

TESIS DOCTORAL



UCAM

UNIVERSIDAD CATÓLICA
DE MURCIA

ESCUELA INTERNACIONAL DE DOCTORADO

Programa de Doctorado Ciencias de la Salud

Análisis multidimensional del Trastorno del Espectro Autista y
la epilepsia en la población pediátrica: implicaciones clínicas y
terapéuticas

Autor:

Alejandro Cano Villagrasa

Directores:

Dr. D. Francisco José Moya y Faz

Dr. D. Miguel López Zamora

Murcia, septiembre de 2024

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La presente Tesis Doctoral titulada “*Análisis multidimensional del Trastorno del Espectro Autista y la epilepsia en la población pediátrica: implicaciones clínicas y terapéuticas*” adopta el formato de COMPENDIO DE PUBLICACIONES. En ella se recoge una síntesis de conceptos derivados de estudios de revisión sistemática de la bibliografía, estudios experimentales y estudios de caso. El compendio consta de seis artículos ya publicados. A continuación, se exponen los seis artículos que forman parte de la Tesis Doctoral:

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- Alejandro Cano-Villagrasa; Miguel López-Zamora. PREMIO a la Mejor Comunicación Oral que lleva por título: *La relación de la epilepsia en las competencias cognitivo-lingüísticas de los niños con un Trastorno del Espectro Autista*. VIII Jornadas de Investigación y Doctorado “Ética en la Investigación Científica”, 2022, Murcia España.
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- Alejandro Cano-Villagrasa; Miguel López-Zamora. *La influencia de la epilepsia en el lenguaje y las funciones ejecutivas del paciente infantil con TEA y epilepsia*. XXV Congreso Internacional de Actualización en Trastornos del Neurodesarrollo, 2023, Valencia, España.
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- Alejandro Cano-Villagrasa; Clara Puig-Herreros; Lucía Domingo-Moscardó. *Diferencias de rendimiento en lectura y escritura entre los menores con TEA y TDAH*. 8th International Congress of Clinical and Health Psychology in Children and Adolescents, 2022, Elche, España.
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- Alejandro Cano-Villagrasa; Miguel López-Zamora; Nadia Porcar-Gozalbo. *Relación entre el procesamiento sensorial y el funcionamiento ejecutivo de menores con TEA y epilepsia*. 9th International Congress of Clinical and Health Psychology in Children and Adolescents, 2023, Valencia, España.
- Alejandro Cano-Villagrasa; Miguel López-Zamora; Francisco José Moya-Faz; Nadia Porcar-Gonzalbo. *Alteraciones en el proceso de lectura de la población infantil con TEA y epilepsia*. XXVI Congreso Internacional de Actualización en Trastornos del Neurodesarrollo, 2024, Valencia, España.

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- Cano-Villagrasa, A. (2024). Trastorno del Espectro Autista y epilepsia, *Casos prácticos en logopedia. Trastornos específicos del desarrollo del lenguaje (parte II)*. Editorial Síntesis.
- Cano-Villagrasa, A., y López-Zamora, M. (2024). Abordaje logopédico en los trastornos del neurodesarrollo. Editorial Tirant Humanidades (Valencia), España. 364 páginas. ISBN: 978-84-1183-697-5. Rol de Autor y Editor. Posición 1 del ranking General del SPI 2022.

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- Cano-Villagrasa, A. y Porcar-Gozalbo, N. (4 de diciembre de 2023). Sí hay relación entre el uso de pantallas y el autismo, pero no es la que pensábamos. *The Conversation*. <https://theconversation.com/si-hay-relacion-entre-el-uso-de-pantallas-y-el-autismo-pero-no-es-la-que-pensabamos-217382#>

AUTORIZACIÓN DEL DIRECTOR DE LA TESIS PARA SU PRESENTACIÓN

El Dr. D. Francisco José Moya y Faz y el Dr. D. Miguel López Zamora como Directores⁽¹⁾ de la Tesis Doctoral titulada “*Análisis multidimensional del Trastorno del Espectro Autista y la epilepsia en la población pediátrica: implicaciones clínicas y terapéuticas*” realizada por D. Alejandro Cano Villagrasa en el Programa de Doctorado de Ciencias de la Salud, **autorizan su presentación a trámite** dado que reúne las condiciones necesarias para su defensa.

Lo que firmo, para dar cumplimiento al Real Decreto 99/2011 de 28 de enero, en Murcia a 18 de septiembre de 2024.

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RESUMEN

El Trastorno del Espectro Autista (TEA) es uno de los trastornos del neurodesarrollo más prevalentes en la actualidad. Esta condición cursa con alteraciones significativas en la comunicación y en la interacción social. Además de ello, suele aparecer de forma comórbida con una serie de trastornos y alteraciones, siendo la epilepsia una de las más comunes, lo que causa que se deterioren no solo aspectos pragmáticos del lenguaje y la interacción, sino que haya otras dimensiones del desarrollo que se vean limitadas. La persona con TEA y epilepsia muestra alteraciones significativas en los procesos relacionados con el lenguaje expresivo y receptivo, la cognición, el funcionamiento ejecutivo, la conducta, el control emocional o los procesos relacionados con la lectura. Por todo esto resulta esencial desarrollar protocolos de evaluación e intervención temprana para poder atender las necesidades de la persona con TEA y epilepsia y mejorar el pronóstico de estas. De este modo, el objetivo general de la presente tesis doctoral fue analizar y explorar las características clínicas y los protocolos de evaluación e intervención existentes en las personas diagnosticadas con TEA y epilepsia. Para cumplir con este propósito, se diseñó una investigación que abarca aspectos relacionados con el estudio de las funciones lingüísticas, cognitivas, ejecutivas, conductuales, trastornos del sueño, protocolos de evaluación y programas de intervención en la población infantil con TEA y epilepsia. Los participantes que se seleccionaron, para la realización de los estudios empíricos que comprenden este compendio, fueron un total de 170 personas con edades comprendidas entre los 7 y los 9 años, divididos en tres grupos en función de su diagnóstico: un grupo con TEA, un grupo con epilepsia y un grupo con TEA y epilepsia. Se registraron con instrumentos estandarizados las medidas relacionadas con el lenguaje, la cognición, la función ejecutiva, los problemas emocionales y conductuales de todos los participantes en un único momento de evaluación. Se realizaron diferentes análisis multivariados de la covarianza con el fin de determinar las diferencias en el rendimiento de estas medidas entre los tres grupos de participantes. Tras el diseño y evaluación de la muestra seleccionada los resultados permitieron articular varios análisis que sirvieron para que en la fase de difusión se creasen 8 artículos. Los resultados obtenidos en la presente tesis doctoral destacan que los participantes con TEA y

