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Identificación y validación de marcadores inflamatorios, daño oxidativo y cardiovascular para el rendimiento neurocognitivo en población con enfermedad mental grave y diabetes mellitus tipo 2

Tesis Doctoral presentada por:

Joan Vicent Sánchez Ortí

Directores y tutor académico:

Dr. Vicent Balanzá Martínez

Dra. Patricia Correa Ghisays

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INFORME DIRECTOR, CODIRECTORA Y TUTOR PARA DEPÓSITO DE TESIS

Directores / Codirectores:

1.- Apellidos y nombre: Vicent Balanzá Martínez, N.I.F.: 25419535G, Departamento: Medicina, Centro: Universitat de València.

2.- Apellidos y nombre: Patricia Correa Ghisays, N.I.F.: 21804343K, Departamento: Psicología Evolutiva y Educación, Centro: Universitat de València.

Tutor o tutora

Apellidos y nombre: Vicent Balanzá Martínez, N.I.F.: 25419535G, Departamento: Medicina, Centro: Universitat de València.

Director, codirectora y tutor, respectivamente, de la tesis doctoral: "*Identificación y validación de marcadores inflamatorios, daño oxidativo y cardiovascular para el rendimiento neurocognitivo en población con enfermedad mental grave y diabetes mellitus tipo 2*" de D. Joan Vicent Sánchez Ortí, estudiante del Programa de Doctorado **3139 Medicina** (RD99/2011) en Medicina de la Universitat de València, emiten informe **FAVORABLE** para la realización del depósito y la defensa de la tesis doctoral.

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PRÓLOGO

La presencia de múltiples enfermedades crónicas en un mismo individuo se ha convertido en uno de los principales desafíos de salud del siglo XXI. El incremento en la esperanza de vida acaecido durante las últimas décadas, entre otros factores, se ha asociado con un crecimiento drástico en la aparición de enfermedades comórbidas. Entre los principales componentes involucrados se encuentran, por un lado, los diversos factores de riesgo cardiometabólicos y, por otro, los estilos de vida poco saludables, como la inactividad física, el sedentarismo, patrones de dieta/nutrición y sueño de pobre calidad, abuso de sustancias, alcohol o tabaco. Se piensa que incrementan el riesgo de desarrollar diferentes enfermedades crónicas y, a su vez, contribuyen al aumento de la carga de enfermedad. El empeoramiento en la calidad de vida y el aumento de la mortalidad en etapas tempranas de la vida se encuentran entre las principales consecuencias para las personas.

Es ampliamente conocido que las personas con trastorno mental grave presentan una mayor probabilidad de desarrollar enfermedades cardiometabólicas en comparación con la población general. Asimismo, las personas con enfermedades metabólicas también tienen mayores probabilidades de desarrollar un trastorno mental a lo largo de su vida. La coocurrencia de estas enfermedades puede ser debida a la aparición de factores de riesgo comunes. De hecho, un porcentaje significativo de los individuos que desarrollan esta comorbilidad presentan un estilo de vida poco saludable.

Desde la perspectiva de la práctica clínica, la intervención de la comorbilidad plantea un reto considerable debido a la escasez de pruebas válidas y fiables para realizar un diagnóstico certero y a la complejidad de las interacciones entre los diferentes fármacos y sus efectos secundarios. En la actualidad, se considera que la prevención es un pilar fundamental para evitar posibles consecuencias adversas, lo que requiere de grupos de trabajo multidisciplinares que trabajen coordinadamente para tratar las diferentes enfermedades.

Desde el punto de vista fisiológico, el reto se centra en comprender el origen del aumento de la coocurrencia o comorbilidad de las enfermedades metabólicas y los trastornos mentales, lo que puede deberse a diversos factores genéticos, ambientales, cambios fisiológicos relacionados con el curso de la enfermedad o el impacto de los efectos secundarios de fármacos en el organismo, actuando de forma aislada o más habitualmente interactiva. En consecuencia, delimitar los mecanismos fisiológicos que subyacen a la coocurrencia de estas enfermedades puede mejorar la precisión en el diagnóstico y proporcionar vías de estudio para nuevas dianas terapéuticas.

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LISTA DE ABREVIATURAS Y SIGLAS

Apo-A1	Apolipoproteína- A1
Apo-B:	Apolipoproteína- B
APA	Asociación Americana de Psiquiatría
BHE	Barrera Hematoencefálica
CCL11	Chemokine (C-C motif) Ligand 11 (Eotaxina-1)
CCL2	Chemokine (C-C motif) Ligand 2 (MCP-1: Monocyte Chemoattractant Protein-1)
CCL3	Chemokine (C-C motif) Ligand 3 (MIP-1α: Macrophage Inflammatory Protein-1α)
CCL20	Chemokine (C-C motif) Ligand 20
CIE	Clasificación Internacional de Enfermedades
COX	Ciclooxigenasa
COX-2	Ciclooxigenasa-2
CS	Control Sano
DMT2	Diabetes Mellitus Tipo 2
DSM	Manual Diagnóstico y Estadístico de los Trastornos Mentales
ECM	Enfermedad Cardiometabólica
EZ	Esquizofrenia
GBD	Global Burden of Disease
HiTOP	Taxonomía Jerárquica de la Psicopatología
ICAM	ICAM: Molécula de Adhesión Intercelular 1
IFN-gamma	IFN-gamma: Interferón gamma
IL-1	Interleucina-1
IL-1β	Interleucina-1 beta
IL-1b	Interleucina-1 beta
IL-1RA	Antagonista del receptor de interleucina-1
IL-4	Interleucina-4
IL-6	Interleucina-6
IL-7	Interleucina-7
IL-8	Interleucina-8
IL-10	Interleucina-10
IL-12	Interleucina-12
IL-17	Interleucina-17
IL-18	Interleucina-18
IL-33	Interleucina-33

IL-6	Interleucina-6
IL-17	Interleucina-17
MAPK	Mitogen-Activated Protein Kinase (Quinasa activada por mitógenos)
NF-κB	Nuclear Factor kappa-light-chain-enhancer of activated B cells (Factor nuclear kappa B)
NLR	Ratio Neutrófilo-Linfocito
OB	Obesidad
OMS	Organización Mundial de la Salud
PCR	Proteína C reactiva
PLR	Ratio Plaqueta-Linfocito
PLT	Plaquetas
RDoC	Criterios de Dominio de Investigación
ROS	Reactive Oxygen Species (Especies reactivas de oxígeno)
RPMN	Recuento de Polimorfonucleares
RVPMN	Recuento de Variación de Polimorfonucleares
SNC	Sistema Nervioso Central
SM	Síndrome Metabólico
sIL-2R	Receptor soluble de la interleucina-2
sIL-6R	Receptor soluble de la interleucina-6
sTNF-R1	Receptor soluble del TNF tipo 1
sTNFR1	Receptor soluble del TNF tipo 1
sTNFR2	Receptor soluble del TNF tipo 2
TDM	Trastorno Depresivo Mayor
TG	Triglicéridos
TLR	Toll-Like Receptors (Receptores tipo Toll)
TNF-a	Factor de necrosis tumoral alfa
TB	Trastorno Bipolar
TMG	Trastorno Mental Grave
VCAM	Molécula de Adhesión Celular Vascular 1
ROS	Especies Reactivas de Oxígeno
mROS	Especies Reactivas de Oxígeno Mitocondriales

RESUMEN

Introducción: Los déficits cognitivos son frecuentes en los trastornos mentales graves (TMGs) y ciertas enfermedades cardiometabólicas (ECMs), asociándose a alteraciones en memoria, atención, velocidad de procesamiento y función ejecutiva. Estos déficits comparten mecanismos biológicos, como inflamación sistémica de bajo grado, disfunción metabólica y estrés oxidativo, que pueden afectar el funcionamiento del sistema nervioso central. Los biomarcadores asociados a estos procesos tienen un impacto diferencial según la presencia de comorbilidades. Esta tesis doctoral integra las perspectivas transdiagnósticas y de comorbilidad para explorar cómo estas interacciones biológicas contribuyen a los déficits cognitivos, proponiendo que los biomarcadores inflamatorios y metabólicos actúan como factores de riesgo transdiagnósticos.

Metodología: Para alcanzar el objetivo principal, se diseñaron tres estudios. Los participantes fueron 165 individuos, 30 con diagnóstico de esquizofrenia (EZ), 42 con diagnóstico de trastorno bipolar (TB), 35 con diagnóstico de trastorno depresivo mayor (TDM), 30 con diagnóstico de diabetes tipo 2 (DMT2) y 28 individuos sanos (CSs). En el estudio I se evaluaron los componentes del síndrome metabólico (SM), el funcionamiento cognitivo y social. El estudio II se centró en los biomarcadores periféricos de inflamación, estrés oxidativo y metabolismo lipídico en relación con la obesidad (OB). En el estudio III se evaluó la relación entre el rendimiento cognitivo y los biomarcadores inflamatorios y lipídicos. Todos los estudios se basan en los resultados de dos evaluaciones realizadas durante el periodo de un año.

Resultados: En primer lugar, los resultados mostraron que los participantes con SM presentaron un mayor deterioro cognitivo en comparación con los que no lo padecían, especialmente en relación con los niveles de triglicéridos y la glucemia en ayunas. En segundo lugar, se observó que los individuos con OB tipo 1 y tipo 2 mostraron un peor rendimiento cognitivo y mayores niveles de marcadores inflamatorios, como la proteína C-reactiva. En tercer lugar, la combinación de biomarcadores inflamatorios y metabólicos fue útil para la identificación del deterioro cognitivo en una muestra transdiagnóstica de TMG.

Conclusiones: Las conclusiones principales indican que (1) la comorbilidad entre TMG y ECM está estrechamente vinculada con el deterioro cognitivo y social. (2) La interrelación entre los mecanismos metabólicos e inmuno-inflamatorios respalda un enfoque transdiagnóstico para abordar tanto trastornos psiquiátricos como metabólicos. (3) Los biomarcadores de inflamación y metabolismo proporcionan un modelo útil para identificar individuos en riesgo de desarrollar deterioro cognitivo, lo que podría permitir una detección temprana y un tratamiento personalizado.

ABSTRACT

Introduction: Cognitive deficits are common in severe mental illnesses (SMIs) and certain cardiometabolic diseases (CMDs), being associated with alterations in memory, attention, processing speed and executive function. These deficits share biological mechanisms, such as low-grade systemic inflammation, metabolic dysfunction and oxidative stress, which can affect the functioning of the central nervous system. Biomarkers associated with these processes have a differential impact depending on the presence of comorbidities. This PhD thesis integrates transdiagnostic and comorbidity perspectives to explore how these biological interactions contribute to cognitive deficits, proposing that inflammatory and metabolic biomarkers act as transdiagnostic risk factors.

Methodology: To achieve the main objective, three studies were designed. Participants were 165 individuals, 30 with a diagnosis of schizophrenia (SZ), 42 with a diagnosis of bipolar disorder (BD), 35 with a diagnosis of major depressive disorder (MDD), 30 with a diagnosis of type 2 diabetes (T2DM) and 28 healthy individuals (HCs). Study I assessed the components of metabolic syndrome (MetS), cognitive and social functioning. Study II focused on peripheral biomarkers of inflammation, oxidative stress and lipid metabolism in relation to obesity (OB). Study III assessed the relationship between cognitive performance and inflammatory and lipid biomarkers. All studies are based on the results of two assessments conducted over a one-year period.

Results: First, the results showed that participants with MS had greater cognitive impairment compared to those without, especially in relation to triglyceride levels and fasting blood glucose. Second, it was observed that individuals with type 1 and type 2 OB showed worse cognitive performance and higher levels of inflammatory markers, such as C-reactive protein. Third, the combination of inflammatory and metabolic biomarkers was useful for the identification of cognitive impairment in a transdiagnostic TMG sample.

Conclusions: The main findings indicate that (1) comorbidity between SMI and CMD is closely linked to cognitive and social impairment. (2) The interrelationship between metabolic and immune-inflammatory mechanisms supports a transdiagnostic approach to address both psychiatric and metabolic disorders. (3) Inflammatory and metabolic biomarkers provide a useful model to identify individuals at risk for developing cognitive impairment, which could allow for early detection and personalized treatment.

1. INTRODUCCIÓN

1.1. Comorbilidad física en salud mental: una perspectiva holística

Los trastornos psiquiátricos son un grupo heterogéneo de enfermedades caracterizadas por síntomas conductuales, emocionales y cognitivos. Según la *Global Burden of Disease* (GBD), los trastornos psiquiátricos se encuentran entre las principales causas de carga de enfermedad a nivel mundial y su prevalencia ha crecido considerablemente en las últimas décadas (GBD, 2022).

Las personas con trastorno mental grave (TMGs), como el trastorno depresivo mayor (TDM), el trastorno bipolar (TB) o la esquizofrenia (EZ), presentan una tasa de comorbilidad más elevada que la población general (GBD, 2020). Esta circunstancia tiene profundas consecuencias en múltiples ámbitos de la vida diaria, por ejemplo, reducción de la calidad de vida, funcionamiento social, y/o rendimiento cognitivo y, se ha relacionado directamente con una disminución considerable en la esperanza de vida de entre 10 y 20 años (GBD, 2024a). Aunque la conducta suicida contribuye a incrementar la morbilidad y la mortalidad prematura, la principal causa son las enfermedades físicas que representan aproximadamente el 70% de la tasa de mortalidad, especialmente, las enfermedades cardiometabólicas (ECMs). Se considera que estas contribuyen a una cuarta parte de la reducción de la esperanza de vida en dicho colectivo (GBD, 2024b; Sánchez-Valle et al., 2020). Los factores de riesgo cardiometabólicos, como la obesidad (OB), la diabetes, la hipertensión arterial, la dislipidemia y el tabaquismo, surgen a una edad más temprana y son más prevalentes en las personas con TMG. Tanto los factores de riesgo como las ECMs comórbidas se asocian con una evolución desfavorable de la enfermedad mental y con peores resultados clínicos, incluyendo una peor respuesta a los psicofármacos y un mayor riesgo de recaídas (de Louw et al., 2019; GBD, 2024c; Liu et al., 2022; Martins et al., 2019). Además, el síndrome metabólico (SM), la hipertensión, la OB y la diabetes se han asociado de forma significativa con el deterioro cognitivo en personas con TMG (Dove y Xu, 2023).

Actualmente, nuestra comprensión sobre los mecanismos causales de la comorbilidad entre los TMGs y las enfermedades físicas, concretamente las ECMs, es limitada. Sin embargo, parecen estar asociados con factores de riesgo socioeconómicos (por ejemplo, bajo nivel educativo y desempleo), estilos de vida (por ejemplo, dieta de calidad pobre, sedentarismo,

insomnio, consumo de sustancias de abuso), mecanismos biológicos y fisiopatológicos compartidos y/o interacciones recíprocas (por ejemplo, efectos secundarios de los psicofármacos) (Fiorillo y Sartorius, 2021). Cabe mencionar que los TMGs se caracterizan por una fisiopatología compleja que involucra a múltiples sistemas fisiológicos, además del sistema nervioso central (SNC). En este contexto, los TMGs se han conceptualizado, no sólo como el resultado de una enfermedad del cerebro, sino también como enfermedades sistémicas (Leboyer et al., 2012; Zumstein y Riese, 2020).

El creciente interés por la comorbilidad y los mecanismos comunes entre los TMGs y las ECMs, su impacto en los resultados clínicos y la comprensión de sus fundamentos fisiopatológicos tienen varias implicaciones. En la práctica clínica, este conocimiento puede orientar las decisiones diagnósticas (por ejemplo, pruebas de cribado diagnóstico), así como las medidas preventivas y terapéuticas (por ejemplo, prevención de los factores de riesgo, mayor precisión en los tratamientos farmacológicos y psicológicos) dirigidas a este colectivo. Por último, desde el ámbito de la investigación, podría contribuir significativamente a identificar nuevas dianas terapéuticas basadas en mecanismos neurobiológicos comunes.

Si bien es cierto que se ha hecho un esfuerzo considerable por parte de las instituciones socio-sanitarias para atajar algunos de los principales problemas de salud física en población con TMG (por ejemplo, campañas de promoción de la salud para prevenir la aparición de los factores de riesgo cardiometabólicos y fomento de los estilos de vida saludables), se considera que estas siguen siendo insuficientes (Chang et al., 2023; Dregan et al., 2020; Moeti et al., 2022).

Las personas con TMG no parecen haberse beneficiado de los avances en prevención y tratamiento de las ECMs en la misma medida que la población general. Así, la mortalidad por enfermedades físicas sigue creciendo en esta población (Peitz et al., 2021). Además, la alta probabilidad de aparición de los factores de riesgo cardiometabólicos se ha mantenido a lo largo del tiempo. Pruebas recientes muestran una mayor incidencia de diabetes y resistencia a la insulina, así como un aumento en los problemas de hipertensión y dislipemia en edades tempranas, lo que puede dar lugar a eventos cardiovasculares adversos (Carney et al., 2021). Asimismo, la calidad de vida se ve notoriamente reducida cuando se comparan ambas poblaciones. Además, aproximadamente el 75% de las personas con TMG con una ECM comórbida necesita apoyo socio-sanitario externo para ser autónomos, en comparación con aquellas con TMG sin una ECM comórbida (Dai et al., 2020; Mejaddam et al., 2022).

1.2. Hacia un nuevo paradigma diagnóstico: abordando la heterogeneidad y la comorbilidad

La comorbilidad, definida como la presencia de más de un trastorno o enfermedad en el mismo individuo, parece ser la norma y no la excepción cuando nos referimos a las enfermedades mentales (Nordgaard et al., 2023). En este sentido, las personas con diagnóstico de trastorno mental, como TDM, TB, ansiedad, trastorno obsesivo-compulsivo y algunos trastornos psicóticos tienen altas tasas de comorbilidad entre sí (Halstead et al., 2024). De hecho, alrededor del 50% de los individuos con TMG han sufrido uno o más episodios de ansiedad a lo largo de su vida (Léda-Rêgo et al., 2024; Wilson et al., 2020), y casi un tercio de las personas con trastornos de ansiedad ha recibido tratamiento antipsicótico o antidepresivo (Garakani et al., 2024; Scholten et al., 2020). De manera análoga ocurre con las ECMs, en las que más de la mitad de los individuos presenta otra enfermedad comórbida, ya sea de carácter cardiovascular, respiratorio o metabólico (Sacramento-Pacheco et al., 2023).

Incluir los factores de riesgo y protección compartidos podría ser una perspectiva adecuada para comprender las elevadas tasas de comorbilidad y los posibles solapamientos neurobiológicos que existan entre los TMGs y otras enfermedades, como las ECMs (Álvarez-Gálvez et al., 2023). Los estilos de vida poco saludables, que suelen caracterizar a la población con TMG, pueden incrementar drásticamente el riesgo de desarrollar alguna ECM (Firth et al., 2020). Las ECMs son la principal causa de muerte en personas con un TMG, quienes presentan tasas más altas de infarto de miocardio, hipertensión arterial y accidentes cerebrovasculares en comparación con la población general (Firth et al., 2019).

En este sentido, las personas con SM tienen, aproximadamente, tres veces más probabilidades de desarrollar trastornos del estado de ánimo y el doble de presentar algún trastorno psicótico (Sotos-Prieto et al., 2021). El SM es un conjunto de enfermedades médicas interrelacionadas que incluyen el perímetro abdominal aumentado (PA), los triglicéridos elevados (TG), niveles bajos de colesterol de lipoproteínas de alta densidad (HDL), glucosa plasmática en ayunas elevada (GA) y presión arterial alta (PA) (Punthakee et al., 2018). Este diagnóstico requiere la presencia de, al menos, tres de los siguientes cinco criterios [Panel de Tratamiento de Adultos III (Adult Treatment Panel III, ATP III) del Programa Nacional de Educación

sobre el Colesterol (National Cholesterol Education Program, NCEP)]: PA aumentado, TG elevados, colesterol HDL reducido, GA elevada y PA elevada. Los valores de corte establecidos, por el NCEP y ATP III, para definir estas alteraciones son los siguientes: (i) PA > 102 cm en hombres y > 88cm en mujeres; (ii) TG ≥ 150 mg/dl o tratamiento específico; (iii) niveles de HDL < 40 mg/dl en hombres y < 50 mg/dl en mujeres o tratamiento específico; (iv) PA sistólica ≥130 mmHg y PA diastólica ≥ 85 mmHg o tratamiento de hipertensión arterial previamente diagnosticada; y (v) niveles de GA ≥ 100 mg/dl o diagnóstico previo de diabetes mellitus tipo 2 (DMT2) (Alberti et al., 2009; Punthakee et al., 2018).

La evidencia reciente ha destacado que las alteraciones metabólicas también están asociadas con un aumento de la morbilidad y mortalidad prematura (Dols, 2019; Pillinger et al., 2018). El diagnóstico de SM permite identificar a individuos con un mayor riesgo de desarrollar enfermedades crónicas, como la DMT2, debido a la relación entre sus componentes, en especial la combinación de TG elevados y HDL reducido (Meamar et al., 2020). Asimismo, la prevalencia de TMG se duplica en individuos con enfermedades crónicas, como diabetes, dislipemia u osteoporosis, y se triplica en aquellos con OB (NCD-RisC, 2017). La OB también es un buen ejemplo, ya que constituye un factor de riesgo común para el desarrollo de ECMs y trastornos mentales, especialmente trastornos del estado de ánimo (Blüher, 2019). Asimismo, comparte mecanismos biológicos con ambos tipos de enfermedades, TMGs y otras ECMs (Sánchez-Valle et al., 2020).

En este sentido, la inflamación sistémica se ha visto implicada en la fisiopatología tanto de los trastornos mentales como cardiometabólicos (Palmer et al., 2024). Otras vías de acción molecular, compartidas por ambos tipos de enfermedades incluyen el estrés oxidativo, la disfunción mitocondrial, las alteraciones en el retículo endoplasmático y la apoptosis (Teixeira et al., 2022). En las últimas décadas, varios estudios centrados en el riesgo poligénico han demostrado la existencia de cierta superposición genética entre los TMGs y las ECMs, principalmente en genes implicados en la respuesta inmuno-inflamatoria (Rodrigue et al., 2022). Estos hallazgos parecen sustentar la idea de que ciertos mecanismos biológicos comunes podrán estar implicados en el desarrollo de estas comorbilidades (**Figura 1**).

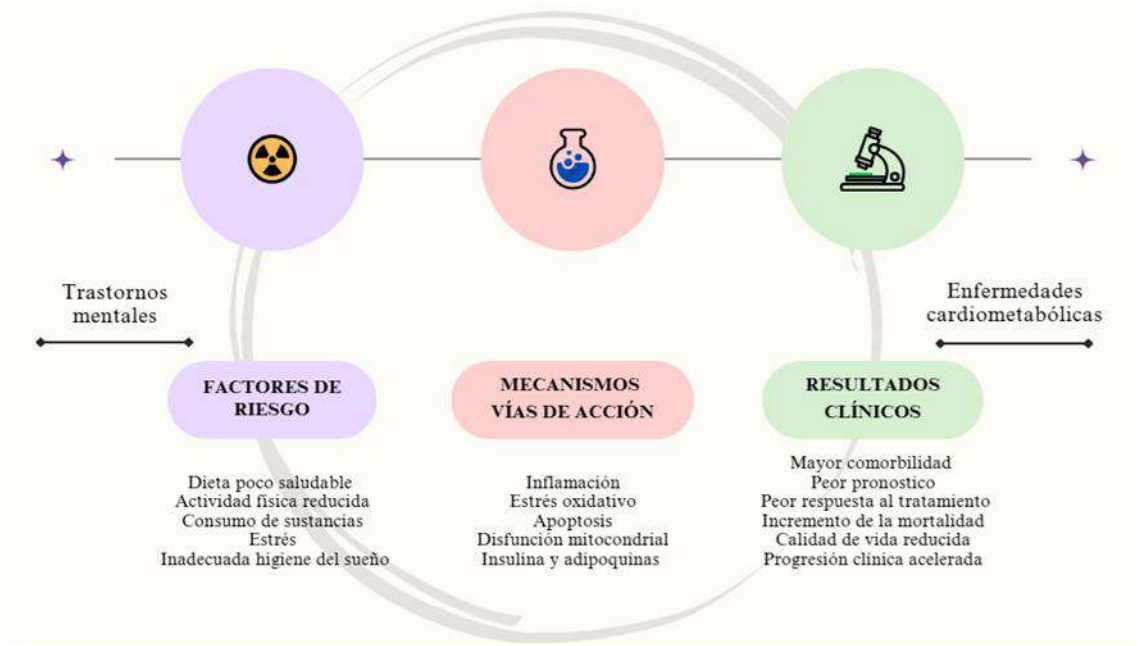

Figura 1. Mecanismos compartidos entre TMGs y ECMs (elaboración propia).

1.2.1. Alternativas a las clasificaciones diagnósticas convencionales: integrando el enfoque dimensional

La perspectiva transdiagnóstica intenta suplir las limitaciones de los modelos nosológicos basados en categorías diagnósticas (Oliver, 2024). Se fundamenta en la idea de que los trastornos mentales no son entidades separadas que se aglutinan en categorías únicas y aisladas, sino que serían la expresión de variaciones en una misma dimensión clínica que puede ser compartida por varias categorías diagnósticas. Dicha perspectiva entiende la naturaleza de la salud y la enfermedad como un continuo con diferentes grados de disfunción en cada uno de los sistemas neurobiológicos fundamentales. El enfoque transdiagnóstico se centra en identificar los procesos subyacentes y compartidos entre los distintos trastornos mentales y comorbilidades (Vogel et al., 2024). Este planteamiento supone un punto de partida para aumentar el conocimiento sobre los componentes y mecanismos neurobiológicos, conductuales, cognitivos y emocionales a través de los cuales ejercen su acción los factores de riesgo y protección en las enfermedades mentales (Waszczuk et al., 2023). Sin embargo, se trata de una propuesta más entre muchas otras que coexisten, cada

una intentando aportar soluciones a la complejidad inherente de los TMGs (Eaton et al., 2023).

En este contexto, parece que el enfoque tradicional basado en categorías diagnósticas, planteado en el Manual Diagnóstico y Estadístico de los Trastornos Mentales (DSM) de la Asociación Americana de Psiquiatría (APA) y la Clasificación Internacional de Enfermedades (CIE) de la Organización Mundial de la Salud (OMS), es insuficiente para abordar el desafío de la comorbilidad y la heterogeneidad de los trastornos mentales. El enfoque categorial fue el primero en implementarse y ofrece algunas ventajas como la facilidad para realizar un diagnóstico en múltiples contextos. La alta fiabilidad de la homogeneización de los criterios diagnósticos, definida por consenso entre expertos y basada en la similitud de las manifestaciones sintomáticas ha sido, hasta ahora, una de sus principales ventajas para el buen funcionamiento de ambos sistemas de clasificación diagnóstica (First et al., 2023; Gaebel et al., 2020). Sin embargo, la utilidad de estas categorías diagnósticas es limitada. Entre otras consecuencias, no permite la identificación de dianas terapéuticas certeras, lo que convierte el manejo clínico y el tratamiento en un proceso de ensayo-error (Köhne et al., 2020).

Según algunos autores (Huda 2021), las críticas principales hacia estos sistemas de clasificación serían tres:

- *Alta comorbilidad entre entidades diagnósticas*. Las personas con un diagnóstico específico suelen cumplir criterios de otros trastornos. Esto cuestiona el enfoque aislado en trastornos individuales, alejándose del contexto clínico donde la comorbilidad es la norma.
- *Heterogeneidad de las manifestaciones clínicas de personas con el mismo diagnóstico*. Dos individuos con el mismo diagnóstico pueden compartir pocos síntomas, lo que dificulta identificar mecanismos neurobiológicos comunes debido a su gran variabilidad clínica.
- *Baja capacidad predictiva de la respuesta al tratamiento*. Clasificar por recuento de síntomas puede ignorar algunos factores como la cronicidad o el desarrollo evolutivo.

Estas circunstancias reflejan la necesidad de profundizar en la comprensión tanto del desarrollo como del tratamiento de los trastornos mentales. Se ha sugerido que el ámbito de la salud mental necesita incorporar una perspectiva holística e integrada que aborde los avances

científicos en el funcionamiento cerebral desde una perspectiva dimensional de lo típico (normal) y atípico (patológico) a lo largo de todo el ciclo vital (Bolton, 2023).

1.2.1.1. Modelo RDoC

En línea con estos planteamientos, los Criterios de Dominio de Investigación (*Research Domain Criteria*, RDoC) introducidos por el Instituto Nacional de Salud Mental de los Estados Unidos se centraron en llevar la investigación más allá de las limitaciones de los enfoques diagnósticos tradicionales, considerando en su lugar dimensiones transdiagnósticas que podrían llegar a validarse a nivel biológico (Cuthbert, 2020).

El enfoque RDoC invierte la perspectiva clásica al considerar la sintomatología clínica en términos de desviaciones en el funcionamiento normal y no utilizar signos o síntomas para definir enfermedades específicas. De este modo, incorpora la perspectiva transdiagnóstica entendiendo que la sintomatología clínica es la expresión fenotípica de alteraciones en los dominios neurobiológicos. El enfoque RDoC no implica reduccionismo biológico ya que no se reduce la sintomatología a causas biológicas, sino que entiende que los síntomas mentales suceden en el SNC y, por tanto, sus manifestaciones también pueden ser detectables a ese nivel (MacNeill et al., 2021; Williams et al., 2024) (**Figura 2**).

