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EDITORIAL

Advancing accessibility to care

Avanzando hacia una atención más accessible

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The current issue of the *Revista Mexicana de Neurociencia* presents works that collectively underscore the transformative potential of neuromodulation, neuroimaging, and targeted therapies in treating complex neurological and psychiatric conditions. These manuscripts not only advance our understanding of brain circuitry but also highlight critical barriers and opportunities for improving patient care in Mexico and beyond.

A pivotal theme in this issue is accessibility. Here, Trejo-Cruz et al. show that high-frequency intermittent Theta-Burst stimulation (iTBS) given 3 times per day for 4 weeks significantly reduced suicidal thoughts in people with depressive disorder who only received one session per day for the same period. This accelerated approach offers promise for rapid crisis intervention, particularly where in-hospital management or other interventions may not be readily available.

For Parkinson´s disease, Martínez-Ramírez et al. identify cost, centralization, and knowledge gaps as major hurdles to deep-brain stimulation (DBS) adoption in Mexico. Interestingly, 71% of physicians surveyed lacked specialized training, signaling an urgent need for education and policy reforms to democratize access to this life-changing treatment.

The DBS survey reveals economic, infrastructural, and educational barriers limiting advanced Parkinson's care in Mexico, while the iTBS trial demonstrates how protocol optimization (e.g., accelerated sessions) can enhance feasibility in resource-constrained settings.

Moving forward, these studies collectively advocate for policy-driven solutions to address cost and infrastructural barriers, such as decentralizing specialized services and funding training programs. As we harness these advances, collaboration across disciplines – neurosurgery, psychiatry, psychology, and policymaking – will be essential to translate laboratory insights into real-world healing.

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ORIGINAL ARTICLE

Clinical effects on semi-structured suicidal thinking with two intermittent Theta-Burst stimulation intervention protocols in depressive disorder

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Abstract

Objective: *To analyze the clinical outcomes of two intermittent theta burst protocols applied to depressed patients with semi-structured suicidal thinking.* **Methods:** *23 participants with Depression according to the Diagnostic and Statistical Manual of Mental Disorders 5th edition criteria, were accepted via informant consent and randomized in Group A: 1 session and Group B: 3 sessions, during 4 weeks, using clinical Scales for depression and suicidal behavior to assess each participant.* **Results:** *Wilcoxon rank test analysis showed statistically significant post-treatment reduction on suicidal thoughts for Group B ($p < 0.01$) with also a larger effect-size (> 0.80) which it was measured with Hedges' g. Hazard Ratio analysis showed a major probability for Group B to decrease suicide-related thinking.* **Conclusions:** *A decrease in suicidal thinking was more observed in the group that received three sessions daily for 4 weeks, indicating more sessions during the day could offer a quicker response to suicidal thinking, especially for prevention of this type of behavior in areas where no hospitalization is available. These results support the feasibility of creating new preventive methods to improve the efficacy in the early eradication of suicidal thoughts.*

Keywords: *Depression. Intermittent Theta Burst. Suicide behavior. Suicidal thinking. Transcranial magnetic stimulation.*

Efectos clínicos sobre el pensamiento suicida semiestructurado con dos protocolos de intervención de estimulación intermitente Theta-Burst en el trastorno depresivo

Resumen

Objetivo: *Analizar los resultados clínicos de dos protocolos de estimulación Theta Burst intermitente aplicados en pacientes deprimidos con ideación suicida semiestructurada.* **Métodos:** *23 participantes con Depresión según los criterios del Manual*

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Diagnóstico y Estadístico de los Trastornos Mentales 5ª edición, fueron aceptados mediante consentimiento informado y aleatorizados en Grupo A: 1-sesión y Grupo B: 3-sesiones, durante 4 semanas, utilizando escalas clínicas de depresión y conducta suicida para evaluar a cada participante. **Resultados:** *El análisis con la prueba de suma de rangos de Wilcoxon mostró una reducción estadísticamente significativa de los pensamientos suicidas después del tratamiento para el Grupo B ($p < 0,01$) con también un mayor tamaño del efecto (> 0,80) que se midió con la g de Hedges. El análisis de Riesgo Relativo mostró una mayor probabilidad de que el Grupo B disminuyera los pensamientos suicidas.* **Conclusiones:** *La disminución de la ideación suicida fue más observada en el grupo que recibió tres sesiones diarias durante cuatro semanas, indicando que más sesiones durante el día podrían ofrecer una respuesta más rápida en la ideación suicida, especialmente para la prevención de este tipo de comportamiento en áreas donde no se dispone de hospitalización. Estos resultados apoyan la viabilidad de crear nuevos métodos preventivos para mejorar la eficacia en la erradicación precoz de los pensamientos suicidas.*

Palabras clave: *Depresión. Estimulación Theta Burst Intermitente. Conducta suicida. Pensamiento suicida. Estimulación magnética transcraneal.*

Introduction

Major depressive disorder (MDD) affects 380 million people worldwide, with 60% linked to suicidal behavior rates, and 25.5% growth rate due to severe acute respiratory syndrome coronavirus 2 (SARS-COV-2). In suicide-related behavior rates, there is a limited pharmacological treatment efficacy, with discomforting side effects in patients. Repetitive transcranial magnetic stimulation (rTMS) and its variant, intermittent theta burst stimulation (iTBS), are a non-invasive, Food and Drug Administration-approved treatment for MDD, the latter applies burst triplets at 50 Hz and a 200-ms interval, helping induce greater changes in synaptic plasticity than rTMS; with some clinical evidence on accelerated protocols (more sessions per-day and less days of treatment)[1]. Some clinical evidence of changes in suicidal thinking using iTBS was found by Desmyter et al. in a Sham/active-iTBS, suggesting 39% (n = 50) remission rates[2]; other studies with a minor sample showed similar outcomes[3]. Recently, Mehta et al., 2022, obtained remission rates of up to 49% (n = 159) in an iTBS/10Hz-rTMS intervention[4]. Based on the latter, we hypothesized that more sessions per day could reduce more effectively the presence of suicide-like thinking.

Our objective was to compare the clinical effectiveness and hazard reduction of two iTBS interventions (once-daily sessions and thrice-daily sessions) on semi-structured suicidal thinking in clinically depressed adult patients.

Materials and methods

The study was conducted from October 2021 to March 2023 at the "Dr. Moisés López González" Neurodiagnostics and Rehabilitation Unit by trained professionals at the Autonomous University of Queretaro, Mexico. The trial was performed according to the Declaration of Helsinki and approved by the Bioethics Committee of the Faculty of Medicine of the Autonomous University of Queretaro. The study was registered in ClinicalTrials.Gov. (NCT05694754). Patients were recruited from private and public health institutions and online surveys.

A total of 149 participants recruited from various clinical private or public centers and online surveys were initially assessed; where 23 patients of both sexes between 18 and 45 years of age met the criteria for major depression and semi-structured suicidal thinking and were accepted (Fig. 1A). Inclusion criteria within the study included DSM-5 clinical based diagnostic for MDD (Table 1). Patients must have had stable pharmacological treatment at least for the last 30 days with adequate adherence to it; electroencephalogram (EEG) with no contraindications to receive iTBS treatment (paroxysmal or epileptic activity). Exclusion criteria included patients with seizure activity or the presence of suicidal attempts in the last 30 days or have structured suicidal ideation, as well as a significant risk of suicide attempts of moderate-to-high lethality during treatment. Participants with intracranial metallic objects, intracranial or metallic plates in the skull, pacemaker, cochlear implant, neuro-stimulation device and/or shunt valves, cochlear implant, neuro-stimulation device, and/or shunt valves were also excluded. Patients with assessment sessions and/or stimulation sessions with at least 3 consecutive absences were excluded. Exclusion criteria took into consideration reports of SARS-CoV-2 Covid-19 symptoms during treatment. All participants signed

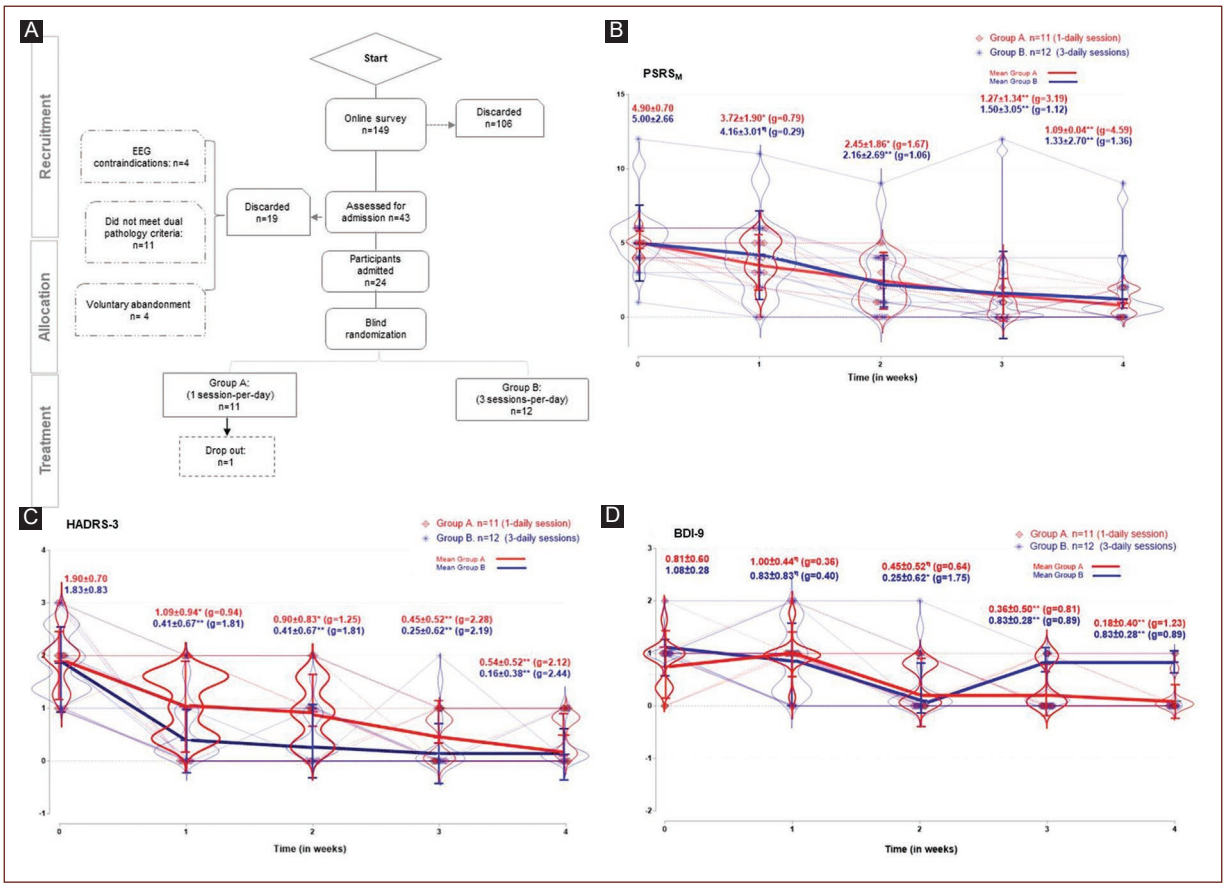

Figure 1. A: the flow diagram illustrates the stages (recruitment, allocation and treatment) of the iTBS protocol: 1 session (Group-A) and 3 sessions (Group-B). Only one drop out occurred during the treatment process. **B:** plutchik Suicide Risk Scale with the modifiable items (PSRS$_M$). Suicidal ideation structure can be assessed with **C:** rating depression scale item-3. **D:** beck depression inventory item-9. The X axis shows the evaluation time in terms of weeks: 0 (baseline), 4 (post treatment). The red (Group-A) and blue (Group-B) violin plots represents the distribution of the subjects throughout time. The Y axis shows the clinical scale scores; p-value ($p < 0.05$*; $p < 0.01$**; $p < 0.001$***; h = non-significant) Group A (n = 11), Group B (n = 12); g = Size Effect with Hedges g.

informed consent and were able to leave the study at their own free will at any time they wanted to.

A controlled triple-masked trial design with a non-probabilistic sample was used. Patients were randomized: Group A: bursts of 3 pulses at 50Hz, repeated at 5Hz for a 2-second period (10-bursts), followed by an 8-s intertrain interval, for a total of 600 pulses.

Group-B: Same parameters with a daily 3-time application and 10-min rest intervals in between each session.

Each patient chose an envelope with a randomization code which placed them in Group A (n = 11) or Group B (n = 12). To reduce bias, we masked the protocol to patients, iTBS provider and rater. The motor threshold was set at 80% (visual method). The treatment intensity consisted in the application of the minimum amount of single-pulse energy for the induction of cortical excitability.

Both groups received 4 weeks of iTBS (5-days per on week days), using a Magventure-Pro-R30 stimulation equipment, and an MCF-B70 stimulation coil.

The coil was positioned on the left dorsolateral prefrontal cortex ($_L$DLPFC). Positioning was determined by the 10-20 EEG system over F3, by means of location software (BA9, BA8, BA43 William-Beam and Jeff Borckardt), using vertex as reference, by marking the nasion-inion and tragus-tragus midpoints.

Primary outcome measures were changes on (A) presence/severity of symptomatology of depression, measured with the Hamilton depression rating scale (HADRS): 21-item version instrument to assess/follow-up severity of symptomatology and response to

Table 1. Mentions the clinical criteria for the diagnose of major depressive disorder according to DSM-5

Assessment scores on two treatment groups. Mean ± SD/(Hedges g)										
	HADRS		MADRS		BDI		HAM-A			
	Baseline	Post treatment	Baseline	Post treatment	Baseline	Post treatment	Baseline	Post treatment		
A	31.36 ± 6.03	8.72 ± 6.97** (2.92)	31.18 ± 5.70	9.09 ± 7.24** (3.29)	34.90 ± 8.43	5.45 ± 7.50** (4.30)	27.27 ± 6.18	9.45 ± 8.11** (2.37)		
B	29.36 ± 3.85	6.20 ± 4.80** (4.63)	31.90 ± 6.67	4.70 ± 3.94** (3.75)	34.36 ± 16.62	6.60 ± 6.85** (2.07)	24.36 ± 4.94	9 ± 6.63* (2.52)		
Weekly assessment scores on suicide risk behavior scales. Mean ± SD/(Hedges g)										
	PSRS					$PSRS_M$				
	Baseline	W1	W2	W3	W4	Baseline	W1	W2	W3	W4
A	10.54 ± 2.33	6.90 ± 2.21** (1.54)	4.45 ± 2.80** (2.27)	3.00 ± 2.75** (2.84)	2.18 ± 2.75** (2.84)	4.90 ± 0.70	3.72 ± 1.90* (0.79)	2.45 ± 1.86* (1.67)	1.27 ± 1.38** (3.19)	0.90 ± 0.94** (4.64)
B	9.81 ± 2.60	6.81 ± 3.54** (0.92)	3.90 ± 3.78** (1.75)	3.00 ± 3.94** (1.96)	3.37 ± 3.40** (2.04)	5.36 ± 2.46	4.54 ± 2.84 (0.29)	2.36 ± 2.73** (1.11)	1.63 ± 3.64** (1.15)	1.60 ± 2.91** (1.34)
Weekly assessment scores on suicide risk behavior scales. Mean ± SD/(Hedges g)										
	BHS									
	Baseline	W1	W2	W3	W4					
A	12.54 ± 4.94	8.27 ± 3.55* (0.95)	4.72 ± 3.03** (1.83)	3.81 ± 3.5* (1.9)	2.36 ± 2.01** (2.59)					
B	10.33 ± 6.47	7.72 ± 4.38 (0.46)	4.63 ± 3.44* (1.06)	3.09 ± 2.7* (1.4)	2.22 ± 2.44** (1.60)					
Weekly assessment on items related to suicide risk behavior on clinical depression scales. Mean ± SD/(Hedges g)										
	HADRS (3)					MADRS (10)				
	Baseline	W1	W2	W3	W4	Baseline	W1	W2	W3	W4
A	1.90 ± 0.70	1.09 ± 0.94 * (0.94)	0.90 ± 0.83* (1.25)	0.45 ± 0.52** (2.26)	0.54 ± 0.52** (2.12)	2.18 ± 0.75	1.63 ± 1.12* (0.55)	1.18 ± 1.07* (1.04)	0.63 ± 0.92* (1.77)	0.90 ± 0.30* (2.15)
B	1.90 ± 0.83	0.63 ± 0.67** (1.61)	0.45 ± 0.68** (1.83)	0.25 ± 0.62** (2.19)	0.20 ± 0.42** (2.48)	1.90 ± 1.04	1 ± 0.89 (0.89)	0.33 ± 0.50* (1.81)	0.08 ± 0.28* (2.48)	0.10 ± 0.28* (2.48)

(*Continues*)

Table 1. Mentions the clinical criteria for the diagnose of major depressive disorder according to DSM-5 (*continued*)

Weekly assessment on items related to suicide risk behavior on clinical depression scales. Mean ± SD/(Hedges g)												
	BDI (9)											
	Baseline	W1	W2	W3	W4							
A	0.81 ± 0.60	1.00 ± 0.44 (0.36)	0.45 ± 0.52 (0.64)	0.36 ± 0.50* (0.81)	0.18 ± 0.40* (1.23)							
B	1.08 ± 0.28	0.83 ± 0.83 (0.40)	0.25 ± 0.62* (1.75)	0.83 ± 0.28** (0.89)	0.83 ± 0.28** (0.89)							
Weekly assessment on absence of suicidal thinking structure with the depression items related to suicide. Percentage (%), n, Hazard Ratio (HR). Without presence of suicidal thinking (1)/ Presence of suicidal thinking (2)												
	HADRS (3)								MADRS (10)			
	W1		W2		W3		W4		W1		W2	
	36.3 (4)	50 (6)	36.7 (4)	50 (6)	54.5 (7)	83.310)	45.5 (5)	75 (9)	9.09 (1)	41.7 (5)	36.4 (4)	58.3 (7)
1	63.64 (7)	50 (6)	63.7 (7)	50 (6)	45.5 (4)	17.7 (2)	54.5 (6)	25 (3)	90.9 (10)	58.3 (7)	63.6 (7)	41.7 (5)
2	0.7272	1.37	0.5	1.37	0.84	1.17	0.555	1.8	0.215	4.58	0.624	1.60
HR=	36.3 (4)	50 (6)	36.7 (4)	50 (6)	54.5 (7)	83.3 (10)	45.5 (5)	75 (9)	9.09 (1)	41.7 (5)	36.4 (4)	58.3 (7)
Weekly assessment on absence of suicidal thinking structure with the depression items related to suicide. Percentage (%), n, Hazard Ratio (HR). Without presence of suicidal thinking (1)/ Presence of suicidal thinking (2)												
	MADRS (10)				BDI (9)							
	W3		W4		W1		W2		W3		W4	
	63.6 (7)	100 (12)	90.9 (10)	91.7 (11)	9.09 (1)	36.7 (4)	63.6 (7)	75 (9)	72.3 (8)	83.3 (10)	90.9 (10)	91.7 (11)
1	36.4 (4)	0 (0)	9.09 (1)	8.3 (1)	90.9 (10)	63.7 (7)	36.4 (4)	25 (3)	27.3 (3)	16.7 (2)	9.09 (1)	8.3 (1)
2	0.636	1.57	0.991	1	0.2476	4.03	0.848	1.17	0.8679	1.15	0.991	1
HR=	63.6 (7)	100 (12)	90.9 (10)	91.7 (11)	9.09 (1)	36.7 (4)	63.6 (7)	75 (9)	72.3 (8)	83.3 (10)	90.9 (10)	91.7 (11)

