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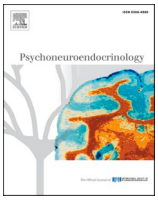

Relationship between immunometabolic status and cognitive performance among major depression disorder patients

Yolanda Sánchez-Carro [a,b,c], Alejandro de la Torre-Luque [c,d], Maria J. Portella [c,e], Itziar Leal-Leturia [a,b,c], Neus Salvat-Pujol [f,g], Clara Massaneda [f], Aida de Arriba-Arnau [f], Mikel Urretavizcaya [c,f,h], Mar Peretó [i], Alba Toll [j], Antonio Martínez-Ruiz [k], Raquel Ferreiros-Martinez [l], Pilar Álvarez [j], Virginia Soria [c,f,h], Pilar López-García [a,b,c,*]

[a] Department of Psychiatry, Universidad Autonoma de Madrid (UAM), Spain
[b] Department of Psychiatry, Instituto de Investigación Sanitaria Princesa (IIS-IP), Madrid, Spain
[c] Center for Biomedical Research in Mental Health (CIBERSAM), Carlos III Health Institute, Madrid, Spain
[d] Department of Legal Medicine, Psychiatry and Pathology, Universidad Complutense de Madrid, Spain
[e] Biomedical Research Institute Sant Pau (IIB-Sant Pau), Universitat Autonoma de Barcelona (UAB), Spain
[f] Bellvitge University Hospital, Department of Psychiatry, Bellvitge Biomedical Research Institute (IDIBELL), Neurosciences Group - Psychiatry and Mental Health, Barcelona, Spain
[g] Corporació Sanitària Parc Taulí, Department of Mental Health, Sabadell, Spain
[h] Department of Clinical Sciences, School of Medicine, Universitat de Barcelona (UB), Spain
[i] Inia Neural SL, Castellón, Spain
[j] Institute of Neuropsychiatry and Addictions, Hospital del Mar, IMIM, Barcelona, Spain
[k] Unidad de Investigación, Hospital Universitario Santa Cristina, Instituto de Investigación Sanitaria Princesa (IIS-IP), Madrid, Spain
[l] Service of Clinical Analysis, Hospital Universitario de la Princesa, Instituto de Investigación Sanitaria Princesa (IIS-IP), Madrid, Spain

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ABSTRACT

Background: Alterations in cognitive performance have been described in patients with major depressive disorder (MDD). However, the specific risk factors of these changes are not yet known. This study aimed to explore whether inmunometabolic parameters are related to cognitive performance in MDD in comparison to healthy controls (HC)

Methods: Sample consisted of 84 MDD patients and 78 HC. Both groups were compared on the results of cognitive performance measured with the Cambridge Neuropsychological Test Automated Battery (CANTAB), the presence of metabolic syndrome (MetS) and an inflammatory/oxidative index calculated by a principal component analysis of peripheral biomarkers (tumor necrosis factor, C-reactive protein and 4-hydroxynonenal). A multiple linear regression was carried out, to study the relationship between inmunometabolic variables and the global cognitive performance, being the latter the dependent variable.

Results: Significant differences were obtained in the inflammatory/oxidative index between both groups ($F_{(1157)}$= 12.93; $p < .001$), also in cognitive performance ($F_{(1157)}$= 56.75; $p < .001$). The inmunometabolic covariate regression model (i.e., condition (HC/MDD), sex, age and medication loading, MetS, inflammatory/oxidative index and the interaction between MetS and inflammatory/oxidative index) was statistically significant ($F_{(7157)}$= 11.24; $p < .01$) and explained 31% of variance. The condition, being either MDD or HD, (B=−0.97; $p < .001$), age (B=−0.28; $p < .001$) and the interaction between inflammatory/oxidative index and MetS (B=−0.38; $p = .02$) were factors associated to cognitive performance.

Limitations: Sample size was relatively small. The cross-sectional design of the study limits the possibilities of analysis.

Conclusions: Our results provide evidence on the conjoint influence of metabolic and inflammatory dysregulation on cognitive dysfunction in MDD patients. In this way, our study opens a line of research in immunometabolic agents to deal with cognitive decline associated with MDD.

* Correspondence to: Department of Psychiatry, School of Medicine, Universidad Autónoma de Madrid, 4 Arzobispo Morcillo Street, Madrid 28029, Spain.
E-mail address: p.lopez@uam.es (P. López-García).

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1. Introduction

Major depressive disorder (MDD) is a common psychiatric disorder and a leading cause of disability worldwide (World Health Organization, 2017). Cognitive symptoms, such as difficulty concentrating, difficulties in making plans, and frequent forgetfulness (Christensen, Baune, 2019) are a prominent feature of the disorder, along with sadness and anhedonia (Culpepper et al., 2015). Domains such as psychomotor speed, memory and executive functions have been found to be affected in MDD patients (Davis et al., 2017; Douglas and Porter, 2009; Eraydin et al., 2019) from the onset of the first episode (Chen et al., 2015; Vicent-Gil et al., 2018) and even after the episode has remitted, as a result of functional and anatomical brain changes (Janssen et al., 2007; Kanner, 2004; Salvat-Pujol et al., 2017).

There is a gap of knowledge, however, regarding the mechanisms underlying the development of cognitive symptoms in MDD. The study of immunometabolic alterations could be a factor of particular interest, as they seem to affect essential cognitive mechanisms such as synaptic plasticity, neurodegeneration and neurogenesis (Bernardino et al., 2008; Hein et al., 2010; McAfoose and Baune, 2009; Sierra et al., 2007) and have an impact on brain function (Livingston et al., 2020; Yates et al., 2012). Alterations in the periventricular and subcortical white matter and a negative correlation between fasting blood glucose levels and hippocampal cell density have been linked to immunometabolic dysregulation (Livingston et al., 2020; Yates et al., 2012).

Immunometabolic alterations have been associated with the presence of atypical symptoms (Lamers et al., 2020; Lasserre et al., 2017; Milaneschi et al., 2020; Penninx et al., 2013), functional status (Baune et al., 2010) and symptom aggravation (Rock et al., 2014) in MDD patients. In this regard, a bidirectional relationship has been described between depression and metabolic risk factors such as obesity and hypertension (Carey et al., 2014; Dunbar et al., 2008; Repousi et al., 2018). The presence of metabolic syndrome (MetS) has been associated with the severity of depressive symptoms (Räikkönen et al., 2002). Concerning the study of the immune system in MDD, two biomarkers have been widely explored (Mac Giollabhui et al., 2020): increases in positive acute phase proteins such as C-reactive protein (CRP) (Howren et al., 2009) and dysregulation of tumor necrosis factor (TNF-α) (Dowlati et al., 2010). However, the mechanisms whereby these inflammatory factors are disbalanced in MDD patients remain largely unknown. If the inflammatory response becomes chronic, then it may contribute to the increase of free radicals, producing a homeostatic imbalance and an increment of oxidative stress (Biswas et al., 2017). It is a well-recognized mechanism in aging and disease, which has also been related to pathophysiology of MDD (Maes et al., 2011). The 4-hydroxy-2-nonenal (HNE) aldehyde is one of the main end products of lipid peroxidation related to health problems (Csala et al., 2015). Patients with depression have an increased circulating plasma level of HNE that is associated to a lower antioxidant protection capacity in these subjects (Liu et al., 2015; Romano et al., 2017).

Therefore, a relationship between immunometabolic alterations and cognitive performance is to be expected in patients with MDD. More research is necessary in this regard, since there are few studies related to this topic (Chang et al., 2012; Grassi-Oliveira et al., 2011; Krogh et al., 2014), not supporting these relationships in all of them (Chen et al., 2020). On the other hand, most of the studies that analyze the relationship between MetS and cognition are focused on the elderly population and dementia (Lai et al., 2020; Segura and Jurado, 2009), being necessary to provide evidence in patients with MDD, as there are very few studies and inconclusive data in this regard (Kopchak and Pulyk, 2017).

In addition to studying both, MetS and inflammation in relation to the cognitive performance of MDD patients, it is important to study their impact jointly. MetS triggered by chronic inflammation could represent a greater risk factor for poor clinical prognosis (Barzilay et al., 2001; Pradhan et al., 2001) and cognitive impairment (Yaffe et al., 2004).

Therefore, the present study aimed at determining differences in the immunometabolic status and cognitive performance between healthy controls (HC) and MDD patients and to examine the relationship between the immunometabolic profiles of MDD patients and its influence on cognitive performance. MDD patients with MetS and high inflammatory profile were hypothesized to have poorer cognitive performance.

