Alteraciones neuroendocrinas en trastornos del espectro impulsivo-compulsivo: implicaciones en el trastorno de juego y la adicción a la comida

Mikel Etxandi Santolaya

ALTERACIONES NEUROENDOCRINAS EN TRASTORNOS DEL ESPECTRO IMPULSIVO-COMPULSIVO: IMPLICACIONES EN EL TRASTORNO DE JUEGO Y LA ADICCIÓN A LA COMIDA

Memoria de tesis doctoral presentada por

Mikel Etxandi Santolaya

para optar al grado de doctor por la Universidad de Barcelona

Dirigida por:

Susana Jiménez Murcia 1,2,3,4

Fernando Fernández Aranda 1,2,3,4

1. Unidad de Psicología Clínica, Hospital Universitari de Bellvitge, L'Hospitalet de Llobregat
2. Grupo de Psiconeurobiología de los trastornos alimentarios y de las conductas adictivas, Programa en Neurociències, Institut d'Investigació Biomèdica de Bellvitge – IDIBELL, L'Hospitalet de Llobregat
3. Departament de Ciències Clíniques, Facultat de Medicina, Universitat 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-R	Anorexia nerviosa restrictiva
AN-P	Anorexia nerviosa purgativa
BN	Bulimia nerviosa
CIE	Clasificación Internacional de Enfermedades
DSM	*Diagnostic and Statistical Manual of Mental Disorders* (Manual Diagnóstico y Estadístico de los Trastornos Mentales)
FA	*Food Addiction* (Adicción a la comida)
GH	Hormona de crecimiento
GHS-R1a	Receptor de la hormona de crecimiento
HUB	Hospital Universitario de Bellvitge
IMC	Índice de masa corporal
LEAP-2	Péptido antimicrobiano hepático enriquecido 2
NPY	Neuropéptido Y
TCA	Trastorno de la conducta alimentaria
TDAH	Trastorno por déficit de atención e hiperactividad
TJ	Trastorno de juego
TOC	Trastorno obsesivo-compulsivo
TUS	Trastorno por uso de sustancias
YFAS	*Yale Food Addiction Scale*

ENUMERACIÓN DE LOS ARTÍCULOS DE LA TESIS

Tesis en formato de compendio de publicaciones.

La presente tesis consta de cinco objetivos y tres artículos. Todos ellos han sido llevados a cabo con muestra recogida en la Unidad de Adicciones Comportamentales del Hospital Universitario de Bellvitge (HUB).

Objetivos:

1. Explorar y comparar las concentraciones plasmáticas de hormonas reguladoras del apetito (leptina, grelina, adiponectina y LEAP-2) entre pacientes con trastorno de juego y sujetos sanos. (Estudio 1)

2. Analizar las correlaciones entre factores endocrinos y aspectos neuropsicológicos y clínicos en el trastorno de juego. (Estudio 1)

3. Explorar si existen diferencias en las concentraciones plasmáticas de las hormonas implicadas en la regulación del apetito (grelina, LEAP-2, adiponectina y leptina) en una muestra de pacientes diagnosticados de trastorno de juego con y sin adicción a la comida. (Estudio 2)

4. Explorar las correlaciones entre los niveles de las hormonas implicadas en trastorno de juego y adicción a la comida y las variables clínicas y psicológicas en el subgrupo con adicción a la comida. (Estudio 2)

5. Evaluar los correlatos clínicos de la adicción a la comida en pacientes con trastorno de juego, teniendo en cuenta rasgos de personalidad, el estado psicológico o el consumo de sustancias y en función del sexo. (Estudio 3)

A continuación, se citan los artículos en el orden en el cual serán referidos a lo largo de este documento:

1. **Etxandi M**, Baenas I, Mora-Maltas B, Granero R, Fernández-Aranda F, Tovar S, Solé-Morata N, Lucas I, Casado S, Gómez-Peña M, Moragas L, Pino-Gutiérrez AD, Codina E, Valenciano-Mendoza E, Potenza MN, Diéguez C, Jiménez-Murcia S. Are Signals Regulating Energy Homeostasis Related to Neuropsychological and Clinical Features of Gambling Disorder? A Case-Control Study. Nutrients. 2022;14(23):5084. (**IF: 5.9; Q1** en la categoría "Nutrition & Dietetics")

2. **Etxandi M**, Baenas I, Mora-Maltas B, Granero R, Fernández-Aranda F, Tovar S, Solé-Morata N, Lucas I, Casado S, Gómez-Peña M, Moragas L, Pino-Gutiérrez A, Codina E, Valenciano-Mendoza E, Potenza MN, Gearhardt AN, Diéguez C, Jiménez-Murcia S. Plasma Concentration of Leptin is Related to Food Addiction in Gambling Disorder: Clinical and Neuropsychological Implications. Journal of Behavioral Addictions. 2023;12(4):1019-1031. (**IF: 7.8; Q1** en la categoría "Psychiatry")

3. **Etxandi M**, Baenas I, Munguía L, Mestre-Bach G, Granero R, Gómez-Peña M, Moragas L, Del Pino-Gutiérrez A, Codina E, Mora-Maltas B, Valenciano-Mendoza E, Potenza MN, Gearhardt AN, Fernández-Aranda F, Jiménez-Murcia S. Clinical Features of Gambling Disorder Patients with and Without Food Addiction: Gender-Related Considerations. J Gambl Stud. 2022; 38(3):843-862. (**IF: 2.4; Q2** en la categoría "Psychology, multidisciplinary")

1

INTRODUCCIÓN

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1.1. CEREBRO Y APARATO DIGESTIVO, UNA MIRADA INTEGRADORA

Durante muchos años en la historia de la medicina imperó un modelo centrado en el estudio de órganos por separado, así como en la búsqueda de explicaciones y tratamientos a los diferentes problemas de salud a través de la identificación de disfunciones aisladas en los mismos. Sin embargo, durante las últimas décadas, ha quedado patente que muchas patologías presentan etiologías y cursos evolutivos complejos, en los que es necesario ampliar el foco, adoptando una mirada sistémica, para entender la interacción entre diferentes órganos y sistemas de cara a comprender su base biológica.

En esta línea, la conexión entre el sistema digestivo y las estructuras cerebrales encargadas de procesar aspectos como las emociones o los recuerdos ha sido ampliamente analizada. Durante los últimos años, y a través de diversos enfoques, han sido muchos los autores que han logrado demostrar la implicación de dicha interrelación en trastornos mentales. Los mecanismos biológicos que subyacen a dicha conexión son variados y complejos, incluyendo sistemas hormonales, aspectos inmunológicos, vías de neurotransmisión y señalización a través de la interacción con la microbiota intestinal (1).

Ejemplos paradigmáticos podrían ser los múltiples estudios que, sin obviar el impacto de factores psicológicos y sociales en la etiopatogenia los trastornos mentales, han logrado identificar asociaciones entre alteraciones en la microbiota intestinal y trastornos depresivos u obesidad (2,3). Por otro lado, y en sentido inverso, es ampliamente conocido que algunos trastornos digestivos se encuentran íntimamente relacionados con el estado mental de los individuos que los padecen, como es el caso de las enfermedades inflamatorias intestinales, en las que se observa una elevada comorbilidad con trastornos de ansiedad y depresión, pudiendo afectar al curso evolutivo de la enfermedad (4). En la misma línea, algunas enfermedades metabólicas como la diabetes mellitus se han relacionado con un aumento en el riesgo de presentar trastornos afectivos como la depresión mayor (5).

Toda esta evidencia ha tenido una repercusión asistencial clara durante los últimos años, y, por ejemplo, es cada vez más frecuente que los profesionales de salud mental recomienden a sus pacientes poner el foco en mantener una dieta saludable y prestar atención a aspectos relacionados con el estado metabólico, como factor fundamental a la hora de cuidar la salud mental.

Los estudios que componen el presente trabajo pretenden ahondar en el análisis de la interacción entre aparato digestivo, estado metabólico y trastornos mentales, analizando una de las diversas vías de comunicación entre ambos sistemas: la señalización a través de factores neuroendocrinos. Se pretende estudiar esta vía de interrelación en trastornos adictivos, en concreto el trastorno de juego (TJ) y la adicción a la comida o *food addiction* (FA), ambas entidades englobadas dentro del denominado espectro impulsivo-compulsivo.

1.2. ESPECTRO IMPULSIVO-COMPULSIVO

1.2.1. Definición y marco teórico

Existe un debate abierto en la comunidad científica acerca de cuál es la aproximación más apropiada a la hora de estudiar y abordar los trastornos mentales. Si bien las principales clasificaciones diagnósticas históricamente han abogado por un planteamiento categorial, son muchos los autores que defienden que una aproximación dimensional puede ser útil a la hora de conceptualizar dichos trastornos y evitar las principales limitaciones del modelo categorial (principalmente la excesiva frecuencia de comorbilidad diagnóstica y la perspectiva dicotómica de ausencia o presencia de enfermedad, sin tener en cuenta posibles diferentes niveles de severidad) (6).

Es en este contexto en el que nace el concepto de espectro impulsivo-compulsivo, constructo que pretende englobar en un mismo continuum distintos trastornos mentales en cuyo desarrollo estarían implicadas disfunciones, en mayor o menor medida, de aspectos neurobiológicos relacionados con la compulsividad y la impulsividad (7). De esta forma, en uno de los extremos del espectro se situaría la compulsividad, definida como la tendencia a incurrir en

conductas repetitivas de forma excesiva, dirigidas a aliviar el malestar emocional y la ansiedad; y en el extremo opuesto se ubicaría la impulsividad, descrita como la tendencia a llevar a cabo conductas buscando una excitación o gratificación inmediatas, infravalorando el potencial daño que puedan derivar de las mismas. Próximas al polo de la compulsividad se situarían entidades diagnósticas como el trastorno obsesivo-compulsivo (TOC), el trastorno dismórfico corporal o la anorexia nerviosa de tipo restrictivo (AN-R) y hacia el polo de la impulsividad se ubicarían patologías como el trastorno por uso de sustancias (TUS), la bulimia nerviosa (BN), la anorexia nerviosa de tipo purgativo (AN-P) o las dos entidades diagnósticas que han sido objeto de estudio en el presente proyecto de tesis doctoral: el trastorno de juego y la adicción a la comida (7).

A lo largo de los últimos años se ha descrito una elevada comorbilidad entre estas entidades diagnósticas, identificándose aspectos clínicos compartidos por diferentes trastornos del espectro impulsivo-compulsivo, lo cual ha llevado a diversos autores a proponer que dicho conjunto de trastornos podrían compartir aspectos neurobiológicos comunes, relacionados con la disfunción de circuitos cerebrales implicados en el desarrollo de alteraciones en la compulsividad y la impulsividad (8). En estudios recientes se han llegado a sugerir que hallazgos neurobiológicos concretos, como una reducción de la activación del estriado ventral durante la fase de anticipación de la recompensa, podría constituir un posible biomarcador común a diferentes trastornos del espectro (9).

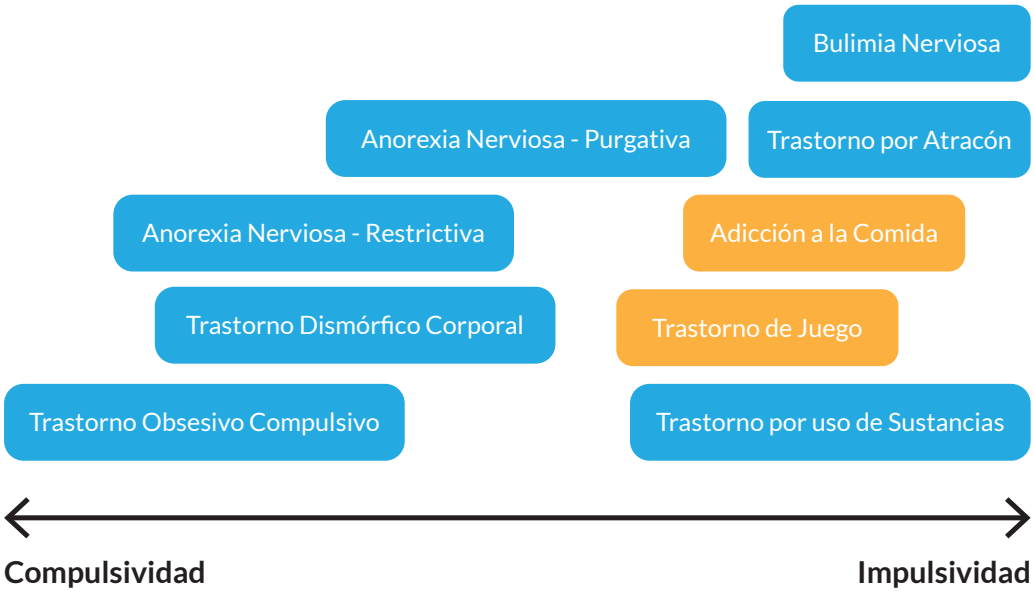

Figura 1. Representación del modelo transdiagnóstico del espectro impulsivo-compulsivo.
Nota: Elaboración propia.

1.2.2. Trastorno de Juego

1.2.2.1. Clasificación y criterios diagnósticos

El juego se define como una actividad que consiste en poner en riesgo algo valioso con la esperanza de obtener algo de mayor valor (10). Dicha conducta se remonta a las primeras civilizaciones humanas y ha evolucionado a lo largo de la historia. Actualmente, las modalidades de juego más populares, especialmente entre la población joven, son las apuestas deportivas, el póquer y algunos juegos de casino. Sin embargo, y especialmente en España, durante décadas, juegos como las máquinas recreativas con premio y, en menor medida, el bingo, han sido mucho más frecuentes. Asimismo, la lotería, especialmente la navideña, constituye un fenómeno social único en el panorama internacional, considerándose como algo casi tradicional. Cabe destacar que el juego puede llevarse a cabo de forma presencial o a través de Internet.

A nivel conceptual se diferencian dos grandes tipos de juego: el juego estratégico (que implica el uso por parte del jugador de conocimientos o habilidades

relacionadas con el juego para poder participar y aspirar a obtener un resultado favorable, como por ejemplo los juegos de cartas o las apuestas deportivas) y el juego no estratégico (en el cual el resultado del juego es completamente aleatorio, como es el caso de las máquinas, la lotería o el bingo).

Este tipo de actividades están muy extendidas y culturalmente arraigadas en nuestra sociedad, pero entrañan riesgos evidentes, especialmente para colectivos vulnerables. Si bien para muchos el juego se limita a una actividad de ocio esporádica en términos de tiempo dedicado, frecuencia y dinero invertido, para algunas personas puede suponer la entrada en una dinámica de ganancias y pérdidas que puede conducir a una pérdida de control en cuanto a la conducta de juego. En este contexto, el TJ es el término utilizado en la quinta edición del Manual Diagnóstico y Estadístico (DSM-5) para definir un patrón persistente y recurrente de conducta de juego que se asocia a un malestar o un deterioro psicosocial significativo (11).

Figura 2. Tipos de jugador según la intensidad y repercusión de la conducta de juego. *Adaptada de Jiménez-Murcia y Aymamí* (12)

El TJ es la adicción comportamental con mayor apoyo empírico y reconocimiento formal por parte de la comunidad científica. Esta entidad diagnóstica apareció por primera vez en el DSM-III bajo la denominación de juego patológico y fue inicialmente clasificado como un trastorno del control de impulsos. Sin embargo, fue posteriormente reclasificado dentro de la categoría de trastornos adictivos con la publicación del DSM-5, modificación que vino justificada por la extensa evidencia científica que demuestra que dicho trastorno comparte múltiples similitudes tanto clínicas como neurobiológicas con los trastornos por uso de sustancias (TUS) y que implicó un importante cambio de paradigma, tanto a nivel de enfoque terapéutico como de investigación de aspectos etiopatogénicos (10). De forma similar, otra de las principales clasificaciones, como es la Clasificación Internacional de Enfermedades, undécima edición (CIE-11), incluye el TJ como categoría diagnóstica dentro de la sección "trastornos debidos al consumo de sustancias o conductas adictivas" (13). Los criterios diagnósticos del TJ según el DSM-5 vienen recogidos en la tabla 1.

Tabla 1. Criterios diagnósticos DSM-5 para el trastorno de juego

A. Trastorno por juego problemático persistente y recurrente, que provoca un deterioro o malestar clínicamente significativo y se manifiesta porque el individuo presenta cuatro (o más) de los siguientes criterios durante un periodo de 12 meses:

1. Necesidad de apostar cantidades de dinero cada vez mayores para conseguir la excitación deseada.
2. Está nervioso o irritado cuando intenta reducir o abandonar el juego.
3. Ha hecho esfuerzos repetidos para controlar, reducir o abandonar el juego, siempre sin éxito.
4. A menudo tiene la mente ocupada en las apuestas (p. ej., reviviendo continuamente con la imaginación experiencias de apuestas pasadas, condicionando o planificando su próxima apuesta, penando en formas de conseguir dinero para apostar).
5. A menudo apuesta cuando siente desasosiego (p. ej., desamparo, culpabilidad, ansiedad, depresión).
6. Después de perder dinero en las apuestas, suele volver otro día para intentar ganar ("recuperar" las pérdidas).
7. Miente para ocultar su grado de implicación en el juego.
8. Ha puesto en peligro o ha perdido una relación importante, un empleo o una carrera académica o profesional a causa del juego.
9. Cuenta con los demás para que le den dinero para aliviar su situación financiera desesperada provocada por el juego.

B. Su comportamiento ante el juego no se explica mejor por un episodio maníaco.

Especificar si:
Episódico: Cumple los criterios diagnósticos en más de una ocasión, si bien los síntomas se apaciguan durante varios meses, por lo menos entre períodos de trastorno por juego.
Persistente: Experimenta síntomas continuamente, cumple los criterios diagnósticos durante varios años.

Especificar si:
En remisión inicial: Tras haber cumplido previamente todos los criterios de trastorno por juego, no ha cumplido ninguno de ellos durante un mínimo de 3 meses, pero sin llegar a 12 meses.
En remisión continuada: Tras haber cumplido previamente todos los criterios de trastorno por juego, no ha cumplido ninguno de ellos durante un mínimo de 12 meses o más.

Especificar la gravedad actual:
Leve: Cumple 4-5 criterios.
Moderado: Cumple 6-7 criterios.
Grave: Cumple 8-9 criterios.

Adaptado del Manual Diagnóstico y Estadístico de los Trastornos Mentales DSM-5 **(11)**

1.2.2.2. Epidemiología

Se estima que la prevalencia a lo largo de la vida del TJ se sitúa entre el 0,4 y el 1% de la población, siendo más frecuente en hombres que en mujeres, si bien está diferencia podría estar reduciéndose en los últimos años, según apuntan diversos estudios (11). Cabe señalar que algunos autores han propuesto que esta tradicional diferencia entre sexos podría tener relación con una posible menor tendencia a consultar en unidades especializadas por parte de las mujeres, debido probablemente a un mayor estigma social, lo cual llevaría a una infraestimación del problema en estudios de prevalencia (14,15).

Más allá de diferencias en prevalencia, existen algunas características diferenciales en el curso de la enfermedad entre hombres y mujeres. Por un lado, los hombres tienden a presentar una edad de inicio menor y en general muestran una preferencia por juegos estratégicos (se ha postulado que por el componente de competitividad que implican) (16), mientras que las mujeres presentan debuts más tardíos pero suelen requerir de un menor intervalo de tiempo desde el inicio de la conducta de juego hasta el desarrollo del trastorno (17).

1.2.2.3. Factores de riesgo

El TJ, como el resto de trastornos adictivos, son un ejemplo paradigmático de interacción de factores de vulnerabilidad biológica con aspectos psicológicos y sociales, que juegan un papel clave tanto en la instauración como en el mantenimiento de la conducta problema. En este contexto, ciertos individuos pueden presentar un mayor riesgo de padecer este trastorno. A continuación, se detallan algunos de los factores de riesgo identificados y respaldados con un mayor nivel de evidencia científica.

- **Sociodemográficos:** Al igual que en otros trastornos mentales y en concreto en las adicciones, los factores sociales y demográficos juegan un papel muy relevante en desarrollo y el mantenimiento del TJ. Estudios previos demuestran que sujetos de grupos de edad concretos, como los adolescentes y los adultos jóvenes o de mediana edad, presentan una mayor vulnerabilidad para

el desarrollo del trastorno. Además, también se han descrito como factores de riesgo un bajo nivel educativo, el hecho de vivir en entornos socialmente desfavorecidos o la ausencia de supervisión parental (10,18,19).

A nivel ambiental, existen estudios recientes que correlacionan la exposición a publicidad relacionada con el juego, así como una mayor accesibilidad al mismo, con un mayor riesgo de desarrollar el trastorno (20).

- **Psicológicos:** Aspectos relacionados con la psicopatología y la personalidad premórbida también constituyen factores clave a la hora de entender las diferencias interpersonales en cuanto a la vulnerabilidad para el desarrollo del TJ.

  Uno de los principales factores psicológicos relacionados con el TJ es la impulsividad. Numerosos estudios han demostrado que diferentes aspectos de la impulsividad (como la urgencia positiva, la urgencia negativa o la dificultad para la supresión de respuestas motoras) pueden verse alterados en individuos con TJ (21–23) y se ha descrito que personas con una elevada impulsividad presentan un mayor riesgo de desarrollar el trastorno (10,19).

  En cuanto a factores de personalidad relacionados con el TJ, si bien no existe un único perfil que caracterice a todas las personas con dicho trastorno, si se han descrito algunos factores de riesgo para desarrollar problemas relacionados con el juego. Éstos incluirían, según estudios previos, una alta tendencia a la búsqueda de sensaciones, una elevada evitación del daño, un alto neuroticismo o una baja auto-dirección (24–27).

  En este sentido, diversos autores han estudiado las características psicológicas de las personas con TJ y, en la búsqueda de modelos teóricos en cuanto a la etiopatogenia se han desarrollado paradigmas psicosociales como el de Blaszczynski y Nower (2002) (28), que actualmente, cuenta con un sólido respaldo empírico (29), y que diferencia tres grupos distintos de individuos con vulnerabilidad para el desarrollo de TJ: los conductualmente condicionados, los emocionalmente vulnerables y los impulsivos con características antisociales.

Según este modelo, el primer grupo de pacientes, conocido como el de jugadores conductualmente condicionados, serían aquellos que oscilan entre el juego regular y el excesivo por los efectos del condicionamiento propio de los juegos de apuesta, así como por distorsiones cognitivas en torno a la probabilidad de ganar y una serie de juicios erróneos o una pobre capacidad para la toma de decisiones, más que por un deterioro en el control conductual (28).

Los segundos, el grupo de los emocionalmente vulnerables, estarían caracterizados por presentar, además de procesos de condicionamiento y distorsiones cognitivas como en el grupo previo, unos mayores niveles de ansiedad y/o depresión premórbidos, dificultades en el desarrollo de estrategias adaptativas de afrontamiento ante el malestar emocional o el estrés y, en muchos casos, eventos vitales adversos que pueden actuar como detonante o factor mantenedor de la conducta problema. En estos individuos es más frecuente la existencia de antecedentes de trauma en la infancia y la conducta de juego estaría motivada por la intención de modular estados afectivos negativos (28).

En el tercer grupo, los jugadores impulsivos con características antisociales, destaca una mayor interferencia de contextos psicosociales adversos en relación a la conducta de juego. En este grupo predomina la impulsividad y es habitual que coexista una historia previa de conductas de riesgo más allá del juego, incluyendo consumo de sustancias y conductas delictivas. Asimismo, sería el grupo en el que existiría mayor implicación de los factores de riesgo neurobiológicos (28).

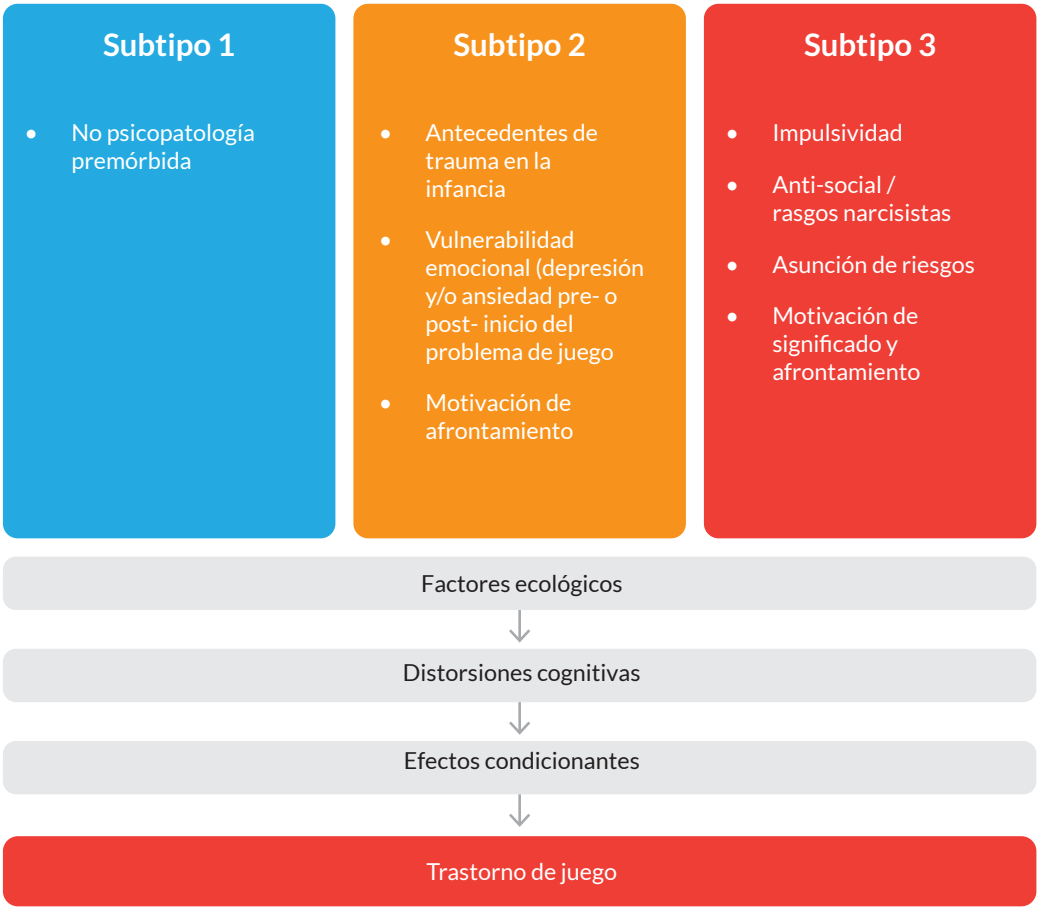

Figura 3. Representación del modelo de Blaszczynski y Nower. *Adaptado de Nower, Blaszczynski et al.*(30)

Cabe señalar que este modelo ha servido como base para estudios más recientes en los que se proponen otras clasificaciones en cuanto a subtipos de individuos con TJ. En este sentido, un estudio llevado a cabo por Jiménez-Murcia y colaboradores en 2019, en el que se analizó una amplia muestra de hasta 2570 personas con TJ, propuso en base a los resultados obtenidos una clasificación en tres subgrupos o clústeres en función del nivel del malestar emocional, que resultó ser la variable más relevante a la hora de identificar subgrupos mutualmente excluyentes. De esta forma, el clúster 1 se definiría como el de sujetos con un "elevado malestar emocional" y se caracterizaría por una mayor edad, gravedad y duración del trastorno, así como una mayor severidad en los niveles de psicopatología. En clúster 2 sería el de "malestar emocional leve" que aglutinó a la mayor parte de la muestra estudiada y que

implicaría una psicopatología general y gravedad del TJ más leve. El clúster 3, definido por un "moderado malestar emocional" estaría compuesto por sujetos jóvenes, con un mayor nivel de educación, duración más corta del trastorno y niveles moderados de psicopatología general (31).