Data are presented as percentages (%), means, and standard deviations (SD). Effect size: Hedges' g. Clinical scales: HAM-D – Hamilton Depression Rating Scale (cut-off: non-depressive 0–7; mild 8–16; moderate 17–23; severe ≥24); HAM-A – Hamilton Anxiety Rating Scale; MADRS – Montgomery–Åsberg Depression Rating Scale (cut-off: non-depressive 0–6; mild 7–19; moderate 20–34; severe ≥ 35); BDI – Beck Depression Inventory (cut-off: minimal 0–9; mild 10–18; moderate 19–29; severe 30–63); PRS – Plutchik Suicide Risk Scale; PRSM – Modifiable items of PRS; BHS – Beck Hopelessness Scale; HAM-D (3), MADRS (10), BDI (9) – suicide-related items. L-DLPFC: left dorsolateral prefrontal cortex. p-values: ***p < 0.001, **p < 0.01, *p < 0.05. Timepoints: baseline, week 1 (W1), week 2 (W2), week 3 (W3), week 4 (W4), and post-treatment. Wilcoxon rank-sum test revealed statistically significant post-treatment differences between groups.

treatment[5]; the Montgomery–Asberg depression rating-scale (MADRS): 10-item interview to assess symptom severity. Items evaluate sadness, internal tension, sleep alterations, lack of concentration, laxity, anhedonia, pessimistic thoughts[6], and suicidal ideation; the Beck depression inventory (BDI): Self-report of symptomatology composed by 21 Likert-type items[7]. Anxiety symptoms were assessed with the Hamilton rating scale for anxiety (HAM-A)[8:] 14-item questionnaire to evaluate the severity of anxiety symptoms. Bias/response set on clinical scales was performed with the 33-item Marlowe Crowne social desirability scale (MCSD). (B) Suicide risk thoughts: beck hopelessness scale (BHS): 20 items with dichotomous answers (true/false), referring own well-being and attitude toward the future. Plutchik suicide risk scale (PSRS): a self-applied 26-item instrument with dichotomous response (Yes/No), which enables the identification of suicide attempts, impulsivity, plans related to self-destruction, hopelessness, depression, and use of sleep-inducing drugs[9].

An evaluation with PSRS, as well as with the items that quantify changes throughout the treatment ($PSRS_M$), was performed and the total score of the scale was obtained. An observation of changes in the structure of suicidal thinking over time was carried out using item 3 of the HADRS-3, and item 9 of the beck depression scale (BDI-9). BHS and item 10 of the MADRS-10 were used as a backup tool to assess the same symptomatology (Figs. 2A and B).

Statistical analysis

We used GraphPad Prism v.6, and the Statistical Package for the Social Sciences v.22. The analysis included the Mann–Whitney *U*-test for intergroup analysis; Friedman and Wilcoxon tests were used for intragroup assessment; effect size was calculated with Hedges' g and hazard ratio (HR) with a 95% confidence interval (CI) to observe risk reduction on suicidal thinking (HR ≥ 1: is considered statistically significant). $p \leq 0.05$ was considered statistically significant[10].

Results

Demographic and clinical data

Table 2 shows sociodemographic data, adverse effects, and clinical results. Assessments with MCSD scores were homogenous (Group A: Mean = 15.75 ± 2.45; Group B: Mean = 15.08 (4.01); p = 0.710) indicating participant unbiased response[11].

Depression and anxiety symptoms assessment with clinical scales

Depression/Anxiety baseline symptoms were in the range of moderate to severe with no differences among groups: HADRS (p = 0.249), MADRS (p = 0.869), BDI (p = 0.666), and HAM-A (p = 0.429) (Table 2).

Pre-post treatment analysis

Group-A

Outcomes showed differences for HADRS, MADRS, BDI (p = 0.003), and HAM-A (p = 0.005). The percentage decrease scores and the effect size were larger for this group on BDI (Table 2).

Group-B

Significant differences were found in the three scales of depression (p = 0.005) and anxiety (p = 0.011). The effect size on clinical scales was larger for this group on HADRS, MADRS, and HAM-A (Table 2). Percentage reduction in depressive symptomatology was larger for Group B with HADRS (86.88%-p = 0.005) and MADRS (85.26%-p = 0.005).

Scales related to suicidal risk behavior

Baseline scores were similar in both groups $PSRS_M$ (p = 0.918), HADRS-3 (p = 0.786), BDI-9 p = 0.90 (Figs. 1B-D). BHS (p = 0.440) and MADRS-10 (p = 0.699) (Fig. 2).

Pre-post treatment analysis

Group-A

Results showed differences $PSRS_M$ and HADRS-3 ($p < 0.05$ and $p < 0.005$, Figs. 1B and C); BDI for the last 2 weeks ($p < 0.05$; Fig. 1D); BHS ($p < 0.05$ and $p < 0.005$).

Group-B

Analyses showed differences in $PSRS_M$ ($p < 0.005$) in the last 3 weeks, HADRS-3 ($p < 0.005$), and BDI-9 ($p < 0.005$) in the last 2 weeks (Table 2 and Figs. 1B-D).

Table 2. Sociodemographic and clinical analysis of both groups under iTBS treatment

Statistical sociodemographic of the participants of the study on both iTBS treatment groups. Demographic data of the participants of the study (n = 23) (Mean ± SD)						
Group	Age	Gender (n)		Years of academic education	Number of lifetime of depressive episodes	Lifetime suicide attempts
		Men (n = 8/36.36%)	Women (n = 15/63.63%)			
A (n = 11)	38.00 ± 12.05	4		7	15.45 ± 2.84	4.63 ± 2.76
B (n = 12)	41.25 ± 10.25	4		8	15.83 ± 2.16	5.41 ± 3.11
Adverse effects during treatment with iTBS (%)						
Headaches after session	Headaches during the day	Dizziness		Nausea	Auditory discomfort	Seizures
A	9.09	0		9.09	0	0
B	9.09	9.09		9.09	0	0

On BHS ($p < 0.05$), HR (CI = 95%) showed a higher percentage of suicidal thoughts absence for Group B (Table 2).

Discussion

To our knowledge, this is the first study comparing an accelerated iTBS protocol (3 sessions) with an approved iTBS procedure to observe clinical effectiveness on non-structured and semi-structured suicide thinking. Regarding the decrease in depressive and anxiety symptoms, both groups achieved ≥ 70% reductions. This is similar to the results found by Desmayter et al.[12] and Baeken et al.[13], in a 4-day Sham versus control study (n = 50 and n = 45, respectively), with reductions of up to 50% for those who received active iTBS (5-daily sessions). Nonetheless, our study seeks a larger follow-up through time, to observe the clinical evolution of our participants and, also evaluating hopelessness and suicidal risk behaviors, where the changes in both groups showed differences ($p \leq 0.05$) in PSRS. Concerning to the clinical outcomes, our study found a decrease in suicidal thinking in a higher percentage of the population, as well as a greater tolerance to pulses compared to rates reported by Richard et al. 2022, on depressed patients with suicidal thinking (n = 22). Their results showed an 18.2% response-to-treatment rate, and an 18.5% rate of tolerance to receive 1,800 pulses daily. This raises the question of whether the differences between this study and ours could be due to the fewer daily sessions with Group B compared to the 5 daily sessions carried out by Richard et al. However, statistically speaking, the percentage decrease in suicidal thinking was greater in our clinical trial, and we were able to measure this effectiveness by also including the effect size. Although we consider the relevance of achieving clinical effectiveness and risk reduction on suicidal thinking in a shorter period, we also seek to maintain this effect over time, as seen in the statistical significance of our study (Table 2). Despite both groups obtaining the outcomes, Group B had a better response to treatment overall. Regarding the absence of suicidal thinking each week, HR analysis showed Group B had a higher chance to see these thoughts reduced, which highlights the relevance of creating preventive approaches by monitoring suicidal thinking at an early onset stage by reducing the risk of impulsive behavior and early suicide attempts, while continuing to assess the evolution of the patients' behavior under treatment. It is important to underline that during the study, none of the patients achieved any structured suicidal ideation or direct lethal behaviors that could threaten at any moment the life of the patient. We secured that by providing the participants, psychiatric and psychological assessments with specialized personnel along with having at all times contact with patient's primary support network and communication and feedback with the patient's adscripted health services. Having this in mind, our purpose, as we stated before, is to look for approaches by monitoring early onset of suicidal thinking instead of acting on the severe stages when there are more threats to the patient's life.

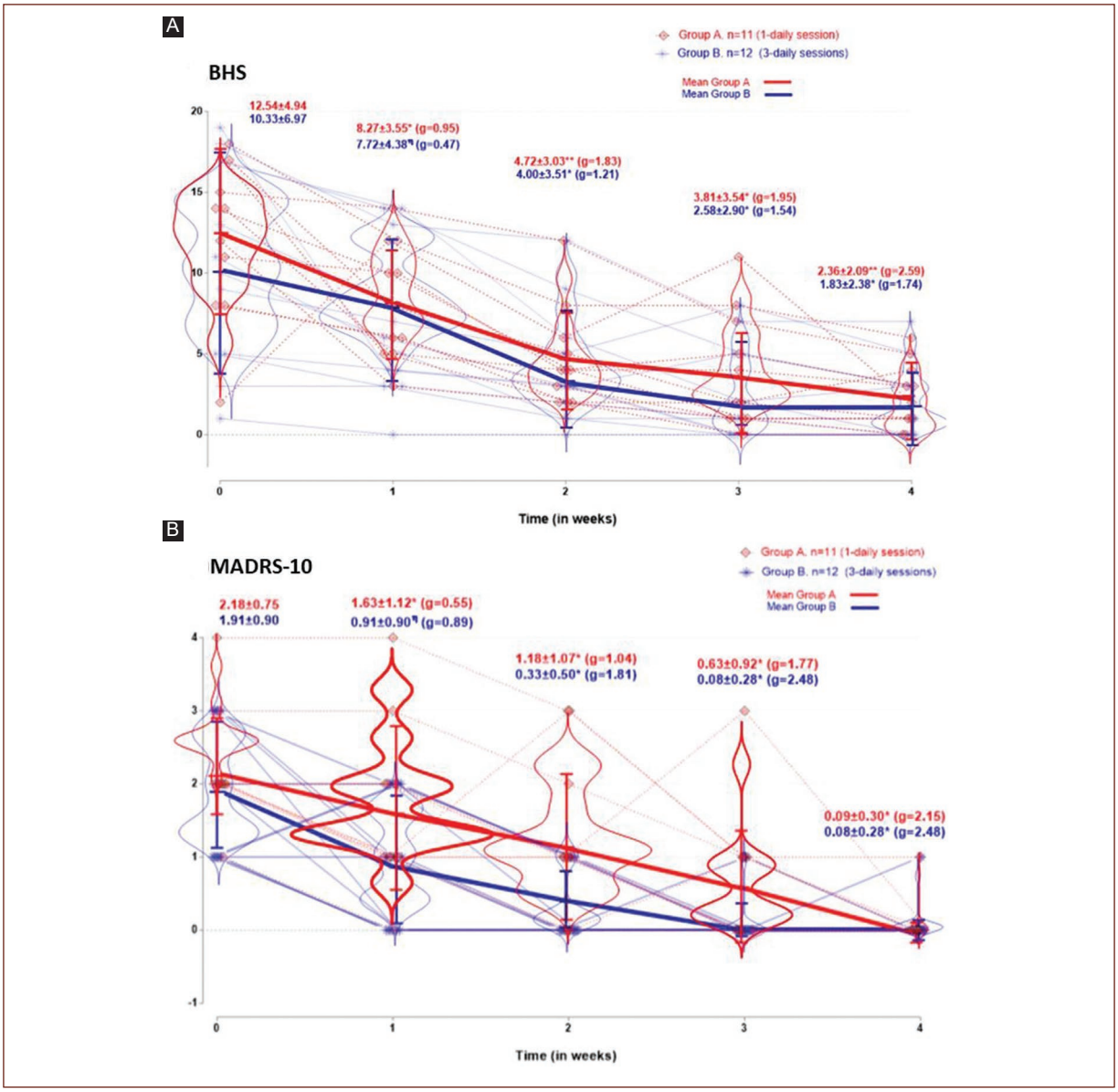

Figure 2. Risk of variables associated with suicidal behavior was assessed with. **A:** beck hopelessness scale. Suicidal ideation structure can be assessed with. **B:** montgomery-asberg rating depression scale item-10. The X axis shows the evaluation time in terms of weeks: 0 (baseline), 4 (post-treatment). The red (Group-A) and blue (Group-B) violin plots represents the distribution of the subjects throughout time. The Y axis shows the clinical scale scores. p-value ($p < 0.05$*; $p < 0.01$**; $p < 0.001$***; h = non-significant). Group A (n = 11); Group B (n = 12). g = Size Effect with Hedges g.

Conclusion

This study is a glimpse into what we can do by comparing several forms of stimulation throughout time to understand more suitable stimulation protocols in response to harmful thinking and behavior. Limitations on the study related to the pandemic did not allow us to compare a 5-sessions per-day protocol. Other limitations are related to the small sample size for each group, which is crucial to understand in the long term the effects of an early onset intervention and the impact of suicidal behavior on clinical depressed patients.

Since we did not face any threats of suicide or more structured suicidal thoughts during the course of the study, we have to look ahead for if this type of intervention represents an innovation in terms of improve the quality of life of the patient without achieve peaks of unnecessary risks that in terms of availability of places for hospitalization, interventions, and resources,

could be represent a more dynamic intervention that does not imply to put a pause in other aspects of the life of the patient such as productivity and a quicker recover from their symptoms.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

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 for 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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ORIGINAL ARTICLE

Knowledge, attitudes, and barriers toward deep brain stimulation for Parkinson's disease in Mexico

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Abstract

Objective: *Parkinson's disease (PD) is the second most prevalent neurodegenerative disorder among individuals over 50 years old and poses a significant public health challenge in Mexico. While deep brain stimulation (DBS) is an effective therapy for improving motor symptoms and reducing medication dependency, its adoption in Mexico faces multiple barriers. This study aimed to evaluate the knowledge, attitudes, and perceived barriers among physicians regarding DBS to identify key areas for optimizing its accessibility for PD patients.* **Methods:** *A descriptive qualitative study was conducted using a 19-question online survey targeting Mexican physicians who treat patients with PD. A total of 69 physicians from various specialties participated. Data were analyzed using descriptive statistics and thematic analysis.* **Results:** *Among respondents, 89.9% considered DBS to be safe, and 94.2% did not perceive it as a last resort treatment. However, 71.0% lacked specialized training in DBS, and 34.8% had no contact with specialized DBS centers. The main reported barriers included the high cost of the procedure (79.7%), centralization of services in major cities (29%), and limited knowledge among physicians and patients (21.7%).* **Conclusions:** *Despite favorable attitudes toward DBS in Mexico, economic, educational, and infrastructural barriers hinder its implementation. It is crucial to develop funding policies, decentralize services, and strengthen medical training to ensure equitable and timely access to this advanced therapy.*

Keywords: *Parkinson's disease. Deep brain stimulation. Access barriers. Medical attitudes. Mexico.*

Conocimiento, actitudes y barreras hacia la estimulación cerebral profunda para Parkinson en México

Resumen

Objetivo: *La enfermedad de Parkinson (EP) es el segundo trastorno neurodegenerativo más prevalente en mayores de 50 años y representa un desafío significativo para la salud pública en México. Aunque la estimulación cerebral profunda (ECP) es una terapia eficaz para mejorar los síntomas motores y reducir la dependencia de medicamentos, su adopción en México enfrenta múltiples barreras. Este estudio tuvo como objetivo evaluar el conocimiento, las actitudes y las barreras percibidas entre los médicos respecto a la ECP para identificar áreas clave que optimicen su accesibilidad para los pacientes con EP.* **Métodos:** *Se realizó un estudio descriptivo cualitativo mediante una encuesta en línea de 19 preguntas dirigida a médicos mexicanos que atienden pacientes con EP. Participaron 69 médicos de diversas especialidades. Los datos fueron analizados*

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utilizando estadísticas descriptivas y análisis temático. **Resultados:** *El 89.9% de los encuestados consideró que la ECP es segura, y el 94.2% no la percibe como una terapia de última línea. Sin embargo, el 71.0% carecía de capacitación especializada en ECP, y el 34.8% no tenía contacto con centros especializados. Las principales barreras reportadas incluyeron el alto costo del procedimiento (79.7%), la centralización de los servicios en ciudades principales (29%) y el conocimiento limitado entre médicos y pacientes (21.7%).* **Conclusiones:** *A pesar de las actitudes favorables hacia la ECP en México, las barreras económicas, educativas y de infraestructura dificultan su implementación. Es fundamental desarrollar políticas de financiamiento, descentralizar servicios y fortalecer la capacitación médica para garantizar un acceso equitativo y oportuno a esta terapia avanzada.*

Palabras clave: *Enfermedad de Parkinson. Estimulación cerebral profunda. Barreras de acceso. Actitudes médicas. México.*

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder worldwide, with an estimated incidence of 40-50 cases/100,000 inhabitants in Mexico[1]. Its prevalence increases significantly in individuals over 50 years old, making it a public health priority[2]. PD is characterized by debilitating motor symptoms such as bradykinesia, resting tremor, and rigidity, alongside a broad range of non-motor symptoms[3]. These symptoms severely impact patients' quality of life, place a significant burden on caregivers, and generate substantial costs for healthcare systems[4]. Despite advancements in pharmacological management, including levodopa and other dopaminergic agents, advanced-stage patients face motor complications such as fluctuations in medication response and treatment-induced dyskinesias[5]. These limitations underscore the need for complementary and more effective treatments to optimize the comprehensive management of advanced-stage disease.

Deep brain stimulation (DBS) has emerged as an advanced and effective therapy for managing PD. Introduced in 1987, this neurosurgical technique involves implanting electrodes in specific brain areas to modulate affected neural circuits[6]. DBS provides substantial improvements in motor symptoms, reduces fluctuations and dyskinesias, and decreases medication dependency. Evidence suggests that these benefits can persist for over 15 years in appropriately selected patients, highlighting its potential as a transformative intervention for PD management[7].

