UNIVERSITAT DE BARCELONA

Clinical and Neurobiological Substrates in Extreme Eating and Weight Disorders

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Doctoral thesis

CLINICAL AND NEUROBIOLOGICAL SUBSTRATES IN EXTREME WEIGHT AND EATING CONDITIONS

presented by **ROMINA A. MIRANDA OLIVOS** for the doctoral degree at the University of Barcelona

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DOCTORAL IN MEDICINE AND TRANSLATIONAL RESEARCH
Neurosciences Program
School of Medicine and Health Sciences
UNIVERSITY OF BARCELONA

October 2023

“Donde haya un árbol que plantar, plántalo tú. Donde haya un error que enmendar, enmiéndalo tú. Donde haya un esfuerzo que todos esquivan, hazlo tú. Sé tú el que aparta la piedra del camino.”

(Gabriela Mistral)

“It's not wrong to be beautiful; what's wrong is the obligation to be beautiful."
(Susan Sontag)

"Is there a good way to categorize bodies? What do categories tell us? Categories tell us more about the need to categorize bodies than about the bodies themselves."

(Judith Buttler)

“Yo canto a la diferencia que hay de lo cierto a lo falso. De lo contrario no canto.”
(Violeta Parra)

ACKNOWLEDGEMENTS / AGRADECIMIENTOS

En primer lugar, quisiera agradecer a todas las mujeres que accedieron voluntaria y generosamente a participar en esta investigación a pesar de no siempre estar en el mejor momento de su vida. Mujeres valientes que llegan aquí buscando ayuda médica y/o psicológica y que, además, aceptan altruista y desinteresadamente formar parte de estos estudios. Siempre os tendré gratitud eterna por vuestra disposición de querer manera colaborar en esta investigación.

Si tuviera que agradecer a todas y cada una de las personas que formaron parte de alguna manera en la materialización de esta tesis doctoral, seguramente necesitaría la misma cantidad de páginas para poder mencionarlas a todas. Desde Marc Via que me animó a picar puertas en el mundo de la investigación y no desistir a pesar de no tener un super expediente académico, pasando por la María Mataró, la Alba y la Noe que me recibieron en el Projecte Moviment sin conocerme y me enseñaron lo más importante que debe saber un investigador: saber llevar un proyecto. Todo lo que aprendí ese año fue tan importante que, hasta día de hoy, atesoro esas enseñanzas ya que me han provisto de las herramientas básicas para llevar un proyecto de investigación con excelencia. Gracias por vuestro rigor. Creo que lo mejor que me pudo haber pasado es haber comenzado mis primeros pasos en la investigación con vosotras. ¡Lo hacéis estupendo! Sea lo que sea en lo que estéis, estoy segura de que es así.

Por supuesto, mis primeros y más grandes agradecimientos son para mis queridos padres académicos, Carles y Fernando. A tu, Carles, moltes gràcies per confiar en mi des del primer dia quan vaig començar el màster de neurociències i em vas dir, tot i que ja no hi havia lloc, que tenies un espai per a mi. Gràcies per obrir-me la porta per formar part del teu equip i treballar a les teves files. Ha estat un honor que espero no perdre mai. Agraeixo molt les teves ensenyances, el teu coaching quan el desànim m'envaïa, els teus consells i correccions que m'han permès perfeccionar-me a l'hora d'escriure, analitzar i ser crítica i rigorosa per fer ciència. A ti Fernando, porque si Carles me abrió la puerta, tú me invitaste a pasar y a sentarme en esta gran mesa de este equipo. Gracias por confiar en mí para gestionar los proyectos de investigación y darme la oportunidad de potenciar mi carrera científica motivándome siempre a estar pensando nuevas ideas y líneas de investigación. Gracias por tu generosidad y tu ambición. Sin este impulso y soporte, no tendría hoy los resultados que sustentan esta tesis y mi curriculum. Como hija académica, espero haber estado a la altura de las expectativas que ambos teníais para conmigo.

A mis compañeros/mentores en este camino, especialmente a Oren, Trevor, Nacho y Zaida. Habéis sido como mis hermanos mayores de la neuroimagen y de papers. Me habéis enseñado casi todo lo que sé. Gracias por regalarme generosamente vuestro tiempo y vuestra paciencia!, a esta pesada que siempre tenía preguntas y dudas e incurría en los mismos errores. A tu Oren per confiar en mi quan encara estaba aprenent a escriure articles cientifics. A Trevor por ser mi mejor mentor en escribir en inglés corrigiéndome una y otra vez, hasta que un día aprendí a expresarme en tu idioma sin frases hard-to-read. Gracias por cuidarme y aconsejarme. A Nacho. Gracias por tu paciencia amigo, gracias por contestar mis llamadas a las 8am de un sábado cuando algo me fallaba en la reso. Todo contigo fueron facilidades. Sin tu cerebro y tus scripts TODO hubiera sido tan dificil y quizás imposible. Lo mismo contigo, Zaida. Ha sido un placer trabajar contigo y aprender de la mejor cuando aterricé en esta unidad.

A mis queridos compañeros del laboratorio de neuroimagen, especialmente a Cris S., Asier, Sara, Víctor, Pablo y Pam, quienes me enseñaron que, además de compañeros de trabajo, también podías encontrar amigos. Especialmente, a Víctor, Pam que, junto con Nacho, Marta, Maci y Mer

se transformaron en mi 'prescripción médica' personal de dosis mensuales de risas, bailes y karaokes; todo lo que necesitaba para seguir y algo que nunca imaginé encontrar y necesitar tanto, al comenzar este viaje en la investigación. Asimismo, a mi familia chileno-italiana, Pablo y Giulia. Gracias, amigos por esas risas y largas conversaciones de cualquier cosa que no fuera de trabajo y esas cenitas tan ricas de completos o pastas.

A mis compis de trincheras, especialmente a la dra. Vintró, a Isa, Lucía y Nacho por hacerme de cojín siempre, siempre, siempre. A Isa, mi compañera de endos, mi compañía durante la estancia en formato audios-podcast, la mejor compañera que he podido tener para escribir novelas científicas. De la misma manera, extiendo estos agradecimientos a Isabel Sánchez y Jéssica Jiménez. Gracias por vuestro compañerismo siempre. He encontrado unas compañeras extraordinariamente generosas, inteligentes y sobre todo, trabajadoras. Nos hemos cuidado entre todas a base de abrazos y buenas dosis de serotonina y endorfinas, al no dejar de reír y reírnos en los dias fáciles y difíciles. Gracias por estar ahí y poner el hombro las unas a las otras para que ninguna desfallezca. Cuidarnos. He sido afortunada de contar con vosotras y ostentar de tener a mi lado personas tan válidas y bonitas como vosotras. Gracias.

También quiero agradecer a mis amigos. A esas personas maravillosas que un día se cruzaron en mi camino y se quedaron en mi corazón. A mi Karla con K por todas las noches de conversaciones soñando que vivíamos en mundos que hoy vivimos. Gracias por tus podcast de 9 minutos de update desde LA, por animarme y quererme, yo también te quiero hasta el infinito, amiga. Soy muy afortunada de tener amigos que me han aguantado antes durante y espero que después de esta etapa. Gracias por sacarme de este planeta cuando vuestros ojos amigos veían que lo necesitaba. A mi querida Anabel. Tu fuiste la primera estrellita que conocí cuando llegue a este país y recorrimos juntas tantos caminos que para mí es una fortuna que la vida nos haya querido volver a tener cerca. A Albert, mi gran amigo y hermano del corazón. Hemos pasado todas las tempestas y días de sol acompañándonos y cuidándonos siempre. No puedo dejar de agradecerte todo el cariño y lealtad que has tenido conmigo. Gracias, Mari.

A mis ángeles que me cuidan desde el cielo. A mi abuelita Sara, porque de ella heredé este carácter lleno del coraje y valor, necesario para enfrentar la vida. A mi Lela que me trenza el cabello mientras duermo y me cuida y me acompaña siempre. Y a mi padre. A ti te agradezco la herencia científica que me tiene hoy aquí. Sé que debes estar orgullosa de tu hija haciéndose doctora.

A mis mujeres. A mi hermana Valentina, porque a pesar de ser tan diferentes, siempre me has enseñado con tu forma de vivir tu maternidad y ser mujer. Gracias por tu complicidad hermana mía y por confiar en mí. A mi reina madre. Qué te voy a decir a ti. Me has aguantado con tu vida. Diste la pelea por mí en los momentos más difíciles. Gracias por tu templanza a pesar de todo. Porque la vida no nos lo ha puesto fácil, pero somos guerreras. Nos levantamos, nos sacudimos el polvo y seguimos adelante. Un día me dijiste que algún día nos reiríamos de todo eso y aquí estamos, riendo y tomando partido de todo aquello que nos ha pasado. Te amo mamita mía.

Finalmente, no puedo dejar de agradecerte a ti, mi incondicional compañero, Quim. Carinyu meu, gràcies per la teva infinita paciencia i per cuidarme, soportarme y no abandonarme a pesar de los días lluviosos de truenos y relámpagos que te hice vivir algunas veces durante esta época. Tienes el poder, como el señor de las nubes que eres, de moverlas a tu antojo y traerme de nuevo el sol y sacarme una sonrisa. Ets el meu superheroi. Sóc molt afortunada que m'estimis, ets com un refugi que trobo cada dia quan estic al teu costat.

FUNDINGS

The studies presented in this present doctoral thesis were conducted by members of the Psychoneurobiology of Eating and Addictive Behaviors Group and the Neuroimaging and Mental Health Lab at the Bellvitge University Hospital and Bellvitge Biomedical Research Institute (IDIBELL), in collaboration with members of the Centro de Investigación Biomédica en Red-Fisiopatología de la Obesidad y Nutrición (CIBEROBN) and Ciber de Salud Mental (CIBERSAM) of the Instituto Salud Carlos III.

All research was carried out within the framework of the Ciències Clíniques at the University of Barcelona Medical School in Barcelona, Spain.

Financial support for this work was provided by the Carlos III Health Institute (Ministry of Economy and Competitiveness, Spain) and CIBEROBN. Specifically, project fundings were obtained from the Carlos III Health Institute (grant numbers PI14/00290, PI17/01167, PI20/00132) and CIBEROBN. Additional support was received from EU-H2020 Grants (Eat2beNICE/ H2020-SFS-2016-2; Ref 728018).

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ABBREVIATIONS AND ACRONYMS

2-AG	2-arachidonoylglycerol
ACC	anterior cingulate cortex
ADHD	attention deficit hyperactivity disorder
AEA	anandamide
AgRP	agouti-related peptide
AN	anorexia nervosa
AN-BP	anorexia nervosa binge-purge type
AN-R	anorexia nervosa restrictive type
ARC	arcuate nucleus
BE	binge episodes
BED	binge eating disorder
BMI	body mass index
BN	bulimia nervosa
BSD	binge spectrum disorder
CART	cocaine- and amphetamine-regulated transcript hormone
CB	cannabinoid
CB1R	cannabinoid 1 receptor
CBT	cognitive-behavioral therapy
CNS	central nervous system
CS	controles sanos
dACC	dorsal anterior cingulate cortex
DBT	Dialectical Behavior Therapy
dlPFC	dorsolateral prefrontal cortex
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, fifth edition
eCB	endocannabinoid
eCBs	endocannabinoids
ED	eating disorders
EWC	extreme weight conditions
fMRI	functional magnetic resonance imaging
HC	healthy controls
IGT	Iowa Gambling Task
IMC	índice de masa corporal
LH	lateral hypothalamus
MH	medial hypothalamus
MRI	magnetic resonance imaging
NAcc	nucleus accumbens
NAcc-Insula	nucleus accumbens and the insula functional connectivity
NAcc-SMA	nucleus accumbens and the supplementary motor area functional connectivity
NPY	neuropeptide Y
OB	obesity

OFC	orbitofrontal cortex
OX	Orexin
PFC	prefrontal cortex
POMC	proopiomelanocortin
PVN	paraventricular nucleus
PYY	peptide YY
RMI	resonance magnetic imaging
rs-fMRI	resting state functional resonance magnetic imaging
SMA	supplementary motor area
SSRIs	selective serotonin reuptake inhibitors
TA	trastorno por atracón / trastorn per afartament
TCA	trastorno de la conducta alimentaria
vACC	ventral anterior cingulate cortex
VS	ventral striatum
VTA	ventral tegmental area
WCST	Wisconsin Card Sorting Test
WHO	World Health Organization
α-MSH	alpha-melanocyte stimulating

LIST OF ARTICLES IN THE THESIS

Thesis in compendium of publications format

The present thesis consists of three main objectives and five published articles. All of them have been carried out with samples collected at the Clinical Psychology and Endocrinology Unit of Bellvitge University Hospital (HUB).

1. Baenas I*, **Miranda-Olivos R***, Granero R, Solé-Morata N, Sánchez I, Pastor A, Del Pino-Gutiérrez A, Codina E, Tinahones FJ, Fernández-Formoso JA, Vilarrasa N, Guerrero-Pérez F, Lopez-Urdiales R, Virgili N, Soriano-Mas C, Jiménez-Murcia S, de la Torre R, Fernández-Aranda F. Association of anandamide and 2-arachidonoylglycerol concentrations with clinical features and body mass index in eating disorders and obesity. **European Psychiatry.** 2023 May 31;66(1): e49. doi: 10.1192/j.eurpsy.2023.2411.
[a]Impact Factor: 7.8; D1 in PSYCHIATRY – SSCI (14/144)

2. **Miranda-Olivos R,** Baenas I, Steward T, Granero R, Pastor A, Sánchez I, Juaneda-Seguí A, Del Pino-Gutiérrez A, Fernández-Formoso JA, Vilarrasa N, Guerrero-Pérez F, Virgili N, López-Urdiales R, Jiménez-Murcia S, de la Torre R, Soriano-Mas C, Fernández-Aranda F. Exploring the influence of circulating endocannabinoids and nucleus accumbens functional connectivity on anorexia nervosa severity. **Molecular Psychiatry.** 2023 Sep 28. doi: 10.1038/s41380-023-02253-2.
[a]Impact Factor: 11; D1 in PSYCHIATRY – SCIE (11/156).

3. **Miranda-Olivos R*,** Steward T*, Martínez-Zalacaín I, Mestre-Bach G, Juaneda-Seguí A, Jiménez-Murcia S, Fernández-Formoso JA, Vilarrasa N, Veciana de La s Heras M, Custal N, Virgili N, Lopez-Urdiales R, Menchón JM, Granero R, Soriano-Mas C, Fernandez-Aranda F. The neural correlates of delay discounting in obesity and binge eating disorder. **Journal of Behavioral Addictions**. 2021. 10(3): 498–507.
[a]Impact Factor: 7.8; - D1 in PSYCHIATRY – SSCI (13/144).

4. **Miranda-Olivos R***, Testa G*, Lucas I, Sánchez I, Sánchez-González J, Granero R, Jiménez-Murcia S, Fernández-Aranda F. Clinical factors predicting impaired executive functions in eating disorders: The role of illness duration. **Journal of Psychiatry Research**. 2021. 144: 87-95.
[a]Impact Factor: 4.8; - Q2 in PSYCHIATRY – SSCI (38/144).

5. Lucas I, **Miranda-Olivos R**, Testa G, Granero R, Sánchez I, Sánchez-González J, Jiménez-Murcia S, Fernández-Aranda F. Neuropsychological Learning Deficits as Predictors of Treatment Outcome in Patients with Eating Disorders. **Nutrients**. 2021. 13(7): 2145.
[a]Impact Factor: 5.9; - Q1 in NUTRITION & DIETETICS – SCIE (17/89).

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[*] Share first authorship

[a] According to the Journal Citation Report (JCR)

THESIS SUMMARY

Introduction: Extreme eating and weight conditions (EWC) represent a construct that emerges as a dimensional and theoretical model that identifies individuals who show inappropriate eating behavior and abrupt weight fluctuations. According to this spectrum of EWC, one extreme can be represented by individuals with anorexia nervosa (AN) characterized by an excessive restriction of food intake and an extreme body mass index (BMI) whereas the other end of this continuum is represented by individuals with obesity (OB) characterized by a BMI over 30. In addition to AN and OB, some eating disorders (ED) are also part of this continuum given the high risk of falling into one of the extremes, such as bulimia nervosa (BN) and binge eating disorder (BED). Studies have described similar alterations at psychological, and neurobiological levels linked to their abnormal patterns of eating behaviors delineating vulnerability pathways related to neurobiological basis. While many studies in this field have primarily been cross-sectional, they have unveiled intricate biopsychosocial interactions warranting an examination of potential underlying factors in the development and persistence of EWC. An integrated and comprehensive view of these conditions, in which an overlap between ED and OB is understood, will enable the diagnostic conceptualization of preventive measures and new treatment strategies.

Hypotheses and Objectives: Based on previous literature, this thesis proposes that individuals suffering from extreme weight disorders would exhibit dysfunctional brain activity in regions associated with emotional reward processing and cognitive control in comparison to healthy controls (HC). Similarly, it is expected that neuroendocrine alterations in EWC will exert an influence on clinical symptomatology. Furthermore, it is hypothesized that executive function impairments observed among individuals with EWC will negatively impact their clinical course. In line with these hypotheses, the main objectives of these studies were to investigate brain function in individuals with EWC, assessed through task-specific paradigm-based assessments, when compared to HC. Additionally, we aimed to assess the impact of the interaction between neuroendocrine factors and brain function on the clinical and anthropometric characteristics of

individuals with EWC. Finally, the final objective was to identify the potential influences of executive functions on the clinical outcomes of individuals with EWC.

Methods: The thesis encompassed five studies conducted at the Clinical Psychology Unit, at the Bellvitge University Hospital-IDIBELL, in collaboration with the Endocrinology Unit and the Institute of Diagnostic Imaging at the same hospital. The variables of interest for each study were collected through diverse measurement instruments. For brain function assessment, magnetic resonance imaging (MRI) data were acquired from the whole brain using a 3.0 Tesla clinical MRI scanner equipped with a 32-channel phased-array head coil. To evaluate the presence or absence of ED diagnosis, DSM-5 criteria were employed. Moreover, all participants completed self-reported psychological and personality assessments through paper-and-pencil-validated questionnaires. Finally, the BMI was determined using a Tanita BC-420MA multifrequency electrical bioimpedance analyzer to estimate body composition. Blood samples were collected after fasting to obtain circulating endocannabinoids (eCBs), specifically 2-arachidonoylglycerol (2-AG) and anandamide (AEA).

Main results: From the results obtained in the studies comprising this doctoral thesis, a dysfunction in the insula was observed in individuals with AN and OB. In OB, a decrease in insula activity was observed through functional magnetic resonance imaging (fMRI) after a delay discounting task, prioritizing immediate rewards over delayed rewards. In the case of individuals with AN, functional neuroimaging analyses revealed low connectivity between the nucleus accumbens (NAcc) and the insula (NAcc-insula) and between NAcc and the supplementary motor area (NAcc-SMA) when compared to the HC group. The connectivity between NAcc-insula and NAcc-SMA in individuals with AN was associated with high circulating eCB concentrations and a lower BMI. Circulating eCBs were positively associated with emotional dysregulation and general psychopathology, indicating a common neurobiological pathway across all clinical groups (i.e., AN, BN, BED, and OB). Likewise, similar performance was observed in executive functions among patients with ED with bulimic-purging characteristics, unlike what was observed in those patients with restrictive symptomatology. However, these results in cognitive functions (especially decision-making and cognitive flexibility) were worse than those observed in the control group. The learning curve related to decision-

making also predicted treatment outcomes in ED. Patients with a favorable treatment outcome showed a better learning curve during a decision-making task compared to those who had a worse outcome. Additionally, a positive association was found between the duration of ED and deficits in executive functions.

Conclusions: Findings largely confirm the initial hypotheses and raise new research questions and challenges in the field of EWC. These results provide relevant information about the neurobiological, neuroendocrine, and neurocognitive deficiencies in EWC and how they can aid in early identification and the design of more personalized therapeutic programs. Firstly, alterations in insular function among individuals with AN and OB suggested a shared neurobiological basis for these conditions. Considering the role of the insula in body awareness and emotional processing, these alterations might influence how individuals perceive and process their bodies and emotions in the context of eating. Secondly, reduced functional connectivity in the NAcc with the insula and the supplementary motor area (SMA) in AN may underlie alterations in the integration of interoceptive, somatosensory, and motor planning related to hedonic information. Circulating eCBs are linked to not only neurobiological changes in EWC, but also to psychological factors such as general psychopathology, impulsivity, and emotional regulation across all clinical groups, highlighting the complex interplay between neuroendocrine signaling and psychological processes in EWC. Results related to executive functions support previous findings that showed poor performance in executive functions in patients with ED, compared to HC, particularly in decision-making and cognitive flexibility. Interestingly, learning in decision-making has proven to be a valuable predictor of treatment outcomes, highlighting the importance of taking cognitive factors into account in the management of ED. A longer duration of the disorder increased the risk of exhibiting deficits in decision-making, cognitive flexibility, and inhibitory control suggesting that early intervention and tailored treatment strategies may be crucial in improving outcomes in these patients. Likewise, these results provide valuable information on neurobiological, neuroendocrine, and neurocognitive impairments in EWC that could help to identify new and more specific therapeutic approaches and improve the prognosis of individuals with EWC.

RESUMEN DE LA TESIS

Introducción: Los trastornos extremos de alimentación y peso (EWC, por sus siglas en inglés) representan un constructo que emerge como un modelo dimensional y teórico que identifica a individuos que muestran comportamientos alimentarios inadecuados y fluctuaciones abruptas de peso. Según este espectro de EWC, un extremo puede estar representado por individuos con anorexia nerviosa (AN), caracterizada por una restricción excesiva de la ingesta de alimentos y un índice de masa corporal (IMC) extremadamente bajo, mientras que el otro extremo está representado por individuos con obesidad (OB), caracterizada por un IMC superior a 30. Además de AN y OB, algunos trastornos de la conducta alimentaria (TCA) también forman parte de este continuum debido al alto riesgo de caer en uno de los extremos, como la bulimia nerviosa (BN) y el trastorno por atracón (TA). Los estudios han descrito alteraciones similares a niveles psicológicos y neurobiológicos vinculados a sus patrones anormales de comportamiento alimentario, delineando vías de vulnerabilidad relacionadas con una base neurobiológica. Aunque muchos estudios en este campo han sido principalmente transversales, han encontrado interacciones biopsicosociales complejas que requieren un examen de posibles factores subyacentes en el desarrollo y persistencia de los EWC. Una visión integral y global de estas condiciones, en la que se sobreentienda una superposición entre los trastornos alimentarios y la obesidad, permitirá la conceptualización diagnóstica de medidas preventivas y nuevas estrategias de tratamiento.

Hipótesis y objetivos: Basándose en la literatura previa, esta tesis postula que las personas que sufren trastornos extremos de peso mostrarán una actividad cerebral disfuncional en regiones asociadas con el procesamiento emocional de recompensas y el control cognitivo en comparación con controles sanos (CS). Del mismo modo, se espera que las alteraciones neuroendocrinas en los EWC ejerzan una influencia en la sintomatología clínica. Asimismo, se plantea la hipótesis de que las alteraciones en las funciones ejecutivas observadas entre las personas con EWC, influirán negativamente en su curso clínico. En línea con estas hipótesis, los objetivos principales de estos estudios son el investigar la función cerebral en personas con EWC, evaluada mediante

paradigmas basados en tareas específicas, al ser comparados con HC. Además, buscamos evaluar el impacto de la interacción entre los factores neuroendocrinos y la función cerebral, sobre las características clínicas y antropométricas de los EWC. Del mismo modo, el último objetivo es identificar las posibles influencias de las funciones ejecutivas en la sintomatología clínica de personas con EWC.

Métodos: La tesis engloba cinco estudios, realizados en la Unidad de Psicología Clínica del Hospital Universitario de Bellvitge-IDIBELL, en colaboración con la Unidad de Endocrinología y el Instituto de la Imagen Diagnóstica del mismo hospital. Las variables de interés para cada uno de los estudios se recogieron mediante diversos instrumentos de medición. Para la evaluación de la función cerebral, se adquirieron datos de resonancia magnética (RM) de todo el cerebro utilizando un escáner MRI clínico de 3.0 Tesla equipado con una bobina de cráneo de 32 canales. Para evaluar la presencia o ausencia de un diagnóstico de TCA, se emplearon los criterios del DSM-5. Además, todos los participantes completaron evaluaciones psicológicas y de personalidad a través de cuestionarios validados en lápiz y papel. Finalmente, se determinó el IMC utilizando un analizador de bioimpedancia eléctrica multifrecuencia, Tanita BC-420MA, para estimar la composición corporal. Se recopilaron muestras de sangre después de ayunar para la obtención de las concentraciones endocannabinoides circulantes (eCBs), específicamente 2-arachidonilglicerol (2-AG) y anandamida (AEA).

Resultados principales: A partir de los resultados obtenidos en las investigaciones que componen esta tesis doctoral, se observó una disfunción en la ínsula, en individuos con AN y OB. En OB, se observó una disminución de la actividad en la ínsula, a través de resonancia magnética funcional (RMf), tras una tarea de descuento de demora, al priorizar recompensas inmediatas sobre recompensas demoradas. En el caso de individuos con AN, los análisis de neuroimagen funcional revelaron una baja conectividad entre el núcleo accumbens (NAcc) y la ínsula (NAcc-ínsula) y el NAcc y el área motora suplementaria (NAcc-SMA), al ser comparados con el grupo HC. La conectividad entre NAcc-ínsula y NAcc-SMA en individuos con AN, se asoció con altas concentraciones circulantes de eCBs y un IMC más bajo. Los eCB circulantes se asociaron positivamente con desregulación emocional y psicopatología general, mostrando una vía neurobiológica común en todos los grupos clínicos (es decir, AN, BN, BED y OB).

Asimismo, se observó un rendimiento similar en las funciones ejecutivas, entre los pacientes con TCA de características bulímico-purgativas, a diferencia del observado en aquellos pacientes con sintomatología restrictiva. Sin embargo, estos resultados en funciones cognitivas (especialmente toma de decisiones y flexibilidad cognitiva) fueron peores que los observados en el grupo control. La curva de aprendizaje, relacionada con la toma de decisiones, también predijo los resultados del tratamiento en TCA. Aquellos pacientes con un buen resultado al tratamiento mostraron una mejor curva de aprendizaje, durante una tarea de toma de decisiones, con respecto a los que obtuvieron un peor resultado. Además, se obtuvo una asociación positiva entre la duración del TCA y déficits en las funciones ejecutivas.

Conclusiones: Los hallazgos en su mayoría confirman las hipótesis iniciales y plantean nuevas preguntas de investigación y desafíos en el campo de EWC. Estos resultados brindan información relevante sobre las deficiencias neurobiológicas, neuroendocrinas y neurocognitivas en EWC y cómo pueden contribuir a la identificación temprana y al diseño de programas terapéuticos más personalizados. En primer lugar, las alteraciones en la función de la ínsula entre individuos con AN y OB sugieren una base neurobiológica compartida para estas condiciones. Teniendo en cuenta el papel de la ínsula en la conciencia corporal y el procesamiento emocional, estas alteraciones podrían influir en cómo los individuos perciben y procesan sus cuerpos y emociones en el contexto de la alimentación. En segundo lugar, la reducción de la conectividad funcional en el NAcc con la ínsula y el área motora suplementaria (SMA) en AN puede subyacer a alteraciones en la integración de información interoceptiva, somatosensorial y planificación motora relacionada con la información hedónica. Los eCB circulantes están relacionados no solo con cambios neurobiológicos en EWC, sino también con factores psicológicos como la psicopatología general, la impulsividad y la regulación emocional en todos los grupos clínicos, destacando la compleja interacción entre la señalización neuroendocrina y los procesos psicológicos en EWC. Los resultados relacionados con las funciones ejecutivas respaldan hallazgos previos que mostraron un bajo rendimiento en las funciones ejecutivas en pacientes con ED en comparación con HC (grupo control), especialmente en la toma de decisiones y la flexibilidad cognitiva. Curiosamente, el aprendizaje en la toma de decisiones ha demostrado ser un predictor valioso de los resultados del

tratamiento, destacando la importancia de tener en cuenta los factores cognitivos en el manejo de ED. Una duración más larga del trastorno aumentó el riesgo de exhibir déficits en la toma de decisiones, la flexibilidad cognitiva y el control inhibitorio, lo que sugiere que la intervención temprana y las estrategias de tratamiento personalizadas pueden ser cruciales para mejorar los resultados en estos pacientes. Del mismo modo, estos resultados brindan información valiosa sobre las deficiencias neurobiológicas, neuroendocrinas y neurocognitivas en EWC que podrían ayudar a identificar enfoques terapéuticos nuevos y más específicos, y mejorar el pronóstico de las personas con EWC.

RESUM DE LA TESI

Introducció: Les condicions extremes de l'alimentació i el pes (EWC, per les seves sigles en anglès) representen un constructe que emergeix com un model dimensional i teòric que identifica a individus que mostren comportaments alimentaris aberrants i fluctuacions abruptes de pes. Segons aquest espectre d'EWC, un extrem pot estar representat per individus amb anorèxia nerviosa (AN), caracteritzada per una restricció excessiva de la ingesta d'aliments i un índex de massa corporal (IMC) extremadament baix, mentre que l'altre extrem està representat per individus amb obesitat (OB), caracteritzada per un IMC superior a 30. A més de AN i OB, alguns trastorns de la conducta alimentaria (TCA) també formen part d'aquest continu donat el gran risc de caure en un dels extrems, com ara la bulímia nerviosa (BN) i el trastorn per afartament (TA). Els estudis han descrit alteracions similars a nivell psicològic i neurobiològic vinculades als seus patrons anormals de comportament alimentari, delineant vies de vulnerabilitat relacionades amb una base neurobiològica. Tot i que molts estudis en aquest camp han estat principalment transversals, han revelat interaccions biopsicosocials complicades que requereixen un examen de possibles factors subjacents en el desenvolupament i la persistència dels EWC. Una comprensió integral permet la integració de mesures preventives i estratègies de tractament, al mateix temps que reconeix la significativa superposició entre els trastorns alimentaris i l'obesitat, una connexió sovint passada per alt en les discussions de salut pública.

Hipòtesi i objectius: Basant-se en la literatura prèvia, aquesta tesi va postular que les persones que pateixen trastorns extrems de pes mostrarien una activitat cerebral disfuncional en regions associades al processament emocional de recompenses i al control cognitiu en comparació amb controls sans (HC). Del mateix mode, s'espera que les alteracions neuroendocrines en els EWC exerceixin una influència en la simptomatologia clínica. Així mateix, es va plantejar la hipòtesi que les alteracions en les funcions executives observades entre les persones amb EWC podrien perjudicar el curs de cada condició clínica. En línia amb aquestes hipòtesis, els objectius principals d'aquest estudi van ser investigar la funció cerebral avaluada mitjançant paradigmes basats en tasques i sense tasques en persones amb EWC en comparació amb HC. A més,

vam buscar avaluar l'impacte de la interacció entre els factors neuroendocrins i la funció cerebral en les característiques clíniques i antropomètriques dels EWC. De la mateixa manera, l'últim objectiu va ser identificar les possibles influències de les funcions executives en els resultats clínics de les persones amb EWC.

Mètodes: La tesi va abastar cinc estudis realitzats a la Unitat de Psicologia Clínica en col·laboració amb la Unitat d'Endocrinologia i l'Institut de la Imatge Diagnòstica de l'Hospital Universitari de Bellvitge. Les variables d'interès per a cada estudi es van recopilar mitjançant diversos instruments de mesura. Per a l'avaluació de la funció cerebral, es van adquirir dades de ressonància magnètica (MRI) de tot el cervell mitjançant un escàner MRI clínic de 3.0 Tesla equipat amb una bobina de crani de 32 canals. Per avaluar la presència o absència d'un diagnòstic de trastorns de la conducta alimentària (TCA) es van emprar els criteris del DSM-5. A més, tots els participants van completar avaluacions psicològiques i de personalitat a través de qüestionaris validats en paper i llapis. Finalment, es va determinar l'índex de massa corporal (IMC) mitjançant un analitzador de bioimpedància elèctrica multifreqüència Tanita BC-420MA per estimar la composició corporal. Es van recollir mostres de sang després de jeure per obtenir endocannabinoids circulants (eCBs), específicament 2-arachidonilglicerol (2-AG) i anandamida (AEA).

Resultats principals: A partir dels resultats obtinguts en les investigacions realitzades en aquesta tesi doctoral, es va observar una disfunció alterada en la ínsula en individus amb AN i OB. En OB, es va observar una disminució de l'activitat a la ínsula en una tasca de descompte de demora durant la ressonància magnètica funcional (fMRI) en triar recompenses immediates sobre recompenses retardades. En el cas d'individus amb AN, els anàlisis de neuroimatge funcional van revelar una connectivitat reduïda entre el nucli accumbens (NAcc) i la ínsula (NAcc-ínsula) i el NAcc i l'àrea motora suplementària (NAcc-SMA) en comparació amb el grup HC. La connectivitat disfuncional entre NAcc-ínsula i NAcc-SMA en individus amb AN es va associar amb concentracions circulants de eCB i l'IMC. Els eCB circulants es van associar amb impulsivitat, desregulació emocional i psicopatologia general, mostrant una via neurobiològica comuna en tots els grups clínics (és a dir, AN, BN, BED i OB). Es va observar un rendiment similar en les funcions executives entre els ED amb simptomatologia bulímica purgativa que difereix d'aquells

pacients amb simptomatologia restrictiva. Tanmateix, es va observar un mal rendiment en la presa de decisions i la flexibilitat cognitiva en comparació amb el grup HC. La corba d'aprenentatge relacionada amb la presa de decisions també va predir els resultats del tractament en TCA. Aquells pacients amb un bon resultat del tractament van mostrar una millora en la corba d'aprenentatge durant una tasca de presa de decisions, però aquells pacients amb un mal resultat del tractament no van mostrar progressió en l'aprenentatge. A més, la durada del TCA es va associar amb dèficits en les funcions executives i una durada més llarga va augmentar el risc de presentar aquests dèficits.

Conclusions: Els resultats en gran part confirmen les hipòtesis inicials i plantegen noves preguntes i reptes en el camp dels EWC. En primer lloc, les alteracions en la funció insular entre les persones amb AN i OB suggereixen una base neurobiològica compartida per a aquestes condicions. Tenint en compte el paper de la ínsula en la consciència corporal i el processament emocional, les alteracions podrien influir en com les persones perceben i processen els seus cossos i emocions en el context de l'alimentació. En segon lloc, la connectivitat funcional reduïda al NAcc amb la ínsula i el SMA en AN podria subjèixer alteracions en la integració d'informació interoceptiva, somatosensorial i de planificació motora relacionada amb la informació hedònica. Els eCB circulants estan vinculats no només a canvis neurobiològics en EWC, sinó també a factors psicològics com la psicopatologia general, la impulsivitat i la regulació emocional en tots els grups clínics, destacant la complexa interacció entre la senyalització neuroendocrina i els processos psicològics en EWC. Els resultats relacionats amb les funcions executives recolzen troballes prèvies que van mostrar un mal rendiment en les funcions executives en pacients amb TCA en comparació amb HC, especialment en la presa de decisions i la flexibilitat cognitiva. Interessantment, l'aprenentatge en la presa de decisions va resultar ser un valuós predictor dels resultats del tractament, la qual cosa destaca la importància de considerar factors cognitius en la gestió dels TCA. Una durada més llarga del trastorn va augmentar el risc de presentar dèficits en la presa de decisions, la flexibilitat cognitiva i el control inhibitori, suggerint que una intervenció precoç i estratègies de tractament personalitzades podrien ser crucials per millorar els resultats del tractament en aquests pacients. A més, aquests resultats proporcionen informació valuosa sobre les deficiències neurobiològiques, neuroendocrines i neurocognitives en

EWC que podrien ajudar a identificar nous enfocaments terapèutics més específics i millorar el pronòstic de les persones amb EWC.

1. INTRODUCTION

Eating behavior is a complex phenomenon, that involves several systems of the organism, with the main objective of maintaining the energetic and nutritional balance that guarantees the functioning of the organism. From a primary perspective, the act of eating represents an intrinsic human response motivated by hunger or satiety signals. However, in addition to being modulated by physiological factors, eating behavior is also influenced by cognitive and emotional processes, environmental and socio-economic factors that can determine eating habits and even the type of dietetic patterns and eating habits.

In recent decades, Western society has witnessed a significant rise in the quantity, variety, and accessibility of foods high in sugar and fat, as highlighted by several studies (1–3). The social context in which eating behaviors take place also plays a crucial role in determining the quality and quantity of food intake, affecting the nutritional status and long-term health outcomes of individuals. Unfortunately, a high-calorie and high-fat food environment has promoted malnutrition and an alarming increase in OB rates (4). Furthermore, the prevalence of cultural and media-driven beauty stereotypes, alongside the consumption of hypercaloric foods, has contributed to the development of an unrealistic ideal of extreme thinness (5). This ideal, in turn, has led to increased body dissatisfaction leading to dieting and weight loss (6). This scenario, in more vulnerable individuals, has contributed to the existence of maladaptive behaviors related to eating and weight control which can lead to the development of extreme eating and weight conditions (EWC).

The EWC construct emerges as a dimensional and theoretical model that identifies individuals who show aberrant eating behavior and abrupt weight fluctuations (6–10). According to this spectrum of weight-related disorders continuum, one extreme can be represented by individuals with anorexia nervosa (AN) characterized by an excessive restriction of food intake and an extremely low and dangerous body mass index (BMI). The other end of this continuum is represented by individuals with OB characterized by a BMI over 30. In addition to AN and OB, some eating disorders (ED) are also part of this continuum given the high risk of falling into one of the extremes (6,8,10). For instance,

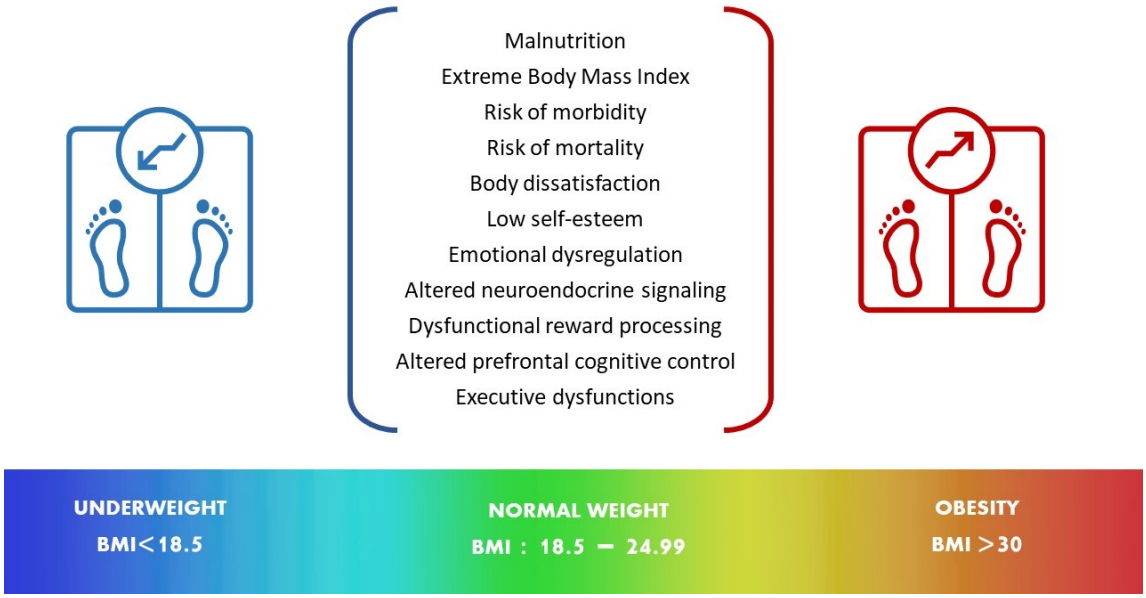
bulimia nervosa (BN) or binge eating disorder (BED), characterized by frequent episodes of excessive intake in a short period, presents a high risk for OB (11) and underweight (12–14).

Although the BMI is generally not considered a useful index of nutritional compromise, there is a broad consensus in using BMI as an indicator to delimit the ranges of normal weight which correlates with total adiposity and life expectancy (15,16). Abrupt changes in BMI are associated with an increased risk of mortality (17) and mental health problems (18,19). Overall, despite individuals being at different ends of the weight spectrum and exhibiting different eating behaviors, studies have reported the presence of similar neurobiological, neurocognitive, and psychosocial alterations (Figure 1). This suggests that EWC may share risk factors in the development or maintenance of each clinical condition, which significantly deteriorates the health and quality of life of these individuals (TABLE 1) (6,10,19–21).

From a nutritional standpoint, an unhealthy diet can compromise body systems such as the cardiovascular, endocrine, and even neurological systems (16,22–24). These risks arising from malnutrition have also been demonstrated to increase the risk of mortality and morbidity (25,26). In individuals with ED, the mortality rates are higher compared to other psychiatric disorders (23). In OB, the presence of comorbid diseases such as hypertension, diabetes, and other related pathologies can also increase the risk of mortality (24,27). For this reason, food choices and eating habits are a fundamental part of maintaining a healthy weight but also ensuring the correct functioning of the organism and being an indicator of life expectancy and quality (28).

