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EDITORIAL

Deficit awareness in patients with neurological lesions: a brief historical note

Consciencia de déficit en pacientes con lesiones neurológicas: breve apunte histórico

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Introduction

Consciousness is a multifaceted concept that, in practical and simplified terms, is divided into 2 components: level of consciousness and content of consciousness.[1] The level of consciousness, "being conscious," arousal or wakefulness is the capacity to awaken and maintain the sleep-wake rhythm. The content of consciousness, "being aware," or awareness is the disposition to integrate different sensory stimuli and create the knowledge that allows a person to become aware of themselves and of their state, as a separate and independent entity from the environment.

In clinical practice, it is common to find patients with neurological lesions who present an alteration in the content of consciousness, "being aware," and are unable to perceive the deficits they have – or appear not to perceive them. Some even deny what is indisputable to the observer. In other cases, they have some awareness but show indifference.[2] The aim of this article is to provide a brief historical review of awareness of deficits in patients with neurological lesions.

History

Around 63 AD, Seneca provided one of the first descriptions of an alteration in awareness of deficit: "that woman (…) suddenly lost her sight, and I will tell you something incredible, but quite true: she does not know that she is blind".[3] However, the beginning of its scientific study did not occur until the second half of the 19th century.

In 1874, Carl Wernicke noted that patients with sensory aphasia are commonly unaware of their linguistic errors, since they do not attempt to correct them.[4] Eleven years later, Constantin von Monakow wrote about a patient with cortical blindness who "is not at all aware of his blindness, while making moving allusions to his frailty and senile stupidity and, from time to time, hinting at the imminent end of his life".[5] In 1893, Joseph Jules Dejerine presented a case with similar characteristics: "Although he no longer distinguishes anything, he does not want to admit his blindness. (…) When convinced of his error, he excuses himself by saying that he has a tear in his eye that prevents him from seeing well".[6]

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In 1899, Gabriel Anton described a patient who showed a clear dissociation between her inability to perceive that she could not see and her concern about the linguistic difficulties arising from her clinical condition.[7] According to Anton, this dissociation demonstrates that awareness of deficit is not a unitary phenomenon and that it may manifest in a fragmented manner, as Von Monakow had already suggested in his 1885 article. Regarding the origin of unawareness of cortical blindness, he suggested that it is caused by disconnection of the occipital lobes from the rest of the brain. He also indicated that patients reject the idea that they are blind because they continue to see through subcortical visual systems.

In the early 20th century, Adolf Meyer pointed out that alterations in awareness of deficit are not exclusive to vascular neurological lesions, but may also arise after traumatic lesions. Meyer described a mill operator who, after hitting his head, attributed his work difficulties to the fact that other workers "put things in his way".[8]

In 1914, Joseph Babinski coined the term "anosognosia" to refer to the lack of knowledge that some patients have regarding their hemiplegia. At the same time, he proposed the term "anosodiaphoria" to designate the affective indifference that some of them show toward their paralysis.[9] In the German scientific literature of the late 19th and early 20th centuries, various authors described cases of patients with neurological lesions who were unable to recognize their hemiplegia: Müller (1892), Anton (1893), Pick (1898), and Zingerle (1913), to name a few.

From a predominantly organic perspective, authors such as Anton, Meyer, and Babinski considered the inability of patients to perceive their deficits to be a direct consequence of their neurological lesions. Other authors, framed within different psychological currents, believed that these phenomena derived from the use of adaptive mechanisms to cope with disability acquired after brain injury. Babinski himself indicated that "we know that many patients, out of coquetry or self-esteem, try to conceal the disorders from which they suffer".[9]

In 1925, Heinz Hartmann and Paul Schilder – influenced by Freud's psychoanalytic ideas – proposed that difficulty recognizing the presence of a deficit is not necessarily explained by the neurological lesion, but derives from a motivational response by the patient.[10] According to these authors, patients exclude from their consciousness the inadmissible presence of the deficit through organically based defense mechanisms – Freud argued that human consciousness has a "filtering system" that keeps outside consciousness unpleasant thoughts that may damage self-image. In a later article, Schilder noted that "it is surprising how little patients worry about their head injuries".[11] This idea is aligned with the concept of anosodiaphoria proposed by Babinski. Kurt Goldstein believed that this disorder is an adaptive device whose purpose is to avoid a catastrophic reaction to the presence of a deficit that may alter the person's capacity for survival. In his work *The Organism*, he wrote: "we are dealing with apparently quite normal biological reactions to a very severe defect".[12] In the mid-1950s, Edwin Weinstein and Robert Kahn proposed that the state of brain function determines the pattern in which denial is expressed and maintained, and to some extent the circumstances that provoke it.[13] According to these authors, neurological lesions provide an altered functional environment in which the patient can deny anything that they feel is wrong.

Final comment

Historically, alterations in awareness of deficit have been explained through two apparently antagonistic hypotheses: one biological and the other psychological. The biological hypothesis currently has greater support. Alterations in awareness of deficit are considered a multidimensional clinical syndrome of neurological origin, generating a series of specific deficits, with multiple levels of complexity and severity, arising from the deterioration of discrete anatomofunctional monitoring systems responsible for the control and monitoring of specific brain processes, motor, sensory, attentional, linguistic, mnemonic, etc.[14]

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ORIGINAL ARTICLE

Development of the synaptic dysfunction index and its association with beta-amyloid in preclinical stages of Alzheimer's disease

Desarrollo del índice de disfunción sináptica y su asociación con beta-amiloide en etapas preclínicas de enfermedad de Alzheimer

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Abstract

Background: *Synaptic dysfunction is an early event in Alzheimer's disease and may be related to amyloid-beta deposits in preclinical stages.* **Objective:** *To develop the Synaptic Dysfunction Index (IDsyn) and evaluate its association with amyloid-beta.* **Method:** *Analytical study with secondary data (n = 375). Principal Component Analysis (PCA) was applied to derive the IDsyn from neurogranin, SNAP25, SYT1, and GAP43. Associations with amyloid-beta were analyzed, and discriminatory capacity was assessed with ROC curves.* **Results:** *PCA explained 86.7% of the variability, with neurogranin, SYT1, and GAP43 as the main contributors. The presence of amyloid-beta was associated with higher IDsyn ($p < 0.001$), especially at high levels (OR: 16.65; 95% CI: 3.80-72.87). The ROC curve showed good discriminatory ability (AUC: 0.794).* **Conclusion:** *IDsyn quantifies synaptic dysfunction and is associated with elevated beta-amyloid levels.*

Keywords: *Alzheimer disease. Amyloid beta-peptides. Synaptic transmission. Principal component analysis. Early diagnosis.*

Resumen

Antecedentes: *La disfunción sináptica es un evento temprano en Alzheimer y puede estar relacionada con depósitos de beta-amiloide en etapas preclínicas.* **Objetivo:** *Desarrollar el índice de disfunción sináptica (IDsyn) y evaluar su asociación con beta-amiloide.* **Método:** *Estudio analítico con datos secundarios (n = 375). Se aplicó análisis de componentes principales (ACP) para derivar el IDsyn a partir de neurogranina, SNAP25, SYT1 y GAP43. Se analizaron asociaciones con beta-amiloide y se evaluó la capacidad discriminativa con curvas ROC.* **Resultados:** *El ACP explicó el 86.7% de la variabilidad, con neurogranina, SYT1 y GAP43 como principales contribuyentes. La presencia de beta-amiloide se asoció con mayor IDsyn ($p < 0.001$), especialmente en valores elevados (OR: 16.65; IC 95%: 3.80-72.87). La curva ROC mostró buena capacidad discriminativa (AUC: 0.794).* **Conclusión:** *El IDsyn cuantifica la disfunción sináptica y se asocia con valores elevados de beta-amiloide.*

Palabras clave: *Enfermedad de Alzheimer. Péptidos beta-amiloides. Transmisión sináptica. Análisis de componente principal. Diagnóstico precoz.*

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Background

Synaptic dysfunction is a key process in the early development of Alzheimer disease (AD), even before the onset of clinical symptoms[1]. In preclinical stages, the accumulation of beta-amyloid (Aβ) in the brain alters neuronal communication and compromises synaptic plasticity[2], suggesting that synaptic biomarkers in cerebrospinal fluid (CSF) may be valuable tools for early detection of the disease.

Among the most relevant biomarkers, neurogranin is associated with synaptic plasticity, and its increase in CSF indicates greater synaptic dysfunction and AD progression[3]; SNAP25 (synaptosomal-associated protein 25 kDa), which is a presynaptic protein essential for synaptic vesicle exocytosis and neurotransmitter release, is reduced in brain tissue and elevated in CSF, reflecting synaptic loss[4]; synaptotagmin-1 (SYT1), involved in regulating the synaptic vesicle fusion process[5], is altered in AD, affecting synaptic transmission; and growth-associated protein 43 (GAP-43), a marker of neuronal plasticity and regeneration, also shows changes associated with cognitive deficits[6].

Although these biomarkers have proven useful, their individual interpretation is complex because they reflect different aspects of synaptic function. To address this limitation, the objective of this research was to develop a synaptic dysfunction index (IDsyn) through principal component analysis (PCA), integrating four synaptic biomarkers into a single quantitative measure based on the cutoff point of this IDsyn. The development of this index could provide a more precise tool for identifying synaptic alterations and facilitate early diagnostic strategies and monitoring of AD progression.

Methods

Study design and study population

We conducted an analytical cross-sectional study using data obtained from an international open-access research data repository. The database used was generated from the original study by Suárez-Calvet et al. entitled *CSF Synaptic biomarkers in the preclinical stage of Alzheimer's disease and their association with MRI and PET markers of neurodegeneration*. The data from that study included synaptic biomarkers obtained from CSF and the presence of Aβ protein detected by CSF and/or positron emission tomography (PET)[7]. Notably, the secondary database available did not include sociodemographic or clinical data, nor the exact concentrations of Aβ. The analyzed population consisted of 396 cognitively healthy adults, with or without the presence of Aβ protein in CSF and/or PET.

The STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines for cross-sectional studies were reviewed and followed, and the necessary modifications were made to ensure compliance with these recommendations.

Variables and measurements

The presence of Aβ protein was classified into three groups: 1) Aβ-negative (CSF Aβ42/40 negative and Aβ PET < 30 centiloids); 2) low Aβ burden (CSF Aβ42/40 positive but PET Aβ < 30 centiloids); and 3) positive (CSF Aβ42/40 positive and Aβ PET ≥ 30 centiloids).

Subsequently, participants were grouped into 2 cohorts: absence (Aβ-negative) and presence of Aβ (including both low and high burden). However, to explore the differential effect of the magnitude of accumulation, a three-level categorization (absence, low burden, and high Aβ burden) was also used for comparative analyses of the IDsyn. This methodological decision allowed evaluation of whether a dose-dependent relationship exists between Aβ values and synaptic dysfunction.

The dependent variable was IDsyn, calculated from the factor loadings of synaptic biomarkers using PCA. Independent variables included concentrations of neurogranin (pg/mL), SYT1 (pM), SNAP25 (pM), and GAP-43 (pM), measured in CSF samples.

Statistical analysis

PCA was applied to calculate the IDsyn based on synaptic biomarkers. Subsequently, the discriminative ability of the IDsyn to identify the presence of elevated Aβ protein levels was evaluated through receiver operating characteristic (ROC) curve analysis. The area under the curve (AUC) was determined, and a cutoff point was selected to classify participants according to high or low synaptic dysfunction.

A composite IDsyn was constructed using PCA including CSF synaptic biomarkers: neurogranin, GAP-43, SNAP-25, and SYT1. The first principal component was retained as the summary index, as it explained the greatest proportion of the joint variance.

For analytical purposes, the IDsyn was subsequently dichotomized using a cutoff point determined by ROC curve analysis, using the presence of Aβ in CSF as the reference variable. The optimal cutoff point identified was 3.400 units, which maximized sensitivity and specificity to discriminate between presence and absence

of Aβ. Based on this threshold, participants were classified into 2 groups: high (IDsyn ≥ 3.400) and low synaptic dysfunction (IDsyn < 3.400).

Ethical considerations

The data used come from an open-access database under a Creative Commons (CC0) license, which guarantees their reuse without restrictions and without including confidential or identifiable participant information. The supplementary information, including the database, is available at the following link: https://datadryad.org/dataset/doi:10.5061/dryad.vdncjsxv4

Results

The results of the descriptive statistics showed that the concentration of neurogranin, a key protein in synaptic plasticity, ranged from 219.30 to 2,172.00 pg/mL, with a mean of 794.81 pg/mL and SD, 321.26 pg/mL. SNAP25, which is involved in synaptic vesicle exocytosis, showed a mean of 21.58 pM, with minimum and maximum values of 15.55 and 31.86 pM, respectively. Regarding SYT1, an essential protein for neurotransmitter release, values ranged from 26.40 to 105.71 pM, with a mean of 51.76 pM and SD, 12.71 pM. Finally, GAP43, a marker of neuronal remodeling, showed wide variability, with a range from 738.42 to 7,170.00 pM, a mean of 2,796.82 pM, and SD, 1,092.88 pM. A total of 396 participants were included in the descriptive analysis of synaptic biomarkers; however, the number of cases with complete data varied slightly between biomarkers because of missing data in the CSF samples. To ensure the validity of the multivariable analysis, PCA and construction of the IDsyn were performed only in the 375 cases with complete data for all 4 biomarkers (Table 1).

The descriptive statistics showed that the concentration of neurogranin, a key protein in synaptic plasticity, ranged from 219.30 to 2,172.00 pg/mL, with a mean of 794.81 pg/mL and SD, 321.26 pg/mL. SNAP25, involved in synaptic vesicle exocytosis, showed a mean of 21.58 pM, with minimum and maximum values of 15.55 and 31.86 pM, respectively. Regarding SYT1, an essential protein for neurotransmitter release, values ranged from 26.40 to 105.71 pM, with a mean of 51.76 pM and SD, 12.71 pM. Finally, GAP43, a marker of neuronal remodeling, showed wide variability, with a range from 738.42 to 7,170.00 pM, a mean of 2,796.82 pM, and SD, 1,092.88 pM (Table 1).

PCA showed that a single component explained most of the variability in the synaptic biomarkers, with high communalities (> 0.72) and high factor loadings in component 1 (> 0.85). SYT1, neurogranin, and GAP43 showed the highest loadings (> 0.95), indicating their strong contribution. The first component had an eigenvalue of 3.469, explaining 86.7% of the variance, which increased to 100% with the 4 biomarkers. Sampling adequacy was optimal (KMO, 0.839), and Bartlett's test was significant ($p < 0.001$), justifying the use of PCA. These results support the integration of the biomarkers into a composite index, such as the IDsyn, to assess synaptic dysfunction, although external validation is required (Table 2).

PCA identified high factor loadings in the 4 synaptic biomarkers (> 0.85), indicating their strong contribution to the variability of the index. Neurogranin, SYT1, and GAP43 showed the highest loadings (> 0.95), reflecting their relevance in synaptic dysfunction. Based on these coefficients, the IDsyn was formulated as a weighted combination of the biomarkers:

IDsyn = (0.956 × neurogranin) + (0.854 × SNAP25) + (0.958 × SYT1) + (0.953 × GAP43) (Table 3).

The results showed that the presence of Aβ was associated with a higher IDsyn, especially when its values were elevated. Initially, participants were grouped into 2 categories, absence vs presence of Aβ, for general descriptive purposes. However, for a more detailed analysis, the variable was subsequently categorized into 3 levels: absence, low values, and high values, based on cutoff points previously established in the database. This stratification allowed evaluation of a possible dose-response effect between Aβ burden and synaptic dysfunction. A significant difference was observed between the groups with and without Aβ ($p = 0.005$), suggesting an important impact on synaptic function. Subsequently, when the subgroup with low values was compared with the group without Aβ, no statistically significant difference was found ($p = 0.291$), whereas individuals with high values showed a significantly higher IDsyn compared with the group without Aβ ($p < 0.001$), reinforcing the relationship between greater Aβ accumulation and increased synaptic dysfunction. These findings highlight the importance of monitoring Aβ accumulation as a possible marker of synaptic dysfunction (Table 4).

The ROC curve of the IDsyn showed good discriminative capacity to differentiate between individuals with and without elevated Aβ protein values. The AUC was 0.794, indicating adequate performance of the index. The 95% CI ranged from 0.719 to 0.868, suggesting

Table 1. Descriptive statistics of synaptic biomarkers

Variable (unit)	n	Minimum	Maximum	Mean	SD
Neurogranin (pg/mL)	396	219.30	2172.00	794.81	321.26
SNAP25 (pM)	386	15.55	31.86	21.58	2.98
SYT1 (pM)	385	26.40	105.71	51.76	12.71
GAP43 (pM)	375	738.42	7170.00	2796.82	1092.88

Units: pg/mL (picograms per milliliter), pM (picomolar). GAP43: growth-associated protein 43; SNAP25: synaptosomal-associated protein involved in synaptic vesicle exocytosis; SYT1: synaptotagmin-1.

Table 2. Principal component analysis of synaptic biomarkers

Variable	Initial communality	Extracted communality	Loading in component 1	Initial eigenvalue	% variance	% cumulative
Neurogranin	1.000	0.913	0.956	3.469	86.727	86.727
SNAP25	1.000	0.728	0.854	0.353	8.818	95.544
SYT1	1.000	0.918	0.958	0.108	2.694	98.239
GAP43	1.000	0.909	0.953	0.070	1.761	100

KMO measure of sampling adequacy, 0.839. Bartlett test of sphericity: $\chi^2 = 1702.280$, df=6, $p < 0.001$.
GAP43: growth-associated protein 43; SNAP25: synaptosomal-associated protein involved in synaptic vesicle exocytosis; SYT1: synaptotagmin-1.