Genéticos: Más allá de factores ambientales y psicológicos, que sin duda juegan un papel crucial en el desarrollo del TJ, estudios de heredabilidad realizados en muestras de gemelos sugieren un componente de predisposición genética para el desarrollo de este trastorno (32), algunos de los mecanismos implicados se enumeran a continuación:

- Genes relacionados con la señalización dopaminérgica: Se ha observado que ciertos polimorfismos en genes asociados con la regulación de la neurotransmisión en vías dopaminérgicas, como DRD1, DRD2 y DRD4, relacionados con procesos de recompensa y motivación, podrían aumentar la vulnerabilidad para el desarrollo de TJ (10,33).

- Genes implicados en el sistema serotoninérgico: Alteraciones en genes que regulan la serotonina, otro neurotransmisor asociado con el control de los impulsos y las emociones, como SLC6A4, MAOA o MAOB, han sido vinculadas con un mayor riesgo de desarrollar el trastorno (10,33).

- Genes relacionados con factores neurotróficos: Recientemente se ha estudiado la posible vinculación de alteraciones en genes que codifican para factores neurotróficos y TJ. Este conjunto de proteínas, entre las que se encuentran en factor de crecimiento nervioso (NGF), el factor neurotrófico derivado del cerebro (BDNF) y las neurotrofinas 3 y 4, se ha vinculado con la fisiopatología de diversos trastornos mentales, entre ellos las adicciones, por su conocida implicación en la regulación de la actividad neuronal y plasticidad sináptica (34–36). Los resultados hasta la fecha indican que algunos polimorfismos, en concreto en NTF3 y NTRK2, podrían estar relacionados con una mayor vulnerabilidad para presentar el trastorno (37).

- Otros: Estudios recientes, usando la técnica de asociación del genoma completo (GWAS) han identificado que distintas variantes de otros genes (MT1X, ATXN1 y VLDLR), previamente relacionados con adicciones y otros trastornos mentales, podrían estar asociadas a TJ (38).

1.2.2.4. Comorbilidades

El TJ, al igual que otros trastornos del espectro impulsivo-compulsivo, frecuentemente se presenta asociado a otros trastornos mentales. Las entidades diagnósticas más frecuentemente relacionadas con dicho trastorno son los TUS (principalmente trastorno por consumo de alcohol), trastornos afectivos y trastornos de personalidad (10,39,40). Sin embargo, también se han descrito asociaciones con otras entidades diagnósticas como trastornos de la conducta alimentaria (TCA), trastornos psicóticos o trastornos del neurodesarrollo (41,42). La comorbilidad, como suele ser habitual, frecuentemente se relaciona con mayor gravedad del trastorno o una mayor dificultad para el tratamiento, lo cual supone un importante reto asistencial (43).

La conducta suicida en personas con TJ requiere una mención especial. La evidencia disponible demuestra una sólida relación entre el TJ y el suicidio en jugadores de todas las edades (44–46), si bien existen autores que cuestionan si dicho fenómeno se explica como elemento intrínseco o complicación del propio trastorno o si se explica mejor como consecuencia de las frecuentes comorbilidades psiquiátricas a las que se asocia, como se ha mencionado previamente (47). Diversos estudios centrados en analizar dicha cuestión reportan resultados contradictorios; si bien hay trabajos recientes que sugieren una asociación entre el TJ y el suicidio, incluso tras ajustar por variables que podrían actuar como factor de confusión, como las comorbilidades psiquiátricas (en concreto depresión, trastornos de ansiedad y TUS) (45), otros no reportan asociaciones significativas en dicho sentido (48–50). En suma, la relación entre el suicidio y el TJ es una realidad clínica, si bien todavía existen dudas respecto a los mecanismos mediante los cuales se produce esta asociación.

1.2.2.5. Aspectos neuropsicológicos

Los individuos con TJ presentan unas alteraciones a nivel neurobiológico que los sitúa en una posición de vulnerabilidad para el desarrollo y mantenimiento de la conducta de juego, así como de otros trastornos del espectro impulsivo-compulsivo, a pesar de la aparición de consecuencias negativas.

En este sentido, las características neurobiológicas relacionadas con los trastornos adictivos incluyen procesos neuropsicológicos alterados no sólo en relación con las funciones ejecutivas, como la inhibición de la respuesta, la autorregulación, la toma de decisiones, la flexibilidad cognitiva o la planificación, sino también con la memoria de trabajo (51–53). Estas funciones cognitivas se han descrito como síntomas centrales en los trastornos adictivos y están especialmente relacionadas con el deterioro de la capacidad de control sobre los impulsos presente en estas entidades (52).

Estas alteraciones neuropsicológicas se han relacionado ampliamente con el TJ, y diversos estudios apuntan a que no sólo implican una mayor probabilidad de desarrollar el trastorno, sino que también se asocian con una mayor duración y gravedad del mismo (54,55). En la misma línea, trabajos recientes apuntan a que disfunciones a nivel neuropsicológico podrían relacionarse con una peor respuesta al tratamiento. En concreto, se ha propuesto que una baja flexibilidad cognitiva en pacientes con TJ podría constituir un predictor de abandono del tratamiento y de una mayor probabilidad de presentar recaídas (56). Por todo ello, algunos autores han propuesto el desarrollo de abordajes específicos en función del perfil neuropsicológico con el fin de ofrecer intervenciones individualizadas que puedan mejorar la eficacia del tratamiento (57,58).

1.2.3. Adicción a la comida (*Food Addiction*)

1.2.3.1. Definición y criterios diagnósticos

La obesidad es un problema de salud pública grave y extendido en sociedades muy diversas en todo el mundo. El constante aumento de la prevalencia de esta patología a lo largo de las últimas décadas ha hecho que se estudien las razones por las que algunas personas consumen ciertos alimentos en exceso de forma crónica y son incapaces de limitar su ingesta pese al desarrollo de consecuencias negativas evidentes.

Cada vez existe una mayor evidencia clínica y neurobiológica que demuestra que, en sujetos vulnerables, la sobrealimentación persistente puede conducir a un patrón de comportamiento compulsivo similar al de los TUS y otros trastornos adictivos. Este hecho condujo a la formulación del constructo de adicción a la comida o, por su nombre en inglés, *Food Addiction* (FA). Pese a no estar actualmente reconocido como diagnóstico en las principales clasificaciones internacionales, su estudio ha ido cobrando mayor interés por parte de la comunidad científica durante los últimos años, centrándose principalmente en aspectos neurobiológicos y fenomenológicos de esta entidad (59).

La definición de este trastorno se ha desarrollado en base a conductas y experiencias subjetivas relacionadas con el consumo de alimentos que se asemejan a los criterios del TUS (60). De esta forma, en 2009 se establecieron unos criterios diagnósticos y se desarrolló un instrumento, la *Yale Food Addiction Scale*, un cuestionario autorreportado que consta de 35 ítems que adapta los criterios diagnósticos de dependencia de sustancias del DSM IV-TR a la conducta alimentaria o al abuso de algunos alimentos específicos (61). En los últimos años este instrumento ha sido actualizado, surgiendo la *Yale Food Addiction Scale 2.0* (YFAS 2.0) para ajustarse a los criterios diagnósticos de los TUS según el DSM-5 (62). Siguiendo este instrumento, el cumplimiento de dos o más criterios (de un total de 11), unido a un deterioro funcional o malestar clínicamente significativo, serían indicadores de FA.

Los ítems de la escala YFAS 2.0, traducida y validada al español se detallan a continuación (63):

Tabla 2. Criterios evaluados en la escala YFAS 2.0

Consumo superior al previsto
Incapacidad para reducir el consumo
Pérdida de tiempo significativa
Renuncia a actividades importantes
Consumo a pesar de los efectos físicos o emocionales negativos
Tolerancia
Abstinencia
Craving
Incumplimiento de obligaciones
Consumo a pesar de los efectos interpersonales negativos
Consumo en situaciones físicamente peligrosas
Malestar o deterioro funcional

Nota. Elaboración propia

Cabe señalar que no todos los alimentos tienen el mismo potencial adictivo. En este sentido, la escala YFAS 2.0 se centra en evaluar la ingesta de alimentos con niveles elevados de carbohidratos refinados y/o grasas añadidas, como golosinas o aperitivos salados (64). Este tipo de alimentos es el que se ha relacionado de forma más sólida con conductas indicadoras de una potencial adicción, como pueden ser un consumo excesivo o la pérdida de control sobre el mismo (65–67).

1.2.3.2. Epidemiología

Meta-análisis recientes en los que se incluyeron hasta 281 estudios de 36 países diferentes reportan una prevalencia poblacional de FA de 14% en adultos y de 12% en población infanto-juvenil (68,69).

En pacientes con obesidad que han sido intervenidos mediante cirugía bariátrica los estudios apuntan una prevalencia de hasta el 32% (70) y, en el caso de individuos con trastorno por atracón, la comorbilidad con FA se eleva hasta el 50% (68). En este sentido, algunos autores han expresado su preocupación por el mencionado solapamiento diagnóstico entre el trastorno por atracón, un TCA caracterizado por episodios recurrentes de atracones en ausencia de conductas compensatorias, y FA. En esta línea, un meta-análisis reciente demuestra que, si bien la presencia de FA en pacientes con trastorno por atracón es elevada, aún lo es más en otros TCA como la BN, y también se observa en sujetos sanos. Los autores el mencionado estudio defienden que dichos resultados apoyan la idea de que se trata de entidades separadas, que reflejan situaciones clínicas diferentes (71).

1.2.3.3. Aspectos neurobiológicos

La conceptualización de la FA como un potencial trastorno adictivo no se justifica únicamente por los aspectos clínicos comunes descritos previamente, sino que viene respaldada por evidencia en cuanto a mecanismos neurobiológicos compartidos entre situaciones de obesidad / consumo excesivo de alimentos con los hallados en individuos con TUS u otras adicciones.

Actualmente los modelos más extendidos en cuanto a la neurobiología de la adicción defienden que durante la fase de intoxicación existe un aumento de la transmisión dopaminérgica y péptidos opioides que median la sensación de placer a nivel de núcleo accumbens y el estridado dorsal (72). En este sentido, hay estudios que demuestran que dichos sistemas de señalización también se activan en relación a la ingesta de alimentos (72). En otras palabras, tanto las sustancias de abuso como la comida activan el sistema de recompensa do-

paminérgico, aunque a través de mecanismos diferentes, y por ello en ambas situaciones existe la posibilidad de que surja un proceso de condicionamiento a través del cual, estímulos previamente neutros se asocien con estímulos gratificantes y acaben convirtiéndose en independientes de las conductas asociadas a la recompensa, dando lugar a conductas propias de trastornos adictivos (73).

Como se ha comentado previamente, algunos alimentos, en concreto aquellos ricos en carbohidratos refinados y/o grasas añadidas, habitual en productos ultra-procesados, tienen un mayor potencial adictivo. A nivel neurobiológico, algunos autores defienden que esta realidad clínica se puede explicar por la mayor capacidad de este conjunto de alimentos de provocar un aumento de niveles de dopamina extracelular en el estriado ventral, similar al que se observa en el consumo de otras sustancias adictivas como la nicotina y el alcohol (67,74–76).

Más allá del contenido de los alimentos, se ha propuesto que la elevada velocidad a la cual estos alimentos ultra-procesados hacen llegar los hidratos de carbono y las grasas al sistema digestivo y al cerebro también puede ser relevante para explicar su potencial adictivo (77). Ello viene justificado por la experiencia en TUS, donde es conocido que las sustancias y vías de administración que afectan más rápidamente al cerebro tienen una mayor capacidad de provocar trastornos adictivos (78).

En esta línea de aspectos neurobiológicos compartidos entre FA y TUS, numerosos estudios de neuroimagen funcional y estructural han dilucidado similitudes neurobiológicas entre las adicciones a sustancias y la obesidad (73). En comparación con los individuos sanos, los sujetos con obesidad o TUS muestran diferencias en regiones cerebrales implicadas en el sistema de recompensa y en la atención (79,80). En este sentido, trabajos previos revelan que una mayor respuesta a estímulos relacionados con alimentos en dichas regiones tiene capacidad predictiva de un futuro aumento de peso (81). Además, estudios de neuroimagen funcional realizados en situación de reposo muestran diferencias de conectividad, principalmente entre regiones de recompensa y áreas prefrontales, entre personas con obesidad y sujetos sanos (82). Por

último, estudios con resonancia magnética estructural muestran reducciones en los volúmenes de materia gris y blanca en regiones cerebrales implicadas en funciones ejecutivas y el control inhibitorio en estos individuos (83,84).

1.2.3.4. Comorbilidad con Trastorno de Juego

Dado que tanto FA como TJ son trastornos adictivos, el estudio de su comorbilidad y aspectos clínicos y neurobiológicos compartidos ha atraído la atención de diversos investigadores (85). Se han descrito características comunes a ambas entidades, como dificultades para el control conductual y un deterioro en funciones ejecutivas (86). Por otro lado, tanto en FA como en TJ se ha descrito una mayor dificultad en la regulación emocional, que, en algunos casos, podría conducir a la sobreingesta alimentaria o la conducta de juego como forma de paliar el malestar emocional (87). Además, como trastornos dentro del espectro impulsivo-compulsivo, la impulsividad se ha asociado con el desarrollo y mantenimiento de ambas entidades, en los que es habitual observar una incursión en las conductas problema (ya sea comer o jugar) de forma poco premeditada y a pesar de la aparición de consecuencias negativas (como pueden ser el aumento de peso o la pérdida de recursos económicos) (88).

Sin embargo, pese a compartir aspectos comunes, también se han discreto diferencias entre ambos trastornos. Por ejemplo, el TJ es más frecuente en hombres (89), mientras que FA lo es en mujeres (90). Se ha propuesto que las mujeres podrían ser más propensas a adoptar conductas adictivas y a ingerir de forma excesiva alimentos por motivaciones de refuerzo negativo que incluyen el afrontamiento del estrés, la depresión y la ansiedad (91).

Aunque estas dos entidades clínicas han comenzado a estudiarse conjuntamente durante los últimos años, las probables diferencias por sexo, los rasgos de personalidad y la psicopatología general apenas se han investigado en individuos con TJ con y sin FA. En un estudio previo, la comorbilidad entre FA y TJ se relacionó con peores estados emocionales y psicológicos. Además, el sexo femenino y tener una edad más joven fueron los dos condicionantes más robustamente asociados a la coocurrencia de FA y TJ. En cuanto a los rasgos

de personalidad, puntuaciones elevadas en evitación del daño y autotrascendencia, así como puntuaciones inferiores en cooperatividad, se asociaron con un mayor riesgo de presentar FA entre las personas con TJ. Sin embargo, los autores no encontraron diferencias significativas en la edad de inicio, la duración de los problemas de juego o el consumo de drogas, entre otros, entre participantes con TJ y aquellos con FA comórbida (85).

1.3. NEUROBIOLOGÍA DEL ESPECTRO IMPULSIVO-COMPULSIVO

Como se ha comentado previamente, la propuesta de englobar distintos trastornos dentro del espectro impulsivo-compulsivo nace, en parte, ante la evidencia que respalda alteraciones a nivel neurobiológicas comunes a entidades como los TCA, TUS, TJ o TOC (8,92). El desarrollo de la neuroimagen funcional y estructural de las últimas décadas ha permitido profundizar en el estudio de dichas alteraciones neurobiológicas compartidas. Dentro de los diversos sistemas y estructuras cerebrales explorados, uno ha emergido como foco de mayor interés para la comunidad científica por su implicación en procesos relacionados con la compulsividad y la impulsividad, así como por la evidencia de su implicación en este conjunto de trastornos: el sistema de recompensa cerebral.

1.3.1 Sistema de recompensa

El sistema de recompensa es el conjunto de estructuras cerebrales que se encargan de reforzar positivamente, a través principalmente de vías de neurotransmisión dopaminérgicas y mediando la sensación de placer, conductas necesarias para la supervivencia en respuesta a determinados estímulos. Este circuito incluye estructuras como el área tegmental ventral (principal implicada en la producción y transmisión proyectada de dopamina), el estriado ventral (lugar de proyección del área tegmental ventral) y otras zonas como el córtex prefrontal ventromedial y el córtex orbitofrontal, que forman parte de las vías mesocorticales.

El estriado ventral, concretamente el núcleo accumbens, contribuye de forma importante al procesamiento de recompensa, activándose ante la anticipa-

ción y recepción de distintos tipos de estímulos. Además, también participa en procesos de aprendizaje (en muchas ocasiones alterados en trastornos del espectro impulsivo-compulsivo). En esta línea, múltiples estudios de neuroimagen han mostrado alteraciones a nivel del estriado ventral en entidades como adicciones comportamentales, TUS o TCA. Teniendo esto en cuenta, y a la luz de los resultados de un interesante meta-análisis en el que se reportó una disminución relativa de la activación del estriado ventral durante la anticipación a la recompensas tanto en TJ como en TUS (93), se ha sugerido que el nivel de activación del estriado ventral podría ser un biomarcador relevante en diferentes trastornos del espectro impulsivo-compulsivo (9,94).

El estriado proyecta a regiones del córtex prefrontal, en concreto al córtex prefrontal ventromedial, estructura clave en la toma de decisiones relacionadas con la recompensa. Existe una robusta evidencia de la implicación de alteraciones neuroanatómicas y funcionales de este circuito cerebral en trastornos adictivos como el TJ. En este sentido, estudios de neuroimagen han demostrado una disminución relativa de la actividad en circuitos frontoestriatales en diversos escenarios (como durante la simulación de juego o en la anticipación de la recompensa) en individuos con trastornos como el TUS y el TJ (95–97).

1.3.2 Sistema de regulación del apetito

Diversos factores endocrinos han sido implicados en la respuesta cerebral a la recompensa y la gratificación (98,99), incluidas ciertas hormonas gástricas (por ejemplo, la grelina) y las adipocitoquinas (por ejemplo, la leptina y la adiponectina) (100,101), clásicamente asociadas con la regulación de la ingesta de alimentos y el equilibrio energético (102). El mecanismo mediante el cual dichos factores neuroendocrinos ejercen su efecto de modulación sobre las vías dopaminérgicas mesolímbicas y mesocorticales implicadas en el procesamiento de la recompensa es complejo y variado. Por ejemplo, estudios previos sugieren que cambios en el estado nutricional modulan la actividad de las células dopaminérgicas del área tegmental ventral y la liberación de dopamina de estas células al núcleo accumbens. De esta forma, existe evidencia que apoya una disminución de la señalización dopaminérgica en situaciones de exposi-

ción crónica a dietas ricas en grasas y un aumento de la misma en situación de restricción alimentaria (103,104). A continuación, se detallan individualmente las hormonas reguladoras del apetito analizadas en los estudios que componen el presente trabajo.

1.3.2.1 Leptina

Descubierta en 1994, la leptina es una hormona peptídica de 167 aminoácidos derivada principalmente por los adipocitos, que actúa como un importante regulador de la ingesta de alimentos y la homeostasis energética. Otros tejidos, como las células endocrinas del sistema gastrointestinal, músculo e hipotálamo también expresan leptina y sus concentraciones plasmáticas están altamente correlacionadas con el índice de masa corporal (IMC) tanto en humanos como en modelos animales (105). Su función principal es la de reducir la ingesta energética suprimiendo el apetito en situaciones en los que el balance energético del organismo así lo requiere. La leptina atraviesa la barrera hematoencefálica por medio de transporte saturado y produce su efecto central a través de la activación de receptores en a nivel hipotalámico, principalmente en su núcleo arqueado. La leptina ejerce su acción anorexigénica por un lado a través de la inhibición de la liberación de neuropeptido Y (NPY), y, por otro, estimulando la secreción de melanocortina, con acción catabólica y anorexígena (106).

En condiciones fisiológicas existe una relación entre la cantidad de tejido adiposo del individuo y la producción de leptina, por lo que sus concentraciones plasmáticas se correlacionan con el IMC, siendo más elevadas en mujeres que en hombres (106). Sin embargo, se ha observado que en situación de sobrepeso existe una elevación significativa de los niveles de leptina, lo que ha llevado a describir el fenómeno de resistencia a la leptina (107). Este escenario implicaría una disfunción en la señalización de leptina, que podría ocurrir a través de diversos mecanismos moleculares, y que implicaría una incapacidad de dicha hormona para ejercer su función fisiológica a través de la activación de sus receptores hipotalámicos y una consecuente elevación de sus concentraciones plasmáticas (108).

Dado que la leptina regula el sistema de recompensa en el cerebro mediante la supresión de la actividad neural posprandial, se ha estudiado en relación a la impulsividad y en trastornos adictivos (109,110). En estudios previos, concentraciones plasmáticas de leptina se han correlacionado inversamente con la gravedad del consumo de sustancias (111), llegándose a proponer como un posible biomarcador en los TUS relacionados con el alcohol y la cocaína (101,112). Sin embargo, los estudios sobre su papel en el consumo de alcohol muestran resultados algo inconsistentes, ya que también hay estudios que describen concentraciones de leptina más elevadas en individuos con trastorno por consumo de alcohol que en controles sanos, asociándose positivamente con la ingesta de alcohol (113).

1.3.2.2 Adiponectina

Se trata de una adipocitoquina descubierta en 1995, compuesta por 244 aminoácidos, secretada por los adipocitos y que, al igual que la leptina, regula el metabolismo energético del organismo. Actúa a través de la estimulación de la oxidación de ácidos grasos, reduce los triglicéridos plasmáticos y mejora el metabolismo de la glucosa mediante un aumento de la sensibilidad a la insulina (114). Múltiples estudios demuestran que tanto la obesidad como la resistencia a la insulina se relacionan con concentraciones plasmáticas de adiponectina reducidas. Es por ello que esta hormona ha atraído la atención de la comunidad científica desde su descubrimiento, principalmente por su papel como biomarcador de enfermedad metabólica (114,115).

A pesar de que hay menos estudios relacionados con la adiponectina y las adicciones, se han descrito concentraciones séricas disminuidas en la obesidad con y sin trastornos alimentarios y en el trastorno por consumo de opiáceos (116,117). La adiponectina también se ha propuesto como biomarcador del *craving*, al igual que la grelina, en el trastorno por consumo de alcohol (118).

1.3.2.3 Grelina

La grelina es una hormona peptídica de 28 aminoácidos identificada en 1999 como el ligando endógeno del receptor secretagogo de la hormona de crecimiento (GHS-R1a). Tiene la función de estimular el apetito, que ejerce aumentado la liberación de péptidos orexigénicos como el NPY en el núcleo arqueado del hipotálamo (108,119). Presenta una relación inversa con el IMC y es secretada principalmente por células endocrinas del estómago, si bien también se produce, aunque en menor cantidad, en tejido intestinal, hipófisis, placenta y páncreas. Las concentraciones plasmáticas de grelina varían en función del estado energético del organismo, se elevan en situación de ayuno y se reducen en la etapa posprandial (119). Además de su función estimulante del apetito, tiene otras muchas funciones como la regulación del sistema cardiovascular modulando la biodisponibilidad de óxido nítrico a nivel endotelial, así como efectos antiinflamatorios que ejerce a través de la inhibición de células T cooperadoras tipo 1 y la secreción de citoquinas proinflamatorias como la interleuquina 6 (108,120,121).

Sin embargo, su efecto más relevante para el presente trabajo es su papel en procesos psicológicos vinculados con el procesamiento de la recompensa, por su acción sobre el sistema dopaminérgico en el área tegmental ventral, donde GHS-R1a se encuentra ampliamente distribuido, estimulando la liberación de dopamina (120,122). La grelina se ha descrito como un reforzador neural hedónico tanto para recompensas naturales (por ejemplo, la comida) como para no naturales (por ejemplo, sustancias de abuso) por su interacción con la dopamina en el circuito mesolímbico y otras vías neuroendocrinas (p. ej., relacionadas con el estrés, el apetito y el procesamiento metabólico) (123). Esta hormona se ha estudiado en diferentes trastornos del espectro impulsivo-compulsivo, como el trastorno por atracón (124) así como en trastornos adictivos (125), especialmente en relación con el consumo de alcohol (126,127). En este sentido, se ha descrito un aumento de la señalización de grelina en los TUS, que se correlaciona positivamente con el deseo de consumo, la abstinencia y las recaídas (127). Además, existe evidencia que apoya la idea de que la administración exógena de grelina aumenta el *craving* y el consumo de sustancias (128), y que

la administración exógena de antagonistas de receptores de grelina producen el efecto contrario (129). Por último, alteraciones genéticas relacionadas con el sistema de la grelina, como polimorfismos de su receptor, se han asociado con comportamientos de búsqueda de recompensa y consumo (130).

1.3.2.4 LEAP-2

Se trata de un antagonista de la función de la grelina descrito recientemente, denominado péptido antimicrobiano hepático enriquecido 2 (LEAP-2) (131,132). Durante muchos años la grelina fue el único ligando endógeno conocido de GHS-R1a, hasta que 2018 Ge y colaboradores describieron LEAP-2 y demostraron que ejercía una función de antagonismo de dicho receptor (131). De esta forma, actualmente se considera que la actividad de GHS-R1a está controlada por dos ligandos endógenos reguladores que ejercen funciones opuestas: la grelina (función activadora) y LEAP-2 (inhibidora). En cuanto a sus funciones biológicas, poco tiempo después se demostró que las concentraciones plasmáticas de LEAP-2 fluctuaban de forma opuesta a las de la grelina en función del estado metabólico, y que se correlacionaba positivamente con el IMC (133). Desde dicho hallazgo este nuevo factor neuroendocrino se ha considerado como una señal reguladora de la homeostasis energética y se ha propuesto que pueda jugar un papel como supresor del apetito. Es por ello que ha despertado el interés de diversos autores durante los últimos años, especialmente por ser una posible diana terapéutica en el tratamiento de la obesidad (134). Sin embargo, aún es pronto para ponderar su posible efecto en esta patología, y su uso farmacológico podría encontrarse con obstáculos como los potenciales efectos adversos de inhibir la secreción de GH.

Cabe señalar que si bien existe poca evidencia al respecto, a nivel neuropsicológico se ha relacionado con la impulsividad y con el funcionamiento cognitivo (135), y es por ello que podría contribuir a disrupciones neurobiológicas relacionadas con la patogenia de las adicciones, especialmente teniendo en cuenta su interacción con la señalización de la grelina.

1.3.3 Alteraciones neuroendocrinas en Trastorno de Juego

La evidencia sobre la implicación de factores endocrinos en adicciones a sustancias ha impulsado algunos estudios en el campo de las adicciones comportamentales en los últimos años. En TJ, un estudio de Sztainert y colaboradores sugiere que la grelina puede predecir el deseo de jugar y la persistencia en el juego (136). Un único estudio que exploró las concentraciones de leptina en TJ no encontró diferencias significativas en comparación con las de controles sanos (137). Hasta la fecha no se han publicado estudios que analicen el papel de la adiponectina ni LEAP-2 en adicciones comportamentales. Queda patente, ante la escasa evidencia en cuanto a la implicación de factores neuroendocrinos en adicciones conductuales como el TJ, que es necesario intensificar la investigación en este ámbito, para profundizar en posibles procesos etiopatogénicos y eventualmente abordar la posibilidad de identificar dianas terapéuticas y marcadores biológicos de estos trastornos.

1.3.4 Alteraciones neuroendocrinas en *Food Addiction*

En cuanto a los correlatos neurobiológicos de FA, estudios previos han explorado posibles alteraciones endocrinas en la patogénesis de este trastorno (138). Por su función reguladora del apetito, se ha propuesto que tanto la grelina como la leptina podrían desempeñar un papel importante en FA (139).