epilepsia muestran mayores alteraciones en las medidas registradas en los estudios que componen el compendio de artículos de investigación en comparación con los otros dos grupos: grupo con TEA y grupo con epilepsia. Asimismo, se determinó que los protocolos de evaluación temprano deben comprender instrumentos de medida estandarizados que evalúen el lenguaje, la cognición, la sensorialidad y la lectura, tales como el CELF-5, el ENFEN, la WISC-V, el PROLEC-R y el SP-2, siendo pruebas de evaluación baremadas y con una alta fiabilidad y validez. Por último, es primordial que se lleve a cabo una intervención farmacológica y en los procesos de comunicación y cognición de las personas con TEA y epilepsia. Por ende, se debe evaluar las alteraciones conductuales y los episodios epilépticos y aplicar un tratamiento farmacológico efectivo con medicación como la Carbamazepina, siendo este un fármaco que se ha demostrado su efectividad en esta población. Además de ello, es necesario instaurar un sistema de comunicación para potenciar los procesos lingüísticos y la interacción con el entorno en el cual se desarrolla la persona con TEA y epilepsia, mejorando su autonomía y su calidad de vida. En conclusión, esta tesis doctoral destaca la necesidad urgente de desarrollar y aplicar protocolos de evaluación e intervención temprana para niños con TEA y epilepsia, abordando sus complejas necesidades desde una perspectiva bio-psico-social. La investigación evidencia la importancia de integrar enfoques multidisciplinarios que incluyan tanto la evaluación estandarizada como intervenciones farmacológicas y comunicativas efectivas. Esto no solo mejorará las capacidades lingüísticas, cognitivas y emocionales de los afectados, sino que también contribuirá significativamente a su autonomía y calidad de vida a largo plazo.

PALABRAS CLAVE

Trastorno del Espectro Autista; epilepsia; infancia; lenguaje; cognición; emoción; funcionamiento ejecutivo; sensorialidad; evaluación; intervención; farmacología

ABSTRACT

The Autism Spectrum Disorder (ASD) is one of the most prevalent neurodevelopmental disorders today. This condition is characterized by significant impairments in communication and social interaction. Additionally, it often appears comorbidly with various other disorders and conditions, with epilepsy being one of the most common. This comorbidity leads to deterioration not only in pragmatic aspects of language and interaction but also in other developmental dimensions. Individuals with ASD and epilepsy exhibit significant alterations in processes related to expressive and receptive language, cognition, executive functioning, behavior, emotional control, and reading processes. Therefore, it is essential to develop early evaluation and intervention protocols to address the needs of individuals with ASD and epilepsy and improve their prognosis. The overall aim of this doctoral thesis was to analyze and explore the clinical characteristics and existing evaluation and intervention protocols for individuals diagnosed with ASD and epilepsy. To achieve this aim, research was designed to encompass aspects related to the study of linguistic, cognitive, executive, behavioral functions, sleep disorders, evaluation protocols, and intervention programs in the pediatric population with ASD and epilepsy. The participants selected for the empirical studies comprising this compendium totaled 170 individuals aged between 7 and 9 years, divided into three groups based on their diagnosis: one group with ASD, one group with epilepsy, and one group with both ASD and epilepsy. Standardized instruments were used to record measures related to language, cognition, executive function, emotional and behavioral problems of all participants in a single evaluation session. Various multivariate analyses of covariance were conducted to determine the differences in the performance of these measures among the three participant groups.

The results of the selected sample design and evaluation facilitated several analyses, resulting in the creation of eight articles during the dissemination phase. The findings of this doctoral thesis highlight that participants with both ASD and epilepsy show greater impairments in the recorded measures compared to the other two groups: the ASD group and the epilepsy group. Furthermore, it was determined that early evaluation protocols should include standardized measurement instruments that assess language, cognition, sensory processing, and reading, such as the CELF-5, ENFEN, WISC-V, PROLEC-R, and SP-2, which are norm-referenced tests with high reliability and validity. Finally, it is crucial to implement pharmacological intervention and interventions targeting communication and cognition processes for individuals with ASD and epilepsy. Behavioral alterations and epileptic episodes should be assessed, and an effective pharmacological treatment, such as Carbamazepine, should be administered, as it has proven effective in this population. Additionally, it is necessary to establish a communication system to enhance linguistic processes and interaction with the environment in which the individual with ASD and epilepsy develops, thereby improving their autonomy and quality of life. In conclusion, this doctoral thesis underscores the urgent need to develop and implement early evaluation and intervention protocols for children with ASD and epilepsy, addressing their complex needs from a biopsychosocial perspective. The research highlights the importance of integrating multidisciplinary approaches that include both standardized assessment and effective pharmacological and communicative interventions. This will not only improve the linguistic, cognitive, and emotional capabilities of those affected but also significantly contribute to their long-term autonomy and quality of life.

KEYWORDS

Autism Spectrum Disorder; epilepsy; childhood; language; cognition; emotion; executive functioning; sensory processing; assessment; intervention; pharmacology

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"Dos de las cosas que puedes controlar son la actitud y el esfuerzo. Por eso, trabaja duro en silencio y deja que el éxito sea el que haga ruido".

ÍNDICE GENERAL

RESUMEN	13
I - INTRODUCCIÓN	35
1.1. El Trastorno del espectro autista.....	35
1.1.1. Características lingüísticas	40
1.1.2. Características cognitivas	44
1.1.3. Comorbilidades.....	45
1.2. La epilepsia.....	46
1.2.1. Características lingüísticas	49
1.2.2. Características cognitivas	50
1.2.3. Comorbilidades.....	52
1.3. El Trastorno del Espectro Autista y la epilepsia	53
1.3.1. Perfil cognitivo-lingüístico	55
1.4. La evaluación de la población infantil con TEA y epilepsia	56
1.4.1. Evaluación del Trastorno del Espectro Autista	56
1.4.2. Evaluación de la epilepsia.....	61
1.5. La intervención de la población infantil con TEA y epilepsia	66
1.5.1. Intervención farmacológica.....	66
1.5.2. Intervención cognitivo-conductual	68
1.5.3. Intervención del lenguaje	72
1.6. Resumen de la introducción	75
II - JUSTIFICACIÓN	83
III - OBJETIVOS.....	87
IV - MATERIAL Y MÉTODO	91