Table 3. Factor loadings from the principal component analysis and formula of the IDsyn

Variable	Loading	Coefficient in the IDsyn formula
Neurogranin	0.956	0.956 × Neurogranin
SNAP25	0.854	0.854 × SNAP25
SYT1	0.958	0.958 × SYT1
GAP43	0.953	0.953 × Protein 43
IDsyn formula	-	IDsyn = (0.956 × Neurogranin) + (0.854 × SNAP25) + (0.958 × SYT1) + (0.953 × Protein 43)

IDsyn: synaptic dysfunction index; GAP43: growth-associated protein 43; SNAP25: synaptosomal-associated protein involved in synaptic vesicle exocytosis; SYT1: synaptotagmin-1.

that its performance was not due to chance. In addition, statistical significance ($p < 0.001$) confirmed that the discrimination provided by the IDsyn was statistically robust. The curve was located above the reference diagonal (AUC, 0.5), reflecting predictive capacity greater than chance. Based on ROC curve analysis, a cutoff point of 3.400 was selected (Fig. 1). The overall presence of Aβ was significantly associated with greater synaptic dysfunction (41.0 vs 27.0%; p = 0.008), with OR, 1.88 (95% CI, 1.17-3.02) vs its absence. However, low Aβ values did not show a significant association with synaptic dysfunction (p = 0.413). In contrast, accumulation at high values was associated with a significantly greater probability of synaptic dysfunction (20.4 vs 1.5%; $p < 0.001$), with OR,16.65 (95% CI, 3.80-72.87).

For comparison, the IDsyn was dichotomized using a cutoff point of 3.400 units, determined from ROC curve analysis, which optimized the ability to discriminate elevated Aβ values. Values equal to or greater than this threshold were classified as "high synaptic dysfunction," and those below this value were classified as "low synaptic dysfunction." These results suggest a possible critical threshold of Aβ accumulation above which synaptic alteration intensifies (Table 5).

Discussion

The present study proposed a composite index (IDsyn) to quantify synaptic dysfunction based on CSF biomarkers. Although the index was generated through PCA, a clinically relevant cutoff point (≥ 3.400 units) was identified through ROC curve analysis, allowing an operational classification of synaptic dysfunction into high and low categories. The results provide evidence of the relationship between the presence of Aβ and

Table 4. Comparison of IDsyn according to the presence and levels of beta-amyloid

Group	n	Mean IDsyn	SD	p
Presence of beta-amyloid				0.005
Yes	105	38,054,117	132,172,290	-
No	212	33,551,357	133,482,938	-
Low beta-amyloid levels vs absence				0.291
Low values	82	35,337,033	119,832,729	
Absence	212	33,551,357	133,482,938	-
High beta-amyloid levels vs absence				< 0.001
High values	23	47,741,112	130,960,614	-
Absence	212	33,551,357	133,482,938	-

SD: standard deviation; IDsyn: synaptic dysfunction index.

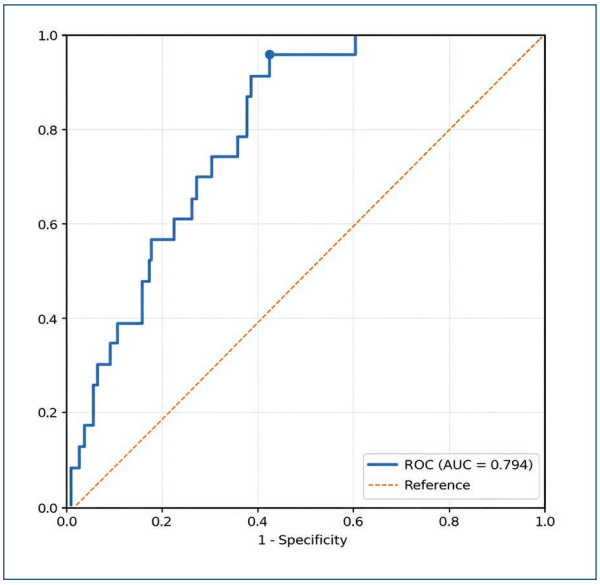

Figure 1. ROC curve of the IDsyn for predicting elevated beta-amyloid values. The blue curve represents the diagnostic performance of the IDsyn for identifying the presence of elevated beta-amyloid. The red diagonal line indicates the reference line (AUC = 0.5), which represents the performance expected by chance. The AUC was 0.794 (95% CI, 0.719-0.868), with $p < 0.001$, indicating adequate discriminative capacity of the index. The optimal cutoff point was 3.400. AUC: area under the curve; 95% CI: 95% confidence interval; IDsyn: synaptic dysfunction index; ROC: receiver operating characteristic.

synaptic dysfunction, quantified by the IDsyn, representing an objective tool for assessing synaptic alteration and its association with neurodegenerative processes.

PCA of the synaptic biomarkers indicated that neurogranin, SNAP25, SYT1, and GAP43 explained most of the variance in synaptic dysfunction. These proteins play key roles in synaptic dynamics, such as regulation of synaptic vesicle exocytosis (SNAP25, SYT1), structural remodeling of dendritic spines (neurogranin), and neuronal plasticity (GAP43)[8]. Their alteration in the presence of Aβ may represent one of the principal pathways of synaptic deterioration in neurodegenerative diseases such as AD. Therefore, this study is framed in the context of preclinical-stage AD, given that participants did not present cognitive impairment at the time of assessment but already showed Aβ accumulation and measurable synaptic alterations in CSF. This preclinical stage is critical for research because it allows identification of early neuropathologic processes that precede the appearance of clinical symptoms. Therefore, the IDsyn could constitute a useful tool for detecting synaptic dysfunction in the initial phases of the disease, facilitating early interventions before the onset of cognitive decline.

Previous studies have documented alterations in CSF synaptic biomarkers in the early stages of the AD continuum. In particular, the study by Milà-Alomà et al., in the ALFA+ cohort, showed that neurogranin, GAP-43, SNAP-25, and SYT1 increase even in cognitively intact individuals with early Aβ burden and are also associated with risk factors such as age, sex, and APOE ε4, as well as with tau markers, neurodegeneration markers (such as NfL), and structural and metabolic neuroimaging markers[7].

In agreement with this, the present study proposes a complementary approach by constructing a composite index, the IDsyn, through PCA, which makes it possible to capture synaptic dysfunction in an integrated manner. This strategy not only reaffirms the individual usefulness of these biomarkers but also enhances their diagnostic value by demonstrating adequate discriminative capacity of the IDsyn against the presence of Aβ. Thus, the relevance and originality of this work in the context of early identification of AD are highlighted.

It was observed that individuals with elevated Aβ values had a significantly higher IDsyn compared with those without the presence of this protein ($p < 0.001$). In addition, the overall presence of Aβ was associated with a greater probability of synaptic dysfunction (OR, 1.88; 95% CI, 1.17-3.02), especially in cases with high values (OR, 16.65; 95% CI, 3.80-72.87). This reinforces the role of the IDsyn as a relevant metric for assessing the magnitude of synaptic dysfunction and its relationship with pathologic Aβ accumulation. These results support the usefulness of the IDsyn as a

Table 5. Association between the presence and levels of beta-amyloid and the synaptic dysfunction index (classification according to a cutoff point > 3.400 units for high synaptic dysfunction determined by ROC curve)

Comparison	Category	High synaptic dysfunction, n (%)	Low synaptic dysfunction, n (%)	Total (n)	p	OR (95% CI)
Presence of beta-amyloid (overall)	Yes	57 (41.0%)	48 (27.0%)	105	0.008	1.88 (1.17-3.02)
	No	82 (59.0%)	130 (73.0%)	212	-	Ref.
Low values vs absence	Low values	36 (30.5%)	46 (26.1%)	82	0.413	1.24 (0.74-2.08)
	Absence	82 (69.5%)	130 (73.9%)	212	-	Ref.
High values vs absence	High values	21 (20.4%)	2 (1.5%)	23	< 0.001	16.65 (3.80-72.87)
	Absence	82 (79.6%)	130 (98.5%)	212	-	Ref.

95% CI: 95% confidence interval; OR: odds ratio; ROC: receiver operating characteristic.

composite measure to capture synaptic dysfunction related to amyloid burden, integrating multiple synaptic biomarkers into a single robust metric.

From a pathophysiologic point of view, these findings reinforce the role of Aβ in altered synaptic function, which is consistent with previous studies on neurodegeneration in diseases such as Alzheimer disease[9,10]. Aβ accumulation is implicated in disruption of neuronal homeostasis through different mechanisms. Among them, Aβ oligomers have been described as interfering with synaptic plasticity and synaptic transmission through alteration of NMDA and AMPA receptor activity, leading to imbalance in neuronal excitability[11]. In addition, Aβ may induce oxidative stress, disruption of the neuronal cytoskeleton, and microglial activation, which contributes to neuroinflammation and progressive synaptic loss[12].

Of note, although the presence of Aβ at low values did not show a significant association with synaptic dysfunction (p = 0.291), its accumulation at high values did generate an important disruption of synaptic function. This suggests the existence of a critical threshold above which Aβ triggers structural and functional alterations that negatively affect synaptic integrity. These mechanisms include the formation of toxic Aβ aggregates that alter intracellular calcium homeostasis, promoting neuronal excitotoxicity and mitochondrial dysfunction[13]. Similarly, overproduction of reactive oxygen species and activation of microglia exacerbate the neuroinflammatory response, contributing to synaptic and neuronal degeneration[14,15].

These findings highlight the importance of Aβ as a possible marker of synaptic dysfunction and reinforce the need to investigate its pathophysiologic mechanisms to develop therapeutic strategies. The IDsyn could be a useful tool for quantifying synaptic dysfunction and facilitating its early detection. For its clinical application, additional studies are required to validate its use across different stages of neurodegeneration and evaluate its predictive capacity, allowing its integration as a biomarker in medical practice.

This study had limitations, such as its cross-sectional design, which precludes establishing causality between Aβ and synaptic dysfunction. Although the IDsyn is based on validated biomarkers, other relevant factors, such as phosphorylated tau or inflammatory markers, were not included. In addition, the database used lacked complete clinical and sociodemographic information, and Aβ was available only as a categorical variable, without data on its concentrations. Such limitations restrict the possibility of performing risk-gradient analyses and could affect the generalizability of the findings. Sample representativeness and the influence of unexplored genetic or environmental factors should also be considered. All of the above highlights the need for longitudinal studies and a broader approach.

Conclusions

The IDsyn emerges as an objective, sensitive, and clinically relevant tool for detecting synaptic alterations associated with the presence and concentration of Aβ, particularly at high values. This finding not only supports the central pathogenic role of Aβ, but also introduces the IDsyn as a useful marker for risk stratification, early identification, and follow-up of synaptic dysfunction in neurodegenerative contexts. Its high discriminative capacity suggests added value compared with current approaches, opening the possibility of its integration into clinical and research protocols.

Taken together, the results of this study provide concrete evidence to consider the IDsyn a key component in the multimodal approach to cognitive impairment. Future longitudinal studies incorporating complementary markers, such as phosphorylated tau, neuroinflammation, and cortical atrophy, will be essential to validate its applicability and broaden the understanding of the pathophysiologic pathways involved in diseases such as Alzheimer disease.

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Conflicts of interest

The author declares no conflicts of interest.

Ethical considerations

Protection of persons and animals. The author declares that no experiments were performed on human beings or animals for this research.

Confidentiality, informed consent, and ethical approval. The study does not involve personal patient data and does not require ethical approval. SAGER guidelines do not apply.

Statement on the use of artificial intelligence. The author declares that no generative artificial intelligence was used in the writing of this manuscript.

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ORIGINAL ARTICLE

The relationship between primary language and short-term outcomes in patients with non-acute subdural hematomas

La relación entre idioma primario y desenlaces en el corto plazo en pacientes con hematomas subdurales no agudos

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Abstract

Background: *Language barriers may contribute to in-hospital outcome disparities, particularly among immigrants with neurosurgical conditions. In patients with non-acute subdural hematomas, effective verbal communication is critical for recovery as they face a significant comorbidity burden. However, the impact of language discordance on outcomes in this population remains unclear.* **Objective:** *To investigate the association between primary language and short-term outcomes in patients with non-acute subdural hematomas (NASDH).* **Methods:** *We conducted a retrospective cohort study of adults treated for NASDH at a single academic center between January 2017 and September 2024. Patients were stratified based on the primary language documented in the electronic health record, categorized as English or non-English. Length of hospitalization was analyzed using Mann–Whitney's U and multivariable linear regression. Adverse events and discharge disposition were assessed using Fisher's exact tests and multivariable logistic regression.* **Results:** *Among 437 patients, 47 (11%) primarily spoke a language other than English, and 301 (69%) were male. Patients with a different primary language were overrepresented in the highest quintile of socioeconomic deprivation ($p < 0.001$). Interpretation services were provided to 87% of patients who had a primary language other than English. There were no significant differences in length of stay (adjusted β: 0.03; 95% confidence interval [CI]: -0.23-0.23; $p = 0.82$), adverse events (adjusted odds ratio [OR]: 0.80; 95% CI: 0.34-1.77; $p = 0.59$), or discharge home (adjusted OR: 1.37; 95% CI: 0.65-2.95; $p = 0.40$).* **Conclusion:** *Primary language was not associated with short-term outcomes in patients with NASDH. Further research is necessary to investigate disparities across neurosurgical patient populations with diverse linguistic backgrounds.*

Keywords: *Language. Subdural hematoma. Communication. Clinical outcomes. Social determinants of health. Interpretation.*

Resumen

Antecedentes: *Las barreras de idioma pueden contribuir a disparidades en desenlaces intrahospitalarios, particularmente entre personas migrantes con condiciones neuroquirúrgicas. Considerando la alta carga de comorbilidades en pacientes con hematomas subdurales no agudos, la comunicación efectiva es fundamental para la recuperación. Sin embargo, el impacto de la discordancia lingüística en esta población específica es incierto.* **Objetivo:** *Investigar la asociación entre el idioma y los desenlaces clínicos a corto plazo en pacientes con hematomas subdurales no agudos.* **Método:** *Se llevó a cabo un estudio de cohorte retrospectivo en adultos tratados por hematomas subdurales no agudos en un centro académico entre enero de 2017 y septiembre de 2024. Los pacientes fueron clasificados de acuerdo con el idioma primario registrado en el*

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expediente médico electrónico, categorizándose como inglés y no inglés. La duración de la hospitalización se analizó mediante la prueba de Mann-Whitney y regresión lineal. Los eventos adversos y la disposición al alta se evaluaron mediante pruebas de Fisher y regresión logística. **Resultados:** *Se incluyeron 437 pacientes, de los cuales 47 (11%) eran no angloparlantes y 301 (69%) eran hombres. Los pacientes cuyo idioma primario no era el inglés estuvieron sobrerrepresentados en el quintil más alto de privación socioeconómica (p < 0.001). El 87% recibió servicios de interpretación. No se observaron diferencias en la duración de la hospitalización (β ajustado: 0.03; IC 95%: 0.23-0.23; p = 0.82), eventos adversos (OR ajustado: 0.80; IC 95%: 0.34-1.77; p = 0.59) ni en el alta a domicilio (OR ajustado: 1.37; IC 95%: 0.65-2.95; p = 0.40).* **Conclusión:** *El idioma principal no se asoció con desenlaces clínicos a corto plazo en pacientes con hematomas subdurales no agudos. Se requieren esfuerzos subsecuentes y continuos para dilucidar disparidades clínicas en poblaciones neuroquirúrgicas en contextos diversos.*

Palabras clave: *Idioma. Hematoma subdural. Comunicación. Desenlaces clínicos. Determinantes sociales en salud. Traducción.*

Background

With more than 200,000 patient encounters throughout a health-care provider's career, communication is the most common medical procedure[1]. In health-care settings where complex interventions are often indicated, clear verbal exchange of information is crucial for accuracy at key points in the patient's journey, such as symptom reporting, informed consent, explanation of treatment implications, and coordination of follow-up care[2].

Physical, cognitive, and communication-related challenges can compromise the quality of care. Particularly, linguistic barriers carry substantial weight in the United States, where more than 21 million people speak English less than "very well" and 10% of the elderly population may struggle to communicate on a daily basis due to only speaking their primary language[3]. Even though U.S. law mandates equitable access to language interpretation services under Title VI[4-6], the dynamic nature of clinical care can make uninterrupted interpretation difficult to achieve.The dynamic nature of clinical care can make uninterrupted interpretation difficult to achieve.

Despite efforts to address language barriers among non-English-speaking patients, evidence suggests that foreign patient populations often experience delayed care, heightened risks of adverse events, and prolonged hospitalizations in pediatric and adult populations[5-7] This is also the case for neurosurgical patients who struggle to communicate in English; previous research in neuro-oncologic patients suggests that those patients with a different primary language have a higher proportion of emergent admission and complications[8], and other authors have established that patients with medically refractory epilepsy who require surgical intervention had longer times to surgery than their English-speaking counterparts[9]. Despite evidence of disparities in relevant outcomes, these issues remain underexplored in other common neurosurgical conditions.

Having an incidence of up to 20 events per 10,000 person-years, non-acute subdural hematomas (NASDH) rank among the most common neurosurgical conditions, frequently requiring surgical intervention and prolonged hospitalization[10,11]. Because NASDH predominantly affects older adults, these patients appear particularly vulnerable to verbal communication barriers, especially in the context of impaired decision-making[12].

In addition, social vulnerability appears inherent to this population; as noted in previous studies, patients with NASDH often experience poorer functional and survival outcomes, compounded by a high comorbidity burden and limited social support[13]. Furthermore, patients may require specialized aftercare and present persistent neurological deficits that demand careful monitoring[14,15], making thorough and accurate communication essential for guiding recovery.

In this context, the relationship between primary language and short-term outcomes in patients with NASDH warrants further examination. While prior work has explored language-related disparities in surgical populations[16], evolving health-care policies and delivery models may alter the nature or magnitude of this association. Therefore, we aimed to assess whether primary language was associated with short-term outcomes in patients with NASDH, and based on indirect evidence from other subpopulations, we hypothesized that having a primary language other than English would be associated with worse in-hospital outcomes.

Methods

This study adheres to the principles of the Declaration of Helsinki. Institutional Review Board approval was obtained (IRB-ID 2015P002352), and given the

retrospective nature of the study, the requirement for consent was waived. All patient data were anonymized before analysis to protect confidentiality. Reporting for this manuscript aligns with the STROBE statement guidelines[17].