From a psychological point of view, a common characteristic of EWC is a highly negative affect and emotional distress toward the own body shape (10,29–31). Authors who propose this spectrum of extreme eating- and weight-related continuum have indicated the body image dissatisfaction could be premorbid to subsequent pathological eating patterns (29,32,33). For instance, increased body dissatisfaction can lead to seeking maladaptive weight control strategies based on excessive exercise, food restriction, or nutritionally deficient diets (10,29,31,34,35) promoting potential pathological eating patterns (36).

Figure 1: Similar alterations in clinical and neurobiological substrates in extreme eating and weight conditions



From a neurobiological perspective, scientific advancements have identified similar neurobiological alterations in the homeostatic and hedonic mechanisms that regulate eating behavior (37). For example, the maintenance of unhealthy eating habits such as persistent starvation or excessive consumption of high-calorie foods in EWC has been shown to alter the peripheral signaling of hormones and peptides responsible for regulating energy homeostasis (38,39). Likewise, alterations at the neuroendocrine level have also been shown to be associated with dysfunctions of brain activity in regions involved in cognitive processes such as reward processing, emotion, and inhibitory control in EWC (40–46).

Exploring the clinical and neurobiological substrates involved in EWC as a continuum could provide a general understanding of why certain individuals may be more vulnerable to developing extreme weight and aberrant eating behaviors. However, the psychological and biological factors contributing to EWC are not fully understood. The identification of clinical and neurobiological substrates of EWC may have significant clinical implications by enabling the development of novel therapeutic targets improving treatment response from a dimensional approach that focuses on reducing symptoms.

1.1. EXTREME EATING AND WEIGHT CONDITIONS: FROM ANOREXIA TO OBESITY

1.1.1. CHARACTERISTICS OF EWC

The Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5) (47) in the section focused on eating behavior and feeding disorders diagnoses refers to nine categories of ED: pica, rumination disorder, avoidant restrictive food intake disorder (ARFID), AN, BN, BED, other specified eating disorder (OSFED) and unspecified feeding or eating disorder (UFED). This doctoral thesis is specifically focused on those that alterations in eating behavior represent a risk for developing EWC, and also have significant medical complications: AN, BN, and BED.

AN is characterized by restrictive eating behavior that seeks to maintain a body mass index below a healthy weight (BMI>17) (47). Depending on the type of maladaptive behaviors to maintain this low weight, AN is classified into restricting type (AN-R) characterized mainly by excessive starvation and/or exercises, or bulimic-purging type AN (AN-BP) characterized by the presence of vomiting and the use of laxatives. According to DSM-5 criteria, it is also specified the presence of high body dissatisfaction and an altered perception of own body image along with four levels of severity based on BMI: BMI 15–15.99 kg/m² (extreme severity), (severe), BMI16–16.99 kg/m² (moderate), and BMI ≥17 kg/m² (mild). Although amenorrhea has been removed as a diagnostic criterion in the DSM-5 version, it is a recurrent sign associated with the severity in women.

BN is characterized by episodes of excessive overeating accompanied by a sense of loss of control followed by vomiting and purging behavior to compensate for these binge episodes (BE) (47). The severity of BN is determined by the frequency of compensatory behaviors and is classified according to the DSM-5 into 4 categories (47): compensatory behaviors occur between 1 and 3 times a week (mild), between 4 and 7 times a week (moderate), between 8 and 13 times a week (severe), and between 14 or more times a week (extreme).

BED was integrated into the latest version of the DSM-5 as an ED separate from AN and BN (47). In the previous edition of the DSM (DSM-IV-R) BED was "Eating Disorders Not Otherwise Specified" (EDNOS). According to DSM-5, BED is characterized by recurrent episodes of overeating in a short period experiencing high distress or guilt, but not compensatory behaviors after BE. These BE must occur at least once a week for at least 3 months. The frequency of BE represents the severity of BED: mild (1–3 BE per week), moderate (4–7 BE per week), severe (8–13 BE per week), or extreme (14 or more BE per week).

OB is defined as a disease characterized by excessive fat accumulation that can chronically affect several body systems (48). OB, as a complex and multifactorial condition, cannot be solely attributed to excessive consumption of food. Several factors can also contribute to the development of OB including genetic factors, metabolism, hormonal and mental disorders, medications, lifestyle, and environmental factors. For instance, hormonal disorders (e.g., polycystic ovary syndrome) and medications (e.g., antidepressants and steroids) can increase the risk of OB. According to the World Health Organization (WHO), the severity is categorized based on BMI being an OB class I (i.e., BMI between 30 and 34.9 kg/m^2), class II (i.e., BMI between 35 and 39.9 kg/m^2), and class III or extreme (i.e., BMI over o equal 40 kg/m^2). Excessive adiposity accumulation is the primary contributor to negative health consequences such as increasing the risk of mortality, morbidity (26), and the development of cardiovascular and metabolic disease and cancer (49). The risk increases when it is accompanied by additional health problems such as type 2 diabetes and arterial hypertension (TABLE 2) (22,50).

TABLE 1. Main risks of medical complications in EWC

	AN	BN	BED	OB
EATING BEHAVIOR	Restriction of energy intake necessary for metabolic needs causing a significantly low body weight.	Recurrent episodes of eating a large amount of food in a discrete period of time, most individuals would eat accompanied by sense of lack of control		Imbalance between energy intake and energy expenditure, resulting in a positive caloric balance that gradually leads to weight gain
Cardiovascular disease	Hypotension bradycardia (51)	Arrhythmias, cardiac failure (51)	Hypertension, cardiac failure, ischemic heart disease (25)	Hypertension, risk of coronary heart disease or failure (52), stroke, and peripheral vascular diseases (53)

Endocrine and metabolic disease	Hypokalemia, hyponatremia, hypothermia, altered thyroid function, hypercortisolemia amenorrhea, (51)	Acidosis, alkalosis (51)	Risk of metabolic and polycystic ovarian syndrome (54)	Metabolic syndrome, type 2 diabetes (55)
Gastrointestinal complications	Prolonged gastrointestinal transit (delayed emptying, gastric atrophy), constipation delayed (51)	Constipation, gastric or duodenal ulcers, pancreatitis, esophageal, gastric erosions, and perforation (51)	Dysphagia, acid reflux, bloating, abdominal pain, diarrhea, constipation (54), and Irritable bowel syndrome (56,57)	Irritable bowel syndrome (58),
Hematological and vascular diseases	Anemia, leukopenia, thrombocytopenia (51)	Leukopenia or lymphocytosis (51)	High blood pressure, hyperglycemia, high serum triglycerides and hypolipidemia (54)	Hypercholesterolemia, dyslipidemia, atherosclerosis, abnormal concentrations of triglycerides (55)
Skeletal	Osteopenia, osteoporosis (51)	No reported	No reported	Osteoarthritis (59)
Dental problems	Dental caries (51)	Dental erosion (51)	No reported	Periodontal diseases and/or multiinflammatory diseases of the periodontal tissues (60), and xerostomia
Renal, kidney and other systems	Renal calculi (from dehydration) (51)	Acute kidney injury (from dehydration and purging), acute renal injury (from laxatives)	Urinary incontinence derived from polycystic ovarian syndrome (54)	Glomerulosclerosis and tubulointerstitial fibrosis, nephrons injury, reduction in renin-angiotensin system (53)

Note: ED: eating disorders. AN: anorexia nervosa. BN: bulimia nervosa. BED: binge eating disorder. OB: obesity

1.1.2. EPIDEMIOLOGY OF EWC

1.1.2.1. Prevalence

OB is currently the most prevalent EWC compared with AN, BN, and BED affecting over 2 billion men and women worldwide, which is approximately 30% of the world's population (61–63). This epidemic problem is particularly prominent in Western societies. (64). Although less prevalent than OB, ED are public health issues because it causes significant personal and familiar distress and individual-societal burden (65). Epidemiological studies indicate that ED are more prevalent in women, although gender

differences in prevalence are particularly prevalent AN and are less distinct in BED (35,66). Specifically in AN, the prevalence is 1-4% in women and 0.3% in men among the total population (67). In BN, the prevalence is 3% in women and close to 1% in men (54) whereas in BED is between 0.6 and 1.8% in adult women and between 0.3 and 0.7% in men among the total population (54,67). Concerningly, a recent review has highlighted that the prevalence of ED has risen sharply from 3% to almost 8% in recent decades (66). However, since the COVID-19 pandemic, there has been a further increase in ED cases among children and adolescents (68,69).

Regarding OB, the prevalence can vary significantly depending on the country. In the United States, the prevalence of adults with OB is over 40% (48,62) and in Spain, a recent study reported a 20% among the total population (70). Currently, OB rates are increasing at a younger age, becoming a medical concern, as health problems that were expected to appear in adulthood are now observed in children (71). A systematic review indicated that 55% of children will develop OB in adolescence and 80% of adolescents with OB will maintain OB in adulthood (72). In this review, the authors also pointed out that most individuals who develop OB in adulthood did not have OB in childhood. In addition to health problems such as diabetes, high cholesterol, or hypertension, children with OB may show low self-esteem and depressive symptoms (73,74). Currently, the prevention of OB in children is particularly important for reducing the substantial future increment of adults with OB and preventing mental health problems related to OB.

1.1.2.2. Etiology of EWC

The etiology of EWC is still unknown. Studies have investigated the etiology from a biological and psychological perspective as well as taking into consideration environmental and socio-cultural risk factors. More biological oriented studies in ED have indicated the existence of a genetic predisposition to develop AN (75,76), BN and BED (54,75,77,78). An early study reported a considerable genetic risk of developing AN and BN during their lifetime in direct relatives compared to families of healthy controls (79). Recently, the Anorexia Nervosa Genetics Initiative has identified specific chromosomal characteristics associated with the metabolic and clinical alterations observed in AN (80). Similarly, studies have investigated whether genetic factors in OB

predispose these individuals to excessive visceral fat accumulation. Thus, single-nucleotide polymorphisms of the fat mass and OB-associated (FTO) gene have been purposed as with a risk for OB (81) and ED (82). This genetic polymorphism in the FTO involved in mechanisms that regulate eating behavior and energy expenditure, has been identified as a potential risk factor that predisposes individuals to gain weight compared to those without this polymorphism (81,82).

From a clinical perspective, some psychological factors seem to play an important role in developing EWC. Personality traits, namely temperamental traits, are enduring and stable characteristics that describe how a person tends to think, feel, and behave according to contexts and to specific stressful situations. As further expanded in section 1.2 (i.e., Clinical substrates of extreme eating and weight conditions), personality traits, , represent risk factors but also characterize a clinical profile in each EWC as maintaining factor. Considering EWC as a continuum sharing vulnerability factors, studies have described common premorbid personality traits. Low self-esteem, difficulty managing negative emotions, and interpersonal difficulties have characterized the entire continuum of EWC (See TABLE 1). In the case of BN, BED, and OB studies have described similar levels of higher impulsivity, lack of self-control, and a higher reward sensitivity that represent shared risk factors (83,84).

In ED, similar personality traits such as perfectionism, neuroticism, low self-esteem, and elevated harm avoidance represent premorbid personality traits, regardless of ED diagnostic (85–88). Specifically, a higher HA has been a predictor of ED symptomatology in individuals with AN, BN, and other ED (87). HA refers to the tendency of individuals to avoid potential harm or punishment being anxious and susceptible to experiencing negative emotions. In AN studies have described that high perfectionism and obsessive-compulsive traits increase the risk for developing AN (89). In the case of individuals with binge eating symptomatology, studies described high levels of impulsivity and novelty seeking linked to the risk of triggering BE (85,90). Regarding individuals with OB, studies have indicated that the presence of extraversion, openness to experience, and agreeableness (91) or the tendency towards emotional eating (92,93) may delineate the premorbid personality traits in OB.

Environmental factors have also been shown to play a key role in the development of EWC (59,78,94–96). As previously mentioned, social stereotypes of beauty can contribute to body dissatisfaction and negative attitudes toward food in more vulnerable individuals. Individuals with EWC are more vulnerable to societal expectations regarding weight and body shape stereotypes (32,97,98). In addition, there are also situational triggers that can increase the risk of developing an EWC. For example, family problems such as divorce, bereavement, and academic or work pressures may trigger or explain an EWC. Additionally, it has been observed that traumatic life experiences such as physical or sexual abuse are associated with an increased risk of developing ED and OB. Studies have indicated that family and social influences, such as parental criticism of body weight and shape can influence the development of EWC (99). In the case of OB, there are additional sociodemographic and socioeconomic well-identified risk factors. Recent studies consistently reported that socio-economic status and educational level are determinants in the raising prevalence of OB (70,100,101). Likewise, individuals with lower education and those who live in rural and suburban areas are more at risk for OB (101).

The similarity of certain risk factors suggests the need to consider a continuum in EWC rather than discrete categories. Such an approach would facilitate a better understanding of shared risk factors and enable the development of interventions based on common characteristics. This perspective acknowledges the presence of overlapping features and underlying factors that contribute to different diagnostic entities, emphasizing the importance of considering these shared aspects in clinical practice. By adopting a dimensional perspective, clinicians can gain a deeper understanding of the complexity of these disorders and tailor interventions accordingly.

1.1.2.3. Progression of the EWC

The onset and duration of ED can vary depending on the individual and the comorbidities associated with the disorder. The onset of the AN is usually observed before 17 years of age (102), with a better prognosis than those patients with a pre-pubertal onset (67,103). Similar to the BN, although its onset is more commonly situated

in early adulthood (67). Conversely, the onset of BED is usually observed in adulthood (54). In the case of OB, onset can occur in childhood, adolescence, or adulthood.

For example, in AN is observed that, on average, the time to complete remission is between 5 and 6 years (104), even though there is a high probability of AN becoming chronic (102). In BN, a recovery rate close to 55% has also been reported (105). However, there is a significant relapse rate in BN, especially in those individuals reporting high levels of body dissatisfaction and poor psychosocial adjustment (106). In BED, although few studies provide information on the long-term prognosis of BED patients, recent reviews reported a worse prognosis for patients with BED if the disorder is associated with comorbidity of substance use disorders, borderline personality disorder, affective disorders, and post-traumatic stress disorder (30,54). Some studies indicate that ED are long-lasting in close to half of the cases (107,108). High dropout rates (108) and relapses (109) may pose a significant risk of these disorders becoming chronic.

In recent years, the focus of interest has been on identifying underlying substrates that facilitate or hinder successful recovery and reduce a potential relapse, which can imply a risk of EWC becoming chronic. In the case of patients with ED, there has been debate about whether a longer duration is associated with greater severity (110,111). Some authors have used the term 'severe-enduring' to suggest that patients with a long duration of the disorder present more severe eating symptoms or general psychopathology (107). However, in recent years, it has been found that a longer duration of the disorder is not necessarily associated with greater severity (108,110). Some individuals with ED might present a longer duration without acute symptoms, maintaining their daily activities without perhaps resorting to treatment throughout their lives (112,113). However, there is another type of patient who has a long duration associated with repeated failed attempts at recovery (108,112). This trajectory of the disorder is characterized by incomplete treatments, dropouts, or symptoms that do not improve or relapse, prolonging the duration of the disorder (108). These cases require greater efforts to identify and develop therapeutic strategies that ensure treatment success and promote greater adherence.

Relapse and chronification of OB are common issues. Individuals who lose excess weight through lifestyle changes or weight loss interventions will eventually regain weight (22,114). Usually, the prevalence of successful OB treatment can vary depending on the length of follow-up (50,115). Some studies have found that a significant proportion of individuals who lose weight will eventually regain it, while others have reported successful weight loss maintenance in a smaller subset of individuals (50). It is important to note that success is not only measured by weight loss, but also by improvements in other health markers, such as blood pressure, cholesterol levels, and blood sugar control (59,116). Factors that can interfere with non-recovery from OB include genetic predisposition, metabolic factors, lifestyle habits, psychosocial factors, lack of social support, medical conditions, and medication use (50,117). Other factors include poor adherence to treatment, low motivation, and limited access to healthcare services. Additionally, relapse can occur after initial success in weight loss and weight regains is common after bariatric surgery (22,117). Furthermore, OB can become chronic if it is untreated or if there are repeated failed attempts at weight loss (118). Successful treatment of OB requires a comprehensive approach that addresses all contributing factors and provides ongoing support and monitoring.

1.1.2.4. Risk of mortality of EWC

The AN is the mental disorder with the highest mortality rate among ED and even any other psychiatric disorders (119,120). Among all ED, AN has the highest mortality rate at 5.1 deaths per 1000 cases annually, with the majority of deaths resulting from natural causes related to eating (67,121). In contrast, BN has an annual mortality rate of 1.9 deaths per 1000 cases, with suicide representing one in five of these deaths (119,121). In OB, the risk of mortality increase when it is associated with medical complications such as cardiovascular diseases, diabetes, or cancer (26,122). A longitudinal study of 6,197 participants reported a total of 56.1% death at 17-year follow-up exhibiting a similar proportion in men and women (122). Moreover, recent epidemiological studies after the COVID-19 pandemic reported a higher mortality rate linked to OB, with excess weight being a risk factor for health complications (123) and death (27) derived from COVID-19.

1.2. CLINICAL SUBSTRATES IN EXTREME EATING AND WEIGHT CONDITIONS

Some psychobehavioral characteristics have represented the whole spectrum of EWC (TABLE 2). However, it is worth noting that as different diagnostic entities (mental disorder vs excessive visceral fat accumulation), they do not share a similar psychological profile. Individuals with ED, compared to OB, exhibit a more psychopathological profile and greater severity of ED symptoms (124–126). Consequently, the psychological distress reported by patients with ED is higher and typically requires psychological intervention, while individuals with OB may not typically require psychological support. Nevertheless, beyond the psychological distress directly associated with OB, a small proportion may experience psychological and emotional problems or develop a psychiatric disorder such as depression or BED throughout their lives (127).

1.2.1. PERSONALITY TRAITS IN EWC

According to Cloninger's model of personality and temperament, patients with ED share a common personality profile characterized by high harm avoidance and low scores in self-directedness and cooperativeness, as well as traits associated with avoidant personality disorder (83,85,92,128). Interestingly, these personality and temperament factors tend to persist even after recovery, suggesting that they are stable traits that extend beyond the resolution of disordered eating behaviors (85,129). These traits typically surface during childhood, before the onset of the disorder, potentially increasing the risk of developing it.

In AN, personality traits can vary depending on AN subtypes (85). The AN-BP subtype tends to show slightly higher levels of impulsivity and novelty seeking (85,130,131) while the restrictive subtype reports higher levels of persistence and perfectionism (85,132). Both AN-R and AN-BP are characterized by high levels of anxiety (130,131), perfectionism (133,134), and high harm avoidance (90). In this regard, it is worth noting a study that found that levels of harm avoidance in individuals with AN can be very similar or even higher than those with a diagnosis of social phobia or avoidant personality disorder (135). Consistent with this notion, a study identified a cluster C of

personality is more frequent in these patients (130). Cluster C refers to a group of personality disorders characterized by anxious and fearful behavior, including avoidant, dependent, and obsessive-compulsive personality disorders. there are problems with behavioral flexibility, which could explain the presence of certain obsessive behaviors related to body shape or eating and exercise habits. Likewise, Individuals with AN present anhedonia and asceticism which is reflected in a low reactivity to reward as well as a high sensitivity to punishment that is observed in acute stages of the disorder and even after recovery (102).

TABLE 2: Shared psychobehavioral features in EWC

	AN	BN	BED	OB
Low self-esteem	+	+	+	+
Body dissatisfaction	+	+	+	+
Perfectionism	+	+	+	
Poor impulse control		+	+	+
Risk of addictive behaviors		+	+	+
Cognitive rigidity	+			
Depression and anxiety	+	+	+	+
Stress				+
Emotional dysregulation	+	+	+	+
Interpersonal difficulties	+	+	+	
Impulsivity		+	+	+
Emotional eating				+
Binge eating		+	+	
Weight concerns	+	+		
Distortion of body image	+			
Childhood traumas or abuse	+	+	+	+

Note: ED: eating disorders. AN: anorexia nervosa. BN: bulimia nervosa. BED: binge eating disorder. OB: obesity

Some authors have integrated BN and BED within the spectrum of binge eating disorders (BSD) (51,136) given the psychological similarities to the problem of impulse control and the inability to self-control during BE (137–139). Both BN and BED have reported alterations from an impulsivity and compulsivity dimension (139,140). While impulsivity heads the lack of control to initiate disruptive behaviors, compulsivity underlies difficulties in cut-off behaviors despite negative consequences, being potential endophenotypic markers in these BSD. In addition, studies have consistently described that individuals with BSD exhibit higher levels of novelty-seeking (86), lack of perseverance, and low self-directedness (11,141) supporting the notion that these

personality traits may contribute to the underlying psychological mechanisms of impulsive and compulsive behaviors observed in individuals with BSD. Likewise, considering BE usually occur in the context of negative emotion (142–144) studies have suggested that the presence of a maladaptive strategy to alleviate intense emotions might be triggering for compulsive BE (145,146). The lack of strategies for coping with strong emotions can rash impulsive behaviors motivated by strong emotional states (i.e., urgency) (147). Findings converged in indicating a high prevalence of impulsivity, negative urgency, low self-directedness, and high levels of sensitivity to reward exert a binge-promoting effect (141,148). Worryingly, high impulsivity and high sensitivity to rewards increase the risk for substance use disorder in BN and BED (149,150). The prevalence of comorbid substance use disorder is higher in BN than in other ED such as BED or AN hindering recovery (149,150).

Personality traits observed in OB include low self-esteem (10), tendencies towards anxiety and depression (151), problems with impulse control (83,152), openness to experience, and extraversion (91,153). Studies found high associations between OB and depressive and anxiety symptomatology (127). Similar to BSD, individuals with OB may also exhibit impulsive behaviors, acting without considering the long-term consequences (154,155). This lack of consideration for long-term consequences can hinder weight loss efforts, which require time for obtaining results and maintaining long-term effects. Likewise, some individuals with OB may have a lower self-efficacy related to the perception of an inability to achieve goals or make lifestyle changes (156). This can undermine weight management efforts, as individuals may feel discouraged and less motivated to make necessary changes. Interestingly, some studies have also observed higher perfectionism in individuals with OB (6). Finally, regarding openness to experience and extraversion, findings are mixed and can vary across different studies (91,153,157). Some research suggests that individuals with OB may exhibit less willingness to explore new experiences and sociability, although these results are not consistent across all studies (153).

1.2.2. EATING DISORDER SYMPTOMATOLOGY AND GENERAL PSYCHOPATHOLOGY IN EWC

There are significant differences in eating symptomatology between EWC. Undoubtedly, individuals diagnosed with an ED exhibit more pronounced eating symptomatology and distress compared to those with OB in terms of eating patterns. Individuals with ED show a tendency to compensatory behaviors and obsessive concern regarding weight and body shape. However, this does not imply that individuals with OB do not experience any symptoms resembling ED.

Some studies suggest that dietary restriction can be a precipitating factor toward an EWC. Dietary restriction has the potential to trigger an ED due to several factors (10,29,31,34,35). Some of them are related to negative psychological responses toward food, displaying obsession, anxiety, or feelings of deprivation toward food (140). Strict caloric restriction can lead to episodes of overeating (158,159). This cycle of restriction and overeating can lead to OB or BSD if the frequency of overeating episodes is accompanied by a sense of loss of control (159,160). Individuals with OB may exhibit disordered eating patterns, but they do not necessarily experience BE (92) as BED which exhibit BE at least once a week accompanied by feelings of guilt, shame, and emotional distress.

In the case of AN patients, the common eating symptomatology, in both diagnostic subtypes, is related to body image distortion and compensatory behaviors, although they differ in type. In the case of AN-R, individuals tend towards starvation and may compensate for food intake with physical exercise, while patients with AN-B engage in purging and vomiting similar to BN (47). The difference with BN is that AN-BP patients usually do experience subjective BE, but they tend to engage in compensatory behaviors to a greater extent than the amount of food consumed.

In individuals with OB, although they are not classified as eating disorders, several studies have highlighted the potential existence of a bidirectional risk between OB and certain mood disorders (157,161–163). For instance, studies in individuals with a history of major depressive disorder or bipolar disorder are more likely to develop OB, and conversely, individuals with OB are at a higher risk of developing mood disorders, such as major depression (162). In OB, some studies are consistent in pointing out OB as a ‘metabolic-mood syndrome’ given the increased risk of mood disorders

symptomatology (157,164). This psychopathological framework in OB is associated with certain premorbid personality traits such as low self-esteem, negative self-evaluation of body shape, and emotional dysregulation (157,161,165). A more psychopathological profile of OB is associated with the presence of depressive psychopathology. Studies have delved into identifying different behavioral phenotypes in OB, differentiating a functional profile influenced almost exclusively by metabolic factors, while another profile, more dysfunctional, is related to dysregulated behavioral patterns and is more vulnerable to a mental disorder (163,166).

As mentioned, individuals with EWC share significant levels of body dissatisfaction. In the context of OB, the presence of body dissatisfaction can serve as a potential risk factor for the onset of an ED (10). Indeed, there is an important interconnection between OB and ED since both can influence the onset of each other. Patients with BN and BED can lead to OB in the same way that individuals with OB may present an ED (11,167). The presence of lifetime OB represents a more severe expression of ED (19,168). Likewise, patients with lifetime ED and OB showed later onset of ED, but greater severity of ED, greater general psychopathology, and worse prognosis (19). Patients with ED and OB referred family history of OB and/or childhood OB compared to those with ED without a lifetime OB (11). In patients with BN and BED, lifetime OB is indicative of extreme BMI fluctuations, greater general psychopathology and ED severity, and a higher onset and duration than those without a history of OB (169). In the same vein, there can be a crossover between the symptomatology and diagnosis of different ED (13,14). For instance, one-third of patients with AN may cross over from restricting-type AN (RAN) or bulimic-purge type AN (AN-BP) to a diagnosis of BN (12–14,170) or UFED (170). Similar to patients with BN who can experience weight fluctuations, switching to AN-BP (171), BED (170) with risk of OB (11,63).

1.2.3. EMOTIONAL DYSREGULATION

Emotions play a significant role in EWC (172–176). In many cases, emotions can act as triggers or contributing factors to maladaptive patterns of eating. In the last decades, studies have emphasized the role of emotion in both the development and maintenance of EWC (177,178).

In AN, studies have indicated that a lack of emotional awareness might be related to food restriction (173,179) describing low tolerance to distress (173). It has been suggested that patients can employ food restriction and weight loss as strategies to avoid negative emotional states intensifying symptomatology (135,180,181). For instance, starvation can be a negative reinforce that diminishes aversive emotional responses (182,183).

In the case of individuals with BN and BED, often turn to food to cope with difficult emotions or as a form of emotional self-compensation (143,184,185). Lavender et al. (186) found that in individuals diagnosed with BN, higher scores in emotional dysregulation were related to symptom severity, as well as difficulties in accepting emotions, lack of adequate emotion regulation strategies, and impulse control deficits. The fear of weight gain often leads to purging, and it is important to highlight that feelings of guilt commonly arise after a BE in individuals with AN-BP (183) and BSD (146,176,187). Likewise, a higher emotional dysregulation has been positively associated with poorer therapy response (188).

Studies in OB have also found that individuals use food to cope with stress, sadness, anxiety, or other negative emotions (157,189,190). These imbalanced eating patterns motivated by emotional states have been defined as emotional eating (157). Emotional eating refers to the behavior of using food to cope with negative emotions or stress (191–193). It has been observed that individuals with OB have a greater tendency to eat emotionally compared to those without OB (190). This emotional eating involves overeating high-calorie and highly palatable foods beyond the satisfaction of physical hunger (194) and may hinder weight loss and maintenance of a healthy weight as well as adherence to OB treatment programs (192).

1.2.4. CURRENT TREATMENTS FOR EWC

Current treatments for EWC involve a multidisciplinary approach that may include medical, psychological, and nutritional interventions. The specific treatment approach can vary depending on the type and severity of the diagnosis. In the case of treatments for ED, they involve various medical disciplines. As mental disorders, AN, BN, and BED are mainly addressed by mental health professionals, while OB is typically treated by

endocrinology and nutrition fields. However, a multidisciplinary approach involving specialists from other healthcare areas, such as psychological care, endocrinology, cardiology, nutrition, and gastroenterology, might be required in all EWC.

In patients with ED, various forms of psychotherapy are used to address the underlying psychological factors contributing to distress and symptomatology. However, cognitive behavioral therapy (CBT) is the first-line treatment for ED (195). For instance, interventions such as virtual reality have been implemented to address body image concerns (196). Likewise, in recent years, other emerging therapies, so called third wave CBT, such as cognitive remediation and emotional skills training have been employed to enhance cognitive flexibility and emotion regulation in AN (197,198), psychoeducational therapy (199), Dialectical Behavior Therapy (DBT) (200), or Family-based Therapy (FBT) (201) have shown to complement for improving treatment response. In the case of AN patients, hospitalization may be necessary for refeeding and weight restoration, especially in cases of extreme thinness. Likewise, some AN patients may also require endocrinological attention due to hormonal disorders that result from starvation (51). In BN, patients may require medical attention for problems at the intestinal and dental levels.

Regarding pharmacological treatment for ED, the focus primarily revolves around managing comorbid conditions such as depression, anxiety, obsessive-compulsive symptoms, physical complications, and malnutrition (75,202). For instance, selective serotonin reuptake inhibitors (SSRIs) and antipsychotics are potential pharmacological options to address specific symptoms of AN, such as body image distortion, anxiety, irritability, and obsessive thoughts related to food, but as a second line approach (203). These pharmacological strategies can be considered in the treatment of patients with AN. Moreover, the use of fluoxetine (an antidepressant) has been used to reduce BE and purging in BN. Additionally, Lisdexamfetamine, a psychostimulant for attention deficit hyperactivity disorder (ADHD) treatment has been used in some countries as a treatment for reducing BE (204).

The primary focus for treatment of OB treatment revolves around lifestyle changes, including adopting a healthy diet, increasing physical activity, and modifying behavior in

coping with stressful situations (117). Furthermore, medications targeting OB-related medical complications, such as hypertension, type 2 diabetes, or dyslipidemia, may include antihypertensives, oral hypoglycemic agents, or insulin, and medications to reduce cholesterol levels (52,53,205). Medications that affect fat metabolism, such as Orlistat, work by blocking fat absorption in the intestine, thereby reducing calorie intake (205). Overall, there is no single gold standard treatment that works for everyone with OB, as the most effective approach will depend on the individual's specific situation, including their overall health, degree of OB, and personal preferences. Lifestyle modifications, such as changes in diet and physical activity, are often the first-line approach for OB treatment (163).

However, it has been observed that a combination of psychological interventions, exercise, dietary strategies, and bariatric surgery can ensure effective treatment for OB (206). In some cases, bariatric surgery may be recommended for individuals with severe OB. Bariatric surgery includes procedures such as gastric bypass and sleeve gastrectomy, which can result in significant weight loss and improvement in weight-related health problems (22). While bariatric surgery can be an effective OB treatment, it is not a guarantee for long-term weight loss if the patient is not able to make lasting lifestyle changes, such as adopting a healthy diet and engaging in regular physical activity (207). Likewise, some patients may experience weight regain or experience complications post-surgery (169,207).

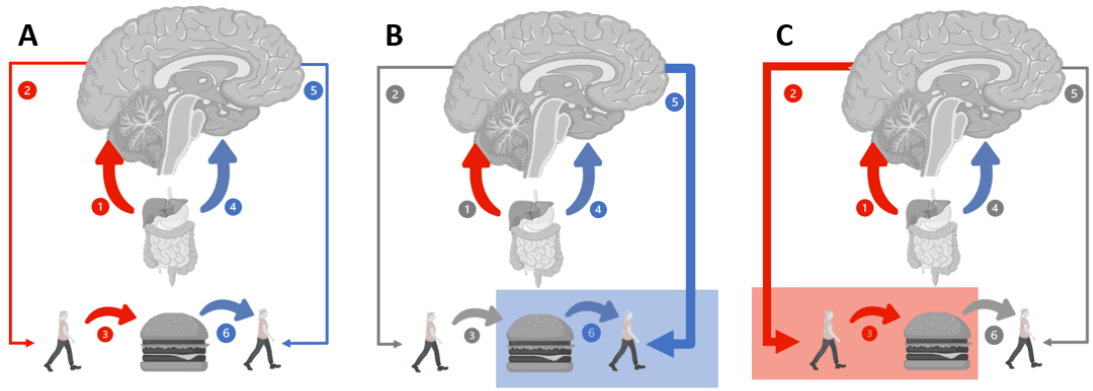
1.3. NEUROBIOLOGICAL SUBSTRATES IN EXTREME WEIGHT CONDITIONS

The neuroscience of eating behavior has focused on the study of underlying biological mechanisms and neural processes involved in regulating and controlling eating behavior to provide insights from normal eating (208) and identify the alterations underlying EWC (38,44,46).

To date, findings have identified the existence of two main mechanisms involved in the regulation of eating behavior: homeostatic and non-homeostatic mechanisms. The homeostatic mechanism acts on eating behavior through physiological signals of hunger and satiety whereas the non-homeostatic mechanism provides the hedonic aspects of

food, increasing the motivation to eat (46,208). The motivation to eat is inherent to humans because food intake ensures survival. As a primary reinforcer, food can increase or decrease the probability of repeating the choice depending on the expectation linked to the value of food. For instance, if a certain food is rewarding for an individual, then this contributes to repeating the experience. In addition to metabolic homeostasis, there is associative learning between the stimulus (i.e., food) and the occurrence of a reinforcer. When eating behavior is motivated by homeostatic needs, food stimulus can be more or less attractive depending on the metabolic state of the individual (208–210). When the metabolic needs of the individual are satisfied (i.e., satiety), the food may still be palatable, but the motivation to eat that food is lower compared to when the metabolic needs require energy consumption (i.e., hunger) (Figure 2) (210,211).

Figure 2. Neurobiology of eating behavior regulation in healthy control, anorexia nervosa, and obesity



Note: The figures show the interaction of mechanism that regulate hunger and satiety considering peripheral and central signaling. The red arrows represent the peripheral signals and brain regions that activate appetite and facilitate the initiation of food consumption whereas the blue arrows represent the peripheral signals and brain regions that inhibit appetite and promote satiety in **A)** healthy control, **B)** anorexia nervosa, and **C)** obesity. **A:** 1) The hypothalamus receives hunger signals; 2) increased responses in the ventral reward pathway, specifically in the dopamine-dependent regions, heighten motivation for food; 3) initiating eating; 4) anorexigenic signals indicate metabolic balance, reducing hunger; 5) decreased responses in the ventral reward pathway but increased activity in brain regions of the dorsal pathway; 6) inhibiting eating behavior. **B:** 1) The hypothalamus receives hunger signals; 2) increased responses in the ventral reward pathway reduce motivation for food; 3) avoiding eating despite homeostatic hunger signals; 4) there is a disruption in anorexigenic signals due to the failure to achieve metabolic energy balance through food intake; 5) Increased activity in the brain's dorsal pathway reinforces cognitive and behavioral control, prioritizing food avoidance over metabolic needs; 6) inhibiting eating behavior. **C:** 1) The hypothalamus receives hunger signals; 2) exacerbated responses in the ventral reward pathway increase the motivation for food, which may be more responsive to high-fat and high-sugar foods; 3) excessive eating; 4) resistance to satiety signals leads to 5) decreased suppression of eating; 6) excessive food consumption beyond metabolic needs.

The evidence converges in suggesting that alterations in eating behavior in EWC would probably be better explained by alterations in non-homeostatic mechanisms than homeostatic mechanisms (46,212). In EWC, differences in brain activity to food stimuli

and even imaging have been observed when compared to healthy controls in regions involved in reward processing and cognitive control (Figure 2) (213,214). This has led to the suggestion that alterations in neural activity may underlie the aberrant eating patterns observed in EWC.

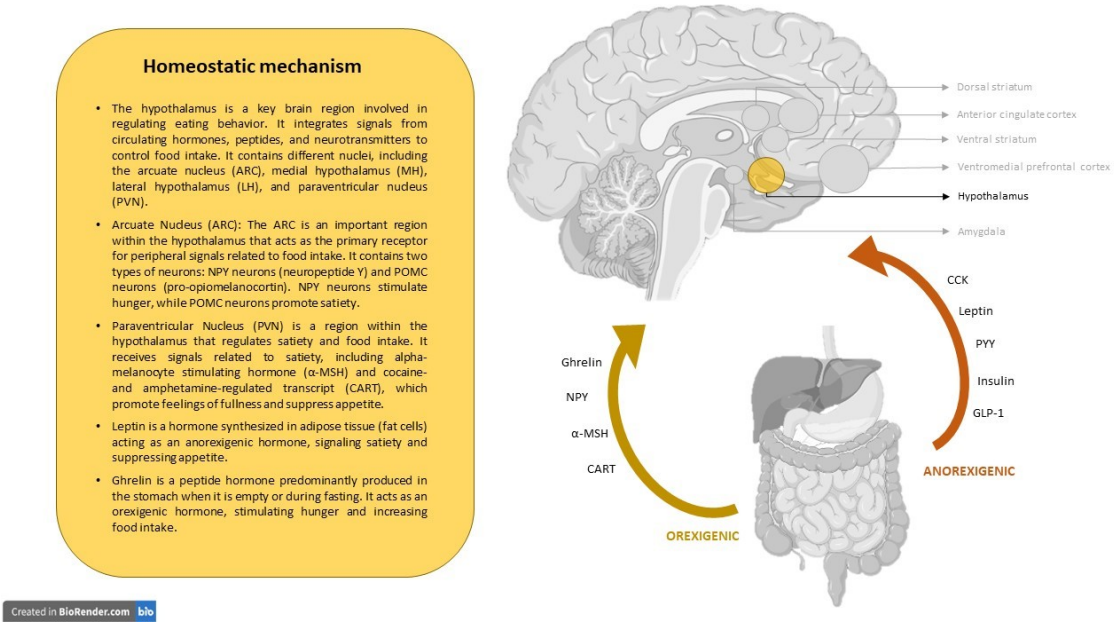
1.3.1. HOMEOSTATIC MECHANISMS IN EWC

Multiple studies have elucidated the intricate interplay between circulating hormones and peptides from peripheral tissues, communicating with the central nervous system to regulate behaviors that either promote or inhibit food intake (215–219). From early studies in animal models, the hypothalamus has been described as the main regulator and integrator of peripheral and central nervous systems receiving signals from hormones, peptides, and neurotransmitters (Figure 3) (220,221). It has been described that lesions in hypothalamic regions can induce alterations in the eating behavior of individuals who, without having an ED, exhibit food restriction or overeating (222). The hypothalamus is comprised of several nuclei, but it is usually divided into three main areas: the medial (MH) and lateral hypothalamus (LH) and the paraventricular nucleus (PVN) (216). The MH is considered the satiety center whereas the LH is the hunger center. Studies have described the arcuate nucleus (ARC), located at the base of the hypothalamus, as the primary receptor of peripheral orexigenic and anorexigenic signals (219,223).

According to their effect on eating behavior, these neuroendocrine signals are classified as orexigenic (for promoting food intake) and anorexigenic (for suppressing food intake). Through two neuronal nuclei (i.e., neuropeptide Y (NPY) neurons and proopiomelanocortin (POMC) neurons, the ARC release NPY and agouti-related peptide (AgRP) to the LH stimulating hunger (217,219) and release the alpha-melanocyte stimulating (α-MSH) and cocaine- and amphetamine-regulated transcript (CART) hormones to the PVN promoting satiety (Figure 3) (224). For example, the ARC receives signaling from ghrelin, an orexigenic peptide that increases its concentration in the stomach when it is empty during fasting (208). Conversely, the peptide YY (PYY) released by gut tissue and the leptin synthesized in adipose tissue, two anorexigenic peptides, arrive at the ARC to cut down on food intake after ingestion (217). Interestingly, it has

been found that leptin also communicates with the prefrontal cortex (PFC), a main brain region part of the non-homeostatic mechanism influencing cognitive control for suppressing eating behavior (225). In the case of the PFC, as discussed later, it is involved in executive functions such as decision-making and self-control, and in this case, plays a crucial role in coordinating behavioral responses with physiological signals associated with satiety (226). This interaction between homeostatic signals mediated by the hypothalamus and specific non-homeostatic brain regions is key to the balance between energy intake and motivation to eat (211,212,223). As described below, regions of cognitive control work together with sensory and reward-related brain regions in the processing of food-related information.

