadas con las funciones ejecutivas (FFEE) (y procesos neuronales subyacentes), que predisponen o mantienen las conductas adictivas (7).

1.4. NEUROPSICOLOGÍA DE LAS FUNCIONES EJECUTIVAS

Las FFEE, tal y como las entendemos, fueron descritas por primera vez por Muriel Lezak (25), señalando que su alteración puede conducir a graves problemas de

iniciación, modificación, control o interrupción de la acción, lo que deriva en una disminución de la conducta espontánea y un aumento de la perseveración e impulsividad. En este sentido, las FFEE se han definido como procesos cognitivos superiores que asocian ideas, movimientos y acciones y los orientan a la resolución de problemas (26–28), con la finalidad de realizar una conducta eficaz, creativa y socialmente aceptada (25,29). Las FFEE permiten prestar y focalizar la atención, razonar, tomar decisiones, tener autocontrol para evitar la impulsividad, considerar alternativas mentalmente o adaptarse de manera flexible a los cambios (30–32).

Existe un consenso a la hora de considerar la flexibilidad cognitiva, la inhibición y la memoria de trabajo como los tres principales componentes de las FFEE (26,33–36), y a partir de estos tres procesos ejecutivos, se construyen las funciones de nivel superior como la toma de decisiones, la planificación o la resolución de problemas (28,37–41). En este sentido, sin estos principales componentes de las FFEE, no hay perspectiva de una actividad mental coherente y las FFEE no podrían operar porque no existiría un campo de actuación estable para que realizaran su función (28,42).

Existen varios modelos que contemplan las FFEE como constructo unitario o como un sistema multimodal con distintos componentes independientes, aunque relacionados (28), sin que ninguno haya sido totalmente aceptado. Del mismo modo, también han surgido varios modelos neuropsicológicos en relación con los trastornos que se trabajan en esta tesis (Tabla 1).

1.4.1. Funciones ejecutivas en el espectro impulsivo-compulsivo

El endofenotipo neurocognitivo del espectro impulsivo-compulsivo se caracteriza por déficits en las FFEE relacionados con el autocontrol o la inhibición de la respuesta (43). La expresión de la impulsividad y la compulsividad es, a menudo, desadaptativa debido a los déficits en el control cognitivo *top-down*, es decir, en el proceso ejecutivo voluntario dirigido a metas (1). Aunque estos constructos comparten mecanismos neuropsicológicos que implican las FFEE, difieren en las funciones cognitivas involucradas que son disociables por diferentes componentes del circuito cortico-subcortical (1). A continuación, los detallamos.

Tabla 1. Modelos neuropsicológicos de los trastornos del espectro impulsivo-compulsivo

AUTORES	MODELOS	DESCRIPCIÓN
Robinson y Berridge (1993) (44)	Sensibilización motivacional: del gustar al necesitar	Proceso mediante el cual la respuesta a un estímulo se intensifica con la exposición repetida, pasando de un placer inicial a una necesidad creciente.
Goldstein y Volkow (2002) (45)	Daño en la atribución de relevancia y la inhibición de respuesta (I-RISA)	Implicaciones en la adicción, donde la capacidad para evaluar la importancia de estímulos se ve afectada, junto con las dificultades para inhibir respuestas inapropiadas.
Koob (2001); Koob y Le Moal (2008) (46,47)	Alostasis y estrés	Teoría que destaca la adaptación continua del organismo a estresores, llevando a cambios neurobiológicos para mantener la estabilidad, pero contribuyendo a la vulnerabilidad a las adicciones.
Damasio et al. (1990, 1991) (48,49)	Marcador somático	Propone que las emociones y respuestas corporales contribuyen a la toma de decisiones. En el contexto de adicciones, los marcadores somáticos podrían influir en la elección de comportamientos relacionados con sustancias.
Everitt y Robbins (2005, 2013, 2016) (17,50,51)	Hábito: de la impulsividad a la compulsividad	Desarrollo de comportamientos automáticos y repetitivos, pasando de impulsividad a compulsividad en el contexto de adicciones.
Aspen et al. (2013) (52)	Sesgo atencional en los TCA	Vulnerabilidades cognitivas predisponen a exhibir un sesgo de atención hacia estímulos relevantes conductas propias del TCA.
Kessler et al. (2016) (53)	Recompensa, control inhibitorio y el comportamiento habitual	Incluye circuitos implicados en el TCA como el control inhibitorio, la recompensa, la motivación y el comportamiento habitual.
Brooks et al. (2012) (54)	Modelo neurobiológico de control de los impulsos	Explora los mecanismos cerebrales involucrados en el control de impulsos y cómo las disfunciones en estas áreas pueden contribuir a comportamientos adictivos.
Robbins et al. (2012) (1)	Modelo neurobiológico impulsivo-compulsivo en TCA	Aplica el concepto de impulsividad-compulsividad específicamente a los TCA, destacando la interacción compleja entre factores neurobiológicos y conductuales en estos trastornos.

Nota. TCA: trastornos de la conducta alimentaria. Elaboración propia.

1.4.1.1. Funciones ejecutivas e impulsividad

Las conductas impulsivas pueden verse como resultante de deficiencias en una o más FFEE, alejándose de ser un sistema unitario (55–57). Varias funciones neuropsicológicas han sido estudiadas para evaluar la impulsividad. Entre ellas, destacan las siguientes:

Toma de decisiones

Habilidad para seleccionar el curso de acción más adaptativo entre un conjunto de posibles alternativas conductuales (58). Se trata de un proceso complejo en el que están implicados diversos aspectos como la consideración de los elementos cognitivos de la situación de decisión, de las contingencias de recompensa y castigo asociadas a cada una de las opciones, y de las señales emocionales asociadas a cada una de las posibles respuestas. Bechara et al. (59) describieron patrones de conducta específicos en pacientes neurológicos, caracterizadas por una tendencia a seleccionar cursos de acción asociados con recompensas inmediatas, incluso cuando éstos conllevan la aparición de importantes consecuencias negativas en el futuro.

Memoria de trabajo

Se define como aquellos mecanismos y procesos que mantienen las representaciones mentales necesarias para el procesamiento de una tarea cognitiva en curso (60). Así, la memoria de trabajo permite mantener y manipular información durante un breve periodo de tiempo en el que ya no está presente el estímulo perceptualmente presente (61–64) posibilitando la ejecución de tareas cognitivas complejas (65–67), y el procesamiento simultáneo de la misma u otra información (68). De esta forma, la memoria de trabajo gestiona el equilibrio de representaciones estables de información frente a interferencias, manteniendo una actualización cuando cambian las demandas de las tareas y requiriendo, por lo tanto, procesos de control cognitivo (69).

Control inhibitorio

Implica la capacidad de controlar la propia atención, comportamiento, pensamientos o emociones para anular una respuesta automática (una fuerte predisposición interna o externa), y realizar lo que se pretende (32,70–73). Algunos autores indican que la inhibición implica que el foco atencional se mantenga fijo en un tipo de estímulo,

facilitando que el sistema de control prevenga la aparición de interferencias (74–76). Diamond (32) destaca que la falta de control inhibitorio deja a la persona sometida a los estímulos externos, impulsos internos, fijaciones o respuestas condicionadas, por lo que su buen funcionamiento nos permite poner en práctica las facultades del cambio y de la elección, o lo que es lo mismo, el control voluntario de cómo reaccionar.

1.4.1.2. Funciones ejecutivas y compulsividad

A diferencia de la impulsividad, la compulsividad se considera una dimensión que incluye otros componentes cognitivos (77). La complejidad de este concepto reside en el hecho de que añade un componente afectivo a las conductas, ya que el objetivo es la reducción del malestar o la prevención de algún acontecimiento negativo (78). El estudio de la compulsividad se ha limitado a menudo a su relación con el trastorno obsesivo-compulsivo (TOC) (79), que puede considerarse la manifestación fenotípica paradigmática. Sin embargo, no es el único, ya que, como se expondrá a lo largo de la presente tesis, también parece ser un elemento central en los TCA y en el trastorno de juego (TJ), así como en otras adicciones conductuales (80). A continuación, se detallan las funciones cognitivas más relevantes referentes a la compulsividad:

Flexibilidad cognitiva

Se define como la capacidad de cambiar la atención de un paradigma conceptual o estrategia a otro, con el fin de adaptar la actividad mental y el comportamiento de acuerdo con las demandas del ambiente (81). En este sentido, permite a la persona considerar una situación desde una perspectiva nueva y diferente, o alternar con facilidad y rapidez entre diferentes perspectivas, ajustándose rápidamente al cambio en función de las demandas o prioridades (32,82). Cuando existe una rigidez cognitiva, se es incapaz de ver las cosas de otra forma (83), predominando enfoques concretos y rígidos a la resolución de problemas y que pueden favorecer la aparición de respuestas inflexibles en forma de comportamientos perseverativos o estereotipados (84–86).

Asimismo, la atención está involucrada de manera importante en la flexibilidad cognitiva, entre otras (87,88). Concretamente, en los subtipos de atención del modelo de Sohlberg y Mateer (89) (Tabla 2), la atención alternante, la selectiva y la dividida, pueden ser consideradas medidas de flexibilidad cognitiva.

Tal como se muestra en la Tabla 2, el modelo actualizado Sohlberg y Mateer (89) consta de cinco componentes:

Tabla 2. Componentes de la atención

Atención focalizada	Habilidad para responder de forma específica a un estímulo. Representaría el nivel más básico de atención.
Atención sostenida	Habilidad para mantener una respuesta constante durante la realización de una actividad continua y repetitiva.
Atención selectiva	Capacidad de mantener una actividad cognitiva o comportamental frente a la presencia de estímulos distractores externos (p.ej., sonidos) e internos (p. ej., preocupaciones).
Atención alternante	Flexibilidad mental que permite cambiar el foco de atención entre tareas con demandas cognitivas distintas, controlando qué información será procesada en cada momento.
Atención dividida	Implica responder simultáneamente a múltiples tareas o múltiples demandas cognitivas. Puede concebirse como una forma rápida y continua de atención alternante, requiriendo al menos una de ellas un procesamiento más automático e inconsciente.

Nota. Elaboración propia en base a Sohlberg y Mateer (89).

1.5. TRASTORNOS DE LA CONDUCTA ALIMENTARIA Y OBESIDAD

Los TCA engloban varios trastornos mentales caracterizados por alteraciones graves en la ingesta de alimentos y en la autoimagen corporal, que implican una serie de problemas físicos y afectan notablemente al funcionamiento psicosocial del individuo (90). La versión actual del Manual Diagnóstico y Estadístico de los Trastornos Mentales (DSM-5 y DSM-5-TR) (91,92) incluye los siguientes TCA: la pica, el trastorno de rumiación, trastorno de evitación/restricción de la ingestión de alimentos, la anorexia nerviosa (AN), la bulimia nerviosa (BN), el trastorno por atracón (TA), otros trastornos de la conducta alimentaria o de la ingesta de alimentos especificados (OSFED por su siglas en inglés: *Other Specified Feeding or Eating Disorder*) y el trastorno de la conducta alimentaria o de la ingesta de alimentos no especificados (TCANE). En la Tabla 3 quedan descritas las características principales de los TCA.

Tabla 3. Características principales de los TCA

TRASTORNO DE LA CONDUCTA ALIMENTARIA	DESCRIPCIÓN	TIPOS
Anorexia Nerviosa (AN)	Se caracteriza por el bajo peso, el miedo intenso a recuperar peso y la distorsión de la imagen corporal.	• Restrictivo (ausencia de atracones o purgas durante los últimos tres meses) • Con atracones/purgas (el individuo ha presentado episodios de atracones y purgas recurrentes)
Bulimia Nerviosa (BN)	Presencia de atracones y conductas purgativas (vómito autoinducido, laxantes, diuréticos) u otras conductas para perder peso (p.ej., ayuno o ejercicio físico compensatorio).	
Trastorno por Atracón (TA)	Presencia de atracones recurrentes sin conducta compensatoria. Un elevado número de personas con dicho trastorno presentan también obesidad.	
Otro Trastorno de la Conducta Alimentaria o de la ingesta de alimentos Especificado (OSFED)	Presencia de algunos síntomas de los trastornos descritos anteriormente.	• AN atípica (se cumplen los criterios para el diagnóstico de AN excepto el de infrapeso) • BN de frecuencia baja y/o duración limitada (las conductas compensatorias se producen menos de una vez a la semana de promedio o bien la duración del cuadro de BN no alcanza los tres meses todavía) • TA de frecuencia baja y/o duración limitada (los atracones se producen menos de una vez a la semana de promedio o bien la duración de éstos no alcanza los tres meses todavía) • Trastorno por Purgas (conductas purgativas en ausencia de atracones con la finalidad de influir en el peso/constitución) • Síndrome de la Ingesta Nocturna de Alimentos (ingesta excesiva de alimentos después de cenar o durante la noche)
Pica	Ingesta recurrente de sustancias no nutritivas en ausencia de otro trastorno mental o afección médica.	
Trastorno de Rumiación	Regurgitación repetida de alimentos en ausencia de afección médica.	
Trastorno de Evitación/Restricción de la Ingestión de Alimentos	Evitación de ciertos alimentos por sus propiedades físicas (textura, sabor…), falta de interés por alimentarse o preocupación sobre las consecuencias repulsivas de la conducta de alimentarse.	
Trastorno de la Conducta Alimentaria o de la Ingesta de Alimentos No Especificada (TCANE)	Presencia de síntomas propios de los TCA sin llegar a cumplir criterios de las categorías diagnósticas previamente descritas.	

Nota. TCA: trastorno de la conducta alimentaria. Elaboración propia en base al DSM-5 (91).

En los estudios del presente trabajo, la pica, el trastorno de rumiación y el trastorno de evitación/restricción de la ingestión de alimentos no se tendrán en cuenta al abordar los TCA. Asimismo, forman parte del espectro bulímico la BN y el TA.

1.5.1. Gravedad de los TCA

El DSM-5 (91,92) expone cuatro criterios de gravedad (leve, moderado, grave y extremo) para la AN, la BN y el TA, que quedan descritos en la Tabla 4. Sin embargo, Dang et al. (93), en un reciente metaanálisis evidenció las limitaciones de la clasificación actual de la gravedad de los TCA. Otros estudios también han destacado que los criterios y puntos de corte utilizados para definir la gravedad de los TCA son controvertidos y carecen de apoyo empírico suficiente (94–99).

Tabla 4. Gravedad de los principales TCA

	AN	**BN**	**TA**
Leve	IMC ≥ 17	1-3 conductas compensatorias/semana	1-3 atracones/semana
Moderado	IMC 16-16,99	4-7 conductas compensatorias/semana	4-7 atracones/semana
Grave	IMC 15-15,99	8-13 conductas compensatorias/semana	8-13 atracones/semana
Extremo	IMC < 15	≥ 14 conductas compensatorias/semana	≥ 14 atracones/semana

Nota. AN: anorexia nerviosa; BN: bulimia nerviosa; TA: trastorno por atracón; IMC: índice de masa corporal. Elaboración propia en base al DSM-5 (91).

1.5.2. Prevalencia

En cuanto a la prevalencia de vida de los TCA, Van Eeden et al. (100) concluyen que la AN asciende al 4% en mujeres y al 0,3% en hombres, mientras que un 3% de mujeres y un 1% de hombres llegan a desarrollar BN a lo largo de su vida. Por lo que refiere al TA, un estudio reciente informa de una prevalencia de vida de 0,6-1,8% en mujeres y del 0,3-0,7% en hombres (101). En general, los TCA son más prevalentes en el sexo femenino y en población occidental (102) y los estudios apuntan a un incremento de la incidencia en estos últimos años, especialmente en el contexto de la pandemia de COVID-19 (100,103,104).

1.5.3. Etiopatogenia

Los TCA son patologías complejas y multicausales que resultan de la interacción de diversos factores médicos, nutricionales, psicológicos, psiquiátricos, familiares y socioculturales que contribuyen al desarrollo y mantenimiento de la enfermedad (105,106). Aun así, se ha procurado identificar factores de riesgo comunes que puedan predecir su inicio (90,106–109). En la misma línea, la academia de trastornos de la alimentación ha informado de evidencias actuales en relación a los factores de riesgo de los TCA (110). Estos son divididos en causas predisponentes (vulnerabilidades de fondo), precipitantes (el contexto ambiental en el momento de inicio) y factores perpetuantes (aspectos secundarios de la enfermedad que hace que ésta sea valorada y mantenida), tal y como se muestra en la Tabla 5.

Factores biológicos

A nivel genético, los estudios de asociación del genoma completo (GWAS, *Genome-Wide Association Studies*) informan de ciertas variantes genéticas asociadas a los TCA (111,112). Los hallazgos obtenidos informan de mayor evidencia en la AN (90,113,114). Una revisión actual informa que las mujeres también tienen mayor riesgo genético de sufrir un TCA, ya que, muestran una mayor heredabilidad al impulso por la delgadez y a la insatisfacción corporal (106). Además, destaca que para los TCA bulímico-purgativos (BN y TA) se observan correlaciones genéticas más robustas con el trastorno por déficit de atención e hiperactividad (TDAH), así como con el sobrepeso y la obesidad. En cambio, en la AN, especialmente el tipo restrictivo (AN-R), tiene fuertes correlaciones con el TOC, el trastorno depresivo mayor (TDM), las tendencias suicidas, la esquizofrenia, el neuroticismo, el autismo y los déficits en el neurodesarrollo. Genes asociados a la AN parecen mantener una relación bidireccional con un índice de masa corporal (IMC) bajo (106).

Los sistemas de neurotransmisores más relevantes en los TCA son la dopamina, que juega un papel en la búsqueda de estímulos relacionados con el apetito y de señales de recompensa, y la serotonina, que está asociada con la inhibición del comportamiento, la reactividad negativa y las emociones desfavorables (115,116).

Tabla 5. Factores de riesgo de los TCA

	TIPOS DE TCA	
	Trastornos de la conducta alimentaria restrictivos	**Trastornos de la conducta alimentaria bulímicos**
Factores biológicos	Predisposición genética Ratio mujer hombre = 10:1 Rasgos TOC/ TEA Desregulación del apetito Vulnerabilidad metabólica Influencias ambientales en etapa perinatal	Predisposición genética Ratio mujer-hombre = 3:1 Vulnerabilidad metabólica Desregulación del apetito
Factores psicológicos	Perfeccionismo Baja tolerancia a la frustración Rigidez cognitiva Alta capacidad para retrasar la recompensa Diminución de la expresividad facial y de interpretar señales no verbales Teoría de la mente reducida Sensibilidad a la clasificación social Pobre capacidad de interacción social Alteración de la imagen corporal Alexitimia	Adversidades en la infancia Rasgos de TDAH Incapacidad para retrasar la recompensa Problemas de cognición social con evitación emocional Alteración de la imagen corporal Alexitimia
Factores psicosociales	Problemas alimentarios de los padres Estrés entre iguales (p.ej., acoso) Exposición a trauma Cultura industrializada/occidental Idealización de la delgadez Nivel socioeconómico medio-alto	Problemas alimentarios de los padres Presión de grupo (p.ej., acoso) Conversaciones sobre aspectos despectivos de la forma del cuerpo Exposición a trauma Cultura industrializada/occidental Idealización de la delgadez
Factores comportamentales	Sobrecontrol del peso y alimentación Preocupación excesiva por el IMC Afrontamiento por evitación Aislamiento social Deterioro de la calidad de vida	Conductas de control de peso Preocupación excesiva por el IMC Afrontamiento por evitación Aislamiento social Deterioro de la calidad de vida

Nota. TOC: trastorno obsesivo-compulsivo. TEA: trastorno del espectro autista. TDAH: trastorno por déficit de atención e hiperactividad. IMC: índice de masa corporal. Elaboración propia adaptada de Treasure et al. (90).

Las hormonas reguladoras del apetito también influyen en el funcionamiento cerebral (117). El hambre y la saciedad están reguladas por el tracto gastrointestinal y los sistemas endocrino y nervioso, a través de la integración de señales hormonales, neuronales, metabólicas, conductuales y cognitivas (118), en las que la estructura central es el hipotálamo (Figura 3) (119). Mediante la estimulación o amortiguación de la respuesta cerebral dopaminérgica, los neuropéptidos hipotalámicos (p. ej., endocannabinoides y opioides) y las hormonas intestinales periféricas como la grelina, insulina y leptina, pueden alterar los circuitos normales de recompensa alimentaria, tal como queda reflejado en la Figura 3 (120–124).

Factores socioambientales

El contexto sociocultural influye tanto en la alimentación como en la imagen corporal, por lo que tiene un papel importante en la etiología de los TCA (90). En este contexto, altos niveles de insatisfacción corporal e internalización del ideal de delgadez son predictores de inicio del trastorno e indicadores de la psicopatología actual de los TCA (125–127). En este sentido, algunas personas llevan a cabo dietas y restricción de ciertos alimentos para poder ajustarse al ideal que se promueve en la sociedad y en los medios de comunicación (109,128–130).

Son muchos otros los factores que pueden influir en que una persona desarrolle y mantenga un TCA. Por ejemplo, la práctica de deportes de élite es un factor de riesgo potencial para conductas alimentarias patológicas entre hombres y mujeres atletas (131–133). Hallazgos recientes también indican que las personas pertenecientes a grupos LGBTQI+ tienen un mayor riesgo de sintomatología TCA y trastornos de la imagen corporal en comparación con individuos heterosexuales (134–136).

Factores psicológicos

A nivel psicológico, una baja autoestima, niveles elevados de evitación al daño y puntuaciones bajas en autodirección y cooperación han sido asociados a la psicopatología alimentaria (137–141). Un elevado neuroticismo también se ha relacionado con el desarrollo de un TCA (138,142,143). Sin embargo, tal y como se observa en la Tabla 5, la prevalencia de rasgos de personalidad y comportamientos parece diferir según la categoría diagnóstica entre los diferentes TCA (90,106). Mientras que niveles elevados de perfeccionismo son comunes entre AN y BN (144–146), los rasgos obsesivos se han

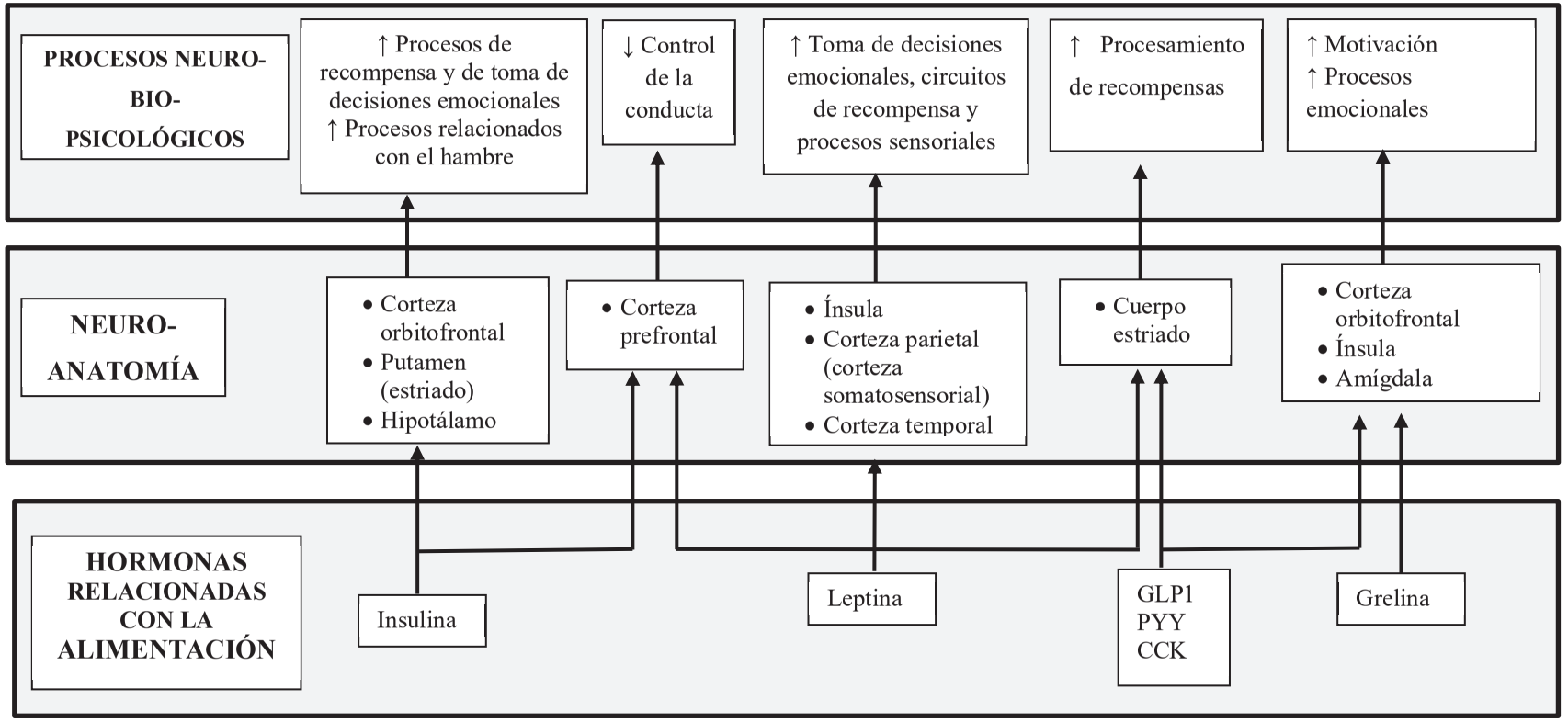

Figura 3. Representación esquemática de las vías de comunicación intestino-cerebro

Nota. GLP1: péptido similar al glucagón tipo 1; PYY: péptido YY; CCK: colecistoquinina. Adaptada de Giel et al. (147).

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asociado con la AN-R, mientras que las conductas de atracones/purgas se han relacionado con la impulsividad y con una mayor desregulación emocional (148–151).

A pesar de que se ha observado la coexistencia entre los TCA y determinados trastornos de personalidad (p. ej., trastorno límite de la personalidad [TLP] y atracones/purgas) (152), los trastornos del estado de ánimo y de ansiedad representan las comorbilidades psiquiátricas más comunes en personas con TCA (p. ej., el TDM afecta a más del 75% de los TCA con atracones/purgas, el trastorno por ansiedad social afecta al 42% de los adultos con TCA) (153–155). Algunos autores sugieren que la presencia de un trastorno de ansiedad diagnosticado en la infancia (p. ej., TOC) puede preceder a la aparición de un TCA (156,157). Otros factores psicológicos que parecen contribuir al riesgo en los TCA incluyen diagnósticos de trastorno de estrés postraumático (TEPT), TDAH o trastorno del espectro autista (TEA) (158–160).

Otro factor de vulnerabilidad psicológica de los TCA son las disfunciones cognitivas que se describen posteriormente, en el apartado 1.5.7.

1.5.4. Curso

El inicio de los TCA suele darse en la adolescencia temprana (161), aunque en ese momento, son más frecuentes los síntomas parciales por lo que no se llega a cumplir criterios diagnósticos (162). Aun así, estos casos tienen un mayor riesgo de desarrollar AN (163), BN (164) o continuar con síndromes parciales del trastorno (162,163). Tales hallazgos plantean la posibilidad de que los TCA se inicien con formas más leves, habiendo una progresión más lenta desde la adolescencia hacia trastornos más graves en la edad adulta temprana (165).

El curso y la evolución de los TCA pueden variar. Además de las altas y frecuentes tasas de abandono (166,167) y de recaídas (168), a lo largo del tratamiento, la investigación sugiere que estas enfermedades pueden ser catalogadas como graves y duraderas en aproximadamente la mitad de los casos (166,169), mientras que otros autores consideran que solo un 10-20% de los casos desarrollan una enfermedad de larga duración (170). El riesgo de mortalidad es elevado, especialmente en la AN (171).

Un gran número de los casos de AN-R pueden desarrollar síntomas bulímicos, con una transición a BN que oscila entre el 20 y el 40% (172–175), y generalmente ocurre en los 5 primeros años (172,176,177). Esto se debe a que comparten una serie de características clínicas, como preocupaciones sobre la imagen corporal y una sobrevaloración de la importancia del peso y la forma corporal (178).

En la BN, las recaídas son frecuentes especialmente en aquellas personas en las que persiste una insatisfacción corporal y un marcado deterioro en el funcionamiento psicosocial (179). A diferencia de la AN y la BN, el TA acostumbra a iniciarse en la ya entrada edad adulta (180). El descontrol en el comer como síntoma central, frecuentemente conduce de un TA a BN (181).

1.5.5. Tratamiento

Existe una variedad de intervenciones, más o menos estandarizadas y evaluadas, para tratar a los pacientes con TCA. Según la guía del Instituto Nacional para la Salud y la Excelencia Asistencial (182), en población adulta, la terapia cognitivo-conductual (TCC) es altamente recomendada para la BN y para el TA. Sin embargo, varios metaanálisis no encuentran resultados concluyentes respecto a la mayor efectividad de los tratamientos psicológicos (183,184). Para los adolescentes con AN, se demostró la eficacia de la terapia familiar (185).

Dadas las tasas de remisión limitadas logradas en los TCA, se han desarrollado nuevos tratamientos dirigidos a aspectos específicos del trastorno. Entre ellos, destacan los tratamientos dirigidos al funcionamiento cerebral que han sido diseñados para reducir los hábitos alimentarios patológicos y promover nuevos aprendizajes. Por ejemplo, la terapia de remediación cognitiva tiene el objetivo de mejorar el funcionamiento neuropsicológico (p.ej., flexibilidad cognitiva) comúnmente afectado en los TCA (186). En el espectro bulímico, se han desarrollado técnicas computarizadas que se centran la modificación de procesos cognitivos como la inhibición, la impulsividad y sesgos atencionales asociados (90) para abordar la conducta de comer en exceso y el aumento de peso (187). Sin embargo, estas técnicas todavía están en progreso (90).

Entre las intervenciones farmacológicas, en la AN los antidepresivos tricíclicos (ATC) y los inhibidores selectivos de la recaptación de serotonina (ISRS) han demostrado ser los más eficaces, mientras que en el TA, la lisdexanfetamina y los antidepresivos son los más utilizados (184). Hay que destacar, sin embargo, que el tratamiento farmacológico no es de

primera elección en los TCA (182) y que, a menudo, se utiliza para el abordaje de ciertas comorbilidades (188).

En conclusión, teniendo en cuenta la diversidad de causas de los TCA, es necesario implementar un enfoque interdisciplinario para conseguir un tratamiento eficaz. La intervención psicológica debe ser complementada con asesoramiento nutricional, manejo de las complicaciones médicas relacionadas con los TCA y, en caso de ser necesario, tratamiento psicofarmacológico.

1.5.6. Obesidad

La obesidad se define como una condición médica que implica una acumulación anormal o excesiva de grasa que supone un riesgo para la salud (189). El cálculo del IMC es el método más común para determinar si una persona adulta presenta sobrepeso u obesidad. Se calcula dividiendo los kilogramos de peso entre el cuadrado de la estatura en metros (IMC = kg/m^2). De este modo, un IMC comprendido entre 25 y 29,9 corresponde al sobrepeso y, cuando es igual o superior a 30, indica obesidad. Por el contrario, se considera normopeso un IMC entre 18,5 y 24,9.

Si bien diversos estudios han demostrado que la obesidad está determinada por factores genéticos, socioeconómicos y ambientales, también se ha examinado la asociación entre factores psicológicos, como la personalidad (190–192). Así, rasgos como la autodirección, la autodisciplina, la prudencia y el autocontrol han resultado ser un factor protector de la obesidad (193,194), mientras que el neuroticismo se ha observado como factor de riesgo (191,195).

La obesidad a menudo se asocia a la BN y, especialmente, al TA así como a trastornos metabólicos (30-40%) (196–198). Existe una relación reconocida desde hace tiempo entre la obesidad y la diabetes mellitus tipo 2 (DM2) que explica claramente la alta prevalencia de DM2 propia de muchos países (199).

La DM2 es un factor de riesgo importante para enfermedades cardiovasculares y, teniendo en cuenta que la obesidad a menudo también se asocia con la hipertensión y la dislipemia, muchos pacientes con obesidad se caracterizan por una agrupación de procesos metabólicos y factores de riesgo cardiovascular (200–202).

1.5.7. Neuropsicología de los TCA como factor transdiagnóstico

La mayoría de las investigaciones relevantes hasta la fecha han analizado el funcionamiento neurocognitivo según el diagnóstico de TCA o el estado de peso. Siguiendo los objetivos de RDoC, explorar la neuropsicología de los TCA desde una perspectiva dimensional puede ayudar a esclarecer si los déficits cognitivos están específicamente ligados a las categorías diagnósticas (tipos de TCA) o más bien se relacionan con tipos y niveles específicos de síntomas. En este sentido, el estudio de muestras mixtas en los TCA puede arrojar luz sobre posibles subtipos neurocognitivos distintos entre los TCA que puedan diferenciar amplios espectros de síntomas, como por ejemplo el espectro bulímico y el restrictivo (203). El modelo transdiagnóstico planteado por Fairburn et al. (144) plantea que los diversos TCA comparten conductas similares y problemas subyacentes, como factores de mantenimiento (p.ej., la sobrevaloración de la forma y el peso). Además, también parecen compartir una base psicopatológica, expresándose en parte como una incapacidad para regular la recompensa y el castigo, y donde la ingesta alimentaria excesiva o restrictiva puede mostrar un perfil cognitivo disfuncional similar (204).

1.5.7.1. Perfil neuropsicológico en los TCA

En un inicio, la literatura existente había planteado la idea de que los TCA (por ejemplo, la AN y la BN) son completamente opuestos entre sí y se sitúan en los extremos opuestos del espectro impulsivo /compulsivo (205,206). No obstante, datos más recientes sugieren que tanto la impulsividad como la compulsividad representan constructos multifacéticos que pueden estar presentes de forma simultánea en los TCA (6,207).

Los déficits neuropsicológicos en los TCA actúan como mediadores entre el funcionamiento neurobiológico subyacente del sistema estriatocortical y los síntomas y comportamientos observados en estos pacientes (208–210). Los estudios iniciales sobre los TCA se enfocaron en los déficits cognitivos generales. Sin embargo, investigaciones posteriores han explorado aspectos específicos del funcionamiento neurocognitivo en relación a las FFEE (211), ya que éstas parecen influir especialmente en la psicopatología (212), aparición y mantenimiento de los TCA (203,209,210). Entre las FFEE donde se han observado más dificultades en los TCA, se encuentran el control inhibitorio, la toma de decisiones, la coherencia central, la flexibilidad cognitiva, el sesgo de atención y la memoria de trabajo (203).

En la actualidad, existe un debate sobre si las funciones cognitivas se consideran un endofenotipo o son consecuencia de los TCA. La evidencia sugiere que algunos pacientes con AN podrían mostrar déficits cognitivos como un marcador de rasgo de la enfermedad (213–215) ya que se ha observado el mantenimiento de los déficits cognitivos tras la recuperación (216–220).

Las FFEE también pueden ser una alternativa a considerar como factor de gravedad de los TCA, y más aún, si tenemos en cuenta que un reciente metaanálisis reconoce las limitaciones de la clasificación de gravedad actual de estos trastornos (93). Concretamente, se ha observado que los déficits en el rendimiento cognitivo en los TCA se han asociado a la gravedad de los síntomas (221–223), comorbilidades (224–226), uso de medicamentos (227,228), cociente de inteligencia (229,230), años de educación (231) y respuesta al tratamiento (232).

En este apartado, nos vamos a centrar especialmente en la toma de decisiones y la flexibilidad cognitiva, los cuales representan medidas neuropsicológicas de las FFEE que evalúan la impulsividad y compulsividad.

Impulsividad cognitiva en los TCA

La toma de decisiones desempeña un papel crucial en las conductas impulsivas relacionadas con los TCA (233–235), ya que se ha hipotetizado que las anomalías en el aprendizaje de recompensas favorecen la consolidación de conductas propias de estos trastornos (236,237). La comida se considera un estímulo gratificante natural (238–240), y hay evidencia que sugiere que la incapacidad para tolerar la demora de las recompensas y para inhibir la conducta de aproximación hacia estímulos gratificantes, en general, contribuyen a la incapacidad de abstenerse de esta recompensa primaria (241). En este sentido, la conducta de atracón indicaría un control deficiente de los impulsos (236,242–245), mostrando una tendencia a preferir consecuencias positivas a corto plazo (p.ej., comida rápida por el buen sabor) que muy probablemente resultan en consecuencias negativas a largo plazo (p.ej., colesterol alto, sobrepeso, sentimiento de culpabilidad) (246). Esta dificultad en el control inhibitorio parece observarse especialmente cuando predominan pensamientos internos relacionados con los alimentos (236) o la imagen corporal (241,247), y en el contexto de una emoción negativa (248). En esta línea, un reciente modelo (Figura 4), descompone el proceso de toma de decisiones en el TA.

Sin embargo, otros TCA se caracterizan también por la persistencia en comportamientos desventajosos, como perseguir conductas de pérdida de peso, a pesar de sus efectos negativos a largo plazo sobre la salud (p.ej., dolencias físicas y dificultades sociales), reflejando una tendencia a preferir el efecto inmediato de estos comportamientos inadaptados a sus consecuencias negativas a largo plazo (249). Por lo tanto, la toma de decisiones desempeña un papel crucial en toda la gama de psicopatología de los TCA (203). No obstante, los tipos restrictivos son menos sensible a la recompensa y se asocian con niveles más altos de inhibición del comportamiento (250–252).

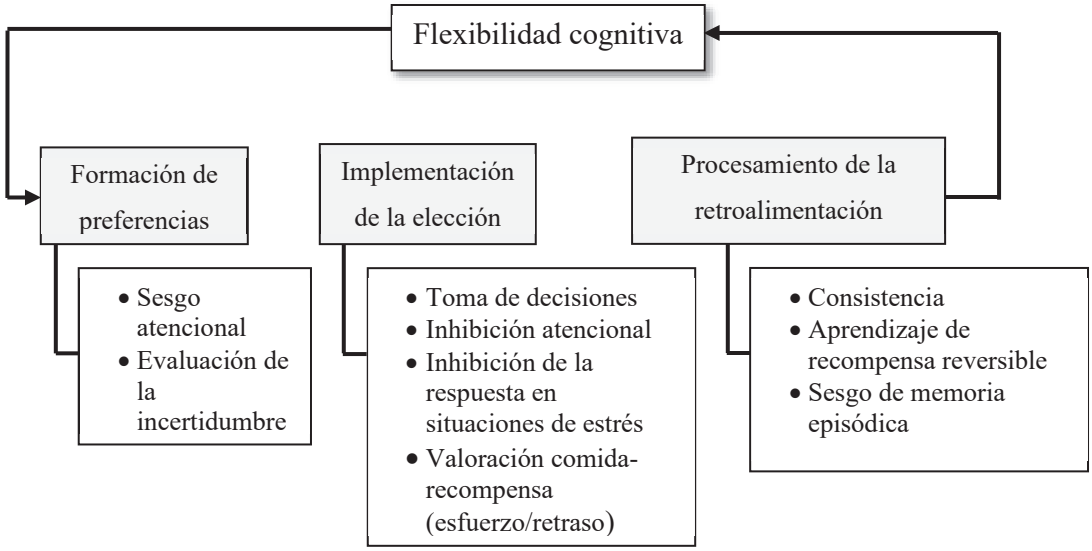

Figura 4. Etapas de la toma de decisiones disfuncional en el trastorno por atracón. Adaptada de Colton et al. (253).

Broomfield et al. (254), en una reciente revisión sistemática, observó que aquellos pacientes con una presentación más severa de la AN demostraron una peor toma de decisiones. En la misma línea, otros estudios también han observado una diferencia significativa en la toma de decisiones de los participantes graves y con mayor duración, sugiriendo que la toma de decisiones puede ser una dificultad específica del perfil severo de la AN (255,256). En el TA, Danner et al. (256) encontraron que la toma de decisiones correlacionaba positivamente con la gravedad de los atracones. Asimismo, las dificultades en la toma de decisiones también parecen afectar a las dificultades para recuperarse (257), ya que el preferir el efecto inmediato de estos comportamientos inadaptados sin tener en cuenta sus consecuencias negativas a largo plazo (258,259) puede entorpecer el tratamiento (259,260).

Compulsividad cognitiva en los TCA

La compulsividad en los TCA involucra la desregulación de los sistemas que llevan a consecuencias negativas debido a errores perseverativos e incapacidad para cambiar la conducta (261). Varios estudios sugieren que las dificultades en la flexibilidad cognitiva son específicas para una subpoblación de pacientes tanto enfermos como recuperados e independientemente de un subtipo diagnóstico (218,219). Sin embargo, el rendimiento en la flexibilidad cognitiva parece verse más afectado en los tipos restrictivos que en los de atracón/purga (210), indicando que la desnutrición también puede afectar a esta función cognitiva (262). Especialmente en la AN, donde la flexibilidad cognitiva se ha considerado un factor predisponente de la enfermedad (ver Figura 5), los patrones alimentarios inflexibles, guiados por reglas, pueden incluir el conteo de calorías, el uso de cifras para controlar las conductas alimentarias y la evitación de ciertos alimentos, como los carbohidratos o aquellos con alto contenido en grasa (215). El ejercicio excesivo también puede seguir patrones repetitivos y sujeto a reglas (263,264).