2. Method

In this cross-sectional study, a sample of 175 participants was recruited (94 MDD patients and 81 HC). All patients were recruited from primary healthcare centres of Madrid and the outpatients´ psychiatric services of University Hospital La Princesa (Madrid, Spain), Bellvitge University Hospital and Hospital del Mar (Barcelona, Spain). Patients had to meet criteria for a current episode of MDD according to the Diagnostic and Statistical Manual of Mental Disorder 4th Edition (DSM-IV-TR) (American Psychiatric Association, 2000), which was confirmed with the Mini International Neuropsychiatric Interview (MINI) (Ferrando et al., 2000). Sex- and age-matched HC were recruited from the community; absence of current or past major psychopathology was confirmed with the MINI interview.

To be included in the study, patients and HC should meet the following inclusion criteria: 18–69 years old, White persons with European ancestry and ability to understand and to sign the informed consent. Patients should meet the criteria for the diagnosis of MDD according to the DSM-IV-TR.

The exclusion criteria were: presence of any neurological or inflammatory disorder, use of antibiotic and/or anti-inflammatory treatment, and pregnancy; absence of current or past mental disorders different from MDD, history of maniac/hipomaniac episodes and treatment with electroconvulsive therapy (ECT) for the current episode and in the last 6 months, for MDD patients.

The study was carried out in accordance with the declaration of Helsinki and following the good practice guidelines. The Local Ethics Committees of each hospital approved the research protocol Clinical Research Ethics Committee (CEIC) of La Princesa University Hospital, CEIC of Bellvitge University Hospital and CEIC of the Parc de Salut Mar.

2.1. Demographic, clinical and lifestyle variables

Demographic variables assessed in all participants were age, sex, marital status, estimated intelligence quotient (IQ) through the vocabulary subtest from the Wechsler Adult Intelligence Scale-Third Edition (Wechsler, 2004), years of education and current job status. Lifestyle was explored through related variables such as tobacco use (subjects were classified as smokers, abstainers and non-ever smokers), alcohol consumption (drinkers, abstainers and non-ever drinkers) and general physical activity measured using the International Physical Activity Questionnaire (IPAQ) (Craig et al., 2003) by ranging “last week activity” into low, moderate and high exercise. All lifestyle factors were self-reported by the subjects.

For the patient sample, the following clinical variables were included: antidepressant medication, recorded as the defined daily dose (DDD); that is, the assumed overall maintenance dose per day for a drug used for its main indication in adults by the World Health Organization Anatomical Therapeutic Chemical Classification System (WHO, 2019) (see Supplementary Materials, Table S1 for more details), severity of the depressive episode measured by Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960) and stage of illness measured by the Maudsley Staging Method (MSM), which is a multidimensional staging model (Fekadu et al., 2009, 2018) that allows staging of resistance to treatment of the patient with MDD along with severity scores from 2 to 13, mild 2–5, moderate 6–9 and severe 10–13 (see the procedure in Supplementary Material, Table S2). To calculate MSM, the following variables were collected: 1) duration of depressive episode, according to the following categories: acute (≤12 months), subacute (13–24 months) and

chronic (> 24 months), 2) severity of current episode measured by the Clinical Global Impression scale (CGI) (Guy, 1976), and 3) treatment failures (resistance) assessed by the Thase and Rush scale (Thase and Rush, 1995).

2.2. Neuropsychological assessment

Cambridge Neuropsychological Test Automated Battery (CANTAB) was used to evaluate cognitive performance of all participants. This battery has been extensively utilized across neuropsychiatric patients (Kim et al., 2014; Levaux et al., 2007), and has been validated for major depression (Sweeney et al., 2000).

Five CANTAB tests were administered on a desktop computer with a touch-sensitive screen, namely:

- Motor Screening Task (MTS): to assess the participant's speed of response measured by mistakes and response latency.
- Rapid visual information process test (RVP): to check visual sustained attention, measured by correct answers, false alarms, and response latency.
- Delayed Matching to Sample (DMS): is a short-term memory task, measured by correct delayed answers and response latency.
- Spatial working memory (SWM): to measure strategy use and working memory, measured by effectiveness of the strategy used to solve the test and response latency.
- One touch Stockings of Cambridge (OTS): to check spatial planning, measured by number of items solved in the first response and response latency.

The assessment covered the cognitive domains of speed of processing (MTS), attention (RVP), visual memory (DMS) and executive function (SWM and OTS).

2.3. Physical examination

All participants underwent a physical examination that included a blood draw, obtaining three samples: a sample for the collection of metabolic biomarkers, a sample for HNE quantification and another sample for TNF-α and CRP concentration analysis. For blood sample drawing, patients were summoned in the early morning, between 8:00 and 10:00 a.m., after a previous fasting night. An indwelling venous catheter was inserted in the antecubital vein. Measures of weight and height to obtain the body mass index (BMI) (kg/m^2), waist circumference (cm) and blood pressure (mm/Hg) were collected at recruitment site by standardized procedures and using the same measurement tools.

According to the guidelines of the Adult Treatment Panel III (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, 2001), indicators for MetS were: waist circumference and blood pressure (systolic blood pressure and diastolic blood pressure), high density lipoprotein cholesterol (HDL-C), triglycerides (mg/dL), and fasting blood sugar level (FBS) (mg/dL). See the Supplementary Material for further details (Table S3).

2.4. Inflammatory and oxidative stress biomarkers

Concentrations of HNE, as an oxidative stress biomarker, and two inflammatory biomarkers, TNF-α and CRP, were quantified. Blood samples were collected in tubes containing ethylenediamine tetra acetic acid (EDTA) for HNE, and tubes without additives to collect TNF-α and CRP. All samples were centrifuged after plasma separation and subsequent storage until quantification analysis. All samples were stored at a temperature of − 80ºC and were analyzed by the same laboratory, blinded for case and control status. The following analysis protocol was followed: TNF-α was quantified by solid phase sandwich ELISA assays on the automated AP22 IF BLOT ELITE system (DAS srl) using a commercial invitrogen™ kit. The minimum detectable dose of Hu TNF-α for this commercial kit is 1.7 pg/mL and inter and intra-assay precision < 10% in both cases (8.5% and 5.2% respectively). On the other hand, CRP quantification was carried out by using serum samples, under the analytical method of immunoturbidimetry, with a Cobas 8000 analyzer (Roche Diagnostics) with reference values of 0.0–0.5 mg / dL. Finally, HNE concentration was quantified in plasma samples by using the OxiSelect HNE adduct competitive ELISA kit (Cell Biolabs, San Diego, CA, USA) using HNE-conjugated bovine serum albumin (HNE-BSA) as standard (range 1.6–200 μg/mL), following the manufacturer's instructions with and inter and intra-assay precision < 15%.

2.5. Data analyses

All data were analysed using IBM SPSS Statistics (IBM SPSS Statistics for Window's, Version 24.0) and R Software. Multiple imputation procedures were conducted to estimate missing values of inflammatory and oxidative stress biomakers, under random forest algorithms, 50 iterations and 10 imputations. As a result, 11.31% of the missing data were imputed (see the Supplementary material to view density plots, Fig. S1).

All variables (including individual scores of demographics, clinical, lifestyle, health-related, cognitive and immunometabolic measures) were compared between HC and MDD patients by means of χ^2 test (or exact *F* test by the Fisher's exact test) for categorical variables and *t-tests* for continuous variables. The Cramer's *V* (for categorical variables) and the Cohen's *d* (for continuous measures) statistic were used as effect size estimates.

Logarithmic transformations were performed for the immunometabolic biomarkers which did not follow a normal distribution. Cognitive scores were standardized so as to have comparable measures; those tests in which higher scores mean worse performance were inverted (i.e., mistakes and response latency of MTS, false alarms, and response latency of RVP and latency of DMS, SWM and OTS) to have a common metric across them. Then, composite scores were calculated to obtain four cognitive domains: processing speed, attention, visual memory and executive function.