Setting and participants

We conducted a retrospective cohort study at a single academic center where English is the primary language, reviewing all consecutive patients aged 18 years or older who underwent intervention for NASDH between January 2017 and September 2024. NASDH was defined as hematomas described as subacute, acute-on-chronic, chronic, or mixed density in the medical reports[18]. We excluded patients whose medical records were not accessible or who were not living at home before the index episode of care. Data was extracted independently by three investigators.

Covariates of interest

Patients were grouped by primary language for verbal communication as documented in the electronic health record, categorizing their primary language as English or non-English. This variable, while not a direct measure of "proficiency," served as a practical proxy for identifying patients who may have encountered language-related challenges in clinical communication or decision-making. We also recorded a binary variable for the use of translation services to complement information about verbal communication in our study population, although it was not deemed as a feature requiring adjustment in the analyses due to a lack of detail.

We collected sociodemographic variables including age, biological sex, and insurance status, as recorded in administrative documents at admission. To describe social determinants of health, we obtained the ZIP-code-based social deprivation index (SDI), a composite measure incorporating seven indicators from the American Community Survey: poverty levels, educational attainment, single-parent households, renter-occupied housing, overcrowded living conditions, vehicle availability, and employment status[19]. A higher score represented more social deprivation, and the feature was presented in quintiles. Primary insurance was categorized as Medicare, Medicaid, private, and uninsured, as noted in the documentation related to the index episode of care. Collected clinical features included history of cognitive impairment, American Society of Anesthesiologists (ASA) score, pre-interventional NIH Stroke Scale (NIHSS), antithrombotic therapy, type of intervention (surgery or middle meningeal artery embolization), and midline shift measured in millimeters. Cognitive impairment was considered present in patients with a documented diagnosis of any class of dementia or a longstanding history of cognitive decline without a specific diagnosis.

Outcomes included length of hospitalization, any adverse events, and discharge setting. Adverse events were noted and classified using the Common Terminology Criteria for Adverse Events (version 5.0) from the US Department of Health and Human Services. Discharge setting was obtained from the discharge summary and noted to be either home, rehabilitation facility, skilled nursing facility, hospice, or in-hospital death.

Confounding control

Potential confounders identified included sex, age, cognitive impairment, SDI, ASA score, type of procedure, NIHSS score at baseline, and time to intervention. Given the limited number of patients in the comparison group, only age, cognitive impairment, and SDI were explored as confounders in the adjusted models to avoid over-fitting.

Missing data

There were no missing data for the primary exposure or outcomes. For variables with < 1% of missingness (SDI and ASA score, with one and two missing values, respectively), median imputation was performed. For NIHSS at baseline, 5% of missingness was observed. Under the assumption that data were missing at random, multiple imputation by chained equations was applied. Comparisons between summary statistics before and after imputation were calculated, with no significant alterations in distributions.

Statistical analysis

We conducted descriptive analyses to characterize the demographic and clinical features of the study groups. Continuous variables, including age, NIHSS score at baseline, and time to intervention, were non-normally distributed and analyzed using the Mann–Whitney U test, with results reported as medians and first and third quartiles. Categorical variables were analyzed using

Fisher's exact test and summarized as frequencies and percentages.

Given the skewness in the length of hospitalization, we applied a logarithmic transformation to approximate normality. Adjusted analyses for length of stay were performed using ordinary least squares (OLS) linear regression, with results reported on the log scale and covariates included as described above.

Secondary outcomes included adverse events and discharge setting, both of which were dichotomized to fit the characteristics and assumptions of the analytic methods of choice, considering a restricted sample size. Adverse events were classified as "any adverse event" versus "none," and discharge settings as "discharged home" versus "non-home" settings. Unadjusted comparisons were conducted using Fisher's exact test, and adjusted analyses were performed using binary logistic regression incorporating the same set of covariates. Associations were reported as odds ratios (OR) with 95% confidence intervals (CI) and corresponding p-values. All statistical analyses were performed using R (version 4.4.2) and RStudio (version 12, Posit PBC, Boston, MA).

Results

From an initial cohort of 462 patients, 437 were included in the analysis; 23 were excluded due to inaccessible medical records, and two were excluded because they were not living at home at baseline. Among the included patients, 390 had English documented as their primary language, and 47 had a different primary language recorded: 26 (62%) Spanish, 6 (13%) Creole, 3 (6.5%) Portuguese, 3 (6.5%) Chinese, and 6 (13%) other less-represented languages. During the study period, every year, there were at least two patients with a language other than English who were treated for NASDH (Fig. 1), and 87% of the total group required in-hospital interpretation at some capacity during their hospitalization, although we could not obtain the specific nature of such service for each patient. No patient with English as the primary language required language interpretation. The median age of the cohort was 73 years (Q1 = 65, Q3 = 80), and 69% were male. Most patients fell into ASA category 3 (n = 286, 65%). There were no observed differences in the use of statin therapy (p = 0.544) or anticoagulation (p = 0.887) (Table 1).

In general terms, this cohort presented unilateral hematomas more commonly (n = 308, 70%), and the mean midline shift measured on their last imaging

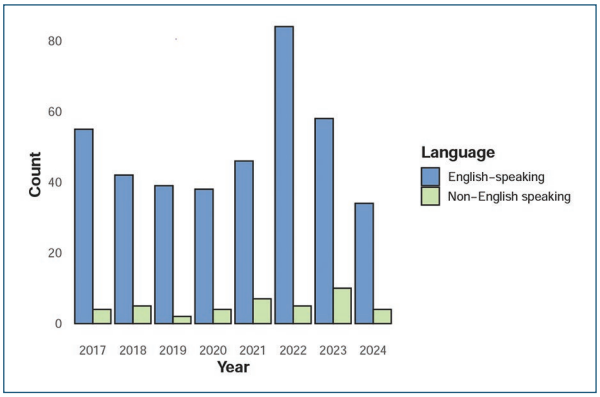

Figure 1. Number of patients treated for non-acute subdural hematomas by year.

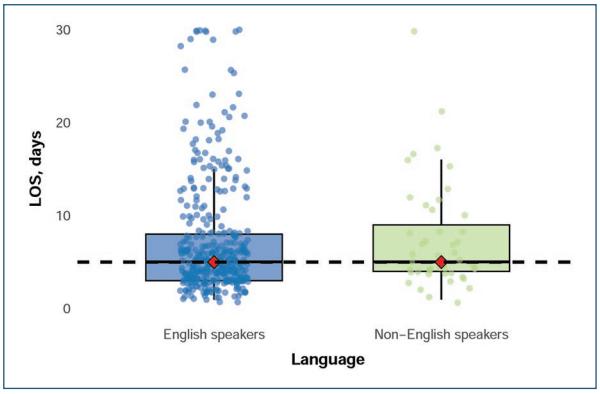

Figure 2. Length of hospitalization by language. This boxplot illustrates the distribution of the length of hospitalization (LOS) by language group. Each scatter dot represents an individual patient. The red diamond indicates the arithmetic mean, whereas the box edges represent the first (Q1) and third (Q3) quartiles. Both groups' patients had a median LOS of 5 days. There was no statistically significant difference in LOS distributions between groups (Mann-Whitney's U test, p = 0.578).

study before the index intervention was 6.6 mm (standard deviation = 4.6). Patients had a median NIHSS score of 1 (Q1 = 0, Q3 = 1), and 41 patients (9.4%) were in a coma before intervention. Most patients underwent surgical evacuation only (n = 342, 78%), with no difference between groups regarding the type of procedure (p = 0.644). The median time between admission and intervention was 1 day (Q1 = 0, Q3 = 1), similar for both groups (p = 0.623).

In the unadjusted analysis of length of hospitalization, both groups had a median length of hospitalization of 5 days, with no observed differences between the distribution of both groups (p = 0.578) (Fig. 2). In terms of

Table 1. Baseline clinical and sociodemographic characteristics

Characteristic	Overall (n = 437) (%)	English as primary language (n = 390) (%)	Primary language other than English (n = 47) (%)	p
Age (years), median (Q1, Q3)	73 (65, 80)	73 (66, 80)	70 (65, 77)	0.108
Biological sex, n (%)				0.587
Male	301 (69)	267 (68)	34 (72)	
Female	136 (31)	123 (32)	13 (28)	
Type of health insurance, n (%)				< 0.001
Medicare	249 (57)	231 (59)	18 (38)	
Medicaid	26 (5.9)	15 (3.8)	11 (23)	
Private	155 (35)	138 (35)	17 (36)	
No insurance	7 (1.6)	6 (1.5)	1 (2.1)	
Socioeconomic deprivation index (quintiles), n (%)				< 0.001
Q1	88 (20)	86 (22)	2 (4.3)	
Q2	91 (21)	88 (23)	3 (6.4)	
Q3	85 (19)	81 (21)	4 (8.5)	
Q4	86 (20)	74 (19)	12 (26)	
Q5	87 (20)	61 (16)	26 (55)	
ASA score, n (%)				0.826
1-2	35 (8)	32 (8.2%)	3 (6.4)	
3	286 (65)	253 (65)	33 (70)	
4-5	116 (27)	105 (27)	11 (23)	
History of dementia or cognitive impairment, n (%)	79 (18)	55 (14)	24 (51)	0.001
Antiplatelet therapy, n (%)	109 (27)	105 (27)	14 (30)	0.677
Anticoagulation, n (%)	53 (12)	47 (12)	6 (13)	0.887
Statins, n (%)	185 (42)	167 (43)	18 (38)	0.544
Coma at baseline, n (%)	41 (9.4)	32 (8.2)	9 (19)	0.029
NIHSS at baseline, median (Q1, Q3)	1 (0, 2)	1 (0, 2)	1 (0, 4)	0.796
Time to intervention, n (%)	1 (0, 1)	1 (0, 1)	1 (0, 1)	0.623
Type of procedure, n (%)				0.644
Surgical evacuation	342 (78)	303 (78)	39 (83)	
Adjunctive MMAE	59 (14)	53 (14)	6 (13)	
Standalone MMAE	36 (8.2)	34 (8.7)	2 (4)	
Midline shift, mean (SD)	6.6 (4.6)	6.5 (4.5)	7.5 (4.8)	0.138
Laterality of hematomas, n (%)				0.331
Unilateral	308 (70)	272 (70)	36 (77)	
Bilateral	129 (30)	118 (30)	11 (23)	

Categorical variables were analyzed with Fisher's exact test. Normally distributed variables display mean and standard deviation and were compared with Student's t-test. Non-normally distributed variables were analyzed with the Wilcoxon test, showing median along with the first and third quartiles of distribution.
SD: standard deviation; Q1: first quartile; Q3: third quartile; MMAE: middle meningeal artery embolization.

adverse events, 86 patients primarily speaking English (22.0%) and 10 patients with a different primary language (21.2%) experienced an adverse event, corresponding to an OR of 0.95 (95% CI: 0.40-2.06 p = 0.999), indicating no differences between groups. Regarding discharge disposition, 220 patients in the first group (56.4%) and 27 in the second (57.4%) were discharged home (OR: 1.04, 95% CI: 0.57-1.92, p = 0.999).

Linear regression models with OLS showed that having a different primary language was not associated with length of hospitalization (β: 0.03, 95% CI: –0.228-0.228, p = 0.820). In contrast, each 1-year increase in age was associated with a 0.6% increase in length of hospitalization on the natural scale (β = 0.006; 95% CI: 0.001-0.120; p = 0.040) (Table 2). In a multivariable logistic regression analysis adjusting for confounders, no difference between groups was found for the occurrence of adverse events (OR: 0.80, 95% CI: 0.336-1.772, p = 0.596) (Table 3). Finally, no evidence was found for differences in the odds of discharge home by language status (OR: 1.37, 95% CI: 0.654-2.953, p = 0.407). Each 1-year increase in age was associated with lower odds of being discharged home (OR: 0.935, 95% CI: 0.915 –0.954, p < 0.001) and patients with cognitive impairment or dementia had 54% lower odds of discharge home compared to those without (OR: 0.453, 95%, CI: 0.256-0.790, p = 0.005), (Table 4).

Table 2. Adjusted analysis for length of hospitalization

Covariate	Estimate (log coefficient)	Lower 95% CI	Upper 95% CI	p
Primary language other than English	0.030	–0.228	0.228	0.820
Age	0.006	0.001	0.120	**0.040***
Cognitive impairment	0.056	–0.141	0.255	0.575
Social deprivation index				
SDI Q2	0.008	–0.217	0.234	0.942
SDI Q3	0.007	–0.220	0.236	0.946
SDI Q4	–0.148	–0.379	0.082	0.206
SDI Q5	0.058	–0.180	0.298	0.630

Bold indicates statistical significance ($p < 0.05$).
Estimates, CI at 95%, and p values calculated using OLS linear regression. Length of hospitalization (days) was log-transformed due to non-normal distribution.
SDI Q: social deprivation index quartile; CI: confidence intervals; OLS: ordinary least squares.

Table 3. Adjusted analysis for adverse events

Covariate	Estimate (OR)	Lower 95% CI	Upper 95% CI	p
Primary language other than English	0.800	0.336	1.772	0.596
Age	1.006	0.986	1.026	0.541
Cognitive impairment	0.953	0.496	1.758	0.882
Social deprivation index				
SDI Q2	0.865	0.425	1.752	0.687
SDI Q3	0.679	0.318	1.420	0.307
SDI Q4	0.767	0.362	1.597	0.481
SDI Q5	1.435	0.704	2.944	0.320

p values calculated using multivariate logistic regression.
Bold indicates statistical significance ($p < 0.05$).
OR: odds ratios; CI: 95% confidence intervals.

Table 4. Adjusted analysis for discharge setting

Covariate	Estimate (OR)	Lower 95% CI	Upper 95% CI	p
Primary language other than English	1.373	0.654	2.953	0.407
Age	0.935	0.915	0.954	**< 0.001***
Cognitive impairment	0.453	0.256	0.790	**0.005***
Social deprivation index				
SDI Q2	1.670	0.886	3.173	0.114
SDI Q3	1.221	0.646	2.312	0.538
SDI Q4	1.701	0.890	3.279	0.109
SDI Q5	0.907	0.457	1.793	0.779

p values calculated using multivariate logistic regression.
Bold indicates statistical significance ($p < 0.05$).
OR: odds ratios; CI: 95% confidence intervals.

Discussion

In these analyses, we found no evidence of primary language influencing outcomes in this cohort. Although we did not encounter comparable prior evidence in patients with NASDH, our findings contrast with prior investigations among neurosurgical populations, which identified disparities between English-speaking patients and their counterparts[20-23]. Three of these studies only included patients treated before 2017; therefore, differences in our findings may reflect changes in the sociocultural landscape of care delivery.

Former studies provide little information on interpretation when language discordance occurs, leaving space for miscommunication to occur during hospitalization. Previous evidence suggests that the availability of interpretation enhances patient satisfaction and improves communication quality, though its impact on clinical outcomes remains unclear[22]. In this study, up to 87% had access to translation, potentially mitigating some of the potential communication imbalances. Although this interrogation fell out of the scope of this work, future efforts may explore whether interpretation services effectively equalize communication within hospital settings.

We expected to encounter a number of variables that were different between both groups, as speaking a different language than English (in the American context) has been associated with social vulnerability[23,24]. A covariate exhibiting imbalance was the socioeconomic deprivation index; while the English-speaking group demonstrated a uniform distribution across quintiles, over half of the patients with a different primary language were in the highest SDI quintile, indicating greater deprivation. This observation aligns with documented health disparities commonly experienced by immigrant populations in cities[25,26]. To assess access to adequate health interventions, we used proxies such as treatment modality, antithrombotic therapy, and statin use. These indicators were similar between language groups. However, since our sample was drawn from a single academic center, selection bias may have contributed to this finding.

Along the same lines, the imbalance noted in SDI and insurance type did not appear to impact outcomes in our analysis. Studies examining the impact of language barriers have described disparities in additional dimensions such as digital communication with healthcare providers after discharge[27], delays in surgery[9], and quality of life[28]. Nevertheless, these measures may be more sensitive to variations in material conditions taking place after discharge.

While elaborating this study, we encountered variability related to language labeling in the existing literature. Many studies use the term "limited English proficiency" to describe individuals lacking fluency in the dominant language of the United States[24,29]. While widely adopted, this term may unintentionally suggest that older immigrants are expected to speak a language they may never have had the opportunity to learn. Other studies have adopted the term "language discordance," emphasizing the linguistic mismatch between patients and their treating physicians[5]. In our study, we chose to explore primary language instead, recognizing that no single descriptor fully captures the complex constraints and lived experiences of individuals facing cultural and communication barriers. Moving forward, researchers and clinicians must adopt terminology that acknowledges systemic barriers and respects cultural identities.

This study has some limitations. The sample size constrained our ability to conduct granular analyses for outcomes such as adverse events and discharge disposition, where multinomial or categorical regression models offer greater nuance. Nevertheless, we believe that the binary approaches employed optimize the utility of our data.

Second, misclassification of the exposure may have occurred, as some individuals with a different primary language might still communicate effectively in English. However, this seems unlikely in our study, as most patients categorized as having a different primary language than English required active language interpretation during their index clinical episode, ultimately suggesting accurate classification. Finally, our study focused exclusively on in-hospital outcomes. We intentionally did not assess post-discharge events due to extensive loss to follow-up, opting instead to analyze endpoints with complete data to minimize selection bias. Despite these limitations, our study offers valuable insights into outcomes of patients with NASDH and lays the groundwork for larger investigations focused on communication barriers in neurosurgical care.

Conclusion

We found no evidence of differential outcomes between patients with NASDH whose primary language was not English and their English-native counterparts, despite significant differences in social deprivation. Future research should prioritize documenting translation practices to enhance understanding of communication beyond hospitals.

Authors' contributions

I. Mesina-Estarrón, K. Huang: conceptualization. I. Mesina-Estarrón: study design. I. Mesina-Estarrón, D. Limbania, and A. Gül: data acquisition. I. Mesina-Estarrón, K. Huang, and D. Limbania: data analysis. I. Mesina-Estarrón and K. Huang: writing.