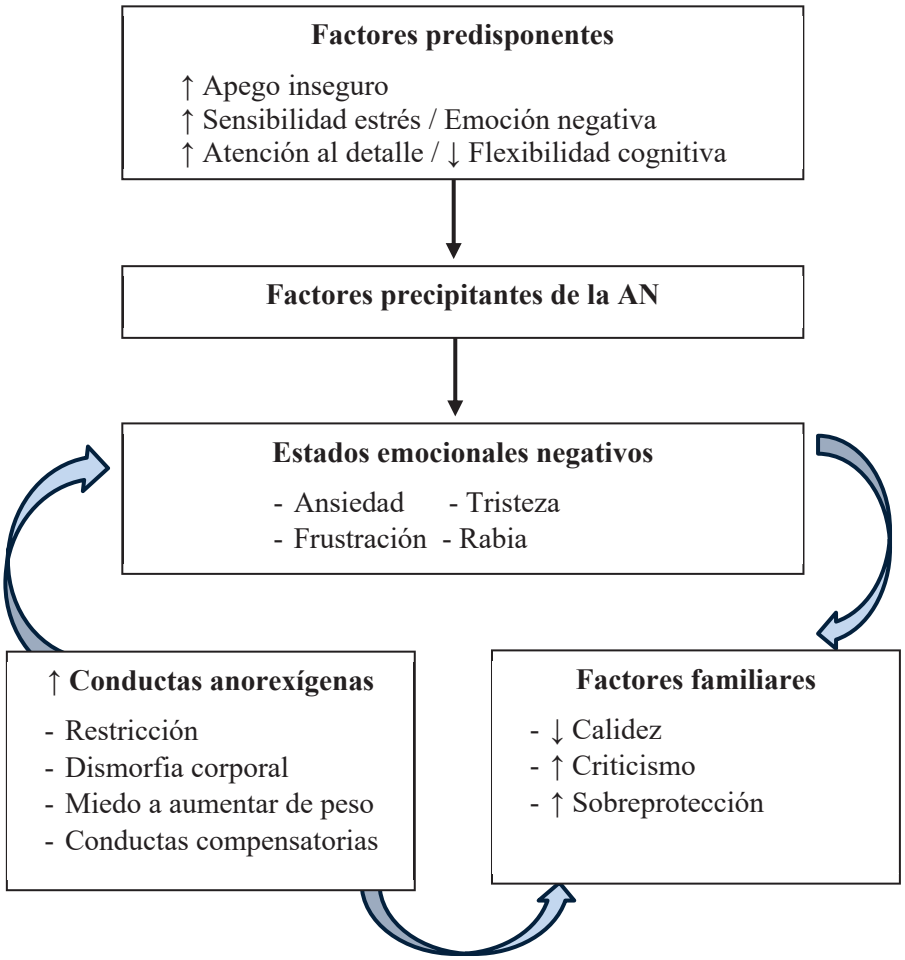

Figura 5. Factores de riesgo en la anorexia nerviosa.
Nota. AN: anorexia nerviosa. Adaptada de Treasure & Schmidt (265).

Los déficits en la flexibilidad cognitiva también se han asociado con la incapacidad de detener el exceso de alimentación compulsiva (210,214,266), aunque otros autores no han encontrado resultados concluyentes en pacientes con BN (267,268).

La gravedad también se ha asociado a dificultades en la flexibilidad cognitiva en los TCA como indica un reciente metaanálisis (269). Varios estudios han sugerido que lo que sustenta los rasgos obsesivo-compulsivos propios de los pacientes con AN es un estilo de procesamiento cognitivo rígido (265,270), lo que sugiere que esta función cognitiva desempeña un papel importante en el desarrollo y manteniendo la enfermedad, en especial en aquellas personas con un TCA grave y con una elevada duración de la enfermedad (254,271). De la misma manera, se ha reportado que la duración de la enfermedad afecta especialmente a la flexibilidad cognitiva (272–274), y se ha demostrado que aquellos pacientes más severos (275) mostraban más alteraciones en este dominio (276,277). Además, una menor duración de la enfermedad se ha relacionado con un resultado favorable de tratamiento (278,279). En este sentido, la inflexibilidad cognitiva también parece ser un importante predictor de la recuperación, puesto que puede dificultar el establecimiento de objetivos, la colaboración y los cambios en el pensamiento (269,271). En relación a la BN y el TA, recientemente se ha demostrado que la duración de la enfermedad predice significativamente la inflexibilidad cognitiva (280). Por tanto, es posible que la inflexibilidad se vuelva más pronunciada en individuos del espectro bulímico a medida que el trastorno progresa.

Comorbilidades en el funcionamiento cognitivo de los TCA

La impulsividad y la compulsividad neuropsicológica se han relacionado con una variedad de condiciones psicopatológicas además de su papel en el TCA. Estas similitudes en el funcionamiento cognitivo pueden conllevar un conjunto de riesgos y vulnerabilidades que favorezcan la aparición y progresión de otros trastornos comórbidos (281).

Patrones de rigidez cognitiva y comportamientos compulsivos repetitivos como es el caso de la AN, también se han encontrado en otros trastornos como el TOC, el trastorno por uso de sustancias (TUS), la esquizofrenia, el TEA o la tricotilomanía (282–287). Además, se han hallado dificultades en la flexibilidad cognitiva en trastornos de ansiedad (TEPT y trastorno de ansiedad generalizada) y en trastornos tradicionalmente impulsivos como serían el TJ u otros trastornos adictivos (288).

Con relación a un funcionamiento más impulsivo propio de los trastornos bulímicos, se hallan similitudes con el TDAH y otros trastornos que figuran formalmente como "Trastornos del control de impulsos" en el DSM-5 (91,289–291). Recientemente, varios modelos han demostrado ser útiles para explicar la toma de decisiones disfuncionales en los TUS (292,293), que tienen manifestaciones neurobiológicas y clínicas superpuestas y son altamente comórbidos con los trastornos bulímicos (294–297).

Particularmente, destaca la comorbilidad entre los TCA y las adicciones comportamentales, como el TJ o, especialmente, la compra compulsiva (CC) (298–304). A pesar de que la etiología específica de la CC es aún desconocida, se trata de una condición de salud mental caracterizada por la compra persistente, excesiva, impulsiva e incontrolable a pesar de las graves consecuencias psicológicas, sociales, laborales y económicas que provocan angustia (305,306).

La evidencia sugiere la existencia de múltiples marcadores biológicos relacionados con la aparición y progresión de los TCA (especialmente del espectro bulímico) y las adicciones comportamentales (302,303), incluidos los procesos neuropsicológicos (307,308) especialmente relacionados con las FFEE, (12), como se describen en esta tesis.

Obesidad

Se ha sugerido la existencia de múltiples marcadores biológicos relacionados con el inicio y la progresión de la obesidad, incluidos factores neuropsicológicos, circuitos cerebrales compartidos y señales metabólicas. Así, se cree que déficits en las FFEE, incluidas la inhibición, flexibilidad cognitiva, memoria de trabajo, toma de decisiones, fluidez verbal y planificación (204,309–313), contribuyen también en la obesidad tanto en la gravedad, (280,314,315), como en los resultados terapéuticos a corto y largo plazo (316–319). De hecho, según algunos autores, los déficits de las FFEE se consideran la causa de actitudes inadecuadas hacia la comida y representan un factor desencadenante en el IMC (320). En esta misma línea, algunas investigaciones que tienen como foco terapéutico las FFEE en personas con obesidad han observado un aumento del funcionamiento ejecutivo y una reducción del IMC confirmando el papel fundamental de las FFEE en la aparición de la obesidad (321–324).

En relación a la obesidad y a la DM2, se ha planteado la posibilidad de que el control del azúcar en sangre y la resistencia a la insulina afecten a los sistemas dopaminérgicos cerebrales (325–330), lo cual podría contribuir a la impulsividad, déficits de

autorregulación y deterioro cognitivo (331–334). A pesar de que aún no se disponga de resultados definitivos, algunos estudios resaltan deficiencias en la impulsividad, especialmente en la impulsividad motora en adultos mayores con DM2 (334). Una investigación reciente indicó una toma de decisiones menos favorable en personas con DM2 en comparación con controles sanos (335). En la actualidad, no hay estudios recientes que analicen la relación entre la compulsividad y la DM2 en individuos con obesidad, por lo que se requieren más investigaciones centradas en esta posible conexión.

1.6. EL TRASTORNO DE JUEGO

1.6.1. Definición y características

Los juegos de azar constituyen una actividad social fácilmente accesible para la población adulta española, así como para los adolescentes (336,337). En este sentido, la conducta de juego se ubica en un continuum que va desde el juego recreativo hasta el uso problemático o patológico de las actividades relacionadas con los juegos de azar (338–340).

El juego patológico fue reconocido como una entidad diagnóstica englobada dentro de los "Trastornos por el control de impulsos no clasificados en otros apartados" en el DSM-III (341). Se caracteriza por una conducta de juego desadaptativa, persistente y recurrente que perdura al menos 12 meses e implica una notable afectación en el funcionamiento psicosocial del individuo (91). La publicación del DSM-5 (91,92) ha conllevado una serie de cambios respecto a las ediciones anteriores. Por un lado, el *Juego patológico* pasa a denominarse *Trastorno de Juego*. Asimismo, pasa a ser considerado la única adicción conductual ("Trastornos no relacionados con sustancias"), incluido en el apartado de "Trastornos relacionados con sustancias y trastornos adictivos". Por último, si bien se mantienen los criterios relativos a la tolerancia, abstinencia, pérdida de control, *craving* y otras características propias de las adicciones, se elimina el criterio referente a la comisión de actos ilegales (91).

El TJ se caracteriza también por su heterogeneidad, que da lugar a distintos perfiles de jugadores. Una de las clasificaciones más utilizadas en la literatura científica y en la práctica clínica es la división según el papel que desempeña el azar, dando lugar a los jugadores estratégicos, donde los conocimientos y las habilidades del individuo pueden influir en el resultado del juego y, por otro lado, los no estratégicos, en los que el resultado depende únicamente del azar (342). Ejemplos de esta última modalidad incluyen la lotería,

las máquinas recreativas con premio o el bingo; mientras que la ruleta (excepto la electrónica), los juegos de cartas, las apuestas deportivas o la inversión en bolsa son considerados juegos estratégicos. Asimismo, se ha clasificado la conducta de juego atendiendo al canal utilizado o a la modalidad: en línea (*online* en inglés) o presencial (*offline* en inglés). Esta diferenciación es también ampliamente reconocida tanto en la investigación como en la práctica clínica. Si bien los resultados sobre si la modalidad estratégica representa una mayor gravedad que la no estratégica no son concluyentes, determinadas variables asociadas a la gravedad (como años de evolución o deudas) apuntan a que el juego estratégico presenta más riesgo en cuanto a impacto funcional y consecuencias negativas para el individuo que el juego no estratégico (343–346). Asimismo, los hallazgos coinciden en que el juego en línea implica un mayor riesgo de desarrollar TJ en comparación con el juego presencial (346–349).

En el marco de esta diversidad propia del TJ, cabe señalar que desde hace décadas, se ha procurado establecer diferentes perfiles o clústeres de las personas que presentaban un uso problemático o patológico del trastorno de juego (349–357).

De entre los distintos modelos teóricos para explicar la heterogeneidad del TJ y la posibilidad de identificar subtipos diferenciados, destaca el conocido como *Pathway Model* de Blaszczynski y Nower (350), que desarrollaron un modelo que distinguía tres tipologías de jugador en base los rasgos de personalidad y otras características clínicas como la gravedad de la conducta de juego o la psicopatología asociada: (1) condicionado conductualmente (perfil menos grave, en el que la conducta desadaptativa del juego se mantiene debido al condicionamiento clásico y operante); (2) emocionalmente vulnerable (en el que la conducta de juego se emplea como una vía de escape frente a estados depresivos y ansiosos) y (3) antisocial e impulsivo (perfil más grave asociado a niveles elevados de impulsividad y posible abuso de sustancias y conductas ilegales, así como mayor implicación de los sustratos neurobiológicos).

Otro de los modelos destacados es el modelo I-PACE (por sus siglas en inglés *Interaction of Person-Affect-Cognition-Execution)* (358). En este modelo, plasmado en la Figura 6, se destaca que los trastornos de adicción a internet, incluido el TJ online, se desarrollan a partir de interacciones entre factores predisponentes (características neurobiológicas y psicológicas), moderadores (estilos de afrontamiento y sesgos cognitivos relacionados con internet) y mediadores (respuestas afectivas y cognitivas a situaciones desencadenantes), junto con un funcionamiento ejecutivo reducido. Dichas interacciones conducen a

experiencias de gratificación o placer en etapas más iniciales. A medida que avanza el proceso de adicción, la experiencia de placer disminuye y aumentan los niveles de compensación y de descontrol conductual. En una actualización reciente de este modelo, se pone de manifiesto su validez en las adicciones comportamentales *offline*, y se expone que una disminución de las FFEE relacionada con el *craving* contribuye al desarrollo de las conductas habituales de estos trastornos (359).

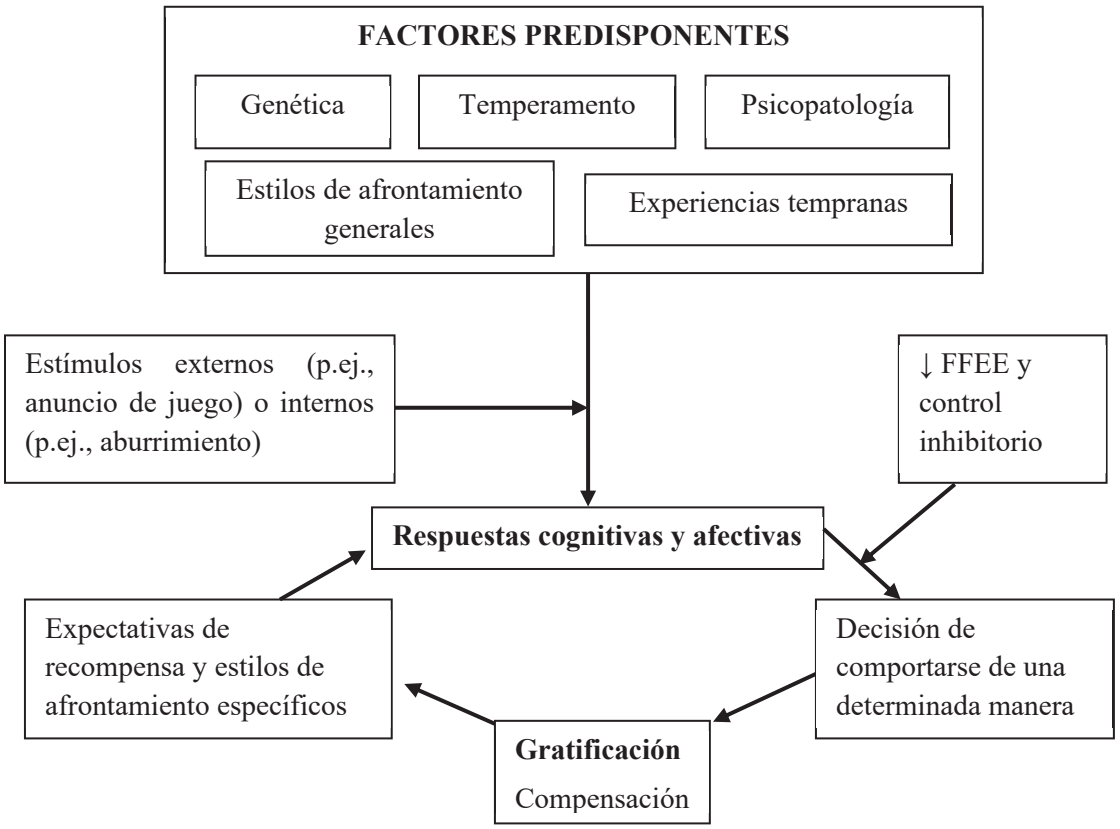

Figura 6. Modelo IPACE.

Nota. FFEE: funciones ejecutivas. Adaptada de Brand et al. (358,359).

1.6.2. Prevalencia

Los estudios de prevalencia del TJ señalan la relación entre conducta de juego problemática y de riesgo y accesibilidad, oferta y disponibilidad, especialmente de los juegos con un alto potencial adictivo (máquinas y ruleta electrónica, en el caso de los juegos no estratégicos y apuestas deportivas, póquer y otros juegos de casino, en cuanto a los de tipo estratégico) (360–363). En este sentido, es importante señalar que la conducta de juego fue legalizada en España en el año 1970 (364) y que la prevalencia ha ido en aumento hasta el momento actual, posiblemente por la aparición del juego en línea, legalizado en 2011 (337,361,365,366). Cabe destacar, sin embargo, que durante el

confinamiento debido a la pandemia del COVID-19, no se reportó un incremento del número de personas solicitando tratamiento para el TJ (367–370). Si bien era esperable que el juego presencial disminuyera debido a las restricciones, no se observó un aumento del juego en línea que, en parte, se puede explicar por la interrupción de las competiciones deportivas y por la convivencia continua con los familiares, así como por la preocupación expresada y el sentido de responsabilidad frente a la emergencia sanitaria mundial (369).

A nivel mundial, una revisión sistemática, que abarcaba estudios realizados entre el 2000 y el 2015, indicó que la prevalencia del juego problemático oscilaba entre el 0,12, y el 5,8% y de entre el 0,12 y el 3,4% en población europea adulta (371). La actualización de este estudio incluye los años comprendidos entre el 2016 y el 2022 y reporta una prevalencia de juego problemático/patológico en adultos de 1,29% (372). Por otro lado, un reciente estudio desarrollado con muestra española, de edades comprendidas entre los 18 y los 64 años, informa de una prevalencia del TJ de un 0,63% (346), evaluada atendiendo a los criterios DMS-5 (91). Concretamente, un 26,21% de estas personas presentaban un TJ grave, seguido de un 28,16% con un TJ moderado y un 45,63% con una gravedad leve del trastorno (346).

Tal como ocurre en otros países, la prevalencia del juego en hombres es mayor que en mujeres (361,371,373,374). Chóliz y colaboradores (361), en una investigación sobre la prevalencia la conducta de juego y el TJ en población española, reportaron una prevalencia del TJ de 1,15% en hombres y de 0,31% en mujeres.

De igual modo, la prevalencia también varía atendiendo a la variable de la edad. Así, los adultos de entre 36 y 50 años son los que presentan una prevalencia de TJ mayor (40 %); seguidos de las personas jóvenes (18-35 años; 31%), que constituyen los principales usuarios del juego en línea, y de los de edad avanzada (51-77 años; 29%) (364), que muestran preferencia por los juegos no estratégicos y presenciales (375,376). En cuanto a la población adolescente, los estudios son más escasos. Sin embargo, apuntan a que un elevado número de menores de edad realizan apuestas tanto de forma presencial como online (377,378). También observan que los varones adolescentes presentan una conducta de juego más problemática en comparación a las mujeres (379) y subrayan la vulnerabilidad propia de la adolescencia y la edad adulta temprana para el desarrollo del juego problemático y el TJ (380), especialmente en la población masculina (373,381).

1.6.3. Curso

El debut del TJ puede tener lugar desde la adolescencia hasta la edad adulta (382). De igual modo, el momento en el que se solicita ayuda para abordar este trastorno es también variable (383,384), manifestando de nuevo la heterogeneidad propia de la conducta de juego y, por ende, de su curso.

El TJ presenta unas tasas de cronicidad significativas (91), especialmente si se da de forma comórbida con otras adicciones (385). En esta línea, se ha demostrado que la presencia de otros trastornos mentales influye en el curso del TJ, siendo la ansiedad, la depresión y la adicción a sustancias, los trastornos más frecuentes en población con TJ (374,386–389). Múltiples estudios informan del uso de la conducta de juego como forma de evadirse del malestar en la población femenina que, a menudo, presenta unas tasas de ansiedad y depresión mayores en comparación con la población masculina (374). Asimismo, en los hombres, la comorbilidad más destacada es con otros trastornos adictivos (390,391).

Tradicionalmente, se ha observado una preferencia por los juegos no estratégicos en el género femenino, y una aparición y desarrollo del trastorno en edades más avanzadas en comparación con los hombres (392–395). Asimismo, en las mujeres se evidencia una menor duración entre la edad de inicio del trastorno y el desarrollo de la conducta problemática de juego (396). Sin embargo, en los últimos años, se han descrito cambios en el patrón de conducta de juego de la mujer, evidenciando un inicio más temprano y un mayor uso de la modalidad en línea (352,397,398).

Cabe destacar también el potencial adictivo del juego en línea, que se ve acentuado por algunas características tales como la fácil accesibilidad –tanto geográfica como horaria–, el anonimato o la inmediatez de la recompensa (366). Se ha descrito la asociación entre el juego en línea y el riesgo de desarrollar un TJ, que puede llegar a ser hasta 10 veces mayor que en el juego presencial (361).

Por último, de forma similar a otros trastornos adictivos (399,400), las recaídas, después de periodos de abstinencia, de mayor o menor duración, son muy frecuentes en el TJ (401–403), por lo que este aspecto debe ser contemplado en el tratamiento de dicha patología.

1.6.4. Etiopatogenia

Son numerosos los factores de riesgo que influyen tanto en el desarrollo como en el mantenimiento de la conducta patológica de juego (358,359,404), tal como queda reflejado en la Figura 7. A continuación, se describe la etiología multicausal del TJ.

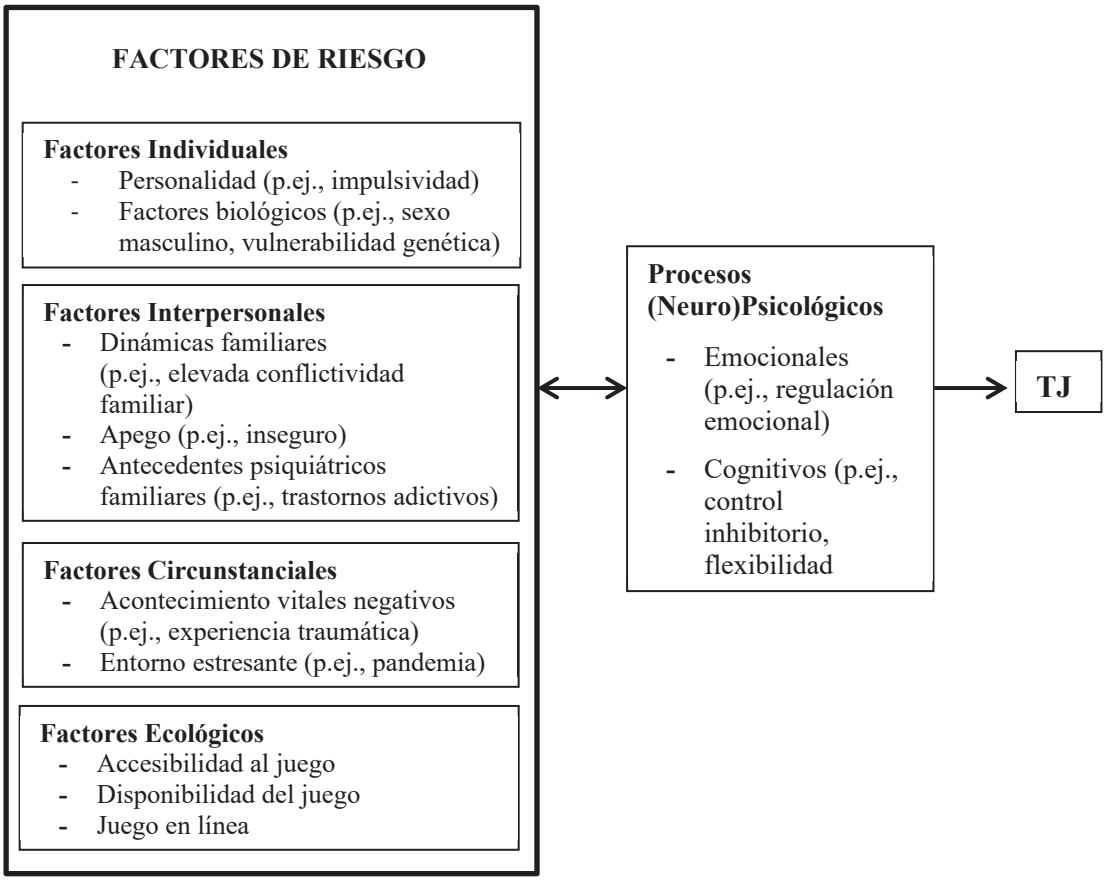

Figura 7. Factores de riesgo de la conducta de juego.
Nota. TJ: trastorno de juego. Adaptada de Kinderman y Tai (405) y de Bonnaire y Billeux (406).

Factores biológicos

Tal como se ha señalado anteriormente, el sexo masculino y la edad temprana (adolescentes y adultos jóvenes) destacan como dos variables de riesgo para el desarrollo del TJ (404).

Por otro lado, si bien la literatura sobre la genética del TJ es escasa, se contempla la influencia de los genes en el desarrollo del TJ , así como una trasmisión intergeneracional a nivel familiar, lo cual sugiere una genética compartida, un entorno familiar compartido y/o la interacción entre ambas variables (407–409). Esta interacción queda patente también en los estudios en gemelos que se han desarrollado para investigar el papel de la genética en dicho trastorno (410–412). Asimismo, los estudios apuntan a una alteración en el sistema serotoninérgico y dopaminérgico (413,414).

Por lo que refiere a las bases neurobiológicas del TJ, son pocos los estudios que se han centrado en los cambios cerebrales estructurales y algunos aportan resultados dispares (415). En general, la mayoría de estudios con resonancia magnética investigan la actividad cerebral presente al realizar determinados procesos neurocognitivos alterados en las personas con TJ, como pueden ser tareas de toma de decisión o tareas que activan el sistema de recompensa y castigo (374). Así, un reciente meta-análisis (415) concluye que se han observado alteraciones en el circuito de recompensa frontoestriatal, en la corteza prefrontal y anterior adyacente, así como en otras estructuras del sistema límbico. También se ha descrito una reducción en la materia gris en las personas con conducta de juego patológica (415). A nivel funcional, de nuevo, destaca la alteración en la dopamina, por su papel destacado en el proceso de adicción (416,417).

Factores socioambientales

Las revisiones sistemáticas centradas en la etiopatogenia del TJ identifican algunos factores de riesgo a nivel social para el desarrollo de dicho trastorno, tales como poseer un nivel educativo bajo o presentar un rendimiento académico deficiente, enfrentarse a una situación económica desfavorable, dificultades familiares, así como el consumo de sustancias o participación en juegos de azar, ya sea dentro de la familia o entre pares, así como comportamientos antisociales (404,408). No obstante, por lo que refiere al juego en línea, el perfil de varón joven con un elevado nivel de estudios y de ingresos económicos es más frecuente (418). Asimismo, la literatura sugiere que participar en múltiples juegos de azar o realizar sesiones largas de juego puede aumentar la vulnerabilidad al desarrollo del TJ (393,404,419,420). Aunque algunos autores vinculan la experiencia temprana de una gran ganancia con el desarrollo de conductas problemáticas relacionadas con el juego (421); otros estudios no encuentran asociaciones significativas entre estas dos variables (422,423).

Otras características socioambientales que cabe destacar son la fácil accesibilidad al juego, la oferta, las políticas de regulación del juego y la publicidad entorno a esta actividad (408,424,425).

Factores psicológicos

Desde los primeros estudios sobre la conducta de juego, se han establecido asociaciones con ciertos rasgos de personalidad. Múltiples investigaciones se han centrado en el papel de la impulsividad en el TJ (426,427), tal como ocurre con el resto de adicciones (428–

432) . De entre los rasgos impulsivos, la urgencia tanto negativa como positiva (tendencia a actuar de forma precipitada al experimentar emociones intensas desagradables, como la ira o la ansiedad, o agradables, como la alegría, respectivamente) (433) se ha asociado estrechamente a la gravedad de la conducta de juego (345,434–436). Asimismo, niveles elevados de búsqueda de sensaciones (definida como la tendencia a implicarse en actividades nuevas) y bajos en autodirección (capacidad para regular y adaptar la conducta propia en miras a un objetivo o valor) han sido también identificados en la mayoría de las personas con TJ (437–439). Destacan también los rasgos propios de la personalidad antisocial, incluyendo las conductas delictivas, como factores de riesgo en el presente trastorno (440,441).

Por otro lado, las dificultades en la regulación de las emociones y las distorsiones cognitivas relativas al juego influyen tanto en el desarrollo como en el mantenimiento de la conducta de juego (442–446).

Finalmente, hay que tener presente que ciertos trastornos mentales están vinculados también a la participación en juegos de azar. Entre ellos, destacan los trastornos por uso de sustancias (447,448), los trastornos depresivos (449,450) y ansiosos (451,452), así como el trastorno por déficit de atención con hiperactividad (TDAH) (453,454).

1.6.5. Tratamiento

Las intervenciones para el TJ se dividen en dos modalidades: las terapias psicológicas y el tratamiento psicofarmacológico. El abordaje psicológico es el más ampliamente estudiado y ha evidenciado mayor efectividad en comparación a los fármacos (455–457). Concretamente, la TCC, mediante el uso de técnicas como restructuración cognitiva, resolución de problemas, control de estímulos, entrenamiento en habilidades sociales y en prevención de recaídas (458), ha demostrado ser eficaz tanto a corto como a medio plazo, ya sea en formato individual como grupal (455,457,459–461). Las intervenciones motivacionales han resultado ser otro enfoque psicológico eficaz en el abordaje del TJ (462). Además, las intervenciones de autoayuda pueden ser beneficiosas para aquellas personas que presentan problemas con la conducta de juego, pero no llegan a cumplir criterios para el TJ propiamente (457).

Por lo que refiere al tratamiento farmacológico, no existe ningún medicamento específicamente recomendado para el abordaje de los síntomas propios del TJ; sin embargo, se podría considerar su uso en casos de comorbilidad psiquiátrica. En este

sentido, se han ensayado algunos fármacos como los antagonistas opioides, antidepresivos, estabilizadores del estado de ánimo y antipsicóticos en pacientes con TJ, a pesar de que los resultados no han sido concluyentes (456,463,464).

1.6.6. Neuropsicología del TJ como factor transdiagnóstico

En el ámbito de las adicciones comportamentales y, en particular en el TJ, se han evidenciado carencias neurocognitivas en diversas funciones, impulsadas por los circuitos motivacionales y de autorregulación, lo que incrementa la probabilidad de iniciar o perpetuar comportamientos adictivos (7,57,465–467). Estas alteraciones neuropsicológicas resultantes de disfunciones en los circuitos cerebrales fronto-subcorticales (45,468–470), han sido consideradas importantes factores transdiagnóstico en los trastornos adictivos (78).

La presencia de estos déficits cognitivos ha sido vinculada a la inclinación a comportarse de manera "impulsiva" y "compulsiva", constituyendo características esenciales que respaldan las conductas propias del TJ (46,77,467,471–477). Considerando la complejidad multifactorial de la impulsividad y la compulsividad (1), en el ámbito de las adicciones conductuales se ha sugerido que la impulsividad está compuesta por al menos tres componentes neuropsicológicos (6,465,478–480) (ver Tabla 6). Por otro lado, la compulsividad es un constructo relativamente reciente que involucra al menos otros cuatro dominios neurocognitivos (6,481) (ver Tabla 6).

Tabla 6. Constructos impulsivo y compulsivo en el TJ

Constructo impulsivo	Constructo compulsivo
Inhibición de la respuesta	Inflexibilidad cognitiva relacionada con contingencias
Toma de decisiones desventajosa	Cambio de tarea o conjunto de atención
Descuento de recompensas	Sesgo de atención o desconexión
	Aprendizaje de hábitos

Nota. Elaborada en base a Lee (78).

1.6.1.1. Perfil neuropsicológico en el TJ

Al analizar la impulsividad y la compulsividad a nivel endofenotípico, la investigación neuropsicológica indica que los déficits en el control cognitivo observados en el TJ están

estrechamente vinculados a las FFEE, siendo uno de los rasgos fundamentales del TJ (1,374,482).

En el TJ, las dificultades en las FFEE como la toma de decisiones (427,483–487), flexibilidad cognitiva (486,488–490), control inhibitorio (485,486,491) o memoria de trabajo (487,492) podrían subyacer a los déficits en el control de los impulsos en el TJ. De hecho, su alteración se ha relacionado con una mayor probabilidad de desarrollar el trastorno (493); además, contribuyen a su mantenimiento (494) e incluso se han considerado un marcador de rasgo para el trastorno (495).

Las medidas de impulsividad y compulsividad neuropsicológicas también pueden considerarse factores importantes en la gravedad del TJ (496). Varios estudios han relacionado las dificultades neuropsicológicas con una peor respuesta de tratamiento (490,497–499), mayor gravedad sintomatológica, número de distorsiones cognitivas (496,500,501), frecuencia del juego, cantidad de dinero perdido e intensidad del impulso de jugar (43,502) y perpetuación del TJ (491,494).

Asimismo, se ha planteado la hipótesis de que las variaciones individuales en el rendimiento cognitivo pueden afectar la inclinación a desarrollar otros procesos cruciales en el TJ, como las distorsiones cognitivas (es decir, creencias sobre el escenario, comportamientos y resultados de la apuesta de juego) (503). En este contexto, el dinero se presenta como una potente recompensa no natural, adquirida a través del aprendizaje cultural, donde algunas de las distorsiones más comunes, como el fenómeno "*near miss*" ("perder por poco") o el fenómeno de control personal (p.ej., apostar por un número de la suerte) se han vinculado al sistema de recompensa (503) y a distintas regiones cerebrales (504–507). Por lo tanto, resulta pertinente investigar las funciones neuropsicológicas asociadas a la impulsividad y la compulsividad, así como su interacción con procesos más complejos, como las distorsiones cognitivas (496).

A nivel neuropsicológico, también se han encontrado resultados interesantes respecto a la preferencia de juego, ya que la exigencia a nivel cognitivo dependerá del grado de azar inherente a cada modalidad de juego (342,344,496,508,509). En este sentido, aunque gran parte de la literatura coincide en que los déficits en las funciones cognitivas contribuyen a la gravedad del juego, algunos estudios han observado que jugadores con preferencia por la modalidad estratégica, aparte de ser un perfil joven con niveles educativos elevados, trabajos bien remunerados y una tendencia a la impulsividad (345,508,510), mostrarían un mejor desempeño neuropsicológico y una mayor gravedad en su TJ (342,511–514), en

comparación con otros perfiles de jugadores (497,515–517). A diferencia de otros perfiles, este tipo de jugadores pueden ser más propensos a realizar apuestas más elevadas y adquirir mayores deudas en un menor periodo de tiempo (342) que, a su vez, se ha asociado a una peor respuesta al tratamiento (518) y a un mayor número de distorsiones cognitivas (519,520).

En este apartado del trabajo, se van a analizar los procesos cognitivos del espectro impulsivo como la toma de decisiones, la memoria de trabajo, y el control inhibitorio, y del espectro compulsivo abordaremos la flexibilidad cognitiva.

Impulsividad cognitiva en el TJ

Los déficits cognitivos más investigados en el TJ están relacionados con la impulsividad. Por ejemplo, se ha observado que la toma de decisiones se ve afectada en estos pacientes (293,496,503,521,522). Esta alteración cognitiva se podría describir en los jugadores como una "insensibilidad a las consecuencias", lo que implica dificultades en la capacidad para aprender de errores anteriores y la incapacidad para renunciar a recompensas (p.ej., dinero) inmediatas y atractivas, en lugar de recompensas menos consistentes pero que maximizan los beneficios a largo plazo (500). Un fallo en el procesamiento emocional, que contribuiría a generar estados somáticos para anticipar beneficios y desventajas (523,524), o la presencia de distorsiones cognitivas (como sentirse afortunado), que llevan a valorar más las recompensas que las pérdidas (496,501,525), son factores que favorecen una toma de decisiones alterada.

La memoria de trabajo está vinculada a diversas funciones cognitivas activadas en la misma región cerebral, que incluye la corteza prefrontal dorsolateral (CPFDL). Precisamente esta área se encuentra alterada en el TJ, lo que sugiere que la memoria de trabajo también puede estar afectada en este trastorno (492). De hecho, algunos estudios han relacionado la dificultad en la toma de decisiones con problemas en la memoria de trabajo en pacientes con TJ (521,526) Asimismo, una reciente revisión sistemática, corrobora el peor rendimiento de la memoria de trabajo en el TJ, y su importante papel como predictor del trastorno al estar asociada a importantes funciones cognitivas como la toma de decisiones, el aprendizaje y el control cognitivo (492).

En el TJ, la recuperación de pérdidas podría surgir de una capacidad de control inhibitorio alterada, dando lugar a una impulsividad como tendencia a tomar decisiones de juego rápidas y precipitadas en busca de la recompensa (527). La falta de control inhibitorio

también puede entenderse como la incapacidad de focalizar la atención en presencia de distractores. En este sentido, en el TJ, una mayor preocupación (búsqueda de recompensa) por la conducta de juego se traduciría en un mayor sesgo atencional hacia estímulos relacionados con el juego (528,529). Desde esta perspectiva, varios estudios han informado de sesgos atencionales en el TJ (530–532).

En relación con la gravedad del TJ, medidas de impulsividad, como la toma de decisiones, se han asociado a la probabilidad de recaer, a la gravedad del TJ (490,533), y a la intensidad de dicha conducta (522,534,535). Incluso en pacientes adolescentes, la dificultad en la toma de decisiones es predictora de la gravedad del TJ y se asocia a mayor consumo de alcohol (500). También se ha vinculado una mala toma de decisiones a un mayor número de distorsiones cognitivas (500,501) pudiendo ser un factor relevante en las formas más graves del TJ (496). Las dificultades en el control inhibitorio se han asociado a la gravedad en el TJ (536–538), a la perpetuación del trastorno (491) y al número de recaídas (498,539). El sesgo atencional también ha sido propuesto como predictor de la gravedad del TJ (540). Por último, una menor capacidad de memoria de trabajo se ha correlacionado con a una mayor gravedad en el TJ (357,492,526), y con otras medidas de impulsividad (521,541).

Compulsividad cognitiva en el TJ

La presentación de la compulsividad en el TJ puede no reflejar lo que se observa típicamente en el trastorno compulsivo más representativo como es el TOC (12). En el TJ, los rasgos y comportamientos compulsivos elevados hallados en jugadores (486,487,542) pueden verse como el punto final de una serie de transiciones que van desde el inicio dirigido a un objetivo, pasando por lo habitual, hasta llegar el comportamiento de juego compulsivo (51). En este sentido, algunos modelos de la adicción han destacado el cambio motivacional de la impulsividad a la compulsividad (543). Sin embargo, otros estudios destacan la compulsividad también como parte del inicio del trastorno, y, por lo tanto, mostrando rasgos comunes con otros trastornos del extremo compulsivo (544,545).

La función cognitiva más representativa de la compulsividad es la inflexibilidad cognitiva. Así, se hipotetiza que una mayor inflexibilidad cognitiva impide a los jugadores cambiar su atención a otras áreas alternativas (p.ej., trabajo), focalizándose en los impulsos relacionados con el juego a pesar de sus consecuencias (6,502,546,547). Asimismo, el intento de recuperar las pérdidas de forma persistente, así como los comportamientos ritualizados, como llevar ropa "de la suerte" o realizar las conductas de juego en un

determinado orden para obtener un resultado más favorable, sugieren patrones rígidos conceptualizados dentro de la compulsividad (527,542,548,549).

Poniendo el foco de atención en el tránsito de la impulsividad a la compulsividad, parece que ésta última se relaciona con formas más graves del TJ y puede tener un efecto negativo a lo largo del tratamiento (43,496). Concretamente, una menor flexibilidad cognitiva se asocia a una mayor gravedad de síntomas de juego (43,550,551) como la frecuencia del juego, la cantidad de dinero perdido, o la intensidad del impulso de jugar (502). Además, una menor flexibilidad cognitiva predijo el abandono del tratamiento, el menor cumplimiento durante el tratamiento, la recaída y el tiempo hasta el abandono y la recaída (497).

Comorbilidades en el funcionamiento cognitivo

Como se ha comentado en apartados anteriores, la expresión neuropsicológica de la impulsividad y la compulsividad es común en varios trastornos, además del TJ, sugiriendo la existencia de mecanismos neurobiológicos comunes (78).

En relación a la impulsividad, la toma de decisiones y el control inhibitorio resultan de especial importancia en todos los trastornos adictivos (552–555). Estos también se han visto alterados en otros trastornos como el TEA (556–558), el TDAH (427,559–561), o los mencionados TCA (298,562,563) sugiriendo déficits similares en el circuito de recompensa cerebral (12). En relación a la compulsividad, en pacientes con TOC se ha observado un patrón de déficits cognitivos similar al TJ (481). En la misma línea, varios estudios observan dificultades cognitivas en la compulsividad similares al TJ en los TUS y en otras adicciones comportamentales (564–567).

Por otro lado, los estados afectivos negativos pueden disminuir el control cognitivo en las personas con problemas de juego (568–571), tal y como se ha observado en otros trastornos psiquiátricos típicamente relacionados con dificultades en la regulación emocional, como el TLP, el TEPT, los TCA, la ansiedad y la depresión (301,572–574). Los pacientes con TJ experimentan altos niveles de estrés debido a las deudas que acostumbran a tener y a las consecuencias psicosociales de la conducta de juego, así que las dificultades cognitivas que muestran (p.ej., control inhibitorio, toma de decisiones), pueden estar relacionadas con los altos niveles de estrés (496). Además, este funcionamiento puede favorecer el uso del juego como mecanismo de afrontamiento

desadaptativo, adquiriéndose y manteniéndose a lo largo del tiempo para hacer frente a emociones desagradables (301,510,575).