A principal component analysis (PCA) was carried out to extract summative profile factors from the inflammatory and oxidative stress markers, as well as from cognitive domain scores. PCA allows extracting uncorrelated factors (components) derived from linear combinations that maximize variance. A factor is retained when its eigenvalue is greater than 1 (i.e., this means that the factor would account for a significant proportion of the total variance explained by the markers/domain scores). To compare the PCA inflammatory/oxidative factors and global cognitive factors between the study groups, analysis of covariance (ANCOVA) was conducted. Participant's sex, age and BMI were used as covariates (i.e., variables to control the analysis for) for the PCA inflammatory/oxidative components; and sex, age and IQ for the PCA cognitive factors. A significant (with *p* value <0.05) *F* statistic value indicates that difference between the study group exists. The $\eta^2_{partial}$ was used as an effect size estimate.

Afterwards, a multiple linear regression was carried out to study whether the sociodemographic and clinical variables would be related to PCA global cognition components. In this regard, a forward covariate entry strategy was followed and four regression models were estimated: 1) Model without covariates, 2) Model with clinical covariates: condition (control/MDD patient), sex (male/female), age and medication loading (meaured by DDD), 3) Model with metabolic covariates (besides the model 2 covariates): MetS (no/yes), 4) Model with inflammatory covariates (besides the model 3 covariates): PCA inflammatory/oxidative factor scores and 5) Model with immunometabolic covariate interaction covariate (besides the model 4 covariates): interaction between MetS and inflammatory/oxidative index. The IQ variable was included in all models as a weighing variable, to control for baseline IQ level. The regression model with a better fit was endorsed by lower levels of the Akaike Information Criterion (AIC). The *B* coefficient (with 95% confidence interval) was used as a loading estimate.

3. Results

Final sample was comprised of 162 participants (78 controls and 84 patients), due to missing data of the drop-out participants. Both groups were comparable in terms of age, sex and civil status. Patients attended fewer years of formal education ($t = 3.14$; $p < .001$; $d = 0.48$) and had a lower premorbid IQ ($t = 3.22$; $p < .01$; $d = 0.51$). On the other hand, there were significant differences in employment status ($\chi^2 = 61.99$; $p < .001$; Cramer's $V = 0.62$), observing a higher percentage of employed HC active in work compared to MDD patients with a higher percentage of people on sick leave (Table 1). A higher percentage of MDD patients had moderate (68.67%) versus mild (22.89%) and severe (8.43%) scores on MSM.

Regarding lifestyle variables, no significant differences were observed in smoking patterns. However, there were significant differences in alcohol consumption ($\chi^2 = 12.32$; $p < .01$; Cramer's $V = 0.28$), and physical activity ($\chi^2 = 14.97$; $p < .001$; Cramer's $V = 0.30$). A higher proportion of alcohol drinkers was found among the HC participants. Conversely, a higher likelihood to follow a sedentary behavior was found among the patients, with a lower percentage of subjects who regularly did moderate or vigorous physical activity.

Metabolic risk markers showed relatively similar levels between both samples (see Table 1). Significant differences were found for CRP and HNE levels. MDD patients had higher levels of CRP ($t = -3.10$; $p = <.01$; $d = -0.50$), and HNE ($t = -2.70$; $p < .01$; $d = -0.49$) than control subjects.

3.1. Cognitive performance

PCA on the cognitive domain scores yielded a one-factor solution based on eigenvalues above 1 ($\lambda = 1.93$). All the four domains saturated on this factor, with loadings >[TS8 0.60 absolute terms (see the loadings in Supplementary Material, Table S4) and explained a 48.28% of variance. Therefore, a global cognition factor was found to embrace cognitive domain scores. Significant between-group differences were found, F (1, 157) = 56.75, $p < .001$, regarding this Global Cognitive Index derived from PCA. More concretely, MDD patients ($m = -0.33$; $sd = 1.04$) showed significantly lower cognition levels than their healthy counterparts ($m = 0.36$; $sd = 0.67$). The magnitude of differences was large, as proven by the effect size estimate, $\eta^2_{partial} = 0.15$.

3.2. Metabolic syndrome and inflammatory/oxidative index

No significant differences were observed between the MDD patients (19.50%) and HC (24.36%) in the presence of MetS ($\chi^2 = 0.40$; $p =$[TS8 0.53amer's $V = 0.06$). In the study of the inflammatory status, a single component was extracted by PCA ($\lambda = 1.26$). The component explained 42.02% of outcome variance and covered the three inflammatory biomarkers: TNF-α, CRP and HNE (see the loadings in Supplementary Material, Table S5), i.e., a general inflammatory/oxidative factor. Significant differences were obtained between patients and HC, $F(1157) = 12.93$; $p < .001$; $\eta^2_{partial} = 0.07$, which indicates a medium effect size of the differences. MDD patients had higher scores in this factor ($m = 0.26$; $sd = 0.99$) compared to the HC ($m = -0.28$; $sd = 0.94$).

3.3. Association and interaction of MetS and inflammatory/oxidative index with cognitive index

Linear regression modeling to explain the PCA cognition score showed that the model including the interaction between the PCA inflammatory/oxidative factor and MetS (model 5) fitted better to data (AIC= 408.67) than the rest of models: clinical covariate model (AIC=409.11), metabolic covariate model (AIC= 410.15), inflammatory/oxidative covariate model (AIC=412.12) and unconstrained model (AIC= 461.51). This model was endorsed by an $F(7154) = 11.24$; $p < .01$ and explained 31% of the variance. In other words, the model

Table 1
Demographics, clinical and health-related variables of HC and MDD patients.

Variables	Healthy Controls $N = 78$	MDD Patients $N = 84$	t-z/χ^2	Effect size
Female (%)	67.95	72.62	-0.23	-0.05
Age, years	48.97 (10.32)	50.37 (10.20)	0.86	0.14
IQ	115.69 (10.65)	110.01 (11.75)	-3.22	-0.51 **
Years of schooling	16.04 (5.51)	13.52 (5.02)	-3.14	-0.48 **
Employment Status (%)	85.90	27.38	-61.99	-0.62
Active in Work	10.26	21.43		***
Unemployed	1.28	46.43		
Sick Leave	2.56	4.76		
Retired				
Marital status (%)	24.36	24.10	-3.45	-0.15
Never married	60.26	56.63		
Married/partnered	7.70	15.66		
Separated/divorced	7.70	3.61		
Widowed				
Tobacco use (%)	17.95	32.14	-5.51	-0.18
Smokers	51.28	35.71		
Non-ever smokers	30.77	32.14		
Abstinent				
Alcohol consumption	65.38	39.28	-12.31	-0.28
(%)	33.33	53.57	-14.97	**
Drinkers	1.28	7.14		-.30
Non-ever drinkers	17.95	46.43		***
Abstinent	60.26	30.10		
Physical activity (%)	21.79	15.48		
Low				
Moderate				
High				
Psychomor Speed	0.22 (0.44)	-0.21 (0.69)	4.74	-0.75 ***
Attention	0.16 (0.59)	-0.15 (0.78)	2.84	-0.45 **
Memory	0.35 (0.50)	-0.33 (0.92)	5.81	-0.91 ***
Executive function	0.75 (1.73)	-0.69 (2.17)	4.64	-0.73 ***
BMI	25.90 (4.47)	26.48 (4.79)	0.80	0.12
SBP (mm/Hg)	126.73 (17.24)	123.08 (17.04)	-1.35	-0.21
DBP (mm/Hg)	78.40 (10.19)	76.56(11.88)	-1.05	-0.16
Waist	88.05 (13.77)	91.50(13.37)	1.62	0.25
HDL-C (mg/dL - log)	61.73 (15.70) 1.77 (0.12)	62.90 (20.63) 1.78 (0.14)	0.06	0.01
Glucose (mg/dL - log)	95.96 (95.95) 1.98 (0.06)	94.79 (94.80) -1.97 (0.07)	-0.64	-0.10
Triglycerides (mg/dL - log)	111.39 (77.77) 1.97 (0.24)	108.13 (62.86) 1.98 (0.20)	0.25	0.04
TNF-α (pg/mL- log)	7.73 (3.25) .84 (0.21)	6.82 (3.41) .78 (0.22)	-1.82	-0.28
CRP (mg/dL - log)	0.17 (0.27) -1.00 (0.43)	0.20 (0.19) -.80 (0.37)	3.10	0.50**
HNE (mg/dL - log)	17.02 (12.43) 1.12 (0.40)	28.45(29.74) 1.31 (0.38)	2.70	0.49**
Antidepressant treatment		2.78 (2.14)		
HDRS		20.76 (5.37)		
Duration of Episode (Months)		17.80 (24.87)		
Treatment Resistant (%)		16.67		
Stage 0		21.43		
Stage I		25.00		
Stage II		14.28		
Stage III		22.62		
Stage IV				
CGI (%)		1.19		
Borderline mentally ill		5.95		
Mildly ill		39.28		
Moderately ill		40.48		
Markedly ill		10.71		
Severely ill		2.38		
Among the most extremely ill patients				