In Mexico, however, access to DBS remains limited compared to developed countries, highlighting significant implementation gaps. These barriers may be linked to economic constraints, the centralization of specialized centers in major cities, and insufficient knowledge and training among physicians regarding the benefits, referral criteria, and safety profile of DBS. Moreover, delayed or absent referrals for eligible patients remain a recurrent issue, preventing many from receiving this therapy at the optimal time.

Physicians play a pivotal role in DBS implementation as they are responsible for identifying and referring patients who may benefit from this intervention. However, physicians' perceptions and attitudes toward DBS can significantly influence referral decisions. International studies have identified similar barriers, including lack of awareness of selection criteria, misconceptions about surgical risks, and disagreement on the optimal timing of the intervention[8]. Addressing these barriers is critical to reducing inequities in DBS access and maximizing its impact on patients' quality of life.

This study aims to explore the knowledge, attitudes, and perceived barriers toward DBS among physicians in Mexico to identify key areas requiring improvement. By analyzing these perceptions, we aim to provide evidence to inform strategies that promote timely and equitable referrals to this advanced therapy, ultimately optimizing PD management in the country. This work aspires to bridge the gap between scientific evidence and clinical practice, improving clinical outcomes and access to advanced treatments like DBS in Mexico.

Materials and methods

A cross-sectional descriptive qualitative study was conducted using an online survey to explore perceptions, knowledge, and barriers related to DBS among physicians treating PD patients in Mexico. This methodological approach enabled a comprehensive and detailed analysis of attitudes and barriers without requiring variable manipulation or group assignment. Participants provided informed consent, which included details on the survey's duration, the purpose of the study, and the absence of incentives. Participation was entirely voluntary, and no incentives were offered. The survey's view rate and participation rate were recorded, and measures were implemented to prevent duplicate entries, ensuring the reliability of the data collected. The study was reviewed and approved by the Institutional

Research Ethics Committee of the Tecnológico de Monterrey (code CA-EMCS-2403-02).

The target population included active physicians in Mexico with experience managing PD patients. Specialties considered included neurology, neurosurgery, internal medicine, geriatrics, and other related fields. Inclusion criteria were physicians actively treating PD patients, while exclusion criteria included those who opted not to participate. Participants were selected through non-probability convenience sampling, yielding a final sample of 69 physicians. A 19-question online survey was designed, covering six thematic areas: demographic data, international recommendations for DBS referral, perceived risks associated with the technique, training in DBS or movement disorders, contact with specialized centers, and perceived barriers to DBS access.

The content of the survey was validated by a panel of experts. A pilot test was conducted with 10 physicians from other regions to assess the clarity and relevance of the questions, leading to adjustments before final implementation. The survey was administered through Google Forms. Participants were invited through email and WhatsApp, with reminders sent to non-respondents after 2 weeks. Recruitment was expanded through national conferences to ensure a diverse sample. Data collection spanned 16 weeks. The survey was distributed to 92 professionals in Nuevo León via WhatsApp and extended to attendees of movement disorders, neurology, and geriatrics conferences, reaching a total of 392 invited participants. Measures were taken to minimize potential selection and information biases. Participants were recruited based on predefined criteria, and the survey was anonymous to reduce social desirability bias. Standardization in questionnaire design and administration aimed to mitigate measurement and interpretation biases.

Survey reliability and internal consistency

The survey was designed to assess knowledge, attitudes, and barriers toward DBS among medical specialists. It consisted primarily of dichotomous (yes/no) questions and one open-ended question. The content of the survey was validated by a panel of experts to ensure relevance and clarity. Given the heterogeneous nature of the questionnaire and the fact that the items did not measure a single underlying construct, internal consistency analysis using Cronbach's alpha was not considered appropriate. Instead, survey validity was ensured through expert panel content validation, clear question wording, and pilot testing to improve reliability.

Statistical analysis

Data analysis was performed using IBM SPSS Statistics version 25. Closed-ended questions were analyzed through frequencies and percentages for categorical variables, while numerical variables, such as age and years of practice, were described using measures of central tendency and dispersion. The open-ended question, which explored perceived barriers to DBS access, underwent thematic analysis to identify and classify responses into key categories, such as cost, infrastructure, and knowledge gaps. This methodological approach ensured robust and in-depth analysis to support the study's findings.

Results

Demographic characteristics

The general characteristics of the participants are detailed in table 1. The mean age was 42.94 years (standard deviation [SD]: 12.48), with a median of 42 years and a range from 29 to 76 years. Age distribution demonstrated a slight positive skewness (1.085) toward younger physicians and moderate kurtosis (0.257). Regarding gender, 53.6% were male (n = 37) and 46.4% were female (n = 32).

Participants reported a mean of 12.78 years of professional practice (SD: 11.67), with a median of 10 years and a range of 1-44 years, reflecting significant variability. The distribution showed a positive skewness (1.272), indicating a greater representation of less experienced physicians. The predominant specialty was Neurology (58%, n = 40), followed by Geriatrics (36.2%, n = 25). Other specialties included Internal Medicine, Neurosurgery, General Medicine, and Psychotherapy (1.4% each). In terms of employment, 53.6% worked in both public and private sectors, 40.6% exclusively in private institutions, and 5.8% exclusively in public institutions. Geographically, most participants practiced in the Central (34.8%, n = 24) and Northeastern (31.9%, n = 22) regions. The remaining participants were distributed across the Western (15.9%, n = 11), Northwestern (8.7%, n = 6), and Southeastern (5.8%, n = 4) regions. A small proportion (2.9%, n = 2) reported practicing internationally.

International recommendations for DBS referral

The presence of a local center or medical group performing DBS was reported by 62.3% of respondents, whereas 37.7% indicated the absence of such services,

Table 1. Demographic characteristics of surveyed physicians

Variable	Category	Frequency (n) / Percentage
Gender	Male	37 (53.6)
	Female	32 (46.4)
Specialty	Neurology	40 (58.0)
	Geriatrics	25 (36.2)
	Internal medicine	1 (1.4)
	Neurosurgery	1 (1.4)
	General practitioner	1 (1.4)
	Psychotherapist	1 (1.4)
Type of institution	Public	4 (5.8)
	Private	28 (40.6)
	Both	37 (53.6)
Nationality	Mexican	67 (97.1)
	Other	2 (2.9)
Geographical practice region in Mexico	Central	24 (34.8)
	Northeast	22 (31.9)
	West	11 (15.9)
	Northwest	6 (8.7)
	Southeast	4 (5.8)
	International	2 (2.9)

reflecting disparities in infrastructure distribution. Most physicians (69.6%) believed that advanced age does not significantly impact the benefits of DBS, while 30.4% disagreed, indicating variability in interpretation of the evidence. Regarding the timing of DBS, 71.0% recommended it 5-10 years after Parkinson's diagnosis, whereas 24.6% suggested earlier intervention (< 5 years) and 4.3% supported a delay (> 10 years).

For atypical Parkinsonism, 60.9% of respondents considered these patients ineligible for DBS, while 39.1% expressed a broader perception of eligibility. In addition, 76.8% of physicians did not view resistance to pharmacological therapy as an essential referral criterion, compared to 23.2% who did. For patients with a poor or absent response to levodopa, 50.7% deemed them eligible for DBS, whereas 49.3% disagreed.

Given the critical role of patient selection in achieving successful outcomes with DBS, we have summarized the key criteria for referral[9,10]. These criteria not only guide specialists but also provide educational value for general practitioners and other healthcare professionals involved in the care of patients with PD. The main factors to consider when identifying potential candidates for DBS include a confirmed diagnosis of idiopathic PD, the presence of disabling motor symptoms such as medication-refractory motor fluctuations or dyskinesias, and a good response to levodopa, which is a strong predictor of favorable outcomes with DBS. Patients with severe comorbidities, uncontrolled psychiatric disorders, or dementia are generally excluded. In addition, a multidisciplinary evaluation involving neurology, neurosurgery, neuropsychology, and psychiatry is essential to assess the suitability of candidates and ensure they have realistic expectations regarding the risks and benefits of DBS. Ultimately, proper patient selection and a thorough preoperative assessment are crucial to optimizing outcomes.

Perception of risk associated with DBS

The majority of participants (89.9%) perceived DBS as a safe technique, while 10.1% expressed concerns about significant risks, particularly surgical complications and device programming issues. In addition, 94.2% believed that DBS should not be limited to a last-resort option, emphasizing its value in earlier stages of the disease.

Training and contact with DBS centers

A total of 71.0% of physicians reported no formal training in movement disorders or DBS, whereas 29.0% had completed specialized education, highlighting a notable gap in advanced medical training. Regarding contact with specialized DBS centers, 65.2% had established connections, while 34.8% lacked these relationships, potentially hindering patient referrals and management.

Perceived barriers to DBS access

Open-ended responses identified four main categories of barriers:

- Economic factors: high procedural and device maintenance costs, coupled with insufficient insurance coverage, were reported by 79.7% of respondents
- Infrastructure and resources: a lack of specialized centers and their centralization in major cities was highlighted by 29%, restricting access for patients in remote areas
- Limited knowledge: a lack of dissemination of information about DBS benefits and referral criteria among both physicians and patients was identified by 21.7%

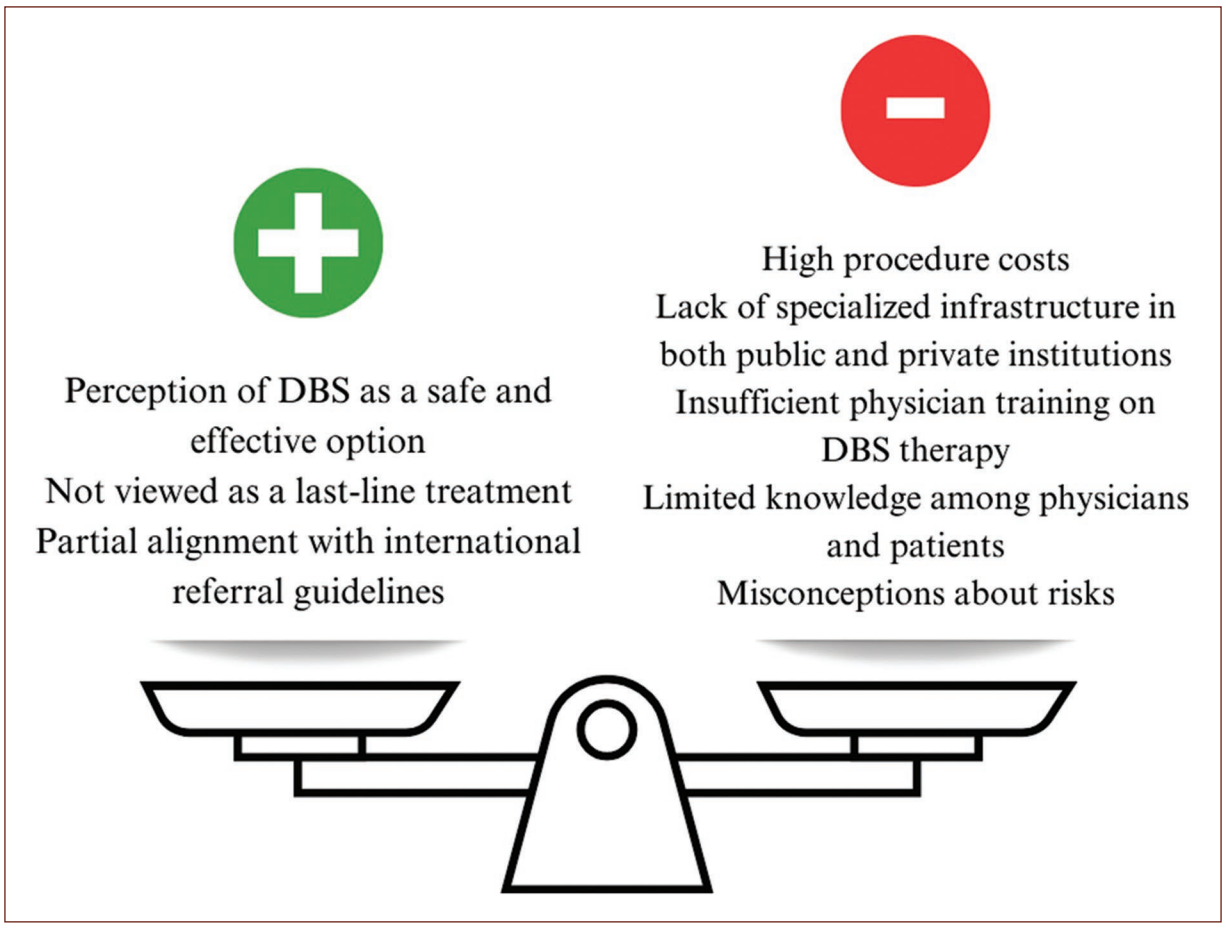

Figure 1. Balance between favorable attitudes and perceived barriers toward deep brain stimulation (DBS) in Mexico. The figure illustrates the balance between favorable attitudes and barriers toward DBS among physicians treating Parkinson's disease patients in Mexico. On the positive side, it highlights the perception of DBS as a safe, effective technique not limited to being a last-line treatment, as well as partial alignment with international guidelines. However, these attitudes contrast with significant barriers, such as the high cost of the procedure, centralized infrastructure, insufficient knowledge among physicians and patients, and erroneous risk perceptions, which limit its implementation and accessibility.

– Perceptual risks: although less common (5.8%), some respondents mentioned fear of the procedure due to misconceptions about surgical risks and uncertain outcomes.

These findings underscore critical areas for improvement to enhance access to and implementation of DBS in Mexico. Figure 1 illustrates the favorable attitudes and perceived barriers toward DBS reported by the surveyed physicians.

Discussion

This study identifies critical factors related to the knowledge, attitudes, and barriers toward DBS in Mexico, highlighting both alignment with international recommendations and discrepancies requiring attention. Nationally, attitudes toward DBS are predominantly positive, with physicians perceiving it as a safe and effective treatment that should not be confined to a last-resort option. However, significant barriers – such as high costs, centralized services, and lack of specialized training – were identified, limiting the accessibility and implementation of this advanced therapy.

The unequal distribution of specialized centers, reported by 37.7% of respondents, underscores structural inequalities that force many patients to travel long distances or face prolonged wait times. This contrasts with studies in more developed settings, such as Shih and Tarsy's work[11], which highlight debates over minimum disease duration before DBS referral as a primary

challenge in well-resourced systems. Similarly, Lange et al. in Germany identified knowledge deficits among physicians, with only 2% accurately identifying key referral criteria[12]. These findings suggest that while barriers differ by context, continuous medical education remains a universal necessity.

Most physicians in this study believed that advanced age does not significantly diminish DBS benefits, aligning with international guidelines. However, the 30.4% expressing contrary opinions underscores variability in evidence interpretation. In addition, while 71.0% of respondents identified 5-10 years post-diagnosis as the ideal DBS window, the 24.6% favoring earlier intervention, and 4.3% supporting later implementation reflect the need to strengthen understanding of evidence-based criteria.

Economic barriers emerged as the most prominent challenge, with 79.7% identifying cost as the primary obstacle to access. This finding aligns with previous studies documenting the critical role of financial constraints, even in more developed healthcare systems[8]. Furthermore, the 21.7% reporting limited knowledge about DBS benefits and safety emphasizes the importance of improving medical training and patient communication.

Although only 5.8% of respondents expressed concerns about surgical risks, these perceptions, combined with knowledge gaps, highlight the need for educational initiatives to dispel misconceptions and promote timely referrals. Collectively, these findings emphasize the necessity of addressing structural, economic, and educational barriers through targeted policies that foster equitable and early access to DBS in Mexico.

This study has several limitations. The small sample size restricts the generalizability of findings to the national level. In addition, the survey-based design may be subject to response bias. Future studies should consider including primary care physicians to broaden the scope of this research and enhance its educational impact. Their involvement could help raise awareness about advanced treatment options for PD among healthcare professionals who play a key role in early diagnosis and patient referral. The exclusion of patient perspectives limits a more comprehensive understanding of barriers to DBS. Finally, the lack of transnational comparisons limits the global contextualization of the results. Despite these limitations, this study provides valuable insights as one of the first systematic investigations into the attitudes, knowledge, and barriers toward DBS in Mexico from the perspective of physicians.