1.6.1.2. Sistema neuroendocrino en el TJ

En los últimos años, se han identificado varios sistemas neuroendocrinos presentes en las adicciones (576–578). Entre ellos, los sistemas neurohormonales clásicamente implicados en la regulación de la alimentación tales como las hormonas intestinales (p. ej., grelina) y las adipocitoquinas (p. ej., leptina, adiponectina) (493,579) (ver Tabla 7). Estas hormonas parecen participar en el procesamiento de la recompensa, y se relacionan con la impulsividad, las funciones cognitivas como la memoria y la regulación del estado de ánimo (577,580–586). En relación con el TJ, algunos estudios han mostrado diferencias en sus concentraciones circulantes entre individuos con TJ y los grupos controles (493,515,581). No obstante, aún son escasas las investigaciones centradas en la identificación de posibles perfiles endofenotípicos basados en estos factores en el TJ, por lo que su inclusión como indicadores para establecer subtipos diferenciados representa una aportación novedosa que abre la puerta a que futuros estudios se centren en los sustratos neuroendocrinos en el TJ.

Tabla 7. Función de las hormonas neuroendocrinas

Hormonas neuroendocrinas	Función en el proceso de adicción
Grelina	Desinhibición motora, toma de decisiones impulsivas, búsqueda de novedades
LEAP2	Implicación con la impulsividad y las funciones cognitivas
Leptina	Contribuye a la regulación de la recompensa
Adiponectina	Marcador de *craving*

Nota. LEAP2: *Liver Enriched Antimicrobial Peptide* 2 (péptido antimicrobiano 2 expresado en el hígado). Elaboración propia.

2. HIPÓTESIS

En base a la literatura existente, se prevé que los pacientes con un diagnóstico de TCA, obesidad, o TJ presenten marcadores neuropsicológicos disfuncionales asociados a rasgos de impulsividad y compulsividad. Asimismo, se espera que estas dificultades cognitivas formen parte de un endofenotipo cognitivo que se asocie a aspectos clínicos y con la gravedad de los trastornos mencionados.

En los TCA, se prevé que un mayor deterioro en el rendimiento cognitivo esté asociado a una mayor gravedad sintomatológica y/o a mayor duración del trastorno. Además, se prevé que aquellos pacientes que presenten comorbilidad con otro trastorno del espectro impulsivo-compulsivo mostrarán un peor rendimiento cognitivo y una peor respuesta al tratamiento.

En el TJ, se hipotetiza que el rendimiento cognitivo podría ir asociado a distorsiones cognitivas específicas y a una mayor impulsividad, así como a un perfil neuroendocrino concreto. Se anticipa que el rendimiento cognitivo tendrá un impacto distinto en la gravedad del trastorno en función de las preferencias del tipo de juego (estratégico / no estratégico).

3. OBJETIVOS

1. Comparar el rendimiento neuropsicológico en pacientes del espectro impulsivo-compulsivo (y concretamente en pacientes con trastorno de la conducta alimentaria, trastorno de juego y obesidad -con y sin diabetes-) y controles sanos.
2. Analizar la asociación entre la gravedad clínica y psicopatológica y el rendimiento neuropsicológico en pacientes del espectro impulsivo-compulsivo.

    a. Explorar si los diferentes niveles de flexibilidad cognitiva están en concordancia con los marcadores clínicos de gravedad (según los criterios diagnósticos DSM-5), con el impulso a la delgadez y/o la duración del trastorno de la conducta alimentaria.

    b. Analizar si los pacientes con trastorno de la conducta alimentaria y, específicamente del espectro bulímico que presentan comorbilidad con otros trastornos del espectro impulsivo-compulsivo, muestran mayor gravedad, mayor psicopatología general y peor funcionamiento neuropsicológico.

    c. Estudiar la relevancia de los niveles de gravedad del trastorno de juego, teniendo en cuenta el peso de cada criterio del DSM-5, tanto en hombres como en mujeres.

    d. Determinar la relación entre el rendimiento neuropsicológico, variables clínicas (distorsiones cognitivas e impulsividad) y neuroendocrinas, considerando la gravedad en el trastorno de juego y las preferencias del tipo de juego.

3. Comparar pacientes con trastorno de la conducta alimentaria, con y sin adicción conductual comórbida, respecto al funcionamiento cognitivo y respuesta a tratamiento.

a. Explorar si los pacientes con trastornos del espectro bulímico que presentan comorbilidad con otros trastornos del espectro impulsivo-compulsivo y, específicamente, compra compulsiva, muestran peor rendimiento cognitivo, peor resultado al tratamiento y mayor tasa de abandono del tratamiento.

4. MATERIAL, MÉTODOS Y RESULTADOS

4.1. ESTUDIO 1

Título del artículo

Transdiagnostic Perspective of Impulsivity and Compulsivity in Obesity: From Cognitive Profile to Self-Reported Dimensions in Clinical Samples with and without Diabetes

Perspectiva Transdiagnóstica de la Impulsividad y la Compulsividad en la Obesidad: Del Perfil Cognitivo a las Dimensiones Autorreportadas en Muestras Clínicas con y sin Diabetes

Objetivos

- Comparar muestras clínicas del espectro impulsivo-compulsivo (pacientes con obesidad (con y sin DM2), pacientes con AN-R y pacientes con TJ) y población sana, a nivel clínico y neuropsicológico.
- Evaluar las diferencias en la impulsividad y la compulsividad en pacientes con obesidad según si presentan o no DM2.

Resumen

Tanto los comportamientos impulsivos como los compulsivos se han descrito en pacientes con obesidad. La coexistencia de obesidad y diabetes tipo 2 (DM2) está estrechamente relacionada con la impulsividad, si bien los resultados en la literatura no son concluyentes. El objetivo del estudio fue llevar a cabo una evaluación exhaustiva de la impulsividad y la compulsividad en personas con obesidad con o sin DM2, en comparación con individuos sanos, pacientes altamente impulsivos (con diagnóstico de trastorno de juego [TJ]) y pacientes altamente compulsivos (con diagnóstico de anorexia nerviosa [AN]). Para medir la impulsividad, se consideró la toma de decisiones y la búsqueda de novedad como rasgo de personalidad y, para medir la compulsividad, se consideró la flexibilidad cognitiva y la evitación al daño como rasgo de personalidad. En cuanto a la impulsividad, los pacientes con obesidad y DM2 mostraron una menor capacidad de toma de decisiones en comparación con los individuos sanos. En cuanto a la compulsividad, los individuos con obesidad sin DM2 presentaron una menor flexibilidad cognitiva y una elevada evitación del daño; estas dimensiones no se asociaron a la obesidad con DM2. Los pacientes con TJ y AN mostraron indicadores tanto de impulsividad como de compulsividad, con una menor capacidad de toma de decisiones y una elevada evitación del daño en comparación con los individuos sanos. Los pacientes con TJ también mostraron una menor flexibilidad cognitiva. Este estudio contribuye al conocimiento de los mecanismos asociados a la DM2 y su asociación con conductas impulsivo-compulsivas, confirmando la hipótesis de que los pacientes con obesidad y DM2 se caracterizarían por mayores niveles de impulsividad.

nutrients

MDPI

Article

Transdiagnostic Perspective of Impulsivity and Compulsivity in Obesity: From Cognitive Profile to Self-Reported Dimensions in Clinical Samples with and without Diabetes

Giulia Testa [1,2,3,†], Bernat Mora-Maltas [1,2,†], Lucía Camacho-Barcia [1,2,3], Roser Granero [3,4], Ignacio Lucas [1,2], Zaida Agüera [1,2,3,5], Susana Jiménez-Murcia [1,2,3,6], Rosa Baños [3,7], Valerie Bertaina-Anglade [8], Cristina Botella [3,9], Mònica Bulló [3,10,11], Felipe F. Casanueva [3,12], Søren Dalsgaard [13], José-Manuel Fernández-Real [3,14], Barbara Franke [15], Gema Frühbeck [3,16], Montserrat Fitó [3,17], Carlos Gómez-Martínez [3,11,18], Xavier Pintó [3,6,19], Geert Poelmans [20], Francisco J. Tinahones [3,21], Rafael de la Torre [3,22,23], Jordi Salas-Salvadó [3,11,18,24], Lluis Serra-Majem [3,25], Stephanie Vos [26], Theresa Wimberley [27] and Fernando Fernández-Aranda [1,2,3,6,*]

1 Department of Psychiatry, University Hospital of Bellvitge, L'Hospitalet de Llobregat, 08907 Barcelona, Spain; gtesta@idibell.cat (G.T.); bmora@idibell.cat (B.M.-M.); lcamacho@idibell.cat (L.C.-B.); ilucas@idibell.cat (I.L.); zaguera@ub.edu (Z.A.); sjimenez@bellvitgehospital.cat (S.J.-M.)
2 Psychiatry and Mental Health Group, Neuroscience Program, Institut d'Investigació Biomèdica de Bellvitge (IDIBELL), L'Hospitalet de Llobregat, 08907 Barcelona, Spain
3 Consorcio CIBER, M.P. Fisiopatología de la Obesidad y Nutrición (CIBERObn), Instituto de Salud Carlos III (ISCIII), 28029 Madrid, Spain; roser.granero@uab.cat (R.G.); rosa.banos@uv.es (R.B.); botella@psb.uji.es (C.B.); monica.bullo@urv.cat (M.B.); felipe.casanueva@usc.es (F.F.C.); jmfreal@idibgi.org (J.-M.F.-R.); gfruhbeck@unav.es (G.F.); mfito@imim.es (M.F.); carlos.gomez@urv.cat (C.G.-M.); xpinto@bellvitgehospital.cat (X.P.); fjtinahones@hotmail.com (F.J.T.); RTorre@imim.es (R.d.l.T.); jordi.salas@urv.cat (J.S.-S.); lluis.serra@ulpgc.es (L.S.-M.)
4 Department of Psychobiology and Methodology, Autonomous University of Barcelona, 08193 Barcelona, Spain
5 Department of Public Health, Mental Health and Perinatal Nursing, School of Nursing, University of Barcelona, L'Hospitalet de Llobregat, 08907 Barcelona, Spain
6 Department of Clinical Sciences, School of Medicine and Health Sciences, University of Barcelona, L'Hospitalet de Llobregat, 08907 Barcelona, Spain
7 Instituto Polibienestar, Universitat de Valencia, 46010 Valencia, Spain
8 Core Lab Department, Biotrial Neurosciences, 35000 Rennes, France; valrie.bertaina-anglade@biotrial.com
9 Department of Basic Psychology Clinic and Psychobiology, Universitat Jaume I, Castellón de la Plana, 12071 Castellón, Spain
10 Department of Biochemistry and Biotechnology, Faculty of Medicine and Health Sciences, University Rovira i Virgili (URV), 43201 Reus, Spain
11 Institut d'Investigació Sanitaria Pere Virgili (IISPV), Hospital Universitari de Sant Joan de Reus, 43204 Reus, Spain
12 Molecular and Cellular Endocrinology Group, Instituto de Investigacion Sanitaria de Santiago de Compostela (IDIS), Complejo Hospitalario Universitario de Santiago de Compostela (CHUS), Santiago de Compostela University (USC) and Centro de Investigacion Biomedica en Red Fisiopatologia de la Obesidad Y Nutricion (Ciberobn), 15705 Santiago de Compostela A Coruña, Spain
13 National Centre for Register-Based Research, Department of Economics and Business Economics, Business and Social Sciences, Aarhus University and iPSYCH, The Lundbeck Foundation Initiative for Integrative Psychiatric Research (Copenhagen-Aarhus), DK-8210 Aarhus, Denmark; sdalsgaard@econ.au.dk
14 Department of Medical Sciences, School of Medicine, Hospital of Girona Dr. Josep Trueta, University of Girona, 17004 Girona, Spain
15 Departments of Human Genetics and Psychiatry, Donders Institute for Brain, Cognition and Behaviour, Radboud University Medical Center, 6525 GA Nijmegen, The Netherlands; Barbara.franke@radboudumc.nl
16 Department of Endocrinology, Instituto de Investigación Sanitaria de Navarra, University of Navarra (IdiSNA), 31008 Pamplona, Spain
17 Unit of Cardiovascular Risk and Nutrition, Hospital del Mar Institute for Medical Research (IMIM), 08003 Barcelona, Spain
18 Universitat Rovira i Virgili, Departament de Bioquímica i Biotecnologia, Unitat de Nutrició, 43201 Reus, Spain
19 Lipids and Vascular Risk Unit, Internal Medicine, University Hospital of Bellvitge (IDIBELL), L'Hospitalet de Llobregat, 08907 Barcelona, Spain

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[20] Department of Human Genetics, Radboud University Medical Center, 6525 GA Nijmegen, The Netherlands; geert.poelmans@radboudumc.nl
[21] Department of Endocrinology and Nutrition, Virgen de la Victoria Hospital, Institute of Biomedical Research in Malaga (IBIMA), University of Malaga, 29016 Málaga, Spain
[22] Integrative Pharmacology and Systems Neurosciences Research Group, Institut Hospital del Mar de Investigaciones Médicas Municipal d'Investigació Mèdica (IMIM), 08003 Barcelona, Spain
[23] IMIM-Hospital del Mar Medical Research Institute and CIBER of Physiopathology of Obesity and Nutrition (CIBEROBN), University Pompeu Fabra (DCEXS-UPF), 08003 Barcelona, Spain
[24] Nutrition Unit, University Hospital of Sant Joan de Reus, 43204 Reus, Spain
[25] Nutrition Research Group, Research Institute of Biomedical and Health Sciences (IUIBS), University of Las Palmas de Gran Canaria, 35001 Las Palmas de Gran Canaria, Spain
[26] Alzheimer Centrum Limburg, Department of Psychiatry and Neuropsychology, School for Mental Health and Neuroscience, Maastricht University, 6211 LK Maastricht, The Netherlands; s.vos@maastrichtuniversity.nl
[27] National Centre for Register-Based Research, Department of Economics and Business Economics, Aarhus University, DK-8000 Aarhus, Denmark; tw@econ.au.dk
* Correspondence: ffernandez@bellvitgehospital.cat; Tel.: +34-93-2607227
† These authors contributed equally to this work.

Abstract: Impulsive and compulsive behaviors have both been observed in individuals with obesity. The co-occurrence of obesity and type 2 diabetes (T2D) is more strongly associated with impulsivity, although there are no conclusive results yet. A multidimensional assessment of impulsivity and compulsivity was conducted in individuals with obesity in the absence or presence of T2D, compared with healthy, normal-weight individuals, with highly impulsive patients (gambling disorders), and with highly compulsive patients (anorexia nervosa). Decision making and novelty seeking were used to measure impulsivity, and cognitive flexibility and harm avoidance were used for compulsivity. For impulsivity, patients with obesity and T2D showed poorer decision-making ability compared with healthy individuals. For compulsivity, individuals with only obesity presented less cognitive flexibility and high harm avoidance; these dimensions were not associated with obesity with T2D. This study contributes to the knowledge of the mechanisms associated with diabetes and its association with impulsive–compulsive behaviors, confirming the hypothesis that patients with obesity and T2D would be characterized by higher levels of impulsivity.

Keywords: impulsivity; compulsivity; decision making; cognitive flexibility; type 2 diabetes; novelty seeking; harm avoidance

1. Introduction

The prevalence of obesity worldwide has alarmingly increased, having nearly tripled in the last 50 years, reaching pandemic levels [1]. As one of the major risk factors for noncommunicable diseases, it has been associated with a reduced quality of life, high presence of disabilities, and decreased life expectancy [2]. Obesity is a complex disorder, usually classified as a metabolic, nutritional, and endocrine disease. Several factors contribute to the physiopathology of this disease, including genetic, social, environmental and psychological aspects [3]. According to the body mass index (BMI), obesity is classified in the following three categories: class I obesity (BMI: 30–34.9 kg/m^2), class II obesity (BMI: 35–39.9 kg/m^2), and class III obesity, or morbid obesity (BMI > 39.9 kg/m^2) [4]. The presence of obesity is associated with multiple comorbidities that significantly contribute to higher rates of morbidity and mortality, including type 2 diabetes (T2D) and insulin resistance (IR), among others [5–7].

Excessive food consumption is one of the main contributors to weight gain in obesity. However, appetite and feeding behavior are not only controlled by energy requirements or metabolic need. Food also acts as a natural reinforcer, and its consumption is motivated by its hedonic properties, which rely on mesolimbic dopamine and opioids systems [8,9]. Processed foods, high in fats, sugars, and salt, are believed to stimulate appetite and increase calorie consumption through stimulation of opiates and dopamine receptors in

the reward center [10,11]. Given the complexity and multicausality of this pathology, understanding the neurobehavioral mechanisms underpinning obesity is crucial to develop effective specific treatments.

Two constructs that have been suggested to play a role in excessive food intake and weight gain are impulsivity and compulsivity [12]. Impulsivity is typically defined as a tendency to act rashly without giving adequate forethought to the consequences of the behaviors, which, in the case of obesity, is reflected by overeating palatable foods [13]. Impulsivity is multidimensional, including personality traits (e.g., sensation seeking, lack of premeditation, and urgency) [14,15], motor impulsivity (e.g., response inhibition), and choice impulsivity (e.g., decision making and deficits in delay gratification) [16–18]. By contrast, compulsivity is characterized by repetitive and persistent behaviors, often harmful, despite their consequences [19]. In the context of overeating and obesity, this is reflected by repetition of maladaptive habits and a failure to shift behavior, despite its negative effects [20]. An important dimension of compulsivity is cognitive flexibility, which is the ability to flexibly adjust behavior to the demands of a changing environment (e.g., attentional set-shifting and task-shifting) [21,22].

Currently, there is a growing interest in analyzing dimensional models, where a spectrum around a specific construct will be considered, in which different disorders share some characteristics. From this point of view, the term dimension is understood as the set of magnitudes that serve to define a psychological phenomenon [23]. Thus, while the categorical model is based on the process of counting symptoms to an arbitrary number, where the presence of more symptoms becomes meaningless, in dimensional approaches, the number of diagnostic features forms an index of severity by taking into account the daily functioning of patients. The clinical utility of adopting dimensional models has been suggested, especially in the case of personality pathologies [24].

This is the case for the impulsive–compulsive spectrum, in which the dimensional approach is especially relevant. Along this spectrum, some mental disorders typically described in the impulsive pole are gambling disorder (GD) and other impulse control disorders, attention-deficit hyperactivity disorder (ADHD), borderline personality disorder, among others [25–27]. Compulsivity is well represented by anorexia nervosa restrictive type (AN-R), obsessive-compulsive disorder, and obsessive-compulsive personality trait [28,29]. Nonetheless, where obesity and obesity plus T2D comorbidity can be placed along the impulsive–compulsive spectrum is still unknown, which could have important implications for developing specific treatments.

Impulsive personality traits have been associated with a greater body mass index (BMI) and weight gain [30,31]. Moreover, strong evidence exists for a positive relation between obesity and cognitive indices of impulsivity, such as poor decision making [32] and deficits in delay gratification [33]. Similarly, a lack of cognitive flexibility has been shown in individuals with obesity and overweight [34,35]. Personality traits related to compulsivity, such as obsessive-compulsive traits and harm avoidance [36], as well as the ability to cope with negative emotions [37], have been suggested to play an important role in the development and perpetuation of obesity [38,39]. Accordingly, some studies showed elevated harm avoidance in individuals with obesity [40–43].

Type 2 diabetes is a metabolic disorder, characterized by pancreatic β-cell dysfunction and insulin resistance, which result in elevated levels of blood glucose [44]. Impaired glycemic control and IR have been suggested to impact brain dopaminergic systems [45–50], which may contribute to impulsivity and deficits in self-regulation, as well as impairment in cognitive functioning [51–54]. Although there are still no conclusive results, some studies highlight impairments in impulsivity, specifically in motor impulsivity in older adults with T2D [54], and recent research showed more disadvantageous decision making in T2D than in healthy controls in the Iowa gambling task (IGT) [55]. To the best of our knowledge, there are no current studies evaluating the association between compulsivity and T2D in individuals with obesity. Taking all this into account, it is unclear whether the

presence of T2D affects different dimensions of impulsivity and compulsivity in individuals with obesity.

The present study aimed to describe and compare different clinical populations along the impulsivity–compulsivity spectrum. It especially focuses on individuals with obesity in the absence or presence of T2D, when compared with highly impulsive patients (namely, patients with GD) highly compulsive patients (namely, patients with AN-R), and healthy, normal-weight individuals. A multiple assessment of various impulsivity and compulsivity dimensions, using self-reported measures and neuropsychological tasks, was conducted to evaluate decision making and novelty seeking as markers of impulsivity, and cognitive flexibility and harm avoidance as markers of compulsivity. Based on the above-mentioned literature, individuals with obesity were expected to present compulsivity-related personality traits and poor cognitive flexibility. For the impulsivity dimensions, we hypothesize an impulsive profile to characterize obesity with T2D, with impulsive decision making and novelty seeking possibly being more pronounced in these individuals than in those with obesity only.

2. Materials and Methods

2.1. Study Design and Population

In the present cross-sectional study, a total of 581 participants along the impulsive–compulsive spectrum were included, as follows: n = 115 individuals with morbid obesity without diabetes (OB-DM), n = 67 individuals with morbid obesity and T2D (OB + DM), n = 107 individuals with anorexia nervosa restrictive subtype (AN-R), n = 121 individuals with gambling disorder (GD) and n = 171 healthy controls (HC). Participants in the AN-R and GD groups who presented with T2D were not included. Seven centers, all part of the Spanish Biomedical Research Centre in Physiopathology of Obesity and Nutrition (CIBERobn), participated in the study. The clinical groups were patients who had been consecutively referred to the clinics mentioned above. Healthy controls were recruited by means of word-of-mouth and advertisements at local universities, from the same catchment area as the clinical groups. The study was conducted according to the guidelines of the Declaration of Helsinki and its amendments, the International Conference on Harmonization Good Clinical Practice guidelines, and local regulatory requirements. The study was approved by the ethics committees of all participating institutions. Informed consent was obtained from all subjects participating in the study.

2.2. Psychometric Measures

The Temperament and Character Inventory—Revised (TCI-R) [56], previously validated in a Spanish adult population [57], consists of 240 items with a five-point Likert scale format. Three character dimensions are evaluated (self-directedness, cooperativeness, and self-transcendence) and also four temperaments (harm avoidance, novelty seeking, reward dependence, and persistence). In this study, harm avoidance and novelty seeking subscales were adopted as measures of compulsivity and impulsivity, respectively. For this sample, the Cronbach's alpha was good, ranging from α = 0.830 (for novelty seeking) to α = 0.889 (for harm avoidance).

The Symptom Checklist—90 Items—Revised (SCL-90-R) [58], which was validated in a Spanish population [59], was administered for evaluating self-reported psychological distress and psychopathology. The instrument is scored on nine primary symptom dimensions (somatization, obsessive-compulsive behavior, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, and psychoticism) and three global indices (global severity index (GSI), positive symptom total (PST), and positive symptom distress index (PSDI)). The internal consistency for the global index in our sample was high, α = 0.980.

2.3. Neuropsychological Measures

The computerized version of the Wisconsin card sorting test (WCST) [60] was used to evaluate cognitive flexibility through a set-shifting task. The WCST consists of matching stimulus cards within one of three of the following available categories: color, shape, or number. For a correct match, participants must identify the sorting rule, receiving the feedback of "right" or "wrong" after each sort. Following 10 consecutive correct matches, the rule is changed and then a new sorting rule must be identified. There are up to six attempts to detect the sorting rule and five rule shifts during the task. Each rule attainment is referred to as "category completed". Participants do not know the correct rules or changes. The test continues until 128 cards are sorted. The following variables were adopted to measure cognitive flexibility: perseverative errors (i.e., failure to change sorting strategy after negative feedback), non-perseverative errors and the number of completed categories.

The Iowa gambling task (IGT) [61] is a computerized task proposed as a measure of choice impulsivity as it evaluates decision making. It is performed by selecting between four decks where each deck provides a specific amount of play money. It consists of a total of 100 turns in which the rewards interspersed between the decks are probabilistic punishments (monetary losses with different amounts). The final objective of the task is to earn as much money as possible and lose as little money as possible by choosing the cards from any deck, and participants are able to change the deck at any time. The score for this test is obtained by the difference of selected cards from decks A and B, and from decks C and D (CD–AB). Higher scores indicate better performance on the task. This means that the subject will have chosen more cards from decks C and D as they are advantageous (less penalties), while decks A and B are not advantageous (more penalties).

2.4. Procedure

The presence of T2D was diagnosed by a physician and the information was retrieved from medical records. Obesity was defined as BMI $\geq$ 30 kg/m^2, calculated using the formula BMI = weight(kg)/(height(m))^2. AN-R and GD samples were diagnosed according to the DSM-5 criteria [62] by clinical psychologists and psychiatrists with more than 15 years of experience in the field, during a face-to-face clinical interview. Regarding the neuropsychological evaluation, it was administered by a trained psychologist in a single session. In addition, the tests were specifically selected to determine various dimensions of executive functions. Other significant information was collected during the clinical interviews, such as sex, age, and education level.

2.5. Statistical Analysis

Statistical analysis was performed with Stata17 for Windows [63]. Comparison between the groups was performed with analysis of covariance (ANCOVA, adjusted for sex, age, educational level, and BMI) for quantitative measures and with logistic regression (also adjusted for the same covariates) for binary measures. Since the groups were ordered according to their position within the compulsivity–impulsivity continuous dimensional spectrum, these models included polynomial contrasts to assess the presence of patterns in data adjusted by linear, quadratic, cubic, and quartic equation/functions (four polynomial trends were assessed, the maximum allowed for variables categorized in five group levels). Pairwise post hoc comparisons also explored differences between group means and proportions.

The Finner method was employed to control type I error due to multiple null hypothesis tests. This is a correction procedure based on a stepwise multiple-test method aimed to adjust p-values whilst controlling the familywise error rate (FWER, defined as the likelihood of achieving at least k false rejections) [64]. Controlling the k-FWER implies fixing a number of $k-1$ of tolerated erroneous rejections, and then combining the unadjusted p-values to obtain a single testing for the group of null hypothesis tests at α-level.

3. Results

3.1. Descriptive for the Sample

Table 1 displays the distribution of the patients' sex, education levels, age, and BMI, as well as the comparison between the groups. The AN-R group included a high proportion of women and patients with secondary or university education levels, the youngest mean age, and the lowest BMI. The OB-DM group was also characterized by a high proportion of women, patients with primary or secondary study levels, and the highest BMI. OB + DM also included mostly women, the highest proportion of participants with primary education levels, the oldest mean age, and the highest mean BMI. The GD group included mostly men and a high proportion of patients with primary education levels.

Table 1. Descriptive for the sample.

	AN-R ***N* = 107**		**OB − T2D** ***N* = 115**		**HC** ***N* = 171**		**OB + T2D** ***N* = 67**		**GD** ***N* = 121**		
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*p*
Sex											
Women	97	90.7%	107	93.0%	144	84.2%	48	71.6%	19	15.7%	**<0.001** *
Men	10	9.3%	8	7.0%	27	15.8%	19	28.4%	102	84.3%	
Education											
Primary	29	27.1%	48	41.7%	16	9.4%	48	71.6%	72	59.5%	**<0.001** *
Secondary	48	44.9%	53	46.1%	104	60.8%	17	25.4%	32	26.4%	
University	30	28.0%	14	12.2%	51	29.8%	2	3.0%	17	14.0%	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	*p*
Age (years)	25.31	8.30	41.39	11.87	29.71	13.28	54.61	11.33	38.30	13.56	**<0.001** *
BMI (kg/m^2)	16.36	2.17	44.60	6.70	22.34	3.14	41.96	8.59	26.38	5.90	**<0.001** *

Note. AN-R: anorexia nervosa restrictive. OB − T2D: obesity without T2D. HC: healthy control. OB + T2D: obesity without T2D. GD: gambling disorder. SD: standard deviation. * Bold: significant comparison.

3.2. Comparison of Impulsivity and Compulsivity Measures

Table 2 contains the ANCOVA results with a comparison between the means registered in the impulsivity and compulsivity measures, adjusted for the covariates of sex, age, educational level, and BMI (see Figure 1 for the performance line graph for the adjusted mean scores). These results provide evidence for differences between the groups. As expected, the HC achieved the highest performance in the neuropsychological measures (highest means in the IGT and lowest means in the WCST errors and perseverative errors), the lowest mean in harm avoidance, and the lowest psychological distress. AN-R showed the worst performance in the IGT task (the scores were similar to those obtained among GD patients), the lowest mean in the novelty seeking trait, and the highest mean in harm avoidance (for this personality trait, the mean score was quite similar to OB-DM). Regarding the IGT total raw score, patients with OB + DM achieved worse performance compared to the HC group, whereas no differences were found between the participants in the OB-DM group and the HC group. The OB-DM condition reported the worst performance in the WCST task and the highest mean in the harm avoidance scale. The GD patients also achieved poor performance in the neuropsychological task, and the highest mean in the novelty seeking dimension. Figure 2 includes the line chart showing the performance learning curve in the IGT task. HC obtained the best performance, followed by OB-DM and OB + DM, while AN-R and GD achieved the worst results.

Regarding polynomial contrasts, most measures did not adjust to a linear trend, while other quadratic–cubic–quartic functions achieved statistical significance (Table 2). These results indicated that other patterns in data with many fluctuations are more likely to appear than simply increasing or decreasing means within the impulsivity–compulsivity continuous spectrum.

Table 2. Comparison between the groups in impulsivity and compulsivity measurements. ANCOVA adjusted by sex, age, education and BMI.

	AN-R *N* = 107		**OB − T2D** *N* = 115		**HC** *N* = 171		**OB + T2D** *N* = 67		**GD** *N* = 121		**Polynomial Contrasts Trends (*p*-Value)**			
Impulsivity	***Mean***	***SD***	***Mean***	***SD***	***Mean***	***SD***	***Mean***	***SD***	***Mean***	***SD***	***O1***	***O2***	***O3***	***O4***
IGT Total raw	−1.62	20.33	7.71	22.12	13.24	28.52	2.10	20.31	1.41	24.58	0.964	**0.004** *	0.106	0.308
IGT Learning	5.84	12.94	6.35	14.65	7.87	16.84	7.08	14.38	3.44	14.38	0.511	0.177	0.477	0.909
IGT Risk index	2.63	13.83	5.89	13.42	8.46	17.02	3.63	13.28	1.96	15.22	0.561	**0.029** *	0.481	0.478
TCI-R Novelty seeking	90.94	12.56	96.53	13.21	100.33	11.45	96.15	12.11	117.82	9.29	**0.001** *	**0.001** *	**0.001** *	**0.035** *
Compulsivity	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*	*O1*	*O2*	*O3*	*O4*
WCST Errors	27.40	16.71	39.19	25.96	23.06	16.04	27.98	24.61	31.04	24.66	0.636	0.733	**0.001** *	**0.027** *
WCST Errors perseve.	12.94	7.71	19.67	14.61	10.84	7.24	13.96	13.21	13.80	10.88	0.348	0.735	**0.001** *	**0.011**
WCST Categ.compl.	5.11	1.20	4.45	2.22	5.25	1.21	5.37	2.12	4.80	1.97	0.650	0.549	**0.001** *	0.416
TCI-R Harm avoid.	106.02	18.63	108.88	16.87	91.38	16.21	100.21	14.07	103.51	18.77	**0.046** *	**0.002** *	**0.015** *	**0.004** *
SCL-90R Obs.-comp.	1.24	0.91	1.26	0.73	0.70	0.56	1.04	0.67	1.45	0.87	0.505	**0.001** *	**0.016** *	0.055
Pairwise	AN-R/		AN-R/		AN-R/		AN-R/	OB − T2D/	OB − T2D/	OB − T2D/	HC/	HC/	OB + T2D/	
comparisons	OB − T2D		HC		OB + T2D		GD	HC	OB + T2D	GD	OB + T2D	GD	GD	η^2
Impulsivity														
IGT Total raw	0.142		**<0.001** *		0.572		0.493	0.291	0.159	0.224	**0.046** *	**0.002** *	0.895	0.048
IGT Learning	0.897		0.307		0.760		0.381	0.638	0.764	0.365	0.821	0.056	0.259	0.008
IGT Risk index	0.407		**0.004** *		0.806		0.807	0.429	0.361	0.222	0.164	**0.005** *	0.605	0.024
TCI-R Novelty seeking	0.068		**<0.001** *		0.102		**<0.001** *	0.133	0.843	**<0.001** *	0.121	**<0.001** *	**<0.001** *	**0.282** †
Compulsivity														
WCST Errors	**0.025** *		0.104		0.915		0.321	**<0.001** *	**0.001** *	0.059	0.288	**0.010** *	0.479	0.043
WCST Errors perseve.	**0.013** *		0.125		0.715		0.647	**<0.001** *	**0.001** *	0.008 *	0.189	0.063	0.943	0.042
WCST Categ.compl.	0.126		0.496		0.555		0.306	**0.023** *	**0.001** *	0.318	0.761	0.072	0.107	0.029
TCI-R Harm avoid.	0.512		**<0.001** *		0.199		0.408	**<0.001** *	**0.002** *	0.132	**0.022** *	**<0.001** *	0.358	**0.124** †
SCL-90R Obs.-comp.	0.937		**<0.001** *		0.314		0.119	**<0.001** *	0.073	0.218	**0.046** *	**<0.001** *	**0.010** *	**0.109** †

Note. AN-R: anorexia nervosa restrictive. HC: healthy control. GD: gambling disorder. OB − T2D: obesity without T2D. OB + T2D: obesity with T2D. IGT: Iowa gambling test. SCL-90: Symptom Checklist—90 Items—Revised. TCI-R: Temperament and Character Inventory–Revised. WCST: Wisconsin card sorting test. SD: standard deviation. O1: order 1, linear. O2: order 2, quadratic. O3: order 3, cubic. O4: order 4, quartic. η^2: partial eta squared. * Bold: significant parameter. † Bold: effect size within the ranges moderate/medium to large/high. Note. AN-R: anorexia nervosa restrictive. OB − T2D: obesity without T2D. HC: healthy control. OB + T2D: obesity with T2D. GD: gambling disorder. IGT: Iowa gambling test. WCST: Wisconsin card sorting test. *Y*-axis represents the means adjusted by sex, age, education, and BMI.

3.3. Comparison of Psychological State

Table S1 (Supplementary) shows the comparison of the psychopathology state between the groups, according to the SCL-90R scales (see Figure S1 for the T-standardized mean scores). A healthier psychology status was registered for the participants within the HC group, followed by the OB + DM patients. On the other hand, the GD and AN-R conditions registered the worse psychology state.

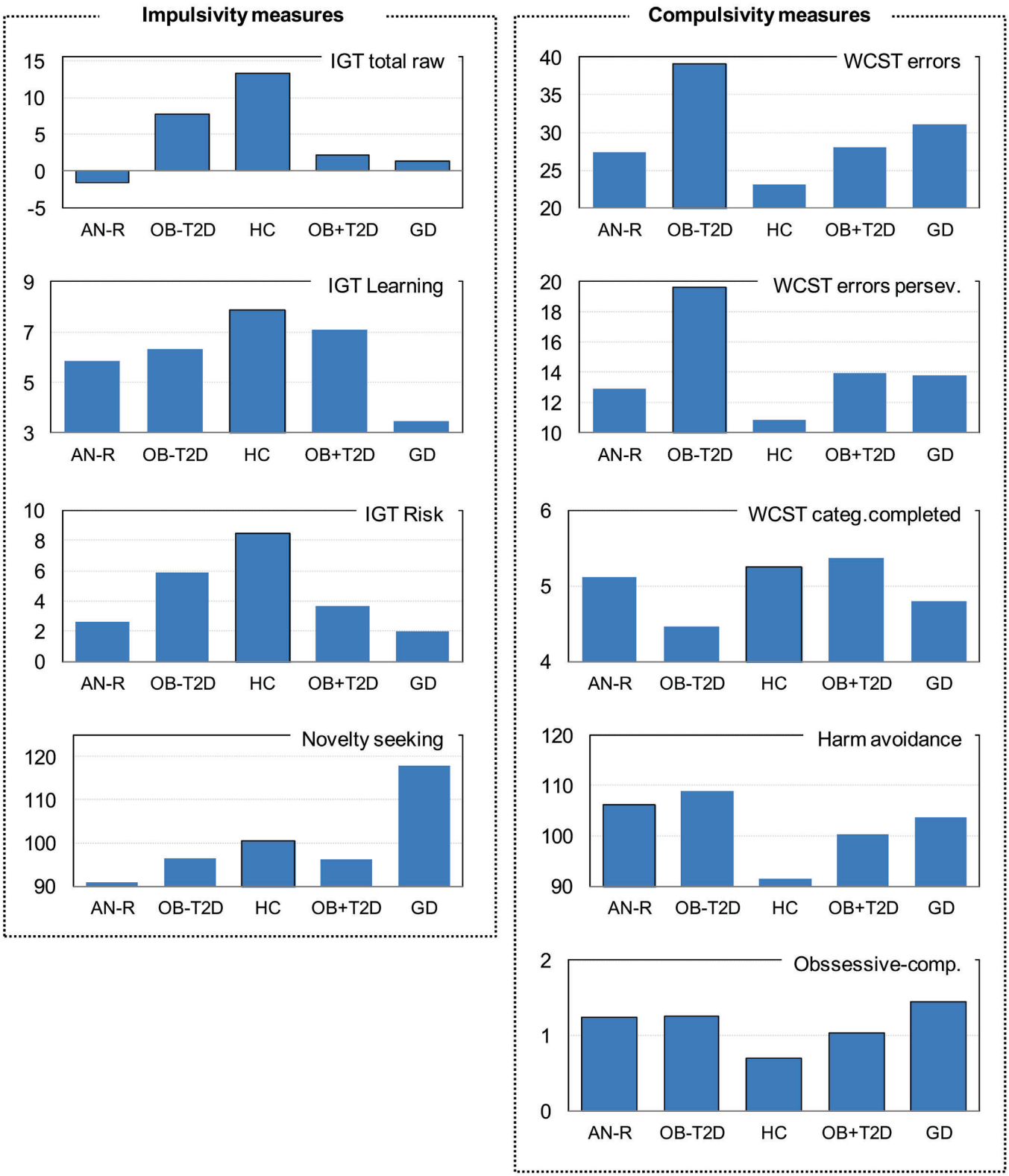

Figure 1. Bar charts with the impulsivity–compulsivity measures in the study (dimensional scores).

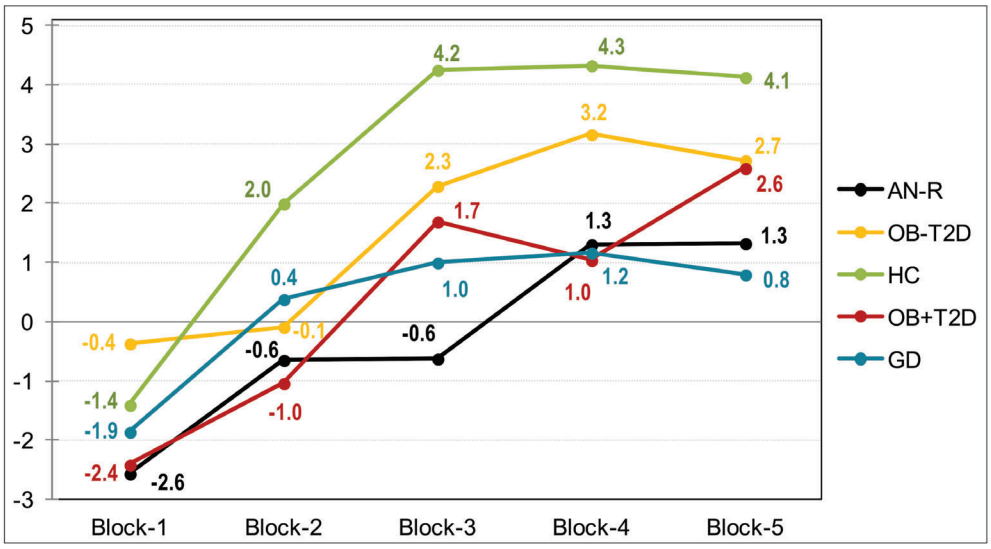

Figure 2. Performance learning curve (IGT task). Note. AN-R: anorexia nervosa restrictive. OB − T2D: obesity without T2D. HC: healthy control. OB + T2D: obesity with T2D. GD: gambling disorder. *Y*-axis represents the means adjusted by sex, age, education, and BMI.

4. Discussion

In the present study, we sought to investigate cognitive and personality traits associated with impulsivity and compulsivity in individuals with obesity in the presence or absence of T2D. Additional groups included in the study were healthy, normal-weight individuals, highly impulsive patients (patients with GD), and underweight, highly compulsive patients (patients with AN-R). Individuals with obesity and T2D showed highly impulsive decision making, whereas the other measure of impulsivity, novelty seeking, was not associated with obesity with T2D, nor with obesity only. For the compulsive pole, individuals with only obesity presented poor cognitive flexibility and high harm avoidance, although these dimensions were not associated with obesity plus T2D.