Por un lado, la señalización de grelina se ha descrito como un regulador clave de la obesidad, y las concentraciones más altas se han asociado con un mayor deseo y consumo de alimentos (140). Sin embargo, y a pesar de que hasta la fecha existen pocos estudios que hayan analizado específicamente la asociación entre FA y grelina, la mayoría de ellos reportan resultados negativos (141,142).

Por otro, se ha planteado la hipótesis de que las concentraciones más altas de leptina en ayunas pueden subyacer a la ingesta excesiva de alimentos y desembocar en conductas compatibles con FA (143). En esta línea, FA se ha asociado con menores concentraciones de leptina en adolescentes con normopeso, y con concentraciones superiores de leptina en individuos con sobrepeso

(144). Los autores de este último estudio plantearon la hipótesis de que la asociación negativa entre las concentraciones de leptina y FA en condiciones de normopeso podría explicarse por una mayor sensación de hambre y una mayor propensión a comer en exceso en estos individuos, lo que podría haber llevado a una mayor gravedad de FA. En individuos con sobrepeso, las altas concentraciones circulantes de leptina pueden reflejar una situación de resistencia a la leptina, en la que el fracaso de la supresión de la ingesta de alimentos inducida por leptina puede conducir al desarrollo de conductas de alimentación compulsiva, compatibles con la definición de FA (116,144).

Es muy interesante resaltar que un estudio reciente aborda por primera vez, hasta la fecha, el análisis de la asociación de concentraciones plasmáticas tanto de leptina como de grelina con la presencia de FA, en una muestra amplia de más de 900 individuos. Los resultados concuerdan con la evidencia previa y sugieren un aumento de niveles de leptina y una ausencia de diferencias en cuanto a concentraciones de grelina, en los sujetos con FA (145).

1.4. Fundamentación de los estudios realizados

Los trastornos del espectro impulsivo-compulsivo, y en concreto las adicciones, son trastornos complejos en cuyo desarrollo y mantenimiento interaccionan factores psicosociales de distinta naturaleza con aspectos de vulnerabilidad neurobiológica. Pese a los grandes esfuerzos realizados a nivel de investigación translacional, hasta la fecha no disponemos de biomarcadores útiles para identificar, en la práctica clínica habitual, aquellos individuos con una mayor predisposición a desarrollar el trastorno. Es por ello que profundizar en el estudio de aspectos neurobiológicos relacionados con estos trastornos, y en concreto con el TJ y FA, supone un reto imprescindible de cara a conocer mejor sus bases biológicas y avanzar hacia el desarrollo de biomarcadores y potenciales dianas terapéuticas que puedan tener un impacto en estos pacientes.

En este contexto y en base a la evidencia disponible en la actualidad, queda patente que la interacción de factores neuroendocrinos relacionados con la regulación del apetito con el sistema de recompensa cerebral juega un papel en

algunos trastornos adictivos como los TUS, si bien su implicación en adicciones conductuales como el TJ u otros constructos como FA no está plenamente contrastada. Además, la posible implicación de dicha interacción en el desarrollo de aspectos clínicos y neuropsicológicos es desconocida. Teniendo esto en cuenta, la principal motivación del presente trabajo es la de avanzar en el conocimiento sobre la posible implicación de alteraciones neuroendocrinas en relación a hormonas reguladoras del apetito y su interacción con variables clínicas y neuropsicológicas en el TJ, así como analizar la comorbilidad de dicho trastorno con FA, tanto a nivel clínico como neurobiológico.

2

HIPÓTESIS

HIPÓTESIS

1. Existirán diferencias significativas en las concentraciones plasmáticas de hormonas reguladoras del apetito entre pacientes con trastorno de juego y sujetos sanos. (Estudio 1)

2. Los pacientes con TJ presentarán una mayor psicopatología, un peor rendimiento neuropsicológico y un perfil de personalidad más disfuncional en comparación con sujetos sanos. (Estudio 1)

3. Las características clínicas y neuropsicológicas diferenciales de los individuos con TJ, en comparación con sujetos sanos, estarán relacionadas con las alteraciones endocrinas. (Estudio 1)

4. Los pacientes con TJ y FA presentarán diferencias significativas en las concentraciones plasmáticas de hormonas reguladoras del apetito en comparación con los que no presenten FA. (Estudio 2)

5. Los niveles de las hormonas alterados en los pacientes con TJ y FA correlacionarán con un peor rendimiento cognitivo y con medidas de impulsividad. (Estudio 2)

6. La presencia de FA, entre los pacientes con TJ, se asociará a un peor perfil clínico, mayor psicopatología y mayor gravedad del trastorno. (Estudio 3)

7. Existirá una mayor frecuencia de FA entre las mujeres (frente a los hombres) con TJ. (Estudio 3)

3

OBJETIVOS

OBJETIVOS

1. Explorar y comparar las concentraciones plasmáticas de hormonas reguladoras del apetito (leptina, grelina, adiponectina y LEAP-2) entre pacientes con trastorno de juego y sujetos sanos. (Estudio 1)

2. Analizar las correlaciones entre factores endocrinos y aspectos neuropsicológicos y clínicos en trastorno de juego. (Estudio 1)

3. Explorar la existencia de diferencias en las concentraciones plasmáticas de las hormonas implicadas en la regulación del apetito (grelina, LEAP-2, adiponectina y leptina), en una muestra de pacientes diagnosticados de TJ con y sin FA. (Estudio 2)

4. Explorar las correlaciones entre los niveles de las hormonas implicadas en TJ y FA y las variables clínicas y psicológicas en el subgrupo con FA. (Estudio 2)

5. Evaluar los correlatos clínicos de FA en pacientes con TJ, teniendo en cuenta rasgos de personalidad, el estado psicológico o el consumo de sustancias y en función del sexo. (Estudio 3)

4

MATERIAL, MÉTODOS Y RESULTADOS

MATERIAL, MÉTODOS Y RESULTADOS

4.1. Estudio 1

Título del artículo: ¿Están relacionadas las señales que regulan la homeostasis energética con las características neuropsicológicas y clínicas del trastorno de juego? Un estudio caso-control.

Resumen:

Introducción: El trastorno de juego (TJ) es una enfermedad grave y de prevalencia moderada cuya neurobiología aún no se conoce por completo. A pesar de que se han estudiado posibles alteraciones de las señales implicadas en la homeostasis energética en trastornos por consumo de sustancias, aún no se han examinado en detalle en el TJ.

Objetivos: Los objetivos del presente estudio fueron comparar diferentes factores endocrinos y neuropsicológicos entre individuos con TJ y controles sanos (CS) y explorar las interacciones endocrinas con variables neuropsicológicas y clínicas.

Métodos: Se llevó a cabo un estudio con diseño de casos y controles en 297 individuos con TJ y 41 individuos sin TJ (controles sanos; CS). Los participantes fueron evaluados mediante una entrevista clínica semiestructurada y una batería psicométrica. Para la evaluación de variables endocrinas y antropométricas, se añadieron 38 CS a los 41 evaluados inicialmente.

Resultados: Los individuos con TJ presentaron mayores concentraciones plasmáticas de grelina en ayunas ($p < 0,001$) y menores concentraciones de LEAP-2 y adiponectina ($p < 0,001$) que los CS, tras ajustar por el índice de masa corporal (IMC). El grupo con TJ presentó un rendimiento neuropsicológico más bajo en relación a la flexibilidad cognitiva y la toma de decisiones, así como un peor estado psicológico, mayores niveles de impulsividad y un perfil de personalidad más disfuncional. A pesar de no encontrar asociaciones significativas entre los

factores endocrinos y aspectos neuropsicológicos o clínicos en el grupo de TJ, algunas dimensiones cognitivas deterioradas (la prueba de vocabulario WAIS y los errores perseverativos WCST) y las concentraciones más bajas de LEAP-2 predijeron estadísticamente la presencia de TJ.

Discusión: Los hallazgos del presente estudio sugieren que disfunciones neuropsicológicas y endocrinas concretas pueden jugar un papel en individuos con TJ, así como predecir la presencia de TJ. En este contexto, parece justificada una mayor exploración de las vías de vulnerabilidad endofenotípica en TJ, especialmente por su potencial implicación a nivel etiopatogénico y terapéutico.

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Article

Are Signals Regulating Energy Homeostasis Related to Neuropsychological and Clinical Features of Gambling Disorder? A Case–Control Study

Mikel Etxandi [1,2,†], Isabel Baenas [1,3,4,†], Bernat Mora-Maltas [1,4], Roser Granero [3,4,5], Fernando Fernández-Aranda [1,3,4,6], Sulay Tovar [3,7], Neus Solé-Morata [1,4], Ignacio Lucas [1,4], Sabela Casado [3,7], Mónica Gómez-Peña [1,4], Laura Moragas [1,4], Amparo del Pino-Gutiérrez [3,4,8], Ester Codina [1], Eduardo Valenciano-Mendoza [1], Marc N. Potenza [9,10,11,12,13], Carlos Diéguez [3,7] and Susana Jiménez-Murcia [1,3,4,6,*]

1 Department of Psychiatry, Bellvitge University Hospital-Bellvitge Institute for Biomedical Research (IDIBELL), 08907 Barcelona, Spain
2 Department of Psychiatry, Hospital Universitari Germans Trias i Pujol, IGTP Campus Can Ruti, 08916 Badalona, Spain
3 Ciber Fisiopatología Obesidad y Nutrición (CIBERObn), Instituto de Salud Carlos III, 28029 Madrid, Spain
4 Psychoneurobiology of Eating and Addictive Behaviors Group, Neurosciences Programme, Bellvitge Institute for Biomedical Research (IDIBELL), 08908 Barcelona, Spain
5 Department of Psychobiology and Methodology, Autonomous University of Barcelona, 08193 Barcelona, Spain
6 Department of Clinical Sciences, School of Medicine and Health Sciences, University of Barcelona, 08907 Barcelona, Spain
7 Department of Physiology, CIMUS, Instituto de Investigación Sanitaria, University of Santiago de Compostela, 15782 Santiago de Compostela, Spain
8 Department of Public Health, Mental Health and Perinatal Nursing, School of Nursing, University of Barcelona, 08907 Barcelona, Spain
9 Department of Psychiatry, Yale University School of Medicine, New Haven, CT 06510, USA
10 Child Study Center, Yale University School of Medicine, New Haven, CT 06510, USA
11 Connecticut Mental Health Center, New Haven, CT 06519, USA
12 Connecticut Council on Problem Gambling, Wethersfield, CT 06106, USA
13 Department of Neuroscience, Yale University, New Haven, CT 06520, USA
* Correspondence: sjimenez@bellvitgehospital.cat
† These authors contributed equally to this work.

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Abstract: Gambling disorder (GD) is a modestly prevalent and severe condition for which neurobiology is not yet fully understood. Although alterations in signals involved in energy homeostasis have been studied in substance use disorders, they have yet to be examined in detail in GD. The aims of the present study were to compare different endocrine and neuropsychological factors between individuals with GD and healthy controls (HC) and to explore endocrine interactions with neuropsychological and clinical variables. A case–control design was performed in 297 individuals with GD and 41 individuals without (healthy controls; HCs), assessed through a semi-structured clinical interview and a psychometric battery. For the evaluation of endocrine and anthropometric variables, 38 HCs were added to the 41 HCs initially evaluated. Individuals with GD presented higher fasting plasma ghrelin ($p < 0.001$) and lower LEAP2 and adiponectin concentrations ($p < 0.001$) than HCs, after adjusting for body mass index (BMI). The GD group reported higher cognitive impairment regarding cognitive flexibility and decision-making strategies, a worse psychological state, higher impulsivity levels, and a more dysfunctional personality profile. Despite failing to find significant associations between endocrine factors and either neuropsychological or clinical aspects in the GD group, some impaired cognitive dimensions (i.e., WAIS Vocabulary test and WCST Perseverative errors) and lower LEAP2 concentrations statistically predicted GD presence. The findings from the present study suggest that distinctive neuropsychological and endocrine dysfunctions may operate in individuals with GD and predict GD presence. Further exploration of endophenotypic vulnerability pathways in GD appear warranted, especially with respect to etiological and therapeutic potentials.

Keywords: gambling disorder; addictive behavior; impulsive–compulsive behavior; gut hormones; adipocytokines; neuropsychology

1. Introduction

Gambling disorder (GD) has been classified as a behavioral addiction (BA) in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) [1], being characterized by recurrent maladaptive gambling behavior, leading to negative consequences in one or more areas of life functioning [2]. Diagnostic criteria include the need to gamble with increasing amounts of money (i.e., tolerance), the tendency to chase losses, irritability when attempting to stop the behavior (i.e., abstinence), the presence of unsuccessful efforts to control gambling behavior, a predominance of thoughts focused on the gambling behavior, the presence of lies or the loss of a significant relationship or job/educational opportunity because of gambling, and the propensity to gamble when feeling distressed or to rely on others to provide money to relieve desperate financial situations caused by gambling [1]. From an etiological perspective, neuroimaging, genetic, and biochemical studies have suggested shared vulnerability factors between addictive-related disorders, such as GD and substance use disorders (SUDs) [3,4]. For instance, dysfunctional neurobiological pathways involved in reward processing [5], which may underlie impulsive and compulsive tendencies, have been described [6].

Several endocrine factors have been implicated in brain responses to rewards and gratification [7,8] including gut hormones (e.g., ghrelin) and adipocytokines (e.g., leptin and adiponectin) [9,10], classically associated with food intake regulation and energy balance [11]. Despite its stimulating appetite role, ghrelin has been described as a hedonic neural reinforcer for natural (e.g., food) and non-natural rewards (e.g., drugs) by its interaction with dopamine signaling in the mesolimbic circuit and other neuroendocrine pathways (e.g., linked to stress, appetite, and metabolic processing) [12]. Ghrelin has been extensively studied in different addictive-related disorders, such as binge eating disorder (BED) and obesity [13,14], as well as in SUDs [15], especially involving alcohol [16,17].

Noticeably, ghrelin up-regulation has been described in SUDs, which positively correlates with craving, abstinence, and relapse [17–19]. Accordingly, exogenous ghrelin administration increases craving and drug consumption [9], contrary to ghrelin antagonists [20,21]. An antagonist of ghrelin named liver enriched antimicrobial peptide 2 (LEAP2) has been recently described [22,23]. It has been related to impulsivity and cognitive functioning [24] and may contribute to addictions due to its interplay with ghrelin. Furthermore, genetic alterations related to the ghrelin system, such as receptor polymorphisms, have been associated with reward-seeking behaviors and consumption [25], which together may have potential therapeutic implications [26,27]. In GD, a study by Sztainert et al. [28] suggests ghrelin as a potential predictor of gambling craving and persistence.

Adipocytokines have also been studied in relation to impulsivity [29] and addiction [30,31]. As in the case of regulation of food intake, opposite effects on craving and abstinence have been attributed to leptin compared with ghrelin [32]. Leptin concentrations have been inversely correlated with consumption severity [33], being proposed as a possible biomarker in SUDs involving alcohol and cocaine [10,34]. However, studies regarding alcohol consumption have shown inconsistent results [30], even describing higher leptin concentrations in individuals with alcohol use disorder than in HCs, positively associated with alcohol intake [30,34]. A single study exploring leptin concentrations in GD did not find significant differences compared with those in HCs [35]. Despite there are fewer studies related to adiponectin and addictions, decreased serum concentrations have been reported in obesity with and without eating disorders and in opioid use disorder [14,36]. Adiponectin has also been proposed as a biomarker of craving, like ghrelin, in alcohol use disorder [37]. Similar to other addictive-related disorders, these endocrine substrates represent potential candidates involved in the pathogenesis of BAs, such as GD [35]. However, this area remains underexplored in GD, and further research is needed.

Other neurobiological features linked to addictive-related disorders include impaired neuropsychological processes not only regarding executive functions, such as response inhibition, self-regulation, decision-making, cognitive flexibility, and planning but also working memory [38–42]. These cognitive functions have been described as core symptoms in BAs [39] and are especially related to impulse control [41]. More severe neuropsychological impairment has been described among older patients with GD and preferences for non-strategic gambling [41,43,44]. Neuropsychological impairment has statistically predicted poorer treatment outcome, with more frequent dropout and relapse [41,45].

Beyond neuropsychological factors, other psychological and clinical features have been implicated in the development of addictive disorders [46]. In GD, for example, certain personality traits such as high levels of novelty-seeking (related to impulsivity) and harm avoidance, especially in women [46,47], together with low self-directedness have been linked to both GD and SUDs [48,49]. Difficulties in emotion regulation and poorer psychological states have been linked to GD [50], particularly in women and older individuals with non-strategic gambling [43,44]. A more dysfunctional psychological profile has been associated with greater neuropsychological impairment [41,43,44]. However, studies have largely not explored relationships between different neurobiological features (i.e., endocrine, and neuropsychological factors) and psychological and clinical variables.

To the best of our knowledge, this is the first study that explores the roles of multiple specific signals implicated in addiction and energy homeostasis, meaning food intake and energy expenditure, and clinical and psychological measures among a clinical population with GD. We aimed to explore and compare plasma concentrations of specific metabolic hormones (i.e., leptin, ghrelin, adiponectin, and LEAP2) between patients with GD and HCs. As a second aim, we analyzed correlations between the mentioned endocrine factors and neuropsychological and clinical features. In line with previous literature in addictive disorders, we hypothesized the existence of significant differences in plasma hormonal concentrations between the GD and HC groups. We also hypothesized poorer cognitive functioning, worse psychopathological state, and a more dysfunctional personality profile among individuals with GD. These features were also hypothesized to be related to endocrine alterations, including being able to statistically predict GD presence.

2. Materials and Methods

2.1. Participants

The sample consisted of n = 297 treatment-seeking adult outpatients with GD (93.6% males) with a mean age of 39.58 years (SD = 14.16), voluntarily recruited at the Behavioral Addictions Unit-Psychiatry Department of Bellvitge University Hospital (Barcelona, Spain). As inclusion criteria, all the patients had a diagnosis of GD according to DSM-5 criteria [1]. The HC group was composed by 41 individuals without GD (90.2% males), with a mean age of 49.27 years (SD = 15.23) and was recruited via advertisement from the same catchment area. Regarding anthropometric and endocrine variables, 79 HCs were evaluated by adding to the initial sample 38 healthy adults from CIMUS, University of Santiago de Compostela (Santiago de Compostela, Spain). General exclusion criteria for all participants were the presence of an organic mental disorder, an intellectual disability, a neurodegenerative disorder (such as Parkinson's disease) or an active psychotic disorder. Recruitment of participants occurred from April 2018 to September 2021, and the evaluation of individuals with GD took place before starting treatment at the Behavioral Addictions Unit-Psychiatry Department of Bellvitge University Hospital (Barcelona, Spain).

Supplementary Materials Table S1 contains the complete description for the participants in the study.

2.2. Measures

2.2.1. Hormonal Assays

Endocrine variables were quantified from peripheral blood sample extraction by venous aspiration with ethylenediamine tetraacetic acid (EDTA; 25 mM final concentration),

all samples were collected at 9 am, after at least 8 h of fasting. The blood was centrifuged at 1700 *g* in a refrigerated centrifuge (4 °C) for 20 min. Plasma was immediately separated from serum and stored at −80 °C until analysis. Parameter determinations were conducted using commercial kits according to the manufacturer's instructions and in a single analysis to reduce inter-assay variability. The quantitative measurement of LEAP-2 in plasma was performed using a commercial enzyme-linked immunosorbent assay (ELISA) kit (Human LEAP-2 [37–76] ELISA kit, Phoenix Pharmaceuticals, Inc., Burlingame, CA, USA), previously validated [51,52]. Intra-assay and inter-assay variation coefficients were <10% and <15%, respectively. The assay sensitivity limit was 0.15 ng/mL. Total ghrelin (pg/mL) was measured by ELISA kit (Invitrogen-Thermo Fisher Scientific, Madrid, Spain) for detection of human ghrelin, with a specificity of 100%. Intra-assay variation coefficient was <6% and inter-assay <8.5%. The assay sensitivity limit was 11.8 pg/mL [53]. Adiponectin (ng/mL) and leptin (ng/mL) plasma measurements were performed using a solid-phase sandwich ELISA kit (Invitrogen-Thermo Fisher Scientific, Madrid, Spain) with a specificity of 100%. Intra-assay and inter-assay variation coefficients were <4% and <5%, respectively, and assay sensitivity limit was 100 pg/mL for adiponectin and <3.5 pg/mL for leptin. The absorbance from each sample was measured in duplicate using a spectrophotometric microplate reader at a wavelength of 450 nm (Epoch 2 microplate reader, Biotek Instruments, Inc., Winooski, VT, USA).

2.2.2. Neuropsychological Variables

Iowa Gambling Task (IGT) [54]. A computerized task to evaluate decision-making, risk, reward, and punishment value. The participant must select 100 cards from four decks (i.e., A, B, C, and D), and after each card selection, an output is given either a gain or a loss of money. The participant is instructed that the aim of the task is to win as much money as possible. 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. While decks A and B are not advantageous as the final loss is higher than the final gain, decks C and D are advantageous since the punishments are smaller. Higher scores point to better performance, while negative scores point to persistently choosing disadvantageous decks.

Wisconsin Card Sorting Test (WCST) [55] is a task for assessing cognitive flexibility and inhibitory control, composed of four stimulus cards and 128 response cards showing different shapes, colors, and numbers of figures in each one. The participant must match response cards with the stimulus cards in a way that it seems justifiable before receiving the feedback (i.e., correct, or incorrect). After ten sequential correct answers the categorization criteria changes. The number of complete categories, percentage of perseverative errors, and percentage of non-perseverative errors are recorded.

Stroop Color and Word Test (SCWT) [56] consists of three different lists, beginning with a word list containing the names of colors printed in black ink; then, a color list that comprises letter "X" printed in color; and, finally, a color-word list constituted of names of colors in a color ink that does not match the written name. Three final scores are obtained based on the number of items that the participant can read on naming on each list in 45 s. It assesses the ability to inhibit cognitive interference, which occurs when the processing of a stimulus feature affects the simultaneous processing of another attribute of the same stimulus.

Trail Making Test (TMT) [57] consists of 25 circles spread out over two sheets of paper (Parts A and B). The participant is told to connect these circles drawing a line between consecutive numbers (part A) and alternating numbers and letters following a sequential order (part B). The task assesses visual conceptual and visual-motor tracking, entailing motor speed, attention, and the capacity to alternate between cognitive categories (set-shifting). Each part is scored according to the spent time to complete the task.

Digits backward task of the Wechsler Memory Scale-Third Edition (WMS-III) [58] consists of two lists of digits presented verbally by the examiner. The participant is asked to repeat the digits in the same order (first list) and in reverse order (second list). It assesses

verbal working memory due to internal manipulation of mnemonic representations of verbal information that is required in the absence of external cues.

Vocabulary subtest of the Wechsler Adult Intelligence Scale, 3rd ed. (WAIS-III) [59] requires defining words of increasing difficulty orally presented, to assess the vocabulary expression and to estimate intellectual capacity [60].

2.2.3. Clinical Variables

South Oaks Gambling Screen (SOGS) [61], Spanish validation [62], is a 20-item instrument for screening past-year gambling problems and related negative consequences. The total score is a measure of problem-gambling severity, with a score of five or more suggestive of "probable pathological gambling". Its internal consistency in the study sample was Cronbach's alpha (α) = 0.735.

Diagnostic Questionnaire for Pathological Gambling According to DSM criteria [63], Spanish validation [64], is a self-report questionnaire with 19 items coded in a binary fashion (yes-no), used for diagnosing GD according to the DSM-IV-TR and DSM-5 criteria [1]. Its internal consistency in the study sample was α = 0.796.

Symptom Checklist-90-Revised (SCL-90-R) [65], Spanish validation [66], is a 90-item self-report questionnaire measured on an ordinal 3-point scale, evaluating a broad range of psychological problems and psychopathology, based on nine primary symptomatic dimensions (Somatization, Obsession–Compulsion, Interpersonal Sensitivity, Depression, Anxiety, Hostility, Phobic Anxiety, Paranoid Ideation, and Psychoticism). It includes three global indices (global severity index, positive symptom distress index, and total positive symptom). The internal consistency in the study was α = 0.979.

Temperament and Character Inventory-Revised (TCI-R) [67], Spanish validation [68], is a questionnaire with 240-items scored on a 5-point Likert scale, measuring personality derived from three character dimensions (Self-Directedness, Cooperativeness, and Self-Transcendence) and four temperament dimensions (Harm Avoidance, Novelty Seeking, Reward Dependence, and Persistence). It is used only for research purposes in a public non-profit hospital, in its Spanish adaptation in which the original author participated [68]. The internal consistency in the study was between α = 0.702 (Novelty Seeking) and α = 0.876 (Persistence).

Impulsive Behavior Scale (UPPS-P) [69], Spanish validation [70], measures five facets of impulsive behavior through self-report on 59 items: negative urgency; positive urgency; lack of premeditation; lack of perseverance; and sensation-seeking. The internal consistency in the study was between α = 0.799 (lack of perseverance) and α = 0.928 (positive urgency).

2.2.4. Other Variables

Additional data (e.g., socio-demographic, socio-economic, anthropometric variables, and GD-related characteristics) were collected in a semi-structured face-to-face clinical interview as described elsewhere [71].

2.3. Procedure

All patients and HCs from the same catchment area were evaluated at the Behavioral Addictions Unit-Psychiatry Department of Bellvitge University Hospital (Barcelona, Spain), by an expert multidisciplinary team in the field of GD. In the first session, a comprehensive semi-structured clinical interview was conducted, in which all aspects related to gambling behavior were assessed. During the second session, the extraction of blood samples occurred. Samples were analyzed in CIMUS, University of Santiago de Compostela (Santiago de Compostela, Spain), where 38 out of 79 HCs were evaluated regarding endocrine and anthropometric measures. The neuropsychological assessment was performed in a third session.

2.4. Statistical Analysis

The statistical analysis was conducted with Stata17 for Windows [72]. Comparison between groups (GD versus HC) were made by Analysis of Covariance (ANCOVA), adjusting for sex, age, and body mass index (BMI) for endocrine variables, and adjusting for sex, age, and education level for neuropsychological variables. The effect size for the mean comparisons was obtained with the standardized Cohen's-d, considering moderate-mild effect values $0.50 < |d| < 0.80$ and high-large effect values $|d| > 0.80$ [73].

Associations between endocrine and neuropsychological and clinical variables were estimated with partial correlation coefficients, adjusting for sex, age, and BMI (associations with the neuropsychological tasks also included adjustment for the education level). Due to strong associations between the null-significance test for the correlation models given the sample sizes (low correlations achieve significance in large samples, and vice versa), in this study mild-moderate correlation was considered for values $|R| > 0.24$ and high-large correlation for values $|R| > 0.37$ [74].

A predictive model was obtained to select the variables with discriminative capacity to identify the presence of GD, through logistic regression. The criterion for the modeling was the diagnosis of GD (presence/absence), and potential predictors included sociodemographic measures, global psychopathological distress, impulsivity levels, personality features, and neuropsychological and endocrine measures. A stepwise selection method was used to automatically select significant contributors. Sex, age, and BMI were included as adjustment/covariables. The goodness-of-fit was measured with the Hosmer–Lemeshow test, the overall predictive capacity with the Cox-Snell's pseudo-R2, and the overall discriminative capacity with the area under the Receiver Operating Curve (ROC).

In this study, the increase in the Type-I error due to the performance of multiple significance tests was controlled with the familywise error Finner's procedure, which has shown greater efficiency than the classic Bonferroni adjustment method [75].