Conclusions

This study highlights predominantly positive attitudes toward DBS among physicians in Mexico, emphasizing its perception as a safe and effective therapeutic option. However, economic barriers, centralized services, lack of knowledge about referral criteria, and misconceptions about risks hinder its implementation and accessibility. Overcoming the identified barriers will require implementing policies focused on adequate financing, decentralization of specialized services, and continuous medical education programs. Informational campaigns targeting physicians and patients could further enhance understanding of DBS as a viable and timely option, optimizing its impact on PD management and patient quality of life. This work underscores the importance of tailoring global strategies to the specific needs of the Mexican context, thereby strengthening equity and effectiveness in access to advanced therapies.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

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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ORIGINAL ARTICLE

The EMDR-PRECI: advancing neurobiological insights into PTSD through fMRI in women with cancer

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Abstract

Objective: *This research aimed to develop an Eye Movement Desensitization and Reprocessing-Protocol for Recent Critical Incidents and Ongoing Traumatic Stress (EMDR-PRECI)-based functional magnetic resonance imaging (fMRI) protocol to explore the neurobiological conditions associated with PTSD diagnosis and to demonstrate the effects of the application of the EMDR-PRECI in general and the EMDR Butterfly Hug (BH) method for self-administered bilateral stimulation in particular on specific brain structures associated with post-traumatic stress disorder (PTSD), and to establish a precedent that can serve as a new tool for advancing our understanding of the neurobiology of PTSD and EMDR treatment. This study is also part of a larger research project examining the neurobiological, psychological, and neuropsychological changes associated with the application of the EMDR-PRECI in women with cancer and PTSD-related diagnoses.* **Methods:** *The authors used a transversal quantitative quasi-experimental study design to develop the EMDR-PRECI-based fMRI protocol, which included T1 spin echo pulse sequences in axial projection and blood oxygenation level dependent-EPI 2D in axial projection.* **Results:** *Results showed that the average deoxygenation change relative to the resting condition increases in each brain region (amygdala, hippocampus, and medial prefrontal cortex) during the treatment condition, using the BH, compared to the control condition (no BH), inferring that these brain regions experienced neuromodulation.* **Conclusions:** *The BH triggered simultaneous changes across multiple brain regions, suggesting the impact of this method in broader brain circuits. This study provides an fMRI research protocol to study PTSD and its treatment through the EMDR-PRECI protocol.*

Keywords: *PTSD. EMDR-PRECI. Butterfly Hug. fMRI. Cancer-related PTSD.*

Protocolo EMDR-PRECI: avances neurobiológicos en el TEPT a través de estudios de RMf en mujeres con cáncer

Resumen

Objetivo: *Esta investigación tuvo como objetivo desarrollar un protocolo de resonancia magnética funcional (fMRI) basado en el Protocolo de Desensibilización y Reprocesamiento por Movimientos Oculares para Incidentes Críticos Recientes y Estrés Traumático Continuado (EMDR-PRECI), para explorar las condiciones neurobiológicas asociadas con el diagnóstico*

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de TEPT y demostrar los efectos de la aplicación del EMDR-PRECI en general, y del método EMDR del Abrazo de la Mariposa (BH) para la estimulación bilateral autoadministrada en particular, en estructuras cerebrales específicas asociadas al trastorno de estrés postraumático (TEPT), y establecer un precedente que pueda servir como nueva herramienta para avanzar en nuestra comprensión de la neurobiología del TEPT y el tratamiento con EMDR. Este estudio también forma parte de un proyecto de investigación más amplio, que examina los cambios neurobiológicos, psicológicos y neuropsicológicos asociados a la aplicación del EMDR-PRECI en mujeres con cáncer y diagnósticos relacionados con el TEPT. **Métodos:** *Los autores utilizaron un diseño de estudio cuantitativo transversal cuasiexperimental para desarrollar el protocolo de resonancia magnética funcional (fMRI) basado en EMDR-PRECI, que incluía secuencias de pulsos de eco de espín T1 en proyección axial y EPI 2D dependiente del nivel de oxigenación sanguínea en proyección axial.* **Resultados:** *Los resultados mostraron que el cambio promedio de desoxigenación en relación con el estado de reposo aumenta en cada región del cerebro (amígdala, hipocampo y corteza prefrontal medial) durante la condición de tratamiento usando el BH, en comparación con la condición de control (sin BH), lo que permite inferir que estas regiones del cerebro experimentaron neuromodulación.* **Conclusiones:** *El BH provocó cambios simultáneos a través de múltiples regiones cerebrales, lo que sugiere el impacto de este método en amplios circuitos cerebrales. Este estudio proporciona un protocolo de investigación de fMRI para estudiar el TEPT y su tratamiento a través del protocolo EMDR-PRECI.*

Palabras clave: *TEPT. EMDR-PRECI. Abrazo de la Mariposa. fMRI. TEPT relacionado con el cáncer.*

Introduction

Over the past 20 years, functional magnetic resonance imaging (fMRI) has provided valuable insights into the psychopathophysiology of various psychiatric disorders, particularly post-traumatic stress disorder (PTSD)[1-3]. fMRI research involves task-based studies in which patients perform activities that engage specific mental processes. The neurons involved in these processes require increased energy, which is primarily supplied by the oxygen in the blood circulating through capillaries near the relevant brain areas. By analyzing variations in the fMRI signal, which reflect changes in oxygenation levels (oxyhemoglobin), researchers can infer functional changes in the brain activity of the regions involved.[4]

There is a growing consensus among researchers[5] that the primary brain regions implicated in PTSD pathology are the amygdala, the medial prefrontal cortex (mPFC), and the hippocampus[6-9]. Shin et al.[7] in their meta-analysis of neuroimaging research on the structure and neurochemistry of these regions in individuals with PTSD have identified the neurocircuitry involved: a hyper-reactive amygdala, leading to an exaggerated response to fear and threat-related stimuli[10,11], the prefrontal cortex (PFC), and the hippocampus. In contrast to the amygdala, the PFC shows decreased responsiveness, which has been linked to the mPFC's partial failure to effectively inhibit the amygdala[12]. Regarding the impact on the hippocampus in individuals with PTSD, there is well-documented evidence of reduced hippocampal volume, decreased neuronal integrity, and impaired hippocampal function, which are associated with deficits in explicit memory[13].

There is some consensus on the neurophysiopathology underlying PTSD[14,15] and studies have shown the impact of certain psychotherapies on specific brain regions. The meta-analysis conducted by Pierce and Black[15] provides a comprehensive study of various trauma-focused psychotherapies and their impact specific brain regions, including nine fMRI studies on Eye Movement Desensitization and Reprocessing (EMDR) Therapy[16-24]. However, no functional neuroimaging studies have yet examined the EMDR-protocol for recent critical incidents and ongoing traumatic stress (PRECI) in real-time. Some Pierce and Black[15] suggest that Trauma-Focused Cognitive Behavioral Therapy (TF-CBT) may lead to significant activity in the mPFC and orbitofrontal cortex compared to other psychotherapy modalities. Similarly, EMDR Therapy has been shown to stimulate the superior frontal gyri and the dorsolateral PFC more effectively than other approaches. In addition, EMDR Therapy demonstrates the greatest potential for deactivating the insula and regions of the hindbrain. These findings align with a recent meta-comparative study on the long-term effectiveness of various psychotherapies for PTSD[25], which identified EMDR Therapy and Cognitive Processing Therapy[26] as having the largest effect sizes for short- and long-term follow-up, respectively.

Some case studies report similar results[27] with the administration of the EMDR Standard Protocol with females with PTSD during an fMRI study, showing significant changes in self-report measures and marked change in brain activation within the PFC, indicating a

ventromedial shift. Invernizzi, et al.[28] demonstrated significant brain functional changes on the right anterior par hippocampal gyrus and the left amygdala (LA) with the provision of EMDR Therapy in first responders that developed PTSD after responding to the 9/11 attacks.

Real-time fMRI studies and PTSD neuromodulation

Recent studies using real-time functional magnetic resonance imaging (rtfMRI) have explored the neurobiology of various disorders, particularly PTSD, and the potential for neuromodulation through specific interventions[29]. A pioneering series of studies[30-32] investigated the use of neurofeedback as a neuromodulation technique. The research question was whether healthy volunteers could be trained to control blood oxygenation level dependent (BOLD) activity levels in the amygdala using rtfMRI neurofeedback while watching positive autobiographical memories. The findings revealed that participants who successfully learned neurofeedback through rtfMRI were able to enhance regional BOLD activity in the amygdala. Notably, the BOLD fMRI signal increased in the LA in response to the number of neurofeedback sessions in the experimental protocol, indicating that amygdala activity can be modulated through neurofeedback during emotional experiences. Later, Zotev et al.[31] confirmed that rtfMRI neurofeedback in veterans with PTSD led to improvements in amygdala functioning, particularly in fMRI connectivity between the LA and the PFC. Similar results were recently observed in the amygdala and the cingulate cortex of patients with major depressive disorder who also received rtfMRI neurofeedback training with EEG[32].

EMDR therapy

EMDR Therapy is a structured eight-phase, three-pronged protocol based on the Adaptive Information Processing (AIP) theoretical model. The AIP theoretical model posits that the basis of psychopathology is memory networks of traumatic events or adverse life experiences that have been inadequately processed and maladaptively stored in a state-specific form. In EMDR Therapy these pathogenic memories are reprocessed, resulting in changes in the way the memory is encoded and subsequently experienced[33]. EMDR Therapy and TF-CBT are the only psychotherapies recommended for children, adolescents, and adults with PTSD by the World Health Organization Guidelines for the Management of Conditions Specifically Related to Stress[34]. EMDR Therapy administered to patients with cancer has been proven to be effective in the reduction of PTSD symptoms and PTSD diagnostic remission[35].

The EMDR-PRECI

The EMDR-PRECI is an evidence-based, eight-phase, and three-pronged individual EMDR Therapy protocol developed in the field specifically designed for the full reprocessing of pathogenic memory networks associated with recent, present, or past prolonged adverse experiences (e.g., ongoing or prolonged traumatic stress of patients with cancer-related PTSD diagnosis, victims of sexual and/or physical violence)[14]. The EMDR-PRECI utilizes eye movements (EM) as a first-choice method of bilateral stimulation (BLS) to reprocess pathogenic memories. Due to the impossibility of applying EM during the protocol's reprocessing phases inside the fMRI machine, the authors decided to use the Butterfly Hug (BH) method for self-administered BLS.

The EMDR BH Method

The EMDR BH method for self-administered BLS was originated by Lucina (Lucy) Artigas during her fieldwork with the survivors of Hurricane Pauline in Acapulco, Mexico in 1998. As of November 2024, over 80 peer-reviewed published studies have shown the effectiveness of EMDR Therapy protocols and treatment intervention procedures (e.g., ASSYST, EMDR-IGTP, EMDR-IGTP-OTS, EMDR-PRECI) using the BH as a self-administered BLS method for the reprocessing of pathogenic memories in various populations (e.g., disasters survivors, individuals living in ongoing geopolitical crises, child victims of severe interpersonal violence, female survivors of domestic violence, cancer patients, survivors of terrorist attacks, individuals living in situations of ongoing war trauma, refugees). The instruction for the BH method is as follows: *"Raise your hands to face level with your palms facing you. Cross your hands and hook your thumbs. Put your hands on your chest, with your middle fingers below your collarbones. Make sure that your fingers are together and as vertical as possible. Now, move your hands alternately as if they were the flapping of a butterfly's wings. Close your eyes, or keep them partially opened, focusing on a spot ahead…* (pause for 3 s) *breathe slowly and deeply, while you observe what is going through your mind and body, without changing it, without judging it, and without pushing your thoughts away…* (pause for 3 s) *you can pretend what you are observing is like clouds passing*

by…stop when you feel in your body that it has been enough and lower your hands to your lap"[36].

Cancer and trauma

There is evidence pointing to a relationship between cancer and trauma, with the prevalence of cancer being higher among the population with trauma compared to the general population. Specifically, women who suffered traumatic experiences, victims of domestic and sexual violence, and adverse childhood experiences have a higher prevalence of cancer[37]. The diagnosis of a chronic illness such as cancer is considered a risk factor for developing PTSD, according to the update made to the diagnostic criteria in the DSM-5 in 2013. This relationship between cancer and trauma may be implicated by chronic inflammation and immune dysregulation induced by changes in the hypothalamic-pituitary-adrenal (HPA) axis[38,39].

Objective

This descriptive and comparative study aimed to develop an EMDR-PRECI-based fMRI protocol to explore neurobiological conditions associated with PTSD and to demonstrate the effects of the application of the EMDR-PRECI in general and the BH in particular, on specific brain structures associated with PTSD.

Material and method

Study design

The authors used a transversal quantitative quasi-experimental study design to develop the EMDR-PRECI-based fMRI protocol.

Research ethics

The research design and proposal were reviewed and approved by the Institutional Review Board of the Central Hospital "Ignacio Morones Prieto" in San Luis Potosí, Mexico and was registered as number 73-16 in September 2016.

Participants

This study was conducted between 2017 and 2021 in San Luis Potosí, Mexico. Potential participants were recruited through social media networks and referrals from other cancer patients. Interested individuals were invited to call for details about the research project. A total of 50 potential participants expressed interest and received information about the study. Of the 50, 20 completed the intake interview and met the inclusion criteria. To ensure eligibility, all participants were initially assessed using the Short Post-Traumatic Stress Disorder Rating Interview (SPRINT)[40]. If a participant scored 16 points or higher, the Global Assessment of Post-Traumatic Stress Scale (EGEP)[41] was administered to confirm a PTSD diagnosis, after which the informed consent document was signed. The patients' ages ranged from 41 to 68 years old, with an average age of 51.6. Among the participants, 15 had breast cancer, two had colon cancer, two had lung cancer, and one had lymphoma.

Inclusion criteria were: (a) Female adult, (b) diagnosis of cancer, (c) having received or currently receiving cancer treatment (e.g., surgery, radiotherapy, and/or chemotherapy), (d) having a PTSD diagnosis related to their cancer diagnosis and treatment, and (e) free of acute infections. Exclusion criteria were: (a) a terminal phase of cancer, (b) ongoing self-harm/suicidal or homicidal ideation, (c) diagnosis of a psychotic or bipolar disorder, (d) diagnosis of a dissociative disorder, (e) an organic mental disorder, (f) present, active chemical dependency problem, (g) significant cognitive impairment (e.g., severe intellectual disability, dementia), (h) at present receiving specialized trauma therapy, (i) receiving psychofarmacotherapy for the management of PTSD symptoms, and (j) receiving any other psychological, psychosocial, or psychoeducational treatment.

fMRI data acquisition

fMRI studies were performed with General Electric 1.5 T HDe high-field equipment. A standard 4-channel quadrature scanning antenna for the skull was used. The protocol included T1 spin echo pulse sequences in axial projection and BOLD-EPI 2D in axial projection (Functional Imaging). The parameters of the pulse sequences were the following: T1 Fast FLAIR Axial 2D: TR 2675, TE minimum, TI 750, FOV 24, Matrix 250 × 224, NEX 2, Frequency band 31.25. BOLD-EPI Axial 2D: TR 3000, TE 28.7, FOV 40, Matrix 64X 64, NEX 1, Frequency Band Dead. The fMRI was planned in axial projection in a dorsoventral direction. Information was acquired every 30 s while the patient was at rest and with interspersed brain activity, with the study starting at rest.

Procedure

After participants completed the intake interview and were determined to have met inclusion criteria, they were randomly assigned to one of four EMDR therapists trained in the EMDR-PRECI participating in the study. The first session of the EMDR-PRECI was conducted in the therapist's private office. During this initial session, the history and treatment planning phase was completed. The therapist asked the patient to provide a brief, general description of the adverse experience from right before the cancer treatment until the present moment. The clinician assessed clinical symptoms and the patient's stabilization skills during the preparation and stabilization phase. The EMDR BH method for self-administered BLS was also taught during this session. The first target for reprocessing inside the fMRI equipment was the worst part identified by the patient by running a mental movie of the whole cancer-related experience from right before the beginning until the present moment or even looking into the future. This unique procedure covers the patient's entire traumatic stress clinical spectrum to identify the targets for reprocessing.

Once the patient and the therapist identified the worst part of the cancer-related adverse experience selected for reprocessing, the patient was scheduled for their first reprocessing session at the Radiology and Imaging Department of Ignacio Morones Prieto Central Hospital in San Luis Potosí, where the patient's brain activity was recorded using fMRI equipment. The selected worst part was reprocessed during this session using the EMDR-PRECI reprocessing phases and the BH as self-administered BLS. The BH was chosen instead of other BLS methods (e.g., EM, bilateral sounds, taping on the knees) because it could be used inside the fMRI machine, and studies have shown that it is a non-pharmacological intervention that has proven to be effective in reducing anxiety in various populations[42]. The EMDR-PRECI protocol was adapted for this fMRI study with specific research objectives.

Treatment

Once the patient was positioned inside the MRI machine, the study commenced with an initial 6-min block dedicated to equipment calibration, during which the patient remained at rest. After completing this phase, the patient received instructions to begin the first block of reprocessing. At this point, the Subjective Units of Disturbance Scale (SUDS) was used to measure the level of disturbance and was recorded for the previously identified worst part of the selected cancer-related adverse experience. Each reprocessing block has duration of 6 min with 24 s. These first 24 s were used for an adjustment period of the FMR equipment after the instruction that must be indicated on each block. As many reprocessing blocks as necessary were used until the SUDS score decreased to 0. The average time inside the MRI machine was 55 min.

Only the first block of reprocessing was divided into two parts of 3 min each (uninterrupted). In the first part, we made a sequence of blocks of exposure of the worst part (of 30 s) without the BH, followed by a block of breathing (30 s of breathing and up to 3 min). After these 3 min, the second part began with a reprocessing sequence (with the BH and breathing until completing another 3 min and adding the 6 min of the first block). This first block was used as a baseline measurement. After this first baseline block, the first (after 24 s) 6 min of the reprocessing block begins. Then, the patient starts with the fragment of 30 s of reprocessing with the BH and 30 s of breathing uninterrupted until completing 6 min, and SUDs are checked. A new reprocessing block was started if the patient reported SUDs >0. More than 6-min blocks were used to reduce the SUDs to 0 or the lowest possible SUD during the 1-h study time frame. When the SUDs reached 0 or when 15 min were remaining in the fMRI study time (even if the SUD did not reach 0), the therapist went to an intermediate 6-min block in which the first 30 s the patient concentrated on the worst part of the adverse experience being reprocessed, but without doing the BH. In the subsequent 30 seconds, they were asked to focus only on breathing.

The final 6-min block for stabilization purposes was done with the patient evoking their pleasant memory or safe place. Finally, when the fMRI study concluded, the therapist scheduled a follow-up appointment to continue the EMDR-PRECI. This protocol consisted of running the mental movie again, looking for any other disturbing parts, which were subsequently reprocessed in the therapist''s private office.