Impulsive decision making (e.g., choice impulsivity) is characterized by the preference for high immediate reward, despite higher future losses, in terms of both physical and psychological outcomes [17]. Poor decision making, shown by a lower IGT total score, was observed in individuals with obesity in the presence of T2D, when compared with the HC group. This was similar to what was observed in GD and AN-R compared to the HC. By contrast, the IGT total score in individuals with obesity in the absence of T2D did not differ from that of the HC group. Our findings are consistent with a previous study [55], which showed more disadvantageous decisions in the IGT total score in individuals with obesity plus T2D than in the HC. A potential explanation for the relation between obesity plus T2D and cognitive components of impulsivity could be, to some extent, the deficiencies in central insulin signaling, which are thought to impact the brain's dopaminergic (DA) systems [45–49]. Given the central role of DA in cognitive functions related to impulsivity [65–67], it is possible that the presence of T2D and the related alterations in insulin signaling in the brain impact these cognitive dimensions of impulsivity [68,69].

Regarding personality traits related to impulsivity, novelty seeking reflects the tendency to seek out new stimuli and experiences, to be easily bored, and be inclined to avoid monotony [70]. The group of patients with GD were the only group that showed high novelty seeking, whereas individuals with obesity in the presence or absence of T2D were not characterized by high novelty seeking when compared with the HC. Although some studies in the general population reported a positive relation between novelty seeking and BMI [70], this was not found in clinical populations of individuals with obesity, in which novelty seeking was not related to BMI [71] or to successful weight loss [72]. Moreover, it has been suggested that higher novelty seeking is more frequently associated with the pres-

ence of eating disorders (e.g., binge eating disorder and night eating disorder) [73], rather than obesity. Impulsive personality traits more strictly linked to decision making, such as urgency [74] and a lack of premeditation [75], may be expected to be more pronounced in individuals with obesity in the presence of T2D, although no studies are available to date.

For the compulsive spectrum, cognitive flexibility refers to the ability to flexibly adapt one's behavior to a changeable environment [76]. We found poor flexibility in individuals with obesity without T2D, compared to the other groups. This is consistent with previous findings, in which deficits in cognitive flexibility have been observed in people with overweight and obesity [34,35]. Difficulties in shifting current behavior in response to different requirements could negatively impact eating behaviors, and this cognitive rigidity could help to maintain unhealthy eating habits and, thus, relate to high body weight [77].

Concerning personality traits, harm avoidance is defined as the tendency to be motivated by a desire to avoid aversive experiences, which is strictly related to compulsive attitudes. We observed higher levels of harm avoidance in the group of individuals with obesity without T2D. This is in line with previous studies in clinical samples, which showed a positive association between harm avoidance and obesity [40–42]. Higher harm avoidance scores have been particularly reported in patients with grade 3 obesity compared with grade 2 and 1 obesity [42]. Nevertheless, higher psychological distress was present in individuals with obesity without T2D compared to the individuals with obesity plus T2D, which could contribute to more rigid behavior and cognition.

Limits and Strengths

The present study was limited by the absence of some important variables, such as the duration of diabetes and the diabetes medication, which could have interfered with the results. Therefore, these findings should be interpreted with caution, and further studies, taking medication and illness duration into account, will need to be undertaken. Furthermore, considering the complex nature of impulsivity and compulsivity, a broader assessment of the other domains of impulsivity/compulsivity would be informative, to better characterize obesity in the presence or absence of T2D.

Despite these limitations, one of the strengths of the study is the inclusion of clinical comparison groups that are representative of impulsivity and compulsivity, such as GD and AN-R. This facilitates the placement of obesity groups along the impulsive–compulsive spectrum. An additional strength is the use of both neurocognitive and personality measures, enabling a more comprehensive assessment.

5. Conclusions

Taken together, the results of this study suggest that the individuals with obesity in the absence of T2D were more rigid in their behavior and showed more compulsive personality traits than those with obesity plus T2D. On the other pole of impulsivity, we found that individuals with obesity in the presence of T2D were more impulsive in their decisions compared to healthy, normal-weight controls; this would allocate them to the impulsive pole of the impulsive–compulsive spectrum. If so, the tendency to make impulsive choices may be expected to negatively impact self-control and diabetes management. However, due to the lack of information about diabetic medication and diabetes duration, which affect insulin signaling in the brain, these findings should be interpreted with caution. Further studies, controlling these variables, are needed to confirm the present findings.

Despite its exploratory nature, this study offers preliminary insights into the personality traits associated with the compulsivity–impulsivity spectrum in individuals with obesity in the presence or absence of T2D. For the health care provider, identifying and understanding the presence of personality traits that could act as a barrier to treatment adherence may improve the success rates of diabetes management and obesity weight loss treatments.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/nu13124426/s1: Table S1: comparison between the groups: ANCOVA adjusted for sex, age, education and BMI; Figure S1: line charts with the SCL-90R profile in the study (mean T-scores).

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4.2. ESTUDIO 2

Título del artículo

Cognitive flexibility and DSM-5 severity criteria for Eating Disorders: Assessing drive for thinness and duration of illness as alternative severity variables

Flexibilidad cognitiva y criterios de gravedad del DSM-5 para los Trastornos de la Conducta Alimentaria: Evaluación de la obsesión por la delgadez y la duración de la enfermedad como variables alternativas de gravedad

Objetivos

- Evaluar si los criterios de gravedad de los TCA, propuestos por el DSM-5, se asocian a déficits en el rendimiento cognitivo (flexibilidad cognitiva).
- Explorar si la obsesión por la delgadez y la duración de la enfermedad, podrían actuar como índices de gravedad alternativos en pacientes con TCA.

Resumen

Los criterios de gravedad para los trastornos de la conducta alimentaria (TCA), propuestos en el DSM-5, carecen de suficiente apoyo empírico. La obsesión por la delgadez (DT por sus siglas en inglés *Drive for Thinness*) y la duración de la enfermedad se han propuesto como dos medidas de gravedad alternativas, si bien su evidencia empírica es limitada. Hasta la fecha, no constan investigaciones que hayan evaluado la validez de los actuales criterios de gravedad de los TCA, teniendo en cuenta el rendimiento cognitivo. La flexibilidad cognitiva suele estar alterada en los TCA y es un posible indicador de gravedad. El presente estudio evaluó por primera vez: 1) si las categorías de gravedad de los TCA propuestas en el DSM-5 se asociaban con déficits en la flexibilidad cognitiva y, 2) si la DT y la duración de la enfermedad, actuaban como índices de gravedad alternativos y relevantes. Para ello, 161 pacientes con TCA fueron clasificados según las categorías de gravedad del DSM-5, la DT y la duración de la enfermedad. Se evaluó la capacidad discriminativa de cada categoría para la flexibilidad cognitiva mediante el Test de Clasificación de Tarjetas de Wisconsin (WCST). Los resultados obtenidos indicaron: a) En el grupo de anorexia nerviosa (AN), los pacientes con gravedad moderada mostraron mejores puntuaciones en el WCST que los pacientes con gravedad leve y grave/extrema según el DSM-5. Asimismo, los pacientes con gravedad moderada mostraron un menor porcentaje de déficits de flexibilidad cognitiva que las otras dos categorías de gravedad; b) En el grupo de TCA con conductas bulímico-purgativas, los pacientes con gravedad leve mostraron una mayor afectación cognitiva (déficits de flexibilidad cognitiva) que las categorías moderada y grave/extrema. Al evaluar el índice de gravedad alternativo de la DT, no se encontraron diferencias en flexibilidad cognitiva en ninguno de los grupos. En cuanto a la duración de la enfermedad, en el grupo AN, el rendimiento de los pacientes con mayor duración de la enfermedad fue peor que el del grupo de corta duración. Por otro lado, el grupo de pacientes con conductas bulímico-purgativas, que además presentaban una mayor duración del TCA, mostraron más déficits en flexibilidad cognitiva que los pacientes con menor duración. Estos hallazgos constatan las limitaciones de los criterios actuales de gravedad del DSM-5 para categorizar la flexibilidad cognitiva en los TCA e indican que la duración de la enfermedad podría considerarse un criterio de gravedad alternativo.

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RESEARCH

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Cognitive flexibility and DSM-5 severity criteria for eating disorders: assessing drive for thinness and duration of illness as alternative severity variables

Bernat Mora-Maltas[1,2†], Ignacio Lucas[1,2,3†], Roser Granero[2,3,4], Cristina Vintró-Alcaraz[1,2,3], Romina Miranda-Olivos[1,2,3], Isabel Baenas[1,2,3], Isabel Sánchez[1,2,3], Jessica Jiménez-del Toro[1,2], Jéssica Sánchez-González[1,2], Isabel Krug[5], Javier Tapia[1,6], Susana Jiménez-Murcia[1,2,3,7] and Fernando Fernández-Aranda[1,2,3,7*]

Abstract

Background The severity criteria for eating disorders (EDs) proposed in the DSM-5 have been established without sufficient empirical support. Drive for thinness (DT) and duration of illness have been proposed as two alternative severity measures, however their empirical evidence is also limited. To date, no research has assessed the validity of current eating disorder (ED) severity criteria regarding cognitive flexibility factors. Cognitive flexibility is often impaired in EDs, becoming a possible severity symptom. The current study assessed for the first time (1) whether the severity indexes for EDs proposed in the DSM-5 were associated with deficits in cognitive flexibility and, (2) whether drive for thinness and illness duration, acted as an alternative, more meaningful severity indices for deficiencies in cognitive flexibility.

Methods Participants were 161 patients diagnosed with an ED, who were categorized according to DSM-5 severity categories, DT and duration of illness. Discriminative capacity of each classification was assessed for cognitive flexibility measured by Wisconsin card sorting test (WCST).

Results The findings for the DSM-5 classification comprised: (a) In the anorexia nervosa (AN) group, patients with moderate severity showed better scores in WCST than patients with mild and severe/extreme severity. Also, patients with moderate severity showed lower percentage of cognitive flexibility deficits than the other two severity categories; (b) For the binge spectrum disorders (BSD) group, the patients with mild severity showed a higher percentage of cognitive flexibility deficits than did the moderate and severe/extreme categories. When assessing the alternative severity index of DT, no differences were found in cognitive flexibility in any of the groups. Regarding illness duration, in the AN group the task performance of the patients with longer illness duration was worse than the performance of the short duration group and, in the BSD group, patients with longer duration also showed more deficits in cognitive flexibility than the patients with shorter duration of illness.

[†]Bernat Mora-Maltas and Ignacio Lucas shared first authorship.

*Correspondence:
Fernando Fernández-Aranda
ffernandez@bellvitgehospital.cat
Full list of author information is available at the end of the article

Conclusions Our findings point out the limitations of the DSM-5 severity criteria to categorize cognitive flexibility in EDs and support illness duration as an alternative severity approach for EDs.

Plain English summary

The current severity criteria for eating disorders were defined without enough evidence and present several limitations. Therefore, some researchers proposed alternative criteria like the drive for thinness or the duration of the disorder. Eating disorders are characterized by cognitive impairments such as deficits in cognitive flexibility. Cognitive flexibility is the ability to adapt our behaviour to the needs of the environment. According to our results, current severity criteria do not classify correctly in terms of cognitive flexibility. Moreover, this study shows that patients with longer illness duration show less cognitive flexibility. Therefore, this study highlights the limitations of current severity criteria for eating disorder to classify according to cognitive flexibility. Our findings also show the importance of taking into account the illness duration in order to assess the severity of the disorder.

Keywords Eating disorders, Neuropsychology, DSM-5-TR, Illness duration, Severity ratings

Background

The fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) [1] and its text revised version (DSM-5-TR) [2] propose four different severity gradients for eating disorders (EDs) ('mild', 'moderate' 'severe' and 'extreme'). The severity of the disorder is determined by the body mass index (BMI = kg/m^2) for anorexia nervosa (AN). Regarding binge spectrum disorders (BSD), a classification previously used in the literature [3] that includes bulimia nervosa (BN) and binge eating disorder (BED), the severity is determined by the weekly frequency of episodes of inappropriate compensatory behaviours for BN, and the number of weekly binge episodes for BED. However, a recent systematic review and meta-analysis presented a compound of scientific evidence that acknowledged the limitations of the current severity classification for EDs [4]. According to the literature, the criteria and cut-offs used for defining the severity of EDs are controversial and lack sufficient empirical support [5–10].

With respect to AN, inconsistent results have been found, maybe because using only BMI does not take into account important factors such as physical (e.g. weight history), psychological or cognitive factors that may reflect different kinds of impairment [11–13]. In this line, several studies assessing individuals with AN did not find significant variation among the different DSM-5 severity groups regarding distress, psychiatric comorbidity or further attitudinal eating disorder (ED) symptoms (i.e., shape concerns/weight) [5, 6, 9, 14–18]. Moreover, Dakanalis et al. [19] found that patients with less severe AN showed more bingeing and purging behaviours than the ones with more severity, and the presence of binge-purge behaviours in AN have been associated with more psychopathology [20–22], more relapses [23] and poorer treatment outcomes [24]. For BSD, incongruous findings regarding the utility of the DSM-5 severity index have been obtained. Studies that support the proposed DSM-5 criteria found that patients with severe and extreme BN had more psychiatric comorbidities, functional impairments, perfectionism, and ED body-related attitudes and behaviours than those in the mild and moderate categories [17, 25–28]. Conversely, a study by Zayas et al. [18] supported the utility of the BN severity index with respect to ED psychopathology in females, but not in males, and other studies found rarely or no differences for these variants across the BN severity groups [5, 29, 30]. Furthermore, in some other studies few patients diagnosed with BN fell into the severe or extreme categories, raising doubts about the cut-off points of the BN classification [17, 31, 32]. The literature has also been contradictory with regard to BED. Some studies reported differences between severity groups in relation to BMI, ED characteristics, comorbidity (personality disorders, biases and emotional difficulties), and other factors of distress and impairment [5, 11, 27, 33, 34]. However, various studies found no differences between severity categories with respect to psychiatric comorbidity, prognostic prediction or body attitude [6, 8, 11, 17, 30, 34, 35]. In addition, as seen in BN, few individuals with BED fall into the severe or extreme BED categories [4–6, 8, 17].

Due to the uncertainty that exists regarding the functionality of the DSM-5 severity index, researchers have introduced transdiagnostic indices to find alternative severity classifications for each ED subtype [4]. In this line, previous research has proposed other alternative measures for ED severity to overcome the limitations presented by the DSM-5 classification. For example, Krug et al. [6] proposed an alternative transdiagnostic indicator of ED severity, the *drive for thinness* (DT) dimension of the eating disorders inventory-2 (EDI-2)

[36]. DT is defined as an extreme fear of weight gain, which reinforces disordered eating patterns (especially restrictive eating) [37–39]. However, DT is just one factor involved in the complex process of EDs [40].

Duration of illness has also been reported as an alternative indicator of severity for EDs. Specifically, the EDs literature has repeatedly demonstrated that a shorter duration of illness is related to a more favourable outcome of treatment for EDs [41–44]. For instance, a study by Fernández-Aranda et al. [45] has shown that duration of illness was linked with poor response to treatment, suggesting that the duration of illness could be a good marker of severity. In this study, the duration cut-off points from which there would be a greater risk of having poor results were: 12 years for patients diagnosed with AN, 13 years for patients with BN, and 21 years for patients with BED. In addition, other empirical studies have reported an association between the duration of illness and deficits in cognitive flexibility in AN [46] and BSD [47].

Cognitive flexibility is defined as the ability to adjust individual's beliefs or behaviour in response to new situations, which is essential for behaviour self-regulation [48]. A common neuropsychological task to measure cognitive flexibility is the Wisconsin Card Sorting Test (WCST; [49]). Although the role of cognitive flexibility in EDs is still being studied, there is increasing support that this cognitive malfunction may be one of the factors that influences the development and maintenance of EDs. A meta-analysis carried out by Wu et al. [50] reported cognitive flexibility impairments in patients with restrictive subtype of AN, BN and BED. In addition, a recent study associated AN and BSD with impairments in different executive domains, including cognitive flexibility [51]. In that study, poor cognitive performance correlated with anxious, depressive, and ED symptoms. Other results also associated cognitive flexibility impairments in EDs with comorbid symptomatology, such as depression or anxiety [52]. In patients with AN, lack of cognitive flexibility has been considered a neurocognitive endophenotype that may contribute to compulsive and rigid behaviour [53–55]. Specific treatments, such as the cognitive remediation therapy, are aimed at the cognitive impairments shown by these patients [56–58]. Complement usual treatment with cognitive remediation therapy have proven to produce a significant improvement in eating disorder-specific health-related quality of life and a greater reduction of eating disorder psychopathology [59]. However, the efficacy of cognitive remediation therapy remains unknown due to a lack of conclusive data from other studies, which have found no evidence that this treatment improves eating disorder symptoms [60, 61]. For BSD, a meta-analysis reported that deficits in cognitive flexibility are associated with the inability to stop compulsive overeating [50]. Moreover, poor performance of BSD patients in the WCST have proven to be a predictor of bad treatment outcome [62]. However, in BSD there are inconsistent results, with studies reporting deficits in cognitive flexibility [50, 63], and others finding no significant differences [64, 65] compared to controls.

Until now, the literature has taken little account of cognitive factors as an effective measure to assess the severity of EDs. In fact, to our knowledge, there are no studies that evaluate cognitive deficits of patients with an ED based on the DSM-5 severity indices.

The current study

The current study assessed, for the first time: (1) Whether the severity indices for EDs proposed in the DSM-5 were associated with deficits in cognitive flexibility and, (2) Whether DT and illness duration, acted as an alternative, more meaningful severity indices for deficiencies in cognitive flexibility.

Methods

Participants

The participants were 161 adults (130 females and 31 males) who met the DSM-5 criteria for an ED. All patients were diagnosed by experienced psychologists. Those who were diagnosed according to DSM-IV-TR criteria [66] were reanalysed and recoded post-hoc using DSM-5 criteria [2]. Most patients were treatment naïve ($n=116$, 72%). The number of patients with one previous treatment was $n=24$ (14.9%), with two previous treatments was $n=10$ (6.2%), and with three or more previous treatments $n=11$ (6.8%). There was a positive correlation between the number of previous treatments and illness duration (non-parametric correlation = 0.333) in the whole sample. The distribution of the ED diagnoses was: 72 AN-Restrictive (AN-R), 28 AN-Binge-eating/Purging type (AN-BP), 34 BN, and 27 BED. Patients with a diagnosis of AN-R and AN-BP were categorized in the AN group, and patients diagnosed with BN and BED were categorized in the BSD group. This classification was based on the common physiological and psychological factors that differentiate ED subtypes [3]. The AN group had a mean age of 27.28 years (SD = 8.99). The BSD group had a mean age of 35.62 years (SD = 10.64). The age range of the total sample is between 17 and 58 years. Table 1 displays a detailed sociodemographic description of each group, and the result of the statistical comparison. Exclusion criteria were having an intellectual disability, the presence of an organic mental disorder or an active psychotic disorder.

Data were collected between November 2007 and January 2020 at the Eating Disorders Unit of the Bellvitge

Table 1 Sample description

	AN group ($n=100$)		BSD group ($n=61$)		*p*
	n	**%**	***n***	**%**	
Sex					
Females	92	92.0	38	62.3	**< 0.001***
Males	8	8.0	23	37.7	
Marital status					
Single	81	81.0	36	59.0	**0.006***
Married	15	15.0	16	26.2	
Divorced	4	4.0	9	14.8	
Education					
Primary	33	33.0	26	42.6	0.324
Secondary	38	38.0	23	37.7	
University	29	29.0	12	19.7	
Employment					
Unemployed	43	43.0	22	36.1	0.384
Employed/student	57	57.0	39	63.9	
Social position					
High	12	12.0	4	6.6	**0.028***
Mean-high	21	21.0	20	32.8	
Mean	24	24.0	23	37.7	
Mean-low	34	34.0	9	14.8	
Low	9	9.0	5	8.2	
	Mean	**SD**	**Mean**	**SD**	***p***
Age (years old)	27.28	8.99	35.62	10.64	**< 0.001***
Onset ED (years old)	21.06	8.58	25.21	11.38	**0.009***
Duration ED (years)	6.22	6.30	10.41	8.12	**< 0.001***
EDI-2 drive for thinness	9.72	7.31	14.38	5.12	**< 0.001***
Body mass index (kg/m^2)	16.21	1.50	30.94	8.93	**< 0.001***
Inappropriate compensatory behaviours	2.67	7.84	4.69	6.57	0.094

AN anorexia nervosa group (*AN-R* anorexia nervosa restrictive, *AN-BP* anorexia nervosa binge-purging), *BSD* binge spectrum disorders symptoms group (*BN* bulimia nervosa, *BED* binge eating disorder), *ED* eating disorder, *SD* standard deviation, *EDI-2* eating disorders inventory-2; Inappropriate compensatory behaviours: number of vomits, laxatives and diuretics per week. *Bold: significant comparison

University Hospital (Barcelona, Spain). All participants received information about the procedure and signed an informed consent form. All procedures were approved by the Ethical Committee of the Bellvitge University Hospital in accordance with the Helsinki Declaration of 1975 as revised in 1983 (Refs. 34/05, 307/06).

Sociodemographic and clinical information

Sociodemographic data were collected from each participant. These data included age, education level, marital status and employment, as well as ED onset and duration. Sex data is also reported, showing a higher proportion of females, but in accordance with prevalence estimates of EDs [67]. Social position was calculated using the Hollinghead method [68].

Psychological assessment

Participants were evaluated using the DT subscale of the Eating Disorders Inventory-2 (EDI-2) [36]. This questionnaire evaluates cognitive and behavioural features related to the ED. DT factor is defined as the extreme fear of weight gain and over-preoccupation about diet and weight. In this study, Cronbach's alpha for the EDI-2 DT subscale was 0.884 (indicating good internal consistency).

Neuropsychological assessment

The computerized version of the Wisconsin Card Sorting Test (WCST) [49, 69] was used to evaluate cognitive flexibility. The WCST includes 128 cards that comprise three available categories: number (*N*), colour (*C*) and shape (*S*). For a right pair, participants must identify the sorting rule, receiving the feedback of "Right" or "Wrong" after each sort. By trial and error, the participant must learn

to change the sorting categories according to the given feedback. Initially, *C* is the correct sorting category, and positive feedback is given only if the card is placed in the pile with the same colour. After 10 consecutive right pairs, the rule is changed, and then, another sorting rule must be identified. There are up to six attempts to detect the sorting rule and five rule shifts during the task. Each rule attainment is referred to as "category completed". The task ends when all 128 cards are sorted or after the six full categories are completed. The number of completed categories is recorded, as well as the percentages of errors, perseverative responses, perseverative errors, non-perseverative errors, and conceptual level responses. The presence of deficits in cognitive flexibility was determined by scores below the 16^{th} percentile in any of the WCST scales perseverative errors, non-perseverative errors, and number of completed categories, based on normative data published in the manual of the task and in accordance with previous literature about cognitive functions [70, 71]. The method to calculate presence of deficits in cognitive flexibility is not described in the manual, but have been previously used in eating disorders [47].

Severity index categorization

DSM-5

The DSM-5 severity classifications were carried out following the criteria proposed in the manual [1]. For the AN group, four severity categories were defined according to patients' BMI: mild (> 17.0 kg/m^2), moderate (16–16.99 kg/m^2), severe (15–15.99 kg/m^2) o extreme (< 15 kg/m^2). The severity of the ED in patients diagnosed with BN was defined by the number of inappropriate compensatory behaviours per week (vomits, laxatives and diuretics): mild (1–3 episodes/week), moderate (4–7 episodes/week), severe (8–13 episodes/week) and extreme (> 14 episodes/week). In patients with a BED diagnosis, the severity categories were defined by the same categorization as for BN but taking into account binge eating episodes per week instead of compensatory behaviours.

Drive for thinness

Krug et al. [6] used an alternative categorization for ED severity based on DT symptomatology using the EDI-2 DT subscale. We used the same cut-off point for classifying low DT (≤ 14) participants and high DT (> 14) participants, based on the recommendations by [72] for screening purposes. This cut-off point has also been used in other previous studies [73].

Illness duration

Illness duration cut-off points were based on a previous recent study that highlighted the importance of the duration of the disorder in the treatment outcome of EDs [45]. This previous study calculated the duration cut-off points from when there would be a higher risk of having poor treatment outcomes in each subtype of ED. Hence, the cut-off points used in this study were 12 years for patients diagnosed with AN-R and AN-BP, 13 years for patients with BN, and 21 years for patients with BED.

Procedure

Evaluations were conducted in two separate sessions prior to the psychological treatment. In the first one, we collected sociodemographic data and conducted the psychological assessment. And, in the second one, participants completed a computerized version of the WCST [49, 69].

Statistical analysis

The statistical analysis was performed with Stata17 (Stata Press, 2021) for Windows. Chi-squared tests (χ^2) were done for the comparison of categorical variables between the groups (e.g. cognitive flexibility deficits), and analysis of variance (ANOVA) was done for the comparison of quantitative measures (e.g. neuro-psychological scores). The effect size of the proportion and mean comparisons was estimated through Cramer's-V coefficient for categorical variables [the thresholds 0.06, 0.15 and 0.30 were considered for low/poor effect size, moderate/medium, and high/large (Cohen, 1998)] and partial eta-squared coefficient (η2) for quantitative measures [the thresholds for low/poor, moderate/medium and high/large were 0.06, 0.10, and 0.25 (Levine and Hullett, 2002)]. Increase of Type-I error due to multiple comparisons was controlled using the Finner Method (Finner, 1993), a family-wise procedure that has proved to be more powerful than the classical Bonferroni correction.

Results

Severity distribution

Figure 1 displays bar-charts for the severity levels according to the three classification methods of the study (DSM-5, DT and illness duration). Among patients in the AN group, the more prevalent categories were: severe-extreme severity based on the DSM-5 severity levels (grouping 40.0% of patients), low score based on the EDI-2 DT scale (66.0%), and short duration (78.0%) based on the illness duration. Among patients of the BSD group, the more prevalent categories were mild severity for the DSM-5 classification system (36.1%), high score based on the EDI-2 DT scale (59.0%), and short duration based on the illness duration (75.4%).

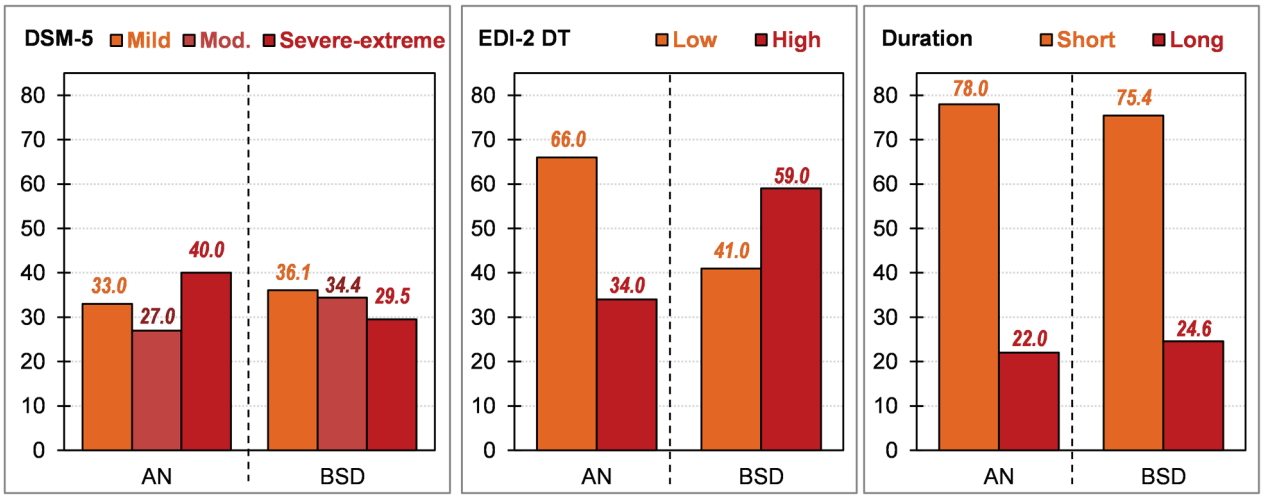

Fig. 1 Severity prevalence estimates according to the three classification methods of the study (DSM-5, drive for thinness and illness duration)

Cognitive flexibility based on the DSM-5 severity classification

Table 2 shows the discriminative capacity of the classification methods for cognitive flexibility based on DSM-5 severity criteria. Among patients in the AN group, the moderate severity group classified by the DSM-5 criteria showed better performance in WCST (PctErrors, PctPersRsps, PctPersErrors, PctCLRsps) than the mild and severe/extreme groups. This classification also reported that patients grouped in the mild and severe/extreme categories showed a higher percentage of deficits in cognitive flexibility than the moderate group. Among BSD group, patients classified in the mild severity category showed higher percentage of deficits in cognitive flexibility than the moderate and severe/extreme categories.

Cognitive flexibility based on alternative severity classifications

Table 3 shows the discriminative capacity of alternative severity classification methods for cognitive flexibility. No differences in cognitive flexibility were obtained for the DT classification in any group. However, regarding duration of the disorder, patients of the AN group and a short duration of the disorder showed a better performance in WCST (PctErrors, PctPersRsps, PctPersErrors, PctNonPersError, PctCLRsps) than the patients with a longer duration. In the patients of the BSD group classified by duration of illness, no differences were found in the task scores. Nevertheless, the duration of the illness differentiated the presence of deficits in cognitive flexibility in patients with BSD, with a higher percentage of deficits in cognitive flexibility for the patients with longer duration.

Discussion

A first aim of the present study was to determine if the DSM-5 severity criteria for EDs were able to assess the presence of deficits in cognitive flexibility, considering that it could be a core symptom of severity in EDs. Our second aim was to evaluate whether other alternatives variables such as DT or illness duration could be associated with poorer cognitive flexibility. Using the DSM-5 severity criteria for AN, we observed that the moderate severity group performed better in the WCST than the mild and severe/extreme groups, which presented a similar performance. In the same line, we found that patients classified in the mild and severe/extreme groups according to DSM-5 criteria, presented a higher percentage of deficits in cognitive flexibility than the moderate severity group. Considering the BSD group, our study did not find significant differences in cognitive flexibility performance between the DSM-5 severity groups. Additionally, the less severe group showed more cognitive flexibility deficits than the other two groups. These results suggest that DSM-5 severity criteria were not able to discriminate between cognitive flexibility levels of patients diagnosed with a BSD. Regarding both clinical groups, the present findings showed that DT did not discriminate poor cognitive flexibility. However, duration of illness did present discriminative capacity to assess poor cognitive flexibility, resulting in an alternative severity classification for EDs. In the AN group, the WCST performance of the long duration group was worse than the performance of the short duration group. Similarly, in the BSD group, the long duration group included a higher percentage of people with cognitive flexibility deficits.

These results illustrate that the DSM-5 severity ratings for AN, that are exclusively based on BMI, do not

Table 2 Discriminative capacity on cognitive flexibility for the DSM-5 severity classification

AN group (n = 100)											
WCST T-scores	***DSM-5 criteria***										
	Mild (G1) *n* = 33		**Mod(G2) *n* = 27**		**S/E (G3) *n* = 40**		**Factor group**		**Pairwise comparisons**		
									G1–G2	***G1–G3***	***G2–G3***
	Mean	***SD***	***Mean***	***SD***	***Mean***	***SD***	***p***	**ES**	***p***	***p***	***p***
WCST: PctErrors	45.36	11.37	52.44	10.31	46.30	11.24	**0.033***	0.068	**0.015***	0.719	**0.028***
WCST: PctPersRsps	46.91	11.91	55.11	10.71	46.33	10.59	**0.004***	**0.108†**	**0.005***	0.823	**0.002***
WCST: PctPersErrors	46.91	11.91	53.74	10.45	46.10	10.63	**0.016***	0.082	**0.019***	0.756	**0.006***
WCST: PctNonPersErrors	45.67	10.69	51.70	10.41	47.23	9.86	0.072	0.053	**0.026***	0.521	0.084
WCST: PctCLRsps	44.79	11.75	52.37	10.15	46.05	11.62	**0.026***	0.072	**0.011***	0.636	**0.027***
Deficit	*n*	%	*n*	%	*n*	%	*p*	ES	*G1–G2*	*G1–G3*	*G2–G3*
Cognitive flexibility	13	40.6%	2	7.4%	11	27.5%	**0.015***	**0.291†**	**0.004***	0.240	**0.041***
BSD group (n = 61)											
WCST T-scores	***DSM-5 criteria***										
	Mild (G1) *n* = 22		**Mod(G2) *n* = 21**		**S/E (G3) *n* = 18**		**Factor group**		**Pairwise comparisons**		
									G1–G2	***G1–G3***	***G2–G3***
	Mean	***SD***	***Mean***	***SD***	***Mean***	***SD***	***p***	**ES**	***p***	***p***	***p***
WCST: PctErrors	41.68	13.12	46.05	9.62	47.94	11.22	0.209	0.052	0.216	0.091	0.608
WCST: PctPersRsps	44.18	14.71	47.05	11.13	50.06	16.48	0.431	0.029	0.510	0.197	0.511
WCST: PctPersErrors	42.95	14.60	46.81	10.98	49.28	16.76	0.367	0.034	0.377	0.166	0.590
WCST: PctNonPersErrors	43.00	11.56	46.86	7.95	48.78	9.06	0.163	0.061	0.198	0.066	0.540
WCST: PctCLRsps	41.73	12.71	45.81	9.71	47.89	11.27	0.219	0.051	0.242	0.092	0.570
Deficit	*n*	%	*n*	%	*n*	%	*p*	ES	*G1–G2*	*G1–G3*	*G2–G3*
Cognitive flexibility	11	50.0%	5	23.8%	2	11.1%	**0.021***	**0.355†**	**0.046***	**0.009***	0.303

AN group anorexia nervosa group, *BSD* group binge spectrum disorders group, *WCST* Wisconsin card sorting test, *PctErrors* percentage of errors, *PctPersRsps* percentage of perseverative responses, *PctPersErrors* percentage of perseverative errors, *PctNonPersErrors* percentage of non-perseverative errors, *PctCLRsps* percentage of conceptual level responses, *Mod* moderate, *S/E* severe/extreme, *SD* standard deviation, *ES* effect size [partial eta-squared for ANOVA (η^2) and Cramer-V for chi-square test (C-V)]; *Bold: significant comparison; †Bold: effect size into the mild/moderate to the high/large range ($\eta^2 > 0.10$ or C-V > 0.15).

correspond to the deficits in cognitive flexibility. In patients diagnosed with AN, poor cognitive flexibility may be associated with the perseveration of maladaptive cognitive and behavioural patterns [74–76]. Therefore, it may contribute to the maintenance of the fixation on weight loss, weight control and calorie counting, excessive exercise routines, or instilled body image distortion [77, 78], all of which are clinical symptoms in AN [30, 79]. Our findings are consistent with previous research that highlighted the limited clinical utility of DSM-5 severity specifiers for AN [4, 5, 9, 18]. Considering the BSD group, taking into consideration that poor cognitive flexibility is frequently linked to the inability to cut off compulsive overeating [50] and difficulties set shifting attention away from ED-related stimuli [80], these findings are consistent with other studies that highlight the limited clinical support for DSM-5 severity criteria for BN [5, 30, 81] and BED [8, 11, 34, 35]. The results highlight the limitations of the DSM-5 severity criteria for EDs, as there are important domains, such as cognitive flexibility, that do not map onto the current, linear severity criteria. In this particular sample, cognitive flexibility seems to be associated with other factors, such as the duration of illness.

The present results suggest that duration of illness could be a better variable than DSM-5 severity criteria to identify poor cognitive flexibility in patients diagnosed with an ED. The poor cognitive flexibility presented by the two clinical groups with longer duration of illness could be suggested as a common EDs feature. Some studies have associated difficulties in cognitive flexibility with a fixed idea and rigid eating style based on idiosyncratic rules and with a greater resistance to be modified by therapy [78, 82]. Therefore, it seems that in EDs, the difficulty to adapt to new behaviour and rules in a changing environment could be associated with longer duration of the disorder. In addition, cognitive rigidity is a variable that is at odds with the notion of change and is likely to present difficulties to therapy and, therefore, is considered one of

Table 3 Discriminative capacity on cognitive flexibility for alternative severity classifications

AN group (n = 100)												
WCST T-scores	**EDI-2 drive for thinness**						**Duration of the disorder**					
	Low *n* = 66		**High *n* = 34**		**Factor group**		**Short *n* = 78**		**Long *n* = 22**		**Factor group**	
	Mean	***SD***	***Mean***	***SD***	***p***	**ES**	***Mean***	***SD***	***Mean***	***SD***	***p***	**ES**
WCST: PctErrors	46.94	11.36	49.03	11.29	0.385	0.008	49.13	10.92	42.41	11.44	**0.013***	0.061
WCST: PctPersRsps	48.62	11.43	49.41	12.09	0.749	0.001	50.54	11.44	43.05	10.43	**0.007***	0.072
WCST: PctPersErrors	48.08	11.25	49.12	11.79	0.667	0.002	50.01	11.15	42.82	10.64	**0.008***	0.069
WCST: PctNonPersError	47.14	10.45	49.44	10.47	0.299	0.011	49.01	10.38	44.05	10.06	**0.049***	0.039
WCST: PctCLRsps	46.59	11.65	48.79	11.54	0.371	0.008	48.78	11.21	42.23	11.76	**0.018***	0.055
Deficit	*n*	*%*	*n*	*%*	*p*	ES	*n*	*%*	*n*	*%*	*p*	ES
Cognitive flexibility	19	29.2%	7	20.6%	0.353	0.093	18	23.4%	8	36.4%	0.222	0.123
BSD group (n = 61)												
WCST T-scores	**EDI-2 drive for thinness**						**Duration of the disorder**					
	Low *n* = 25		**High *n* = 36**		**Factor group**		**Short *n* = 46**		**Long *n* = 15**		**Factor group**	
	Mean	***SD***	***Mean***	***SD***	***p***	**ES**	***Mean***	***SD***	***Mean***	***SD***	***p***	**ES**
WCST: PctErrors	46.32	11.98	44.14	11.36	0.474	0.009	46.43	11.74	40.73	10.21	0.098	0.046
WCST: PctPersRsps	48.40	13.11	45.86	14.89	0.495	0.008	48.80	14.95	41.07	9.42	0.065	0.057
WCST: PctPersErrors	47.68	12.99	45.08	15.05	0.487	0.008	48.13	14.99	40.07	9.33	0.055	0
WCST: PctNonPersErrors	46.40	10.16	45.78	9.75	0.810	0.001	47.09	9.97	42.80	9.01	0.144	0.036
WCST: PctCLRsps	46.68	11.90	43.75	11.10	0.329	0.016	46.35	11.57	40.67	10.16	0.095	0.047
Deficit	*n*	*%*	*n*	*%*	*p*	ES	*n*	*%*	*n*	*%*	*p*	ES
Cognitive flexibility	9	36.0%	9	25.0%	0.354	0.119	10	21.7%	8	53.3%	**0.020***	**0.298†**

AN group anorexia nervosa group, *BSD group* binge spectrum disorders group, *WCST* Wisconsin card sorting test, *PctErrors* percentage of errors, *PctPersRsps* percentage of perseverative responses, *PctPersErrors* percentage of perseverative errors, *PctNonPersErrors* percentage of non-perseverative errors, *PctCLRsps* percentage of conceptual level responses, *Mod* moderate, *S/E* severe/extreme, *SD* standard deviation, *ES* effect size [partial eta-squared for ANOVA (η^2) and Cramer-V for chi-square test (C-V)]; *Bold: significant comparison; †Bold: effect size into the mild/moderate to the high/large range ($\eta^2 > 0.10$ or C-V > 0.15).

the factors associated with a worse prognosis [74]. In fact, in EDs, the lack of response to treatment has been linked to the illness duration and therefore, with chronicity [45]. Regarding duration and cognition, while some studies have observed that longer illness duration and severity in ED symptomatology were associated with executive dysfunctions [47, 83, 84], other studies did not find significant associations between longer illness duration and cognitive deficits [85, 86]. Therefore, the literature on the impact of illness duration on executive functions requires further investigation.

The preceding leads us to suggest that the DSM severity classification may not adequately reflect the severity from a neurocognitive point of view. Consequently, it may be beneficial to consider alternative factors in order to define severity classifications for EDs. Our results do not support DT as a transdiagnostic measure of severity for EDs. This variable may present some limitations as a transdiagnostic measure to assess eating disorders severity as, for example, some individuals could have different concerns, such as muscularity [87]. According to our results, duration of illness seems to be a better severity variable in terms of cognitive deficits. Although cognitive features are not yet considered an important severity measure in EDs, several studies have focused intervention on improving executive functions as alternative treatment with promising results [57, 88]. Therefore, the improvement of executive functions, such as cognitive flexibility, could influence a greater ability to adapt and guide problematic behaviours. However, a wide range of commonly shared features (i.e. affective, cognitive, biological, or personality) that can occur across all ED diagnoses have to be taken into account as well.

Limitations and strengths

The results of this study must be interpreted in light of its limitations. First, our sample size was limited to test the discriminative power of DSM-5 severity criteria regarding cognitive flexibility across all ED subtypes. Second, related to the previous one, due to the heterogeneity of each group it is not possible to reach conclusions about differences between all the ED subtypes included in the study (e.g., BN, BED). Future studies should include a sufficient sample of each subtype to better identify

the characteristics of each. Third, people diagnosed with an ED usually present deficits in different cognitive domains, hence, other cognitive domains could also have been explored, such as decision making or working memory. Fourth, although the study used for establishing the duration thresholds is representative of the population included in this study, using the thresholds proposed in a single study could represent a limitation. Fifth, it is important to highlight that this study included only a treatment seeking adult ED population. Consequently, our findings might not generalize to other populations, such as adolescents with an ED, for which some studies [89] revealed that cognitive impairment was not linked to AN. Future studies need to verify the DSM-5 severity index for EDs and other transdiagnostic severity indicators across a range of different treatment seeking and community samples.

