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EDITORIAL

Cognitive and behavioral manifestations in neurological and psychiatric diseases as models to understand the complexity of human biology

Manifestaciones cognitivas y conductuales en enfermedades neurológicas y psiquiátricas como modelos para comprender la complejidad de la biología humana

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Human cognition and behavior are complex functions of the brain. Our insights for comprehension of its intricate neurobiology came to a large extent from neurological and psychiatric diseases, principally through lesional models and more recently through functional models using technological advances.

The classical vascular models apported strong evidence for our comprehension of human cognition and behavior. These models are still useful today and are essential for comprehension of brain function, such as the Upper Motor Neuron Syndrome, Wernicke's Aphasia, and other syndromes such as the controverted "Vascular Depression," a syndrome that originally was described by Robinson and consists of late-life depression with executive cognitive dysfunction and subcortical hyperintensities in brain imaging, which has apported important knowledge in the comprehension of mood syndromes[1,2]. Furthermore, other kind of lesional models corresponding to focal neurodegeneration have been very helpful to understand the regional anatomy, including circuits and cortical hubs closed to particular cognitive or behavioral functions. That is the case of our comprehension on behavioral social skills, behavioral inhibition and semantic information storage in cases of behavioral variant Frontotemporal Dementia or Semantic Variant Primary Progressive Aphasia affecting the anterior temporopolar region(s)[3]; or the understanding that we have learned in terms of visual processing through syndromes such as cortical posterior atrophy, commonly secondary to Alzheimer Disease Pathology, and less frequently by Lewy Body Disease or Prion Diseases[4,5].

On the other hand, the majority of Primary Psychiatric syndromes, with less precision have an affected particular brain region explaining the complete load of the disease. A known research biomarker in people with Primary Depression is the change in function or/and volume of the anterior cingulate gyrus, particularly the subgenual area, a brain structure implicated in the processing of cognitive and affective information[6,7]. Although several trials focusing on the stimulation of the anterior cingulate region for depression have been developed, results are controversial and costs are elevated, leading to deep stimulation as an experimental treatment until now[8].

Why deep brain stimulation directed to the anterior cingulate, which is a known structural biomarker in depression, does not work in all cases to treat depression? The answer relies on understanding the behavioral and cognitive manifestations of Primary Psychiatric Disorders as "non focal brain diseases" but circuit diseases that may

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be affected in different patterns in different persons, as recent research supports[9]. In addition, Behavioral and Cognitive Manifestations of Psychiatric Disorders also are influenced and modulated by the social-environmental situations and the psychological load of every individual as the biopsychosocial model proposes.

In this issue of Revista Mexicana de Neurociencia interesting research related to behavioral and cognitive manifestations in disease models is exposed, including findings in cognitive function and depression and their correlation to academic performance, as well as an interesting assessment of creative thinking in people affected by frontal meningiomas. Research that contribute evidence to the field of behavioral and cognitive manifestations of neurological and psychiatric diseases.

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ORIGINAL ARTICLE

Chronic infection and malignancy screening in Mexican patients with multiple sclerosis

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Abstract

Objective: *Screening studies are recommended to rule out neoplasms and chronic infections before starting disease-modifying therapies (DMTs). To illustrate the importance of screening before DMT initiation and to show, the most frequent findings in patients with multiple sclerosis (MS) in a developing country.* **Methods:** *We analyzed patients admitted to the MS clinic from 2020 to 2023 who underwent screening before the initiation of DMT. All patients were sampled for: quantiFERON for tuberculosis (TB), varicella zoster immunoglobulin G levels, human immunodeficiency virus, Hepatitis B, Hepatitis C virus, venereal disease research laboratory, papanicolaou smear, and mammogram in women over 40.* **Results:** *We analyzed 103 patients, 74 of whom were women (71.8%), with a mean age of 42.8 ± 15. Pathological findings were detected in 21 (20%) patients: latent TB in 12 (11.6%), cervical human papillomavirus infection in 3 (2.9%), benign thyroid nodule in 2 (1.9%), liver TB in 1 (0.9%), penile squamous carcinoma in 1 (0.9%), thyroid carcinoma in 1 (0.9%), and breast papilloma in 1 (0.9%). Patients who received DMT did not develop any complications.* **Conclusions:** *The pathological findings did not influence the final treatment decision. However, screening tests are essential for the early detection and management of chronic conditions. Conducting these tests before initiating DMTs helps identify potential co-morbidities or contraindications to immunosuppressive treatments, ensuring safer and more effective patient care.*

Keywords: *Chronic infections. Multiple sclerosis. Prevention. Screening. Treatment initiation.*

Tamizaje de infecciones crónicas y malignidad en pacientes mexicanos con esclerosis múltiple

Resumen

Objetivo*: Los estudios de cribado se recomiendan para descartar neoplasias e infecciones crónicas antes de las terapias modificadoras de la enfermedad. (TME). Ilustrar la importancia del cribado previo al inicio de TME, mostrar los hallazgos más frecuentes en pacientes con esclerosis multiple (EM) en un país en vías de desarrollo.* **Métodos***: Se analizaron los pacientes ingresados en la consulta de EM entre 2020-2023, a quienes se les realizó un perfilamiento previo al inicio de TME. A todos los pacientes se les tomaron muestras de: quantiFERON para tuberculosis, niveles de IgG varicela zoster, virus de la inmunodeficiencia humana, hepatitis B, hepatitis C, VDRL, citología vaginal y mamografía en mujeres mayores de 40 años.* **Resultados***: Se analizaron 103 pacientes, de los cuales 74 eran mujeres (71.8%), la edad media fue de 42.8 ± 15 años. Se detectaron hallazgos patológicos en 21 (20%) pacientes: tuberculosis latente 12 (11.6%), infección cervical por VPH 3 (2.9%), nódulo tiroideo benigno 2 (1.9%), tuberculosis hepática 1 (0.9%), carcinoma escamoso de pene 1 (0.9%), carcinoma de tiroides 1 (0.9%) y papiloma*

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de mama 1 (0.9%). Los pacientes que recibieron TME no desarrollaron ninguna complicación. **Conclusiones***: Los hallazgos patológicos no influyeron en la decisión final del tratamiento. Sin embargo, el perfilamiento es esencial para la detección temprana y el tratamiento de enfermedades crónicas. La realización de estas pruebas ayuda a identificar posibles comorbilidades o contraindicaciones para los tratamientos inmunosupresores, lo que garantiza una atención al paciente más segura y eficaz.*

Palabras clave: *Esclerosis múltiple. Tamizaje. Infecciones crónicas. Prevención. Inicio del tratamiento.*

Introduction

Multiple sclerosis (MS) is a chronic, demyelinating, and neurodegenerative disease of the central nervous system. It is the leading cause of non-traumatic disability among young adults, affecting 2.3 million people worldwide[1].

The growing number of approved disease-modifying therapies (DMTs) increases the possibility of adapting treatment plans to individual patient needs, in terms of efficacy, safety issues, and preferences[2]. Current trends toward initiating high-efficacy DMTs have gained ground due to accumulating evidence supporting their efficacy in slowing disease progression and reducing clinical disability[3].

Depending on their mechanisms of action, immunomodulatory and immunosuppressive DMTs increase the risk of infections, including reactivation of latent pathogens, as well as asymptomatic chronic or new infections[4].

People living with MS are a risk group for chronic infections, with studies reporting hazard ratios between 2.5 and 3.5 times higher for MS patients compared with controls[5]. People with MS also experience a reduced life expectancy of up to 7-14 years compared to the general population[6,7].

While these therapies claim an acceptable safety profile, they exert a considerable immunosuppressive effect, potentially heightening the theoretical risk of infections and malignancies. Given these considerations, it is advisable to conduct screening studies before starting DMTs to identify and exclude any neoplasms or chronic infections that might pose contraindications to their use[8].

The Delphi consensus statement provides a comprehensive list of screening studies recommended for baseline infectious disease evaluation before initiating any DMT[9]:

- Serologic assessment: Toxoplasma immunoglobulin G (IgG), Hepatitis B core antibody (HBcAb), surface antigen (HBsAg), surface antibody (HBsAb), Hepatitis C virus antibody (HCVAb), human immunodeficiency virus (HIV), venereal disease research laboratory (VDRL)
- Immunoglobulins for varicella-zoster virus (VZV IgG), cytomegalovirus (CMV IgG), Epstein-Barr virus (EBV IgG), measles IgG, and rubella IgG
- Papanicolaou (Pap) smear with human papillomavirus (HPV) test
- Tuberculosis (TB) testing: Interferon-γ release assay (IGRA) or purified protein derivative intradermal (PPD- intradermal reaction) test.

Methods

An observational retrospective study was performed, with the approval of the Ethics Committee of our institution. We analyzed patients admitted to the MS Clinic of the Instituto Nacional de Ciencias Médicas y Nutrición “Salvador Zubirán” in Mexico City, from January 2020 to December 2022, who underwent screening before the initiation of DMT.

We based our profiling on the recommendations of the Delphi consensus, adapting them to suit our population. Patients were sampled for IGRA with QuantiFERON®-TB Gold for TB, VZV IgG, HIV, HBcAb, HBsAg, HBsAb, HCVAb, and VDRL. Women underwent a Pap smear with a cervical HPV test, and those over 40 years of age also had a mammogram.

Toxoplasma IgG, CMV IgG, EBV IgG, Measles IgG, and Rubella IgG tests were not included, as they are not routinely recommended before starting DMTs.

In the applicable cases, thoracic radiography, thyroid function tests, and thyroid ultrasound were performed. Fourteen patients who were not completely evaluated and lost to follow-up were excluded.

The rest of the demographic variables, clinical characteristics, pharmacological treatment, and comorbidities were obtained from medical records. Patient data were collected and captured in a database in the Statistical Package for the Social Science V25 program for analysis. Descriptive analysis of nominal variables was performed using percentages and proportions, and for numeric variables, mean and standard deviation were used. Bivariate analysis was performed with numeric variables using the Student’s t-test.

Results

We analyzed 103 patients, 74 were women (71.8%), and the average age was 42.8 ± 15, the mean time living with MS was 12.75 years, average expanded disability status scale score was 2.72 ± 1.8. Sixty-six patients (65%) presented with relapsing-remitting MS, 26% with secondary progressive MS, and 9% with primary progressive MS.

Previous comorbidities were found in 26 patients (25%) patients, which were: hypothyroidism 9 (8%), diabetes mellitus type 2 6 (5%), hypertension 3 (2%), lupus 3 (2%), inflammatory colitis 1 (0.9%), neurofibromatosis 1 (0.9%), uveitis 1 (0.9%), Type 1 diabetes mellitus (0.9%), and ischemic stroke 1 (0.9%).

Pathological findings were detected in 21 (20%) patients, as seen in table 1. In our series, we identified three cases of cervical HPV infection which resolved with electrofulguration. A patient with a verrucous dermal lesion on the penis was found to have a low-grade HPV+ neoplasia, which was resolved with excisional biopsy. No other male patient reported genital lesions, so no further screening tests were performed. None of our patients with latent TB (LTB) exhibited any pathological findings on chest tomography indicative of active TB. All individuals received prophylactic treatment in collaboration with infectious disease specialists, and no complications arose at the beginning of the DMT.

An extra-pulmonary manifestation of TB was observed in only one patient, a 35-year-old woman, previously treated with alemtuzumab in 2016, who underwent screening tests in 2023 following a clinical relapse. She presented persistent elevation of liver function tests, with a liver biopsy revealing granulomatous inflammation and a positive *Mycobacterium tuberculosis* polymerase chain reaction. At present, she is under surveillance and has not initiated DMT yet.

Patients with other pathological findings were effectively treated and subsequently administered DMT, as described in table 1. As of now, they have not experienced any complications.

The interval between screening tests and the initiation of DMT was 21.3 ± 14 days for patients without pathological findings. In contrast, for patients with pathological findings, this interval increased significantly to 96.2 ± 78 days. This delay was statistically significant (p = 0.001), likely due to the need for additional tests and evaluations by other specialties.

Discussion

Our study results align with those documented in other international series, underscoring the significance of conducting profiling studies prior to starting a DMT. In accordance with Global Consensus Standards, clinicians are advised to evaluate DMT eligibility within 6 weeks of diagnosis[10].

We perform the same screening tests for all patients, regardless of the intended DMT. This standardized approach simplifies the process and helps prevent delays if a treatment change becomes necessary later. Although we recognize that this may not be applicable to all centers, we consider it a good clinical practice for efficient patient management.

At our center, we were able to initiate DMT within 3 weeks of diagnosis for patients without abnormalities in their screening tests. In contrast, this period extended to 3 months for patients with pathological findings. Our MS clinic is part of a tertiary care hospital, ensuring access to all necessary specialties for comprehensive case management. However, it is important to emphasize that healthcare in Mexico is highly variable, and the time required to initiate DMT is likely even longer in many other settings.