4.1.	Participantes	91
4.2.	Instrumentos y materiales	93
4.2.1.	Evaluación Clínica de Fundamentos del Lenguaje 5	93
4.2.2.	CEG. Test de Comprensión de Estructuras Gramaticales	93
4.2.3.	BRIEF-2 de Evaluación Conductual de la Función Ejecutiva	94
4.2.4.	ENFEN, Evaluación Neuropsicológica de las Funciones Ejecutivas en Niños	94
4.2.5.	Wechsler Intelligence Scale for Children - Fourth Edition	95
4.2.6.	Cuestionario SENA, sistema de evaluación de niños y adolescentes	95
4.2.7.	BASC-3, sistema de evaluación de la conducta de niños y adolescentes - 3	96
4.3.	Procedimiento	97
4.3.1.	Procedimiento de recolección de datos.....	97
4.3.2.	Procedimiento para la aprobación del comité de ética	98
4.4.	Diseño y análisis de datos	98
V -	COMPENDIO DE ARTÍCULOS.....	101
5.1.	Artículo 1.....	101
5.2.	Artículo 2.....	115
5.3.	Artículo 3.....	131
5.4.	Artículo 4.....	149
5.5.	Artículo 5.....	160
5.6.	Artículo 6.....	172
5.7.	Artículo 7.....	183
5.8.	Artículo 8.....	192
VI -	RESULTADOS Y DISCUSIÓN.....	207
6.1.	RELACIÓN DE LA EPILEPSIA EN LAS ALTERACIONES COGNITIVAS Y LINGÜÍSTICAS DE LAS PERSONAS CON TEA	208

6.2.	LOS TRASTORNOS DEL SUEÑO Y SU RELACIÓN CON LA DISFUNCIÓN NEUROBIOLÓGICA Y LAS ALTERACIONES COGNITIVAS EN LA PERSONA CON TEA Y EPILEPSIA	210
6.3.	COMPARACIÓN DEL RENDIMIENTO EN EL FUNCIONAMIENTO EJECUTIVO Y EL LENGUAJE ENTRE LA POBLACIÓN INFANTIL CON TEA, EPILEPSIA Y TEA CON EPILEPSIA	212
6.4.	COMPARACIÓN DEL PATRÓN EMOCIONAL, CONDUCTUAL Y DE FUNCIONAMIENTO EJECUTIVO ENTRE LA POBLACIÓN INFANTIL CON TEA, EPILEPSIA Y TEA CON EPILEPSIA	218
6.5.	COMPARACIÓN DEL PROCESAMIENTO Y LA COMPRENSIÓN AUDITIVA ENTRE LA POBLACIÓN INFANTIL CON TEA, EPILEPSIA Y TEA CON EPILEPSIA	227
6.6.	PROTOCOLO PARA LA EVALUACIÓN DEL LENGUAJE, LA COGNICIÓN Y EL PERFIL SENSORIAL DE LA PERSONA CON TEA Y EPILEPSIA	231
6.7.	EL TRATAMIENTO FARMACOLÓGICO EN LAS PERSONAS CON TEA Y EPILEPSIA	234
6.8.	LA INTERVENCIÓN DEL LENGUAJE Y LA COMUNICACIÓN EN LAS PERSONAS CON TEA Y EPILEPSIA	238
VII -	CONCLUSIONES	245
VIII -	LIMITACIONES Y FUTURAS LÍNEAS DE INVESTIGACIÓN	249
IX -	REFERENCIAS BIBLIOGRÁFICAS	253
X -	ANEXOS	301

SIGLAS Y ABREVIATURAS

ABA, Análisis Conductual Aplicado

ANCOVA, Análisis de la covarianza

CDC, Centros para el Control y la Prevención de Enfermedades

CI, Cociente Intelectual

CT, Tomografía computarizada

DI, Discapacidad Intelectual

EEG, Electroencefalograma

EIBI, Intervenciones Conductuales Intensivas Tempranas

ESDM, Modelo de Denver de Inicio Temprano

fMRI, Resonancia magnética funcional

ILAE, Liga Internacional Contra la Epilepsia

ISRS, Inhibidores selectivos de la recaptación de serotonina

ISRSN, Inhibidores selectivos de la recaptación de serotonina y noradrenalina

MANCOVA, Análisis de la covarianza multivariada

MEG, Magnetoencefalografía

MRI, Resonancia Magnética

NDBI, Intervenciones Conductuales del Desarrollo Natural

OMS, Organización Mundial de la Salud

PECS, Sistema de comunicación por intercambio de imágenes

SAAC, Sistemas Alternativos y Aumentativos de Comunicación

SISCOM, SPECT interictal-ictal co-registrada con MRI

SLK, Síndrome de Landau Kleffner

TCC, Terapia cognitivo-conductual

TCE, Traumatismo Craneoencefálico

TDAH, Trastorno por Déficit de Atención con Hiperactividad

TEA, Trastorno del Espectro del Autismo

TEACCH, Treatment and Education of Autistic and related Communication Handicapped Children

TOC, Trastorno Obsesivo Compulsivo

TS, Trastornos del sueño

ÍNDICE DE FIGURAS, DE TABLAS Y DE ANEXOS

ÍNDICE DE FIGURAS

Figura 1. Comparación de las puntuaciones medias entre el grupo TEA (G1), el grupo Epilepsia (G2) y el grupo TEA y epilepsia (G3) en las medidas correspondientes a la prueba CELF-5.....	213
Figura 2. Comparación de las puntuaciones medias entre el grupo TEA (G1), el grupo Epilepsia (G2) y el grupo TEA y epilepsia (G3) en las medidas correspondientes a la prueba BRIEF-2.	215
Figura 3. Comparación de las puntuaciones medias entre el grupo TEA (G1), el grupo Epilepsia (G2) y el grupo TEA y epilepsia (G3) en las medidas correspondientes a la prueba ENFEN.	216
Figura 4. Comparación de las puntuaciones medias entre el grupo TEA (G1), el grupo Epilepsia (G2) y el grupo TEA y epilepsia (G3) en los problemas conductuales y emocionales interiorizados en la prueba SENA.....	219
Figura 5. Comparación de las puntuaciones medias entre el grupo TEA (G1), el grupo Epilepsia (G2) y el grupo TEA y epilepsia (G3) en los problemas conductuales y emocionales exteriorizados en la prueba SENA.....	220
Figura 6. Comparación de las puntuaciones medias entre el grupo TEA (G1), el grupo Epilepsia (G2) y el grupo TEA y epilepsia (G3) en las medidas de funcionamiento ejecutivo en el ENFEN.	225
Figura 7. Comparación de las puntuaciones medias entre el grupo TEA (G1), el grupo Epilepsia (G2) y el grupo TEA y epilepsia (G3) en la comprensión de estructuras gramaticales de las pruebas CEG y CELF-5.....	228