However, our study also presents some remarkable strengths. First, our results are in line with previous studies that reported the limitations of the DSM-5 severity criteria. Moreover, this study includes further evidence that strengthens the conclusions derived from those studies, because these limitations seem to extrapolate to cognitive domains such as cognitive flexibility. Second, these results encourage the application of a transdiagnostic severity indicator based on illness duration.

Conclusions

The present study makes noteworthy contributions to evidence the limitations of the DSM-5 and DSM-5-TR severity criteria for EDs. The proposed severity classification does not demonstrate good discrimination in terms of cognitive flexibility levels, a core significant feature of EDs. Furthermore, our findings show that the ED duration is associated with cognitive flexibility deficits, confirming that illness duration can be a good marker of severity in EDs. Future studies should aim to further demonstrate all the limitations of the DSM-5 and DSM-5-TR severity classification for EDs and also to propose alternative severity variables.

Abbreviations

AN	Anorexia nervosa
ANOVA	Analysis of variance
AN-BP	Anorexia nervosa, binge-purgative subtype
AN-R	Anorexia nervosa, restrictive subtype
BED	Binge eating disorder
BMI	Body mass index
BN	Bulimia nervosa
BSD	Binge spectrum disorders
DT	Drive for thinness dimension of the eating disorders inventory-2
DSM-5	Diagnostic and statistical manual of mental disorders, fifth edition
DSM-5-TR	Diagnostic and statistical manual of mental disorders, fifth edition, text revision
ED	Eating disorder
EDs	Eating disorders
EDI-2	Eating disorders inventory-2
ES	Effect size
Mod	Moderate severity
PctErrors	Percentage of errors in the Wisconsin Card Sorting Test
PctPersRsps	Percentage of perseverative responses in the Wisconsin Card Sorting Test
PctPersErrors	Percentage of perseverative errors in the Wisconsin Card Sorting Test
PctNonPersErrors	Percentage of non-perseverative errors in the Wisconsin Card Sorting Test
PctCLRsps	Percentage of conceptual level responses in the Wisconsin Card Sorting Test
S/E	Severe/extreme severity
SD	Standard deviation
WCST	Wisconsin Card Sorting Test

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Availability of data and materials
The datasets generated during and/or analyzed during the current study are not publicly available due to ethical restrictions in order to protect the confidentiality of the participants, but are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
All participants received information about the procedure and signed an informed consent form. All procedures were approved by the Ethical Committee of the Bellvitge University Hospital in accordance with the Helsinki Declaration of 1975 as revised in 1983 (Refs. 34/05, 307/06).

Consent for publication
Not applicable.

Competing interests
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Author details
[1]Clinical Psychology Unit, University Hospital Bellvitge and CIBERobn, Feixa Llarga s/n 08907 L'Hospitalet del Llobregat, Barcelona, Spain. [2]Psychoneurobiology of Eating and Addictive Behaviours Group, Bellvitge Biomedical Research Institute (IDIBELL), Barcelona, Spain. [3]CIBER de Fisiopatología de la Obesidad y Nutrición (CIBERobn), Instituto de Salud Carlos III, Barcelona, Spain. [4]Departament de Psicobiologia i Metodologia, Universitat Autònoma de Barcelona, Barcelona, Spain. [5]Melbourne School of Psychological Sciences, The University of Melbourne, Melbourne, Australia. [6]Gerencia Territorial Metropolitana Sud. Hospital Universitari de Bellvitge, Barcelona, Spain. [7]Department of Clinical Sciences, School of Medicine and Health Sciences, University of Barcelona, Barcelona, Spain.

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Publisher's Note

4.3. ESTUDIO 3

Título del artículo

Executive functions in Binge Spectrum Eating Disorders with comorbid Compulsive Buying

Funciones ejecutivas en los Trastornos de la Conducta Alimentaria del espectro bulímico-purgativo con compra compulsiva comórbida

Objetivos

- Explorar si los pacientes con trastornos del espectro bulímico que presentan comorbilidad con compra compulsiva muestran mayor gravedad, mayor psicopatología general y peor rendimiento cognitivo en comparación a pacientes con trastornos del espectro bulímico sin comorbilidad y controles sanos.
- Analizar si los pacientes con trastornos del espectro bulímico que presentan comorbilidad con compra compulsiva muestran un peor resultado al tratamiento y mayor tasa de abandonos en comparación a pacientes con trastornos del espectro bulímico sin comorbilidad y controles sanos.

Resumen

Los trastornos de la conducta alimentada (TCA) del espectro bulímico (específicamente bulimia nerviosa [BN] y trastorno por atracón [TA]) acostumbran a presentar altos niveles de impulsividad y una elevada complejidad. Esta característica es también propia de algunas adicciones conductuales, como la compra compulsiva (CC). Los objetivos de este trabajo fueron explorar si los pacientes con TCA del espectro bulímico que presentaban comorbilidad con CC mostraban una mayor gravedad clínica y complejidad, así como un peor funcionamiento cognitivo. Se pretendía, además, analizar si este grupo de pacientes obtenía un peor resultado al tratamiento y una mayor tasa de abandonos. Este estudio, de diseño longitudinal, contaba con una muestra de n = 75 mujeres diagnosticadas de TCA de tipo bulímico, con o sin CC asociada, y Controles Sanos (CS). Todas las participantes completaron una evaluación sobre flexibilidad cognitiva, toma de decisiones, sintomatología del TCA, estado psicopatológico y rasgos de personalidad. Se observó que el grupo de TCA con CC presentaba un perfil clínico más grave, un peor resultado al tratamiento y una mayor afectación neuropsicológica, en comparación a los otros grupos. Los resultados mostraron también que los déficits en la toma de decisiones se asociaban a un peor resultado del tratamiento, mientras que los déficits en flexibilidad cognitiva, a la presencia de comorbilidad. Determinados rasgos de personalidad, tales como la autodirección y la búsqueda de novedades, se asociaron con el rendimiento neuropsicológico y la comorbilidad. Se concluyó que las pacientes con TCA del espectro bulímico, con CC comórbida presentan un peor perfil clínico y neuropsicológico, así como un peor resultado al tratamiento. Estas características clínicas deberían tenerse en cuenta para el diseño de abordajes terapéuticos específicos y personalizados.

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RESEARCH ARTICLE

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Executive functions in binge spectrum eating disorders with comorbid compulsive buying

Lucero Munguía[1,2] | Ignacio Lucas[1] | Susana Jiménez-Murcia[1,2,3] | Bernat Mora-Maltas[1] | Roser Granero[3,4] | Romina Miranda-Olivos[1,3] | Isabel Sánchez[1] | Giulia Testa[1,3] | María Lozano-Madrid[1,3] | Robert Turton[5] | Jose M. Menchon[1,2,6] | Fernando Fernández-Aranda[1,2,3]

[1]Department of Psychiatry, Bellvitge University Hospital-IDIBELL, Barcelona, Spain

[2]Department of Clinical Sciences, School of Medicine and Health Sciences, University of Barcelona, Barcelona, Spain

[3]Ciber Physiopathology, Obesity and Nutrition (CIBERObn), Instituto de Salud Carlos III, Barcelona, Spain

[4]Department of Psychobiology and Methodology of Health Sciences, Universitat Autònoma de Barcelona, Barcelona, Spain

[5]Department of Clinical, Educational and Health Psychology, University College London, London, UK

[6]Ciber Salud Mental (CIBERsam), Instituto Salud Carlos III, Barcelona, Spain

Correspondence
Susana Jiménez-Murcia and Fernando Fernández-Aranda, University Hospital of Bellvitge-IDIBELL and CIBEROBN, Feixa Llarga, L'Hospitalet del Llobregat, 08907 Barcelona, Spain.
Email: sjimenez@bellvitgehospital.cat and f.fernandez@ub.edu

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Abstract

Objective: The aims were to explore if bulimic spectrum disorders (BSD) patients, who also present comorbid compulsive buying (CB), could represent a specific subtype considering its neuropsychological performance; to present a descriptive analysis of different clinical features; and to explore how these variables could influence treatment outcome. It was hypothesised that the comorbid group will present worse neuropsychological performance that will lead to a worse treatment outcome.

Method: The study has a longitudinal design. Women ($N = 75$) diagnosed with BSD, BSD + CB and Healthy Controls (HC); completed an evaluation of: cognitive flexibility, decision making, eating disorder (ED) symptomatology, psychopathological state and personality traits.

Abbreviations: ANOVA, analysis of variance; BA, behavioural addiction; BMI, body mass index; BN, bulimia nervosa; BSD, bulimic spectrum disorders; BSD + CB, bulimic spectrum disorder with comorbid compulsive buying; C, colour; CB, compulsive buying; CBT, cognitive behavioural therapy; CFI, Bentler's Comparative Fit Index; DSM-5, Diagnostic and Statistical Manual of Mental Disorders 5; ED, eating disorder; EDI-2, Eating Disorder Inventory-2; GSI, Global Severity Index; HC, healthy controls; ICD-11, International Classification of Diseases 11; IGT, Iowa Gambling Task; N, number; PSDI, Positive Symptom Distress Index; PST, Positive Symptoms Total; RMSEA, root mean square error of approximation; S, shape; SCL-90-R, Symptom Checklist-90 Items-Revised; SD, standard deviation; SEM, structural equation model; SRMR, standardised root mean square residuals; TCI-R, Temperament and Character Inventory–Revised; TLI, Tuker–Lewis Index; WCST, Wisconsin Card Sorting Test.

Lucero Munguía and Ignacio Lucas are co-first authors.

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Results: BSD + CB was the group with the most severe clinical profile, worst treatment outcome and higher neuropsychological impairment, than other groups. Path-analysis evidenced that deficits in decision making were associated with bad treatment outcome, while deficits in flexibility with the presence of the comorbidity. Self-directedness and novelty seeking were associated with the neuropsychological performance and the comorbidity.

Conclusion: BSD + CB exhibit a worse clinical and neuropsychological profile that seems to be related with the treatment outcome, which should be taken into account for the establishment of specific treatment approaches.

KEYWORDS

binge spectrum disorders, compulsive buying, eating disorders, executive functions

Highlights

- Bulimic spectrum disorders comorbid with compulsive buying present with the most severe clinical profile and the worst treatment outcome
- The comorbid group exhibit more neuropsychological deficits than the non-comorbid one and the healthy controls
- Deficits in decision making were directly and positively associated with bad treatment outcome, while deficits in flexibility with the comorbid presence of the disorders
- Personality traits were associated with the neuropsychological performance and the comorbidity

1 | INTRODUCTION

Impulsivity has been defined as a tendency to respond with little forethought, often with disregard to the negative consequences to the impulsive behaviour to the individual or others (Moeller et al., 2001). It has been related to psychopathological conditions, such as eating disorders (EDs) or behavioural addictions (BA) (Lee et al., 2019; Mallorquí-Bagué et al., 2020; Waxman, 2009).

ED subtypes that are associated with high impulsive traits usually present with binge eating behaviours. According to the taxonomy of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5; American Psychiatric Association, 2013), bulimia nervosa (BN) is characterised by recurrent episodes of binge eating (eating large amounts with loss of control) and compensatory behaviours to prevent weight gain, which can include self-induced vomiting, inappropriate use of medicines, fasting or extreme exercise, whereas binge eating disorder (BED) is characterised by distressing, recurrent episodes of binge eating, with fewer compensatory behaviours. These binge-related impulsive behaviours, BN and BED, are known as binge spectrum disorders (BSD) (Treasure et al., 2020). Likewise, BA have been defined referring to persistent and maladaptive behaviours, in spite of the negative later repercussions, implying loss of control, craving, onset of tolerance and abstinence (Grant et al., 2010). Therefore, impulsivity traits are also highly related to BA (Lee et al., 2019).

BSD diagnosis have usually showed comorbidity with BA (Fernández-Aranda et al., 2006, 2008). The aforementioned link between BSD, and BA has motivated research into the presence of common core factors between them, including aspects of biological, neurocognitive and psychological nature.

According to biological models, dopamine has been associated with addictive processes and BSD. BED patients have shown greater density and higher binding potential of the dopamine D2 receptor, both related with enhanced dopamine signalling. This condition may predispose to reward hypersensitivity (Davis et al., 2012) and changes in dopamine release, as predictors of binge eating (Wang et al., 2011). The same dopamine receptors (D2) have been found to be related with the control of reward-associated behaviours, as in substance use disorders (Baik, 2013; Volkow & Li, 2005). Related with neurocognition, patients diagnosed with BED have shown impaired response inhibition and cognitive planning (Grant & Chamberlain, 2020). In a similar way,

individuals with BA perform disadvantageously on decision-making tasks (Bechara, 2003), as well as presenting with a diminished performance on tests of inhibition, cognitive flexibility and planning tasks (Ko et al., 2010). Considering personality traits, in BN patients with a lifetime comorbid BA the presence of high impulsive tendencies, harm avoidance and novelty seeking, as well lower self-directedness, and lower cooperativeness have been found (Álvarez-Moya et al., 2007; Del Pino-Gutiérrez et al., 2017; Fischer & Smith, 2008; Jiménez-Murcia et al., 2013). Additionally, in ED patients, the presence of a BA is associated with greater severity of the eating symptomatology (Fernández-Aranda et al., 2006, 2008; Jiménez-Murcia et al., 2015), greater general psychiatric morbidity and psychopathology (Bulik et al., 2004; Fernández-Aranda et al., 2008; Mitchell et al., 2002) and poorer prognosis than those without comorbid BA (Fernández-Aranda et al., 2006, 2008). All these findings suggest that at the clinical level, BSD with comorbid BA could be a different subtype.

Among the BA that are usually found in BSD, higher rates of comorbidity have been found with compulsive buying disorder (CB) (Faber et al., 1995; Fernández-Aranda et al., 2006, 2008; Jiménez-Murcia et al., 2015; Mitchell et al., 2002). Even though the specific aetiology of CB is still unknown, it is a mental health condition characterised by the persistent, excessive, impulsive and uncontrollable purchase of products in spite of severe psychological, social, occupational, financial consequences which lead to distress (McElroy et al., 1994; Müller et al., 2015).

As well, it follows the same addictive process as other BA, as positive feelings are initially experienced while shopping and buying, but over time the shopping episodes are used to alleviate negative moods (Christenson et al., 1994; Kellett & Bolton, 2009), as well as a strategy to cope with stress, and other materialism values such as gaining social approval/recognition, and improve their self-image (Estévez et al., 2020; Lejoyeux & Weinstein, 2010; McQueen et al., 2014; Roberts et al., 2014). Even though studies on CB prevalence report diverse results (Harvanko et al., 2013; Mueller et al., 2011), women tend to present this dysfunctional behaviour with a higher percentage than men (Fernández-Aranda et al., 2019; Granero et al., 2016; Jiménez-Murcia et al., 2015; Maraz et al., 2016; Mueller et al., 2011). Although it has not been included in the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (American Psychiatric Association, 2013), several authors keep proposing that it should be included in the 11th revision of the International Classification of Diseases (ICD-11) (Müller et al., 2019). In concordance with the aforementioned, in the comorbid presence of CB and BSD high impulsivity, novelty seeking and eating symptomatology, as well as bad psychopathological state, have been found (Fernández-Aranda et al., 2019; Jiménez-Murcia et al., 2015).

The reinforcing effect of some impulsive behaviours, such as gambling, buying, binge eating and purging, support the hypothesis that these disorders are associated with dysfunctions in the brain's reward system (Fineberg et al., 2010; Probst & Van Eimeren, 2013). Consequently, people with CB usually present altered activity in the brain's reward system. When performing purchasing decisions, they show higher activation in the striatum than people without this disorder, specifically in the nucleus accumbens (Raab et al., 2011). This may be related to decreased activity in the ventromedial prefrontal cortex, which plays an important role in planning and decision making processes (Hiser & Koenigs, 2018; Wagar & Thagard, 2004). However, to the best of our knowledge, no study has explored if patients with comorbid BSD + CB show worse neuropsychological functioning than those BSD patients without the comorbidity.

Therefore, the aim of the present study was to explore if patients with comorbid BSD + CB, could represent a specific subtype, considering its neuropsychological performance. Additionally, to present a descriptive analysis of clinical features of patients with comorbid BSD + CB, and to explore how the mediation-interaction of these variables could influence treatment outcome. Attending the previous results, BSD patients, who are characterised by high impulsive traits, also report poor neurocognitive performance. Then, this impaired performance could be even worse in those patients who also present poor impulse control in other behaviours such as CB. Therefore, we hypothesised that the comorbid group will present worse neuropsychological performance, more maladaptive personality traits, higher ED symptomatology, worse psychopathological state and worse treatment outcome, than the patients without comorbidity.

The implications of the present study are that if a subtype of the comorbid presence of BSD and CB is identified, and is related with a bad treatment outcome, proper treatment approaches could be offered to the patients considering the characterisation of the comorbid subtype. This may be helpful considering that a progressive significant impairment of overall individual functioning has been found in both, BSD (American Psychiatric Association, 2013) and CB, in which patients may present feelings of regret/remorse over purchases, shame, guilt, legal and financial problems, and other interpersonal difficulties (Thege et al., 2015).

2 | MATERIALS AND METHODS

2.1 | Participants

Regarding the clinical groups, the participants consecutively referred for assessment and treatment at the Unit of Eating Disorders of the Department of Psychiatry of the University Hospital of Bellvige in Barcelona. From an initial sample of 97 BSD patients (51 with BN and 46 with BED) that conducted neuropsychological assessment, 25 patients presented CB (25.77%) life time, being the ones that was selected for the present study. For the same sample, 25 patients with only BSD, with the same age range and similar education level, were randomly selected. Following the same line, 25 healthy controls from the same geographic area were matched for age and education level, recruited via word-of-mouth and advertisements. To be eligible for the study, participants could not have a lifetime history of an eating disorder and current obesity or any behavioural addiction.

Therefore, the total sample comprised 75 women, 25 with BSD, 25 with BSD and comorbid CB and 25 healthy controls. All participants from the clinical groups included in the study were diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria (American Psychiatric Association, 2013).

2.2 | Psychological assessment

Temperament and Character Inventory–Revised (TCI-R) (Cloninger, 1999) is a 240-item questionnaire with a five-point Likert scale format. It measures four temperaments (harm avoidance, novelty seeking, reward dependence and persistence) and three character dimensions (self-directedness, cooperativeness and self-transcendence). This questionnaire has been validated in a Spanish adult population (Gutiérrez-Zotes et al., 2004). The Cronbach's alpha for the different scales in the current sample were into the good range, from $\alpha = 0.80$ (for novelty seeking) to $\alpha = 0.87$ (for harm avoidance).

Symptom Checklist-90 Items-Revised (SCL-90-R) (Derogatis, 1994) is a 90-item questionnaire used for assessing self-reported psychological distress and psychopathology. It evaluates nine primary symptom dimensions: somatisation, obsessive-compulsive, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation and psychoticism, as well as three global indices: Global Severity Index (GSI), Positive Symptom Total (PST), and Positive Symptom Distress Index (PSDI). This instrument has been validated in a Spanish population (Derogatis, 2002). The internal consistency for the global index in our sample was $\alpha = 0.97$.

Eating Disorder Inventory-2 (EDI-2) is a 91-item multidimensional self-report questionnaire that assesses psychological and behavioural characteristics relevant to eating disorders. The questionnaire consists of 11 subscales, answered on a six-point Likert scale: drive for thinness, body dissatisfaction, bulimia, ineffectiveness, perfectionism, interpersonal distrust, interoceptive awareness, maturity fears, asceticism, impulse regulation and social insecurity. This instrument have been validated in a Spanish population (Garner, 1998). The internal consistency of the EDI-2 total score in our sample was $\alpha = 0.93$.

Compulsive buying assessment. We conducted a face to face semi-structured interview exploring buying attitudes, associated feelings, underlying thoughts and the extent of preoccupation with buying and shopping, as recommended (Müller et al., 2015). Diagnostic criteria were determined for CB in accordance with the guidelines set by McElroy et al. (1994). These criteria have received considerable acceptance in the research community, even though their validity and reliability have not yet been determined (Tavares et al., 2008).

Other measures. Additional information was collected through a semi-structured interview with the clinicians. This interview included sex, age and education level, as well as information regarding the presence or absence of impulsive behaviours (including alcohol abuse, drugs abuse, binge episodes, theft and kleptomania).

2.3 | Neuropsychological measures

Executive function performance was evaluated considering two subdomains: cognitive flexibility and decision-making.

The Wisconsin Card Sorting Test (WCST) (Heaton & PAR Staff, 2003) is a computerised set-shifting task for assessing cognitive flexibility. It includes 128 cards that vary according to three attributes: number (N), colour (C) and shape (S). The participant has to pile the cards beneath four reference cards that also vary along these same dimensions, and in order to succeed, they have to settle upon a predetermined sorting rule. The only feedback given to the participant is the word 'right' or 'wrong' after each sorting. Initially, C is the correct

sorting category, and positive feedback is given only if the card is placed in the pile with the same colour. After 10 consecutive correct sorts, the rule changes. Thus, the positive feedback is only given when the sorting matches the new category. By trial and error, the participant must learn to change the sorting categories according to the given feedback. There are up to six attempts to derive a rule, providing rule shifts in the following category sequence: C-S-N-C-S-N. Participants are not informed of the correct sorting principle and that the sorting principle shifts during the test. The test is completed when all 128 cards are sorted or after the six full categories are completed. The number of completed categories, the percentage of perseverative errors (i.e., failures to change sorting strategy after negative feedback) and the percentage of non-perseverative errors are recorded. Other measures include total trials, total errors, conceptual, perseverative responses and trials to complete first category.

The Iowa Gambling Task (IGT) (Bechara et al., 1994) is a computerised task to evaluate decision-making, which has also been proposed as a measure of choice impulsivity (Eisinger et al., 2016). It involves a total of 100 turns distributed across four decks of cards (A, B, C and D), and each time the participant selects a deck, a specified amount of play money is awarded. The interspersed rewards among these decks are probabilistic punishments (monetary losses with different amounts). Participants are instructed that the final aim of the task is to win as much money as possible and to avoid losing as much money as possible. Moreover, they may choose cards from any deck, and switch decks at any time. This test is scored by subtracting the number of cards selected from decks A and B from the number of cards selected from decks C and D. Decks A and B are not advantageous as the final loss is higher than the final gain; however, decks C and D are advantageous since the punishments are smaller. Higher scores indicate better performance on the task.

The IGT is divided into five blocks. The first blocks are supposed to assess the decision-making process under ambiguity conditions while the last blocks (after the 40th selection) are used to assess the decision-making capabilities under risk conditions due to the rules have been figured out at this point (Brand et al., 2006).

Several indices were used to analyse performance in the IGT: the total score for each block of 20 cards (the first block is thought through a measure of decision making under ambiguity); the IGT total score, which would be the difference among the total number of cards selected from the Decks A and B (disadvantageous ones) and those selected from the Decks C and D (advantageous ones); the IGT learning score, that is, the difference among the net score in the last two blocks and the net score in the first two; the IGT risk score, that is, the score of the last two blocks added together (a measure of decision making under risk or certainty) (Giannunzio et al., 2018).

2.4 | Treatment outcome

Patients with BSD received 16 weekly outpatient group therapies based on CBT, previously described (Fernández-Aranda & Turón-Gil, 1998), by an experienced psychologist. Patients were re-evaluated at discharge and categorised into three categories: 'full remission', 'partial remission' and 'non-remission'. Voluntary treatment discontinuation was categorised as 'dropout' (i.e., not attending treatment for three consecutive sessions was considered dropout). Following the guidelines of treatment outcome according to DSM-5 criteria (American Psychiatric Association, 2013), the working definition of a 'full remission' outcome was a total absence of symptoms meeting diagnostic criteria for at least four consecutive weeks, 'partial remission' was defined as substantial symptomatic improvement but the continued presence of residual symptoms for at least four consecutive weeks, finally, patients who presented 'non-remission' and dropout were labelled as poor outcome, these categories were previously used to assess treatment outcome in other published studies (Agüera et al., 2013, 2015; Lucas et al., 2021; Sauchelli et al., 2016; Steward et al., 2016). These categories were based on the consensus judgement of the senior clinical staff who considered all aspects of the patient's treatment outcome, such as normalisation of nutritional dietary patterns, frequency of binge episodes and compensatory behaviours (such as self-induced vomiting or laxative and diuretics misuse), weight restoration, improvement in attitudes regarding weight and shape and ED cognitions.

2.5 | Procedure

All participants in our sample voluntarily sought treatment for ED and were diagnosed according to the DSM-5 criteria (American Psychiatric Association, 2013) by clinical psychologists and psychiatrists with more than 15 years of experience in the field. They conducted two face-to-face clinical interviews, before and after a psychometric evaluation. The neuropsychological tests were selected to cover various aspects of executive functions and were administered by a trained psychologist in a single session, prior to treatment onset. The patients

included in this study did not receive any kind of compensation for their participation.

The present study was approved by the appropriate research committee, according to the Declaration of Helsinki. Written and signed informed consent was obtained from all participants.

2.6 | Statistical analysis

Statistical analysis was carried out with Stata16 for windows (Stata-Corp, 2019). Comparisons between the groups were based on chi-square tests (χ^2) for categorical variables and analysis of variance (ANOVA) for quantitative measures. Effect size for mean differences was estimated through the standardised Cohen's-*d* coefficient (it was considered null for $|d|<0.20$, low-poor for $|d|>0.20$, moderate-medium for $|d|>0.50$ and large-high for $|d|>0.80$). Effect size for proportion differences was obtained through Cohen's-*h* coefficient, based on the difference of the arcsine transformation of the rates obtained in the groups. The rule of thumb for the interpretation of the resulting coefficient is the same than Cohen's-*d* (cut of 0.20, 0.50 and 0.80 are interpreted as small effect, mild-medium effect size and high-large effect size, respectively) (Cohen, 1988).

In this work, two categorical-binary measures were calculated for measuring the presence of deficit in the decision making and flexibility areas. These two classifications were based in the normative data published in the manuals of each test. Percentile 16th was selected as the threshold (this cut-off is usually considered for identifying the high risk of impairing performance). Impairing decision making was assigned to participants with IGT total score under the percentile 16th, while impairing flexibility was assigned to participants with scores under the percentile 16th in any of the WCST scales perseverative errors, non-perseverative errors and number of categories completed.

Path analysis carried out through structural equation models (SEM) estimate the role/s, magnitude/s and significance of the associations between personality measures, deficit in the neuropsychological performance, diagnostic group and treatment outcome, obtained for the clinical subsamples (BSD and BSD + CB groups). Path analysis constitutes a multivariate procedure for testing direct, indirect and total effects (including mediational links). The model was adjusted with the maximum-likelihood estimation method of parameter estimation and goodness-of-fit was measured with χ^2 test, root mean square error of approximation (RMSEA), Bentler's Comparative Fit Index (CFI), Tuker–Lewis Index (TLI) and standardised root mean square residuals (SRMR) (adequate fitting was considered for non-significant result in the χ^2 test, RMSEA < 0.08, CFI > 0.95, TLI > 0.95 and SRMR < 0.08 (Barrett, 2007).

In this study, increase in the Type I error due to the multiple significance tests was controlled through the Finner-method (Finner & Roters, 2001), a Familywise error rate stepwise procedure which has proved more powerful than the classical Bonferroni correction.

3 | RESULTS

3.1 | Characteristics of the sample

The top block of Table 1 shows the sociodemographic descriptive data for the sample. The control group mainly included single subjects, with secondary or higher education and in an active work situation (the mean age of this group was 31.2 years old, *SD* = 10.2). BSD patients were mainly single or married, with primary studies levels and employed (mean age was 35.0, *SD* = 10.3). BSD + CB also grouped mainly single patients, with primary studies levels and unemployed (mean age was 34.2, *SD* = 10.6).

Regarding the clinical profiles (bottom part of Table 2), as expected the control group showed better psychopathological status (lower means in the ED severity and psychological distress) and less harm avoidance and higher self-directedness than the two clinical groups. BSD + CB was the group with the most impaired clinical profile (higher means in the ED severity and the psychological distress, as well as higher novelty seeking, higher harm avoidance and less self-directedness). BSD + CB also registered later age of onset of the eating related problems.

3.2 | Comparison of the neuropsychological measures

Table 2 contains the comparison between the groups for the neuropsychological measures analysed in the study. Regarding the IGT task, the BSD + CB condition registered the worse profile with the lowest scores in the Learning and the Risk constructs. Regarding the WCST, no differences between the groups were found. For the binary scores identifying the high risk of deficit (in the decision making and flexibility areas) the worse performance was registered for BSD + CB, followed by BSD, while HC registered the lowest risks of deficit.

TABLE 1 Descriptive for the sample

	HC (*n* = 25)		BSD (*n* = 25)		BSD + CB (*n* = 25)		BSD versus HC		BSD + CB versus HC		BSD + CB versus BSD	
	n	**%**	***n***	**%**	***n***	**%**	***p***	**|*h*|**	***p***	**|*h*|**	***p***	**|*h*|**
Marital status												
Single	20	80.0%	12	48.0%	17	68.0%	**0.045***	**0.68**[a]	0.591	0.28	0.167	0.41
Married	3	12.0%	10	40.0%	4	16.0%		**0.66**[a]		0.12		**0.55**[a]
Divorced/separated	2	8.0%	3	12.0%	4	16.0%		0.13		0.25		0.12
Education												
Primary	4	16.0%	12	48.0%	13	52.0%	**0.046***	**0.71**[a]	**0.024***	**0.79**[a]	0.927	0.08
Secondary	12	48.0%	8	32.0%	8	32.0%		0.33		0.33		0.00
University	9	36.0%	5	20.0%	4	16.0%		0.36		**0.51**[a]		0.10
Employment												
Unemployed	3	12.0%	11	44.0%	15	60.0%	**0.012***	**0.74**[a]	**0.001***	**1.06**[b]	0.258	0.32
Employed/student	22	88.0%	14	56.0%	10	40.0%						
	Mean	***SD***	**Mean**	***SD***	**Mean**	***SD***	***p***	**|*d*|**	***p***	**|*d*|**	***p***	**|*d*|**
Age (years)	31.20	10.23	34.96	10.31	34.20	10.56	0.204	0.37	0.310	0.29	0.796	0.07
Onset of ED (years)	–	–	22.00	8.86	32.20	21.43	–	–	–	–	**0.033***	**0.62**[a]
Duration of ED (years)	–	–	13.16	8.55	11.44	8.80	–	–	–	–	0.487	0.20
BMI (kg/m^2)	–	–	36.22	12.93	32.35	8.95	–	–	–	–		0.35
EDI-2 total	33.16	27.65	106.80	39.39	131.88	26.97	**0.001***	**2.16**[b]	**0.001***	**3.61**[b]	**0.007***	**0.74**[a]
SCL-90R GSI	0.63	0.41	1.67	0.79	2.21	0.61	**0.001***	**1.67**[b]	**0.001***	**3.05**[b]	**0.003***	**0.77**[a]
TCI-R novelty seeking	103.48	9.82	99.88	14.62	112.48	15.60	0.352	0.29	**0.022***	**0.69**[a]	**0.002***	**0.83**[b]
TCI-R harm avoidance	91.44	15.83	121.52	17.34	131.88	14.96	**0.001***	**1.81**[b]	**0.001***	**2.63**[b]	**0.026***	**0.64**[a]
TCI-R reward dep.	108.60	10.36	104.60	15.92	103.96	18.62	0.360	0.30	0.289	0.31	0.883	0.04
TCI-R persistence	114.64	23.55	100.56	15.28	103.44	20.79	**0.016***	**0.71**[a]	0.053	0.46	0.615	0.16
TCI-R self-directedness	143.72	17.61	119.12	20.24	99.80	16.25	**0.001***	**1.30**[b]	**0.001***	**2.59**[b]	**0.001***	**1.05**[b]
TCI-R cooperativeness	135.68	26.63	139.76	15.62	130.76	19.44	0.496	0.19	0.412	0.21	0.135	**0.51**[a]
TCI-R self-transcendence	67.80	22.71	63.04	13.49	67.04	14.71	0.338	0.25	0.878	0.04	0.421	0.28

Abbreviations: BMI, body mass index; BSD, bulimic spectrum disorder; BSD + CB, bulimic spectrum disorder with compulsive buying; HC, healthy control; SD, standard deviation.

[a]Bold: effect size into the medium range ($50 \leq |d| < 0.80$ or $50 \leq |h| < 0.80$).

[b]Bold: effect size into the large range ($|d| \geq 0.80$ or $|h| \geq 0.80$).

*Bold: significant comparison.

Figure 1 shows the performance learning curve in the IGT obtained in each group (mean IGT scores on the five consecutive blocks of the card draws). Dash lines represent the trend line with the best fit within each diagnostic condition (linear trend for HC and BSD, and polynomial cubic trend for BSD + CB). As expected, the best performance learning was achieved by HC controls, followed by BSD patients. BSD + CB group did not reach adequate performance in the learning task.

3.3 | Therapy outcome

Table 3 contains the distribution of the therapy outcome in the clinical groups, as well as the results of the

TABLE 2 Comparison between the neuropsychological measures

	HC (n = 25)		BSD (n = 25)		BSD + CB (n = 25)		BSD versus HC		BSD + CB versus HC		BSD + CB versus BSD	
	Mean	*SD*	Mean	*SD*	Mean	*SD*	*p*	|*d*|	*p*	|*d*|	*p*	|*d*|
IGT: Block1	−1.20	7.14	−3.12	3.92	−1.53	4.85	0.219	0.33	0.832	0.05	0.308	0.36
IGT: Block2	0.40	7.90	−1.76	5.49	1.29	3.41	0.199	0.32	0.594	0.15	0.071	**0.67**[a]
IGT: Block3	1.84	9.07	−1.44	3.94	−0.35	6.12	0.088	0.47	0.252	0.28	0.568	0.21
IGT: Block4	1.68	9.99	−0.40	5.60	−2.00	7.12	0.348	0.26	0.099	0.42	0.470	0.25
IGT: Block5	2.08	10.34	0.08	5.55	−3.06	7.07	0.374	0.24	**0.025***	**0.58**[a]	0.165	**0.52**[a]
IGT: total	4.80	30.84	−6.64	15.28	−5.65	19.39	0.080	0.47	0.110	0.41	0.878	0.06
IGT: learning	4.56	16.56	4.56	8.71	−4.82	9.87	0.999	0.00	**0.008***	**0.69**[a]	**0.008***	**1.01**[b]
IGT: risk	3.76	16.51	−0.32	8.77	−5.06	10.05	0.243	0.31	**0.013***	**0.65**[a]	0.176	**0.50**[a]
WCST: trials	94.84	20.72	96.53	17.78	91.56	12.71	0.732	0.09	0.507	0.19	0.315	0.32
WCST: errors	26.36	24.30	28.47	20.61	25.78	14.43	0.713	0.09	0.919	0.03	0.639	0.15
WCST: conceptual	62.36	17.64	60.06	15.96	59.22	8.12	0.577	0.14	0.447	0.23	0.839	0.07
WCST: completed categ.	5.12	1.94	5.06	1.64	5.11	1.06	0.893	0.03	0.983	0.01	0.910	0.04
WCST: Persev.responses	14.56	13.96	14.65	10.74	15.50	12.21	0.980	0.01	0.789	0.07	0.808	0.07
WCST: persev.errors	13.28	12.21	13.53	9.06	14.33	9.76	0.933	0.02	0.723	0.10	0.787	0.09
WCST: non-persev. Errors	13.08	12.96	14.94	14.29	11.44	5.55	0.572	0.14	0.619	0.16	0.289	0.32
WCST: trials-first-category	25.60	34.99	27.76	31.41	20.33	10.03	0.784	0.07	0.504	0.20	0.347	0.32
	n	%	*n*	%	*n*	%	*p*	|*h*|	*p*	|*h*|	*p*	|*h*|
Deficit: decision making	10	40.0%	14	56.0%	17	68.0%	0.258	0.32	**0.047***	**0.57**[a]	0.382	0.25
Deficit: flexibility	6	24.0%	12	48.0%	18	72.0%	0.077	**0.51**[a]	**0.001***	**1.00**[b]	0.083	**0.50**[a]

Abbreviations: BSD, bulimic spectrum disorder; BSD + CB, bulimic spectrum disorder with compulsive buying; HC, healthy control; SD, standard deviation.

[a]Bold: effect size into the medium range ($50 \leq |d| < 0.80$ or $50 \leq |h| < 0.80$).

[b]Bold: effect size into the large range ($|d| \geq 0.80$ or $|h| \geq 0.80$).

*Bold: significant comparison.

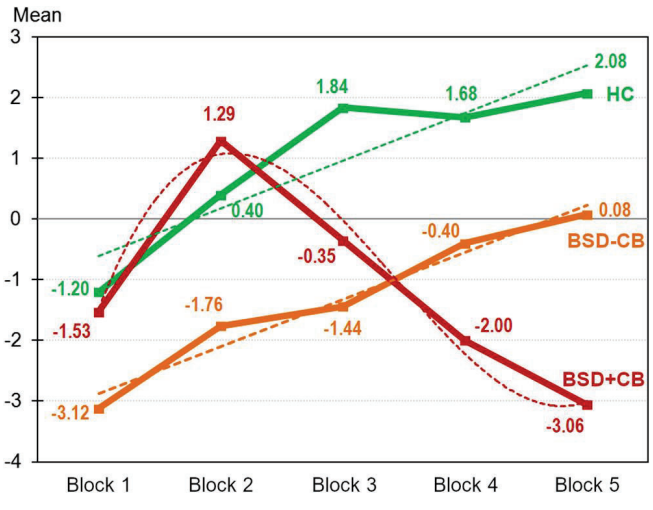

FIGURE 1 Performance learning curve in the IGT. BSD-CB, bulimic spectrum disorder without compulsive buying (n = 25); BSD + CB, bulimic spectrum disorder with compulsive buying (n = 25); HC, healthy control (n = 25) [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 3 Therapy outcome and deficit in the neuropsychological performance in the study

	BSD; (n = 25)		BSD + CB; (n = 23)			
	n	%	*n*	%	*p*	|*h*|
Treatment outcome						
Dropout	3	12.0%	10	43.5%	**0.025***	**0.73**[a]
Non-remission	4	16.0%	1	4.3%		0.40
Partial-remission	5	20.0%	7	30.4%		0.24
Full-remission	13	52.0%	5	21.7%		**0.64**[a]

Abbreviations: BSD, bulimic spectrum disorder; BSD + CB, bulimic spectrum disorder with compulsive buying.

[a]Bold: effect size into the medium range ($50 \leq |d| < 0.80$ or $50 \leq |h| < 0.80$).

*Bold: significant comparison.

statistical comparison. Differences between the groups were obtained, being the comorbid BSD + CB associated to worse efficiency.

3.4 | Path analysis

Figure 2 includes the path diagram with the standardised coefficients obtained in the SEM. Continuous line represent significant coefficients ($p \leq 0.05$) and dash-lines non-significant coefficients. Adequate goodness-of-fit was obtained for the model: $\chi^2 = 3.82$ ($p = 0.80$), RMSEA = 0.002, CFI = 0.998, TLI = 0.999 and SRMR = 0.047. Lower scores in the self-directedness personality traits increased the risk of deficit in the decision making area and the presence of the comorbid condition BSD + CB. The concurrent presence of both disorders was also directly associated with higher scores in the novelty seeking personality trait and the presence of deficit in the flexibility cognitive area. Bad treatment outcome (considered in the study as dropout or non-remission) was directly related with the presence of deficit in decision making, and this neuropsychological score also mediated within the relationship between self-directedness and bad outcome (lower scores in the personality trait increased the risk of deficits in decision making, which predicted higher risk of bad therapy outcome).

4 | DISCUSSION

The present study compared the neuropsychological performance and psychological profiles of patients with BSD + CB comorbidity, BSD patients and HC participants. The objectives were to assess if BSD + CB comorbidity could be a specific subtype according to their neuropsychological functioning, present a descriptive analysis of different clinical features and to explore how the mediation-interaction of these variables could influence treatment outcome.

Regarding our first objective, we observed that patients with BSD + CB comorbidity presented poorer learning performance in the IGT than the patients without comorbidity and the HC group. Both BSD and HC groups showed a tendency to increase their selections from the advantageous decks with respect to the initial blocks. On the contrary, BSD + CB group showed the inverse trend, as they selected more cards from the disadvantageous decks as the task progressed. The initial blocks of the IGT represent a context of uncertainty, where the results cannot be predicted, and the decisions are made under ambiguity, whereas the last trials of the task represent decisions made under risk (Giannunzio et al., 2018). Therefore, the learning performance requires the participant to learn from previous experience in order to achieve better results. Also, the BSD + CB group presented with a higher percentage of impaired cognitive flexibility than the HC group. Our findings support the hypothesis that the BSD + CB comorbidity is associated with a poorer performance in a neuropsychological task related with decision making and cognitive flexibility.

The results agree with previous research that pointed towards an impaired executive planning in patients with binge-eating behaviours (Grant & Chamberlain, 2020), and also with those that indicated a poorer performance in decision making and cognitive flexibility of patients diagnosed with a BA (Bechara, 2003; Ko et al., 2010). These neurocognitive variables may influence in part the tendency toward the comorbidity. However, to the best of our knowledge, this is the first approximation that confirms this neurocognitive profile in BSD with comorbid CB patients.