TB

The global prevalence of LTB stood at 24.8% as determined by IGRA, and 21.2% when using a 10 mm PPD cut-off[11]. In a major MS center in the United States, fewer than 10% of patients exhibited abnormal IGRA results: 2.0% tested positive, while 6.1% yielded indeterminate results[12]. In Mexico, there are an estimated 23,000-37,000 new cases of TB reported annually, resulting in a rate of 23 cases/100,000 inhabitants[13]. We observed an incidence of LTB of 11.9%, consistent with rates reported by other centers in Mexico[14]. The PPD or tuberculin test is recommended as the first choice for diagnosing LTB due to its cost-effectiveness. This test has a sensitivity of 75% for detecting *M. tuberculosis* infection in patients who are not vaccinated with Bacillus Calmette-Guérin (BCG) and 59% in those who are vaccinated. IGRAs have better specificity than the tuberculin test and are not affected by BCG vaccination under normal conditions[15].

LTB linked with immunosuppressive risk factors poses a yearly risk of active TB ranging from 5% to 10%[16].

LTB screening is suggested for patients with MS who will be started on teriflunomide, fingolimod, natalizumab, alemtuzumab, rituximab, ocrelizumab or dimethyl fumarate (DMF). The use of alemtuzumab, cladribine, and teriflunomide is correlated with a slightly elevated risk of active TB compared with the general population, particularly in areas endemic to TB[17].

Table 1. Pathological findings in MS patients, treatment strategies, and the selection of DMTs post-screening

Pathological finding	Patients, n (%) (n = 103) (%)	Treatment	DMT chosen after screening
Latent tuberculosis	12 (11.6)	Rifampicine or isoniazide for 6 months	Cladribine Ocrelizumab Fingolimod
Pap smear with atypical HPV+cells	3 (2.9)	Electrofulguration	Cladribine Ocrelizumab
Benign thyroid nodule	2 (1.9)	Surveillance	Siponimod Cladribine
Liver tuberculosis	1 (0.98)	Six-month RIPE TB treatment (rifampicine, isoniazid, pyrazinamide, ethambutol)	In surveillance
Low-grade neoplasia in penis HPV+	1 (0.98)	Excisional biopsy	Ocrelizumab
Papillary thyroid cancer	1 (0.98)	Thyroidectomy with radioiodine	Cladribine
Intraductal breast carcinoma	1 (0.98)	Excisional biopsy	Dimethyl fumarate

MS: multiple sclerosis; DMT: disease-modifying therapies; HPV: human papillomavirus; RIPE TB: tuberculosis.

However, there is no evidence of an elevated risk of active TB associated with interferons, glatiramer acetate, DMF, fingolimod, natalizumab, and anti-CD20 monoclonal antibodies[18].

Patients with Grade 3 or worse lymphopenia, recent methylprednisolone use, and those using fingolimod or DMF are at a significantly higher risk of having indeterminate IGRA test. Clinicians should be mindful of these factors, as adequate screening for LTB is crucial for safety with certain DMTs[19].

According to international recommendations, patients with MS who test positive for LTB should have a chest X-ray and TB preventive therapy with isoniazide or rifampicine should be considered, regardless of the treatment chosen[19].

The timing for starting a DMT depends on the urgency of disease control. Typically, DMT initiation is delayed for four to 8 weeks after starting LTB prophylaxis, mainly due to the potential risk of hepatotoxicity when both treatments are started concurrently. Therefore, periodic monitoring of clinical status and liver function is necessary[20].

In our study, all patients received preventive treatment without any complications or elevations in liver enzyme levels, enabling them to begin DMT 4 weeks after starting prophylaxis.

In MS patients who develop active TB, it is essential to promptly initiate a full course of anti-TB therapy. MS treatment should be paused until the intensive phase of treatment is completed. The decision to restart DMT should be made in collaboration with an infectious disease specialist[21].

Viral hepatitis

No cases of viral hepatitis were identified within our series. Clinical trials for MS typically exclude patients with evidence of HBV or HCV infection, consequently, determining the risk of hepatitis reactivation is challenging. This risk is relatively elevated in patients receiving B-cell-depleting agents or alemtuzumab[22].

Other risk factors for HBV infection include unvaccinated patients and profound lymphocytopenia. The risks of HBV activation in patients treated with fingolimod, DMF, and teriflunomide have not been well established but are likely low[23].

Considering the risk of HBV flares or reactivation among patients receiving immunosuppressant agents, it is recommended that all patients undergo screening for HBV infection. If HBcAb and HBsAb are negative, Hepatitis B vaccine (three doses) should be administered[24].

We recommend Hepatitis B vaccination for all patients with negative HBsAb serology. The recombinant Hepatitis B vaccine has an established safety profile, and current evidence indicates that it does not contribute to the development or reactivation of MS. Therefore, its administration can be safely considered whenever clinically indicated[25].

For patients planning to initiate anti-CD20 therapies (e.g., ocrelizumab, rituximab), evidence supports the effectiveness of administering the Hepatitis B vaccine at least 1 month before treatment initiation. In such cases, using an accelerated vaccination schedule has been shown to enhance the production of antibody titers[26,27].

Malignancy

In our study, we identified three malignancies: papillary thyroid carcinoma, intraductal breast papilloma, and penile carcinoma. All were detected in their early stages, and effective control was achieved, allowing all patients to subsequently initiate DMT. Importantly, none of these patients have experienced any complications following the initiation of immunosuppression. In a Danish population-based study, no increased incidence of malignancy was observed in patients with MS compared to the general population[28]. In addition, in another case–control study, the probability of developing cancer was 0.8 in the MS group, which did not show a significant difference from healthy subjects[29]. However, some studies have reported an increase in malignancy, particularly for the brain and urinary tract. This bias may be attributed to the periodic evaluation of patients by brain magnetic resonance imaging and urological assessment[30,31].

Sexually transmitted diseases (STDs)

Few studies have been conducted on sexual risk behaviors or STDs in patients with MS. It seems that individuals living with MS are at similar risk as the general population. No significant difference was found in sexual debut, number of partners, or risk behaviors for STDs[32].

In our series, we identified three cases of cervical HPV infection which resolved with electrofulguration. A patient with a verrucous dermal lesion on the penis was found to have a low-grade HPV + neoplasia, which was resolved with excisional biopsy. No other male patient reported genital lesions, so no further screening tests were performed.

The primary HPV-related concern is cervical cancer, with 96% of cases attributed to HPV infections[33]. Cell-mediated immunosuppression is indeed a risk factor for preneoplastic and neoplastic HPV-related diseases. Several cases of cervical dysplasia have been reported with alemtuzumab, fingolimod, and natalizumab[34].

VZV

The presence of anti-VZV antibodies is approximately 92-95% in both MS patients and controls[35]. The risk of reactivation of latent herpesvirus infection is indeed heightened by immunosuppressive therapy, especially treatments that affect cellular immunity. Monitoring of VZV IgG levels is recommended, and vaccination is necessary before initiating DMTs for patients who test negative for antibodies[36].

Immune reconstitution therapies such as alemtuzumab or cladribine are associated with a higher risk of VZV reactivation. Prophylaxis with acyclovir is recommended during the 1st month of treatment with alemtuzumab and in cases of grade 3 lymphopenia with cladribine[37].

Ocrelizumab and fingolimod have been linked to an elevated risk of herpes virus infections, although usually presenting as mild cases. Routine antiviral prophylaxis is generally not necessary[38,39].

Other MS treatments, such as teriflunomide and DMF, do not appear to be clearly associated with an increased risk of frequency or severity of herpesvirus infections, although there are scattered case reports[40].

The main limitations of this study include its single-center design and its setting in a referral hospital specializing in internal medicine. This context may lead to a higher prevalence of comorbidities compared to the general population or patients treated at other neurological centers.

Conclusion

The implementation of screening tests before initiating DMTs facilitates the identification of potential comorbidities or contraindications to immunosuppressive treatments. Although our study did not observe any complications when starting DMTs, screening tests play a crucial role in detecting and managing chronic conditions early, which might otherwise remain undiagnosed until symptoms develop.

In Mexico and other developing countries, neurologists often act as the primary point of contact for managing patients with MS. This role encompasses the responsibility of addressing all relevant clinical factors and conducting comprehensive screenings. Access to other medical specialties and a collaborative approach to managing comorbidities are critical components of effective MS patient care.

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The authors declare that this work was carried out with the authors' own resources.

Conflicts of interest

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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ORIGINAL ARTICLE

The effectiveness of vagus nerve stimulation in rheumatoid arthritis: a systematic review

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Abstract

Objective: *This review aims to assess the effectiveness of vagus nerve stimulation (VNS) in relieving RA symptoms.* **Methods***: A systematic review was performed in seven databases to identify randomized clinical trials that investigated the use of VNS on the symptom improvement of adults with RA. The review adhered to PRISMA guidelines and assessed bias risk using the RoB 2.0 Tool.* **Results***: A total of 1131 documents were identified, but only four were included. It was found no significant difference between active and sham stimulation in ACR20 response rates at week 12 (25.0% vs. 26.9%, p = 0.823), with similar results for Disease Activity Score 28 with C-reactive protein (DAS28-CRP) and HAQ-DI. However, high-disease activity participants showed significant reductions in DAS28-CRP, CRP levels, and interferon-y with non-invasive VNS (n-VNS), whereas low-disease activity participants did not benefit and experienced a decrease in cardiac vagal tone and interleukin-10 levels. Overall, n-VNS was well tolerated. VNS with a small neurostimulator was safe and effective in alleviating RA symptoms in drug-resistant patients. Two patients experienced significant improvements in various measures between the screening visit and day 42, but after device deactivation, they experienced worsened DAS28 and VAS pain scores.* **Conclusions:** *VNS was well-tolerated and yielded favorable results, indicating its potential as a viable treatment option. Its efficacy in treatment-resistant RA patients offers promising prospects.*

Keywords: *Rheumatoid arthritis. Vagus nerve stimulation. Treatment outcome.*

La eficacia de la estimulación del nervio vago en artritis reumatoide: una revisión sistemática

Resumen

Objetivo: *Esta revisión tiene como objetivo evaluar la eficacia de la estimulación del nervio vago (ENV) para aliviar los síntomas de la AR.* **Métodos:** *Se realizó una revisión sistemática en siete bases de datos para identificar ensayos clínicos aleatorizados. que investigaran el uso de la ENV en la mejora de los síntomas de los adultos con AR. La revisión se adhirió a las pautas PRISMA y evaluó el riesgo de sesgo utilizando la herramienta RoB 2.0.* **Resultados:** *Se identificaron un total de 1131 documentos, pero solo se incluyeron 4. No se encontró ninguna diferencia significativa entre la estimulación activa y simulada en las tasas de respuesta ACR20 en la semana 12 (25,0% frente a 26,9%, p = 0,823), con resultados similares para DAS28-CRP y HAQ-DI. Sin embargo, los participantes con alta actividad de la enfermedad mostraron reducciones significativas en DAS28-CRP, niveles de CRP e interferón-y con estimulación no invasiva del nervio vago (n-VNS), mientras*

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que los participantes con baja actividad de la enfermedad no se beneficiaron y experimentaron una disminución en el tono vagal cardíaco y los niveles de interleucina-10. En general, la n-VNS fue bien tolerada. La VNS con un pequeño neuroestimulador fue segura y efectiva para aliviar los síntomas de AR en pacientes resistentes a los medicamentos. Dos pacientes experimentaron mejoras significativas en varias medidas entre la visita de selección y el día 42, pero después de la desactivación del dispositivo, experimentaron un empeoramiento de las puntuaciones de dolor DAS28 y VAS. **Conclusiones:** *La VNS fue bien tolerada y arrojó resultados favorables, lo que indica su potencial como una opción de tratamiento viable. Su eficacia en pacientes con AR resistente al tratamiento ofrece perspectivas prometedoras.*

Palabras clave: *Artritis reumatoide. Estimulación del nervio vago. Resultado del tratamiento.*

Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease that causes joint inflammation, pain, stiffness, and deformities. RA involves chronic synovial inflammation, joint erosion, and physical abnormalities[1]. While current treatments have improved RA management, there is a need for more effective therapies. Despite progress in current treatments, some patients face challenges in treatment response, and disease progression can occur[2,3].

Research on the autonomic nervous system, specifically on the autonomic portion of the vagus nerve, shows promise for innovative treatments. The vagus nerve regulates immune and inflammatory responses. Studies using advanced neuroimaging confirm its potential in modulating these responses, especially in autoimmune diseases such as RA[4-6]. The "vagus nerve-brain-immunity axis" plays a vital role in immune regulation. Experimental studies demonstrate that vagus nerve stimulation (VNS) can reduce pro-inflammatory cytokines while increasing anti-inflammatory ones[7,8].

Recent research suggests a potential link between vagus nerve dysfunction and RA development[9]. Insufficient activation of the vagus nerve may lead to imbalanced immune responses, perpetuating chronic joint inflammation. Pre-clinical studies on animal models of RA have shown that VNS can reduce synovial inflammation and limit joint damage, providing encouraging evidence of its effectiveness[4]. This review aims to consolidate scientific evidence on the effectiveness of VNS in the treatment of people with RA.

Materials and methods

Protocol and registration

This systematic review strictly followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and was registered on the International Prospective Register of Systematic Reviews (PROSPERO) database under registration number CRD42023452467.

Eligibility criteria

The study employed the PICOTS strategy: population (adults older than 18 years old diagnosed with RA according to the American College of Rheumatology and/or European League Against Rheumatism [EULAR]), intervention (electrical stimulation of the vagus nerve), comparison (other interventions), outcome (improvement in clinical symptoms), publication period (no specific limitation), and study design (randomized clinical trials).