ÍNDICE DE TABLAS

Tabla 1. <i>Criterios diagnósticos del Trastorno del Espectro Autista según el DSM-5 TR.</i>	35
Tabla 2. <i>Criterios diagnósticos del grado de la necesidad de apoyo del Trastorno del Espectro Autista según el DSM-5 TR</i>	37
Tabla 3. <i>Instrumentos de evaluación y diagnóstico del TEA</i>	57
Tabla 4. <i>Tipos de pruebas de neuroimagen para el diagnóstico de la epilepsia</i>	63
Tabla 5. <i>Características de los participantes incluidos en el estudio</i>	92
Tabla 6. <i>Diferencias entre los grupos: TEA (G1), Epilepsia (G2) y TEA y epilepsia (G3) en las medidas del lenguaje obtenidas en la prueba CELF-5</i>	212
Tabla 7. <i>Diferencias entre los grupos: TEA (G1), Epilepsia (G2) y TEA y epilepsia (G3) en las medidas del funcionamiento ejecutivo obtenidas en la prueba BRIEF-2</i>	215
Tabla 8. <i>Diferencias entre los grupos: TEA (G1), Epilepsia (G2) y TEA y epilepsia (G3) en las medidas del funcionamiento ejecutivo obtenidas en la prueba ENFEN</i>	216
Tabla 9. <i>Diferencias entre las medidas de los grupos: TEA (G1), Epilepsia (G2) y TEA con epilepsia (G3) en los problemas conductuales y emocionales interiorizados en la prueba SENA</i>	219
Tabla 10. <i>Diferencias entre las medidas de los grupos: TEA (G1), Epilepsia (G2) y TEA con epilepsia (G3) en los problemas conductuales y emocionales exteriorizados en la prueba SENA</i>	220
Tabla 11. <i>Diferencias entre las medidas de los grupos: TEA (G1), Epilepsia (G2) y TEA con epilepsia (G3) en el perfil conductual registrados por los padres y los profesores en el BASC-3</i>	221
Tabla 12. <i>Comparación de las puntuaciones medias entre el grupo TEA (G1), el grupo Epilepsia (G2) y el grupo TEA y epilepsia (G3) en las medidas de funcionamiento ejecutivo en el ENFEN</i>	225
Tabla 13. <i>Diferencias entre las medidas de los grupos: TEA (G1), Epilepsia (G2) y TEA con epilepsia (G3) en la comprensión de estructuras gramaticales de las pruebas CEG y CELF-5</i>	227

Tabla 14. <i>Protocolo de evaluación de las competencias lingüísticas, cognitivas y de perfil sensorial de la persona con TEA y epilepsia.</i>	231
Tabla 15. <i>Tratamiento farmacológico de síntomas asociados con el TEA</i>	235
Tabla 16. <i>Tratamiento farmacológico preferido para abordar la epilepsia en la población pediátrica con TEA</i>	236
Tabla 17. <i>Protocolos de intervención en los procesos de comunicación a través de Sistemas Aumentativos de Comunicación en la persona con TEA y epilepsia</i>	240

ÍNDICE DE ANEXOS

ANEXO 1. Aceptación del Comité de Ética de la UCAM	301
ANEXO 2. Consentimiento informado	302
.....	302
ANEXO 3. Renuncia de los coautores no doctores.....	303
ANEXO 4. Aceptación de los coautores	304
ANEXO 5. Declaración jurada de originalidad del trabajo.....	305

I – INTRODUCCIÓN

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1.1. EL TRASTORNO DEL ESPECTRO AUTISTA

El Trastorno del Espectro Autista (TEA) es un trastorno del neurodesarrollo caracterizado por déficits en la comunicación social y la presencia de intereses restringidos y comportamientos repetitivos (APA, 2013). En 2013, se publicó la quinta edición del Manual Diagnóstico y Estadístico de los Trastornos Mentales (DSM-5; APA, 2013), actualizando los criterios diagnósticos (Tablas 1 y 2) para el TEA desde la edición anterior (DSM-IV; APA, 2000), y se mantiene hasta la última versión registrada de este (DSM-5 TR; APA, 2022).

Tabla 1. *Criterios diagnósticos del Trastorno del Espectro Autista según el DSM-5 TR*

A. Deficiencias persistentes en la comunicación social y en la interacción social en diversos contextos, manifestado por lo siguiente, actualmente o por los antecedentes (los ejemplos son ilustrativos, pero no exhaustivos):

1. Las deficiencias en la reciprocidad socioemocional, varían, por ejemplo, desde un acercamiento social anormal y fracaso de la conversación normal en ambos sentidos pasando por la disminución en intereses, emociones o afectos compartidos hasta el fracaso en iniciar o responder a interacciones sociales.
2. Las deficiencias en las conductas comunicativas no verbales utilizadas en la interacción social, varían, por ejemplo, desde una comunicación verbal y no verbal poco integrada pasando por anomalías del contacto visual y del lenguaje corporal o deficiencias de la comprensión y el uso de gestos, hasta una falta total de expresión facial y de comunicación no verbal.
3. Las deficiencias en el desarrollo, mantenimiento y comprensión de las relaciones, varían, por ejemplo, desde dificultades para ajustar el comportamiento en diversos contextos sociales pasando por

dificultades para compartir juegos imaginativos o para hacer amigos, hasta la ausencia de interés por otras personas.

Especificar la gravedad actual:

La gravedad se basa en deterioros de la comunicación social y en patrones de comportamiento restringidos y repetitivos.