3. Results

3.1. Comparison of Endocrine Measures

Adjusting for sex, age, and BMI, the GD group reported higher ghrelin and lower LEAP2 and adiponectin values compared with HCs (Table 1 and first panel of Figure 1). No differences were found regarding leptin values.

3.2. Comparison of Neuropsychological and Clinical Measures

ANCOVAs comparing the mean values of the neuropsychological measures and clinical variables are displayed in Table 2 (see also second panel of Figure 1). Compared to HCs, the GD group displayed worse performance on the WCST, WAIS-vocabulary test, and performance-learning curve during IGT performance (Figure 2). The GD group also reported worse psychopathological states (higher mean scores on the SCL-90 R), higher impulsivity (except on the UPPS-P sensation-seeking scale) and more dysfunctional personality profiles (except on the TCI-R persistence scale).

Table 1. Comparison of clinical characteristics via ANCOVA.

	Control (*N* = 79)		GD (*N* = 297)			
	Mean	**SD**	**Mean**	**SD**	***p***	**|d|**
1 Ghrelin (pg/mL)	544.92	673.59	958.48	753.26	**<0.001 ***	**0.58 †**
1 LEAP2 (ng/mL)	8.41	3.99	5.28	2.88	**<0.001 ***	**0.90 †**
1 Leptin (ng/mL)	9.00	8.13	8.18	7.85	0.402	0.10
1 Adiponectin (ng/mL)	12784.98	14084.20	8381.47	4374.29	**<0.001 ***	0.42
2 BMI (kg/m^2)	24.99	2.36	26.57	5.04	**0.005 ***	0.40

Note. GD: gambling disorder. LEAP2: liver enriched antimicrobial peptide 2. BMI: body mass index. SD: standard deviation. |d|: Cohen's-d coefficient. * Bold: significant comparison. 1 Adjustment by sex, age, and BMI. 2 Adjustment by sex and age. † Bold: effect size into the range mild-moderate ($|d| > 0.50$ and <0.80) to high-large ($|d| > 0.80$).

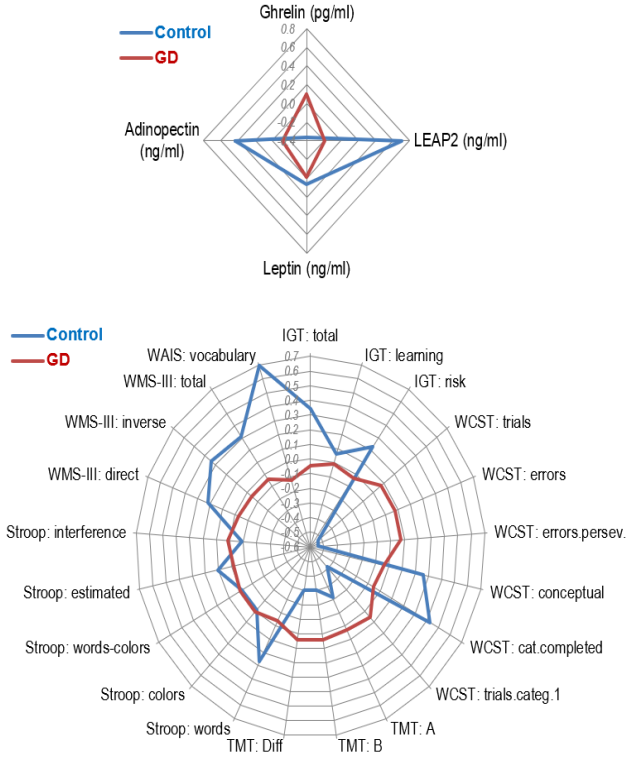

Figure 1. Radar-charts (z-standardized means are plotted). Note. GD: gambling disorder (n = 297). Control (n = 41). LEAP2: liver enriched antimicrobial peptide 2. IGT: Iowa Gambling Test. WCST: Wisconsin Card Sorting Test. TMT: Trail Making Test. WMS-III: Wechsler Memory Scale Third Edition. WAIS: Wechsler Adult Intelligence Scale. Due the different measurement scale for the variables in the graph, Z-standardized means are plotted to facilitate interpretation.

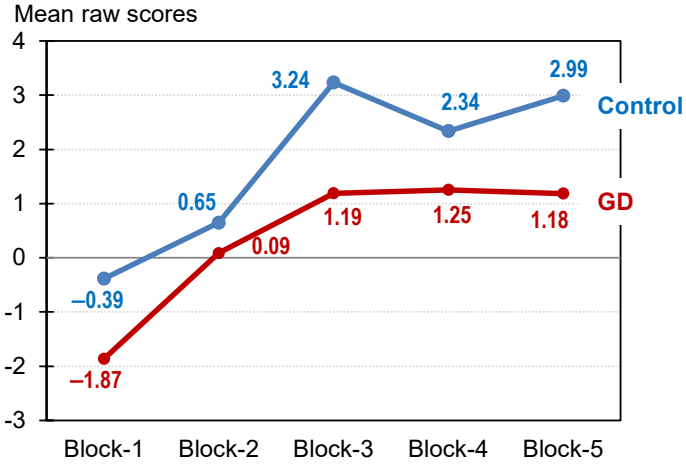

Figure 2. Performance-learning curve in the Iowa Gambling Test task. Note. GD: gambling disorder (n = 297). Control (n = 41).

Table 2. Comparison of the clinical characteristics via ANCOVA.

	Control (*N* = 41)		**GD (*N* = 297)**			
1 Neuropsychological Measures	Mean	SD	Mean	SD	*p*	|d|
IGT: block-1	−0.39	4.87	−1.87	5.16	0.115	0.30
IGT: block-2	0.65	5.87	0.09	5.52	0.583	0.10
IGT: block-3	3.24	9.50	1.19	6.97	0.126	0.25
IGT: block-4	2.34	9.85	1.25	7.46	0.446	0.12
IGT: block-5	2.99	8.33	1.18	8.56	0.249	0.21
IGT: total	8.88	28.10	2.10	21.94	0.104	0.27
IGT: learning	5.07	15.12	4.22	13.77	0.739	0.06
IGT: risk	5.33	15.78	2.44	13.64	0.257	0.20
WCST: trials	91.61	19.76	102.98	19.58	**0.001** *	**0.58** †
WCST: errors	20.04	16.28	33.14	21.77	**<0.001** *	**0.68** †
WCST: errors perseverative	9.13	6.27	15.09	10.06	**<0.001** *	**0.71** †
WCST: conceptual	65.77	8.66	60.60	16.25	0.063	0.40
WCST: categories completed	5.59	1.07	4.76	1.80	**0.006** *	**0.56** †
WCST: trials to complete 1-cat	17.64	6.52	26.79	28.09	0.053	0.45
TMT: A	28.81	8.10	31.77	10.51	0.088	0.32
TMT: B	70.67	22.07	78.41	36.38	0.202	0.26
TMT: Diff	41.74	18.48	47.75	32.35	0.271	0.23
Stroop: words	101.50	13.27	98.13	13.91	0.173	0.25
Stroop: colors	67.82	9.97	68.28	11.00	0.812	0.04
Stroop: words-colors	43.07	10.25	42.97	10.55	0.955	0.01
Stroop: estimated	40.48	5.20	40.11	5.53	0.700	0.07
Stroop: interference	2.59	7.71	2.86	7.75	0.838	0.04
WMS-III: direct	8.91	1.93	8.96	2.02	0.902	0.02
WMS-III: direct-span	5.99	1.12	6.01	1.16	0.947	0.01
WMS-III: inverse	6.55	1.89	6.18	1.99	0.304	0.19
WMS-III: inverse-span	4.80	0.98	4.64	1.15	0.427	0.15
WMS-III: total	15.46	3.36	15.14	3.62	0.617	0.09
WAIS: vocabulary	45.30	5.29	38.50	8.52	**<0.001** *	**0.96** †
2 Psychological measures	Mean	SD	Mean	SD	*p*	|d|
SCL-90R Somatization	0.43	0.35	0.99	0.78	**<0.001** *	**0.92** †
SCL-90R Obsessive/compul.	0.68	0.52	1.19	0.84	**<0.001** *	**0.74** †
SCL-90R Interp.sensitivity	0.40	0.38	0.99	0.80	**<0.001** *	**0.95** †
SCL-90R Depressive	0.51	0.59	1.54	0.93	**<0.001** *	**1.32** †
SCL-90R Anxiety	0.36	0.34	1.00	0.80	**<0.001** *	**1.05** †
SCL-90R Hostility	0.43	0.50	0.96	0.87	**<0.001** *	**0.76** †
SCL-90R Phobic anxiety	0.06	0.16	0.41	0.61	**<0.001** *	**0.77** †
SCL-90R Paranoid Ideation	0.46	0.47	0.95	0.79	**<0.001** *	**0.75** †
SCL-90R Psychotic	0.22	0.26	0.90	0.75	**<0.001** *	**1.20** †
SCL-90R GSI score	0.43	0.34	1.08	0.70	**<0.001** *	**1.18** †
SCL-90R PST score	26.37	16.45	47.53	20.77	**<0.001** *	**1.13** †
SCL-90R PSDI score	1.41	0.33	1.86	0.59	**<0.001** *	**0.95** †
UPPS-P Lack premeditation	20.98	4.02	24.32	5.51	**<0.001** *	**0.69** †
UPPS-P Lack perseverance	19.26	4.13	21.97	4.83	**0.001**	**0.60** †
UPPS-P Sensation seeking	28.13	7.41	28.51	7.89	0.770	0.05
UPPS-P Positive urgency	20.70	5.85	31.92	9.22	**<0.001** *	**1.45** †
UPPS-P Negative urgency	23.02	5.55	32.25	6.44	**<0.001** *	**1.54** †
UPPS-P Total	112.13	18.36	138.83	22.37	**<0.001** *	**1.30** †
TCI-R Novelty seeking	99.34	10.63	110.82	13.13	**<0.001** *	**0.96** †
TCI-R Harm avoidance	88.04	17.86	98.79	16.83	**<0.001** *	**0.62** †
TCI-R Reward dependence	103.95	13.99	97.97	13.50	**0.009** *	0.43
TCI-R Persistence	112.65	18.18	109.02	18.90	0.259	0.20
TCI-R Self-directedness	148.17	19.03	130.13	20.52	**<0.001** *	**0.91** †
TCI-R Cooperativeness	136.98	15.25	130.18	15.42	**0.010** *	0.44
TCI-R Self-transcendence	66.73	15.93	61.38	13.83	**0.025** *	0.36

Note. GD: gambling disorder. SD: standard deviation. IGT: Iowa Gambling Test. WCST: Wisconsin Card Sorting Test. TMT: Trail Making Test. WMS-III: Wechsler Memory Scale Third Edition. WAIS: Wechsler Adult Intelligence Scale. SCL-90R: Symptom Checklist-90-Revised. UPPS-P: Impulsive Behavior Scale. TCI-R: Temperament and Character Inventory-Revised. * Bold: significant comparison. 1 Adjustment by sex, age, and education. 2 Adjustment by sex and age. † Bold: effect size into the range mild-moderate (|d| > 0.50) to high-large (|d| > 0.80).

3.3. Associations between Endocrine Variables and Neuropsychological and Clinical Measures

Supplementary Materials Table S2 displays the partial correlation matrix between the endocrine profile with neuropsychological and clinical variables (psychopathology,

impulsivity, and problem-gambling severity). No relevant associations were found within the GD subsample. Among HCs, lower ghrelin values were related to higher values on the IGT-block 5 and, on the WCST scales, number of trials and number of perseverative errors. Higher LEAP2 values were associated with worse psychological states and poorer performance on the TMT, Stroop task, and WMS digits-direct task. Higher leptin was also related to higher levels of phobic anxiety and worse performance on the IGT, WCST conceptual portion, and TMT. Finally, higher adiponectin values were correlated with lower scores on the UPPS-P lack of premeditation scale, and worse performance on the WMS direct and total scales.

3.4. Predictive Model for GD Presence

Table 3 shows the results of the logistic regression. The likelihood of being identified as GD was higher for individuals with lower education levels, lower social position indexes, greater psychopathological distress, higher impulsivity, lower self-transcendence, worse neuropsychological performance (specifically for WCST perseverative errors and on the Stroop color and WAIS vocabulary tasks), and lower LEAP2 levels.

Table 3. Predictive logistic regression model for identifying GD.

Dependent Variable: 1 = GD vs. 0 = HC	B	SE	*p*	OR	95% CI OR	
Covariates Sex (0 = women; 1 = men)	−0.781	1.498	0.602	0.458	0.024	8.623
Age (years-old)	−0.100	0.033	0.002	0.905	0.848	0.965
BMI (kg/m^2)	0.508	0.149	0.001	1.662	1.241	2.226
Education (low levels)	2.875	0.754	0.001	17.724	4.045	77.665
Socioeconomic status (low levels)	1.099	0.543	0.043	3.000	1.035	8.696
Psychopathology distress (SCL-90R GSI)	2.483	0.896	0.006	11.973	2.069	69.290
Impulsivity (UPPS-P total)	0.082	0.023	0.001	1.086	1.038	1.135
Personality: TCI-R self-transcendence	−0.071	0.031	0.023	0.932	0.877	0.990
WCST Perseverative errors	0.180	0.068	0.008	1.198	1.048	1.368
Stroop Color	0.093	0.047	0.046	1.098	1.002	1.203
WAIS Vocabulary	−0.175	0.064	0.007	0.840	0.740	0.953
LEAP2 (ng/mL)	−0.326	0.126	0.009	0.722	0.564	0.923
Fit statistics	H-L = 0.985; R2 = 0.427; AUC = 0.986 (95% CI: 0.973 to 0.998)					

Note. GD: gambling disorder (n = 297). HC: healthy control (n = 41). Stepwise logistic regression adjusted by sex, age, and BMI. SE: standard error. OR: odds ratio. H-L: Hosmer–Lemeshow test (p-value). R2: Cox-Snell R2. AUC: area under the ROC curve (95% confidence interval (CI)). List of statistical predictors: sociodemographics (marital status, studies levels, and socioeconomic position), psychopathology distress (SCL-90R GSI), impulsivity level (UPPS-total), personality features (TCI-R), psycho-neurological profile, and endocrine measures (ghrelin, leptin, LEAP2 and adinopectin).

4. Discussion

The present work studied gut hormones and adipocytokines, based on their association with reward and impulsive–compulsive processes, in people with GD compared with HCs. Likewise, neuropsychological, and clinical features were also evaluated, as well as its relationship with endocrine factors. Individuals with GD presented altered endocrine profiles compared to HCs, and regardless of BMI, were characterized by higher plasma ghrelin and lower LEAP2 and adiponectin concentrations, without significant differences in leptin levels. A worse neuropsychological performance, higher emotion dysregulation, greater psychopathological scores, higher impulsivity, and a more dysfunctional personality profile were also described in individuals with GD. Although significant correlations between endocrine factors and neuropsychological and clinical features were largely lacking, some neuropsychological domains and lower LEAP2 concentrations predicted GD presence. Implications are described below.

Increased plasma ghrelin concentrations in patients with GD seem consistent with results in SUDs, where ghrelin upregulation has been described [17,18], These findings suggest not only that this hormone could be involved in addictive processes [76] but also shared neurobiological substrates [3,4]. Despite not predicting GD presence, ghrelin up-

regulation could speculatively contribute to maintenance of gambling due to its reinforcing properties [28], as well as being a risk factor for relapse, related to intensify craving [28]. If such possibilities received empirical support, similar to in SUDs, they may have important therapeutic implications for GD [27].

Although this is the first study to explore LEAP2 in GD, lower concentrations among individuals with GD suggest a possible dysfunction in the ghrelin system also involving LEAP2. The findings raise the intriguing possibility as to whether altered ghrelin production may influence LEAP2 release, supporting LEAP2 antagonism [22] and favoring lower LEAP2 concentrations. Moreover, both ghrelin and LEAP2 concentrations are subject to BMI in both animals and humans but in opposite ways [52]. Thus, persistent differences in ghrelin and LEAP2 after adjustment by BMI between groups, together with the finding that lower LEAP2 concentrations statistically predicted the presence of GD, suggest that these potential disturbances may be intrinsically associated with GD. Going one step further, our results raise the question of whether LEAP2 could be a potential therapeutic target in GD and other addictive-related disorders because of the neutralization of ghrelin's possibly deleterious actions in craving, abstinence, and relapse. However, as LEAP2 has only been recently described and there is lack of extensive or consistent data in the literature, future research is needed [22].

The results regarding adiponectin agree with those reported in other addictive disorders [14,37]. Some protective functions have been linked to adiponectin, such as anti-inflammatory, anti-diabetic, and anti-atherogenic properties [77]. Thus, the results may in part explain a neurobiological basis for a worse metabolic state and a higher cardiometabolic risk associated with addiction, including individuals with GD, who had a significant higher BMI than HCs in our sample [77]. Speculatively, they may also in part explain incident cardiovascular conditions in relation to GD symptomatology in older adults [78]. Interestingly, our findings support the previous work by Geisel et al. [35], regarding leptin concentrations in GD. On the one hand, intrinsic compensatory mechanisms exist associated with endocrine dysfunctions in addiction, based on changes in receptors' activity and/or hormones' biosynthesis [79], which may be a possible rationale to explain the lack of differences between individuals with GD and HCs. Nevertheless, due to the heterogeneous methodology and mixed conclusions described in other addictive disorders, as well as limited work in GD, further studies are lacking to replicate these extend the current results.

Regarding neuropsychological performance, patients with GD had poorer cognitive flexibility and more perseverative errors than HCs, in line with previous findings [80]. Although we failed to find significant differences in the IGT trials, the GD group showed numerically less learning on the task, which may suggest a potential worse decision-making performance [41]. However, given the absence of statistically significant differences, the findings also resonate with prior reports showing similar patterns but no group differences in independent samples [81].

Patients with GD presented poorer estimated cognitive reserves compared to HCs. Lower scores on intellectual performance scales may be associated with a greater tendency to make risky decisions and may thus be a potential risk factor for the development of GD [82]. As a distinguishing finding, worse performance on the WAIS Vocabulary and WCST Perseverative errors predicted the presence of GD. Taken together, the results are in line with previous research suggesting that compulsive responding is in part mediated by impulsive decisions [39], since perseverative behavior has been "normalized" when feedback-response pause is increased in cognitive flexibility tasks [83]. One possibility is that low cognitive reserve may promote impulsivity, leading to an increase in perseverative behaviors in patients with GD. Even though significant correlations between endocrine and neuropsychological factors were largely absent, it may be worth further investigating possible common links based on relationships with reward-related neurocircuitry [84].

Patients with GD scored higher on general psychopathology and impulsivity measures [85], with more dysfunctional personality features (i.e., higher novelty-seeking and harm avoidance and lower reward dependence, self-directedness, cooperativeness, and

self-transcendence) [85]. This profile has been linked to younger age of GD onset and problem-gambling severity [86,87]. Particularly, in our study, lower self-transcendence, and younger age, described as a possible risk factor of GD [2] also predicted the presence of GD. Self-transcendence seems to be a protective factor delaying the age of GD onset [86,88]. On the other hand, younger age has been positively linked to earlier GD onset, male sex, and higher novelty-seeking, and therefore, with problem-gambling severity [89]. Socio-demographic differences related to educational and socio-economic levels aligned with previous studies of our group [85]. From a social perspective, having a lower educational status and less social support have been previously implicated in GD [90].

Newly, relationships between endocrine and clinical variables were largely not observed. However, some previous studies revealed a relationship of appetite-related hormones with impulsivity domains and mood regulation [29,91]. Considering the complexity of addictive disorders and the limitations of cross-sectional studies, prospective studies with larger samples are warranted to understand better relationships over time.

Limitations and Strengths

Some limitations should be mentioned. As the cross-sectional nature of this study limits causal attributions, future longitudinal studies are needed to better understand the involvement of neuroendocrine alterations and their roles in GD. Moreover, endocrine measurements were analyzed from peripheral blood samples, which could limit the inference of their functioning at a neural level. The lower number of individuals in the HC group with respect to the GD group may also limit the interpretation of the results, studies with a larger sample size are necessary to confirm the findings. Moreover, the GD group was principally composed of treatment-seeking males referred to a specialized unit in Catalonia, Spain. As such, studies of other compositions from other jurisdictions are warranted to determine generalizability of the results. Nonetheless, the representation of women in the study is consistent with the prevalence estimates in clinical treatment-seeking samples in GD, and comparable to their frequency in the control group. On the other hand, other strengths of this work is an adequate sample size, the well-characterized clinical and neuropsychological profile of both groups, and the adjustment in models for potentially confounding factors.

5. Conclusions

The present study provides evidence about underlying neuropsychological and endocrine dysfunctions related to reward processing in GD. The results have identified specific endocrine, neuropsychological, and clinical factors statistically predicting the presence of GD. Despite the cross-sectional design, this study supports a multifactorial nature of GD. Additionally, it supports the existence of potential neurobiological targets, known for involvement in other addictive disorders, with possible therapeutic implications. Hence, future research in this area may contribute to the development of more specific psychological and biological treatment strategies in GD.

Supplementary Materials: The following supporting information can be downloaded at https://www.mdpi.com/article/10.3390/nu14235084/s1, Table S1: Characteristics of the sample; Table S2: Partial correlation matrix.

Author Contributions: M.E., I.B., B.M.-M. and S.J.-M. contributed to the development of the study concept and design. R.G. performed the statistical analysis. M.E., I.B., M.G.-P., L.M., A.d.P.-G., B.M.-M., E.V.-M. and S.J.-M. aided with data collection. I.B., A.d.P.-G., E.C., S.T., S.C. and C.D. carried out the procedures related to blood extraction and hormone analysis. M.E., I.B., B.M.-M., N.S.-M. and S.J.-M. aided in the interpretation of data and the writing of the manuscript. F.F.-A., M.N.P., C.D., S.J.-M. and I.L. revised the manuscript and provided substantial comments. F.F.-A. and S.J.-M. obtained funding. All authors have read and agreed to the published version of the manuscript.

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

Data Availability Statement: Individuals may inquire with Jiménez-Murcia regarding the availability of the data as there are ongoing studies using the data. To avoid overlapping research efforts, Jiménez-Murcia will consider requests on a case-by-case basis.

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4.2. Estudio 2

Título del artículo: La concentración plasmática de leptina está relacionada con la adicción a la comida en el trastorno de juego: Implicaciones clínicas y neuropsicológicas.

Resumen:

Introducción: Existen datos que apuntan a un solapamiento en las vías neurobiológicas implicadas en la regulación del apetito y los trastornos adictivos. A pesar de que se han asociado diferentes medidas neuroendocrinas tanto con el trastorno de juego (TJ) como con la adicción a la comida (FA), hasta la fecha se desconoce la manera en la que alteraciones en hormonas reguladoras del apetito pueden estar relacionadas con la coexistencia de ambas entidades.

Objetivos: Comparar las concentraciones plasmáticas de grelina, leptina, adiponectina y LEAP-2 entre pacientes con TJ, con y sin FA, y explorar la asociación entre las concentraciones hormonales circulantes y las características neuropsicológicas y clínicas en individuos con TJ y FA.

Métodos: La muestra incluyó 297 pacientes diagnosticados de TJ (93,6% varones). Ninguno de los pacientes con TJ tenía diagnóstico de trastorno de la conducta alimentaria a lo largo de su vida. La FA se evaluó con la escala YFAS 2.0. Todos los pacientes fueron evaluados mediante una entrevista clínica semiestructurada y una batería psicométrica que incluía pruebas neuropsicológicas. También se obtuvieron muestras de sangre para medir variables hormonales y se recogieron variables antropométricas.

Resultados: De la muestra total, se observó FA en 23 individuos (FA+) (7,7% de la muestra, 87% varones). Cuando se comparó a los sujetos con y sin FA, aquellos con FA+ presentaron tanto un mayor índice de masa corporal (IMC) ($p < 0,001$) como concentraciones de leptina más elevadas, tras ajustar por IMC ($p = 0,013$). En los pacientes con FA, las concentraciones de leptina se correlacionaron positivamente con una mayor impulsividad, una menor flexi-

bilidad cognitiva y un peor control inhibitorio. Otras medidas endocrinas no difirieron entre los grupos.

Discusión: El presente estudio implica a la señalización de leptina en la coexistencia de TJ y FA. Entre estos pacientes, la concentración de leptina se ha asociado con características clínicas y neuropsicológicas comunes a ambas entidades, como la impulsividad y el rendimiento cognitivo en ciertos dominios.

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FULL-LENGTH REPORT

Plasma concentration of leptin is related to food addiction in gambling disorder: Clinical and neuropsychological implications

MIKEL ETXANDI[1,2,3], ISABEL BAENAS[1,3,4,5], BERNAT MORA-MALTAS[1,3,5], ROSER GRANERO[4,5,6], FERNANDO FERNÁNDEZ-ARANDA[1,4,5,7], SULAY TOVAR[4,8], NEUS SOLÉ-MORATA[1], IGNACIO LUCAS[1,4,5], SABELA CASADO[4,8], MÓNICA GÓMEZ-PEÑA[1,5], LAURA MORAGAS[1,5], AMPARO DEL PINO-GUTIÉRREZ[4,5,9], JAVIER TAPIA[1,3,5,10], EDUARDO VALENCIANO-MENDOZA[1], MARC N. POTENZA[11,12,13,14,15], ASHLEY N. GEARHARDT[16], CARLOS DIÉGUEZ[4,8] and SUSANA JIMÉNEZ-MURCIA[1,4,5,7*]

[1] Clinical Psychology Unit, Bellvitge University Hospital, Barcelona, Spain

[2] Department of Psychiatry, Hospital Universitari Germans Trias i Pujol, IGTP Campus Can Ruti, Badalona, Spain

[3] Doctoral Program in Medicine and Translational Research, University of Barcelona (UB), Barcelona, Spain

[4] Ciber Physiopathology of Obesity and Nutrition (CIBERObn), Instituto de Salud Carlos III, Madrid, Spain

[5] Psychoneurobiology of Eating and Addictive Behaviors Group, Neurosciences Programme, Bellvitge Biomedical Research Institute (IDIBELL), Barcelona, Spain

[6] Department of Psychobiology and Methodology, Autonomous University of Barcelona, Barcelona, Spain

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

[8] Department of Physiology, CIMUS, University of Santiago de Compostela, Instituto de Investigación Sanitaria, Santiago de Compostela, Spain

[9] Department of Public Health, Mental Health and Perinatal Nursing, School of Nursing, University of Barcelona, Barcelona, Spain

[10] Medical Direction of Ambulatory Processes, South Metropolitan Territorial Management, Bellvitge University Hospital, Barcelona, Spain

[11] Department of Psychiatry, Yale University School of Medicine, New Haven, CT, USA

[12] Child Study Center, Yale University School of Medicine, New Haven, CT, USA

[13] Connecticut Mental Health Center, New Haven, CT, USA

[14] Connecticut Council on Problem Gambling, Wethersfield, CT, USA

[15] Department of Neuroscience, Yale University, New Haven, CT, USA

[16] Department of Psychology, University of Michigan, Ann Arbor, USA

*Corresponding author.
E-mail: sjimenez@bellvitgehospital.cat

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ABSTRACT

Background: Data implicate overlaps in neurobiological pathways involved in appetite regulation and addictive disorders. Despite different neuroendocrine measures having been associated with both

gambling disorder (GD) and food addiction (FA), how appetite-regulating hormones may relate to the co-occurrence of both entities remain incompletely understood. *Aims:* To compare plasma concentrations of ghrelin, leptin, adiponectin, and liver-expressed antimicrobial peptide 2 (LEAP-2) between patients with GD, with and without FA, and to explore the association between circulating hormonal concentrations and neuropsychological and clinical features in individuals with GD and FA. *Methods:* The sample included 297 patients diagnosed with GD (93.6% males). None of the patients with GD had lifetime diagnosis of an eating disorder. FA was evaluated with the Yale Food Addiction Scale 2.0. All patients were assessed through a semi-structured clinical interview and a psychometric battery including neuropsychological tasks. Blood samples to measure hormonal variables and anthropometric variables were also collected. *Results:* From the total sample, FA was observed in 23 participants (FA+) (7.7% of the sample, 87% males). When compared participants with and without FA, those with FA+ presented both higher body mass index (BMI) ($p < 0.001$) and leptin concentrations, after adjusting for BMI ($p = 0.013$). In patients with FA, leptin concentrations positively correlated with impulsivity, poorer cognitive flexibility, and poorer inhibitory control. Other endocrine measures did not differ between groups. *Discussion and conclusions:* The present study implicates leptin in co-occurring GD and FA. Among these patients, leptin concentration has been associated with clinical and neuropsychological features, such as impulsivity and cognitive performance in certain domains.