Studies exclusively involving human subjects were included, without restrictions on publication date, country of publication, or language. Duplicates were removed, and the authenticity of the information was verified.

Studies with missing or incomplete data, scientific papers presented at conferences, letters, conference abstracts, expert opinions, case reports, studies involving patients with other forms of arthritis (e.g., psoriatic arthritis and juvenile idiopathic arthritis), stimulation of the vagus nerve associated with another intervention studies involving animals and studies that stimulate the vagus nerve in a non-electrical way were excluded.

Search strategy and selection process

An extensive exploration was undertaken across various databases, including PubMed, Scopus, Cochrane Central, SciELO, Web of Science, Science Direct, and Google Scholar (see Table S1 in supplementary material). Key terms included: Rheumatoid Arthritis and Vagus Nerve Stimulation. The search covered data until July 2023, with PubMed encompassing records from 1947, Scopus from 1960, Cochrane Central from 1992, SciELO from 1998, Science Direct from 1997, and Google Scholar from 2004.

After the removal of duplicates, these articles were rigorously screened on the Rayyan platform by two independent evaluators (DD and VB) based on titles and abstracts. A third researcher (JF) resolved any conflicts. Population characteristics, eligibility criteria, intervention protocol, and results of individual studies were extracted by a single reviewer (DD) and cross-checked with the assistance of two additional reviewers (VB and JF). All data were recorded in a table adapted from the Cochrane Consumers and Communication Review Group data collection handbook[10].

Risk of bias assessment

The risk of bias was assessed using the Cochrane Risk of Bias (RoB 2) tool for randomized clinical trials, categorizing the risk into five domains of bias as high, uncertain, or low. Two investigators (DD and VM) independently evaluated the risk of bias in each trial included with the updated RoB tool version 2. Any discrepancies were resolved by discussion and intervention of a third reviewer (JF) whenever necessary. Following the methodological quality appraisal of each study, the Kappa coefficient of inter-rater reliability was calculated (IBM SPSS Statistics) (IBM, 2021). Values range from near perfect, 0.81-1.00, substantial, 0.61-0.80, moderate, 0.41-0.60, fair, 0.21-0.40, and slight 0.0-0.2[11].

Ethical approval

As a secondary study of systematic reviews, formal ethics committee approval, and informed consent were unnecessary.

Data synthesis and analysis

The data were meticulously organized in a Google spreadsheet. Study comparisons between intervention and control groups utilizing mean differences and standard deviation were grouped according to outcomes. A meta-analysis was not attempted due to the heterogeneity of the study protocols.

Certainty of evidence

The certainty of evidence for individual results was assessed through the Grading of Recommendation Assessment, Development, and Evaluation (GRADE) approach[12]. Certainty of evidence ratings was conducted independently by two authors (DD and VB), with disagreements resolved through discussion with a third author (JF). Certainty of evidence across results was graded high, medium, low, or very low certainty Grading of Recommendation Assessment, Development, and Evaluation (GRADE) approach[12]. Due to all included studies being randomized controlled trials, each outcome began with a high certainty rating. Studies were downgraded for the following reasons: (1) risk of bias or limitations in the detailed design and implementation, (2) unexplained heterogeneity or inconsistency of results, (3) indirectness of evidence, (4) imprecision of results, (5) high probability of publication bias.

Results

Study selection

Initially, 1,131 documents were identified in our database searches and after removing duplicates, 950 articles remained. After analyzing the title and summary of these records, 20 documents were searched for retrieval and subsequently screened by reading and studying the full text. Conflicts between the two reviewers (DD and VB) were resolved by consensus with a third reviewer (JF), and four articles met the inclusion criteria for qualitative synthesis[8,13-16]. The exclusions that occurred in the full-text screening were justified in a PRISMA flowchart together with the complete screening and selection process (Fig. 1).

Study characteristics (Table 1 and Table S2)

The included articles, dated from 2016 to 2023, were conducted in Denmark, Croatia, and the United States, involving 165 participants, 136 women, and 29 men. The average age ranged between 49.3 and 56.22; however, the Danish study did not specify the age of the patients included in the study[14] (Table 1). Among the four articles included, two did not have a control group. Once the intervention was carried out on all research participants, the evaluation of the effectiveness of the intervention was carried out by comparing parameters before and after stimulation of the vagus nerve. All participants in the included studies[8,13,14,15] were adults and diagnosed with RA. The full outlined eligibility criteria for studies are reported in table S2 (see Table S2 in supplementary material). Various types of vagal stimulation were used, including auricular transcutaneous stimulation[13], miniaturized cervical devices[8,15], and subcutaneous pulse generators[14]. These interventions were applied over periods ranging from 5 days to 12 weeks.

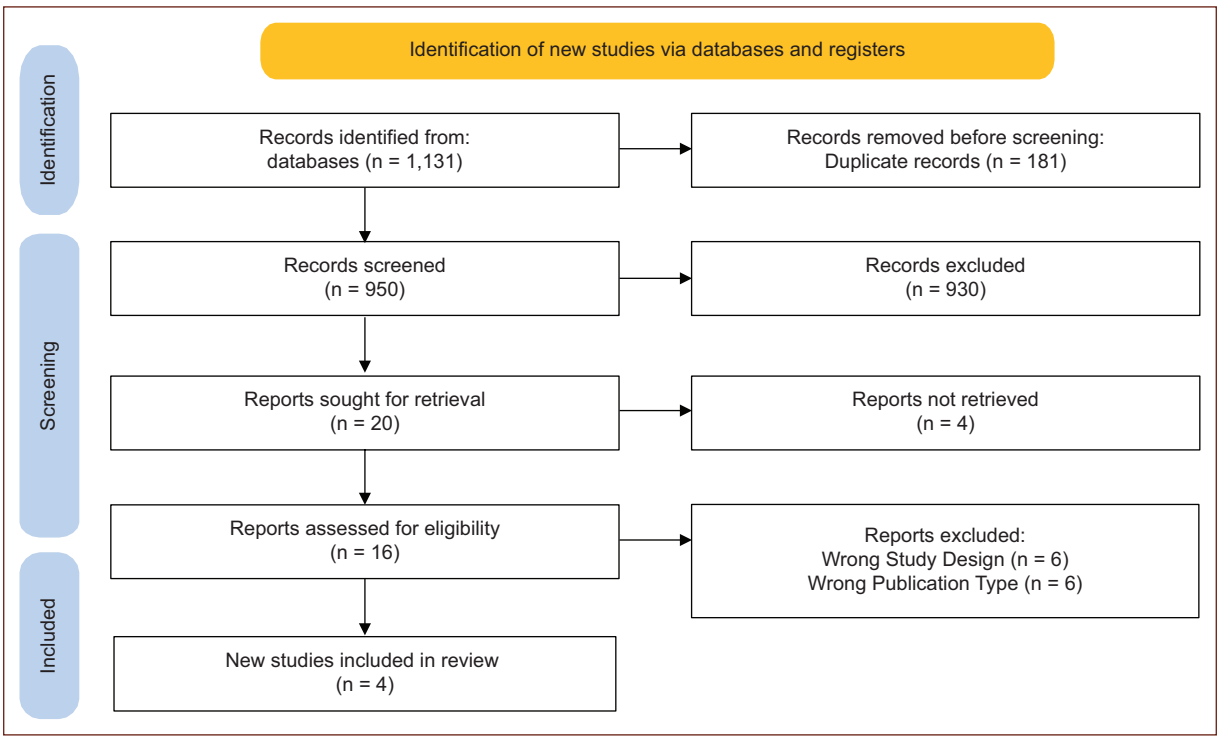

Figure 1. Prisma flow chart of the search, screening, and selection process.

Table 1. Baseline study and participant characteristics of included studies

Author, year, country	Title	Control			Experimental		
		No. of participants	Sex (M/F)	Mean age years (SD)	No. of participants	Sex (M/F)	Mean age years (SD)
Baker et al., 2023, USA	A randomized, double-blind, sham-controlled, clinical trial of auricular vagus nerve stimulation for the treatment of active RA	52	10/42	53.8	61	10/51	54.9
Drewes et al., 2020, Denmark†	Short-term transcutaneous non-invasive vagus nerve stimulation may reduce disease activity and pro-inflammatory cytokines in RA: results of a pilot study	-	-	-	36	5/31	56.22
Genovese et al., 2020, USA	Safety and efficacy of neurostimulation with a miniaturized vagus nerve stimulation device in patients with multidrug-refractory RA: a two-stage multicentre, randomized pilot study	4	2/2	55.0	10	1/9	49.3
Doko et al., 2016, Croatia†	Elektrostimulacija vagalnog živca u liječenju bolesnika s reumatoidnim artritisom - rezultati hrvatskog centra do 84. dana u sklopu međunarodnog pilot-istraživanja	-	-	-	2	1/1	Not reported

†The intervention was carried out on all study participants and, therefore, there is no control group.

Risk of bias assessment (Fig. 2)

Three studies raised some concerns[8,13,14], whereas one had a low risk of bias[15], as detailed in figure 2, outlining the assessed domains and overall risk of bias. The agreement between individual scores produced a Cohen's Kappa result of 0.744, demonstrating substantial agreement between the reviewers (see Table S3 in supplementary material). The level of evidence[16] for each outcome has been presented in figure 2.

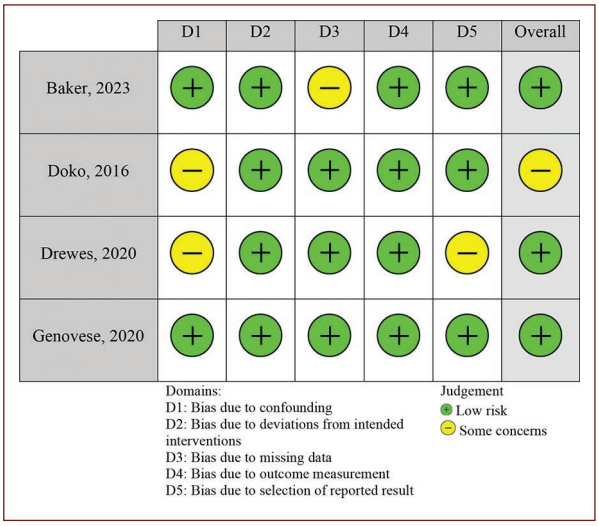

Figure 2. Risk of bias according to RoB 2.0 tool.

Study interventions and outcomes (Table 2)

Baker et al. instructed patients to use the device for 15 min daily[13]. The device emitted 20 kHz stimulation pulses with non-sensible amplitudes tailored to patient tolerance (median 2.6 mA, range 1.0-2.6, IQR 2.6-2.6). A total of 113 patients (mean age 54 years, 82% female) were enrolled, and 101 patients (89.4%) completed week 12. The American College of Rheumatology criteria 20 (ACR20) response at week 12 was 25.0% for active stimulation versus 26.9% for placebo (difference vs. placebo [95% CI]: –1.9 [–18.8-14[9], p = 0.823). The change in mean least squares in Disease Activity Score 28 with C-reactive protein (DAS28-CRP) was –0.95 ± 0.16 for active stimulation versus –0.66 ± 0.16 for placebo (p = 0.201); in the Health Assessment Questionnaire Disability Index (HAQ-DI), it was -0.19 ± 0.06 for active stimulation versus –0.02 ± 0.06 for placebo (p = 0.044). Adverse events occurred in 17 patients (15%), all mild or moderate. Auricular VNS did not significantly improve RA activity.

Doko et al. used stimulation for 60 s at 10 Hz, with a pulse duration of 250 μs and output currents from 0.25 to 2.0 mA[14]. Follow-ups were on the 1st and 4th days to assess blood biomarkers, and on the 7th day, patients received another 60-s stimulation and were instructed to use a magnet for daily at-home electrostimulation. VNS showed positive effects in both patients: DAS28 (7.00 and 6.22 vs. 4.03 and 2.13), Patient Global Assessment (PGA) (70 and 53 vs. 27 and 16), PtGA (48 and 43 vs. 15 and 14), tender joints (26 and 28 vs. 4 and 0), swollen joints (24 and 14 vs. 8 and 2), pain intensity (72 and 87 vs. 21 and 7), HAQ (2.25 and 2.25 vs. 1.5 and 1.375), and CRP (23.8 and 5.58 vs. 13 and 4.61). Fourteen days post-deactivation (day 56), CRP levels increased (13-16.3; 4.61-5.33), DAS28 (4.03-5.04; 2.13-2.18), and pain Visual Analog Scale (VAS) (21-73; 7-19). On day 84, subject 2's DAS28 (5.04-4.58) and VAS pain (73-28) decreased, whereas subject 1's DAS28 (2.18-3.19), and VAS pain (19-29) increased. The study concluded that VNS is effective in reducing clinical symptoms and inflammation in RA patients unresponsive to methotrexate therapy.