B. Patrones restrictivos y repetitivos de comportamiento, intereses o actividades, que se manifiestan en dos o más de los siguientes puntos, actualmente o por los antecedentes (los ejemplos son ilustrativos, pero no exhaustivos):

1. Movimientos, utilización de objetos o habla estereotipados o repetitivos (p. ej., estereotipias motoras simples, alineación de los juguetes o cambio de lugar de los objetos, ecolalia, frases idiosincrásicas).
2. Insistencia en la monotonía, excesiva inflexibilidad de rutinas o patrones ritualizados de comportamiento verbal o no verbal (p. ej., gran angustia frente a cambios pequeños, dificultades con las transiciones, patrones de pensamiento rígidos, rituales de saludo, necesidad de tomar el mismo camino o de comer los mismos alimentos cada día).
3. Intereses muy restringidos y fijos que son anormales en cuanto a su intensidad o foco de interés (p. ej., fuerte apego o preocupación por objetos inusuales, intereses excesivamente circunscritos o perseverantes).
4. Hiper- o hiporeactividad a los estímulos sensoriales o interés inhabitual por aspectos sensoriales del entorno (p. ej., indiferencia aparente al dolor/temperatura, respuesta adversa a sonidos o texturas específicos, olfateo o palpación excesiva de objetos, fascinación visual por las luces o el movimiento).

Especificar la gravedad actual:

La gravedad se basa en deterioros de la comunicación social y en patrones de comportamiento restringidos y repetitivos.

C. Los síntomas han de estar presentes en las primeras fases del período de desarrollo (pero pueden no manifestarse totalmente hasta que la demanda social supera las capacidades limitadas, o pueden estar enmascarados por estrategias aprendidas en fases posteriores de la vida).

D. Los síntomas causan un deterioro clínicamente significativo en lo social, laboral u otras áreas importantes del funcionamiento habitual.

E. Estas alteraciones no se explican mejor por la discapacidad intelectual (trastorno del desarrollo intelectual) o por el retraso global del desarrollo. La discapacidad intelectual y el trastorno del espectro del autismo con frecuencia coinciden; para hacer diagnósticos de comorbilidades de un trastorno del espectro del autismo y discapacidad intelectual, la comunicación social ha de estar por debajo de lo previsto para el nivel general de desarrollo.

Fuente: *adaptado de APA (2022)*

Tabla 2. *Criterios diagnósticos del grado de la necesidad de apoyo del Trastorno del Espectro Autista según el DSM-5 TR*

Grado 1: “Necesita ayuda”

Sin ayuda in situ, las deficiencias en la comunicación social causan problemas importantes. Dificultad para iniciar interacciones sociales y ejemplos claros de respuesta atípicas o insatisfactorias a la apertura social de otras personas. Puede parecer que tiene poco interés en las interacciones sociales.

Grado 2: “Necesita ayudas notables”

Deficiencias notables de las actitudes de comunicación social verbal y no verbal, problemas sociales aparentes incluso con ayuda in situ, inicio limitado de las interacciones sociales y reducción de la respuesta o respuestas no normales a la apertura social de otras personas.

Grado 3: “Necesita ayuda muy notable”

Las deficiencias graves de las aptitudes de comunicación social verbal y no verbal causan alteraciones graves del funcionamiento, inicio muy limitado de las interacciones sociales y respuesta mínima a la apertura social de otras personas.

Fuente: *adaptado de APA (2022)*

El TEA es un trastorno neurobiológico influenciado tanto por factores genéticos como ambientales que afectan al desarrollo del cerebro (Bentenuto *et al.*, 2021). Los estudios publicados sobre el perfil neuropatológico son heterogéneos, pero han revelado diferencias en la arquitectura y conectividad cerebelosa, anomalías del sistema límbico y alteraciones corticales de los lóbulos frontal y temporal, junto con otras malformaciones del sistema nervioso central (Crowell *et al.*, 2019; Thomas *et al.*, 2018). Los factores genéticos juegan un papel importante en el TEA, puesto los hermanos de pacientes con TEA tienen un mayor riesgo de presentar un diagnóstico de este trastorno. Además de ello, se ha observado una correlación significativa entre el TEA y el proceso embrionario en gemelos monocigóticos (Majhi *et al.*, 2023). Los estudios de asociación a nivel del genoma y los métodos de secuenciación del exoma completo han ampliado la comprensión de los genes relacionados con el diagnóstico de TEA (Ji *et al.*, 2020). Por ejemplo, los genes vinculados al TEA incluyen aquellos que desempeñan un papel en el desarrollo del cerebro, la función de los neurotransmisores, o genes que afectan a la excitabilidad neuronal (Courchesne *et al.*, 2020). Muchas de las alteraciones genéticas asociadas al TEA codifican proteínas relevantes en la sinapsis neuronal, además de estar involucradas en cambios dependientes de la actividad en las neuronas (Parellada *et al.*, 2023). Las redes de riesgo genético del TEA incluyen vías involucradas en la neurotransmisión y la neuroinflamación del sistema nervioso central (Friedman *et al.*, 2006). En última instancia, el TEA sigue siendo uno de los trastornos del neurodesarrollo genéticamente más heterogéneos con variantes raras de novo con más de 700 genes (Chevallier *et al.*, 2014).

Si bien la genética claramente juega un papel fundamental en la etiología del TEA, la expresión fenotípica a nivel genético es también de suma importancia (Grove *et al.*, 2019). El riesgo genético puede ser modulado por factores ambientales

prenatales, perinatales y postnatales en algunos pacientes (Trost *et al.*, 2022). Por ejemplo, la exposición prenatal a la talidomida y el ácido valproico aumenta el riesgo, mientras que los estudios sugieren que los suplementos prenatales de ácido fólico en pacientes expuestos a medicamentos antiepilépticos pueden reducir el riesgo (Honybun *et al.*, 2021).

La edad materna y paterna avanzada han demostrado tener una relación con un mayor riesgo de tener un hijo con TEA (Modabbernia *et al.*, 2017). Por ello, se han hecho revisiones exhaustivas de la historia materna de enfermedades autoinmunes, como diabetes, enfermedad tiroidea o psoriasis, pero los resultados de los estudios siguen siendo contradictorios, ya que los resultados no reflejan una relación significativa entre estos factores y el riesgo de que el feto contraiga un trastorno como el TEA (Li *et al.*, 2019; Hornig *et al.*, 2018). En la misma línea, la infección materna o la activación inmunitaria durante el embarazo es otra área de interés y puede ser un factor de riesgo potencial según investigaciones recientes (Cheng *et al.*, 2019). Además de ello, tanto los intervalos inter-gestacionales más cortos como los más largos también se han informado que aumentan el riesgo de TEA (Schieve *et al.*, 2015). Los bebés nacidos de forma prematura también han demostrado tener un mayor riesgo de TEA, además de otros trastornos del neurodesarrollo (Yong *et al.*, 2021). En una revisión epidemiológica previa, los factores obstétricos, como el sangrado uterino, el parto por cesárea, el bajo peso al nacer, el parto prematuro y los bajos puntajes de Apgar, se informaron como los pocos factores más consistentemente asociados con el TEA (Getahun *et al.*, 2017). De igual manera, un metaanálisis informó sobre varios factores de riesgo pre, peri y postnatales que resultaron en un riesgo relativo elevado de TEA en la descendencia, pero también reveló una heterogeneidad significativa, lo que resulta en una incapacidad para hacer una determinación verdadera con respecto a la importancia de estos factores (Brumbaugh *et al.*, 2020).