Figure 3. Homeostatic brain mechanism involved in the regulation of eating behavior



In the context of EWC, studies have described an altered function between neuroendocrine signaling and hypothalamic activity (45,227–231). For instance, studies on AN have suggested that dietary restriction and persistent ignoring of physiological signals of hunger may lead to alterations in hypothalamic functioning (227,232). In the same way, in OB, excessive energy intake beyond metabolic needs might alter satiety signaling and induce an imbalance in the homeostatic mechanism that regulates food intake (227,228). Consistent with this notion, a recent study reported decreased activity in the hypothalamus during glucose ingestion in individuals with AN and OB compared

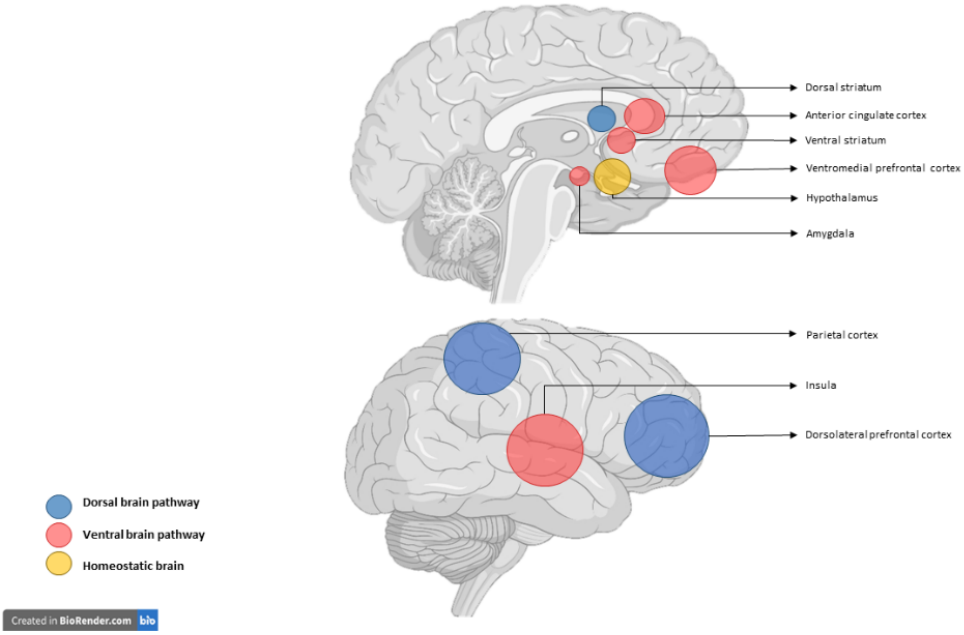
to healthy controls (227). During glucose ingestion, both AN and OB showed a similar increase in blood insulin, but only the OB group showed elevated functional connectivity between the hypothalamus and the brain reward system compared to the AN group. Likewise, while normal-weight participants showed the expected responses in hypothalamic activity, both AN patients and OB individuals showed weakened hypothalamic reactivity. During glucose ingestion, patients with AN displayed reduced responsiveness in the nucleus accumbens (NAcc) and amygdala, along with impaired functional connectivity between the hypothalamus and reward-related brain regions. These pioneering findings suggest that altered hypothalamic reactivity during the processing of food stimuli be linked to the pathophysiology of AN and a similar reduced hypothalamic activity in the AN and OB groups although being in opposite extremes of weight and eating behavior (227).

1.3.2. NON-HOMEOSTATIC MECHANISMS IN EWC

The non-homeostatic mechanisms are primarily characterized by neural pathways involved in appetite-related processes, cognitive control, and limbic circuits (46). The LH represents this link between physiological hunger and satiety signals and appetite phenomena (209,224,233). As the hunger center, the LH releases orexin (OX), a brain-gut peptide that stimulates dopaminergic neurotransmission in the brain reward circuit promoting eating by the reinforcing value of food even independently of the homeostatic energy balance (209,234,235). These appetite-related processes involve motivational and emotional higher-order processing encompassing the valuation of food stimuli, and the integration of interoceptive signals (236). When a food is ingested, sensory signals are processed by the gustatory cortex, olfactory cortex, and somatosensory cortex, which are involved in the perception of the flavors, odors, and textures of the foods (46). Then, these primary signals are transmitted to the NAcc, which is a key component of the reward circuit in the brain. The NAcc is responsible for regulating dopaminergic neurotransmission, which influences pleasure and reward processing (216) and interacts with cognitive and emotional brain regions to regulate eating behavior.

Thanks to animal models and neuroimaging techniques, it has been possible to study non-invasively brain activity "in vivo" while eating behavior takes place or while visual (237) or olfactory (238) food stimuli are processed. Based on this evidence, some authors have proposed theoretical models to identify the neural pathways by which the non-homeostatic circuitry processes food signals to regulate intake beyond the physiological signals of hunger and satiety (46,239). Thus, Kaye and collaborators (239) proposed a neural network to explain the modulation of eating behavior by non-homeostatic mechanisms composed of two brain pathways: the ventral and the dorsal pathway (Figure 4).

Figure 4. Brain regions associated with homeostatic and non-homeostatic mechanisms involved in the regulation of eating behavior

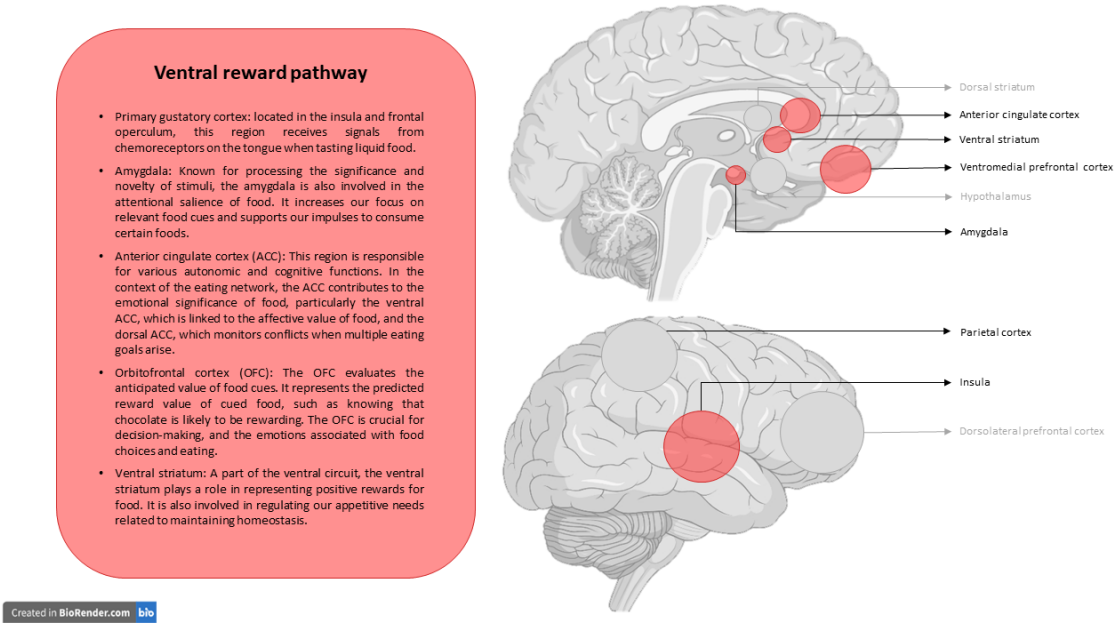


1.3.2.1. The ventral brain pathway of eating behavior in EWC

The ventral pathway is composed of brain regions involved in the evaluation of the motivational properties of food, as well as in the attribution of affective meaning to food stimuli such as the orbitofrontal cortex (OFC), amygdala, insula, ventral striatum (VS), and ventral regions of the anterior cingulate cortex (vACC). The reward brain system is considered an important piece of the ventral pathway because it is associated with the processing of food rewards and focuses on the emotional and motivational response to food-related stimuli. In the context of visual processing of food cues, visual information

about food is sent from the primary visual cortex to the fusiform gyrus, where the object depicted in the image is recognized. From there, the information is transmitted to brain regions that process attention (amygdala), taste (insula/frontal operculum), and reward (i.e., the OFC, ACC, and VS) (Figure 5). This ventral pathway is associated with the pleasurable experience associated with food and the desire to consume it.

Figure 5. The ventral brain pathway involved in the non-homeostatic regulation of eating behavior



Studies have consistently described that dysfunctions in the ventral pathway could underlie altered reward sensitivity and attentional biases toward food cues in individuals with EWC (240–242). For instance, studies on OB have described higher reward sensitivity linked to increased activity in the insular cortices and the VS in response to high-caloric food stimuli (241). Similarly, studies on individuals with AN have shown that an increased response in the NAcc to underweight body shape stimuli indicates aberrant reward function in these patients (242) as well as may also play a role in determining the duration (243).

As part of the ventral pathway, the reward system is composed of interconnected brain circuits including the mesostriatal, mesolimbic, and mesocortical circuits comprising the mesocorticolimbic circuit mediated by the dopaminergic, eCB, and opioid systems (244).

The mesostriatal pathway projects dopaminergic transmission from the ventral tegmental area (VTA) to the NAcc and the ventral pallidum (VP) (209); the mesolimbic pathway from the VTA to limbic brain regions such as the insula, amygdala, and the hippocampus (245,246), and the mesocortical pathway, dopamine transmission projects directly to the PFC (247). The NAcc is rich in dopamine and cannabinoid (CB) receptors which are activated when experiencing pleasure and reward stimuli (248,249). Dopamine serves as the primary transmission pathway from the VTA to NAcc whereas the eCB and opioid systems co-localize with dopaminergic neurons, modulating dopamine functionality depending on the context (244).

The dopaminergic system in individuals with ED may be less stable during development and more susceptible to environmental influences (44,126,250). Specifically, in patients with AN, disruptions in dopaminergic neurotransmission have been associated with obsessive or ritualistic behaviors in AN (43) Based on this premise, it has been argued that patients with AN have a deficit in the reward circuitry (44). However, studies have observed that the functioning of the reward circuitry could not merely be deficient but rather aberrant. For instance, it has been suggested that the reduced activity observed in brain reward circuits during gustatory reward tasks in individuals with AN may be linked to a fear of weight gain when they recognize the caloric nature of food stimuli (44,251). However, patients with AN can also show greater activation in the striatum circuitry in response to disorder-related stimuli such as underweight body images than normal-weight controls (243).

Studies in BN and BED focused on investigating the mechanisms underlying BE have described a desensitized dopamine system, suggesting this alteration might override cognitive control and drives the urge to binge (252). Studies in animals have demonstrated that excessive sugar consumption can lead to the sensitization of dopamine-related reward systems, potentially contributing to addictive-like cravings (253,254). Similarly, excessive consumption of highly palatable foods can result in disproportionate dopamine release and subsequent desensitization of dopamine circuits, leading to a diminished response to rewards (255). This hyperresponsivity in reward regions may be a consequence of persistent overeating, driving individuals to

consume larger quantities of food to compensate for the reduced reward response (255,256).

Interestingly, the eCB system has been demonstrated to be an important constituent of neural substrates involved in the homeostatic (257) and non-homeostatic mechanism (258) modulating dopaminergic transmission in the mesocorticolimbic circuit (259) and exerting orexigenic function on homeostatic and non-homeostatic circuits (260). CB receptors type 1 (CB1R) are expressed in the VTA (261,262), the NAcc, the amygdala, frontal and limbic cortices (249,263), and even the hypothalamus (264,265). The most studied eCBs are anandamide (AEA) and 2-arachidonoylglycerol (2-AG). Both eCBs and CB receptors comprise the eCB system. Under normal conditions, fasting is known to result in elevated concentrations of AEA and 2-AG in the central nervous system. These concentrations subsequently return to their baseline during food consumption (264).

Several studies have highlighted the existence of a dysfunctional eCB system in patients with EWC (258,260,266–268). Specifically, studies have observed that AN and OB exhibit a divergent activation of eCB system: AN has been associated with a hypoactive eCB system whereas in OB a hyperactivated eCB system (264,269). Interestingly, in patients with AN, evidence has been observed of an upregulation of CB1R suggesting this availability might response to a compensatory mechanism induced by starvation in AN which could contribute to tolerating prolonged energy restriction (269,270). The upregulation of CB1R has been observed in the insular cortex, a region involved in integrating interoceptive information, gustatory processing, reward mechanisms, and emotional responses (269). Consistent with this notion, elevated levels of CB1R mRNA have been found in the blood of women with AN (271).

Some authors have purposed that both DA and eCBs can modulate two main psychological processes related to the hedonic impact of food named ‘wanting’ and ‘liking’ processing (209,258,272–274). The processing of 'liking' attributes hedonic value to foods, enhancing the anticipation and expectation based on the palatability of specific food stimuli, even in the absence of them (273,274). On the other hand, 'wanting' is defined as the motivational processes that promote behavior toward food stimuli (273,274). These psychological processes of ‘liking’ and ‘wanting’ are closely related to

learning associated with the incentive salience of a stimulus recognized as rewarding based on previous experiences (275). In the context of EWC, studies have observed that binge symptomatology may be primarily associated with the anticipation of a food reward ("wanting") experience rather than the actual intake of the food reward (210,276).

In the ventral pathways, it is worth emphasizing the significant role of the insula. As part of the ventral pathway, the insula is involved in the integration of sensory and interoceptive information (46,277). Likewise, the insular function has been demonstrated to be involved in the processing of emotions in functional activity with the amygdala and the vACC (278). Regarding eating behavior, the insula has been implicated in the perception and processing of tastes and food texture (279) and in responding to homeostatic signals of hunger and satiety (277). Specifically, the amygdala and the hippocampus are part of the limbic circuit, a brain network of interconnected subcortical structures that play an important role in emotional processing and memory centers that recall the pleasurable and satisfying aspects of the stimulus (280). These limbic regions can regulate the non-homeostatic mechanism of eating by dopaminergic neurotransmission. For instance, the dopaminergic response can be attributed to the activation of the hippocampus and amygdala, recalling the rewarding or emotional aspect of food, increasing the desire to eat (274). A positive experience related to food regarding its smell, taste, or the feeling of satisfaction can be attributed to the hippocampus and amygdala function which activate the dopamine system in the NAcc. Therefore, individuals may experience a ‘wanting to eat’ process (appetite/incentive motivation) for a rewarding stimulus without it being present but increasing the motivation to obtain it. However, if individuals are satiated individuals, they may experience a ‘liking’ (pleasure/palatability), but motivation may be lower than in hunger (281).

Likewise, an experimental task developed by Frank and collaborators pioneered the study of increased activity in the OFC during taste stimuli (282). The milkshake neuroimaging paradigm consists of evaluating brain activity during the administration of different taste stimuli (e.g., sweet, salty, bitter, or neutral). These authors observed that the OFC increased activity during a sweet glucose solution vs. a saline solution taste

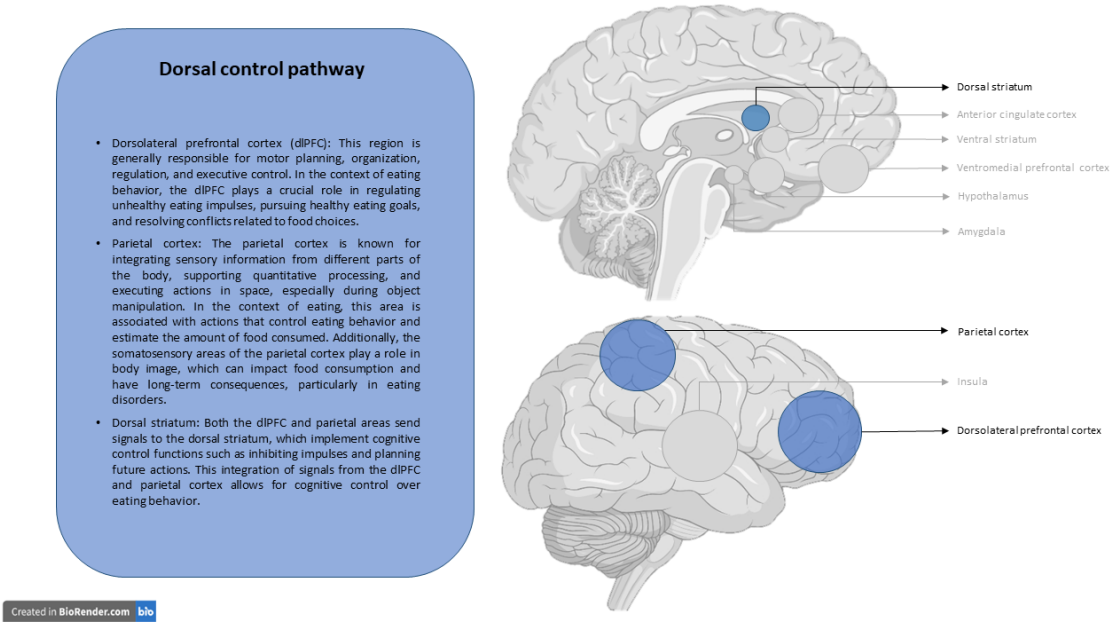
condition, suggesting this region is involved in conferring hedonic value to foods (282). In the context of EWC, it has been observed that individuals with BN had hyperactivity of the OFC and anterior cingulate cortex (ACC) and decreased activity in the PFC associated with increased craving (283), which supports the abovementioned notion that reward expectancy may impair inhibitory control (256). In an interventional study applying Transcranial Magnetic Stimulation in the OFC was observed a reduction in BE in individuals with BN (283). Similar to patients with BED, increased reward sensitivity to food has been positively associated with the OFC (284) and VS activity compared to HC. (285). Consistently, structural differences in the OFC have also been reported in individuals with AN and BN (286). In both AN and BN patients, the OFC may be larger or smaller compared to individuals with BED or OB (286). Considering the role of the OFC in conferring hedonic value to foods, these structural differences in the OFC might be implicated in the maladaptive eating behavior in AN and BN.

Likewise, a dysfunctional modulation of the amygdala with the PFC in OB is linked to emotional eating (287). It has been suggested that a lack of emotional regulation in OB is associated with dysfunctional activation of the anterior insula (288). In the context of visual stimuli of palatable foods, individuals with OB display differential brain activation patterns in regions such as the VS, OFC, insula, ACC, and amygdala compared to HC, indicating an attentional bias toward specific types of food (287,289,290). These regions are associated with encoding the reward value of food stimuli and may contribute to food cravings and increased risk of weight gain (234). Under the same premise that was maintained regarding the neurobiological functioning in patients with BN and BED, it is observed that the risk of overeating in OB is associated with emotional processes and biases towards highly calorically dense food stimuli. Additionally, in OB, it has been observed alterations in emotional processing linked to increased activity of the amygdala suggesting an aberrant function in the processing of emotional information (287,291). Likewise, reduced activity in the anterior insula has been associated with emotional regulation in OB (292) suggesting these neural circuits might underlie emotional dysregulation in EWC and emotional eating in OB (126)

1.3.2.2. The dorsal brain pathway of eating behavior in EWC

The dorsal pathway is mainly involved in processes engaging the executive such as behavioral planning and decision-making processes, as well as in the emotional regulation derived from the ventral pathway. This pathway is composed of brain regions such as the dorsal part of the ACC (dACC), the dorsolateral PFC (dlPFC), the hippocampus, and the parietal cortex, key hubs for the effective functioning of cognitive control (Figure 6) (293). These regions play a crucial role in higher-level cognitive processes that are essential for goal-directed behavior, planning, problem-solving, and inhibitory control (46,294). Chen and collaborators (46) suggest that this dorsal pathway, under normal conditions, could be involved in orienting eating behavior toward healthy eating goals.

Figure 6. The dorsal brain pathway involved in the non-homeostatic regulation of eating behavior



Specifically, the network consisting of the frontal and parietal cortices is mainly involved in executive functions, which include cognitive processes such as attention, working memory, decision-making, and behavioral control (294). The PFC is structurally and functionally divided into subregions involved in various cognitive functions (295). Specifically, the dlPFC is associated with the ability to regulate and control behavior (296). The parietal cortex is involved in spatial processing, and attentional control as well

as the integration of sensory information related to stimulus perception, interoception, and the coordination of motor responses (297).

Impairments in cognitive control have been considered a common feature across the continuum of EWC (298). For instance, individuals with AN tend to exhibit excessive self-control, cognitive inflexibility, and difficulties in shifting between tasks (299). These deficits in cognitive flexibility and set-shifting abilities have been associated with decreased activity in the dlPFC in individuals with AN compared to HC (300). Moreover, it has been observed that, after treatment, this lower activity in the dlPFC and an improvement in cognitive flexibility is associated with recovery, indicating that dlPFC function may serve as a predictor of improvements in cognitive flexibility following treatment (301), suggesting the dlPFC might play a crucial role in the cognitive rigidity which contributes to difficulties in adapting their behaviors and responses to changing circumstances. Likewise, during the cognitive emotional reappraisal task, it was observed that a dissociation between the dlPFC and the amygdala may be related to deficits in emotional regulation and the severity of the ED symptomatology in patients with AN (302). Studies exploring other regions of the dorsal pathway such as the dorsal anterior cingulate cortex (dACC) have shown that reduced activity in the dACC is associated with perseverative errors during set-shifting tasks (299). Considering that the dACC is involved in the regulation and execution of cognition and the control of attention, alterations in this brain area in AN could be related to difficulties in changing rigid and persistent behaviors associated with eating and body image.

In contrast, individuals with BN and symptoms of BED are more likely to show increased impulsivity related to food (303). A weaker cognitive control mechanism may lead to difficulties in stopping eating, even when an individual has been satiated. In these cases, a lack of resources of the prefrontal control network when individuals are exposed to palatable food stimuli may explain impulsive eating behavior that goes beyond hunger or satiety physiological signals (126,304). Conversely, increased activity in the dlPFC is associated with enhanced self-control during decision-making related to food in individuals with a normal weight (34,305,306). In this vein, it has been suggested that an attentional bias toward high-calorie foods in OB, BN, and BED might trigger subsequent overeating and alter neuroendocrine signaling in brain regions linked to

inhibitory control (38,40,225). Studies comparing individuals with or without ED have shown that impaired cognitive control in individuals with OB appears to be more altered if individuals with OB had ED (307,308), especially when exposed to images of high-calorie foods (309–311).

As discussed in the section on the ventral pathway, a plausible explanation for the alterations observed in patients with BN, BED, and OB is related to the existence of disruptions in the mesocorticolimbic circuitry that control behavior but also process reward signals (308,312). These changes have been reported in the corticostriatal circuitry belonging to the ventral pathway of the non-homeostatic mechanism (i.e., the PFC, insular cortex, OFC, and striatum) (256). In other words, studies suggest that disruptions in the crosstalk of both the ventral and dorsal pathways could explain the impulsive and unpremeditated behavior towards highly appetitive or other rewarding stimuli (313). For instance, during the anticipation of food stimuli, patients with binge symptomatology compared to controls exhibited reduced activation in the dACC. However, during the taste of food, increased activity in the medial OFC, medial PFC, and posterior cingulate cortex is observed (314). These divergent patterns of brain activation in response to food-related stimuli, when tasted or viewed, may suggest that less involvement of self-control regions and greater activity in reward brain regions may promote BE. A similar pattern of weakened activation of dopamine signaling associated with increased striatum activity and decreased activity of the PFC has also been observed in OB (315) when they were confronted with high-caloric food stimuli (311,316,317). Studies in patients with BED indicated that changes in the configuration of corticostriatal circuits resemble the alterations observed in substance abuse (126,318). In line with this, the presence of altered activity in the PFC and the ventral pathway such as the insula during the execution of the Stroop task has been observed in individuals with OB with and without ED (313). However, these altered patterns of brain activity appear to be more pronounced in individuals with BED compared to those with OB without ED, suggesting that this bias toward high-calorie food could be explained by specific underlying brain mechanisms that contribute to a potential BE in exposure to high-calorie food (319).

1.4. NEUROCOGNITION OF EXTREME EATING AND WEIGHT CONDITIONS

The main cognitive functions studied in EWC are executive functions. The executive functions are a set of mental processes that allow controlling and adapting goal-directed behaviors according to internal states and environmental context (320). It is comprised of several sub-domains such as decision-making, set-shifting, planning, working memory, and inhibitory control among others. These processes are essential for daily activities controlling behavior based on long-term goals. In EWC, while studies have focused on other cognitive functions such as memory and processing speed, alterations in executive functions have been consistently related to eating behavior (321–325). Considering its complexity, alterations in cognitive processes could underlie maladaptive eating behaviors. For example, in AN, ignoring physiological hunger signals requires excessive control over behavior to maintain restriction, whereas, in OB, exaggerated attention to food stimuli can displace satiety signals to the background, leading to eating beyond energy needs.

1.4.1. EXECUTIVE FUNCTION

As it has been described, executive function is mainly located in the PFC, but it currently recognized the involvement of other brain regions such as basal ganglia or amygdala (326–328). Evidence of this localization was initially observed in patients with lesions sustained in the PFC (329–331). These patients can display adequate performance in other cognitive functions such as memory, language, or visuospatial or vasoconstrictive skills, but deficits in tasks requiring planning, sequencing, or flexibility, in addition to exhibiting alterations in emotion regulation, social behavior, or abstract thoughts (332–334). Here, the mesocorticolimbic circuit plays a fundamental role in regulating executive functions by integrating processes of motivation, reward, and emotions (335,336). Dysfunctions in this circuit can significantly impact a person's ability to plan, make decisions, control impulses, and regulate emotional responses. It has been demonstrated that alterations in the mesocorticolimbic circuit can affect executive functions (296,337,338). These alterations can contribute to psychiatric disorders such as addiction, depression, and impulse control disorders.

1.4.1.1. Decision-Making

Decision-making is a psychological construct consisting of different cognitive processes that allow the selection of an adequate behavioral response based on the evaluation of context and stimuli as well as the predictability of the possible consequences associated with these decisions based on learning from previous experiences (334). Nevertheless, in addition to being a mainly rational process, decision-making processes are also carried out under uncertainty or based on emotional heuristics (339,340). Damasio was a pioneer in postulating the existence of both components involved in decision-making processes: a rational component that evaluates the pros and cons and emotional processing that emerges from the anticipation of possible consequences (335,341).

An experimental task designed to assess decision-making in situations of uncertainty is the Iowa Gambling Task (IGT) (342). This task involves participants choosing between four decks of cards, each deck has different probabilities of winning and losing money. Participants learn through feedback provided after each choice. Two of the decks are considered "disadvantageous decks" in the long run, as they have high gains but also high losses, resulting in a net loss of money over time. The other two decks are considered "advantageous decks" as they have smaller gains but also smaller losses, resulting in a net gain of money in the long run. As participants make repeated choices, it is expected that they learn to avoid the disadvantageous decks and prefer the advantageous decks. Performance on this task is used to assess individuals' ability to make adaptive decisions in uncertain situations and evaluate their propensity for risk-taking or loss avoidance.

The research focused on investigating decision-making impairments in individuals with AN reveals differences in performance based on diagnostic subtypes (343,344). Overall, in AN, decision-making can be influenced by rigid and extreme thinking patterns, leading to a preference for choices that restrict food intake and avoid weight gain. Studies have shown that individuals with AN-BP tend to make more impulsive decisions compared to those with AN-R (343). Indeed, it has been observed that this neurocognitive profile in decision-making exhibits similar performance to patients with BSD (344). Studies have observed a positive correlation between impaired decision-making and the acute phase

of the disorder (345,346) which can improve after remission of ED symptomatology, displaying a performance similar to HC (345–347). For this reason, some authors point out that the deficits in decision-making observed in AN and even in BN may be attributed to a transient impairment rather than a stable trait (343).

Moreover, within the context of decision-making, there is a cognitive process known as delay discounting (336,348–350). The delay discounting task is an experimental paradigm used to assess an individual's capacity to value and make decisions based on long-term rewards versus immediate rewards. In this task, participants are presented with different scenarios in which they must choose between receiving a smaller but immediate reward or waiting for a period of time to receive a larger reward. The objective is to measure the individual tendency to discount or devalue future rewards compared to present rewards. The decisions made during the task provide information about the ability to resist immediate gratification over larger but delayed rewards. These reward-based decisions involve cognitive processes in which individuals subjectively value the potentially rewarding stimulus before deciding on a choice (36,351). The inability to tolerate the delay of even a larger reward may contribute to risky and impulsive decision-making, where the valuation of the reward trumps the valuation of future consequences (336,348).

This inability to delay gratification has been associated with impulsivity, since biased decisions may be made based solely on the rewarding value of the stimulus without premeditating future consequences (336,352). Specifically, individuals with BN and BED show a tendency to prioritize immediate but unfavorable outcomes, neglecting options that offer long-term advantages (353). In the context of eating, individuals with BN and BED tend to show greater impulsivity and risky decisions related to food. For instance, it has been observed that a predisposition to make risky and immediate decisions is more pronounced when the stimulus is food in BED compared to OB (354,355). Although this attentional bias towards high-calorie food is a characteristic feature observed in both individuals with OB and BED., studies have found that individuals with ED and OB tend to respond more impulsively than HC and OB (without ED) if tasks involving food cues or body images stimuli (139,303,354,355). In this regard, some studies have suggested this stimulus-specific bias could collaborate in increasing negative emotional states,

cravings, and overeating in BED (140,154). The heightened impulsive responses and preference for immediate rewards observed in both BED and OB may contribute to difficulties in regulating their eating behavior and maintaining a healthy balance between immediate gratification and long-term consequences (139,354).

1.4.1.2. Cognitive Flexibility

Cognitive flexibility refers to the ability to shift or adapt behaviors or thoughts adjusting them in accordance with the demands of context (328,356). This cognitive process implies identifying incorrect responses and taking advantage to correct and resolve them with an alternative response that can be effective (320,328). For example, if a behavior has no longer generated the expected result, the ability to set-shifting in thoughts and behavior is key to finding alternative solutions and responding successfully to changing environmental demands (328,331). Conversely, cognitive rigidity shows a behavior of persevering and maintaining a certain strategy even having experienced a bad result or loss associated with the use of that strategy (139).

One widely used neuropsychological assessment to measure cognitive flexibility is the Wisconsin Card Sorting Test (WCST) (357). The WCST involves presenting participants with a series of cards varying in shapes, colors, and numbers, and instructing them to classify the cards based on a specific rule initially provided. However, the rule unpredictably changes during the test, requiring participants to shift their mental strategies, overcome perseverative responses, and adapt to the new rules for accurate card classification. The primary objective of the WCST is to evaluate an individual's ability to flexibly transition between different cognitive strategies, effectively responding to changing situations. It assesses various cognitive domains, including attentional capacity, inhibitory control of automatic responses, and the capacity to plan and execute tasks. To quantify performance on the WCST, several parameters are considered. These include the number of errors made, reflecting difficulties in adjusting to rule changes, the number of perseverative responses, indicating tendency to adhere to previous rules despite new instructions, and the individual's ability to learn and apply new rules throughout the test.

In the context of EWC, differences in cognitive flexibility compared to HC have been observed. In AN, evidence of cognitive rigidity and difficulties in shifting focus and adapting to new situations has been found (358). Individuals with AN tend to display rigid thought patterns and a tendency to persevere in restrictive eating behaviors and obsessive concerns related to weight and body shape (358–360). This lack of cognitive flexibility has been associated with the severity disorder and a longer duration of illness in AN and BN (361,362). In AN, a high cognitive rigidity might be reflected in persisting in starvation or maintaining unhealthy habits despite the negative health consequences (361,363). Worryingly, these rigid behaviors and maladaptive habits in AN have demonstrated a substantial reduction after weight recovery (364).

In the case of individuals within the BSD, poor cognitive flexibility is frequently linked to patterns of compulsive overeating due to the inability to shift these behavioral responses that are causing psychological distress and physical discomfort (140,365). Specifically, cognitive flexibility in BN is characterized by difficulties in the ability to quickly switch between different strategies or approaches. For instance, individuals with BN may struggle to change their eating behavior and may be trapped in patterns of recurrent binge eating and purging (365,366). In patients with BED, compulsivity has been observed in the inability to cut off compulsive overeating, which has been demonstrated to contribute to the development and maintenance of the disorder (140,154,367).

Deficits in cognitive flexibility have also been reported in OB (9,368). Indeed, studies have reported that individuals with OB reported worse performance in cognitive flexibility compared to patients with ED (9,368) and compared with HC (9). These difficulties in cognitive flexibility may be related to food consumption regulation and the ability to change unhealthy eating habits (368). Individuals with OB may struggle to adapt to new dietary strategies or change their eating behavior, contributing to the persistence of OB. For instance, a recent study observed that in patients undergoing bariatric surgery, poorer performance on cognitive flexibility tasks was associated with worse treatment outcomes (369). Specifically, the number of perseverative responses was a relevant predictor of weight loss at 12 months. These individuals showed

difficulties in adapting to new lifestyle habits which was reflected in lower weight loss during the critical period after bariatric surgery.

1.4.1.3. Inhibitory Control

Inhibitory control is the ability to maintain attention and control behavior, thoughts, or emotions to perform a specific response and/or behavior. Three main types of inhibitory control have been distinguished: cognitive, attentional, and behavioral inhibitory control (370–372). Cognitive inhibitory control refers to the ability to suppress undesired thoughts or previously learned information to carry out an activity satisfactorily (373). Attentional control is related to efforts in ignoring unnecessary stimuli to focus attention on those that are congruent with the demanding environment (372). Finally, behavioral control is related to self-control and impulsivity and refers to the ability to inhibit certain behaviors which are an obstacle to achieving an immediate or long-term objective (374). In the long term, behavioral inhibitory control is associated with discipline, since it requires maintaining specific behaviors to complete long-term outcomes, inhibiting others that hinder that outcome.

For assessing cognitive inhibitory control, the Stroop task is a widely used paradigm for assessing cognitive interference and the ability to inhibit automatic responses (375). In this task, participants are presented with a series of words written in different colors. The challenge is to name the color of the ink in which the words are written while ignoring the semantic content of the words. For example, if the word "green" is written in red ink, the correct response would be to say "red" instead of "green”. Then, the interference occurs when the word content and the color of the ink conflict, leading to an incorrect automatic response based on the word's reading. Performance on the Stroop task is evaluated based on response time and accuracy in identifying the color of the ink. Longer response times or a higher number of errors indicate greater difficulty in inhibiting automatic responses and reduced selective attention capacity.

Numerous investigations have reported variations in performance among different subtypes of ED (240,360,376). For instance, in the context of AN-R, there is evidence of heightened inhibitory control exerted over food intake, resulting in dietary restraint despite the potential negative health consequences (240,376). In AN, individuals often

display rigid and inflexible thinking patterns that may impair their ability to inhibit maladaptive thoughts especially if they are related to body image and weight (99). Nevertheless, AN is associated with high levels of self-control and restraint, this heightened control can be selective to eating-related behaviors and not extend to other domains of cognitive control (43,99).

Conversely, individuals with BSD exhibit deficits in inhibitory control, which are associated with impulsivity and difficulties in emotional regulation. These deficits might contribute to the occurrence of BE (377). For instance, studies have shown that individuals with ED such as AN or BN exhibit impairments in Stroop task performance compared to HC. They tend to have longer response times and higher error rates, indicating. Overall, the findings from research on the Stroop task in EWC highlight difficulties in inhibiting automatic responses and managing cognitive interference. In BN, deficits in cognitive inhibitory control have been observed, particularly in the context of impulsivity and difficulties in suppressing intrusive thoughts related to binge eating and purging behaviors. Similarly, individuals with BN may experience challenges in inhibiting impulsive motor responses associated with binge eating and purging episodes. Research on cognitive inhibitory control in BED is limited, but some evidence suggests deficits in inhibitory control related to food-related cues and impulsivity. BED may also be associated with difficulties in inhibiting motor responses, particularly in the context of impulsive eating behaviors.

Individuals with OB may exhibit deficits in both cognitive and motor inhibitory control, including difficulties in resisting temptations and making adaptive decisions related to food consumption (378). Motor inhibitory control deficits have been observed in individuals with OB, particularly in tasks that require inhibiting prepotent responses or suppressing automatic eating behaviors (379). BED and OB may share similarities in terms of challenges in inhibiting impulsive motor responses related to food consumption (139,354). However, further research is needed to fully understand the specific differences and similarities in inhibitory control among these disorders and OB.

2. HYPOTHESIS

I. Individuals with extreme weight disorders would display alterations in brain activity and functional connectivity in regions involved in the non-homeostatic mechanism compared to healthy controls.
    a. Individuals with anorexia nervosa will show differences in the pattern of functional connectivity compared to healthy controls.
    b. Altered circulating endocannabinoid concentrations will be associated with altered functional connectivity of the nucleus accumbens in individuals with anorexia nervosa.
    c. During a decision-making task, in comparison to healthy controls, individuals with extreme weight disorders will display dysfunctional activity in brain regions involved in cognitive, reward, and emotional processing.

II. Neuroendocrinological alterations observed in extreme weight disorders will influence clinical features.
    a. Circulating endocannabinoid concentrations and nucleus accumbens functional connectivity will be associated with the severity of extreme weight disorders.
    b. Psychological and clinical features of extreme weight disorders will be distinctively correlated with circulating endocannabinoid concentrations compared to healthy controls.

III. Individuals with extreme weight disorders will exhibit deficits in executive function, such as decision-making and impulse control, which will have an impact on the progression of the disorder.
    a. Individuals with extreme weight disorder will perform worse in executive functions compared to healthy controls.
    b. A longer duration of EWD will increase deficits in executive functioning.
    c. Deficits in decision-making will have an impact on treatment outcome.

3. OBJECTIVES

I. To investigate the regional brain activity and interregional functional connectivity in individuals with extreme weight disorders in comparison to healthy controls.
    a. To compare neural activity during a delay discounting functional magnetic resonance imaging paradigm between individuals with obesity with and without eating disorders and healthy controls.
    b. To evaluate differences in functional connectivity of the nucleus accumbens between individuals with anorexia nervosa and healthy controls.

II. To explore the association between neuroendocrine signaling and brain function in extreme weight disorders.
    a. To examine the influence of circulating endocannabinoids concentrations on nucleus accumbens functional connectivity in anorexia nervosa.
    b. To assess differences in circulating endocannabinoids concentrations between individuals with extreme weight disorders and healthy controls.
    c. To analyze the association between circulating endocannabinoids concentrations and clinical features of individuals with extreme eating and weight disorders.

III. To identify the role of neurocognitive function in the clinical features of individuals with extreme eating and weight disorders.
    a. To characterize performance in executive function in individuals with extreme eating and weight disorders compared to healthy controls.
    b. To investigate the role of eating disorder duration on executive function.
    c. To evaluate the role of decision-making abilities on treatment outcomes in patients with eating disorders.

4. MATERIALS, METHODS, AND RESULTS

4.1. Study 1: The neural correlates of delay discounting in obesity and binge eating disorder

4.2. Study 2: Exploring the influence of circulating endocannabinoids and nucleus accumbens functional connectivity on severity in anorexia nervosa

4.3. Study 3: Association of anandamide and 2-arachidonoylglycerol concentrations with clinical and anthropometric features in eating disorders and obesity

4.4. Study 4: Clinical factors predicting impaired executive functions in eating disorders: the role of illness duration

4.5. Study 5: Neuropsychological learning deficits as predictors of treatment outcome in patients with eating disorders

4.1. STUDY 1

THE NEURAL CORRELATES OF DELAY DISCOUNTING IN OBESITY AND BINGE EATING DISORDER

Miranda-Olivos R, Steward T, Martínez-Zalacaín I, Mestre-Bach G, Juaneda-Seguí A, Jiménez-Murcia S, Fernández-Formoso JA, Vilarrasa N, Veciana de Las Heras M, Custal N, Virgili N, Lopez-Urdiales R, Menchón JM, Granero R, Soriano-Mas C, Fernandez-Aranda F. *The neural correlates of delay discounting in obesity and binge eating disorder.* **J Behav Addict**. 2021 Apr 26;10(3):498–507. doi: 10.1556/2006.2021.00023.

AKADÉMIAI KIADÓ

Journal of Behavioral Addictions

10 (2021) 3, 498–507

Special Section on Overweight, obesity and eating disorders in relation to addiction

DOI:
10.1556/2006.2021.00023

FULL-LENGTH REPORT

The neural correlates of delay discounting in obesity and binge eating disorder

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Received: October 3, 2020 • Revised manuscript received: November 30, 2020; January 22, 2021; March 19, 2021 • Accepted: March 23, 2021
Published online: April 26, 2021

ABSTRACT

Background and aims: Increased delay discounting is associated with obesity and binge eating disorder (BED). Although BED and obesity frequently co-occur, the neural mechanisms underlying delay discounting in these conditions remain poorly understood. *Methods:* Thirtyfive women with obesity, including 10 participants with obesity and BED and 31 controls completed a monetary delay discounting task during functional magnetic resonance imaging. *Results:* We identified that increased discounting rates were associated with decreased activity in the left anterior insula in participants with obesity compared to controls when choosing immediate rewards over delayed rewards ($P_{FWE} < 0.05$). An exploratory analysis comparing the BED subsample to the other groups did not detect significant differences. *Discussion and conclusions:* Our findings suggest decreased activity in the anterior insula may underlie heightened delay discounting in individuals with obesity, contributing the probability of choosing immediate rewards over delayed rewards based on emotional states. Future studies including larger, more diverse samples are required to confirm these effects.

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KEYWORDS

delay discounting, obesity, binge eating disorder, eating disorders, fMRI

INTRODUCTION

Delay discounting is a cognitive process describing how individuals value a reward to a lesser extent the farther into the future it is received; thereby devaluing delayed rewards as a function of time. Delay discounting differs substantially among individuals (Lempert, Steinglass, Pinto, Kable, & Simpson, 2019), and high delay discounting is understood to reflect an inability to resist immediate reward over positive prospective outcomes. Steeper individual discounting rates (i.e., a preference for sooner, smaller reward) are associated with multiple clinical conditions characterized by deficits in impulse control (e.g., addictive disorders or gambling disorder) (Leeman & Potenza, 2012; Steward, Mestre-Bach, Fernández-Aranda, et al., 2017; Steward et al., 2017).