(continued on next page)

Table 1 (*continued*)

Variables	Healthy Controls *N*= 78	MDD Patients *N*= 84	*t*-*z*/χ^2	Effect size
MSM (%)		22.89		
Mild		68.67		
Moderate		8.43		
Severe				

Note. Percentage of cases are displayed for dichotomous and categorical variables. Means and standard deviation (between brackets) are displayed for continuous variables. Effect size estimates (Cohen's *d* for continuous outcomes and Cramer's *V* for non-continuous outcomes).
Mean scores and standard deviations for HDL-C, glucose, ttriglycerides, TNF-α CRP and HNE are given in mg/dL or pg/mL and on a logarithmic scale.
IQ= Intelligent quotient, BMI = Body mass index, SBP= Systolic blood pressure, DBP= Diastolic blood pressure, HDL-C = High-density lipoprotein cholesterol, TNF-α = Tumor necrosis factor, CRP= C-reactive protein, HNE= 4-Hydroxynonenal, HDRS= Hamilton Depression Rating Scale, CGI= Clinical Global impression scale, MSM= Maudsley staging method.
* $p < .05$
** $p < .01$
*** $p < .001$

comprising clinical, metabolic, inflammatory and metabolic*inflammatory interaction covariates explained better the PCA cognition score than the remaining ones. In this model, the clinical condition (B= −0.97; CI= −1.32, −0.61), age (B= −0.28; CI= −0.41, −0.14) and the interaction between MetS and the inflammatory/oxidative index (B= −0.38; CI= −072, −0.05) showed a significant loading related to global cognitive performance. Regression coefficients of covariates are displayed in Table 2. Being a patient with major depression, being older and having metabolic syndrome together with higher levels in the inflammatory/oxidative index, were related to poor cognitive performance.

The results indicated that the presence of MetS, and the alterations in the inflammatory/oxidative index were not independently related to cognitive performance. In this way, as we can see displayed in Fig. 1, the interaction between the presence of MetS and high levels of inflammation scores were related to poorer cognitive performance in our sample.

Thus, cognitive performance scores showed a significant relationship with the inflammatory/oxidative index in those subjects who presented MetS (F (1,33) = 9.16; p <[TS8 0.01) compared to those who did not (F (1125) = 0.08; p = .77) (see supplementary material,Table S6 for more details).

Table 2
Regression coefficients by predictors in the realization of the linear regression model for the study of the relationship with cognitive performance.

	B	CI	t-value	SE
(intercept)	0.38	(0.06,0.70)	2.32	0.16*
Condition (reference=healthy control)	-0.97	(−1.32, −0.61)	-5.42	0.17 ***
Sex (reference=man)	0.16	(−0.13,0.45)	1.09	0.14
Age	-0.28	(−0.41, −0.14)	-4.18	0.06 ***
Medication load	0.05	(−0.12, 0.23)	0.62	0.09
MetS (reference=no)	0.19	(−0.14, 0.51)	1.14	0.16
Inflammatory/oxidative index	0.05	(−0.09, 0.20)	0.72	0.07
Interaction between MetS and Inflammatory/oxidative index	-0.38	(−0.72, −0.05)	-2.30	0.17*

Note. MetS =Metabolic syndrome. B= Beta coefficient, CI= 95% confidence interval, SE=Standar Error.
* * $p < .01$
* $p < .05$
*** $p < .001$

4. Discussion

According to our results, we observe that some factors are involved in cognitive function of the study participants: the condition of being either a depressive patient or control, age and the interaction between MetS and the inflammatory/oxidative score. More specifically, belonging to the group of patients, being older and having MetS, together with high levels of the inflammatory/oxidative index, is associated with a worse cognitive performance.

In previous studies, it has already been observed that, in a specific way, MDD may lead to transient decline in varying cognitive domains such as verbal learning, verbal fluency, psychomotor speed, memory and executive functions (Douglas and Porter, 2009; Davis et al., 2017; Eraydin et al., 2019). This transient decline may become enduring cognitive deficits after the disorder being overcome due to anatomical and functional changes at the brain level (Kanner, 2004; Janssen et al., 2007; Salvat-Pujol et al., 2017).

On the other hand, age was revealed as a relevant covariate to explain general cognition decline. It has been well supported that one of the main risk factors for cognitive decline is aging in both community and clinical samples (Kirova et al., 2015; Romero-Ayuso et al., 2021). In turn, depression is more prevalent in older adults (Andreas et al., 2017), leading to an increasing risk of conversion to dementia (Butters et al., 2008; Byers and Yaffe, 2011).

Our study supports the impact of the interaction MetS together with alterations in the inflammatory/oxidative index on cognitive performance. More concretely, we found that individuals showing at least three metabolic risk factors (in other words, MetS), together with higher levels in the inflammatory/oxidative index would be related to poorer cognitive performance. These results are in line with those found by Yaffe's team in their study with healthy older people. in which subjects with MetS and high inflammatory levels, measured with CRP and IL-6, were at risk of deterioration in their mental state (Yaffe et al., 2004).

Alterations in the immune and metabolic system and the presence of oxidative stress are closely related, with a link between them derived from dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis (Horowitz et al., 2020; Fiksdal et al., 2019; Rhen and Cidlowski, 2005). In addition, low-grade chronic inflammation has been proven to be a characteristic pathological feature of obesity and MetS, with high levels of fatty acids contributing to an increase in the release of pro-inflammatory cytokines, with some studies linking the presence of obesity and cognitive decline with inflammation with a mediating role (Chan, 2019; Miller and Spencer, 2014).

Metabolic dysregulation contributes to neuronal alterations and synaptic relationships, with a reduction in serum adiponectin concentration (APN) related to being overweight, which contributes to the accumulation of amyloid-β protein and an increase in microglia and astroglia, related to cognitive impairment (Wang et al., 2021). In addition, hypertension, another risk factor for the presence of MetS, is a risk factor for the appearance of arterial smooth muscle hyperplasia and the formation of atherosclerosis, which in turn promotes the production of reactive oxygen species production and inflammation in cerebral blood vessels (Wang et al., 2021). The excessive action of cytokines also promotes oxidative stress, that favors a homeostatic imbalance (Biswas et al., 2017) with an even greater hyperactivation of the microglia that has neurotoxic effects and consequences on learning and memory (McAfoose and Baune, 2009). In this way, subjects with immunometabolic alterations could be more vulnerable to the presence of cognitive deleterious changes, seeing their brain circuits such as the basal ganglia or anterior cingulate cortex altered, due to the altered action of essential pathways such as kinurenine (Miller et al., 2013) or changes in the white matter and cell density of the hippocampus (Yates et al., 2012; Livingston et al., 2020).

Recent evidence shows that not all patients with depression have immunometabolic alterations and suggests a link between atypical depression (i.e., MDD featured by atypical behavioural symptoms, such