Deoxygenation change (DC) calculation

The DC between the treatment condition (TC) and the rest condition (RC) was calculated using the formula: $DC = 100 \times (EC - RC)/RC$. Since reduced oxygenation levels in the blood correspond to increased oxygen consumption, smaller values on the deoxygenation scale indicate higher oxygen consumption. Therefore, a positive DC relative to rest ($DCExp - DCRest > 0$) means that oxygen consumption in the experimental condition

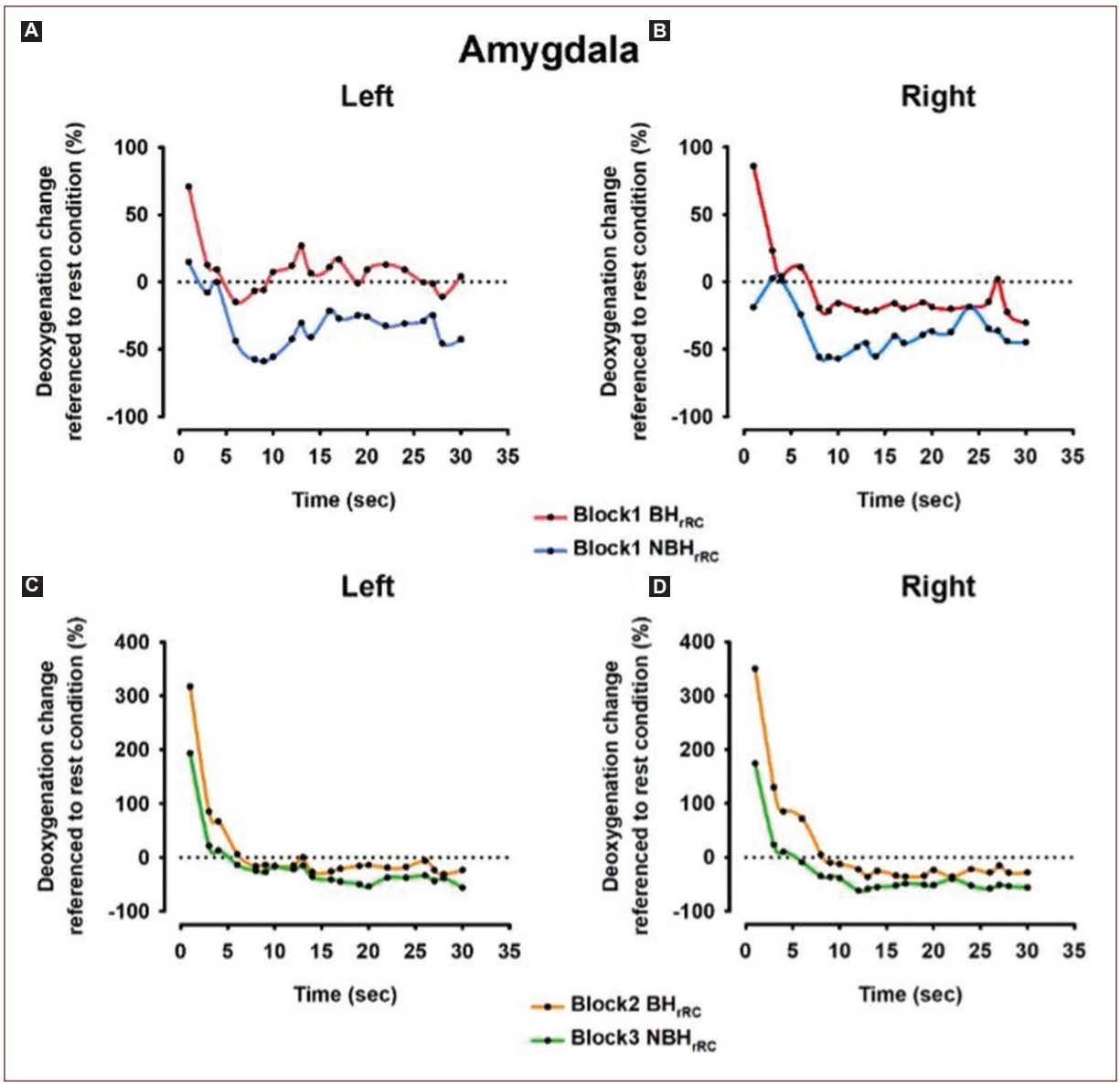

Figure 1. Time series of deoxygenation changes in the amygdala during the experimental conditions. **A:** the "butterfly hug" condition reduces deoxygenation levels compared to the "no butterfly hug" condition in the left amygdala. **B:** similarly, the "butterfly hug" condition reduces deoxygenation levels compared to the "no butterfly hug" condition in the right amygdala. **C:** the deoxygenation reduction profile in the left amygdala is similar between the "butterfly hug" and "no butterfly hug" conditions. **D:** the deoxygenation reduction profile in the right amygdala is also similar between the "butterfly hug" and "no butterfly hug" conditions. rRC = referenced to rest condition.

(BH, non-Butterfly Hug [NBH], in protocols B1, B2, and B3) was lower than at rest. Conversely, a negative DC (DCExp–DCRest < 0) indicates that oxygen consumption in the TC was higher than at the RC, reflecting an increase in oxygen consumption during the TRn.

Statistical analysis

As the time series did not meet the normality assumption (Shapiro–Wilk $p < 0.05$), non-parametric tests were used to evaluate differences in medians across the TCs. A Friedman Analysis of Variance (ANOVA) will be conducted to test for intragroup differences. This non-parametric test is suitable when the assumptions of parametric tests, such as normality or homogeneity of variance, are violated. The Friedman ANOVA is applied to assess differences across multiple conditions, where the same participants provide data for all conditions (i.e., repeated measures). If the Friedman ANOVA result is significant,

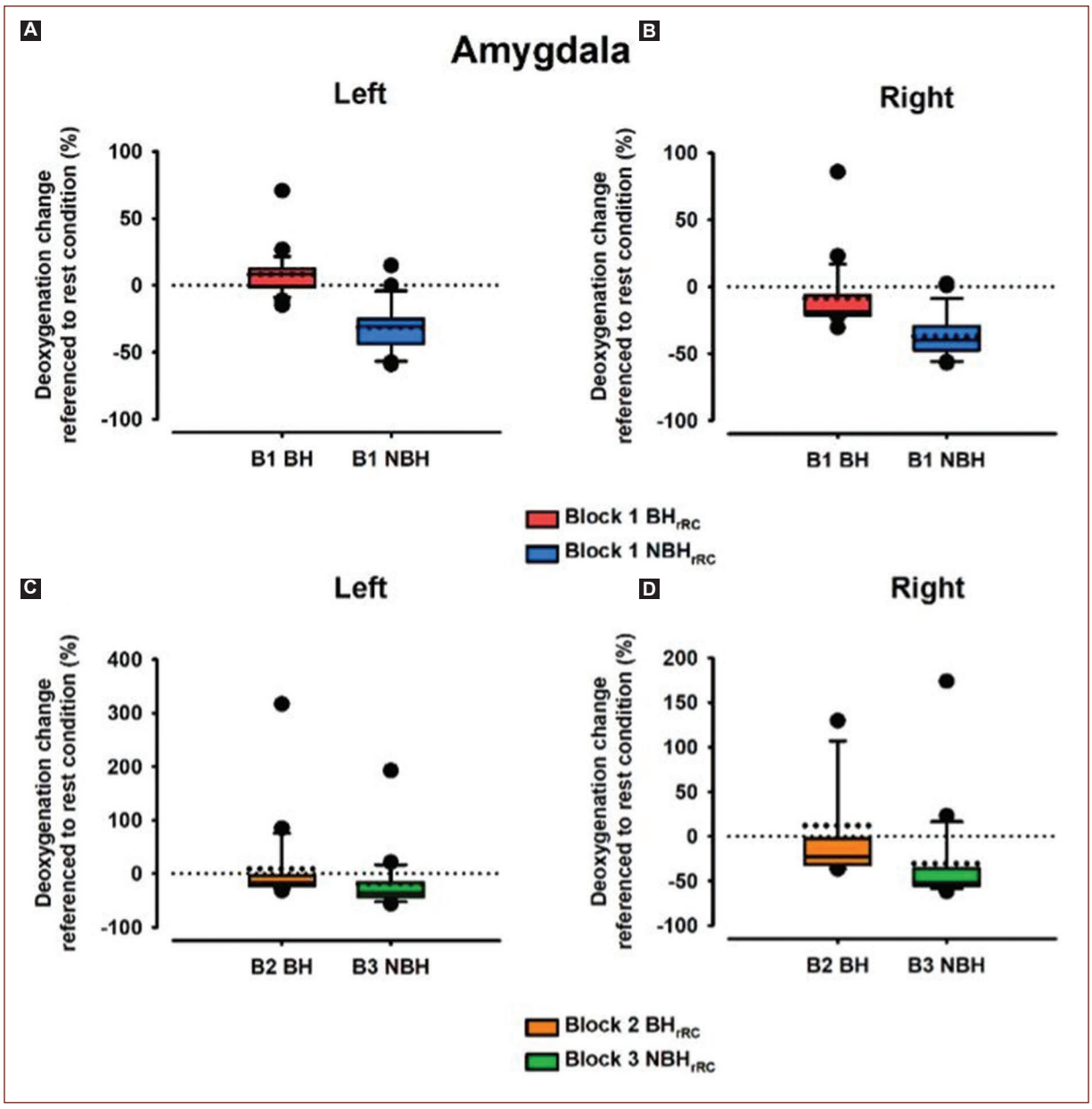

Figure 2. Box Plots for deoxygenation Change (DC) in the Amygdala. **A:** left amygdala DC for Block 1 (B1) under the butterfly hug (BH) and no butterfly hug (NBH) conditions. **B:** right amygdala DC for Block 1 (B1) under the butterfly hug (BH) and no butterfly hug (NBH) conditions. **C:** left amygdala DC for Block 2 (B2) under the butterfly hug (BH) condition and for Block 3 (B3) under the no butterfly hug (NBH) condition. **D:** right amygdala DC for Block 2 (B2) under the butterfly hug (BH) condition and for Block 3 (B3) under the no butterfly hug (NBH) condition. rRC: referenced to rest condition.

post hoc analyses will be carried out using the non-parametric Wilcoxon test. The Wilcoxon test compares two sets of scores from the same participants, serving as the non-parametric equivalent of the dependent t-test for repeated measures data. Statistical significance will be determined using a two-tailed test. To control for Type I error, the Bonferroni correction will be applied to all Wilcoxon tests, adjusting the significance threshold to $p < 0.0125$. In addition, effect sizes (r) will be reported, with $r > 0.5$ indicating a large effect.

Results

This study measured changes in brain dynamics by analyzing blood oxygen levels between the resting state and the TC. The aim was to identify differences between pathogenic memory reprocessing moments

and non-reprocessing moments. It was hypothesized that variations in blood oxygen levels would increase or decrease as an effect of the experiment, specifically during the reprocessing of pathogenic memories in the fMRI study.

Amygdala

Figure 1 illustrates the changes in blood oxygen levels within the amygdala across different phases of the study. The findings indicate that reprocessing during the fMRI study, particularly using the BH method during the reprocessing phases of the EMDR-PRECI, leads to a reduction in blood oxygen consumption in the amygdala. The literature reports that the amygdala tends to show hyperactivation in individuals with PTSD, which is linked to increased oxygen consumption due to higher energy demands[10,43]. Therefore, our results suggest a neuromodulator effect, implying that reprocessing through the application of the EMDR-PRECI in general, and the BH in particular, may help restore the amygdala to its baseline neurobiological state, facilitating emotional stabilization.

Figure 1 shows the time series of DCs in the amygdala during the experimental conditions BH and NBH for B1, B2, and B3. Figure 2 shows the Box Plots for DC in the amygdala across different blocks of the study. Friedman's ANOVA revealed that DCs in the amygdala were significantly influenced by the protocol (BH versus NBH), χ^2 (7) = 85.3, $p < 0.0001$. Paired comparisons showed the following: in the LA during Block 1 (B1), deoxygenation was significantly smaller in the BH condition (median = 8.15) compared to the NBH condition (median = –30.83), Z = –3.92, $p < 0.0001$, r = –0.62. A similar pattern was observed in the right amygdala, where deoxygenation during B1 was also significantly smaller in the BH condition (median = –18.66) compared to the NBH condition (median = –39.97), Z = –3.92, $p < 0.0001$, r = –0.62. In addition, when comparing Blocks 2 (B2) and 3 (B3), the LA showed significantly smaller deoxygenation in the B2 BH condition (median = –15.95) than in the B3 NBH condition (median = –35.10), Z = –3.92, $p < 0.0001$, r = –0.62. A similar trend was found in the right amygdala, where deoxygenation was significantly smaller in the B2 BH condition (median = –23.26) compared to the B3 NBH condition (median = –51.59), Z = –3.92, $p < 0.0001$, r = –0.62 (Table 1). These results indicate that, compared to the RC, both amygdalae exhibited smaller oxygen consumption in the BH condition than in the NBH condition during the B1 and B2-B3 protocols, except only for the LA during B1-BH (Fig. 2A).

Table 1. Summary of the Wilcoxon test results for the Amygdala

Condition	Median (a.u.)	Effect size	Difference	Significance
Amygdala left				
B1-BH	8.15	–0.62	38.98	0.0001
B1-NBH	–30.83			
B2-BH	–15.95	–0.62	–19.15	0.0001
B3-NBH	–35.10			
Amygdala right				
B1-BH	–18.66	–0.62	–21.31	0.0001
B1-NBH	–39.97			
B2-BH	–23.26	–0.62	–28.33	0.0001
B3-NBH	–51.59			

B1: block 1; B2: block 2; B3: block 3; BH: butterfly hug; NBH: non-butterfly hug; a.u.: arbitrary units.

Hippocampus

Figure 3 shows the time series of DCs in the hippocampus during the experimental conditions BH and NBH for B1 and B2 and B3. Figure 4 shows the Box Plots for DC in the hippocampus across different blocks of the study. Friedman's ANOVA revealed that DCs in the hippocampus were significantly influenced by the protocol used (BH and NBH), Chi 2 (7) = 79.2, $p < 0.0001$.

In the left hippocampus during B1, deoxygenation was significantly smaller in the BH condition (median = –27.79) compared to the NBH condition (median = –40.61), Z = –3.9, $p < 0.0001$, r = –0.87. A similar pattern was observed in the right hippocampus, where deoxygenation during B1 was significantly smaller in the BH condition (median = –25.38) compared to the NBH condition (median = –29.30), Z = –3.5, $p < 0.001$, r = –0.78.

On the other hand, when comparing B2 and B3, the left hippocampus showed significantly greater deoxygenation in the B2 BH condition (median = –28.66) compared to the B3 NBH condition (median = –23.67), Z = –3.2, $p < 0.001$, r = –0.71. However, in the right hippocampus, no significant difference in deoxygenation was found between the B2 BH condition

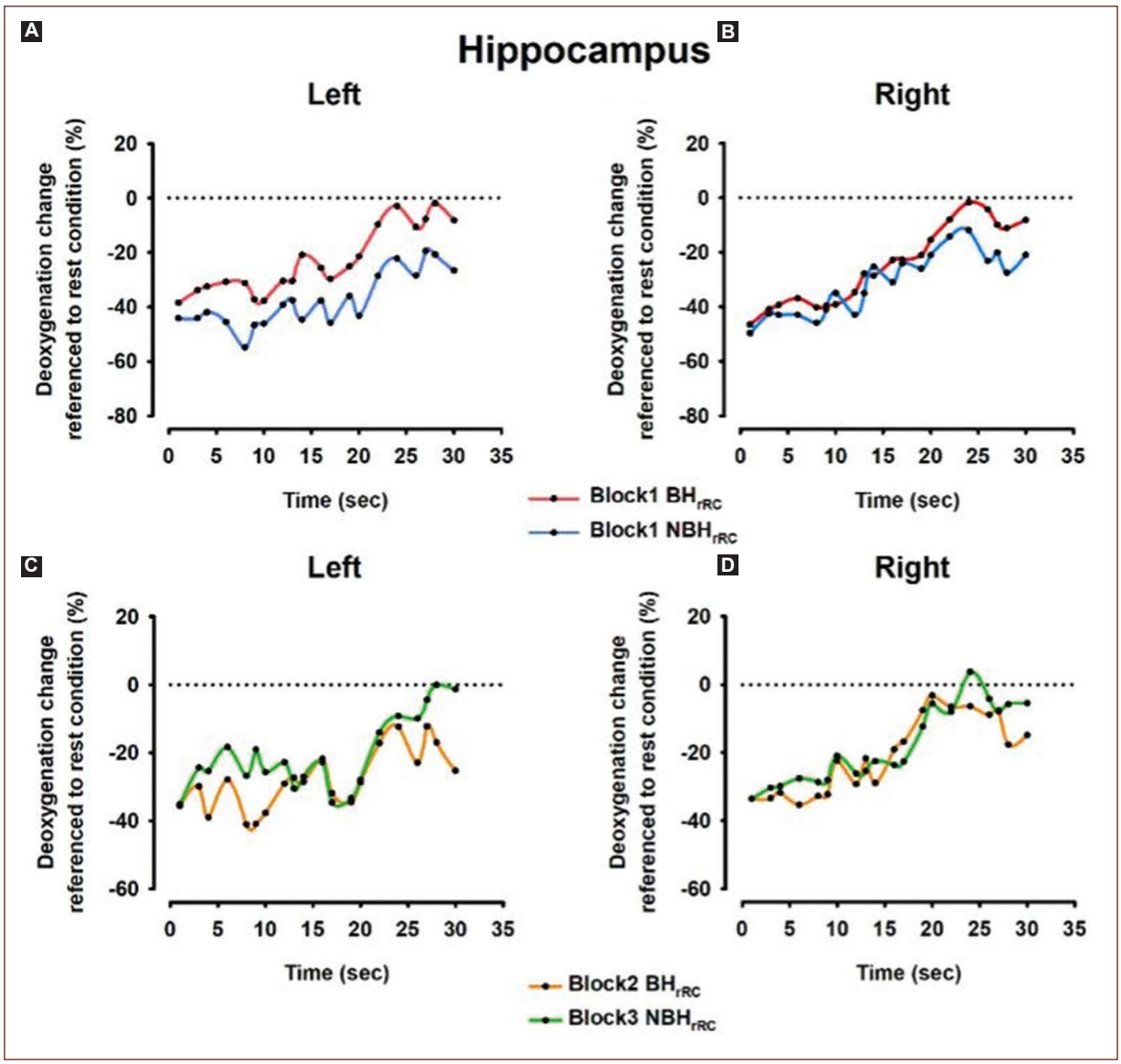

Figure 3. Time series of deoxygenation changes in the hippocampus during the experimental conditions. **A:** the "butterfly hug" condition reduces deoxygenation levels more rapidly compared to the "no butterfly hug" condition in the left hippocampus. **B:** in the right hippocampus, the "butterfly hug" condition also reduces deoxygenation levels, though at a similar pace to the "no butterfly hug" condition. **C:** the deoxygenation profile in the left hippocampus is similar between the "butterfly hug" and "no butterfly hug" conditions. **D:** the deoxygenation profile in the right hippocampus is also similar between the "butterfly hug" and "no butterfly hug" conditions. rRC: referenced to rest condition.

(median = –20.45) and the B3 NBH condition (median = –22.66), Z = –1.6, p > 0.05, r = –0.36 (Table 2).

These findings indicate that, compared to the RC, both hippocampi exhibited smaller oxygen consumption in the BH condition in comparison to the NBH condition, during the B1 protocol. However, in the left hippocampus, there was smaller oxygen consumption in the NBH condition than in the BH condition during the B2-B3 protocols (Fig. 4).

mPFC

Figure 5 shows the time series of DCs in the mPFC during the experimental conditions BH and NBH for B1 and B2 and B3. Figure 6 shows the Box Plots for DC in the mPFC across different blocks of the study. Friedman's ANOVA revealed that DCs in the mPFC were significantly influenced by the protocol used (BH and NBH), Chi 2 (7) = 104.6, p < 0.0001.