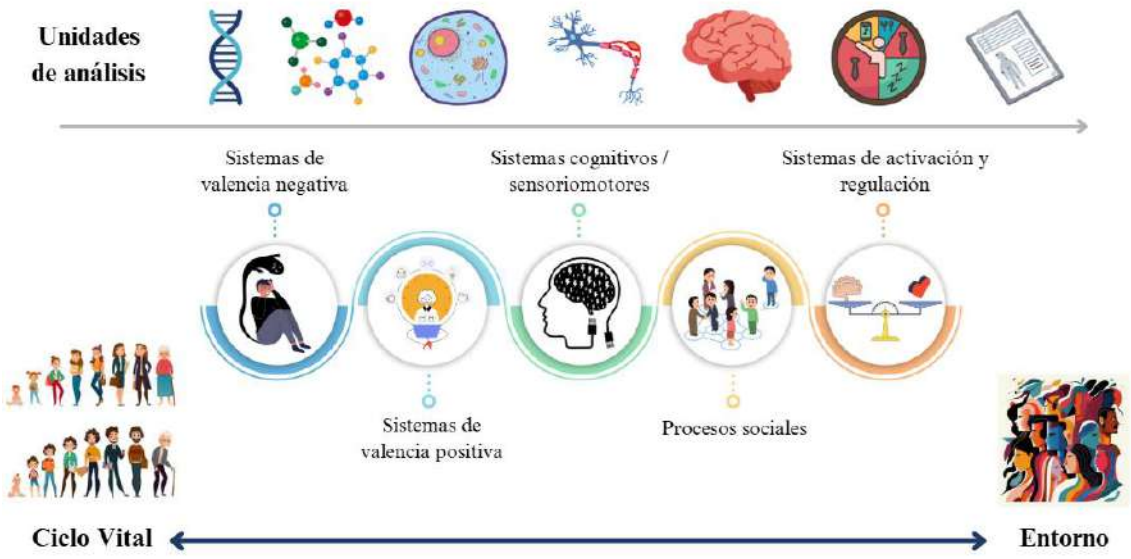

Figura 2. Esquema RDoC que recoge los constructos o dominios funcionales y sus unidades de análisis que hacen referencia a los niveles metodológicos del estudio de sus componentes (elaboración propia).

1.2.1.2. Modelo HiTOP

Otro enfoque dimensional, la Taxonomía Jerárquica de la Psicopatología (*Hierarchical Taxonomy of Psychopathology*, HiTOP), fue diseñado de manera similar para abordar los problemas relacionados con los límites diagnósticos arbitrarios, como la heterogeneidad y la comorbilidad, pero también para ser más inmediatamente relevante en la clínica (Conway et al., 2022). HiTOP se desarrolla a partir de investigaciones clínicas, particularmente mediante análisis factorial y análisis de clúster latentes aplicados a los síntomas psiquiátricos (Kotov et al., 2017; 2022; Ringwald et al., 2023).

En este sentido, mientras que el RDoC busca comprender los fundamentos etiológicos del comportamiento normal y patológico a través de dimensiones fundamentadas en la neurociencia, HiTOP propone un sistema diagnóstico alternativo enfocado en su aplicación práctica en el ámbito clínico, priorizando la descripción de síntomas, signos y comportamientos clínicos (Kotov et al., 2021). Sin embargo, ambos enfoques son complementarios, ya que HiTOP ha desarrollado un modelo jerárquico de dimensiones

psicopatológicas altamente sólido, capaz de orientar la investigación neurocientífica dentro del marco del RDoC (Michelini et al., 2021) (**Figura 3**).

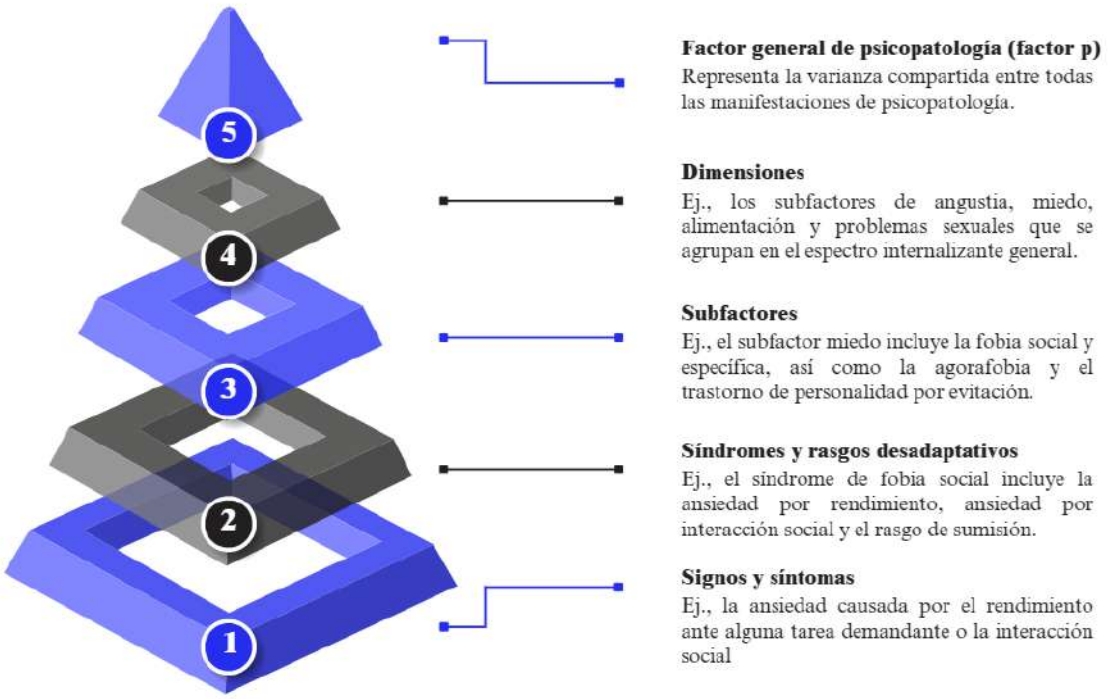

Figura 3. Esquema HiTop que recoge los principales niveles de análisis (elaboración propia).

En este sentido, los enfoques dimensionales RDoC y HiTOP surgieron para abordar esta necesidad. Se centraron en superar las limitaciones de los enfoques categoriales, postulando un cambio de paradigma que considerase dimensiones transdiagnósticas con potencial para ser validadas mediante marcadores biológicos (Cuthbert, 2020; Kotov et al., 2022) (**Figura 4**).

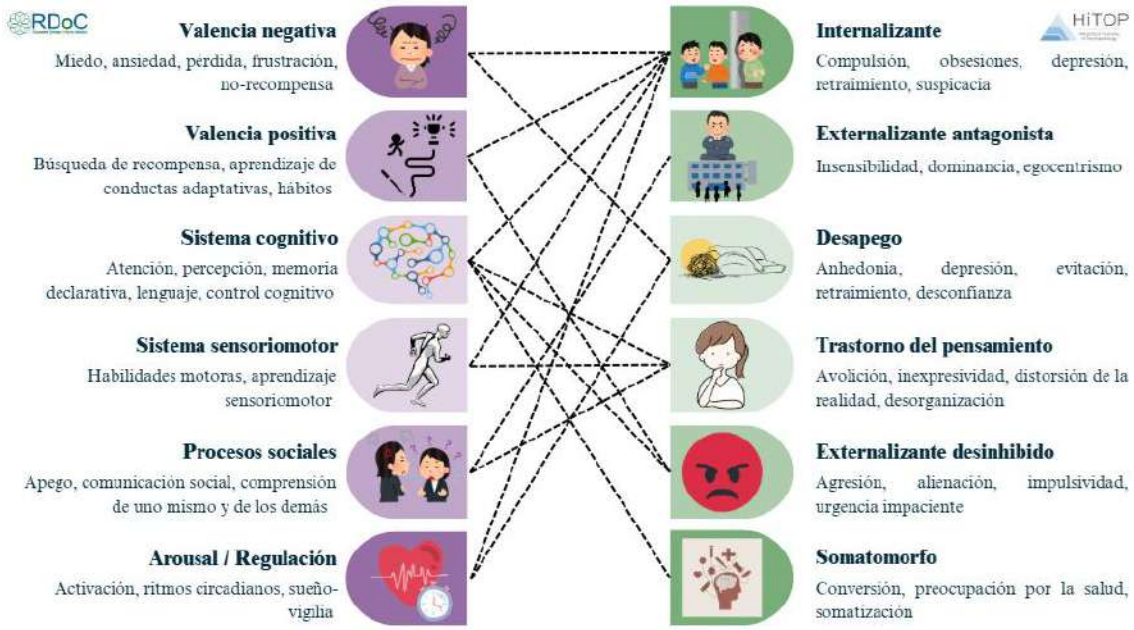

Figura 4. Resumen de las principales relaciones entre los enfoques RDoC y HiTOP (elaboración propia).

En consecuencia, se han producido algunos avances en la identificación de características transdiagnósticas en los TMG (como síntomas de ansiedad, anhedonia y algunos déficits cognitivos) que estaban relacionadas con niveles de análisis más básicos como genes o conectividad neuronal, mientras que se han logrado menos avances en relación con los biomarcadores moleculares en sangre periférica (Parkes et al., 2020; Petersen y Miskowiak, 2021). Sin embargo, los últimos estudios apuntan a que los biomarcadores inmune-inflamatorios pueden llegar a ser fiables en la mayoría de TMG (Goldsmith et al., 2023). Así pues, parece que existe una creciente necesidad de identificar biomarcadores válidos para predecir la respuesta al tratamiento y la mejora de los resultados clínicos.

1.3. Medicina de precisión: integrando constructos y perspectivas

La medicina de precisión se caracteriza por promover tratamientos específicos y personalizados basados en la especificidad de los síntomas, características biológicas y experiencias (conductas, emociones y cognición) de cada persona. Estos tratamientos tienen el potencial de mejorar sustancialmente la calidad de vida y el funcionamiento diario de las personas con TMG y enfermedades relacionadas (Scala et al., 2023).

En la actualidad, las tasas de adherencia al tratamiento, farmacológico y/o psicológico, varían entre el 30% y el 60% y la remisión completa se produce en menos de un tercio de las personas con un diagnóstico de TMG. Asimismo, existen grandes diferencias interindividuales relacionadas, sobre todo, con las comorbilidades y la gravedad de la sintomatología. De modo que aquellas personas con TMG y un peor estado físico y/o mental tienen una menor probabilidad de recuperación y la remisión es más prolongada en el tiempo (Rødevand et al., 2022).

La medicina de precisión también está relacionada con las enfermedades físicas. Por ejemplo, se han identificado con éxito algunos biomarcadores para ciertos tipos de cáncer (Hacking et al., 2022; Lin et al., 2020). Sin embargo, por el momento, los marcadores biológicos en el ámbito de los trastornos mentales no han alcanzado ese desarrollo (McQuaid, 2021). La gran heterogeneidad en la sintomatología entre individuos con un mismo diagnóstico y la permeabilidad en las zonas limítrofes de las categorías diagnósticas podrían explicar la dificultad a la hora de identificar biomarcadores específicos para los TMGs.

La medicina de precisión, con su enfoque en tratamientos personalizados basados en características individuales, establece un marco prometedor para abordar la complejidad de los TMGs y sus comorbilidades. No obstante, las limitaciones en la identificación de biomarcadores específicos resaltan la necesidad de un enfoque más amplio que integre tanto factores compartidos como interacciones bidireccionales entre los TMG y las ECMs. Este enfoque holístico permite entender cómo la inflamación, la neuroinflamación y otros mecanismos moleculares compartidos contribuyen al desarrollo y la cronicidad de ambas condiciones, ofreciendo una perspectiva más integrada para avanzar en la investigación y el tratamiento de estas complejas interacciones.

1.4. Mecanismos moleculares compartidos por los TMGs y las ECMs

Hasta ahora, la investigación en biomarcadores se ha centrado en categorías diagnósticas concretas. Si bien parece una buena estrategia de investigación, es importante destacar que las comorbilidades existentes entre los TMGs obstaculizan la identificación de las características clave de un trastorno en particular.

En este sentido, la evidencia reciente apunta a que la inflamación crónica de bajo grado contribuye al desarrollo de ECMs, incluidas la diabetes y la OB (Evans et al., 2021). Se han investigado algunas vías de acción a través de las cuales las moléculas pro-inflamatorias pueden transmitirse desde la periferia del organismo al cerebro, lo que se conoce como neuroinflamación. Las citoquinas periféricas pueden cruzar la barrera hematoencefálica (BHE) a través de canales de transporte y zonas permeables, activando la microglía y contribuyendo así a la neuroinflamación. La activación de la microglía puede provocar una cascada de acciones donde las citoquinas liberadas por la microglía activada puedan aumentar aún más la inflamación y activar nuevas células microgliales. Asimismo, la inflamación y la actividad celular asociada (por ejemplo, aumento de las especies reactivas de oxígeno (ROS) y los mecanismos de adhesión celular) pueden alterar la BHE, provocando que aumente la presencia de moléculas inflamatorias en el encéfalo. Los niveles de inflamación pueden influir en los niveles de neurotransmisores y los factores neurotróficos, teniendo como consecuencia, la afectación de los circuitos neuronales implicados en la cognición, la emoción y el comportamiento (Dias-Carvalho et al., 2024). Cabe destacar que la neuroinflamación es un mecanismo importante involucrado en la fisiopatología de algunos TMGs (Almeida et al., 2019).

Numerosos sistemas biológicos, como los procesos inmuno-inflamatorios y metabólicos, que se encuentran afectados en algunos TMGs, se alteran de manera similar bajo ciertas circunstancias como padecer alguna ECM comórbida (Amo-Aparicio et al., 2024). Por un lado, algunos estudios clínicos muestran que, si bien la gravedad de los síntomas psicóticos no está asociada con los niveles de citoquinas, los niveles de los biomarcadores cardiometabólicos se asocian, de forma positiva, con los niveles de citoquinas [interleucina (IL)-6, IL-7, IL-12/23 y IL- 16] y, de forma negativa, con el factor de necrosis tumoral alfa

(TNF-a) (Foiselle et al., 2022). De manera similar, las personas con trastornos del estado de ánimo mostraron niveles inflamatorios [IL-6, TNF-a y proteína c-reactiva (PCR)] elevados relacionados con perfiles metabólicos, especialmente cuando predominan los síntomas depresivos (Huang et al., 2023). Asimismo, varias revisiones recientes indican que los marcadores inflamatorios elevados asociados con parámetros cardiometabólicos pueden tener un fuerte impacto sobre la cronicidad en la enfermedad y la resistencia al tratamiento (Mucci et al., 2020; Prestwood et al., 2021). Por otro lado, los estudios genéticos han puesto de manifiesto la necesidad de considerar los mecanismos cardiometabólicos en el contexto de la interacción genoma-ambiente como punto de partida para comprender las interacciones que se producen entre las diferentes comorbilidades (Peedicayil, 2023). De hecho, numerosos estudios han identificado algunos cambios epigenéticos relacionados con ECMs como precursores de la aparición de sintomatología psiquiátrica en algunos grupos de individuos con TMG (Garcia-Rizo y Bitanihirwe, 2020; Huang et al., 2024). Asimismo, sigue sin esclarecerse si los mecanismos inflamatorios relacionados con las ECMs aumentan el riesgo de desarrollar un TMG, y viceversa, o si ambas condiciones son consecuencia de factores de riesgo compartidos que impulsan la inflamación. También es posible que dicha interacción pueda ser bidireccional, en que ambos tipos de enfermedades se retroalimentan mutuamente y los factores genéticos y ambientales aumentan el riesgo de cada una de ellas (Kramer et al., 2019; Roomruangwong et al., 2020).

Asimismo, existen otros mecanismos relevantes, algunos de ellos relacionados con la inflamación. Los mecanismos moleculares de estrés oxidativo implican un desequilibrio entre la producción de ROS y la capacidad del sistema antioxidante [enzimas catalasa, superóxido dismutasa (SOD) y glutatión peroxidasa (GSH), principalmente] del organismo para neutralizarlas. El estrés oxidativo puede causar daño a macromoléculas celulares como lípidos, y proteínas, y está asociado con diversas enfermedades, incluyendo las cardiovasculares, las neurodegenerativas y el cáncer. En el caso de los TMGs, en personas con TDM, el estrés oxidativo [ROS, ROS mitocondriales (mROS), y SOD] se ha relacionado con la regulación de biomarcadores periféricos y genéticos, lo que puede contribuir a la disfunción celular y al inicio de la inflamación sistémica. Según Ait Tayeb et al. (2023), el desequilibrio entre los radicales libres y los antioxidantes genera un ambiente proinflamatorio que afecta no solo a las células nerviosas, sino también a las moléculas de adhesión (Ait Tayeb et al., 2023).

Por último, las moléculas de adhesión celular, como las selectinas, las integrinas y las cadherinas, son proteínas que median la interacción entre las células o entre las células y la matriz extracelular. Estas moléculas desempeñan un papel esencial en procesos como la inflamación, la migración celular y la reparación tisular, pero también pueden estar involucradas en procesos como la metástasis tumoral cuando sus funciones están desreguladas. En individuos con EZ se observó que la elevación de las moléculas de adhesión [Molécula de adhesión intercelular 1 (ICAM), Molécula de adhesión celular vascular 1 (VCAM), Recuento de polimorfonucleares (RPMN), Recuento de variación de polimorfonucleares (RVPMN), E-, L-, y P-selectina, entre otras] refleja un estado inflamatorio crónico que podría contribuir a la patogénesis de la enfermedad (Zinellu y Mangoni, 2024). Estos hallazgos subrayan que el estrés oxidativo y la alteración de las moléculas de adhesión pueden potenciar la inflamación sistémica. En esta tesis, se usará "perfil inflamatorio" o términos similares para referirse a la inflamación sistémica y otros mecanismos moleculares relacionados, como el estrés oxidativo y las moléculas de adhesión celular.

1.5. La inflamación como mecanismo transdiagnóstico subyacente

Varios mecanismos biológicos podrían explicar el fenotipo inflamatorio encontrado en las personas con TMGs. Cabe destacar que los mediadores inflamatorios son producidos fisiológicamente por diferentes tejidos, incluyendo las células del sistema inmune, el tejido adiposo (es decir, adipocinas), las fibras musculares (es decir, miocinas), el intestino y el cerebro. Por lo tanto, es probable que múltiples mecanismos contribuyan a la inflamación crónica de bajo grado asociada con diversos TMGs (Kramer et al., 2019; Roomruangwong et al., 2020; Thylur y Goldsmith, 2022) (**Tabla 1**).

Tabla 1. Principales alteraciones en biomarcadores moleculares asociadas con enfermedades mentales y metabólicas

Enfermedad	Biomarcadores moleculares	Referencias
TDM	Incrementos de IL-6, PCR, TNF-a, COX-2. Alteraciones en los receptores inflamatorios sTNF-R1, sIL-2R.	(Kalkman, 2020; Kouba et al., 2024; Min et al., 2023; Nguyen et al., 2021; Ruiz et al., 2022).
TB	Niveles elevados de IL-6, IL-1b, TNF-a, COX-2, IL-17 Alteraciones en los receptores inflamatorios sTNF-R1, sIL-2R, sIL-6R. Aumento del estrés oxidativo.	(Bavaresco et al., 2020; Huang et al., 2023; Jones et al., 2021; Kloiber et al., 2022; Polat et al., 2023; Queissner et al., 2021; Wu et al., 2023).
EZ	Aumento de IL-6, IL-8, TNF-a, PCR, albúmina, glóbulos blancos, IgG. Disminución de IL-4, IL-10.	(Halstead et al., 2023; Misiak et al., 2024; Warren et al., 2024).
Otros trastornos psicóticos	Incremento de IL-6, IL-1b, IL-12, IFN-gamma, TNF-a, IL-8, IL-10, sIL-2R. Disminución de IL-4, IL-10.	(Misiak et al., 2021; Warren et al., 2024).
PEP	Aumento de IL-6, IFN-gamma, IL-12, IL-7.	(Dunleavy et al., 2022; Warren et al., 2024).

OB	Incremento de IL-6, IL-12, IL-18, TNF-a, PCR. Desregulación del estrés oxidativo Disfunción mitocondrial.	(Le Thuc y García-Cáceres, 2024; Martins et al., 2019; Mörkl et al., 2021).
DMT2	Incremento de IL-6, PCR.	(Nguyen et al., 2021; Panagi et al., 2022)

Abreviaturas: COX-2: Ciclooxigenasa-2, IFN-gamma: Interferón gamma, IL-6: Interleucina-6, IL-1b: Interleucina-1 beta, IL-8: Interleucina-8, IL-4: Interleucina-4, IL-10: Interleucina-10, IL-12: Interleucina-12, IL-17: Interleucina-17, IL-18: Interleucina-18, IL-7: Interleucina-7, IgG: Inmunoglobulina G, PCR: Proteína C reactiva, sTNF-R1: Receptor soluble del TNF tipo 1, sIL-2R: Receptor soluble de la interleucina-2, sIL-6R: Receptor soluble de la interleucina-6, TNF-a: Factor de necrosis tumoral alfa

La asociación entre las enfermedades mencionadas puede ser bidireccional e involucrar múltiples mecanismos biológicos interconectados, de manera que establecer la causalidad en dicha relación es un tema actual de debate. Como se mencionaba anteriormente, los individuos con TMGs suelen presentar hábitos de vida poco saludables que a su vez son importantes factores de riesgo para las ECMs y que, además, inciden en el desarrollo de la inflamación sistémica de bajo grado (Kip y Parr-Brownlie, 2023). Por ejemplo, los síntomas depresivos y ansiosos pueden aumentar el deseo de consumir alimentos ultraprocesados que a su vez puede impactar en el aumento de peso y riesgo de OB (Salwa et al., 2023). Del mismo modo, diversos antipsicóticos, pueden inducir un aumento de peso y adiposidad como efecto secundario (Stogios et al., 2023). Varios antidepresivos también pueden promover el aumento de peso así como el riesgo a desarrollar OB y DMT2 (Kukucka et al., 2024; Solmi et al., 2024).

Asimismo, las vías inmuno-inflamatorias se relacionan con la trayectoria de enfermedad de los TMGs. En las personas con TDM, la disfunción inmuno-inflamatoria ha sido vinculada con la recurrencia y gravedad de los episodios depresivos, así como con la respuesta al tratamiento y la recuperación funcional (Debnath et al., 2021). En el TB, los niveles elevados de inflamación pueden acelerar la progresión de la enfermedad (Grewal et al., 2023). De manera similar, en la EZ, una mayor duración de la enfermedad se asocia con marcadores

inflamatorios elevados, especialmente durante episodios psicóticos (Bhikram y Sandor, 2022; Özdin y Böke, 2019).

La activación de las vías inflamatorias promueve el desarrollo de la resistencia a la insulina a través de la activación de vías moleculares que bloquean la señalización intracelular (Al-Mansoori et al., 2022). La resistencia a la insulina se ha asociado con peores resultados clínicos en individuos con TMGs y representa un factor crítico en la fisiopatología de las complicaciones metabólicas en estos individuos. Por ejemplo, las personas con trastornos del estado de ánimo y resistencia a la insulina presentan tasas más elevadas de ciclado rápido, resistencia al tratamiento y dificultades funcionales en comparación con aquellas sin resistencia a la insulina (Sen et al., 2021). De manera similar ocurre con individuos con EZ (Zhuo et al., 2024). De hecho, la comorbilidad entre DMT2 y TMG repercute en el aumento de eventos cardiovasculares y las tasas de mortalidad (Borovcanin et al., 2023). Asimismo, la resistencia a la insulina se ha asociado con la respuesta fisiológica al estrés que, a su vez, puede perjudicar los procesos de adhesión celular que están relacionados con eventos cardiovasculares (Banks y Rhea, 2021).

Se ha sugerido que la inflamación crónica de bajo grado también puede ser resultado de respuestas inmunes, específicamente, de una inmunorregulación deteriorada. Por ejemplo, se han observado recuentos elevados de células inmunes activadas (monocitos, linfocitos, neutrófilos, y macrófagos), así como mecanismos de señalización intracelular involucrados en la inflamación, activación y proliferación celular en individuos con TMGs (Misiak et al., 2021; Ruiz et al., 2022) (**Tabla 2**).

Tabla 2. Resumen de la evidencia actual que relaciona la inflamación sistémica de bajo grado con la fisiopatología de las enfermedades estudiadas

Niveles de acción	**Mecanismos de inflamación sistémica**
Molecular	Aumento de la expresión y polimorfismos de genes relacionados con la inmunidad (p.ej., IL-1β, TNF-α y PCR)
	Activación de vías intracelulares (p. ej., MAPK y NF-κB)
	Sensores activados (p.ej., TLR e inflamasoma)

Sangre periférica o SNC	Niveles elevados de citocinas proinflamatorias (p.ej. TNF-α, IL-1β, IL-6, IL-17, IL-33)
	Niveles elevados de receptores solubles de citocinas (p.ej., sTNFR1 y sTNFR2)
	Niveles elevados de quimiocinas (p.ej., CCL11, CCL2, CCL3, CCL20, IL-8)
	Niveles elevados de proteínas de fase aguda (p.ej., PCR)
	Más marcadores de activación de células endoteliales
	Mayores niveles de adipoquinas
	Más marcadores de estrés oxidativo
	Niveles elevados de autoanticuerpos
Clínica	Mayor prevalencia de enfermedades autoinmunes
	Mayor prevalencia de comorbilidades médicas generales (enfermedades cardiovasculares, diabetes y OB)
	Mediadores proinflamatorios asociados con la sintomatología, la progresión clínica y la respuesta al tratamiento
	Remisión asociada a la normalización de los marcadores inflamatorios

Abreviaturas: CCL2: Chemokine (C-C motif) Ligand 2 (MCP-1: Monocyte Chemoattractant Protein-1), CCL3: Chemokine (C-C motif) Ligand 3 (MIP-1α: Macrophage Inflammatory Protein-1α), CCL11: Chemokine (C-C motif) Ligand 11 (Eotaxina-1), CCL20: Chemokine (C-C motif) Ligand 20, IL-1β: Interleucina-1 beta, IL-6: Interleucina-6, IL-17: Interleucina-17, IL-33: Interleucina-33, MAPK: Mitogen-Activated Protein Kinase (Quinasa activada por mitógenos), NF-κB: Nuclear Factor kappa-light-chain-enhancer of activated B cells (Factor nuclear kappa B), PCR: Proteína C reactiva, sTNFR1: Receptor soluble del TNF tipo 1, sTNFR2: Receptor soluble del TNF tipo 2, TLR: Toll-Like Receptors (Receptores tipo Toll), TNF-α: Factor de necrosis tumoral alfa.

1.6. Funcionamiento cognitivo y social en TMGs y ECMs

Los déficits cognitivos son una de las principales causas de discapacidad física y mental en todo el mundo. Esta carga está aumentando debido a la mayor esperanza de vida y al crecimiento de la población mundial (Mukadam et al., 2024). Los déficits cognitivos asociados con los TMGs incluyen, entre otros, problemas de memoria, déficits de velocidad de procesamiento, déficits de atención y concentración y deterioro de la función ejecutiva (GBD, 2024d). Estos son una característica compartida por los TMGs. Los déficits cognitivos están presentes en la mayoría de individuos con diagnóstico de EZ (Jester et al., 2023), mientras que en los individuos con diagnóstico de TB y TDM, los déficits cognitivos son una manifestación clínica frecuente (Elefante et al., 2024). Además, se han observado hallazgos parecidos en ECM, como diabetes y OB (Jung y Mok, 2022) (**Tabla 3**).

Tabla 3. Principales déficits cognitivos asociados a las enfermedades estudiadas

Función Cognitiva	**Diagnósticos**	**Referencias**
Déficits en atención	TDM, TB, EZ, OB	Adraoui et al., 2023; Kriesche et al., 2023; Lin et al., 2020; Naomi et al., 2023
Déficits en memoria a corto y largo plazo	TDM, TB, EZ, OB, DMT2	Fanelli et al., 2022; Millett et al., 2021; Tanaka et al., 2020; Wachowska y Gałecki, 2021
Déficits en velocidad de procesamiento	TDM, TB, EZ, DMT2	Habtewold et al., 2020; Kriesche et al., 2023; Ortiz et al., 2022; Peters et al., 2022
Déficits en funciones ejecutivas	TDM, TB, EZ, DMT2	Adraoui et al., 2023; Fanelli et al., 2022; Millett et al., 2021; Wachowska y Gałecki, 2021
Déficits en fluidez verbal	EZ, OB	Adraoui et al., 2023; Olsthoorn et al., 2021
Déficits en habilidades visuoespaciales	DMT2	Ortiz et al., 2022

Abreviaturas: TDM: Trastorno Depresivo Mayor, TB: Trastorno Bipolar, EZ: Esquizofrenia, DMT2: Diabetes Mellitus Tipo 2, OB: Obesidad

Si bien los déficits cognitivos son una síntoma constante de los TMGs y algunas ECMs, en muchos casos, los mecanismos moleculares de este deterioro cognitivo siguen siendo desconocidos. Como se ha mencionado con anterioridad, los TMG también se asocian con alteraciones en las concentraciones de moléculas inflamatorias, alteraciones en el metabolismo lípido de las células, estrés oxidativo, entre otras, tanto a nivel sistémico como en el SNC. De manera similar, ocurre en algunas enfermedades físicas, especialmente en las ECMs. Estas moléculas, además de su papel en la respuesta inmunitaria, también son neuromoduladoras y pueden afectar al correcto funcionamiento del sistema nervioso (Ettinger, 2022; Pacholko y Iadecola, 2024). Esto plantea la posibilidad de que las alteraciones en los biomarcadores revisados previamente puedan estar relacionadas con el déficit cognitivo en las enfermedades estudiadas en esta tesis doctoral (**Tabla 4**).