In a manner similar to monetary reward, studies have suggested that individuals with obesity assign a higher value to the receipt of immediate food reward, even when satiated (Appelhans et al., 2011). Accordingly, delay discounting has been proposed as a potential psychological factor contributing to obesity (Amlung, Petker, Jackson, Balodis, & Mackillop, 2016; Appelhans et al., 2011), as the choices of individuals with obesity might be swayed by a stronger preference for immediate rewards (i.e., unhealthy foods) over larger future rewards (i.e., improved health). Compared to healthy-weight controls, women with obesity tend to exhibit steeper discount patterns (Weller, Cook, Avsar, & Cox, 2008). Likewise, studies have demonstrated high discounting rates to be positively associated with body mass index (BMI) (Jarmolowicz et al., 2014; Tang, Chrzanowski-Smith, Hutchinson, Kee, & Hunter, 2019) and overeating (Appelhans et al., 2011). Steeper discount patterns could hamper efforts by individuals with obesity to reach a healthy weight as the tendency to choose immediate rewards is often incompatible with sustained dietary control and changes in eating habits (Maxwell, Gardiner, & Loxton, 2020).

Delay discounting tasks performed during functional magnetic resonance imaging (fMRI) have provided insights into the neurobiological mechanisms underlying impulsive choices (Figner et al., 2010; Smith et al., 2016; Steward, Miranda-Olivos, Soriano-Mas, & Fernández-Aranda, 2019). Multiple neural systems are believed to be involved in delay discounting, including those implicated in assigning value (the ventral striatum and ventromedial prefrontal cortex (vmPFC)), prospection (the posterior cingulate, precuneus, medial temporal lobe, and dorsomedial prefrontal cortex (dmPFC)), and executive control (anterior cingulate cortex (ACC) and dorsolateral prefrontal cortex (dlPFC)) (Lempert et al., 2019; Marco-Pallarés, Mohammadi, Samii, & Münte, 2010; McClure, Laibson, Loewenstein, & Cohen, 2004). Moreover, activity in the insula is believed to influence the probability of selecting smaller, sooner rewards over larger, delayed rewards based on affective states (Volkow & Baler, 2015). Studies in healthy controls have found a bias to choose smaller immediate rewards over delayed reward to be associated with increased activity in the striatum, insula, and vmPFC (Koffarnus et al., 2017; Wittmann, Lovero, Lane, & Paulus, 2010), whereas increased activity, in the dlPFC and parietal regions, is associated with choosing larger delayed rewards (McClure et al., 2004; Wittmann, Leland, & Paulus, 2007).

Neuroimaging studies have shown biases to immediate rewards in obesity to be associated with altered activity in prefrontal and parietal regions (Kishinevsky et al., 2012; Stoeckel, Murdaugh, Cox, Cook, & Weller, 2013). Activity in these regions contributes to the inhibition of impulses and the planning future of actions by weighing possible long-term consequences (Chen, Papies, & Barsalou, 2016). In the context of delay discounting, higher functional activity in the prefrontal cortex (PFC) and lower discounting rates have been associated with achieving (Kishinevsky et al., 2012; Weygandt et al., 2013) and maintaining weight loss (Weygandt et al., 2015). For instance, lower discounting rates associated with stronger activity in the dlPFC can predict, before a dietary intervention, successful weight loss at 12 weeks (Weygandt et al., 2013) and one-year following treatment (Weygandt et al., 2015). Relatedly, discounting rates have been observed to decrease after bariatric surgery in patients with morbid obesity (Budría et al., 2012). These studies demonstrate neural activity during decision-making can be a prognostic factor in dietary success and maintaining weight loss (Kishinevsky et al., 2012; Weygandt et al., 2013, 2015).

Binge eating disorder (BED) is characterized by distressful and frequent episodes of excessive food intake accompanied by a sense of loss of control (American Psychiatric Association, 2013). Although not all patients with BED have obesity, lack of control over food intake and increased binge frequency contribute to an 87% prevalence of obesity in individuals with BED (Villarejo et al., 2012). Some researchers support a framework wherein patients with BED represent a subgroup within a heterogeneous obesity phenotype (Hege et al., 2015; Jiménez-Murcia et al., 2019; Schag, Schönleber, Teufel, Zipfel, & Giel, 2013). In pattern akin to behavioral addictions and substance abuse (Minhas et al., 2021; Steward, Mestre-Bach, Fernández-Aranda, et al., 2017), studies have also identified an association between higher discount rates and symptomatology in individuals with obesity and BED (Kekic et al., 2020; Manwaring, Green, Myerson, Strube, & Wilfley, 2011). Women with BED and obesity have been found to present steeper discounting rates to food reward, compared to women with obesity without BED (non-BED) (Manwaring et al., 2011) and to monetary rewards, compared to control participants (Bartholdy et al., 2017; Steward, Mestre-Bach, Vintró-Alcaraz, et al., 2017). Moreover, theoretical models in obesity based on hedonic hunger and delay discounting have been designed to classify BED or non-BED according to individuals' scores (Manasse et al., 2015). In this study, high discounting rates and worse inhibitory control were associated with an increased probability of belonging to the BED group.

While no study to date has examined delay discounting in individuals with BED using fMRI, there is evidence to suggest that individuals with BED present distinct neural activation patterns during tasks involving inhibitory control in comparison to individuals with obesity without BED. For example, Balodis et al. (2013) found that individuals with BED presented diminished activity in the vmPFC, inferior frontal gyrus (IFG), and insula during incongruent trials on the Stroop task when compared to non-BED and controls. Voon (2015) suggests impulsive behaviors in individuals with BED are associated with greater cognitive impairment compared to those with non-BED obesity. In particular, impulsive behavior in BED is associated with greater behavioral inflexibility, compulsivity, and psychopathology compared to non-BED obesity (Voon, 2015).

In the study at hand, we examined monetary delay discounting during fMRI in women with obesity compared to controls. First, we aimed to investigate whether there were differences in neural activity associated with discounting rates between all participants with obesity and a control group. Second, in an exploratory sub-analysis, activation patterns during delay discounting in participants with BED were compared to participants with obesity and controls. We also sought to explore if differences in neural activity were associated with impulsive traits and eating disorder severity.

Based on prior literature, we hypothesized participants with obesity as a whole (OB-all) would exhibit higher discounting rates than controls and that this would be associated with reduced activation in the PFC, insula, and parietal regions, as well as increased activity in brain regions involved reward processing. Moreover, we hypothesized that BED participants would exhibit a differential activation pattern to non-BED participants with obesity during delay discounting. Considering the lack of fMRI studies in BED and the limited sample size of our BED group in this study, we have chosen not to further specify our hypotheses for this exploratory analysis.

METHODS

Participants

Sixtysix adult women (18–56 years of age) were included in the present study. Thirtyfive individuals belonged to the OB-all group defined as having a BMI over 30. Within the OB-all group, 10 women had BED and 25 women did not have BED (non-BED). All women in the BED group met the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria for BED following a standardized structured interview conducted by clinical psychologists and psychiatrists. The BED and the non-BED groups were recruited from the Eating Disorders Unit and the Endocrinology and Nutrition Unit, respectively, at Bellvitge University Hospital in Barcelona, Spain. Participants in the non-BED group were patients seeking treatment for obesity and were required to a psychiatric screening in order to be considered a candidate for bariatric surgery. The BED and the non-BED groups were compared to 31 female controls (BMI = 18–24.99), recruited via advertisements from the same University Hospital catchment area.

All participants underwent the Mini-International Neuropsychiatric Interview (M.I.N.I.) to assess the presence of a psychiatric disorder. In the case of controls, exclusion criteria were a lifetime history of an eating disorder, based on DSM-5 diagnostic criteria, having had obesity, and current diagnosis of psychiatric disorder. The study exclusion criteria for all participants were being male, the presence of an organic mental disorder or an intellectual disability, being pregnant or currently breastfeeding, and any contraindication for magnetic resonance imaging (MRI) scanning.

Procedures

Participants underwent assessments over two separate sessions. The first session consisted of collecting clinical and anthropometric measures (outside-scanner measures), while the MRI scanning was conducted at a second session.

Measures

Body composition. Initially, the participant height was measured by a stadiometer without wearing shoes. Then, this information was introduced in a leg-to-leg body composition analyzer using a Tanita BC-420MA (Tanita BC-420MA, Tanita Corp. Tokyo, Japan) to collect body composition variables and to obtain BMI. This instrument is a validated, non-invasive bioelectrical impedance analyzer that estimates body composition, considering age and sex.

Eating Disorders Inventory-2 (EDI-2). Eating disorder symptomatology was assessed via a validated Spanish version of the EDI-2 (Garner, Olmstead, & Polivy, 1983). This is a self-report instrument to screen symptomatology related to eating disorders on a six-point Likert scale. It consists of 91 items and provides scores on 11 subscales: drive for thinness, body dissatisfaction, bulimia, ineffectiveness, perfectionism, interpersonal distrust, interoceptive awareness, maturity fears, asceticism, impulse regulation, and social insecurity. The sum of all subscales provides an eating disorder measure, which is considered a global scale of eating disorder severity. The internal consistency for the scale estimated through Cronbach's alpha was excellent ($\alpha = 0.96$).

Impulsivity measure (UPPS-P). This 59-item questionnaire is a multi-dimensional assessment of impulsivity using five distinct personality traits related to impulsive behavior. Specifically, it measures lack of perseverance, lack of premeditation, sensation seeking, negative urgency, and positive urgency. It contemplates acts or incidents that occurred during the last 6 months, scoring on a Likert scale of 1–5. The current study used the Spanish validation of the UPPS-P, which has demonstrated good reliability and validity (Verdejo-García, Lozano, Moya, Alcázar, & Pérez-García, 2010). Internal consistency was between good ($\alpha = 0.82$ for

lack of premeditation) to excellent (α = 0.92 for positive urgency).

MRI delay discounting paradigm. The items for our delay discounting task were initially designed by Kirby, Petry, and Bickel (1999). This questionnaire consists of 27 items evaluating intertemporal decision-making, and participant choice between two amounts of hypothetical monetary reward (e.g., between €55 "NOW" or €81 in 30 days). Each trial, considering its temporal gap and two rewards, is computed to provide a specific discounting rate (k). Thus, the 27 discount rates derived from each item delineate a hyperbolic function rating from 0 to 0.25. A higher k indicates a greater devaluing of future rewards and a tendency to select smaller, immediate rewards.

The fMRI delay discounting task used in this study was adapted from prior work by Marco-Pallarès et al. (2010), and it was implemented using Presentation (Version 18.3, build 03.11.16, Neurobehavioral Systems, Albany, USA, www.neurobs.com). This task contained 4 runs with 27 trials included in each run. The total duration of each trial was 11 seconds beginning with the presentation of a cross fixation for 5 seconds to minimize carry-over effects, followed by the task block for 6 seconds. During the initial 3 seconds of the block, monetary choices were presented, and participants were required to give their responses during the final 3 seconds. Participants provided responses on an MRI-compatible button-box (Lumina 3G Controller, Cedrus Corporation), and the task was displayed via an angled mirror system using an MRI-compatible LCD screen (BOLD-screen 32, Cambridge Research Systems) located at the end of the scanner bore.

Individual discounting rates (k) were calculated by identifying the switch-point of preference. In other words, the point when individuals change their preferences and begin to select delayed rewards over immediate rewards. Due to the hyperbolic distribution of discount parameter (Kirby & Maraković, 1996), individual means were obtained by calculating the geometric mean across runs between trials, where the switch-point took place, and which produced choices consistent with individuals' k. In order to work with a linear distribution of individuals' k rates, these were transformed using natural logarithmic (ln) transformation. Thus, ln(k) values range from −9 to 0 with 0 representing higher k rates, and −9 representing lower k rates.

Data analysis

Imaging data acquisition, preprocessing, and analysis. MRI data were obtained using a 3.0 Tesla MRI scanner (Intera, Philips Medical Systems, Eindhoven, Best, Netherlands) equipped with a 32-channel phased-array head coil. For the delay discounting task, 151 volumes per run were obtained with following parameters: repetition time of 2,000 ms, echo time of 25 ms, and a pulse angle of 90°; in a 24-cm field of view (FOV); and an 80 × 80 pixel matrix delivering voxel sizes of 3 × 3 × 3 mm with no gap and 40 interleaved slices, parallel to the anterior-posterior commissure line. Each run had a duration of 4.95 min. A high-resolution T1-weighted anatomical scan was also acquired to facilitate registration of the EPI data into standard space. A three-dimensional fast-spoiled gradient, an inversion-recovery sequence with 233 contiguous slices (repetition time, 10.43 ms; echo time, 4.8 ms; flip angle, 8°) in a 24-cm field of view with a 320 × 320 pixel matrix and isotropic voxel size of 0.75 × 0.75 × 0.75 mm, was used.

fMRI preprocessing. All images were preprocessed using BrainWavelet Toolbox, which allows for the removal of high- and low-frequency artifacts from a time series by denoising the synchronized signal transients induced by head motion. The realigned functional sequences were co-registered to each participant's anatomical scan, which had been previously co-registered and normalized to the SPM-T1 template. Further preprocessing took place using a pipeline in the CONN toolbox (version 19b, Massachusetts Institute of Technology, Cambridge, USA, http://www.nitrc.org/projects/conn) running on MATLAB R2019b. For each participant, preprocessing of functional data underwent the following steps: (1) motion correction, (2) slice-time correction, (3) ART-based identification of outlier scans for scrubbing, (4) spatial normalization applying the anatomical normalization parameters, which were then re-sliced to a 2mm isotropic resolution in Montreal Neurological Institute (MNI) space, and (5) smoothing using a Gaussian filter with an 8 mm full width at half maximum (FWHM) kernel.

Next, denoising was applied to remove residual movement and physiological noise. Blood oxygen level-dependent (BOLD) time series were regressed against the six head motion parameters obtained from realignment and physiological noise deriving from white matter, cerebrospinal fluid (CSF), and global (BOLD) time-series were included as confounding factors. Last, temporal frequencies below 0.008 Hz or above 0.09 Hz were removed from the BOLD signal in order to remove additional artifacts.

First-level analyses. First-level (single subject) maps were estimated using statistical parametric mapping software (SPM 12, Welcome Department of Imaging Neuroscience, London, England; www.fil.ion.ucl.ac.uk/spm). A general linear model (GLM) was performed comparing the hemodynamic response during the 6 seconds of NOW and LATER choice blocks, across 4 runs. First-level activation was computed for each individual on NOW > LATER trials by convolving the time course of activation with the canonical hemodynamic response function (HRF). Heart rate frequency recorded during the fMRI paradigm was introduced as an individual regressor of hemodynamic response. The BOLD signal at each voxel was convolved using the SPM12 canonical HRF and a 128 s high-pass filter was applied.

Second-level analyses. First-level contrast images were then carried forward to a group-level random effects analysis, using a summary statistics approach (i.e., ANOVA). First, between-group comparisons (OB-all vs. controls or BED vs. non-BED vs. controls) examined differences in neural activation during NOW > LATER associated with discounting

rates. Discounting rates represented by ln(k) were included as main variable of interest to explore brain activations during NOW > LATER trials. Given the significant differences between groups, age was introduced as a confounding variable. As a first step, a two-sample t-test was carried out comparing activation between participants in the OB-all group and the control group. Next, in order to investigate the distinctive brain activity within the obesity groups (BED and non-BED) in comparison to the control group, a one-way ANOVA was performed between these three groups. Significance thresholding from all derived differences in activation was set to satisfy a family-wise error (FWE) rate correction of $P_{FWE} < 0.05$ (spatial cluster extent) as well as, a threshold of $P < 0.001$ as recommended by Woo, Krishnan, and Wager (2014) and Eklund, Nichols, and Knutsson (2016).

In order to explore the association between significant brain-derived differences between groups from the delay discounting task and clinical measures, derived peak activation eigenvalues from regions displaying significant differences were extracted.

Statistical analyses of non-imaging data. Statistical analyses of clinical measures and brain-derived eigenvalues were conducted with SPSS 23 (IBM Corp; Armonk, NY). One-way ANOVA was employed for the global comparison of study variables between groups including post hoc pairwise comparisons via Scheffé's procedure. Effect sizes for mean differences were measured using Cohen's d coefficient ($|d| > 0.2$ was considered low-poor, $|d| > 0.5$ mild-moderate, and $|d| > 0.8$ high-large) (Kelley & Preacher, 2012). The Finner method was also used to control Type-I error due to multiple comparisons (this method is included in FWE stepwise procedures) (Finner, 1993).

Associations within-groups were examined using Pearson's parametric correlations (R). Due to the strong association for these parameters between significance test and sample size (low correlations estimated within large samples tend to provide significant results, whereas high correlations within low samples tend to provide non-significant values), the R-coefficients were interpreted attending to effect sizes ($|R| > 0.24$ was considered mild-moderate and $|R| > 0.37$ high-large; these thresholds corresponds to Cohen's-d of 0.20, 0.50, and 0.80 respectively) (Rosnow & Rosenthal, 1996).

Ethics

The study procedures were carried out in accordance with the Declaration of Helsinki. The Clinical Research Ethics Committee of Bellvitge University Hospital (PR146/14) approved the study. Written informed consent was obtained from all participants before taking part in the study.

RESULTS

Delay discounting and behavioral results

Table 1 summarizes sociodemographic, anthropometric information, and psychological measures in the three groups.

Table 1. Sample description

	Control group (n = 31)		Obesity group (n = 35)											
			non-BED; n = 25		BED; n = 10			Control vs non-BED		Control vs BED			non-BED vs BED	
	Mean	SD	Mean	SD	Mean	SD	F	P	$\|d\|$	P	$\|d\|$	P	$\|d\|$
Age (years-old)	29.65	12.64	37.56	10.13	39.70	8.87	4.86	**0.011***	**0.69**†	**0.028***	**0.92**†	0.652	0.22
Education (years)	15.35	1.92	12.96	3.37	12.60	3.13	6.73	**0.002***	**0.87**†	**0.015***	**1.06**†	0.727	0.11
BMI (kg/m2)	21.24	1.99	42.48	7.24	38.98	4.16	140.26	**0.000***	**4.00**†	**0.001***	**5.44**†	0.150	0.59†
Discount rates (k)[a]	-4.90	0.97	-4.29	1.02	-4.72	1.46	2.30	**0.049***	**0.62**†	0.651	0.14	0.424	0.35
EDI-2: Total score	27.58	18.08	63.88	32.71	107.10	38.14	33.89	**0.000***	**1.37**†	**0.001***	**2.66**†	**0.001***	**1.21**†
UPPS-P: lack of premeditation	22.42	5.42	23.52	5.05	25.10	6.62	0.95	0.394	0.493	0.21	0.201	0.44	0.567	0.27
UPPS-P: lack of perseverance	20.03	5.17	22.04	4.77	25.60	5.95	4.49	**0.015***	0.185	0.40	**0.010***	**1.00**†	0.150	0.66†
UPPS-P: sensation seeking	28.35	7.54	24.68	6.20	22.80	7.83	3.08	0.053	0.096	0.53†	**0.047***	**0.72**†	0.567	0.27
UPPS-P: positive urgency	22.77	7.90	21.24	4.77	27.30	13.47	1.99	0.146	0.493	0.24	0.155	0.41	0.150	0.60†
UPPS-P: negative urgency	25.55	6.34	28.50	6.29	35.80	7.64	9.36	**0.000***	0.142	0.47	**0.001***	**1.46**†	**0.021***	**1.04**†

Note: non-BED: obesity without binge eating disorder. BED: binge eating disorder.
[a] Values correspond to the ln(k).
*Bold: significant comparison.
† Effect size in the moderate ($|d|$>0.50) to high range ($|d|$>0.80).

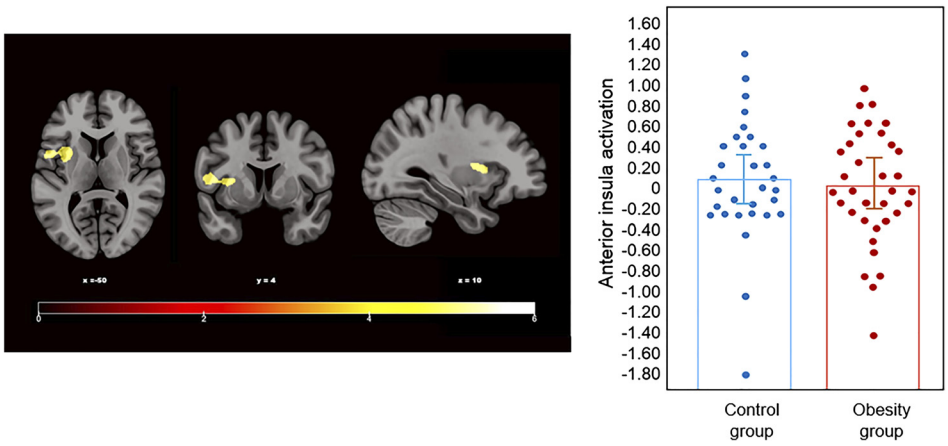

Fig. 1. The left panel depicts the identified increased activation in the left anterior insula associated with discount rates in the control group in comparison to the obesity group (OB-all) during NOW > LATER. Color bar represents t-values. Results are displayed at family-wise error (FWE) probability ($P_{FWE} < 0.05$), ($P < 0.001$), cluster-extent. The right panel depicts individual participant activation levels according to group

As expected, BMI was significantly different between the control group and clinical groups ($P < 0.001$). Likewise, there were significant differences in age ($P = 0.006$) between groups.

Concerning the behavioral delay discounting measure, the three groups did not significantly differ in discounting rates ($P = 0.109$; Table 1). However, a significance was observed when comparing the non-BED and control groups ($P = 0.049$: Table 1). As would be expected, the BED group endorsed higher scores of eating disorder severity on the EDI-2 compared to control group ($P < 0.001$) and the non-BED group ($P < 0.001$). The BED group endorsed higher levels in lack of perseverance ($P = 0.010$) and negative urgency ($P = 0.001$) compared to controls on the UPPS-P. Likewise, the BED group had higher negative urgency levels ($P = 0.021$) compared to the non-BED group.

Imaging data

Group comparisons using independent sample t-tests during NOW >. LATER found that discounting rates were positively associated with decreased activation in the left anterior insula extending laterally through the temporal cortex in the OB-all group compared to the control group ($P_{FWE} = 0.029$; Fig. 1; Table 2).

Group comparisons using a one-way ANOVA during NOW > LATER found no significant differences between the BED and the non-BED group, or the BED and the control group ($P_{FWE} > 0.05$).

Table 2. Second-level fMRI delay discounting task results

Contrast NOW > LATER	Region	MNI Coordinates (x, y, z)	ke[a]	t
Controls<OB-all	Left anterior insula	−50; 4; 10	232	4.87

Note: OB-all: obesity group (non-BED and BED). A general linear model (GLM) was performed comparing the hemodynamic response during the 6 seconds of NOW and LATER choice blocks of the delay discounting task, with NOW > LATER trials serving as our primary contrast of interest. Results satisfied a family-wise error (FWE) probability ($P_{FWE} < 0.05$) and ($P < 0.001$) cluster-extent threshold.
MNI: Montreal Neurological Institute.
[a] Cluster extent in voxels.

DISCUSSION

The present study investigated the neurobiological substrates of delay discounting in obesity with and without BED. We found a negative association between left anterior insula activation during NOW > LATER and individual discount rates in all participants with OB in comparison to controls. Contrary to our hypotheses, our exploratory analysis in BED patients did not identify differences in activation associated with discount rates during NOW > LATER. This lack of identified differences between groups is most likely due to a lack of power and are discussed in the limitations section.

The insula is understood to play a modulatory role in decision making by incorporating interoceptive and emotional processes during the deliberation between NOW vs LATER choices (Volkow & Baler, 2015). In healthy controls, the anterior insula has been found to increase in activation when choosing immediate reward over delayed choices (Carter et al., 2010; Wittmann et al., 2010). Our finding associating higher delay discounting with decreased anterior insula activity suggests that individuals with obesity may experience impairments in integrating interoceptive signals with higher-level cognitive processing (Simmons et al., 2013; Zaki, Davis, & Ochsner, 2012). Analogous results have been found in individuals with obesity and poor sleep quality (Martin et al., 2015). This study found diminished insula activity in individuals with obesity and poor sleep

quality when making immediate and smaller monetary choices compared to a baseline condition. Similarly, recent research has identified decreased anterior insula activity during risky decisions following a loss in participants with obesity, which indicates that maladaptive signaling in the insula may underpin alterations in weighing the costs and benefits of decisions in obesity (Steward, Juaneda-Seguí, et al., 2019). Decreased modulation of putative executive function regions has also been found in women with obesity during difficult vs. easy trials of a delay discounting task (Stoeckel et al., 2013), suggesting that dysfunctional interactions between executive control and interceptive networks could contribute to excessive food intake (Steward, Menchon, et al., 2017; Syan et al., 2019). This compulsive eating pattern is associated with addictive-like eating behavior in obesity and is often defined using symptoms parallel to those of substance use disorders and behavioral addictions (Kakoschke, Aarts, & Verdejo-García, 2019; Kekic et al., 2020). Likewise, addictive behaviors have been robustly associated with steep discounting to delayed reward (Volkow & Baler, 2015), suggesting the presence of overlapping brain systems mediating appetitive and addictive behaviors (Volkow & Baler, 2015).

It is plausible that reduced insula activation may partly underpin the emotionally driven impulsivity and decision-making impairments that characterize emotional eating in OB and BED (Steward & Berner, 2020). In the case of patients with BED, a similar response to rewarding cues may manifest in the form of compulsive eating (Kakoschke et al., 2019). Food intake itself can become a source of distress as entrenched eating habits conflict with goals to normalize eating behaviors (Chao et al., 2016; Munsch, Meyer, Quartier, & Wilhelm, 2012). It should be noted that the BED group also showed higher negative urgency scores than the non-BED and control groups. For individuals with BED, negative urgency is often associated with excessive eating, which is used to alleviate negative emotions (Aloi et al., 2020; Lavender & Mitchell, 2015; Munsch et al., 2012). However, any inferences emerging from these preliminary results must be interpreted with caution given the limited sample size featured in this study. As such, future studies with larger samples are required to confirm this effect.

Last, in contrast to other studies, our results did not identify significant behavioral differences when comparing discounting rates between all participants with obesity and controls and only a marginal significance was found when comparing the non-BED group to controls. Our findings are partly supported by a systematic review by McClelland et al. (2016), which identified mixed results when comparing individuals with obesity to controls. While most studies identified high discount rates in individuals with obesity compared to controls, a relevant proportion of studies did not report differences (McClelland et al., 2016). The authors underscored the importance of examining whether the use of hypothetical (vs. real) monetary rewards can influence discounting rates. Similarly, food vs non-food rewards are known to influence delay discounting in individuals with obesity and BED and controls (Manwaring et al., 2011; McClelland et al., 2016).

Although this study has its strengths, some limitations should be considered when interpreting its results. First, our sample does not fully represent the general population with obesity as our participants were recruited from a hospital setting and seeking treatment (i.e., bariatric surgery or psychotherapy). Second, our study cannot make inferences regarding causality due to its cross-sectional design. Third, this study only recruited women and future studies should aim to include larger and diverse samples, especially in patients with BED. It would be of interest to examine whether higher discount rates are a risk factor for compulsive overeating and whether interventions targeted at orienting individuals with BED to increase the value of future rewards could produce a meaningful decrease in binge eating behaviors (Juarascio, Manasse, Espel, Kerrigan, & Forman, 2015). Likewise, it would have been of interest to consider hormonal factors (e.g., estrogens levels), which are known to modulate reward response (Diekhof, 2015). Finally, our sample size was limited and our failure to identify significant differences between groups is likely due to a lack of statistical power.

CONCLUSIONS

Our findings provide evidence of alterations in anterior insula function in individuals with obesity and BED during delay discounting. Future studies with larger samples and using delay discounting paradigms may shed light as to why a subset of individuals with obesity may be prone to binge eating episodes. Likewise, it would be of interest for future studies to integrate both general and food-specific tasks with neuroimaging in order to further delineate the neural circuitry that contributes to BED (Berner et al., 2017).

Funding sources: This manuscript and research were supported by grants from the Ministerio de Economía y Competitividad (PSI2015-68701-R), Ministerio de Sanidad, Servicios Sociales e Igualdad (PR338/17), Instituto de Salud Carlos III (ISCIII) (FIS PI14/00290, PI17/01167 and PI20/132) and co-funded by FEDER funds/European Regional Development Fund (ERDF), a way to build Europe. CIBERObn and CIBERSAM are both initiatives of ISCIII. This research was supported by a PNSD (PR338/17-MSSSI) grant. Additional support was received from EU Grant Eat2beNice (H2020-SFS-2016-2; Ref 728018). TS is supported by a NHMRC/MRFF Investigator Grant (MRF1193736), a BBRF Young Investigator Grant, and a University of Melbourne McKenzie Fellowship. GMB is supported by a postdoctoral grant from FUNCIVA. We thank CERCA/the Generalitat de Catalunya for institutional support. The funders had no role in the study design, data collection, and analysis, decision to publish, or preparation of the manuscript.

Author's contributions: R.M-O.: Conceptualization, Investigation, Methodology, Project administration, Data curation, Writing—original draft; T.S.: Conceptualization, Investigation, Methodology, Project administration, Data curation, Writing—original draft; I.M.-Z.: Formal analysis, Investigation, Methodology, Data curation; G.M.-B.: Investigation, Project administration, Data curation; A.S.-J.: Methodology, Data curation; S.J.-M.: Funding acquisition; J.A.F.-F.: Funding acquisition; N.V. (Nuria Vilarrasa): Resources; M.V.d.l.H.: Resources; N.C.: Resources; N.V. (Nuria Virgili): Resources; R.L.-U.: Resources; J.M.M.: Funding acquisition; C.S.-M.: Conceptualization, Investigation, Project administration, Data curation, Writing - original draft; F.F.-A.: Conceptualization, Investigation, Project administration; Funding acquisition, Writing-original draft.

Conflict of Interest: FF-A declares having received consultation honoraries from Novo Nordisk and editorial honoraries from Wiley. The rest of the authors declare no conflict of interest.

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4.2. STUDY 2

EXPLORING THE INFLUENCE OF CIRCULATING ENDOCANNABINOIDS AND NUCLEUS ACCUMBENS FUNCTIONAL CONNECTIVITY ON SEVERITY IN ANOREXIA NERVOSA

Miranda-Olivos R, Baenas I, Steward T, Granero R, Pastor A, Sánchez I, Juaneda-Seguí A, Del Pino-Gutiérrez A, Fernández-Formoso JA, Vilarrasa N, Guerrero-Pérez F, Virgili N, López-Urdiales R, Jiménez-Murcia S, de la Torre R, Soriano-Mas C, Fernández-Aranda F. *Exploring the influence of circulating endocannabinoids and nucleus accumbens functional connectivity on anorexia nervosa severity*. **Mol Psychiatry.** 2023 Sep 28. doi: 10.1038/s41380-023-02253-2.

ARTICLE OPEN

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Exploring the influence of circulating endocannabinoids and nucleus accumbens functional connectivity on anorexia nervosa severity

Romina Miranda-Olivos[1,2,3,4,16], Isabel Baenas[1,2,3,4,16], Trevor Steward[5], Roser Granero[2,3,6], Antoni Pastor[2,7], Isabel Sánchez[1,2,3], Asier Juaneda-Seguí[4,8,9], Amparo del Pino-Gutiérrez[2,3,10], José A. Fernández-Formoso[2], Nuria Vilarrasa[11,12], Fernando Guerrero-Pérez[11], Nuria Virgili[11], Rafael López-Urdiales[11], Susana Jiménez-Murcia[1,2,3,13], Rafael de la Torre[2,7,14], Carles Soriano-Mas[8,9,15]✉ and Fernando Fernández-Aranda[1,2,3,13]✉

Anorexia nervosa (AN) is a severe psychiatric disorder characterized by a harmful persistence of self-imposed starvation resulting in significant weight loss. Research suggests that alterations in the nucleus accumbens (NAcc) and circulating endocannabinoids (eCBs), such as anandamide (AEA) and 2-arachidonoylglycerol (2-AG), may contribute to increased severity and maladaptive behaviors in AN, warranting an examination of the interplay between central reward circuitry and eCBs. For this purpose, we assessed NAcc functional connectivity and circulating AEA and 2-AG concentrations in 18 individuals with AN and 18 healthy controls (HC) to test associations between circulating eCBs, NAcc functional connectivity, and AN severity, as defined by body mass index (BMI). Decreased connectivity was observed between the NAcc and the right insula (NAcc-insula; $p_{FWE} < 0.001$) and the left supplementary motor area (NAcc-SMA; $p_{FWE} < 0.001$) in the AN group compared to HC. Reduced NAcc-insula functional connectivity mediated the association between AEA concentrations and BMI in the AN group. However, in HC, NAcc-SMA functional connectivity had a mediating role between AEA concentrations and BMI. Although no significant differences in eCBs concentrations were observed between the groups, our findings provide insights into how the interaction between eCBs and NAcc functional connectivity influences AN severity. Altered NAcc-insula and NAcc-SMA connectivity in AN may impair the integration of interoceptive, somatosensory, and motor planning information related to reward stimuli. Furthermore, the distinct associations between eCBs concentrations and NAcc functional connectivity in AN and HC could have clinical implications for weight maintenance, with eCBs being a potential target for AN treatment.

Molecular Psychiatry; https://doi.org/10.1038/s41380-023-02253-2

INTRODUCTION

Anorexia nervosa (AN) is an eating disorder (ED) characterized by food restriction, body image disturbances, and a harmful drive for weight loss despite negative consequences [1–4]. Significant weight loss has been shown to have increasingly pronounced adverse effects on both mental and physical well-being as individuals with AN continue to lose weight [5–7]. As such, the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) categorizes the severity of AN based on body mass index (BMI), ranging from mild (BMI ≥ 17 kg/m^2) to extreme (BMI < 15 kg/m^2) [8].

Aberrant eating behavior in AN is believed to be underpinned by dysfunctional reward processing and diminished response to homeostatic signals [9–11]. Neuroimaging and behavioral research have identified alterations in brain reward and cognitive control systems in patients with AN [9, 11–15], with initial evidence suggesting brain activation and connectivity measures may be associated with AN treatment outcomes [16, 17].

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Received: 1 June 2023 Revised: 31 August 2023 Accepted: 5 September 2023
Published online: 28 September 2023

The nucleus accumbens (NAcc) is a crucial region for assessing rewards. It receives dopaminergic projections from various brain areas, including the ventral tegmental area (VTA), prefrontal cortex, insula, amygdala, and lateral hypothalamus [18–20]. These projections play a role in metabolic homeostasis and influence both the motivation to eat ("wanting") and the hedonic evaluation of food preferences ("liking") [21–25]. Both psychological processes (i.e., "wanting and liking") have been described by Berridge [26] as mesolimbic processes associated with the representation of rewarding stimuli. The valuation of an external stimulus perceived as rewarding increases motivation and approach to it, just as cognitive processing can increase the desire for an external rewarding stimulus in its absence.

Studies in individuals with AN have found decreased activity in the NAcc and insula in response to taste stimuli compared to healthy controls (HC) [27]. Although patients with AN respond to hedonic stimuli (such as palatable food), they report not "wanting" to be motivated by these types of stimuli for fear of gaining weight [9, 27, 28]. By contrast, when viewing underweight body images, patients with AN exhibited increased NAcc activation [29, 30]. NAcc alterations have been associated with the AN severity [31] and can persist even after weight recovery [32], suggesting that this region contributes to aberrant reinforcement, promoting behaviors such as starvation or over-exercising. For this reason, the NAcc has been used as a therapeutic target for deep brain stimulation (DBS) in AN [17, 33]. Preliminary results have demonstrated NAcc DBS can help improve AN treatment outcomes [17] and to reduce depressive and anxious symptoms [33].

A growing body of evidence supports the implication of the endocannabinoid system (eCB system) in the brain reward circuitry. The eCB system is composed of endogenous cannabinoid (CB) receptors type 1 and 2 (CB1R and CB2R) expressed in the central and the peripheral nervous system and two main lipidic endogenous ligands: anandamide (AEA) and 2-arachidonoylglycerol (2-AG) [34]. In the brain, the endocannabinoids (eCBs) are released from VTA to the NAcc, the amygdala, and the frontal cortex [35, 36], modulating extracellular levels of dopamine in the NAcc [24, 37]. Most studies focused on the eCB system have converged on describing its involvement in wanting and liking processes [25, 26]. For instance, studies in animals have demonstrated that an injection of 2-AG in the NAcc promotes orexigenic function in the lateral hypothalamus via inhibition of GABAergic signaling in rats [38, 39].

Based on this knowledge, some pharmacological studies have focused on the CB1R as a potential target in the treatment of AN, reporting limited evidence regarding safety and efficacy [40–42]. For instance, some interventional studies have tested the efficacy of a synthetic cannabinoid called dronabinol in patients with AN [40, 42]. This compound acts as a CB1R agonist, promoting appetite. While initial results did not show a significant increase in body weight and revealed adverse effects in some patients [42], a subsequent study demonstrated a modest weight gain without tolerability problems [40]. It is currently considered a potential pharmacological option for AN treatment albeit with limited evidence regarding its effectiveness [41].

Research focused on exploring the eCB system in AN has provided mixed results. While some studies comparing individuals with AN and HC reported elevated AEA concentrations in AN [14, 43], other research has identified decreased AEA concentrations [13] or no significant differences [44]. These alterations in AEA concentrations observed in AN were maintained even after weight restoration [13, 14]. Regarding 2-AG, most studies have found no significant differences comparing patients with AN and HC [13, 14, 43, 44]. Likewise, studies investigating the activity and expression of CB receptors have also shown inconsistent results. For instance, a study observed CB1R up-regulation in patients with AN and BN compared to HC [45]. Frieling et al. [45] reported a negative association between CB1R availability and ED severity, with higher symptomatology being associated with lower CB1R expression [45]. However, another study reported down-regulation only in patients with EDs presenting self-injurious behavior compared to those who did not report such behavior and HC [46]. Despite these divergent results, both studies converged in linking a down-regulation of CB1R with a more severe presentation of the disorder.

Neuroimaging studies support that the eCB system can mediate brain reward circuits involved in the control of appetite and motivation toward food. A recent study in HC reported that circulating AEA concentrations were associated with functional connectivity between the lateral hypothalamus and the ventral striatum during satiety and between the anterior cingulate cortex and the insula during fasting [47]. In EDs, one positron emission tomography study (PET) investigated CB1R availability in the brain of patients with AN and observed an increased availability in the insula in AN and BN compared with HC [48], as well as in the frontal and temporal lobes. Gérard et al. [48] hypothesized that this up-regulation of the CB1R in the insular, frontal, and temporal regions in AN could represent a compensatory mechanism in response to altered concentrations of circulating eCBs as a consequence of chronic hunger.

A deeper understanding of the interaction between the brain reward system and the eCB system could help to better elucidate the modulation that they exert on motivational and homeostatic processes related to altered food intake in AN. Likewise, the identification of the neurobiological substrates of maladaptive behavior in AN could allow for the delineation of potential therapeutic targets aimed at counteracting their impact. As such, the present study sought to investigate the intrinsic functional architecture of the NAcc using resting-state functional magnetic resonance imaging (fMRI) and fasting circulating AEA and 2-AG concentrations in individuals with AN compared to HC. We aimed to explore whether circulating eCBs concentrations would have an influence on NAcc functional connectivity and BMI, as a measure of AN severity [8]. We hypothesized that individuals with AN would exhibit reduced NAcc resting-state functional connectivity (rsFC) with prefrontal regions, the insula, temporal, and parietal regions, compared with HC. Likewise, we expected alterations in the functional connectivity patterns of the NAcc and eCBs concentrations would influence AN severity.

METHODS

Participants

A cross-sectional study was conducted on 36 adult women (18–47 years old): 18 individuals belonging to AN (BMI < 18 kg/m^2) and 18 HC (BMI = 18–24.99 kg/m^2). All patients in the AN group were diagnosed with restrictive subtype (AN-R) using DSM-5 criteria [8] based on a semi-structured interview (SCID-5) [49] carried out by experienced clinical psychologists and psychiatrists. The selection of a clinical sample composed exclusively of patients with AN-R aimed to focus on a specific subtype of AN and to minimize the potential effect of purging behaviors on eCBs concentrations [43]. Likewise, BMI was used as a severity criterion in AN according to the DSM-5 [8]. Patients were recruited between 2016 and 2021 from the Eating Disorders Unit at the Bellvitge University Hospital (Barcelona, Spain). All patients were admitted to a three-month day-hospital treatment program consisting of refeeding treatment and daily group cognitive-behavioral therapy (CBT) sessions. The HC group was recruited via advertisements from the same catchment area.

In order to detect the presence of a psychiatric disorder, all participants were evaluated using the Mini International Neuropsychiatric Interview (M.I.N.I.) [50]. Considering that anxiety or depressive disorders frequently co-occur in patients with AN [51], the presence of these comorbidities was not exclusionary. For HC, the exclusion criteria were having had a lifetime diagnosis of ED or obesity and/or a current DSM-5 diagnosed psychiatric disorder or obesity. For all participants, the exclusion criteria were being male, having an organic mental disorder, having had head trauma with a loss of consciousness for more than 2 min, having a learning or intellectual disability, being pregnant or currently breastfeeding, and any contra-indication for magnetic resonance imaging (MRI) scanning.

The study procedures were carried out in accordance with the Declaration of Helsinki. The Clinical Research Ethics Committee of the Bellvitge University Hospital approved the study (PR319/20). Written informed consent was obtained from all participants before taking part in the study.

Procedure

The assessment was performed in two separate sessions. Anthropometric and clinical variables, as well as blood samples to evaluate circulating eCBs concentrations (i.e., 2-AG and AEA), were collected during the first session. This was conducted before starting treatment in the AN group. Participants completed functional magnetic resonance imaging (fMRI) scanning during a second session. Patients with AN underwent assessments and fMRI scanning at the start of treatment.