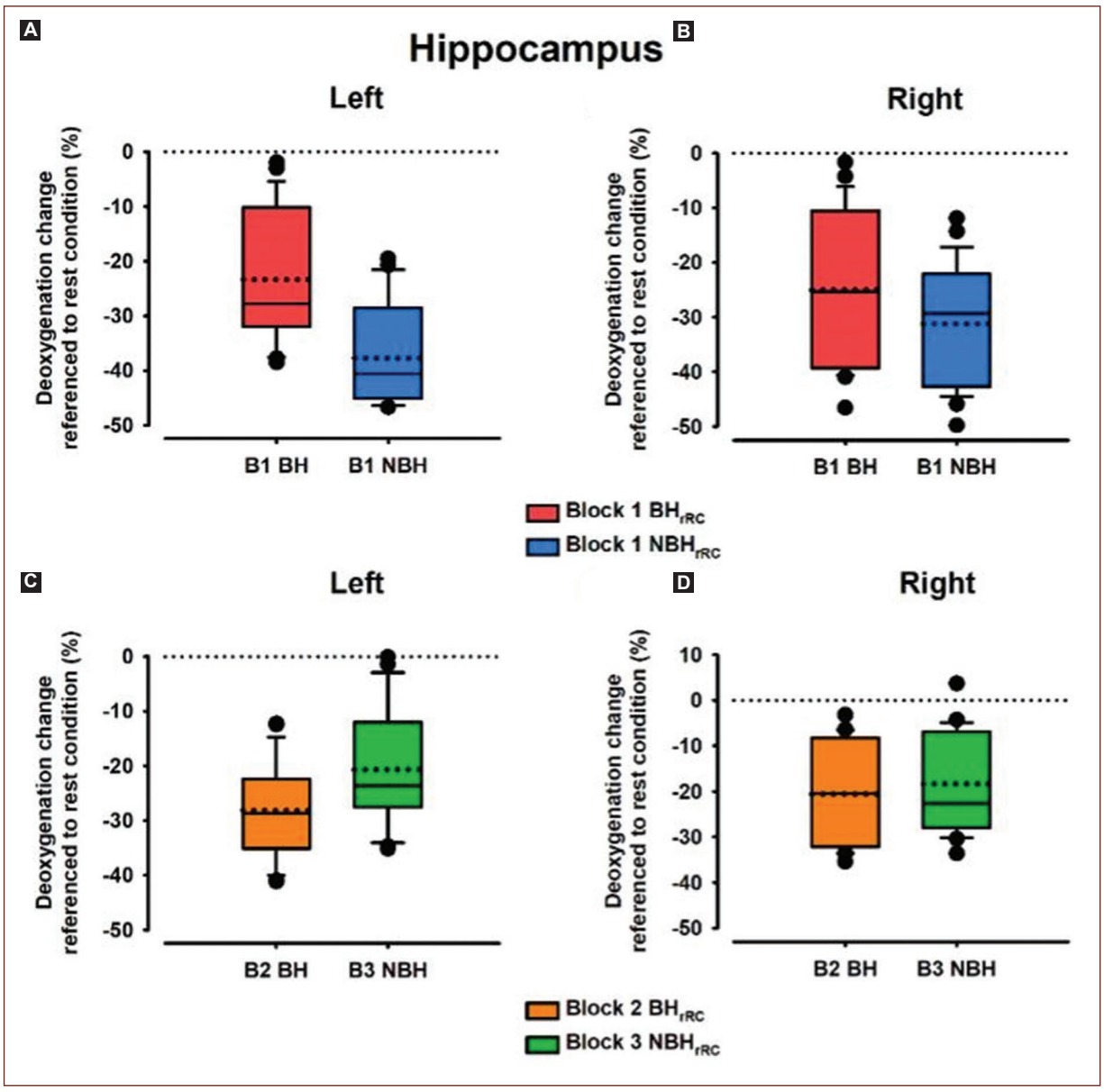

Figure 4. Box Plots for Deoxygenation Change (DC) in the Hippocampus. **A:** left hippocampus DC for Block 1 (B1) under the butterfly hug (BH) and no butterfly hug (NBH) conditions. **B:** right hippocampus DC for Block 1 (B1) under the butterfly hug (BH) and no butterfly hug (NBH) conditions. **C:** left hippocampus DC for Block 2 (B2) under the butterfly hug (BH) condition and for Block 3 (B3) under the no butterfly hug (NBH) condition. **D:** right hippocampus DC for Block 2 (B2) under the butterfly hug (BH) condition and for Block 3 (B3) under the no butterfly hug (NBH) condition. rRC: referenced to rest condition.

In the left mPFC during Block 1 (B1), deoxygenation was significantly smaller in the BH condition (median = –6.73) compared to the NBH condition (median = –12.62), $Z = -3.7$, $p < 0.0001$, $r = -0.58$. A similar pattern was found in the right mPFC, where deoxygenation during B1 was significantly smaller in the BH condition (median = –11.42) compared to the NBH condition (median = –23.39), $Z = -3.8$, $p < 0.0001$, $r = -0.60$.

In addition, when comparing B2 and B3, the left mPFC showed significantly smaller deoxygenation in the B2 BH condition (median = 16.36) compared to the B3 NBH condition (median = –9.34), $Z = -3.9$, $p < 0.0001$, $r = -0.61$. A similar trend was observed in the right mPFC, where deoxygenation was significantly smaller in the B2 BH condition (median = 5.29) compared to the B3 NBH condition (median = –15.51), $Z = -3.9$, $p < 0.0001$, $r = -0.61$ (Table 3).

These results indicate that, compared to the RC, both mPFC regions exhibited lower oxygen consumption in the BH condition than in the NBH condition during the B1 and B2-B3 protocols. The positive DC observed in figure 6C and D indicates that oxygen consumption was higher at rest than during the BH condition, indicating

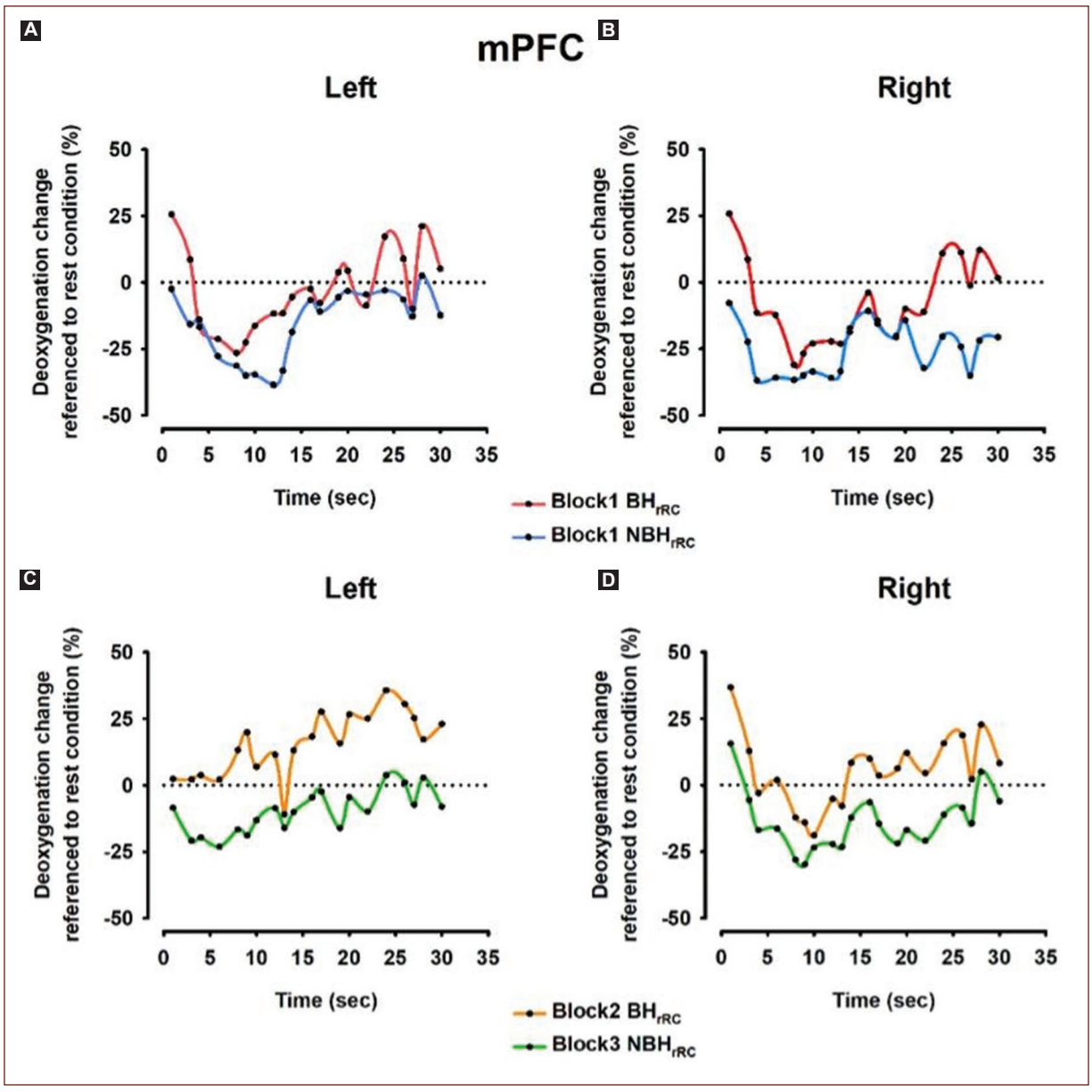

Figure 5. Time series of deoxygenation changes in the Medial prefrontal cortex (mPFC) during the experimental conditions. **A:** the "butterfly hug" condition shows similar deoxygenation profiles compared to the "no butterfly hug" condition in the left mPFC. **B:** in the right mPFC, the "butterfly hug" condition reduces deoxygenation levels compared to the "no butterfly hug" condition, particularly after 20 seconds. **C:** the "butterfly hug" condition reduces deoxygenation levels in the left mPFC compared to the "no butterfly hug" condition. **D:** similarly, the "butterfly hug" condition reduces deoxygenation levels in the right mPFC compared to the "no butterfly hug" condition. rRC: referenced to rest condition.

a decrease in oxygen consumption during the experimental condition (Fig. 6).

Discussion

Over the past 20 years, psychology and neuroscience have generated significant evidence on how psychological disorders affect the human brain[44]. This has allowed us to understand the neurobiology underlying various disorders, particularly PTSD. In addition, advances in brain imaging technology, such as fMRI, have enabled us to examine the effects of different psychotherapy modalities on brain activity associated with these conditions. The literature suggests that PTSD is characterized by specific neurobiological changes that few psychotherapy approaches – apart from EMDR therapy and EMDR therapy protocols – are capable of effectively modifying and restoring[15-45].

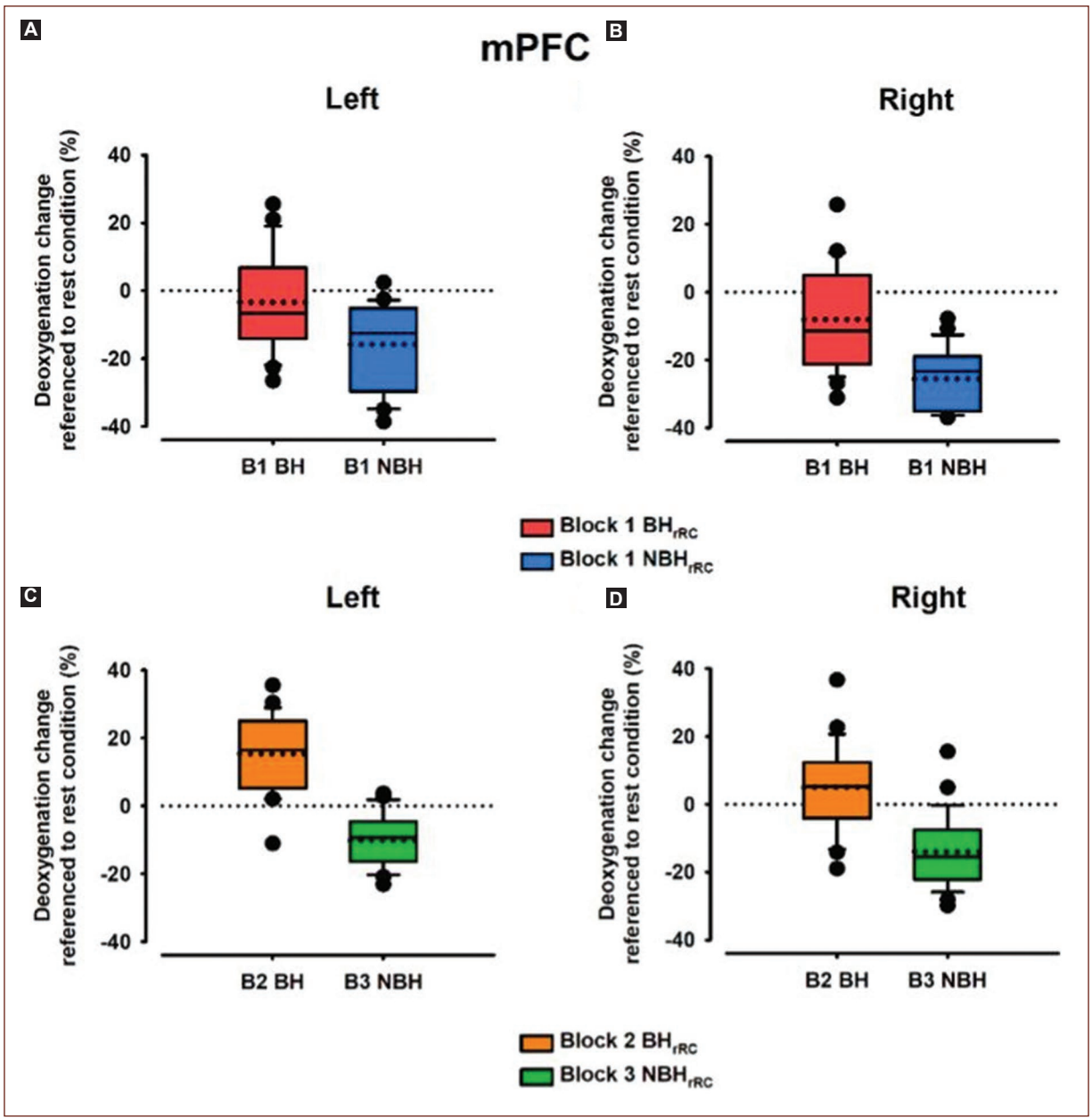

Figure 6. Box Plots for Deoxygenation Change (DC) in the Medial prefrontal cortex (mPFC). **A:** left mPFC DC for Block 1 (B1) under the butterfly hug (BH) and no butterfly hug (NBH) conditions. **B:** right mPFC DC for Block 1 (B1) under the butterfly hug (BH) and no butterfly hug (NBH) conditions. **C:** left mPFC DC for Block 2 (B2) under the butterfly hug (BH) condition and for Block 3 (B3) under the no butterfly hug (NBH) condition. **D:** right mPFC DC for Block 2 (B2) under the butterfly hug (BH) condition and for Block 3 (B3) under the no butterfly hug (NBH) condition. rRC: referenced to rest condition.

The preset study has found some evidence of neurobiological changes associated with the reprocessing phases of the EMDR-PRECI using the BH as a self-administered BLS method. These changes may include modifications in brain activity related to memory and emotional regulation. The BH method, a form of self-administered BLS used in EMDR therapy, was used in our study to reprocess cancer-related pathogenic memories and induce behavioral changes related to the patient's overall emotional stabilization. The BH appears to trigger simultaneous changes across multiple brain regions, suggesting that this method impacts broader brain circuits. Our findings indicate that the brain areas consuming the most oxygen during this process include the right and LA, the right and left hippocampus, and the mPFC on both sides. This neurobiological system may play a key role in generating responses related to post-traumatic stress.

Table 2. Summary of the Wilcoxon test results for the Hippocampus

Condition	Median (a.u.)	Effect size	Difference	Significance
Hippocampus left				
B1-BH	–27.79	–0.87	–12.82	0.001
B1-NBH	–40.61			
B2-BH	–28.66	–0.71	4.99	0.001
B3-NBH	–23.67			
Hippocampus right				
B1-BH	–25.38	–0.78	–3.92	0.001
B1-NBH	–29.30			
B2-BH	–20.45	–0.36	–2.21	>0.05 n.s.
B3-NBH	–22.66			

B1: block 1; B2: block 2; B3: block 3; BH: butterfly hug; NBH: non-butterfly hug; a.u.: arbitrary units; n.s.: non-significative.

Table 3. Summary of the Wilcoxon test results for the medial prefrontal cortex

Condition	Median (a.u.)	Effect size	Difference	Significance
Medial prefrontal cortex left				
B1-BH	–6.73	–0.58	–5.89	0.0001
B1-NBH	–12.62			
B2-BH	16.36	–0.61	–25.70	0.0001
B3-NBH	–9.34			
Medial prefrontal cortex right				
B1-BH	–11.42	–0.60	–11.97	0.0001
B1-NBH	–23.39			
B2-BH	5.29	–0.61	–20.80	0.0001
B3-NBH	–15.51			

B1: block 1; B2: block 2; B3: block 3; BH: butterfly hug; NBH: non-butterfly hug; a.u.: arbitrary units.

Furthermore, the effect sizes were consistently large, except in B2 and B3 of the right hippocampus. This suggests that the BH condition exerts a strong effect in reducing oxygen consumption. A decrease in oxygen consumption during an emotional state, such as that induced by the BH, has various clinical implications depending on the physiological and pathological context in which it occurs.

One possible interpretation is autonomic regulation and relaxation. A reduction in oxygen consumption may indicate a shift toward parasympathetic activation, promoting a state of relaxation and reducing right hippocampus activation[46]. Some reports indicate that emotional regulation techniques, such as meditation and diaphragmatic breathing, can lower cerebral and systemic oxygen metabolism, fostering a sense of calm.

Conversely, a decrease in cerebral metabolism has been associated with certain psychiatric conditions. For example, in major depressive disorder, reduced metabolic activity in specific brain regions, particularly those involved in emotional regulation has been linked to lower oxygen demand[47]. Similarly, altered metabolic patterns have been observed in states of dissociation and ineffective emotional regulation. Research suggests that trauma-induced dissociative states or extreme stress can lead to decreased activity in limbic structures such as the amygdala and mPFC, which in turn reduces oxygen consumption[48].

In addition, an abnormal decrease in oxygen consumption in response to emotional stimuli has been associated with affective dysregulation, as seen in PTSD. Furthermore, some PTSD patients exhibit altered cerebral oxygen dynamics, potentially due to hyperactivation of the HPA axis, which affects cerebral blood flow regulation[7]. This mechanism could underlie the significant changes in oxygen consumption observed in our study, particularly given the large effect sizes associated with the BH condition.

These findings highlight the complex interplay between emotional states, autonomic regulation, and cerebral metabolism, suggesting that the observed reduction in oxygen consumption may reflect either a beneficial relaxation response or a pathological state, depending on the broader clinical context.

The data suggest that oxygen consumption in both the right and LA during the BH condition is associated with participants being exposed to distressing memories. This aligns with the assertion[1] that the amygdala assigns emotional significance to various stimuli. Similarly, other authors[2,3] propose that the amygdala processes exteroceptive information, regardless of sensory modality, further supporting the idea that the BH method strongly stimulates this region.

In addition, the mPFC shows higher oxygen consumption during the BH condition compared to the NBH condition. Previous studies[4] suggested that this region is involved in processing emotions related to complex social and personal situations. This could explain why

patients in highly stressful conditions may experience a lack of initiative or akinesia. Activating this area through the use of the BH method likely facilitates patients' re-experiencing of their emotional state.