Tabla 4. Relación entre la disfunción cognitiva y las alteraciones en los biomarcadores moleculares en las enfermedades estudiadas

Enfermedad	**Biomarcadores asociados a déficits cognitivos**	**Referencias**
TDM	Niveles elevados de biomarcadores proinflamatorios, como IL-6, PCR, TNF-a, IL1-RA.	(Kriesche et al., 2023; Malhi y Mann, 2018; Pike et al., 2024; Mac-Giollabhui et al., 2021; Wachowska y Gałecki, 2021; Wu y Zhang, 2023)
TB	Estado pro-inflamatorio (PCR, IL-6, TNF-α), estrés oxidativo (ROS), y actividad inmunitaria (leucocitos).	(Lin et al., 2020; Lima et al., 2022; McIntyre et al., 2020; Millett et al., 2020, 2021; Peters et al., 2022; Poletti et al., 2024; Zazula et al., 2022).

EZ	Incremento de actividad inflamatoria mediada por citocinas (TNF-α, PCR, IL-6).	Adraoui et al., 2023; Habtewold et al., 2020; Jauhar et al., 2022; Patlola et al., 2023; Zeng et al., 2021).
DMT2	Resistencia a la insulina y con el incremento de citocinas proinflamatorias (IL-1, PCR, TNF-a).	(Du et al., 2023; Dutta et al., 2022; Espeland et al., 2022; Roy et al., 2023; Ortiz et al., 2022).
OB	Niveles elevados de citocinas proinflamatorias (IL6, IL-1b y PCR).	(Fanelli et al., 2022; Lingvay et al., 2024; Naomi et al., 2023; Tanaka et al., 2020).

Abreviaturas: IL-1: Interleucina-1, IL-1b: Interleucina-1 beta, IL-1RA: Antagonista del receptor de interleucina-1, IL-6: Interleucina-6, PCR: Proteína C reactiva, ROS: Reactive Oxygen Species (Especies reactivas de oxígeno), TNF-α: Factor de necrosis tumoral alfa.

Los mecanismos biológicos que conducen a la inflamación sistémica de bajo grado suelen estar alterados en individuos con TMG, especialmente en aquellos con alguna comorbilidad asociada (Teixeira et al., 2022). En este contexto, se ha observado que las asociaciones entre algunos parámetros inflamatorios y los déficits cognitivos varían en función de las ECMs (como la OB y diabetes) en esta población (Erichsen et al., 2022; Olsthoorn et al., 2021). Estos hallazgos sugieren que las comorbilidades de las personas con TMGs podrían estar estrechamente relacionadas con la inflamación y los procesos cognitivos (To et al., 2022).

En este sentido, el funcionamiento cognitivo y social juega un papel determinante en este grupo de individuos. Según la literatura reciente, el incremento de la respuesta inmune-inflamatoria se ha relacionado con la disminución de los rendimientos en algunas funciones cognitivas y el funcionamiento social diario en individuos con TMGs. Asimismo, aquellas personas con comorbilidades (como OB) tenían niveles de inflamación más elevados y mayores probabilidades de desarrollar deterioro cognitivo (Du et al., 2023; Naomi et al., 2023). Algunos estudios actuales han demostrado que, entre las personas con trastornos del estado de ánimo y comorbilidades cardiometabólicas, los niveles altos de citoquinas proinflamatorias y la disfunción en los mecanismos cardiometabólicos se asocian con un empeoramiento de algunas funciones cognitivas, como la memoria, la velocidad de

procesamiento y las funciones ejecutivas (Dionysopoulou et al., 2021). Del mismo modo, la actividad inflamatoria se ha relacionado con un menor rendimiento cognitivo y una peor calidad de vida en personas con diagnóstico de psicosis con alguna ECM comórbida (Kowalski et al., 2023).

Además, se ha observado que las alteraciones en el funcionamiento cognitivo y social pueden servir como indicadores de la trayectoria de enfermedad (McCleery y Nuechterlein, 2019). Los déficits cognitivos están asociados con un peor pronóstico y podrían predecir el estado clínico en individuos con TMGs (Herold et al., 2021). Asimismo, un peor funcionamiento social se ha relacionado con trayectorias clínicas desfavorables (Hall et al., 2019). Cabe mencionar que las ECMs pueden agravar el deterioro cognitivo asociado al transcurso de la enfermedad (Borovcanin et al., 2020). De manera similar, aunque existen pocos estudios sobre los biomarcadores de metabolismo lipídico, se ha observado que los niveles de apolipoproteínas, especialmente Apo-A1, están relacionados con el deterioro de la memoria a medio y largo plazo. Además, la Apo-A1 parece estar implicada en las fases tempranas del deterioro cognitivo en adultos mayores. De hecho, una disminución en los niveles sanguíneos de Apo-A1 se ha relacionado con la transición de un deterioro cognitivo leve a demencia (Slot et al., 2017). En este sentido, los estudios longitudinales posibilitan un análisis más idóneo de las asociaciones entre todas estas variables de interés.

En esencia, parece que algunos biomarcadores podrían considerarse factores de riesgo transdiagnósticos para el desarrollo de deterioro cognitivo en diversos TMGs, mientras que otros podrían servir como factores protectores. Es evidente que la comprensión de los fundamentos fisiopatológicos de las enfermedades mentales debe integrar los mecanismos biológicos para obtener una comprensión profunda y holística de los factores trandiagnósticos involucrados. En esta tesis se usará "perfil inflamatorio" o términos similares para referirse a la inflamación sistémica y otros mecanismos moleculares relacionados, como el estrés oxidativo y las moléculas de adhesión celular.

A modo de resumen de la introducción de esta tesis, se ha identificado que:

1. Los déficits cognitivos son una característica frecuente y potencialmente incapacitante en los TMG (EZ, TB, TDM) y algunas ECMs (DMT2, OB). Estas alteraciones incluyen principalmente problemas en la memoria, atención, velocidad de procesamiento y función ejecutiva. Además, parece existir un solapamiento a nivel cognitivo entre las diferentes enfermedades que se estudiarán en esta tesis.

2. De forma similar, existen alteraciones moleculares comunes entre los TMGs y las ECMs, como inflamación sistémica de bajo grado, disfunción metabólica y estrés oxidativo. Estas alteraciones pueden impactar el SNC a través de mecanismos neuromoduladores, contribuyendo a los déficits cognitivos observados.
3. En los TMGs, los biomarcadores asociados a la inflamación y la disfunción metabólica se relacionan de forma diferente con los déficits cognitivos en función de la presencia o no de comorbilidades cardiometabólicas, como OB y DMT2.

Integrar las perspectivas transdiagnóstica y de comorbilidades cardiometabólicas ofrece una visión novedosa sobre cómo los mecanismos biológicos comunes en los TMGs y las ECMs contribuyen a los déficits cognitivos. Aunque existe evidencia que respalda estas relaciones, los estudios previos no han abordado sistemáticamente esta interacción desde esa doble perspectiva.

De este modo, planteamos que los biomarcadores asociados a la inflamación y la disfunción cardiometabólica actuarían como factores de riesgo transdiagnósticos que exacerban los déficits cognitivos en personas con TMGs, especialmente en presencia de ECMs comórbidas. Esta hipótesis se apoya en hallazgos preliminares, pero resulta innovadora al combinar las dos perspectivas mencionadas. Además, se adopta una perspectiva longitudinal para comprender mejor cómo estos procesos evolucionan a lo largo del tiempo. Se espera que este enfoque permita identificar biomarcadores específicos que puedan servir tanto para el diagnóstico temprano como para intervenciones terapéuticas personalizadas en estos trastornos complejos.

2. HIPÓTESIS

2.1. Hipótesis principales

1. La variabilidad fenotípica del deterioro cognitivo y del perfil inflamatorio en individuos con TMG (TDM, TB, EZ) será similar a la descrita en la literatura reciente.

2. La determinación conjunta de los déficits cognitivos y las alteraciones en el perfil inflamatorio contribuirán a clasificar correctamente a los individuos con diagnóstico de TMG con o sin comorbilidad cardiometabólica.

2.2. Hipótesis secundarias

1. Los individuos con TMG y ECMs comórbidas tendrán un peor funcionamiento cognitivo y social, así como un aumento en el perfil inflamatorio que las personas con TMG sin dichas comorbilidades y los individuos sanos.

2. El funcionamiento cognitivo y social, junto con el perfil inflamatorio será similar entre los individuos con diferentes TMG.

3. Los déficits en el funcionamiento cognitivo y social, junto con las alteraciones en el perfil inflamatorio estarán vinculados con desenlaces clínicos desfavorables en la población de estudio.

3. OBJETIVOS

3.1. Objetivos principales

1. Ahondar en la caracterización del funcionamiento cognitivo y social, así como del perfil inflamatorio de los individuos con TMG desde una doble perspectiva transdiagnóstica y de comorbilidad.

2. Examinar las relaciones de las comorbilidades cardiometabólicas (SM, OB, DMT2) sobre la cognición y el perfil inflamatorio de las personas con TMG.

3.2. Objetivos secundarios

1. Describir la magnitud del deterioro cognitivo y social, así como del perfil inflamatorio en individuos con TMG con o sin comorbilidad cardiometabólica.

2. Analizar las diferencias en el funcionamiento cognitivo y social, así como los parámetros inflamatorios entre los individuos con diferentes TMG.

3. Explorar la contribución relativa del perfil inflamatorio al funcionamiento cognitivo y social en la muestra de estudio.

4. MÉTODOS Y RESULTADOS

4.1. Estudio I

Título: Specific metabolic syndrome components predict cognition and social functioning in people with type 2 diabetes mellitus and severe mental disorders

Autores: Joan Vicent Sánchez-Ortí, Vicent Balanzá-Martínez, Patricia Correa-Ghisays, Gabriel Selva-Vera, Joan Vila-Francés, Rafael Magdalena-Benedito, Constanza San-Martin, Víctor M. Victor, Irene Escribano-Lopez, Antonio Hernández-Mijares, Juliana Vivas-Lalinde, Benedicto Crespo-Facorro, Rafael Tabarés-Seisdedos.

Autores de correspondencia: Vicent Balanzá-Martínez y Rafael Tabarés-Seisdedos

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Ver publicación completa en el ANEXO I.

4.2. Estudio II

Título: Inflammation and weight change related to neurocognitive and functional impairment in diabetes and psychiatric disorders

Autores: Joan Vicent Sánchez-Ortí, Vicent Balanzá-Martínez, Patricia Correa-Ghisays, Gabriel Selva-Vera, Joan Vila-Francés, Rafael Magdalena-Benedito, Constanza San-Martin, Víctor M Victor, Irene Escribano-Lopez, Antonio Hernandez-Mijares, Juliana Vivas-Lalinde, Benedicto Crespo-Facorro, Rafael Tabarés-Seisdedos

Autor de correspondencia: Rafael Tabarés-Seisdedos

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Ver publicación completa en el ANEXO II.

4.3. Estudio III

Título: Inflammation and lipid metabolism as potential biomarkers of memory impairment across type 2 diabetes mellitus and severe mental disorders

Autores: Joan Vicent Sánchez-Ortí, Patricia Correa-Ghisays, Vicent Balanzá-Martínez, Gabriel Selva-Vera, Joan Vila-Francés, Rafael Magdalena-Benedito, Constanza San-Martin, Víctor M Victor, Irene Escribano-Lopez, Antonio Hernandez-Mijares, Juliana Vivas-Lalinde, Benedicto Crespo-Facorro, Rafael Tabarés-Seisdedos

Autores de correspondencia: Vicent Balanzá-Martínez y Rafael Tabarés-Seisdedos

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5. DISCUSIÓN

Los objetivos principales de la presente tesis doctoral son profundizar en la caracterización del funcionamiento cognitivo y del perfil inflamatorio de los individuos con TMG (TDM, TB, EZ) y examinar el impacto de las comorbilidades cardiometabólicas (SM, OB, DMT2) sobre la cognición y el perfil inflamatorio desde una perspectiva transdiagnóstica y longitudinal.

En primer lugar, nuestros resultados revelan un peor funcionamiento cognitivo en personas con SM, incluyendo aquellas con un TMG, en comparación con aquellas sin esta comorbilidad, aunque el funcionamiento social fue similar en ambos grupos. Entre los componentes del SM, los niveles de TG y la GA se destacaron como predictores clave del funcionamiento cognitivo y social de las personas con TMG, independientemente de presentar o no SM, en esta muestra transdiagnóstica combinada. Además, la PA se identificó como un factor relevante para predecir el funcionamiento cognitivo en personas con SM. Los niveles de TG mostraron ser el componente del SM más preciso para identificar a aquellos individuos con mayor deterioro cognitivo (estudio I).

En segundo lugar, los individuos con OB, incluyendo aquellos con un TMG, mostraron una disminución general del funcionamiento cognitivo y social junto con un aumento de la inflamación sistémica. El aumento de los biomarcadores antiinflamatorios y la disminución de los proinflamatorios fueron importantes para detectar cambios significativos en el peso corporal a lo largo del tiempo, teniendo en cuenta los diferentes grados de OB. En lo que respecta a los cambios de peso corporal, los biomarcadores inflamatorios, de estrés oxidativo y las moléculas de adhesión fueron factores comunes para predecir el funcionamiento cognitivo y social, con mayor fiabilidad en aquellos individuos que experimentaron una pérdida de peso. Específicamente, un estado antiinflamatorio elevado predijo de forma significativa una mejor función cognitiva en esta muestra transdiagnóstica combinada (estudio II).

En tercer lugar, observamos que el rendimiento en tareas de memoria se asoció de forma significativa con cambios en dos de los biomarcadores analizados. En concreto, en comparación con los individuos con un mejor rendimiento mnésico, aquellos que presentaban un mayor deterioro tenían niveles más altos de TNF-α y concentraciones más bajas de apolipoproteína (Apo)-A1. Además, el análisis discriminante mostró que un modelo que combinaba biomarcadores proinflamatorios (IL-6, TNF-α y PCR) y biomarcadores de metabolismo lipídico (Apo-A1 y Apo-B) era capaz de distinguir a los individuos con

diferentes grados de rendimiento de la memoria. Sin embargo, los biomarcadores de estrés oxidativo y la citocina antiinflamatoria IL-10 no se asociaron con la función de la memoria en esta muestra transdiagnóstica combinada (estudio III).

5.1. Caracterización del funcionamiento cognitivo y del perfil inflamatorio en personas con TMG

En cuanto al primer objetivo secundario de la tesis, en lo que respecta a la magnitud del deterioro cognitivo y el perfil inflamatorio en individuos con TMG con o sin comorbilidad cardiometabólica (estudios I, II y III), más de la mitad de los participantes en nuestros estudios presentaron comorbilidades. Específicamente, el 49,6% cumplieron criterios para SM y el 75,7% para OB, lo que demuestra una prevalencia notablemente elevada en consonancia con la evidencia reciente (de Louw et al., 2019; Martins et al., 2019; Sánchez-Valle et al., 2020).

En este contexto, nuestros resultados revelan que las personas con diagnóstico de TMG con alguna comorbilidad cardiometabólica presentan, de forma consistente, un peor funcionamiento cognitivo y social independientemente del diagnóstico primario, lo que se traduce en un considerable malestar y pérdida en la calidad de vida. Asimismo, cabe destacar que las asociaciones significativas se extienden al perfil inflamatorio que se encuentra alterado, incluyendo niveles elevados de biomarcadores proinflamatorios (entre ellos, IL-6, TNF-α, PCR, NLR y PLR), así como cambios más acentuados en los parámetros metabólicos en las personas con comorbilidades (por ejemplo, Apo-A1 y Apo-B). Sin embargo, no se observaron diferencias en los biomarcadores de actividad endotelial o de adhesión celular ni de estrés oxidativo estudiados.

De forma conjunta, estos hallazgos coinciden con los publicados previamente en personas con EZ y trastornos del estado de ánimo (Hiller et al., 2023; Patel et al., 2022; Suseelan et al., 2023). En la literatura reciente se observó que los individuos con un mayor número de comorbilidades mostraban un peor funcionamiento cognitivo y social. Por un lado, en cuanto al funcionamiento cognitivo de las personas con TMG, se evidenció una estrecha relación entre la cantidad y el tipo de comorbilidades, especialmente las ECMs. Además, a lo largo del

tiempo, el deterioro cognitivo se asoció con peores resultados clínicos en individuos con TMG y múltiples comorbilidades. Asimismo, aunque en menor medida, se han encontrado resultados similares para el funcionamiento social (Temedda et al., 2024). Por otro lado, se ha observado una fuerte relación entre los niveles de inflamación sistémica y las comorbilidades físicas en personas con TMG (Teixeira et al., 2022). Este hallazgo respalda la idea de que un incremento en la inflamación sistémica se asocia con una mayor probabilidad de desarrollar comorbilidades en personas con TMG. Estas enfermedades están infradiagnosticadas e infratratadas en este colectivo, lo que contribuye a su mayor morbilidad y mortalidad (Noortman et al., 2023). En este contexto, parecen influir múltiples niveles de análisis, desde factores de riesgo compartidos (por ejemplo, un estilo de vida poco saludable) hasta vías fisiopatológicas comunes, interacciones bidireccionales e incluso deficiencias en el acceso de las personas a los servicios sanitarios (GBD, 2024b; GBD 2024c; Teixeira et al., 2022).

Cabe destacar que la comprensión de la patogénesis y la contribución específica de cada uno de estos mecanismos al escenario de comorbilidad están en ciernes en la actualidad. La posibilidad de identificar clusters o subconjuntos de individuos que presentan fenotipos específicos (por ejemplo, “fenotipo inflamatorio”) aún debe repensarse antes de su aplicación a la práctica clínica, ya que es necesario confirmar los resultados con muestras mayores y estudios independientes. Por ejemplo, Chae et al. (2023) identificaron un subtipo "inmunometabólico" de depresión asociado a síntomas atípicos, inflamación y actividad metabólica (Chae et al., 2023). También queda por definir si un tratamiento dirigido a mecanismos fisiopatológicos compartidos entre personas con TMG y ECM puede ser eficaz en ambas enfermedades. De hecho, gran parte de la evidencia presentada hasta ahora se basa en clasificaciones categoriales, mientras que nuestros resultados se fundamentan en una muestra transdiagnóstica, lo que plantea la pregunta de cómo comparar nuestros hallazgos con los de la literatura previa ya que apenas existen estudios similares al nuestro. Este contraste conceptual destaca la diferencia entre enfoques categoriales y transdiagnósticos.

Por lo tanto, los resultados de nuestros estudios confirmaron la primera hipótesis secundaria de la tesis ya que, en términos generales, los individuos con TMG y ECM comórbidas presentaron un peor funcionamiento cognitivo así como cambios en los parámetros inflamatorios en comparación con las personas con TMG sin comorbilidad y con individuos sanos.

5.1.1. Estrategias terapéuticas centradas en la inflamación y los mecanismos relacionados para la prevención de comorbilidades en las personas con TMG

Como se ha comentado anteriormente, los mecanismos inflamatorios son un aspecto importante de la fisiopatología de los TMG, que no solo están fuertemente asociados con las ECMs, sino que también tienen efectos directos e indirectos sobre la actividad cerebral y, por tanto, sobre los síntomas cognitivos, emocionales y conductuales (Almeida et al., 2019; Dias-Carvalho et al., 2024; Evans et al., 2021). En este contexto, es razonable postular que las intervenciones antiinflamatorias pueden tener un gran valor terapéutico para los individuos con TMG y ECMs comórbidas.

Por un lado, hay amplia evidencia de que los tratamientos farmacológicos convencionales para los trastornos del estado de ánimo y psicóticos tienen efectos antiinflamatorios (Fitton et al., 2022). Por ejemplo, los antidepresivos y el litio tienen efectos antiinflamatorios y antioxidantes bien establecidos, disminuyendo la producción de citocinas proinflamatorias (TNF-α, IL-1, IL-6, y PCR), aumentando la liberación de citocinas antiinflamatorias (IL-4, IL-8, IL-10), regulando la expresión de las ROS y SOD (Hall et al., 2024; Szałach et al., 2023). Por otro lado, antiinflamatorios no esteroideos (como la aspirina y el celecoxib), biológicos o anticuerpos monoclonales (como infliximab) y otros medicamentos (como la memantina y el dextrometorfano) dirigidos a las citocinas se han investigado para el tratamiento de los trastornos del estado de ánimo y la EZ, con resultados prometedores (Amerio et al., 2024; Bavaresco et al., 2020; Rizk et al., 2024; Ruiz-Sastre et al., 2024). En consecuencia, parece que los beneficios clínicos de estos fármacos podrían lograrse mediante la regulación de los desequilibrios neuroquímicos y mediante la reducción de la inflamación sistémica. A pesar de que estos resultados aún son preliminares, las terapias antiinflamatorias podrían desempeñar un papel en el manejo clínico de individuos con TMG y las complicaciones metabólicas.

Además, estudios previos han identificado efectos beneficiosos de los fármacos antidiabéticos como estrategia terapéutica para prevenir la aparición de la DMT2 en individuos con TMG (Mishu et al., 2021). Más recientemente, varios ensayos clínicos han demostrado el efecto antidepresivo y de mejora del funcionamiento cognitivo de los fármacos antidiabéticos (como pioglitazona y liraglutida) y reductores de peso (como las

tiazolidinedionas) (Khan et al., 2020; Possidente et al., 2023). Además, los fármacos antidiabéticos se han propuesto como una estrategia eficaz para mitigar los efectos metabólicos de los antipsicóticos, prevenir el aumento de peso y mejorar los parámetros del metabolismo glucídico en individuos con diagnóstico de TMG que reciben dicho tratamiento (Verhaegen y Van Gaal, 2021).

Por otro lado, estrategias no farmacológicas, como las intervenciones dietéticas/nutricionales y la actividad física/ejercicio regular, pueden mejorar los resultados clínicos de las personas con TMG, así como retrasar la aparición de complicaciones metabólicas. De hecho, los ensayos clínicos aleatorizados sobre el impacto específico de estas intervenciones son prometedores, dado su potencial para prevenir y mejorar estas condiciones (Balanzá-Martínez et al., 2020; Bradley et al., 2022; Simjanoski et al., 2023). Por ejemplo, una mayor adherencia a un patrón dietético de alta calidad, como la dieta mediterránea, se ha identificado como un factor protector para reducir la gravedad clínica y mejorar el pronóstico en individuos jóvenes con TMG, así como para prevenir la aparición de síntomas psicóticos y del estado de ánimo en individuos con problemas de salud mental en la adultez (Camprodon-Boadas et al., 2024; Jacka et al., 2017). Otro ejemplo lo encontramos en los efectos beneficiosos de realizar actividad física regular, entre ellos, mejorar la salud mental, reducir las complicaciones metabólicas y prevenir la muerte prematura en población con TMG (Brobakken et al., 2022).

Adicionalmente, abundante literatura reciente sugiere el papel que ejerce la microbiota intestinal en la salud mental y el funcionamiento cognitivo (Berding y Cryan, 2022). En estudios clínicos, las estrategias de modulación de la microbiota intestinal, como el uso de probióticos, el consumo de fibra dietética y el trasplante de microbiota fecal mejoraron las complicaciones metabólicas (por ejemplo, OB, diabetes y dislipidemia) (Berding et al., 2021). Asimismo, la suplementación con prebióticos, simbióticos y alimentos fermentados apuntan a una reducción de los niveles circulantes de biomarcadores inflamatorios (PCR, IL-6,) y de estrés oxidativo, así como algunas mejoras clínicas en individuos con TMG, con una mayor evidencia en el TDM (Ribera et al., 2024).

En resumen, diversas estrategias farmacológicas y no farmacológicas dirigidas a prevenir y tratar complicaciones metabólicas muestran potencial para mejorar la salud mental y la cognición de las personas con TMG. Sin embargo, se requieren más estudios para identificar las mejores intervenciones terapéuticas y especialmente, mediante la estratificación, quiénes

podrían obtener los mayores beneficios. Es crucial investigar también sus efectos a largo plazo en parámetros cognitivos y sociales.

5.2. Comparación del funcionamiento cognitivo y de los parámetros inflamatorios entre las enfermedades estudiadas y el grupo control

Siguiendo el segundo objetivo secundario de la tesis, "analizar las diferencias en el funcionamiento cognitivo y parámetros inflamatorios entre las enfermedades estudiadas y el grupo control" (estudios I y II), cuando examinamos el desempeño entre los diferentes grupos diagnósticos (TDM, TB, EZ, DMT2) no se observaron diferencias significativas en el funcionamiento cognitivo ni en el perfil inflamatorio. Sin embargo, sí se encontraron diferencias significativas entre aquellos individuos con alguna de estas enfermedades y los sanos. Además, este resultado se mantuvo consistente durante el periodo de seguimiento. Así pues, los resultados del estudio I muestran que el funcionamiento cognitivo es similar dentro de cada grupo de individuos; con independencia de la comorbilidad con SM. Asimismo, el funcionamiento social es similar entre grupos. En el estudio II se observa que los funcionamientos cognitivo y social fueron similares entre los diferentes grupos con OB comórbida, pero inferiores a los de los individuos sanos. Estos hallazgos son congruentes con un amplio conjunto de estudios que evidencian un solapamiento fenotípico sustancial entre los diferentes TMG e, incluso, con enfermedades somáticas (Abdolmaleky et al., 2021; Piché et al., 2020). Asimismo, los estudios I y II muestran que los individuos con mayor carga de enfermedad presentan un perfil inflamatorio distinto y significativamente más elevado en comparación con personas sanas o con menor carga de enfermedad. En este sentido, nuestros resultados respaldan la idea de que el perfil inflamatorio podría ser un mecanismo biológico común entre los TMG y algunas ECMs, como sugieren estudios recientes (Amo-Aparicio et al., 2024; Thylur y Goldsmith, 2022).

Lo mencionado hasta ahora concuerda con nuestra segunda hipótesis secundaria, es decir, no se encontraron diferencias en el funcionamiento cognitivo ni en el perfil inflamatorio entre los individuos con diferentes TMG.

Los resultados obtenidos sugieren la existencia de aspectos compartidos y solapamientos entre los TMG definidos de forma categorial. Este patrón se alinea con la idea de que en psiquiatría las categorías diagnósticas no poseen unos límites claramente definidos que los distingan entre sí. En este contexto, el enfoque transdiagnóstico aportaría ciertas ventajas al permitir estudiar los TMG sin las restricciones impuestas por estas categorías, facilitando además el reclutamiento de muestras más amplias.

Los hallazgos actuales, tanto de la literatura revisada como de esta tesis, refuerzan la idea de que los individuos con TMG podrían reagruparse de forma diferente a como se establece en los manuales diagnósticos actuales. Es posible que las clasificaciones convencionales, como el DSM o la CIE, no sean suficientes para comprender adecuadamente los trastornos psicóticos o del estado de ánimo (Cuthbert, 2020; Kotov et al., 2017, 2021). En lugar de ser entidades cualitativamente distintas, los TMG podrían concebirse como un continuo de síntomas psicóticos y del estado de ánimo, con niveles de gravedad diferentes (Conway et al., 2022; Kotov et al., 2022).

A pesar de que los TMG se diagnostican principalmente por criterios psicopatológicos y conductuales, es fundamental destacar que las medidas neuropsicológicas y los biomarcadores ofrecen información valiosa y complementaria que puede mejorar la validez de los diagnósticos (MacNeill et al., 2021; Ringwald et al., 2023; Williams et al., 2024). Estos resultados sugieren la utilidad de incorporar evaluaciones neuropsicológicas detalladas y pruebas de biomarcadores en el diagnóstico de los trastornos mentales. En este sentido, los resultados de la presente tesis doctoral apoyan que el diagnóstico tradicional resulta eficaz para identificar a los individuos con sintomatología clínica evidente (entre ellos, delirios, alucinaciones, euforia, depresión), pero no permitiría distinguir entre perfiles de individuos con diferentes déficits cognitivos y sociales. Consecuentemente, parece necesaria la incorporación de una perspectiva holística y transdiagnóstica para una mejor comprensión y manejo de dichas enfermedades.

Por lo tanto, los resultados de nuestros estudios confirmaron la primera hipótesis principal de la tesis ya que, en términos generales, la variabilidad fenotípica del deterioro cognitivo y del perfil inflamatorio en individuos con diagnóstico de TMG y DMT2 fue similar a la descrita en la literatura reciente.

5.3. Contribución relativa del perfil inflamatorio y metabólico al funcionamiento cognitivo y social en población con TMG y ECM

En cuanto al tercer objetivo secundario de la presente tesis doctoral, "explorar la contribución relativa del perfil inflamatorio al funcionamiento cognitivo en la muestra de estudio" (estudios I, II y III), encontramos que diversos biomarcadores inflamatorios predicen el funcionamiento cognitivo y social en población con TMG, ejerciendo un rol diferencial según ciertas variables clínicas. Además, algunos parámetros inflamatorios y metabólicos actuarían como elementos mediadores en el funcionamiento en ciertos dominios cognitivos, como la memoria. El perfil inflamatorio y metabólico es capaz de clasificar correctamente el 70% de individuos con indicadores de una mayor gravedad clínica [SM, aumento del índice de masa corporal (IMC), y déficit de memoria].

Los biomarcadores inflamatorios pueden predecir el funcionamiento cognitivo y social, a nivel basal y al año de seguimiento. Estos hallazgos ya han sido identificados en estudios previos con muestras de EZ (Adamowicz et al., 2024), TB (Millett et al., 2021), TDM (Zainal et al., 2021) y algunas ECMs, como la diabetes (Sluiman et al., 2022). Sin embargo, hasta ahora no se habían identificado en una muestra conjunta, desde una perspectiva transdiagnóstica del TMG, lo que representa una innovación de la presente tesis doctoral.