Body mass index measure. The height of the participants was determined using a stadiometer. This information was entered into a Tanita Multi-Frequency Body Composition Analyzer BC-420MA (Tanita BC-420MA, Tanita Corp. Tokyo, Japan). This is a bioelectrical impedance analyzer and a non-invasive instrument that measures weight and estimates body composition. These data were used to calculate BMI.

Peripheral endocannabinoids measures. Blood samples were obtained after overnight fasting. Blood was centrifuged at 1700g in a refrigerated centrifuge (4 °C) over 20 min. Plasma was separated immediately and stored at −80 °C until eCBs (i.e., 2-AG and AEA) were analyzed, by liquid chromatography-mass spectrometry (LC/MS-MS) following a previously validated method [52].

Neuroimaging analysis

Imaging data acquisition. Whole-brain resting-state fMRI (rsfMRI) data were obtained using a 3.0 Tesla clinical MRI scanner equipped with a 32-channel phased-array head coil (Intera Achieva Philips Medical Systems, Eindhoven, Netherlands). During an 8-minute sequence, participants were instructed to relax, stay awake, and lie still with their eyes open while observing a fixation cross. 240 whole-brain volumes were acquired using T2*-weighted echo-planar imaging (EPI) with a repetition time (RT) of 2000 msec, an echo time of 25 msec, and a pulse angle of 90°, in a 24-cm field of view (FOV) and an 80×80-pixel matrix, providing isotropic voxel sizes of $3 \times 3 \times 3$ mm with no gap. A structural MRI scan was acquired for each participant. Specifically, a high-resolution T1-weighted anatomical scan was acquired to facilitate registration of the EPI data into standard MNI space, and for extracting individual global gray matter volume. A three-dimensional fast-spoiled gradient, an inversion-recovery sequence with 233 contiguous slices (repetition time, 10.43 msec; echo time, 4.8 msec; flip angle, 8°) in a 24-cm field of view, with a 320×320-pixel matrix and isotropic voxel sizes of $0.75 \times 0.75 \times 0.75$ mm was used. In addition, participants had their heart rate frequency recorded with a BIOPAC MP150 data acquisition system and AcqKnowledge 4.4 software (BIOPAC Systems Inc., Goleta, CA).

fMRI preprocessing. fMRI data were processed and analyzed using MATLAB version 2019b (The MathWorks Inc., Natick, Massachusetts) and CONN toolbox version 2019b [53]. First, the BrainWavelet Toolbox was used to denoise all functional images. rsfMRI data underwent the following preprocessing steps: (1) functional realignment and unwarping, (2) slice-timing correction, (3) structural segmentation and normalization, (4) functional normalization, (5) ART-based identification of outlier scans for scrubbing according to previous recommendations [54], and (6) smoothing using a Gaussian filter (FWHM 8 mm). Physiological noise potentially disturbing the blood oxygen level-dependent (BOLD) signal (i.e., white matter, cerebrospinal fluid (CSF), and global BOLD time-series), as well as motion parameters (3 translational and 3 rotational axes) were introduced as confounders in an additional denoising step by the aCompCor [55] using the CONN toolbox [53]. Additional steps after denoising included the band-pass filtering of the BOLD time series (between 0.008 and 0.09 Hz), linearly detrending, and despiking to remove additional artifacts.

Seed-based functional connectivity analysis. We obtained a reward brain mask using Neurosynth inference maps (https://neurosynth.org). Neurosynth [56] is a meta-analytic neuroimaging database that uses a large series of previous studies to create empirical maps based on the probability that activation in specific brain regions would be associated with a specific term, such as "reward". Choosing the "reward" term, a total of 922 studies were reported showing a forward-inference statistical map comprising several brain regions such as striatal regions, midbrain, cortices, hippocampus, amygdala, insulae, and cingulate, frontal, and intraparietal cortices (see Fig. S1a). The seed region within the reward system was selected by restricting the level of statistical significance of the empirical reward map. That is, we only included voxels with a high statistical probability ($p_{FDR} = 0.00001$) of association with the term "reward". These resulted in a seed including 219 voxels within the ventral striatum/NAcc area (see Fig. S1a).

First-level (single-subject) maps were estimated in bivariate correlation analyses (Pearson's *r*) of the resting-state BOLD time series, and NAcc-seeded connectivity maps were obtained for each subject. Heart rate frequency recorded during the rsfMRI was introduced as an individual regressor. A high-pass filter (128 s) was used to remove low-frequency drifts.

Second-level analysis (between-group effects) was carried out comparing NAcc functional connectivity between the AN group and the HC group. Given the significant age differences between groups, all analyses were controlled for this variable and corrected for multiple comparisons as recommended by Woo et al. [57] and Eklund et al. [58]. All derived differences in functional connectivity were analyzed under a statistical significance threshold satisfying a family-wise error (FWE) rate correction of $p_{FWE} < 0.05$ (spatial cluster extent).

Statistical analyses of non-imaging data

Stata17 for Windows was used for the statistical analysis. The comparisons between groups were done with the analysis of variance (ANOVA) procedures, including age as confounding for the tests focused on the BMI, circulating eCBs concentrations, and eigenvalues from regions displaying significant between-group differences in functional connectivity. The assumptions of normality and homoscedasticity, required for the ANOVA, were met in this study ($p > 0.05$ in the Shapiro-Wilk tests and F-variance ratio test). The statistical power analysis yielded values ranging from $\beta = 0.6$ to 1 for mean comparisons.

The path analysis procedure explored the underlying associations between circulating eCBs, NAcc functional connectivity, and BMI. A multi-group model was tested including the diagnostic subtype as the group to assess the invariance of the structural coefficients between the AN and HC groups. Maximum likelihood estimation was used, and all parameters were freely estimated (any value was assumed and estimated by SEM). In order to obtain a more parsimonious model and increase statistical power, parameters with non-significant tests were deleted and then, the model was respecified and refitted. Goodness-of-fit was evaluated using standard statistical measures: chi-square test (χ^2), the root mean square error of approximation (RMSEA), Bentler's Comparative Fit Index (CFI), the Tucker-Lewis Index (TLI), and the standardized root mean square residual (SRMR). Adequate model fit was considered non-significant by χ^2 tests if the following criteria were met: RMSEA < 0.08, TLI > 0.9, CFI > 0.9, and SRMR < 0.1 [59]. The global predictive capacity of the model was measured by the coefficient of determination (CD). In addition, due to the small sample size and the underpowered test for the SEM [60], in this analysis, relevant coefficients were considered for |standardized coefficient| ≥ 0.24.

RESULTS

Sample description

Table 1 describes the study sample. The AN group was younger ($M = 22.89 \pm 4.66$) than the HC group ($M = 34.22 \pm 7.78$; $t = 5.30$; $p < 0.001$). Likewise, the AN group had a lower BMI ($M = 16.28 \pm 1.40$) than the HC group ($M = 21.63 \pm 2.06$; $p < 0.001$). In the AN group, the mean age of onset was 17.11 years old, and the mean illness duration was 5.78 years. Likewise, an ANCOVA (adjusted for age) compared differences between groups in the 2-AG and AEA concentrations revealed no significant differences in 2-AG ($F_{(1,33)} = 0.008$; $p = 0.930$; $|d| = 0.04$) and AEA ($F_{(1,33)} = 1.18$; $p = 0.285$; $|d| = 0.50$) concentrations.

Between-group differences in NAcc functional connectivity. In comparison to HC, individuals with AN showed lower rsFC between the NAcc and the insula encompassing the adjacent temporal gyrus and operculum ($p_{FWE} < 0.001$) and the supplementary motor area ($p_{FWE} < 0.001$) (Fig. 1; Table 2).

Table 1. Sample description.

	HC ($n = 18$)		AN ($n = 18$)		p	$\|d\|$
	Mean	***SD***	***Mean***	***SD***		
Age (years old)	34.22	7.78	22.89	4.66	**<0.001***	**1.77†**
BMI (kg/m^2)[a]	21.63	2.06	16.28	1.40	**<0.001***	**3.04†**
Duration (years)	--	--	5.78	4.58	--	--
Onset (years old)	--	--	17.11	3.98	--	--
2-AG[a]	6.16	4.73	6.34	4.18	0.930	0.04
AEA[a]	0.24	0.09	0.20	0.08	0.285	**0.50†**

HC healthy controls, *AN* anorexia nervosa, *SD* standard deviation, *BMI* body mass index, *SD* standard deviation, *2-AG* 2-arachidonoylglycerol, *AEA* anandamide.
*Bold: significant comparison ($p < 0.05$). †Effect size in the moderate to high range.
[a]Comparison between groups: ANCOVA adjusted for age.

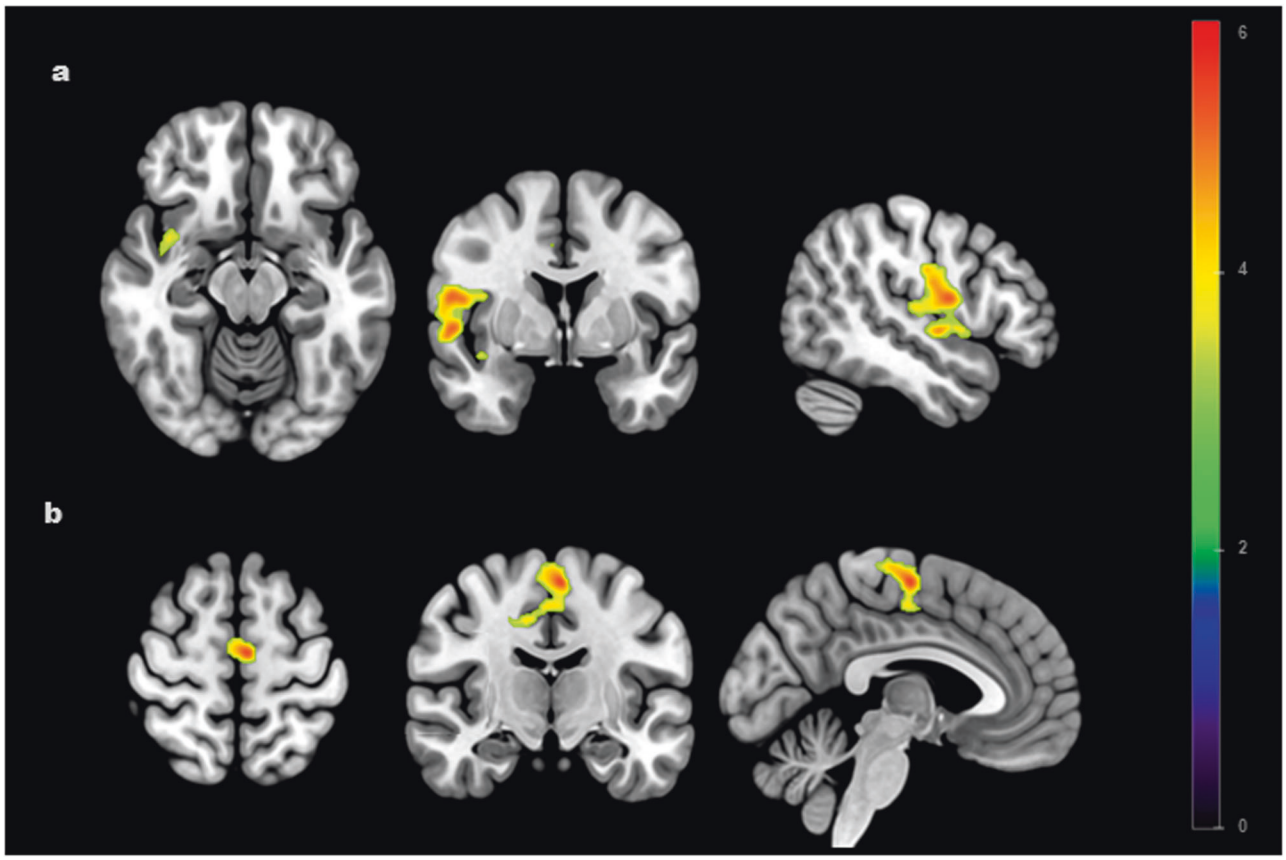

Fig. 1 Between-group differences (AN < HC) in the functional connectivity of bilateral nucleus accumbens seeds. Figures (**a**, **b**) display lower functional connectivity between the nucleus accumbens and (**a**) the right insula (NAcc-insula; $p_{FWE} < 0.001$); (**b**) the left supplementary motor area (NAcc-SMA; $p_{FWE} < 0.001$) in the AN group compared to HC. Color bar represents t-values. Results are corrected and displayed at family-wise error (FWE) probability $p_{FWE} < 0.05$ threshold, cluster-extent. AN anorexia nervosa, HC healthy controls.

Path analyses. Our multigroup SEM obtained achieved adequate goodness-of-fit ($\chi 2 = 2.15$ [$p = 0.341$], RMSEA = 0.066, CFI = 0.989, TLI = 0.906, and SRMR = 0.038) and a global predictive capacity around 41% (CD = 0.411). A quasi-significant result was obtained in the joint test assessing the invariance of structural coefficients by group ($\chi 2 = 16.28$, $p = 0.092$), suggesting the existence of different structures within AN and HC groups. Figure 2 shows the path diagrams with the standardized coefficients. Within the AN group (marked in red in the figure), AEA and 2-AG showed a direct influence on BMI, whereas NAcc-insula functional connectivity had a dual role: a direct impact on the BMI and a mediational role on the relationship between AEA and BMI. Within the HC group (marked blue in the figure), AEA had a direct influence on the BMI, whereas NAcc-SMA functional connectivity had a dual role by contributing directly to BMI and mediating the relationship between AEA, 2-AG, and BMI.

DISCUSSION

The present study investigated NAcc functional connectivity and circulating eCBs concentrations in AN compared with HC, and their potential influence on BMI. In line with our hypothesis, we identified alterations in the functional connectivity patterns of the NAcc with the insula (NAcc-insula) and the supplementary motor area (NAcc-SMA) in individuals with AN compared to HC. Likewise, our results showed NAcc-insula and NAcc-SMA functional

Table 2. Second-level analysis showed reduced NAcc functional connectivity in the AN group compared to the HC group.

Functional connectivity	Region	MNI Coordinates (x, y, z)	ke[a]	t
AN < HC	Insula	54; −6; −2	1368	5.89
	Supplementary Motor Area	−4; −12; 62	605	4.54

AN anorexia group, *HC* healthy control.
A familywise error (FWE) probability (pFWE < 0.05) cluster-extent threshold was used.
Coordinates (x, y, z) are given in Montreal Neurological Institute (MNI) atlas space.
[a]Cluster extent in voxels.

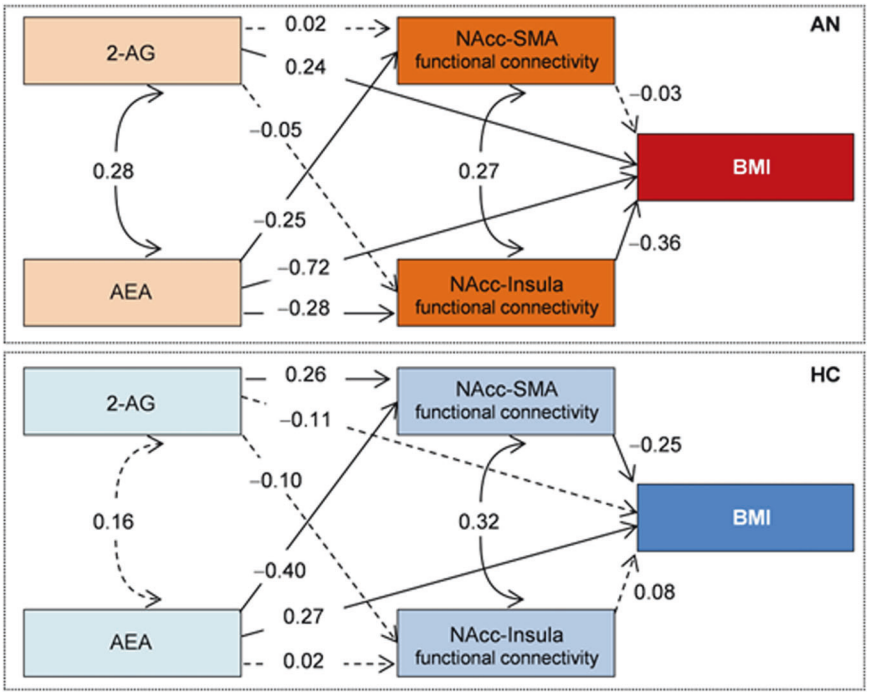

Fig. 2 Path-diagram with the standardized coefficients (SEM model adjusted for age). AN anorexia nervosa, HC healthy controls, 2-AG 2-arachidonoylglycerol, AEA anandamide, NAcc nucleus accumbens, SMA supplementary motor area, BMI Body Mass Index. Continuous line: relevant coefficient. Dash line: non-relevant coefficient. Standardized coefficients ≥0.24 were considered relevant.

connectivity distinctively mediated the association between eCBs and BMI in each group.

Alterations in NAcc functioning have been widely reported in patients with AN [17, 27, 29–31, 33]. We identified NAcc-insula and NAcc-SMA hypoconnectivity in AN. The insula is the core of sensory, interoceptive, and gustatory processing regions [61], being part of the salience network (SN) [62], whereas the SMA plays an important role in motor planning and execution of voluntary movements, as well as in somatosensory processing, being part of the sensorimotor network (SMN) [62, 63]. In AN, aberrant communication between the insula and striatal regions has been associated with altered sensitivity to interoceptive and reward cues, which could be responsible for the development of maladaptive eating behavior and distorted perceptions surrounding hunger, satiety, and body weight and shape [32, 64, 65]. Insular dysfunction has been observed during the processing of taste and food rewards, which has been postulated as a possible mechanism underlying these behavioral and interoceptive disturbances in these patients [65]. Similarly, dysfunctional activity in the SMA has been related to alterations in body perception and severity of the disorder [66, 67]. For instance, a negative evaluation of body image in AN has been associated with lower functional connectivity of the SMA compared to HC [67]. Individuals in the acute stage of AN exhibited a lower SMA functional connectivity in comparison to both those who have recovered from AN and HC [66]. As speculative, this finding suggests that SMA functional connectivity could be affected in acute states of the disorder.

Concentrations of eCBs were not significantly different between groups, consistent with previous studies that observed no differences in 2-AG [13, 43] and AEA [44] concentrations. However, our findings revealed a specific interaction between eCBs and distinct NAcc functional connectivity in HC and AN concerning BMI. Higher AEA concentrations were associated with reduced NAcc-SMA functional connectivity and higher BMI in the HC group. The strength of NAcc-SMA functional connectivity in HC was a mediator in the association between both eCBs and BMI, but only AEA concentrations showed a positive direct association with BMI. A recent study also reported that circulating AEA concentrations influenced brain functional connectivity in HC evaluating changes during fasting and satiety [47]. However, in contrast to our findings, they observed that higher AEA concentrations were associated with increased functional connectivity in the caudate/NAcc with the insula and the anterior cingulate cortex [47]. Moreover, this study did not find a link between 2-AG and brain functional connectivity whereas we observed that higher 2-AG concentrations were associated with increased NAcc-SMA functional connectivity. Findings in HC support the notion that AEA and 2-AG may play distinct and independent roles in regulating BMI by exerting influence on reward and somatosensory circuits [24, 47]. While an increase in AEA concentrations would

downregulate functional connectivity promoting weight gain, an increase in 2-AG would upregulate the strength of functional connectivity between NAcc-SMA counteracting weight gain. In other words, the influence of the NAcc-SMA functional connectivity on BMI could be distinctively regulated by AEA and 2-AG. These findings could have important clinical implications for the development of new therapeutic strategies aimed at maintaining a healthy weight, as a treatment for weight disorders.

In AN, both AEA and 2-AG were found to influence the association between the NAcc-insula and NAcc-SMA functional connectivity and BMI, a DSM-5 criterion of severity for AN [68]. Specifically, elevated AEA concentrations were directly associated with lower BMI, whereas 2-AG was associated with higher BMI. Based on the existence of compensatory mechanisms involving the eCB system [11, 48, 69], increasing AEA concentrations could represent an attempt to improve eating behavior and favor weight gain. However, the negative association between AEA and BMI in these patients could suggest resistance to this neuroendocrine signaling involved in the regulation of homeostatic and hedonic mechanisms related to food intake [70]. In contrast, the positive association between BMI and 2-AG may suggest that mutual regulation of AEA and 2-AG serves as a mitigator of severity in AN by modulating BMI. Consistent with this, studies using animal models have shown that infusion of cannabinoid agonists can elevate circulating 2-AG concentrations and CB1R activation in the NAcc, stimulating food intake and weight gain [38, 39].

Our SEM analysis in the AN group also showed a negative association between AEA concentrations and NAcc-insula and NAcc-SMA functional connectivity. In contrast to HC, NAcc-insula functional connectivity played a mediating role between AEA and BMI. That is, elevated AEA concentrations had a diminishing effect on NAcc-insula functional connectivity, which increased as a function of BMI. It is noteworthy that results derived from the association between AEA and NAcc-insula functional connectivity are opposite to those observed in the study by Martín-Pérez and collaborators [47], being argued that the influence of AEA on reward-related brain circuits would help to promote feeding in calorie-deprived situations [47, 71]. As this study was conducted in HC, our results might purpose the existence of a biological vulnerability pathway that could contribute to ignoring the somatosensory and interoceptive response to hedonic information in AN. Despite being speculative, the association of this described pathway with higher BMI in AN leads to the hypothesis of whether the existence of an underlying compensatory mechanism in the eCB system would involve an up-regulation of CB receptors in these regions. This up-regulation could be a response to the resistance of hedonic signaling mediated by AEA and the reduced NAcc-insula connectivity. Consistent with this rationale, in individuals with AN, an up-regulation of CB1R found in insular, frontal, and temporal regions suggested a compensatory response to altered circulating eCBs concentrations as a result of chronic starvation [48]. Given the preliminary nature of our results and the scarcity of evidence to dovetail with these findings, future studies should further confirm these assumptions.

This study should be interpreted considering some limitations. For example, its cross-sectional design does not allow the establishment of causal links. Likewise, there was a significant age difference between groups. Although this variable was controlled for in our analysis, future age-matched studies should be designed to minimize this potential age-related bias. In addition, due to the limited sample size used in this study, the mediation model exclusively used BMI as the clinical parameter of severity in order not to compromise the statistical power of the SEM analyses. Future studies with larger samples and further clinical parameters (in addition to BMI) could provide more evidence for these novel findings. Furthermore, the sample does not fully represent the population with AN because all patients were women recruited from a hospital setting. Finally, this study has not considered other variables of potential interest such as some hormonal factors (e.g., estrogen concentrations) [72, 73], or the well-known effect of physical activity on patients with AN that can modulate the eCB system tone [14]. However, the exclusive selection of the AN-R subtype was intended to eliminate the effect that purgative behaviors could potentially have on NAcc functional connectivity [33] and on circulating eCBs [43]. Future studies should examine the role of brain functioning and the interaction of eCBs in patients with EDs and purgative symptomatology. Additionally, this study also provides some noteworthy strengths. To the best of our knowledge, this is the first study exploring the association between deficits in brain reward function based on NAcc functional connectivity and circulating eCBs concentrations in patients with AN. From this perspective, the eCB system might be a potential target for treatment in AN and other EDs. Likewise, this study can also contribute to a deeper understanding of the neuroendocrine interplay between the eCB system and other neuroendocrine systems, considering the modulatory role that this system may have on the dopaminergic reward circuitry in AN.

CONCLUSIONS

Dysfunctional connectivity between NAcc-insula and NAcc-SMA in AN may underlie alterations in the integration of interoceptive, somatosensory, and motor planning information, which could override responsiveness to hedonic information. Results from the multivariate SEM modeling indicate different association pathways between eCBs, functional connectivity, and BMI in AN and HC groups. These findings suggest that eCBs play a crucial role in influencing the relationship between brain networks and BMI in AN, shedding light on the neurobiological mechanisms underlying severity. The clinical implications of our results could contribute to the development of novel therapeutic strategies aimed at maintaining a healthy weight, as a treatment for weight and ED. Future research should investigate whether a potential causal relationship would exist between eCBs, NAcc connectivity, and the development of AN symptoms, such as restrictive eating behaviors.

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ACKNOWLEDGEMENTS

We thank CERCA Programme/Generalitat de Catalunya for institutional support. We also want to thank the Institut d'Investigació Biomèdica de Bellvitge (IDIBELL) and the Integrative Pharmacology and Systems Neuroscience research group-Hospital del Mar Research Institute (IMIM). This manuscript and research were supported by grants from Instituto de Salud Carlos III (ISCIII) (FIS PI20/00132) and co-funded by FEDER funds/European Regional Development Fund (ERDF), a way to build Europe. CIBERObn and CIBERSAM are both initiatives of ISCIII. Additional support was received from the Delegación del Gobierno para el Plan Nacional sobre Drogas (2021I031) and Ministerio de Ciencia e Innovación (grant PID2021-124887OB-I00). Additional funding was received by AGAUR-Generalitat de Catalunya (2021-SGR-00824), European Union's Horizon 2020 research and innovation program under Grant agreement no. 847879 (PRIME/H2020, Prevention and Remediation of Insulin Multimorbidity in Europe) and the European Union's Horizon Europe research and innovation program under grant agreement No 101080219 (eprObes). This work was partially supported by Instituto de Salud Carlos III through the grant CM21/00172 (IB) (co-funded by European Social Fund. ESF investing in your future). RG is supported by the Catalan Institution for Research and Advanced Studies (ICREA-Academia, 2021-Programme). TS is supported by a National Health and Medical Research Council (NHMRC)/Medical Research Future Fund (MRFF) Investigator Grant (MRF1193736), a Brain & Behavior Research Foundation (BBRF) Young Investigator Grant, and a University of Melbourne McKenzie Fellowship. The funders had no role in the study design, data collection, analysis, decision to publish, or preparation of the manuscript.

AUTHOR CONTRIBUTIONS

RM-O: Conceptualization, Investigation, Methodology, Data curation, Writing-original draft; IB: Conceptualization, Investigation, Methodology, Data curation, Writing-original draft. TS: Data curation, Methodology, Investigation, Project administration, Draft review; RG: Methodology, Data curation; AP: Methodology, Draft review; IS: Data collection; AJ-S: Methodology, Data curation; AP-G: Data collection; JAF-F: Resources; NV (Nuria Vilarrasa): Data collection; FG-P: Data collection; NV (Nuria Virgili): Data collection; RL-U: Data collection; S.J.-M: Funding acquisition; RdT: Conceptualization, Methodology, Draft review; CS-M: Conceptualization, Investigation, Data curation, Writing-original draft, Draft review; FF-A: Conceptualization, Investigation, Project administration; Funding acquisition, Writing-original draft, Draft review.

COMPETING INTERESTS

FFA and SJM received consultancy honoraria from Novo Nordisk and FFA editorial honoraria as EIC from Wiley. The rest of the authors have nothing to disclose.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41380-023-02253-2.

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4.3. STUDY 3

ASSOCIATION OF ANANDAMIDE AND 2-ARACHIDONOYLGLYCEROL CONCENTRATIONS WITH CLINICAL AND ANTHROPOMETRIC FEATURES IN EATING DISORDERS AND OBESITY

Baenas I, **Miranda-Olivos R**, Granero R, Solé-Morata N, Sánchez I, Pastor A, Del Pino-Gutiérrez A, Codina E, Tinahones FJ, Fernández-Formoso JA, Vilarrasa N, Guerrero-Pérez F, Lopez-Urdiales R, Virgili N, Soriano-Mas C, Jiménez-Murcia S, de la Torre R, Fernández-Aranda F. *Association of anandamide and 2-arachidonoylglycerol concentrations with clinical features and body mass index in eating disorders and obesity*. **Eur Psychiatry**. 2023 May 31;66(1):e49. doi: 10.1192/j.eurpsy.2023.2411.

European Psychiatry

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Association of anandamide and 2-arachidonoylglycerol concentrations with clinical features and body mass index in eating disorders and obesity

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Abstract

Background. Anandamide (AEA) and 2-arachidonoylglycerol (2-AG) play a pivotal role in stimulating motivational behavior toward food and energy metabolism. Aberrant functioning of the endocannabinoid system has been observed in extreme weight conditions (EWCs), suggesting it may influence pathophysiology. Then, we aimed to analyze fasting AEA and 2-AG plasma concentrations among individuals with EWC (i.e., anorexia nervosa [AN] and obesity with and without eating disorders [EDs]) compared with healthy controls (HCs), and its association with clinical variables and body mass index (BMI).

Methods. The sample included 113 adult women. Fifty-seven belonged to the obesity group, 37 without EDs (OB-ED) and 20 with ED (OB+ED classified within the binge spectrum disorders), 27 individuals from the AN group, and 29 from the HC group. Peripheral blood samples, several clinical variables, and BMI were evaluated.

Results. Unlike 2-AG, AEA concentrations showed significant differences between groups ($p < 0.001$). Increased AEA was observed in the OB-ED and OB+ED compared with both HC and AN group, respectively. Likewise, AEA was differentially associated with emotional dysregulation, general psychopathology, food addiction, and BMI in all clinical groups.

Conclusions. These results support the interaction between biological and clinical factors contributing to delineating vulnerability pathways in EWC that could help fit personalized therapeutic approaches.

Introduction

The extreme weight condition (EWC) construct has been used to classify individuals with unhealthy eating behaviors, altered body adiposity, metabolism, and nutrition patterns [1–3]. These clinical conditions would be distributed within a continuum where, at one extreme anorexia nervosa (AN) is found, whereas the other end is represented by obesity [1–3]. While AN is an eating disorder (ED) characterized by a low body mass index (BMI) (i.e., BMI < 18 kg/m^2), obesity is defined as a metabolic disorder with a BMI ≥ 30 kg/m^2, according to the World Health Organization [4]. EDs are mental illnesses with multifactorial etiopathogenesis involving

Research Article

Cite this article: Baenas I, Miranda-Olivos R, Granero R, Solé-Morata N, Sánchez I, Pastor A, del Pino-Gutiérrez A, Codina E, Tinahones FJ, Fernández-Formoso JA, Vilarrasa N, Guerrero-Pérez F, Lopez-Urdiales R, Virgili N, Soriano-Mas C, Jiménez-Murcia S, de la Torre R, Fernández-Aranda F (2023). Association of anandamide and 2-arachidonoylglycerol concentrations with clinical features and body mass index in eating disorders and obesity. *European Psychiatry*, **66**(1), e49, 1–11
https://doi.org/10.1192/j.eurpsy.2023.2411

Received: 27 October 2022
Revised: 20 January 2023
Accepted: 07 March 2023

Keywords:
2-arachidonoylglycerol; anandamide; eating disorders; endocannabinoids; obesity

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biological to psychosocial factors [5, 6]. Bulimia nervosa (BN) and binge eating disorder (BED) are also EDs, which could be understood under the umbrella of the so-called binge spectrum disorders (BSDs) [7], with an important lifetime prevalence of obesity [8–10]. In fact, the frequency of binge eating episodes (BEs) can increase the risk for obesity in almost half of the individuals with BSD [8, 9], suggesting the existence of shared biological and environmental vulnerability factors between both entities [11–16].

In the last decades, the endocannabinoid (eCB) system has emerged as a biological factor implicated in the pathogenesis of EWC, given its modulating role in eating behavior, energy metabolism, and food-related reward processing [17–20]. This system is composed of endogenous ligands (i.e., endocannabinoids, eCBs), cannabinoid receptors (CBRs), and the enzymatic machinery in charge of the synthesis and degradation of the eCBs [20]. In addition to being the two best-known eCBs [21], anandamide (AEA) and 2-arachidonoylglycerol (2-AG) are involved in homeostatic and hedonic aspects of feeding by pleiotropic actions [22, 23], mostly through their union with the type-1 CBR (CB1R) [24]. While AEA has a higher affinity than 2-AG, acting as a partial agonist, 2-AG is considered a full CB1R agonist [25]. This receptor is predominantly located in the central nervous system (CNS) [19, 26], where brain 2-AG concentrations are almost 200 times higher than those of AEA [27], but also found peripherally (e.g., adipose tissue, gastrointestinal tract, liver, pancreas, skeletal muscle, and kidney) [24, 28].

Globally, the eCB system exerts a central orexigenic function [29] as a retrograde inhibitor of dopaminergic neurotransmission in both regulatory pathways of intake, homeostatic and hedonic [30, 31]. As part of the homeostatic mechanism, the eCB system is involved in the integration of peripheral and central hunger and satiety signals in the hypothalamus, promoting behaviors toward food acquisition [20, 32]. In the hedonic pathway, the eCB system modulates mesolimbic circuits that are involved in increasing motivation toward food (i.e., "wanting to eat" psychological process) and reinforcing the rewarding properties of food (i.e., "liking eating" psychological process) [32, 33]. AEA has been classically defined as a physiological meal initiator, increasing motivation toward food (i.e., "wanting to eat") [30] and the hedonic aspects of food (i.e., "liking eating") [34, 35]. 2-AG has been mostly related to reinforcing the rewarding properties of food (i.e., "liking eating") [36], suggesting a distinctive role to each one [36, 37]. In addition, the eCB system promotes peripherally anabolic processes toward energy storage [38], with increased concentrations during fasting and decreased after feeding at both CNS and peripheral tissues [39]. A bidirectional cannabinoid signaling between brain regions and peripheral tissues has been described, which might contribute to intrinsically regulating the activity of the eCB system [37, 40–45]. Interestingly, in recent years, the gut–brain vagal axis has received special attention due to its potential role in regulating energy balance [46]. This axis seems to modulate central homeostatic and hedonic feeding pathways through the signaling of several peripheral endocrine factors (e.g., ghrelin, leptin, etc.), including peripheral eCBs [40].

In the context of EWC, studies have hypothesized alterations in the eCB system could underlie maladaptive behavior [47]. In obesity, a hyperactive eCB system has been described, with increased CB1R availability [48], as well as AEA and/or 2-AG concentrations during fasting [38, 49–51]. In patients with BED, higher AEA concentrations have been observed compared with healthy controls (HCs), hypothesizing that increased AEA in BED could be a risk factor for BEs [52]. However, in patients with BN, who also report BE, no significant differences have been found compared with HC [52]. Although a hypoactive eCB system has been stated in AN [53–55], describing a lower CB1R availability [56], findings related to the amount of eCBs remain still inconclusive [52, 57]. Monteleone et al. [52] described higher plasma AEA concentrations in AN compared with HC, whereas a recent study reported lower AEA concentrations in acute phases of the disorder and post-recovery [57], which was also supported in animal models [56]. Regarding 2-AG, studies in EDs have shown no significant differences in 2-AG concentrations when comparing BSD or AN with HC [45, 52, 57].

The association between eCBs and body composition has been explored with the intent to provide further insight into the potential underlying neurobiological mechanisms among EWC [58, 59]. In this line, a study in individuals with EDs and obesity described a negative association between BMI and CB1R availability in both hypothalamic (i.e., homeostatic pathway) and mesolimbic regions (i.e., hedonic pathway), supporting the existence of compensatory mechanisms that seek to counteract the abnormal activity of the eCB system in EWC [58]. On the other hand, in HC, CB1R availability was inversely linked to BMI, but only regarding the homeostatic pathway [58]. In the general population, a study exploring a wide range of BMI observed higher 2-AG concentrations in subjects with obesity and lower AEA in individuals with underweight [49]. These interactions between the eCB system and anthropometric measurements such as BMI might preliminarily indicate the existence of different functional links among individuals with different body compositions.

From a psychological perspective, the eCB system has shown to be involved in the pathogenesis of mood disturbances and impulse control problems [60–67]. Indeed, the role of eCBs has been explored in some psychiatric disorders such as addictive-related disorders [60, 61], borderline personality disorder [62, 63], post-traumatic stress disorder (PTSD) [64–66], and depression [67]. However, findings are mixed so far. For instance, while studies have described an elevated availability of CB1R in the brain of patients with PTSD [65], other studies have shown elevated [63] or reduced [62, 68] circulating eCBs concentrations. In the context of EWC, the evidence exploring the clinical interactions of eCBs is scarce. Preliminary results have reported an association between CB1R down-regulation and EDs severity and personality traits such as novelty-seeking and perfectionism [69, 70], suggesting a potential role in the psychopathology of EWC.

In this line, some investigations have explored the eCB system as a potential pharmacological target for treating mood-related disorders [71] and obesity with BE [72]. While studies have suggested that increased AEA concentrations might have an antidepressant and anxiolytic effect in both animal and human models [73–75], in obesity with BE, the CB1R blockade has shown effects in reducing food intake and, even, weight and adiposity [47, 76]. However, clinical trials have not been successful given the side effects of pharmacological treatments [71, 77]. To date, the evidence obtained requires further studies to consolidate these findings. The peripheral eCB system should be considered as a potential therapeutic target [78], supported by the existence of bottom-up cannabinoid signaling (e.g., gut–brain axis) [40, 41, 43] potentially involved in the pathophysiology of EWC [40, 44] and opening the possibility of minimizing side effects [47].

Given this background, our initial objective was to evaluate differences in fasting circulating AEA and 2-AG concentrations in individuals with EWC compared with HC. Furthermore, aiming to explore the interaction between circulating AEA and 2-AG concentrations, BMI, and clinical variables, we investigated the

underlying role of eCBs in each clinical group. We hypothesized obesity groups without (OB-ED) and with ED (OB+ED) would exhibit increased eCBs concentrations compared with the AN and HC group while the AN group would report the lowest eCBs concentrations. Considering the distinctive role of both 2-AG and AEA on food intake, we expected characteristic associations with BMI and clinical variables in each clinical group.

Methods

Participants

A total of 113 adult women (18–56 years old) were recruited: 57 individuals had obesity, 37 OB-ED and 20 OB+ED (3 BN and 17 BED); and 27 individuals had AN (25 restrictive and 2 binge-purging subtypes). Clinical groups were compared with 29 HC (BMI = 18–24.99 kg/m^2). Individuals with EDs were diagnosed according to DSM-5 criteria [5], using a semi-structured interview based on the SCID-5 [79]. Participants from the AN and OB+ED group were recruited from the Eating Disorders Unit at the Bellvitge University Hospital (Barcelona, Spain), while those individuals with OB-ED were recruited from the Endocrinology and Nutrition Unit at the same hospital. The HC group was recruited via advertisements from the same catchment area. In those with EDs, inclusion in the study occurred within the first week of treatment admission.

All participants underwent the Mini-International Neuropsychiatric Interview (M.I.N.I.) [80] to assess the presence of a psychiatric disorder. In the case of HC, exclusion criteria were a lifetime history of ED, based on DSM-5 diagnostic criteria, and/or obesity, and a current diagnosis of a psychiatric disorder. The study deferral criteria for all participants were male sex, the presence of an organic mental disorder, or an intellectual disability, as well as current problematic use of alcohol and illicit drugs (e.g., cannabis or cocaine).

Procedures

Participants were evaluated at Eating Disorders Unit (Bellvitge University Hospital, Barcelona, Spain) by experienced clinical psychologists and psychiatrists in two separate sessions. The first session consisted of a semi-structured clinical interview and self-report questionnaires that are part of the standardized psychometric assessment routinely performed in the initial clinical evaluation in our treatment unit. These psychometric instruments are designed at assessing general psychopathology, emotion regulation, and impulsivity. The second session consisted of measuring BMI and collecting fasting blood samples to assess circulating AEA and 2-AG concentrations.

Ethics

The study was carried out according to Good Clinical Practice and the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of the Bellvitge University Hospital (PR146/14). All participants were thoroughly informed of the procedures and provided written informed consent.

Assessments

Anthropometric measures

Height was measured by a stadiometer without wearing shoes. This information was introduced in a leg-to-leg body composition analyzer using a Tanita BC-420MA (Tanita BC-420MA, Tanita Corp., Tokyo, Japan) to collect body composition variables and obtain BMI. This instrument is a noninvasive bioelectrical impedance analyzer that estimates body composition, considering age and sex.

Biological measures

Blood samples were obtained in the morning, after at least 12 hours of fasting. Blood was processed at 1,700 g in a refrigerated centrifuge (4°C) over 20 min. Plasma was separated immediately and stored at −80°C until its analysis. AEA and 2-AG were analyzed by liquid chromatography-mass spectrometry (LC/MS–MS) with a previously validated method [59].

Clinical measures

Symptom Checklist-90 Items-Revised (SCL-90-R) [81]**;** Spanish validation [82]. The SCL-90-R assesses nine scales on general psychopathology: somatization, obsessive–compulsive, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, and psychoticism. In addition, it assesses three global psychological distress indices: Global Severity Index (GSI), Positive Symptom Total (PST), and Positive Symptom Distress Index (PSDI). The internal consistency in our sample was $\alpha = 0.98$.

Yale Food Addiction Scale 2.0 (YFAS 2.0) [83]**;** Spanish validation [84]. This is a self-reported scale to assess food addiction (FA) based on the 11-substance dependence-related symptoms adapted to the context of food consumption. The YFAS 2.0 consists of 35 items and produces two measurements: (a) a continuous symptom count score that reflects the number of fulfilled diagnostic criteria (ranging from 0 to 11), and (b) a binary measurement (present versus absent) based on the number of symptoms (at least 2) and the self-reported clinically impairment or distress. Additionally, it gives the severity cut-offs: mild (2–3 symptoms), moderate (4–5 symptoms), and severe (6–11 symptoms). The internal consistency of our sample was $\alpha = 0.97$.