Furthermore, the increased oxygen consumption observed in the hippocampus during the BH condition appears to support the retrieval of long-term memories, particularly those consolidated over an extended period of learning or experiencing significant events[5]. The co-activation of cortical and subcortical regions during the BH condition suggests a coordinated effort that underpins the formation of signs and symptoms associated with PTSD.

This description of the brain circuit activated by the BH highlights that the EMDR-PRECI in general, and the BH in particular, not only aids in recovery from stressful events, modulating brain activity in the regions associated with PTSD but also has a strong scientific basis, offering valuable insights into the neurobiological mechanisms of PTSD.

The EMDR-PRECI-based fMRI protocol opens the doors to explore neurobiological conditions associated with PTSD diagnosis on specific brain structures associated with PTSD and establish a precedent that can serve as a new tool for advancing our understanding of the neurobiology of PTSD and EMDR Therapy treatment.

Conclusion

This study sheds new light on understanding the effectiveness of the EMDR-PRECI in general, as it is an EMDR therapy protocol designed explicitly for populations with recent, present, or past prolonged adverse experiences, and the BH method in particular, during the reprocessing of pathogenic memories, triggering simultaneous changes across multiple brain regions, suggesting the impact of this method in broader brain circuits. Our findings suggest that EMDR-PRECI, particularly using the BH, induces neurobiological changes associated with PTSD recovery. It also provides a fMRI protocol for future neurobiological research using the EMDR-PRECI for a better understanding of PTSD treatment. Future research should explore these effects in diverse populations and assess long-term outcomes.

The perspective that suggests the use of neuroscience tools in psychotherapy could be one of the most promising practices since it assumes that any action (psychotherapeutic procedure) inevitably has an effect on some brain system. The present work suggests that there is a possible order of activation (successive series of oxygen expenditure) during the application of the EMDR PRECI and the BH method in those patients suffering from PTSD.

Limitations and future directions

fMRI is a powerful tool in neuroscience research; however, it has several methodological and technical limitations, as well as potential confounding factors that can impact the interpretation of results. For instance, its spatial resolution is insufficient to capture neuronal activity at the level of microscopic circuits or individual synapses, while its temporal resolution is lower than that of techniques such as EEG or MEG, limiting the ability to record rapid neural dynamics[49]. In addition, fMRI relies on the BOLD signal, an indirect measure of neural activity that can be influenced by vascular and metabolic factors[50].

Motion artifacts, even from minor head movements, can distort data, posing particular challenges in studies involving children, psychiatric populations, or neurodegenerative patients[51]. Many fMRI studies also suffer from small sample sizes (n < 20-30), reducing statistical power and increasing the likelihood of false positives[52]. Moreover, uncontrolled physiological variables – such as emotional states, fatigue, attentional fluctuations, and individual differences in cerebral vasculature – can introduce additional noise into the data, further complicating result interpretation[53].

Thus, while fMRI provides valuable insights into brain function, its inherent limitations and confounding factors must be carefully addressed to ensure the validity of findings in future studies. Adopting rigorous methodological practices, including larger sample sizes, appropriate statistical corrections, and the control of physiological variables, is essential for improving the reproducibility and reliability of research in cognitive and clinical neuroscience. Other limitations of this study are the sample size (n = 20), lack of a randomized controlled trial (RCT) study design, and subsequent absence of a control group. Future studies must have access to hospitals, cancer treatment centers, or NGOs focused on providing mental health services to women with cancer to facilitate a larger sample size. Therefore, to enhance the robustness of this study, we suggest future RCT studies with a longitudinal design, a larger sample size with long-term follow-up to evaluate change stability of treatment, and populations with recent, present, or past prolonged adverse experiences and related PTSD diagnosis, with treatment as usual control group or control group Solomon four-group design with other treatment groups receiving another trauma-focused

treatment, such as TF-CBT, psychological transpersonal treatments, such as holotropic breathwork[54], multi-modal motion-assisted memory desensitization, and reconsolidation (3MDR)[55].

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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 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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REVIEW ARTICLE

The relation between the dopaminergic system, drug addiction, and brain structures related to reward behaviors and decision-making

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Abstract

Drug addiction is a serious global health problem that affects the brain, behavior, and decision-making of people, leading to an inability to control drug use. The pharmacological effects of drugs, experienced as a reward, are driven by a variety of genetic, environmental, developmental, and psychosocial factors and are mainly regulated by the dopaminergic system in the reward circuit, with the ventral tegmental area and nucleus accumbens being the most important. Dopamine, the main neurotransmitter, is responsible for regulating physiological functions, including reward-related behaviors. When substance abuse occurs, dopamine is released in greater quantities, forming a connection between the substance and the feeling of reward, thus creating a desire for more pleasurable effects. Dopamine receptors also play a direct role in generating intracellular signals related to pleasure and rewards. Drugs with addictive potential can downregulate the activity and expression of dopamine receptors in the brain. This review focuses on understanding the role of dopamine, the dopaminergic system, and brain structures related to rewards and associated behaviors in drug addiction.

Keywords: *Addiction. Drugs. Reward. Decision-making. Dopamine.*

La relación entre el sistema dopaminérgico, la drogadicción y las estructuras cerebrales relacionadas con las conductas de recompensa y la toma de decisiones

Resumen

La drogadicción es un grave problema de salud global que afecta al cerebro, la conducta y la toma de decisiones de las personas, lo que lleva a una incapacidad para controlar el consumo de sustancias. Los efectos farmacológicos de las drogas, experimentados como una recompensa, están impulsados por una variedad de factores genéticos, ambientales, del desarrollo y psicosociales, y están regulados principalmente por el sistema dopaminérgico en el circuito de recompensa, siendo el área tegmental ventral y el núcleo accumbens las regiones más importantes. La dopamina, el principal neurotransmisor, es responsable de regular funciones fisiológicas, incluidas las conductas relacionadas con la recompensa. Cuando se produce el consumo de sustancias, se libera dopamina en mayores cantidades, formando una conexión entre la sustancia y la sensación de recompensa, lo que genera el deseo de experimentar nuevamente esos efectos placenteros. Los

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receptores de dopamina también desempeñan un papel directo en la generación de señales intracelulares relacionadas con el placer y la recompensa. Las drogas con potencial adictivo pueden disminuir la actividad y la expresión de los receptores de dopamina en el cerebro. Esta revisión se centra en comprender el papel de la dopamina, el sistema dopaminérgico y las estructuras cerebrales relacionadas con la recompensa y las conductas asociadas en la adicción a las drogas.

Palabras clave: *Adicción. Drogas. Recompensa. Toma de decisiones. Dopamina.*

Introduction

The use and consumption of psychoactive substances dates back to prehistoric times. Archeological data suggest that the use of such substances, mostly plants, has been around for at least 10,000 years, and there is historical evidence of their cultural use for the past 5,000 years[1]. A clear example is the chewing of coca leaves, which dates back more than 8,000 years in Peruvian society.

Psychoactive substances are natural or synthetic compounds that, when introduced by any route (e.g., buccal, nasal, oral, and intravenous) and passing into the bloodstream, have a direct effect on the central nervous system (CNS), causing specific changes in its functions. The CNS is a target for many types of drugs of abuse as well as specific prescribed medications. These drugs affect the brain by binding to receptors, resulting in changes in neuronal activity. The effects of drugs vary, depending on the drug, its concentration, and the type of receptor to which it binds. Drug use is driven by the pharmacological effects of drugs in the CNS, which are experienced as rewards and influenced by genetic, developmental, and psychosocial factors that mediate access to the drug, social norms, and support systems[2]. All drugs of abuse modulate gene expression involved in neuroplasticity through epigenetic and, possibly, transcriptional modifications, leading to addictive behaviors as a result of allostatic maladaptation of neuronal circuits[3]. These modifications disrupt intracellular signaling mechanisms and neural circuits, the dysfunction of which has been implicated in the long-lasting changes associated with addiction.

This review presents a synthesis of the existing literature on the relationship between the dopaminergic system, drug addiction, and brain structures related to reward behavior and decision-making. It was conducted as a narrative review, an approach that allows for the exploration of the breadth and complexity of the topic, identification of the key trends, and provision of a descriptive overview. This narrative review is characterized by a thematic organization of the information, synthesizing study findings in a descriptive manner to provide a comprehensive understanding of the topic.

Drug addiction is a chronic, recurrent, progressive, and sometimes fatal condition that manifests in various mental and physical states throughout the addiction cycle, from craving to drug intake, intoxication, withdrawal, and remission (preoccupation/anticipation, binge/intoxication, and negative affect/withdrawal). It worsens over time and involves changes in brain's reward and stress systems[4]. Structures considered to be part of these reward systems are located along the primary dopaminergic pathway of the brain. When exposed to rewarding stimuli, the brain responds by releasing increased amounts of dopamine, the main neurotransmitter associated with rewards and pleasure during addiction states[5]. Other behavioral and cognitive disturbances, such as impulsivity or impairments in learning, conditioning, reward processes, and executive function, are thought to play a role in the development and maintenance of addiction[6]. Addiction can cause long-lasting changes in brain circuits related to reward, stress, and self-control, even after a person has stopped taking a drug[7]. The current data suggest that most drugs of abuse initially reinforce their effects by activating reward circuits in the brain and that drug experimentation is largely voluntary. Chronic drug use impairs brain function by interfering with a person's ability to self-control addictive drug-using behaviors, making the brain more sensitive to stress and negative moods[8]. This is why drug abuse can have rewarding effects and why it is consumed by humans or self-administered by laboratory animals. Brain imaging studies of people with addiction show physical changes in areas of the brain that are critical for judgment, decision-making, learning, memory, and behavior control. Imaging studies such as positron emission tomography (PET) provide new ways to investigate and understand how individual biological factors integrate with one another and relate to behavior, as well as how biological and environmental variables interact during drug addiction[9]. Most PET studies on drug addiction have focused on the dopaminergic system of the brain, as this system is believed to be through which most drugs of abuse exert their reinforcing effects[10]. Dopamine lies at the core of drug reward and pleasure and is involved

in all stages of drug addiction, from induction to maintenance to relapse after a period of withdrawal[11]. All drugs of abuse, directly or indirectly, affect the brain's reward system, causing a release of high amounts of dopamine a neurotransmitter found in various regions of the brain that modulates movement, emotions, cognition, motivation, and feelings of pleasure.

Process addiction, also known as behavioral addiction, is characterized by an overwhelming impulse to engage in a certain behavior, despite the negative consequences that may result. Upon engaging in said behavior, the individual often experiences an elevated mood, followed by a sense of shame or guilt upon its completion. Common process addictions include shopping, gambling, sexual activity, pornography, eating disorders, internet use, exercise, work, and compulsive criminal behavior. These addictions can harm the individual's physical and emotional health, damage interpersonal relationships, and may even lead to legal or financial problems. Process addiction should not be confused with an addiction to drugs or alcohol. Although process addiction and addiction to drugs are distinct disorders, they often co-occur, a phenomenon referred to as dual diagnosis. All addictions share similar characteristics, such as the inability of the addicted person to stop or limit compulsive behavior, even when it has a negative impact on many aspects of their life[12].

The reward system and mesolimbic pathway

Rewards are a natural process in which the brain associates various stimuli – such as substances of abuse, situations, events, or activities – with positive or pleasant outcomes, causing adjustments in an individual's behavior, also known as appetitive or preparatory and consummatory behavior, ultimately leading them to seek out that particular positive stimulus again and again[13]. Dopamine has been extensively implicated in the processing of all types of rewards at a cerebral level, including the valence of food, drink, sex, social interaction, and substance abuse[14].

The mesolimbic system is a key component of the reward system, playing an important role in motivating behavior and providing positive reinforcement. This system is mainly composed of the ventral tegmental area (VTA) and nucleus accumbens (NAc), along with their afferent and efferent connections. The mesolimbic system is a CNS circuit in which dopamine inputs from the VTA innervate brain regions involved in executive, affective, and motivational functions, including the prefrontal cortex (PFC), amygdala, and NAc[15]. This circuitry is crucial for establishing the relationship between rewards and stimuli, thereby guiding behavior. Changes in dopamine mesolimbic neurotransmission modify behavioral responses to various environmental stimuli associated with reward behaviors. Psychostimulants, drugs of abuse, and natural rewards such as food and sex can cause substantial synaptic changes in the dopaminergic mesolimbic system[16].

The reward system is primarily composed of the VTA and consists of dopaminergic projections to the NAc and other brain targets, including PFC, amygdala, and hippocampus[17]. The VTA, located in the midbrain, is a small region that is an important source of dopamine, particularly in the limbic regions. This region is composed of dopaminergic, gamma-aminobutyric acid neurons, and glutamate neurons, with the dopaminergic neurons being the most abundant (up to 60%)[8]. The VTA is a heterogeneous structure in the midbrain and plays an important role in reinforcement, reward, learning, motivation, cognition, aversion, and addictive behavior[18]. In the VTA, drugs of abuse directly influence the release of dopamine in this area, leading to addiction and associated behaviors compared to those of non-addicted individuals. Dopaminergic neurons in the VTA (VTA-DA neurons) project to the NAc, a central hub of the reward circuit and a major driver of goal-directed actions that are sensitive to the current salience (estimated value) of an associated goal[19]. Furthermore, these neurons project to the amygdala and hippocampus, mediating memory and emotional associations, as well as to PFC regions, which mediate salience attribution and self-regulation. Collectively, these regions contribute to reinforcement and conditioning that follow chronic drug consumption[20]. The activity of VTA-DA neurons is linked to all reward-predicting processes, including the psychostimulatory effect of rewards. Addictive drugs, such as cocaine, amphetamine, morphine, nicotine, and ethanol, induce characteristic changes in synaptic plasticity in VTA-DA neurons within 24 h of acute exposure. VTA is an anatomical site critical for behavioral sensitization following repetitive drug administration[19]. Therefore, VTA-DA neurons have been an interesting topic and are considered the main therapeutic target for treating reward and pleasure-related disorders, such as drug addiction and mood disorders, owing to their key role in directing reward-related responses[21].

The NAc is located in the rostral region of the basal forebrain, below the ventral striatum. It consists of two parts: the NAc shell and the NAc core. This structure

is responsible for regulating an individual's reward circuit, with the NAc shell receiving information from the limbic system and the NAc core mainly receiving information from the motor system[22]. The NAc acts as a functional interface between these two systems, converting motivation into action. It is also responsible for modulating the response to reward-related signals, which are encoded through projections to and from the amygdala, thalamic nuclei, and PFC[23]. The VTA-NAc circuit is the primary reward pathway in the brain, in which drugs of abuse have important effects on the release and increase of dopamine concentrations. Rewarding stimuli primarily stimulate VTA-DA neurons to release dopamine into the NAc, thereby driving the activity of medium spiny neurons (MSNs) and subsequent reward-seeking behaviors[22,23]. In the NAc, MSNs make up 90-95% of all neurons[23]. These, along with cholinergic interneurons, have been shown to be the two main groups of neurons in this structure that are important for studying addiction comorbidity[24]. The NAc plays a crucial role in various forms of adaptive and pathologically motivated behavior. Several studies have demonstrated a strong association between this structure and a range of neurological and psychiatric disorders, including depression, obsessive-compulsive disorder, bipolar disorder, anxiety disorders, Parkinson's disease, Alzheimer's disease, Huntington's disease, obesity, drug abuse, and addiction[24,25].

The habenula is another important brain structure in reward circuitry; it receives information from the limbic system, sends signals to the VTA, regulates dopamine levels in the striatal region, and plays a role in modulating reward and reward-associated learning[26]. However, the ventral striatum, including the NAc, is the major structure involved in reward processing.

The dorsal striatum is critically involved in action selection and initiation components of decision-making, and it also appears to mediate feedback properties such as valence and magnitude in habitual behavior control and addiction[27,28]. Therefore, both the ventral and dorsal regions of the striatum play collaborative roles in mediating rewards[27].

Recent studies have shown that reward is subjective and highly influenced by the chemistry of the individual, homeostatic state, genetics, and epigenetics[29]. The main function of the reward system is to determine the valence of a stimulus, signal whether it should be avoided or approached and assign priority to one stimulus over another. Substances of abuse, whether illicit (e.g., cocaine and heroin) or licit (e.g., alcohol, nicotine), hijack the mesolimbic system by offering a reward with no obvious biological function. However, the pleasure and reward attached to the initial substance use are later lost through abuse, leading to a vicious cycle of addiction. All drugs of abuse acutely lower reward thresholds at the brain level, thereby increasing or facilitating rewards[30].

Addiction is a complex process that involves multiple networks in the brain, with one of the most important being the VTA. It is now widely accepted that repeated exposure to addictive substances leads to adaptive changes at the molecular and cellular levels in the mesolimbic dopamine pathway, which is responsible for regulating motivational behavior and organizing emotional and contextual behaviors[31]. These modifications in the mesolimbic pathway led to drug dependence, a chronic relapsing disorder characterized by compulsive drug-seeking and drug-use behaviors that persist despite the severe negative consequences of the drugs[32] (Fig. 1). Animal models of addiction and depression have chosen the NAc as a primary research target because of experimental evidence showing that addictive drugs increase dopamine release or alter synaptic plasticity in this structure, while non-addictive drugs generally do not affect basal dopamine release or plasticity[33,34]. Neurons in this structure are activated by stimuli that produce rewarding experiences, such as drugs of abuse, exercise, food, sex, and music. Alterations in dopaminergic signaling are common mechanisms in several motivational and reward disorders, including addiction. Drugs of abuse, while sharing the common effect of increasing dopamine levels in the NAc, achieve this through diverse mechanisms. Some drugs, such as cocaine, directly block dopamine reuptake, while others like opioids indirectly increase dopamine release by disinhibiting dopaminergic neurons in the VTA[35-37]. These increases in dopamine contribute to the reinforcing that promotes drug-taking behavior. In humans, functional imaging studies have shown that environmental cues associated with addictive drugs can release dopamine into the NAc region[38]. Thus, alterations in dopaminergic signaling play a critical role in the development and maintenance of addiction.