Específicamente, en el estudio I, el perfil metabólico mostró una adecuada capacidad de predicción del funcionamiento cognitivo de las personas con TMG al año de seguimiento (varianza explicada: 10.8% – 12.6%), especialmente en el grupo con SM (12.6%). En mayor medida, también explicó su funcionamiento social (varianza explicada: 14.3% - 19.1%). Estos resultados son consistentes con los obtenidos previamente en individuos con diferentes diagnósticos específicos de TMG (Barton et al., 2020; Meamar et al., 2020). Asimismo, componentes del SM mostraron capacidad para discriminar a los individuos con resultados clínicos desfavorables (75% - 87.1%), siendo especialmente útiles los niveles de TG elevados. Este hallazgo respalda la idea de que las alteraciones metabólicas se asociarían con una peor evolución cognitiva y social en individuos con TMG (Schmitt et al., 2020).

En el estudio II, sobre OB como comorbilidad, se encontraron resultados similares. Asimismo, los cambios de peso al año de seguimiento también se relacionaron con el perfil inflamatorio (IL-6, IL-10 y PLT). Estos resultados son consistentes con la literatura existente, que indica que el aumento de la actividad inflamatoria se relaciona con el deterioro cognitivo y social, así como con los cambios de peso en individuos con TMG (Naomi, 2023; Schmitt y Gaspar, 2023). En un metaanálisis reciente, se encontraron correlaciones significativas entre parámetros pro-inflamatorios (IL-6 y PCR) y resultados clínicos desfavorables (peor funcionamiento cognitivo y social, así como aumento del IMC) en individuos con TMG, lo que sugiere que los mecanismos de inflamación tienen un impacto sustancial en la trayectoria de la enfermedad que se mantiene a lo largo del tiempo (Le Thuc y García-Cáceres, 2024).

En el estudio III se analizó la relación de los biomarcadores con el funcionamiento mnésico, controlando las comorbilidades (SM y OB), con el fin de poder clarificar el impacto real del perfil inflamatorio sobre la cognición. Como se esperaba, un mayor grado de inflamación sistémica se relacionó con peores resultados clínicos (por ejemplo, peor funcionamiento cognitivo) en individuos con TMG (Safari y Mashayekhan, 2023) (**Figura 5**).

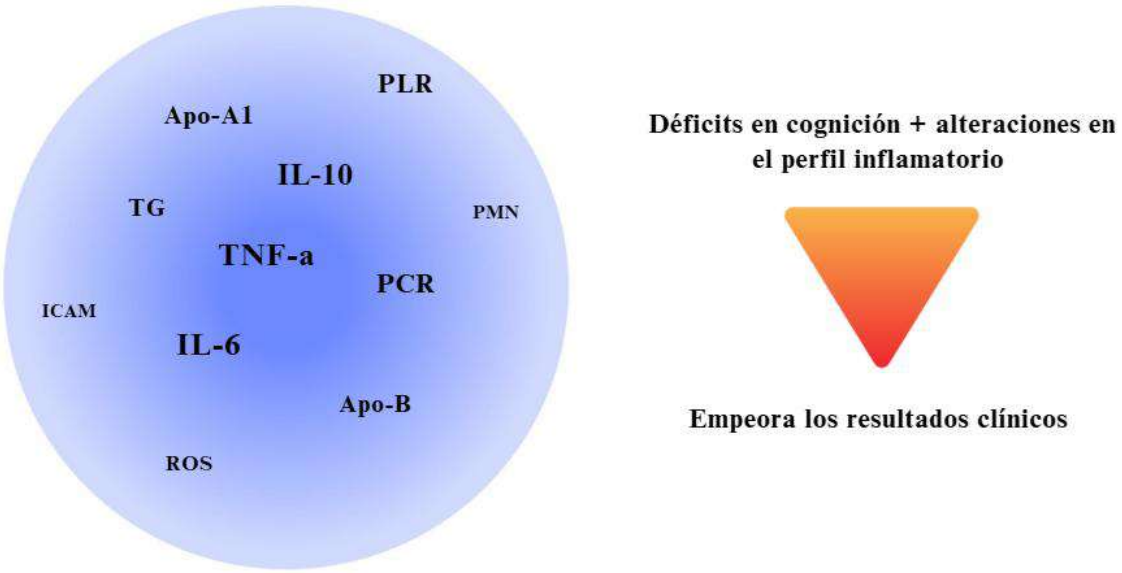

Figura 5. Resumen de los principales biomarcadores moleculares (inmuno-inflamatorios, metabolismo lipídico, moléculas de adhesión y estrés oxidativo) y su relación con el funcionamiento cognitivo (elaboración propia).

Nota: Los biomarcadores cuyas siglas aparecen con un tamaño de fuente mayor y más cerca del centro del círculo indican una relación más significativa con el funcionamiento cognitivo. Por el contrario, aquellos que se encuentran más alejados del centro y con un tamaño de fuente menor reflejan una relación menos significativa con el funcionamiento cognitivo.

De forma conjunta, nuestros resultados confirmaron la tercera hipótesis secundaria de la tesis, aportando evidencia a favor de que los déficits cognitivos y las alteraciones en el perfil inflamatorio se relacionan con peores resultados clínicos en las personas con TMG.

5.3.1. Conexión entre el déficit cognitivo y la inflamación y mecanismos moleculares relacionados

Los hallazgos descritos en nuestros estudios postulan que algunas moléculas inflamatorias (IL-6, TNF-α y CRP), inmunológicas (NLR y PLR), lipídicas (TG, Apo-A1 y Apo-B) y de adhesion molecular (VCAM, RPMN) serían potenciales determinantes de los déficits cognitivos. Según la literatura revisada, y en línea con nuestros hallazgos, parece que estos biomarcadores podrían ser compartidos en las enfermedades estudiadas (Elefante et al., 2024; Jester et al., 2023; Jung y Mok, 2022).

Nuestros resultados mostraron que la disminución en el funcionamiento cognitivo y social está asociada con el aumento en la inflamación sistémica (IL-6, PCR, TNF-a). Esta relación ha sido documentada en los trastornos estudiados en esta tesis. Por ejemplo, se ha encontrado que el TNF-α y sus receptores están negativamente asociados con el declive de la cognición en el TB (Chakrabarty et al., 2019; Hua et al., 2020) y en TMG (Hoseth et al., 2016). Asimismo, en adultos de mediana edad con DMT2, los niveles elevados de TNF-α en el suero se correlacionaron con un peor rendimiento en memoria de trabajo (Dyer et al., 2020).

Estos hallazgos coinciden con la literatura reciente que sugiere que la inflamación crónica puede interferir directamente con las conexiones neuronales y su funcionamiento. Citocinas como la IL-6 y el TNF-α, involucradas en respuestas inmunitarias, pueden afectar procesos neuronales esenciales como la plasticidad sináptica, contribuyendo a déficits en dominios cognitivos como la memoria y la atención (Jorgensen et al., 2023).

La evidencia meta-analítica refuerza esta relación entre biomarcadores inflamatorios y deterioro cognitivo. Por ejemplo, Morrens et al. (2022) destacaron que niveles elevados de

La evidencia meta-analítica refuerza esta relación entre biomarcadores inflamatorios y deterioro cognitivo. Por ejemplo, Morrens et al. (2022) destacaron que niveles elevados de PCR, IL-6 y TNF-α están significativamente relacionados con déficits en la memoria verbal, visual y de trabajo en individuos con TMG (Morrens et al., 2022). De manera similar, en individuos con TB y EZ, los niveles elevados de IL-6, IL-1β, TNF-α y CRP están relacionados con un peor rendimiento en dominios cognitivos como atención, velocidad de procesamiento, función ejecutiva y aprendizaje verbal y visual (Patlola et al., 2023; Vares et al., 2020).

Además, el vínculo entre la inflamación sistémica y el deterioro cognitivo en la TMG está respaldado por estudios que destacan el impacto de moléculas inflamatorias en la neurofisiología. Según Patlola et al. (2023), estas citocinas no solo interfieren con la comunicación neuronal, sino que también promueven la neuroprotección o neurotoxicidad (Patlola et al., 2023).

En el caso de individuos con DMT2, se dispone de evidencia similar. Un metanálisis de Anita et al. (2022) respalda la asociación entre inflamación crónica y deterioro cognitivo (Anita et al., 2022). Por ejemplo, niveles elevados de IL-6 y TNF-α están relacionados con un peor desempeño en memoria y otras funciones cognitivas (Marioni et al., 2010). Este panorama refuerza la idea de que las respuestas inflamatorias desreguladas desempeñan un papel central en la patogénesis del deterioro cognitivo y subraya la necesidad de explorar enfoques terapéuticos dirigidos a la inflamación para abordar estas alteraciones.

Del mismo modo, en cuanto a los biomarcadores inmunitarios, nuestros resultados revelan una estrecha relación con el funcionamiento cognitivo y social. La literatura reciente muestra que la producción de diferentes tipos de leucocitos puede tener un rol crucial en la fisiopatología, ya que su transcripción y secreción están estrechamente relacionadas con el desarrollo cerebral humano (Zeng et al., 2024). Por ejemplo, los niveles de monocitos se asociaron negativamente con el funcionamiento cognitivo en individuos con EZ (Feng et al., 2020) y con un mayor riesgo de progresión a lo largo del tiempo (Adamowicz et al., 2024). De manera similar, niveles reducidos de monocitos están asociados con peores resultados clínicos en el TB (Karthikeyan et al., 2022) y en el TDM (Moriarity et al., 2020). Evidencia reciente ha demostrado que las diferencias en los perfiles inmunitarios pueden ayudar a identificar a individuos con depresión unipolar y bipolar (Brunoni et al., 2020; Sanchez-Autet et al., 2022) y a aquellos con trayectorias de enfermedad más graves (Poletti et al., 2021).

Además, un perfil inmunoinflamatorio deteriorado puede aumentar la vulnerabilidad a DMT2 (Blériot et al., 2023) y se ha postulado como un predictor significativo de peores resultados clínicos con el tiempo (Sluiman et al., 2022; Vreijling et al., 2024).

En cuanto a los biomarcadores de estrés oxidativo (ROS, mROS, SOD), nuestros hallazgos evidencian una relación positiva con el funcionamiento cognitivo y social. Hasta donde sabemos, no se dispone de estudios que exploren la relación de estos biomarcadores en una muestra con características parecidas a la nuestra. Sin embargo, estudios en individuos con enfermedades neurodegenerativas, como el estudio de Nantachai et al. (2022) revela que los individuos con deterioro cognitivo presentan un aumento significativo del estrés oxidativo, evidenciado por una mayor peroxidación lipídica y toxicidad asociada. Además, se observa una disminución de las defensas antioxidantes, especialmente en los niveles de GSH, lo que indica una capacidad reducida para contrarrestar el daño oxidativo. También se encuentran niveles elevados de homocisteína, un marcador relacionado con el estrés oxidativo y el riesgo cardiovascular (Nantachai et al., 2022; Peng et al., 2025). Por otro lado, una alta actividad pro-oxidativa en edades tempranas puede ser un factor de riesgo para el desarrollo de demencia, por el contrario, puede ser un factor neuroprotector en situaciones donde los niveles de estrés son muy elevados (Franzoni et al., 2021).

Asimismo, en referencia a los biomarcadores de metabolismo lipídico, nuestros resultados revelan una estrecha relación entre los TG y algunas apolipoproteínas (Apo-A1 y Apo-B) con el funcionamiento cognitivo. La mayoría de los estudios se han centrado en explorar la relación entre el metabolismo lipídico y el deterioro cognitivo en personas con enfermedades neurodegenerativas. Así pues, múltiples estudios sugieren que las apolipoproteínas también están implicadas en el deterioro relacionado con la edad (Hui et al., 2017; Zhang et al., 2022; Rao et al., 2021). Se han realizado muchos menos estudios sobre la relación entre las apolipoproteínas y la cognición en los TMG.

Por ejemplo, los niveles elevados de TG se asociaron de manera significativa con el deterioro de la cognición en individuos con TMG y ECMs (Dimache et al., 2021). Asimismo, los niveles séricos de Apo-B predijeron de manera independiente el rendimiento de la memoria en el TDM (Hui et al., 2017), mientras que los niveles de Apo-B se asociaron negativamente con la cognición en una muestra mixta de TDM y TB (Zhang et al., 2022). Además, tanto los niveles de Apo-A1 como los de Apo-B predijeron el deterioro de la memoria en un estudio

amplio en individuos con EZ (Rao et al., 2021). No tenemos conocimiento de estudios similares realizados en DMT2.

Por último, nuestros resultados muestran que el funcionamiento cognitivo y social estuvo significativamente asociado con los biomarcadores de adhesión molecular (ICAM, VCAM, RPMN, RVPMN). Estos biomarcadores pueden ser más específicos de algunos tipos de enfermedades (en este caso, ECM) en lugar de ser indicadores de inflamación general. Sin embargo, también es posible que las moléculas de adhesión ejerzan un papel potencial en el deterioro cognitivo (Pacholko y Iadecola, 2024). Así, hay evidencia preliminar sobre la asociación entre las moléculas de adhesión celular y los déficits cognitivos en individuos con TMG (Erichsen et al., 2022). Además, ciertas moléculas de adhesión celular están estrechamente relacionadas con el deterioro cognitivo tanto en enfermedades neurodegenerativas, como en enfermedades somáticas, como la diabetes (Rundek et al., 2022). Por ello, los mecanismos de adhesión celular podrían representar nuevas dianas en el tratamiento de la disfunción cognitiva asociada con TMG.

Se corroboró la segunda hipótesis principal que afirma que la determinación conjunta de los déficits en cognición y las alteraciones en el perfil inflamatorio contribuye a clasificar correctamente a individuos con TMG.

Replicar los hallazgos que relacionan la alteración del perfil inflamatorio y mecanismos relacionados con el deterioro cognitivo en una muestra transdiagnóstica representa una innovación significativa en la investigación en salud mental. Este enfoque permite identificar patrones comunes y diferencias entre diversos trastornos, enriqueciendo nuestra comprensión de los mecanismos subyacentes. La inclusión de condiciones como la DMT2 en estos estudios es especialmente valiosa, ya que esta enfermedad crónica se asocia con alteraciones inflamatorias y cognitivas. Ampliar esta investigación a poblaciones con otras comorbilidades podría revelar interacciones específicas entre la inflamación, la cognición y las enfermedades metabólicas, abriendo nuevas vías para intervenciones terapéuticas personalizadas.

5.4. Líneas de investigación futuras

A lo largo de la presente tesis doctoral se ha puesto de manifiesto la necesidad de abordar la comorbilidad en población con TMG, así como la utilidad de los modelos predictivos a la hora de identificar posibles efectos diferenciales del perfil inflamatorio sobre el funcionamiento cognitivo y social de dicho colectivo.

Una de las principales innovaciones de esta tesis radica en la adopción de un enfoque transdiagnóstico para el análisis de los TMG. Este enfoque tiene el potencial de superar las limitaciones inherentes a las categorías diagnósticas tradicionales, permitiendo ampliar las muestras de estudio al incluir personas con características compartidas entre distintos diagnósticos. De esta manera, se abre la posibilidad de diseñar tratamientos más personalizados y eficaces que consideren las dimensiones compartidas por los diferentes trastornos. En este sentido, futuras investigaciones podrían profundizar en cómo operativizar y extender la aplicación del enfoque transdiagnóstico en la práctica clínica. Sería de gran valor el desarrollo de herramientas metodológicas que permitan estratificar a los individuos en función de patrones sintomáticos transdiagnósticos, lo que podría ampliar aún más el impacto de este enfoque en el tratamiento de los TMG.

La creciente prevalencia de comorbilidades, particularmente las ECMs, junto con la mortalidad prematura asociada a estas en individuos con TMG, resalta la necesidad de personalizar las intervenciones. En particular, se debe priorizar la mejora de los estilos de vida, como sugieren estudios recientes (Rødevand et al., 2022), y mejorar tanto los procedimientos de detección como el tratamiento de las ECMs en esta población (Ronaldson et al., 2020). Además, la creciente evidencia sobre la relevancia de los biomarcadores en el diagnóstico y tratamiento de los TMG subraya la importancia de integrarlos de manera más efectiva en el proceso terapéutico. Un aspecto crucial que debe explorarse es la identificación de mecanismos comunes entre los TMG y las ECMs, lo que podría facilitar el desarrollo de herramientas predictivas transdiagnósticas para prevenir de manera más ajustada el desarrollo de estas comorbilidades en individuos con TMG (Nees et al., 2021).

Si bien en la actualidad existen intervenciones farmacológicas centradas en reducir los parámetros cardiometabólicos, su efectividad en la mejora de las comorbilidades y el funcionamiento cognitivo sigue siendo limitada (Solmi et al., 2021). En este contexto, los enfoques centrados en la promoción de estilos de vida saludables se han mostrado

prometedores en población con comorbilidades cardiometabólicas, no sólo en la reducción de comorbilidades metabólicas, sino también en la mejora del funcionamiento cognitivo (Wiedeman et al., 2021). Sin embargo, estas intervenciones suelen centrarse principalmente en la salud física, como el control del peso y el IMC, sin priorizar suficientemente la mejora de la cognición (Bauer et al., 2016; Simjanoski et al., 2023). Este aspecto puede ser relevante, ya que el control de los parámetros metabólicos podría contribuir significativamente a mejorar la calidad de vida y el funcionamiento general de las personas con TMG, especialmente en un contexto donde los psicofármacos actualmente disponibles tienen el potencial de agravar los problemas metabólicos, y las terapias nutricionales aún no han demostrado eficacia suficiente en TMG (Sud et al., 2021).

Un enfoque preventivo integral debe considerar el cambio de expectativas y percepciones sobre hábitos saludables, tales como la importancia de la actividad física regular y combatir el sedentarismo, los cuales pueden contribuir a la aparición de ECMs en personas con TMG. De forma similar, prevenir el deterioro cognitivo podría mejorar el funcionamiento psicosocial y la calidad de vida, e incluso retrasar la aparición de las ECMs (Reuben et al., 2024). Para lograr resultados sostenibles en la mejora del funcionamiento cognitivo, los enfoques terapéuticos transdiagnósticos deben alinearse con estrategias sociales más amplias que promuevan la inclusión social, la educación y el empleo (Bolster-Foucault et al., 2021; Oswald et al., 2024; Shah et al., 2021). Esto implica la necesidad de desarrollar herramientas predictivas para el déficit cognitivo y social en personas con TMG, guiando intervenciones preventivas más eficaces, y teniendo en cuenta las comorbilidades cardiometabólicas.

Además, una línea prometedora de investigación se refiere a las implicaciones en la relación entre el perfil inflamatorio y la disfunción cognitiva en pacientes con TMG. Si la inflamación y otros biomarcadores asociados contribuyen a las alteraciones cognitivas, esto podría redefinir el enfoque terapéutico, especialmente si se incorporan estrategias antiinflamatorias. A pesar del creciente interés en estas terapias para los síntomas clínicos de los TMG, las intervenciones antiinflamatorias han abordado de manera limitada las disfunciones cognitivas. Identificar estrategias pro-cognitivas eficaces basadas en reducir la inflamación permitiría ofrecer un tratamiento más integral para las personas con TMG.

Asimismo, la estratificación de las muestras clínicas mediante el uso de biomarcadores es un área que merece atención prioritaria para personalizar las intervenciones y definir perfiles de pacientes que se beneficien más de estas estrategias. La identificación de subgrupos

específicos de individuos según sus perfiles de biomarcadores permitiría diseñar intervenciones más personalizadas (Balanzá-Martínez et al., 2020).

En consecuencia, existen varios temas clave que considero esenciales para continuar avanzando en este campo. Un aspecto de gran interés es la exploración de los mecanismos subyacentes a la interacción entre los diferentes marcadores moleculares, más allá de los inflamatorios, y las alteraciones cognitivas y sociales. A pesar de los avances logrados, aún se desconocen las rutas precisas a través de las cuales estos mecanismos influyen en el comportamiento y en las funciones cognitivas de los individuos con TMG. Sería relevante investigar cómo las variaciones individuales en el perfil metabólico e inmuno-inflamatorio podrían predecir de manera más precisa la aparición o la gravedad de las dificultades cognitivas y sociales, lo que permitiría personalizar las estrategias terapéuticas.

5.5. Limitaciones y fortalezas

Varias limitaciones deben ser consideradas a la hora de interpretar los resultados presentados en esta tesis. En primer lugar, el tamaño relativamente pequeño de la muestra limita la capacidad de generalizar los resultados a otras poblaciones clínicas. Esta limitación se agrava por la relativamente alta tasa de mortalidad experimental observada después de un año de seguimiento, lo que ha podido introducir un sesgo de retención al incluir principalmente a individuos que completaron las evaluaciones y que presumiblemente se encontraban en mejor estado clínico al inicio del estudio.

En segundo lugar, aunque el IMC y los parámetros de SM son medidas comúnmente utilizadas para evaluar la OB y el SM, respectivamente; su capacidad para representar el estado de salud global es limitada. Medidas de actividad lipídica más extensas, como los parámetros genéticos del metabolismo, habrían sido preferibles para reflejar mejor los riesgos inflamatorios y metabólicos asociados y aportar información más exhaustiva.

En tercer lugar, el uso de un score cognitivo global y mnésico como medida principal puede dificultar la comparación directa con investigaciones previas que han explorado la relación entre las variables analizadas y la cognición a un nivel más específico, considerando funciones o dominios concretos.

En cuarto lugar, la imposibilidad de controlar el impacto de ciertas variables relevantes sobre los resultados principales. Los parámetros de inflamación, mecanismos metabólicos y de estrés oxidativo pueden fluctuar dependiendo del estado clínico y los tratamientos farmacológicos recibidos, lo que introduce variabilidad en los resultados. Además, variables como el estatus de fumador no fueron recopiladas al inicio del estudio, lo que puede haber afectado la interpretación de los hallazgos (Felger y Capuron, 2021). Estas limitaciones metodológicas subrayan la necesidad de estudios futuros con diseños más robustos (por ejemplo, experimentales) y parámetros clínicos mejor definidos.

A pesar de las limitaciones mencionadas, la presente tesis doctoral presenta algunas fortalezas. En primer lugar, el enfoque transdiagnóstico empleado es novedoso. Consideramos que permitiría evaluar el funcionamiento cognitivo y social en individuos con diferentes comorbilidades, abarcando poblaciones con diferentes enfermedades somáticas y mentales aparentemente no relacionadas entre sí.

En segundo lugar, la naturaleza multicéntrica del estudio puede incrementar la validez externa de los resultados y favorecer la aplicabilidad de los hallazgos a diferentes contextos clínicos.

En tercer lugar, el diseño longitudinal permite explorar posibles relaciones causales entre las vías de inflamación, metabólicas y de estrés oxidativo asociadas a las ECMs y el funcionamiento cognitivo y social de las personas con TMG a lo largo del tiempo.

6. CONCLUSIONES

Las principales conclusiones que se pueden extraer de los diferentes artículos que integran la tesis son:

1. La variabilidad fenotípica observada en el deterioro cognitivo y el perfil inflamatorio de individuos con TMGs (TDM, TB, EZ) coincide con los patrones descritos en la literatura actual.
2. La evaluación simultánea de los déficits cognitivos y las alteraciones inflamatorias podría ser útil para una clasificación más precisa de los individuos con TMGs, con independencia de que presenten comorbilidades cardiometabólicas.
3. Los individuos con TMGs y comorbilidades cardiometabólicas presentan un funcionamiento cognitivo y social más deteriorado y un perfil inflamatorio más elevado que aquellos sin comorbilidades y que los individuos sanos.
4. El perfil de funcionamiento cognitivo y social, así como los patrones inflamatorios, no difieren significativamente entre los individuos con distintos tipos de TMGs, lo que sugiere que las alteraciones cognitivas y el perfil inflamatorio podrían representar aspectos transdiagnósticos.
5. Los déficits en el funcionamiento cognitivo y social, junto con las alteraciones en el perfil inflamatorio, se asocian con peores desenlaces clínicos (aparición de comorbilidades) en la población de estudio. Este hallazgo subraya la relevancia de monitorizar estos factores para predecir y gestionar los riesgos de complicaciones a largo plazo en individuos con TMGs.
6. Los componentes específicos del SM se asocian significativamente con el deterioro cognitivo en personas con TMGs y ECMs, lo que indica que el efecto acumulativo de estos componentes podría representar un factor transdiagnóstico en la predicción del funcionamiento cognitivo y social.
7. La inflamación y el metabolismo lipídico parecen estar asociados con el funcionamiento mnésico en personas con TMGs y DMT2, lo que sugiere que los biomarcadores podrían ser una herramienta útil para identificar a individuos con mayor riesgo de deterioro cognitivo.

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ANEXO I

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ORIGINAL ARTICLE

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Specific metabolic syndrome components predict cognition and social functioning in people with type 2 diabetes mellitus and severe mental disorders

Joan Vicent Sánchez-Ortí[1,2,3] | **Vicent Balanzá-Martínez**[1,2,4,5,6] | **Patricia Correa-Ghisays**[1,2,3,4,5] | **Gabriel Selva-Vera**[1,2,4,5] | **Joan Vila-Francés**[7] | **Rafael Magdalena-Benedito**[7] | **Constanza San-Martin**[2,8] | **Víctor M. Victor**[9,10,11] | **Irene Escribano-Lopez**[9] | **Antonio Hernández-Mijares**[9] | **Juliana Vivas-Lalinde**[12] | **Benedicto Crespo-Facorro**[2,13] | **Rafael Tabarés-Seisdedos**[1,2,4,5]

[1]INCLIVA – Biomedical Research Institute, Valencia, Spain

[2]TMAP – Evaluation Unit in Personal Autonomy, Dependency and Serious Mental Disorders, University of Valencia, Valencia, Spain

[3]Faculty of Psychology, University of Valencia, Valencia, Spain

[4]Center for Biomedical Research in Mental Health Network (CIBERSAM), Health Institute, Carlos III, Madrid, Spain

[5]Teaching Unit of Psychiatry and Psychological Medicine, Department of Medicine, University of Valencia, Valencia, Spain

[6]Mental Health Unit of Catarroja, Valencia, Spain

[7]IDAL - Intelligent Data Analysis Laboratory, University of Valencia, Valencia, Spain

[8]Department of Physiotherapy, University of Valencia, Valencia, Spain

[9]Service of Endocrinology and Nutrition, University Hospital Dr. Peset, Valencia, Spain

[10]Foundation for the Promotion of Health and Biomedical Research in the Valencian Region (FISABIO), Valencia, Spain

[11]Department of Physiology, University of Valencia, Valencia, Spain

[12]Department of Psychiatry, Mental Health Service, Manises, Valencia, Spain

[13]Department of Psychiatry, Faculty of Medicine, University of Sevilla, HU Virgen del Rocío IBIS, Sevilla, Spain

Correspondence
Vicent Balanzá-Martínez, Teaching Unit of Psychiatry and Psychological Medicine, Department of Medicine, University of Valencia, Blasco-Ibáñez 17, 46010 Valencia, Spain.
Email: vicente.balanza@uv.es

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Abstract

Objective: Obesity and metabolic diseases such as metabolic syndrome (MetS) are more prevalent in people with type 2 diabetes mellitus (T2DM), major depressive disorder (MDD), bipolar disorder (BD), and schizophrenia (SZ). MetS components might be associated with neurocognitive and functional impairments in these individuals. The predictive and discriminatory validity of MetS and its components regarding those outcomes were assessed from prospective and transdiagnostic perspectives.

Methods: Metabolic syndrome components and neurocognitive and social functioning were assessed in 165 subjects, including 30 with SZ, 42 with BD, 35 with MDD, 30 with T2DM, and 28 healthy controls (HCs). A posteriori, individuals were classified into two groups. The MetS group consisted of those who met at least three of the following criteria: abdominal obesity (AO), elevated triglycerides

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(TG), reduced high-density lipoprotein cholesterol (HDL), elevated blood pressure (BP), and elevated fasting glucose (FPG); the remaining participants comprised the No-MetS group. Mixed one-way analysis of covariance and linear and binary logistic regression analyses were performed.

Results: Cognitive impairment was significantly greater in the MetS group (n = 82) than in the No-MetS group (n = 83), with small effect sizes ($p < 0.05$; $\eta^2 p = 0.02 – 0.03$). In both groups, the most robust associations between MetS components and neurocognitive and social functioning were observed with TG and FPG ($p < 0.05$). There was also evidence for a significant relationship between cognition and BP in the MetS group ($p < 0.05$). The combination of TG, FPG, elevated systolic BP and HDL best classified individuals with greater cognitive impairment ($p < 0.001$), and TG was the most accurate ($p < 0.0001$).

Conclusions: Specific MetS components are significantly associated with cognitive impairment across somatic and psychiatric disorders. Our findings provide further evidence on the summative effect of MetS components to predict cognition and social functioning and allow the identification of individuals with worse outcomes. Transdiagnostic, lifestyle-based therapeutic interventions targeted at that group hold the potential to improve health outcomes.

KEYWORDS

cognition, metabolic syndrome, severe mental disorder, social functioning, type 2 diabetes mellitus

1 | INTRODUCTION

Obesity and metabolic problems have reached pandemic proportions in recent decades, representing an increased socioeconomic burden that in turn is associated with increased morbimortality.[1] For instance, people with type 2 diabetes mellitus (T2DM) and severe mental illness (SMI), such as major depressive disorder (MDD), bipolar disorder (BD), and schizophrenia (SZ), have a higher prevalence of metabolic syndrome (MetS) than the general population.[2,3] MetS is a cluster of certain medical conditions, such as abdominal obesity (AO), elevated triglycerides (TG), low- and high-density lipoprotein cholesterol (HDL), elevated fasting plasma glucose (FPG), and elevated blood pressure (BP).[4,5] Unhealthy lifestyle behaviors, including smoking, poor eating habits and diet quality and reduced physical activity, are major drivers of the increase in MetS among individuals with SMI and T2DM.[6,7] All these factors are strongly associated with poor quality of life, poor treatment adherence, and increased mortality in these populations.[8] Moreover, treatment with psychopharmacological medications, especially certain mood stabilizers and antipsychotics, may cause weight gain and further increase the risk of metabolic disorders.[9,10]

Significant outcomes

- Metabolic syndrome is linked with neurocognitive decline across somatic and psychiatric disorders over time.
- Specific metabolic syndrome components predict cognition and social functioning.
- Abdominal obesity did not play any significant role for neurocognitive performance and social functioning.