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The authors declare that they have no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The authors have obtained approval from the Ethics Committee for the analysis of routinely obtained and anonymized clinical data, so informed consent was not necessary. Relevant guidelines were followed.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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CASE REPORT

Intravascular large B-cell lymphoma as a mimic of primary vasculitis of the central nervous system

Linfoma intravascular de células B grandes como simulador de vasculitis primaria del sistema nervioso central

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Abstract

Intravascular lymphoma (IVL) is a rare variant of non-Hodgkin lymphoma characterized by the proliferation of neoplastic lymphoid cells within small- and medium-caliber blood vessels.This unusual localization makes it a "great imitator", presenting with nonspecific signs and symptoms that vary depending on the affected organ. Systemic and cutaneous manifestations are not always present, and due to its aggressive, heterogeneous, and infrequent nature, diagnosis is often delayed or made post mortem. We present the case of a patient with IVL isolated to the central nervous system, who presented with multiple cerebrovascular events leading to rapidly progressive dementia, ataxia, and sensorineural hearing loss —the latter not previously reported in the literature. In patients with progressive, multifocal neurological syndromes and imaging findings suggestive of vasculitis, IVL should be considered in the differential diagnosis. Histopathological confirmation is essential for timely diagnosis and to guide appropriate treatment.

Keywords: *Intravascular lymphoma. Diffuse large B cell lymphoma. Central nervous system. Primary vasculitis of the central nervous system. Case report.*

Resumen

El linfoma intravascular (LIV) es una rara variante de linfoma no Hodgkin, caracterizada por la proliferación de células linfoides neoplásicas dentro de vasos sanguíneos de pequeño y mediano calibre. Esta localización inusual le convierte en un «gran simulador», con signos y síntomas inespecíficos que dependen del órgano afectado. Los síntomas sistémicos y cutáneos no siempre están presentes, y su presentación heterogénea, agresiva y poco frecuente dificulta el diagnóstico, que en muchos casos se realiza post mortem. Presentamos el caso de una paciente con LIV aislado del sistema nervioso central, cuyo debut clínico incluyó eventos cerebrovasculares múltiples, demencia rápidamente progresiva, ataxia e hipoacusia, esta última no reportada previamente en la literatura. Ante cuadros neurológicos multifocales progresivos con hallazgos vasculíticos, se debe considerar el LIV como diagnóstico diferencial. La confirmación histopatológica es esencial para establecer el diagnóstico oportuno y guiar el tratamiento adecuado.

Palabras clave: *Linfoma intravascular. Linfoma difuso de células B grandes. Sistema nervioso central. Vasculitis primaria del sistema nervioso central. Informe de caso.*

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Introduction

Intravascular lymphoma (IVL), also known as angiotropic lymphoma, is a rare extranodal variant of non-Hodgkin lymphoma characterized by the growth of neoplastic lymphoid cells within the lumen of small- and medium-caliber vessels.[1] The age-adjusted incidence of IVL is approximately 0.095 cases per million persons per year.[2]

Isolated involvement of the central nervous system (CNS) is extremely rare, and most cases are diagnosed only *post mortem* because of the nonspecific nature of the clinical presentation and diagnostic findings.[3]

The coexistence of general symptoms, such as fatigue and edema, as well as skin involvement, is common, especially in Western and Asian countries.[4]

In Asian patients, GI involvement is more common, as is the association with hemophagocytic syndrome.[5]

This case report was written following the CARE guideline recommendations to ensure transparency and quality in reporting.

Case report

A 66-year-old woman, previously independent and with no cardiovascular risk factors, presented in March 2022 with vertigo and gait instability after 1 year of progressive neurological symptoms that began with an acute cerebrovascular event in February 2021, characterized by left hemiparesis of undetermined etiology. Six months after the event, she continued to have difficulties with language fluency, limb and oroalimentary apraxia, worsening gait and balance, and progressive hearing loss. There was no family history of dementia or cerebrovascular disease.

On initial examination, vital signs were normal. Neurological examination showed disorientation in time and space, nonfluent language, and anomic blocks. The presence of kinetic and orolingual apraxia, alexia without agraphia, and mild flaccid dysarthria was notable. Hearing loss was clinically documented by whispered voice, Rinne, and Weber tests, and later confirmed by audiometry as sensorineural hearing loss. Muscle strength and tone were normal. Stereotypy-like movements were observed in the right hand, which the patient recognized as involuntary, and gait was ataxic, requiring bilateral support.

Initial laboratory tests showed no hematologic or hydroelectrolytic abnormalities. Renal and liver function were normal, and infectious disease and autoimmunity profiles were negative. Brain magnetic resonance imaging showed multiple subacute cortico-subcortical infarcts involving bilateral watershed territories; old lesions in different territories, predominantly in both frontal lobes and middle cerebellar peduncles; and extensive microangiopathic leukoencephalopathy (Fig. 1). Given the distribution of the infarcts and the suspicion of vasculitis, a lumbar puncture was performed, and cerebrospinal fluid analysis revealed no abnormalities. Cerebral angiography demonstrated areas of stenosis and dilatation, with irregularities of the distal branches of medium-caliber arteries, predominantly involving both anterior cerebral arteries (Fig. 2). Because primary CNS vasculitis was suspected, intravenous methylprednisolone (500 mg daily for 3 days) was initiated, and a brain biopsy was performed. Histopathology showed atypical intravascular B cells with positive CD20 and PAX5 staining and Ki-67 of 50%, compatible with intravascular diffuse large B-cell lymphoma (Fig. 3). Extension studies were performed to rule out systemic disease, including computed tomography of the chest and abdomen, whole-body positron emission tomography, and bone marrow aspiration, all of which were negative. Based on these data, the diagnosis of CNS-restricted IVL was established.

Systemic chemotherapy with the R-CHOP regimen (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone) was initiated. At the last follow-up, she had completed seven cycles and tolerated treatment well. Eighteen months after diagnosis, she remained dependent for activities of daily living, with persistent hearing loss and cognitive impairment within the dementia range. However, she had regained independent ambulation.

Discussion

IVL is defined in the World Health Organization classification of hematopoietic tumors as an extranodal diffuse large B-cell lymphoma characterized by neoplastic lymphoid cells residing within the lumen of small or intermediate vessels, particularly capillaries.[6]

It is a very rare condition, with an incidence of less than 1 case per million population. It occurs in adults, with a median age of 70 years, and no sex predominance.[2]

It can affect any organ, although it particularly involves the bone marrow, and usually does not affect lymph nodes, which clinically makes it a “great mimicker,” as it can present with a variety of nonspecific signs and symptoms due to the involvement of one or

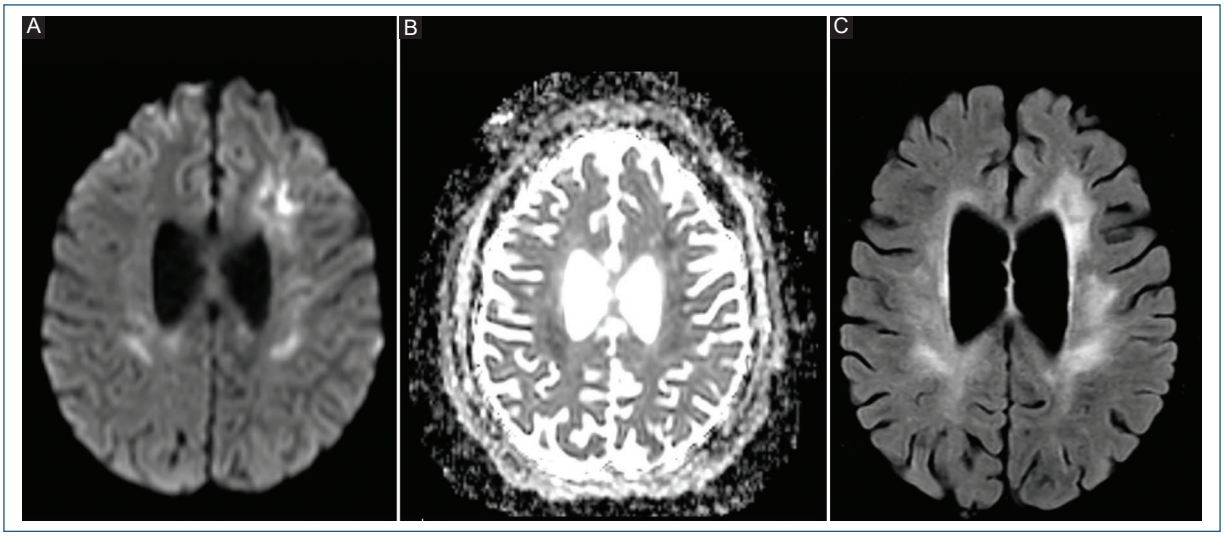

Figure 1. Brain magnetic resonance imaging showing areas of infarction in different acute and chronic stages. **A:** axial diffusion-weighted imaging (DWI) sequence showing diffusion restriction in the left frontal and right parietal regions. **B:** axial apparent diffusion coefficient (ADC) image confirming the areas of restriction. **C:** axial fluid-attenuated inversion recovery (FLAIR) sequence additionally showing old infarcts in the left frontal region.

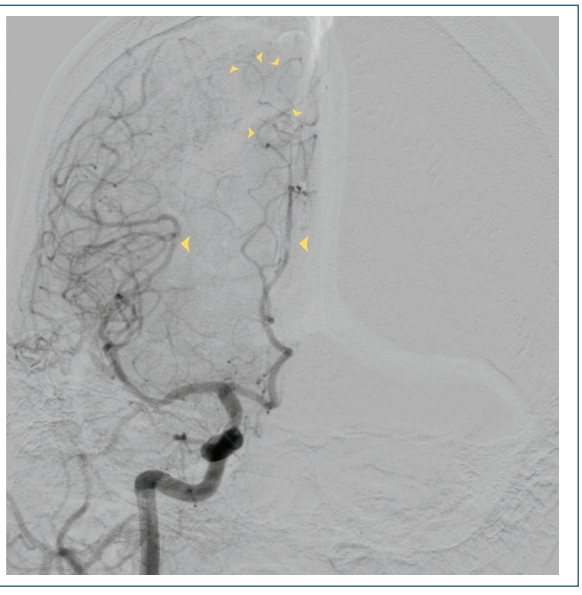

Figure 2. Cerebral angiography showing areas of diffuse arterial narrowing followed by areas of dilatation; arrows indicate the areas of narrowing.

several systems.[7] Two clinical presentations have been described. The classic form is characterized by neurological manifestations and is frequently associated with cutaneous involvement, particularly in patients from the Western hemisphere. The less frequent form is associated with hemophagocytic syndrome, particularly in Asian patients.[5]

Neurological symptoms are the most common, followed by nonspecific skin lesions, fever of unknown origin, and adrenal masses. Neurological manifestations primarily involve various ischemic symptoms. They typically have a subacute onset and a progressive course. Multiple clinical presentations have been described, including syncope,[8] behavioral changes,[9] rapidly progressive cognitive decline, seizures, recurrent stroke-like presentations, and symptoms of myelopathy or cranial neuropathies. It is not uncommon for patients to be mute and have significant impairment of consciousness at the first neurological evaluation.[10]

Although systemic symptoms are common, systemic involvement is not always present[4], as in our patient, who had no fever or cutaneous involvement and presented with rapidly progressive dementia, impaired motor and gait function, and hearing loss, without involvement of other organs. Hearing loss is, to our knowledge, a previously unreported manifestation and highlights the importance of considering IVL in the differential diagnosis of unexplained sensorineural hearing loss.

In the literature, reported cases of IVL with a variety of neurological manifestations were initially evaluated by considering alternative diagnoses.[11] In our case, secondary causes of vasculopathies were exhaustively ruled out.

The most frequent laboratory findings are anemia, elevated lactate dehydrogenase levels, and increased

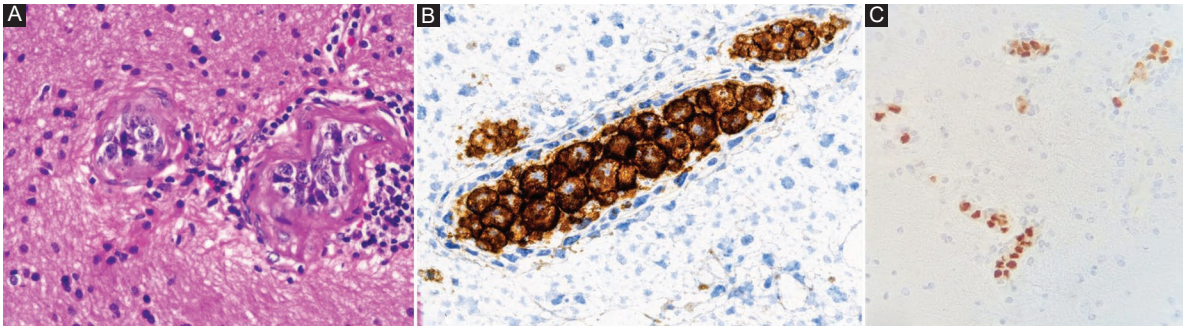

Figure 3. Brain biopsy. **A:** hematoxylin-eosin staining showing proliferation of neoplastic lymphoid cells within the lumen of blood vessels. **B:** positive CD20, indicating B-cell lineage. **C:** positive PAX5, a B-cell marker.

erythrocyte sedimentation rate. Malignant lymphoid cells are occasionally detected in peripheral blood smears, and given the tendency of B cells to remain intravascular, positron emission tomography is usually negative.[7,12]

From a radiological perspective, CNS involvement in IVL usually shows nonspecific findings on magnetic resonance imaging, such as multifocal ischemic lesions with diffusion restriction, white matter hyperintensities, meningeal enhancement, mass-like lesions, and, occasionally, hemorrhagic changes. These patterns, especially in patients with subacute neurological symptoms and systemic abnormalities, should raise suspicion of IVL.[13]

Cerebral angiography may show findings similar to those of other vasculopathies, limiting its specificity. In our patient, findings suggestive of vasculitis were reported, which may lead to misdiagnosis, such as primary angiitis of the CNS.[13]

A high index of suspicion is required to achieve an *ante mortem* diagnosis, and it is not uncommon for the diagnosis to be established *post mortem* at autopsy. The definitive *ante mortem* diagnosis of IVL can only be established by histopathological confirmation,[14] demonstrating, both morphologically and by immunohistochemistry, the confinement of large neoplastic lymphoid cells within the lumen of small blood vessels, without invasion of the surrounding tissue.[6] Most reported cases highlight the importance of performing brain biopsy in patients with white matter lesions of unknown cause or aggressive clinical presentations.[9] In this context, brain biopsy is particularly relevant, especially in cases such as that of our patient, with atypical or unexplained white matter disease, absence of vascular risk factors, young age, and confluent lesions.

Is generally aggressive, except in cases limited to the skin. The most robust data indicate overall survival rates at 1, 3, and 5 years of approximately 66, 52, and 46%, respectively, despite treatment.[2] Currently, treatment is based on the R-CHOP regimen. Other regimens, such as high-dose methotrexate (≥ 3 g/m^2 intravenously every 21 days), which constitutes the cornerstone of treatment for primary CNS lymphomas, have not shown benefit in IVL.

These patients are considered to have disseminated disease and should always be treated with systemic chemotherapy. Experience with CNS-directed therapy is limited.[3] Chemotherapeutic regimens that include rituximab have improved clinical outcomes in these patients, although the prognosis remains unsatisfactory.[15] Some studies have reported that chemotherapy treatment is associated with a significant reduction in mortality. A hazard ratio (HR) of 0.40 for death has been reported among patients receiving chemotherapy compared with those not receiving it, corresponding to an approximately 60% reduction in mortality risk.[2] In the CNS, recurrences occur in 25% of cases and may be associated with extravascular brain masses. Clinical presentation and paraclinical studies do not allow prediction of CNS relapse.[3]

Conclusions

CNS-restricted IVL is extremely rare and difficult to diagnose due to the heterogeneity of its manifestations. Angiographic findings may be indistinguishable from those of vasculitis. This case highlights the role of biopsy in patients with suspected vasculitis and atypical presentations, as it remains the only method for establishing a definitive diagnosis, thus allowing initiation of appropriate chemotherapy, which may

improve survival and neurological outcomes. Sensorineural hearing loss may represent a manifestation of this rare condition.

Authors' contributions (CRediT)

J.S. Saavedra-Moreno: conceptualization, supervision, writing-review, and editing. D.A. Jiménez-Trespalacios: research, writing of the original draft. A.C. Ibáñez-Acosta: research, collection of clinical data. V. Serna-Loaiza: literature review, writing of the original draft. L. Triviño-Charry: literature review, manuscript editing. R. López: clinical supervision, diagnostic validation. G.J. Varela-Aguirre: histopathological analysis, image visualization, validation. All authors reviewed and approved the final version of the article.

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Ethical considerations

Protection of humans and animals. The authors declare that they followed the ethical standards of the relevant experimentation committee, in accordance with the World Medical Association and the Declaration of Helsinki. The procedures were approved by the institutional Ethics Committee.

Confidentiality, informed consent, and ethical approval. The authors followed the protocols of their healthcare center/institution for access to medical record data. Informed consent was obtained from the patient, and approval was granted by the Ethics Committee. The recommendations of the SAGER guidelines were followed.

Declaration on the use of artificial intelligence. The authors declare that no type of generative artificial intelligence was used for the writing or creation of content in this manuscript.

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EVIDENCE SYNTHESIS

CB1 receptor and obesity: from the rimonabant controversy to new therapeutic perspectives

Receptor CB1 y obesidad: de la controversia del rimonabant a las nuevas perspectivas terapéuticas

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Abstract

Obesity is a chronic and multifactorial disease associated with metabolic alterations, hormonal resistance, and systemic inflammation. The endocannabinoid system regulates functions in both the central nervous system and peripheral tissues, including appetite, energy metabolism, hepatic lipogenesis, insulin and leptin sensitivity, as well as the gut-brain axis. Its dysfunction is linked to visceral obesity, insulin resistance, and neuroimmune imbalance. Among its targets, the cannabinoid receptor type 1 (CB1) stands out as a therapeutic candidate. Rimonabant, a CB1 antagonist, reduced body weight and improved cardiometabolic parameters, but was withdrawn due to neuropsychiatric side effects. This prompted the development of peripheral CB1 antagonists with limited blood-brain barrier penetration and improved safety profiles. In parallel, pharmacogenomic studies have identified variants in CNR1 and SLC6A4 that influence efficacy and adverse effects, paving the way for personalized medicine. This article reviews the role of CB1, the clinical trajectory of rimonabant, and advances in peripheral antagonists.