Difficulties in Emotion Regulation Strategies (DERS) [85]; Spanish validation [86]. This is a 36-item self-reported scale to assess emotional dysregulation, divided into six subscales: lack of emotional awareness, lack of emotional clarity, nonacceptance of emotional responses, difficulties engaging in goal-directed behavior, limited access to emotional regulation strategies, and impulse control difficulties. Participants responded using a five-point Likert scale ranging from 1 (rarely) to 5 (almost always). Higher scores indicate greater problems in emotion regulation. The internal consistency of the DERS total score in our sample was $\alpha = 0.96$.

Impulsive Behavior Scale (UPPS-P) [87]; Spanish validation [88]. It 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 this study was $\alpha = 0.90$.

Statistical analysis

Statistical analysis was carried out with Stata17 for Windows [89]. Comparisons between groups were done with chi-square tests (χ^2) for categorical variables, and analysis of variance (ANOVA) for quantitative variables. A statistical power calculation was previously performed for the mean comparisons displaying values ranging from $1 - \beta = 0.81$ to $1 - \beta = 0.89$, a threshold usually considered acceptable in medical science ($1 - \beta = 0.80$). Differences between groups in 2-AG and AEA concentrations were done with an analysis of covariance (ANCOVA), adjusted by the participants'

age. Fisher's least significant difference method was employed for multiple comparisons, and standardized Cohen's-*d* statistic assessed the effect size of the mean differences (low–poor effect size was interpreted for $|d| > 0.20$, moderate–medium for $|d| > 0.50$, and large–high for $|d| > 0.80$) [90].

Finally, a path analysis procedure was conducted to explore underlying relationships between biological variables and clinical features. This statistical procedure is an extension of multiple regression modeling and estimates the magnitude and significance of a set of relationships between variables, including mediational links (direct and indirect effects) [91]. Path analysis was run as a case of structural equation modeling (SEM) with the maximum-likelihood estimation method. To assess the invariance of the structural coefficients between the diagnostic types a multi-group model was defined and tested. Goodness-of-fit was evaluated using standard statistical measures and adequate fitting was considered for: nonsignificant result for the χ^2 test, the root mean square error of approximation (RMSEA) < 0.08, Bentler's Comparative Fit Index (CFI) > 0.90, Tucker–Lewis Index (TLI) > 0.90, and the standardized root mean square residual (SRMR) < 0.10 [92]. The coefficient of determination (CD) measured the global predictive capacity of the model. In this study, SEM was obtained for each clinical group.

Results

Descriptive of the sample

Table 1 displays the distribution of the socio-demographic, BMI, and clinical variables (total scores), and the comparison between groups. As expected, significant differences between groups were found in BMI ($p < 0.001$*), UPPS-P ($p = 0.001$*), SCL-90R GSI ($p < 0.001$*), DERS ($p < 0.001$*), Y-FAS 2.0 ($p < 0.001$*), but also in age ($p < 0.001$*). For this reason, age was considered confounding.

Comparison of biological measures between the groups

Table 2 displays the results of the ANCOVA (adjusted by age), comparing 2-AG and AEA between groups. Regarding 2-AG, differences between HC and obesity groups (i.e., OB-ED and OB+ED) were observed, displaying the HC group with significantly higher mean concentrations. On the other hand, obesity groups registered the highest AEA mean concentrations (0.45 and 0.38, respectively), which statistically differed from those registered in the AN and HC groups (0.22 and 0.25, respectively). Figure 1 shows the scatterplots displaying the relationships between 2-AG and AEA with BMI. The plots evidence the moderator role of the ED subtype: (a) for 2-AG a negative relationship was identified with BMI among HC and AN, while no significant association was found between OB+ED and OB-ED group; and (b) for AEA, a positive association was found with BMI among OB-ED, a negative association among AN, and a nonsignificant association was identified among HC and OB+ED conditions.

Path analysis

The multi-group model assessing the invariance by the diagnostic types achieved adequate fitting: $\chi^2 = 16.06$ ($p = 0.378$), RMSEA = 0.050, CFI = 0.991, TLI = 0.948, and SRMR = 0.090. The global predictive capacity of the model was CD = 0.187. The joint test for invariance obtained significant results ($\chi^2 = 72.35$, $p = 0.001$), indicating that the set of relationships between variables was different among diagnostic groups.

Figure 2 shows the path diagram with standardized coefficients for each clinical group. To facilitate interpretation, only significant relationships have been plotted (nonsignificant parameters have been deleted in the figure). Coefficients with statistical differences between groups are represented in red lines whereas black lines represent no statistical differences. Multi-group SEM for the complete sample can be viewed in the Supplementary Material (Figure S1).

In the AN group, higher 2-AG concentrations predicted a worse psychopathological state, while lower AEA concentrations predicted higher BMI and higher emotional dysregulation levels (DERS). The UPPS-P and YFAS scores were also higher for patients with higher emotional dysregulation levels, while the BMI was also higher in patients with higher DERS scores but lower general psychopathology.

In the OB+ED group, higher AEA concentrations contributed to increasing YFAS scores and BMI and decreased DERS total score. UPPS-P and YFAS were also increased for patients with higher emotional dysregulation levels. Higher impulsivity levels were related to a worse psychopathological state. In the model, no significant associations were observed for 2-AG with other variables.

In the OB-ED group, higher AEA concentrations predicted higher YFAS scores and BMI, and lower DERS total scores. UPPS-P was increased for patients with higher emotional dysregulation scores, while YFAS total score was higher for patients with a worse psychopathological state. In the model, no significant associations were observed for 2-AG with other variables.

A common mediational link was observed between AEA concentrations and specific clinical features within the three diagnostic groups: lower AEA concentrations predicted a higher DERS total score, which, in turn, predicted a worse psychopathological state.

Discussion

The present study found higher AEA concentrations in the obesity groups compared with the HC and AN group, as well as higher 2-AG concentrations in the HC group compared with the OB-ED group. Interestingly, AEA concentrations showed a distinct association with BMI among EWC. In AN, higher AEA concentrations predicted lower BMI, whereas, in the obesity groups, increased AEA concentrations were linked to higher BMI and FA. In all clinical groups, higher AEA concentrations were related to lower emotional dysregulation and indirectly predicted lower general psychopathology. Emotional dysregulation also mediated the relationship between AEA and impulsivity. Higher 2-AG concentrations predicted greater general psychopathology in the AN group.

Differences between groups in circulating eCBs concentrations partially supported our hypotheses. On the one hand, the obesity groups (i.e., OB-ED and OB+ED) exhibited similar AEA concentrations, which were significantly higher than in the HC and AN group, respectively. We expected to obtain elevated circulating eCBs concentrations in individuals with obesity, according to previous studies [38, 49, 50, 52]. Increased AEA concentration supported the rationale that AEA could be a vulnerability factor for overeating in obesity and BSD [20, 52, 93], as well as a risk factor for the onset and maintenance of BE [52, 94]. Considering peripheral eCBs also influence vagal-dependent activity at the central level, our results raise the question of whether AEA specifically may play a key role in the pathophysiology of obesity and BED through the gut–brain vagal axis, underlying BE by triggering both homeostatic

Table 1. Descriptive of the sample

	HC; *n* = 29		AN; *n* = 27		OB+ED; *n* = 20		OB-ED; *n* = 37		
	Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*	*p*
Age (years-old)	37.38	10.51	22.96	5.47	37.35	9.90	39.92	9.70	**<0.001***
Education (years)	7.66	6.05	11.89	5.06	6.25	5.84	8.59	5.80	**0.006***
Body mass index (kg/m^2)	22.31	2.29	16.63	1.69	40.35	7.46	43.05	8.63	**<0.001***
UPPS-P: Total	113.38	19.25	127.44	24.32	135.75	19.45	121.30	14.49	**0.001***
SCL-90R: GSI score	0.63	0.64	1.69	0.61	1.95	0.76	0.98	0.54	**<0.001***
DERS: Total	70.62	19.97	109.19	26.49	109.90	24.84	80.92	21.01	**<0.001***
YFAS-2: Total	1.21	2.60	4.63	3.13	8.90	1.92	3.95	3.02	**<0.001***

Abbreviations: AN, anorexia nervosa; DERS, Difficulties in Emotion Regulation Scale; HCs, healthy controls; OB+ED, obesity with eating disorder; OB-ED, obesity without eating disorder; SCL-90-R GSI, Symptom Checklist-90-Revised, global severity index; SD, standard deviation; UPPS-P, Impulsive Behavior Scale; YFAS-2, Yale Food Addiction Scale.
*Bold: Significant comparison (0.05 level).

Table 2. Comparison between groups: ANCOVA adjusted by age

	HC; *n* = 29		AN; *n* = 27		OB+ED; *n* = 20		OB-ED; *n* = 37				
	Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*	*F-stat*	*df*	*p*
2-AG	6.72	4.86	5.35	3.92	5.78	3.00	4.77	2.46	1.59	3/108	0.195
AEA	0.25	0.07	0.22	0.07	0.38	0.09	0.45	0.24	13.08	3/108	**<0.001***

	Pairwise comparisons											
	HC vs. AN		HC vs. OB+ED		HC vs. OB-ED		AN vs. OB+ED		AN vs. OB-ED		OB+ED vs. OB-ED	
	p	|*d*|	*p*	|*d*|	*p*	|*d*|	*p*	|*d*|	*p*	|*d*|	*p*	|*d*|
2-AG	0.224	0.36	0.376	0.23	**0.035***	**0.51**†	0.724	0.12	0.614	0.18	0.328	0.37
AEA	0.632	0.31	**0.002***	**1.68**†	**<0.001***	**1.13**†	**0.002***	**1.99**†	**<0.001***	**1.26**†	0.110	0.37

Abbreviations: 2-AG, 2-arachidonoylglycerol; AEA, anandamide; AN, anorexia nervosa; HCs, healthy controls; OB+ED, obesity with eating disorder; OB-ED, obesity without eating disorder; SD, standard deviation.
*Bold: Significant comparison (0.05 level).
†Bold: Effect size into ranges mild–moderate (|*d*| > 0.50) to high–large (|*d*| > 0.80).

and hedonic brain circuits [40]. Besides, due to the modulation of eCBs on other endocrine processes in peripheral tissues such as the gastrointestinal tract and liver [42, 45, 48], this increase of AEA would also underlie other metabolic disorders, which are highly comorbid in obesity (with and without EDs) (e.g., diabetes mellitus, dyslipidemia, etc.) [10, 38].

On the other hand, only the OB-ED group significantly differs in 2-AG concentrations from the HC group, surprisingly showing lower 2-AG concentrations. Considering this unexpected result, we emphasize the need for experimental research to explore the different factors, physiological pathways, and biofeedback mechanisms that seem to be involved in promoting the eCB system actions [37, 40, 44, 95, 96]. In this line, genetic alterations modifying the enzymatic activity of the eCB system could be involved in a dysfunctional eCBs synthesis [95–98]. For example, fatty acid amide hydrolase (FAAH) gene polymorphisms have been described in obesity [95, 98], an enzyme aimed at eCBs degradation, specially AEA [78, 99]. Other animal and human works have described increased eCBs concentrations linked to a reduced central and peripheral expression of FAAH in obesity [95, 98], being this enzyme even proposed as a potential biomarker of BE [96]. Although our study did not further investigate genetic factors underlying eCBs concentrations, future studies should assess whether specific genetic polymorphisms such as those related to FAAH or more specific enzymes responsible for the metabolism of 2-AG [47] would underlie differences in circulating eCBs.

In the AN group, the lack of differences in 2-AG concentrations when compared with HC were in line with previous studies [52, 57]. Regarding AEA, this group showed significantly lower AEA concentrations compared with the obesity groups, although these differences were not observed between the AN and HC group. Despite this latter finding contrasted with previous works [52, 57], this lack of differences could respond to a compensatory mechanism secondary to a hypoactive eCB system in AN [53–55]. As speculative, this fact could be understood as an intent of the eCB system to promote food intake in AN through the stimulation of the homeostatic pathway [54, 55, 69]. In addition, considering the role of AEA in motivational reward processing [32, 33], a plausible hypothesis addressed by Monteleone [94] would suggest that increased AEA concentrations may also act by reinforcing self-starvation which would allow patients with AN to cope with the sensation of hunger despite prolonged restriction [94]. Whether this hypothesis [94] may help to explain our result, the cross-sectional nature of our study did not allow us to confirm it. However, the association between AEA and BMI in the clinical groups could preliminarily support this rationale.

Noticeably, the SEM analysis showed that higher AEA predicted lower BMI in AN whereas higher BMI in the obesity groups,

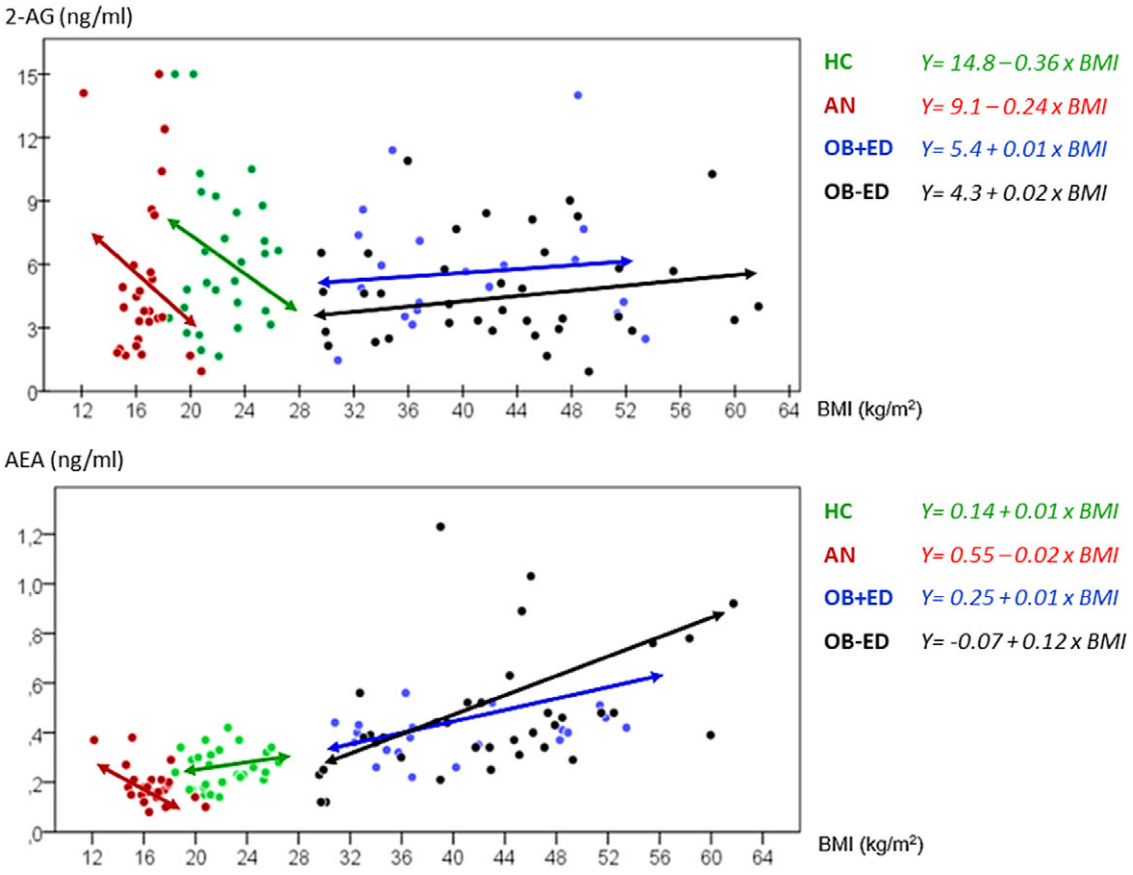

Figure 1. The scatterplot displays regression analysis of the association of circulating 2-arachidonoylglycerol (2-AG) and anandamide (AEA) concentrations with body mass index (BMI). Continuous line: regression line. Green line: regression line in healthy controls. Red line: regression line in anorexia nervosa. Blue line: regression line in obesity with eating disorder. Black line: regression line in obesity without eating disorder. 2-AG, 2-arachidonoylglycerol (ng/ml); AEA, anandamide (ng/ml); BMI, body mass index (kg/m^2); HCs, healthy controls; AN, anorexia nervosa; OB+ED, obesity with eating disorder; OB-ED, obesity without eating disorder.

suggesting that an elevated AEA might be a potential indicator of a more extreme BMI in each clinical condition. Besides, as we expected, AEA and 2-AG showed different links with BMI and psychological variables in the clinical groups. For instance, 2-AG was only related to BMI in the AN group. In this case, similar to a previous study [74], higher 2-AG concentrations were related to greater general psychopathology, which acted as a mediational factor in predicting a lower BMI. This result is interesting because previous studies have pointed to the association of general psychopathology (e.g., anxiety, depressive symptoms, hostility, etc.) with lower BMI and greater severity in AN [100, 101]. Then, our SEM analysis may delineate the existence of a potential endophenotype characterized by the interplay between 2-AG and general psychopathology that would particularly predict BMI in AN, a criterion of severity in this disorder [102].

Interestingly, all clinical groups showed a common pathway related to AEA and some clinical factors. Thus, lower AEA predicted higher emotional dysregulation, which also mediated greater general psychopathology. In addition, a higher emotional dysregulation predicted greater impulsivity. The clinical associations observed in the SEM analysis were in line with previous literature [103–105], as well as the potential association between these psychological variables and BMI in EWC [100, 101, 106]. Moreover, AEA has been linked to emotional processing and impulsivity in other psychiatric disorders [60–67, 107, 108] being, for example, lower AEA concentrations linked to higher emotion dysregulation [65, 68]. In EWC, these results pointed to the possible participation of peripheral eCBs along with psychological processes involved in impulsivity, emotional regulation, and mood that may modulate feeding behavior [103–105]. Besides, higher AEA concentrations predicted higher FA, which is highly prevalent in individuals with obesity [84, 109–113]. Particularly, the association between AEA and FA was also mediated by emotional dysregulation in the OB+ED group and by general psychopathology in the OB-ED group. In individuals with BSD, the co-occurrence of ED and FA has been associated with greater emotional dysregulation and general psychopathology compared with those without FA [109]. In obesity, the presence of FA has been related to depressive symptoms and impulsivity traits [114]. The specific clinical pathways of AEA could imply a differential pattern characterizing individuals with obesity with or without a diagnosis of ED. However, higher FA scores in OB-ED could draw a clinical profile more similar to OB+ED. These findings reinforce the notion that AEA may represent a shared vulnerability factor underlying transdiagnostic psychological features not only among different psychiatric disorders including EDs [115, 116], but also in OB-ED in the context of EWC.

Altogether, the eCB system could be a crucial pharmacological target regarding its involvement in the regulation of food intake and weight management [77, 117–119], as well as in psychopathological processes among individuals with EWC. Consistent with this notion, the eCB system has been proposed as a therapeutic target in EWC to manage the metabolic comorbidities and cardiovascular

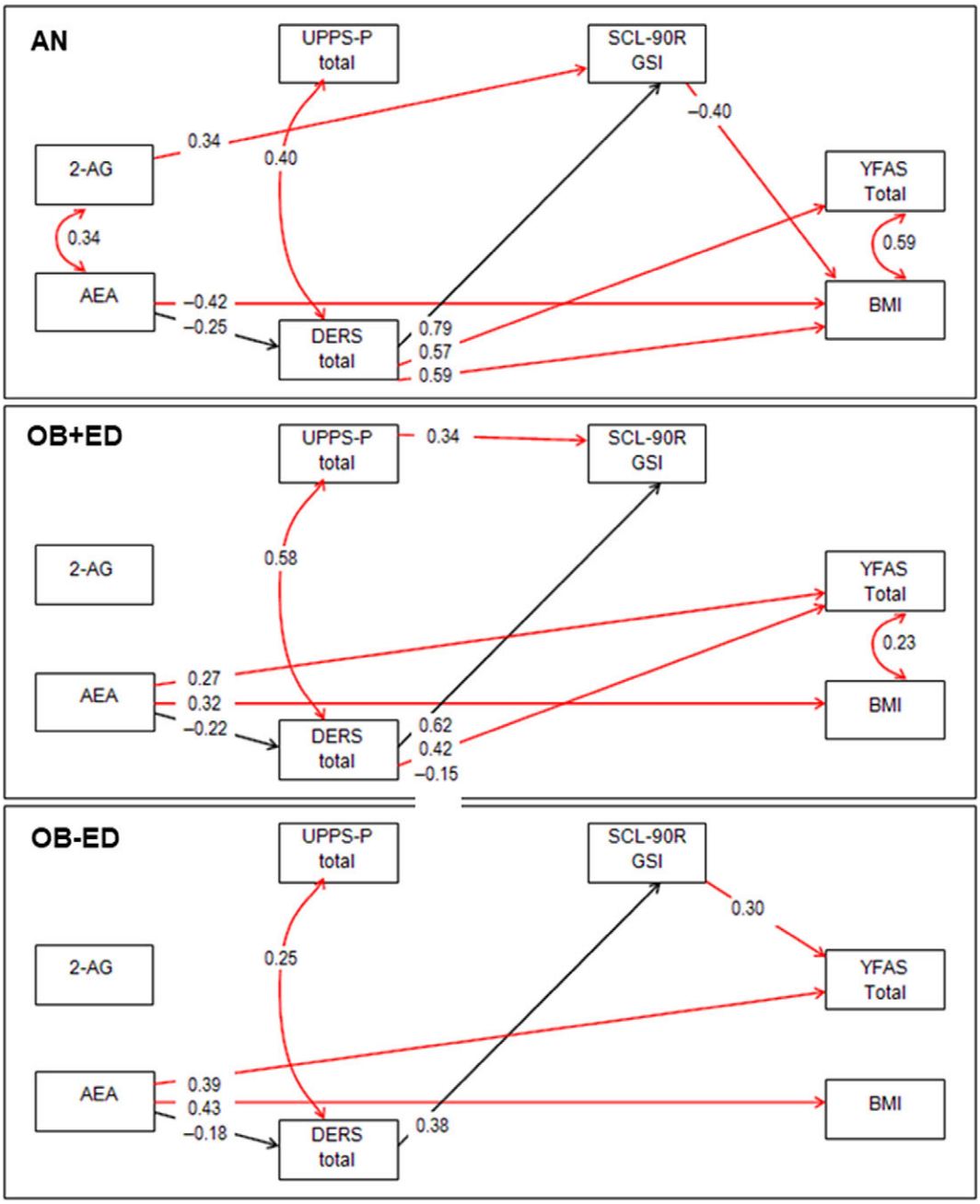

Figure 2. Path diagram: standardized coefficients (results adjusted by age) (in color). Continuous line: significant parameter. Dash line: nonsignificant parameter. Black line: invariant parameter (the coefficient is statistically equal between the diagnostic subtypes). Red line: noninvariant parameter (the coefficient is statistically different between the diagnostic subtypes). 2-AG, 2-arachidonoylglycerol; AEA, anandamide; AN, anorexia nervosa; BMI, body mass index; DERS, Difficulties in Emotion Regulation Scale; OB+ED, obesity with eating disorder; OB-ED, obesity without eating disorder; SCL-90-R GSI, Symptom Checklist-90-Revised, global severity index; UPPS-P, Impulsive Behavior Scale; YFAS-2, Yale Food Addiction Scale.

risk factors linked, for example, to obesity such as dyslipidemia and diabetes mellitus [119, 120]. Likewise, it has been postulated effective drugs to treat endocrine-related diseases, which contemplate interrelations between the eCB system and other endocrine pathways (e.g., thyroid hormones, estrogens, glucose metabolism, etc.), might be potential candidates to essay among EWC [121].

The present study should be considered in light of some limitations, such as a sample consisting of women seeking treatment. Therefore, it does not represent the general population with AN and obesity (with and without ED). Besides, the cross-sectional design did not allow us to infer causality from our results. Moreover, our study did not investigate the effect of purging behaviors (in the OB+ED group), as well as some factors such as sex hormones, medication, or the effect of excessive physical activity (in AN), which would influence the eCB system functioning [122]. Likewise, although the use of cannabis and other illicit drugs was controlled, tobacco use was not an exclusion criterion. In the future, studies should not disregard its effect on eCBs concentrations. Finally, considering the influence of physiological hunger and satiety signals, further research should analyze circulating eCBs in both fasting and postprandial conditions to accurately report the changes in circulating concentrations of 2AG and AEA and

evaluate if there are differences between them. Notwithstanding these limitations, to the best of our knowledge, this is the first study to show the complex interplay between eCBs and psychological variables in EWC. Although several variables could be considered in future studies as confounders, this study did include the use of a previously validated procedure to obtain plasma eCBs concentrations, the presence of a control group, and adjusting for age.

Conclusions

Our results support the notion that AEA and 2-AG have different functional roles in EWC, where AEA predominantly influences BMI and psychological features. In individuals with EDs and obesity, AEA emerges as a possible biological marker of a more extreme BMI and psychopathological profile. In the case of individuals with obesity, although AEA concentrations were similar, the presence or absence of an ED was differentiated by the association of AEA with clinical variables. However, the increase of AEA in OB-ED defined a clinical profile more closely resembling the OB +ED group. Likewise, the interplay between 2-AG and BMI, mediated by general psychopathology, could underlie a more severe profile in individuals with AN. As a result, these findings evidence the implication of eCBs in abnormal eating behavior, weight disturbances, and psychopathological features, which could represent a potential pharmacological target in EWC.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1192/j.eurpsy.2023.2411.

Acknowledgments. We thank CERCA Programme/Generalitat de Catalunya for institutional support. We also thank Instituto de Salud Carlos III (ISCIII), CIBERobn, CIBERSAM and CIBERDEM are initiatives of ISCIII), FEDER funds/European Regional Development Fund (ERDF), a way to build Europe, and the European Social Fund. ESF investing in your future.

Financial support. We thank CERCA Programme / Generalitat de Cataluny a for institutional support. This manuscript and research were supported by grants from the Delegación del Gobierno para el Plan Nacional sobre Drogas (2021I031), Ministerio de Ciencia e Innovación (PDI2021-124887OB-I00), Instituto de Salud Carlos III (ISCIII) (FIS PI20/00132) and cofounded by FEDER funds/European Regional Development Fund (ERDF), a way to build Europe. CIBER Obn, CIBERSAM, and CIBERDEM are initiatives of ISCIII. Additional funding was received by AGAUR- Generalitat de Catalunya (2021-SGR-00824 and 2021 SGR 00253) and European Union's Horizon 2020 research and innovation program under Grant agreement no. 728018 (H2020-SFS-2016-2, Eat2beNice), no. 847879 (PRIME/H2020, Prevention and Remediation of Insulin Multi morbidity in Europe) and no. 101080219 (eprObes). This study has also been funded by Instituto de Salud Carlos III through the grant CM21/00172 (IB) (Co-funded by European Social Fund. ESF investing in your future). RG is supported by the Catalan Institution for Research and Advanced Studies (ICREA-Academia, 2021-Programme). The funders had no role in the study design, data collection, analysis, decision to publish, or preparation of the manuscript.

Competing interest. F.F.-A. and S.J.-M. received consultancy honoraria from Novo Nordisk and Fernando Fernández-Aranda editorial honoraria as EIC from Wiley. The remaining authors declared no competing interests.

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4.4. STUDY 4

CLINICAL FACTORS PREDICTING IMPAIRED EXECUTIVE FUNCTIONS IN EATING DISORDERS: THE ROLE OF ILLNESS DURATION

Miranda-Olivos R, Testa G, Lucas I, Sánchez I, Sánchez-González J, Granero R, Jiménez-Murcia S, Fernández-Aranda F. Clinical factors predicting impaired executive functions in eating disorders: The role of illness duration. **J Psychiatr Res**. 2021 Dec;144:87-95. doi: 10.1016/j.jpsychires.2021.09.042.

Journal of Psychiatric Research 144 (2021) 87–95

Contents lists available at ScienceDirect

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Clinical factors predicting impaired executive functions in eating disorders: The role of illness duration

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ARTICLE INFO

Keywords:
Executive function
Eating disorder
Decision-making
Cognitive flexibility
Inhibitory control
Illness duration

ABSTRACT

Poor performance in executive functions is observed in individuals with eating disorders (EDs). These impairments have usually been associated with the presence of comorbid psychopathology or with higher severity of EDs. However, few studies have explored the interaction between illness duration and deficits in executive functions. The present study investigates the association between ED duration and performance in decision-making, inhibitory control, and cognitive flexibility in the anorexia nervosa restrictive subtype (AN-R), bulimic/purging subtype (AN-BP), and binge spectrum disorders (BSDs) (namely, bulimia nervosa and binge eating disorder) among 116 women with EDs compared with 123 women healthy controls (HCs). Using cumulative survival analysis, we estimated the risk of deficits related to illness duration. Predictors of executive dysfunctions were assessed by regression analysis, including as potential predictors illness duration, severity of general psychopathology, and ED symptomatology. Results showed poor decision-making and cognitive flexibility in participants with EDs compared with HCs. ED duration was associated with poor inhibitory control in the AN-BP group and poor cognitive flexibility in the BSD group. The illness duration increased the risk of presenting early deficits in executive function. In decision-making and inhibitory control, the AN-R group showed the earliest deficits, whereas in cognitive flexibility it was the BSD group. ED duration predicted impaired cognitive flexibility in the BSD group and impaired inhibitory control in the AN-BP group, whereas the severity of general psychopathological symptoms was a predictor of impaired cognitive flexibility in individuals with AN-R. These results highlight the relevance of illness duration in executive dysfunctions in EDs.

1. Introduction

Executive functions are a set of mental processes that facilitate controlling and adapting goal-directed behaviors to internal states and environmental context (Diamond, 2013). They consist of several subdomains that include decision-making, set-shifting, planning, working memory, cognitive function, and inhibition, as well as other cognitive domains important for the functioning of human behavior. For this reason, executive dysfunctions can involve difficulties at the cognitive, behavioral, and emotional levels, exerting substantive problems on individuals' everyday life activities (Rabinovici et al., 2015).

In the case of eating disorders (EDs), previous studies have reported dysfunctions in different executive processes, such as cognitive flexibility (Wu et al., 2014), decision-making (Guillaume et al., 2015), and inhibitory control (Bartholdy et al., 2016), suggesting that executive dysfunctions play a key role in problems related to maladaptive eating behaviors. Consistent with this hypothesis, a recent study detected that poor cognitive functioning in childhood was also associated with the risk of developing EDs in adolescence (Schaumberg et al., 2020). Likewise, a recent review suggested that impaired cognitive functions can

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https://doi.org/10.1016/j.jpsychires.2021.09.042
Received 21 April 2021; Received in revised form 8 September 2021; Accepted 22 September 2021
Available online 27 September 2021

contribute to the etiology and maintenance of the disorder (Smith et al., 2018). However, to date, it remains unclear whether executive dysfunctions are a vulnerability factor for ED symptoms or whether ED symptoms are influencing executive deficits (Hirst et al., 2017).

Cognitive flexibility, understood as the ability to shift thoughts or actions according to situational demands, is frequently impaired in EDs (Tchanturia et al., 2012; Wu et al., 2014). In individuals with anorexia nervosa restrictive subtype (AN-R), it is observed a lack of cognitive flexibility associated with rigid behaviors and habits, contributing to increased severity of ED symptomatology, such as intake restriction (Abbate-Daga et al., 2014; Roberts et al., 2010). But on the other hand, a recent review has recently been described that the recovery of normal weight in these individuals can improve cognitive flexibility in children and adolescents with AN (Hemmingsen et al., 2020). In the case of individuals within the bulimic-binge spectrum of eating disorders (BSDs) — namely, bulimia nervosa (BN) and binge eating disorder (BED) — poor cognitive flexibility is frequently linked to the inability to cut off compulsive overeating (Wu et al., 2014).

Similarly, deficits in decision-making have been widely described in individuals with EDs (Guillaume et al., 2015). Decision-making involves several processes that require the evaluation and selection of stimuli to execute a planned behavior based on preferences formation (Ernst and Paulus, 2005). Interestingly, studies in AN-R have described how poor decision-making is positively associated with an acute phase of the disorder (Lindner et al., 2012; Tchanturia et al., 2007) that improves when there is remission of ED symptomatology in these individuals, displaying similar performance to healthy controls (Lindner et al., 2012; Steward et al., 2016; Tchanturia et al., 2007). Accordingly, Guillaume and collaborators (2015) suggested that these observed deficits in decision-making can be a state rather than a trait impairment in AN and BN. In the case of individuals with BED, it has been observed a predisposition to make decisions that provide immediate but negative results, disregarding options that provide long-term benefits (Steward et al., 2019). Deficits in decision-making in BED are also associated with problems in attentional skills and low adaptability to change according to the context (Aloi et al., 2015).

Regarding inhibitory control, understood as the ability to suppress or interrupt behavioral or cognitive responses (Bari and Robbins, 2013), several studies have described an altered performance in each ED subtype (Howard et al., 2020; Smith et al., 2018; Wierenga et al., 2014). In the case of AN-R, an exacerbated inhibitory control over intake can lead to dietary restraint despite negative health consequences (Howard et al., 2020; Wierenga et al., 2014), whereas in individuals within the BSD, inhibitory control deficits are associated with impulsivity and emotional regulation difficulties that can lead to binge episodes (Kittel et al., 2015).

In the same way that executive functions interact with ED symptomatology, some studies point out a reciprocal association between executive function deficits and the presence of comorbid symptomatology with other psychiatric disorders (Billingsley-Marshall et al., 2013; Matsumoto et al., 2015). For instance, it has been observed that anxiety and depressive symptoms can predict poor performance on executive functions in AN-R, anorexia binge/purging (AN-BP), specified feeding or eating disorder (OSFED) (Billingsley-Marshall et al., 2013), and BN (Matsumoto et al., 2015). The presence of comorbid psychopathology has been associated with a worse prognosis of EDs, hampering recovery and a good treatment outcome (Forrest et al., 2018) thereby extending illness duration (Ambwani et al., 2020; Fernández-Aranda et al., 2021; Flynn et al., 2020).

Overall, illness duration in psychiatric disorders has been associated with poor cognitive performance (Galimberti et al., 2020). In EDs, the role of illness duration has been widely studied because it is closely connected with nonresponders to treatment and therefore, with chronicity (Fernández-Aranda et al., 2021). Although this finding is inconsistent with other studies that found no relationship between ED duration and treatment outcome (Radunz et al., 2020). Results in this area are still unclear, reinforcing the need to explore the impact of ED duration on treatment outcome. Concerning cognition, a longer ED duration could be expected to have an adverse effect on executive functions, according to previous evidence (Galimberti et al., 2020). However, the literature on the impact of disease duration on executive function is contradictory and requires further research. For instance, a study in individuals with AN and BN observed how longer illness duration and severity in ED symptomatology were associated with executive dysfunctions (Grau et al., 2019; Roberts et al., 2010) whereas other studies did not find significant associations (Cavedini et al., 2004; Galimberti et al., 2012).

In light of the above, there is a lack of studies addressing how ED duration affects each ED subtype differently. Given the impact of illness duration on individuals with eating disorders (Fernández-Aranda et al., 2021), and the role of executive functions on the treatment outcome (Billingsley-Marshall et al., 2013; Juarascio et al., 2015), the present study investigates performance in executive functions within three main cognitive domains: cognitive flexibility, decision-making, and inhibitory control in women with AN-R, AN-BP, and BSD (i.e., BED, BN), compared to a healthy control group. To explore the impact of illness duration on executive dysfunction in each ED subtype, we explored whether illness duration was associated with decision-making, cognitive flexibility, and inhibitory control performance within each ED subtype. Furthermore, we sought to identify the point estimate throughout the EDs where there is an associated risk for executive dysfunction. Finally, to explore the potential factors contributing to executive dysfunctions, we also assessed the predictive role of ED duration, ED symptomatology, and general psychopathology in observed deficits within these executive subdomains for each ED subtype.

Based on prior literature, we would expect poorer executive function performance across all ED subtypes compared to healthy controls. Regarding illness duration, we hypothesized a negative association between illness duration and executive function performance among ED subtypes. Finally, we postulated that longer ED duration, higher ED symptomatology, and more severe general psychopathology would distinctively predict executive dysfunctions in each ED subtype.

2. Methods

2.1. Participants

The present study recruited 239 female participants. A total of 116 individuals had a diagnosis of ED and 123 belonged to the healthy control (HC) group. The ED groups were classified according to three ED subtypes: AN-R (n = 59), AN-BP (n = 27), and BSD (n = 30) based on the DSM-5 diagnostic criteria (APA, 2013). The current diagnosis of ED was considered irrespective of whether patients had another ED subtype during their lifetime. All participants of the ED groups were previously admitted to the EDs Unit of the Bellvitge University Hospital (Barcelona, Spain). Patients were asked to voluntarily participate in the study and were assessed by experienced clinicians using a semi-structured interview based on the SCID-5 (First et al., 2015). During the clinical interview, individuals with EDs reported onset and duration of problematic eating. It should be noted that this study did not generate the illness duration as the difference between age and onset, but rather both onset and duration were self-reported.

Neuropsychological and clinical assessments were conducted in the first week of treatment. Women in the control group were recruited from the same hospital catchment area. The exclusion criteria applied in this study were as follows: (1) being male; (2) individuals with a history of chronic medical illness or neurological condition that might affect cognitive function; (3) individuals with head trauma with a loss of consciousness for more than 2 min, learning disability or intellectual disability; and (4) individuals age under 18 or over 60 years of age.

Written informed consent was obtained from all participants before they took part in the study. The study procedures were carried out in

accordance with the Declaration of Helsinki as revised in 1989, and the Clinical Research Ethics Committee of Bellvitge University Hospital (PR146/14) approved the study.

2.2. Procedures

Participants underwent two separate sessions: the first session consisted of a psychological assessment, and the subsequent session consisted of an executive function assessment.

2.2.1. Psychological assessment

Temperament and Character Inventory-Revised (TCI-R). This 240-item questionnaire is a self-report instrument that assesses temperament and character traits on a 5-point Likert scale (Cloninger et al., 1993). Temperamental dimensions are novelty-seeking, harm avoidance, reward dependence, and persistence, whereas character dimensions are self-directedness, cooperativeness, and self-transcendence. The current study used the validated Spanish version of the questionnaire, which demonstrated a Cronbach's alpha of 0.87 (Gutiérrez-Zotes et al., 2004).

Symptom Checklist-Revised (SCL-90-R). This 90-item questionnaire is a self-report instrument that measures perceived psychopathological symptoms on a 5-point Likert scale (Derogatis and Savitz, 1999). Items are subdivided into nine dimensions: somatization, obsessive-compulsive, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, and psychoticism. These dimensions enable the determination of the Global Severity Index (GSI). The current study used the validated Spanish version of the questionnaire, which has demonstrated a Cronbach's alpha of 0.75 (Derogatis, 2002).

Eating Disorders Inventory-2 (EDI-2). ED symptomatology was assessed via a validated Spanish version of the Eating Disorders Inventory-2 (Garner, 1991). The EDI-2 is a self-report instrument to screen symptomatology related to eating disorders on a six-point Likert scale. The EDI-2 consists of 91 items and provides scores on 11 subscales: drive for thinness, body dissatisfaction, bulimia, ineffectiveness, perfectionism, interpersonal distrust, interoceptive awareness, maturity fears, asceticism, impulse regulation, and social insecurity. The sum of all subscales provides an eating disorder measure, which is considered a global scale of ED severity. The EDI-2 has been validated in the Spanish population, showing a Cronbach's alpha of 0.63 (Garner, 1998).

2.2.2. Executive function assessment

Executive function performance was evaluated considering three subdomains: cognitive flexibility, inhibitory control, and decision-making. Deficits in executive functions were established when individuals' scored below the 16th percentile based on normative values regarding age and education according to previous studies examining cognitive performance (Reitan, 2004; Tanner-Eggen et al., 2015).

Wisconsin Card Sorting Test (WCST) (Heaton and Staff, 1990). Cognitive flexibility was evaluated using the computerized WCST (version 4). The WCST consists of matching stimulus cards within one of three available categories: color, shape, or number. For a correct match, participants must identify the sorting rule, receiving the feedback of "Right" or "Wrong" after each sort. Following 10 consecutive correct matches, the rule is changed and then a new sorting rule must be identified. There are up to six attempts to detect the sorting rule and five rule shifts during the task. Each rule attainment is referred to as "category completed". Participants do not know the correct rules or changes. The test continues until 128 cards are sorted. Two types of errors exist: perseverative errors (i.e., the number of errors when continuously responding to an incorrect rule) and nonperseverative errors (i.e., the number of errors when changing a rule). Both are summarized in terms of total errors as an index of cognitive flexibility.

IOWA Gambling Task (IGT) (Bechara et al., 1997). Decision-making was assessed using a computerized version of the IGT. This task consists of selecting 100 cards distributed in four decks (A, B, C, and D). Participants have five blocks (20 cards in each trial). There are two advantageous decks (C and D) providing overall gains, whereas the disadvantageous decks (A and B) provide overall losses. Participants are instructed to choose cards to obtain as much money as possible with minimal losses. Higher scores involve advantageous decks (better performance), whereas lower scores involve a persistent choice of disadvantageous decks (poor performance). Scores from five blocks facilitate obtaining a learning curve and total IGT score, which are the sum of the five blocks.