Limitations

- High experimental mortality at one-year follow-up.
- Relatively small sample size.
- Not information about dietary habits.

In recent years, the importance of a multimorbidity view that brings together the effects of mental and physical health has been increasingly recognized.[11,12] Indeed, recent reviews highlight that abnormal metabolic pathways promote the onset of several SMI, such us SZ, and it is related to increased early morbimortality.[13,14] MetS

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diagnosis allows the identification of individuals at a higher risk of developing chronic conditions. MetS components, such as FPG levels and especially the combination of elevated TG and reduced HDL, predict the risk of developing T2DM.[15] Likewise, a recent study found that individuals with SMI who meet the criteria for MetS suffer from multiple comorbidities in comparison with healthy controls (HCs).[16] Moreover, individuals with SMI and MetS have a more severe condition, a worse response to pharmacological treatments and a worse prognosis than individuals without MetS.[17,18] On the other hand, recent studies have reported that MetS is significantly associated with cognitive impairment in individuals with SMI, which could in turn contribute to a decline in social functioning.[19,20] Other studies have suggested that BP, HDL, and TG are important predictors of cognition in individuals with SMI, whereas AO is one of the predictors of cognitive impairment and quality of life.[21] These relationships also apply to several nonpsychiatric conditions, including cardiometabolic illnesses.[22] Indeed, individuals with T2DM who meet the criteria for MetS have worse cognitive performance and poorer quality of life than individuals without MetS.[23,24] Likewise, metformin treatment has been associated with decreased cardiovascular risk and improved neurocognitive outcomes in patients with T2DM.[25] In summary, increasing evidence supports the notion that MetS and its components are relevant risk factors or predictors of neurocognitive and social dysfunction across common noncommunicable diseases. Therefore, it is likely that the former represents a transdiagnostic component with implications for relevant outcomes.

To our knowledge, no study has evaluated the contribution of MetS and its components to both neurocognitive and social functioning in people with SMI and T2DM. Moreover, the great heterogeneity of possible combinations of MetS components makes it difficult to estimate the risk of developing impaired cognitive or social functioning. No previous studies have been conducted to determine whether some combinations of MetS components predict cognitive performance and social functioning better than others in individuals with or without MetS diagnosis across T2DM and SMI. While MetS components might aid in the early detection of neurocognitive and functional impairment in at-risk populations, evidence supporting their potential application in clinical practice is scarce. To our knowledge, the discriminatory ability of MetS components for classifying individuals with greater cognitive impairment has not been tested. Therefore, research using samples of individuals with T2DM, MDD, BD, and SZ may help to determine the risk of neurocognitive and social dysfunction associated with MetS more effectively in these populations.

1.1 | Aims of the study

The aims of this study were threefold: (a) to explore whether baseline MetS components are significant predictors of cognitive performance and social functioning at the one-year follow-up, (b) to examine the discriminatory ability of specific MetS components for classifying individuals with greater cognitive impairment, and (c) to analyze the differences between specific MetS components, cognitive performance, and social functioning in people with or without MetS diagnosis across T2DM and SMI.

2 | MATERIALS AND METHODS

2.1 | Study design and ethical considerations

This article is part of a project aimed at identifying and validating peripheral biomarkers for neurocognitive deficits in MDD, BD, SZ, and T2DM. This prospective and comparative cohort project was conducted between April 2015 and January 2018, and it investigated the association and evolution of certain peripheral blood biomarkers and neurocognitive impairments in a unique longitudinal cohort of individuals with somatic and psychiatric disorders. Demographic and clinical data, neurocognitive and social functioning data, and biomarkers of peripheral blood were collected at baseline (T1) and after one year (T2). Individuals with SMI were recruited from mental health units (MHUs) in several towns in the province of Valencia, Spain (Foios, Catarroja, Paterna, and Sagunto); the psychiatry outpatient clinic and endocrinology department of the University Hospital Dr. Peset; and the Miguel Servet MHU in Valencia City. HCs were residents of the same areas as the individuals with SMI. Participants were demographically matched. All participants provided informed consent after the study procedures were explained. The ethical committees or an institutional review board at each participating center approved the study protocol, and the study was conducted in accordance with the ethical principles of the Declaration of Helsinki. For this article, only those variables related to this study aims were included in the analyses.

2.2 | Participants

SZ, BD, and MDD were diagnosed based on the criteria of the Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM 5).[26] T2DM was diagnosed based on the Standards of Care criteria of the American Diabetes Association.[27] Participants with MDD and BD had to meet

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the remission criteria[28] of an acute affective episode, and individuals with SZ had to be clinically stable.[29] Individuals with T2DM had to be free of severe diabetic neuropathy and kidney disease (serum creatinine <1.5 mg/dl) and, at baseline and at 1-year follow-up, FPG levels were previously checked in this group to reduce possible biases due to overlapping of the glycemic pathway between HC and those with T2DM. For HC recruitment, the absence of physical illness, pharmacological treatments, and family history of SMI in first-degree relatives was required. An ability to understand study procedures and willingness to give written consent were required for participation. General exclusion criteria for all groups included current hospitalization, documented cognitive impairment not secondary to psychiatric disorder (intellectual disability or major neurocognitive disorder, i.e., dementia), disability or inability that prevented understanding of the protocol, current substance abuse disorder (except for nicotine), pregnancy, intake of steroids, corticosteroids, antioxidants, antibiotics, and immunologic therapies, fever over 38°C, and history of vaccination within 4 weeks of the evaluation. The same inclusion and exclusion criteria were used at T1 and T2.

MetS diagnosis was assessed at both times following the revised criteria of the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III).[4,30] This diagnosis requires the presence of at least three of the following five criteria: AO, elevated TG, reduced HDL, elevated BP, and elevated FPG. NCEP ATP III cut-off values to define these alterations are as follows: (i) waist circumference (WC) >102 cm for men and >88 cm for women will hereafter be used as a measure of AO, (ii) TG ≥150 mg/dl or specific treatment for this lipid abnormality, (iii) HDL levels <40 mg/dl for men and <50 mg/dl for women or specific treatment for this lipid abnormality, (iv) systolic BP (SBP) ≥130 mmHg and diastolic BP (DBP) ≥85 mmHg or treatment of previously diagnosed hypertension, and (v) fasting FPG levels ≥100 mg/dl or previously diagnosed T2DM. Following this definition, the participants with alterations in at least three criteria were defined as having MetS, and the remaining participants were classified as not having MetS.

The following MetS components were collected as follows: weight (kg), height (m), WC (cm), TG, HDL, SBP/DBP (mmHg), and FPG. Body weight, height, and WC were measured by calibrated scales. WC was measured in the standing position at the end of normal expiration and at the midway between the inferior costal margin and the superior border of the iliac crest. BP was measured on the right arm using an automatic sphygmomanometer with participants in the sitting position after resting for 5 minutes. Average SBP and DBP values of at least two repeated measurements were calculated. Under aseptic conditions, fasting venous blood samples were collected between 8 and 9 am to measure TG, HDL and FPG levels. Individuals with diseases followed the prescribed pharmacological treatment throughout the study.

2.3 | Assessments

The assessments were conducted by the same experienced psychologists and psychiatrists of the research group. Sociodemographic data, including sex, age, years of education, occupational status and laterality (defined as manual, ocular and crural dominance), were collected.

Clinical evaluations were conducted using the following scales: (i) Kaplan–Feinstein Scale (KFS),[31] (ii) Charlson Comorbidity Index (CCI),[32] (iii) 17-item Hamilton Rating Scale for Depression (HRSD),[33] (iv) Young Mania Rating Scale (YMRS),[34] (v) Positive and Negative Syndrome Scale (PANSS),[35] and (vi) Clinical Global Impression (CGI) scale.[36] For smokers, current tobacco consumption, expressed as the number of cigarettes per day (CPD), and breath carboxyhemoglobin (COHb) level, a validated measure of smoke exposure, were collected.[37] The total number of prescribed psychopharmacological medications and other medications were also registered.

Cognitive performance was evaluated using a comprehensive battery of neuropsychological tests and subtests previously used by our group.[38-41] Seven cognitive domains were assessed: (i) *verbal learning and memory*: Complutense Verbal Learning Test (TAVEC) total immediate recall, short-term free recall and long-term free recall variables[42]; (ii) *cognitive flexibility*: Stroop Color and Word test (SCWT) color/word subtest[43] and Wisconsin Card Sorting Test (WCST) categories completed and perseverative errors[44]; (iii) *verbal fluency*: FAS and animal naming test for phonemic and semantic fluency, respectively[45]; (iv) *working memory*: Trail Making Test (TMT) Part B[45] and Wechsler Adult Intelligence Scale III edition (WAIS-III) digit span backwards[46]; (v) *short-term memory*: TAVEC immediate recall of the first learning trial and immediate recall of the interference list[42] and WAIS-III digit span forward[46]; (vi) *visual memory*: Rey-Osterrieth Complex Figure Test (ROCFT) figure two minutes after the copy (fRey2) and 20 minutes after the copy (fRey20)[47]; and (vii) *processing speed*: finger tapping test (FTT) left unimanual, right unimanual, left bimanual, right bimanual and average four scores,[45,48] WAIS-III digit symbol coding subtest,[46] SCWT color and word subtests[43] and TMT Part A.[45] A global cognitive score (GCS) was calculated by averaging the seven cognitive domain scores.

Social functioning was evaluated using (i) the Functional Assessment Short Test (FAST),[49] (ii) the Short Form-36 Health Survey questionnaire (SF-36),[50] and (iii)

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the World Health Organization Quality of Life brief scale (WHO-QoL-Bref).[51] A global social functioning score (GSFS) was calculated by averaging the total scores on the three scales.

2.4 | Statistical analyses

Data were analyzed using Statistical Package for Social Sciences (SPSS) version 26.0 for Windows.[52] Descriptive analyses were conducted using Student's t-tests for independent samples for continuous variables and chi-square tests for categorical variables. Normality was assumed for all continuous variables because the sample was sufficiently representative of the target population, which was statistically verified. This fact guarantees that the variables are distributed in a normalized way. The differences between groups for MetS components, cognitive performance, and social functioning at T1 and T2 and their evolution overtime were assessed using a mixed one-way analysis of covariance (ANCOVA), with diagnosis (SMI and T2DM) and sex as covariables. It was adjusted for diagnosis and sex because these factors were differentially distributed between the two groups and were a confounding variable. The direct scores obtained for GCS and GSFS were transformed into Z-scores. For the calculation of the Z-scores, the mean and standard deviation of the individuals without MetS (No-MetS) at T1 were taken as reference values. Thus, a valid measure was obtained to contrast the objective condition of the study (exposure or not to MetS). To test the predictive capacity of MetS components at baseline to explain the variance in cognitive performance and social functioning at T2, a linear regression analysis was performed using a predictive model that included only MetS components that were significant for each MetS group. Other variables relevant to cognitive performance and social functioning were not included because the MetS components were optimal predictors per se. Likewise, to test the ability to discriminate individuals with greater cognitive impairment at T2 from MetS components at T1, a binary logistic regression was performed using a predictive model that included only MetS components that were significant for each group. Greater cognitive impairment was defined by scores greater than one standard deviation below the mean on the GCS. Subsequently, a receiver operating characteristic (ROC) curve was generated for the variables identified in the binary logistic regression as explanatory factors of cognitive performance. From this curve, optimal performance levels were delimited based on sensitivity and specificity values for each of the selected variables. For all analyses, $p < 0.05$ was considered statistically significant. The procedure to create the predictive models was as follows: first, a predictive analysis was performed with MetS components one by one, then predictive models were generated that included and combined the statistically more powerful variables; finally, the optimal predictive combination was obtained. No more than five variables were included in each model, thus guaranteeing the correct performance of the analysis.

3 | RESULTS

3.1 | Sample description

At T1, the sample consisted of 165 persons, including 30 with SZ, 42 with BD, 35 with MDD, 30 with T2DM, and 28 HCs. The total sample was classified into two groups: 83 in the No-MetS group (T2DM = 4, MDD = 27, BD = 22, SZ = 8 and HC = 22) and 82 in the MetS group (T2DM = 26, MDD = 8, BD = 20, SZ = 22 and HC = 6).

Forty participants were lost to follow-up at T2 (retention rate: 75.7%). The sample consisted of 70 individuals in the No-MetS group (T2DM = 3, MDD = 18, BD = 18, SZ = 12 and HC = 19) and 55 individuals in the MetS group (T2DM = 22, MDD = 7, BD = 11, SZ = 15 and HC = 0).

A summary of the sociodemographic and clinical characteristics of the participants is presented in Table 1. Women represented half of the total sample (48%). The mean age of the whole sample was 49.9 (SD: 10.2) years. The MetS group was characterized by a significantly lower percentage of women than the No-MetS group. Age, mean number of years of education and laterality were similar in both groups. Moreover, the MetS group had significantly higher levels of multimorbidity and use of medications other than psychopharmacological agents.

3.2 | Between-group comparisons of MetS components, cognitive performance and social functioning at T1 and T2

MetS components at T1 and T2 for both groups are shown in Table 2. Overall, at T1, MetS components were significantly higher in the MetS group ($p < 0.01$; $\eta^2p = 0.03$ to 0.26). Similar findings were observed at T2 ($p < 0.0001$; $\eta^2p = 0.11$ to 0.32). At both assessments, moderate effect sizes were observed for all MetS components when compared between groups. As expected, individuals with MetS had significantly higher WC than those without MetS ($p < 0.0001$; $\eta^2p = 0.12$). Furthermore, HDL was significantly lower in the MetS group ($p < 0.0001$; $\eta^2p = 0.15$). The within-group presence of MetS components did not significantly differ over time.

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TABLE 1 Sociodemographic and clinical characteristics of the sample at T1

Variables[a]	No-MetS ($n = 83$)	MetS ($n = 82$)	Statistical analyses t or χ^2 (p)[i,j]
Sociodemographic			
Sex[b]	53 (64%)	26 (32%)	17.0***
Age	48.8 (9.2)	51.1 (11.2)	NS
Years of education	12.4 (4.8)	12.5 (4.6)	NS
Dependent status[c]	18 (22%)	23 (28%)	NS
Occupation status[d]	50 (60%)	54 (66%)	NS
Laterality[e]	80 (96%)	77 (94%)	NS
Clinical			
Tobacco[f]	37 (44%)	32 (39%)	NS
COHb	0.9 (1.0)	1.1 (1.3)	NS
KFS	0.9 (1.5)	1.6 (1.9)	2.5**
CCI	0.7 (1.2)	1.3 (1.6)	2.9**
HRSD[g]	6.5 (6.5)	6.3 (5.9)	NS
YMRS[g]	1.8 (2.7)	2.8 (4.4)	NS
PANSS-P[g]	7.3 (1.4)	8.7 (3.9)	2.9**
PANSS-N[g]	8.7 (5.0)	11.7 (8.4)	2.7**
PANSS-G[g]	19.7 (8.0)	23.4 (11.2)	2.4**
CGI[g]	2.8 (1.4)	3.0 (1.5)	NS
Psychiatric medications[h]	2.0 (2.1)	2.2 (2.1)	NS
General medications[h]	3.0 (3.1)	4.3 (2.7)	2.6**

Abbreviations: CCI, Charlson Comorbidity Index; CGI, Clinical Global Impression; COHb, carboxihemoglobina; G, general; HRSD, Hamilton Rating Scale for Depression; KFS, Kaplan-Feinstein Scale; MetS, metabolic syndrome; N, negative; NS, not significant; P, positive; PANSS, Positive and Negative Syndrome Scale; T1, time 1; YMRS, Young Mania Rating Scale.

NS = $p > 0.05$; *$p \leq 0.05$; **$p \leq 0.01$; ***$p \leq 0.001$; ****$p \leq 0.0001$.

[a]Expressed as the mean (standard deviation) except when indicated.

[b]Female n (%).

[c]Dependent n (%).

[d]Not active n (%).

[e]Right-handers n (%).

[f]Yes n (%).

[g]Lower scores represent a better outcome.

[h]Number

[i]t-test for independent samples.

[j]Chi-square test.

Neurocognitive performance and social functioning at T1 and T2 for both groups are shown in Table 3. Individuals with MetS showed worse cognitive performance than individuals without MetS at T1 ($p < 0.05$; $\eta^2 p = 0.02$) and T2 ($p < 0.05$; $\eta^2 p = 0.03$). At both assessments, small effect sizes were observed for neurocognitive performance and social functioning when compared between groups. However, social functioning was similar ($p > 0.05$) at both assessments. The within-group cognitive performance and social functioning did not significantly differ over time.

3.3 | Predictive capacity of MetS components at T1 of neurocognitive performance and social functioning at T2

The results of the relative contributions of MetS components at T1 to explain the variation in GCS and GSFS scores at T2 are shown in Table 4. For individuals with MetS, TG alone was the most powerful predictor of GCS at T2 (12.6%), followed by the combination of SBP and DBP, which were the MetS components that explained 10.8% of GCS variance at T2. Moreover, the combination of TG and FPG significantly predicted GSFS at T2 and explained 19.1% of the variance.

For the No-MetS group, 12.5% of GCS variance at T2 could be explained by the combination of TG and FPG. Moreover, WC alone significantly predicted 14.3% of the variance in GSFS at T2, while the combination of TG, HDL, and FPG explained the largest percentage of variance (18.8%) of GSFS at T2.

3.4 | Discriminatory ability of MetS components at T1 to classify individuals with greater cognitive impairment at T2

The results regarding the ability of MetS components at T1 to discriminate individuals with greater cognitive impairment at T2 are shown in Table 5. The combination of four components (TG, FPG, SBP, and HDL) was the model that best classified these individuals, with a correct classification rate of 87.1%. Next, the combination of TG, SBP, and FPG (86.3%), the combination of TG and SBP (81.5%), and TG alone (75%) were successively the best classifiers. ROC curve analysis was performed to assess the diagnostic usefulness of TG, which, as seen in the binary logistic regression, proved to be the most useful component in the classification of individuals with greater cognitive impairment (Figure 1). The analysis showed that the area under the ROC curve for the identification of individuals with greater cognitive impairment was 83.9% with TG (95% CI = 0.77–0.91). As seen in the figure, the TG level that best discriminates individuals with greater cognitive impairment will likely be between those points of the curve, with sensitivity between the 0.75 and 0.80 values.

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TABLE 2 Components related to metabolic syndrome at T1 and T2

	No-MetS		MetS		*Statistical analyses*				
Variables[a]	**T1 (*n* = 83)**	**T2 (*n* = 70)**	**T1 (*n* = 82)**	**T2 (*n* = 55)**	**T1 F (*p*)**[b]	**η^2p**[c]	**T2 F (*p*)**[b]	**η^2p**[c]	**T1-T2 F (*p*)**[b]
WC	92.9 (18.3)	94.9 (16.1)	107.3 (11.1)	110.0 (12.5)	23.4****	.12	15.1****	.11	NS
TG	94.5 (39.6)	100.9 (47.6)	160.0 (60.4)	191.7 (88.1)	58.2****	.26	57.7****	.32	NS
HDL	55.4 (12.2)	54.9 (12.8)	43.0 (9.9)	42.4 (10.3)	30.0****	.15	16.6****	.12	NS
SBP	119.3 (12.7)	118.4 (13.4)	133.3 (17.2)	136.4 (17.9)	25.5****	.13	24.4****	.16	NS
DBP	73.9 (10.3)	73.0 (9.5)	79.2 (9.9)	81.8 (10.0)	5.0**	.03	20.4****	.14	NS
FPG	94.5 (20.5)	96.2 (18.4)	121.7 (46.9)	128.9 (41.4)	24.2****	.13	33.6****	.21	NS

Abbreviations: ANCOVA, analysis of variance; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HDL, high-density lipoprotein; MetS, metabolic syndrome; NS, not significant; SBP, systolic blood pressure; T1, time 1; T2, time 2; TG, triglycerides; WC, waist circumference.

NS = $p > 0.05$; *$p \le 0.05$; **$p \le 0.01$; ***$p \le 0.001$; ****$p \le 0.0001$. Effect size: η^2p: small ≈ 0.02; moderate ≈ 0.15; large ≈ 0.35.

[a]Expressed as the mean (standard deviation).

[b]ANCOVA.

[c]Partial eta-squared (η^2p).

TABLE 3 Cognitive performance and social functioning at T1 and T2

	No-MetS		MetS		Statistical analyses				
Variables[a]	**T1 (*n*=83)**	**T2 (*n*=70)**	**T1 (*n*=82)**	**T2 (*n*=55)**	**T1 F (*p*)**[b]	**η^2p**[c]	**T2 F (*p*)**[b]	**η^2p**[c]	**T1-T2 F (*p*)**[b]
GCS	0.0 (1.0)	0.0 (0.9)	−0.3 (0.9)	−0.3 (0.9)	3.9*	.02	4.3*	.03	NS
GSFS	0.0 (1.0)	0.0 (1.0)	0.1 (0.9)	0.0 (1.0)	NS		NS		NS

Abbreviations: ANCOVA, analysis of covariance; GCS, global cognitive score; GSFS, global social functioning score; MetS, metabolic syndrome; NS, not significant; T1, time 1; T2, time 2.

NS = $p > 0.05$; *$p \le 0.05$; **$p \le 0.01$; ***$p \le 0.001$; ****$p \le 0.0001$. Effect size: η^2p: small ≈ 0.02; moderate ≈ 0.15; large ≈ 0.35.

[a]Z-scores expressed as the mean (standard deviation).

[b]ANCOVA.

TABLE 4 Predictive MetS components at T1 of cognitive performance and social functioning at T2.

Dependent variables at T2	**Predictors at T1**	***β***	**95% CI**	***t***	**Percent of variance explained (adjusted R^2)**
Group: No-MetS					
GCS	TG	−0.29	−0.01 to 0.00	2.39*	12.5
	FPG	−0.19	−0.02 to 0.00	1.65*	
GSFS	WC	−0.37	−0.04 to 0.00	3.11***	14.3
	TG	−0.21	−0.01 to 0.00	1.77*	18.8
	HDL	0.28	0.00 to 0.04	2.33*	
	FPG	−0.23	−0.02 to 0.00	1.96*	
Group: MetS					
GCS	SBP	0.35	0.00 to 0.03	2.48**	10.8
	DBP	−0.32	−0.05 to 0.00	2.28*	
	TG	−0.35	−0.009 to −0.002	2.98**	12.6
GSFS	TG	−0.44	−0.01 to 0.00	3.71***	19.1
	FPG	−0.19	−0.008 to 0.001	1.60*	

Abbreviations: DBP, diastolic blood pressure; FPG, fasting plasma glucose; GCS, global cognitive score; GSFS, global social functioning score; HDL, high-density lipoprotein; MetS, metabolic syndrome; NS, not significant; SBP, systolic blood pressure; T1, time 1; T2, time 2; TG, triglycerides; WC, waist circumference.

NS = $p > 0.05$; *$p \le 0.05$; **$p \le 0.01$; ***$p \le 0.001$; ****$p \le 0.0001$.

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TABLE 5 MetS components at T1 with ability to discriminate individuals with greater cognitive impairment at T2

Dependent variables at T2	Predictors at T1	β	Wald	Percent of variance explained	Global percentage correctly predicted
GCI	TG	0.02	26.9****	0.31 to 0.42	75.0
	TG	0.03	26.2****	0.44 to 0.58	81.5
	SBP	0.08	16.5****		
	TG	0.03	24.2****	0.51 to 0.68	86.3
	SBP	0.04	12.3****		
	FPG	0.07	11.9****		
	TG	0.03	19.9****	0.53 to 0.71	87.1
	FPG	0.05	12.1****		
	SBP	0.07	9.7***		
	HDL	−0.06	4.9*		

Abbreviations: FPG, fasting plasma glucose; GCI, greater cognitive impairment; HDL, high-density lipoprotein; MetS, metabolic syndrome; NS, not significant; SBP, systolic blood pressure; T1, time 1; T2, time 2; TG, triglycerides.

NS = $p > 0.05$; *$p \leq 0.05$; **$p \leq 0.01$; ***$p \leq 0.001$; ****$p \leq 0.0001$.

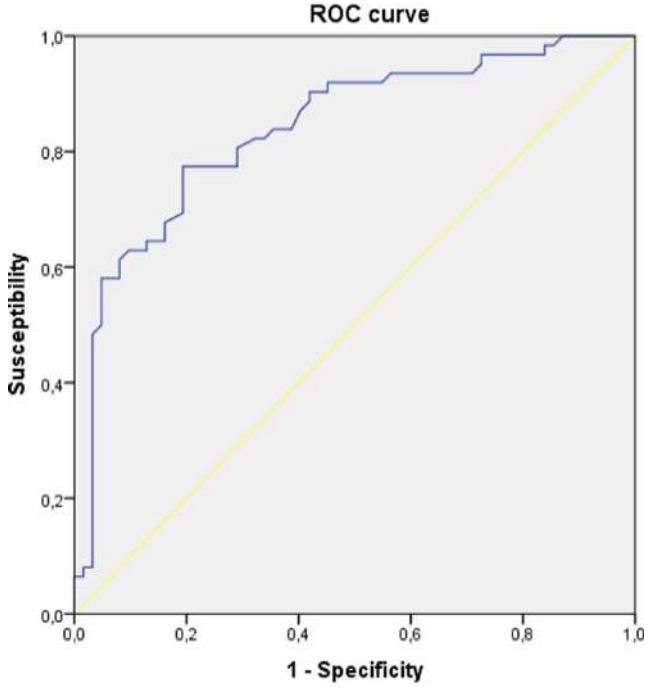

FIGURE 1 Identification of individuals with greater cognitive impairment based on TG levels

4 | DISCUSSION

The growing and dramatic impact of overweight/obesity and metabolic illnesses on physical and mental health is becoming increasingly well known. It is therefore crucial to determine the MetS components that play a key role in this relationship. To our knowledge, this is the first study to evaluate the predictive and discriminatory validity of MetS and its components regarding cognitive and social functioning across people with T2DM and SMI using a longitudinal design and a transdiagnostic perspective.

The results indicated that cognitive performance was significantly worse in individuals with MetS than in those without MetS, while social functioning was similar in both groups. In addition, TG and FPG were found to be key MetS components for predicting cognitive performance and social functioning across SMI and T2DM, regardless of MetS status. Moreover, BP was a significant predictor of cognitive function in individuals with MetS. Regarding discriminatory ability, TG seemed to be the most accurate MetS component for identifying individuals with greater cognitive impairment.[15,16,19,20]

These findings build upon growing evidence suggesting that individuals with SMI and T2DM, who also meet criteria for MetS, have worse cognitive performance than those without MetS.[20,23] Moreover, evidence indicates that individuals with SMI and T2DM have an unhealthy lifestyle that, in addition to psychopharmacological medication intake, increases the risk of developing MetS.[6,9] Thus, people with SMI and T2DM appear to be particularly vulnerable to cognitive and functional impairments linked to MetS. This could be explained by underlying pathophysiological pathways common to somatic and psychiatric diseases, such as immune-inflammatory processes, epigenetic regulatory mechanisms, or the microbiota-gut-brain system.[15,17]

These results have potential implications for the prevention and management of functional impairment in individuals with SMI and T2DM who meet criteria for MetS and individuals with MetS only. MetS is currently considered a major risk factor for the development of chronic diseases that involve high morbimortality, such as T2DM and SMI,[53] and therefore, early detection and

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intervention for those at high risk of developing MetS is crucial. Based on the results of this study, it is proposed that some MetS components are especially useful to discriminate between individuals with disease and healthy individuals, thereby representing key elements for agile and accurate prevention. Thus, early detection of changes in those MetS components offers an opportunity to promote healthy lifestyle behaviors in individuals with SMI and T2DM, which in turn may reduce the risk of developing cardiometabolic complications. In this respect, we emphasize the importance of including MetS components as promising illness diagnostic markers for individuals with SMI and T2DM.[18] Furthermore, our findings converge with the current therapeutic strategy of increasing physical activity and improving the quality of the dietary patterns to address MetS. On the other hand, the recently issued Royal Australian and New Zealand College of Psychiatrists (RANZCP) clinical guidelines for depression place lifestyle-based interventions as the first step in the primary healthcare approach.[54] In keeping with current views that lifestyle is a multidimensional construct,[55] our results further emphasize the need to implement therapeutic interventions that are sensitive to lifestyle changes, thus encouraging regular physical exercise, restorative sleep patterns, improved diet quality, and increased social interaction, among others. Of note, all these behaviors are modifiable. The efficacy of lifestyle-based interventions is widely acknowledged for the prevention and treatment of several noncommunicable diseases and represents the grounds of lifestyle medicine.[56] The recent development of lifestyle psychiatry is gaining momentum.[57] Lifestyle modifications reportedly have a positive impact on symptom severity and neurocognitive function for individuals with SMI,[58,59] which goes beyond their known efficacy to treat metabolic comorbidities. Moreover, the negative impact of several MetS components on cognition might be prevented with nutritional and dietary interventions specifically designed to improve cognition in individuals with SMI and T2DM.[60,61] However, further studies are needed to determine whether lifestyle modifications have sustained, long-term effects in the SMI population.[62] This evidence should be urgently translated into clinical practice, given the poor literacy for nutritional and lifestyle medicine among healthcare professionals and trainees.[63,64]

This paper cannot be concluded without pointing out some of its limitations and strengths. Thus, the limitations of the study include its relatively small sample size, which reduces the generalization of the results to populations of individuals with clinical characteristics similar to those studied. Moreover, after a year of follow-up, high experimental mortality was observed. This may have led to a potential bias in the retention of individuals who completed the assessments and were thus in a presumably better clinical condition. Despite these limitations, this study is characterized by a novel transdiagnostic approach and a comprehensive assessment of cognitive and functional outcomes in individuals with or without MetS across populations with somatic and psychiatric disorders. Furthermore, being a multicenter study increases the external validity of the results.