KEYWORDS

gambling disorder, food addiction, leptin, impulsivity, addictive behaviors

INTRODUCTION

Gambling disorder (GD) is classified as a behavioral addiction in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) (APA, 2013). It is characterized by a recurrent and maladaptive gambling behavior, impaired control and increasing priority given to gambling, as well as continuation or escalation of gambling despite the occurrence of negative consequences in different domains of patients' daily lives (Potenza et al., 2019). GD shares clinical and etiological aspects with substance use disorders (SUDs), including neurobiological features (Griffiths, 2017; Linnet, 2020; Solé-Morata et al., 2022).

Although food addiction (FA) is not currently recognized as a formal diagnostic entity, the concept has been supported through clinical and biological studies (Gearhardt, Davis, Kuschner, & Brownell, 2011). This construct may in part explain high and rising rates of obesity in contemporary society that might relate to addictive properties of food promoting the consumption of densely caloric, hyperpalatable, inexpensive, processed foods (Gearhardt, Grilo, Dileone, Brownell, & Potenza, 2011). However, there is a lack of consensus regarding some aspects of this construct, such as the most appropriate conceptual framework to explain FA (Gearhardt & Hebebrand, 2021; Treasure, Leslie, Chami, & Fernández-Aranda, 2018). There are authors who define FA as addictive-like eating (Hebebranda et al., 2014), while others propose a substance-based addiction model (Fernandez-Aranda, Karwautz, & Treasure, 2018; Schulte, Avena, & Gearhardt, 2015). The latter model suggests that some foods, especially palatable ones with large amounts of processed sugars and fats, may lead to overeating and addictive-like behaviors by activating brain reward pathways, in a similar way to what occurs in SUDs (Gearhardt, Phil, & Corbin, 2011; Schulte et al., 2015). Moreover, many clinical and neurobiological similarities have been identified between FA and addictive disorders, such as an excessive preoccupation and desire for rewarding consumption, the development of tolerance and abstinence, and difficulties decreasing consumption despite negative consequences (Fletcher & Kenny, 2018; Gearhardt, Phil, & Corbin, 2011; Pursey, Contreras-Rodriguez, Collins, Stanwell, & Burrows, 2019; Volkow, Wang, Fowler, Tomasi, & Baler, 2012). Some authors have raised concerns regarding the diagnostic overlap between binge eating disorder (BED), an eating disorder (ED) characterized by recurrent episodes of bingeing in the absence of compensatory behaviors and FA, although recent studies provide evidence supporting that they are separate entities, which reflect different clinical situations (di Giacomo et al., 2022).

Along these lines, previous work has suggested a potential association between FA and GD (Etxandi et al., 2021; Jiménez-Murcia et al., 2017). The prevalence of FA in patients with GD has been estimated at around 7.8% (Granero et al., 2018), and co-occurrence between GD and FA has been related to specific clinical features in individuals with GD, such as higher body mass index (BMI), more psychopathology, and elevated harm avoidance (Etxandi et al., 2021). Moreover, some works hypothesized that the comorbidity with FA could be associated with gambling patterns indicative of more protracted or severe GD, which makes its study of special interest to identify possible preventive and early detection strategies (Etxandi et al., 2021).

Interestingly, one area of recent attention when studying the neurobiology of addictive disorders involves neurohormonal systems implicated in appetite regulation, with such systems linked to brain reward pathways (Etxandi et al., 2022; Iovino et al., 2022). Among endocrine factors involved in the reward circuit, ghrelin (an appetite stimulating hormone) has been shown to be a neural reinforcer for both natural (e.g., food) and non-natural (e.g., money) rewards, which influences dopamine signaling in brain areas related to reward processing (e.g., mesolimbic regions) (Farokhnia et al., 2018; Vengeliene, 2013). The liver-expressed antimicrobial peptide 2 (LEAP-2) is a recently described endocrine factor involved in appetite regulation that antagonizes the effects of ghrelin (Ge et al., 2018; Lugilde et al., 2022). Although there is currently less evidence of its involvement in addictive disorders, it has been related to impulsivity (Voigt et al., 2021), which has been linked to addictions including GD (Brewer & Potenza, 2008). Other endocrine factors such as adipocytokines (i.e., leptin and adiponectin) produced by adipose tissue have also been studied in relation to addictive disorders (Escobar et al., 2018; Housová et al., 2005; Novelle & Diéguez, 2018). Leptin is an important

peripheral signal regulating food intake, with appetite-suppressing functions and circulating concentrations related to BMI (Hellström et al., 2004). Both leptin and adiponectin have also been linked to impulsivity (Sutin et al., 2013) and craving in SUDs (Hillemacher et al., 2009; Martinotti et al., 2017). Noticeably, these endocrine factors linked to SUDs have prompted investigations in behavioral addictions such as GD (Geisel, Hellweg, Wiedemann, & Müller, 2018). A recent case-control study described an increase in ghrelin concentrations, but a decrease in LEAP-2 and adiponectin in individuals with versus without GD, after adjusting for BMI (Etxandi et al., 2022).

Regarding neurobiological correlates of FA, prior efforts have explored possible endocrine alterations (Leigh & Morris, 2018). Both ghrelin and leptin may play a significant role in FA (Piccinni et al., 2021). On the one hand, ghrelin signaling has been suggested as a key regulator of obesity, and higher concentrations have been associated with increased food craving and consumption (Lopez-Aguilar, Ibarra-Reynoso, & Malacara, 2018). It has also been hypothesized that higher fasting leptin concentrations may underlie excessive food intake (Miller et al., 2014). FA has been associated with lower leptin concentrations in adolescents with normal weight whereas with higher leptin concentrations in individuals with overweight (Peters et al., 2018). The authors hypothesized that the negative association between leptin concentrations and FA under normal-weight conditions could be explained by a stronger sense of hunger and a greater propensity for overeating in these individuals, which could have led to greater FA severity. In individuals with overweight, high circulating leptin concentrations may reflect leptin resistance, in which the failure of leptin-level-induced feeding suppression may lead to the development of FA (Peters et al., 2018; Yu, Fernandez, Meng, Zhao, & Groth, 2021).

To the best of our knowledge, no previous studies have investigated hormonal factors in the co-occurrence of FA and a behavioral addiction such as GD. The main aim of the present study was to explore whether there were differences in plasma concentrations of hormones involved in appetite regulation (namely ghrelin, LEAP-2, adiponectin, and leptin) in a sample of patients diagnosed with GD, with and without FA. Moreover, we aimed to explore correlates between concentrations of any implicated hormones and clinical and neuropsychological variables in the subgroup with FA. These included measures of cognitive domains described as core features in well-known neuroscientific models of addiction and especially related to impulse control, that we hypothesized to co-occur in GD and FA, such as prefrontally mediated executive functions (i.e., cognitive flexibility, inhibitory control, decision making, working memory, attention, and set-shifting) (Bechara & Van Der Linden, 2005; Blaszczynski & Nower, 2002; Mallorquí-Bagué et al., 2018; van Timmeren, Daams, van Holst, & Goudriaan, 2018). We hypothesized that circulating concentrations of appetite-regulating hormones would differ between GD patients with and without FA, with levels of implicated hormones correlating with impulsivity measures in the FA subgroup.

METHODS

Participants

The sample consisted of $n = 297$ seeking-treatment outpatient adults with GD. Participants were mostly male ($n = 278$, 93.6%) and with a mean age of 39.58 years ($SD = 14.16$). They were voluntarily recruited from April 2018 to September 2021 at the Behavioral Addictions Unit within the Clinical Psychology Unit of Bellvitge University Hospital (Barcelona, Spain). All patients had a diagnosis of GD according to DSM-5 criteria (APA, 2013). None of them presented a lifetime ED, which constituted an exclusion criteria together with the presence of an organic mental disorder, an intellectual disability, a neurodegenerative disorder (such as Parkinson's disease), or an active psychotic disorder.

Measures

Hormonal assays. Peripheral blood samples were collected by venous aspiration with ethylenediamine tetraacetic acid (EDTA) (25 mM final concentration), obtained at 9 am after at least 8 h of overnight fasting. Blood was centrifuged at 1,700 g in a refrigerated (4°C) centrifuge for 20 min. The plasma was immediately separated from the serum and stored at −80°C until analysis. Parameter determinations were conducted using commercial kits according to the manufacturer's instructions and in a single analysis to reduce inter-assay variability. Quantitative plasma LEAP-2 measurement was performed using a commercial enzyme-linked immunosorbent assay (ELISA) kit (Human LEAP-2 ELISA kit, Phoenix Pharmaceuticals, Inc), previously validated (Barja-Fernández et al., 2021; Mani et al., 2019). Intraassay and interassay coefficients of variation were <10% and <15%, respectively. The sensitivity limit of the assay was 0.15 ng/mL. Total ghrelin (pg/mL) was measured using an ELISA kit (Invitrogen-Thermofisher scientific) for the detection of human ghrelin, with a specificity of 100%. The intra-assay variation coefficient was <6%, and the inter-assay variation coefficient <8.5%. The sensitivity limit of the assay was 11.8 pg/mL (Pena-Bello et al., 2015). Plasma adiponectin (ng/mL) and leptin (ng/mL) were measured using a solid-phase sandwich ELISA kit (Invitrogen-Thermofisher scientific) with a specificity of 100%. The intraassay and interassay coefficients of variation were <4% and <5%, respectively, and the assay sensitivity limit was 100 pg/mL for adiponectin and <3.5 pg/mL for leptin. Each sample's absorbance was measured in duplicate using a microplate spectrophotometric reader at a wavelength of 450 nm (Epoch 2 microplate reader, Biotek Instruments, Inc).

Neuropsychological variables. *Vocabulary subtest of the Wechsler Adult Intelligence Scale, 3rd edition (WAIS-III)* (Wechsler, 1999): The WAIS-III involves defining words of increasing difficulty presented orally. It was used to assess vocabulary expression, as a measure of estimated intelligence (De Oliveira, Nitrini, Yassuda, & Brucki, 2014).

Iowa Gambling Task (IGT) (Bechara, Damasio, Damasio, & Anderson, 1994, 2000): The IGT is a computerized task for evaluating risk-/reward-based and punishment-influenced decision-making. Participants must select 100 cards from four decks of cards (i.e., A, B, C, and D) and, after each card selection, either a monetary gain or a loss is obtained. The participants are told that the ultimate goal of the task is to win as much money as possible. The 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. Whereas decks A and B are not advantageous, since the final loss is greater than the final gain, decks C and D are advantageous since the penalties are smaller (as are the rewards). Higher scores indicate better performance, while negative scores reflect more choices from disadvantageous decks. The test score for each block (IGT-1, 2, 3, 4, and 5) is calculated by subtracting the number of choices from disadvantageous decks to the number of choices from advantageous decks draws. The total task score (IGT-Total) is obatined by adding the scores of the five blocks. The learning score (IGT-Learning) measures the differences between the two first blocks (where the participant has not learned which decks are advantageous and disadvantageous) and the two last blocks (where the participant could have already detected which decks involve a risky choice and then, the experience gained through the trial can produce changes in choice patterns). Additionally, the risk score (IGT-Risk) is measured considering the scores from the two last blocks.

Wisconsin Card Sorting Test (WCST) (Grant & Berg, 1948): The WCST evaluates cognitive flexibility. It is comprised of four types of stimulus cards and 128 response cards that show different shapes, colors, and numbers of figures on each one. Participants must match the response cards to the stimulus cards in a way that seems justifiable to them before they receive feedback (i.e., correct or incorrect). After ten correct consecutive responses, the categorization criteria change. Total trials, total errors, perseverative errors and non-perseverative errors, the number of complete categories, conceptual, and trials to complete first category are recorded.

Trail Making Test (TMT) (Reitan, 1958): TMT part A consists of 25 circles on a piece of paper with the numbers 1 to 25 written randomly in each. The person is tasked with drawing a line from one circle to the next in ascending numerical order, from 1 to 25, as quickly as possible. The lines between the circles are referred to as the "trail." For part B, the dots go from 1 to 13 and include letters from A to L. As in the first part, the person must connect the dots in order while alternating letters and numbers, as in 1-A-2-B-3-C…, in the shortest time possible without lifting the pen from the paper. The task assesses visual conceptual and visual-motor tracking, entailing motor speed, attention, and the capacity to alternate between cognitive categories (set-shifting). Each part is scored according to the time spent to complete the task.

Stroop Color and Word Test (SCWT) (Golden, 1978): The SCWT consists of three separate lists. First, a word list contains the names of colors in black ink. Then, a color list includes the letter "X" printed in different colors. Lastly, a color word list consisting of color names in a color ink that does not match the written name. Three final scores are obtained based on the number of items the participant can read on each of the three lists within 45 seconds. The SCWT assesses cognitive interference, which occurs when the processing of one stimulus feature affects the simultaneous processing of another attribute.

Clinical variables. *Yale Food addiction Scale 2.0 (YFAS 2.0)* (Gearhardt, Corbin, & Brownell, 2016): The YFAS 2.0 consists of a self-report scale for assessing FA based on 11 symptoms related to SUDs that are adapted to the context of food consumption. The YFAS 2.0 consists of 35 items and produces two measurements: (1) a continuous symptom count score that reflects the number of diagnostic criteria met (from 0 to 11), and (2) a binary measure (present vs. absent) that is based on the number of symptoms (at least 2) and self-reported clinical distress or impairment. In addition, it also provides severity thresholds: mild (2-3 symptoms), moderate (4-5 symptoms) and severe (6-11 symptoms). The Spanish validation of the YFAS-2 (Granero et al., 2018) generated an internal consistency of Cronbach's alpha (α) = 0.94. The internal consistency of our sample was $\alpha = 0.97$.

South Oaks Gambling Screen (SOGS) (Lesieur & Blume, 1987): The SOGS includes 20 items for the identification of problem gambling and associated negative consequences. Total scores obtained as the summation of the items have been used as a measure of problem-gambling severity, with a score of five or more reflecting "probable pathological gambling." The Spanish validation of the scale showed very good psychometric results in the adaptation study (test-retest reliability $R = 0.98$, internal consistency $\alpha = 0.94$ and convergent validity $R = 0.92$) (Echeburúa, Baez, Fernández-Montalvo, & Páez, 1994). The internal consistency for this scale in the study sample was $\alpha = 0.74$.

Diagnostic Questionnaire for Pathological Gambling According to DSM criteria (Stinchfield, 2003): Spanish adaptation (Jiménez-Murcia et al., 2009). This instrument is a self-report questionnaire containing 19 items coded on a binary scale (yes-no), which is used for the diagnosis of GD according to the DSM-IV-TR (APA, 2000). This questionnaire has been updated according to DSM-5 (APA, 2013) criteria. The internal consistency of this scale in the study sample was $\alpha = 0.80$.

Symptom Checklist-90-Revised (SCL-90-R) (Derogatis, 1994): The SCL-90-R is a self-report questionnaire of 90 items that assesses a broad range of psychological problems and psychopathology, based on nine primary symptom dimensions (Somatization, Obsessive-Compulsion, Interpersonal Sensitivity, Depression, Anxiety, Hostility, Phobic Anxiety, Paranoid Ideation, and Psychoticism). Three global indexes are included (global severity index, positive symptom distress index and total positive symptom). The validation of the scale in the Spanish population (Derogatis, 2002) showed a mean internal consistency of $\alpha = 0.75$. The internal consistency in the study was $\alpha = 0.98$.

Temperament and Character Inventory-Revised (TCI-R) (Cloninger, 1999): The TCI-R is a 240-item questionnaire

scored on a 5-point Likert scale that measures personality features derived from three character dimensions (Self-Directedness, Cooperativeness, and Self-Transcendence) and four temperament dimensions (Harm Avoidance, Novelty Seeking, Reward Dependence and Persistence). Evaluation of the Spanish revised version (Gutiérrez-Zotes et al., 2004) had an internal consistency of $\alpha = 0.87$. This questionnaire was administered in its Spanish adaptation, in which the original author participated (Gutiérrez-Zotes et al., 2004). The internal consistency in the study was between $\alpha = 0.70$ (Novelty Seeking) and $\alpha = 0.88$ (Persistence).

Impulsive Behavior (UPPS-P) (Whiteside, Lynam, Miller, & Reynolds, 2005). Through 59 self-report items, the UPPS-P assesses five aspects of impulsive behavior: negative urgency; positive urgency; lack of premeditation; lack of perseverance; and sensation-seeking. The Spanish validation of the UPPS-P demonstrated good reliability (Cronbach's α between 0.79 and 0.93) and external validity (Verdejo-García, Lozano, Moya, Alcázar, & Pérez-García, 2010). The internal consistency in the study varied between $\alpha = 0.80$ (lack of perseverance) and $\alpha = 0.93$ (positive urgency).

Difficulties in Emotion Regulation Strategies (DERS) (Gratz & Roemer, 2004). The DERS is a self-reported 36-item scale that assesses emotion dysregulation. The scale is divided into six subscales (non-acceptance of emotional responses, difficulties in performing goal-directed behaviors when experiencing strong emotions, difficulties in controlling impulses, lack of emotional awareness, limited access to emotion regulation strategies, and lack of emotional clarity). The participants are asked to answer each item using a five-point Likert scale ranging from 1 (almost never) to 5 (almost always). Higher scores suggest greater problems in emotion regulation. The instrument has been validated in the Spanish population (Hervás & Jódar, 2008). The internal consistency of the DERS total score in our sample was $\alpha = 0.92$.

Other variables. Additional data (e.g., socio-demographic, and socio-economic, anthropometric variables, and GD-related characteristics) were collected in a semi-structured face-to-face clinical interview, as described elsewhere (Jiménez-Murcia, Aymamí-Sanromà, Gómez-Pena, Álvarez-Moya, & Vallejo, 2006).

Procedure

The participants were assessed at the Behavioral Addictions Unit of the Clinical Psychology Unit of Bellvitge University Hospital (Barcelona, Spain). A multidisciplinary team (psychology, psychiatry, and nursing) with more than 15 years of experience in the field of GD and other behavioral addictions conducted the evaluation and data collection. In a first session, a comprehensive semi-structured clinical interview was performed, focusing on gambling behaviors. Moreover, lifetime ED was also assessed. In a second session, the psychometric evaluation and the extraction of biological samples took place. The biological samples were subsequently analyzed at the Singular Center for Research in Molecular Medicine and Chronic Diseases (CIMUS), University of Santiago de Compostela (Santiago de Compostela, Spain). Finally, in a third session, the psychological assessment was performed by an experienced neuropsychologist for 60 min. We also administered the WAIS-III (Wechsler et al., 1999) vocabulary subtest as a measure of estimated intelligence (Lezak et al., 2004). All measures used in this study correspond to the evaluation done prior to the beginning of specialized treatment in our Unit.

Statistical analysis

Statistical analysis was performed with Stata17 for Windows (Stata-Corp, 2021). Comparison of socio-demographic and gambling-related problems between the YFAS 2.0 positive versus negative screening groups was done with chi-square tests (χ^2) for categorical data and *T*-tests for quantitative data. For these models, effect sizes of relationships were measured with Cohen's-*h* and Cohen's-*d* coefficients, interpreting mild-moderate effect sizes for values above 0.50 and less than 0.80 and high-large effect size for values above 0.80 (Kelley & Preacher, 2012).

Comparisons of hormonal measures between groups were performed with analysis of covariance (ANCOVA), adjusting for sex, age, and BMI. The association between leptin concentrations and clinical and neuropsychological variables was assessed through partial correlation coefficients, adjusted for sex, age, BMI, and WAIS-vocabulary scores, the latter used to adjust the between-group comparisons for estimated intelligence. Given the relationship between the significance of correlations with sample sizes (small coefficients can achieve highly significant *p*-values in large samples, and vice versa), correlation values with size $|R|>0.24$ (medium-moderate effect size) or $|R|$ (large-high effect size) were considered relevant in this study (Rosnow, 1996).

This study used Finner's procedure for controlling the increase in the Type-I error due to the use of multiple statistical comparisons. This procedure is sustained by the familywise error rate stepwise multiple method, and it is aimed to adjust significance levels (*p*-values) by controlling for the probability that the statistical tests make at least k false rejections (Finner & Roters, 2001).

Ethics

The latest version of the Declaration of Helsinki guided conduct in the present study. The Clinical Research Ethics Committee of Bellvitge University Hospital approved this study (ref. PR329/19 and PR338/17), as part of the scientific production within national and competitive research projects developed by our research group (RTI2018-101837-B-I00; 2019I47). Signed informed consent was obtained from all participants.

RESULTS

Descriptive for the sample

Most participants in the study were single (53.2%), men (93.6%), with low education levels (52.9%), and of low social status (44.8%). The mean age was 39.6 years old (SD =

14.2), mean age of onset of the gambling problems 29.1 years old (SD = 12.4), and mean duration of gambling problems 5.23 years (SD = 6.0). The percentage of patients who reported non-strategic gambling preference was 49.8%, while 31.0% reported strategic, and 19.2% both non-strategic and strategic gambling. The prevalence of patients with gambling-related debts was 58.9%.

Comparison of the measures between FA groups

A small percentage (7.7%) of the sample met criteria for FA. Table 1 presents sociodemographic and GD variables stratified by FA status, with significant differences in the SOGS total score and the BMI levels (higher means among patients with FA + group).

The results of the ANCOVA comparing ghrelin, LEAP-2, leptin, and, adiponectin concentrations between patients with and without FA evidenced differences for the leptin values (higher mean concentrations among the FA + group) (see Table 2 and Fig. 1, with the radar chart).

The ANCOVA procedure with the comparison of the clinical profiles between patients with and without FA is showed in Table S1 (supplementary material). Differences between groups were found for the psychopathological state (higher SCL-90R mean scores in the FA + group), and the emotion regulation capacity (higher scores in DERS among the FA+ group, showing concretely difficulties engaging in goal-directed behaviors, limited access to emotion regulation strategies, lack of emotional clarity, and higher total score).

Table 1. Comparison between the groups for the sociodemographic and the GD profiles

	Total (*n* = 297)		FA− (*n* = 274)		FA+ (*n* = 23)			
	n	%	*n*	%	*n*	%	*p*	|*h*|
Sex								
Women	19	6.4%	16	5.8%	3	13.0%	0.175	0.25
Men	278	93.6%	258	94.2%	20	87.0%		
Education								
Primary	157	52.9%	143	52.2%	14	60.9%	0.160	0.18
Secondary	112	37.7%	107	39.1%	5	21.7%		0.38
University	28	9.4%	24	8.8%	4	17.4%		0.26
Marital								
Single	158	53.2%	146	53.3%	12	52.2%	0.074	0.02
Married	103	34.7%	98	35.8%	5	21.7%		0.31
Divorced	36	12.1%	30	1.9%	6	26.1%		0.40
Social index								
High	8	2.7%	7	2.6%	1	4.3%	0.875	0.10
Mean-high	19	6.4%	18	6.6%	1	4.3%		0.10
Mean	24	8.1%	23	8.4%	1	4.3%		0.17
Mean-low	113	38.0%	105	38.3%	8	34.8%		0.07
Low	133	44.8%	121	44.2%	12	52.2%		0.16
	Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*	*p*	|*d*|
Age (years-old)	39.58	14.16	39.44	14.15	41.26	14.45	0.554	0.13
Age of onset of GD (years)	29.10	12.42	28.80	12.37	32.74	12.69	0.144	0.31
Duration of GD (years)	5.23	6.02	5.24	6.11	5.04	4.88	0.880	0.04
DSM-5 criteria	7.13	1.80	7.09	1.82	7.70	1.40	0.119	0.37
SOGS total	10.85	3.23	10.74	3.17	12.13	3.73	**0.048***	0.40
	n	%	*n*	%	*n*	%	*p*	|*h*|
Preference								
Non-strategic	148	49.8%	139	5.7%	9	39.1%	0.551	0.23
Strategic	92	31.0%	83	3.3%	9	39.1%		0.19
Mixed	57	19.2%	52	19.0%	5	21.7%		0.07
Debts due to the GD								
No	122	41.1%	113	41.2%	9	39.1%	0.843	0.04
Yes	175	58.9%	161	58.8%	14	60.9%		
	Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*	*p*	|*d*|
Body mass index (Kg/m^2)	26.48	5.04	25.99	4.37	32.34	8.15	**<0.001***	**0.97**†

Note. GD: gambling disorder. SD: standard deviation.
FA−: food addiction negative screening group. FA+: food addiction positive screening group.
*Bold: significant comparison. †Bold: effect size into the ranges mild-moderate to high-large.

Table 2. Comparison of hormonal measures: ANCOVA (adjusted by sex, age, and BMI)

	Total (*n* = 297)		FA− (*n* = 274)		FA+ (*n* = 23)				YFAS-total
	Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*	*p*	|*d*|	*R*
Ghrelin (pg/mL)	941.59	753.26	945.03	758.78	938.15	643.10	0.967	0.01	0.006
LEAP-2 (ng/mL)	5.26	2.88	5.31	2.87	5.21	3.09	0.661	0.03	0.007
Leptin (ng/mL)	10.05	7.85	7.88	7.42	12.23	10.47	**0.013***	**0.52**†	0.106
Adiponectin (ng/mL)	8,678.79	4,374.29	8,374.86	4,429.37	8,982.71	3,710.43	0.543	0.15	0.022

Note. SD: standard deviation. R: Partial correlation.
FA−: food addiction negative screening group. FA+: food addiction positive screening group.
*Bold: significant comparison. †Bold: effect size into the ranges mild-moderate to high-large.

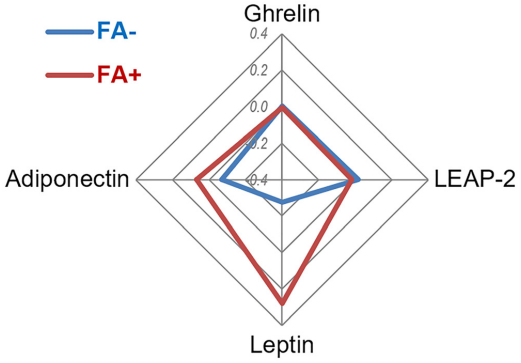

Fig. 1. Radar chart with the hormonal profile (z-standardized means are plotted).
Note. Z-standardized means are plotted in the graph. Total sample (*N* = 297).