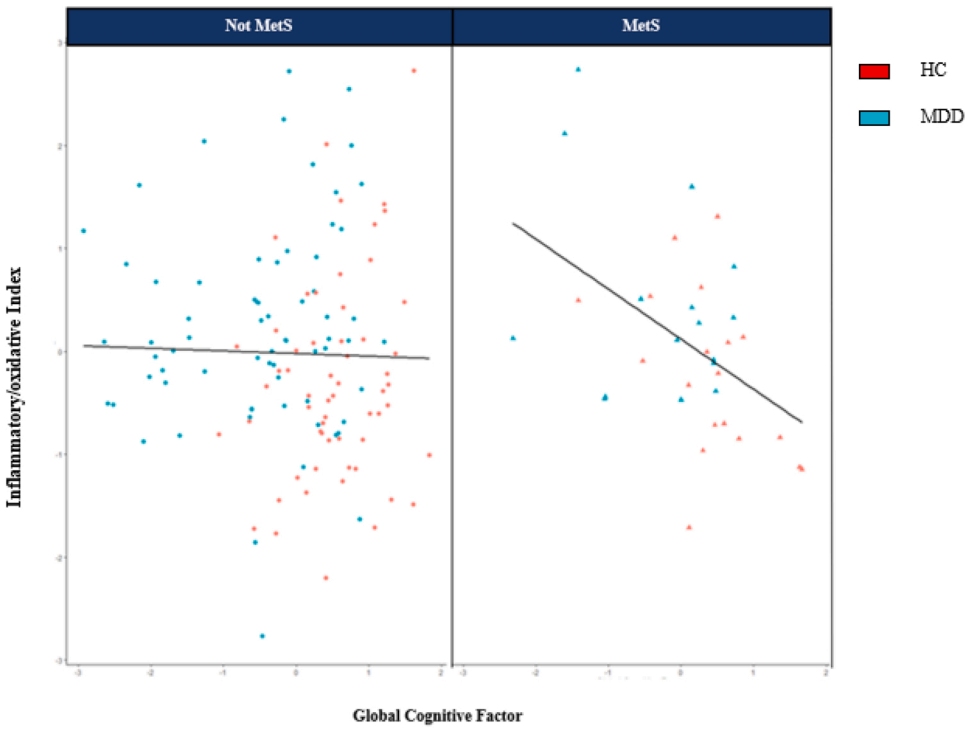

Fig. 1. Interaction between MetS and inflammatory factor in the regression model for cognitive performance, **Note.** MetS= Metabolic syndrome. The dots represent the participants without MetS, the triangles represent the participants with MetS. HC values are displayed in red and MDD patient values are displayed in blue color. The relationship between the global cognitive factor and the inflammatory/oxidative index was significant in the case of the participants with MetS ($r = -.46$, $p < .01$), but not significant in the case of the participants without MetS (r= -.02, p=.77).

as hyperphagia, weight gain, hypersomnia, fatigue) and inflammatory imbalance (i.e., increased pro-inflammatory levels) (Lamers et al., 2020; Milaneschi et al., 2020) and an elevated risk of MetS (Lasserre et al., 2017; Penninx et al., 2013). With our results, we observe that the cognitive symptoms also experienced by these patients are also related to the immunometabolic alteration they suffer. In this way, patients with a greater number of vegetative and cognitive symptoms could be a more inflamed group.

This inflammation could lead to the appearance of metabolic diseases comorbid with depression, especially in this group of patients, since it seems to have a mediating role in both pathologies, for example, patients with depression have a greater risk of arterial hypertension and patients with type 2 diabetes were 1.2–2.3 times more likely to have depressive symptoms than the general population (Qiu et al., 2021). The relationship between the two appears to be measured by inflammation, since it has been observed that NLRP3 inflammatory bodies can mediate hippocampal neuroinflammation and depression-like behavior and at the same time, can cause changes in the levels of hormones, mediators and inflammatory factors in endocrine regulation, and abnormal function or expression of some receptors (Feng et al., 2019; Qiu et al., 2021).

Besides, our results suggest an interactive pattern of relationships between the immunometabolic dysregulation, age (Wang et al., 2021) and depression (Dunbar et al., 2008; Carey et al., 2014; Mazereeuw et al., 2015; Chan, 2019). We speculate that a link between the onset and maintenance of cognitive problems may be related to higher-order dysregulation of the HPA axis (affecting both inflammation and metabolic processes), vascular disease and microglial changes (Butters et al., 2008; Byers and Yaffe, 2011; Wang et al., 2021).

Bearing our results in mind, we show that the evaluation of cognitive performance and the inmunometabolic status in patients with MDD seems as an essential step to prevent possible subsequent alterations and to carry out an effective and comprehensive treatment. Treatments that prevent increases in inflammatory levels such as physical exercise or that aim to reduce them, such as anti-inflammatories are already being tested with MDD patients with different results (Eyre et al., 2015; Kappelmann et al., 2018; Kopschina Feltes et al., 2017; Lee et al., 2021; Repple, Opel, 2021). The relationship found in our work of these biomarkers with cognition could mean that this type of treatment could be effective for the cognitive ailments expressed by patients with depression, therefore a further study in this regard is pertinent.

The study opens a line of research in immunometabolic agents (but not only inflammatory) to deal with cognitive decline associated with MDD and it would be important to continue with longitudinal lines of research that consider the evolution of cognitive performance, in the presence of these related factors, being able to establish trajectories and risk scores.

Regarding the limitations of the study, we must point out that our results were derived from analyses using a relatively limited sample size. Note that our sample would be large enough for parametric analysis based on linear modelling (e.g., ANCOVA models) (Shieh, 2020). On the other hand, the sample was somewhat heterogenous as patients from the clinical sample had a lower IQ and different employment features than HC. Both variables have been related to cognitive performance (Fisher et al., 2014; Mohn et al., 2014). Note that the employment status is often associated with the IQ level (Richardson and Norgate, 2015). Moreover, analysis on cognitive performance was controlled for the IQ in our study.

Another limitation is precisely its cross-sectional design, which limits the possibilities of analysis and prevents infering causal relationships.

Another possible limitation is that the analyses were carried out on composite scores (factors) and not on individual tests scores. However, composite scores have the benefit of reducing the number of variables to be tested and thus, increase the statistical power when using limited sample sizes.

5. Conclusions

In summary, our results show the relevance of the study of immunometabolic biomarkers and their interactions in relation to cognitive performance, opening a line of research in patients with MDD. Specifically, in our study we provide evidence of the joint association of metabolic and inflammatory dysregulation with cognitive symptoms suffered by these patients.

Further research should be done to support our results. It would also be pertinent to carry out studies in these specific populations,

considering factors related to depressive symptomatology and cognition, such as active lifestyles (Katayama et al., 2021; Sánchez-Carro et al., 2021), sleep patterns (Hu et al., 2021) and interventions that have shown positive results in reducing inflammation and exert protective effects on the brain, such as physical exercise (Erickson et al., 2019; De la Rosa et al., 2020) and adjuvant treatment with anti-inflammatory drugs (Salagre et al., 2017).

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Conflict of Interest

The authors report no biomedical financial interests or potential conflicts of interest regarding this work.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.psyneuen.2021.105631.

References

American Psychiatric Association, 2000. Diagnostic and statistical manual of mental disorde[rs]. text rev, 4th ed..,. American Psychiatric Association, Washington, DC.

Andreas, S., Schulz, H., Volkert, J., Dehoust, M., Sehner, S., Suling, A., Ausín, B., Canuto, A., Crawford, M., Da Ronch, C., Grassi, L., Hershkovitz, Y., Muñoz, M., Quirk, A., Rotenstein, O., Santos-Olmo, A.B., Shalev, A., Strehle, J., Weber, K., Wegscheider, K., Härter, M., 2017. Prevalence of mental disorders in elderly people: the European MentDis_ICF65+ study. Br. J. Psychiatry 210 (2), 125–131. https://doi.org/10.1192/bjp.bp.115.180463.

Barzilay, J.I., Abraham, L., Heckbert, S.R., Cushman, M., Kuller, L.H., Resnick, H.E., Tracy, R.P., 2001. The relation of markers of inflammation to the development of glucose disorders in the elderly: the cardiovascular health study. Diabetes 50 (10), 2384–2389. https://doi.org/10.2337/diabetes.50.10.2384.

Baune, B.T., Miller, R., McAfoose, J., Johnson, M., Quirk, F., Mitchell, D., 2010. The role of cognitive impairment in general functioning in major depression. Psychiatry Res. 176 (2–3), 183–189. https://doi.org/10.1016/j.psychres.2008.12.001.

Bernardino, L., Agasse, F., Silva, B., Ferreira, R., Grade, S., Malva, J.O., 2008. Tumor necrosis factor-α modulates survival, proliferation, and neuronal differentiation in neonatal subventricular zone cell cultures. Stem Cells 26 (9), 2361–2371. https://doi.org/10.1634/stemcells.2007-0914.

Biswas, S., Das, R., Banerjee, E.R., 2017. Role of free radicals in human inflammatory diseases. AIMS Biophys. 4 (4), 596–614. https://doi.org/10.3934/biophy.2017.4.596.

Butters, M.A., Young, J.B., Lopez, O., Aizenstein, H.J., Mulsant, B.H., Reynolds 3rd, C.F., DeKosky, S.T., Becker, J.T., 2008. Pathways linking late-life depression to persistent cognitive impairment and dementia. Dialog-. Clin. Neurosci. 10 (3), 345–357. https://doi.org/10.31887/DCNS.2008.10.3/mabutters.

Byers, A.L., Yaffe, K., 2011. Depression and risk of developing dementia. Nat. Rev. Neurol. 7 (6), 323–331. https://doi.org/10.1038/nrneurol.2011.60.