Keywords: *Obesity. Endocannabinoid system. CB1 receptor. Rimonabant. Pharmacotherapy. Personalized therapy.*

Resumen

La obesidad es una enfermedad crónica y multifactorial asociada con alteraciones metabólicas, resistencia hormonal e inflamación sistémica. El sistema endocannabinoide regula funciones en el sistema nervioso central y los tejidos periféricos, incluyendo el apetito, el metabolismo energético, la lipogénesis hepática, la sensibilidad a la insulina y a la leptina, así como el eje intestino-cerebro. Su disfunción se asocia con obesidad visceral, resistencia a la insulina y desequilibrio neuropsiquiátricos. Entre sus blancos, el receptor cannabinoide tipo 1 (CB1) destaca como diana terapéutica. El rimonabant, antagonista del receptor CB1, reduce el peso y mejora los parámetros cardiometabólicos, pero fue retirado por sus efectos neuropsiquiátricos. Esto impulsó el desarrollo de antagonistas periféricos del receptor CB1 con menor penetración de la barrera hematoencefálica y mayor seguridad. Paralelamente, los estudios farmacogenómicos han revelado variantes en CNR1 y SLC6A4 que influyen en la eficacia y en los efectos adversos, abriendo paso a la medicina personalizada. Este artículo revisa el papel del receptor CB1, la experiencia clínica del rimonabant y los avances en antagonistas periféricos.

Palabras clave: *Obesidad. Sistema endocannabinoide. Receptor CB1. Rimonabant. Farmacoterapia. Terapia personalizada.*

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Introduction

Obesity is a multifactorial disorder characterized by excessive accumulation of adipose tissue, resulting from an imbalance between caloric intake and energy expenditure. It is currently recognized by the World Health Organization as a chronic disease of neurobehavioral nature, associated with a persistent systemic inflammatory state that entails important metabolic, cardiovascular, endocrine, and psychological repercussions.[1]

In clinical practice, the most widely used diagnostic tool to estimate body adiposity is the body mass index (BMI), calculated by dividing weight (kg) by height squared (m^2). According to the criteria of the Centers for Disease Control and Prevention, a BMI < 18.5 kg/m^2 indicates underweight, 18.5-24.9 kg/m^2 indicates normal weight, 25.0-29.9 kg/m^2 indicates overweight, and ≥ 30 kg/m^2 corresponds to obesity. The latter is classified into three grades: class I (BMI: 30.0-34.9 kg/m^2), class II (BMI: 35.0-39.9 kg/m^2), and class III (BMI: ≥ 40 kg/m^2), or morbid obesity.[2,3] However, BMI has important limitations, as it does not distinguish between adipose tissue and muscle mass, nor does it provide information on body fat distribution. In addition, it does not consider factors such as biological sex, age, or hormonal composition, which significantly influence the storage and distribution of adipose tissue.[1] In general, women tend to accumulate subcutaneous fat in the gluteal and femoral regions (gynoid pattern), whereas men show greater visceral adiposity (android pattern), associated with a higher cardiometabolic risk.[4] These physiological differences may generate biases in BMI interpretation, since the same value may represent different body compositions in men and women.

These differences acquire a particularly relevant epidemiological dimension in Mexico, where obesity constitutes one of the main public health crises. According to the 2018 National Health and Nutrition Survey, 36.1% of the adult population had obesity, more frequently women (40.2%) than men (30.5%).[5] This condition significantly increases the risk of developing chronic noncommunicable diseases, such as type 2 diabetes mellitus, systemic arterial hypertension, and dyslipidemia, in addition to increasing the demand for health services and the costs associated with their complications.[6] Against this background, various strategies have been developed for the treatment of obesity, ranging from lifestyle changes to pharmacological interventions aimed at reducing caloric intake, inhibiting lipid absorption, or increasing energy expenditure.[7] In cases of severe obesity or obesity refractory to conservative treatments, surgical interventions, such as gastric bypass, have proven highly effective in achieving sustained weight loss and significantly improving metabolic comorbidity. In this context, cannabinoid type 1 receptor (CB1) antagonists have emerged as promising pharmacological alternatives.[8] During states of stress or caloric restriction, the activity of the endocannabinoid system (ECS) increases, favoring hyperphagia, visceral fat storage, and metabolic dysfunction.[9]

The purpose of this article is to review the role of the CB1 receptor in the regulation of energy metabolism, as well as to analyze pharmacological advances in the development of peripheral antagonists aimed at its selective modulation as a therapeutic strategy for obesity.

Role of the endocannabinoid system in appetite and metabolism regulation

The ECS consists of 3 main components: 1) endogenous ligands or endocannabinoids, mainly anandamide and 2-arachidonoylglycerol; 2) cannabinoid receptors, CB1 and CB2; and 3) the enzymes responsible for their synthesis and degradation. These compounds, derived from arachidonic acid, are bioactive lipids that act as neuromodulators and are synthesized "on demand" in response to specific physiological signals.[10] After synthesis, they diffuse through the cell membrane into the extracellular space, where they exert their effects through activation of cannabinoid receptors. Their inactivation occurs mainly through enzymatic hydrolysis: anandamide is degraded by fatty acid amide hydrolase (FAAH), and 2-arachidonoylglycerol by monoacylglycerol lipase.[11] Additionally, both endocannabinoids can be metabolized by cyclooxygenase-2, generating biologically active oxidized derivatives.[12]

CB1 is a G protein-coupled receptor and is expressed predominantly in the central nervous system (CNS), with high density in key regions for appetite and reward regulation, such as the hypothalamus, nucleus accumbens, amygdala, hippocampus, and prefrontal cortex.[13,14] Its activation modulates the hedonic response to highly palatable foods, enhancing the perception of pleasure and stimulating reward-driven eating behaviors.[15] At the peripheral level, the CB1 receptor is also found in metabolically active organs, such as the liver, adipose tissue, skeletal muscle, pancreas, and gastrointestinal tract. At these sites, it regulates functions such as lipogenesis, insulin sensitivity, digestive hormone secretion, and energy storage, thus participating in metabolic homeostasis.[16] (Fig. 1).

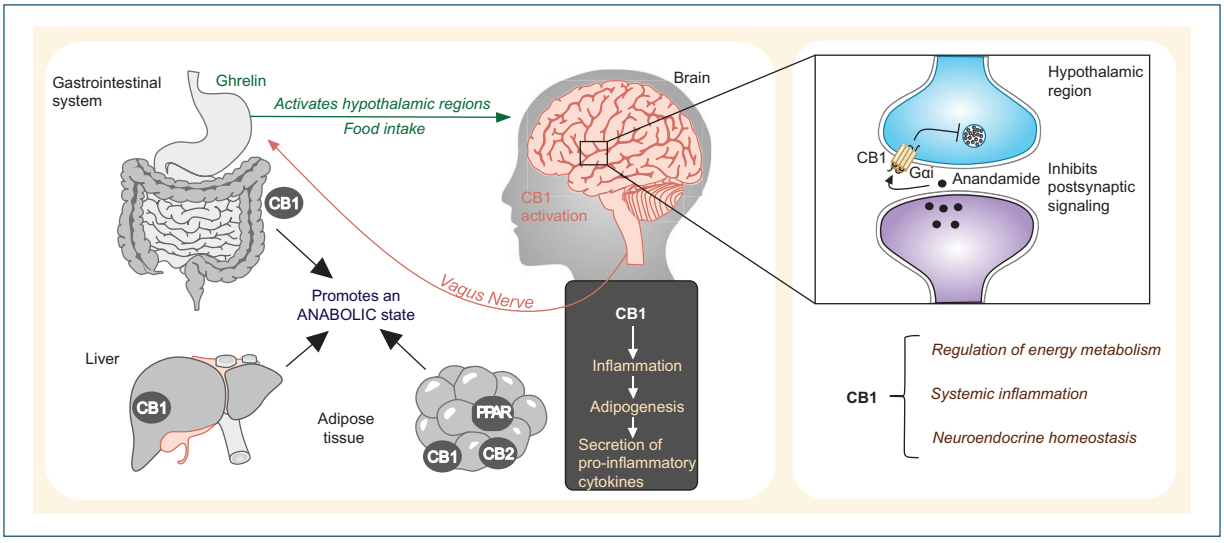


Figure 1. Modulation of appetite and metabolism by the CB1 receptor. This receptor, present in the central nervous system and in peripheral tissues, regulates energy balance by integrating neuroendocrine and metabolic signals. Ghrelin, secreted by the gastrointestinal tract, activates orexigenic hypothalamic regions, and its effect is enhanced by activation of the CB1 receptor. In the hypothalamus, endocannabinoids such as anandamide activate the CB1 receptor, inhibiting postsynaptic signaling and promoting food intake. At the peripheral level, activation of the CB1 receptor in the liver, intestine, and adipose tissue favors an anabolic state characterized by adipogenesis, inflammation, and secretion of proinflammatory cytokines. The CB2 receptor, expressed in adipocytes, also participates in the regulation of metabolism and local inflammation. Taken together, these mechanisms promote energy storage and contribute to systemic homeostasis.

Activation of the ECS, particularly of the CB1 receptor, promotes an anabolic state characterized by increased appetite, accumulation of body fat, and reduced energy expenditure. In experimental models, genetic deletion of the CB1 receptor produces hypophagia, reduction of fat mass, and increased basal metabolism, reinforcing its orexigenic role.[16,17] This effect is enhanced by CB1 receptor-induced stimulation of ghrelin synthesis and release, a hormone secreted mainly by the stomach that acts on the hypothalamus to increase food intake. Additionally, activation of the CB1 receptor modulates the hypothalamic-pituitary-adrenal axis, integrating neuroendocrine signals that favor energy storage.[18] This effect is manifested through the release of glucocorticoids, which stimulate appetite, promote lipogenesis, and decrease energy expenditure, thereby consolidating a metabolic profile oriented toward reserve accumulation (Fig. 1).

Overall, these findings show that the CB1 receptor acts as a regulator of energy metabolism, integrating peripheral and central signals that promote an anabolic state. However, its function is not limited solely to metabolic control; it also actively participates in the behavioral mechanisms that regulate food intake at the neuronal level.[14,15] In this context, eating behavior can be understood as the interaction of two functional components: the homeostatic and the hedonic, which are closely interrelated.[16]

Homeostatic and hedonic components of eating behavior

Eating behavior is regulated by 2 main systems: 1) the homeostatic system, responsible for maintaining energy balance through physiological processes, and 2) the hedonic system, which drives food consumption for pleasure or reward.[16] The ECS constitutes a bridge between both mechanisms. In the homeostatic component, the CB1 receptor is expressed in the hypothalamus and acts as a modulator of neuronal activity by producing neuropeptide Y and agouti-related protein, favoring intake when energy reserves decrease.[17] In addition, CB1 receptor activation enhances the orexigenic effects of ghrelin and reduces the anorexigenic signals mediated by leptin and insulin, contributing to the maintenance of a positive energy balance.[17,18] On the other hand, the hedonic component involves dopamine-mediated reward circuits, particularly in regions such as the nucleus accumbens, amygdala, and prefrontal cortex. In these areas, endocannabinoids promote dopamine release in response to highly palatable food stimuli, intensifying the perception of pleasure and

reinforcing food-seeking behaviors.[15,16] This mechanism explains why stimulation of the CB1 receptor can induce both eating driven by physiological need and "eating for pleasure." However, hyperactivation of the ECS, especially in the context of hypercaloric diets or chronic stress, favors dominance of the hedonic system over the homeostatic system, promoting overeating, visceral fat accumulation, and hormonal resistance.[14,15]

Furthermore, the actions of the ECS on eating behavior and emotional state depend on its communication with other neurotransmission systems that modulate reward and motivation; among these, in addition to mesolimbic dopaminergic circuits, serotonergic systems stand out, whose interaction with the ECS amplifies its influence on appetite and mood regulation.[19,20]

In general terms, the ECS acts as a dynamic regulator of the balance between the homeostatic and hedonic impulses of eating, integrating metabolic, hormonal, and emotional signals that determine eating behavior and, ultimately, the body's energy and emotional state.

Interaction of the endocannabinoid system with dopaminergic and serotonergic circuits

The influence of the ECS on eating and emotional behavior depends on its functional communication with other neurotransmission systems, including mesolimbic dopaminergic circuits and serotonergic systems. In the ventral tegmental area, activation of the CB1 receptor in GABAergic interneurons produces disinhibition of dopaminergic neurons, increasing dopamine release toward the nucleus accumbens and the prefrontal cortex.[13,14] This mechanism enhances the sensation of pleasure and reinforces reward-motivated behaviors, such as the intake of highly palatable foods.[14]

In addition, the ECS regulates serotonergic tone through the interaction between CB1 receptors and 5-HT1A/5-HT2C receptors in regions such as the hypothalamus and hippocampus. This bidirectional relationship influences both appetite modulation and mood, integrating metabolic and emotional functions.[19,20] Central inhibition of the CB1 receptor, as occurs with the antagonist rimonabant, alters serotonin release and reduces mesolimbic dopaminergic signaling, contributing to the development of depressive and anxious symptoms observed in treated patients.[19,20] Taken together, these interactions confirm that the ECS acts as an integrative modulator between the homeostatic pathways of appetite and the hedonic and emotional circuits of the brain, consolidating its role as an essential neurometabolic axis in the physiology of eating behavior and in the effects derived from its pharmacological modulation, including those observed with CB1 receptor antagonists.

Although the CB2 receptor is located mainly in immune system cells, some studies have reported its expression in the CNS. Its role is more closely associated with modulation of inflammation and immunometabolic homeostasis, which is relevant in conditions such as chronic obesity and metabolic syndrome. Its expression has also been identified in adipocytes, where it participates in processes such as adipogenesis, lipid metabolism, and secretion of pro- and anti-inflammatory cytokines. These functions suggest an active role of the CB2 receptor in adipose tissue remodeling and in the regulation of local inflammation, thereby contributing to energy balance and overall metabolic status.[21,22]

Interestingly, in addition to their action on the canonical CB1 and CB2 receptors, endocannabinoids can also interact with other nonconventional molecular targets, thereby expanding the diversity of their physiological effects.[23] For example, anandamide can activate the TRPV1 ion channel, the transient receptor potential vanilloid type 1 receptor, which is involved in nociception and thermal signaling. This may generate responses opposite to those induced by CB1 receptor activation, such as stimulation of excitatory or inflammatory pathways. Similarly, at high concentrations, anandamide can act as an agonist of peroxisome proliferator-activated receptor gamma, modulating gene transcription and participating in the regulation of inflammatory and metabolic processes.[24,25]

In addition to classic endocannabinoids, there are related compounds, such as N-oleoylethanolamide and N-palmitoylethanolamide, which do not activate CB1/CB2 receptors but exert their effects through receptors such as PPAR alpha and TRPV1, with relevant functions in the regulation of appetite, lipid metabolism, and inflammation. Another example is 2-oleoylglycerol, an agonist of the orphan receptor GPR119, whose activation in the intestine stimulates the release of glucagon-like peptide 1, a key incretin in the promotion of satiety and blood glucose control.[26] Although these noncanonical receptors show less direct signaling than CB1 and CB2 receptors, their participation in metabolic and neuroendocrine pathways suggests a complementary, yet significant, role in energy homeostasis.

This landscape has led to the proposal of an expanded view of the ECS, known as the endocannabinoidome, which includes not only classic endocannabinoids, their

receptors, and enzymes, but also a broader network of related lipids, additional receptors, and convergent signaling pathways.[27] The promiscuity of its ligands, enzymatic redundancy, and interaction with other physiological control systems make the ECS a complex and highly versatile system. This complexity represents both a challenge and an opportunity for the development of new therapeutic strategies targeting metabolic disorders such as obesity, type 2 diabetes mellitus, and metabolic syndrome.[28]

Finally, although recreational cannabis use, particularly of compounds with activity on the CB1 receptor, such as Δ9-tetrahydrocannabinol (THC), has traditionally been associated with a transient increase in appetite, a phenomenon known as "munchies," several epidemiological studies have reported a lower prevalence of obesity and a lower BMI in regular users compared with the general population. This apparent paradox has generated interest in the scientific community, as it contrasts with the acute orexigenic profile of cannabis. One possible explanation lies in physiological adaptation to chronic cannabinoid use, which could induce desensitization or downregulation of the CB1 receptor, especially in peripheral tissues related to energy metabolism. In addition, sustained cannabis use has been proposed to activate compensatory mechanisms, such as increased basal energy expenditure, activation of thermogenic pathways, possibly mediated by brown adipose tissue, or changes in the gut microbiota profile. However, these mechanisms remain a matter of debate, and the influence of sociodemographic, genetic, or lifestyle factors that could bias the results observed in population studies cannot be ruled out.[29]

The CB1 receptor as a neurometabolic integrator: implications for the gut-brain axis, hormonal resistance, and thermogenesis

In addition to its role in appetite control and eating behavior, the CB1 receptor exerts functions in the regulation of multiple physiological axes involved in energy metabolism, systemic inflammation, and neuroendocrine homeostasis. Its expression both in the CNS and in peripheral tissues, including components of the gut-brain axis, positions it as a relevant neurometabolic integrator in the pathophysiology of obesity.[30]

In this context, the ECS, through the CB1 receptor and its endogenous ligands, modulates processes within the gut-brain axis. These include vagal afferent signaling, enteric neuron function, and secretion of GI peptides such as peptide YY, glucagon-like peptide 1, and cholecystokinin.[31] In addition, the ECS plays a key role in the regulation of the intestinal barrier, the local immune response, and microbiota composition. The CB1 receptor, present in the intestinal epithelium, and CB2, expressed in mucosal immune cells, modulate tight junction integrity, cytokine secretion, and immune cell differentiation.[32] In turn, by influencing motility, inflammation, and secretion of antimicrobial factors, the ECS indirectly impacts the balance of the gut microbiota.[33] Experimental evidence indicates that a high-fat diet alters endogenous endocannabinoid production, promoting chronic activation of the CB1 receptor, which is associated with increased intestinal permeability, metabolic endotoxemia, and hypothalamic inflammation.[34] In contrast, pharmacological inhibition of the CB1 receptor favors restoration of intestinal barrier integrity, reduction of neuroinflammation, and greater sensitivity to satiety signals.[35]

Furthermore, the CB1 receptor modulates the regulation of leptin and insulin sensitivity. In obesity, activation of the CB1 receptor in the hypothalamus interferes with leptin signaling through overexpression of SOCS3, suppressor of cytokine signaling 3, an intracellular inhibitor of the JAK/STAT pathway, Janus kinase/signal transducer and activator of transcription, and promotes central leptin resistance. At the peripheral level, the CB1 receptor inhibits insulin receptor phosphorylation and decreases translocation of glucose transporter type 4 to the cell membrane in tissues such as skeletal muscle and adipocytes.[36,37] These effects translate into hyperglycemia, hyperinsulinemia, and ectopic lipid accumulation. Pharmacological inhibition of the CB1 receptor has been shown to restore insulin signaling in the liver and muscle, improving glucose tolerance and promoting fatty acid oxidation.[38]

An additional relevant aspect in the pathophysiology of obesity is modulation of brown adipose tissue by the CB1 receptor. Its activation has been shown to negatively regulate thermogenic activity by decreasing the expression of key genes such as *UCP1*, *PGC-1α*, and *PRDM16*, which limits the body's capacity to dissipate energy as heat.[39,40] In contrast, CB1 receptor antagonism reverses this effect, promoting activation of brown adipose tissue and browning, beige transdifferentiation, of white adipose tissue, that is, its conversion toward a more thermogenic phenotype. These actions translate into a sustained increase in basal energy expenditure and constitute a promising complementary therapeutic strategy in the management of obesity, since they not

only contribute to reduced caloric intake but also favor lipid oxidation and energy dissipation as heat.[41]

These data suggest that the CB1 receptor acts as a systemic modulator of several metabolic and neuroendocrine processes. Moreover, pharmacological intervention on the CB1 receptor, in addition to being able to regulate appetite, could also improve intestinal homeostasis, restore hormonal sensitivity, and activate thermogenic mechanisms, reinforcing its potential as a therapeutic target in the treatment of obesity and its comorbidity.