Our current findings emphasize the need to promote lifestyle-based interventions for people with SMI and T2DM. The use of mobile health (m-health) technologies offers a promising opportunity to gather real-time data on lifestyle changes and self-care, which may be particularly useful for the prevention, tracking, and management of metabolic complications during the course of chronic illnesses. Further research is required to address the mental health effects derived from metabolic complications and changes in lifestyle. In this regard, studies that include more longer-term observations of concomitant lifestyle behaviors could serve to detect changes in metabolic conditions that allow the prevention of neurocognitive impairment among those with somatic and mental disorders. Therefore, considering lifestyle from a holistic perspective, rather than assessing individual behaviors in isolation, becomes essential to understanding the interactions between lifestyle and mental health. Additionally, rigorous further research on the identification of other clinical markers related to changes in lifestyle could not only improve our understanding of mental and physical health but also help to achieve excellence in clinical practice and improve precision psychiatry, which is likely to change the current compartmentalized mental health approach.

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CONFLICT OF INTERESTS

None.

AUTHORS' CONTRIBUTION

JVS-O, VB-M, PC-G, and RT-S: conception and design of the study; acquisition and analysis of data; drafting the manuscript and figures. GS-V, CS-M, VMV, IE-L, AH-M, JV-L, and BC-F: drafting the manuscript and figures. JV-F and RM-B: Formal analysis. All authors have read and agreed to the published version of the manuscript.

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PEER REVIEW

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Joan Vicent Sánchez-Ortí https://orcid.org/0000-0002-8209-6688
Vicent Balanzá-Martínez https://orcid.org/0000-0001-7772-7396
Patricia Correa-Ghisays https://orcid.org/0000-0002-1752-7349
Gabriel Selva-Vera https://orcid.org/0000-0001-9895-8361
Joan Vila-Francés https://orcid.org/0000-0001-8293-8235
Rafael Magdalena-Benedito https://orcid.org/0000-0003-3752-8231
Constanza San-Martin https://orcid.org/0000-0003-0347-5442
Antonio Hernández-Mijares https://orcid.org/0000-0003-4099-1905
Benedicto Crespo-Facorro https://orcid.org/0000-0003-0033-7132
Rafael Tabarés-Seisdedos https://orcid.org/0000-0002-1089-2204

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ANEXO II

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Original

Inflammation and weight change related to neurocognitive and functional impairment in diabetes and psychiatric disorders

Joan Vicent Sánchez-Ortí[a,b,c,d,1], Vicent Balanzá-Martínez[a,b,c,e,f,1], Patricia Correa-Ghisays[a,b,c,d,e,1], Gabriel Selva-Vera[a,b,c,e], Joan Vila-Francés[g], Rafael Magdalena-Benedito[g], Constanza San-Martin[c,h], Víctor M. Victor[a,i,j,k], Irene Escribano-Lopez[i], Antonio Hernandez-Mijares[i], Juliana Vivas-Lalinde[l], Benedicto Crespo-Facorro[b,m], Rafael Tabarés-Seisdedos[a,b,c,e,*]

[a] *INCLIVA – Health Research Institute, Valencia, Spain*
[b] *Center for Biomedical Research in Mental Health Network (CIBERSAM), Health Institute, Carlos III, Madrid, Spain*
[c] *TMAP – Evaluation Unit in Personal Autonomy, Dependency and Serious Mental Disorders, University of Valencia, Valencia, Spain*
[d] *Faculty of Psychology, University of Valencia, Valencia, Spain*
[e] *Teaching Unit of Psychiatry and Psychological Medicine, Department of Medicine, University of Valencia, Valencia, Spain*
[f] *Mental Health Unit of Catarroja, Valencia, Spain*
[g] *IDAL – Intelligent Data Analysis Laboratory, University of Valencia, Valencia, Spain*
[h] *Department of Physiotherapy, University of Valencia, Valencia, Spain*
[i] *Service of Endocrinology and Nutrition, University Hospital Dr. Peset, Spain*
[j] *Foundation for the Promotion of Health and Biomedical Research in the Valencian Region (FISABIO), Valencia, Spain*
[k] *Department of Physiology, University of Valencia, Valencia, Spain*
[l] *Department of Psychiatry, Mental Health Service, Manises, Valencia, Spain*
[m] *Department of Psychiatry, Faculty of Medicine, University of Sevilla, HU Virgen del Rocío IBIS, Spain*

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ABSTRACT

Introduction: Obesity is a global pandemic associated with various cardio-metabolic and psychiatric disorders. Neurocognitive and functional deficits have been associated with several somatic and psychiatric disorders. Adiposity-related inflammation has recently emerged as a key risk factor for neurocognitive and functional impairments. This prospective transdiagnostic study aimed to investigate the role of adiposity-related inflammatory markers in neurocognitive and functional outcomes associated with weight changes.
Methods: Peripheral blood inflammatory and oxidative stress biomarkers and neurocognitive and functional performance were assessed twice over 1 year in 165 individuals, including 30 with schizophrenia, 42 with bipolar disorder, 35 with major depressive disorder, 30 with type 2 diabetes mellitus (T2DM), and 28 healthy controls. Participants were stratified by body mass index into categories of type 2 obesity (T2OB; $n = 30$), type 1 obesity (T1OB; $n = 42$), overweight (OW; $n = 53$), and average weight (NW; $n = 40$). Mixed one-way analysis of covariance and linear and binary logistic regression analyses were performed.
Results: Compared with NW, T2OB and T1OB were significantly associated with impaired neurocognitive and functional performance ($p < 0.01$; $\eta^2 p = 0.06–0.12$) and higher levels of C-reactive protein and platelets (PLT) ($p < 0.01$; $\eta^2 p = 0.08–0.16$), with small-to-moderate effect sizes. IL-6, IL-10, and PLT were key factors for detecting significant weight changes in T1OB and T2OB over time. Regression models revealed that inflammatory and oxidative stress biomarkers and cellular adhesion molecules were significantly associated with neurocognitive and functional performance ($p < 0.05$).

* Corresponding author.
E-mail address: rafael.tabares@uv.es (R. Tabarés-Seisdedos).
[1] These authors contributed equally to this work.

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Discussion: Obesity is characterized by neurocognitive and functional impairments alongside low-grade systemic inflammation. Adiposity-related inflammatory biomarkers may contribute to neurocognitive and functional decline in individuals with T2DM and psychiatric disorders. Our data suggest that these biomarkers facilitate the identification of specific subgroups of individuals at higher risk of developing obesity.
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Introduction

Obesity (OB) has emerged as a global pandemic over the past few decades. OB constitutes a major public health problem that causes a substantial societal and economic burden associated with a greater risk of morbimortality.[1,2] Evidence suggests that OB and increased body fat/adiposity are bi-directionally associated with poor mental health outcomes.[3] Indeed, several psychiatric disorders are strong risk factors for the development and maintenance of OB.[4] Additionally, OB is frequently complicated by cardio-metabolic diseases, such as type 2 diabetes mellitus (T2DM). In this regard, T2DM appears to be related to body mass index (BMI), whereby individuals with severe OB have a higher risk of developing T2DM.[5] Moreover, decreased quality of life and increased functional impairments are frequently observed in individuals with OB, predominantly owing to higher rates of treatment resistance and relapse.[6]

Psychiatric and cardio-metabolic multimorbidities may contribute to neurocognitive and functional decline in individuals with OB.[7] In individuals with psychotic and mood disorders, more severe OB significantly increases neurocognitive deficits than average weight (NW).[8,9] Of note, an extensive neurocognitive overlap has been observed between individuals with T2DM and psychotic and mood disorders.[10] This overlap is associated with more significant functional impairment in individuals with comorbid OB. Fernando et al. recently reported that T2DM is associated with an increased risk of developing earlier neurocognitive impairments in individuals with overweight (OW)/OB.[11] Furthermore, the presence of weight gain (WG) and high comorbidity rates among individuals with OB are associated with an increased risk of neurocognitive decline and poorer functional outcomes over time.[12]

Lifestyle factors, such as dietary patterns that are poor in nutrients and high in saturated fats and refined sugars, in conjunction with increased sedentary behaviors and reduced physical activity, have been shown to contribute significantly to increased weight, particularly in more vulnerable populations such as individuals with psychotic and mood disorders.[13,14] Psychopharmacological treatments prescribed to individuals with psychotic and mood disorders have been associated with metabolic complications that also contribute to WG.[15] Conversely, weight loss (WL) is associated with improved cognition. For instance, a recent review highlighted a positive effect of WL on neurocognitive performance in individuals with OW/OB over time.[16]

The association of weight changes with neurocognitive and functional performance may be mediated by inflammatory processes.[17] OB is associated with chronic low-grade inflammation, which in turn is commonly observed in cardio-metabolic and psychiatric disorders.[18] Recent meta-analyses have identified that increased concentrations of pro-inflammatory biomarkers, including C-reactive protein (CRP), tumor necrosis factor-alpha (TNF-α), and interleukin-6 (IL-6), alongside oxidative stress and mitochondrial dysfunction are associated with neurocognitive and functional impairments in a large proportion of individuals with OB and related comorbidities.[19,20] Similarly, a meta-analysis that tracked weight changes revealed that heightened inflammation is consistently associated with WG, such that individuals with more severe OB and elevated inflammatory biomarkers have poorer neurocognitive and functional outcomes than those with OB alone.[21] Collectively, increasing evidence suggests that adiposity-related inflammatory processes lead to neurocognitive and functional impairments across psychiatric disorders and T2DM. Therefore, regardless of the primary condition, inflammatory changes associated with excess body fat/adiposity may represent a transdiagnostic component with relevant implications for WG prevention and OB management.

To our knowledge, no study to date has evaluated the contribution of inflammatory markers to the detection of weight changes in individuals with OB and comorbid psychiatric disorders and T2DM. Moreover, more studies need to examine the ability of inflammatory biomarkers to predict neurocognitive and functional performance in individuals stratified by WG/WL from a transdiagnostic and longitudinal perspective. The aims of the present study were three-fold: (a) to compare inflammatory biomarkers and neurocognitive and functional performance across individuals with psychiatric disorders and T2DM stratified by BMI, (b) to examine the usefulness of inflammatory biomarkers for detecting significant weight changes, and (c) to explore whether baseline inflammatory biomarkers were significant predictors of neurocognitive and functional performance at the 1-year follow-up.

Materials and methods

Study design and ethical considerations

This article is part of a project that aims to identify and validate peripheral biomarkers for neurocognitive deficits in major depressive disorder (MDD), bipolar disorder (BD), schizophrenia (SZ), and T2DM. This prospective comparative cohort study was conducted between April 2015 and January 2018 to investigate the association and evolution of specific peripheral blood biomarkers and neurocognitive impairments in a unique longitudinal cohort of individuals with somatic and psychiatric disorders. Demographic and clinical data, neurocognitive and functional data, and information on peripheral blood biomarkers were collected at baseline (T1) and after one year (T2). Individuals with psychiatric disorders were recruited from mental health units (MHUs) in several towns in the province of Valencia, Spain (Gandía, Foios, Catarroja, Paterna, and Sagunto); the psychiatry outpatient clinic and endocrinology department of the University Hospital Dr. Peset; and Miguel Servet MHU in Valencia City. Healthy controls (HCs) were residents of the same areas as those of individuals with SMI. Participants were demographically matched. All participants provided written informed consent after the study procedures were fully explained. The ethics committees and institutional review boards at each participating center approved the study protocol, and the study was conducted in accordance with the ethical principles of the Declaration of Helsinki. For this study, only variables related to the present study aims were included in the analyses.

Participants

SZ, BD, and MDD were diagnosed according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders 5.[22] T2DM was diagnosed based on the Standards of Care criteria of the American Diabetes Association.[23] Participants with MDD and BD were required to meet the remission criteria[24] of an acute affective episode. Individuals with SZ were required to be clinically stable.[25] Individuals with T2DM were required to be free of severe diabetic neuropathy and kidney disease (serum creatinine <1.5 mg/dL). For recruitment as HCs, the absence of physical illness, pharmacological treatments, and family history of psychiatric disorders in first-degree relatives was required. The ability to understand the study procedures and willingness to provide written consent were required for participation. General exclusion criteria for all groups included current hospitalization; documented cognitive impairment not secondary to psychiatric disorders such as intellectual disability or major neurocognitive disorders, i.e., dementia; disability or inability that prevented understanding of the protocol; current substance use disorders (except for nicotine); pregnancy; intake of steroids, corticosteroids, antioxidants, antibiotics, and immunologic therapies; fever with temperature over 38 °C; and history of vaccination within 4 weeks of the evaluation. The same inclusion and exclusion criteria were used at T1 and T2.

Anthropometric variables of height (m) and body weight (kg) were measured using calibrated scales. The exposure of interest was BMI, calculated as kilogram per meter squared, as a measure of overall OB. BMI, measured at study baseline, was examined continuously and categorically. Considering the World Health Organization (WHO) criteria, the following references were used: NW ($\leq$24.9 kg/m^2), OW (25–29.9 kg/m^2), type 1 obesity (T1OB) (30–34.9 kg/m^2), and type 2 obesity (T2OB) (35–39.9 kg/m^2).[26,27] Accordingly, participants with a BMI $\geq$25 kg/m^2 were defined as having OW and different OB degrees (type 1 and type 2), and the remaining participants were classified as having NW. None of the participants were classified as having type 3 obesity (T3OB), since the criterion of BMI $\geq$40.0 kg/m^2 was not met. Thus, a valid measure was obtained to analyze the objective condition of the study (exposure or not to OW/OB). Considering the revised criteria of the Guidelines for the Management of Overweight and Obesity in Adults, WG and WL were defined as the difference per year in kilograms. Values were calculated as the difference between weights measured at T1 and T2 and were categorized into "weight gain >3 kg," "weight loss <3 kg," and "stable weight of 0.1–2.99 kg".[28]

Clinical and neuropsychological assessments

Assessments were conducted by the same experienced psychologists and psychiatrists of the research group. Sociodemographic data, including sex, age, years of education, dependent and occupational status, and motor laterality (defined as manual, ocular, and crural dominance), were collected.

Clinical evaluations were conducted using the following instruments: (i) Kaplan–Feinstein Scale (KFS),[29] (ii) Charlson Comorbidity Index (CCI),[30] (iii) 17-item Hamilton Rating Scale for Depression,[31] (iv) Young Mania Rating Scale,[32] (v) Positive and Negative Syndrome Scale,[33] and (vi) Clinical Global Impression Scale.[34] The total number of prescribed psychopharmacological medications and other medications was also registered.

Cognitive performance was evaluated using a comprehensive battery of neuropsychological tests and subtests previously used by our group (CB/07/09/0021). The battery included the premorbid Intelligence Quotient, which was calculated using the WAIS-III Vocabulary subtest, considered a classical measure of intelligence level before the onset of a mental disorder.[35] Seven cognitive domains were assessed: (i) *verbal learning and memory*: Complutense Verbal Learning Test (TAVEC) for total immediate recall, short-term free recall, and long-term free recall variables[36]; (ii) *cognitive flexibility*: Stroop Color and Word test (SCWT) color/word subtest[37] and Wisconsin Card Sorting Test categories for completed and perseverative errors[38]; (iii) *verbal fluency*: FAS and animal-naming test for phonemic and semantic fluency, respectively[39]; (iv) *working memory*: Trail-Making Test (TMT) Part B[39] and Wechsler Adult Intelligence Scale III edition (WAIS-III) digit span backwards[40]; (v) *short-term memory*: TAVEC immediate recall of the first learning trial, immediate recall of the interference list,[36] and WAIS-III digit span forward[40]; (vii) *visual memory*: Rey–Osterrieth Complex Figure Test (ROCFT), Figure 2 minutes after the copy (fRey2) and 20 minutes after the copy (fRey20)[41]; and (vii) *processing speed*: finger-tapping test left unimanual, right unimanual, left bimanual, and right bimanual and average of the four scores[39,42]; WAIS-III digit symbol coding subtest[40]; SCWT color and word subtests[37]; and TMT Part A.[39] A global cognitive score (GCS) was calculated by averaging the seven cognitive domain scores.

Functional performance was evaluated using the Functional Assessment Short Test,[43] Short Form-36 Health Survey questionnaire (SF-36),[44] and World Health Organization Quality of Life Brief Scale (WHO-QoL-Bref).[45] A global functional score (GFS) was calculated by averaging total scores on the three scales.

Determination of biomarkers in peripheral blood

Venous blood extraction was performed, and serum and plasma samples were stored in a freezer at −80 °C. Serum cytokine concentrations were determined using Luminex® X-MAP technology (Luminex Corp., Austin, TX, USA) based on flow cytometry. The following cytokines were analyzed: IL-6, IL-10, and TNF-α. Sample processing and data analysis were performed according to the manufacturer's instructions. CRP levels were determined using an immunonephelometric assay (Behring Nephelometer II, Dade Behring, Inc., Newark, DE, USA). Oxidative stress in leukocytes was evaluated using fluorimetry techniques with a fluoroscan (Synergy MX). In total, 100,000 cells were plated in each well of 96-well plates and were incubated for 30 min at 37 °C with the corresponding fluorochromes, as follows: dichlorofluorescein diacetate to measure reactive oxygen species (ROS) production (485 nm excitation, 535 nm emission), MitoSOX to measure mitochondrial ROS (mROS) (510 nm excitation, 580 nm emission), tetramethylrodamin methyl ester to assess mitochondrial membrane potential (552 nm excitation, 574 nm emission), nonylacridin orange mitochondrial mass (495 nm excitation, 519 nm emission), and 5-chloromethylfluorescein diacetate to measure intracellular glutathione (492 nm excitation, 517 nm emission). The monocyte cell line U-937 was used as an internal control to avoid potential fluctuations in fluorescence over time. Serum lipid peroxidation levels were measured using a commercial thiobarbituric acid reactive substances (TBARS) kit according to the manufacturer's instructions (Olympus, Hamburg, Germany). A Luminex 200 flow analyzer system (Austin, TX, USA) was employed to analyze adhesion molecules in serum. To measure immunological markers, citrated blood samples were incubated with dextran (3%) for 45 min to isolate human polymorphonuclear leukocytes (PMNs). The supernatant was layered over Ficoll–Hypaque (GE Healthcare, Barcelona, Spain) and centrifuged for 25 min at room temperature at 650× *g*. Lysis buffer was added to erythrocytes remaining in the pellet, which were incubated at room temperature for 5 min and then spun at 240× *g* for 5 min. PMNs were isolated. A 1.2-mL aliquot of PMNs was obtained from the peripheral blood of HCs and patients at a density of 10^6 cells/mL in complete RPMI (RPMI 1640 medium supplemented with 10% fetal bovine serum, 1% penicillin/streptomycin, 1% glutamine, and 1% sodium pyruvate). Prior to this, primary cultures of human umbilical cord endothelial cells

(HUVECs) were established. HUVECs were isolated. On the day of experimentation, PMNs were monitored through the endothelial monolayer at a speed of 0.3 mL/min over a 5-min period. Activity was recorded, and the number, velocity, and adhesion to the endothelial monolayer of rolling PMNs were determined. The number of rolling PMNs was measured as those rolling for 1 min. Velocity was assessed by determining the time in which 15 rolling PMNs covered 100 μm. Adhesion was analyzed by counting the number of PMNs adhering to the endothelium for at least 30 s in five fields. Platelet (PLT) levels were evaluated to be within the normal range in each participant at baseline and at the 1-year follow-up ($150–400 \times 10^9$/L).

Statistical analyses

Data were analyzed using Statistical Package for Social Sciences version 26.0 for Windows.[46] The sample size was calculated using Ene 2.0 software, which estimated that twenty-five individuals for each sample group were sufficient to ensure the representativeness.[47] Descriptive analyses were conducted using a one-way analysis of variance (ANOVA) for continuous variables and the chi-square test for categorical variables. Differences between groups in neurocognitive and functional performance and biomarkers at T1 and T2 and their evolution over time were assessed using a mixed one-way analysis of covariance (ANCOVA), with diagnosis (psychiatric disorders and T2DM) and sex as co-variables. Normality was assumed for all continuous variables because the sample was sufficiently representative of the target population, which was statistically verified. This guaranteed that the variable groups for T1 and T2 could be assessed using ANOVA/ANCOVA. A post hoc analysis with Bonferroni-corrected pairwise *t*-test and the Mann–Whitney *U* were performed to examine differences between groups. The effect size was calculated with partial eta-squared ($\eta^2 p$), and the following values were used as reference: small = 0.02, moderate = 0.15, and large = 0.35. The direct scores obtained for GCS and GFS were transformed into *Z*-scores. For calculation of *Z*-scores, the mean and standard deviation of individuals with NW at T1 were used as reference values. To test the predictive ability of biomarkers at T1 to discriminate individuals with significant WG/WL over time, binary logistic regression was performed using a predictive model that only included biomarkers that were significant for each group based on WG/WL. Similarly, to test the predictive capacity of biomarkers at baseline to explain the variance in neurocognitive and functional performance over time, linear regression analysis was performed using a predictive model that only included biomarkers and BMI that were significant for each group. Other variables relevant to neurocognitive and functional performance were not included because they were not the focus of this study, and the biomarkers were considered optimal predictors per se. For all analyses, $p < 0.05$ indicated statistical significance. The procedure to generate the predictive models was performed as follows. First, a predictive analysis was performed with single biomarkers, then predictive models were generated that included and combined variables that were statistically more powerful. Finally, the optimal predictive combination was obtained. No more than five variables were included in each model, thus guaranteeing correct performance of the analysis.

Results

Sample description

At T1, the sample consisted of 165 individuals, including 30 with SZ, 42 with BD, 35 with MDD, 30 with T2DM, and 28 HCs. The total sample was classified into four groups according to BMI categories, comprising 40 in the NW group (T2DM = 3, MDD = 9, BD = 9, SZ = 2, and HC = 17), 53 in the OW group (T2DM = 12, MDD = 12, BD = 15, SZ = 8, and HC = 6), 42 in the T1OB group (T2DM = 9, MDD = 9, BD = 10, SZ = 11, and HC = 3), and 30 in the T2OB group (T2DM = 6, MDD = 5, BD = 8, SZ = 9, and HC = 2). A summary of the baseline main outcomes for each diagnostic group (T2DM, MDD, BD, SZ, and HC) is presented in supplementary material 1.

In total, 40 participants were lost to follow-up at T2 (retention rate: 75.7%). The sample consisted of 27 individuals in the NW group (T2DM = 1, MDD = 6, BD = 6, SZ = 1, and HC = 13), 43 in the OW group (T2DM = 12, MDD = 5, BD = 12, SZ = 9, and HC = 5), 31 in the T1OB group (T2DM = 8, MDD = 8, BD = 7, SZ = 8, and HC = 0), and 24 in the T2OB group (T2DM = 4, MDD = 6, BD = 4, SZ = 9, and HC = 1).

Additionally, the sample was divided into three groups based on WG/WL over follow-up, comprising 34 individuals with WG (T2DM = 6, MDD = 8, BD = 7, SZ = 8, and HC = 5), 24 individuals with WL (T2DM = 2, MDD = 6, BD = 7, SZ = 9, and HC = 0) and 67 individuals with stable weight (SW) (T2DM = 17, MDD = 11, BD = 15, SZ = 10, and HC = 14).

There were no differences by primary diagnosis (T2DM, MDD, BD, and SZ) in any of the groups related to obesity ([NW, OW, T1OB, and T2OB] and [WG, WL, and SW]) and the interaction between primary diagnosis and obesity was non-significant.

A summary of the baseline sociodemographic and clinical characteristics of participants in each group (NW, OW, T1OB, and T2OB) is presented in supplementary material 2. Of the total sample, 48% were women. The mean age of the total sample was 46.2 (SD: 12.3) years. The percentage of women was significantly higher in the NW group other groups. Age, years of education, dependent status, occupational status, and laterality were similar among groups. The NW group exhibited significantly lower levels of multimorbidity as measured with the KFS and CCI as well as lower prescriptions of psychopharmacological and non-psychopharmacological medications.

Between-group comparisons of neurocognitive and functional performance

Neurocognitive and functional performance of the four groups at T1 and T2 is presented in Table 1. Neurocognitive performance was significantly higher in the NW group than in the T1OB and T2OB groups at T1 ($p < 0.01$; $\eta^2 p = 0.08$) and in the OW group at T2 ($p < 0.01$; $\eta^2 p = 0.09$). Individuals with NW exhibited significantly higher functional performance than individuals with T2OB at T1 ($p < 0.01$; $\eta^2 p = 0.06$) and individuals with T1OB at T2 ($p < 0.001$; $\eta^2 p = 0.12$). Functional performance was significantly higher in individuals with OW than in those with T2OB ($p < 0.001$; $\eta^2 p = 0.12$). At both assessments, small-to-moderate effect sizes were observed for neurocognitive and functional performance in between-group comparisons. No significant within-group differences were observed in neurocognitive and functional performance over time.

Between-group comparisons of immune-inflammatory biomarkers

Levels of CRP were significantly higher in the T2OB group than in the NW group at T1 ($p < 0.001$; $\eta^2 p = 0.09$) and in the OW group at T2 ($p < 0.0001$; $\eta^2 p = 0.16$) (Table 2). Similarly, PLT concentrations were significantly higher in the T1OB and T2OB groups than in the NW group at both assessments ($p < 0.01$; $\eta^2 p = 0.08–0.11$). In all cases, the effect sizes were small-to-moderate. No significant within-group differences were noted over time.

Table 1
Neurocognitive and functional performance at T1 and T2.

Variables[a]	NW		OW		T1OB		T2OB		Statistical analyses					
	T1 ($n=40$)	T2 ($n=27$)	T1 ($n=53$)	T2 ($n=43$)	T1 ($n=42$)	T2 ($n=31$)	T1 ($n=30$)	T2 ($n=24$)	T1 (p)[b]	Post hoc test[c]	η^2p[d]	T2 (p)[b]	Post hoc test[c]	η^2p[d]
GCS	0.0(1.0)	0.1(0.9)	−0.5(1.2)	−0.6(1.1)	−0.9(1.1)	−0.7(0.9)	−0.9(1.2)	−0.7(1.1)	5.0**	T2OB, T1OB<NW	.08	4.2**	T2OB,T1OB, OW<NW	.09
GSFS	0.0(1.0)	0.1(0.8)	−0.3(0.9)	−0.1(0.8)	−0.3(1.0)	−0.4(1.1)	−0.6(1.1)	−0.8(1.2)	3.4**	T2OB<NW	.06	5.7***	T2OB,T1OB <NW T2OB<OW	.12

Abbreviations: T1: time 1; T2: time 2; NW: normal-weight; OW: overweight; T1OB: type 1 obesity; T2OB: type 2 obesity; GCS: global cognitive score; GSFS: global functional score; NS: not significant (NS = $p > 0.05$; **$p \leq 0.01$; ***$p \leq 0.001$). Effect size (η^2p: small ≈ 0.02; moderate ≈ 0.15; large ≈ 0.35).
[a] *Z*-scores expressed as mean(standard deviation).
[b] ANCOVA.
[c] Bonferroni test.
[d] Partial eta-squared (η^2p).

Discriminatory ability of baseline biomarkers for detecting significant weight changes

The ability of inflammatory biomarkers at T1 to detect significant weight changes at T2 was analyzed, and the results are presented in Table 3. The combination of two interleukins (IL-6 and IL-10) and PLTs resulted in a model that best discriminated individuals with WG/WL at T2, with a correct classification rate of 69.4%. There was a strong positive relationship between IL-10 ($p < 0.05$) and PLT ($p < 0.0001$) and a negative correlation with IL-6 ($p < 0.05$).

Predictive ability of baseline biomarkers for neurocognitive and functional performance at T2

The results of the relative contributions of inflammatory markers at T1 to explain the variation in GCS and GFS scores at T2 are presented in Table 4. For individuals with WG, the combination of anti-inflammatory (IL-10) and oxidative stress biomarkers (ROS), mitochondrial reactive oxygen species (mROS), mitochondrial membrane potential ($\Delta\Psi m$), and adhesion molecules (P-selectin [PSEL]) significantly predicted GCS at T2 and explained 31.3% of the variance. Of note, rolling polymorphonuclear cells (RPMNs) alone significantly predicted GCS at T2 and explained 26.6% of the variance. Moreover, oxidative stress biomarkers (glutathione [GSH], mROS, superoxide dismutase [SOD]), adhesion molecules (myeloperoxidase [MPO]), and PLT significantly predicted GFS at T2 and explained 34.7% of the variance.

Similarly, in the WL group, the combination of anti-inflammatory (IL-10) biomarker, adhesion molecules (vascular cellular adhesion molecule [VCAM] and MPO), and PLT significantly predicted GCS at T2 and explained 49.4% of the variance. Moreover, BMI, oxidative stress biomarkers (mROS and SOD), and adhesion molecules (intercellular adhesion molecule [ICAM] and PLT) significantly predicted GFS at T2 and explained 56.3% of the variance.

In the SW group, the combination of pro-inflammatory (TNF-α) biomarkers, adhesion molecules (ICAM, leukocyte–endothelium adhesion polymorphonuclear cells [LEPMN], and RPMN), and WBC explained 27.1% of the GCS variance at T2, while the combination of BMI and VCAM explained 13.1% of the GFS variance at T2.