Correlational analysis

Table 3 includes the partial correlation matrix assessing the relationship between leptin concentrations and clinical measures, separately for patients with and without FA, and adjusted for sex, age, BMI, and WAIS-vocabulary scores. All correlation coefficients involving the FA− group were into the low effect-size range, suggesting no relationships between leptin and psychological performance, GD severity, psychological state, impulsivity, and emotion regulation capacity among these patients. Within the FA+ group, higher leptin concentrations were related to worse performance on neuropsychological measures (including the WCST, TMT, and SCWT), greater problem-gambling severity (reflected in the number of DSM-5 GD criteria and SOGS scores), higher scores on the SCL-90R obsessive-compulsive and phobic anxiety scales, higher impulsivity levels (UPPS-P: lack of premeditation, sensation-seeking, positive urgency, and total score), and more emotion-

Table 3. Partial correlation with the leptin level (adjusted by sex, age, BMI and WAIS-vocabulary)

	FA− (*n* = 274)	FA+ (*n* = 23)		FA− (*n* = 274)	FA+ (*n* = 23)
IGT: block 1	−0.026	−0.055	SCL-90R Somatization	0.024	−0.129
IGT: block 2	−0.023	−0.092	SCL-90R Obsessive/compulsive	0.020	**0.322**†
IGT: block 3	0.030	−0.071	SCL-90R Interpersonal sensitivity	−0.081	0.019
IGT: block 4	−0.030	**−0.334**†	SCL-90R Depressive	0.004	−0.134
IGT: block 5	0.013	0.071	SCL-90R Anxiety	−0.002	0.009
IGT: total	−0.006	−0.141	SCL-90R Hostility	−0.073	0.138
IGT: learning	0.012	−0.076	SCL-90R Phobic anxiety	0.061	**0.300**†
IGT: risk	−0.008	−0.143	SCL-90R Paranoid Ideation	−0.069	0.153
WCST: trials	0.035	**0.375**†	SCL-90R Psychotic	−0.041	0.140
WCST: errors	−0.034	**0.244**†	SCL-90R GSI score	−0.023	0.042
WCST: errors perseverant	−0.031	**0.278**†	SCL-90R PST score	−0.041	0.110
WCST: conceptual	0.071	0.222	SCL-90R PSDI score	−0.007	0.002
WCST: categories completed	0.045	0.023	UPPS-P Lack premeditation	−0.056	**0.285**†
WCST: trials for the 1st-categ.	−0.029	0.182	UPPS-P Lack perseverance	0.019	−0.029
TMT: A	−0.043	0.109	UPPS-P Sensation seeking	−0.145	**0.318**†
TMT: B	−0.052	**0.326**†	UPPS-P Positive urgency	−0.155	**0.435**†
TMT: Diff	−0.046	**0.324**†	UPPS-P Negative urgency	−0.077	0.226
Stroop: words	0.062	−0.174	UPPS-P Total	−0.142	**0.348**†
Stroop: colors	−0.002	−0.064	DERS Non acceptance emotions	−0.056	0.068
Stroop: words-colors	−0.018	**−0.289**†	DERS Difficulties directed behav.	0.007	**0.282**†
Stroop: estimated	0.029	−0.116	DERS Impulse control difficult.	−0.025	0.139
Stroop: interference	−0.042	**−0.353**†	DERS Lack emotional aware.	0.043	**−0.234**†
DSM-5 criteria	0.049	**0.240**†	DERS Limited access emotions	−0.045	0.163
SOGS total	−0.038	**0.406**†	DERS Lack emotional clarity	0.047	0.085
			DERS Total	−0.022	0.135

Note. †Bold: effect size into the range mild-moderate (|*R*|>0.24) to high-large (|*R*|>0.37).

regulation difficulties (DERS) related to goal-directed behaviors and lack of emotional clarity.

DISCUSSION

The present work studied differences in plasma concentrations of appetite-regulating hormones between individuals with and without FA in a sample of patients diagnosed with GD. Likewise, neuropsychological and clinical features were assessed. The results suggested that subjects with FA presented higher BMI, more severe GD measured by the SOGS, greater emotion dysregulation, worse general psychopathological state, and an altered endocrine profile characterized by an elevation of leptin concentrations (after adjusting for BMI), without differences in the other analyzed endocrine factors. Moreover, correlations between leptin concentrations and certain psychological and clinical features were observed in the FA+ group. Higher concentrations of leptin were associated with phobic anxiety and obsessive-compulsive dimensions (SCL-90R), impulsivity, emotion dysregulation, and poorer cognitive flexibility and inhibitory control. Furthermore, in the FA+ group, leptin concentrations were also associated with more severe GD.

The prevalence of FA in the sample (7.7%) was similar to that described in the literature (Granero et al., 2018). As expected, considering both the nature of the studied comorbidity and results from previous studies, patients with FA presented higher SOGS scores and BMI, supporting the notion of more severe GD and a worse metabolic profile in this subgroup of patients (Etxandi et al., 2021; Jiménez-Murcia et al., 2017). This finding reinforces the idea that individuals with GD and FA may benefit from specific therapeutic strategies (e.g., improving healthy eating habits, increasing physical exercise) and that screening for FA in patients with GD may help optimize preventive and therapeutic approaches (Etxandi et al., 2021). No other significant differences were found between sociodemographic profiles nor gambling preferences between both groups, which has also been reported in a prior publication from our group (Etxandi et al., 2021).

Elevated adjusted plasma leptin concentrations in patients with FA, who presented a higher BMI, is consistent with previous studies (Peters et al., 2018) and support the notion that elevated concentrations of this adipocytokine may represent leptin resistance in patients with overweight. According to this hypothesis, leptin would not adequately exert its appetite-suppressing function and could underlie the development of addictive-like eating in these individuals (Peters et al., 2018). Moreover, leptin concentrations showed a positive correlation with trait impulsivity, which is in line with previous studies (Sutin et al., 2013). Leptin can modulate mesolimbic activity both through receptors expressed on dopaminergic cells in the midbrain, and indirectly via its actions in upstream hypothalamic circuits (Adams et al., 2018). Our findings suggest that patients with GD and FA may have leptin resistance that might contribute to dysfunctions in this signaling system and lead to an increased impulsivity. However, increased impulsivity may underlie FA-related eating behaviors leading to increased leptin concentrations, or other possibilities (relating to synergism) may also exist. Elevated impulsivity has been previously reported in both GD and FA (Mestre-Bach et al., 2020; Schulte & Gearhardt, 2021). In patients with GD and co-occurring FA, the dysfunction of circuits linked to impulsivity and leptin signaling may underlie not only the incursion into behaviors related to excessive food intake, but also some common clinical and psychological features related to both GD and FA.

Poor cognitive performance, such as low cognitive flexibility and disadvantageous decision-making, has been implicated in both GD and FA (Etxandi et al., 2022; Lacroix & von Ranson, 2021; Steward et al., 2018). To our knowledge, this is the first study to evaluate the association between leptin concentrations and cognitive performance in people with GD and FA. Interestingly, our results showed a positive correlation between leptin concentrations and poorer cognitive flexibility, as measured by WCST and TMT performance, in GD patients with FA. Some studies focusing on populations of lean body mass have suggested a possible protective factor of this adiponectin (Holden et al., 2017; Lieb et al., 2009), while poorer cognitive performance (specifically in cognitive flexibility and other executive functions) has been related to elevated circulating leptin concentrations in individuals with overweight (Labad et al., 2012). Considering that leptin has an influence on hippocampus-dependent learning and memory (Harvey, Solovyova, & Irving, 2006) and that the hippocampus has been related to cognitive flexibility (Leirer et al., 2010), these results as a whole may suggest that leptin resistance could be involved in the impairment of cognitive flexibility in GD patients with FA (Gunstad et al., 2008).

Recent studies have reported a potential association between leptin concentrations and neuropsychological performance, particularly involving measures of inhibitory control (Wollenhaupt et al., 2019). Interestingly, the results of the present study also demonstrate a positive correlation of leptin concentrations with deficits in inhibitory control, as measured by the SCWT, in patients with FA. Taking all the above into account, the relationship between adjusted leptin concentrations and measures related to impulsivity is highly suggestive, especially when observed in the FA+ group (with higher BMI) and not in the FA-group. Although future studies are warranted to further clarify its role, the results would be in line with the hypothesis that leptin signaling could underlie impulsivity-related dysfunctions in patients with GD and co-occurring FA. Moreover, these results may also contribute to the ongoing debate on the theory and classification of FA. In this regard, the potential involvement of neurobiological factors in the development of impairments in dopaminergic pathways that regulate neural systems associated with reward sensitivity and incentive motivation in FA can reinforce its conceptualization as an addictive disorder.

Individuals with GD, with versus without FA, had higher scores in general psychopathology and emotion dysregulation,

consistent with previous studies (Etxandi et al., 2021; Jiménez-Murcia et al., 2017). FA-related behaviors have been proposed as maladaptive responses to emotional distress, with serious metabolic and clinical implications (Etxandi et al., 2021). Bearing in mind the involvement of leptin signaling in the potential development of anxiety-related behaviors (Liu, Guo, & Lu, 2016), the positive correlation between leptin concentrations and emotion dysregulation and phobic anxiety results resonate with prior findings. Although preliminary, these findings suggest that leptin could be a biological mechanism related to the higher emotion dysregulation found in patients with GD and FA.

Noticeably, in the present study no significant alterations in other endocrine factors concentrations (i.e., ghrelin, LEAP-2, and adiponectin) were identified between GD patients with and without FA. It is very suggestive that in a previous study of our group comparing the same hormones between patients with GD and healthy subjects, differences were observed in ghrelin and adiponectin signaling, but not in leptin concentrations, adjusted for BMI (Etxandi et al., 2022). This finding leads us to hypothesize that leptin could play a specific role in FA, independent of GD, that involves specific neuropsychological and psychopathological domains, including impulsivity, cognitive flexibility, and inhibitory control.

In sum, our results suggest that leptin is linked to FA in patients with GD, underlying clinical and neuropsychological characteristics that exist when adjusting for BMI and other potential confounders. Leptin appears linked to more severe GD symptomatology in the FA+ group. Although promising, these preliminary exploratory results would benefit from more investigation into leptin signaling disturbances in patients with GD and FA.

Strengths and limitations

Some limitations should be considered when interpreting the results of this study. The cross-sectional nature of the study precludes causal attributions. Future longitudinal research is needed to better characterize a role for leptin in co-occurring GD and FA. The sample was principally composed of treatment-seeking males with GD referred to a specialized unit. The extent to which these findings generalize to other populations, including women with GD, warrants direct investigation. However, the percentage of women in the study is consistent with those in treatment-seeking GD samples. The last limitation is the lack of analysis for potential interaction effects (this was not an objective of the study). Given the pioneering nature of the work, as well as the large number of variables considered (particularly for the neuropsychological area), the number of the potential moderation parameters was too large. We considered more appropriate to provide the results of this first study, aimed to explore and identify the key endocrine and neuropsychological variables within the GD profile, and to plan future studies with larger samples and a limited number of measures (those selected as the most relevant and therefore candidate to analyze the moderation effects).

Some strengths of the present study include a sizable sample, the well-characterized clinical and neuropsychological assessments, and the adjustment of analyses for potential confounding factors. Also, we used several measurement tools, including global scales and subscales, which provide a broad visualization of the psychopathological and functional profile for the patients.

CONCLUSIONS

The present study provides insight into possible underlying endocrine dysfunctions related to reward processing in FA among patients with GD. Despite its cross-sectional design, this study suggests that leptin signaling may underlie clinical and neuropsychological aspects, especially in terms of impulsivity, cognitive flexibility, and GD severity in the subgroup with FA, with potential therapeutic implications. Future research in this area may contribute to a better understanding of the biology of GD and FA, as well as to the development of more specific psychological and biological treatment strategies in this clinical population.

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Authors' contribution: ME, IB, BM-M, and SJ-M contributed to the development of the study concept and design. RG performed the statistical analysis. ME, IB, BM-M, MG-P, LM, AP-G, EV-M, and SJ-M aided with data collection. IB, AP-G, ST, SC, and, CD carried out the procedures related to neuroendocrine variables extraction and analysis. ME, IB, BM-M, IL, NS, and SJ-M aided with interpretation of data

and the writing of the manuscript. MNP, AG, FF-A, JT, and SJ-M revised the manuscript and provided substantial comments. FF-A and SJ-M obtained funding.

Conflict of interest: Mikel Etxandi, Isabel Baenas, Bernat Mora-Maltas, Roser Granero, Sulay Tovar, Neus Solé-Morata, Ignacio Lucas, Mónica Gómez-Peña, Laura Moragas, Amparo del Pino-Gutiérrez, Javier Tapia, Eduardo Valenciano-Mendoza, Sabela Casado, Ashley N. Gearhardt, and Carlos Diéguez report no disclosures. Fernando Fernández-Aranda and Susana Jiménez-Murcia received consultancy honoraria from Novo Nordisk, and Fernando Fernández-Aranda received editorial honoraria from Wiley. Marc N. Potenza has consulted for and advised Opiant Pharmaceuticals, Idorsia Pharmaceuticals, Baria-Tek, AXA, Game Day Data and the Addiction Policy Forum; has been involved in a patent application with Yale University and Novartis; has received research support from the Mohegan Sun Casino and Connecticut Council on Problem Gambling; has participated in surveys, mailings, or telephone consultations related to drug addiction, impulse control disorders, or other health topics; has participated in trainings, medical education and journal editorial work; and has consulted for law offices and gambling entities on issues related to impulse control or addictive disorders.

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SUPPLEMENTARY MATERIAL

Supplementary data to this article can be found online at https://doi.org/10.1556/2006.2023.00051.

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4.3. Estudio 3

Título del artículo: Características clínicas de los pacientes con trastorno de juego con y sin adicción a la comida: Consideraciones relacionadas con el sexo.

Resumen:

Introducción: Si bien la adicción a la comida (FA) es una entidad debatida, que actualmente no está reconocida como un diagnóstico formal, comparte características con otras adicciones, como el trastorno de juego (TJ). Sin embargo, la prevalencia de la FA en el TJ y los correlatos clínicos de su comorbilidad no se conocen completamente, especialmente en relación a posibles diferencias entre hombres y mujeres.

Objetivos: Estudiar las características clínicas diferenciales en pacientes con TJ que presentan FA.

Métodos: Se llevó a cabo un estudio observacional transversal. La muestra incluyó 867 pacientes diagnosticados de TJ (798 hombres y 69 mujeres) que acudieron a una unidad especializada en adicciones conductuales. La comorbilidad con FA fue evaluada a través de la escala YFAS 2.0.

Resultados: Se observó FA en el 8,3% de los pacientes con TJ (18,8% de las mujeres, 7,4% de los hombres). La presencia de FA se asoció con una mayor psicopatología general y evitación del daño, mayores índices de masa corporal y menor autodirección y cooperatividad. En las mujeres, FA se asoció a una mayor duración del TJ. En los hombres, FA se asoció a un inicio más temprano y a una mayor gravedad del TJ, así como al consumo problemático de alcohol. Entre los pacientes con TJ, FA se asoció con patrones de juego sugestivos de un TJ más prolongado o grave en ambos sexos.

Discusión: El cribado y abordaje de FA en pacientes con TJ puede ayudar a optimizar enfoques preventivos y terapéuticos. Estudios futuros deberían considerar la posibilidad de instaurar pautas para mejorar los hábitos alimentarios saludables, aumentar el ejercicio físico y trabajar en estrategias adaptativas de afrontamiento ante el estrés y otras emociones negativas con el fin de abordar FA en TJ.

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ORIGINAL PAPER

Clinical Features of Gambling Disorder Patients with and Without Food Addiction: Gender-Related Considerations

Mikel Etxandi[1] · Isabel Baenas[1,2] · Lucero Munguía[1,3] · Gemma Mestre-Bach[1,4] · Roser Granero[2,5] · Mónica Gómez-Peña[1] · Laura Moragas[1] · Amparo del Pino-Gutiérrez[2,6] · Ester Codina[1] · Bernat Mora-Maltas[1] · Eduardo Valenciano-Mendoza[1] · Marc N. Potenza[7,8,9,10] · Ashley N. Gearhardt[11] · Fernando Fernández-Aranda[1,2,3] · Susana Jiménez-Murcia[1,2,3]

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Abstract
Although food addiction (FA) is a debated condition and it is not currently recognized as a formal diagnosis, it shares features with other addictions, such as gambling disorder (GD). However, the prevalence of FA in GD and the clinical correlates are incompletely understood, especially within women versus men. To investigate FA in patients presenting with GD. The sample included 867 patients diagnosed with GD (798 males and 69 females) attending a specialized behavioral addictions unit. FA was observed in 8.3% of GD patients (18.8% of women, 7.4% of men). More psychopathology and harm avoidance, greater body mass indices and less self-directedness and cooperativeness were associated with FA. In women, FA was associated with a longer GD duration. In men, FA was associated with earlier GD onset, greater GD and problematic alcohol use severities. Among patients with GD, FA was associated with more psychopathology and gambling patterns suggestive of more protracted or severe GD. Screening for and addressing FA condition in patients with GD may help optimize preventive and therapeutic approaches. Future studies should consider testing guidelines to improve healthy eating habits, increase physical exercise and better manage stress and other negative emotions in order to target FA in GD.

Keywords Addictive behaviors · Food addiction · Gambling disorder · Alcohol · Gender

✉ Susana Jiménez-Murcia
sjimenez@bellvitgehospital.cat

Extended author information available on the last page of the article

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Introduction

Gambling disorder (GD) is considered a behavioral addiction and defined as a persistent and recurrent maladaptive pattern of gambling behavior associated with impaired functioning in personal, social, and occupational domains (APA, 2013; Fauth-Bühler et al., 2017; Potenza et al., 2019). GD frequently co-occurs with other psychiatric disorders including substance use, mood, anxiety and personality disorders (Grant & Chamberlain, 2015; Karlsson et al., 2019; Kim et al., 2018; Petry et al., 2005; Tackett et al., 2017). Although food addiction (FA) is not a formal diagnostic entity, a possible association between GD and FA has been suggested (Jiménez-Murcia et al., 2017). The prevalence of FA has been estimated at 7.8% in individuals with GD, and an association between body mass index (BMI) and FA symptomatology has been described for patients with GD (Granero, Jiménez-Murcia, et al., 2018).

At least two frameworks have been proposed when conceptualizing FA: addictive-like eating and substance-based addiction models (Fernandez-Aranda et al., 2018; Hebebranda et al., 2014; Schulte et al., 2017). This lack of consensus may in part contribute to FA not being considered as a formal mental disorder in the current editions of the Diagnostic and Statistical Manual (DSM-5) or the International Classification of Diseases (ICD-11) (APA, 2013; The World Health Organisation, 2019). The substance-based addiction framework purports that some foods, especially palatable ones with large amounts of processed sugars and fats, may promote both overeating and addictive-like behaviors by activating brain reward systems (Schulte et al., 2015a). Therefore, FA may show similarities with other addictions, such as substance use disorders (SUDs) (Gearhardt et al., 2011; Schulte et al., 2015b). Proposed similarities include a preoccupation with obtaining the desired substance, the development of tolerance, abstinence, excessive use, difficulties reducing consumption despite negative physical and psychological consequences and similar neural processes (Carter & Davis, 2010; Gearhardt et al., 2011; Volkow et al., 2011,Fletcher & Kenny, 2018; Gordon et al., 2018; Pursey et al., 2019).

Given GD's classification as a behavioral addiction, common features between FA and GD may exist (Jiménez-Murcia et al., 2017). Both are associated with difficulties in controlling behavior (Hardy et al., 2018; Saunders et al., 2017), and impaired executive functions (Mestre-Bach, Fernández-Aranda, et al., 2020a; Steward et al., 2018). As with GD, psychopathology has been associated with FA (Burrows et al., 2018; Jiménez-Murcia et al., 2019). As well, GD and FA may involve maladaptive emotional regulation, engaging in gambling or eating for negative reinforcement motivations; i.e., to alleviate negative emotions (Innamorati et al., 2017; Mestre-Bach, Fernández-Aranda, et al., 2020b). Finally, impulsivity is another common feature between both disorders (Kandeger et al., 2019; Mestre-Bach, Steward et al., 2020), that has been highly associated with the development and maintenance of behavioral addictions (Lee et al., 2019), considering the tendency to respond with little forethought with the maladaptive behaviors, in spite of the negative later repercussions(Grant & Chamberlain, 2020). Same characteristics has been found in binge-related impulsive behaviors presents in Bulimia Nervosa and Binge eating disorders (Treasure et al., 2020), that has also been related with FA (Jiménez-Murcia, Agüera, Paslakis & Munguia, 2019; Penzenstadler et al., 2018).

Differences between GD and FA have also been described. For example, GD is more frequently observed among men, although the gender gap appears to be narrowing (Abbott et al., 2018; Subramaniam et al., 2015). Gender-related differences in types of gambling, age of onset and other features have been reported in GD (Zakiniaeiz et al., 2017). In

contrast, FA is more frequently observed among women (Pursey et al., 2014). Women as compared with men are also more likely tendencies to engage in addictive behaviors and eating for negative reinforcement motivations that include coping with stress, depression and anxiety (Zakiniaeiz & Potenza, 2018). Thus, there is a need to consider gender in understanding how FA may relate to clinical features in GD patients.

Although these two clinical entities have begun to be studied together, gender, personality traits and psychopathology have been scarcely investigated in GD individuals with and without FA. In the study from Jimenez-Murcia et al. (2017), the comorbidity between FA and treatment-seeking patients with GD was related to poorer emotional and psychological states. Being female and younger were two condition more associated with the co-occurrence of FA and GD. Regarding personality traits, high scores in harm avoidance and self-transcendence, and low scores in cooperativeness were associated with a higher risk of presenting FA among subjects with GD. However, the authors did not find significant differences in age of onset, duration of gambling problems or drug use among others, between participants with GD and those with comorbid FA.

Therefore, the present study aimed to assess the clinical correlates of FA among GD patients, considering personality features, psychological state or substance consumption, examined in men and women separately, anticipating potential gender-related differences as the literature points out. Our main hypothesis is that the presence of FA among GD would be associated with worse clinical profiles, greater psychopathology and more severe GD. We also anticipated more frequent FA among women (versus men) with GD.

Methods

Participants

The study sample consisted of 867 GD patients including 798 men and 69 women. Participants were referred for treatment to the Pathological Gambling Unit in the Psychiatry Department at a General University Hospital, in Spain, between May of 2016 and June of 2020. This hospital is part of the Spanish Public Assistance Network and of a Public University Campus, having its own research institute. It is the local reference center for a population of around 343,000 inhabitants and the territorial tertiary reference center for more than 2 million people. Participants were diagnosed according to the DSM-5 (APA, 2013) criteria for GD by clinical psychologists and psychiatrists with more than 20 years of experience in the field of behavioral addictions and eating disorders. None met DSM-5 diagnostic criteria for any current eating disorder, being a comorbid diagnostic of ED an exclusion criteria for the present study.

Measures

The South Oaks Gambling Screen (SOGS) (Lesieur & Blume, 1987) is a 20-item screen for problem gambling behaviors and consequences during the prior twelve months. The total score reflects problem gambling severity, with a score of 4 or more indicating problem gambling. The Spanish validation of the scale achieved very good psychometric results in the adaptation study (test-retest reliability $R = 0.98$, internal consistency $\alpha = 0.94$ and convergent validity $R = 0.92$) (Echeburúa et al., 1994). The internal consistency for this scale in the study sample was adequate ($\alpha = 0.74$).

The Diagnostic Questionnaire for Pathological Gambling (Stinchfield, 2003) is a self-report questionnaire with 19 items coded in a binary fashion (yes-no) that permits assessing DSM-IV (American Psychiatric Association, 2010) and DSM-5 (APA, 2013) diagnostic criteria for GD. Itwas used in the present study for assessing GD. Based on the DSM-5 taxonomy, several GD-related measures may be generated: thepresence/absence of each DSM inclusion criterion, the presence/absence of GD diagnosis, a dimensional measure of problem gambling severity (total number of DSM criteria, obtained as the sum of the individual criteria), and GDseverity grouped in four levels [non-problem gambling (0 criteria), problem gambling (for 1–3 criteria), mild GD (4–5 criteria), moderate GD (6–7 criteria) and severe GD (8–9 criteria)]. The Spanish adaptation of the questionnaire obtained satisfactory psychometric properties: internal consistency with a Cronbach's alpha equal to 0.95 for the combined sample, satisfactory convergent validity (moderate to large correlations with other measures of problem gambling severity), and high discriminative capacity (sensitivity = 0.92 and specificity = 0.99) (Jiménez-Murcia et al., 2009). The internal consistency for this scale in the study sample was good ($\alpha = 0.80$).

The Symptom Checklist-90-Revised (SCL-90-R) (Derogatis, 1994) is a 90-item self-report questionnaire measured on an ordinal 3-point scale that evaluates a broad range of psychological problems and symptoms of psychopathology by measuring nine primary symptom dimensions: Somatization, Obsession-Compulsion, Interpersonal Sensitivity, Depression, Anxiety, Hostility, Phobic Anxiety, Paranoid Ideation, and Psychoticism. It includes three global ratings, named global severity index (overall psychological distress), positive symptom distress index (the intensity of symptoms), and positive symptom total (self-reported symptoms). The global severity index can be used as a summary of the test. The validation of the scale in a Spanish population (Derogatis, 2002) obtained a mean internal consistency of 0.75 (coefficient alpha). The internal consistency in the study was excellent for the global ratings ($\alpha = 0.98$) and the one for the subscales range from adequate to excellent ($\alpha = 0.80$ for Paranoid Ideation to $\alpha = 0.92$ for Depressive).

The Temperament and Character Inventory-Revised (TCI-R) (Cloninger, 1999) is a questionnaire with 240 items scored on a 5-point Likert scale, which measures personality factors related to three character dimensions (Self-Directedness, Cooperativeness, and Self-Transcendence) and four temperament dimensions (Harm Avoidance, Novelty Seeking, Reward Dependence and Persistence). Evaluation of the Spanish revised version (Gutiérrez-Zotes et al., 2004) had an internal consistency of 0.87 (coefficient alpha). The internal consistency in this study for the subscales ranged from adequate to very good ($\alpha = 0.70$ for Novelty Seeking to $\alpha = 0.87$ for Self-Directedness).

The Yale Food Addiction Scale 2.0 (YFAS-2) (Gearhardt et al., 2016) is a 35-item self-report questionnaire for measuring FA during the prior year. The original YFAS was based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) (APA, 2010) criteria for substance dependence and was adapted to the context of food consumption. The YFAS-2 is based on DSM-5 criteria for SUDs (APA, 2013) and evaluates 11 symptoms. Two measurements may be calculated: (a) a continuous symptom count score reflecting the number of fulfilled criteria (ranging from 0 to 11), and (b) a FA threshold based on the number of symptoms (at least 2) and self-reported clinically significant impairment or distress. This final measurement allows for the binary classification of FA (present versus absent). Based on the revised DSM-5 taxonomy, it is possible to establish severity cut-offs: mild (2–3 symptoms), moderate (4–5 symptoms), and severe (6–11 symptoms). The Spanish validation of the YFAS-2 (Granero, Jiménez-Murcia, et al., 2018) generated an internal consistency of 0.94 (coefficient alpha). In this study, internal consistency for the total score was excellent ($\alpha = 0.96$).

The Alcohol Use Disorders Identification Test (AUDIT) (Saunders et al., 1993) is a 10-item screening questionnaire for hazardous alcohol consumption. It includes questions about the amount and frequency of drinking, alcohol dependence, and problems caused by alcohol. A score of 8 or more is considered to indicate harmful alcohol use and a score of 12 or more in women (15 or more in men) is likely to indicate alcohol dependence. This questionnaire has shown adequate validity in Spanish samples (Delgado, 1996).

The Drug Use Disorders Identification Test (DUDIT) (Berman et al., 2003) is an 11-item self-administered instrument to identify non-alcohol drug use patterns and related problems in individuals likely to meet criteria for a substance dependence diagnosis. The total score can range from 0 to 44 (as a result of the sum of the 11 items scored from 0 to 4); higher scores reflect more severe drug use problem. The first nine items are scored on a 5-point Likert scale ranging from 0 to 4, and the last two are scored on 3-point scales (values of 0, 2, and 4).