La Organización Mundial de la Salud (OMS) estima la prevalencia internacional del TEA en 0.76%; sin embargo, esto solo representa aproximadamente el 16% de la población infantil mundial (Salari *et al.*, 2022). Los Centros para el Control y la Prevención de Enfermedades (CDC) estiman que alrededor del 1.68% de los niños en Estados Unidos de 8 años son diagnosticados con TEA (LaSalle, 2023; Maenner *et al.*, 2023). En Europa, los diagnósticos de TEA informados por los padres en 2016 tuvieron un promedio ligeramente mayor, del

2.5% (Solmi *et al.*, 2022). La prevalencia de TEA a nivel internacional se duplicó más del doble en la última década según estimaciones de la Red de Monitoreo del Autismo y las Discapacidades del Desarrollo (CDC, 2014).

El TEA es más común en hombres (Baio *et al.*, 2018). Sin embargo, en una revisión reciente (Green *et al.*, 2019) reveló que la proporción entre hombres y mujeres es más cercana a 3:1 que a la reportada previamente de 4:1, aunque este estudio no se realizó utilizando los criterios del DSM-5 TR (APA, 2022). Este estudio también sugirió que las niñas que cumplen con los criterios para TEA tienen un mayor riesgo de no recibir un diagnóstico clínico. El fenotipo de TEA femenino puede desempeñar un papel en que las niñas sean diagnosticadas erróneamente, diagnosticadas más tarde o pasadas por alto. No solo las mujeres tienen menos probabilidades de presentar síntomas evidentes, sino que también son más propensas a enmascarar sus déficits sociales a través de un proceso de enmascaramiento, lo que dificulta aún más un diagnóstico adecuado (Ochoa-Lubinoff *et al.*, 2023).

1.1.1. Características lingüísticas

Específicamente, las personas con TEA tienen antecedentes de desarrollo muy diversos y difieren significativamente en la medida en que dominan, vocalizan y expresan el lenguaje en forma de gramática y vocabulario (Thomas *et al.*, 2023). En general, 3 de cada 4 niños con TEA muestran algunas habilidades lingüísticas deterioradas para cuando ingresan en la escuela, que pueden ser leves o graves, mientras que 1 de cada 4 niños con TEA muestra habilidades lingüísticas típicas o incluso excepcionales antes de los 5 años (Cermak *et al.*, 2022). Aunque las dificultades en el lenguaje funcional son un indicador importante de TEA en la primera infancia, las dificultades en la comunicación a través del lenguaje oral no son uniformes, y este hecho indica que proporcionar un pronóstico y diseñar intervenciones ajustadas puede suponer un reto (Prescott y Ellis Weismer, 2022). Sin embargo, el nivel de habilidades y competencias lingüísticas en la infancia predice significativamente los resultados futuros de las personas con TEA (McKernan y Kim, 2022), como el éxito académico y la autonomía en las actividades de la vida diaria (Braconnier y Siper, 2021). Por lo tanto, es particularmente

importante que los investigadores obtengan una comprensión de las variables que afectan y causan los niveles heterogéneos de adquisición del lenguaje en la población infantil con TEA (Sourvinos *et al.*, 2021).

La semántica, como campo de estudio, se enfoca en entender cómo los idiomas estructuran y expresan significados. Es fundamental en el dominio del lenguaje y puede influir en trastornos en los que se presentan alteraciones lingüísticas, como en el TEA (Silva y Feitosa, 2019). Varias investigaciones han demostrado que los niños con TEA tienden a tener un vocabulario operativo más limitado en comparación con niños con un desarrollo normotípico de la misma edad (Ambridge *et al.*, 2021; Gladfelter *et al.*, 2019; Vogindroukas *et al.*, 2022). Algunos estudios, como el de Goodwin *et al.* (2012) y Schaeffer *et al.* (2023), sugieren que en ocasiones no hay diferencias importantes en el desarrollo del vocabulario expresivo o la comprensión de palabras en las personas con TEA y aquellos con desarrollo típico. Sin embargo, los niños con TEA tienden a mostrar patrones lingüísticos peculiares, como el uso de coloquialismos, parafasias, o nombrar objetos de manera inapropiada, lo que puede reflejar dificultades para representar mentalmente el significado deseado o inseguridad al comunicarse. Estudios recientes, como el realizado por Vigliocco *et al.* (2018), han investigado cómo los niños con TEA aprenden conceptos y palabras abstractas, y si esto puede predecir un trastorno en el desarrollo del lenguaje. Aunque se ha observado un deterioro generalizado en el vocabulario para niños con TEA que tienen trastorno del lenguaje, no se ha encontrado un rendimiento alterado específicamente en palabras abstractas. Esto sugiere que las dificultades sociales y emocionales en el TEA pueden tener mecanismos subyacentes diferentes a la adquisición de vocabulario de carácter abstracto.

Además, estudios como los de Taylor *et al.* (2020) indican que el desarrollo del lenguaje en individuos con TEA puede ser independiente de otros rasgos autistas y no está relacionado ni genética ni clínicamente con la gravedad de los síntomas del TEA. Esto destaca la complejidad de este trastorno y la heterogeneidad en el desarrollo del lenguaje que caracterizan a las personas con esta condición. A pesar de los avances en la comprensión del perfil sintomatológico del TEA en las competencias lingüísticas, aún no existe una hipótesis única que pueda explicar todas las peculiaridades y dificultades encontradas en individuos con esta condición (Neuhaus *et al.*, 2022).

Con respecto a la pragmática del lenguaje, es decir, su uso apropiado y ajustado en contextos sociales, plantea dificultades significativas para las personas con diagnóstico de TEA (Hage *et al.*, 2021). Aunque muchas teorías psicológicas han intentado explicar el autismo en términos de factores neurológicos y cognitivos, las dificultades pragmáticas, que incluyen la incapacidad para determinar el tipo de lenguaje apropiado para diferentes situaciones sociales, son comunes en personas con TEA (Choque Olsson *et al.*, 2017). Estas dificultades lingüísticas a menudo se consideran secundarias a los problemas cognitivos o sociales asociados con el TEA (Shaw *et al.*, 2021). Sin embargo, los déficits en el lenguaje pragmático pueden complicar las relaciones sociales y generar ansiedad social, ya que los individuos con TEA pueden exhibir comportamientos lingüísticos inapropiados en situaciones sociales, como la falta de respuesta a preguntas de otros agentes comunicativos o tener una conversación bidireccional (Rodas *et al.*, 2017).