Drewes et al. used a device that administered 120 seconds of non-invasive transcutaneous VNS (n-VNS)[8]. Participants self-stimulated the left and right cervical vagus nerves three times daily (morning, afternoon, and evening) over 4 days. The device delivered approximate sinusoidal wave electrical pulses (1 ms [five waves, each 200 μs]), at 25 Hz with a maximum current of 60 mA, and voltage capped at 24 V. In participants with high RA disease activity, n-VNS did not change cardiac vagal tone (CVT), heart rate (HR), or diastolic blood pressure (BP), but reduced systolic BP by 12 mmHg (p = 0.003); DAS28-CRP decreased on days 2 and 5 (p = 0.02), as did interferon-gamma (p = 0.02), without changes in other cytokines. In those with low RA activity, n-VNS decreased CVT (p = 0.03) without changing HR or BP, and DAS28-CRP remained unchanged, though interleukin 10 decreased (p = 0.02). Participants with high RA activity had lower baseline CVT than those with low activity (3.6 ± 2 vs. 4.9 ± 3, p = 0.03).

Genovese et al. found the intervention safe and well-tolerated, reducing RA symptoms in patients resistant to multiple drug therapies[15]. They assessed outcomes using DAS28, PCR response, 20% improvement in ACR 20, ACR50, ACR70 responses, and EULAR response criteria.

Grading the evidence

The GRADE certainty of evidence rating and rationale used for each outcome measure are reported in full in

Table 2. Study methodology and summarized results of individual studies

Author, year	Intervention and its parameters	Intervention duration, N° of sessions, session duration	Usual care (control group)	Functional outcome measures	Measurement tool	Assessment timing (weeks)
Baker et al., 2023	VNS auricular nerves of the external ear, through customized auricular devices. – Pulse shape: biphasic square waves, current-controlled, and charge-balanced. – Stimulation frequency: 20 kHz. – Current amplitude: individually adjusted to imperceptible levels, with a median of 2.6 mA (range: 1.0 to 2.6 mA, interquartile range: 2.6-2.6 mA). – Session duration: 15 minutes, once daily.	12 weeks 84 sessions 15 min	Usual medications for RA	RA activity	ACR20; DAS28-CRP; HAQ-DI	0 (start of the study) 6th week 12th week
Drewes et al., 2020	VNS Cervical part of the vagus nerve (left and right sides) – Pulse frequency: 25 Hz (every 40 ms). – Maximum output current: 60 mA. – Adjustable voltage: Up to 24 V, depending on patient tolerance.	4 days 12 sessions 2 min	-	Vital signs RA activity	CVT HR BP DAS28-CRP IFN-γ	1st day (start of the study) 2nd day 5nd day
Genovese et al., 2020	VNS Left vagus nerve in the cervical region – Pulse frequency: 10 Hz. – Pulse duration: 250 μs. – Current intensity: Increased by 0.1 mA weekly until reaching the maximum tolerated level, with a limit of 2.5 mA.	12 weeks 84 or 252 sessions 1 min	Usual medications for RA	RA activity	DAS28-CRP ACR 20 ACR50 ACR70 EULAR	6 weeks before the study start 0 (start of the study) 1th week 2th week 3th week 4th week 5th week 6th week 8th week 12th week
Doko et al., 2016	VNS Left vagus nerve in the cervical region – Stimulation frequency: 10 Hz. – Pulse duration: 250 μs. – Current intensity: individually adjusted to the maximum tolerable level: range between 0.25 mA and 2.0 mA. The initial intensity was set at 0.75 mA for one participant and 1.0 mA for the other.	12 weeks (There was a break in intervention from week 6 to 8) 70 sessions 1 min	-	RA activity	DAS28; PGA PtGA HAQ PCR VSA pain	Day 1 Day 4 Day 7 2th week 3th week 4th week 6th week 8 th week 12 th week

RA: rheumatoid arthritis; ACR: American College of Rheumatology criteria; DAS28-CRP: disease activity score 28 with C-reactive protein; HAQ-DI: health assessment questionnaire disability index; CVT: cardiac vagal tone; HR: heart rate; BP: diastolic blood pressure; IFN-γ: interferon-gamma activity; EULAR: European League Against Rheumatism response criteria; PGA/PtGA: patient global assessment; VSA: Visual Analog Scale.

table S4 (see Table S4 in supplementary material). We found only one low-quality evidence (downgraded by one point due to some concerns regarding the risk of bias; inconsistency and imprecision, respectively) for the Disease Activity Score in 28 joints (DAS-28-CRP), as the articles present methodologies considerably heterogeneous, small samples and some concerns about the risk of bias, especially in Doko et al. in this aspect[14].

Discussion

The systematic review in this study presented a spectrum of VNS modalities administered over varying durations as a potential therapeutic intervention for RA. Some contrasts across the studies need careful analysis of stimulation techniques and possibly the demographic compositions of the studied populations. Such disparities underscore the critical need for discernment when considering the application of VNS in the context of RA treatment, particularly given that the studies were conducted in different countries and formulated different methodologies for intervention and participant inclusion.

The convergence in some studies results with broader literature validates the potential of VNS as a mechanism-based neuromodulating therapy for RA. The multifaceted anti-inflammatory effects of VNS, mediated through the cholinergic anti-inflammatory pathway and α7 nicotinic acetylcholine receptor subunit (α7nAChR), coalesce seamlessly with the theoretical framework underpinning VNS's role in autoimmune diseases. Acetylcholine acts as the cognate or "natural" ligand for α7 nicotinic acetylcholine receptors (α7nAChR) expressed on monocytes, macrophages, and cytokine-producing stromal cells, inhibiting inflammasome activation in macrophages exposed to lipopolysaccharide and other pro-inflammatory stimuli. This receptor serves as a central axis in the inhibition of pro-inflammatory cytokine release, thereby acting as a key mediator in the anti-inflammatory cascade. Acetylcholine's instrumental role in inhibiting inflammation through the α7 nicotinic acetylcholine receptor subunit dovetails with the tangible reductions in inflammation indicators and clinical symptoms evidenced in the reviewed studies[4,17,18].

The efficacy of VNS in RA treatment originates in the intricate interplay between the autonomic nervous system and the innate and adaptive immune responses[5]. The vagus nerve, as the principal parasympathetic nerve, plays a pivotal role in modulating inflammation. Recent research has unraveled the anti-inflammatory potential of the vagus nerve through various pathways[7]. This includes, first, the anti-inflammatory hypothalamic-pituitary-adrenal axis, cortisol release reduces pro-inflammatory cytokines, but its dysfunction in RA may impair the anti-inflammatory effect, second, the cholinergic anti-inflammatory pathway, which involves the interaction of acetylcholine with nicotinic receptors (α7nAChR) on macrophages, as previously mentioned and, finally, the splenic sympathetic anti-inflammatory pathway, which uses norepinephrine released by splenic nerves to inhibit the release of TNF-α, is also dysregulated in chronic inflammatory states[4,19,20]. One of the circuits widely described in the literature and worthy of note is the so-called "inflammatory reflex." This signaling mechanism, enhanced by vagal stimulation, has been shown to reduce the production of pro-inflammatory cytokines, thereby mitigating the severity of RA in experimental models[4]. These mechanisms collectively contribute to the suppression of pro-inflammatory cytokines, thereby dampening the immune response.

Looking ahead, the future of VNS in RA treatment appears promising. A pioneering study shed light on the critical involvement of the α7nAChR in the cholinergic anti-inflammatory pathway[19]. This revelation laid the foundation for exploring VNS as a potential therapeutic avenue for RA. Further studies have advanced our understanding of VNS techniques, ranging from invasive implantation to non-invasive transcutaneous stimulation, and their impact on musculoskeletal diseases[6,18,21-23].

Current research endeavors are steering toward refining VNS protocols, optimizing stimulation parameters, and delving into personalized approaches tailored to individual patient profiles. With the advent of novel device technologies, such as the AspireSR® and SenTiva™ VNS therapy systems, the landscape of VNS is undergoing rapid evolution, providing an increasingly precise and personalized treatment based on the best therapeutic approach for the patient, and consequently, making it safer and more effective overall[4,23-25]. Although the self-stimulant provides greater convenience for the patient and offers the described anti-inflammatory benefits, we have not yet found evidence in the literature suggesting an immediate response, as seen in the preventive treatment of epileptic seizures. These new technologies herald a new era in the application of VNS for not only epilepsy and depression but also for chronic inflammatory conditions such as RA[8,26,27].

Moreover, ongoing clinical trials are exploring the expansive potential of VNS in diverse domains. The investigation of VNS in stroke rehabilitation, chronic

heart failure, and inflammatory bowel disease represents a paradigm shift in our approach to utilizing this therapy[17]. In addition, studies investigating the effects of VNS on depression and cluster headaches hint at the far-reaching impact of this modality[28].

The exploration of VNS in the context of RA unveils a multifaceted approach to modulating inflammation. Understanding the relationship between the vagus nerve and RA could lead to innovative therapies, offering hope for an improved quality of life for RA patients. As we stand at the cusp of a new era in medical technology, the future of VNS in RA treatment holds great promise. With ongoing research endeavors and the advent of innovative device technologies, we are poised to unlock new dimensions in the therapeutic potential of VNS, not only in RA but across a spectrum of chronic inflammatory conditions.

This review highlights VNS as a promising frontier in innovative RA therapies, supported by its validation in the literature as a neuromodulatory therapy with anti-inflammatory mechanisms. Divergences among studies indicate the need for further exploration of confounding variables. Limitations include the lack of standardization in VNS characteristics, a limited number of studies, and research conducted in a few countries, necessitating testing in diverse populations and contexts. Ongoing research, exploring varied VNS protocols and advanced devices, promises new therapeutic perspectives, suggesting a shift in RA treatment. More studies are required to validate these findings and address the identified limitations.

Conclusion

From this perspective, the evidence supporting the use of VNS in RA appears to offer promising prospects, particularly for patients resistant to conventional pharmacological treatment. VNS was well tolerated and demonstrated relative safety in the studies reviewed, as most adverse events were mild and/or moderate, indicating its potential as a viable treatment option. Patients with high disease activity exhibited more notable reductions in inflammatory markers–C-reactive protein (CRP) and interferon-γ–and in the attenuation of clinical symptoms, compared to milder outcomes in patients with low disease activity. Thus, the integration of VNS as part of a multidisciplinary treatment approach seems to foster a new perspective in the management of RA, promoting significant improvements in patient's quality of life by alleviating symptoms and the functional impact of the disease. However, the limitations of this review may affect the quality of the presented results. Future research with greater methodological rigor in clinical trials, larger sample sizes, and longer intervention periods is essential to better evaluate clinical outcomes, the most benefited populations, and the long-term adverse events of the therapy.

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The authors declare that this work was carried out with the authors' own resources.

Conflicts of interest

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 study does not involve patient personal data nor requires ethical approval. The SAGER guidelines do not apply.

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

Supplementary data

Supplementary data are available at DOI: 10.24875/RMN.24000037. These data are provided by the corresponding author and published online for the benefit of the reader. The contents of supplementary data are the sole responsibility of the authors.

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ORIGINAL ARTICLE

Anxiety, depression, stress, executive functions, and academic performance: a post-COVID-19 study

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Abstract

Objective: *Low academic performance (LAP) is a concerning phenomenon in Mexico. Neuropsychology has emerged as a discipline to address this issue through executive functions. This study analyzed how anxiety, depression, academic stress, and executive dysfunctions (EDs) influence the academic performance (AP) of adolescents.* **Methods:** *A quantitative, non-experimental approach with correlational and explanatory scope was employed. 147 high school students from the state of Puebla (Mexico) participated.* **Results:** *Depression and coping with academic stress explained AP (R^2 = 0.089, F = 7.013, p ≤ 0.001). Furthermore, better performance in tasks assessing inhibitory control (R^2 = 0.190, F = 16.938, p ≤ 0.001), verbal working memory (R^2 = 0.176, F = 10.185, p ≤ 0.001), phonological and semantic verbal fluency (R^2 = 0.207, F = 12.415, p ≤ 0.001), abstract attitude, and comprehension of figurative meaning (R^2 = 0.179, F = 10.403, p ≤ 0.001) also explained AP.* **Conclusions:** *The importance of considering depression, academic stress, and ED to understand and address LAP is highlighted, which will guide effective educational interventions.*

Keywords: *Anxiety. Depression. Academic stress. Executive functions. Academic performance.*

Ansiedad, depresión, estrés, funciones ejecutivas y rendimiento académico: un estudio post COVID-19

Resumen

Objetivo: *El bajo rendimiento académico (BRA) es un fenómeno preocupante en México. La neuropsicología ha surgido como una disciplina para abordar este problema a través de las funciones ejecutivas (FE). Este estudio analizó cómo la ansiedad, la depresión, el estrés académico y las disfunciones ejecutivas influyen en el rendimiento académico (RA) de los adolescentes.* **Métodos:** *Se empleó un enfoque cuantitativo, no experimental, con un alcance correlacional y explicativo. Participaron 147 estudiantes de secundaria del estado de Puebla (México).* **Resultados:** *La depresión y el afrontamiento al estrés académico explicaron el RA (R^2 = 0.089, F = 7.013, p ≤ 0.001). Además, un mejor desempeño en tareas que evalúan el control inhibitorio (R^2 = 0.190, F = 16.938, p ≤ 0.001), la memoria de trabajo verbal (R^2 = 0.176, F = 10.185, p ≤ 0.001), la fluidez verbal fonológica y semántica (R^2 = 0.207, F = 12.415, p ≤ 0.001), la actitud abstracta y la comprensión del sentido figurado (R^2 = 0.179, F = 10.403, p ≤ 0.001) también explicaron el RA.* **Conclusiones:** *Se destaca la importancia de considerar la depresión, el estrés académico y las disfunciones ejecutivas para comprender y abordar el BRA, lo que guiará intervenciones educativas efectivas.*

Palabras clave: *Ansiedad. Depresión. Estrés académico. Funciones ejecutivas. Rendimiento académico.*

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Introduction

Academic performance (AP) is often reflected in numerical terms or grades, representing students' level of learning, effort, and success in an educational. When students fail to meet the objectives and competencies set by teachers, they are identified as cases of low AP (LAP)[1]. In Mexico, LAP is a significant concern, evidenced by the PISA 2022 results showing a marked decline in Mathematics and Science performance compared to 2018. Mexico ranked third worst in Mathematics and reading comprehension and had the lowest score in Science[2].