Carey, M., Small, H., Yoong, S.L., Boyes, A., Bisquera, A., Sanson-Fisher, R., 2014. Prevalence of comorbid depression and obesity in general practice: a cross-sectional survey. Br. J. Gen. Pr. 64 (620), e122–e127. https://doi.org/10.3399/bjgp14X677482.

Chan, K.L., Cathomas, F., Russo, S.J., 2019. Central and Peripheral Inflammation Link Metabolic Syndrome and Major Depressive Disorder. Physiology 34 (2), 123–133. https://doi.org/10.1152/physiol.00047.2018.

Chang, H.H., Lee, I.H., Gean, P.W., Lee, S.Y., Chi, M.H., Yang, Y.K., Lu, R.B., Chen, P.S., 2012. Treatment response and cognitive impairment in major depression: association with C-reactive protein (https://doi:). Brain Behav. Immun. 26 (1), 90–95. https://doi.org/10.1016/j.bbi.2011.07.239.

Chen, M.H., Hsu, J.W., Huang, K.L., Tsai, S.J., Su, T.P., Li, C.T., Lin, W.C., Tu, P.C., Bai, Y.M., 2020. Role of obesity in systemic low-grade inflammation and cognitive function in patients with bipolar I disorder or major depressive disorder. CNS Spectr. 1–7. https://doi.org/10.1017/S1092852920001534.

Chen, Y., Wang, C., Zhu, X., Tan, Y., Zhong, Y., 2015. Aberrant connectivity within the default mode network in first-episode, treatment major depressive disorder. J. Affect Disord. 183, 49–56. https://doi.org/10.1016/j.jad.2015.04.052.

Christensen, M.C., Baune, B.T., 2019. Differences in perceptions of major depressive disorder symptoms and treatment priorities between patients and health care providers across the acute, post-acute, and remission phases of depression. Front Psychiatry 10, 335. https://doi.org/10.3389/fpsyt.2019.00335.

Craig, C.L., Marshall, A.L., Sjöström, M., Bauman, A.E., Booth, M.L., Ainsworth, B.E., Pratt, M., Ekelund, U., Yngve, A., Sallis, J.F., Oja, P., 2003. International physical activity questionnaire: 12-country reliability and validity. Med Sci. Sports Exerc 35 (8), 1381–1395.

Csala, M., Kardon, T., Legeza, B., Lizák, B., Mandl, J., Margittai, É., Puskás, F., Száraz, P., Szelényi, P., Bánhegyi, G., 2015. On the role of 4-hydroxynonenal in health and disease. Biochim Biophys. Acta 1852 (5), 826–838. https://doi.org/10.1016/j.bbadis.2015.01.015.

Culpepper, L., Muskin, P.R., Stahl, S.M., 2015. Major depressive disorder: understanding the significance of residual symptoms and balancing efficacy with tolerability. Am. J. Med 128 (9 Suppl), S1–S15. https://doi.org/10.1016/j.amjmed.2015.07.001.

Davis, M., DellaGioia, N., Matuskey, D., Harel, B., Maruff, P., Pietrzak, R.H., Esterlis, I., 2017. Preliminary evidence concerning the pattern and magnitude of cognitive dysfunction in major depressive disorder using cogstate measures. J. Affect Disord. 218, 82–85. https://doi.org/10.1016/j.jad.2017.04.064.

De la Rosa, A., Olaso-Gonzalez, G., Arc-Chagnaud, C., Millan, F., Salvador-Pascual, A., García-Lucerga, C., Blasco-Lafarga, C., Garcia-Dominguez, E., Carretero, A., Correas, A.G., Viña, J., Gomez-Cabrera, M.C., 2020. Physical exercise in the prevention and treatment of Alzheimer's disease. J. Sport Health Sci. 9 (5), 394–404. https://doi.org/10.1016/j.jshs.2020.01.004.

Douglas, K.M., Porter, R.J., 2009. Longitudinal assessment of neuropsychological function in major depression. Aus N. Z. J. Psychiatry 43 (12), 1105–1117. https://doi.org/10.3109/00048670903279887.

Dowlati, Y., Herrmann, N., Swardfager, W., Liu, H., Sham, L., Reim, E.K., Lanctôt, K.L., 2010. A meta-analysis of cytokines in major depression. Biol. Psychiatry 67 (5), 446–457. https://doi.org/10.1016/j.biopsych.2009.09.033.

Dunbar, J.A., Reddy, P., Davis-Lameloise, N., Philpot, B., Laatikainen, T., Kilkkinen, A., Bunker, S.J., Best, J.D., Vartiainen, E., Kai Lo, S., Janus, E.D., 2008. Depression: an important comorbidity with metabolic syndrome in a general population. Diabetes care 31 (12), 2368–2373. https://doi.org/10.2337/dc08-0175.

Eraydin, I.E., Mueller, C., Corbett, A., Ballard, C., Brooker, H., Wesnes, K., Aarsland, D., Huntley, J., 2019. Investigating the relationship between age of onset of depressive disorder and cognitive function. Int J. Geriatr. Psychiatry 34 (1), 38–46. https://doi.org/10.1002/gps.4979.

Erickson, K.I., Hillman, C., Stillman, C.M., Ballard, R.M., Bloodgood, B., Conroy, D.E., Macko, R., Marquez, D.X., Petruzzello, S.J., Powell, K.E., FOR 2018 PHYSICAL ACTIVITY GUIDELINES ADVISORY COMMITTEE*, 2019. Physical activity, cognition, and brain outcomes: a review of the 2018 physical activity guidelines. Med. Sci. Sports Exerc. 51 (6), 1242–1251. https://doi.org/10.1249/MSS.0000000000001936.

Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, 2001. Executive summary of the third report of the national cholesterol education program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III). JAMA 285 (19), 2486–2497. https://doi.org/10.1001/jama.285.19.2486.

Eyre, H.A., Air, T., Proctor, S., Rositano, S., Baune, B.T., 2015. A critical review of the efficacy of non-steroidal anti-inflammatory drugs in depression. Prog. Neuropsychopharmacol. Biol. Psychiatry 57, 11–16. https://doi.org/10.1016/j.pnpbp.2014.10.003.

Fekadu, A., Wooderson, S.C., Markopoulou, K., Cleare, A.J., 2009. The Maudsley staging method for treatment-resistant depression: prediction of longer-term outcome and persistence of symptoms. J. Clin. Psychiatry 70 (7), 952–957. https://doi.org/10.4088/JCP.08m04728.

Fekadu, A., Donocik, J.G., Cleare, A.J., 2018. Standardisation framework for the Maudsley staging method for treatment resistance in depression. BMC Psychiatry 18 (1), 100. https://doi.org/10.1186/s12888-018-1679-x.

Feng, X., Zhao, Y., Yang, T., Song, M., Wang, C., Yao, Y., Fan, H., 2019. Glucocorticoid-driven NLRP3 inflammasome activation in hippocampal microglia mediates chronic stress-induced depressive-like behaviors. Front. Neurosci. 12, 210. https://doi.org/10.3389/fnmol.2019.00210.

Ferrando, L., Bobes, J., Gibert, J., Soto, M., Soto, O., 2000. 1.1. MINI Entrevista neuropsiquiátrica internacional (MINI international neuropsychiatric interview, MINI). Instrum. Detección Orientac. Diagnóstica.

Fiksdal, A., Hanlin, L., Kuras, Y., Gianferante, D., Chen, X., Thoma, M.V., Rohleder, N., 2019. Associations between symptoms of depression and anxiety and cortisol responses to and recovery from acute stress. Psychoneuroendocrinology 102, 44–52. https://doi.org/10.1016/j.psyneuen.2018.11.035.

Fisher, G.G., Stachowski, A., Infurna, F.J., Faul, J.D., Grosch, J., Tetrick, L.E., 2014. Mental work demands, retirement, and longitudinal trajectories of cognitive functioning. J. Occup. Health Psychol. 19 (2), 231–242. https://doi.org/10.1037/a0035724.