Stroop Color-Word Test (SCWT) (Golden, 1978). Cognitive inhibitory control was evaluated using the SCWT. This paper-and-pencil test is composed of three different trials. In the first trial, participants read the color names displayed on a page. Next, participants must indicate the color in which an "X" is printed. Finally, there is a trial involving the names of colors printed in an incongruent color (e.g., the word "blue" printed in red). Participants must complete each trial in 45 s. Collectively, these results enable the determination of the "interference score", where a high interference score indicates good cognitive inhibitory control.

2.3. Statistical analysis

Statistical analysis was carried out with Stata16 for Windows (StataCorp, 2019). First, comparisons between the groups were based on chi-square tests for categorical measures and the analysis of variance (ANOVA) for quantitative variables.

Second, Cox regression analysis estimated the survival function between the duration of the ED in years and the presence of a deficit in the cognitive measures of the study. This methodology is a statistical procedure commonly used to explore changes over time for a specific event with censored data. Third, separate survival functions were used to assess the relationship between the EDs and the risk of presenting impaired cognitive functioning, as well as the potential moderator/interaction role in each ED subtype.

Finally, stepwise logistic regressions explored the main contributors to the presence of impaired performance in decision-making, cognitive flexibility, and inhibitory control. These models implemented the duration of eating-related symptoms, ED severity (EDI-2 total), and global psychopathological distress (SCL-90R GSI) as potential predictive variables. Impaired performance was identified when participants scored below the 16th percentile (Reitan, 2004; Tanner-Eggen et al., 2015) according to the normative data published in the manuals of each test. Concretely, scores below the 16th percentile in the IGT total score were considered to indicate impaired decision-making, and scores below the 16th percentile in perseverative errors, nonperseverative errors, and numbers of categories completed were considered to indicate impaired cognitive flexibility. Likewise, impaired inhibitory control was assigned to participants scoring below the 16th percentile on the Stroop interference scale. Goodness-of-fit was valued with Hosmer-Lemeshow test ($p > 0.5$ was considered for adequate fitting) and the global prediction capacity with the Nagelkerke's pseudo-R^2 coefficient.

Analyses involving executive functions were adjusted for age and education levels, and the BMI as confounding variables. The effect size for the mean differences in the ANOVA was estimated with Cohen's d coefficient (poor effect size was considered for $|d|>0.20$, mild-moderate for $|d|>0.50$, and high-large for $|d|>0.80$) (Cohen, 1988; Granero et al., 2020; Kelley and Preacher, 2012). For the correlation estimates, the effect size was considered mild-moderate for $|R|>0.24$ and high-large for $|R|>0.37$ (these thresholds correspond to Cohen's $d = 0.50$ and $d = 0.80$, respectively) (Rosnow and Rosenthal, 1996). Finally, Finner correction was also used to control for Type-I error due to multiple statistical comparisons (Finner and Roters, 2001). This correction carries out by adjusting the rejection criteria for each hypothesis fixing the familywise error rate no higher than a certain prespecified significance level. The procedure starts sorting into order lowest-to-highest the p(unadjusted)-values p1, …, pk obtained in

k-independent null-hypothesis tests and then applying the next algorithm: p(adjusted) = (1 – (1-p(non-adjusted)) ^ (total tests/position within the ordered tests). This study applied the Finner method separately for each Table/procedure.

3. Results

3.1. Description of the sample

Table 1 describes the clinical groups (AN-BP, AN-R, BSD) and the healthy controls, including age, body mass index (BMI), age at the onset of ED, and the duration of the ED (in years). Both onset and duration were directly reported by individuals with EDs. Significant differences between groups were found in age, the duration of the ED, and BMI. The age of onset of the disorder did not differ between ED subtypes.

The first block of Table 2 shows the clinical measures and neurocognitive performance, including the frequency distribution of the former: the severity of the ED symptoms (EDI-2 total) and global psychopathological distress (SCL-90R GSI). Differences between the groups appeared, except for the comparison between BSD and AN-BP.

3.2. Differences between ED subtypes and healthy controls in executive function performance

The second block of Table 2 contains the comparison between groups (adjusted by the covariates age and education, and BMI) for the mean scores obtained in each executive function. All clinical groups showed poor decision-making scores compared to controls; lower cognitive flexibility was detected for individuals with AN-BP and BSD than for controls. The AN-R group obtained better performance in decision-making and cognitive flexibility than the AN-BP and BSD groups. No differences were found between the BSD and AN-BP groups. Finally, as to inhibitory control, no differences were observed between any of the ED groups and HCs or between clinical groups.

Fig. 1 includes the neurocognitive profile of executive subdomains in the study: the first line graph represents the prevalence of participants within the deficit condition, and the second line graph represents the z-standardized means (standardized values within the sample).

Likewise, deficits in executive functions were mainly represented by the BSD group. Considering the cutoff point for identifying impaired performance (i.e., scores below the 16th percentile), 66% of individuals with BDS exhibited deficits in decision-making, whereas 48.1% and 40.7% of individuals in the AN-BP and AN-R groups, respectively, exhibited deficits in decision-making. Deficits in cognitive flexibility were observed in 33% of the BSD and AN-BP groups and 18.6% in the AN-R group. The smallest deficit gaps were observed in inhibitory control. In the BSD group, 33% of participants demonstrated deficits in inhibitory control, whereas 22% and 18.6% of participants in the AN-BP and AN-R groups, respectively, demonstrated deficits in inhibitory control. There was a lower proportion of individuals with deficits in the control group than in the clinical groups (Fig. 1).

3.3. Associations between ED duration and executive function performance among ED subtypes

Table 3 includes the correlation matrix between ED duration and performance on the executive functions (partial correlations adjusted by age and education, and BMI were calculated). For the AN-BP group, ED duration was negatively correlated with Stroop interference. For the BSD group, ED duration was negatively correlated with the WCST number of categories completed. Also, ED duration was positively correlated with the number of WCST errors and perseverant errors, in this group.

3.4. Association between ED duration and the risk of deficits in executive function

The risk associated with executive impairment is represented in Fig. 2, which contains the survival functions (adjusted by age and education level, and BMI) obtained for each executive domain: the ED duration is plotted on the X-axis and the cumulative proportion of participants "surviving" without the presence of impaired executive function is plotted on the Y-axis (functional deficits were assigned to individuals with performance scores below the 16th percentile based on normative data). Each graphic includes a horizontal dashed line drawn on the value 0.75 for the Y-axis (representing the probability of *surviving* without cognitive deficit, corresponding to the 75th percentile) and three vertical dashed lines for the cutoff of the 75th percentile, with the cumulate curves estimated for each diagnostic subtype. Dashed lines within each plot identify the duration of the disorder associated with a high risk of impaired cognitive performance (at least 25% of risk).

Therefore, an ED duration of 3 years among AN-R demonstrated at least a 25% risk of deficits in decision-making (that is, at least 25% of AN-R experienced impaired decision-making after an ED duration of 3 years). For BSD, ED duration of 7 years was associated with at least a 25% probability of reporting impaired decision-making while, for AN-BP, ED duration of 8 years was associated with a 25% or higher risk of impaired decision-making. As to cognitive flexibility, BSD duration of 8 years, AN-R duration of 9 years, and AN-BP duration of 11 years were the thresholds for a 25% or more risk of achieving impaired levels. For the inhibitory control domain, the risk of impaired performance was 25% or greater after a duration of 5 years for AN-R, 12 years for AN-BP, and 15 years for BSD.

3.5. Predictors of deficits in executive functions

The results of the logistic regressions exploring whether ED duration, among other clinical indexes, was a predictor of executive dysfunctions among ED subtypes are included in Table 4. For the AN-R group, psychopathological distress was associated with a higher likelihood of deficits in cognitive flexibility. For the AN-BP group, a higher likelihood of deficits in inhibitory control was related to longer ED duration. Finally, in the BSD group, increased odds of impaired flexibility were also related to longer ED duration.

Table 1
Descriptive of the sample.

	Control *(N = 123)*		AN-R *(N = 59)*		AN-BP *(N = 27)*		BSD *(N = 30)*		
	Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*	*p*
Chronological age (years-old)	26.21	7.91	26.36	8.50	28.67	8.91	35.63	10.28	**<.001***
Onset of disorder (years-old)	–	–	20.88	8.14	21.00	8.06	23.17	9.86	.469
Duration of disorder (years)	–	–	5.22	6.07	8.41	4.89	9.98	7.80	**.003***
Body mass index (BMI,kg/m^2)	21.66	2.68	16.10	1.50	16.74	1.95	30.80	9.17	**<.001***
Frequency of binges/week	–	–	–	–	2.30	3.24	6.40	4.48	**<.001***
Frequency of vomits/week	–	–	–	–	5.74	5.55	3.53	5.08	.123

Note. AN-R: anorexia nervosa restrictive. AN-BP: anorexia nervosa bulimic purgative. BSD: binge spectrum disorder.
SD: standard deviation. *Bold: significant comparison (0.05 level). — Not applicable.

Table 2
Comparison for clinical measures and neurocognitive performance.

	Control		AN-R		AN-BP		BSD		Factor group		AN-R vs Control		AN-BP vs Control		BSD vs Control		AN-BP vs AN-R		BSD vs AN-R		BSD vs AN-BP	
	N = 123		*N = 59*		*N = 27*		*N = 30*															
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	*p*	*power*	*p*	|*d*|	*p*	|*d*|	*p*	|*d*|	*p*	|*d*|	*p*	|*d*|	*p*	|*d*|
Clinical measures																						
EDI-2 Total score	26.4	20.8	63.5	38.9	101.2	38.4	112.3	43.3	**.001***	1.00	**.001***	**1.19**†	**.001***	**2.42**†	**.001***	**2.53**†	**.001***	**0.98**†	**.001***	**1.18**†	.188	0.27
SCL-90R GSI	0.58	0.42	1.30	0.72	1.88	0.62	1.86	0.83	**.001***	1.00	**.001***	**1.21**†	**.001***	**2.45**†	**.001***	**1.94**†	**.001***	**0.87**†	**.001***	**0.72**†	.890	0.03
[a]**Executive functions**																						
Decision making																						
IGT Trail-1	−1.54	7.16	−3.05	4.36	−2.35	4.81	−1.98	3.87	.585	.185	.184	0.26	.561	0.13	.774	0.08	.619	0.15	.595	0.26	.862	0.09
IGT Trail-2	3.19	8.22	−1.25	4.59	−1.85	4.34	−1.55	6.27	**.001***	.994	**.001***	**0.67**†	**.001***	**0.77**†	**.006***	**0.65**†	.701	0.13	.892	0.05	.901	0.05
IGT Trail-3	5.45	8.43	1.18	5.35	−1.73	5.32	−1.32	4.26	**.001***	1.000	**.001***	**0.60**†	**.001***	**1.02**†	**.001***	**1.01**†	.072	**0.55**†	.281	**0.52**†	.868	0.08
IGT Trail-4	5.60	9.68	2.59	7.39	−1.78	5.36	−0.52	7.12	**.001***	.988	.058	0.35	**.001***	**0.94**†	**.005***	**0.72**†	**.026***	**0.68**†	.268	0.43	.671	0.20
IGT Trail-5	4.24	10.48	3.17	8.94	−3.36	6.57	−1.59	6.16	**.001***	.969	.538	0.11	**.001***	**0.87**†	**.015***	**0.68**†	**.003***	**0.83**†	.124	**0.62**†	.589	0.28
IGT Total	16.95	29.82	2.64	21.96	−11.08	17.48	−6.97	17.41	**.001***	1.000	**.003***	**0.55**†	**.001***	**1.15**†	**.001***	**0.98**†	**.019***	**0.69**†	.250	**0.51**†	.643	0.24
Cognitive flexibility																						
WCST Total errors	19.07	15.90	18.98	18.73	33.43	32.52	28.78	26.25	**.002***	.914	.983	0.00	**.002***	**0.56**†	.060	0.45	**.002***	**0.54**†	.141	0.43	.510	0.16
WCST Persever.errors	9.98	7.17	8.33	8.61	14.49	19.59	17.67	16.38	**.004**	.885	.410	0.21	.070	0.31	**.005***	**0.61**†	**.013***	0.41	**.009***	**0.71**†	.399	0.18
WCST Categ.compl.	5.58	1.24	5.57	1.38	4.55	2.41	4.92	2.10	**.007**	.850	.996	0.00	**.005***	**0.54**†	.103	0.38	**.004***	**0.52**†	.207	0.37	.488	0.17
Inhibitory control																						
STROOP Interference	6.25	9.23	5.52	8.02	5.16	9.94	6.77	9.02	.944	.073	.658	0.08	.592	0.11	.821	0.06	.858	0.04	.670	0.15	.604	0.17

Note. SD: standard deviation. AN-R: anorexia nervosa restrictive. AN-BP: anorexia nervosa bulimic purgative. BSD: binge spectrum disorder.
IGT: Iowa Gambling Test. WCST: Wisconsin Card Scoring Test. [a] Comparison between the groups (ANCOVA, adjusted by age, education and BMI).
*Bold: significant comparison (0.05 level). †Bold: effect size into ranges mild-moderate (|d|>0.50) to high-large (|d|>0.80).

4. Discussion

The present study initially set out to examine cognitive flexibility, inhibitory control, and decision-making across individuals with ED subtypes (i.e., AN-R, AN-BP, and BSD) compared to controls. In addition, the study explored the association between executive dysfunctions and ED duration. We found that ED subtypes showed poorer decision-making and cognitive flexibility than the HC group, whereas we observed similar executive functioning performance between the AN-BP and BSD groups. Concerning ED duration, our results showed that ED duration was specifically associated with poor inhibitory control in individuals with AN-BP and poor cognitive flexibility in the BSD group (i.e., BN and BED). By contrast, in the AN-R group, we were not able to find a significant association. Cumulative survival analysis found that illness duration increased the risk of presenting early deficits in decision-making and inhibitory control in the AN-R group, whereas the BSD group was the first to exhibit deficits in cognitive flexibility. Likewise, ED duration predicted the executive impairment in the BSD and AN-BP groups, whereas the severity of general psychopathological symptoms predicted executive impairment in the AN-R group.

The comparative analysis of the performance in executive functioning showed, as expected, poorer performance in the ED groups than in the HC group in terms of cognitive flexibility and decision-making, in accordance with previous studies (Aloi et al., 2015; Guillaume et al., 2010; Tamiya et al., 2018). However, no significant differences were reported in inhibitory control. There were pronounced deficits in decision-making in the BSD and AN-BP groups compared to the AN-R and HC groups according to previous literature (Guillaume et al., 2015; Hirst et al., 2017), whereas the AN-R group showed poor decision-making compared to the HC group. The IGT evaluates risky decision-making based on monetary gain or losses, where participants must decide between four decks that offer an immediate reward, aiming to obtain as much money as possible. Individuals with BSD tend to prefer risky immediate rewards over future and safe gains, disregarding long-term outcomes (Steward et al., 2017). These individuals reported greater risk-seeking and inflexible choices irrespective of changes in context, as reflected in binge episodes (Voon, 2015). Performance in cognitive flexibility was remarkably dysfunctional in the AN-BP and the BSD groups, displaying increased total errors and perseverative errors. Although cognitive rigidity has been often associated with AN-R, most of the studies did not clearly distinguish between the subtypes of AN (Roberts et al., 2010; Wu et al., 2014). In the case of inhibitory control, previous studies have focused on adopting tasks using disorder-relevant stimuli (e.g., food or weight-/shape-related), proposing that problems in inhibition are more related to food stimuli than unrelated stimuli (Bartholdy et al., 2016; Wu et al., 2013). Therefore, the lack of significant differences between groups in our study could be due to the stimuli used in the Stroop task. Overall, it is remarkable that the AN-BP group shared more similarities with the BSD group, as reported previously (Mandelli et al., 2019; Reichenberger et al., 2021). Both groups presented a severe clinical profile in comparison to the AN-R group.

ED duration was associated with executive function performance in the AN-BP and BSD groups. Our results showed a negative association between the duration of BSD and cognitive flexibility. Binge eating episodes, characterized by frequent excessive food intake and a sense of a loss of control (APA, 2013), can underlie a behavioral inflexibility in these individuals reflected in an inability to change their response despite the context. Likewise, illness duration in the AN-BP group displayed a negative association with inhibitory control. The AN-BP group has been consistently differentiated from the AN-R group difficulties in control over intake, increasing complications to regulate a normal weight, and becoming gradually worse as EDs progress (Berkowitz et al., 2016; Lantz et al., 2017), in addition to higher impulsivity and emotional dysregulation (Culbert et al., 2016; Mallorquí- Bagu é et al., 2020; Vervaet et al., 2021). This might also explain why individuals with AN-BP, over the years, are at risk of conversion to BN (Monteleone et al.,

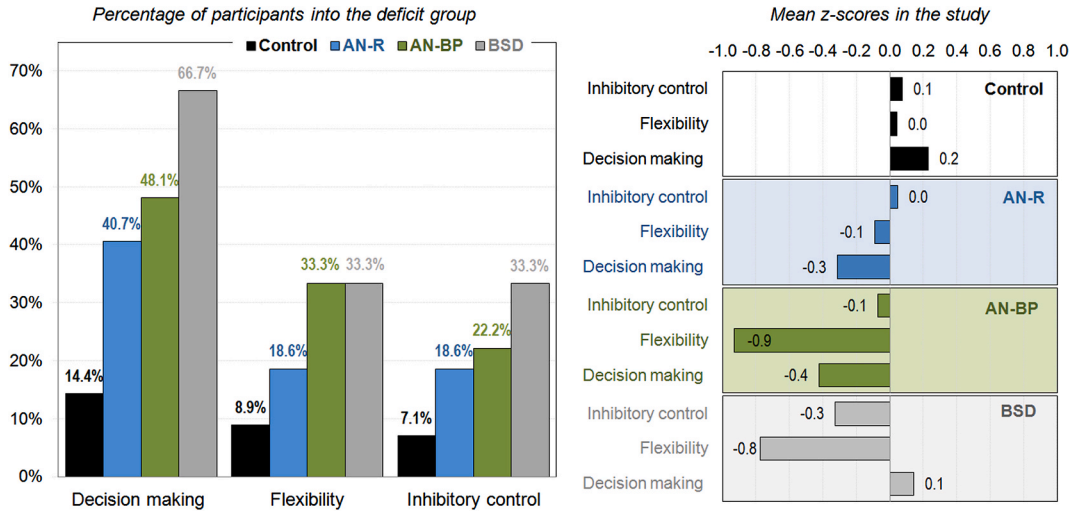

Fig. 1. Neurocognitive profile on executive function sub-domains in the study. *Note.* AN-R: anorexia nervosa restrictive. AN-BP: anorexia nervosa bulimic purgative. BSD: binge spectrum disorder.

Table 3
Association between the eating disorder duration and performance in executive function: partial correlations adjusted by age, education, and BMI.

	Total ED *N = 116*	AN-R *N = 59*	AN-BP *N = 27*	BSD *N = 30*
Decision making				
IGT Total	.001	.217	-.143	.008
Flexibility				
WCST Total errors	.092	-.048	-.052	**.275**[a]
WCST Perseverative errors	.118	-.079	-.051	**.333**[a]
WCST Categories completed	-.095	.086	-.021	**-.270**[a]
Inhibitory control				
STROOP Interference	-.113	-.120	**-.274**[†]	-.084

Note. IGT: Iowa Gambling Test. WCST: Wisconsin Card Scoring Test.
ED: eating disorder. AN-R: anorexia nervosa restrictive. AN-BP: anorexia nervosa bulimic purgative. BSD: binge spectrum disorder.
[a] Bold: effect size into ranges mild-moderate ($|R|>0.24$) to high-large ($|R|>0.37$).

2011). In this context, when further investigating the role of illness duration as a risk factor for executive dysfunctions, we modeled the time needed for 25% of individuals with ED to present deficits within each executive subdomain to identify a time point for a risk linked to illness duration. Using a cumulative survival model, our results showed that throughout the disorder there was an early risk of presenting deficits in decision-making as compared to other subdomains. Early risk of cognitive impairment was mainly observed in the AN-R and BSD groups in contrast to the AN-BP group. As the disorder progresses, our results show an increased risk of early cognitive impairment in decision-making in the AN-R group (up to 3 years of duration), followed by the BSD group (up to 7 years of duration) and the AN-R group (up to 8 years of duration). Concerning impaired cognitive flexibility, the BSD group showed an increased likelihood of early risk, closely followed by the AN-BP and AN-R groups. In inhibitory control, the AN-R group showed the earliest deficits (up to 5 years of duration) while in the AN-BP and BSD the time required to present deficits was 12 and 15 years, respectively. These results confirm an interaction between illness duration and cognitive functions (Galimberti et al., 2020) providing evidence on how executive dysfunctions are associated with a specific time point of duration for each ED subtype. Further studies focused on risk and maintenance models related to executive functions are required to confirm these findings.

ED duration had a consistently predictive role on executive dysfunction in the BSD and AN-BP groups, whereas greater general psychopathology predicted deficits in the AN-R group. Specifically, illness duration in the BSD group predicted deficits in cognitive flexibility, suggesting that individuals could increase their risk for exhibiting behavioral or/and cognitive rigidity at more advanced stages of the disorder. In individuals with AN-R, more severe psychopathology predicted deficits in cognitive flexibility. In general, there is consistent evidence that psychopathologic symptomatology can impact executive function, supporting the notion that other factors involve cognitive deficits (Abbate-Daga et al., 2014; Billingsley-Marshall et al., 2013; Dingemans et al., 2020; Kanakam et al., 2013). Studies in AN-R showed increased inflexibility in individuals with obsessive-compulsive (Kanakam et al., 2013), anxiety, and depression symptomatology

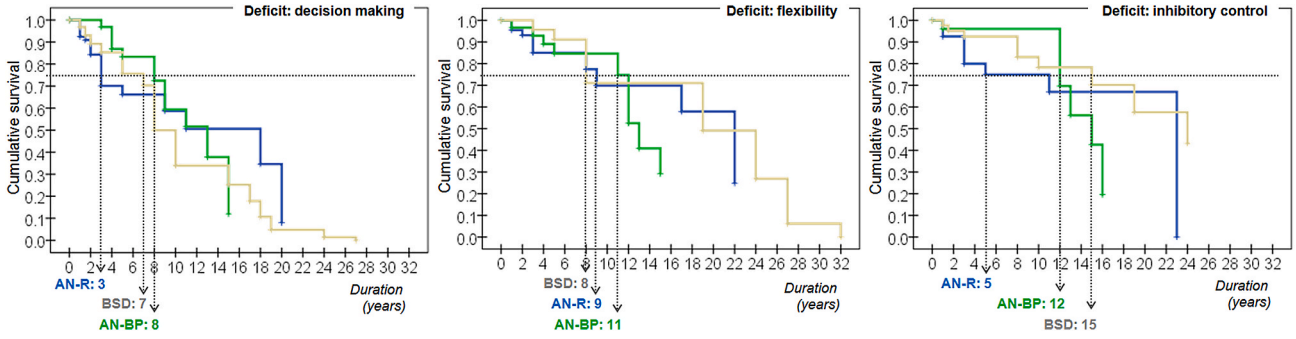

Fig. 2. Cumulate survival functions (adjusted by age, education, and BMI). *Note.* AN-R: anorexia nervosa restrictive. AN-BP: anorexia nervosa bulimic purgative. BSD: binge spectrum disorder.

Table 4
Contribution of age, ED duration, ED symptomatology (EDI-2 total), and general psychopathology (SCL-90R GSI) on executive dysfunction in each ED groups (logistic regression).

			Coefficients						Fitting statistics	
Group	Criteria	Predictors	B	SE	p	OR	95% CI OR		H-L	NR^2
AN-R *(n = 59)*	Deficits in decision making	*No significant predictors*								
	Deficits in flexibility	Psychopath. distress	0.935	0.472	.048	2.547	1.010	6.423	.125	.111
	Deficits in inhibitory control	*No significant predictors*								
AN-BP s*(n = 27)*	Deficits in decision making	*No significant predictors*								
	Deficits in flexibility	*No significant predictors*								
	Deficits in inhibitory control	Duration of ED (years)	0.183	0.109	.045	1.200	1.001	1.485	.333	.174
BSD *(n = 30)*	Deficits in decision making	*No significant predictors*								
	Deficits in flexibility	Duration of ED (years)	0.113	0.059	.045	1.120	1.001	1.257	.252	.194
	Deficits in inhibitory control	*No significant predictors*								

Note. ED: eating disorders. AN-R: anorexia nervosa restrictive. AN-BP: anorexia nervosa bulimic purgative. BSD: binge spectrum disorder.
H-L: Hosmer-Lemeshow test (p-value). N-R^2: Nagelkerke's pseudo-R^2 coefficient.
OR: odds ratio. List of predictors: ED duration, ED symptomatology (EDI-2 total) and psychopathological distress (SCL-90R GSI).

(Abbate-Daga et al., 2014), which, in turn, has been shown to negatively affect treatment outcomes, increasing the risk of a long-term disorder (Flynn et al., 2020).

Impaired executive functions could be related to the risk of developing and maintaining ED symptomatology and, at the same time, ED symptomatology can be affecting executive functions, presenting a reciprocal interaction between them. However, the results obtained do not allow a direct causal effect to be inferred. Therefore, longitudinal studies would be necessary to identify causality. A better understanding regarding the influence of top-down mechanisms in ED could facilitate efforts to develop suited interventions with respect to which factors play a direct role in treatment outcomes. Currently, interventional programs, such as cognitive remediation therapy oriented to improve executive functions, have been shown to be effective in EDs (Juarascio et al., 2015) and in severe and enduring patients (Dandil et al., 2020; Dingemans et al., 2013; Leppanen et al., 2018). Future studies should also consider ED duration and general psychopathology as main factors to be taken into consideration when fitting cognitive treatments to each ED subtype.

Although this study has its strengths, some limitations should be considered when interpreting these results. Inferences emerging from these results must be interpreted with caution due to the limited sample size: some statistical procedures could be underpowered with the consequence of missing real relationships in the population (Table 2 includes the power coefficient for the ANCOVA procedures). Likewise, our sample does not fully represent the general population with EDs because all participants were recruited from a hospital setting and were seeking treatment. Moreover, this study cannot be generalized to men with EDs, since only women were represented in the current sample. Further studies with larger samples are needed to confirm our findings. Finally, our study was not able to control the medication prescribed in individuals with EDs. Future studies should consider this aspect and verify if there is an impact on executive functions.

Other issues should also be considered when interpreting our results, such as the possible effect of other factors that the scientific literature has associated with cognitive functioning, mainly BMI. It should be outlined that we performed a statistical analysis stratified by the diagnostic subtype (separately for individuals with AN-R, AN-BP, and BSD, which also allowed obtaining the potential moderator-interaction role of this measures) and that BMI has been additionally included as a covariate to avoid confounding biases.

In conclusion, altered decision-making and poor cognitive flexibility were observed in individuals with EDs, highlighting similar neurocognitive profiles in the AN-BP and BSD groups. ED duration was associated with executive dysfunctions, showing different time points of increased risk of executive impairment within each ED subtype. The results confirmed our hypothesis predicting the role of ED duration in executive dysfunctions in individuals with BSD and AN-BP.

CRediT authorship contribution statement

Romina Miranda-Olivos: Conceptualization, Investigation, Methodology, Project administration, Data curation, Writing – original draft. **Giulia Testa:** Conceptualization, Investigation, Methodology, Project administration, Data curation, Writing – original draft. **Ignacio Lucas:** Conceptualization, Methodology, Writing – original draft. **Isabel Sánchez:** Data acquisition, Methodology. **Jessica Sánchez-González:** Data acquisition, Methodology. **Roser Granero:** Methodology, Formal analysis, Writing – original draft. **Susana Jiménez-Murcia:** Funding acquisition. **Fernando Fernández-Aranda:** Conceptualization, Investigation, Project administration, Funding acquisition, Writing – original draft.

Funding information

This manuscript and research were supported by grants from the Ministerio de Economía y Competitividad (PSI2015-68701-R), Ministerio de Sanidad, Servicios Sociales e Igualdad (PR338/17), Instituto de Salud Carlos III (ISCIII) (FIS PI17/01167 and PI20/132) and co-funded by FEDER funds/European Regional Development Fund (ERDF), a way to build Europe. CIBERObn is an initiative of ISCIII. Additional support was received from EU Grant Eat2beNice (H2020-SFS-2016-2; Ref 728018). We thank CERCA/the Generalitat de Catalunya for institutional support. The funders had no role in the study design, data collection, and analysis, decision to publish, or preparation of the manuscript.

Declaration of competing interest

FFA 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.

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4.5. STUDY 5

NEUROPSYCHOLOGICAL LEARNING DEFICITS AS PREDICTORS OF TREATMENT OUTCOME IN PATIENTS WITH EATING DISORDERS

Lucas I, **Miranda-Olivos R**, Testa G, Granero R, Sánchez I, Sánchez-González J, Jiménez-Murcia S, Fernández-Aranda F. Neuropsychological Learning Deficits as Predictors of Treatment Outcome in Patients with Eating Disorders. **Nutrients.** 2021 Jun 23;13(7):2145. doi: 10.3390/nu13072145.

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Neuropsychological Learning Deficits as Predictors of Treatment Outcome in Patients with Eating Disorders

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Citation: Lucas, I.; Miranda-Olivos, R.; Testa, G.; Granero, R.; Sánchez, I.; Sánchez-González, J.; Jiménez-Murcia, S.; Fernández-Aranda, F. Neuropsychological Learning Deficits as Predictors of Treatment Outcome in Patients with Eating Disorders. *Nutrients* **2021**, *13*, 2145. https://doi.org/10.3390/nu13072145

Academic Editor: Stefano Erzegovesi

Received: 21 April 2021
Accepted: 17 June 2021
Published: 23 June 2021

Abstract: Eating disorders (EDs) are severe psychiatric illnesses that require individualized treatments. Decision-making deficits have been associated with EDs. Decision-making learning deficits denote a lack of strategies to elaborate better decisions that can have an impact on recovery and response to treatment. This study used the Iowa Gambling Task (IGT) to investigate learning differences related to treatment outcome in EDs, comparing between patients with a good and bad treatment outcome and healthy controls. Likewise, the predictive role of impaired learning performance on therapy outcome was explored. Four hundred twenty-four participants (233 ED patients and 191 healthy controls) participated in this study. Decision making was assessed using the Iowa Gambling Task before any psychological treatment. All patients received psychological therapy, and treatment outcome was evaluated at discharge. Patients with bad outcome did not show progression in the decision-making task as opposed to those with good outcome and the healthy control sample. Additionally, learning performance in the decision-making task was predictive of their future outcome. The severity of learning deficits in decision making may serve as a predictor of the treatment. These results may provide a starting point of how decision-making learning deficits are operating as dispositional and motivational factors on responsiveness to treatment in EDs.

Keywords: eating disorders; decision making; learning; treatment outcome

1. Introduction

Eating disorders (EDs) are important psychiatric illnesses that involve abnormal eating behavior. Patients affected with EDs may present excessive concern over food, body weight, and shape dissatisfaction. These conditions could also lead to serious physical problems and impaired psychosocial functioning [1]. Moreover, there is an increased risk of suicide in people with EDs compared to the non-ED population [2–5]. A recent systematic review regarding the diagnosis prevalence of EDs established that worldwide, around 8.4% of women and 2.2% of men will be diagnosed with this condition at some point in their lifetime [6]. The main treatments for EDs, which are based on cognitive–behavioral therapy (CBT), have been demonstrated to be useful in reducing symptoms [7,8]; however, these current treatments have not always reported successful outcomes [9–12].

A systematic review [13] reported ED remission rates between 18% and 62%. Several individual circumstances might underlie the response to treatment in EDs, increasing the risk of having bad treatment outcomes, resulting in low remission rates or poor adherence to treatment [14–19]; therefore, assessing which functions act as predictors for the treatment outcome of the ED is crucial in order to design optimized individual treatments [20–22].

Some of the most studied cognitive features in patients with EDs are their executive function impairments in comparison to the healthy population [16,23–28]. Executive functions optimize cognitive processes to solve demanding situations where instinct or intuition is insufficient [29]. Complex cognitive processes, such as decision making, are strongly related to executive functions [30]. Decision making involves high-level processes, including option generation, evaluation of risks and consequences, and choosing between different possibilities in order to achieve a certain personal objective [31]. Therefore, decision-making processes require complex high-level processing to make advantageous decisions taking different variables into account. These processes are commonly related to prefrontal cortex activity [32,33]. Psychiatric illnesses, such as EDs, are usually associated with significant impairments in prefrontal, fronto-limbic, and fronto-striatal neural systems [34].

Even though each ED subtype has been related to its own specific neurocognitive impairments [35], decision-making deficits have been found among all ED conditions [25,27,36–40]. Patients with EDs reported poor learning during decision-making paradigms [41,42], showing a tendency to persist in decisions/choices, despite negative consequences. Learning deficits in the decision-making tasks of patients diagnosed with EDs may be related to an excessive sensitivity to reward or punishment, which could be associated with the persistence of their dysfunctional behavior [42]. Some studies have hypothesized that in EDs, as reported in obsessive-compulsive disorders, observed impairments in decision making may be related to biological markers [26,43]; however, decision-making deficits in EDs do not have to be considered a completely permanent feature. Neurocognitive training on executive functions has been tested in patients with EDs, showing improvement in cognitive flexibility, inhibitory control, and working memory [16]. Furthermore, in another study, patients with anorexia nervosa showed great improvement in decision making after CBT treatment in patients in full remission of their ED symptoms but not in patients with no remission [40]. Just as patients with EDs who improve their symptoms showed an improvement in their performance post-treatment, it could be expected that better decision making at baseline would also predict a better treatment outcome; however, the literature examining neurocognitive predictors of treatment outcome in EDs is scarce [44] and there is a lack of studies focusing on neuropsychological profiles as predictors of therapy outcome [45]. Cavedini et al. [14] observed how the function of decision making might be linked to treatment outcomes in women with anorexia nervosa. Still, they pointed toward the necessity of understanding which neurocognitive feature linked to decision making can be used as a criterion for selecting the proper treatment.

Based on the facts described above, this research was designed with two aims: first, to assess baseline learning differences related to decision-making between patients with EDs who recovered from their symptoms and those who did not; second, to explore the predictive capacity of impaired learning performance on therapy outcome.

According to the above-mentioned aims, we propose two hypotheses. First, if learning decision-making skills influence treatment efficacy, EDs with bad treatment outcomes will show impaired learning performance, even before the treatment. Second, if there is an impaired neurocognitive functioning in ED patients with bad treatment results, the decision-making learning skill will help discriminate between having good or bad treatment outcomes.

2. Materials and Methods

2.1. Participants

A total of 424 participants were included in the present study: 341 women and 83 men, with a ratio similar to recent studies [6]. The ED group contained 190 women and 43 men,

with a mean age of 30.52 (SD = 10.9), whereas the healthy control (HC) group (151 women and 40 men) had a mean age of 25.65 (SD = 8.5). In terms of the highest level of education, for the HC group, 5.8% attained a primary education, 56% attained a secondary education, and 38.2% attained a tertiary degree. For the ED group, 35.2% attained a primary education, 40.8% attained a secondary education, and 24% attained a tertiary degree. Table S1 (Supplementary Material) contains the sociodemographic characteristics of the groups at baseline. To avoid potential biases in the results, all the comparisons were adjusted for the covariates of age and education level at baseline. Patients with EDs were recruited from the Eating Disorders Unit at Bellvitge University Hospital in Barcelona, Spain. All patients within the ED group met the Diagnostic and Statistical Manual of Mental Disorders (DSM-5; American Psychiatric Association, Philadelphia, PA, USA) [46] criteria for EDs, following standardized structured interviews. The ED group was composed of 85 patients with anorexia nervosa (AN) restrictive subtype, 41 patients with AN bulimic/purging subtype, 44 with bulimia nervosa (BN), 45 patients with binge eating disorder (BED), and 18 patients with other specified feeding or eating disorder (OSFED). Once diagnosed, they were asked to voluntarily participate in this study. Neuropsychological and clinical assessments were conducted in the first week of their treatment. The exclusion criteria for the HC group were a body mass index below 18.5 or above 25 and a lifetime history of EDs, according to a semi-structured interview and following DSM-5 diagnostic criteria.

Data were collected between May 2008 and November 2020. All participants were adults, received information about the procedure, and signed an informed consent form. All procedures were approved by the Ethical Committee of the Bellvitge University Hospital in accordance with the Helsinki Declaration of 1975 as revised in 1983.

2.2. Procedure

Participants completed a computerized version of the Iowa Gambling Task (IGT) [47]. Additionally, the patients' psychopathology symptoms were evaluated via the Spanish version of the Symptom Checklist-Revised (SCL-90-R) [48], and their ED symptoms were assessed with the Spanish version of the Eating Disorders Inventory-2 (EDI-2) [49]. All these evaluations were conducted prior to the psychological treatment.

2.2.1. Decision-Making Assessment

The computerized version of the IGT was used to assess decision-making processes [50]. This task consists of 100 trials in which the participants must draw a card from one of the four presented decks (A, B, C, and D). Each card represents a monetary gain but can also result in monetary loss. There are two advantageous decks and two disadvantageous ones. The first ones produce less monetary incomes but with an overall gain, whereas the second presents larger gain amounts and an overall monetary loss. The participant has to gain as much as possible by the end of the task. It is subdivided into five blocks of twenty trials performed consecutively. The first blocks allow measuring decision making under ambiguity, whereas in the last blocks, the task switches to decision making under risk because the rules may have been figured out [51].

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 calculated by adding the scores of the five blocks. The task also allows us to calculate a learning score (IGT-Learning) and a risk score (IGT-Risk) [42]. IGT-Learning is calculated with the difference between the scores of the two first blocks and the two last ones. This approach/procedure allows us to assess the differences between the first and final blocks. The first blocks are assessed because the participant has not learned which decks are advantageous and disadvantageous; the last blocks are assessed because the experience gained through the trial can produce changes in choice patterns. Furthermore, IGT-Risk considers only the scores from the two last blocks, where a participant could have already detected which decks involve a risky choice.

2.2.2. Treatment

As described elsewhere [9,52], patients diagnosed with AN attended a day hospital treatment program, including CBT group therapy sessions, lasting 90 min each, for 15 weeks. Treatment for the other ED diagnosis (BN, BED, and OSFED) consisted of 16 weekly outpatients CBT group therapy sessions, lasting 90 min each. Patients were re-evaluated at discharge and categorized as either in full remission (i.e., total absence of symptoms meeting criteria for at least 4 weeks), partial remission (i.e., a substantial symptomatic improvement but with residual symptoms), and non-remission. These categories were previously used as the threshold to assess treatment outcomes in patients with EDs [9,19,52]. The treatment outcomes categories were based on the judgments of senior clinical staff considering normalization of nutritional dietary patterns, frequency of binge episodes and compensatory behaviors, weight restoration, and improvement in attitudes regarding weight and shape. Voluntary treatment discontinuation was categorized as dropout (i.e., not attending treatment for at least three consecutive sessions). Patients were subdivided into two groups depending on their treatment outcome. Those who showed full or partial remission of their symptoms were included in the good outcome group (n = 166; 71.2%), and those who did not show remission or abandoned the treatment were included in the bad outcome group (n = 67; 28.8%). The treatment results obtained were similar to those reported previously [53].

2.3. Data Analysis

Statistical analysis was done with Stata16 for windows (College Station, TX, USA). The association between the baseline measures with the CBT efficiency (bad versus good outcome) was based on the chi-square test (χ^2) for categorical measures and analysis of variance (ANOVA) for quantitative measures. An increase in the Type-I error due to the multiple significance tests was based on the Finner method [54], which is a family-wise procedure that has proved more powerful than the standard Bonferroni correction.

The comparison of the learning curves in the IGT was based on 3 × 5 mixed ANOVA (adjusted by the participants' age and education level), which is defined as the between-subjects factor of the group (bad CBT outcome, good CBT outcome, and control condition) and as the within-subjects factor for the score in each block. Polynomial contrasts for the within-subject factor assessed linear, quadratic, cubic, and quartic trends in the learning curves. Comparing the IGT-Learning score between the three groups was also based on analysis of variance, which was adjusted by age and education (ANCOVA).

The discriminative capacity of the IGT-Learning score to discriminate between good versus bad outcomes in the CBT was based on Receiver Operating Characteristics (ROC) analysis. This methodology is used in clinical areas to obtain the optimal cut-off in measurement tools using an external reference criterion. In this work, ROC analysis was applied within the ED subsample to obtain the best cut-off in the IGT index to discriminate between patients with bad versus good CBT outcomes. Since selecting the optimal cut-off depends on the prevalence of the criteria and the costs/risks of false classifications [55], the analysis was performed considering a distribution for the CBT outcome equal to the sample and a cost for a false negative double compared to the cost for a false positive.

Logistic regression valued the capacity of the optimal cut-off point in the IGT-Learning global measure to differentiate between bad and good outcomes. Goodness-of-fit was assessed with the Hosmer and Lemeshow test.

In this study, the effect size was based on the eta-squared coefficient (η^2) for quantitative measures (values of 0.06, 0.10, and 0.25 were interpreted as low–poor, moderate–medium, and large–high effect size) [56], and in Cramer's-V coefficient for categorical (values of 0.10, 0.30, and 0.50 were interpreted as low–poor, moderate–medium, and large–high effect size) [57].