This decline is largely attributed to the COVID-19 pandemic lockdowns, as online classes significantly impacted learning. Parents and caregivers reported a deterioration in AP, with teachers noting greater difficulties in subjects such as Reading and Mathematics[3]. LAP's adverse consequences include school dropout, which exposes adolescents to risks like joining criminal gangs or adopting antisocial behaviors, and developing issues such as alcoholism or drug addiction. In addition, psychological consequences have been identified in adolescents with LAP, including suicidal behavior, depression, and low self-esteem due to frustration at not achieving academic success.

During the COVID-19 pandemic, there was a significant increase in these symptoms. In regions like North America, psychological impacts such as anxiety, stress, and depression were reported[4], negatively affecting students' concentration and mood, especially during the transition from distance to in-person education, resulting in a sense of disconnection impacting AP[5]. In addition, executive functions (EF), including inhibitory control, working memory, and cognitive flexibility, essential for managing academic tasks, were also negatively affected.

This study aims to evaluate anxiety, depression, academic stress, and executive dysfunction in secondary school students and their relationship with AP post-pandemic.

Materials and methods

A quantitative, non-experimental, cross-sectional study with correlational and explanatory scope was conducted.

A total of 162 adolescents from a secondary school in the state of Puebla (Mexico) participated, of which 147 (51.7% male and 48.2% female) met the inclusion criteria: (1) adolescents without learning difficulties, (2) without physical or sensory limitations, (3) active and enrolled in the educational institution where the research was conducted, (4) voluntary participation with parental or guardian consent. Table 1 describes the sample characteristics.

Although the sample is not representative of the entire state of Puebla, it is representative of the secondary school where the study took place, which had a total of 232 students at the time of the evaluation. The representativeness of the sample was determined by calculating a margin of error of 5% and a confidence level of 95%, resulting in a required sample size of approximately 146 students. However, the sample was selected through convenience sampling, meaning that participation was voluntary and limited to those who were willing to participate.

To assess anxiety, the Spanish version of the "Generalized Anxiety Disorder 7-item scale" was used. This screening tool evaluates the frequency of generalized anxiety symptoms through seven Likert-type questions ranging from 0 (never) to 3 (almost every day). A score ≥ 10 could indicate the presence of moderate-to-severe generalized anxiety disorder. The instrument's reliability in Mexican population was 0.93[6]. For this study, Cronbach's α reliability was 0.80.

To assess depression, "The Patient Health Questionnaire (PHQ-9)" was used. This screening tool evaluates the frequency of depressive symptoms through nine items with responses ranging from 0 (None) to 3 (Almost every day). A score ≥ 10 could indicate the presence of moderate-to-severe depressive disorder. The reliability in Mexican population was 0.81[7]. For this study, it was 0.80.

To assess academic stress, the Systemic Cognitive Inventory (SV-21) was used[8]. It consists of 23 items, a dichotomous first filter with yes and no options to determine if the participant is a candidate for evaluation, and a second item that evaluates the intensity of academic stress with responses from 1 = little to 5 = a lot. The remaining 21 items are grouped into three dimensions with seven items each: (1) stressors, (2) symptoms or reactions to stressors, and (3) coping strategies. Each factor includes response anchors from 0 = never to 5 = always. A mean of 0 to 2.38 indicates a low level of academic stress, 2.39-3.0 a moderate level, and 3.1-5.0 a severe level. The reliability was 0.83 for the stressor's subscale, 0.87 for symptoms, and 0.85 for coping strategies. In this study, it was 0.78 for stressors, 0.86 for symptoms, and 0.85 for coping strategies.

The overall average for the school year (2022-2023) was considered. AP was classified into low, medium, and high categories based on the following criteria:

Table 1. Sample characteristics (n = 147)

Variable	F (%)
Sex	
Male	76 (51.7)
Female	71 (48.2)
Age	
12	51 (34.6)
13	51 (34.6)
14	35 (23.8)
15	10 (6.8)
School grade	
1st year	70 (47.6)
2st year	77 (52.4)
Schooling	
7 years	64 (43.5)
8 years	77 (52.3)
9 years	6 (4.0)
Handedness	
Right-handed	135 (91.8)
Left-handed	11 (7.5)
Ambidextrous	1 (0.7)
Academic performance	
Low	93 (63.2)
Medium	48 (32.6)
High	6 (4.0)

a score below 7 indicates LAP, 8 indicates medium AP, and between 9 and 10 indicates high AP.

The Neuropsychological Battery of EFs and Frontal Lobes-3 was applied[9]. This instrument, validated for the Mexican population, consists of 15 tests for ages 6-90. The battery evaluates functions corresponding to the orbitofrontal, medial, dorsolateral, and anterior prefrontal cortex. It includes tasks to assess: inhibitory control, rule-following, risk-benefit processing, visual self-directed working memory, verbal-serial working memory, sequential visuospatial working memory, verbal fluency, productivity, mental flexibility, visuospatial planning, sequential planning, reverse sequencing, coding control, metamemory, comprehension of figurative meaning, and abstract attitude. The normalized scores classify performance as high normal (> 116), normal (85-115), mild-moderate impairment (70-84), and severe impairment (< 69).

The battery has shown adequate psychometric properties, with inter-rater reliability reported at 0.80, ensuring consistent scoring between examiners.

A meeting was held with the school principal to obtain permission for the study, explaining the objectives and purpose of the research. Upon consent, a meeting with parents or guardians was conducted to request permission, and those who provided consent signed the informed consent. Their children were then contacted to request informed assent, explicitly detailing confidentiality, anonymity, and voluntary participation guarantees[10].

Before its implementation, the project was reviewed in its methodological and ethical aspects by a committee of researchers designated by the Subdirectorate of Graduate Studies at the Faculty of Psychology of the *Universidad Autónoma de Nuevo León*.

The neuropsychological battery and questionnaires were administered 5 months after resuming in-person classes post-COVID-19 lockdown, from December 2022 to April 2023. The evaluation was conducted individually in a designated, interference-free space provided by the educational institution. The evaluation time was 60-90 min.

The Jeffrey's Amazing Statistics Program was used. First, descriptive statistics such as mean and standard deviation (SD) were obtained for each variable. Then, Spearman's rho non-parametric correlations were conducted, interpreting correlation strength using the following criteria: 0.1-0.3 = weak, 0.4-0.6 = moderate, 0.7-0.9 = strong.

A stepwise multiple regression analysis was also conducted to select a subset of AP predictor variables. This analysis was performed in separate models, considering psychological variables and cognitive function variables related to orbitofrontal, anterior prefrontal, and dorsolateral regions. This strategy aimed to reduce model overfitting risk and simplify result interpretation. For supplementary analyses comparing anxiety symptoms among students with low, medium, and high AP, the Kruskal–Wallis H test was used.

Results

More than half of the participants were male, with an average age of 13.02 (SD = 0.929) and schooling of 7.60 (SD = 0.568). The average AP was 7.68 (SD = 0.743), and over 60% had low AP (Table 1).

The average levels of anxiety, depression, and academic stress symptoms in the sample were mild. Weak and negative correlations were found between AP and both depression and academic stress symptoms. In addition, both positive and negative correlations were observed in the Stroop A and B indicators. Negative correlations were also found with verbal working memory tasks, with the most notable being with alphabetical ordering (trial number 2). Finally, phonological verbal fluency was one of the main variables associated with AP (Table 2).

Table 2. Descriptive statistics and correlations with academic performance

Psychological and neuropsychological variables	$\bar{X}$	SD	Rho
Psychological variables			
Anxiety	8.06	4.950	–0.058
Depression	7.75	5.512	–0.235**
Stressors	1.70	0.738	–0.110
Academic stress symptoms	1.47	0.846	–0.176*
Academic stress coping	1.83	0.832	0.070
Orbitofrontal region			
Mazes (crossing)	0.476	0.960	0.005
Cards (risk percentage)	35.9	8.732	0.017
Card game (total score)	17.5	12.29	0.058
Stroop A (stroop errors)	3.14	4.589	–0.339***
Stroop A (time)	116.9	37.70	–0.401***
Stroop A (correct)	79.0	6.323	0.357***
Stroop B (Stroop errors)	2.95	5.229	–0.353***
Stroop B (time)	95.8	32.52	–0.463***
Stroop B (correct)	80.9	5.255	0.334***
Classification (errors)	0.918	0.955	0.119
Total (natural)	186.5	13.42	0.436***
Anterior prefrontal region			
Semantic classification (abstracts)	1.53	1.406	0.164*
Proverbs (time)	128.6	50.95	–0.283***
Proverbs (correct)	3.27	0.965	0.275***
Metamemory (negative errors)	3.18	2.867	0.085
Metamemory (positive errors)	3.14	2.674	–0.068
Total (natural)	14.14	2.700	0.265**
Dorsolateral region - working memory			
Self-directed pointing (perseverations)	2.96	3.001	–0.070
Self-directed pointing (time)	74.7	48.74	–0.157
Self-directed pointing (correct)	18.1	3.844	0.122
Subtracting 40-3 (time)	68.5	44.32	–0.202*
Subtracting 40-3 (correct)	9.57	3.103	0.157
Subtracting 100-7 (time)	156.9	82.10	–0.216**
Subtracting 100-7 (correct)	7.42	4.409	0.209*
Adding (time)	67.8	40.61	–0.158
Adding (correct)	17.65	4.001	0.196*
Alphabetical order (Trial 1)	3.21	1.602	–0.252**
Alphabetical order (Trial 2)	5.59	0.881	–0.323***
Alphabetical order (Trial 3)	5.69	0.816	–0.281***
Visuospatial memory (max level)	2.51	0.982	–0.022
Visuospatial memory (perseverations)	0.279	0.649	0.144
Visuospatial memory (order errors)	3.00	2.348	–0.046
Dorsolateral region - executive function			
Mazes (planning - dead end)	0.646	0.985	–0.114
Mazes (time)	36.3	14.03	–0.178*
Card sorting (correct)	36.7	10.45	0.203*
Card sorting (perseverations)	7.85	5.451	–0.172*
Card sorting (delayed perseverations)	7.72	4.456	–0.136
Card sorting (time)	350.8	104.3	–0.099
Semantic classification (categories)	3.32	1.277	0.218**
Semantic classification (animal average)	6.57	2.078	0.075
Semantic classification (total score)	7.88	3.618	0.207*
Verbal fluency (correct)	9.84	3.878	0.360***
Verbal fluency (perseverations)	0.701	0.925	0.014
Tower of Hanoi (3 discs - moves)	10.74	5.657	0.127
Tower of Hanoi (3 discs - time)	128.6	50.95	0.106
Tower of Hanoi (4 discs - moves)	26.63	13.07	0.139
Tower of Hanoi (4 discs - time)	106.5	65.26	0.047
Total (natural)	166.7	23.17	0.321***

*p < 0.05; **p < 0.01; ***p < 0.001. $\bar{X}$: mean; SD: standard deviation; Rho: correlation coefficient.

Table 3. Multiple regression between anxiety, depression, academic stress, and academic performance

Predictor variables	β	t	p	Collinearity	
				Tolerance	VIF
Model with anxiety variable					
(Intercept)		49.596	< 0.001		
Depression	–0.481	–3.917	< 0.001	0.411	2.434
Coping strategies	0.207	2.430	0.016	0.855	1.170
Anxiety	0.250	2.066	0.041	0.423	2.365
Model without anxiety variable					
(Intercept)		51.521	< 0.001		
Depression	–0.361	–3.469	< 0.001	0.862	1.160
Coping strategies	0.199	2.600	0.010	0.862	1.160

β: regression coefficient; t: student's t; p: statistical significance; VIF: variance inflation factor.

A relationship was found between psychological variables and AP (R^2 = 0.115, F = 6.204, p ≤ 0.001); specifically, depression (β = –0.481), coping with academic stress (β = 0.207), and anxiety (β = 0.250). To obtain a more precise model of the psychological variables explaining AP, anxiety was excluded from the analysis as it did not show a significant correlation with AP (Table 2). The result of the final model indicated a statistical relationship (R^2 = 0.089, F = 7.013, p ≤ 0.001); with the variables of depression (β = –0.361) and coping with academic stress (β = 0.199) (Table 3).

In addition, to analyze the role of anxiety in AP, the Kruskal–Wallis test revealed no significant differences (χ^2 = 1.032; p = 0.597) (Fig. 1), between the low AP group (8.32 ± 4.762), medium AP group (7.75 ± 5.261), and high AP group (6.66 ± 5.785), although a trend in the mean can be observed, where the low AP group exhibits the highest levels of anxiety.