Grassi-Oliveira, R., Bauer, M.E., Pezzi, J.C., Teixeira, A.L., Brietzke, E., 2011. Interleukin-6 and verbal memory in recurrent major depressive disorder. Neuro Endocrinol. Lett. 32 (4), 540–544.
Guy, W., 1976. Clinical global impression. Assess. Man. Psychopharmacol. 217–222.
Hamilton, M., 1960. Rating scale for depression. J. Neurol. Neurosurg. Psychiatry 23, 56–62.
Hein, A.M., Stasko, M.R., Matousek, S.B., Scott-McKean, J.J., Maier, S.F., Olschowka, J. A., Costa, A., O'Banion, M.K., 2010. Sustained hippocampal IL-1β overexpression impairs contextual and spatial memory in transgenic mice (https://doi:). Brain Behav. Immun. 24 (2), 243–253. https://doi.org/10.1016/j.bbi.2009.10.002.
Horowitz, M.A., Cattaneo, A., Cattane, N., Lopizzo, N., Tojo, L., Bakunina, N., Musaelyan, K., Borsini, A., Zunszain, P.A., Pariante, C.M., 2020. Glucocorticoids prime the inflammatory response of human hippocampal cells through up-regulation of inflammatory pathways. Brain, Behav. Immun. 87, 777–794. https://doi.org/10.1016/j.bbi.2020.03.012.
Howren, M.B., Lamkin, D.M., Suls, J., 2009. Associations of depression with C-reactive protein, IL-1, and IL-6: a meta-analysis. Psychosom. Med 71 (2), 171–186. https://doi.org/10.1097/PSY.0b013e3181907c1b.
Hu, M., Shu, X., Feng, H., Xiao, L.D., 2021. Sleep, inflammation and cognitive function in middle-aged and older adults: a population-based study. In: J Affect Disord, 284. Advance online publication,, pp. 120–125. https://doi.org/10.1016/j.jad.2021.02.013.
Janssen, J., Hulshoff Pol, H.E., de Leeuw, F.E., Schnack, H.G., Lampe, I.K., Kok, R.M., Kahn, R.S., Heeren, T.J., 2007. Hippocampal volume and subcortical white matter lesions in late life depression: comparison of early and late onset depression. J. Neurol. Neurosurg. Psychiatry. ;78(6):638–40. https://doi. https://doi.org/10.1016/j.biopsych.2004.09.011.
Kanner, A.M., 2004. Structural MRI changes of the brain in depression. Clin. EEG Neurosci. 35 (1), 46–52. https://doi.org/10.1177/155005940403500111.
Kappelmann, N., Lewis, G., Dantzer, R., Jones, P.B., Khandaker, G.M., 2018. Antidepressant activity of anti-cytokine treatment: a systematic review and meta-analysis of clinical trials of chronic inflammatory conditions. Mol. Psychia 23 (2), 335–343. https://doi.org/10.1038/mp.2016.167.
Katayama, O., Lee, S., Bae, S., Makino, K., Shinkai, Y., Chiba, I., Harada, K., Shimada, H., 2021. Lifestyle changes and outcomes of older adults with mild cognitive impairment: A 4-year longitudinal study. In: Arch Gerontol Geriatr, 94. Advance online publication,, 104376. https://doi.org/10.1016/j.archger.2021.104376.
Kim, H.S., An, Y.M., Kwon, J.S., Shin, M.S., 2014. A preliminary validity study of the cambridge neuropsychological test automated battery for the assessment of executive function in schizophrenia and bipolar disorder. Psychiatry Investig. 11 (4), 394. https://doi.org/10.4306/pi.2014.11.4.394.
Kirova, A.M., Bays, R.B., Lagalwar, S., 2015. Working memory and executive function decline across normal aging, mild cognitive impairment, and Alzheimer's disease. Biomed. Res. Int. 2015, 748212 https://doi.org/10.1155/2015/748212.
Kopchak, O., Pulyk, O., 2017. Association between depressive symptoms and cognitive impairment in patients with metabolic syndrome. Wiad. Lek. 70 (4), 737–741.
Kopschina Feltes, P., Doorduin, J., Klein, H.C., Juárez-Orozco, L.E., Dierckx, R.A., Moriguchi-Jeckel, C.M., de Vries, E.F., 2017. Anti-inflammatory treatment for major depressive disorder: implications for patients with an elevated immune profile and non-responders to standard antidepressant therapy. J. Psychopharmacol. (Oxf., Engl.) 31 (9), 1149–1165. https://doi.org/10.1177/0269881117711708.
Krogh, J., Benros, M.E., Jørgensen, M.B., Vesterager, L., Elfving, B., Nordentoft, M., 2014. The association between depressive symptoms, cognitive function, and inflammation in major depression. Brain, Behav., Immun. 35, 70–76. https://doi.org/10.1016/j.bbi.2013.08.014.
Lai, M., Ames, D.J., Cox, K.L., Ellis, K.A., Sharman, M., Hepworth, G., Desmond, P., Cyarto, E.V., Szoeke, C., Martins, R., Masters, C.L., Lautenschlager, N.T., 2020. Association between cognitive function and clustered cardiovascular risk of metabolic syndrome in older adults at risk of cognitive decline. J. Nutr. Health Aging 24 (3), 300–304. https://doi.org/10.1007/s12603-020-1333-4.
Lamers, F., Milaneschi, Y., Vinkers, C.H., Schoevers, R.A., Giltay, E.J., Penninx, B., 2020. Depression profilers and immuno-metabolic dysregulation: Longitudinal results from the NESDA study. Brain Behav. Immun. 88, 174–183. https://doi.org/10.1016/j.bbi.2020.04.002.
Lasserre, A.M., Strippoli, M.F., Glaus, J., Gholam-Rezaee, M., Vandeleur, C.L., Castelao, E., Marques-Vidal, P., Waeber, G., Vollenweider, P., Preisig, M., 2017. Prospective associations of depression subtypes with cardio-metabolic risk factors in the general population. Mol. Psychiatry 22 (7), 1026–1034. https://doi.org/10.1038/mp.2016.178.
Lee, J., Gierc, M., Vila-Rodriguez, F., Puterman, E., Faulkner, G., 2021. Efficacy of exercise combined with standard treatment for depression compared to standard treatment alone: a systematic review and meta-analysis of randomized controlled trials. JAD, S0165-0327(21)01002-8. Adv. Online Publ. https://doi.org/10.1016/j.jad.2021.09.043.
Levaux, M.N., Potvin, S., Sepehry, A.A., Sablier, J., Mendrek, A., Stip, E., 2007. Computerized assessment of cognition in schizophrenia: promises and pitfalls of CANTAB. Eur. Psychiatry 22 (2), 104–115. https://doi.org/10.1016/j.eurpsy.2006.11.004.
Liu, T., Zhong, S., Liao, X., Chen, J., He, T., Lai, S., Jia, Y., 2015. A meta-analysis of oxidative stress markers in depression (https://doi:). PloS One 10 (10). https://doi.org/10.1371/journal.pone.0138904.
Livingston, J.M., McDonald, M.W., Gagnon, T., Jeffers, M.S., Gomez-Smith, M., Antonescu, S., Cron, G.O., Boisvert, C., Lacoste, B., Corbett, D., 2020. Influence of metabolic syndrome on cerebral perfusion and cognition. Neurobiol. Dis. 137, 104756 https://doi.org/10.1016/j.nbd.2020.104756.
Mac Giollabhui, N., Ng, T.H., Ellman, L.M., Alloy, L.B., 2020. The longitudinal associations of inflammatory biomarkers and depression revisited: systematic review, meta-analysis, and meta-regression. Mol. Psychiatry, 10. 1038/s41380-020-00867-4. Adv. Online Publ. https://doi.org/10.1038/s41380-020-00867-4.
Maes, M., Galecki, P., Chang, Y.S., Berk, M., 2011. A review on the oxidative and nitrosative stress (O&NS) pathways in major depression and their possible contribution to the (neuro)degenerative processes in that illness. Prog. NeuroPsychopharmacol. Biol. Psychiatry 35 (3), 676–692. https://doi.org/10.1016/j.pnpbp.2010.05.004.
Mazereeuw, G., Herrmann, N., Andreazza, A.C., Khan, M.M., Lanctôt, K.L., 2015. A meta-analysis of lipid peroxidation markers in major depression. Neuropsychiatr. Dis. Treat. 11, 2479–2491. https://doi.org/10.2147/NDT.S89922.
McAfoose, J., Baune, B.T., 2009. Evidence for a cytokine model of cognitive function. Neurosci. Biobehav Rev. 33 (3), 355–366. https://doi.org/10.1016/j.neubiorev.2008.10.005.
Milaneschi, Y., Lamers, F., Berk, M., Penninx, B., 2020. Depression heterogeneity and its biological underpinnings: toward immunometabolic depression. Depress Biol. Psychiatry 88 (5), 369–380. https://doi.org/10.1016/j.biopsych.2020.01.014.
Miller, A.A., Spencer, S.J., 2014. Obesity and neuroinflammation: a pathway to cognitive impairment. Brain Behav. Immun. 42, 10–21. https://doi.org/10.1016/j.bbi.2014.04.001.
Miller, A.H., Haroon, E., Raison, C.L., Felger, J.C., 2013. Cytokine targets in the brain: impact on neurotransmitters and neurocircuits. Depress Anxiety 30 (4), 297–306. https://doi.org/10.1002/da.22084.
Mohn, C., Sundet, K., Rund, B.R., 2014. The relationship between IQ and performance on the MATRICS consensus cognitive battery. Schizoph Res Cog 1 (2), 96–100. https://doi.org/10.1016/j.scog.2014.06.003.
Penninx, B.W., Milaneschi, Y., Lamers, F., Vogelzangs, N., 2013. Understanding the somatic consequences of depression: biological mechanisms and the role of depression symptom profile. BMC Med. 11, 129. https://doi.org/10.1186/1741-7015-11-129.
Pradhan, A.D., Manson, J.E., Rifai, N., Buring, J.E., Ridker, P.M., 2001. C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. JAMA 286 (3), 327–334. https://doi.org/10.1001/jama.286.3.327.
Qiu, W., Cai, X., Zheng, C., Qiu, S., Ke, H., Huang, Y., 2021. Update on the relationship between depression and neuroendocrine metabolism. Front. Neurosci. 15, 728810 https://doi.org/10.3389/fnins.2021.728810.
Räikkönen, K., Matthews, K.A., Kuller, L.H., 2002. The relationship between psychological risk attributes and the metabolic syndrome in healthy women: antecedent or consequence? Metabolism 51 (12), 1573–1577. https://doi.org/10.1053/meta.2002.36301.
Repousi, N., Masana, M.F., Sanchez-Niubo, A., Haro, J.M., Tyrovolas, S., 2018. Depression and metabolic syndrome in the older population: a review of evidence. J. Affect Disord. 23756–23764. https://doi.org/10.1016/j.jad.2018.04.102.
Repple, J., Opel, N., 2021. Sport und körperliche Bewegung bei unipolarer Depression: prävention, therapie und neurobiologische wirkmechanismen [Sport and physical exercise in unipolar depression: Prevention, therapy, and neurobiological mechanisms of action]. Der Nervenarzt 92 (5), 507–514. https://doi.org/10.1007/s00115-021-01113-0.
Rhen, T., Cidlowski, J.A., 2005. Antiinflammatory action of glucocorticoids–new mechanisms for old drugs. N. Engl. J. Med 353 (16), 1711–1723. https://doi.org/10.1056/NEJMra050541.
Richardson, K., Norgate, S.H., 2015. Does IQ really predict job performance? Appl. Dev. Sci. 19 (3), 153–169. https://doi.org/10.1080/10888691.2014.983635.
Rock, P.L., Roiser, J.P., Riedel, W.J., Blackwell, A.D., 2014. Cognitive impairment in depression: a systematic review and meta-analysis. Psychol. Med 44, 2029–2040. https://doi.org/10.1017/S0033291713002535.
Romano, A., Serviddio, G., Calcagnini, S., Villani, R., Giudetti, A.M., Cassano, T., Gaetani, S., 2017. Linking lipid peroxidation and neuropsychiatric disorders: focus on 4-hydroxy-2-nonenal. Free Radic. Biol. Med. 111, 281–293. https://doi.org/10.1016/j.freeradbiomed.2016.12.046.
Romero-Ayuso, D., Cuerda, C., Morales, C., Tesoriero, R., Triviño-Juárez, J.M., Segura-Fragoso, A., Gallud, J.A., 2021. Activities of daily living and categorization skills of elderly with cognitive deficit: a preliminary study. Brain Sci. 11 (2), 213. https://doi.org/10.3390/brainsci11020213.
Salagre, E., Solé, B., Tomioka, Y., Fernandes, B.S., Hidalgo-Mazzei, D., Garriga, M., Jimenez, E., Sanchez-Moreno, J., Vieta, E., Grande, I., 2017. Treatment of neurocognitive symptoms in unipolar depression: a systematic review and future perspectives. J. Affect Disord. 221, 205–221. https://doi.org/10.1016/j.jad.2017.06.034.
Salvat-Pujol, N., Labad, J., Urretavizcaya, M., de Arriba-Arnau, A., Segalàs, C., Real, E., Ferrer, A., Crespo, J.M., Jiménez-Murcia, S., Soriano-Mas, C., Menchón, J.M., Soria, V., 2017. Hypothalamic pituitary-adrenal axis activity and cognition in major depression: the role of remission status (https://doi:). Psychoneuroendocrinology 76, 38–48. https://doi.org/10.1016/j.psyneuen.2016.11.007.
Sánchez-Carro, Y., Portella, M.J., Leal-Leturia, I., Salvat-Pujol, N., Etxandi, M., de Arriba-Arnau, A., Urretavizcaya, M., Pousa, E., Toll, A., Álvarez, P., Soria, V., López-García, P., 2021. Age at illness onset and physical activity are associated with cognitive impairment in patients with current diagnosis of major depressive disorder. J. Affect Disord. 279, 343–352. https://doi.org/10.1016/j.jad.2020.10.032.
Segura, B., Jurado, M.A., 2009. Metabolic syndrome and ageing: cognitive impairment and structural alterations of the central nervous system. Rev. Neurol. 49 (8), 417–424.
Shieh, G., 2020. Power analysis and sample size planning in ANCOVA designs. Psychometrika 85 (1), 101–120. https://doi.org/10.1007/s11336-019-09692-3.