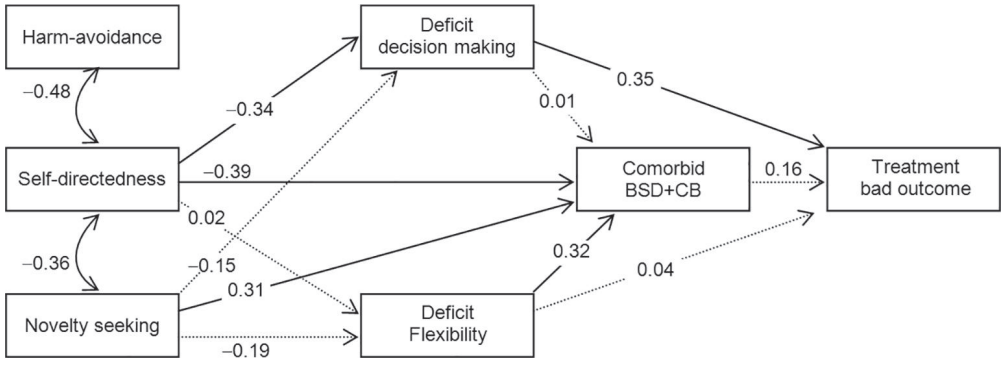

FIGURE 2 Path-diagram with the standardised coefficients. Continuous line: significant coefficient. Dash-line: non-significant coefficient. Sample: clinical conditions (BSD and BSD + CB groups, $n = 48$). BSD, bulimic spectrum disorder; BSD + CB, bulimic spectrum disorder with compulsive buying

The second aim of this study was to present a descriptive clinical characterisation of BSD + CB population. The comorbid group presented with a more severe profile than the patients with only BSD, considering higher general psychopathology and severity of the ED symptomatology; as well as predominant personality traits usually associated with more dysfunctional behaviour, called higher novelty seeking and harm avoidance and lower self-directedness (Álvarez-Moya et al., 2007; Del Pino-Gutiérrez et al., 2017; Jiménez-Murcia et al., 2013). According to the literature, a comorbid BA in ED patients has been already associated to these results (Fernández-Aranda et al., 2006, 2008; Jiménez-Murcia et al., 2015), which also seems to influence a poor treatment response (Fernández-Aranda et al., 2006, 2008), as was found in the present study by the comorbid group whom presented more dropouts and less full-remission indices than the non-comorbid one.

In relation to the aim of identifying if our target population (BSD + CB) could be a different subtype, we hypothesised that the neuropsychological performance would be determinant in this respect. However, even if this group present a worse performance in the neuropsychological tasks than the no comorbid one, the personality traits were the variables that had a mediation and predictive role to present the comorbidity. Novelty seeking was positively associated to present with the comorbidity, while self-directedness was negatively associated. Both variables may be related with the impulsive behaviours found in BSD and other BA (Álvarez-Moya et al., 2007; Del Pino-Gutiérrez et al., 2017; Jiménez-Murcia et al., 2013) including CB (Fernández-Aranda et al., 2019; Jiménez-Murcia et al., 2015). Interestingly, only a low self-directedness was significantly associated with more deficits in decision making, and this low neuropsychological performance mediated the relationship between self-directedness and bad outcome. Self-directedness indicates the ability to regulate and adapt behaviour to the demands of a situation in order to achieve personally chosen goals and values (Cloninger, 1999), which, according our results, influences the decision making process, and, as has been mentioned in the literature, it is related with difficulties in following therapy goals and achieving a good treatment outcome in BSD and other BA (Fernández-Aranda et al., 2021; Granero et al., 2020; Wagner et al., 2015). Also, the path-analysis showed that deficits in cognitive flexibility were positively associated with the presence of the comorbidity. People with BSD + CB seem to act impulsively despite its negative consequences, and they also show less cognitive flexibility that could relate to the repetition and maintenance of their unadjusted behaviours (Tchanturia et al., 2012).

Therefore, even the executive functions could be compromised in the comorbid group, it is a higher impulsivity which seems to have an important role in the characterisation of the BSD + CB profile, and could explain the co-occurrence of both disorders, as happens in other BA comorbid to ED (Jiménez-Murcia et al., 2013; Von Ranson et al., 2013). These results may be taken into account in considering an adequate treatment approach, in order to offer a precise therapy to those patients that present with this comorbidity. Considering the characteristics of the comorbid group, therapies that improve impulsive response, motivation and adherence to treatment, as well as cognitive process may be helpful. Mindfulness has shown positive results improving impulse behaviours motivated by planning capacity deficits (Korponay et al., 2019), as well as in the reduction of compulsive eating behaviours (Radin et al., 2019). Serious games may be another valuable tool for this comorbid group due to the fact that it may help to improve the motivation, help to develop positive relationships between patients and therapists, in this way dismissing the dropout rates and reinforcing the adherence to treatment (Tárrega et al., 2015).

4.1 | Limitations and future directions

The following limitations of this study need to be considered. Aspects such as: the sample size, the inclusion of only female, adult participants and from a specific geographic area, limits the generalisation of the results. Future studies should aim to use larger, more balanced samples in order to overcome this drawback. It is also important to consider that the present study only explored neuropsychological performance in patients with comorbid BSD and CB, future studies focusing on other behavioural addictions, rather than only CB, could be important in order to define a possible subtype of BSD and behavioural addictions. As well, other cognitive process, such as memory and attention, will be of interest to be explored in this population.

5 | CONCLUSIONS

According to our results, people with this high impulsive profile would also present more deficits in decision making and cognitive flexibility as well as worse treatment outcome. These results could indicate that the high impulsive traits and subsequent impaired neuropsychological performance are features that directly influence the presence of the comorbid BSD + CB, as well as relate to poor treatment outcomes of the people who present

this comorbidity. This study may represent a first exploration of the neurocognitive profile in BSD with comorbid CB patients, and it could be possible to hypothesise that the comorbidity may be a specific subtype of BSD, but further research should be performed in order to be able to establish it.

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CONFLICT OF INTERESTS

Fernando Fernández-Aranda received consultancy honoraria from Novo Nordisk and editorial honoraria as EIC from Wiley. The other authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

Lucero Munguía, Ignacio Lucas, Susana Jiménez-Murcia and Fernando Fernández-Aranda contributed to the development of the study concept and design. Roser Granero performed the statistical analysis. Romina Miranda-Olivos, Bernat Mora-Maltas, Giulia Testa, Isabel Sánchez, María Lozano-Madrid, aided with data collection. Lucero Munguía, Ignacio Lucas, Susana Jiménez-Murcia, Bernat Mora-Maltas and Fernando Fernández-Aranda aided with interpretation of data and the writing of the manuscript. Robert Turton aided with supervision, review and editing of the manuscript.

DATA AVAILABILITY STATEMENT

The datasets generated during and/or analysed during the current study are not publicly available due to ethical restrictions in order to protect the confidentiality of the participants, but are available from the corresponding author on reasonable request.

ORCID

Lucero Munguía https://orcid.org/0000-0002-9751-810X
Ignacio Lucas https://orcid.org/0000-0001-9426-5082
Susana Jiménez-Murcia https://orcid.org/0000-0002-3596-8033
Bernat Mora-Maltas https://orcid.org/0000-0002-4142-3208
Roser Granero https://orcid.org/0000-0001-6308-3198
Romina Miranda-Olivos https://orcid.org/0000-0003-2360-5830
Isabel Sánchez https://orcid.org/0000-0001-5874-8204
Giulia Testa https://orcid.org/0000-0003-4200-8062
María Lozano-Madrid https://orcid.org/0000-0003-3833-317X
Robert Turton https://orcid.org/0000-0001-6435-456X
Jose M. Menchon https://orcid.org/0000-0002-6231-6524
Fernando Fernández-Aranda https://orcid.org/0000-0002-2968-9898

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4.4. ESTUDIO 4

Título del artículo

Network analysis of DSM-5 criteria for Gambling Disorder: considering sex differences in a large clinical sample

Análisis en red de los criterios DSM-5 para el trastorno de juego: consideración de las diferencias de sexo en una amplia muestra clínica

Objetivos

- Utilizar el enfoque de análisis de redes en una amplia muestra clínica para determinar la centralidad de cada criterio del DSM-5 en el TJ.
- Analizar las diferencias respecto al género de los criterios propios del TJ.

Resumen

La quinta versión del Manual Diagnóstico y Estadístico de los Trastornos Mentales (DMS-5) y su versión revisada (DSM-5-TR) proponen niveles de gravedad para el trastorno del juego (TJ) basados en el número de criterios que cumple el paciente. El objetivo del presente estudio fue evaluar la centralidad de cada criterio y su relación, mediante la realización de un análisis de redes, teniendo en cuenta las diferencias de sexo. Se analizó la centralidad de cada criterio en 4.203 pacientes con TJ (3836 hombres y 367 mujeres), así como la importancia de otras variables clínicas y sociodemográficas. Los resultados mostraron que el criterio de abstinencia ("Inquieto o irritable cuando intenta reducir o dejar de jugar") presentaba los valores de centralidad más altos en ambos sexos. En los hombres, el segundo criterio más central fue el de tolerancia ("Necesita jugar con cantidades crecientes de dinero para conseguir la excitación deseada"); mientras que, entre las mujeres, el segundo fue el de persecución de pérdidas ("Después de perder dinero jugando, suele volver otro día para recuperar lo perdido"). Los criterios más centrales identificados están asociados a las conductas compulsivas del proceso adictivo. Teniendo en cuenta la gran relevancia del síndrome de abstinencia tanto en hombres como en mujeres, así como la tolerancia en hombres y la intención de recuperar las pérdidas en mujeres, el reconocimiento y comprensión de estos síntomas resultan fundamentales para el diagnóstico preciso del TJ.

Network analysis of DSM-5 criteria for gambling disorder: considering sex differences in a large clinical sample

Running title: Network analysis DSM-5 gambling disorder

Ignacio Lucas[1,2,3*], Bernat Mora-Maltas[1,2*], Roser Granero[2,3,4], Zsolt Demetrovics[5, 6], Víctor Ciudad-Fernández[7], Giovanna Nigro[8], Marina Cosenza[8], Magda Rosinska[9], Javier Tapia-Martínez[1, 10], Fernando Fernández-Aranda[1,2,3,11], Susana Jiménez-Murcia[1,2,3,11#]

[1]Clinical Psychology Unit, Bellvitge University Hospital, Barcelona, Spain
[2]Psychoneurobiology of eating and addictive behaviours group, Bellvitge Biomedical Research Institute (IDIBELL), Barcelona, Spain
[3]CIBER de Fisiopatología de la Obesidad y Nutrición (CIBERobn), Instituto de Salud Carlos III, Barcelona, Spain
[4]Departament de Psicobiologia i Metodologia, Universitat Autònoma de Barcelona, Spain
[5]Institute of Psychology, ELTE Eötvös Loránd University, Budapest, Hungary
[6]Centre of Excellence in Responsible Gaming, University of Gibraltar, Gibraltar, Gibraltar
[7]Department of Personality, Assessment and Psychological Treatment, Faculty of Psychology, University of València, Valencia, Spain
[8]Department of Psychology, Università degli studi della Campania "Luigi Vanvitelli", Viale Ellittico, Caserta, Italy
[9]Body Image Assessment and Intervention Unit, Department of Clinical Health and Psychology, Autonomous University of Barcelona, Barcelona, Spain
[10]Gerencia Territorial Metropolitana Sud. Hospital Universitari de Bellvitge, Barcelona, Spain
[11]Department of Clinical Sciences, School of Medicine and Health Sciences, University of Barcelona, Spain

*Contributed equally
#Corresponding author:
Susana Jiménez-Murcia
Department of Psychiatry, University Hospital Bellvitge and CIBERobn, Barcelona, Spain.
Feixa Llarga s/n 08907 L'Hospitalet del Llobregat (Barcelona, Spain).
Tel. +34-93-2607227, Fax. +34-93-2607193.
Email: sjimenez@bellvitgehospital.cat

Ignacio Lucas, PhD, ORCID 0000-0001-9426-5082
Bernat Mora-Maltas, MSc, ORCID 0000-0002-4142-3208
Roser Granero, PhD, ORCID 0000-0001-6308-3198
Zsolt Demetrovics, PhD, ORCID 0000-0001-5604-7551
Víctor Ciudad- Fernández, MSc, ORCID 0000-0003-1366-0625

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Giovanna Nigro, PhD, ORCID 0000-0003-3518-2468
Marina Cosenza, PhD, ORCID 0000-0002-5813-017X
Magda Rosinska, MSc, ORCID 0009-0009-9918-7592
Javier Tapia-Martínez, MD
Fernando Fernández-Aranda, PhD, ORCID 0000-0002-2968-9898
Susana Jiménez-Murcia, PhD, ORCID 0000-0002-3596-8033

Authors' contribution

Conceptualization: I.L., B.M.-M., F.F.-A., S.J.-M.; Investigation: I.L., B.M.-M., R.G., F.F.-A., S.J.-M.; Formal Analysis: R.G.; Writing- Original draft: I.L., B.M.-M., R.G., V.C.-F.; Writing – review & editing: Z.D., G.N., M.C., M.R., J.T.-M., F.F.-A., S.J.-M.; Funding acquisition: F.F.-A., S.J.-M.. All authors approved the final version of the manuscript.

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ABSTRACT

Background: The fifth version of the Diagnostic and Statistical Manual for Mental Disorders (DMS-5) and its revised version (DSM-5-TR) propose severity levels for gambling disorder (GD) based on the number of criteria met. However, this taxonomy presents some limitations. We aimed to assess the centrality of each criterion and their relationship by conducting a network analysis while considering sex differences. **Methods:** We performed a network analysis with the DSM-5 criteria for GD with data from 4,203 treatment-seeking patients (3,836 men and 367 women) diagnosed with GD who sought for treatment in a general tertiary hospital which has a unit specialized in behavioural addictions. **Results:** The withdrawal criterion ("Restless or irritable when attempting to cut down or stop gambling") showed the highest centrality values in both sexes. In men, the second most central criterion was the tolerance criterion ("Needs to gamble with increasing amounts of money in order to achieve the desired excitement"); while among women, the second was the chasing losses criterion ("After losing money gambling, often returns another day to get even"). **Conclusions:** The most central criteria identified are associated with compulsivity-driven behaviours of the addictive process. Taking into account the high relevance and transitive capacity of withdrawal in both men and women, as well as tolerance in men and chasing losses in women, the recognition and understanding of these symptoms are fundamental for the accurate diagnosis and severity assessment of GD.

Keywords: Gambling disorder; Network analysis; Withdrawal; Tolerance; Chasing losses

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INTRODUCTION

Gambling disorder (GD) is the only behavioural addiction (BA) included in the main section of the DSM-5 [1] and the DSM-5-TR [2]. The fifth edition of the DSM introduced changes aimed to improve the diagnostic accuracy of GD [3–5]. For instance, GD was relocated from the Impulse-Control Disorders Not Classified Elsewhere category to the Substance-Related and Addictive Disorders category, the illegal acts criterion was removed [6,7], and the threshold of the diagnosis was reduced from five to four criteria [8–10]. However, while the International Classification of Diseases (ICD-11) [11] difference between essential and additional features of GD, the DSM-5 give the same significance to all the symptoms, taking into account only the number of fulfilled criteria. Furthermore, in contrast to categorical approaches, other models such as The Research Domain Criteria (RDoC) from the National Institute of Mental Health (NIMH) [12] and the Hierarchical Taxonomy of Psychopathology (HiTOP) [13] propose dimensional frameworks for the study of psychopathology, including GD. The DSM-5 integrated this dimensional approach, resulting in the inclusion of severity ratings for GD. Replicating the severity classification for Substance Use Disorders (SUD), three severity categories were proposed for GD, depending on the number of criteria met: mild (4 or 5 criteria), moderate (6 or 7) or severe (8 or 9) [1,2]. For SUD, the number of fulfilled criteria has proven to be a good severity indicator [14]. However, for GD, this taxonomy showed some limitations regarding the lack of significant differences between the moderate and severe categories in terms of psychopathology and functional impact. Also, no differences have been observed in terms of treatment outcome between the three categories of severity [15,16]. One possible reason for these limitations could be that each diagnostic criterion may have a different level of significance to the disorder [8,17,18]. In this same vein, an increase in the weight of the most central criteria could improve the accuracy of the severity level diagnosis for GD [8,17]. Thus, it would be important to determine the core criteria that have a stronger influence in GD severity, as proposed for other behavioural addictions [19–21]. However, there is no clear agreement among researchers as to which would be the core criteria of GD. One recognized model of addiction, the ‘components’ model, proposes six core features: salience, mood modification,

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tolerance, withdrawal, conflict and relapse [22,23]. But, others argue that the addiction process, rather than the symptoms, should be the primary focus, as it serves as the foundation for symptom development and maintenance [20,24]. In this regard, the transition from impulsive-related behaviours (positive reinforcement) to later compulsivity-driven behaviours (negative reinforcement) have been described as one of the key mechanisms underlying addiction [25,26]. This crossover from goal-directed to compulsive behaviour has also been described for BA [27–29]. These later compulsive motives may eventually produce withdrawal syndrome/negative affect when the objective cannot be achieved [30]. Therefore, the GD criteria associated with the promotion of the addictive process through negative reinforcement, such as withdrawal, may be directly related to the course and severity of the addictive process [31]. Moreover, several studies suggested that withdrawal would be one of the symptoms most closely related to the severity of GD [17,18,32–34].

In addition, when describing the more central features of GD severity, it is essential to consider the differences between men and women [35–37]. Although studies about GD in women are scarce [38], the literature reports that women present more of a preference than men for non-strategic gambling forms (e.g., lottery or slot machines), have a lower socioeconomic status and higher psychopathology related to comorbidities, such as affective disorders [5,35,36,39–42]. In general, women tend to use gambling more as a way to regulate their emotional state [7,43–46], and men tend to use it more as a thrilling activity [47]. In summary, these distinctions may constitute differences in terms of the weight of each criterion between women and men.

With the objective of defining the weight and relationship of each criterion, network analysis (NA) is an appropriate approach to determine the spatial/functional structures of psychological constructs based on the relevance and relationships of their features [48,49]. In clinical research, NA has already been used to determine the relevance of each symptom and their inter-connection for different psychopathological conditions such as depression [50], posttraumatic stress disorder [51], eating disorders [52,53] or addictive disorders [49,54,63,64,55–62].

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In addictive disorders, NA has already yielded interesting results about the relevance and relationship of the symptoms. Analysis of the centrality and connections of SUD symptoms across different substance classes determined that the highest centrality for using a substance more than planned had a strong interaction with tolerance [49]. In the specific case of alcohol use disorder, loss of control [55] and physiological dependence (withdrawal) have been reported as the most central features [54]. Likewise, other research analysed the factors of multiple substances and behavioural addictions using NA, finding unique features for each taxonomy [56].

Some studies also showed the utility of NA in determining the centrality of the symptoms in different types of BA. For instance, the most central features of internet gaming disorder were conflict, withdrawal, and tolerance [57], while for problematic smartphone use, these were loss of control and continued excessive use [58], regarding problematic pornography use were salience, mood modification and withdrawal [64], and for problematic social media they were problems in self-regulation and preference for online communication [59]. However, in line with these differences found between SUD and different types of BA [56], NA of potentially addictive behaviours also suggests that different internet based behaviours should be considered as separate entities, with specific features for each activity [60,62,63]. This evidence emphasises the necessity of analysing the centrality of the specific symptoms related to each type of BA. On the basis of these results, GD should be analysed independently from other types of BA. Furthermore, NA of problematic gambling in women showed more association with gambling machines, while in men was more associated with sports betting, poker and casino games [61], consistent with the higher preference for strategic gambling in men and non-strategic gambling in women [65]. In this regard, to our knowledge, no study has used a NA approach to examine the relevance and interconnections of each GD criteria of the DSM-5 in a large sample of treatment-seeking patients with GD, considering differences between men and women.

Aims and hypotheses

The aim of this study was to use the NA approach to determine the centrality of each DSM-5 criterion for GD in a large clinical sample, with a special focus on sex differences. In this regard, criteria

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that are directly related to the negative reinforcement process, such as withdrawal, could have more relevance and influence in the co-occurrence of other symptoms. Moreover, bearing in mind the differences that have been described between men and women diagnosed with GD, we hypothesise that both sexes would present different key symptoms.

METHOD

Participants

The sample was composed of 4,203 patients (3,836 men and 367 women) diagnosed with GD. All of them sought treatment at the Behavioural Addictions Unit of the University Hospital of Bellvitge, a public hospital in Spain certified as a tertiary care centre for the treatment of GD. The recruitment process took place between January-2005 and March-2023. They were evaluated by experienced clinical psychologists in two sessions prior to the start of treatment. During the first session, the clinical psychologist conducted a semi-structured interview to confirm the diagnosis of GD and explored various aspects of gambling behaviour and sociodemographic data, including age, age of onset of the GD, duration of GD, marital status, highest academic level achieved, employment situation, personal income, family income (social position was calculated by the Hollingshead's index [66]). During this first session, they also signed the informed consent to participate in the study. During the second assessment session, participants completed a battery of validated psychometric instruments, including the Diagnostic Questionnaire for Pathological Gambling According to DSM Criteria [9,10]. All patients had a diagnosis of GD according to DSM-5 criteria (≥4 criteria). This study was carried out in accordance with the Declaration of Helsinki. The University Hospital of Bellvitge's Ethics Committee of Clinical Research approved the study (Refs. 34/05, 307/06).

DSM-5 criteria

Diagnostic criteria for Gambling Disorder (Table 1) were assessed prior to the start of treatment using the Spanish adaptation of the Diagnostic Questionnaire for Pathological Gambling [9,10]. This

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instrument have showed satisfactory reliability and validity. It should be noted that with the release of the DSM-5, pathological gambling was reclassified and renamed as gambling disorder. So, all patients' diagnoses were re-evaluated and recodified *post hoc* according to DSM-5 criteria. This instrument is a self-report measure composed of 19 items coded in a binary scale (Yes/No). The internal consistency for this study was α=.761.

--- Insert Table 1 ---

Statistical analysis

Stata18 for Windows was used for the analysis of the sociodemographic data [67], with chi-square analysis for categorical variables and t-test for quantitative measures. The Gephi 9.2 for Windows program was used to obtain the network in this work [68] (available at http://gephi.org). This statistical software has been specifically developed for exploring and visualising networks within diverse datasets, and it allows a powerful spatialisation process and the computation of essential parameters of centrality, linkage and density. In this work, each node represents a DSM-5 criterion for GD, and the edges of the underlying relationship pattern. The centrality indices calculated for the nodes provide the measure of the relevance of each criterion, while the linkage indices can be interpreted as the transitive capacity of each node towards the co-occurrence of the other criteria. The analysis was not pre-registered and the results should be considered exploratory.

Two separate networks were visualised in this study, collected from subsamples of men and women. The weights of the edges (the effect size and the signal [indicating positive versus negative relationships]) were calculated as the partial correlation coefficient between each of the two nodes, adjusted to the rest of the nodes. This correlation matrix provided the specific degree of association between two DSM-5 criteria, controlling the potential effect of the other DSM-5 criteria, which were removed. The initial data structure for the network resulted in 9 nodes and 36 potential edges, some of which had very low weights (partial correlations around 0). To simplify this initial complex structure, as per usual in NA, only edges that reached significance ($p<.05$) were modelled.

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The relevance and the linkage capacity of the nodes were measured through two centrality indices [69]: a) eigenvector centrality, which provided the relative prominence of each node based on the weighted sum of centrality measures of all nodes connected to a node; and b) closeness centrality, which provided the relative connection capacity based on how close the node is to all the other nodes in the graph (these values are calculated as the reciprocal of the sum of the length of the shortest paths between the node and all other nodes in the graphon). High eigenvector centrality indicated that the information contained in a specific node is highly valuable for the whole graph. High closeness centrality indicated a short average distance between one node and all the other nodes (these nodes have a high capacity to promote relevant changes in other areas of the network structure).

In addition to the centrality measures, other indices interpreted in the study were: a) the (average) path length, calculated as the mean of the shortest paths between all pairs of nodes (this value represents a measure of the efficiency of information transport in the network); and b) the diameter, calculated as the greatest distance between the two furthest nodes (representing the maximum eccentricity of any vertex in the graph) [70]. The density of the graph was also estimated as the number of connections divided by the number of possible connections, which provides a measure of how close the network is to being complete (a complete graph includes all possible edges and achieves a density measure equal to 1).

RESULTS

Sociodemographic data

Table 2 presents the distribution and differences in sociodemographic features between the subsamples of women and men. The sample of men were younger than women (41.41 (SD=12.81) vs. 50.18 (SD=13.45) years old). Same for the age of GD onset (29.22 (SD=12.29) years for men, 37.48 (SD=11.63) for women). Both groups showed no differences in the duration of the GD. Mean personal and family income were higher in the sample of men (1248.02 and 2122.30 euros, respectively) than in women (898.39 and 1691.16). There were differences in the distribution of marital status, employment,

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and social position between men and women groups. Women had higher rates of divorce, unemployment, and lower social position. No differences were observed in their education level.

--- Insert Table 2 ---

DSM-5 criteria distribution

Table 3 displays the prevalence of each DSM-5 criterion within women and men subsamples, as well as the proportion comparisons. The most frequent criterion was A7 ("lies related to gambling activity") (95.1% of women reported this behaviour and 94.3% of men; $p = .536$). The least frequent criterion was A1 "gambling with an increasing amount of money" (63.2% of women reported this behaviour and 62.5% of men; $p = .798$). Differences between sexes were found for A3 "lack of control" (more frequent among men), A5 "gamble as a way of escaping" (more frequent among women") and A8 "social impact" (more frequent among men).

--- Insert Table 3 ---

Table S1 (supplementary material) contains the prevalence of the DSM-5 criteria stratified (separately) by sex and by the GD severity group.

Network analysis

The first panel of Figure 1 displays the visualization of the network obtained among the women subsample, and the left panel of Figure 2 displays the bar charts with the nodes ordered according to the eigenvector and the closeness centrality. The network for women achieved a density equal to 0.417 (around 42% of the potential edges were modelled), an average path length equal to 1.639 and a diameter equal to 3.0. According to the eigenvector centrality indices, the node with the highest relevance in the network was A2 "withdrawal" (this specific DSM-5 criterion was identified as the behaviour with the greatest influence in the graphon, with an eigenvector centrality equal to 1). According to the closeness centrality, the highest linkage capacity was achieved by A2 "withdrawal" and A6 "chasing one's losses"

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(the activation of these specific DSM-5 criteria, which achieved a closeness coefficient equal to 0.73, had the greatest impact on the other nodes).

--- Insert Figure 1 ---

--- Insert Figure 2 ---

The network obtained among the subsample of men (the right panel of Figure 1) achieved a density equal to 0.583 (resulting in 58.3% of the potential edges modelled), an average path length equal to 1.417 and a diameter equal to 2.0. The centrality indices (the right panel of Figure 2), indicated that A2 "withdrawal" was the DSM-5 criterion with the highest relevance and linkage capacity (both eigenvector and closeness centrality indexes achieved a value equal to 1).

Table S2 (supplementary material) contains the complete results obtained in the NA among women and men subsamples.

DISCUSSION

This study explored the network structure of the GD criteria defined by the DSM-5 taxonomy in a large sample of treatment-seeking patients with GD, considering differences between men and women. The NA results reported that withdrawal criterion ("Restless or irritable when attempting to cut down or stop gambling") had the highest centrality values, regardless of sex. This result confirms our initial hypothesis about withdrawal being closely related to the course and severity of the addictive process [31], and fits with previous literature that emphasised the relevance of withdrawal to the severity of the GD [17,18,32–34]. This might indicate that the gambling addiction process could be driven by compulsive motives with the aim of avoiding the discomfort associated with not gambling (negative reinforcement) [27–29], and suggest that, if the patient reports withdrawal, they may be more likely to also present with other GD criteria and, following the definition of the DSM-5, present greater severity of the disorder.

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Regarding our second hypothesis, the rest of the hierarchy extracted from the NA reported differences between sexes. Women and men differ in their second core node. In the sample of men diagnosed with GD, the tolerance symptom ("Needs to gamble with increasing amounts of money in order to achieve the desired excitement") is the second most relevant and transitive criterion of the network. Whereas, in the sample of women diagnosed with GD, the chasing losses criterion ("After losing money gambling, often returns another day to get even" ("chasing" one's losses) is the second most central criterion. These findings fit with previous longitudinal data having related tolerance and chasing losses with a more severe progression of GD [71]. It might be possible that the relevance of chasing losses in women would be affected by their socioeconomic status [72]. In our sample, women had a lower social position with higher unemployment rates and lower economic income. These factors may produce a stigma that emphasises the relevance of trying to recover money through gambling due to the higher impact of incurring economic losses [72]. As well, it should be noted that tolerance and chasing one's losses have been seen to be closely related, as the latter could be a different form of expression of tolerance [30], perhaps a more planned one.

Previous literature already reported that the DSM-5 severity classification for GD presents important limitations regarding psychopathology, functional impact, and treatment outcome [15,16]. Moreover, these results show that most patients who seek treatment for GD usually present moderate or severe forms of the disorder. According to the DSM-5, each criterion would exert the same influence on the severity of the disorder, as in SUD [14]. However, the results presented in this study are in line with previous research that support the different significance of each GD criterion [8,17,18]. In light of these results, more weight should be given to those symptoms that concur with the physiological hallmarks of SUD, withdrawal and tolerance [32]. Both symptoms would be directly involved in the development of the addictive process and, therefore, in the course and severity of the GD [20].

This study provides empirical evidence of the importance of withdrawal and tolerance in GD severity [34]. The conceptualization of withdrawal and tolerance as core features of GD severity would comply with the addiction models that highlight the importance of the 'components' [22,23], as these

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criteria are considered core features of the addiction. And also with the proposals that focus on the process of addiction [20,24], as these criteria may be directly related to the transition from goal-directed behaviours to compulsivity-driven behaviours [27–29]. However, although negative reinforcement processes have been historically associated with development and maintenance of an addiction disorder [73], both withdrawal and tolerance have been criticized in GD and other BA due to the lack of empirical support [24,74–76]. These findings also reaffirm the need for further research that acknowledges the precise description of withdrawal and tolerance symptoms in GD, and their differences with those observed in SUD. For instance, withdrawal symptoms in GD do not have to be analogous to those present in SUD. Most studies that acknowledge the importance of withdrawal in GD, have obtained this symptomatology by self-report from the participants [17,18,32,33]. Moreover, regarding tolerance, the necessity to gamble with increased amounts of money to achieve the same excitement could be associated with the accumulated debts or erroneous perceptions about gambling [30]. Therefore, more research about withdrawal and tolerance in GD would help to precisely define these processes in GD and clarify their strong influence towards the severity of the disorder. Additionally, these results give rise to consider the relevance of other features that are not yet GD criteria, such as craving, which is associated with GD severity [77].

These results emphasise an important aspect of GD, suggesting that patients who report restlessness or irritability when attempting to reduce or stop gambling may signify more severe cases of GD. Withdrawal symptoms may indicate the need for personalized treatments tailored to address severe GD in clinical practice. Recognizing these symptoms as markers of severity underscores the importance of distinguishing varying degrees of GD and implementing targeted interventions for more effective support. In this line, the dimensional approach already proposed by models such as RDoC [12] and HiTOP [13] could be a promising avenue for studying the clinical features of GD [78]. Just as the DSM-5 revised its diagnostic criteria for GD to improve diagnostic accuracy, future editions of the diagnostic manual should consider the relevance of each criterion to determine the severity of GD.

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This study is not exempt from limitations. Firstly, the cross-sectional design does not allow for the temporal sequence to be demonstrated in the hierarchy which was extracted from these results. Longitudinal data would be necessary to test if the presence of one criterion would predict the future development of additional symptomatology. Secondly, although sex differences were considered, not all existing gambling profiles were assessed, to which the significance of the criteria may vary (e.g. gambling preference, age, impulsivity traits). Thirdly, the absence of control over possible complementary pharmacological treatment. And lastly, the sample was non-probabilistic and intentional, since data were collected from patients with GD who sought treatment. This makes it difficult to draw conclusions about the whole population with GD.

The study also has several strengths. First, the use of network methodology to describe the structure of interrelations between the DSM-5 criteria for GD. This analytical approach has rapidly grown in psychopathology during the last decades with promising results. It greatly expands the capacity to easily visualise the dynamics of the mental symptoms through a topological explanatory strategy. Network theory underlies the conceptualization of complex psychiatric conditions as the phenomenological manifestation of relatively stable network structures of interacting symptoms. Graph theory provides the tools to mathematically quantify the dynamics of the complex systems by their topological properties (i.e., centrality, path length, density). Furthermore, the external validity of these results and their generalization to clinical practice are supported by the use of a large clinical sample of patients formally diagnosed with GD and by the networks obtained for both men and women.

CONCLUSIONS

Defining the relevance and transitional capacity of each criterion may have important implications in the specification of GD severity. Also, defining specific profiles for men and women may help in adapting the criteria to obtain a more precise diagnosis of the disorder. Overall, these results show that certain criteria bear more significance in the severity of GD and, thus, provide additional evidence concerning the limitations of the severity classification for GD proposed in the DSM-5 and the

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DSM-5-TR. Considering the higher weight of withdrawal in both men and women, as well as tolerance in men and chasing losses in women, such criteria may be helpful in being able to identify the most severe cases of GD. In conclusion, the recognition and understanding of these symptoms are fundamental for the accurate diagnosis of GD, emphasizing their pivotal role in guiding effective treatment strategies and improving patient outcomes.

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Conflict of interest

F.F.-A. and S.J.-M. received consultancy honoraria from Novo Nordisk and F.F.-A. editorial honoraria as EIC from Wiley. The University of Gibraltar receives funding from the Gibraltar Gambling Care Foundation, an independent, not-for-profit charity. ELTE Eötvös Loránd University receives funding from Szerencsejáték Ltd. (the gambling operator of the Hungarian government) to maintain a telephone helpline service for problematic gambling. None of these funding sources are related to this study, and the funding institution had no role in the study design or the collection, analysis, and interpretation of the data, the writing of the manuscript, or the decision to submit the paper for publication.

Data aviability

The datasets generated during and/or analysed during the current study are not publicly available due to ethical restrictions in order to protect the confidentiality of the participants, but are available from the corresponding author on reasonable request.

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FIGURE CAPTIONS

Figure 1. Visualization of the networks among women (left) and men (right) subsamples

Note. Edge thickness represents the relative edge weight strength. Node size represents the relative weight in the network. All the edges obtained a positive signal.

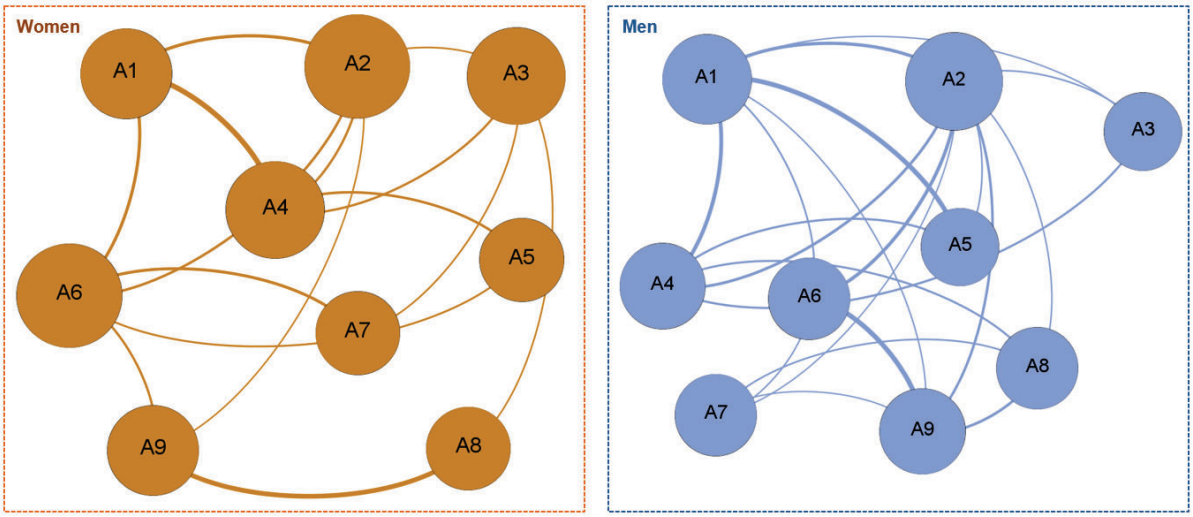

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Figure 2. Relevance of centrality and linkage of the nodes among women (left) and men (right) subsamples.

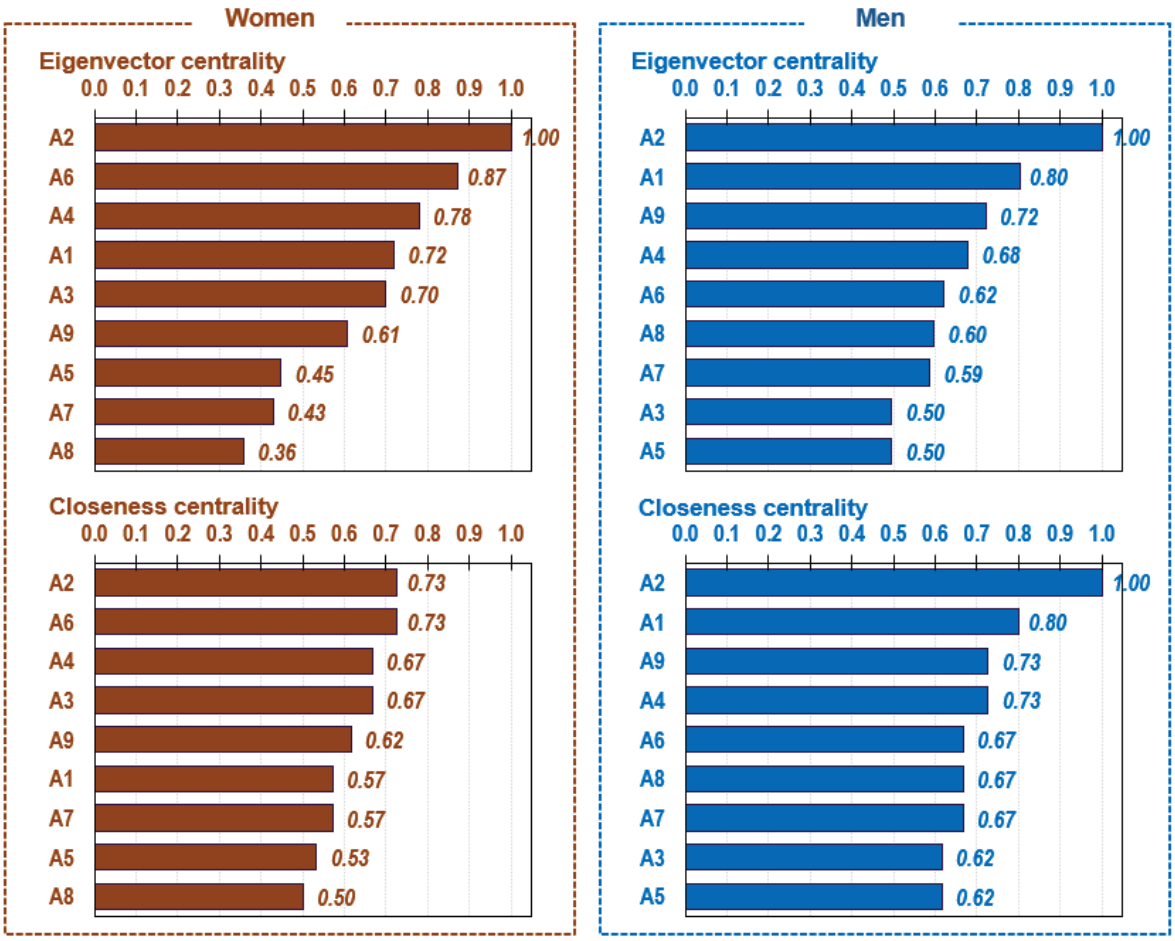

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Table 1. DSM-5 and DSM-5-TR diagnostic criteria for gambling disorder

A1. Needs to gamble with increasing amounts of money in order to achieve the desired excitement.
A2. Is restless or irritable when attempting to cut down or stop gambling.
A3. Has made repeated unsuccessful efforts to control, cut back, or stop gambling.
A4. Is often preoccupied with gambling (e.g., having persistent thoughts of reliving past gambling experiences, handicapping or planning the next venture, thinking of ways to get money with which to gamble).
A5. Often gambles when feeling distressed (e.g., helpless, guilty, anxious, depressed).
A6. After losing money gambling, often returns another day to get even ("chasing" one's losses).
A7. Lies to conceal the extent of involvement with gambling.
A8. Has jeopardized or lost a significant relationship, job, or educational or career opportunity because of gambling.
A9. Relies on others to provide money to relieve desperate financial situations caused by gambling.

Note: Severity: Mild (4 or 5 criteria), Moderate (6 or 7 criteria) and Severe (8 or 9 criteria). Extracted from DSM-5 (APA, 2013) and DSM-5-TR (APA, 2022).