Discussion

To our knowledge, this is the first study to evaluate the predictive validity of inflammatory and oxidative stress biomarkers for neurocognitive and functional performance and their discriminatory ability to detect significant weight changes in individuals with psychiatric disorders and T2DM stratified by BMI using a longitudinal design and transdiagnostic perspective.

Individuals with OB exhibited an overall decrease in neurocognitive and functional performance alongside an increase in systemic inflammation. Increased anti-inflammatory and decreased pro-inflammatory factors were critical for detecting significant weight changes over time, considering different degrees of OB. Regarding WG/WL, inflammatory biomarkers, oxidative stress, and adhesion molecules were common factors for predicting the neurocognitive and functional performance of individuals with T2DM and psychiatric disorders, with higher reliability in the WL group. Specifically, elevated anti-inflammatory status significantly predicted improved neurocognitive function in individuals with WG/WL (Fig. 1).

Our findings build upon growing evidence suggesting that OB, T2DM, and psychiatric disorders share several pathogenic pathways, including adiposity-related systemic inflammation.[3,5] The intricate relationship between weight status and inflammatory processes may influence neurocognitive and functional performance. The results of our study converge with previous findings suggesting that the chronic low-grade inflammation characteristic of OB increases the risk of neurocognitive and functional impairments over time.[17,18] According to our findings, extant evidence indicates that inflammatory factors such as IL-6 and TNF-α modulate weight changes in individuals with psychiatric disorders and T2DM.[19,48] Furthermore, the association between WG and systemic inflammation may increase the risk of neurocognitive and functional decline in individuals with OW/OB.[21] Recent evidence suggests that better neurocognitive performance of individuals with OB is associated with WL and decreased inflammation.[12] Therefore, from a transdiagnostic and comorbidity perspective, our findings provide evidence of overlapping inflammatory pathways that influence weight changes and lead to neurocognitive and functional impairments in OB.

Healthy lifestyles and nutritional strategies are associated with a lower frequency of WG, improved neurocognitive performance, and better functional outcomes.[49] In our study, lower weight was associated with better neurocognitive and functional outcomes, and adiposity-related inflammatory processes potentially mediated this relationship. Mechanistically, the prevention and management of weight changes may contribute to normalizing adiposity-related inflammatory processes.[50,51] Accordingly, an obesogenic diet rich in saturated fat and refined sugars is associated with systemic inflammation, leading to dysregulation of brain circuits involved in appetitive behaviors, thereby promoting WG.[52] Thus, treatments to reduce systemic inflammation may improve neurocognitive and functional performance and reduce the risk of morbimortality in individuals with OB.[53,54] In this regard, weight-loss interventions, including regular exercise, healthy lifestyles, and bariatric surgery, have been reported to reduce low-grade

Table 2
Biomarkers at T1 and T2.

Variables[a]	NW		OW		T1OB		T2OB		Statistical analyses					
	T1 ($n=40$)	T2 ($n=27$)	T1 ($n=53$)	T2 ($n=43$)	T1 ($n=42$)	T2 ($n=31$)	T1 ($n=30$)	T2 ($n=24$)	T1 (p)[b]	Post hoc test[c]	η^2p[d]	T2 (p)[b]	Post hoc test[c]	η^2p[d]
Inflammatory markers														
IL-6	2.2(1.2)	2.7(2.1)	3.2(3.0)	3.4(2.7)	2.5(1.8)	3.0(1.6)	3.1(2.0)	3.5(1.6)	NS			NS		
IL-10	29.2(24.4)	14.9(15.9)	24.0(19.8)	11.7(14.8)	29.3(35.5)	13.1(12.8)	41.3(45.5)	10.3(12.4)	NS			NS		
TNF-α	9.4(3.1)	10.3(2.7)	9.5(2.7)	11.2(5.7)	9.1(3.1)	11.3(3.6)	9.8(3.2)	11.6(3.0)	NS			NS		
CRP	1.9(2.3)	1.5(1.3)	4.0(4.9)	2.5(2.8)	3.5(3.0)	4.6(6.2)	6.3(6.5)	6.9(6.2)	5.8***	NW<T2OB	.09	7.6****	NW,OW <T2OB	.16
Oxidative stress markers														
GSH	189.5(75.7)	202.8(84.8)	198.1(97.6)	205.3(72.1)	174.1(99.5)	174.4(93.9)	177.6(93.8)	165.6(77.9)	NS			NS		
ROS	139.1(60.5)	320.0(165.0)	132.8(65.4)	300.6(165.4)	129.4(63.4)	329.9(186.6)	122.3(45.3)	267.3(151.3)	NS			NS		
mROS	156.5(60.9)	209.4(96.2)	173.0(68.2)	201.0(75.2)	177.0(60.4)	217.0(109.0)	156.6(42.6)	207.5(131.4)	NS			NS		
SOD	51.5(26.3)	49.4(33.7)	44.0(22.9)	41.4(26.4)	43.1(26.2)	40.3(34.7)	40.5(22.3)	33.9(11.9)	NS			NS		
ΔΨm	98.2(23.0)	99.4(21.2)	99.5(19.3)	99.3(18.1)	102.8(22.1)	107.1(46.5)	100.6(14.5)	97.5(14.8)	NS			NS		
Adhesion molecules														
ICAM	97.5(39.8)	99.9(38.7)	114.4(57.1)	112.6(49.0)	122.0(47.1)	121.8(52.3)	117.3(41.5)	128.3(42.5)	NS			NS		
VCAM	564.3(165.3)	779.2(208.6)	620.1(178.5)	798.2(257.6)	612.3(153.0)	793.3(212.1)	570.1(124.2)	784.9(204.0)	NS			NS		
LEPMN	14.5(20.2)	7.3(7.4)	12.4(13.3)	10.6(9.1)	11.2(9.6)	8.6(8.0)	14.7(19.1)	11.3(9.1)	NS			NS		
RPMN	158.0(102.8)	151.6(60.2)	185.5(102.7)	161.5(78.3)	164.6(91.6)	199.9(116.6)	210.4(114.9)	180.4(78.9)	NS			NS		
RVPMN	564.0(215.7)	509.8(189.6)	535.7(212.0)	531.2(213.9)	573.4(199.3)	527.4(198.6)	493.6(177.0)	451.1(205.7)	NS			NS		
PSEL	121.8(38.6)	116.2(45.1)	126.4(35.3)	116.9(43.7)	126.3(34.5)	109.6(37.1)	131.2(38.5)	111.7(31.5)	NS			NS		
MPO	578.3(268.9)	658.5(341.4)	691.7(382.1)	613.8(447.3)	643.0(419.1)	638.3(478.6)	524.4(233.5)	623.5(329.7)	NS			NS		
Immunological markers														
WBC	7.0(2.0)	7.0(2.1)	8.1(2.4)	7.7(2.3)	7.3(1.6)	7.8(2.0)	7.8(1.9)	7.9(1.9)	NS			NS		
PLT	222.5(53.8)	219.2(50.7)	231.5(62.9)	241.0(54.8)	257.4(60.7)	264.5(69.4)	263.1(66.1)	265.6(66.3)	4.5**	NW<T1OB, T2OB	.08	4.8**	NW<T1OB, T2OB	.11

Abbreviations: T1: time 1; T2: time 2; NW: normal-weight; OW: overweight; T1OB: type 1 obesity; T2OB: type 2 obesity; IL-6: interleukin-6; IL-10: interleukin-10; TNF-α: tumor necrosis factor-alpha; CRP: C-reactive protein; GSH: glutathione; ROS: reactive oxygen species; mROS: mitochondrial reactive oxygen species; SOD: superoxide dismutase; ΔΨm: mitochondrial membrane potential; CAM: cellular adhesion molecule; PMN: polymorphonuclear cells; I: inter; V: vascular; LE: leukocyte–endothelium adhesion; R: rolling; RV: rolling velocity; PSEL: P-selectin; MPO: myeloperoxidase; WBC: white blood cell; PLT: blood platelets; NS: not significant (NS = $p > 0.05$; **$p \leq 0.01$; ***$p \leq 0.001$; ****$p \leq 0.0001$). Effect size (η^2p: small ≈ 0.02; moderate ≈ 0.15; large ≈ 0.35).

[a] Expressed as mean(standard deviation).

[b] ANCOVA.

[c] Bonferroni test.

[d] Partial eta-squared (η^2p).

Table 3
Discriminatory capacity of baseline inflammatory markers to detecting significant weight changes.

Dependent variables at T2	Predictors at T1 associated	β	Wald	Percent of variance explained	Global percentage correctly predicted
WL/WG	IL-6	−0.25	3.7*	0.16–0.21	69.4
	IL-10	0.01	5.1*		
	PLT	0.01	12.1****		

Abbreviations: T1: time 1; T2: time 2; WL: weight loss; WG: weight gain; IL-6: interleukin-6; IL-10: interleukin-10; PLT: blood platelets; NS: not significant (NS = $p > 0.05$; *$p \leq 0.05$; ****$p \leq 0.0001$).

Table 4
Predictive biomarkers at T1 of neurocognitive and functional performance at T2.

Dependent variables at T2	Predictors at T1 associated	β	95% CI	t	Percent of variance explained (adjusted R^2)
Group: WG					
GCS	IL-10	0.33	0.00 to 0.02	1.9*	31.3
	ROS	0.42	0.00 to 0.01	2.4*	
	mROS	0.58	0.00 to 0.02	3.0**	
	ΔΨm	0.39	0.00 to 0.05	2.0*	
	PSEL	−0.35	−0.02 to 0.00	2.0*	
GSFS	RPMN	−0.51	−0.01 to 0.00	3.4**	26.6
	GSH	−0.46	−0.01 to 0.00	2.5**	
	mROS	0.48	0.00 to 0.01	2.6**	34.7
	SOD	−0.48	−0.06 to 0.00	2.4*	
	MPO	0.43	0.00 to 0.003	2.3*	
	PLT	−0.56	−0.01 to 0.00	3.0**	
Group: WL					
GCS	IL-10	0.45	0.00 to 0.02	2.3*	49.4
	VCAM	−0.64	0.00 to −0.002	3.6**	
	MPO	0.31	0.00 to 0.002	1.9*	
	PLT	−0.48	−0.01 to 0.00	2.5**	
GSFS	BMI	−0.45	−0.13 to −0.01	2.4*	56.3
	mROS	−0.47	−0.01 to 0.00	2.7**	
	SOD	−0.52	−0.05 to −0.01	3.2**	
	ICAM	0.44	0.00 to 0.01	2.4*	
	PLT	0.5	0.00 to 0.01	1.9*	
Group: SW					
GCS	TNF-α	−0.34	−0.18 to −0.03	2.8**	27.1
	ICAM	−0.32	−0.01 to 0.00	2.8**	
	LEPMN	0.28	0.00 to 0.03	2.4**	
	RPMN	−0.40	0.00 to −0.002	3.2**	
	WBC	0.26	0.00 to 0.21	2.1*	
GSFS	BMI	−0.28	−0.09 to 0.00	2.38*	13.1
	VCAM	0.24	0.00 to 0.003	2.05*	

Abbreviations: T1: time 1; T2: time 2; WG: weight gain; WL: weight loss; SW: stable weight; GCS: global cognitive score; GSFS: global functional score; IL-10: interleukin-10; TNF-α: tumor necrosis factor-alpha; GSH: glutathione; ROS: reactive oxygen species; mROS: mitochondrial reactive oxygen species; SOD: superoxide dismutase; ΔΨm: mitochondrial membrane potential; CAM: cellular adhesion molecule; PMN: polymorphonuclear cells; I: inter; V: vascular; LE: leukocyte–endothelium; R: rolling; PSEL: P-selectin; MPO: myeloperoxidase; PLT: blood platelets; NS: not significant (*$p \leq 0.05$; **$p \leq 0.01$).

inflammation in OB and improve neurocognitive performance simultaneously.[55]

This study has some limitations. Although BMI is the most common measure of OB, it does not fully represent body fat distribution. More reliable anthropometric measures, such as waist circumference or waist-to-hip ratio, may have been preferable. The present study did not evaluate other parameters involved in OB pathophysiology, such as metabolic disruptions, changes in the microbiota gut–brain axis, and vascular dysfunction biomarkers. Moreover, after one year of follow-up, high sample mortality was observed. This may have led to a potential bias in retaining individuals who completed the assessments and were thus in a presumably better clinical condition. Despite these limitations, the strengths of this study include its novel transdiagnostic approach and comprehensive assessment of cognitive and functional outcomes in individuals stratified by BMI across populations with T2DM and psychiatric disorders. Moreover, the longitudinal design permits the establishment of potential causal relationships between adiposity-related inflammation and neurocognitive and functional outcomes. Finally, the study's multicenter nature increases the results' external validity.

In conclusion, OB is associated with neurocognitive and functional impairments. The mechanisms underlying this association may involve the exacerbation of inflammatory pathways. Aberrant cellular adhesion molecule-related mechanisms in OB may trigger a pro-inflammatory response, impairing neurocognitive performance. Oxidative damage also plays a crucial role in maintaining inflammatory processes.[19,56] A deeper understanding of shared pathways underscoring the link between OB, T2DM, and psychiatric disorders may contribute to the development of transdiagnostic anti-inflammatory therapeutic strategies for these disorders. For instance, a randomized cross-over trial reported a significant positive relationship between elevated cerebral blood flow and improved neurocognition following non-pharmacological, short-term supplementation with a ketone monoester.[57] These data provide new clinical approaches for OB phenomenology in the context of cardio-metabolic and psychiatric disorders. The combined use of several biomarkers may facilitate the identification of individuals with an increased risk of developing OB and improve the management of specific patient subgroups with cardio-metabolic and psychiatric comorbidities. We propose that managing the biological bases of OB may contribute to maintaining healthy

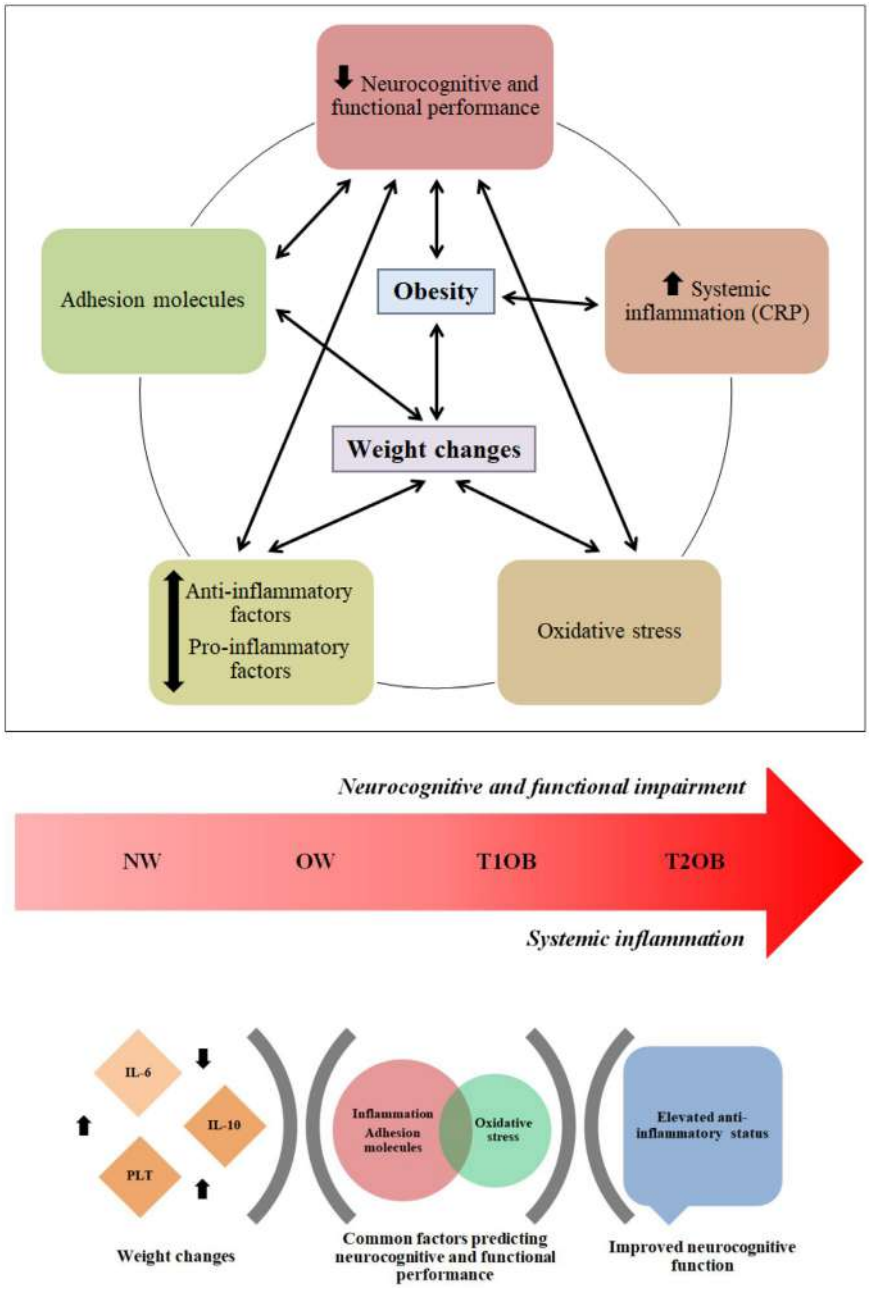

Fig. 1. Summary of main findings.

eating behaviors while identifying clinical phenotypes associated with different neurocognitive and functional trajectories.[58] Therefore, combinations of inflammatory, oxidative stress and adhesion molecule biomarkers hold promise for improving innovative and personalized treatment strategies targeting cardio-metabolic and inflammatory processes in individuals with T2DM and psychiatric disorders with comorbid OB.

Authors' contributions

JVS-O, VB-M, PC-G, VMV and RT-S: conception and design of the study; acquisition and analysis of data; drafting the manuscript and figures. GS-V, CS-M, IE-L, AH-M, JV-L, and BC-F: drafting the manuscript and figures. JV-F and RM-B: Formal analysis. All authors have read and agreed to the published version of the manuscript.

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Conflicts of interest

None declared.

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Appendix A. Supplementary data

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ANEXO III

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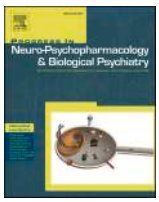

Inflammation and lipid metabolism as potential biomarkers of memory impairment across type 2 diabetes mellitus and severe mental disorders

Joan Vicent Sánchez-Ortí [a,c,d,1], Patricia Correa-Ghisays [a,b,c,d,e,1,*], Vicent Balanzá-Martínez [a,b,c,e,f,*], Gabriel Selva-Vera [a,b,c,e], Joan Vila-Francés [g], Rafael Magdalena-Benedito [g], Constanza San-Martin [b,c,h], Víctor M. Victor [i,j,k], Irene Escribano-Lopez [i], Antonio Hernandez-Mijares [i], Juliana Vivas-Lalinde [l], Benedicto Crespo-Facorro [b,m], Rafael Tabarés-Seisdedos [a,b,c,e]

[a] INCLIVA - Health Research Institute, Valencia, Spain
[b] Center for Biomedical Research in Mental Health Network (CIBERSAM), Health Institute, Carlos III, Madrid, Spain
[c] TMAP - Evaluation Unit in Personal Autonomy, Dependency and Serious Mental Disorders, University of Valencia, Valencia, Spain
[d] Faculty of Psychology, University of Valencia, Valencia, Spain
[e] Teaching Unit of Psychiatry and Psychological Medicine, Department of Medicine, University of Valencia, Valencia, Spain
[f] Mental Health Unit of Catarroja, Valencia, Spain
[g] IDAL - Intelligent Data Analysis Laboratory, University of Valencia, Valencia, Spain
[h] Department of Physiotherapy, University of Valencia, Valencia, Spain
[i] Service of Endocrinology and Nutrition, University Hospital Dr. Peset, Spain
[j] Foundation for the Promotion of Health and Biomedical Research in the Valencian Region (FISABIO), Valencia, Spain
[k] Department of Physiology, University of Valencia, Valencia, Spain
[l] Department of Psychiatry, Mental Health Service, Manises, Valencia, Spain
[m] Department of Psychiatry, Faculty of Medicine, University of Sevilla, HU Virgen del Rocío IBIS, Spain

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ABSTRACT

Introduction: Neurocognitive impairment is a transdiagnostic feature across several psychiatric and cardiometabolic conditions. The relationship between inflammatory and lipid metabolism biomarkers and memory performance is not fully understood. This study aimed to identify peripheral biomarkers suitable to signal memory decline from a transdiagnostic and longitudinal perspective.

Methods: Peripheral blood biomarkers of inflammation, oxidative stress and lipid metabolism were assessed twice over a 1-year period in 165 individuals, including 30 with schizophrenia (SZ), 42 with bipolar disorder (BD), 35 with major depressive disorder (MDD), 30 with type 2 diabetes mellitus (T2DM), and 28 healthy controls (HCs). Participants were stratified by memory performance quartiles, taking as a reference their global memory score (GMS) at baseline, into categories of high memory (H; $n = 40$), medium to high memory (MH; $n = 43$), medium to low memory (ML; $n = 38$) and low memory (L; $n = 44$). Exploratory and confirmatory factorial analysis, mixed one-way analysis of covariance and discriminatory analyses were performed.

Results: L group was significantly associated with higher levels of tumor necrosis factor-alpha (TNF-α) and lower levels of apolipoprotein A1 (Apo-A1) compared to those from the MH and H groups ($p < 0.05$; $\eta^2p = 0.06$–0.09), with small to moderate effect sizes. Moreover, the combination of interleukin-6 (IL-6), TNF-α, c-reactive protein (CRP), Apo-A1 and Apo-B compounded the transdiagnostic model that best discriminated between groups with different degrees of memory impairment ($\chi^2 = 11.9$–49.3, $p < 0.05$–0.0001).

Conclusions: Inflammation and lipid metabolism seem to be associated with memory across T2DM and severe mental illnesses (SMI). A panel of biomarkers may be a useful approach to identify individuals at greater risk of neurocognitive impairment. These findings may have a potential translational utility for early intervention and advance precision medicine in these disorders.

* Corresponding authors at: Teaching Unit of Psychiatry and Psychological Medicine, Department of Medicine, University of Valencia, Blasco Ibáñez 15, 46010 Valencia, Spain Phone: +34 963983349
E-mail addresses: patricia.correa@uv.es (P. Correa-Ghisays), vicente.balanza@uv.es (V. Balanzá-Martínez).
[1] Contributed equally to this work

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1. Introduction

Memory is a core construct for human neurocognition. The ability to encode, manipulate, consolidate and retrieve information is a critical determinant of daily performance and quality of life across different clinical populations (Millan et al., 2012). Important differences in memory performance exist that are strongly related to health and disease states variability between individuals (McWhirter et al., 2020). Likewise, memory impairments have been observed in a significant proportion of individuals with severe mental illness (SMI) and certain cardio-metabolic disorders, such as type 2 diabetes mellitus (T2DM) (Abramovitch et al., 2021; Arvanitakis et al., 2020; Martinez-Aran and Vieta, 2015). Memory deficits are prevalent across these disorders, and contribute significantly to patients' social functioning, quality of life and occupational outcomes (Cambridge et al., 2018; Green et al., 2019; Sánchez-Moreno et al., 2018). In this regard, growing evidence supports the idea that neurobiological factors subserving disrupted memory processes transcend diagnostic categories (Bourgognon and Cavanagh, 2020).

At the molecular level, it is now generally accepted that complex memory processes involve dynamic interactions with immune-inflammation, oxidative stress and metabolic pathways. There are consistent findings supporting that pro- and anti-inflammatory cytokines, such as interleukin (IL)-1, IL-4, IL-6, IL-10 and tumor necrosis factor-alpha (TNF-α) play a key role in information processing in the human brain (Levin et al., 2021). Importantly, immune-inflammatory biomarkers are found at higher concentrations in individuals with memory deficits (Süβ et al., 2021). Thus, it has been suggested that an increased pro-inflammatory response makes difficult for individuals to use effective cognitive strategies for encoding, manipulating and retrieving information (Tetlow et al., 2019). Likewise, oxidative stress and metabolic changes may have a direct influence on memory impairment and cognitive rehabilitation (Franzoni et al., 2021; Hua et al., 2021a). Recent findings support that abnormal blood lipid profiles are risk factors for memory impairment among healthy individuals (Sanjana et al., 2021). Overall, increasing evidence suggests that, regardless of clinical diagnoses, similar immune-inflammation, oxidative stress, and metabolic pathways could subserve disrupted memory processes, suggesting common pathways for memory impairment.

To date, significant overlap in neurobiological factors, neural substrates, and genetic underpinnings promote an integrative rather than a reductionist approach to neurocognitive performance. The National Institute of Mental Health (NIMH) Research Domain Criteria (RDoC) project provides an integrative framework for translational research that is focused on functional dimensions of behavior and cognitive/affective processes, and transcends traditional DSM/ICD categories of psychiatric disorders (Insel, 2014). These dimensions are studied along a span of functioning from normal to abnormal, with the understanding that each one is situated in, and affected by, environmental and neurodevelopmental contexts. In this regard, RDoC suggest that memory processes should be one of core domains in the human brain functioning and that memory deficits are a core feature across somatic and psychiatric disorders. Accordingly, the identification of neurobiological changes underlying these deficits seems relevant (Cuthbert, 2020). To our knowledge, no previous studies have identified valid biomarkers for memory dysfunction in a sample of individuals with T2DM and SMI. This research gap hampers better understanding whether immune-inflammatory, oxidative stress and metabolic biomarkers can be used to identify individuals with memory impairment. This study aimed to identify peripheral biomarkers valid for memory dysfunction from a combined, transdiagnostic sample of individuals with T2DM and SMI.

2. Materials and methods

2.1. Study design and ethical considerations

This study is part of a project aimed at identifying and validating peripheral biomarkers for neurocognitive deficits in major depressive disorder (MDD), bipolar disorder (BD), schizophrenia (SZ) and T2DM. This prospective and comparative cohort project was conducted between April 2015 and January 2018, and it investigated the association and evolution of certain peripheral blood biomarkers and neurocognitive impairments in a unique longitudinal cohort of individuals with somatic and psychiatric disorders. Demographic, clinical, neurocognitive and functional data, and biomarkers of peripheral blood were collected at baseline (T1) and after one year (T2). Individuals with SMI were recruited from mental health units (MHUs) in several towns in the province of Valencia, Spain (Foios, Catarroja, Paterna, and Sagunto); the psychiatry outpatient clinic and endocrinology department of the University Hospital Dr. Peset; and the Miguel Servet MHU in Valencia City. Healthy controls (HC) were extracted from the general population residing/living in the same areas as the individuals with SMI. Participants were demographically matched. All participants provided informed consent after the study procedures were explained. The ethic committees or institutional review boards at each participating center approved the study protocol, and the study was conducted in accordance with the ethical principles of the Declaration of Helsinki. For this article, only those variables related to the present study aims were included in the analyses.

2.2. Participants

SZ, BD, and MDD, were diagnosed according to Diagnostic and Statistical Manual of Mental Disorders - DSM-5 (APA, 2014) criteria. T2DM was diagnosed based on the Standards of Care criteria of the American Diabetes Association (ADA, 2015). Participants with MDD and BD should meet the remission criteria (Tohen et al., 2009) of an acute affective episode, defined as Young Mania Rating Scale (YMRS) score ≤ 6 and Hamilton Rating Scale for Depression (HRSD) score ≤ 8, and individuals with SZ had to be clinically stable, defined as Positive and Negative Syndrome Scale (PANSS) score ≤ 36 (Andreasen et al., 2005). Individuals with T2DM had to be free of severe diabetic neuropathy and kidney disease (serum creatinine <1.5 mg/dl). For recruitment as HC, the absence of physical illness, pharmacological treatments, and family history of SMI in first-degree relatives were required. Ability to understand study procedures and willingness to give written consent was required for participation. General exclusion criteria for all groups included: current hospitalization, documented cognitive impairment not secondary to psychiatric disorder (intellectual disability or major neurocognitive disorder, i.e. dementia), disability or inability that prevented understanding of the protocol, current substance abuse disorder (except for nicotine), pregnancy, intake of steroids, corticosteroids, antioxidants, antibiotics, and immunologic therapies, fever over 38 °C, and history of vaccination within 4 weeks of the evaluation. The same inclusion and exclusion criteria were used at T1 and T2.

2.3. Clinical and neuropsychological assessments

The assessments were conducted by the same experienced psychologists and psychiatrists of the research group. Sociodemographic and clinical data, including sex, age, years of education, body mass index (calculated as kg/m^2), number of prescribed psychopharmacological medications, laterality (defined as manual, ocular and crural dominance) and comorbidity measured from Kaplan-Feinstein Scale (KFS) (see **supplementary material**) (Rosas-Carrasco et al., 2011), were collected.

Neurocognitive performance was evaluated using a comprehensive battery of neuropsychological tests and subtests previously used by our

group (Aliño-Dies et al., 2020; Correa-Ghisays et al., 2017, 2019, 2022; Garés-Caballer et al., 2022; Luperdi et al., 2021; Salazar-Fraile et al., 2009; San Martín-Valenzuela et al., 2020; Sánchez-Ortí et al., 2022; Selva-Vera et al., 2010; Tabarés-Seisdedos et al., 2008). Memory performance was assessed with the following neuropsychological tests: (i) Verbal memory and learning were assessed by California Verbal Learning Test (CVLT) (Delis et al., 1987) in its Spanish version Complutense Verbal Learning Test (TAVEC) immediate recall of the first learning trial, total immediate recall, immediate recall of the interference list, short-term free recall, long-term free recall variables (Benedet and Alejandre, 2014); (ii) Visual memory was assessed by Rey-Osterrieth Complex Figure Test (ROCFT) two minutes after the copy (fRey2) and 20 min after the copy (fRey20) (Rey, 1999); (iii) Working memory was assessed by Wechsler Adult Intelligence Scale III edition (WAIS-III) digit span forward and backwards (Weschler, 1999); (iv) Working and immediate memory were assessed by Trail Making Test (TMT) Part B (Reitan and Wolfson, 1985). A global memory score (GMS) was calculated by averaging performance scores on each test, resulting from prior factorial analysis.