Sierra, A., Gottfried-Blackmore, A.C., McEwen, B.S., Bulloch, K., 2007. Microglia derived from aging mice exhibit an altered inflammatory profile (https://doi:). Glia 55 (4), 412–424. https://doi.org/10.1002/glia.20468.

Sweeney, J.A., Kmiec, J.A., Kupfer, D.J., 2000. Neuropsychologic impairments in bipolar and unipolar mood disorders on the CANTAB Neurocognitive Battery. Biol. Psychiatry 48, 674–685. https://doi.org/10.1016/s0006-3223(00)00910-0.

Thase, M.E., Rush, A.J., 1995. Treatment resistant depression. In Psychopharmacology: The Fourth Generation of Progress. Bloom FE. Kupfer DJ. Raven Press Ltd, New York, pp. 1081–1097.

Vicent-Gil, M., Keymer-Gausset, A., Serra-Blasco, M., Carceller-Sindreu, M., de Diego-Adeliño, J., Trujols, J., Mur, M., Pérez, V., Alvarez, E., Cardoner, N., Portella, M.J., 2018. Cognitive predictors of illness course at 12 months after first-episode of depression. Eur. Neuropsychopharmacol.: J. Eur. Coll. Neuropsychopharmacol. 28 (4), 529–537. https://doi.org/10.1016/j.euroneuro.2018.02.001.

Wang, X., Ji, L., Tang, Z., Ding, G., Chen, X., Lv, J., Chen, Y., Li, D., 2021. The association of metabolic syndrome and cognitive impairment in Jidong of China: a cross-sectional study. BMC Endocr. Disord. 21 (1), 40. https://doi.org/10.1186/s12902-021-00705-w.

Wechsler, D., 2004. WMS-III Escala de memoria Wechsler-III. TEA ediciones.

WHO, 2019. WHO (World Health Organization) Collaboration Centre for Drug Statistics Methodology Anatomical Therapeutic Chemical (ATC) Classification System (2019). Available at: http://www.whocc.no/.

World Health Organization. (2017). Depression and other common mental disorders: global health estimates (No. WHO/MSD/MER/2017.2).

Yaffe, K., Kanaya, A., Lindquist, K., Simonsick, E.M., Harris, T., Shorr, R.I., Tylavsky, F. A., Newman, A.B., 2004. The metabolic syndrome, inflammation, and risk of cognitive decline. JAMA 292 (18), 2237–2242. https://doi.org/10.1001/jama.292.18.2237.

Yates, K.F., Sweat, V., Yau, P.L., Turchiano, M.M., Convit, A., 2012. Impact of metabolic syndrome on cognition and brain: a selected review of the literature. Arterioscler. Thromb. Vasc. Biol. 32 (9), 2060–2067. https://doi.org/10.1161/ATVBAHA.112.252759.