3. Results

3.1. Comparison of the IGT Measures between the Groups

Table 1 contains the results obtained in the mixed ANOVA (adjusted by age and education) comparing the proficiency in the IGT between the groups (see also the first panel in Figure 1). The interaction of the within- and between-subjects factors was statistically significant (F = 4.09, p < 0.001, η^2 = 0.019), indicating that the learning curves had a specific shape depending on the group. No statistically significant differences between the blocks were found among patients in the bad outcome group (F = 1.63, p = 0.166, η^2 = 0.015), suggesting the absence of a learning curve. Within patients with a good outcome, significant linear (F = 23.3, p < 0.001, η^2 = 0.124) and quadratic (F = 6.49, p = 0.012, η^2 = 0.038) trends appeared: increasing means with blocks were registered (from −2.4 in block 1 to 1.2 in block 5), the difference being lower comparing blocks 4 versus 5 (1.23 versus 1.21). The same pattern was obtained in the control group: significant linear (F = 79.71, p < 0.001, η^2 = 0.296) and quadratic (F = 27.99, p < 0.001, η^2 = 0.128) trends.

Table 1. Performance learning curves in the Iowa Gambling Task (2 × 5 ANOVA adjusted by age and education).

	IGT Raw Scores									
	Block 1		**Block 2**		**Block 3**		**Block 4**		**Block 5**	
Group (outcome)	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Bad (n = 67)	−2.45	3.85	−0.05	4.28	−0.87	5.82	−0.32	7.78	−0.41	7.64
Good (n = 166)	−2.38	4.66	−0.61	5.53	0.24	5.87	1.23	7.42	1.21	8.45
Control (n = 191)	−1.72	5.92	2.22	7.06	4.68	8.35	5.32	9.03	4.93	9.90
Multivariate tests	F	df	p	η^2						
Int. BxG	4.09	8; 419	**0.001** *	0.019						
Block	0.80	4; 419	0.401	0.002						
Group	22.34	2; 419	**0.001** *	0.096						
Factor Block Within Group	F	p	η^2							
Bad	1.63	0.166	0.015							
Good	6.51	**0.001** *	0.059							
Control	30.89	**0.001** *	0.229							
Polynomial contrast for Block	Linear (order 1)			Quadratic (order 2)			Cubic (order 3)			Quartic (order 4)		
	F	p	η^2	F	p	η^2	F	p	η^2	F	p	η^2
Group: bad	1.14	0.289	0.017	3.94	0.051	0.056	1.20	0.277	0.018	1.73	0.193	0.026
Group: good	23.32	**0.001** *	0.124	6.49	**0.012** *	0.038	0.15	0.701	0.001	1.02	0.314	0.006
Group: control	79.71	**0.001** *	0.296	27.99	**0.001** *	0.128	0.55	0.457	0.003	0.53	0.468	0.003

Note. SD: standard deviation; * Bold: significant comparison (0.05 level); η^2: partial eta-squared.

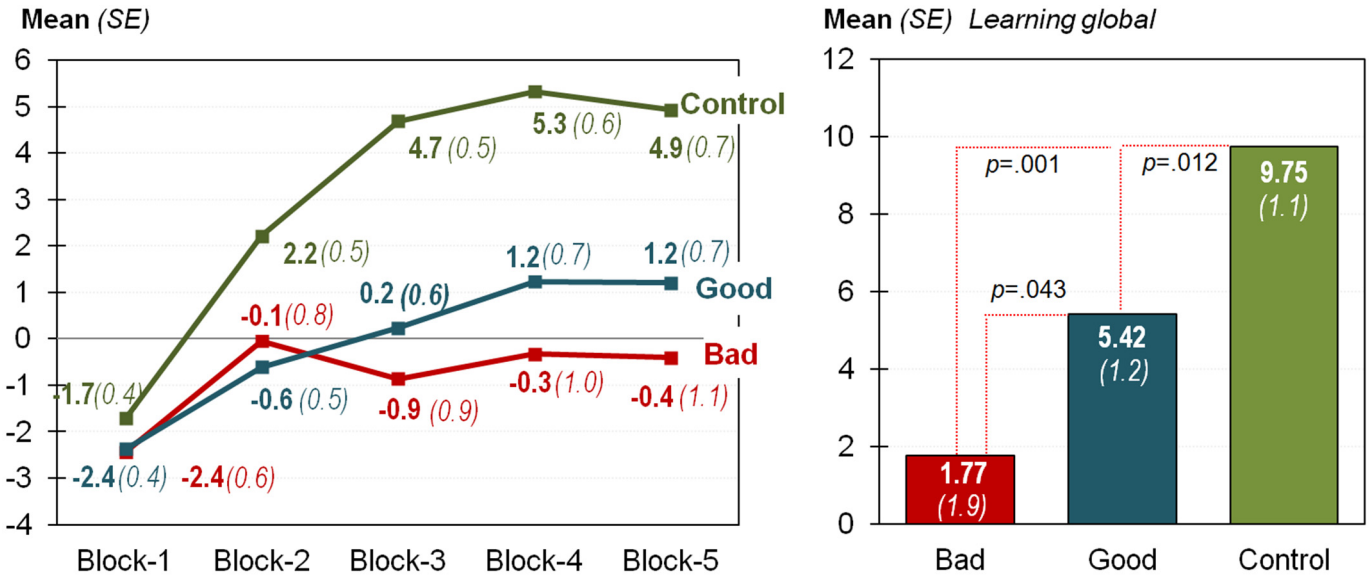

Figure 1. Iowa Gambling Task (IGT) performance–learning curves (**left**) and IGT global scores by group (**right**). Note. Sample size n = 424. SE: standard error.

Table 2 contains the results of the ANCOVA (adjusted by age and education) comparing the IGT-Learning score between the groups (see the second panel in Figure 1). Statistical differences between the groups appeared (F = 7.14, p < 0.001, η^2 = 0.124). Pairwise comparisons (contrasts between the groups) also achieved differences between all the groups.

Table 2. Comparison of the IGT learning global score: ANCOVA adjusted by age and education.

	Bad Outcome		**Good Outcome**		**Control**	
Descriptives	Mean	SD	Mean	SD	Mean	SD
	1.77	14.04	5.42	13.15	9.75	16.67
Factor group	*F*	*df*	*p*	η^2		
	7.14	2; 423	**0.001** *	0.033		
Pairwise comparisons	*F*	*p*	η^2			
Bad vs. good	4.84	**0.043** *	0.014			
Bad vs. control	12.93	**0.001** *	0.030			
Good vs. control	6.44	**0.012** *	0.015			

Note. SD: standard deviation; * Bold: significant comparison (0.05 level); η^2: partial eta-squared.

3.2. Discriminative Capacity of the IGT-Learning Score

Figure 2 contains the results of the ROC analysis obtained in the ED subsample. The optimal cut-off point in the IGT-Learning index to discriminate between good and bad CBT outcomes was 2, which achieved a sensitivity (Se), or true positive rate, of 64.2% and a specificity (SP), or true negative rate, equal to 54.8%.

Figure 3 shows the percentage of patients with a poor performance in the IGT in each group (based on the classification obtained for the cut-off = 2 in the global learning measure). The logistic regression (adjusted by age and education) valuing this cut-off's capacity for differentiating between the two groups achieved a significant parameter for differentiating between bad versus good groups (B = 0.754, SE = 0.301, OR = 2.12, p = 0.012). Goodness-of-fit was achieved (Hosmer and Lemeshow test: χ^2 = 5.95, df = 8, p = 0.653).

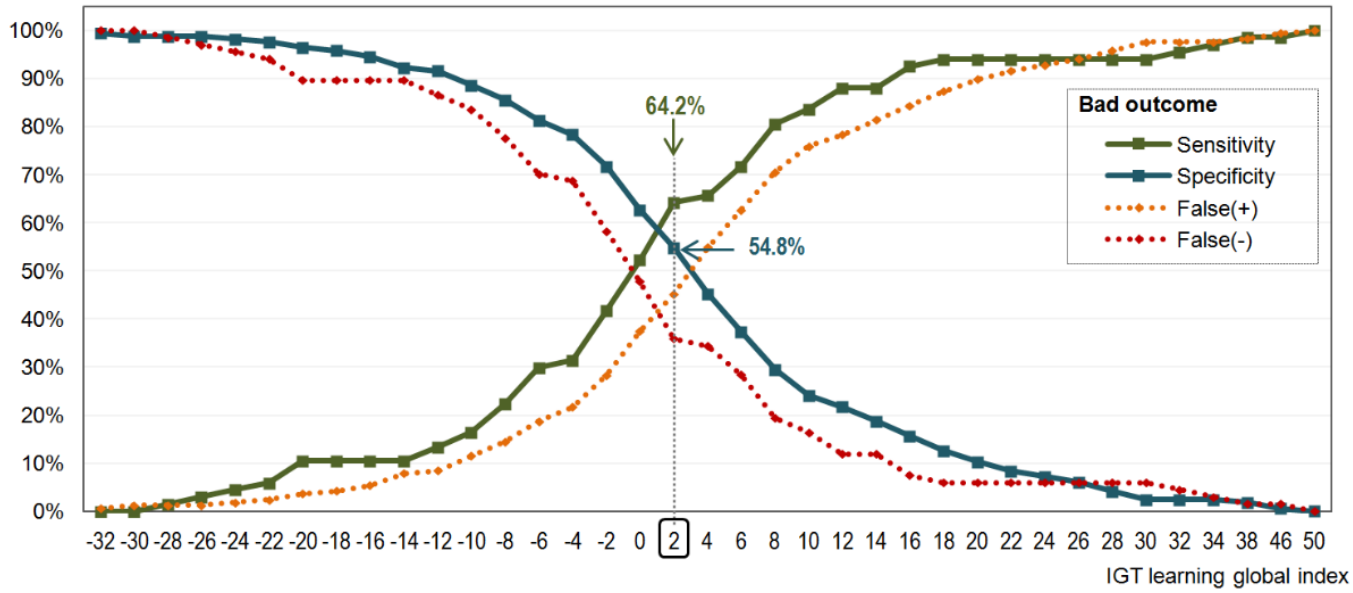

Figure 2. Valuation of the IGT-Learning raw score to predict the treatment outcome. Note. Results obtained for the ED subsample (n = 233).

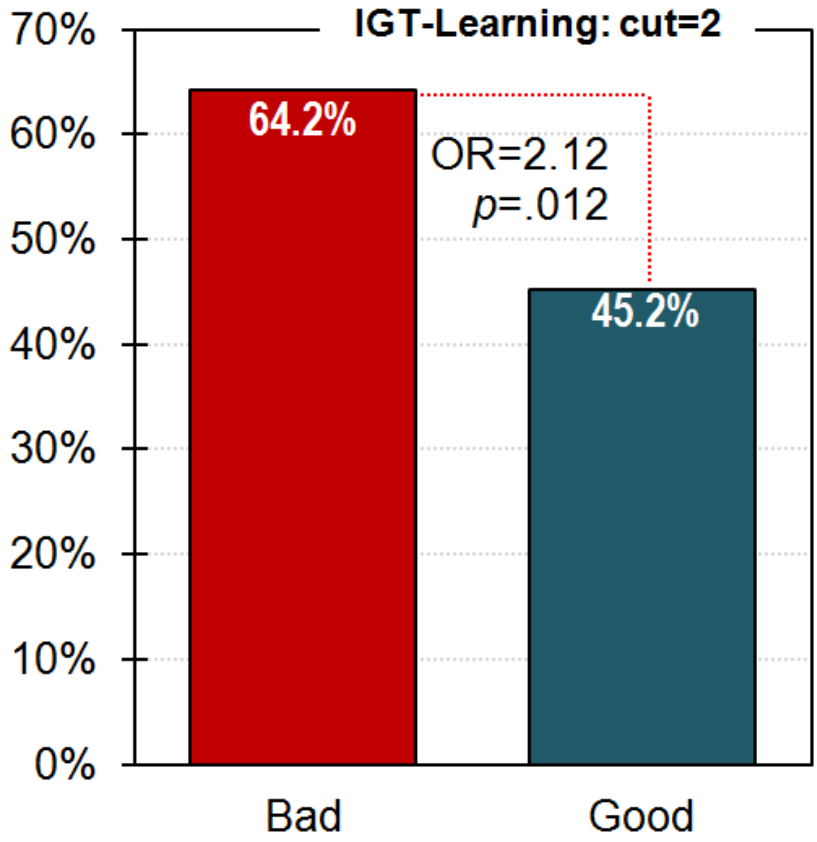

Figure 3. Capacity of the IGT-Learning score to predict the treatment outcome. Each bar represents the percentage of participants with poor IGT-Learning in each group with a cut-off point equal to 2. Note. Results obtained for the ED subsample (n = 233).

3.3. Variables Associated with the CBT Outcome

Table 3 contains the comparison between patients classified according to the CBT outcome (bad versus good) at baseline. No differences were found between groups in any of the variables.

Table 3. Association between baseline measures with the cognitive–behavioral therapy outcome.

		Bad Outcome (n = 67)		Good Outcome (n = 166)			
		n	%	n	%	p	V
Sex	Women	59	88.1%	131	78.9%	0.103	0.202
	Men	8	11.9%	35	21.1%		
		Mean	SD	Mean	SD	p	η^2
Chronological age (years-old)		28.99	9.50	31.13	11.39	0.174	0.008
Duration of disorder (years)		9.57	8.36	7.79	8.65	0.152	0.009
EDI-2: Drive for thinness		11.78	7.14	11.71	6.45	0.946	0.001
EDI-2: Body dissatisfaction		15.22	8.17	14.74	8.84	0.700	0.001
EDI-2: Interoceptive awareness		10.39	6.59	9.73	6.89	0.504	0.002
EDI-2: Bulimia		6.28	5.85	5.41	5.34	0.273	0.005
EDI-2: Interpersonal distrust		5.39	4.61	5.74	5.23	0.630	0.001
EDI-2: Ineffectiveness		10.84	7.08	9.40	7.24	0.169	0.008
EDI-2: Maturity fears		8.37	6.09	7.48	5.19	0.257	0.006
EDI-2: Perfectionism		6.07	4.89	5.05	4.08	0.103	0.011
EDI-2: Impulse regulation		5.43	5.30	5.36	5.81	0.925	0.001
EDI-2: Ascetic		6.70	4.24	6.05	4.25	0.289	0.005
EDI-2: Social insecurity		7.00	4.66	6.90	5.57	0.901	0.001
EDI-2: Total score		93.48	46.79	87.56	45.95	0.377	0.003
SCL-90R: Somatization		1.78	1.02	1.60	0.90	0.198	0.007
SCL-90R: Obsessive/compulsive		1.78	0.97	1.73	0.92	0.734	0.001
SCL-90R: Interpersonal sensitivity		1.90	0.99	1.88	1.00	0.848	0.001
SCL-90R: Depressive		2.25	0.98	2.06	0.99	0.196	0.007
SCL-90R: Anxiety		1.63	0.91	1.46	0.91	0.194	0.007
SCL-90R: Hostility		1.17	0.88	1.19	0.90	0.898	0.001
SCL-90R: Phobic anxiety		0.84	0.86	0.88	0.91	0.736	0.001
SCL-90R: Paranoid Ideation		1.43	0.89	1.28	0.84	0.253	0.006
SCL-90R: Psychotic		1.36	0.82	1.17	0.72	0.081	0.013
SCL-90R: GSI score		1.69	0.78	1.58	0.78	0.300	0.005
SCL-90R: PST score		61.43	19.63	60.36	18.86	0.697	0.001
SCL-90R: PSDI score		2.35	0.59	2.22	0.61	0.127	0.010

Note. EDI-2: V: Cramer's-V. η^2: partial eta-squared. Eating Disorders Inventory-2 [49]. SCL-90R: Symptom Checklist—Revised [48]. GSI: Global Severity Index. PST: Positive Symptom Total. PSDI: Positive Symptom Distress Index.

4. Discussion

We examined baseline differences in decision making in patients with EDs, differentiating between those who improved vs. those who did not after CBT, and analyzed its therapy outcome predicting value. As the first objective, our study addressed whether ED patients with different outcomes present learning differences related to decision making before the treatment. This study's main results showed how both the patients with good outcomes and the healthy control group showed a learning curve through the IGT task; however, the bad outcome group was the only group that did not show progression across the blocks. Based on these results, the first hypothesis is verified, as different outcomes present differences in learning, even before the intervention. The second main finding was that the IGT-Learning score predicted treatment outcome. These findings support our second hypothesis, as the capacity of learning through a decision-making task seems to discriminate between having a successful or a bad treatment outcome. There would be a chance that these learning deficits were related to higher depressive symptoms; nevertheless, there were no observed differences in depression between ED groups.

These results fit not only with previous studies that point toward decision-making deficits in patients with EDs [25,27,36,38–40] but also with the ones that report how individual differences correlate with distinct treatment outcomes [9,15–19]. Regarding a previous study that presented decision making as a predictor of treatment outcome in EDs [14], our study reported its predictive value using a bigger sample, with patients of both sexes and

with different EDs subtypes. In addition, among the neuropsychological variables that discriminate between the treatment results, the learning skills showed differences depending on therapy outcomes and are good predictors of the treatment result. It is noteworthy to mention that patients with EDs who had a poor treatment outcome did not show changes in their answers across the IGT blocks; this could mean that perhaps they neither changed their behavior due to immediate rewards (as in disadvantageous decks) nor to delayed recompenses (as in advantageous decks) [36]. According to Hiroto and Seligman [58], this lack of change is probably related to learned helplessness, and therefore, they may not feel capable of changing the result of the task through their decisions. This behavior could explain why they do not believe in the possibility of improving their symptoms with psychological intervention, leading to poor treatment efficacy and less treatment adherence. Steward et al. [40] reported how patients with EDs who recover from their symptoms also improve their performance in decision-making tasks; therefore, they enhance their learning skills. If that is true, a potential treatment effect would be a patient believing in their ability to change negative situations via their actions and decisions. There were no observed differences in ED symptoms nor in general psychopathology, so, in this sample, the different treatment outcomes do not seem to be directly related to these parameters.

Previous research showed how patients with EDs tend to report high levels of sensitivity to punishment [42,59,60]; however, in our study, some of them still did not seem to learn from the negative feedback; this may be due to the fact that despite stimuli producing a great emotional impact, those patients do not change their behavior because they do not believe they can change situations via their decisions. The main characteristic of learned helplessness is that it highly correlates with depressive states [61,62]. Nevertheless, regarding our results, these learning impairments would be related to a worse treatment outcome independently from the depressive symptoms. The patients with EDs who show impaired learning behaviors and tend to have negative treatment outcomes would need to change their belief in the possibility of improving their symptoms; therefore, individualized treatments for those patients will require focusing on improving their locus of control.

Our study has certain limitations, and the results and conclusions of our study must take these into account. First, using a neuropsychological task such as the IGT may not be practical for the clinical assessment; it would be necessary to design more accessible tools to assess these impairments. Second, our sample size was limited to test the predictive role of IGT performance across ED subtypes. Therefore, inferences emerging from these results must be interpreted with caution considering no discrimination by ED diagnosis. Future studies with larger samples could elucidate the predictive role of decision-making learning in each ED subtype. Third, as seen in other psychological disorders, impaired motivation may influence the performance in cognitive tasks [63]. Future research should include some motivational measure to assess this effect. Fourth, it will still be necessary to evaluate whether there are differences between those patients who do not recover from their symptoms and those that show poor treatment adherence. This study presents an understanding of how neurocognitive deficits may underlie possible treatment outcomes in ED. Future studies should consider our results to develop individualized treatments so that patients with different features and symptoms can benefit from the treatment.

5. Conclusions

In sum, our results show how ED treatment outcomes could be related to cognitive functioning even before the treatment, as patients with different outcomes seem to present different learning skills related to decision making. This learning skill also demonstrated a predictive value for the treatment outcome, possibly indicating that patients who do not change their behavior despite its consequences tend to present greater difficulties with the treatment. It may indicate that these patients show a lack of belief in changing their situation through their behavior. These results point toward the importance of taking into account neuropsychological variables to develop and apply individualized treatments that successfully deal with EDs.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/nu13072145/s1, Table S1: Descriptives of the sample.

Author Contributions: Conceptualization, I.L., R.M.-O., G.T., S.J.-M. and F.F.-A.; methodology, I.L., R.M.-O., G.T., R.G., S.J.-M. and F.F.-A.; formal analysis, R.G.; data curation, R.M.-O., G.T., I.S. and J.S.-G.; writing—original draft preparation, I.L., R.M.-O., G.T. and R.G.; writing—review and editing, I.L., R.M.-O., G.T., R.G., S.J.-M. and F.F.-A.; supervision, S.J.-M. and F.F.-A.; funding acquisition, S.J.-M. and F.F.-A. All authors have read and agreed to the published version of the manuscript.

Funding: We thank CERCA Programme/Generalitat de Catalunya for institutional support. This manuscript and research was supported by grants from the Instituto de Salud Carlos III (ISCIII) (FIS PI14/00290, PI17/01167 and PI20/132), by the SLT006/17/00246 grant, funded by the Department of Health of the Generalitat de Catalunya by the call "Acció instrumental de programes de recerca orientats en l'àmbit de la recerca i la innovació en salut" (PERIS) and co-funded by FEDER funds/European Regional Development Fund (ERDF), a way to build Europe. CIBERObn is an initiative of ISCIII. The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Institutional Review Board Statement: All procedures were approved by the Clinical Research Ethics Committee (CEIC) of Bellvitge University Hospital (ethic approval code: PR146/14) in accordance with the Helsinki Declaration of 1975 as revised in 1983.

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

Data Availability Statement: Data are not available in any repository. Contact with the corresponding author.

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

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5. DISCUSSION

The present thesis adopted a dimensional perspective to investigate individuals with EWC from both a clinical and neurobiological point of view. Samples of individuals with AN and OB represented the opposite ends of this continuum whereas samples of individuals with BN and BED were included to characterize ED with a higher risk of leading towards either extreme, due to compensatory and purgative behaviors following episodes of excessive overeating. Thus, to fulfill the stated objectives and test the proposed hypotheses, various data sources were used including functional neuroimaging, circulating endocannabinoid concentrations, cognitive performance (executive functions), clinical variables, and personality traits. The obtained results have provided substantial support for our initial postulations, while also raising new questions and challenges in the field of research on EWC.

5.1. CLINICAL SUBSTRATES IN EWC

At a clinical level, differences were found in patients with AN depending on the diagnostic subtype, in relation to personality traits and eating symptomatology. However, as expected, no differences were found in terms of general psychopathology across ED diagnoses but did compare with HC and OB. Within the diagnoses of ED, patients with AN-BP often exhibited a psychological profile similar to patients BSD (study 4) who are characterized by recurrent BE such as BN and BED. AN-BP and BSD groups showed marked traits of impulsivity and harm avoidance compared to other ED (51,185). In the case of BED, it was a diagnosis individually addressed in only one study (study 1) comparing its clinical profile with OB (without an ED) and HC. As expected, patients with BED showed higher ED symptomatology and negative urgency compared to individuals with OB without ED and the HC group. Consistent with previous evidence (6,10,19–21), these findings confirm that individuals with EWC and ED represent a more severe presentation of eating and weight-related disturbances characterized by a greater psychological distress in comparison to individuals with EWD but without a comorbid ED diagnosis.

5.2. NEUROBIOLOGICAL SUBSTRATES IN EWC

Regarding our first objective, this thesis investigated brain function in individuals with EWC compared to HC (studies 1 and 2). We expected that individuals with EWC would exhibit alterations in brain regions involved in inhibitory control, emotional regulation, and reward processing. Brain function was analyzed using two different methodological approaches brain function was analyzed: resting-state functional magnetic resonance imaging (rs-fMRI) and task-based fMRI (study A and B). Both approaches provide information about the structural and functional integrity of the brain. The rs-fMRI method allows the assessment of brain function by assessing the synchronicity in spontaneous low-frequency fluctuations across different regions that are synchronously interacting despite being activity-free (380). It has been observed that certain characteristics of the rs-fMRI, such as functional connectivity, have been shown to characterize various neurological and psychiatric disorders (297). On the other hand, task-based fMRI allows the acquisition of brain images to evaluate neuronal activations during the presentation of specific stimuli or after specific instructions. This information offers valuable insights into the active brain areas involved in cognitive and psychological processes.

Studies investigating brain function consistently reported alterations in insula activity in individuals with EWC (as observed in both study 1 and 2), in line with prior research findings (240,292,381). During a decision-making fMRI task known as delay discounting, individuals with OB with or without EDs exhibited a reduced activity in the anterior insula when preferring smaller but immediate rewards over larger but delayed rewards, although no differences in discounting rates were observed. Likewise, during a task-free functional magnetic resonance session (i.e., rs-fMRI), individuals with AN showed a hypoconnectivity between the insula with the NAcc which is the core of the reward brain circuit. The insula has exponentially gained significant scientific interest in recent years. Early evidence from studies examining the role of the insula has indicated its significant involvement in various cognitive processes (279,382,383), ranging from basic functions such primary gustatory processing (279), to interoceptive and emotional integration processes, as well as behavioral self-control (383). As for the delay discounting task, a dysfunctional insula activity during reward-based decision-making has been associated with difficulties in properly evaluating and weighing the long-term consequences of

their decisions (384,385). Therefore, reduced activity in the insula, when individuals choose immediate small rewards over, could contribute to impulsive decision-making and difficulties in considering long-term consequences (385). In the context of our results, this may indicate that individuals with OB exhibit a disruption in the brain region responsible for perceiving and regulating internal body signals during reward-related decision-making. The involvement of the insula in evaluating the temporal aspect and value of rewards may be crucial for promoting more deliberate and forward-thinking decision-making in the context of OB. Prioritizing immediate rewards, a decreased insula activity may be associated with a preference for immediate gratification, potentially hindering efforts to adopt healthier behaviors and maintain weight control (292). This lack of consideration for their decisions and actions could be translated to problematic eating behaviors and maladaptive strategies for weight control in EWC: persistent starvation in AN and an excessive food intake in OB, despite negative health consequences (study 1 and 2).

Furthermore, when assessing functional connectivity in the NAcc in individuals with AN and HC, the findings revealed significant alterations in the functional connectivity patterns of this brain region with the insula and the SMA in AN as compared to HC (study 2). According to previous findings, disruptions in the connectivity between the NAcc and the insula may underlie disturbances in the perception and integration of internal bodily signals which may struggle to perceive their own body, resulting in body image distortions (381,386). In the context of the ventral pathway outlined by Kaye and colleagues (239), hypoconnectivity between the NAcc and the insula may contribute to the observed deficits in reward processing among patients with AN (38,44,239). These deficits may contribute to increase negative emotional responses to food and aversions to this primary rewarding stimulus, even in a hungry state, as suggested by other studies (38,44,239). Additionally, a hypoconnectivity between the NAcc and the SMA in AN compared to HC. The SMA could also participate in deficits in the proposed model of reward deficits in AN (44). The SMA is a brain region involved in the planning and execution of voluntary movements, as well as in the inhibitory control of automatic or impulsive responses (294,387) toward food stimuli (305). Abnormal connectivity in AN between the insula and the SMA with the core of regions of the reward brain system

(i.e., NAcc) may hinder the integration of interoceptive, somatosensory, and motor planning information associated with reward stimuli (study 2). Overall, these results provide a better understanding of the cognitive distortions commonly observed, not only in individuals with AN, but also in individuals with OB with or without ED (studies 1 and 2). In these individuals, common psychobehavioral features such as higher levels of body dissatisfaction, intense weight concern, or body image distortion led to maladaptive eating behavior, such as food restriction (as seen in AN), overeating (as in BN and BED), or compensatory behaviors (as seen in AN and BN) exacerbating the severity of each clinical condition and reducing the likelihood of recovery. For this reason, several studies have invested efforts in identifying underlying neurobiological factors that may be hindering successful recovery and increasing the severity of EWC. Most studies pointing in this direction have investigated potential pharmacological interventions to improve recovery or treatment response, as a complementary approach to psychological treatment, targeting symptomatology, impulsivity levels, or weight control (204,224,388). For example, the identification of specific neurobiological specific neurobiological mechanisms has led to the development of innovative interventions, such as deep brain stimulation (DBS), which is used to modulate aberrant activity in the NAcc in individuals with AN (389,390). DBS in the NAcc has been demonstrated to enhance treatment outcomes (389) and reduce comorbid depressive and anxious symptoms in these patients (390).

5.3. NEUROENDOCRINOLICAL SUBSTRATES IN EWC

Under this premise, a step further in this thesis was sought by exploring the influence of NAcc functional connectivity and circulating eCBs on AN severity (study 2). The observed alterations in NAcc functional connectivity and its interaction with AEA and 2-AG concentrations, particularly in individuals with AN, revealed significant insights. In AN, AEA and 2-AG distinctly impact the relationship between NAcc-insula and NAcc-SMA connectivity and BMI, as indicators of AN severity. Higher AEA concentrations are associated with lower BMI in individuals with AN, might imply a potential resistance to neuroendocrine signaling related to eating behavior and weight regulation. Conversely, elevated levels of 2-AG are linked to higher BMI, suggesting a compensatory mechanism

that may moderate AN severity by influencing BMI. The intricate interplay between circulating eCBs and brain function implies a disrupted bidirectional communication, potentially contributing to the challenges in managing abnormal eating behaviors in AN and exacerbating severity.

As shown in study 3, furthermore, as the eCBs play a crucial role in in modulating two main psychological processes related to motivation and hedonic evaluation of food ('wanting' and 'liking' processing) (209,273,274), a dysregulation of the eCBs system may contribute to the disruption of these psychological processes (41,260,281,391). According to the evidence, an altered eCBs system may contribute to aberrant patterns of eating impacting the motivation to and the rewarding properties of food (39,41,392). The two main eCBs, AEA and 2-AG have distinct functions, with AEA primarily associated with increasing motivation to eat (‘wanting’) and 2-AG linked to reinforcing the rewarding properties of food (‘liking’). Considering these neuroendocrine underpinning, we hypothesized that these neuroendocrine factors would show a distinct association with clinical features in EWC compared to HC (study 2 and 3). Specifically, AEA appears to play a more significant role in motivated behavior and psychopathological processes than 2-AG. 2-AG concentrations showed an association with general psychopathology in the anorexia nervosa (AN) group but did not in other EWC groups (study 3). Higher levels of general psychopathology were directly related to increasing AN severity, as indicated by lower BMI. This suggests that alterations in 2-AG concentrations may contribute to the general psychopathological and indirectly influence the AN severity. Regarding AEA, interestingly, individuals with EWC exhibited a common pathway associated with higher emotional dysregulation, which, in turn, mediated increased general psychopathology and impulsivity. However, emotional dysregulation demonstrated to play a differentiated role among the clinical groups of EWC. For instance, emotional dysregulation mediated the influence of AEA on general psychopathology and the presence of food addiction (FA) in both AN and OB. However, in the case of OB, this emotional dysregulation mediated FA through an increase in general psychopathology. These findings could suggest the existence of a common vulnerability factor influenced by AEA in all individuals with EWC (study 2 and 3) supporting the notion that there is a link between circulating eCBs with psychopathological features and the severity of

symptomatology in EWC, as previous studies have described (12,267,269). In this regard, a better understanding of the specific function of AEA and 2-AG on clinical features in EWC may be able to develop more targeted interventions and to improve the treatment outcomes.

Overall, our results supported the notion that alterations in brain circuits are more involve reward and emotional processing than in brain regions implicated in cognitive control (study 1 and 2). According to the model of non-homeostatic brain circuits purposed by Kaye and collaborators (239). Altered regions found in this study might represent the involvement of the ventral brain pathway rather than the dorsal control pathway (Figure 4). The ventral pathway primarily governs motivation and reward, whereas the dorsal control pathway is responsible for the cognitive and executive regulation of feeding-related phenomena in humans (46,239). By integrating the role eCBs and specific brain regions involved in regulating eating behavior, researchers can gain a comprehensive understanding of the neurobiological mechanisms underlying EWC. Future research and treatment approaches could be tailored to elucidate the underlying mechanisms and identify potential therapeutic targets within the eCB system for individuals with EWC.

5.4. NEUROCOGNITIVE FEATURES IN EWC

In addition to examining the neurobiological aspects, neuropsychological tasks oriented to evaluate cognitive flexibility, inhibitory control, and decision-making were employed to assess the impact of cognitive performance on the prognosis of the EWC, taking into account the aforementioned severity (study 2), duration of the disorder (study 4), and treatment outcome (study 5). Firstly, under the hypothesis that individuals with EWC would exhibit impaired executive function compared to HC, results partially demonstrated the presence of alterations in this cognitive domain (studies 1, 4, and 5). Particularly, performance in both delay discounting decision-making and Stroop inhibitory control tasks did not show differences comparing individuals with EWC and HC (studies 1 and 4). In the fMRI delay discounting task, although we observed differences in brain activity between individuals with OB and HC, both groups showed similar performance in discounting future rewards (study 1). This result could indicate

that, although behavioral similarities (i.e., similar discount rates), there are distinct underlying neural mechanisms involved in reward evaluation when individuals choose immediate but smaller rewards over delayed larger rewards. Further research is needed to explore these neural differences and their implications for understanding decision-making processes in individuals with OB. Similarly, our analysis comparing inhibitory control performance across individuals with AN, OB with ED, and HC did not reveal significant differences (study 4). However, when individuals participate in decision-making tasks that encompass long-term risk and reward considerations, such as the IGT, where they must assess and learn from the outcomes of their choices over time, distinctions in decision-making performance become apparent (study 4). During the IGT, participants are required to make a series of choices from multiple decks of cards, each associated with different probabilities of gaining or losing money. This task simulates real-life decision-making scenarios that involve uncertain outcomes and potential long-term consequences. Hence, in contrast to the delay discounting task, the IGT incorporates the capacity to derive insights from decision outcomes during the task by considering the consequences of choices made over an extended period. In the context of these results, individuals with EWC did exhibit poor performance on the IGT compared to HC group. Also, under the hypothesis that longer duration of the ED would have an adverse impact on executive function, our results showed that duration increased the risk of executive function deficits (study 4). Although most alterations in executive function in ED appear to be reversible during recovery (347), this result highlights the existence of an accumulative risk of presenting deficits associated with duration of the EWC. Although a longer duration of the disorder does not necessarily imply greater severity, the chronification of the EWC has been associated with a prognosis characterized by incomplete treatments, relapse, or persistent symptoms even after completing treatment (108). The risk of non-recovery and chronic relapse underscores the importance of understanding factors that may increase this risk. Our results align with previous research (393,394), highlighting the relationship between illness duration and cognitive functions. Recognizing the impact of ED duration on cognitive flexibility is crucial, especially for patients with BSD and AN-R, where deficits in cognitive flexibility may also indicate greater general psychopathology. These insights reveal the complexity of factors influencing cognitive deficits in ED, including the

prognosis of the disorders (363,395,396). Understanding these dynamics is essential for tailoring interventions that promote both ED recovery and the restoration of critical executive functions for daily life. However, further research using longitudinal designs is necessary to investigate the potential relationship between the cumulative duration-associated risk model and deficits in executive function, as well as to explore its interrelationship with the maintenance of ED. In this regard, we also examined the impact of decision-making learning on treatment outcomes. Decision-making is closely intertwined as learning involves acquiring knowledge and skills that directly influence our ability to make informed decisions based on past experiences and future consequences. Our results showed that patients with better treatment outcomes progressed gradually through the blocks of the decision-making task demonstrating better learning than those who reported worse treatment outcomes. This learning curve of decision-making also discriminated between better or poor treatment outcomes in EWC, supporting previous findings that demonstrated decision-making skill acquisition can serve as a predictor of treatment (397,398). For example, longitudinal studies in OB have observed that good decision-making performance was associated with successful weight loss at 12 weeks (397) and one-year following treatment (398). The ability to learn from previous experiences could be crucial in the recovery of patients with EWC because it is entailed successful discrimination between behaviors that should be maintained and those that should be discarded for achieving favorable outcomes.

In summary, our findings underscore the substantial influence of neurobiological and cognitive deficits on maladaptive eating behaviors in EWC, as evident from their associations with clinical features such as severity, duration, and treatment outcomes. This research reinforces the call for increased attention and resources from the scientific community to explore non-invasive cognition-based strategies for both the intervention and assessment of EWC. A promising avenue includes adopting a biomarker approach that integrates neuroimaging, cognitive assessments, and other biological measures to develop precise and efficacious treatments. It is essential to acknowledge that our comprehension of the neurobiological and neuropsychological mechanisms behind maladaptive eating behaviors necessitates further investigation to advance robust translational science.

5.5. LIMITATIONS AND STRENGTHS

The present thesis should be considered within the context of several limitations. First, the sample consists of patients seeking medical help. It is known that only near 20% of patients with ED seek psychological assistance (399,400). Therefore, there is a significant percentage of this clinical population that remains silent and cannot be represented in our studies. Another weakness is the age differences in the clinical study populations, which do not allow for age-matched samples. Patients with AN usually represent a young clinical group, whereas most individuals with OB and patients with BED may take years to seek medical or psychological help, often motivated by health problems associated with excess weight or psychological distress caused by their uncontrolled eating behavior. Additionally, the male population in this thesis is underrepresented. Both age and gender are almost intrinsic characteristics of each EWC. Women are more vulnerable to social and cultural pressures related to appearance, making them more susceptible to developing dysfunctional relationships with food and their bodies. The generalizability of the results to other populations is limited due to the small sample size in the highlighted studies and the recruitment of all patients with EWC from a single center, which does not represent this entire clinical population. In addition, the inclusion of patients under pharmacological treatment introduces a potential bias, and future studies should systematically assess the impact of medication on the variables of interest. Furthermore, most studies presented in this thesis used a cross-sectional design, highlighting the need for powered longitudinal studies to examine whether the neurobiological and clinical alterations persist after weight and eating symptomatology recovery (in the case of patients with ED), as well as to investigate whether the disturbances precede the onset of the disorder.

Notwithstanding these limitations, the study also has several strengths that should be noted. This thesis addresses the first objective by exploring brain function through activity and resting-state approaches, thereby testing our hypotheses from two different technical approaches. MRI has the potential to provide us with a non-invasive investigation of the whole brain allowing the observation of complex patterns of change in space and time, which can be correlated with behavioral measures. This thesis also

sought to go a step further by using biological variables to complement neurobehavioral findings and explore whether endocrine factors could also help to better understand the mechanisms underlying EWC.

5.6. CLINICAL IMPLICATIONS AND FUTURE DIRECTIONS

Our global understanding of the neurobiology of the brain and its role in EWD is still not ready regarding the use of sophisticated techniques such as fMRI to be reliably employed in clinical settings to diagnose or determine the severity. The range and diversity of methodological approaches used in fMRI studies for ED, coupled with the lack of reproducibility studies in the literature, pose challenges in terms of generalizing recent findings. However, despite these challenges, the body of research indicates commonalities in specific neural network alterations across ED, suggesting the potential benefits of employing a dimensional approach to explore the neurobiology of specific behavioral constructs. To make progress in this direction, this thesis considered a biomarker approach that combines various measures such as neuroimaging, cognitive assessments, and other biological markers. The integration of these approaches may have possible a developing of effective treatments. Additionally, a transdiagnostic approach considering EWC as a continuum could be advantageous for the field of ED and OB. By adopting a dimensional perspective, researchers aim to uncover commonalities and underlying mechanisms that contribute to disordered eating and weight-related problems. By studying shared characteristics, such as hormonal dysregulation, altered neural pathways, and psychological factors, a more comprehensive understanding of the neurobiological and clinical substrates of EWC can be achieved. However, it is important to recognize that our understanding of the neuropsychological mechanisms underlying eating behaviors is still in its early stages. Moving forward, first steps in this direction could be adopting a biomarker approach that integrates neuroimaging, cognitive assessments, and other biological measures to facilitate the development of precise endophenotypes and effective treatments.

6. CONCLUSIONS

1. The study supports our initial hypotheses while also presenting new research questions and challenges in the field of extreme eating and weight conditions.
2. Individuals with eating disorders, especially those with obesity, exhibit a more severe clinical profile within the spectrum of extreme eating and weight conditions.
3. The altered brain regions identified in this study may indicate the involvement of the ventral pathway rather than the dorsal control pathway.
4. Neural correlates of delay discounting in individuals with obesity suggest altered insula activations, which may contribute to impulsive decision-making and to focus on short-term consequences.
5. Hypoconnectivity between the core of reward brain system and the insula and the supplementary motor area in anorexia nervosa may underlie difficulties in integrating sensory and motor planning information, potentially overriding responses to rewarding stimuli.
6. The interaction between nucleus accumbens connectivity and endocannabinoid concentrations distinguishes anorexia nervosa from healthy controls, suggesting a role of endocannabinoids in the eating disorder severity based on DSM-5 criteria.
7. Circulating anandamide levels are associated with body mass index and various psychopathological traits across clinical groups, potentially serving as a common neurobiological marker.
8. Elevated anandamide levels in anorexia nervosa may indicate resistance to neuroendocrine signals involved in regulating eating behavior.
9. Higher levels of 2-arachidonoylglycerol in anorexia nervosa may represent a compensatory mechanism influencing body mass index and overall psychopathology.
10. Neurocognitive performance in extreme eating and weight conditions is characterized by impaired decision-making and cognitive flexibility, while cognitive inhibitory control remains relatively intact compared to individuals without these disorders.

11. There is an early risk of deficits in decision-making, cognitive flexibility, and inhibitory control across eating disorders, particularly in cases with longer illness durations.
12. Skill acquisition in decision-making appears to be a valuable predictor of positive treatment outcomes, emphasizing the importance of considering cognitive factors in the management of eating disorders.

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