Tasks related to the orbitofrontal region showed an association with inhibitory control tasks (R^2 = 0.190, F = 16.938, p ≤ 0.001), specifically in time (β = –0.352) and the number of errors in Stroop B (β = –0.173). Tasks related to the anterior prefrontal region also showed a statistical relationship, especially those related to abstract attitude and understanding figurative meaning (R^2 = 0.179, F = 10.403, p ≤ 0.001); such as time (β = –0.255) and the number of correct responses in the proverbs test (β = 0.201). In addition, the number of abstract categories generated by participants during the semantic classification task (e.g., categories like 'marine animals' or 'carnivores') showed a positive association (β = 0.161).

An association was also identified in working memory tasks (R^2 = 0.176, F = 10.185, p ≤ 0.001), specifically in verbal working memory tasks, such as the number of trials in list three (β = –0.231) and two (β = –0.190), as well as

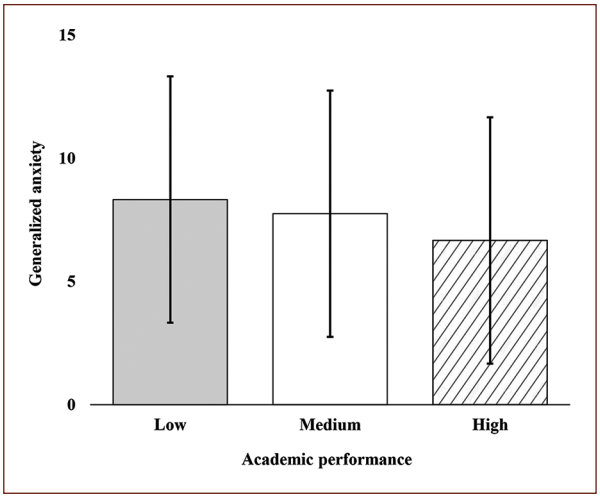

Figure 1. Comparison of generalized anxiety among groups.

the time in the consecutive subtraction 100-7 (β = –0.183). Finally, in EF tasks, a relationship with AP was found (R^2 = 0.207, F = 12.415, p ≤ 0.001), especially with tasks of phonological verbal fluency, in the number of correct responses (β = 0.373) and semantic fluency, in the total number of categories (β = 0.183); and finally, the time to solve the three-disc Tower of Hanoi (β = 0.166) (Table 4).

A statistical association was also found in the natural scores of each region (R^2 = 0.202, F = 18.173, p ≤ 0.001), especially the total score of the orbitofrontal region (β = 0.018) and the anterior prefrontal region (β = 0.062) (Table 5).

Discussion

The aim of the study was to evaluate the psychological variables of anxiety, depression, and academic

Table 4. Multiple regression between the functions of each region evaluated by BANFE-3 and academic performance

Neuropsychological tests by region	β	t	p	Collinearity	
				Tolerance	VIF
Orbitofrontal					
(Intercept)		48.925	< 0.001		
Stroop B (time)	−0.352	−4.484	< 0.001	0.910	1.098
Stroop B (stroop errors)	−0.173	−2.198	0.030	0.910	1.098
Prefrontal anterior					
(Intercept)		27.067	< 0.001		
Proverbs (time)	−0.255	−3.271	0.001	0.943	1.061
Proverbs (correct)	0.201	2.523	0.013	0.903	1.107
Abstract categories	0.161	2.058	0.041	0.943	1.060
Dorsolateral. Working memory					
(Intercept)		21.822	< 0.001		
List 3 (trials)	−0.231	−2.830	0.005	0.861	1.161
Subtracting 100-7 (time)	−0.183	−2.377	0.019	0.970	1.031
List 2 (trials)	−0.190	−2.300	0.023	0.845	1.184
Dorsolateral. Executive function					
(Intercept)		30.917	< 0.001		
Verbal fluency (correct)	0.373	4.879	< 0.001	0.948	1.055
Semantic (categories)	0.183	2.403	0.018	0.955	1.047
Tower of Hanoi (3 discs-time)	0.166	2.201	0.029	0.979	1.021

β: regression coefficient; t: student's t; p: statistical significance; VIF: variance inflation factor; BANFE-3: battery of EF and frontal lobes.

Table 5. Multiple regression between the total scores of each region and academic performance

Total scores by prefrontal cortex region	β	t	p	Collinearity	
				Tolerance	VIF
(Intercept)	3.382	4.362	< 0.001		
Orbitofrontal	0.018	4.290	< 0.001	0.925	1.081
Prefrontal anterior	0.062	2.898	0.004	0.925	1.081

β: regression coefficient; t: student's t; p: statistical significance; VIF: variance inflation factor.

stress and the executive dysfunction that explains AP after the pandemic. In the first model of psychological variables, anxiety was identified to have a positive effect on AP, contradicting the direction of the direct correlation found, which was not significant. Considering this and the absence of significant differences in the comparison between AP groups, the variable was excluded and a second model was presented where the results showed that lower frequency of depressive symptoms and higher frequency of coping strategies for academic stress explained AP.

The negative relationship between depression and AP contrasts with previous studies that found no significant relationship[11]. However, these data align with other research[12,13], which can be explained by the effects that depression can have on adolescents, such as lack of concentration, constant fatigue, sleep disorders, and loss of appetite, which affect school performance[14]. It is important to highlight that the evaluation was carried out 5 months after the return to face-to-face classes due to the COVID-19 confinement. Meta-analytic reviews have shown that mental health problems, including depressive symptoms, persisted in children and adolescents after the pandemic[15].

The positive relationship between coping strategies for academic stress and AP has been supported by other research. Even during the COVID-19 pandemic, it was found that having adequate coping strategies could help adolescents reduce their stress levels, make clear and rational decisions, increase resilience, and

emotional well-being, which would benefit AP[16,17]. On the other hand, regarding EFs and AP, it was found that better performance in inhibitory control indicators is related to better AP. This is because inhibitory control is responsible for regulating automatic and impulsive responses, both at the level of attention and behavior. Students with difficulties in inhibitory control tend to be easily distracted by external stimuli and exhibit excessive motor restlessness[18,19]. This cognitive function gained special relevance after the COVID-19 pandemic, as negative effects of prolonged time in front of electronic devices on students were reported[20]. It was also found that better performance in tasks evaluating verbal working memory, such as the number of trials in the second and third-word list, can predict AP. These findings are in line with other research highlighting the importance of verbal working memory, especially in subjects such as Reading and Mathematics[21-23]. It has been explained that verbal working memory has important implications in language comprehension and production, as well as in long-term retention of information. Therefore, better performance could provide significant advantages in the ability to understand and remember concepts presented in class, as well as to express ideas clearly and coherently[24].

The model revealed that performance in phonological and semantic verbal fluency is related to better AP. These results are consistent with research in university students and adolescents that identified lower performance in these two functions in students with LAP[25-27]. In the case of semantic verbal fluency, neuroimaging studies have shown greater activation in the left temporal cortex, which is mainly associated with language processing and semantic memory, including the comprehension and production of word meanings and the knowledge of concepts[28]. This function facilitates effective communication, critical thinking, and the assimilation of new knowledge, fundamental aspects for achieving better AP[29].

On the other hand, phonological verbal fluency involves linguistic mechanisms associated with fronto-temporal regions, essential for communication[30]. The application of this test involves evoking as many verbs in the infinitive as possible in 1 min, which also requires other skills such as strategy searching, sustained attention, anticipation ability before a task, goal setting and achievement, time planning and organization, essential aspects for academic success[1,31,32]. Even the assessments of semantic and phonological verbal fluency have been proposed as effective tools to detect academic difficulties in students[25].

Within the model, it was also observed that longer time in solving the three-disc Tower of Hanoi was associated with better AP. This test evaluates planning and problem-solving ability. Although no similar studies were found that could explain these results, they could be attributed to the fact that students require more time because they use a more methodical and reflective approach to solve it. However, caution is suggested when interpreting these results, as the main indicator of the Tower of Hanoi (number of moves) did not show a significant relationship. In addition, during its application, it was observed that not all students solved it with the correct number of moves and without making errors (moving two discs at a time and without placing a smaller disc under a larger one). It has been reported that the temporal parameters of this test do not show stability when measured and related to other variables due to various factors, both individual and related to the nature of the test[33]. This suggests that the resolution time alone may not be a completely reliable indicator of cognitive performance.

On the other hand, it was found that better performance in the proverb test, which evaluates the ability to understand figurative meaning, explains AR. These results differ from those obtained in university students, where no significant associations were found[34]. However, they may align with other findings, which showed that students with learning difficulties perform worse in tests of figurative understanding compared to students without learning difficulties[35]. This is explained by the fact that the academic context often involves the use of figurative language, which requires students to go beyond the literal meaning of words. This approach fosters critical thinking and the ability to analyze problems from different perspectives, essential skills in various academic disciplines. It was also found that a higher number of abstract categories explains AP, results that resonate with other studies conducted on university students[36]. This can be explained by the fact that the ability to think abstractly allows for identifying patterns, formulating hypotheses, and solving problems effectively. Furthermore, an abstract attitude facilitates the development of original and creative ideas, which is essential for solving problems in the educational field[37].

Finally, it was revealed that the raw scores of the orbitofrontal and anterior prefrontal regions are the best predictors of AP. This aligns with research suggesting that the orbitofrontal region plays an important role in behavior control, decision-making, and emotional

processing[38]. Deficits in this area can influence behavioral problems that affect learning[39]. It has been suggested that stimulating cognitive processes in this region allows for academic success[40]. On the other hand, the anterior prefrontal region houses "metafunctions," which are higher-order cognitive processes, such as metamemory, understanding figurative meaning, and abstract attitude which are essential for tackling academic problems creatively and unconventionally[9].

The study presents some limitations. First, the sample was not representative of the entire state of Puebla, making it difficult to generalize the results; however, the sample size is adequate for the conclusions reached, and the study has adequate internal validity. The GAD-7 and PHQ-9 instruments are screening tools for initial assessment and cannot replace a complete clinical diagnosis. In addition, being self-report questionnaires, there is the possibility of social desirability bias. In the statistical analysis of EFs, only quantitative measures were used, which might not fully capture the complexity of cognitive processes.

Conclusion

The study evaluated anxiety, depression, academic stress, executive dysfunctions, and their relationship with AP post-pandemic. It was found that a lower frequency of depression symptoms and better management of academic stress were associated with higher AP. In addition, better performance in inhibitory control, verbal working memory, verbal fluency, understanding figurative meaning, and abstract attitude were related to better AP. These findings highlight the importance of addressing both psychological and cognitive aspects to understand AP post-pandemic.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that the procedures followed complied with the ethical standards of the responsible human experimentation committee and adhered to 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 have followed their institution's confidentiality protocols, obtained informed consent from patients, and received approval from the Ethics Committee. The SAGER guidelines were followed according to the nature of the study.

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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ORIGINAL ARTICLE

Assessment of creative thinking and executive functions in patients with frontal lobe meningioma

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Abstract

Objective: *To describe the effect of a pathology such as a meningioma-type tumor in the frontal lobe on executive functions (EF) and creative thinking, as well as determining if differences are found according to their hemispheric location and by frontal regions (medial, dorsolateral and orbitofrontal).* **Methods:** *12 patients with frontal meningioma and 12 controls were evaluated with EF tests. For creative thinking, the Torrance Test of Creative Thinking (TTCT) was used in its two verbal and figural dimensions.* **Results:** *In the comparison between patients and controls, no significant differences were observed in the scores of the TTCT. In the EF, differences were found in the components of visuospatial working memory, semantic fluency, inhibition, flexibility, abstraction, and processing speed. Regarding the laterality of the tumor, patients showed a greater deterioration in flexibility and inhibition components when the tumor was located in the left hemisphere. According to the frontal regions, when the tumor was located in the dorsolateral and orbitofrontal regions, it impaired performance in cognitive flexibility and decision-making. In the properties of elaboration and abstraction of titles of the figural scale of the TTCT, patients presented poor performance when the tumor was located in the dorsolateral region, compared to the medial region. Significant relationships were found between visuospatial working memory and the properties of the creative thinking test.* **Conclusions:** *Changes were observed in patients with frontal tumors in the evaluated processes due to the structural and functional compromise caused by its location.*

Keywords: *Creative thinking. Executive function. Pre-frontal cortex. Laterality. Meningioma.*

Evaluación del pensamiento creativo y funciones ejecutivas en pacientes con meningioma del lóbulo frontal

Resumen

Objetivo: *Describir el efecto de una patología como un tumor tipo meningioma en el lóbulo frontal, sobre las Funciones Ejecutivas (FE) y el pensamiento creativo. Así como, si se encuentran diferencias según la localización hemisférica y por regiones frontales (medial, dorsolateral y orbitofrontal).* **Métodos:** *Se evaluaron 12 pacientes con meningioma frontal y 12 controles con pruebas de FE, y para pensamiento creativo se utilizó el Test de Torrance de Pensamiento Creativo (TTPC) en sus dos dimensiones verbal y figural.* **Resultados:** *En la comparación entre pacientes y controles, no se observaron diferencias significativas en las puntuaciones del TTCT. En el EF, se encontraron diferencias en los componentes de memoria*

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de trabajo visoespacial, fluidez semántica, inhibición, flexibilidad, abstracción y velocidad de procesamiento. En cuanto a la lateralidad del tumor, los pacientes mostraron un mayor deterioro en los componentes de flexibilidad e inhibición cuando el tumor se localizaba en el hemisferio izquierdo. Según las regiones frontales, cuando el tumor se localizaba en las regiones dorsolateral y orbitofrontal, perjudicaba el rendimiento en flexibilidad cognitiva y toma de decisiones. En las propiedades de elaboración y abstracción de títulos de la escala figural del TTCT, los pacientes presentaron un pobre rendimiento cuando el tumor se localizaba en la región dorsolateral, en comparación con la región medial. Se encontraron relaciones significativas entre la memoria de trabajo visoespacial y las propiedades del test de pensamiento creativo. **Conclusiones:** *Finalmente, se observaron cambios en los pacientes con tumor frontal en los procesos evaluados, debido al compromiso estructural y funcional que ocasiona su localización.*

Palabras clave: *Pensamiento creativo. Función ejecutiva. Corteza pre-frontal. Lateralidad. Meningioma.*

Introduction

Creativity, as a cognitive process, is studied based on creative or divergent thinking[1]. It has two defining characteristics: the ability to produce responses that are both novel (original, rare, and unexpected) and appropriate (adaptive and useful according to the task constraints)[2]. Thanks to advances in neuroimaging techniques, the involvement of the pre-frontal cortex (PFC) in creativity has been documented[3-5]. This may be because the PFC regulates all higher cognitive functions, also known as executive functions (EF).