Other variables, including sociodemographic variables and other gambling-related measures (e.g. age of onset and duration), were obtained via face-to-face clinical interviews. The interviews also assessed participants' educational attainment. Socioeconomic status was assessed using the Hollingshead Four Factor Index of Socioeconomic Status (Hollingshead, 2011).

Procedure

All participants in our sample voluntarily sought treatment for GD. Experienced psychologists and psychiatrists conducted two face-to-face clinical interviews, before and after completing study instruments. The first visit was a clinical interview, in which the medical/psychiatric history was assessed, and the subsequent visit consisted of an interview to report the results of the tests and information about the treatment, according to their clinical characteristics and factors associated with GD.

The participants included in this study met criteria for GD and did not present other comorbid behavioral addictions and did not receive any compensation for participating in the study.

Statistical Analyses

Statistical analysis was conducted with Stata16 for Windows (Stata-Corp, 2019). Between-group comparisons for personality (TCI-R), psychopathology (SCL-90R), substance use and BMI measures were based on analysis of variance adjusted for age (ANCOVA) (gender was not considered as a covariate because results stratified for men and women were obtained). Effect sizes for mean differences were estimated through Cohen's d coefficient, poor-low for $|d|>0.20$, mild-moderate for $|d|>0.50$ and large-high for $|d|>0.80$ (Kelley & Preacher, 2012). Between-group comparisons for categorical variables were based on logistic regression also adjusted for age. Type-I error related to multiple comparisons was controlled using the Finner's method, a family-wise procedure with higher power than a Bonferroni correction (Finner & Roters, 2001).

Path analysis was used to assess the set of relationships between gender, age, the personality domains of self-directedness and harm avoidance, FA severity, global psychopathological distress and gambling preference. Path analysis constitutes an extension of multiple regression modeling, used with the aim of estimating magnitudes and significance of simultaneous associations in a set of variables, including direct and indirect effects

(mediational links) (Kline, 2005). This technique is currently used for both exploratory and confirmatory purposes, and therefore it contributes to theory testing and theory development (MacCallum & Austin, 2000). This study modeled path analyses through structural equation modeling (SEM), with the maximum-likelihood estimation method. Goodness of fit was assessed with standard indexes, and it was considered adequate fitting (Barrett, 2007) for: non-significant result in the chi-square test (χ^2), root mean square error of approximation RMSEA < 0.08, Bentler's Comparative Fit Index CFI > 0.90, Tucker-Lewis Index TLI > 0.90, and standardized root mean square residual SRMR < 0.10. Global predictive capacity was estimated with the coefficient of determination (CD).

Ethics

The present study was conducted in accordance with the latest version of the Declaration of Helsinki. The General University Hospital Clinical Research Ethics Committee approved the study, and signed informed consent was obtained from all participants (Ref: PR329/19).

Results

Sample Characteristics

Most patients were single ($n = 454$, 52.4%) or married ($n = 313$, 36.1%), achieved primary ($n = 460$, 53.1%) or secondary ($n = 331$, 38.2%) education levels, were of medium-low or low socioeconomic status ($n = 723$, 83.4%) and were employed ($n = 527$, 60.8%). Mean age was 40.5 years (SD = 13.8). Most patients reportedonly non-strategic gambling ($n = 449$; 51.8%), and 26.1% ($n = 226$) and 22.1% ($n = 192$) reported only strategic gambling and both gambling forms, respectively. Strategic gambling activities are those wherethe gambler can use knowledge of the game to influence or predict the outcome, while nonstrategic gambling implies little or no possibility of influencing the outcome (Potenza et al., 2001). The gambling activity reported as the main reason for seeking treatment in the sample was slot-machines (60.1%), followed by casino or gambling saloons (24.7%), sports-betting (16.0%), and lotteries (14.4%).

Comparison Between Patients with Positive Versus Negative FA Screening

Seventy-two participants (8.3%) screened positive for FA. FA was observed among 18.8% of women and 7.4% of men. Table 1 contains the comparison for individuals with negative versus positive FA screening, stratified by gender (separate comparisons were performed for women and men due the potential moderator role of gender). Among women, FA was associated with harm avoidance, less self-directedness and cooperativeness, greater psychopathology and higher BMI. Among men, FA was associated with harm avoidance and self-transcendence, less self-directedness and cooperativeness, greater psychopathology, greater alcohol use problem severity and higher BMI.

Table 2 includes the prevalence of patients outside the normative ranges for the main psychological variables of the study (estimates represent proportions of participants in subclinical or clinical severity levels). Among women, FA was associated with obesity, greater psychopathology and more self-directedness. Among men, FA was associated

Table 1 Associations between FA and clinical variables with the FA measures

	Women						Men					
	FA − (n = 56)		FA + (n = 13)				FA − (n = 739		FA + (n = *59*)			
	Mean	SD	Mean	SD	*p*	|d|	Mean	SD	Mean	SD	*p*	|d|
TCI-R Novelty seeking	108.3	12.2	106.4	8.8	.585	0.19	110.9	13.0	111.8	12.5	.371	0.07
TCI-R Harm avoidance	108.2	17.4	118.3	17.2	**.046***	**0.59**†	98.4	15.8	107.4	15.4	**.001***	**0.58**†
TCI-R Reward depend	101.1	14.7	99.8	10.6	.763	0.11	97.3	13.8	95.4	16.1	.324	0.12
TCI-R Persistence	105.5	18.1	103.4	21.7	.729	0.10	108.2	18.5	105.1	22.7	.228	0.15
TCI-R Self-directedness	128.4	20.6	108.8	18.7	**.003***	**1.00**†	130.4	21.2	117.4	18.8	**.001***	**0.65**†
TCI-R Cooperativeness	137.7	12.2	129.3	13.8	**.035***	**0.65**†	129.6	15.6	122.9	18.8	**.002***	0.39
TCI-R Transcendence	62.7	13.7	67.4	11.2	.255	0.38	61.2	14.1	67.7	14.7	**.001***	0.46
SCL-90R Somatization	1.40	0.90	2.34	0.89	**.001***	**1.05**†	0.89	0.76	1.54	0.99	**.001***	**0.75**†
SCL-90R Obsessive/comp	1.32	0.87	2.16	0.99	**.004***	**0.90**†	1.11	0.77	1.93	0.93	**.001***	**0.97**†
SCL-90R Interp. sensitive	1.21	0.85	2.32	0.84	**.001***	**1.32**†	0.97	0.80	1.74	0.95	**.001***	**0.87**†
SCL-90R Depressive	1.87	1.00	2.74	0.82	**.005***	**0.95**†	1.50	0.92	2.20	0.93	**.001***	**0.75**†
SCL-90R Anxiety	1.20	0.84	2.06	0.72	**.001***	**1.10**†	0.97	0.78	1.59	0.98	**.001***	**0.69**†
SCL-90R Hostility	0.90	0.78	1.67	0.73	**.002***	**1.02**†	0.94	0.84	1.53	1.10	**.001***	**0.61**†
SCL-90R Phobic anxiety	0.54	0.51	1.25	1.09	**.001***	**0.85**†	0.42	0.61	0.97	0.90	**.001***	**0.73**†
SCL-90R Paranoid	1.09	0.84	2.21	0.86	**.001***	**1.32**†	0.94	0.80	1.60	0.99	**.001***	**0.74**†
SCL-90R Psychotic	0.98	0.82	1.68	0.70	**.007***	**0.92**†	0.89	0.75	1.57	0.95	**.001***	**0.80**†
SCL-90R GSI score	1.28	0.72	2.13	0.65	**.001***	**1.24**†	1.03	0.68	1.72	0.83	**.001***	**0.91**†
SCL-90R PST score	51.20	20.16	65.91	15.96	**.018***	**0.81**†	46.42	21.96	62.03	18.86	**.001***	**0.76**†
SCL-90R PSDI score	2.08	0.60	2.89	0.61	**.001***	**1.33**†	1.85	0.56	2.37	0.71	**.001***	**0.82**†
Tobacco (cigarettes/day)	9.91	11.51	7.55	13.77	.531	0.19	9.45	10.90	9.31	13.12	.925	0.01
Alcohol (AUDIT total)	2.41	4.01	1.06	1.87	.254	0.43	5.20	5.68	7.25	8.31	**.011***	0.29
Drugs (DUDIT total)	1.25	4.02	0.10	0.00	.320	0.40	2.75	6.61	3.80	8.18	.247	0.14

Table 1 (continued)

	Women						Men					
	FA − (n = 56)		FA + (n = 13)				FA − (n = 739		FA + (n = *59)*			
	Mean	SD	Mean	SD	*p*	|d|	Mean	SD	Mean	SD	*p*	|d|
Body mass index (kg/m^2)	27.43	5.96	33.43	6.89	.002*	**0.93**†	26.08	4.35	30.34	6.87	.001*	**0.74**†

SD: standard deviation; FA − : food addiction negative screening; FA + : food addiction positive screening

TCI-R: Temperament and Character Inventory – Revised

SCL-90R: Symptom Checklist-90-Revised

AUDIT: Alcohol Use Disorders Identification Test

DUDIT: Drug Use Disorders Identification Test

*Bold: significant parameter (.05 level)

†Bold: effect size into the range mild-moderate (|*d*|> 0.50) to large-high (|*d*|> 0.80)

Results adjusted by the covariate age

Table 2 Comparison of clinical measures by gender and FA status

	Women						Men					
	FA − (n = 56)		FA + (n = 13)				FA − (n = 739)		FA + (n = 59)			
	n	%	n	%	*p*	|*d*|	n	%	n	%	*p*	|*d*|
GD (8–9 DSM-5 criteria)	30	53.6	8	61.5	.603	0.16	354	47.9	42	71.2	**.001***	**0.51**†
Obesity (BMI > 30)	18	32.1	9	69.2	**.014***	**0.76**†	129	17.5	32	54.2	**.001***	**0.79**†
SCL-90R Somatization	22	39.3	10	76.9	**.013***	**0.78**†	288	39.0	41	69.5	**.001***	**0.62**†
SCL-90R Obsessive/comp	24	42.9	10	76.9	**.027***	**0.71**†	304	41.1	46	78.0	**.001***	**0.77**†
SCL-90R Interp. sensitive	30	53.6	11	84.6	**.040***	**0.69**†	323	43.7	48	81.4	**.001***	**0.80**†
SCL-90R Depressive	30	53.6	12	92.3	**.010***	**0.94**†	439	59.4	47	79.7	**.001***	**0.50**†
SCL-90R Anxiety	17	30.4	10	76.9	**.002***	**0.97**†	321	43.4	41	69.5	**.001***	**0.53**†
SCL-90R Hostility	14	25.0	10	76.9	**.001***	**1.09**†	207	28.0	31	52.5	**.001***	**0.51**†
SCL-90R Phobic anxiety	13	23.2	7	53.8	**.028***	**0.64**†	196	26.5	37	62.7	**.001***	**0.75**†
SCL-90R Paranoid	23	41.1	11	84.6	**.005***	**0.94**†	219	29.6	36	61.0	**.001***	**0.64**†
SCL-90R Psychotic	30	53.6	12	92.3	**.010***	**0.94**†	363	49.1	45	76.3	**.001***	**0.57**†
SCL-90R GSI score	31	55.4	13	100.0	**.003***	**1.46**†	419	56.7	50	84.7	**.001***	**0.63**†
SCL-90R PST score	35	62.5	11	84.6	.128	**0.51**†	420	56.8	48	81.4	**.001***	**0.54**†
SCL-90R PSDI score	8	14.3	8	61.5	**.001***	**1.03**†	160	21.7	31	52.5	**.001***	**0.65**†
TCI-R Novelty seeking	30	53.6	4	30.8	.138	0.47	324	43.8	22	37.3	.328	0.13
TCI-R Harm avoidance	28	50.0	7	53.8	.803	0.08	263	35.6	33	55.9	**.002***	0.41
TCI-R Reward depend	21	37.5	6	46.2	.565	0.18	260	35.2	25	42.4	.267	0.15
TCI-R Persistence	16	28.6	6	46.2	.220	0.37	267	36.1	25	42.4	.338	0.13
TCI-R Self-directedness	41	73.2	12	92.3	.142	**0.53**†	465	62.9	47	79.7	**.010***	0.37
TCI-R Cooperativeness	16	28.6	6	46.2	.220	0.37	277	37.5	37	62.7	**.001***	**0.51**†
TCI-R Transcendence	16	28.6	4	30.8	.875	0.05	286	38.7	19	32.2	.323	0.14

SD: standard deviation; GD: gambling disorder

FA −: food addiction negative screening. FA +: food addiction positive screening. BMI: Body Mass Index

SCL-90R: Symptom Checklist-90-Revised

TCI-R: Temperament and Character Inventory-Revised

*Bold: significant parameter (.05 level)

†Bold: effect size into the range mild-moderate (|*d*| > 0.50) to large-high (|*d*| > 0.80)

Results adjusted by the covariate age

with higher GD severity, obesity, greater psychopathology, more self-directedness and harm avoidance and less cooperativeness.

Table S1 (supplementary) contains the comparison between patients with negative versus positive FA screening for socio-demographics, gambling profile, and problem gambling severity measured as the total number of DSM-5 criteria for GD and SOGS scores. Among women, FA was associated with lower socioeconomic status, unemployment, non-strategic gambling preference, and longer durations of gambling problems. Among men, FA was associated with higher socioeconomic status, greater GD severity and earlier age of onset of gambling.

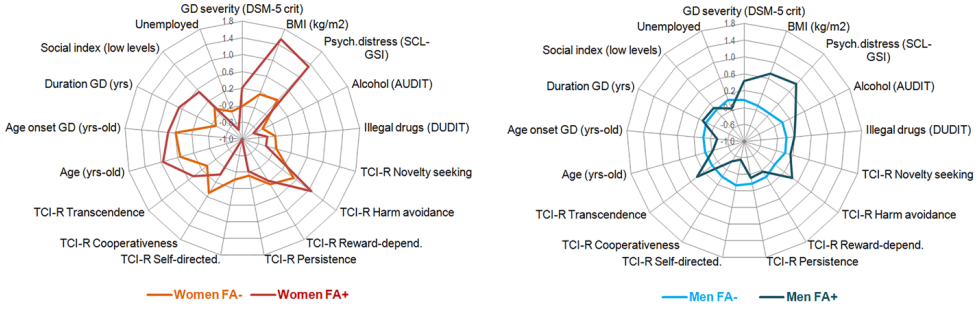

Fig. 1 Radar chart (n = 867)

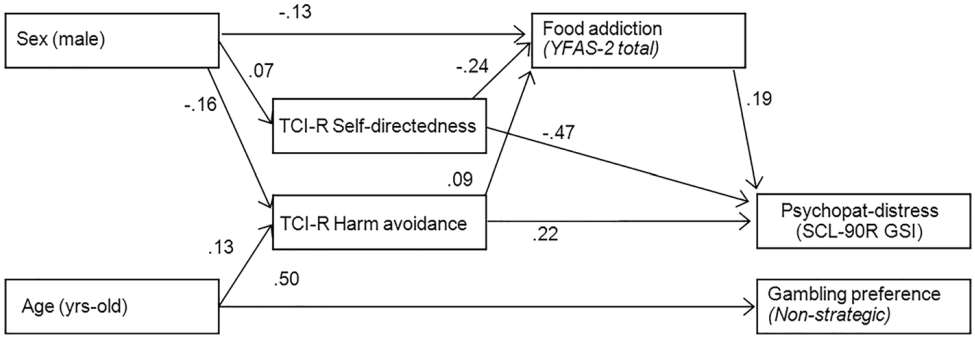

Fig. 2 Path diagram with the results of the structural equation model (n = 867). *Note* Only significant coefficients were retained in the model

Figure 1 displays a radar chart with the profiles related to FA, separately for women and men. Standardized scores are plotted in this graphic to allow easy interpretation as original scales had different ranges.

Path Analysis

Figure 2 displays a path diagram with standardized coefficients obtained in the path analysis (Table S2 includes the complete results for this model, including tests for direct, indirect and total effects). Only significant coefficients were retained in the final model. Only two personality domains were retained (self-directedness and harm avoidance) because the other TCI-R scales did not achieve significant effects. Adequate goodness-of-fit was achieved: $\chi^2 = 10.71$ ($p = 0.296$), RMSEA = 0.015 (95% confidence interval: 0.001 to 0.043), CFI = 0.999, TLI = 0.997, and SRMR = 0.019. Global predictive capacity was also good (CD = 0.299).

FA severity level (defined as the YFAS-2 total score) was higher for women and participants with lower self-directedness scores and higher harm avoidance level. Both personality domains also showed mediational links between gender and age with FA severity: being female was associated with decreased self-directedness and increased harm avoidance, while older age was associated with increased harm avoidance. Path analysis also suggested that FA levels led to higher psychopathology, which also was directly related to

lower self-directedness and higher harm avoidance. Gambling preference was also directly related to age, with older age linked to preferences for non-strategic gambling.

Discussion

The present work studied among GD patients, clinical features associated with FA in women and men. The prevalence of FA in the total sample was 8.3% (18.8% among women, 7.4% among men), similar than the 7.8% reported in other similar studies (Granero, Jiménez-Murcia, et al., 2018). Besides, this percentage is lower than the one corresponding to the presence of FA in non-clinical population (Gearhardt et al., 2016), the study of the common features between both disorders responds to the similar aspects involved in the addictive process, already mentioned in the literature (Innamorati et al., 2017; Jiménez-Murcia et al., 2017; Mestre-Bach, Steward, et al., 2020).

Although no relation between FA and age was found, significant differences in socioeconomic level and employment state were evidenced only among women. In this vein, women with FA had lower socioeconomic status and unemployed. Higher scores in general psychopathology and certain personality traits, namely higher harm avoidance and lower self-directedness and cooperativeness were found in both genders. However, men with FA presented higher self-transcendence, although a numerical difference in the same direction with a similar effect size was observed in women, suggesting a similar relationship in the smaller female sample. Regardless of gender, FA was associated with a higher BMI and obesity. Association between FA and types of gambling were largely negligible. Implications are discussed below.

Although a higher prevalence of GD is described in men than women (Blanco et al., 2006; Husky et al., 2015), previous studies have reported that women are more likely to engage in FA behaviors (Schulte & Gearhardt, 2018) and experience abnormal eating and weight disorders (Jiménez-Murcia et al., 2019; Romero et al., 2019; Schulte & Gearhardt, 2018), with initial studies suggesting similar relationships in patients with GD (Granero et al., 2018; Jiménez-Murcia et al., 2017). Lower socioeconomic status has been associated with GD severity among women (Jiménez-Murcia et al., 2020). Higher psychopathology, particularly depressive and anxiety symptoms, and some specific personality features, such as low self-directedness and perseverance or high reward dependence, have been linked to FA in both medical and mental conditions (Brunault et al., 2018; Imperatori, 2014; Wolz et al., 2016). FA may impact global health, with a special influence on BMI and overweight/obesity (Murphy et al., 2014; Meseri et al., 2020). Our findings among GD patients suggest a poor socioeconomic context and work difficulties (e.g., unemployment), higher emotional vulnerability (e.g., anxiety and depressive symptoms, particularly for women) and poor adaptive coping strategies to deal with stress (e.g., higher harm avoidance and lower self-directedness and cooperativeness) may characterize GD patients with FA.

Regarding clinical features, women with GD and FA had higher duration of GD in comparison with those who did not fulfill FA criteria. Male patients with both disorders were characterized by lower age of onset and higher severity of the GD. These results differ from previous studies were no differences in age of onset and duration of GD were found among patients with GD and FA (Jiménez-Murcia et al., 2017). Moreover, no significant differences were found in gambling modality associated with the presence of FA in neither gender group. Thus, our results could suggest that the presence of FA in patients with GD might be associated with a more severe GD clinical profile in both genders.

Both men and women with GD and FA appear to fit the emotionally vulnerable subtype from the pathway model proposed by Blaszczynski & Nower (2002), and also within the cluster 2–3 (moderate-functional clusters) described among FA individuals with obesity by Jimenez-Murcia (2019). In this group of patients, gambling and eating behaviors might represent potential elements of addiction as these behaviors are seen as strategies to relieve emotional discomfort they may experience in daily situations, usually perceived as threatening and stressful, or which they may not have the proper skills to manage adequately. Therefore, the identification of a vulnerable clinical profile at baseline among GD patients with FA suggests a need for early systematic identification of FA by clinicians. Although both genders have similarities, this subtype may be especially important among women, who appear more likely to experience FA, overweight/obesity and fewer socio-economic resources. Moreover, the creation and/or optimization of specific and individualized social and therapeutic approaches are needed, taking into account that the lack of social support, economic difficulties or physical limitations (e.g., related to obesity) may result in decreased access to medical services. As suggested in previous studies (Jiménez-Murcia et al., 2019), some approaches may target better nutritional and weight management, but also emotional regulation and problem-solving strategies to cope with stress may also be needed.

To the best of our knowledge, this is the first study that analyzes clinical correlates of FA in GD patients from a gender-informed perspective. The results suggest a negative influence of FA on GD, in terms of a higher presence of poor prognosis factors for GD in patients with comorbid FA, that are both similar across genders and differ by gender. With respect to the latter, a longer duration of the GD was associated with FA in women, and in men, FA was associated with an earlier age of onset and higher severities of GD and problematic alcohol use. Of note, some of these differences (particularly with respect to relationships with GD severity) may also pertain to women, as evidenced by largely similar effect sizes and the smaller sample of women.

The clinical characteristics associated with FA have been reported as having deleterious impacts on the course of GD (del Pino-Gutiérrez et al., 2017; Jiménez-Murcia et al., 2016; Valero-Solís et al., 2018). Low socioeconomic status or co-occurring psychopathology (e.g. depression, anxiety) may be particularly relevant to FA in women with GD. These factors could delay medical consultation for GD, resulting in a longer duration of GD when receiving a GD diagnosis. In the case of men, early age of gambling onset and problematic alcohol use appear particularly relevant. Previous studies have reported a relationship between FA and tobacco use among a male predominant sample with GD (Jiménez-Murcia et al., 2017). Apart from gambling and food, men with GD and FA may also use alcohol as a mechanism to cope with stress and negative emotions.

FA was more prevalent among women (versus men) with GD. These results suggest that assessing for FA in treatment-seeking individuals with GD may be particularly helpful for women's health and useful in general for identifying vulnerable patients presenting with the potential for worse courses of GD. The detection and simultaneous treatment of co-occurring psychiatric concerns among GD patients is important. Our findings suggest that the design of specific protocols to detect FA is needed, as is the testing of treatment approaches used in other care settings for addressing FA in GD populations.

In considering the pathway analyses, relationships between gender and personality features with appear mediated by FA. Therefore, the results reinforcement the interpretations of a specific vulnerable group of GD patients (i.e., women with dysfunctional personality features) in whom FA may represent a maladaptive way of dealing with higher levels of psychological distress. Similar conclusions may extend to GD, as has been also proposed

previously (Di Trani et al., 2017; Jiménez-Murcia et al., 2017), with poor emotional regulation contributing importantly to behavioral addictions (Estévez et al., 2017; Mestre-Bach, Fernández-Aranda, et al., 2020b). In thissense, the detection of FA among GD patients could lead to a greater emphasis on approaches to improve emotional regulation (e.g., with mindfulness-based or stress-reduction treatments) within GD treatment. The acquisition of adaptive emotional skills may be translated into a better stress management and reduced gambling and eating to manage such negative states.

A relationship between age and gambling preferences was found, with preferences for non-strategic gambling with older age, consistent with prior findings (Potenza, Steinberg, et al., 2006). Among patients with FA the relationship with GD subtype was only indirect, and specifically in females. This result is consistent with previous works regarding GD samples (Assanangkornchai et al., 2016; Odlaug et al., 2011). Men (particularly younger ones) tend to prefer and have problems with strategic gambling, whereas women (particularly older ones) tend to prefer and have problems with non-strategic gambling (Moragas et al., 2015; Odlaug et al., 2011; Potenza et al., 2001; Potenza et al., 2006; Stevens & Young, 2010).

Strength and Limits

Strengths of this study, such as the large clinical sample, should be mentioned. To date, this is the first study to consider FA in GD patients in a gender-sensitive manner. As the sample consisted of patients treated at a specific unit, assessments were consistently conducted. However, study limitations should also be mentioned. For instance, the treatment-seeking sample was from a region of Spain; as such, the findings may not generalize to non-clinical samples or those from other jurisdictions. The use of self-report assessments for psychiatric conditions may decrease reliability. Future studies should consider alternate assessments (e.g., structured clinical interviews). However, as FA remains a debated construct, its evaluation with a self-report measure is presently most reasonable. Another limitation of the study was the small sample size for the group of patients who met criteria for FA: the underpowered statistical accuracy reduces the change of detecting a true effect, reproducibility of the results and generalization capacity. In addition, the cross-sectional nature of the study did not allow the study of the progression of the concurrent condition of GD with FA, nor examining the underlying mechanisms contributing to the course of this complex clinical condition.

Conclusions

In conclusion, this study characterizes the clinical profile of GD patients with and without FA from a gender-informed perspective. GD patients, especially women, with specific personality characteristics and psychopathology may be particularly prone to FA. Further, a lower socioeconomic status may also be relevant for women with GD to experience FA. Speculatively, the findings taken together suggest that GD patients may engage in FA behaviors to manage high levels of psychological distress. Alcohol and consumption, early age of onset, and severity of GD may contribute to a worse GD prognosis in the presence of FA, particularly in men. In women, a longer duration of GD was linked to FA, suggesting the need for enhancing early intervention efforts to

improve women's health. Therefore, these results support the existence of a specific vulnerable group of GD patients and suggest the relevance of designing specific screening and treatment protocol to address FA in GD patients. Further studies are necessary to increase knowledge about FA and its influence not only in GD, but also in other addictive disorders and mental health conditions. Addressing areas such as underlying mechanisms and neurobiological factors related to FA could be helpful for a better understanding of this condition and its clinical relevance.

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Authors' Contribution ME, IB, LM, GM-B and SJ-M contributed to the development of the study concept and design. RG performed the statistical analysis. ME, IB, MG-P, LM, AP-G, EC, BM-M and EV-M aided with data collection. ME, IB, LM, GM-B and SJ-M aided with interpretation of data and the writing of the manuscript. MNP, ANG, FF-A, and SJ-M revised the manuscript and provided substantial comments. FF-A and SJ-M obtained funding.

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Data Availability and Material (Data Transparency) Individuals may inquire with Dr. Jiménez-Murcia regarding availability of the data as there exist ongoing studies using the data. In order to avoid overlapping research efforts, Dr. Jiménez-Murcia will consider request on a case-by-case bases.

Code Availability Not applicable.

Declarations

Conflict of interest Dr. Potenza has consulted for and advised Game Day Data, the Addiction Policy Forum, AXA, Idorsia, and Opiant Therapeutics; has received research support from the Veteran's Administration, Mohegan Sun Casino, and the National Center for Responsible Gaming (no the International Center for Responsible Gambling); has participated in surveys, mailings, or telephone consultations related to addictions, impulse-control disorders or other health topics; has consulted for law offices and the federal public defender's office in issues related to impulse-control and addictive disorders; has provided clinical care in the Connecticut Department of Mental Health and Addiction Services Problem Gambling Services Program; has performed grant reviews for the National Institutes of Health and other agencies; has edited journals and journal sections; has given academic lectures in grand rounds, CME events and other clinical/scientific venues; and has generated books or chapters for publishers of mental health texts. Other authors report no disclosures. Dr. Fernandez-Aranda received consultancy honoraria from Novo Nordisk and editorial honoraria as EIC from Wiley. The rest of the authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

Ethical Approval The present study was carried out in accordance with the latest version of the Declaration of Helsinki. The Bellvitge University Hospital Clinical Research Ethics Committee approved the study, and signed informed consent was previously obtained from all participants (Ref: PR329/19).