The dopaminergic system

The dopaminergic system undergoes late maturation in the brain, suggesting its essential role in stabilizing and integrating functions in neural circuits throughout the lifespan, such as motivation, motor control, and reward processing. Shortly after its identification, the roles of dopamine in reward theory and addiction were

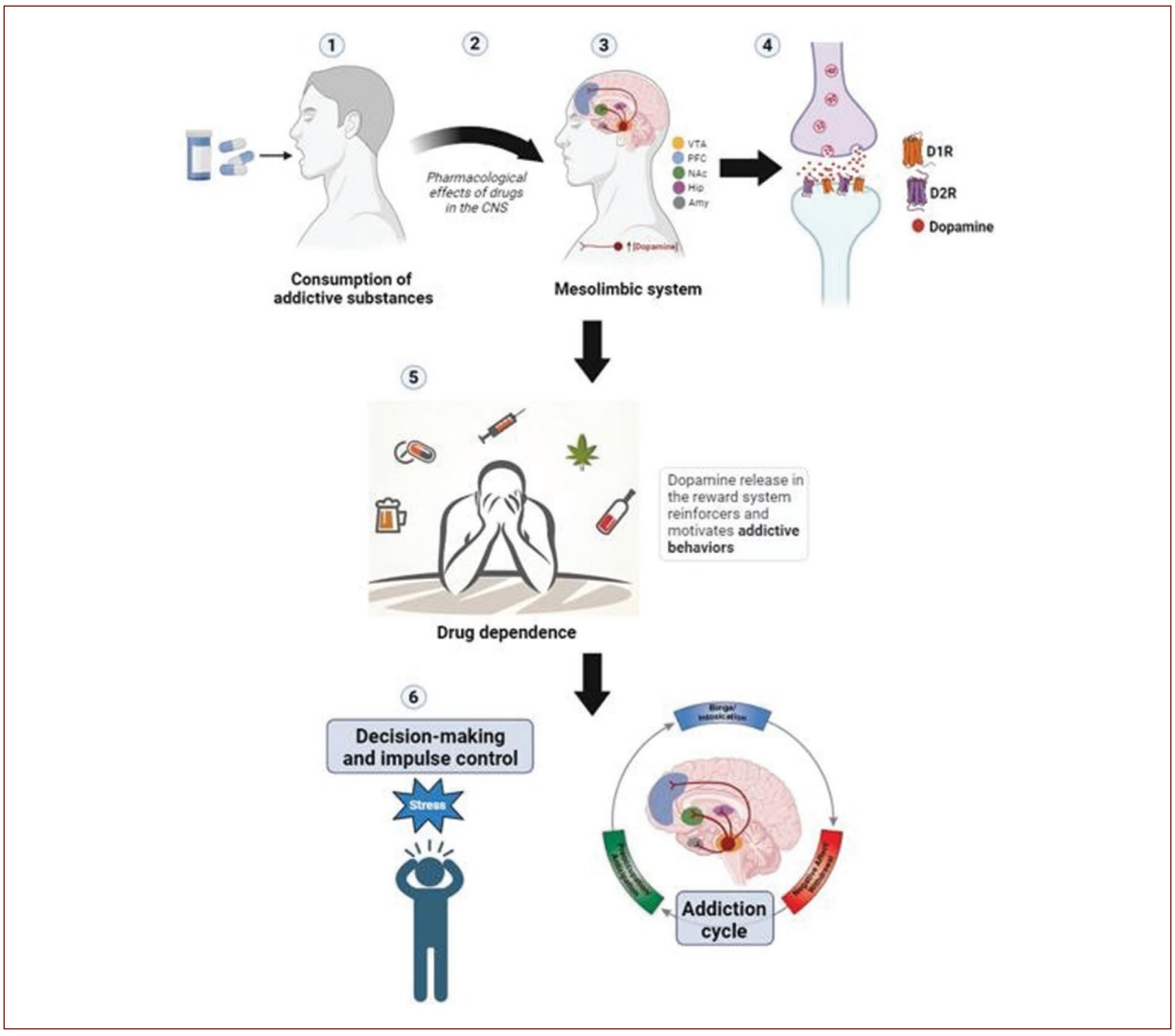

Figure 1. Behavioral addictions to drugs. (1) Psychoactive substances are natural or synthetic compounds that, when introduced into the bloodstream by any route, directly affect the CNS, causing specific changes in its functions. (2) Drug use is driven by the pharmacological effects of drugs in the CNS, which are experienced as rewards or relief from pain. The effects of drugs vary, depending on the drug, its concentration, and the type of receptor to which it binds. (3) The mesolimbic system is a key component of the reward system, mainly composed of the ventral tegmental area (VTA) and nucleus accumbens (NAc), along with their afferent and efferent connections. When exposed to rewarding stimuli, the brain releases increased amounts of dopamine, the main neurotransmitter associated with rewards and pleasure during addiction states. (4) The release of dopamine causes the stimulation of specific receptors, the dopamine receptors (DARs). D1R and D2R are the most abundantly expressed DAR in the brain and G-protein-coupled integral membrane receptors. D1R and D2R contribute to distinct rewarding and addictive behaviors. (5) Modifications to the mesolimbic pathway led to drug dependence, a chronic relapsing disorder characterized by compulsive drug-seeking and drug-use behaviors that persist despite the severe negative consequences of the drugs' effects. (6) Alterations in prefrontal cortex (PFC) function can result in the loss of inhibitory control, leading to compulsiveness and drug-seeking despite severe negative consequences in substance use disorders. Craving is a major challenge in overcoming addiction. This figure was created using BioRender.com.

established, based on anatomical and pharmacological evidence[2,14]. The dopaminergic system is activated by three types of external stimuli: rewards, punishments, and novel stimuli. When activated by rewards or punishments, parts of the dopamine system are activated in bursts that can last up to several seconds, whereas other portions are inhibited in response to negative reinforcement[39].

Dopaminergic neurons fire either in stable, tonic mode (1-8 Hz), which is important for momentary sensitivity to external stimuli and setting the background dopaminergic tone for behavior, or in transient, high-frequency phasic mode (> 15 Hz). Under normal conditions, DA neurons contain a pool of dopamine that is insensitive to stimulation, and more than half of the synaptic dopamine release sites are functionally silent when stimulated[40].

The release of dopamine causes the stimulation of specific receptors, the dopamine receptors (DAR), which are G-protein-coupled integral membrane receptors. The dopaminergic system sends signals through five DAR subtypes, divided into two main subclasses: D1-like (D1R and D5R) and D2-like (D2R, D3R, and D4R) receptors[41]. The role of DAR in different neuronal populations of the striatum illustrates their complexity. Neurons expressing D1R and D2R contribute to distinct rewarding and addictive behaviors. D1R responds primarily to dopamine burst signals, while optogenetic studies have shown that the effect of dopamine burst firing on D2R is not occluded by the presence of a background dopamine tone, suggesting that D2R can respond to a broader range of stimuli. Tonic activation of dopamine leads to the release of dopamine from extra-synaptic release sites, where it binds to high-affinity dopamine D2R and is linked to motivational arousal in response to external stimuli[41,42]. Phasic activation of dopamine causes high extracellular concentrations of dopamine, which activates low-affinity D1R and are linked to conditioning to positive and negative reinforces. This phasic pattern of dopamine activity has been observed in association with drug and reward-seeking behaviors[42].

All drugs of abuse with addictive potential increase dopamine levels, either directly or indirectly affecting dopaminergic neurons in the VTA, resulting in the release of dopamine in the NAc[4]. People with drug addiction show a significant reduction in the function of D2R in the striatum, including in the NAc[41]. This reduction of striatal D2R, which modulates the indirect striatocortical pathway, has been implicated in impulsive and compulsive behaviors[40-42]. The activation of D1R by different stimuli, such as food and drugs, fulfills a reinforcing action, which consolidates the memory traces of the reception of the reward and the events that preceded it. In animal models, the activation of the D1R, through exposure to a reinforcer or predictor (for example, food and drugs of abuse), causes the animal to remember more (in subsequent trials) about the associated internal and external stimulus conditions, leading to the progressive identification of earlier predictive stimuli.

Decision-making and drug use: the role of prefrontal cortex

Decision-making is a complex process that requires the coordination of multiple brain regions, with the PFC playing a major role. This region of the brain is responsible for controlling emotions, forming judgments, and making decisions based on available information[43]. Adolescents are particularly vulnerable to the effects of drug abuse because of the ongoing neurodevelopmental process, particularly in regions such as the PFC, which is crucial for decision-making and impulse control. Imaging studies have shown that the adolescent brain undergoes significant changes in dopamine pathways and PFC development that may increase vulnerability to addiction[6,36,37,43-50]. Alterations in PFC function can result in the loss of inhibitory control, leading to compulsiveness and drug-seeking despite severe negative consequences in substance use disorders. Reward-sensitive processes occur in three key subdivisions of the PFC: the anterior cingulate cortex (ACC), ventromedial prefrontal cortex (vmPFC), and orbitofrontal cortex (OFC)[44,45]. Craving is a major challenge in overcoming addiction and is associated with activation of the ACC, vmPFC, OFC, striatal areas, and insula. Neuroimaging studies in individuals with addiction problems have shown overactivation of the ACC and OFC during drug-related signaling activities, including craving, and hypoarousal during cognitive tasks with neutral valence[45,46].

The OFC in primates and humans is a key for emotion, representing the values of reward and non-reward. It has been established as a critical brain region in adaptive decision-making when the expected reward fails to occur[44]. This structure has been implicated in the pathology of drug and behavioral addiction. Disruptions in OFC function may explain decision-making impairments in some substance-dependent individuals. The vmPFC is involved in various social, cognitive, and affective functions commonly disrupted during mental illness. It is connected to other brain regions implicated in drug abuse behaviors related to impulsive consumption[46].

Amygdala: role in emotional processing, conditioning, and craving

The amygdala, a structure located in the temporal lobe of the mammalian brain, is associated with the

experience of fear and anxiety. It is composed of different nuclei and has traditionally been related to emotional responses, which has been supported by various studies using fear conditioning paradigms. These studies have demonstrated that damage to the amygdala results in deficits in learning and memory of emotionally relevant stimuli[47]. The amygdala is a highly conserved structure of the temporal lobe limbic system, composed of basolateral (BLA), central (CeA), and medial (MeA) subcomponents[47,48]. It interacts with both the cortex and striatum to influence motivated behavior. The BLA, the primary input region of the amygdaloid complex, receives inputs from across the brain, including the hippocampus, NAc, PFC, thalamus, and other amygdala nuclei. Furthermore, the BLA has been found to mediate conditioned drug-seeking behavior for cocaine, alcohol, and heroin[47].

In addition, research has shown that both the BLA and CeA nuclei play different roles in representing the value of primary and conditioned rewards[49].

The amygdala projects to the mesolimbic system in a similar manner to that by which the NAc is activated when cravings occur in cocaine addicts[48,49]. It is suggested that the NAc translates drug-related motivation into drug-seeking actions, and the amygdala is thought to mediate the emotional impact associated with the craving[49]. The BLA encodes Pavlovian incentive associations, and through its projections to the NAc, it underlies the performance of prolonged drug-seeking sequences reinforced by drug-associated conditioned stimuli, which act as conditioned and delayed drug-seeking behaviors. Recent studies have found that low functional connectivity between the amygdala and OFC circuits is associated with greater weekly alcohol intake in binge-drinking young adults and is predictive of future alcohol use, suggesting that this circuit mediates drug use susceptibility[50].

Material and methods

A literature review was conducted using a methodological search strategy in the PubMed database, part of the National Library of Medicine (NIH), to identify relevant studies published between 2000 and 2023. The search strategy used a combination of keywords including “addiction,” “behavior and rewards,” “brain reward system,” “dopamine,” “limbic system,” “dopaminergic system,” “drug abuse,” “decision-making,” “prefrontal cortex,” and “drug addiction”. Boolean operators (AND, OR, NOT) were used to refine the results. Search terms were adapted to the specific syntax of the PubMed database to ensure comprehensive retrieval.

The inclusion criteria were human studies, animal studies, reviews, and meta-analyses without language restrictions. Studies in any language were included to minimize the risk of bias in the review; gray literature (such as dissertations and unpublished reports), and non-peer-reviewed sources were excluded. The selection process included a review of titles, abstracts, and where necessary, full texts of articles to determine their relevance to the review.

Results

The literature review demonstrates that drug addiction remains a prevalent global health issue, with a notable rise in the number of individuals using illicit drugs in the last two decades. Chronic drug use impacts behavior and decision-making, leading to a loss of control over drug consumption. The pharmacological effects of drugs cause structural and neurobiological alterations in crucial brain circuits, particularly those related to reward and pleasure. The dopaminergic system is crucial in modulating these effects.

Dopamine, the primary neurotransmitter involved in reward, regulates various physiological functions, including reward-related behaviors. Drugs of abuse increase the release of dopamine in the brain, strengthening the association between the substance and pleasure and promoting the desire to use the drug more. Dopamine receptors are also directly involved in generating intracellular signals related to pleasure and reward. However, chronic drug use can lead to a downregulation of dopamine receptor activity and expression in the brain.

Several brain structures are involved in addiction, including the VTA and NAc, which are key components of the reward circuitry. The VTA is a major source of dopamine and plays a role in reward, learning, motivation, and addictive behavior. The NAc is a central structure in the reward circuitry that receives information from other brain areas and translates motivation into action. Other brain structures involved in addiction are the PFC and the amygdala. The PFC is critical for decision-making, judgment, and emotional control, while the amygdala processes emotions and is involved in the conditioning associated with drug use.

Repeated exposure to drugs of abuse induces adaptive changes at the molecular and cellular levels in the mesolimbic dopaminergic system, a circuit crucial for motivation, emotion, and reward. These changes, which occur in response to addictive substances, alter the

Table 1. Key studies on brain structures and neurobiology of addiction

Study/Reference	Study design	Study focus	Key findings
Volkow et al.[10]	Human neuroimaging study (PET)	Function of the dopaminergic system in cocaine addiction	Cocaine addicts show a decrease in D2 receptor availability in the striatum, which increases compulsivity in drug use.
Di Chiara and Bassareo[11]	Theoretical review	Role of dopamine in reward and addiction	Dopamine is involved in all stages of addiction, from induction to maintenance and relapse.
Nestler and Carlezon Jr.[15]	Theoretical review	Mesolimbic dopaminergic system in depression and addiction	Modifications in the mesolimbic dopaminergic pathway play a crucial role in drug dependence.
Lüscher and Malenka[19]	Theoretical review	Drug-evoked synaptic plasticity in addiction	Exposure to drugs of abuse induces adaptive changes in the synapses of dopaminergic neurons.
Koob and Volkow[4]	Review	Neurocircuitry análisis of addiction	Addiction involves changes in brain's reward and stress system.
Schultz[5]	Physiological review	Neuronal reward and decision signals	Dopamine has been extensively implicated in the processing of all types of rewards at a cerebral level.
Volkow et al.[2]	Physiological review	Neuroscience of drug reward and addiction	The review discusses the neuroscience of drug reward and addiction.

normal function of this system and contribute to the development of addiction, a chronic, relapsing disorder characterized by compulsive drug seeking and use.

At the molecular level, drugs of abuse modulate gene expression and intracellular signaling in dopaminergic system neurons. These modifications can affect the synthesis, release, reuptake, and metabolism of dopamine, as well as the expression and function of dopamine receptors and other proteins involved in synaptic transmission. At the cellular level, drugs of abuse can induce changes in synaptic plasticity, that is, in the strength and efficacy of connections between neurons. These changes can strengthen connections between neurons involved in reward and motivation processing, leading to increased sensitivity to drug-related stimuli and a higher probability of relapse. Furthermore, drugs can alter the morphology and function of neurons, as well as communication between different brain regions.

To more clearly illustrate the relationship between dopaminergic pathways, brain structures, and addiction, the following table summarizes the key findings from relevant studies in this area (Table 1)[2,4,5,10,11,15,19].

Discussion

Drug addiction alters brain structure and function, leading to maladaptive and potentially harmful behaviors. These behaviors, caused by excessive drug use, lead to changes in the brain circuits related to pleasure and reward. The reward circuit plays a fundamental role in the development and maintenance of addiction, as it is responsible for regulating pleasant and rewarding sensations, facilitating learning, and memorizing contextual stimuli which can serve as triggers for the repetition of addictive behaviors. The dopaminergic system modulates the reward system associated with addictive behavior; this system is a crucial element in addictive disorders and behaviors, and its implications and importance have been confirmed by numerous animal and human studies. Dopamine, a key brain-reward neurotransmitter, is activated by addictive drugs, and its dopamine receptors play a critical role in the development of addiction and are associated with sensitization induced by chronic drug use.

The phenomenon of addiction must be explained in a complex system of interrelated subsystems, at least including the biomedical, sociocultural, and psychological. In particular, neuroscience stands out in its relevance to the circuits involved in addiction (Fig. 2). Therefore, it is essential to continue investigating the consequences and effects of drugs on reward circuits at the behavioral level, which cause addiction. In the

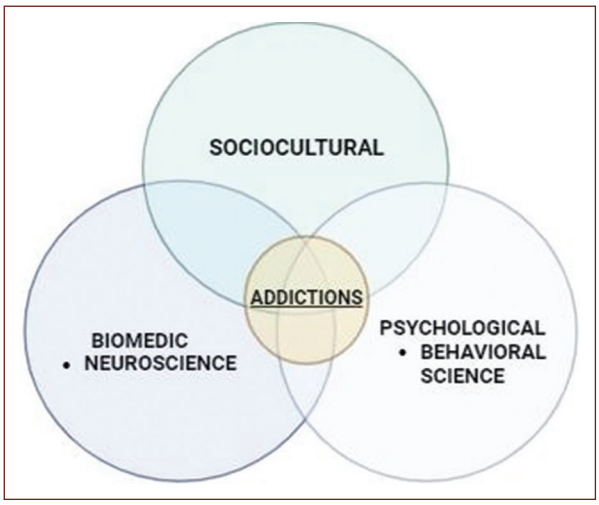

Figure 2. Complex diagram of interrelated subsystems for understanding the phenomenon of addictions.

future, it will be possible to study and analyze potential treatments to avoid these aggravating circumstances.

While this review highlights the common neurobiological pathways involved in drug addiction, there are still gaps in our understanding, particularly regarding the differences between substance addiction and behavioral addiction. Although both share the involvement of the reward system, the specific neurobiological mechanism may differ. For example, the degree of involvement of certain neurotransmitters or the specific patterns of brain activation may differ between these types of addiction. More research is needed to clarify these differences and their implications for treatment.

Emerging therapies offer promising avenues for the treatment of addiction. For instance, deep brain stimulation has shown potential in modulating brain circuits involved in addiction[51], particularly in severe cases refractory to conventional treatments. In addition, research on the modulation of dopamine receptors, such as through targeted pharmacological interventions, may lead to the development of more effective treatments for addiction. Future research should also explore other promising areas, such as gene therapy and treatment of addiction.

Conclusion

The review highlights the significant impact of addictive drugs on the dopaminergic system, the reward circuitry, and decision-making processes, ultimately leading to altered behavior. These findings have important clinical and transnational implications. A deeper understanding of the neurobiological mechanisms underlying addiction can inform the development of more targeted interventions, such as pharmacological therapies aimed at modulating dopaminergic activity or behavioral therapies designed to counteract maladaptive reward learning. In addition, this knowledge can contribute to public health strategies aimed at preventing drug use, particularly among vulnerable populations such as adolescents, who are particularly susceptible to the long-lasting effects of drugs on the developing brain. By translating research findings into clinical practice and public health initiatives, we can strive to mitigate the devastating consequences of addiction for individuals and society.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

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