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Table 2 Sociodemographic data of the sample

		Women		Men			
		N=367		N=3,836			
		Mean	SD	Mean	SD	p	η^2
Age (yrs)		50.18	12.81	41.41	13.45	**<.001***	.033
Age of onset of GD (yrs)		37.48	12.29	29.22	11.63	**<.001***	.038
Duration of GD (yrs)		6.08	6.11	6.15	6.10	.846	.001
Income (euros)	Personal	898.39	742.10	1248.02	976.35	**<.001***	.011
	Family	1691.16	1288.49	2122.30	1499.75	**<.001***	.007
		n	%	n	%	p	V
Marital status	Single	157	42.8%	1609	41.9%	**<.001***	.067
	Married - Couple	135	36.8%	1727	45.0%		
	Divorced - separated	75	20.4%	500	13.0%		
Education	Primary	227	61.9%	2209	57.6%	.210	.027
	Secondary	115	31.3%	1379	35.9%		
	University	25	6.8%	248	6.5%		
Employment	Unemployed	196	53.4%	1595	41.6%	**<.001***	.068
	Employed	171	46.6%	2241	58.4%		
Social position index	High	3	.8%	61	1.6%	**<.001***	.099
	Mean-high	11	3.0%	190	5.0%		
	Mean	42	11.4%	396	10.3%		
	Mean-low	71	19.3%	1280	33.4%		
	Low	240	65.4%	1909	49.8%		

*Note.*GD: Gambling Disorder. SD: standard deviation. V: Cramer's V coefficient. η^2: Eta-squared coefficient.

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Table 3. Distribution of the DSM-5 criteria for GD in the study

	Women *N=367*		Men *N=3,836*			
	n	*%*	*n*	*%*	*p*	*V*
A1. Gambling with increasing amount-money ("tolerance")	232	63.2%	2,399	62.5%	.798	.004
A2. Withdrawal	273	74.4%	2,938	76.6%	.342	.015
A3. Lack of control	324	88.3%	3,539	92.3%	**.008***	.041
A4. Preoccupied	248	67.6%	2,426	63.2%	.099	.025
A5. Gamble as a way of escaping	328	89.4%	2,667	69.5%	**.001***	.124
A6. After losing returns ("chasing" one's losses)	301	82.0%	3,225	84.1%	.306	.016
A7. Lies related to gambling	349	95.1%	3,618	94.3%	.536	.010
A8. Social impact	299	81.5%	3,295	85.9%	**.021***	.035
A9. Relies on others to provide money	271	73.8%	2,953	77.0%	.174	.021
	Mean	*SD*	*Mean*	*SD*	*p*	η^2
DSM-5 Total number of criteria	7.18	1.62	7.10	1.60	.381	.001

Note. SD: standard deviation. V: Cramer's V coefficient. η^2: Eta-squared coefficient. Comparison between the prevalences based on chi-square tests, and comparison between means based on T-test.

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4.5. ESTUDIO 5

Título del artículo

Association between endocrine and neuropsychological endophenotypes and gambling disorder severity

Asociación entre los endofenotipos endocrinos y neuropsicológicos y la gravedad del trastorno del juego

Objetivos

- Analizar la relación entre las variables endocrinas, neuropsicológicas, las medidas potencialmente mediadoras (distorsiones cognitivas relacionadas con el juego y la impulsividad) y la gravedad del TJ, siguiendo un análisis de trayectorias (*path analysis*).
- Identificar si las características endocrinas y neuropsicológicas se asocian a variables relacionadas con la gravedad del TJ y el tipo de juego (estratégico frente a no estratégico).

Resumen

Determinadas características neurobiológicas se relacionan con la gravedad del trastorno de juego (TJ). Los objetivos de este estudio fueron: (1) examinar, a través de un análisis de trayectorias (*path analysis*), si existía relación entre las características neurobiológicas (endocrinas y neuropsicológicas), variables potencialmente mediadoras del TJ, y la gravedad del TJ, y (2) asociar variables endocrinas y neuropsicológicas, con variables relacionadas con la gravedad del TJ y las preferencias de juego (estratégico *vs* no estratégico). La muestra incluyó 297 pacientes con TJ que buscaban tratamiento. Se analizaron las concentraciones endocrinas circulantes de diferentes hormonas relacionadas con el apetito (tales como la grelina, el péptido antimicrobiano hepático 2 [LEAP-2], la leptina y la adiponectina), y el rendimiento neuropsicológico (memoria de trabajo, flexibilidad cognitiva, toma de decisiones, atención y expresión verbal). El análisis de trayectorias evaluó los mecanismos directos y mediadores, entre las características neurobiológicas, y la gravedad del TJ. Se incluyeron variables sociodemográficas y mediadoras del TJ (impulsividad y distorsiones cognitivas relacionadas con el juego). Las correlaciones parciales evaluaron las asociaciones entre las variables neurobiológicas, incluidos los rasgos de impulsividad, y las variables relacionadas con la gravedad del TJ. En cuanto a los resultados, las concentraciones más bajas de adiponectina predijeron una mayor gravedad del TJ, mientras que las concentraciones más altas de LEAP-2 predijeron más distorsiones cognitivas relacionadas con el juego. Asimismo, la interacción entre el rendimiento neuropsicológico y la gravedad del TJ mostró dos vías diferentes: en primer lugar, un mejor rendimiento neuropsicológico predijo directamente la gravedad del TJ; en segundo lugar, un peor rendimiento neuropsicológico se asoció a la gravedad a través de las variables mediadoras de impulsividad y las distorsiones cognitivas. También se identificaron asociaciones entre funciones neuropsicológicas y distorsiones cognitivas específicas, que diferían entre jugadores estratégicos y no estratégicos. Estos resultados proporcionan información actualizada sobre la comprensión de la interacción entre las características neuroendocrinas, las variables clínicas y la gravedad del TJ. Así, las funciones neurobiológicas parecen estar fuertemente relacionadas con la gravedad del TJ. De igual modo, los diferentes perfiles neuropsicológicos que presentan los jugadores estratégicos y no estratégicos también parecen estar estrechamente asociados a distorsiones cognitivas específicas.

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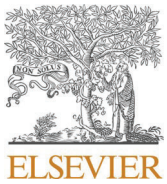

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Association between endocrine and neuropsychological endophenotypes and gambling disorder severity

Bernat Mora-Maltas [a,b,c,1], Isabel Baenas [a,b,c,d,1], Mikel Etxandi [a,c,e], Ignacio Lucas [a,b,d], Roser Granero [b,d,f], Fernando Fernández-Aranda [a,b,d,g], Sulay Tovar [b,h], Neus Solé-Morata [a], Mónica Gómez-Peña [a,d], Laura Moragas [a,d], Amparo del Pino-Gutiérrez [b,d,i], Javier Tapia [c,d,j], Carlos Diéguez [b,h], Anna E. Goudriaan [k,l,m], Susana Jiménez-Murcia [a,b,d,g,n,*]

[a] Clinical Psychology Department, Bellvitge University Hospital- Bellvitge Biomedical Research Institute (IDIBELL), Barcelona, Spain
[b] Ciber Physiopathology of Obesity and Nutrition (CIBERObn), Instituto de Salud Carlos III, Barcelona, Spain
[c] Doctorate in Medicine and Traslational Research Programme, University of Barcelona (UB), Barcelona, Spain
[d] Psychoneurobiology of Eating and Addictive Behaviors Group, Neurosciences Programme, Bellvitge Biomedical Research Institute (IDIBELL), Barcelona, Spain
[e] Department of Psychiatry, Hospital Universitari Germans Trias i Pujol, IGTP Campus Can Ruti, Badalona, Spain
[f] Department of Psychobiology and Methodology, Autonomous University of Barcelona, Barcelona, Spain
[g] Department of Clinical Sciences, School of Medicine and Health Sciences, University of Barcelona, Barcelona, Spain
[h] Department of Physiology, CIMUS, University of Santiago de Compostela, Instituto de Investigación Sanitaria, Santiago de Compostela, Spain
[i] Department of Public Health, Mental Health and Perinatal Nursing, School of Nursing, University of Barcelona, Barcelona, Spain
[j] Medical Direction of Ambulatory Processes, South Metropolitan Territorial Management, Bellvitge University Hospital, Barcelona, Spain
[k] Arkin Mental Health Care, Jellinek, Amsterdam Institute for Addiction Research, Amsterdam, the Netherlands
[l] Amsterdam UMC, Department of Psychiatry, University of Amsterdam, Amsterdam, the Netherlands
[m] Amsterdam Public Health Research Institute, Amsterdam, the Netherlands
[n] Centre for Psychological Services, University of Barcelona, Spain

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ABSTRACT

Background: Neurobiological characteristics have been identified regarding the severity of gambling disorder (GD). The aims of this study were: (1) to examine, through a path analysis, whether there was a relationship between neuroendocrine features, potentially mediational GD variables, and GD severity, and (2) to associate neuroendocrine variables, with GD severity-related variables according to gambling preferences. **Methods:** The sample included 297 outpatients with GD. We analyzed endocrine concentrations of different appetite-related hormones (ghrelin, liver antimicrobial peptide 2 [LEAP-2], leptin, adiponectin), and neuropsychological performance (working memory, cognitive flexibility, inhibition, decision making, premorbid intelligence). Path analysis assessed mechanisms between neuroendocrine features and GD severity, including mediational GD variables (impulsivity traits and gambling-related cognitive distortions). Partial correlations evaluated the associations between neuroendocrine variables, including impulsivity traits, and variables related to GD severity (DSM-5, South Oaks Gambling Screen, illness duration, and gambling-related cognitive distortions). **Results:** Lower adiponectin concentrations predicted greater GD severity, while higher LEAP-2 concentrations predicted more gambling-related cognitive distortions. Likewise, better neuropsychological performance directly predicted GD severity, but worse neuropsychological performance was associated with GD severity through the mediational variables of impulsivity traits and gambling-related cognitive distortions. Also, in non-strategic individuals with GD, poor working memory was associated with gambling expectancies and predictive control. In strategic individuals with GD, poor cognitive flexibility was associated with illusion of control, predictive control, and inability to stop gambling. **Conclusions:** These results provide updated information about the comprehension of the interaction between neuroendocrine features, clinical variables, and severity of GD. Thus, neurobiological functions seem to be strongly related to GD severity.

* Corresponding author at: Head of Clinical Psychology Department, Hospital of Bellvitge-IDIBELL and CIBEROBN, Feixa Llarga s/n 08907. L'Hospitalet del Llobregat, Barcelona, Spain.
E-mail address: sjimenez@bellvitgehospital.cat (S. Jiménez-Murcia).
[1] **Shared first authorship**.

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1. Introduction

Gambling disorder (GD) is a behavioral addiction characterized by an uncontrolled impulse to gamble despite its social and financial consequences, resulting in clinically significant impairment or distress (American Psychiatric Association [APA], 2013). Similar to substance use disorder (SUD), several studies have identified multiple features related to the development and maintenance of gambling behavior and its severity (Potenza et al., 2019). Beyond the Diagnostic and Statistical Manual of Mental Disorders (DSM-5; APA, 2013) which established GD severity based on the number of fulfilled clinical criteria, other alternative indicators of GD severity have been described. For instance, the South Oaks Gambling Screen (SOGS) questionnaire (Holtgraves, 2009; Lesieur & Blume, 1987; Stinchfield, 2002) has been considered to operationalize clinical severity, showing high correlations with DSM-IV (APA, 1994; Stinchfield, 2002) and DSM-5 (Goodie et al., 2013). The presence of gambling-related cognitive distortions (i.e., beliefs about gambling settings, behaviors, and outcomes) is another important predictor of the development of the disorder (Barrault & Varescon, 2013; Chrétien et al., 2017; Emond & Marmurek, 2010; Mathieu et al., 2018), and a severity indicator of GD (Cunningham et al., 2014; Tang & Oei, 2011). Regarding illness duration, some studies have reported a positive relationship with gambling severity (Ledgerwood et al., 2020; Medeiros et al., 2017), relapse, and dropout risk (Lucas et al., 2023; Roberts et al., 2020).

Neurobiological variables such as endocrine factors and neuropsychological performance have also been related to GD severity. Some studies uphold that endocrine factors classically linked to feeding regulation could be involved in addiction-related disorders. For instance, in the mesolimbic circuit, ghrelin has proved to be a neural reinforcer for both natural (e.g., food) and non-natural (e.g., money) rewards, interacting with other neuroendocrine factors related to impulsivity and reward processing (e.g., dopamine, serotonin, opioids) (Anderberg et al., 2016; Farokhnia et al., 2018; Vengeliene, 2013). Thus, an up-regulation of ghrelin has been observed to positively correlate with craving, abstinence, and relapse risk in SUD (Addolorato et al., 2006; Akkişi Kumsar & Dilbaz, 2015; Leggio et al., 2012), and it has also been linked with novelty-seeking (i.e., trait impulsivity), motor disinhibition (i.e., motor impulsivity), and impulsive decision-making (i.e., choice impulsivity) (Anderberg et al., 2016; Skibicka & Dickson, 2011). Until now, only one study investigated the relation between ghrelin and GD, hypothesizing a similar association in individuals with GD (Etxandi et al., 2022), and higher fasting ghrelin plasma level was reported. Moreover, lower concentrations of a ghrelin antagonist called liver antimicrobial peptide 2 (LEAP-2) was found and it predicted the presence of GD-(Etxandi et al., 2022). Similarly, LEAP-2 have been linked to impulsivity and cognitive functions (Ge et al., 2018; Lugilde et al., 2022; Voigt et al., 2021) showing a possible role in the addiction process due to its interaction with ghrelin. Also, adipocytokines (i.e., leptin, adiponectin) have been studied in relation to impulsivity (Sutin et al., 2013) and addiction (Bach et al., 2021; Novelle & Diéguez, 2018; Peters et al., 2018) due to the presence of adipocytokine receptors widely distributed in brain regions including the neocortex and hippocampal regions (Cao et al., 2018). As in the case of food intake regulation, leptin concentrations have been inversely correlated with the severity of consumption (Escobar et al., 2018), being proposed as a possible biomarker in SUD (i.e., alcohol, cocaine) (Martinotti et al., 2017; Mehta et al., 2020). The presence of leptin receptors on dopaminergic neurons within the limbic system has prompted speculation about their involvement in the regulation of reward-related behaviors (e.g. food, gambling, drugs) (Micioni Di Bonaventura et al., 2021; von der Goltz et al., 2010), contributing to neuroinflammation, oxidative stress, and motivating changes in brain plasticity (Heber & Carpenter, 2011; Montalvo-Martínez et al., 2018). Adiponectin has been proposed as a biomarker of craving in alcohol use disorder (Hillemacher et al., 2009), similar to ghrelin. However, decreased serum concentrations have been shown in GD (Etxandi et al., 2022), in individuals with obesity with and without eating disorders (Baenas et al., 2023), and in opioid use disorder (Shahouzehi et al., 2013; Yu et al., 2021). While some endocrine markers have been linked to SUD and GD, studies on endocrine factors remain scarce and their association with GD severity has not been evaluated.

Regarding neuropsychological variables, impaired cognitive flexibility, decision-making, and response inhibition have been linked to GD severity (Brevers et al., 2012; Cosenza et al., 2019; Leppink et al., 2016; Odlaug et al., 2011) and may predict relapse (Goudriaan et al., 2008). Interestingly, some gambling activities involve more executive function than others, considering the level of chance between gambling modalities (Jiménez-Murcia et al., 2020; Odlaug et al., 2011). In this sense, several studies have observed a specific subtype of individuals with GD who use strategic games (e.g., poker, sports betting, stock market). The majority of these individuals were young men, with high levels of education, well-paid employment and high levels of impulsivity (Jiménez-Murcia et al., 2019; Navas et al., 2017; Vintró-Alcaraz et al., 2022), as well as better neuropsychological performance (Lorains et al., 2014; Mallorquí-Bagué et al., 2018). This gambling profile also showed greater gambling severity (Gainsbury et al., 2012; Gainsbury, Russell, Blaszczynski, et al., 2015; Jiménez-Murcia et al., 2020; Mallorquí-Bagué et al., 2017; Wood & Williams, 2011). Regarding non-strategic games (e.g., slot-machines, bingo, lotteries), some studies demonstrated that this form was commonly correlated with women and older individuals (Assanangkornchai et al., 2016; Potenza, 2014) who showed poorer neuropsychological performance (Boggio et al., 2010; Di Rosa et al., 2017). Likewise, impulsivity traits have also been associated with GD severity (Billieux et al., 2012; Savvidou et al., 2017; Vintró-Alcaraz et al., 2022) and with cognitive distortions (Del Prete et al., 2017; Mallorquí-Bagué et al., 2018). Finally, although several studies have related cognitive distortions to brain areas (Clark et al., 2009; Dymond et al., 2014; Lu et al., 2019; Ruiz de Lara et al., 2018), as far as authors know, there are no studies linking extended neuropsychological functions to different types of cognitive distortions.

The primary aim of this study was to analyze the link between endocrine (ghrelin, LEAP-2, leptin and adiponectin) and neuropsychological (working memory, cognitive flexibility, decision making, inhibition, and premorbid intelligence) variables, potentially mediational GD measures (gambling-related cognitive distortions, and impulsivity), and the severity of GD (measured by SOGS), through a path analysis. The second aim was to identify whether, according to gambling preferences (strategic *vs* non-strategic), endocrine and neuropsychological features, including impulsivity traits, were associated with GD severity-related variables (DSM-5, SOGS, duration of illness, and gambling-related cognitive distortions). The authors hypothesized: 1) Endocrine markers would be associated to reward related executive functions (e.g., impulsivity, decision making), showing a targeted pathway to the GD severity. 2) Neuropsychological performance could have a different influence on GD severity considering gambling preferences.

2. Methods

2.1. Participants

The sample was made up of 297 treatment-seeking adult outpatients with GD (diagnosed according DSM-5 criteria) attending at the Behavioral Addictions Unit within the Clinical Psychology Department of Bellvitge University Hospital for treatment of GD. They were voluntarily recruited between April-2018 and September-2021. A structured interview was carried out to check for the existence of an organic mental disorder, an intellectual disability, a neurodegenerative disorder (e.g., Parkinson's disease), or an active psychotic disorder, all of which were considered exclusion criteria.

2.2. Assessments

Neuroendocrine and clinical variables were collected using standardized instruments, which are properly described in the supplementary material. Briefly, blood samples (25 mM final concentration) were collected using a venous aspiration method with ethylenediamine tetraacetic acid (EDTA). A minimum fasting period of eight hours was conserved prior to blood collection. The blood was centrifuged at 1700g for 20 min at 4 °C in a refrigerated centrifuge. Clinical variables were measured using the Spanish adaptation of the following questionnaires: SOGS-(Echeburúa et al., 1994; Lesieur & Blume, 1987); Diagnostic Questionnaire for Pathological Gambling According to DSM criteria (Jiménez-Murcia et al., 2009; Stinchfield, 2003); Impulsive Behavior Scale (UPPS-P) (Verdejo-García et al., 2010; Whiteside et al., 2005); Gambling-related cognitions scale (GRCS) (Del Prete et al., 2017; Raylu & Oei, 2004). Neuropsychological data has been collected by the following instruments: Iowa Gambling Task (IGT) (Bechara et al., 1994, 2000); Wisconsin Card Sorting Test (WCST) (Grant & Berg, 1948); Stroop Color and Word Test (SCWT) (Golden, 1978); Trail Making Test (TMT) (Reitan, 1958); Digits task of the Wechsler-Memory-Scale, Third Edition (WMS-III) (Wechsler, 1997); Vocabulary task of the Wechsler Adult Intelligence Scale, Third Edition (WAIS-III) (Wechsler, 1999).

Socio-demographic, anthropometric, and clinical variables related to GD were collected in a semi-structured face-to-face clinical interview, as described elsewhere (Jiménez-Murcia et al., 2006).

2.3. Procedure

All participants were evaluated at the Behavioral Addictions Unit of the HUB-IDIBELL institution. A multidisciplinary team (psychology, psychiatry, and nursing), with an extensive experience (more than 25 years) in the study of GD and other behavioral addictions, collected the data. A completed semi-structured clinical interview was conducted in the first session (45–60 min) in which sociodemographic, gambling-related, and anthropometric variables were assessed. In the first part of the second visit (10 min), the collection of blood samples occurred between 8 and 10 am in the morning, before food intake. After that, participants underwent a 90-minute session (approximately) to complete psychometric assessments related to gambling and psychological variables. Endocrine variables were analyzed at the Singular Center for Research in Molecular Medicine and Chronic Diseases (CIMUS), University of Santiago de Compostela (Spain). The neuropsychological assessment was completed by experienced neuropsychologists in the third session, which lasted 50–60 min. The three sessions took place on three different days over the course of a week. All the measures used in this study correspond to the assessment carried out prior to the beginning of specialized treatment at the Unit.

2.4. Statistical analysis

Data analysis was done with Stata17 for Windows (Stata Press Publication, 2021). Path analysis tested the underlying associations (direct and indirect links) between endocrine, neuropsychological, and gambling measures. In this work, all parameters were free-estimated, and with the aim to achieve a parsimonious model with easier interpretation, statistically non-significant parameters were excluded. The maximum-likelihood estimation was used and goodness-of-fit was evaluated using standard statistical measures: chi-square test (χ^2), the root mean square error of approximation (RMSEA), Bentler's Comparative Fit Index (CFI), the Tucker-Lewis Index (TLI), and the standardized root mean square residual (SRMR). It was considered an adequate model fit for non-significant χ^2 tests, RMSEA < 0.08, TLI > 0.90, CFI > 0.90 and SRMR < 0.10 (Barrett, 2007). The global predictive capacity for the final model was measured by the coefficient of determination (CD).

Partial correlations adjusted by the patients' sex and age assessed the relationships between GD severity-related variables (DSM-5 criteria, SOGS total, duration of illness, and gambling-related cognitive distortions) with the endocrine and neuropsychological variables. The correlation estimates were interpreted considering the effect size measures (due the strong association between statistical significant for the R-coefficients and the sample size): mild-moderate effect for $|R|>0.24$ and large-high for $|R|>0.37$ (Rosnow & Rosenthal, 1996).

2.5. Ethics

The latest version of the Declaration of Helsinki was used to conduct the present study. The Clinical Research Ethics Committee of Bellvitge University Hospital approved this study (ref. PR329/19 and PR338/17). Signed informed consent was obtained from all participants.

3. Results

3.1. Descriptive for the sample

Table 1 displays the descriptives for the sociodemographic and the GD profile in the total sample (descriptive for the remaining variables of the study are shown in Table S1, supplementary material). Most patients in the study were men, with primary education level, single, and pertained to mean-low to low social position indexes. Mean age was 39.58 years ($SD = 14.16$), mean age of onset of the problematic gambling 29.1 years ($SD = 12.42$) and duration of the GD related problems 5.23 years ($SD = 6.02$). Most participants reported non-strategic games as the preferred gambling activity.

Table 1
Descriptive for the sociodemographic and the GD profile (total sample, n = 297).

	n	%		*Mean*	*SD*
SexWomen	19	6.4 %	Age (yrs-old)	39.58	14.16
Men	278	93.6 %	Age of onset of GD (yrs)	29.10	12.42
EducationPrimary	157	52.9 %	Duration of GD (yrs)	5.23	6.02
Secondary	112	37.7 %	DSM-5 criteria	7.13	1.80
University	28	9.4 %	SOGS total	10.85	3.23
MaritalSingle	158	53.2 %		*n*	%
Married	103	34.7 %	PreferenceNon-strategic	166	55.9 %
Divorced	36	12.1 %	Strategic	131	44.1 %
Social indexHigh	8	2.7 %			
Mean-high	19	6.4 %			
Mean	24	8.1 %			
Mean-low	113	38.0 %			
Low	133	44.8 %			

Note. SD: standard deviation. GD: gambling disorder. DSM: diagnostic and statistical manual of mental disorders. SOGS: South Oaks Gambling Screen.

3.2. Path analysis

Fig. 1 contains the standardized coefficients of the path diagram obtained in the study. With the aim of easier interpretation, only significant coefficients retained in this final model. Adequate goodness of fit was achieved ($\chi^2 = 127.61$ ($p = .278$); RMSEA = 0.016 (95 %CI: 0.001 to 0.034); CFI = 0.987; TLI = 0.984; SRMR = 0.049), and the global predictive capacity was around 42 % (CD = 0.422). The neuropsychological measures used to define the latent variable (labeled as "cognition" in the path diagram) achieved statistical significance, the higher scores (except TMT that score is reversed) in the latent variable were associated with better performance in the IGT, WCST, Stroop, Digits and WAIS vocabulary tasks.

Results of the SEM indicated that higher GD severity (SOGS total) was directly associated with lower adiponectin concentrations, more gambling-related cognitive distortions, higher impulsivity traits, and better performance in the neuropsychological tasks. Some indirect links explaining the GD severity were also identified: a) being a woman and higher LEAP2 concentrations predicted higher gambling-related cognitive distortions, which increased the likelihood of GD severity; b) younger age was related to higher impulsivity traits, which contributed to higher GD severity; and c) younger age also contributed to better performance in the neuropsychological tasks, which was related to higher GD severity. The path diagram also evidenced a positive correlation between ghrelin and adiponectin concentrations, a positive correlation between gambling-related cognitive distortions with impulsivity, and negative correlations between scores in the latent class cognition with impulsivity and gambling-related cognitive distortions. Finally, younger age was also a variable associated with the higher probability of strategic gambling activity.

3.3. Correlation analysis

Table 2 contains the partial correlations (adjusted by the patients' sex and age) between GD severity-related variables (DSM-5, SOGS, duration of illness and GRCS scores) with the neuroendocrine variables. This correlation matrix was obtained for the total sample ($N = 297$). Only relevant correlation coefficients were found for the impulsivity traits: a) lack of perseverance correlated with gambling-related expectancies; b) positive urgency, negative urgency, and UPPS total score

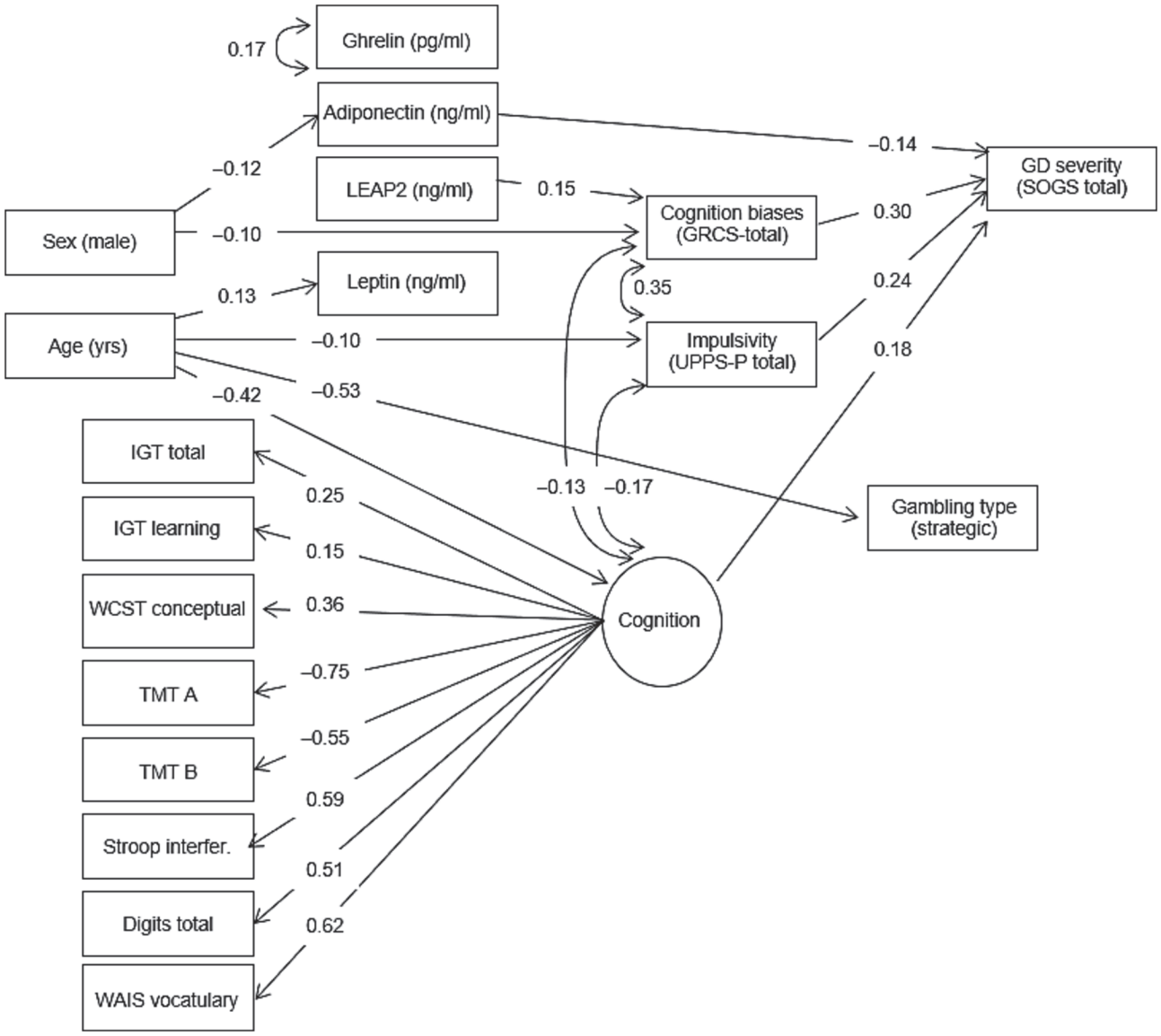

Fig. 1. Path-diagram: standardized coefficients (total sample, n = 297) Note. Only significant coefficients retained in the model. GD: gambling disorder. GRCS: Gambling Related Cognition Scale. UPPS-P: Impulsive Behavior Scale. LEAP2: liver enriched antimicrobial peptide 2. IGT: Iowa Gambling Test. WCST: Wisconsin Card Sorting Test. TMT: Trail Making Test. WAIS: Wechsler Adult Intelligence Scale.

Table 2
Association between the GD severity measures with the clinical profile: partial correlations adjusted by the patients' sex and age (total sample, n = 297).

	DSM-5 criteria	SOGS total	Duration of GD	GRCS GE	GRCS IC	GRCS PC	GRCS IS	GRCS IB	GRCS total
Ghrelin (pg/ml)	0.03	0.07	0.04	0.07	−0.01	−0.03	0.05	0.04	0.03
LEAP2 (ng/ml)	0.01	0.02	0.05	0.04	0.13	0.13	0.05	0.07	0.10
Leptin (ng/ml)	0.08	0.02	−0.05	0.05	0.04	0.09	0.12	0.08	0.10
Adiponectin (ng/ml)	−0.04	−0.14	0.03	−0.03	0.01	0.04	−0.02	0.04	0.01
UPPS-P Lack premeditation	0.14	0.13	0.08	0.10	0.04	0.02	0.12	0.10	0.10
UPPS-P Lack perseverance	0.19	0.16	0.15	**0.26**†	0.11	0.11	0.15	0.13	0.19
UPPS-P Sensation seeking	0.10	0.07	0.02	0.10	0.12	0.13	0.06	0.15	0.14
UPPS-P Positive urgency	**0.31**†	**0.29**†	0.15	**0.37**†	**0.27**†	**0.27**†	**0.31**†	**0.27**†	**0.37**†
UPPS-P Negative urgency	**0.41**†	**0.33**†	0.19	**0.43**†	0.19	**0.24**†	**0.40**†	**0.28**†	**0.39**†
UPPS-P Total	**0.36**†	**0.31**†	0.18	**0.37**†	0.21	**0.24**†	**0.32**†	**0.28**†	**0.36**†
IGT Block 1	0.07	−0.02	−0.06	−0.03	−0.06	0.03	−0.01	−0.08	−0.03
IGT Block 2	0.04	−0.06	−0.08	−0.08	0.01	−0.02	0.01	0.03	−0.01
IGT Block 3	−0.01	0.01	0.01	−0.04	−0.03	−0.01	0.03	0.02	0.00
IGT Block 4	−0.05	−0.10	−0.05	−0.13	−0.11	−0.03	−0.09	0.00	−0.09
IGT Block 5	−0.05	−0.13	−0.08	−0.13	−0.07	−0.04	−0.13	−0.06	−0.11
IGT Total	−0.02	−0.10	−0.08	−0.13	−0.08	−0.02	−0.07	−0.02	−0.08
IGT Learning	−0.10	−0.11	−0.02	−0.11	−0.08	−0.04	−0.13	−0.02	−0.10
IGT Risk	−0.06	−0.14	−0.08	−0.15	−0.10	−0.04	−0.13	−0.04	−0.11
WCST Trials	0.04	0.01	−0.14	0.11	0.06	0.05	0.13	0.08	0.11
WCST Errors perseverative	0.06	0.03	−0.04	0.13	0.08	0.07	0.10	0.10	0.12
WCST Conceptual	−0.03	0.04	−0.02	0.06	0.02	0.10	0.08	0.01	0.07
WCST Categories completed	0.00	0.07	0.06	0.02	0.00	0.07	0.02	−0.01	0.03
TMT A	−0.01	−0.04	−0.07	0.05	0.07	0.04	0.05	0.07	0.07
TMT B	−0.04	−0.08	−0.04	0.02	0.15	0.11	0.05	0.04	0.09
TMT Diff	−0.03	−0.08	−0.02	0.03	0.16	0.12	0.05	0.04	0.10
Stroop words	−0.02	−0.02	−0.02	0.02	−0.13	−0.07	−0.06	−0.08	−0.08
Stroop colors	0.03	0.07	0.02	−0.03	−0.10	−0.15	−0.03	−0.09	−0.10
Stroop words-colors	0.02	0.02	0.06	−0.07	−0.14	−0.17	−0.03	−0.09	−0.12
Stroop interference	0.02	−0.01	0.07	−0.09	−0.11	−0.12	−0.02	−0.05	−0.10
Digits direct	−0.05	0.07	−0.01	−0.09	−0.18	−0.15	−0.06	−0.02	−0.12
Digits direct-span	−0.04	0.05	−0.04	−0.08	−0.16	−0.15	−0.04	0.00	−0.11
Digits inverse	−0.03	0.06	0.02	−0.14	−0.13	−0.14	−0.02	0.00	−0.11
Digits inverse-span	−0.05	0.06	0.02	−0.13	−0.13	−0.14	−0.02	−0.02	−0.11
Digits total	−0.04	0.07	0.01	−0.13	−0.17	−0.16	−0.05	−0.01	−0.13
WAIS Vocabulary	0.02	0.04	0.12	−0.14	−0.13	−0.10	−0.07	−0.07	−0.12

Note. †Bold: effect size into the ranges mild-moderate to high-large. GD: gambling disorder. DSM: diagnostic and statistical manual of mental disorders. SOGS: South Oaks Gambling Screen. GRCS: Gambling Related Cognition Scale. GRCS-GE: gambling related expectancies. GRCS-IC: illusion of control. GRCS-PC: predictive control GRCS-IS: perceived inability to stop gambling. GRCS-IB: interpretative bias. UPPS-P: Impulsive Behavior Scale. LEAP2: liver enriched antimicrobial peptide 2. IGT: Iowa Gambling Test. WCST: Wisconsin Card Sorting Test. TMT: Trail Making Test. WAIS: Wechsler Adult Intelligence Scale.

correlated with all GRCS scales (except for illusion of control, which only correlated with positive urgency).

The partial correlation obtained within the group of patients who reported non-strategic gambling preference (Table 3) informed that: a) lack of perseverance correlated with gambling- related expectancies and the inability to stop gambling; b) positive urgency, negative urgency and UPPS total score correlated with GRCS total score, DSM-5 criteria and SOGS total; additionally, negative urgency was associated with longer duration of the illness; and c) worse performance in the Digits Inverse was associated with gambling-related expectancies and predictive control, and Digits total was associated with illusion of control and predictive control.

Within the group of patients with strategic gambling preference (Table 4), higher scores in positive urgency, negative urgency and UPPS total score correlated with DSM-5 criteria, SOGS total, and all GRCS scales (except illusion of control). Regarding the neuropsychological measures: a) worse performance in the IGT total was related to more gambling-related expectancies; b) worse performance in the WCST (number of trials) correlated with the inability to stop gambling; and c) more difficulties in the TMT (TMT-B and difference scales) were associated with more gambling-related illusion of control, predictive control and total GRCS score.

4. Discussion

The present study analyzed whether neuroendocrine variables predict the severity of GD, as well as its relationship with other potentially mediational GD variables. This study also evaluated whether these neuroendocrine factors were associated with GD severity-related variables according to gambling preferences. Although the results are not in agreement with our first hypothesis (endocrine markers could be related to reward-related executive function, showing a targeted pathway to the GD severity), we found that lower concentrations of adiponectin predicted more GD severity, while higher LEAP-2 concentrations predicted more gambling-related cognitive distortions. Likewise, we found that better neuropsychological performance, higher impulsivity traits, and a higher number of gambling-related cognitive distortions predicted GD severity. However, a worse neuropsychological performance predicted more gambling-related cognitive distortions and impulsivity traits, leading to greater GD severity. These results are consistent with our second hypothesis. Although we did not find other associations between endocrine variables and GD severity-related variables, we identified associations between poorer neuropsychological functions, specific gambling-related cognitive distortions and DSM-5 criteria.

Results regarding adiponectin and GD severity are in line with Etxandi et al. (2022), who found lower adiponectin concentrations in a GD sample. Low adiponectin concentrations have also been associated with greater severity in other addictive disorders (Hillemacher et al., 2009; Yu et al., 2021). This hormone has been associated with anti-inflammatory, anti-diabetic and anti-atherogenic properties (Benchebra et al., 2019). Therefore, the results could suggest that lower concentrations of adiponectin are related to the severity of gambling along with a worse metabolic state and a higher cardiometabolic risk associated with addiction-related disorders, which are usually linked to

Table 3
Association between the GD severity measures with the clinical profile: partial correlations adjusted by sex and age (non-strategic gambling, n = 166).

	DSM-5 criteria	SOGS total	Duration of GD	GRCS GE	GRCS IC	GRCS PC	GRCS IS	GRCS IB	GRCS total
Ghrelin (pg/ml)	0.05	0.10	0.04	0.10	0.01	0.06	0.04	0.08	0.08
LEAP2 (ng/ml)	0.02	−0.02	0.02	0.06	0.14	0.11	0.07	0.07	0.11
Leptin (ng/ml)	0.04	−0.02	−0.06	0.02	0.01	0.07	0.14	0.06	0.08
Adiponectin (ng/ml)	0.06	−0.11	0.12	0.01	0.09	0.08	0.06	0.07	0.07
UPPS-P Lack premeditation	0.06	0.09	0.07	0.02	0.06	−0.04	0.05	0.09	0.04
UPPS-P Lack perseverance	0.19	0.15	0.17	**0.36**†	0.15	0.07	**0.24**†	0.10	0.22
UPPS-P Sensation seeking	0.20	0.08	0.02	0.13	0.11	0.15	0.06	0.19	0.16
UPPS-P Positive urgency	**0.27**†	0.19	0.14	**0.42**†	**0.33**†	**0.31**†	**0.33**†	**0.25**†	**0.40**†
UPPS-P Negative urgency	**0.33**†	**0.27**†	**0.25**†	**0.40**†	0.22	0.22	**0.39**†	0.21	**0.36**†
UPPS-P Total	**0.34**†	**0.25**†	0.20	**0.39**†	**0.24**†	0.22	**0.32**†	**0.25**†	**0.35**†
IGT Block 1	0.13	−0.03	−0.02	−0.01	0.01	0.06	−0.02	−0.03	0.00
IGT Block 2	0.09	−0.05	−0.05	−0.01	0.10	0.09	0.03	0.10	0.08
IGT Block 3	0.07	0.06	0.02	0.10	0.04	0.08	0.10	0.10	0.11
IGT Block 4	−0.03	−0.12	−0.01	−0.05	−0.07	0.04	−0.05	0.05	−0.02
IGT Block 5	−0.01	−0.05	−0.07	−0.13	−0.06	−0.03	−0.11	−0.08	−0.10
IGT Total	0.06	−0.06	−0.05	−0.04	0.00	0.06	−0.03	0.04	0.01
IGT Learning	−0.11	−0.07	−0.03	−0.11	−0.12	−0.06	−0.10	−0.05	−0.11
IGT Risk	−0.02	−0.10	−0.05	−0.11	−0.07	0.00	−0.09	−0.02	−0.07
WCST Trials	0.00	−0.05	−0.18	0.03	−0.01	0.04	0.04	0.02	0.03
WCST Errors perseverative	0.04	0.03	−0.02	0.09	0.09	0.13	0.03	0.13	0.11
WCST Conceptual	−0.11	−0.01	−0.07	0.04	−0.03	0.05	0.09	−0.08	0.03
WCST Categories completed	−0.05	0.03	0.03	0.07	0.01	0.06	0.09	−0.03	0.06
TMT A	0.02	−0.02	−0.10	0.07	0.12	0.07	0.09	0.10	0.11
TMT B	−0.08	−0.12	−0.06	−0.02	0.04	0.02	−0.02	−0.03	0.00
TMT Diff	−0.09	−0.13	−0.04	−0.02	0.02	0.02	−0.03	−0.04	−0.02
Stroop words	−0.05	0.00	−0.02	−0.05	−0.20	−0.12	−0.13	−0.15	−0.16
Stroop colors	0.01	0.13	0.03	−0.08	−0.12	−0.20	0.00	−0.19	−0.14
Stroop words-colors	0.03	0.09	0.08	−0.09	−0.17	−0.23	−0.01	−0.12	−0.15
Stroop interference	0.05	0.06	0.09	−0.07	−0.13	−0.16	0.01	−0.03	−0.09
Digits direct	−0.08	0.08	0.03	−0.14	−0.22	−0.20	−0.08	−0.07	−0.17
Digits direct-span	−0.07	0.08	−0.03	−0.14	−0.19	−0.19	−0.08	−0.05	−0.16
Digits inverse	−0.09	0.08	0.04	**−0.25**†	−0.20	**−0.24**†	−0.06	−0.09	−0.20
Digits inverse-span	−0.08	0.10	0.05	**−0.24**†	−0.16	−0.20	−0.05	−0.11	−0.18
Digits total	−0.09	0.09	0.04	−0.21	**−0.23**†	**−0.24**†	−0.08	−0.09	−0.21
WAIS Vocabulary	0.04	0.05	0.19	−0.14	−0.18	−0.16	−0.07	−0.11	−0.16

Note. †Bold: effect size into the ranges mild-moderate to high-large. GD: gambling disorder. DSM: diagnostic and statistical manual of mental disorders. SOGS: South Oaks Gambling Screen. GRCS: Gambling Related Cognition Scale. GRCS-GE: gambling related expectancies. GRCS-IC: illusion of control. GRCS-PC: predictive control GRCS-IS: perceived inability to stop gambling. GRCS-IB: interpretative bias. UPPS-P: Impulsive Behavior Scale. LEAP2: liver enriched antimicrobial peptide 2. IGT: Iowa Gambling Test. WCST: Wisconsin Card Sorting Test. TMT: Trail Making Test. WAIS: Wechsler Adult Intelligence Scale.

weight disturbances in terms of higher BMI and other medical comorbidities (Baenas et al., 2024; Benchebra et al., 2019). Curiously, LEAP-2 concentrations predicted high GRCS scores. Similarly, in non-clinical population, higher LEAP-2 concentrations have been related to impulsivity (Voigt et al., 2021). Particularly in GD, lower concentrations of LEAP-2 predicted the presence of GD (Etxandi et al., 2022). Although LEAP-2 has been recently described, with a lack of extensive and consistent data in the literature, we hypothesized that LEAP-2 concentrations could be a neurobiological factor underlying cognitive distortions, which have not only been associated with the presence of GD, but also with the severity of GD. Altogether, our results reinforce the potential involvement of endocrine factors well-known for its role in food intake regulation in the pathophysiology of addiction-related disorders, including GD. Although preliminary, these findings contribute deeper understand the neurobiology of GD and its severity turning the focus of future research into biological targets as potential treatment strategies.