Much of our knowledge of cognitive processes has been obtained by studying individuals who have suffered damage in structures of the brain. It is no different for the issue of creativity. Lesions in the medial area (mPFC) can produce a decreased creative drive. The importance of the dorsolateral area (DLPFC) for working memory and flexible problem-solving suggests a greater role in creative skill, while orbitofrontal (oPFC) lesions may have a partly opposing effect[6]. Besides, in the study by Perfil'ev et al.[7], left pre-frontal damage showed a tendency to decrease verbal creativity and the fluency component of visual creativity.

Therefore, the purpose of this study was to describe the effect of frontal damage on verbal and figural creative thinking and EF. Although several studies have attempted to determine the participation of the PFC and each of its areas, they all have methodological deficiencies. In some, the type of pathology studied has generalized effects due to diffuse deterioration, which makes it difficult to establish a relationship with a specific area. Examples of this include reports on patients with neurodegenerative diseases[8] or brain lesions such as head injury, strokes[9], and surgery for epilepsy or brain tumors[7-10]. Another issue is that the pre-frontal areas have not yet been delimited, so it is not possible to know the specific participation of each one.

Materials and methods

Participants

Patients with meningioma-type tumor in the frontal lobe were recruited from the National Institute of Neurology and Neurosurgery (NINN) in Mexico City, Mexico, where they had received medical attention and were within the surgical protocol for tumor resection. The diagnosis was made according to the histopathological report performed on the biopsies of patients. They were evaluated before treatment (surgery, chemotherapy, or radiotherapy). Furthermore, healthy control participants matched by age, gender, and education were evaluated. The exclusion criteria applied were as follows: concomitant neurological or psychiatric diseases, antecedents of drug abuse, visual impairment, severe language deficits, and motor limitations that might affect their ability to perform creative tasks.

Instruments

Creative thinking was assessed using the two scales of the Torrance Test of Creative Thinking (TTCT): figural (TTCT-F)[11], and verbal (TTCT-V)[12], using the validated Spanish version in both cases[13]. The equivalent A and B forms were applied. TTCT generates scores for the following dimensions of the creative process. For the verbal scale: (1) fluency, that is, the number of relevant responses defined in terms of the requirements of the specific tasks or activities; (2) flexibility, or the number of different categories represented, which measures the ability to move from one conceptual field to another; and (3) originality, which reflects the number of unusual responses, understood as statistically-infrequent ideas (Fig. 1A). For the Figural (graphic) scale, meanwhile, the properties assessed were: (1) fluency; (2) originality–as defined above–(3) elaboration, or the number of details in each response; (4) resistance to

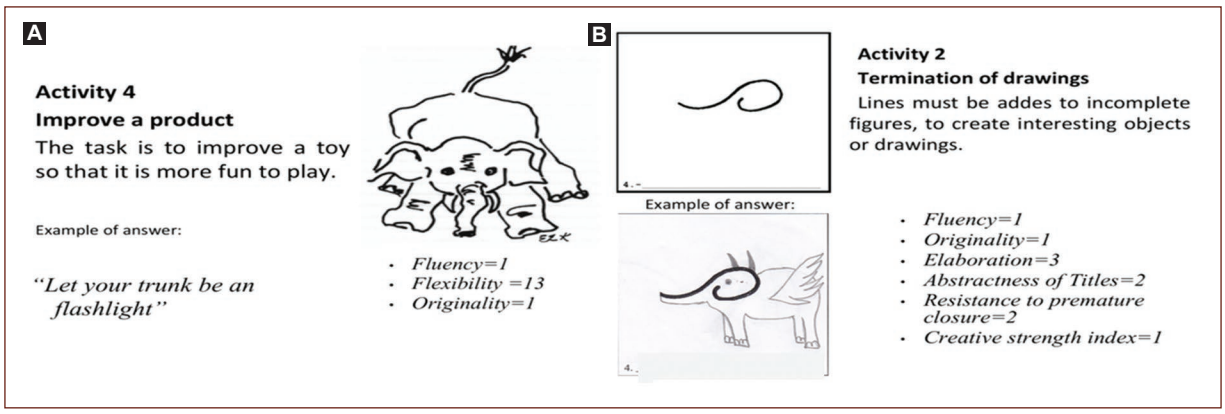

Figure 1. A and **B**: examples of items, response and score of the verbal and figural Torrance Test of Creative Thinking.

pre-mature closure, which reflects the ability to remain open to uncertainty; and (5) abstractness of titles, or the degree of abstraction versus concreteness. In addition, scores are given for such creative strengths as emotional expressiveness, storytelling articulateness, movement or action, expressiveness of titles, synthesis of incomplete figures, unusual visualization, internal visualization, extending or breaking boundaries, humor, richness of imagery, colorfulness of imagery, and fantasy (Fig. 1B).

To evaluate executive functioning, the neuropsychological tests described in table 1 were used.

Procedure

A descriptive-correlational study was carried out, which was approved by the bioethics committee of the NINN (protocol number 49/12). All participants were given an informed consent to sign (Table 1)[14]. The main components related to the functioning of the PFC are shown below, as well as the neuropsychological instruments for its evaluation and its specific location.

To determine the frontal area involved by the meningioma (due to compression effect of the cranial region) in the medial, orbital, and dorsolateral regions, the hemispheric laterality, and the measurement of volume and edema, brain images were analyzed by structural Magnetic Resonance Imaging (sMRI) using 8-channel Magnetic Resonance GE Signa Excite II, Tesla 3 equipment. Volumetry of the tumor mass was obtained using the program IPlan® (BrainLAB, Heimstetten, Germany). Sequence T1 and T2 MRI was utilized. For the anatomical mapping of lesions, the study had the support of expert neuroradiologists from the NINN who were blind to our hypotheses.

To identify the specific area of the frontal lobe where the tumor was located, the following criteria were considered:[15] (1) mPFC area, where damage involved the area between the superior frontal sulcus and medial orbitofrontal gyrus (Brodmann areas 8,9,10,11,12,24,32); (2) oPFC area, when the tumor was located between the medial sulcus of the H-shaped gyrus and the lateral surface of the third frontal convolution (Brodmann areas 10,11,13,47); and (3) dlPFC area, where the tumors affected the region from the superior frontal sulcus to the inferior frontal sulcus (Brodmann areas 8,9,10,11,44,45,46,47). To obtain the volume (space occupied by the tumor) and the edema (pathological increase in the amount of water in the brain with an increase in the volume of the brain parenchyma), the dimension of the lesion in cm^3 was recorded in the longitudinal, transverse and coronal planes, and its volume was calculated using the volumetric measurement technique.

All patients were evaluated individually from 1 to 30 days before tumor resection, in a consulting room or in the NINN hospitalization area; both spaces had optimal environmental conditions and no distractions. In the case of the control group, these were healthy participants who met the selection criteria. They were evaluated individually in one to two sessions, in an isolated room under suitable conditions and without environmental distractions.

Statistical analysis

All statistical analyses were carried out using the software IBM Statistical Package for the Social Sciences (SPSS) 21 (SPSS Inc., Chicago, IL, USA). The level of statistical significance was set at p = 0.05 for

Table 1. The main components related to the functioning of the PFC are shown below, as well as the neuropsychological instruments for its evaluation and its specific location (*adapted from Climent-Martínez et al.*[14])

Components	Test	Frontal cortex areas involved
Working memory (verbal and visuospatial)	Indirect visual and Verbal spans	PFC dorsolateral
Access to semantic and phonological memory	Verbal fluency	PFC dorsolateral Medial frontotemporal cortex
Planning	Tower of London (TOL-DX)	PFC dorsolateral
Alternating/divided attention Processing speed	Trail Making Test (TMT)	Frontoparietal circuit White substance
Inhibition	Stroop test	Anterior cingulate cortex PFC orbital
Flexibility	Wisconsin Card Sorting Test (WCST)	PFC dorsolateral PFC medial
Decision making	Iowa Gambling Task (IGT)	PFC orbital PFC dorsolateral
Abstraction	Kenningar Examination	PFC medial PFC dorsolateral

PFC: pre-frontal cortex.

all analyses. The Mann-Whitney U test was performed to evaluate differences between tests of creative thinking and EF of patients with frontal brain tumors and control participants, as well as in the laterality of the tumor. The location by frontal region (medial, orbital, and dorsolateral) was compared by means of the Kruskal-Wallis test. In case statistically significant differences were found, *post hoc* analyses were carried out using the Mann-Whitney U test to determine where these differences came from. To know if executive functioning and creative thinking are related to each other and to volume and peritumoral edema, the Spearman correlation coefficient was used.

Results

Sample description

The sample consisted of twelve patients (9 women and 3 men with a mean age of = 44.2 years, standard deviation [SD] = 10.5, and mean education = 10.9 years, SD = 4.1) and twelve control participants (9 women and 3 men with mean age = 43.4, SD = 10.8 and mean education = 11.3 years, SD = 3.4). The application of the Mann-Whitney U test found no significant differences in age ($p = 0.862$) or education ($p = 0.726$) between patients and control participants that might have affected their performance on the tests.

In terms of laterality, in six patients the tumor was in the right hemisphere, in four it was in the left hemisphere, and in two it had spread bilaterally, predominantly in the left hemisphere in terms of total volume. The Mann-Whitney U test did not detect any significant differences ($p > 0.05$) in performance between patients with tumors located in the left hemisphere and those with bilateral extension, so it was decided to put them together in the same group.

Regarding the localization of the tumors by the pre-frontal region due to compression effect and regardless of laterality, four were found in the medial area, four in the orbital area, three in the dorsolateral area, and one spread through the three areas but with predominance in the dorsolateral area, so that patient was placed in this final group.

Comparisons of creative thinking and EF between patients and health controls

In creative thinking, no significant differences were found in TTCT verbal and figural performance ($p > 0.05$). Regarding EF, in general, patients presented a lower performance in comparison to the control group in all the tests, showing a lower score, presenting more errors, and taking longer to perform the tests.

In the following processes, a disturbance in the performance of patients is observed according to the

Table 2. Significant differences in executive function tests between patients and control group

Test		Patients	Control group	Mann–Whitney U test	
		Mean (standard error)		Z	p
Fluency	Semantic score	14.4 (1.66)	20.6 (1.11)	–2.7	0.007**
Tower of London (TOL-DX)	Execution time	389.9 (66.49)	201.2 (25.33)	–2.60	0.009**
	Resolution time	478.3 (85.57)	245.5 (25.76)	–2.43	0.015*
Trail making test	Time B	292.5 (53.08)	117.3 (26.03)	–2.89	0.004**
	Total errors B	4.1 (1.26)	0.9 (.452)	–2.16	0.030*
Stroop test	Word-color score	28.2 (3.68)	43 (1.72)	–3.21	0.001**
	Interference score	–3.1 (2.11)	7 (1.26)	–3.18	0.001**
Indirect visual span	Score	4 (0.389)	5.1 (0.288)	–2.02	0.043*
Examination Kenningar	Score	5.6 (0.514)	7.8 (0.808)	–2.29	0.022*
Iowa gambling task	Time	552.2 (78.77)	365.8 (26.07)	–1.96	0.05*

*Significant at the level 0.05 (bilateral); **Significant at the level 0.01 (bilateral).

normalized scores: Semantic fluency, planning (movements more than the TOL-DX test), inhibition (interference score of Stroop test), and speed processing (execution and resolution times, TMT A and B times). It should be noted that in flexibility (assessed by the Wisconsin Card Sorting Test [WCST]), both patients and controls maintain an impaired performance.

Significant differences were found in visuospatial working memory, semantic fluency, processing speed (execution and resolution time of TOL-DX test, TMT B time and execution time in the Iowa Gambling Task), inhibition (interference scores of Stroop Test), and abstraction (assessed by the number of correct answers in the Kenningar examination). No differences were observed in verbal working memory, phonological fluency, or flexibility (WCST) (Table 2).