There are no consensus-based clinical thresholds for the categorization of memory performance so that the participants were stratified by memory performance quartiles, taking as a reference their GMS at baseline. The distribution by quartile was: ≤ -22.90 (quartile-4 group: low GMS magnitude), -22.91 to 28.25 (quartile-3 group: low-medium GMS magnitude), 28.26 to 68.10 (quartile-2 group: high-medium GMS magnitude), $\geq$ 68.10 (quartile-1 group: high GMS magnitude). The groups created at T1 were maintained at T2, with prior verification of stability in GMS.

2.4. Determination of biomarkers in peripheral blood

Venous blood extraction was performed, and the serum and plasma samples were kept in a freezer at −80 °C. (i) Cytokines: serum cytokine concentration was determined using Luminex® X-MAP technology (Luminex Corp., Austin, TX, USA) based on flow cytometry. The following cytokines were analyzed: IL-6, interleukin 10 (IL-10) and TNF-α. Sample processing and data analysis were performed according to the manufacturer's instructions. (ii) Oxidative stress markers and mitochondrial metabolism: oxidative stress in leukocytes was evaluated using fluorimetry techniques in a fluoroscan (Synergy MX). Plated in 96-well plates, 100,000 cells in each, were incubated 30 min at 37 °C with the corresponding fluorochrome: dichlorofluorescein diacetate indicated reactive oxygen species (ROS) production (485 nm excitation, 535 nm emission), MitoSOX measured mitochondrial ROS (mROS) (510 nm excitation, 580 nm emission), tetramethylrodamin methyl ester (552 nm excitation, 574 nm emission) assessed membrane potential, nonylacridin orange mitochondrial mass (495 nm excitation, 519 nm emission), and 5-chloromethylfluorescein diacetate measured intracellular glutathione (492 nm excitation, 517 nm emission). We used the monocyte cell line U-937 as an internal control to avoid the possible fluctuation of fluorescence associated with time. Serum lipid peroxidation levels were measured using a commercial thiobarbituric acid reactive substances kit, and performed according to the manufacturer's instructions. CRP levels were determined by an immunonephelometric assay (Behring Nephelometer II, Dade Behring, Inc., Newark, DE, USA). (iii) Lipid markers. Venous blood was extracted into Vacutainer® tubes and centrifuged at 1500*g* for 10 min at 4 °C, after which biochemical parameters were evaluated. A Beckman LX-20 autoanalyzer (Beckman Coulter, La Brea, CA, US) was employed to assessed lipid metabolism, apolipoprotein A1 (Apo-A1) and apolipoprotein B (Apo-B), content was estimated with Friedewald's formula (Behring Nephelometer II, Dade Behring, Inc., Newark, DE, USA).

2.5. Statistical analyses

Data were analyzed using Statistical Package for Social Sciences (SPSS) version 26.0 for Windows (IBM Corp, 2019).

2.5.1. Preliminary analysis

Exploratory factorial analysis (EFA) was carried out with the variables that make up the memory variables at T1 and confirmatory factorial analysis (CFA) with the same variables at T2. Both analyses were performed with the main axis extraction method. Cronbach's Alpha (α) statistic was calculated in both occasions to assess the internal consistency of the variables included in the analysis (Cortina, 1993; Cronbach, 1951). For all analyses, $\alpha > 0.70$ was considered appropriate. To confirm if this analysis is correct, the Kaiser-Meyer-Olkin (KMO) tests and the Bartlett sphericity test were performed. Following previous literature, the agglomerated neuropsychological tests quantifies different types of memory composing a valid indicator of memory function (Donders, 2020; Sánchez-Cubillo et al., 2009).

2.5.2. Primary analysis

Descriptive analyses were conducted using a one-way analysis of variance (ANOVA) for continuous variables and the chi-squared test for categorical variables. The differences between groups for biomarkers at T1 and T2 and their evolution over time were assessed using a mixed one-way analysis of covariance (ANCOVA), with diagnosis (psychiatric disorders and T2DM), sex, age, years of education, BMI and psychopharmacological medications as co-variables. Adjusting for co-variables was used because the distribution of those factors significantly differed across the groups and was a confounding variable. The stability of the GMS scores over time was assessed using intra-ANCOVA. Normality was assumed for all continuous variables because the sample was statistically verified using Kolmogorov-Smirnov test. In turn, this guaranteed that the variables for T1 and T2 could be assessed using an ANOVA/ANCOVA. A post hoc analysis with a Bonferroni corrected pairwise *t*-test and Mann-Whitney U were performed to examine the differences between groups.

2.5.3. Model analysis

To test the ability of peripheral biomarkers to discriminate between groups with different degrees of memory performance, a discriminant analysis was performed, comparing by pairs of groups, in which used all biomarkers. This procedure was performed at both times separately in order to ensure the consistency of the biomarkers tested. Subsequently, a single model using only significant biomarkers was tested in each group stratified by GMS in order to inform how well the model discriminates between different degrees of memory performance. For all analyses, $p < 0.05$ was considered statistically significant.

3. Results

3.1. Sample description

At T1, the sample consisted of 165 participants, including 30 with SZ, 42 with BD, 35 with MDD, 30 with T2DM, and 28 HCs. Participants were stratified by memory performance quartiles, taking as a reference their GMS at baseline, into categories: 40 in the high memory (H) group (SZ = 1, BD = 8, MDD = 11, T2DM = 4 and HC = 16), 43 in the medium-high memory (MH) group (SZ = 7, BD = 5, MDD = 10, T2DM = 10 and HC = 11), 38 in the medium-low memory (ML) group (SZ = 8, BD = 12, MDD = 6, T2DM = 11 and HC = 1), and 44 in the low memory (L) group (SZ = 14, BD = 17, MDD = 8, T2DM = 5 and HC = 0).

Forty participants were lost to follow-up at T2 (retention rate: 75.7%). At T2, the sample consisted of 125 individuals: 34 in the H group (SZ = 1, BD = 8, MDD = 9, T2DM = 4 and HC = 12), 30 in the MH group (SZ = 7, BD = 4, MDD = 5, T2DM = 7 and HC = 7), 27 in the ML group (SZ = 6, BD = 8, MDD = 6, T2DM = 8 and HC = 0), and 34 in the L group (SZ = 13, BD = 9, MDD = 7, T2DM = 5 and HC = 0).

A summary of the sociodemographic and clinical characteristics of the participants is presented in Table 1. Females represented half of the

total sample (48%). The mean age of the whole sample was 46.2 (SD: 12.3) years. The H group was characterized by a significantly higher years of education and significantly lower BMI than the other groups. The comorbidity and laterality were similar in all groups. Moreover, the L group was prescribed a significantly higher number of psychiatric medications than the other groups. These outcomes were maintained over time. GMS scores remained stable at one-year follow-up ($F = 0.54$; $p > 0.05$).

3.2. Memory as a neurocognitive domain

The results of the EFA and CFA analyses are shown on Table 2. Cronbach's α value indicated an appropriate internal consistency at both times (α = 0.84–0.85, respectively). This high stability over time supports of quality assurance regarding the memory construct. Once the reliability of the neurocognitive domain was verified, the dimensionality of tests set was analyzed. For that purpose, we carried out an EFA. Since KMO showed a value close to 1, the sample was considered to be sufficiently representative of the population. Moreover, Bartlett's sphericity test showed a significance level < 0.0001, which evidences a significant relationship between the variables included. Kaiser's rule provided a factor structure with one factor that explained 54.11% of the total variance. Thus, the existence of a single factor was considered, which was termed GMS. In order to confirm that the adjustment of the set of tests into a single factor was adequate, a CFA was performed. The neuropsychological battery was administered again at T2, to 125 participants; repeating the previous process and guiding the analysis to the confirmation of a single factor.

3.3. Between-group comparisons of peripheral biomarkers

Peripheral serum markers at T1 and T2 for the four groups are shown in Table 3**.** Overall, individuals with low memory obtained significantly higher scores for TNF-α biomarker. Significant differences existed between L group compared to MH and H groups for TNF-α at T1 ($p < 0.01$; $\eta^2p = 0.07$) and at T2 only with H group ($p < 0.05$; $\eta^2p = 0.06$). However, members of the L group showed significantly lower concentrations of apolipoprotein A1 (Apo-A1) compared to MH and H groups at both assessments ($p < 0.01$; $\eta^2p = 0.07–0.09$). In all cases, the effect size was small to moderate. Differences between the time points within each group were not significant.

3.4. Discriminatory ability of peripheral biomarkers for memory performance

The results regarding the discriminatory ability of serum peripheral markers showed that the combination of IL-6, TNF-α, CRP, Apo-A1 and Apo-B was the transdiagnostic model that best discriminated between groups with different memory performance degree ($\chi^2 = 11.9–49.3$, $p < 0.05–0.0001$) (Fig. 1). According to the model, elevated pro-inflammatory activity and impaired lipid metabolism allows for the differentiation of individuals with impaired memory performance.

4. Discussion

To our knowledge this is the first study aimed to identify peripheral biomarkers valid for memory decline from a transdiagnostic sample of HC and individuals with T2DM and psychiatric disorders.

The present results show, on the one hand, that memory performance was significantly associated at both assessments with changes in two of the biomarkers analyzed in this study. Specifically, compared to individuals with better memory performance, those with highest memory impairment had higher levels of TNF-α and lower concentrations of Apo-A1, with small to moderate effect sizes. On the other hand, the discriminant analysis showed that a model combining all three pro-inflammatory biomarkers (IL-6, TNF-α, and CRP) and the two biomarkers of impaired lipid metabolism (Apo-A1 and Apo-B) was able to distinguish individuals with different degrees of memory performance. However, biomarkers of oxidative stress and the anti-inflammatory cytokine IL-10 were not associated with memory function in this combined transdiagnostic sample.

Regarding the nature of the two biomarkers associated with the highest memory impairment, TNF- α is one of the most studied biomarkers in relation to cognitive functions. More specifically, its relationship with memory impairment has been reported in the disorders included in our study. For instance, memory decline has been found to

Table 1
Peripheral serum markers at T1 and T2.

	H		MH		ML		L		*Statistical analyses*			
Variables[a]	T1 ($n = 40$)	T2 ($n = 34$)	T1 ($n = 43$)	T2 ($n = 30$)	T1 ($n = 38$)	T2 ($n = 27$)	T1 ($n = 44$)	T2 ($n = 34$)	T1 (p)[e]	Post hoc test[g]	T2 (p)[e]	Post hoc test[g]
Sex[b, f, h]	27(67%)	25(73%)	19(44%)	13(43%)	12(32%)	9(35%)	21(48%)	16(47%)	10.4**	ML,MH < H	11.3**	ML,MH < H
Age	39.0 (12.2)	40.6 (12.3)	44.7 (14.5)	46.0 (13.6)	51.2 (10.5)	52.3 (11.1)	52.4 (10.2)	51.9 (10.8)	10.9****	H < ML,L MH < L	6.6****	H < ML,L
Years of education	16.1 (4.1)	16.8 (3.8)	13.6 (4.3)	14.0 (3.8)	11.4 (3.7)	12.5 (5.1)	8.7(2.9)	9.1(2.9)	28.5****	L,ML,MH < H L < ML, MH	22.1****	L,ML,MH < H L < ML, MH
BMI	25.5 (4.9)	26.5 (4.9)	29.9 (5.4)	31.5 (6.3)	30.5 (5.2)	30.9 (5.2)	30.9 (5.9)	30.1 (5.1)	8.3****	H < MH, ML,L	5.3**	H < MH, ML,L
KFS	0.7(1.3)	1.0(1.4)	1.5(2.1)	1.8(2.3)	1.5(1.5)	1.4(1.7)	1.5(1.8)	1.2(1.7)	2.3$^{p=0.08}$		2.4$^{p=0.07}$	
Psychiatric medicines[c]	1.2(1.5)	1.0(1.4)	1.5(1.7)	1.6(1.8)	2.0(1.8)	2.3(1.9)	3.7(2.4)	3.5(2.2)	14.5****	H,MH,ML < L	10.2****	H,MH < L
Laterality[d, f, h]	35(88%)	29(85%)	39(90%)	26(87%)	35(92%)	25(93%)	41(93%)	31(91%)	2.6$^{p=0.84}$		6.3$^{p=0.38}$	

Abbreviations: T1 = time 1, T2 = time 2, H = high, MH = medium-high, ML = medium-low, L = low, BMI = body mass index, KFS = Kaplan-Feinstein Scale. ANOVA = Analysis of variance. (Significant level: *$p \leq 0.05$; **$p \leq 0.01$; ***$p \leq 0.001$; ****$p \leq 0.0001$).

[a] Expressed as mean(standard deviation) except when indicated.
[b] female n(%).
[c] number.
[d] right-handers n (%).
[e] ANOVA.
[f] Chi-squared test.
[g] Bonferroni test.
[h] Mann-Whitney *U* test.

Table 2
Exploratory and confirmatory factorial analysis.

FA[a]	Time	Factor	Value KMO	$\chi^2(p)$[b]	Test	Saturation levels	Total percent of variance explained	Cronbach's Alpha (α)
E	1	1	0.84	1478.8****	Tav-IRF	0.76	54.11	0.84
					Tav-TIR	0.91		
					Tav-IRI	0.59		
					Tav-ST	0.80		
					Tav-LT	0.80		
					ROCFT-fRey2	0.79		
					ROCFT-fRey20	0.77		
					WAIS-DSF	0.52		
					WAIS-DSB	0.60		
					TMT-B	0.70		
C	2	1	0.85	1237.4****	Tav-IRF	0.77	57.58	0.85
					Tav-TIR	0.92		
					Tav-IRI	0.68		
					Tav-ST	0.84		
					Tav-LT	0.85		
					ROCFT-fRey2	0.79		
					ROCFT-fRey20	0.80		
					WAIS-DSF	0.54		
					WAIS-DSB	0.58		
					TMT-B	0.73		

Abbreviations: FA = Factorial analysis, E = Exploratory, C = Confirmatory, KMO = Kaiser-Meyer-Olkin sample adequacy measure, TAVEC = Complutense Verbal Learning Test, Tav-IRF = immediate recall of the first learning trial, Tav-TIR = total immediate recall, Tav-IRI = immediate recall of the interference list, Tav-ST = short-term free recall, Tav-LT = long-term free recall variables, ROCFT = Rey-Osterrieth Complex Figure Test, fRey2 = figure two minutes after the copy, fRey20 = 20 min after the copy, WAIS-III = Wechsler Adult Intelligence Scale III edition, DSF = digit span forward, DSB = digit span backwards, TMT = Trial Making Test, B = Part B. KMO: 1–0.9 excellent; 0.8–0.9 good; 0.7–0.8 moderate; 0.6–0.7 poor; 0.5–0.6 low; < 0.5 very low. NS = Not Significant. (NS = $p > 0.05$; *p ≤ 0.05; **p ≤ 0.01; ***p ≤ 0.001; ****p ≤ 0.0001). Saturation levels >0.40. Cronbach's Alpha (α) > 0.70.

[a] Oblique rotation: Oblimin with Kaiser, Extraction method: Main axis.

[b] Chi-squared test (Bartlett sphericity test).

be negatively associated with TNF-α and its receptors in BD (Chakrabarty et al., 2019; Hua et al., 2021b) and SMI (Hoseth et al., 2016) and, in middle-aged adults with T2DM, serum TNF-α level were negatively associated with working memory performance (Dyer et al., 2020). Although few studies exist on lipid markers, levels of apolipoproteins seem to be related to memory impairment. Moreover, Apo-A1 seems to be implicated in the early phases of cognitive decline. Indeed, a decrease in the blood levels of Apo-A1 has been related to the transition from mild cognitive impairment to dementia (Slot et al., 2017). In this line, the lower levels of Apo-A1 found in the group with the highest memory impairment could be interpreted as a correlate of a similar cognitive decline in individuals without diagnosed dementia in our study. Conversely, it could be speculated that levels of Apo-A1 within the normal range could protect from cognitive impairment in that population. Nevertheless, the analyses in our study do not allow to test that hypothesis. Likewise, TNF-alpha and Apo-A1 may be more sensitive (true positives) to phenotypic changes in memory, which is why they are higher in the group with worse cognitive performance; while the remaining significant markers (IL-6, CRP, and Apo-B) are more specific (true negatives) for such changes. These hypotheses remain to be tested in future studies. As mentioned, memory dysfunction in individuals with T2DM and SMIs has been shown to be associated with several peripheral biomarkers signalling abnormalities in systemic inflammation and lipid metabolism. However, previous research has mostly assessed this relationship for each disorder separately, by using several memory variables, and/or by means of correlational analysis, instead of stratifying performance on a global memory score, as made in the present study. In a combined transdiagnostic sample, individuals at one extreme of overall memory performance, e.g., highest impairment, had changes in two biomarkers only. Given the absence of similar studies, the present findings should be considered preliminary and await confirmation.

Regarding the results of the discriminant analysis, we found that a biomarker-based model was able to distinguish individuals with different degrees of memory performance. The model included all three pro-inflammatory biomarkers (TNF-a, IL-6 and CRP) and the two biomarkers of lipid metabolism (Apo-A1 and Apo-B). These results concur with previous evidence supporting these relationships in the disorders analyzed. There is meta-analytic evidence that plasma levels of pro-inflammatory biomarkers are negatively associated with cognitive impairment, and specifically memory decline, in individuals with SMI (Misiak et al., 2018; Bora, 2019; Morrens et al., 2022; Patlola et al., 2023). Indeed, higher CRP levels were significantly, although weakly associated with verbal, visual and working memory impairment across MDD, BD and SZ (Morrens et al., 2022). Similarly, IL-6 correlated with worse verbal memory, whereas TNF-α showed a trend for working memory (Morrens et al., 2022). In individuals with SZ, pro-inflammatory biomarkers (higher IL-6, IL-1β, TNF-α and CRP plasma levels) are significantly related with worse performance in five cognitive domains – attention-processing speed, executive function, working memory, verbal and visual learning and memory (Patlola et al., 2023). In individuals with T2DM, meta-analytic evidence also supports this relationship (Anita et al., 2022). For instance, elevated plasma IL-6 and TNF-α were related with worse cognition, including memory decline (Marioni et al., 2010). Far less studies have been conducted on the relationship between apolipoproteins and cognition in SMI. The present results suggest that apolipoproteins are also involved in memory decline and converge with those of recent studies (Hui et al., 2017; Zhang et al., 2022; Rao et al., 2021). Serum Apo-B levels independently predicted memory performance in MDD (Hui et al., 2017), whereas Apo-B and CRP levels were negatively associated with global cognition in a mixed sample of MDD and BD (Zhang et al., 2022). Moreover, both the Apo-A1 and Apo-B levels predicted memory decline in a large study of chronic SZ (Rao et al., 2021). Interestingly, biomarkers of systemic inflammation have been associated with decreased levels of Apo-A1 across SZ, BD, and MDD (Morris et al., 2021). We are not aware of similar studies conducted in T2DM.

The overlapping etiopathological pathways subserving cardiometabolic and psychiatric disorders has fueled the search for biomarkers related to neurocognitive decline. Previous studies have examined whether a panel of peripheral biomarkers can predict cognitive dysfunction in SMI. For instance, Apo-B and CRP levels were negatively associated with global cognition in a mixed sample of MDD and BD (Zhang et al., 2022). Concise panels of biomarkers have been associated with neurocognitive outcomes also in non-psychiatric

Table 3
Peripheral serum markers at T1 and T2.

	H		MH		ML		L		*Statistical analyses*					
Variables[a]	T1 (n = 40)	T2 (n = 34)	T1 (n = 43)	T2 (n = 30)	T1 (n = 38)	T2 (n = 27)	T1 (n = 44)	T2 (n = 34)	T1 (p)[b]	Post hoc test[c]	η^2p[d]	T2 (p)[b]	Post hoc test[c]	η^2p[d]
Inflammatory markers														
IL-6	2.3 (1.3)	2.8(1.4)	2.8(1.5)	3.0(1.7)	3.5(3.7)	3.1(2.6)	2.7 (2.1)	3.0(1.8)	$2.4^{p=0.06}$			$0.2^{p=0.86}$		
IL-10	29.7 (27.4)	15.6 (15.7)	28.6 (26.4)	13.2 (8.2)	27.0 (32.5)	14.0 (17.9)	35.0 (34.8)	16.2 (23.9)	$0.4^{p=0.70}$			$0.5^{p=0.67}$		
TNF-α	8.6 (2.0)	9.2(2.2)	8.6(2.5)	10.9 (2.7)	10.0 (2.8)	11.1 (2.8)	10.7 (3.8)	12.9 (6.7)	3.9**	H,MH < L	0.07	2.6*	H < L	0.06
CRP	2.3 (2.5)	2.5(2.4)	4.6(6.6)	3.7(4.6)	3.5(3.1)	3.7(3.9)	4.2 (4.2)	3.8(5.8)	$1.8^{p=0.13}$			$.05^{p=0.98}$		
Oxidative stress markers														
GSH	208.0 (95.9)	191.1 (89.6)	202.2 (116.3)	190.4 (92.4)	206.0 (100.4)	179.0 (84.7)	193.4 (94.7)	188.2 (105.6)	$0.3^{p=0.79}$			$0.5^{p=0.68}$		
ROS	157.6 (86.7)	306.1 (133.2)	137.5 (97.4)	319.1 (181.9)	141.6 (82.5)	270.4 (186.9)	122.2 (41.3)	323.9 (204.4)	$2.2^{p=0.09}$			$0.8^{p=0.46}$		
mROS	177.0 (66.6)	203.9 (96.5)	168.6 (71.9)	211.1 (95.6)	171.3 (70.8)	215.7 (96.3)	163.6 (60.8)	205.4 (129.8)	$.04^{p=0.98}$			$0.1^{p=0.95}$		
SOD	108.9 (47.3)	97.5 (37.1)	105.6 (50.1)	101.9 (34.5)	106.0 (50.0)	102.7 (25.2)	101.1 (19.4)	97.7 (18.0)	$.06^{p=0.97}$			$0.6^{p=0.60}$		
ΔΨm	48.7 (30.3)	42.2 (28.5)	41.4 (21.2)	46.8 (39.9)	46.3 (33.7)	42.2 (32.3)	49.1 (55.3)	40.1 (30.5)	$0.2^{p=0.83}$			$0.5^{p=0.67}$		
Lipid metabolism markers														
Apo-A1	161.0 (27.3)	170.6 (32.5)	155.6 (29.8)	157.4 (31.1)	145.7 (17.2)	147.6 (22.2)	139.1 (24.6)	129.6 (27.3)	4.0**	L < MH,H	0.07	3.9**	L < MH,H	0.09
Apo-B	92.7 (20.2)	98.0 (22.7)	93.7 (25.3)	91.5 (25.5)	98.7 (26.2)	102.5 (24.0)	96.8 (24.7)	101.5 (21.0)	$0.3^{p=0.76}$			$1.0^{p=0.39}$		

Abbreviations: T1 = Time 1, T2 = Time 2, H = high, MH = medium-high, ML = medium-low, L = low, IL-6 = Interleukin-6, IL-10 = Interleukin-10, TNF-α = Tumor Necrosis Factor alpha, CRP = C-reactive protein, GSH = Glutathione, ROS = Reactive Oxygen Species, mROS = Mitochondrial Reactive Oxygen Species, SOD = Superoxide Dismutase, ΔΨm = Mitochondrial membrane potential, Apo-A1 = Apolipoprotein A1, Apo-B = Apolipoprotein B. (Significant level: *p ≤ 0.05; **p ≤ 0.01; ***p ≤ 0.001; ****p ≤ 0.0001). Effect size (η^2p: small ≈ 0.02; moderate ≈ 0.15; large ≈ 0.35).

[a] Expressed as mean(standard deviation).

[b] ANCOVA.

[c] Bonferroni test.

[d] Partial Eta-Squared (η^2p).

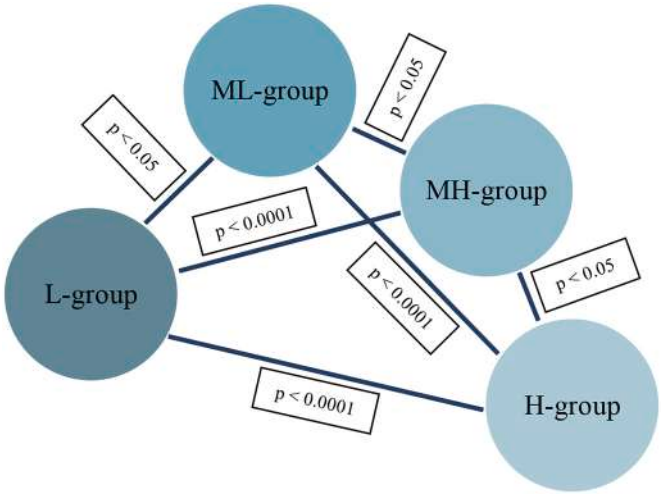

Fig. 1. Discriminatory capacity of the biomarkers-based model to differentiate between groups.

populations, such as individuals living with HIV (Marcotte et al., 2013) and those with ischemic stroke (Peng et al., 2021). However, fewer studies have assessed a larger set of biomarkers, such that used in our study. Moreover, the biomarker-based model found in this study could be framed into the "allostatic load" model. Allostatic load (AL) represents the cumulative 'wear and tear' on body systems that results from chronic stress and/or inefficient management of the systems that promote adaptation (McEwen and Stellar, 1993). Indeed, the primary mediators of AL include biomarkers such as pro- and anti-inflammatory cytokines, as well as stress hormones and their antagonists (McEwen, 2003), and make part of the set of biomarkers composing the AL index (McCrory et al., 2023). Interestingly, increased AL has been linked to cognitive decline among older adults (Juster et al., 2010). Moreover, an increase in AL has been inversely related to cognitive flexibility among overweight adults, and to inhibitory control and working memory among normal-weight adults (Ottino-González et al., 2019). In individuals with psychosis, a higher AL index was associated with worse scores on overall cognitive performance (Piotrowski et al., 2019).

However, oxidative stress biomarkers were not significantly associated with memory impairment in the present study. These results converge with those of a recent review, which show not significant relationships between oxidative damage and cognitive performance (Nantachai et al., 2022). Nevertheless, oxidative damage has been associated with neurocognitive impairment in individuals with SZ (Yang et al., 2022) and diabetes (Li et al., 2023).

The present findings support that a transdiagnostic biomarker-based model is related to cognitive impairment, with potential implications for clinical practice and research. For example, a biomarker-based model indicative of the development of altered lipid metabolism has been recently validated, which in turn can be useful to prevent the neurocognitive decline associated with cardiovascular complications in individuals with T2DM and SZ (Veitch et al., 2022). Transdiagnostic

models of cognition in high comorbidity disorders represent a shift towards a more dimensional and mechanism-based understanding of psychopathology. Growing evidence supports that variability of cardiometabolic and immune-inflammatory activity play a key role in the neurocognitive decline and that stabilization of these parameters may serve as a therapeutic target for improving neurocognitive performance, especially in the comorbidities population (Arnoriaga-Rodríguez and Fernández-Real, 2019; Zhou et al., 2021). Furthermore, these biomarkers could be useful for early detecting neurocognitive impairment across a range of disorders, thereby preventing clinical progression (Liu et al., 2021; Menculini et al., 2021; Kupka et al., 2021). The RDoC approach has the potential to inform the development of more effective treatments that could be applicable to broader range of disorders. For example, inflammatory biomarkers, specifically elevated CRP level, can be relevant for diagnosis and monitoring for individuals with psychosis (Ullah et al., 2021). Furthermore, given the close relationship between the effects of psychotropic drugs and inflammation, it could be useful in predicting the adherence of individuals to future treatments. This targeted approach can contribute to expedite the efficiency and improve the specificity of clinical trials and psychopharmacological treatment (Song et al., 2020; Zhang et al., 2022). Thus, RDoC perspective generates an opportunity to investigate common and differential patterns of neurocognitive performance across different disorders that could improve treatment in those individuals where traditional therapies have not worked well due to the inflammation.

Several limitations of this study should be considered. First, the inflammatory processes among participants could fluctuate depending on the type and clinical status of the disorder and pharmacological treatments (Tatay-Manteiga et al., 2017). Second, several relevant variables were not collected at baseline, such as current smoker status. Third, after a year of follow-up, high sample attrition was observed. Fourth, the relatively small sample size and single follow-up assessment may reduce the generalizability of the present results. However, the multicenter design of the study may increase the external validity of the results.

In conclusion, this study emphasizes the potential relationship of immune-inflammatory and lipid metabolism activity in the memory processes across several conditions. Specifically, the biomarker-based model presented in this study is able to discern the memory impairment in individuals with T2DM and psychiatric disorders. If confirmed by future studies, this model could facilitate a more accurate and early detection and treatment of memory deficits. Moreover, our findings further support that keeping healthy immunological system and metabolism may be essential for information processing and memory consolidation. Therefore, whether these assumptions eventually fulfill the aim of transcending the limitations of current psychiatric nosologies, will enable us to move forward in our understanding of physiological and molecular bases from transdiagnostic perspective.

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Declaration of Competing Interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pnpbp.2023.110817.

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