On the other hand, the association between a better neuropsychological performance and GD severity could suggest that those individuals with GD with preserved cognitive skills tend to gamble with greater amounts of money and greater complexity therefore, showing high GD severity scores. This profile usually occurs in young strategic individuals with GD (Gainsbury, Russell, Blaszczynski, et al., 2015; Gainsbury, Russell, Hing, et al., 2015; Jiménez-Murcia et al., 2019; Moragas et al., 2015) that could be very accurate at capturing statistical information from gambling devices, and together with preserved executive functioning, may contribute to false mastery (Navas et al., 2019). False mastery is a false sense of confidence and control over gambling activities due to the knowledge that one perceives to have. It is important to note that false mastery has not been assessed in the present study, since the GRCS measures other types of gambling-related cognitive distortions with a superstition component. The literature has reported a large heterogeneity among individuals with GD regarding not only socio-demographic, personality traits, and clinical variables (Bonnaire et al., 2013; Grant et al., 2012; Moragas et al., 2015), but also cognitive style (Mouneyrac et al., 2018; Navas et al., 2019). In this vein, some authors have stated that those individuals who exhibit a greater need to engage in demanding cognitive tasks, require more time and recruit working memory and attentional resources (De Neys & Bonnefon, 2013), particularly gambling for intellectual stimulation (Binde, 2013; Jiménez-Murcia et al., 2019; Mestre-Bach et al., 2019). This could explain why these individuals get involved and present serious gambling problems. Still, the literature has suggested that poorer neuropsychological performance is associated with greater severity of GD (Brevers et al., 2012; Leppink et al., 2016). Although this link was not directly observed in our path analysis, the results have shown an indirect alternative way. Specifically, poorer neuropsychological performance would affect GD severity by a positive association with impulsivity and gambling-related cognitive distortions. These two variables have been extensively studied in the field of GD and broadly connected to GD severity (Buen & Flack, 2022; Cunningham et al., 2014; Devos et al., 2020; Savvidou et al., 2017). These results would highlight the double role that neuropsychological performance may have in GD severity. In strategic individuals with GD, better neuropsychological performance would be related to GD severity because it may contribute to false

Table 4
Association between the GD severity measures with the clinical profile: partial correlations adjusted by sex and age (strategic gambling, n = 131).

	DSM-5 criteria	SOGS total	Duration of GD	GRCS GE	GRCS IC	GRCS PC	GRCS IS	GRCS IB	GRCS total
Ghrelin (pg/ml)	−0.02	0.04	0.03	0.01	−0.07	−0.17	0.05	0.00	−0.05
LEAP2 (ng/ml)	−0.02	0.01	0.09	0.01	0.13	0.13	0.04	0.04	0.09
Leptin (ng/ml)	0.09	0.02	−0.02	0.05	0.09	0.09	0.07	0.05	0.09
Adiponectin (ng/ml)	−0.10	−0.13	−0.13	−0.06	−0.10	0.00	−0.08	−0.01	−0.06
UPPS-P Lack premeditation	0.23	0.17	0.09	0.21	0.00	0.11	0.22	0.14	0.18
UPPS-P Lack perseverance	0.17	0.16	0.12	0.12	0.07	0.16	0.00	0.19	0.14
UPPS-P Sensation seeking	0.01	0.09	0.04	0.05	0.13	0.10	0.07	0.10	0.11
UPPS-P Positive urgency	**0.42**†	**0.45**†	0.17	**0.33**†	0.17	**0.24**†	**0.30**†	**0.33**†	**0.35**†
UPPS-P Negative urgency	**0.52**†	**0.38**†	0.08	**0.46**†	0.15	**0.27**†	**0.41**†	**0.41**†	**0.44**†
UPPS-P Total	**0.41**†	**0.40**†	0.15	**0.36**†	0.18	**0.27**†	**0.32**†	**0.36**†	**0.38**†
IGT Block 1	−0.05	−0.03	−0.14	−0.07	−0.16	−0.02	0.01	−0.17	−0.09
IGT Block 2	−0.09	−0.13	−0.17	−0.18	−0.14	−0.18	−0.04	−0.07	−0.15
IGT Block 3	−0.15	−0.08	−0.02	−0.22	−0.13	−0.14	−0.08	−0.12	−0.17
IGT Block 4	−0.10	−0.10	−0.13	−0.22	−0.20	−0.13	−0.14	−0.06	−0.19
IGT Block 5	−0.07	−0.21	−0.12	−0.10	−0.09	−0.03	−0.13	−0.01	−0.09
IGT Total	−0.14	−0.18	−0.17	**−0.25**†	−0.23	−0.15	−0.13	−0.12	−0.22
IGT Learning	−0.04	−0.11	−0.02	−0.08	−0.04	−0.01	−0.13	0.05	−0.06
IGT Risk	−0.10	−0.19	−0.15	−0.19	−0.17	−0.09	−0.16	−0.04	−0.16
WCST Trials	0.17	0.13	−0.06	0.21	0.18	0.08	**0.27**†	0.17	0.23
WCST Errors perseverative	0.16	0.09	−0.06	0.19	0.08	−0.03	0.23	0.04	0.13
WCST Conceptual	−0.01	0.03	0.07	0.07	0.10	0.17	0.02	0.19	0.14
WCST Categories completed	−0.03	0.02	0.09	−0.06	−0.04	0.08	−0.12	0.03	−0.03
TMT A	0.02	0.00	0.04	0.03	−0.01	−0.01	0.02	0.00	0.01
TMT B	0.13	0.06	0.02	0.12	**0.35**†	**0.28**†	0.21	0.17	**0.28**†
TMT Diff	0.14	0.07	0.03	0.13	**0.38**†	**0.29**†	0.22	0.19	**0.30**†
Stroop words	−0.05	−0.13	−0.04	0.11	−0.01	−0.01	0.03	0.03	0.04
Stroop colors	−0.06	−0.10	−0.01	0.01	−0.10	−0.13	−0.13	0.04	−0.08
Stroop words-colors	−0.08	−0.16	0.00	−0.05	−0.11	−0.09	−0.09	−0.04	−0.09
Stroop interference	−0.05	−0.13	0.02	−0.11	−0.09	−0.04	−0.07	−0.08	−0.10
Digits direct	−0.03	0.03	−0.08	−0.04	−0.11	−0.09	−0.06	0.06	−0.06
Digits direct-span	−0.02	0.01	−0.06	0.01	−0.11	−0.09	0.00	0.07	−0.03
Digits inverse	0.02	−0.02	−0.05	0.03	0.00	0.03	0.03	0.17	0.06
Digits inverse-span	−0.01	−0.03	−0.07	0.03	−0.09	−0.04	0.02	0.13	0.02
Digits total	−0.01	0.01	−0.08	0.00	−0.07	−0.04	−0.02	0.13	0.00
WAIS Vocabulary	−0.20	−0.14	−0.06	−0.19	−0.03	−0.04	−0.15	−0.04	−0.12

Note. †Bold: effect size into the ranges mild-moderate to high-large. GD: gambling disorder. DSM: diagnostic and statistical manual of mental disorders. SOGS: South Oaks Gambling Screen. GRCS: Gambling Related Cognition Scale. GRCS-GE: gambling related expectancies. GRCS-IC: illusion of control. GRCS-PC: predictive control GRCS-IS: perceived inability to stop gambling. GRCS-IB: interpretative bias. UPPS-P: Impulsive Behavior Scale. LEAP2: liver enriched antimicrobial peptide 2. IGT: Iowa Gambling Test. WCST: Wisconsin Card Sorting Test. TMT: Trail Making Test. WAIS: Wechsler Adult Intelligence Scale.

mastery and to use gambling as a form of intellectual stimulation. In non-strategic individuals with GD, worse neuropsychological performance could be related to higher severity, as higher impulsivity and gambling-related cognitive distortions may exert more effect when neuropsychological functioning is poorer. Indeed, impulsivity could be seen as the lack of executive functioning.

Based on the interesting and unexplored association between poorer neuropsychological performance and gambling-related cognitive distortions, we observed that impulsive traits (positive and negative urgencies) are associated with most of the gambling-related cognitive distortions (gambling expectancies, predictive control, inability to stop gambling, and interpretative bias). In addition, lack of perseverance (another impulsive trait) was associated with gambling expectancies. In our study, urgencies were also associated with DSM-5 criteria. An amount of literature supports that positive and negative urgencies are linked with gambling-related cognitive distortions (Del Prete et al., 2017; Michalczuk et al., 2011) and with DSM-5 criteria (Vintró-Alcaraz et al., 2022). Moreover, in non-strategic individuals with GD, our results suggested that working memory -meaning scores in Digits invers- could be negatively associated with gambling expectancies. Specifically, we hypothesize that worse capacity to manipulate information, planning and monitoring the task -which is reported in non-strategic individuals with GD-, would support a more intuitive reasoning, tending to process information in a more automatic way and favoring unconscious gambling (Navas et al., 2019). In this sense, positive rewards may be highly valued and risk undervalued as an emotional regulation strategy (Navas et al., 2019), resulting in maintaining positive expectations and remaining motivated to gamble after negative results (Gibson & Sanbonmatsu, 2004). In addition, predictive control, is also negatively associated with working memory. In fact, working memory has a key role in the ability to fully integrate gains and losses experienced during the task, as continuously updating relevant information and predicting future results is the essence of working memory (Dretsch & Tipples, 2008). In strategic individuals with GD, due to more analytical thinking, cognitive inflexibility (measured by TMT-B score) seems to have an association with gambling-related cognitive distortions. Specifically, we found a negative association between cognitive flexibility and illusion of control, that characterize strategic subjects with GD (Mallorquí-Bagué et al., 2019). We hypothesize that strategic individuals with GD would tend to show a certain reluctance to change their way of thinking because they believe that their skills or superstitions can influence the game, contributing to exacerbate this distortion, and therefore, maintain gambling behavior (Langer, 1975; Toneatto et al., 1997). Relatedly, the association between cognitive inflexibility and predictive control could be explained because strategic persons with GD show a greater perception of control (Navas et al., 2017). Hence, the skill element could create a false sense of higher control over the game (Myrseth et al., 2010). In the same line, lower cognitive flexibility (more trials in WCST), were associated with the inability to stop gambling. These results support the idea that GD, and particularly in strategic subjects with GD, are characterized by compulsivity-related neuropsychological impairments, as exemplified in perseveration and cognitive inflexibility (van Timmeren et al., 2018). Lastly, the association between worse decision-making on the IGT and gambling expectations could be

interpreted due to a decreased sensitivity to rewards, leading to excessive responses to immediate and large gains observed in GD samples (Goudriaan et al., 2006). However, we could not explain why the association has only been observed in strategic gambling. It is worth noting that the negative association between IGT and cognitive distortions has also been reported in previous studies (Ciccarelli et al., 2016, 2017).

4.1. Limitations

This study must be interpreted considering its limitations. For instance, the cross-sectional nature of this study restricts causal attributions. Further longitudinal studies are required to better understand the implication of neuroendocrine factors and their functions in GD. Additionally, endocrine measurements were analyzed from peripheral blood samples, which could limit the inference of their functioning at a neural level. Our study also did not investigate the effect of some factors such as circadian rhythms that might influence variations in plasma concentrations of neuroendocrine substrates. Moreover, as the sample was only composed of treatment-seeking individuals, this fact could limit the generalization of the results. Nonetheless, it should be emphasized that the frequency of women in the study is in agreement with prevalence estimates in samples of GD patients who seek therapeutic treatment (Blanco et al., 2006), and their involvement in the research supports its ecological validity. The results may also be limited in their interpretation due to the absence of variables related to emotional regulation and psychiatric comorbidity (e.g., major depression or anxiety disorders) that could influence cognitive functioning (Thoma et al., 2011). Conversely, some of the strengths of this work are the use of a path analysis procedure to gain a broad comprehensive understanding of how neuroendocrine variables could determine the severity of GD and the well-characterized neuroendocrine profile.

4.2. Conclusions

These results offer new insights to understand the role of neuroendocrine factors in GD severity. Better and worse performance in cognitive tasks seems to influence the severity of GD through different pathways (in strategic individuals with GD would be a direct pathway between better neuropsychological performance and GD severity); in non-strategic individuals with GD, worse neuropsychological performance is associated with more impulsivity traits and gambling-related cognitive distortions, leading to greater GD severity), suggesting the importance of cognitive skills regarding GD severity. These results also provide updated information about the comprehension of the interaction between neuropsychological features and core GD variables, like cognitive distortions. In this sense, this work may open a new route to modify cognitive distortions through neuropsychological rehabilitation. Intervening in executive functions is likely to benefit not only those individuals who gamble and present greater difficulties in executive functions, but also could help to decrease cognitive distortions and impulsivity. Even though studies on neuromodulation and neuropsychological training in GD are largely insufficient, they have been observed in addictive disorders with promising results (Anderson et al., 2023; Verdejo-García et al., 2019), and may provide a way to improve neuropsychological functions.

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CRediT authorship contribution statement

Bernat Mora-Maltas: Conceptualization, Investigation, Writing – original draft. **Isabel Baenas:** Conceptualization, Investigation, Writing – original draft. **Mikel Etxandi:** Conceptualization, Investigation, Writing – original draft. **Ignacio Lucas:** Investigation. **Roser Granero:** Methodology, Formal analysis. **Fernando Fernández-Aranda:** Funding acquisition, Writing – review & editing. **Sulay Tovar:** Investigation. **Neus Solé-Morata:** Investigation. **Mónica Gómez-Peña:** Investigation. **Laura Moragas:** Investigation. **Amparo del Pino-Gutiérrez:** Investigation. **Javier Tapia:** Investigation. **Carlos Diéguez:** Investigation. **Anna E. Goudriaan:** Supervision. **Susana Jiménez-Murcia:** Conceptualization, Funding acquisition, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The datasets analyzed during the study are not publicly available due to patient confidentiality and other ethical reasons but are available from the corresponding author on reasonable request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.addbeh.2024.107968.

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5. DISCUSIÓN

La presente tesis se ha centrado en el estudio de pacientes con TCA, obesidad y TJ desde una perspectiva neuropsicológica. El objetivo principal fue analizar el funcionamiento cognitivo y su relevancia en estos trastornos, dada su estrecha relación con aspectos clínicos y de gravedad cruciales para su desarrollo. Para lograr este propósito, se realizaron multitud de evaluaciones que recopilaron datos que incluían variables neuropsicológicas, clínicas y neuroendocrinas. Todo ello se abordó mediante un enfoque dimensional que se centró en el endofenotipo neuropsicológico impulsivo-compulsivo subyacente en estos trastornos.

Endofenotipo cognitivo del espectro impulsivo-compulsivo

El primer propósito de esta tesis fue comparar el rendimiento cognitivo de pacientes del espectro impulsivo-compulsivo y de controles sanos para estudiar los procesos neuropsicológicos alterados comunes o endofenotipo en los TCA, la obesidad y el TJ. El estudio de endofenotipos pretende utilizar un enfoque transdiagnóstico clasificando la psicopatología a través de la observación del comportamiento y de medidas neurobiológicas (4,5) para establecer constructos dimensionales que ayuden a la comprensión de los trastornos mentales (6). En el caso de la presente tesis, a través de las variables neuropsicológicas, se pretendía conceptualizar los constructos de impulsividad y compulsividad.

En concordancia con la primera hipótesis, una de las primeras conclusiones que se desprende de los resultados obtenidos es que el rendimiento neuropsicológico que evalúa la impulsividad y la compulsividad presenta alteraciones en los trastornos estudiados.

En relación con los TCA, los **estudios 1** y **3** reflejan cómo los pacientes con diagnóstico de trastorno del espectro bulímico con y sin CC comórbida, y obesidad con y sin DM2 muestran indicadores cognitivos de impulsividad y compulsividad, mientras que en la AN-R, los resultados muestran indicadores de impulsividad cognitiva. El trastorno del espectro bulímico y la CC se han asociado a un funcionamiento impulsivo (291,299,587,588). Sin embargo, aunque la literatura indica también marcadores

cognitivos de compulsividad en los trastornos del espectro bulímico (210,214), asociados a la repetición y mantenimiento de sus conductas desadaptativas (220), en la CC, la evidencia es menos clara (588–590). En la AN-R, también se han observado marcadores de compulsividad, en este caso auto-informados [escala de evitación del daño del inventario de temperamento y carácter (TCI-R) (439), y escala de obsesividad-compulsividad en el inventario de 90 síntomas (SCL-90-R) (591)], así como impulsividad cognitiva, con dificultades en la toma de decisiones, situándola en niveles similares al TJ. En este sentido, la toma de decisiones desventajosa se relaciona con conductas de pérdida de peso en la AN y, por lo tanto, no solo se identifican conductas impulsivas en el espectro bulímico o en la obesidad. De hecho, varios autores han sugerido que la resistencia a las tentaciones alimentarias en la AN se ve reforzada por sentimientos inmediatos de éxito, logro, autocontrol y autoestima (592,593). En el **estudio 1,** se observa que los pacientes con obesidad también presentan marcadores cognitivos de impulsividad y compulsividad. El hecho de que se hallen mayores niveles de impulsividad cognitiva en el grupo de obesidad con DM2 va en línea con algunos estudios que destacan la relación entre la DM2 y la impulsividad (334,335). En concreto, es posible que las alteraciones en las señales cerebrales de la insulina puedan afectar a dimensiones mediadas por la dopamina, como es la impulsividad (594,595). En cambio, en el grupo de obesidad sin DM2, se observan mayores niveles de compulsividad cognitiva. Este resultado está en concordancia con otros estudios que informan que la rigidez cognitiva podría contribuir a mantener hábitos alimentarios poco saludables y, por tanto, relacionarse con un peso corporal elevado (596).

En el TJ, el **estudio 1** señala que los pacientes con TJ no solo muestran conductas impulsivas reflejadas en dificultades en la toma de decisiones, sino que además es uno de los trastornos con más errores perseverativos en el Test de Clasificación de Tarjetas de Wisconsin (WCST)(597), mostrando así marcadores de compulsividad cognitiva. De forma similar, el **estudio 4** también destaca que la conducta compulsiva referente a la abstinencia (“mostrarse inquieto o irritable al intentar reducir o dejar de jugar”) es el criterio del DSM-5 (91) con mayor relevancia en el TJ. Estudios previos han mostrado que la compulsividad también está presente en el TJ, especialmente en etapas avanzadas del trastorno, en las que la búsqueda de gratificación y el placer por jugar han ido desapareciendo, ganando relevancia la necesidad por jugar para aliviar estados emocionales negativos (51,543). Es decir, en estas etapas posteriores, primaría el uso

del juego como un refuerzo negativo (598). Esta funcionalidad también se ha descrito especialmente en el género femenino (393,394,599). Sin embargo, otros estudios han señalado que la compulsividad puede estar presente incluso al inicio del trastorno, debido al solapamiento de rasgos obsesivo-compulsivos en el TJ (544,545). De hecho, la presencia simultánea de síntomas obsesivo-compulsivos y el TJ podría deberse a influencias genéticas compartidas (545).

A nivel global, estos resultados indican la coexistencia de síntomas impulsivos y compulsivos en los trastornos del espectro estudiado (17,19,20) y discreparían de la idea clásica de que los extremos del espectro impulsivo-compulsivo serían opuestos, existiendo trastornos puramente "impulsivos" o "compulsivos" (16). Además, reforzarían la idea de que los procesos neuropsicológicos alterados de estos trastornos podrían constituir un mecanismo fisiopatológico común (1,22,23). La literatura también destaca las dificultades en aquellas FFEE que forman parte del constructo impulsivo-compulsivo, tanto en los TCA (203,211) como en procesos adictivos como el TJ (7,427). Asimismo, modelos actuales también informan de la relevancia de las FFEE en el desarrollo y mantenimiento de estos trastornos (253,358,359). Es necesario tener en cuenta que las FFEE son las encargadas, entre otras funciones, de planificar acciones con un fin, de tomar las decisiones adecuadas contemplando las ventajas y desventajas de cada una de ellas, y de adaptarse de forma flexible (31,32). Estos procesos están especialmente afectados en los trastornos estudiados y, por lo tanto, tiene sentido sugerir que los déficits en las FFEE pueden subyacer en las conductas desadaptativas que definen parte de la psicopatología de estos trastornos.

Neuropsicología como predictor de gravedad

El objetivo de esta tesis no era únicamente estudiar el endofenotipo cognitivo asociado a la impulsividad y a la compulsividad. Se pretendía ir un paso más allá, explorando la relación entre la gravedad clínica y psicopatológica, y el rendimiento neuropsicológico de los trastornos estudiados.

Los resultados de los diversos estudios que conforman este trabajo están en concordancia con la hipótesis inicial en la que se esperaba identificar endofenotipos neuropsicológicos comunes relacionados con características clínicas y con la gravedad de los trastornos. Así, en los **estudios 2, 3** y **5**, se observó que un peor rendimiento

cognitivo en funciones que evalúan impulsividad y compulsividad se relacionaban con marcadores de gravedad (duración del trastorno, intensidad de los síntomas, respuesta al tratamiento, rasgos desadaptativos de personalidad y estado psicopatológico) en los TCA y en el TJ.

Respecto a los TCA, el **estudio 2** mostró que los déficits en la flexibilidad cognitiva se asociaban a una mayor duración de la enfermedad en pacientes con AN y con trastornos del espectro bulímico, mientras que los criterios de gravedad del DSM-5 (leve, moderado, grave) y la obsesión por la delgadez no lograron discriminar las dificultades cognitivas. En la misma línea, el **estudio 3**, mostró que el grupo de pacientes con trastornos del espectro bulímico y CC comórbida eran los que presentaban una peor flexibilidad cognitiva y toma de decisiones, así como un perfil de mayor gravedad en comparación con el grupo control y los pacientes con trastornos del espectro bulímico sin comorbilidad. Concretamente, quienes padecían un TCA junto a la CC mostraron mayores niveles de psicopatología general, mayor gravedad de sintomatología alimentaria, peor respuesta al tratamiento y un perfil de personalidad con rasgos impulsivos (búsqueda de sensaciones), compulsivos (evitación del daño) y con baja capacidad de planificación, toma de decisiones y organización de la conducta en base a objetivos (autodirección).

Diversos estudios han indicado que en los TCA, las dificultades en la toma de decisiones y en la flexibilidad cognitiva se asocian a pacientes con un perfil de mayor gravedad (254,256,269) y con una mayor duración de la enfermedad (254,280), por lo que estas funciones parecen tener una relevancia importante. Los déficits en la toma de decisiones no solo influyen en la incapacidad para esperar la comida, característica de las conductas de atracones, sino también en la persistencia y el efecto inmediato de la pérdida ponderal a pesar de sus efectos negativos a largo plazo (236,241,249). De la misma manera, el presentar dificultades en la flexibilidad cognitiva no solo es relevante en la AN, en la que la incapacidad para cambiar la conducta y la presencia de patrones alimentarios inflexibles define parte de la clínica del trastorno, sino que también se ha asociado a la incapacidad de limitar el exceso de alimentación compulsiva en los trastornos bulímicos (210,214,261). La literatura también indica que las dificultades cognitivas se relacionan con más comorbilidades psiquiátricas (224–226). Asimismo, existe un alto nivel de comorbilidad entre los trastornos del espectro impulsivo-

compulsivo, compartiendo rasgos de personalidad (p.ej., búsqueda de sensaciones, evitación del daño, baja autodirección) (438,600) y, cuando estos trastornos co-ocurren, tienden a ser más graves (21). Estos hallazgos son coherentes con los resultados de este trabajo e investigaciones previas que sugieren la existencia de marcadores neuropsicológicos comunes en trastornos del espectro impulsivo-compulsivo (307,308). Esto es indicativo de que aquellos pacientes con marcadores cognitivos de impulsividad y compulsividad podrían tener mayor vulnerabilidad a padecer otros trastornos con características impulsivas y compulsivas. Además, el hecho de que las dificultades a nivel cognitivo se asocien a una peor respuesta al tratamiento indica no solo la relevancia que puedan tener estas dificultades en la eficacia los tratamientos convencionales, sino que plantea la idea de que estos pacientes puedan beneficiarse de un tratamiento neuropsicológico específico. Diversos estudios señalan que ciertas dificultades en las FFEE entorpecen al proceso de tratamiento en los trastornos del espectro impulsivo-compulsivo (357), incluidos los TCA (259,260), predisponiendo al mismo tiempo a una mayor duración de la enfermedad. Desde un punto de vista clínico, los déficits en la flexibilidad cognitiva pueden favorecer la aparición de pensamientos, comportamientos y actitudes más rígidas y persistentes que dificulten cambios de punto de vista (259). Las dificultades en la toma de decisiones también pueden estar implicadas en la respuesta al tratamiento (222), debido a que, a menudo, las personas afectadas por estos trastornos pueden ignorar las consecuencias a largo plazo de sus acciones, negando o subestimando las consecuencias físicas y sociales de la enfermedad. Con toda esta evidencia, se puede sugerir que el rendimiento cognitivo puede ser un factor que predispone a una mayor gravedad de la enfermedad.

No obstante, mientras que algunas investigaciones destacan que en los TCA estas funciones cognitivas tienen un papel importante en el desarrollo de la enfermedad (214,215,219), otros estudios argumentan que los déficits cognitivos son consecuencia de la enfermedad (273,274), por ejemplo, debido a la malnutrición (269). Aunque probablemente ninguna de las explicaciones sea descartable, ello sugiere que las dificultades cognitivas pueden ser un factor destacado en la etiología de los TCA, ya que, como muestran los resultados del **estudio 2**, los criterios del DSM-5 (91) que se basan exclusivamente en el peso, no identifican los déficits neuropsicológicos de estos pacientes. Esta idea es reforzada por estudios que señalan el mantenimiento de los déficits cognitivos tras la recuperación (218–220). Además, algunos estudios han

establecido un perfil neuropsicológico con alteraciones significativas en un 19% de niños y adolescentes con AN, que coincidiría con el 20% de pacientes que desarrollan un perfil grave de la enfermedad, con una larga duración (mayor a 7 años) (601,602). Estos hallazgos sugerirían una predisposición neuropsicológica a desarrollar en un futuro el trastorno y que repercutiría en la gravedad del mismo.

Por lo que refiere al TJ, el **estudio 5** mostró que los déficits en el rendimiento cognitivo (en toma de decisiones, flexibilidad cognitiva, memoria de trabajo y control inhibitorio) se asociaban a la gravedad del TJ, mediante las variables mediadoras de impulsividad auto-informada y de las distorsiones cognitivas. La literatura indica que las dificultades en marcadores cognitivos de impulsividad y compulsividad se han relacionado con la gravedad del trastorno (357,502,533,538,540). Del mismo modo, la impulsividad y las distorsiones cognitivas se han asociado a dificultades cognitivas (500,501,503) y también a la gravedad del TJ (356,434,603). Sin embargo, el **estudio 5** también indicó, sorprendentemente, que un mejor rendimiento cognitivo se asocia de forma directa con una mayor gravedad del TJ. En la misma línea, la literatura también señala la existencia de un subtipo de jugadores, aquellos que hacen uso de la modalidad de juego estratégico, que mostrarían un mejor desempeño neuropsicológico en comparación con otros perfiles de jugadores (497,515–517) y una mayor gravedad del TJ (342,512,513). A diferencia de otros perfiles, este tipo de jugadores, además, serían más jóvenes, con niveles educativos elevados, trabajos bien remunerados y una tendencia a la impulsividad (345,508,510). Asimismo, podrían estar más inclinados a realizar apuestas más elevadas y adquirir mayores deudas en un menor periodo de tiempo (342).

Los resultados, pues, confirman la hipótesis planteada en esta investigación sugiriendo que la identificación del endofenotipo neurocognitivo se asocia a distorsiones cognitivas específicas y a una mayor impulsividad, aunque no se relaciona con un perfil neuroendocrino concreto. Además, como se ha señalado previamente, el papel de la neurocognición en la gravedad del TJ no resulta tan evidente como en los TCA. Probablemente, la explicación de los resultados subyace en la heterogeneidad de los pacientes con TJ que se viene señalando. De hecho, la heterogeneidad en el TJ no se observa únicamente en relación con la modalidad de juego. El **estudio 4** también observa diferencias entre hombres y mujeres en los criterios de gravedad y, por lo tanto, refuerza la necesidad de seguir estudiando y describiendo de forma precisa las

características de los pacientes con TJ. La heterogeneidad a nivel cognitivo puede explicarse considerando que las FFEE, encargadas del autocontrol para evitar llevar a cabo conductas impulsivas, la capacidad para razonar, tomar decisiones o considerar alternativas mentales, resultan alteradas. Su afectación puede implicar que la impulsividad y las distorsiones cognitivas, características propias del TJ, influyan de forma más notoria a conductas descontroladas de juego que aumenten la gravedad del trastorno. En cambio, en pacientes con TJ con unas FFEE preservadas, el hecho de que tengan la sensación de que puedan ser muy precisos a la hora de capturar información estadística de los dispositivos de juego, puede contribuir a una falsa sensación de confianza y control sobre las actividades de juego debido al conocimiento que uno percibe tener, e influir en la gravedad del TJ, tal como han indicado algunos expertos (510).

Relacionado con la heterogeneidad de los pacientes con TJ, cabe destacar que los resultados también señalan que, dependiendo de la modalidad de juego, los déficits neuropsicológicos se asociaban a diferentes distorsiones cognitivas. Esta relación entre los déficits y las distorsiones cognitivas en el TJ ha sido poco estudiada hasta el momento. En los individuos con preferencia por el juego no estratégico, los déficits en la memoria de trabajo se asociaron a distorsiones cognitivas de expectativa y de control predictivo. La literatura indica que, en los pacientes con juego no estratégico, un estilo de pensamiento más intuitivo y automático favorece un juego inconsciente y, por lo tanto, podría implicar mayores dificultades en aquellas funciones propias de la memoria de trabajo (p. ej., manipular la información, planificar y hacer un seguimiento de la tarea tales como las ganancias y las pérdidas durante la conducta de juego) (510). Por otro lado, las dificultades en la flexibilidad cognitiva en aquellas personas con juego estratégico se asociaron a distorsiones de ilusión de control, control predictivo e incapacidad para parar de jugar. Esta asociación podría sugerir que, en línea con la argumentación anterior de la falsa de percepción de control en el juego estratégico, este tipo de pacientes tendería a mostrar cierta reticencia a cambiar su forma de pensar por la creencia de que sus habilidades o intuiciones pueden influir en el juego, contribuyendo a exacerbar esta distorsión y, por tanto, a mantener la conducta de juego (604–606). En conclusión, los resultados sugieren la posible influencia del rendimiento cognitivo en las distorsiones cognitivas, un aspecto clave para entender la conducta de juego.

Por último, con la idea de relacionar marcadores neuropsicológicos con variables biológicas que proporcionaran robustez a posibles correlatos neurobiológicos, este trabajo incluyó el estudio de variables neuroendocrinas en personas con TJ. Aunque el rendimiento cognitivo no mostró asociaciones con las variables neuroendocrinas estudiadas, se observó que bajos niveles de adiponectina se relacionaban con la gravedad del TJ. Bajas concentraciones de esta hormona también han sido encontradas en personas con TJ (493). Algunos autores han planteado la hipótesis de que una adiponectina disminuida podría estar relacionada con un mayor riesgo de enfermedades metabólicas en pacientes con trastornos relacionados con las adicciones, como el TUS y el TJ (493,607). A pesar de ser preliminares, estos hallazgos contribuyen significativamente a una comprensión más profunda de la neurobiología del TJ y de su gravedad, lo que destaca la importancia de orientar futuras investigaciones hacia objetivos biológicos como posibles estrategias de tratamiento.

IMPLICACIONES CLÍNICAS

Los resultados de esta investigación tienen diversas implicaciones para la práctica clínica. A través del estudio neuropsicológico, se identifican algunas limitaciones del enfoque categorial y se defiende la importancia del enfoque transdiagnóstico en la comprensión y tratamiento de los trastornos mentales (22,23). A través del estudio del endofenotipo cognitivo de los TCA y del TJ, se aportan nuevas evidencias para analizar la impulsividad y la compulsividad desde una perspectiva neurobiológica. Mediante el uso de mediciones neuropsicológicas cuantitativas más precisas, en lugar de depender exclusivamente de cuestionarios clínicos, se mejora la comprensión de los procesos conductuales y cognitivos que predisponen o mantienen estos trastornos (7,608). Esto podría conducir a mejoras en la atención a estos trastornos, favoreciendo diagnósticos más exactos, reduciendo las tasas de comorbilidad y permitiendo una mayor flexibilidad al considerar las diferencias entre individuos.

Asimismo, un mayor conocimiento del funcionamiento cognitivo de estas problemáticas permite identificar subtipos clínicos, teniendo en cuenta la impulsividad y la compulsividad cognitiva. Aquellos individuos con mayores déficits cognitivos tienden a presentar perfiles de mayor gravedad que marcan el curso clínico y el proceso terapéutico. Aquellas personas que presenten dificultades en las FFEE puede que no se beneficien de los tratamientos tradicionales, precisamente debido a sus características

neuropsicológicas. Por lo tanto, el desarrollo de intervenciones terapéuticas centradas en la alteración de la toma de decisiones, la flexibilidad cognitiva, la memoria de trabajo o el control inhibitorio entre otros aspectos esenciales podrían ser eficaces para abordar estos aspectos que forman parte, tanto directa como indirectamente, de la sintomatología de estos trastornos, y garantizando un adecuado enfoque terapéutico para estas personas. En esta línea, se han logrado avances prometedores mediante intervenciones centradas en mejorar el funcionamiento cognitivo en trastornos adictivos y TCA, como señalan algunos autores (186,609).

LIMITACIONES

Esta tesis debe ser analizada considerando varias limitaciones. En primer lugar, la muestra se compone de pacientes adultos que están buscando atención especializada. Esto significa que los resultados no pueden generalizarse a personas que no buscan tratamiento, ni a otras muestras comunitarias. En segundo lugar, la mayor parte de los estudios comparten un diseño transversal, lo que dificulta el establecimiento de relaciones causales, especialmente cuando se investigan fenómenos tan complejos. Futuros estudios longitudinales podrían contribuir a determinar si las alteraciones neuropsicológicas persisten en función de variables como el peso, la edad o factores neuroendocrinos. En tercer lugar, la interpretación de los resultados puede estar restringida debido a la falta de variables asociadas al estado emocional, a la presencia de trastornos psiquiátricos comórbidos, como la depresión mayor o los trastornos de ansiedad, o al uso de psicofármacos que podrían tener un impacto en el rendimiento cognitivo (610). Por ello, sería aconsejable que estas variables se tuvieran en consideración en el diseño de próximos estudios. Por último, en referencia a los trabajos que incluyen personas con TCA, estas suelen presentar dificultades cognitivas en diferentes dominios cognitivos, lo que también podrían haberse considerado funciones cognitivas como la memoria de trabajo o la atención.

FORTALEZAS

A pesar de estas limitaciones, los estudios descritos también presentan varios puntos fuertes que conviene destacar. Esta tesis dirige sus objetivos al estudio de endofenotipos cognitivos, aportando descripciones objetivas más precisas. Además, el estudio de variables cognitivas contribuye al establecimiento de las bases neurobiológicas,

permitiendo la observación de patrones cognitivos que pueden ser correlacionados con medidas clínicas. Las herramientas neuropsicológicas utilizadas están expresamente especificadas para los trastornos evaluados. Asimismo, cuentan con una validez, fiabilidad y estandarización sensibles y útiles para identificar y cuantificar los cambios cognitivos propios de estos trastornos. Esta tesis también trató de ir un paso más allá utilizando medidas biológicas para cumplimentar los hallazgos neuropsicológicos y explorar si determinados factores endocrinos pueden también ayudar a entender los mecanismos de los trastornos estudiados. Por último, los estudios incluidos en este trabajo cuentan con amplios tamaños muestrales en los dos trastornos estudiados. Es importante también destacar que se han hecho análisis conjuntos de muestra con TJ y TCA para evidenciar el papel transdiagnóstico del funcionamiento cognitivo.

6. CONCLUSIONES

Generales:

1) Las alteraciones neuropsicológicas relacionadas con las funciones ejecutivas en los trastornos del espectro impulsivo-compulsivo (como los trastornos de conducta alimentaria, la obesidad y el trastorno de juego), forman parte de un endofenotipo cognitivo donde coexisten síntomas impulsivos y compulsivos, actuando como un factor transdiagnóstico.

2) Las alteraciones neuropsicológicas influyen en la gravedad clínica, psicopatológica y en la respuesta al tratamiento. Por ello, son necesarios abordajes centrados en mejorar las funciones cognitivas.

TCA:

3) El rendimiento en procesos neuropsicológicos como la toma de decisiones y la flexibilidad cognitiva es inferior en personas con trastorno del espectro bulímico con y sin compra compulsiva comórbida, anorexia nerviosa restrictiva, y obesidad con y sin diabetes en comparación con personas sanas.

4) Las personas con obesidad y diabetes muestran mayores niveles de impulsividad cognitiva, mientras que las personas con obesidad sin diabetes muestran mayores niveles de compulsividad cognitiva con relación a personas sanas.

5) Las dificultades en flexibilidad cognitiva se asocian a una mayor duración del trastorno en aquellas personas con anorexia nerviosa y trastorno del espectro bulímico. Los criterios de gravedad del DSM-5 y la obsesión por la delgadez no logran discriminar los déficits en flexibilidad cognitiva.

6) Pacientes con trastorno del espectro bulímico y compra compulsiva comórbida presentan un peor rendimiento en la flexibilidad cognitiva y la toma de decisiones en comparación con aquellas personas con trastorno del espectro bulímico sin comorbilidad y personas sanas. Las personas con ambos trastornos muestran mayores

niveles de psicopatología general, mayor gravedad de sintomatología alimentaria y un perfil de personalidad con rasgos impulsivos y compulsivos.

7) Las dificultades a nivel cognitivo en las personas con trastorno bulímico y compra compulsiva se asocian a una peor respuesta al tratamiento, indicando la relevancia del rendimiento cognitivo en la eficacia de tratamientos convencionales y el planteamiento de tratamientos neuropsicológicos específicos para estas personas.

TJ:

8) El rendimiento en procesos neuropsicológicos como la toma de decisiones y la flexibilidad cognitiva es inferior en personas con trastorno de juego en comparación con personas sanas.

9) El criterio del DSM-5 referente a la abstinencia es el criterio con mayor relevancia en el DSM-5, reforzando la idea que factores compulsivos también están presentes en el trastorno de juego.

10) Las dificultades cognitivas en personas con trastorno de juego están relacionadas con la gravedad del trastorno debido a su conexión con la impulsividad rasgo y las distorsiones cognitivas. No obstante, un mejor rendimiento cognitivo se asocia directamente con una mayor gravedad en los individuos con TJ.

11) En los pacientes con preferencia por el juego no estratégico, las dificultades en la memoria de trabajo están vinculadas a distorsiones cognitivas de expectativa y control predictivo. En aquellos con preferencia por el juego estratégico, las dificultades en la flexibilidad cognitiva se relacionan con distorsiones cognitivas de ilusión de control, control predictivo e incapacidad para parar de jugar.

12) Aunque el rendimiento cognitivo no muestra asociaciones con las variables neuroendocrinas estudiadas, bajos niveles de adiponectina se relacionan con la gravedad del trastorno de juego.

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