Rimonabant: rise, fall, and controversies

The development of rimonabant marked a milestone in ECS pharmacology. In the 1980s, structural modification of THC began with the aim of obtaining a selective CB1 receptor antagonist.[40] In 1994, Rinaldi-Carmona et al.[42] synthesized rimonabant, SR141716A, the first CB1 receptor antagonist/inverse agonist, later marketed as Acomplia®.[42,43] In 2006, the European Medicines Agency approved its use as an adjuvant in the treatment of overweight and obesity, especially in patients with metabolic comorbidity such as dyslipidemia, type 2 diabetes mellitus, and cardiovascular diseases.[44]

From a molecular standpoint, rimonabant acts as an inverse agonist of the CB1 receptor, which is a Gi/o protein-coupled receptor. Its activation inhibits the enzyme adenylate cyclase, reducing intracellular levels of cyclic adenosine monophosphate (cAMP) and, consequently, activation of protein kinase A (PKA) and other intracellular pathways related to energy metabolism and lipolysis. By acting as an inverse agonist, rimonabant not only blocks this signaling but also reverses its constitutive basal activity; that is, it inhibits spontaneous activation of the CB1 receptor in the absence of ligand, further decreasing intracellular signaling mediated by cAMP and PKA.[45] In animal models of obesity, chronic administration of 10 mg/kg for 40 days reduced body fat mass by 50% and restored white adipocyte morphology. These effects were associated with increased lipolysis, expression of β-oxidative enzymes, and a sustained increase in basal energy expenditure.[46]

The clinical efficacy profile of rimonabant was evaluated in several double-blind clinical trials, with the RIO studies, Rimonabant In Obesity, being the most relevant. In one of these studies, conducted in more than 6,700 patients with BMI > 27 kg/m^2, 48.6% of those treated with 20 mg/day achieved weight loss ≥ 5%, compared with 20.0% of the placebo group. For losses ≥ 10%, the figures were 25.2 and 8.5%, respectively. In the second year of follow-up, mean weight loss was 7.5 kg in the treated group vs 2.5 kg in the placebo group. These results positioned rimonabant as a promising agent in the treatment of obesity and its metabolic complications.[47]

Initially, the potential of rimonabant in the management of smoking and alcohol addiction was also explored, owing to its ability to modulate dopamine-mediated reward circuits in the mesolimbic system.[48] However, the anorexigenic effects observed in early clinical trials directed its use toward body weight control. Nevertheless, as its use increased, significant psychiatric adverse effects began to be reported frequently, including anxiety, depression, insomnia, fatigue, and even suicidal ideation. A meta-analysis of the RIO studies revealed that 26% of patients treated with 20 mg/day experienced neuropsychiatric symptoms, compared with 14% in the placebo group, and that treated patients were 2.5-3 times more likely to discontinue therapy because of these effects.[49]

It has been proposed that these events are related to the high lipophilicity of rimonabant, which allows it to cross the blood-brain barrier (BBB) and block CB1 receptors in brain regions involved in mood, such as the amygdala, hippocampus, and prefrontal cortex. The BBB is a highly selective structure that regulates the transport of molecules from the blood into the CNS, maintaining cerebral homeostasis. In particular, lipophilic substances can cross it through the transcellular route by dissolving in the lipid bilayer of endothelial membranes.[19,50] Because of this property, rimonabant can exert undesirable central effects, which would partly explain the appearance of neuropsychiatric symptoms. Subsequent genetic studies suggested that certain polymorphisms in the CB1 receptor gene (CNR1) and the serotonin transporter gene (SLC6A4) could predispose some individuals to anxiety- or depression-type adverse responses. Although the number of completed suicides was low, suicidal ideation was reported in 39 patients treated with 20 mg, in 6 treated with 5 mg, and in 13 in the placebo group, which generated growing concern about its safety profile.[51,52]

In 2009, and following a comprehensive review of its risk-benefit profile, the European Medicines Agency decided to withdraw rimonabant from the European market because of increasing evidence of severe psychiatric adverse effects. For its part, the US Food and Drug Administration never approved its marketing, considering that the possible mental health risks outweighed the

therapeutic benefits observed in body weight control and metabolic comorbidity.[53] This experience marked a turning point in ECS research, underscoring the need to develop CB1 receptor antagonists with selective peripheral action, capable of preserving metabolic benefits without affecting the CNS. Currently, several compounds, such as TM38837 and JD5037, are being evaluated using this approach and offer new perspectives for the safe treatment of obesity and its comorbidity.[54]

Challenges of new chemical structures targeting the CB1 receptor and their therapeutic potential

Clinical experience with rimonabant redirected development toward peripheral CB1 receptor antagonists, with tissue selectivity and emphasis on neurobehavioral safety. After rimonabant was withdrawn from the market in 2009 because of severe neuropsychiatric adverse effects, clinical trials of other first-generation CB1 receptor antagonists, such as surinabant, taranabant, otenabant, and ibipinabant, were also suspended. In light of the neuropsychiatric events observed with these first-generation compounds, the current strategy prioritizes the development of peripheral antagonists with lower lipophilicity and greater polar surface area in order to limit their penetration through the BBB and preserve metabolic benefits with a better neurobehavioral safety profile.[55] Additionally, these drugs show greater polarity, higher molecular weight, and lower lipophilicity, which restricts their ability to cross the BBB. A physicochemical parameter, polar surface area, has been used as a criterion to estimate restriction to the extracerebral space, as it correlates inversely with CNS permeability.[56]

In this context, CB1 receptor antagonists have been classified into 3 generations based on their chemical structure, pharmacokinetic profile, and stage of clinical development.[56] (Table 1):

- 1st generation: compounds with high lipophilicity, central action, and a high incidence rate of neuropsychiatric effects. Examples: rimonabant, taranabant, and otenabant.
- 2nd generation: peripheral antagonists designed to avoid penetration through the BBB and minimize central adverse effects. Examples: AM6545 and JD5037.
- 3rd generation: new experimental derivatives with optimized profiles for the treatment of specific metabolic disorders, such as obesity, liver fibrosis, and chronic kidney disease. Examples: PMG-505-010, PMG-505-013, and zevaquenabant.

As shown in table 1, only 1st-generation antagonists can cross the BBB, which is associated with their central effect and adverse profile. In contrast, 2nd- and 3rd-generation antagonists have been designed to act selectively in peripheral tissues such as the liver, adipose tissue, pancreas, and skeletal muscle, without compromising the patient's neurobehavioral stability.

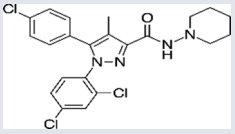
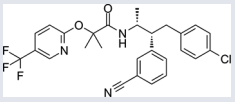
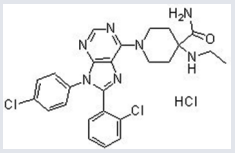
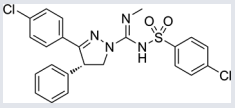
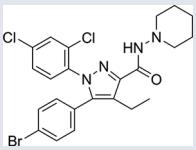
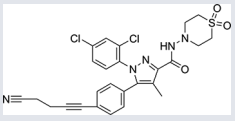
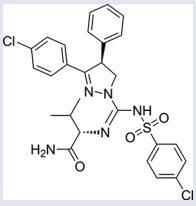
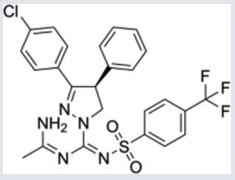
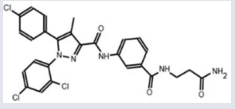
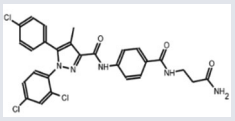
In addition, structural derivatives of rimonabant have been developed with specific changes aimed at reducing its central action. For example, Yang et al.[57] designed the compounds PMG-505-010 and PMG-505-013 by introducing an amide function to increase their polarity and reduce lipophilicity.[57] In a murine model of obesity, oral administration for 4 weeks increased cAMP levels, improved glucose tolerance, corrected the lipid profile, and reduced the expression of proinflammatory cytokines, without causing neurobehavioral alterations. These derivatives have also shown hepatic antifibrotic effects by reducing the expression of genes such as *TGF-β1, αSMA,* and *COL-1α1*, positioning them as therapeutic candidates in both obesity and liver fibrosis.[57]

Similarly, new agents, such as zevaquenabant, have been designed with dual pharmacological activity: CB1 receptor antagonism and modulation of inducible nitric oxide synthase, with potential applications in metabolic diseases such as chronic nephropathy associated with obesity.[58] These structural strategies reflect the transition from centrally acting antagonists toward more selective, specific, and safer compounds.

Nevertheless, despite advances in the chemistry of these new generations, many formulations continue to fail in advanced clinical phases. This limitation has driven interest in incorporating pharmacogenomic tools into the design of therapies targeting the ECS. Variants in genes such as CNR1, which encodes the CB1 receptor, and FAAH, which degrades anandamide, have been shown to modify the response to treatment. For example, the rs1049353 (G1359A) polymorphism in CNR1 has been associated with alterations in receptor density and functionality, as well as with obesogenic phenotypes. It has also been observed that the rs324420 polymorphism in FAAH can alter basal endocannabinoid levels, conditioning the efficacy of, or tolerance to, its antagonism.[58,59]

Pharmacogenomic studies, such as that by Lazary et al.,[60] have documented that the presence of the 5-HTTLPR polymorphism in the serotonin transporter gene (*SLC6A4*) is associated with a higher incidence of neuropsychiatric effects in patients treated with rimonabant. These findings, together with the variants

Table 1. Classification of CB1 receptor antagonists according to generation, structure, clinical stage, and ability to cross the blood-brain barrier

Generation	Generic name (compound)	Structure	Clinical stage	BBB permeability	Therapeutic indication
1st	Rimonabant (SR141716A)		Phase IV (withdrawn)	Yes	Obesity, dyslipidemia, type 2 diabetes mellitus
	Taranabant (MK-0364)		Phases II and III (discontinued)	Yes	Obesity
	Otenabant (CP-945598)		Phase III (discontinued)	Yes	Obesity
	Ibipinabant (BMS-646256)		Phase II (discontinued)	Yes	Obesity
	Surinabant (SR14778)		Phase II (discontinued)	Yes	Obesity, addictions
2nd	AM6545		Preclinical research only	No	Obesity (selective peripheral use)
	JD5037		Preclinical research only	No	Obesity, hepatic steatosis
3rd	Zevaquenabant (MRI-1867)		Preclinical research only	No	Fibroinflammatory disease, obesity-induced chronic kidney disease
	PMG-505-010		Preclinical research only	No	Obesity, liver fibrosis
	PMG-505-013		Preclinical research only	No	Obesity, liver fibrosis

described in *CNR1* and *FAAH*, support the usefulness of identifying genetic profiles that allow patient stratification and prediction of individual sensitivity to adverse effects of CB1 receptor antagonists, guiding the development of precision therapies and personalized medicine.

The recognition of these genetic biomarkers opens the possibility of developing patient stratification strategies.[20,60] These could be used to identify individuals at high risk of developing depression or anxiety induced by CB1 receptor antagonists, predict therapeutic efficacy according to the receptor's genetic profile, and select the type of compound, central or peripheral, most appropriate for each patient. Although these personalized medicine strategies are not yet part of routine clinical practice, they represent a research line with great potential to optimize the benefit-risk ratio in therapies targeting the ECS. Their validation through multicenter and integrative clinical studies combining genetic, clinical, neurobehavioral, and metabolic data will be key for the design of more effective and safer treatments against obesity and its comorbidity.

Conclusions

The CB1 receptor represents a relevant therapeutic target in the approach to obesity, given its central role in appetite regulation and energy homeostasis. Although rimonabant marked a milestone in ECS pharmacology, its withdrawal highlighted the need to develop molecules with a better safety profile. The new peripheral CB1 receptor antagonists, by not penetrating the CNS, offer a promising alternative for the treatment of metabolic disorders. The integration of pharmacogenomic strategies could optimize the individualized therapeutic response, minimizing risks and maximizing benefits. Further preclinical research and clinical trials are required to consolidate the safety and efficacy of these new-generation drugs.

Authors' contributions

J. Díaz-Luis: research, writing of the original draft, and conceptualization. F. Patricio: validation, conceptualization, writing of the original draft, review and editing, visualization, and research. J. Camargo-Meneses: research and writing of the original draft. A. Patricio-Martínez: writing of the original draft, visualization, research, validation, and supervision. D. Limón: funding acquisition, research, writing of the original draft, visualization, supervision, conceptualization, validation, review, and editing.

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Conflicts of interest

The authors declared no conflicts of interest whatsoever.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The study does not involve personal data, medical records, or human biological samples and therefore does not require ethical approval. The SAGER guidelines do not apply.

Declaration on the use of artificial intelligence. The authors declare that no type of generative artificial intelligence was used for the writing or creation of content in this manuscript.

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EVIDENCE SYNTHESIS

Late life depression as a disconnection syndrome: a RAMESES realist synthesis of neurocognitive and neurofunctional correlates

Depresión en la vejez como un síndrome de desconexión: una síntesis realista RAMESES de correlatos neurocognitivos y neurofuncionales

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Abstract

Background: *Late-life depression (LLD) is a prevalent syndrome in older adults, characterized by neuropsychiatric symptoms and multidomain cognitive impairments.* **Objective:** *To examine how contexts and mechanisms interact to generate cognitive outcomes in LLD, and how these patterns support its conceptualization as a disconnection syndrome.* **Method:** *Following the RAMESES publication standards, we performed iterative searches in PubMed for articles published between January 2013 and January 2024. Inclusion was based on relevance (contribution to theory-building or testing) and rigour (credibility of the data). Forty-eight studies were retained.* **Results:** *Findings consistently showed impairments in global cognition, executive functions, processing speed, and memory. These deficits emerged through distinct context-mechanism-outcome (C-M-O) configurations. For example, in older adults with late-onset depression and vascular comorbidity (C), white matter hyperintensities (M) disrupted fronto-subcortical connectivity, leading to executive dysfunction and cognitive slowing (O). In cases of persistent depression (C), hypothalamic-pituitary-adrenal-axis hyperactivation and inflammation (M) produced memory decline and increased dementia risk (O). Importantly, neurofunctional disruptions also played a key role: in women with moderate-severe depression (C), hyper-synchronization of the default mode network (M) impaired sustained attention and cognitive flexibility (O); while in patients with limited SSRI response (C), inefficiency of the cognitive control network (M) explained persistent deficits in planning and judgment (O).* **Conclusion:** *These C-M-O patterns demonstrate that LLD involves interconnected neuroanatomical and neurofunctional mechanisms. Recognizing LLD as a disconnection syndrome has significant implications for tailoring pharmacological and psychotherapeutic interventions and for preventive strategies aimed at strengthening cognitive reserve in late life.*

Keywords: *Late-life depression. Cognitive impairment. Aging. Connectivity. Brain networks.*

Resumen

Antecedentes: *La depresión en la vejez es un síndrome prevalente en adultos mayores, caracterizado por síntomas neuropsiquiátricos y alteraciones cognitivas.* **Objetivo:** *Examinar cómo interactúan los contextos y los mecanismos para generar resultados cognitivos en la depresión en la vejez, y cómo estos patrones respaldan su conceptualización como un síndrome de desconexión.*

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Método: *Siguiendo los estándares de publicación RAMESES se realizaron búsquedas iterativas en PubMed de artículos publicados entre enero de 2013 y enero de 2024. La inclusión se basó en criterios de relevancia (aporte a la teoría) y rigor (credibilidad de los datos). Se incluyeron 48 estudios.* **Resultados:** *Los hallazgos mostraron alteraciones en cognición global, funciones ejecutivas, velocidad de procesamiento y memoria. Estas disfunciones emergieron de configuraciones contexto-mecanismo-resultado (C-M-O). En adultos con depresión de inicio tardío y comorbilidad vascular (C), las hiperintensidades de la sustancia blanca (M) interrumpieron la conectividad frontosubcortical, generando disfunción ejecutiva (O). En la depresión persistente (C), la hiperactivación del eje hipotalámico-hipofisario-adrenal (M) derivó en declive de la memoria y mayor riesgo de demencia (O). Las alteraciones neurofuncionales también fueron relevantes: en las mujeres con depresión moderada-grave (C), la hipersincronización de la red por defecto (M) afectó la atención (O), mientras que en pacientes con respuesta limitada a los inhibidores selectivos de la recaptación de serotonina (C) la ineficiencia de la red de control cognitivo (M) explicó los déficits en planificación (O).* **Conclusiones:** *Estos patrones demuestran que la depresión en la vejez implica mecanismos neuroanatómicos y neurofuncionales interconectados. Reconocerla como un síndrome de desconexión tiene implicaciones clínicas para intervenciones adaptadas y estrategias preventivas que fortalezcan la reserva cognitiva.*

Palabras clave: *Depresión en la vejez. Deterioro cognitivo. Envejecimiento. Conectividad. Redes cerebrales.*

Introduction

Mood disorders are among the most prevalent forms of mental illness[1]. Depression affects more than 280 million people worldwide[2]. This condition can lead to numerous impairments, some of which are mood fluctuations, extreme feelings of sadness, weight gain, anhedonia, psychomotor retardation, sleep disorders, and cognitive deficits,[3,4] and can result in suicide[2].