Cuando existen alteraciones en el lenguaje y en la comunicación, es común que la persona que las presenta emita mensajes lingüísticos repetitivos, debido, en parte, a las dificultades para la gestión y ajuste de esos enunciados. La ecolalia, entendida como la repetición de palabras o frases del habla de otros, es un fenómeno notable en niños con TEA y puede ser más frecuente y persistente en comparación con individuos con un desarrollo normotípico. Aunque se necesita más investigación sobre su naturaleza y función, la ecolalia puede servir como una estrategia de comunicación cuando los individuos con TEA no están seguros de cómo responder en interacciones verbales (Pruccoli *et al.*, 2021). Además, las personas con TEA pueden presentar estilos de habla distintivos, como hablar demasiado suavemente o fuerte, usar un tono emocional inapropiado o crear palabras y expresiones neológicas (Lau *et al.*, 2018). También pueden tener dificultades para entender el lenguaje figurativo y la ironía, así como para narrar historias. Algunos recurren al habla pedante, utilizando un lenguaje formal y repleto de información innecesaria para impresionar a los demás. Es interesante destacar que algunos niños con TEA desarrollan habilidades lingüísticas en idiomas que no son su lengua materna, adquiridas a través del uso de tecnología (programas, televisión, aplicaciones...) en lugar de interacciones sociales (Shield *et al.*, 2017). Esto sugiere una relación entre las dificultades sociales y pragmáticas observadas en el TEA y la forma en que estos individuos aprenden idiomas. Las

dificultades pragmáticas no solo están relacionadas con problemas en otros componentes del lenguaje, sino que también pueden influir en el rendimiento social general (Reindal *et al.*, 2023).

En cuanto al apartado de la fonología, la cual estudia las formas en que los sonidos se distribuyen y se despliegan dentro de idiomas particulares (Shriberg *et al.*, 2011). La alta prevalencia de trastornos en las funciones del habla identificados en perfiles clínicos del TEA ha llevado a un estudio extenso de habilidades fonológicas y articulatorias en los últimos años (Petinou, 2021). Más específicamente, los resultados indican que la prevalencia de la comorbilidad del TEA con los trastornos del habla varía entre el 15% y el 20%. Sin embargo, la sintomatología y la gravedad del TEA en los trastornos del habla siguen sin estar claras dentro de los niños con esta condición del neurodesarrollo (Kissine *et al.*, 2019). Aunque estudios más clásicos sobre el desarrollo de la fonología, la conciencia fonológica y la prosodia informaron perfiles de habla apropiados para la edad en las personas con TEA, en la actualidad, las investigaciones coinciden en que el patrón articulatorio y fonológico de estos perfiles clínicos no son los ajustados para su edad cronológica (Kjelgaard y Tager-Flusberg, 2001). En los individuos con TEA, se observa una estructura inmadura de las sílabas, una variedad restringida de fonética, deformaciones del sonido del habla, una producción inconsistente de palabras, un uso inconsistente de procesos fonológicos, el desarrollo tardío de vocabulario expresivo significativo y un uso restringido de contrastes fonológicos (Tager-Flusberg, 2006).

Por último, en lo relativo a la morfosintaxis, que se refiere al estudio de las propiedades morfológicas y sintácticas de unidades lingüísticas o gramaticales, las reglas que determinan la relación entre una forma lingüística y otra, los niños con TEA presentan dificultades notorias en las competencias morfológicas del lenguaje expresivo, como la repetición de pseudopalabras y la flexión verbal. En los últimos años, varias investigaciones han estudiado la morfosintaxis de los niños con TEA revelando que ciertos aspectos de esta están alterados significativamente. Roberts *et al.* (2004) investigaron la producción de frases en niños de 5 a 15 años con TEA. El estudio mostró que esta población mostraba puntuaciones más bajas en tareas de creación de frases, organización de elementos sintácticos y producción de un discurso coherente y conexo gramaticalmente en comparación con un grupo control de personas con un trastorno del lenguaje. En la misma línea, Perovic *et al.*

(2012) investigaron la emisión y uso de los pronombres en niños con TEA de 6 a 18 años. Este estudio concluyó que estos perfiles también presentaban dificultades en la interpretación de pronombres reflexivos.

Por lo tanto, la población pediátrica con diagnóstico de TEA muestra alteraciones significativas en los diferentes procesos lingüísticos. Pueden presentar dificultades en la fonología con problemas en la articulación de los sonidos del habla, retraso en la adquisición del lenguaje oral y el vocabulario, la comprensión de instrucciones y órdenes, configuración de frases coherentes y conexas, así como en la interacción y uso del lenguaje en entornos o contextos comunicativos.

1.1.2. Características cognitivas

El TEA ha sido descrito como un trastorno que presenta déficits en los principales componentes de las funciones ejecutivas, sobre todo en aquellas de orden superior. Numerosos estudios han encontrado que la población infantil con TEA muestra dificultades significativas en tareas que miden el control inhibitorio (Pellicano *et al.*, 2017; Van Eylen *et al.*, 2015), flexibilidad cognitiva (Pellicano, 2010; Semrud-Clikeman *et al.*, 2014), y memoria de trabajo (Pellicano *et al.*, 2017).

Las investigaciones que han examinado las habilidades de funciones ejecutivas de orden superior en niños con TEA han encontrado, además de los mencionados anteriormente, déficits en la planificación, organización, razonamiento y resolución de problemas (Diamond, 2013; Pellicano, 2010; Unterrainer *et al.*, 2016). Aunque la mayor parte de la evidencia indica que, como grupo, los niños con TEA muestran déficits en las funciones ejecutivas, hay algunos hallazgos contradictorios dentro de la literatura. Por ejemplo, Demetriou *et al.* (2018), Liang *et al.* (2022) y Robinson *et al.* (2009), no encontraron déficits significativos en la flexibilidad cognitiva en niños con diagnóstico de TEA, pero sí reportaron dificultades con la inhibición, la planificación y el autocontrol. Las inconsistencias en estos hallazgos de investigación probablemente se deban a la variedad de diferentes tareas utilizadas para medir los constructos de las funciones ejecutivas, los sesgos durante la realización de las tareas en la medición (Van Eylen *et al.*, 2015), diferentes criterios de emparejamiento de grupos y heterogeneidad de

los participantes dentro del grupo de TEA (por ejemplo, nivel cognitivo, habilidades lingüísticas, gravedad del trastorno).