Volume and peritumoral edema

The average volume of tumors was 47.9 cm^3, in a range of 0.72-108.6 cm^3. Regarding peritumoral edema, an average of 16.7 cm^3 was observed, in a range of 0.19-88.1 cm^3. In addition, a grouping was carried out according to the size of the volume and edema of the meningiomas into small (< 10 cm^3), medium (between 10.001 and 50 cm^3) and large (> 50 cm^3).

In the evaluation of creativity, no significant relationships were found with the size of the volume and peritumoral edema. Regarding executive functioning, with respect to volume, it presents a moderate negative correlation with the planning process (total number of correct answers in the TOL-DX test) with a $\rho = -0.7$ ($p = 0.02$). While edema, processes such as phonological fluency ($\rho = -0.7$, $p = 0.03$), present a moderate negative correlation, and processes such as planning and inhibition, evaluated by the type I error (move more than one ball at a time) ($\rho = 0.6$, $p = 0.05$) of the test of TOL-DX test, present a moderate positive correlation.

Hemispheric differences

Upon comparing creative thinking in relation to the laterality of tumors, no significant differences associated with hemispheric tumor location were found.

For the EF tests, significant differences were found in the inhibition process (interference score of the Stroop test) ($Z = -2.647$, $p = 0.01$), with a higher mean score (better performance) when the tumor was in the right hemisphere. Similarly, in cognitive flexibility, it was observed that patients whose tumor was in the left hemisphere carried out the test in the greatest number of attempts possible, while those with a tumor in the right hemisphere required fewer attempts ($Z = -2.286$, $p = 0.02$).

Differences among the pre-frontal areas (medial, orbital, dorsolateral)

With respect to creative thinking, the statistical analyses of the Kruskal–Wallis test and subsequent *post*

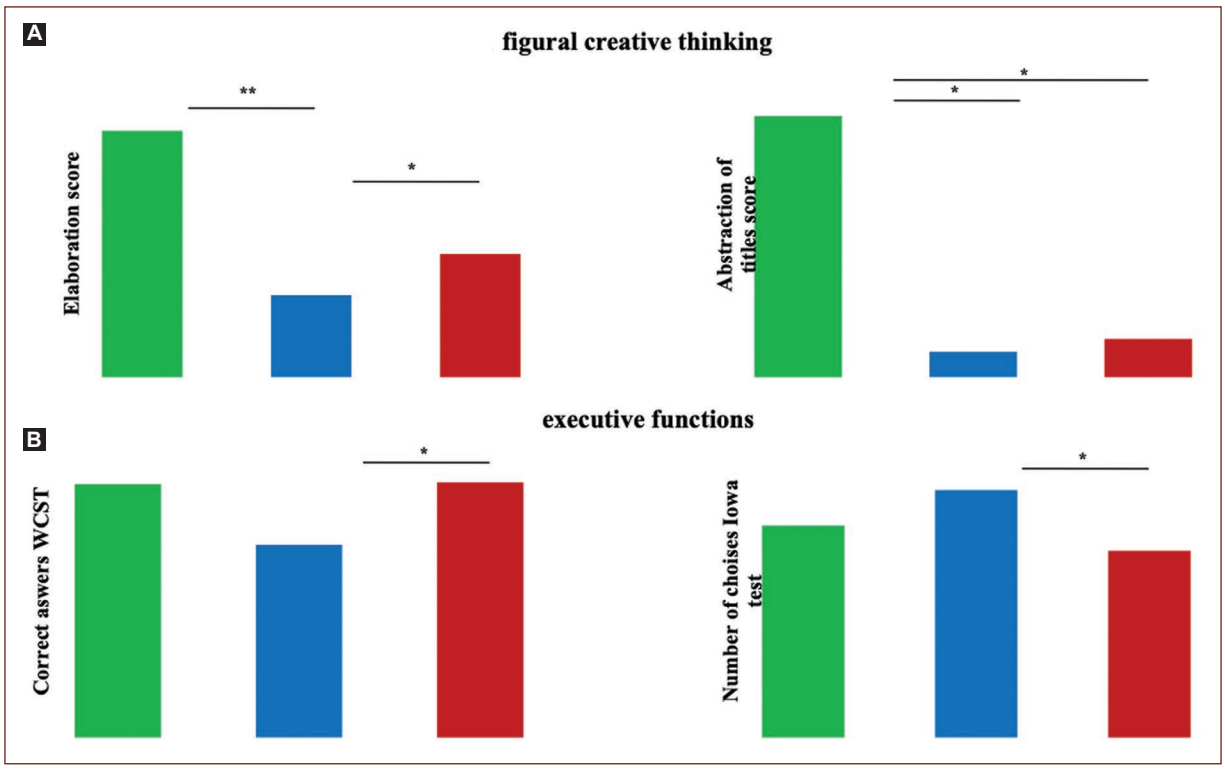

Figure 2. A and **B:** differences among the pre-frontal areas in figural creative thinking and executive functions in patients with meningioma.
*Significant at the level 0.05 (bilateral).
**Significant at the level 0.01 (bilateral).

hoc analyses with the Mann–Whitney U test did reveal significant differences in two of the properties of the figural TTCT, namely, elaboration ($X^2 = 8.261$, $p = 0.02$) and abstraction of titles ($X^2 = 7.700$, $p = 0.02$), where patients with tumor in the dorsolateral region showed a lower score in elaboration compared to the other two regions (medial $Z = –2.477$, $p = 0.01$ and orbital $Z = –2$, $p = 0.05$). Patients whose tumor developed in the medial region obtained a higher score in the abstraction of titles property compared to the dorsolateral ($Z = –2.323$, $p = 0.02$) and orbital ($Z = –2.309$, $p = 0.02$) (Fig. 2A).

In EF, significant differences were found in cognitive flexibility. Through the number of correct answers in the WCST ($X^2 = 5.857$, $p = 0.05$), it is observed that patients with tumors in the dorsolateral frontal region have a lower number of correct answers, compared to those with a tumor in the other regions. Such differences are significant with patients with a tumor in the orbital region ($Z = –2.309$, $p = 0.02$), who have the highest scores. In decision making, differences were found between the three regions ($X^2 = 6.575$, $p = 0.03$); specifically, those whose tumor was in the dorsolateral region presented a greater number of choices of deck 3 (advantageous) in the test Iowa compared with patients whose tumor was in the orbital region ($Z = –2.309$, $p = 0.02$) (Fig. 2B).

Relation between creative thinking and EF

A correlation was found between EF and creative thinking, only in the visuospatial working memory component (inverse Corsi cubes). A moderate positive correlation is observed between this component of EF, both with verbal creativity (in its properties of fluency, flexibility, originality, and the total score), and with figurative creativity (Figural Creativity Index).

Discussion

The purpose of this study was to determine the effect of frontal damage on verbal and figural creative thinking and EF. To accomplish this, patients with frontal pathologies caused by tumors were evaluated and their

performance was compared to that of a control group. It is well-known that patients with meningioma-type tumors have focal deficits that are location-dependent[16,17]. Therefore, this is a type of pathology that offers an ideal paradigm for studying the impact of a lesion in a specific area on cognitive processes.

There were no significant differences in the scores on the two TTCT scales (verbal and figural) between patients and controls. Thus, it is possible to infer that the involvement of other cerebral regions, both cortical and subcortical, are indispensable in this process[18-20], though other studies have emphasized the participation of such brain networks as the default mode and frontoparietal control networks[10,21,22].

However, it is important to keep in mind that the meningioma-type tumors diagnosed in the participants of this study are benign and characterized by slow growth patterns, which means that they can become quite large before causing symptoms. In addition, the brains of participants had been adapting to the growth of the mass, and a plasticity effect had occurred, which can induce a functional reorganization and may be a possible explanation to why no significant changes were observed in the assessment of creative thinking in patients with frontal tumors. It is believed that this explains why neurological deficits do not appear immediately with the onset of pathological lesions, even when they develop within the so-called eloquent areas[23]. This is, then, a possible explanation of why significant changes were observed in the assessment of creative thinking in patients with frontal tumors.

Regarding the components of executive functioning, it was found that the presence of a tumor causes deficits in the execution of patients since in general terms their performance was lower compared to the control group. The results obtained agree in part with data from previous studies[24], where it was found that patients with frontal meningiomas have deficits in working memory, fluidity, shifting, and flexibility. However, it should be noted that in the present investigation, other components of EF were also evaluated, such as: planning through the TOL-DX test, inhibition with the Stroop test, abstraction through the Kenningar Examination for the exploration of metaphorical thinking and decision-making with the IGT, in which significant differences were found compared to the control group, for which these results highlight the importance of deepening the study of EF and in these patients.

In this study, it was found that both the volume and the peritumoral edema presented in the patients showed variability, which was reflected in the executive functioning tests, but not in the creativity evaluation. As to the impact of tumor laterality on creative thinking, no hemispheric differences were found. This result was not unexpected, since creativity also leads to producing useful, relevant, and effective ideas, a process that is driven by the left hemisphere. This result agrees with the findings reported by Mihov et al.[25] who did not observe any differences in the predominantly right hemispheric activation on verbal tasks compared to figural tasks. Finally, according to Lindell[26], creativity is not a lateralized function but rather derives from the interaction and integration of information across the left and right hemispheres.

Significant differences were found in terms of tumor laterality though, since it was found that those that developed tumors in the left hemisphere present deficits in cognitive flexibility (through the WCST test), which is justified by the participation of this hemisphere, specifically of the DLPFC, in tasks that require changing a scheme of action or thought in relation to the evaluation of its results[27]. Significant differences were also found for this same hemisphere in the inhibition process (assessed by the Stroop test), since the patients showed a lower capacity for resistance to interference, which is consistent with studies that indicate that the inhibitory processes that occur during mental tasks that require cognitive activity produce activations lateralized to the left hemisphere[28].

With respect to the differences among the areas of the PFC, it should be noted that significant variations were found in the properties of elaboration (development, ornamentation, or beautification of an idea) and abstraction of titles (i.e., the ability to capture the essence of the information involved) of the figural scale of the Torrance test. In general, observations showed that the patients with tumors in the dorsolateral area had lower performance than those with tumors in the other regions (medial and orbital). This finding can be explained by the fact that alterations in this area are related to deficits in cognitive processes that could impair performance on such creative tasks as abstraction, working memory, flexibility, and fluency, among others[29]. Specifically, a study that analyzed the cerebral bases of originality found that patients with right mCPF lesions obtained lower scores for originality on creativity tests[9], indicating the participation of this area in this component of creativity. Another study, this one of patients with focal frontal lesions, revealed critical prefrontal nodes that were related to the ability to generate and combine remote semantic associations when damage occurred in the pre-frontal medial and pre-frontal

rostrolateral regions, respectively[10]. Finally, according to Gonen-Yaacovi et al.[30] this area appeared to be organized along a rostro-caudal axis, with rostral regions involved in combining ideas creatively and more posterior regions active in freely-generating novel ideas.

Regarding the differences between the regions of the PFC in the EF, it was observed that patients with a tumor in the dorsolateral region show greater deficits in cognitive flexibility tasks (WCST), which corresponds with previous studies[31]. Patients whose tumor was found in the orbitofrontal region presented a lower number of advantageous choices (choice from Deck 3), which agrees with what has been reported in the literature, which states that whose region participates in the processing of related information to the reward[32].

According to the relationship between EF and creative thinking, significant relationships were also found in visuospatial working memory, with both verbal and figural TTPC properties; therefore, this process is considered crucial for our ability to see connections between items that are apparently not connected and to separate elements, since the essence of creativity is being able to integrate and/or recombine elements in a new and different way, and to consider something from a new perspective[33], for which working memory is required in the creative process.

One of the limitations of this study was the small sample size, which has an impact in terms of lower statistical power; therefore, it is necessary to analyze a larger number of patients, since this would allow us to obtain more representative data that can be generalized to the population. In addition, every effort was made to ensure that the participants fulfilled all the necessary requirements and that the tests applied were the ideal ones for evaluating the processes proposed in this research.

Conclusions

There were no differences between patients and controls in verbal and figurative creative thinking, so in addition to the frontal regions, the participation of other cortical and subcortical regions is indispensable to this process. However, some processes were more vulnerable to such damage, for example, those primarily concerned with this area, such as some EF components.

Patients with a tumor in the left hemisphere present less execution in the processes of flexibility and inhibition. Nevertheless, this study did not find evidence that the laterality of the tumor impacted creative thinking. Therefore, this process is derived from the interaction and integration of information in the left and right hemispheres.

With respect to the areas of the PFC, these can play a critical role in creativity, and this emphasizes the importance of determining the participation of these areas of the PFC in greater detail. Significant relationships were found between EF components, mainly visuospatial working memory and the properties of the creative thinking test.

Finally, a developing tumor can invade and destroy the brain tissue in the area in which it is located, creating a specific deficit in the patient which depends on the tumor location. Therefore, this type of tumors that cause alterations in the proper functioning of the frontal lobes, indirectly helps us to better understand the organization of creative thinking in this region.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

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Ethical disclosures

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

Confidentiality of data. The authors declare that they have followed their center's protocols on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the corresponding author.

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