The diagnosis of depressive disorders is typically conducted by clinicians following standardized diagnostic criteria, such as those outlined in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision. This manual distinguishes major depressive disorder (MDD) and persistent depressive disorder (previously Dysthymia), which differ mainly in the duration, intensity, and functional impact of symptoms[3].

Although the symptoms of depression have been well characterized in adulthood, aging introduces distinct clinical features such as depressed mood, fatigue, apathy, somatic complaints, and motivational decline, along with a higher prevalence of cognitive and psychomotor disturbances[5]. Despite increasing evidence, the neurocognitive mechanisms underlying these impairments in late-life depression (LLD) remain only partially understood[6-8]. Understanding this interaction is clinically relevant because most depressive symptoms are modifiable through pharmacological and therapeutic interventions, suggesting that their contribution to neuropathological progression could potentially be mitigated[9,10].

Recent advances in neuroimaging and cognitive neuroscience have highlighted that LLD involves disruptions in large-scale brain networks rather than isolated regional deficits. However, the specific mechanisms linking these neurofunctional alterations to cognitive impairment (CI) remain poorly understood.

Therefore, this study aimed to synthesize recent evidence (2013-2024) on the neurocognitive and neurofunctional correlates of LLD using the realist and meta-narrative evidence synthesis (RAMESES) framework. This approach allows identifying context-mechanism-outcome (C-M-O) configurations that explain how biological, clinical, and demographic contexts interact with neural mechanisms to produce cognitive outcomes. Through this synthesis, we sought to clarify the extent to which LLD can be conceptualized as a disconnection syndrome and to discuss its implications for prevention and treatment in aging by integrating findings from neuroimaging, neuropsychology, and neuroendocrinology studies.

Review method

This review was conducted following the Realist and Meta-narrative Evidence Syntheses: Evolving Standards (RAMESES publication standards), which belong to the EQUATOR Network guidelines for transparent health research reporting. The realist synthesis approach was selected because it allows exploring how and why specific contexts (C) and mechanisms (M) generate cognitive outcomes (O) in LLD.

The article selection process comprised four iterative stages, identification, screening, selection, and inclusion, summarized in figure 1.

During the identification stage, iterative searches were performed in the electronic database PubMed, using the combination of keywords “Depression” AND “cognition”

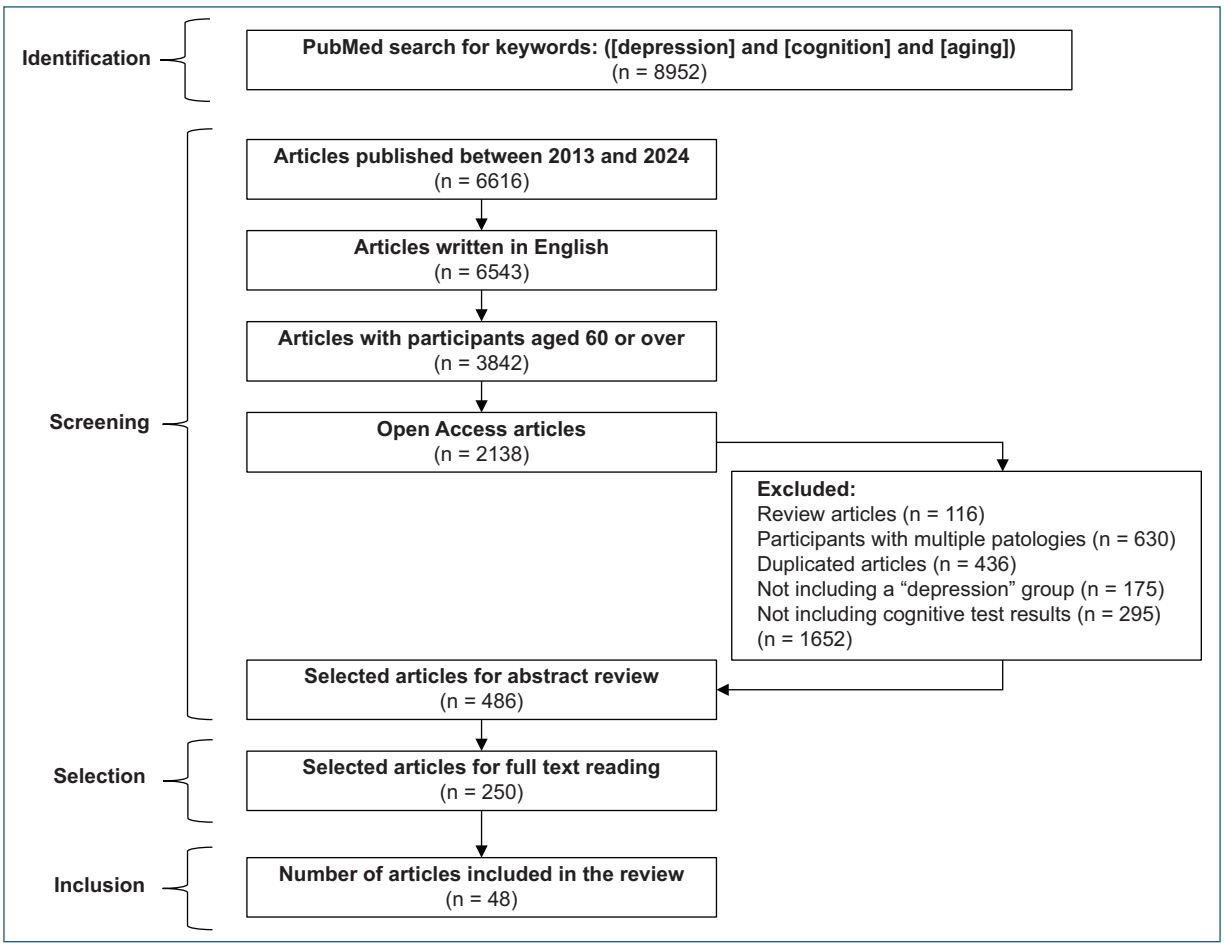

Figure 1. Step-by-step flow diagram of the article search and selection process.

AND "aging." Filters were applied for publication date (January 2013-January 2024) and English-language peer-reviewed articles. The last search was completed on March 10, 2024. In addition, reference lists of included studies were hand-searched to identify potentially relevant papers missed in the database search.

In the screening stage, we excluded articles that did not meet basic eligibility criteria (e.g., unpublished manuscripts, editorials, letters, and book chapters). Two reviewers independently assessed the abstracts according to the principles of relevance (the extent to which the study contributes to theory-building or testing) and rigor (credibility and transparency of the methods used for the data). Discrepancies were resolved through discussion until consensus was reached.

During the selection stage, full texts of eligible studies were retrieved and reviewed in detail. In the inclusion stage, 48 studies met the criteria and were retained for synthesis. For each study, data extraction focused on identifying contexts (C), mechanisms (M), and outcomes (O) relevant to cognitive function in LLD. Using realist logic of analysis, we searched for demi-regularities across studies (recurrent cross-study patterns), compared alternative explanations, and progressively refined the emerging theory conceptualizing LLD as a disconnection syndrome.

Results

The synthesis identified 48 studies exploring cognitive and neurofunctional aspects of LLD. The findings are organized according to the main cognitive domains affected and their associated neurobiological mechanisms, following the C-M-O framework proposed by RAMESES.

Late-life depression and CI

LLD is defined as an episode of MDD occurring for the 1st time in a person older than 60 years, although

the age ranges from 50 to 65 years[11,12]. LLD's estimated prevalence ranges between 4 and 9%[13]. People with LLD are up to 22% more likely to present CI compared to older adults without depression[14]. LLD has been described as a syndrome characterized by neuropsychiatric symptoms and multidomain CI[15-17]. Recently, due to its neurofunctional abnormalities, LLD has come to be known as a "brain disconnection syndrome"[18].

People with late-onset depression (LOD) have more severe cognitive deficits than those with early-onset depression (EOD) where the symptoms are present before the age of 60; in particular, people with EOD report more mood dysregulation symptoms (anxiety, sadness, or anhedonia), in contrast, people with LOD report a combination of mood dysregulation symptoms and cognitive alterations, these results lead to hypothesize that LOD could indicate the presence of a mild neuropathological disorder that contributes to both cognitive deterioration and mood dysregulation[14]. From a neurofunctional perspective, these differences are consistent with evidence of fronto-subcortical disconnection and reduced efficiency in large-scale executive control networks (ECNs), as previously described in neuroimaging research on LLD.

Depressive symptoms are frequent in people with diseases that have a subcortical etiology, such as vascular dementia, Parkinson's disease, Huntington's disease, supranuclear palsy, among others[19]. This interaction between symptoms of depression and cognitive pathology presents a high percentage of comorbidity that ranges between 20 and 50% of adults over 65 years of age. Similarly, 60% of older adults with MDD present CI even in the absence of dementia pathology[20,21]. These comorbidities share common neurobiological mechanisms, including dopaminergic dysregulation, inflammatory processes, and disruption of cortico-subcortical pathways, that may explain the overlap between depressive and cognitive symptoms in late life.

Multiple cognitive domains have been assessed in the search for alterations associated with depression; among them are executive functions, memory, attention, and perception processes[5,21,22]. These alterations have been frequently correlated to the severity of the depressive symptoms, where older adults with high depressive symptomatology perform worse in verbal learning tasks, verbal recovery, visuospatial tasks, verbal fluency, visual memory, and orientation, in contrast to those who do not have depression[23]. Neuroimaging findings suggest that this multidomain impairment reflects reduced efficiency of brain networks involved in cognitive control and self-referential processing, a mechanism also discussed later in this synthesis.

Regarding the temporal course of depression, defined as the history of depressive episodes and their chronicity, it has been found that global CI are more prevalent in older adults with persistent depression in contrast to those without depression[24], and said CI depend on significant fluctuations in depressive symptomatology[25] and not necessarily on the number of depressive episodes[12]. This pattern may reflect sustained biological alterations, such as chronic hyperactivation of stress-related neuroendocrine systems and inflammatory signaling, that interfere with neural plasticity and cognitive flexibility.

Similarly, when longitudinally evaluating the relationship between symptoms of depression and cognition, it was observed that the most severe symptoms of depression occurred in participants with severe CI, however, this relationship becomes statistically weaker in successive evaluations, where participants expressed less symptoms; this could be explained by the inability of the person to identify the presence of depressive symptoms due to the severity of the CI[26]. Such attenuation may also reflect progressive neural disconnection, in which damage to fronto-parietal and limbic circuits reduces awareness of emotional and cognitive changes.

In aging, subjective CI is frequent and is characterized by the self-perception that one's own cognitive processes are in significant decline compared to a previous state[27]. The subjective memory complaints (SMC) are the most reported and have been associated with the presence of depressive symptoms and not with performance in objective cognitive assessments[27,28]. Therefore, in depression, there is the possibility of perceiving that self-cognition is worsening and consequently affecting mood and motivation to do daily activities. At the neurofunctional level, this phenomenon has been linked to increased synchronization within the default mode network (DMN), promoting self-referential rumination and negative cognitive bias.

Regarding daily activities, physical and leisure activities are considered cognitively stimulating activities; the latter act as mediators between depressive symptomatology and global cognition, including cognitive domains such as memory, language, processing speed, and executive functioning[8]. A reduced participation in cognitively stimulating activities increases the risk of cognitive decline in older adults with LLD, becoming a negative cycle where depression affects the ability to participate in stimulating activities and therefore ends up affecting cognition[8]. This reduced engagement also limits activation of compensatory neural pathways, weakening cognitive reserve and reinforcing the disconnection processes underlying cognitive decline in LLD.

Cognitive dysfunctions in LLD

The impact of depressive symptoms on cognitive processes is diverse; there is multiple evidence of alterations in most of the cognitive domains, where the most studied ones are: global cognition, executive functions, processing speed, and memory. These disruptions are dependent on differential factors such as symptom severity, temporal course of depression, and other sociodemographic characteristics, although some research has shown independent effects of each of these variables[23]; there are differences worth describing, for instance, participants with LOD perform worse in tasks associated with verbal learning and memory in contrast to participants with EOD[12]. Neurobiological evidence suggests that these cognitive alterations correspond to specific patterns of brain network dysfunction. In particular, decreased integrity of white matter tracts and reduced synchronization between the cognitive control and DMNs have been linked to the severity of CI in LLD, supporting the view of depression as a disorder of disrupted connectivity[16,17].

Global cognition

It is possible to observe that compared to healthy individuals, older adults with depression perform worse on global cognition tasks, as well as on episodic memory, attention, processing speed, and visuospatial abilities[6,29,30]. Even though alterations in multiple cognitive domains have been reported, it is still unknown which neuropsychological process is more sensitive to depression[31]. These generalized cognitive deficits are consistent with global reductions in functional connectivity (FC) efficiency, particularly within the fronto-parietal and cingulo-opercular networks (CONs), which play central roles in maintaining cognitive control and attention.

Cognitive differences have been found between older adults who had suffered depressive episodes, those who had never suffered depression, and those who had suffered depression but recovered. Regarding this, when longitudinally contrasting the cognitive alterations in older adults who have not had depression, against those who were found to be depressed and then recovered, it was found that the latter had worse cognitive performance from the start in contrast to non-depressed participants, however, in subsequent assessments, participants who were found to be still depressed performed worse on verbal fluency tasks[23]. This persistence of impairment even after remission suggests an enduring disruption in neural network efficiency rather than a temporary state-dependent effect, implying long-term neurofunctional vulnerability.

Furthermore, worse cognitive performance in all domains (except visual memory) was observed in participants who developed symptoms of depression on successive assessments, in contrast to stable non-depressed subjects. Similarly, participants who presented persistent symptoms of depression in both assessments had worse cognitive performance than the other groups[23]. These findings align with longitudinal neuroimaging studies reporting that chronic depressive symptoms predict decreased fronto-subcortical connectivity and reduced global efficiency in cognitive networks, further supporting the hypothesis of LLD as a disconnection syndrome.

Executive functions

Other investigations[15] report that in older adults with a persistent pattern of depressive symptoms, more significant decreases in executive functions and attention are observed.

Executive functions and processing speed seem to be some of the cognitive processes that are most affected by depression; the dysfunction of these processes can explain why people with depression have more disabilities[14]. One of the clinical implications of executive dysfunction is the impairment in the ability to perform instrumental activities of daily living, leading to complications in independent functioning[15]. Neuroimaging and electrophysiological studies have shown that these executive deficits are frequently associated with altered activity in the cognitive control network (CCN) and reduced fronto-subcortical connectivity, mechanisms that compromise inhibitory control and goal-directed behavior. Functional inefficiency within these circuits has been proposed as one of the neural substrates of the "depression-executive dysfunction syndrome" often observed in LLD[18].

Processing speed

In aging, depression alters the speed of processing, usually observed as a slowdown in the ability to perform cognitive tasks, specifically, the speed of processing functions as a mediator process between symptoms of depression and performance in instrumental activities of daily life, but also for other cognitive processes such as executive functions and memory[32].

In the long term, the increase in the severity of depression symptoms produces a more pronounced

deterioration in processing speed, indicating that the severity of the initial symptoms is not the most relevant risk factor at a cognitive level, but rather the time of onset and the trajectory of worsening of depression symptoms[5]. At the neurofunctional level, processing speed deficits have been related to decreased fronto-parietal connectivity and reduced dopaminergic signaling, leading to slower information transfer between cortical regions. This network inefficiency contributes to both psychomotor retardation and generalized cognitive slowing frequently reported in LLD.

Memory

When considering memory alterations, there are two general clinical approaches: assessing the participant's SMC or analyzing the results of neuropsychological evaluations, which do not always correlate. SMC has a greater association with the presence of depressive symptomatology[33], in comparison to the results of neuropsychological tests[33,34]. However, SMC has not been proven to be a viable predictor for the development of mild CI (MCI) or dementia, suggesting that SMC may indicate the presence of depression rather than neuropathology[34]. Functional neuroimaging has revealed that memory-related alterations in LLD are accompanied by disrupted hippocampal connectivity and increased synchronization within the DMN, mechanisms that hinder efficient encoding and retrieval processes.

Some differences by sex have been found regarding depressive symptomatology and cognition. For instance, verbal learning is affected to a greater extent in men with depressive symptomatology in subsequent assessments, which would indicate that the degree of cognitive deterioration associated with depression is greater in men[23]. Furthermore, mild symptoms of depression in men (but not in women) are associated with a 2:1 increased risk of developing amnesic-type mild CI compared to those without symptoms, whereas moderate and severe symptoms of depression in women (but not in men) increase the risk in a ratio of 2:1 of developing non-amnestic mild CI[35]. These sex-related differences may reflect distinct patterns of neural network engagement: men tend to exhibit more pronounced fronto-hippocampal disconnection, whereas women show abnormal hyperconnectivity within the DMN and salience networks (SNs), potentially accounting for the differential cognitive profiles.