Consent to Participate All subjects were informed about the study and all provided a written informed consent.

Consent for Publication Consent for publication of this article has been obtained from all authors.

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Authors and Affiliations

Mikel Etxandi[1] · Isabel Baenas[1,2] · Lucero Munguía[1,3] · Gemma Mestre-Bach[1,4] · Roser Granero[2,5] · Mónica Gómez-Peña[1] · Laura Moragas[1] · Amparo del Pino-Gutiérrez[2,6] · Ester Codina[1] · Bernat Mora-Maltas[1] · Eduardo Valenciano-Mendoza[1] · Marc N. Potenza[7,8,9,10] · Ashley N. Gearhardt[11] · Fernando Fernández-Aranda[1,2,3] · Susana Jiménez-Murcia[1,2,3]

Mikel Etxandi
mikeletxandi@gmail.com

Isabel Baenas
ibaenas@bellvitgehospital.cat

Lucero Munguía
laarcreed_lm@hotmail.com

Gemma Mestre-Bach
gemma.mestre.bach@gmail.com

Roser Granero
Roser.granero@uab.cat

Mónica Gómez-Peña
monicagomez@bellvitgehospital.cat

Laura Moragas
lmoragas@bellvitgehospital.cat

Amparo del Pino-Gutiérrez
adelpino@ub.edu

Ester Codina
ecodina@bellvitgehospital.cat

Bernat Mora-Maltas
bmora@idibell.cat

Eduardo Valenciano-Mendoza
edu.valenciano@gmail.com

Marc N. Potenza
marc.potenza@yale.edu

Ashley N. Gearhardt
agearhar@umich.edu

Fernando Fernández-Aranda
ffernandez@bellvitgehospital.cat

[1] Department of Psychiatry, Bellvitge University Hospital-IDIBELL, Feixa Llarga s/n 08907. Hospitalet del Llobregat, Barcelona, Spain

[2] Ciber Fisiopatología Obesidad y Nutrición (CIBERObn), Instituto de Salud Carlos III, Madrid, Spain

[3] Department of Clinical Sciences, School of Medicine, University of Barcelona, Barcelona, Spain

[4] Universidad Internacional de la Rioja, La Rioja, Spain

[5] Department of Psychobiology and Methodology, Autonomous University of Barcelona, Barcelona, Spain

[6] Department of Public Health, Mental Health and Perinatal Nursing, School of Nursing, University of Barcelona, Barcelona, Spain

[7] Department of Psychiatry and Child Study Center, Yale University School of Medicine, New Haven, Connecticut, USA

[8] Connecticut Council on Problem Gambling, Wethersfield, Connecticut, USA

[9] Connecticut Mental Health Center, New Haven, Connecticut, USA

[10] Department of Neuroscience, Yale University, New Haven, Connecticut, USA

[11] Department of Psychology, University of Michigan, Ann Arbor, USA

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DISCUSIÓN

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La interacción de factores neuroendocrinos relacionados con la regulación del apetito con el sistema de recompensa cerebral, así como la evidencia de su implicación en adicciones a sustancias, hace emerger la hipótesis, hasta la fecha no plenamente contrastada, de su posible papel en adicciones conductuales como el TJ u otras entidades englobadas dentro del constructo de espectro impulsivo-compulsivo, como FA. Con esta idea en mente, el principal objetivo del presente trabajo es el de profundizar en el conocimiento de la posible implicación de alteraciones hormonales y su interacción con variables neuropsicológicas y clínicas en el TJ, así como estudiar la comorbilidad de dicho trastorno con FA, tanto a nivel clínico como neurobiológico.

5.1. Alteraciones neuroendocrinas, clínicas y neuropsicológicas en Trastorno de Juego

En el estudio 1 se analizaron las hormonas leptina, grelina, LEAP-2 y adiponectina, por su conocida asociación con procesos de recompensa e implicación en la impulsividad y la compulsividad, en personas con TJ comparadas con controles sanos. Además, se compararon características neuropsicológicas y clínicas, así como su relación con los factores neuroendocrinos previamente mencionados. Los individuos con TJ presentaron un perfil endocrino alterado en comparación con los controles sanos, tras corregir por IMC, caracterizado por una mayor concentración plasmática de grelina y menor de LEAP-2 y adiponectina, sin diferencias significativas en los niveles de leptina.

El hecho de que los individuos con TJ presentaran niveles más elevados de grelina es consistente con los resultados de estudios previos en TUS, en los que, como se ha señalado en la introducción, se ha descrito un exceso de señalización por parte de esta hormona (127) y se ha propuesto su vinculación a procesos relacionados con la neurobiología de la adicción por su conocida actividad reforzadora del sistema de recompensa cerebral a través de la modulación de la neurotransmisión dopaminérgica (146). De esta forma, estos hallazgos se situarían en la línea de la creciente evidencia que respalda la existencia de un

sustrato neurobiológico común entre los TUS y adicciones comportamentales como el TJ (92), lo cual podría tener potenciales repercusiones terapéuticas.

Además, cabe resaltar que los individuos con TJ no sólo presentaron niveles elevados de grelina en comparación con el grupo control, sino también concentraciones inferiores de LEAP-2, una hormona de reciente descubrimiento y descrita previamente, con función antagónica a la grelina. Este resultado resulta interesante, ya que permite especular con la posibilidad de una potencial alteración en el sistema de señalización de grelina, en forma de un aumento de la producción de grelina y una disminución de la liberación de LEAP-2, que podría jugar un papel en la disfunción de la activación del sistema de recompensa presente en individuos con TJ. En esta línea, y a pesar de que se requieren más estudios para confirmar los hallazgos descritos, estos resultados sugieren la hipótesis de que LEAP-2 podría constituir una potencial diana terapéutica en trastornos adictivos como el TJ, y que ejercería su acción neutralizando el posible efecto perjudicial de la grelina en procesos como el *craving*, la abstinencia y las recaídas.

Las concentraciones plasmáticas inferiores de adiponectina en individuos con TJ en comparación con sujetos sanos está en línea con estudios previos realizados en TUS. Como se ha mencionado previamente, esta hormona está ampliamente relacionada con aspectos metabólicos y se le atribuyen algunas funciones protectoras por su conocido efecto antiinflamatorio, antidiabético y antiaterogénico (147). Estos resultados podrían explicar en parte el peor estado metabólico y la mayor prevalencia de enfermedades cardiovasculares en pacientes con trastornos adictivos, como el TJ, que según la literatura previa y al igual que en los resultados del estudio 1, también se relacionan con un mayor IMC (147,148). En cuanto a las concentraciones de leptina, los resultados del estudio 1 coinciden con los hallazgos de estudios previos en TJ, en los que no se han descrito alteraciones en la señalización de dicha hormona (137), que sí parece estar implicada intrínsecamente en otros procesos como la adicción a la comida, como se discutirá más adelante.

A nivel neuropsicológico, tal y como era esperable teniendo en cuenta la evidencia previa, los individuos con TJ presentaron una menor flexibilidad cognitiva y una mayor tendencia a incurrir en errores perseverativos que los controles sanos (149). Además, y pese a que en el estudio 1 no se alcanzó la significación estadística en la comparación entre grupos, los sujetos con TJ también presentaron una mayor dificultad en el aprendizaje en el *Iowa Gambling Test*, hallazgo que está en línea con trabajos previos en los que se ha descrito una peor capacidad de toma de decisiones en estos pacientes (150). Además, los sujetos con TJ también presentaron un menor rendimiento intelectual estimado, lo cual podría estar asociado con una mayor tendencia a tomar decisiones arriesgadas sin tener en cuenta los potenciales efectos nocivos de las mismas (151). Todo ello dibuja un perfil de funcionamiento neuropsicológico más disfuncional en los individuos con TJ en comparación con los sujetos sanos, que es compartido con otros trastornos adictivos y del espectro impulsivo-compulsivo, que podría explicar en parte su vulnerabilidad para el desarrollo del trastorno. A pesar de que el estudio 1 no logró correlacionar de forma significativa los diferentes factores neuroendocrinos analizados con variables neuropsicológicas concretas, consideramos probable que aspectos neurobiológicos (y potencialmente factores neuroendocrinos) jueguen un papel en el desarrollo y mantenimiento de las mismas, por lo que es necesario ampliar en el conocimiento de la interacción de ambos tipos de factores para entender mejor la etiopatogenia del trastorno, avanzar hacia potenciales dianas terapéuticas y el desarrollo de biomarcardores específicos.

En cuanto a otras variables clínicas de interés, destaca que los pacientes del grupo con TJ presentaron niveles más elevados de impulsividad y de psicopatología general, así como un perfil de personalidad más disfuncional, caracterizado por un lado por una mayor búsqueda de novedad y evitación al daño y, por otro, una menor dependencia a la recompensa, autodirección, cooperación y autotrascendencia. Estos hallazgos se alinean con los resultados de estudios previos, en los que, como se ha comentado en la introducción, este perfil de personalidad se ha asociado con el TJ (24–27). Además, existe evidencia que apunta a que el perfil clínico descrito se asocia una menor edad de inicio y una mayor severidad del trastorno (152,153). A nivel sociodemográfico, los

resultados también son consistentes con trabajos previos. En líneas generales, tener un menor nivel educacional y menor soporte social se confirman como factores de riesgo para el desarrollo del trastorno (154).

Por último, cabe destacar que en el modelo predictivo llevado a cabo, las variables que asociadas a la presencia de TJ en la muestra de este estudio, comprendieron factores socioeconómicos (un menor nivel educativo y menor apoyo social), clínicos (mayor impulsividad y psicopatología general), relacionados con la personalidad (niveles más bajos de autotrascendencia), neuropsicológicos (peor rendimiento en cuanto a errores perseverativos y menor inteligencia estimada) y neuroendocrinos (menores concentraciones plasmáticas de LEAP-2). Todo ello ilustra de forma clara la complejidad de la etiología del trastorno y la heterogeneidad de los elementos que influyen en su desarrollo y mantenimiento, dentro de los cuales los factores neuroendocrinos podrían tener un papel que todavía requiere de mayor investigación.

5.2. Comorbilidad entre Trastorno de Juego y *Food Addiction*

Los estudios 2 y 3 se centraron en analizar la comorbilidad entre el TJ y FA, dos trastornos del espectro impulsivo-compulsivo que comparten múltiples características comunes, como la dificultad para el control conductual y déficits a nivel de funciones ejecutivas (86,155). Se investigaron posibles alteraciones neurobiológicas y características clínicas diferenciales en este subgrupo de pacientes, con posibles implicaciones terapéuticas.

5.2.1. Alteraciones hormonales asociadas: resistencia a la leptina

En el estudio 2 se evaluaron las diferencias en las concentraciones plasmáticas de hormonas reguladoras del apetito entre individuos con y sin FA en una muestra de pacientes diagnosticados de TJ. Asimismo, se evaluaron las características neuropsicológicas y clínicas diferenciales en este subgrupo de pacientes, cuyas implicaciones se discutirán en el siguiente apartado.

A nivel neuroendocrino, destaca el hallazgo de un perfil alterado en el grupo de pacientes que presentaba comorbilidad con FA, en forma de una elevación de las concentraciones plasmáticas de leptina, una vez corregido por IMC, sin diferencias en los demás factores endocrinos analizados (grelina, LEAP-2 y adiponectina). Este aumento de las concentraciones de leptina en pacientes con FA, que además también presentaban un mayor IMC, es consistente con estudios previos (144). La explicación de la elevación de las concentraciones de leptina en este subgrupo de pacientes podría estar relacionada con la resistencia a la leptina, que, como ya se ha comentado en la introducción, implicaría que dicha hormona no puede ejercer su función fisiológica de supresión del apetito y podría acabar promoviendo conductas de sobrealimentación y consumo compulsivo de comida, a pesar de éstas deriven en consecuencias negativas para el individuo. En esta línea, es muy interesante observar que en el estudio 2 se encontró una correlación positiva entre los niveles de leptina y la impulsividad rasgo, especialmente teniendo en cuenta que estudios previos ya han descrito una posible relación entre la señalización de esta hormona y la impulsividad (156). El mecanismo de dicha relación podría ser la implicación de la leptina como modulador de la actividad mesolímbica tanto a través de receptores dopaminérgicos en el mesencéfalo como, indirectamente, a través de sus acciones en circuitos hipotalámicos (157). Siguiendo esta hipótesis, se puede especular que en este subgrupo de pacientes la resistencia a la leptina podría contribuir a disfunciones en dicho sistema de señalización cerebral, condicionando una mayor impulsividad. De forma paralela, en los pacientes con TJ y FA, también se encontró una correlación significativa entre las concentraciones de leptina y diferentes dimensiones neuropsicológicas, entre ellas un peor control inhibitorio (evaluado mediante el *Stroop Color and Word Test*), lo que concuerda con trabajos previos, en los que se ha descrito una posible relación entre los niveles de esta hormona y un deterioro en el rendimiento cognitivo a dicho nivel (158). Teniendo en cuenta todo lo todo lo anterior, la relación entre las concentraciones leptina, corregidas por IMC, y las medidas relacionadas con la impulsividad (impulsividad rasgo y control inhibitorio) es muy reveladora, especialmente cuando se observa únicamente en el grupo con FA (que presentaron mayor IMC). Aunque son necesarios futuros estudios para aclarar mejor su papel, los resultados obtenidos estarían en consonancia con

la hipótesis de que la señalización de la leptina podría subyacer a disfunciones relacionadas con la impulsividad en estos pacientes.

En los pacientes con TJ y FA, también se encontró una asociación positiva entre las concentraciones de leptina con una menor flexibilidad cognitiva. Es interesante resaltar que este no es el primer estudio que evalúa la posible implicación de la leptina a este nivel. Así, trabajos previos obtuvieron resultados similares, sugiriendo que una menor flexibilidad cognitiva y un peor rendimiento en otras funciones ejecutivas se relacionarían con concentraciones elevadas de leptina plasmática en individuos con sobrepeso (159). En este sentido, cabe recordar que la leptina tiene influencia sobre el aprendizaje y la memoria dependientes del hipocampo (160), y que esta estructura cerebral se ha relacionado con la flexibilidad cognitiva (161), por lo que los presentes resultados permiten hipotetizar que la resistencia a la leptina podría jugar un papel en el desarrollo o mantenimiento de esta disfunción en pacientes con TJ y FA.

Además, en el estudio 2 también se describe una asociación positiva entre concentraciones de leptina y variables clínicas como la ansiedad fóbica y la desregulación emocional, en los individuos con FA y TJ. Teniendo en cuenta la posible implicación de la señalización de leptina en el desarrollo de conductas relacionadas con la ansiedad descrita en trabajos previos (162), estos resultados permiten especular con la posibilidad de que la resistencia a la leptina puede condicionar alteraciones a nivel neurobiológico, concretamente a nivel de señalización del área tegmental ventral que expliquen, en parte, la elevada desregulación emocional en este subgrupo de pacientes.

Por último, es muy interesante observar que en el grupo de personas con FA y TJ, los niveles de leptina también se correlacionaron positivamente con la gravedad del TJ. Esta asociación permite hipotetizar que las alteraciones a nivel de impulsividad, regulación emocional y flexibilidad cognitiva relacionadas con una posible resistencia a la leptina, descritas previamente, podrían tener un correlato clínico en forma de una mayor severidad del TJ. La naturaleza transversal del estudio impide, en cualquier caso, realizar asociaciones de causalidad, pero parece justificada la realización de estudios longitudinales

abordando esta cuestión, ya que podría suponer implicaciones terapéuticas relevantes para este grupo de pacientes.

Es de destacar que en el estudio 2 no se observaron alteraciones significativas en las concentraciones de otros factores endocrinos (grelina, LEAP-2, y adiponectina), entre pacientes con TJ y FA, con respecto a aquellos que no presentaban dicha comorbilidad. Tanto la evidencia previa, que como se ha apuntado en la introducción sugiere una implicación de leptina pero no de otras hormonas como grelina en FA (145) como los resultados del estudio 1 (diferencias en la señalización de la grelina y la adiponectina entre individuos con TJ y sujetos sanos), plantean la hipótesis de que la leptina podría desempeñar un papel específico en FA, independiente del TJ, que implicaría alteraciones en dominios neuropsicológicos y psicopatológicos concretos, incluyendo la impulsividad, la flexibilidad cognitiva y el control inhibitorio.

5.2.2. Implicaciones a nivel clínico

En los estudios 2 y 3 se obtuvo una prevalencia de FA similar a la descrita en la literatura (7,7% y 8.3%, respectivamente) (63). Como era de esperar, tanto por la propia naturaleza de la comorbilidad estudiada como por resultados previos, los pacientes con TJ y FA presentaron un mayor IMC, lo cual refuerza la idea de que este subgrupo de pacientes podría presentar un peor perfil metabólico, que se podría beneficiar de estrategias terapéuticas específicas (relacionadas con ejercicio físico, fomentar hábitos saludables…). Sin embargo, más allá de las consecuencias metabólicas de la adicción a la comida, es interesante observar que en ambos estudios los pacientes con FA comórbida presentaron una mayor gravedad del TJ, lo cual coincide con estudio previos y sugiere que ambas entidades presentan elementos en común y una potencial influencia perjudicial entre ellas (85).

Por otro lado, ambos estudios (2 y 3) coinciden en reflejar un peor estado psicopatológico general en los individuos con FA y TJ con respecto a los pacientes con TJ que no presentaban dicha comorbilidad. Además, los resultados del estudio 2 sugieren una mayor desregulación emocional en el grupo con FA.

Todo ello permite hipotetizar que los comportamientos relacionados con FA pueden surgir como respuestas poco adaptativas ante el malestar emocional, encajando dentro del grupo de jugadores emocionalmente vulnerables del modelo de Blaszcynski y Nower descrito previamente (28).

El estudio 3 se llevó a cabo con el objetivo de analizar de forma más concreta las implicaciones clínicas y neuropsicológicas de la comorbilidad de TJ con FA, en una amplia muestra de pacientes, analizando posibles diferencias entre hombres y mujeres. La prevalencia de FA fue superior entre las mujeres en comparación con los hombres. Estas diferencias son las esperadas teniendo en cuenta que, si bien, como se ha descrito previamente en la introducción, la prevalencia de TJ es superior en hombres (163), la frecuencia de conductas relacionadas con FA y en general de un patrón de alimentación anormal es más elevada en mujeres (164,165).

En el estudio 3, se encontraron diferencias en el nivel socioeconómico y en la situación laboral de los pacientes con FA, en relación a los que no presentaban dicha comorbilidad, aunque sólo en el grupo de las mujeres. En este sentido las mujeres con FA presentaban un nivel socioeconómico más bajo y estaban más frecuentemente desempleadas. Cabe señalar que estudios previos han descrito una mayor gravedad del TJ, en mujeres en contexto de dificultades socioeconómicas (25), lo cual estaría alineado con los resultados obtenidos. Más allá de diferencias a nivel de status socioeconómico, tanto en hombres como en mujeres, se han descrito rasgos de personalidad específicos y diferenciales asociados a la presencia de FA. Así, una baja autodirección y perseverancia y una mayor dependencia a la recompensa se asociarían a FA, tanto en personas con trastornos mentales como con otras condiciones médicas (166–168). En el presente estudio, este subgrupo de pacientes mostró una mayor evitación al daño y una menor autodirección y cooperatividad y, sólo en el caso de los hombres, se observaron mayores niveles de autotrascendencia. Todo ello sugiere que un contexto socioeconómico bajo, dificultades a nivel laboral, mayor vulnerabilidad emocional (mayor ansiedad e intensidad de síntomas depresivos, así como dificultades en la regulación emocional) y escasas estra-

tegias de adaptación para afrontar el estrés (en base a rasgos desadaptativos de personalidad) podrían caracterizar a los pacientes de TJ con FA.

Como se ha mencionado previamente, tanto en el estudio 2 como en el 3, los pacientes con FA presentaron una mayor gravedad del TJ y un perfil clínico con características sugestivas de una peor evolución (en el estudio 3 se observó una mayor duración del trastorno en el caso de las mujeres y una menor edad de inicio en los hombres). Además, es interesante observar que en el estudio 3 también se identificó una mayor frecuencia de consumo perjudicial de alcohol, entre los hombres con FA. En este sentido, cabe señalar que en estudios previos se ha descrito una relación entre FA y el consumo de tabaco en una muestra con predominio masculino de individuos con TJ (85). Todo ello permite especular con la existencia de una vulnerabilidad compartida, en la línea del planteamiento del espectro impulsivo-compulsivo, que podría explicar en parte la tendencia de estos individuos a incurrir tanto en el juego como en el consumo compulsivo de comida, pero también de alcohol o tabaco, como mecanismo de afrontamiento ante el estrés o emociones negativas.

5.2.3. Limitaciones y fortalezas de los resultados

Es imprescindible tener en cuenta algunas limitaciones de los estudios que componen este trabajo, de cara a interpretar adecuadamente los resultados. En primer lugar, es importante destacar que los participantes de los tres estudios fueron reclutados a través de su consulta en una unidad específica de tratamiento en Cataluña, que fueron principalmente de sexo masculino y que solicitaron tratamiento para su trastorno. Esta realidad exige cautela a la hora de generalizar las conclusiones a otras poblaciones, como muestras no clínicas, procedentes de otras áreas geográficas o en mujeres.

En segundo lugar, los tres estudios comparten un diseño transversal, lo cual, como se ha mencionado previamente, impide realizar atribuciones causales, especialmente cuando el foco de la investigación son entidades tan complejas como las adicciones. En este sentido, futuros estudios longitudinales podrían

contribuir a caracterizar, de forma más precisa, tanto el papel de los diferentes factores neuroendocrinos en TJ y FA como las características diferenciales y el curso evolutivo del subgrupo de pacientes que presentan comorbilidad entre ambas condiciones.

En cuanto a las mediciones endocrinas en los estudios 1 y 2, conviene recordar que se analizaron a partir de muestras de sangre periférica, lo cual podría limitar la inferencia de su funcionamiento a nivel neuronal. Además, el menor número de individuos del grupo de controles sanos con respecto al grupo con TJ en el estudio 1 y de individuos que cumplían criterios para FA en el estudio 2, también pueden limitar la interpretación de los resultados, por lo que son necesarios estudios con un tamaño de muestra mayor para confirmar los hallazgos.

Por último, y en relación al uso del cuestionario YFAS 2.0 para despistaje de FA, el uso de evaluaciones de naturaleza autoinformada para trastornos mentales puede disminuir la fiabilidad. Estudios futuros deberían considerar evaluaciones complementarias como, por ejemplo, entrevistas clínicas semiestructuradas similares a las que se han llevado a cabo para la evaluación del TJ.

Más allá de las limitaciones mencionadas, también cabe resaltar algunas fortalezas en relación a lo estudios que componen el presente trabajo. Por un lado, el hecho de haber llevado a cabo los análisis estudiando una amplia muestra clínica, caracterizada de forma sistemática por profesionales expertos en cuanto a perfil clínico y evaluaciones neuropsicológicas, así como el haber efectuado correcciones por potenciales factores de confusión en las distintas comparaciones. Por otro, y pese a que ya se ha comentado que la baja representación de mujeres en los tres estudios realizados es una limitación a tener en cuenta, cabe señalar que el porcentaje de mujeres en los mismos coincide con las estimaciones de prevalencia en muestras clínicas de pacientes que buscan tratamiento para el TJ, y que en el caso del estudio 1 es comparable a su frecuencia en el grupo control. Además, el hecho de haber analizado las posibles diferencias en función del sexo en estudio 3 aporta información novedosa en este sentido.

5.2.4. Líneas de investigación futuras

Los resultados de los estudios que componen este trabajo sugieren la implicación de alteraciones neuroendocrinas, junto con otros aspectos clínicos, neuropsicológicos y sociales, en el TJ y en FA. Como se ha mencionado previamente, la naturaleza transversal de los mismos impide llegar a conclusiones de causalidad, por lo que la primera línea de investigación de cara a profundizar en el conocimiento en este ámbito implicaría necesariamente el diseño de estudios longitudinales prospectivos. Analizar la evolución de dichas alteraciones hormonales y su relación con el resto de factores implicados en el curso evolutivo de los diferentes trastornos del espectro impulsivo, y en concreto de TJ y FA, permitiría dilucidar de una forma más precisa su implicación en la patogénesis de los mismos, así como eventualmente identificar dianas terapéuticas sobre las que poder incidir a nivel farmacológico.

En relación a hallazgos concretos del presente trabajo, es destacable la identificación de una disminución de las concentraciones plasmáticas de LEAP-2, junto con un aumento en la señalización de grelina, en individuos con TJ en comparación con sujetos sanos en el estudio 1. Como ya se ha comentado, dicha relación hace emerger la hipótesis de que LEAP-2 podría jugar un papel como posible diana terapéutica, por su función antagónica respecto al efecto de la grelina. Para avanzar en dicha posibilidad, sería útil analizar LEAP-2 (que al ser una hormona recientemente descrita no ha sido tan estudiada) en relación a grelina en otros trastornos del espectro impulsivo-compulsivo (como las adicciones a sustancias) y estudiar su potencial implicación en procesos como la frecuencia de recaídas o la abstinencia.

Por otro lado, también cabe señalar la interesante relación identificada entre concentraciones de leptina y rendimiento cognitivo en diferentes dominios descrita en pacientes con TJ y FA en el estudio 2, con una importante repercusión a nivel clínico. Teniendo en cuenta que la resistencia a la leptina es una situación potencialmente reversible, sería interesante estudiar esta relación en procesos médicos en los que, ya sea a través de medidas dietéticas u otras intervenciones (como la cirugía bariátrica) se logra una reversión del esta-

do de resistencia a la leptina. Estos resultados, así como estudios previos en este ámbito, permiten hipotetizar que una normalización en la función de la leptina podría tener consecuencias no sólo a nivel metabólico, sino también neurocognitivo y psicológico. Para contrastar dicha hipótesis sería interesante diseñar estudios prospectivos en pacientes con obesidad que se vinculan a un tratamiento específico y analizar posibles variaciones en aspectos neuropsicológicos y clínicos (incluyendo comorbilidades con trastornos del espectro impulsivo-compulsivo) en función de su evolución.

6

CONCLUSIONES

CONCLUSIONES

1. El presente trabajo apoya la naturaleza multifactorial del trastorno de juego, identificando factores clínicos, neuropsicológicos y neuroendocrinos relacionados con dicho trastorno.

2. Alteraciones en el sistema de señalización de grelina, en el que LEAP-2 juega un papel como antagonista, podrían estar implicadas en el trastorno de juego, a través de su potencial interacción con el sistema de recompensa cerebral.

3. La resistencia a la leptina podría estar implicada específicamente en la comorbilidad de trastorno de juego con la adicción a la comida.

4. En individuos con trastorno de juego y adicción a la comida, la alteración en la señalización de leptina podría subyacer aspectos clínicos y neuropsicológicos comunes a ambas entidades, como la impulsividad y la flexibilidad cognitiva. Además, podría estar relacionada con una mayor severidad del trastorno de juego, lo cual podría tener implicaciones terapéuticas en un futuro.

5. Los individuos con trastorno de juego que presentan adicción a la comida presentan características clínicas diferenciales, que varían entre hombres y mujeres, así como indicadores sugestivos de una mayor gravedad del trastorno de juego, que podrían beneficiarse de intervenciones específicas.

7

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