Prevalence of depression and CI

The prevalence of depressive symptoms in patients with MCI is around 32%[30], in contrast to older adults with dementia, where the prevalence varies between 9 and 68%[14]. Depression has a high comorbidity in these pathologies and can be considered a risk factor that could increase the incidence or worsening of dementia[9,34,36].

The simultaneous presentation of depression and cognitive symptoms during aging may be related to similar brain correlates, which means that the neuropathological conditions that cause cognitive decline may also cause symptoms of depression[19,26]. These shared mechanisms include white matter damage, neuroinflammation, and dysregulation of large-scale networks such as the default mode and ECNs, contributing to both affective and cognitive manifestations.

For instance, some biological factors that could be present in both MCI and depression are vascular disease, increased amyloid-beta plaques, neuroinflammation, alterations in neuroendocrine and neurotransmission systems, and hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis[15,26,35-37]. The association of amyloid-beta, depression, and CI is usually observed in the early stages of Alzheimer's pathology, so increases in depressive symptoms can be used as a marker of changes in cognition that facilitate the detection of people who are at risk of developing Alzheimer's disease[10]. Altogether, these findings reinforce the interpretation of LLD as a multifactorial condition where molecular, vascular, and network-level alterations converge to produce progressive cognitive deterioration.

Multiple anatomical cerebral correlates of depression have been investigated, finding non-conclusive evidence of alterations in the cerebral gray matter, for which it was hypothesized that there were no significant decreases in the general volume of the brain areas, which led researchers to analyze anatomical brain connectivity and it was discovered that, in participants with depression, there are alterations called white matter hyperintensities (WMH)[38]. These WMH represent one of the most consistent structural mechanisms explaining the disconnection processes underlying cognitive and affective symptoms in LLD.

WMH in late-life depression

WMH are cerebral white matter lesions that are reactive and observable by means of their hyperintensity

in magnetic resonance imaging when using the fluid-attenuated inversion recovery sequence. Their presence has been related to Alzheimer's disease and CI[39], and it has also been described that they negatively impact mood[40].

WMH is related to less brain connectivity between regions responsible for attentional, sensorimotor processes, and between certain subcortical regions in patients with LLD, which leads to difficulties in making attentional changes during a task, to slower processing speeds, and to dysexecutive behavior[18]. This structural disconnection pattern explains why executive functions and processing speed, both dependent on fronto-subcortical loops, are consistently impaired in LLD.

WMH has been correlated with changes in cognition, specifically in processes such as executive functions and processing speed[38], due to demyelination of neuronal tracts that connect the prefrontal cortex with subcortical and posterior structures of the brain[19]. These demyelinating processes reduce conduction velocity and compromise the integration of information across distributed cortical areas, reinforcing the conceptualization of WMH as key structural mechanisms of disconnection.

In depressive disorders, symptoms of depression can moderate CI through these WMH, hypercortisolism, inflammation, increased levels of cytokines, and even the suppression of neurotrophic factors such as the brain-derived neurotrophic factor and the insulin-like growth factor binding protein-5[22,35]. This interaction between vascular and neuroendocrine alterations suggests a multimodal mechanism in which inflammation and stress-related hormones exacerbate network inefficiency and neurodegeneration.

Regarding the heterogeneity of the symptoms in LLD, at least two differential neuroanatomical dimensions (clusters) have been found in LLD using magnetic resonance imaging, the first dimension included patients with relatively preserved brain anatomy and larger subcortical regional volumes, whereas patients in the second dimension displayed brain and WM atrophy, impaired cognitive function, and increased depression severity; patients in the second dimension were more vulnerable to Alzheimer's disease and brain aging[39]. These neuroanatomical subtypes indicate that structural disconnection is not homogeneous in LLD but reflects individual variations in vulnerability to aging and neurodegenerative processes.

Because of the identification of alterations produced by WMH, theories such as the "disconnection theory" have been proposed, where it is postulated that depression in aging should be seen as a disorder of neurocognitive networks that involve multiple neuronal circuits, specifically, those networks involving cortical-subcortical regions[39], leading to reduced interhemispheric connectivity and lower efficiency of cognitive networks[39]. Consequently, WMH serves as the anatomical substrate of disrupted communication between hemispheres and subcortical hubs, establishing the biological foundation of the disconnection syndrome. This disruption in interhemispheric connectivity and reduced cognitive network efficiency may contribute to depressive symptoms. Given that dopamine deficiency is a common factor in aging, this dysfunction could be exacerbated. Therefore, dopamine-stimulating agents hold promising potential in managing depression in older adults, as they may address both the neurocognitive and neurochemical deficiencies that contribute to the chronicity of depressive disorders[40].

Late-life depression as a disconnection syndrome

FC can be defined as a measure of the relationships between different cerebral signals over time. FC allows conclusions to be made regarding the functional interaction between multiple brain areas. In this line, alterations have been reported in the FC of the uncinate fasciculus, which is responsible for the interconnection between the prefrontal cortex and subcortical and limbic structures, including the amygdala and the hippocampus. During cognitive performance, less activation is observed in participants with depression in contrast to healthy participants[41,42], suggesting differences in neuronal network activation, which can lead to less cognitive and brain network efficiency. This finding provides direct neurofunctional evidence that depression in late life is characterized by inefficient recruitment of critical fronto-limbic pathways supporting executive and emotional regulation.

Neurofunctional networks can be described from multiple quantitative measurements, among which are efficiency, efficacy, network segregation, and network integration, with all of them being sensitive to pathology. Theoretically, more efficient networks are associated with better cognitive performance, and said efficiency decreases with age both in healthy participants and in those with depression[43]. In LLD, such reductions in network efficiency are amplified by age-related loss of white matter integrity, leading to a cascade of compensatory hyperactivation across cortical regions.

In recent years, multiple functional brain networks have been described; the most prevalent in the field of cognitive research are the ECN, also known as the fronto-parietal network, DMN, SN, CCN, CON, and the working memory network.

There is evidence of neuronal network dysfunction as an explanatory mechanism in LLD, specifically, alterations in the efficiency of ECN, DMN, and SN have been found in participants with depression, which could contribute to the presence of cognitive and behavioral impairments[16]. These alterations reflect a broader dysregulation of network segregation and integration, where excessive DMN coupling and reduced ECN efficiency predict cognitive slowing, attentional lapses, and impaired goal maintenance.

In fact, impairments of the CCN can result in depression-executive dysfunction (DED), characterized by the difficulty to inhibit irrelevant stimuli and to maintain behaviors aimed at goal completion[18,44], as well as alterations in working memory, episodic memory, processing speed, attention, cognitive control, judgment, and decision-making ability[16,45]. Apart from the depressive symptomatology that is present in DED, which includes anhedonia, psychomotor retardation, lack of introspection, and depressive-type ideation[19]. The overlap of these cognitive and affective symptoms supports the idea that DED arises from dysfunction within fronto-subcortical loops and reduced dopaminergic modulation of the CCN, which together produce both motivational and cognitive rigidity.

Compensatory mechanisms have been proposed regarding the neuronal homogeneity of the CCN, specifically in subcortical areas such as the anterior cingulate cortex (ACC) and the medial temporal gyrus, however, only the activity of the ACC is associated with greater cognitive flexibility, this increase in the regional homogeneity of the ACC may support executive functions through the functional integration of neurocognitive networks that include the posterior parietal cortices and the lateral prefrontal cortex[44]. Thus, ACC hyperactivation represents an adaptive but metabolically costly process that maintains short-term performance at the expense of long-term efficiency.

In older adults with LLD, increased activation of the CCN is considered a compensatory mechanism during cognitive tasks, specifically, greater activation can be observed in right precentral and anterior cingulate areas, bilateral middle frontal gyrus, basal ganglia, and supramarginal gyrus[44,45], in addition to increased activation in areas that do not belong to the CCN, for example, limbic areas, the right cuneus, and fusiform gyrus[44,45]. This compensatory recruitment beyond canonical control regions supports the notion that cognitive effort in LLD relies on diffuse, non-specific neural activation patterns.

The increased non-specific network activation would indicate that in MDD and LLD, a diffuse pattern of brain network activation represents the need to compensate for the inefficiency of functional networks, therefore, resulting in the activation of non-cognitive regions during cognitive tasks[44,45]. Such compensatory hyperactivation reflects the brain's attempt to preserve performance in the face of disconnection but may also accelerate cognitive fatigue and decline.

Similarly, the DMN, which is characterized by a set of regions that present increased activity during resting conditions and decreased activity in cognitively demanding tasks, also shows a differential pattern between depressed and healthy participants, where increased activity is observed during attentional tasks in depressed participants, where an increase in the synchronization of the DMN with other networks such as CCN has also been observed[17,45]. This abnormal cross-network synchronization underlies ruminative and self-referential thinking, reducing cognitive flexibility and attentional control.

FC can be affected globally[16,17], for instance, disturbance in the connectivity of the precuneus with structures responsible for higher cognitive functions is associated with cognitive alterations such as difficulties in sustained attention, cognitive flexibility, and the ability to switch objectives during a task (task-switching), and with manifestations of thought such as "self-referential" thinking and first-person perspective taking[44,45], showing that the CI and thought perturbations found in depression could be related to FC between multiple brain areas. Altogether, these functional alterations converge with the structural evidence of WMH, demonstrating that both disconnection at the white-matter level and inefficient network integration contribute to the multidomain impairments observed in LLD.

The studies reviewed in this section converge on the idea that LLD is best understood as a disorder of disrupted connectivity rather than as the sum of isolated cognitive deficits. Alterations in large-scale brain networks, including the DMN, CCN, and ECN, interact with structural changes such as WMH to produce multidomain impairments. To integrate this evidence, we organized the findings into C-M-O configurations (Table 1). This synthesis illustrates how specific clinical contexts (e.g., late onset, persistent symptoms, sex differences, and treatment response) activate neurobiological mechanisms (e.g., WMH-related disconnection,

Table 1. Synthesized C-M-O patterns linking clinical contexts, neurobiological mechanisms, and cognitive outcomes in late-life depression

Context	Mechanism	Cognitive domain affected	Observed outcome	Reference(s)
Late-onset depression (≥ 60) with vascular comorbidity	WMH → fronto-subcortical disconnection	Executive functions; processing speed	Executive dysfunction, cognitive slowing, functional disability	17,38,39
Persistent depression with high symptom burden	HPA-axis hyperactivation and inflammation	Episodic and verbal memory	Memory decline; ↑ dementia risk	5,35
Female sex, moderate-severe depression	DMN hyper-synchronization/ abnormal DMN-CCN coupling	Sustained attention; cognitive flexibility	Task interference, non-amnestic MCI	16,33,45
Male sex, mild depression	Dopaminergic dysfunction	Verbal memory and learning	↑ Risk of amnestic MCI	33,40
LLD with executive dysfunction, poor SSRI response	CCN inefficiency → Depression-Executive Dysfunction	Planning, judgment, inhibitory control	Persistent executive deficits	18,44
Severe symptoms during cognitive tasks	Reduced efficiency of ECN/ FPN	Working memory; cognitive control	Failures in working memory updating, inhibition	41,42
LLD with task performance	Compensatory hyperactivation (↑ ACC, basal ganglia, MFG, non-CCN)	Executive functions, working memory	Transient support, inefficient long-term compensation	43,44
Geriatric depression (general)	Decreased inter-hemispheric connectivity and lower network efficiency	Global cognition (multidomain)	Broad deficits	38
WMH burden disrupting attentional/ sensorimotor-subcortical tracts	Structural connectome disruption	Set shifting; processing speed	Dysexecutive behavior, slowed processing	17,18
Disturbed precuneus connectivity	Global functional connectivity disturbance	Sustained attention, task-switching, self-referential cognition	Attention lapses; intrusive self-referential thought	44,45
Low participation in cognitively stimulating activities	Reduced cognitive reserve	Global cognition	Negative cycle: depression → ↓ activity → ↓ cognitive reserve→accelerated decline	8,46,47

Arrows represent conceptual relationships between contexts, mechanisms, and outcomes. A rightward arrow (→) indicates a proposed directional relationship (i.e., may contribute to or may lead to). An upward arrow (↑) indicates an increase, a downward arrow (↓) indicates a decrease, and a bidirectional arrow (↔) indicates an interaction or reciprocal association.
C-M-O: context-mechanism-outcome; WMH: white matter hyperintensities; HPA: hypothalamic-pituitary-adrenal; DMN: default mode network; CCN: cognitive control network; MCI: mild cognitive impairment; LLD: late-life depression; SSRI: selective serotonin reuptake inhibitor; ECN: executive control network; FPN: fronto-parietal network; ACC: anterior cingulate cortex; MFG: middle frontal gyrus.

HPA-axis hyperactivation, network inefficiency, and compensatory hyperactivation), which in turn result in characteristic cognitive outcomes. By framing the results in this way, the table provides a clear empirical basis for conceptualizing LLD as a disconnection syndrome.

In summary, the neurofunctional findings reviewed here complement the structural evidence of WMH, reinforcing the notion that LLD represents a convergence of vascular, neurochemical, and network-level disconnection processes.

Discussion

Summary of findings and theoretical implications

This realist synthesis identified multiple C-M-O configurations that explain the neurocognitive heterogeneity of LLD. Across studies, contexts such as late onset, vascular comorbidity, persistent symptoms, and sex differences interacted with neurobiological mechanisms, including WMH, HPA-axis hyperactivation, dopaminergic dysfunction, and

reduced efficiency in large-scale brain networks. These mechanisms produced characteristic cognitive outcomes, primarily executive dysfunction, slower processing speed, and memory decline. Altogether, the evidence supports the conceptualization of LLD as a disconnection syndrome, in which both structural and functional network inefficiency mediate the interaction between mood symptoms and cognitive deterioration.

Treatment implications

In general, we must consider depression as a disease with multiple etiologies, leaving aside reductionist or isolated points of view (for example, explaining depression only as a perturbation in the concentrations of serotonin). In older adults, depressive symptoms could be related to anatomical modifications such as WMH, to functional disturbances, such as hyperactivation of the HPA-axis, to brain network alterations, such as inefficiency due to the recruitment of multiple brain areas in the need to compensate for the cognitive demands, and many more.

Consequently, clinicians should note multiple factors when assessing the presence of depression in older adults and its progression through time[45], for example, when considering sex, it has been reported that males are more reluctant to disclose or underreport depressive symptoms, therefore, delaying early treatments that could reduce the risk of progression to cognitive decline[35].

Furthermore, CIs in specific processes such as executive functions negatively impact a person's ability to do daily activities, affecting their independence and self-care, whereas increasing health risks, hopelessness, and self-criticism, therefore worsening depressive symptoms[6,14,15,32,33,45].

Regarding the treatment approaches, the LLD co-occurring CIs are found to modify the efficacy of pharmacotherapy with selective serotonin reuptake inhibitors (SSRIs) antidepressants, for instance, in persons with DED less SSRIs efficacy has been reported due to a dysfunction in the dopamine system, more research is needed to assess the efficacy of D2/D3 agonists as a more suitable treatment for DED[18,19,21,44]. Some symptoms of diminished dopamine brain levels, such as slowness of movement and thought processing, anhedonia, and psychomotor retardation, are also present in LLD, in conjunction with greater antidepressant response to SSRIs in combination with dopamine enhancers, leads to the hypothesize that dopamine deficiency could be an underlying cause of LLD[40].

Along these same lines, it has been described that a large proportion of older adults who suffer from both depression and CI will continue to present alterations in cognition even after finishing treatment with antidepressants[21,25], thus implying that the use of pharmacological treatments does not always reduce the incipient risk of dementia associated with LLD[9].

Similarly, verbal learning and executive function impairments can also affect psychotherapeutic treatment interventions[12], as the "Gold Standard" psychotherapy for depression is the cognitive behavioral therapy, in which most of the techniques require the ability to learn new ways of thinking and to put new behaviors in practice[6,36]; for this reason, LLD presents treatment difficulties for the mental health professionals that try to apply the traditional approaches with their patients.

A preventive approach in the face of depression and CI could be the constant participation in cognitively stimulating activities, which helps to build cognitive reserve[46,47]. Multiple studies show that cognitive reserve acts as a neuroprotective factor against neuropathology by allowing the person to functionally allocate cognitive resources to compensate for cognitive task demands[48,49], thus helping older adults to maintain daily functioning. These findings suggest that interventions aimed at enhancing cognitive reserve and promoting dopaminergic balance may mitigate both affective and cognitive decline in LLD.

Comparison with previous literature and limitations

The results of this synthesis converge with previous evidence highlighting WMH and network inefficiency as core biomarkers of CI in depression. However, unlike traditional reviews, the realist approach clarifies how these mechanisms operate within specific clinical contexts. Limitations include the exclusive use of PubMed-indexed studies, potential language bias (English-only selection), and the heterogeneity of neuroimaging methods across sources. Moreover, causal inferences remain limited due to the predominance of cross-sectional designs.

Future directions

Future studies should combine multimodal imaging (structural, functional, and metabolic) with longitudinal designs to clarify the temporal sequence linking depressive symptoms, network disconnection, and cognitive decline. Evaluating individualized profiles of structural and functional disconnection may help tailor pharmacological and psychotherapeutic strategies in older adults.

Conclusion

The co-occurrence of depressive symptoms and CI in older adults suffering from LLD should be analyzed as a bidirectional relationship, where the worsening of the first affects the latter and vice versa. This interaction might be due to shared anatomical and functional brain correlates, such as WMH, hyperactivation of the HPA-axis, neurotransmitter imbalance, and network inefficiency. The findings suggest that while several cognitive processes are sensitive to LLD, impairments in executive functions and language have the greatest impact on functional autonomy and treatment prognosis. Recognizing LLD as a disconnection syndrome provides a unifying theoretical framework with clear implications for prevention, early detection, and intervention.

Author contributions

All authors contributed to the formulation of the research goals and aims, as well as to the writing of the initial and final drafts. J.D. López-Sánchez contributed to the development of the methodology and the selection of the articles. D.E. Granados-Ramos and B. Bernal-Morales oversaw the execution of the review.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. This study does not involve personal patient data, medical records, or biological samples, and does not require ethical approval. SAGER guidelines do not apply.

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