Uno de los errores clásicos a nivel metodológico en los estudios focalizados en la evaluación de las funciones ejecutivas y la cognición en personas con TEA era hacer coincidir grupos en habilidades cognitivas no verbales, con una amplia heterogeneidad en su rendimiento y habilidad lingüística. Kercood et al. (2014) señalaron que ninguno de los 24 estudios que examinaron la memoria de trabajo en individuos con TEA, que incluyeron en su revisión, consideró las implicaciones de las habilidades lingüísticas. Sin embargo, algunos estudios han informado que los niños con TEA ya no mostraron déficits en funciones ejecutivas en comparación con controles cuando se covarían las diferencias en las habilidades lingüísticas (Joseph *et al.*, 2005; Liss *et al.*, 2001). Otra variable por considerar dentro de esta población es la discapacidad intelectual, ya que es común encontrar alteraciones de este tipo en aproximadamente el 20% de la población con un diagnóstico de TEA. Debido a que la discapacidad intelectual puede estar presente de forma comórbida en el TEA, y que esta a su vez tiene una influencia significativa en las funciones ejecutivas, la cognición no verbal a menudo se iguala en los grupos en un intento de aislar específicamente las diferencias en los componentes de las funciones ejecutivas.

1.1.3. Comorbilidades

Con respecto a la comorbilidad, las tres cuartas partes de los niños con un diagnóstico de TEA también cursan con otro trastorno médico, psiquiátrico o neurológico que desemboca en una mayor discapacidad física y/o psíquica, un aumento en el costo del tratamiento y una mayor demanda de cuidados por parte de las familias de los pacientes (Bauman, 2010). Es necesario tener conciencia de las altas tasas de asociación del TEA con trastornos comórbidos para guiar el diagnóstico y el tratamiento de forma adecuada, con el fin de mejorar el pronóstico y los resultados clínicos de estos perfiles clínicos (Pardo *et al.*, 2005). Existe un amplio abanico de condiciones o trastornos diferentes que están frecuentemente asociados con el TEA, incluyendo el trastorno por déficit de atención e hiperactividad (TDAH), ansiedad, trastorno bipolar, enfermedad inflamatoria

intestinal, epilepsia, síndrome del cromosoma X frágil, disforia de género, discapacidad intelectual, trastornos inmunológicos, trastorno del aprendizaje, trastorno obsesivo-compulsivo (TOC), esquizofrenia, problemas sensoriales, trastornos del sueño, esclerosis tuberosa, síndrome de Tourette y trastornos de tics (Erickson *et al.*, 2005; Glidden *et al.*, 2016; Zafeiriou *et al.*, 2007).

1.2. LA EPILEPSIA

La epilepsia es una enfermedad neurológica que afecta de forma significativa al correcto funcionamiento cerebral. En la actualidad, la manifestación más común de epilepsia se suele registrar en síndromes, siendo este un conjunto de signos y síntomas que definen una condición epiléptica (Fine y Wirrell, 2020). Los síndromes se clasifican en función de los tipos de convulsiones, el contexto clínico, la neurofisiología y la localización del foco epiléptico registrado a través de las técnicas de neuroimagen (Gonzalez y Wrennall, 2020). La epilepsia puede ser generalizada, si todas las convulsiones y las anomalías en el registro del EEG no son específicas de un área cortical, o focal (parcial) si las manifestaciones clínicas y del EEG sugieren un inicio focal (Specchio *et al.*, 2022). Además de ello, los episodios de epilepsia pueden ser de etiología desconocida o derivada de un daño neurológico principal. Por un lado, las epilepsias idiopáticas no están asociadas con lesiones cerebrales; son causadas por una predisposición genética compleja o, raramente, por una herencia monogénica (Vrščaj *et al.*, 2020). Por otro lado, las epilepsias sintomáticas resultan de una lesión cerebral, que no necesariamente se detecta mediante neuroimagen. El diagnóstico del síndrome es útil para orientar investigaciones y manejo, y es un indicador pronóstico temprano (Symonds *et al.*, 2021).

A nivel mundial, se estima que 10.5 millones de niños menores de 15 años tienen epilepsia activa (Poke *et al.*, 2023), lo que representa aproximadamente el 25% de la población mundial de epilepsia (Cowan, 2002). De los 3.5 millones de personas que desarrollan epilepsia anualmente, el 40% tiene menos de 15 años y más del 80% vive en países en desarrollo (Schubert-Bast *et al.*, 2023). Estudios basados en la población sobre epilepsia de inicio en la infancia indican tasas de incidencia anual de 61–124 por 100,000 en países en desarrollo, y 41–50 por 100,000

en países en vías de desarrollo (Ackermann *et al.*, 2019). La incidencia disminuye progresivamente desde alrededor de 150 por 100,000 en el primer año de vida hasta 45–50 por 100,000 después de los 9 años (Specchio *et al.*, 2022). Los estudios de incidencia acumulativa indican que, hasta los 15 años de edad, el 1.0–1.7% de los niños tendrán al menos una convulsión no provocada, y el 0.7–0.8% tendrán convulsiones repetidas. Las tasas de frecuencia en Europa y América del Norte varían de 3.6–6.5 por 1000 (Schubert-Bast *et al.*, 2023), mientras que los estudios africanos y latinoamericanos informan tasas de 6.6–17 por 1000 (Ackermann *et al.*, 2019).

Casi todos los estudios sobre las causas de las epilepsias infantiles se han realizado combinando todos los tipos de epilepsia. Una serie de investigaciones recientes ha examinado los factores de riesgo para tipos específicos de convulsiones, incluyendo la generalizada tónico-clónicas (Donner *et al.*, 2017), las ausencias simples (Fine y Wirrell, 2020) y las convulsiones parciales complejas (Manford, 2017). Los estudios específicos de cada tipo de convulsión recogen una información más fiable, ya que es probable que diferentes tipos de convulsiones y síndromes epilépticos tengan diferentes factores de riesgo, provocando sesgos en la comparación de los resultados obtenidos por los perfiles clínicos de la epilepsia (Ali, 2018; Steriade *et al.*, 2021).

Considerando todos los tipos de epilepsia combinadas, aproximadamente del 55% al 75% de todas ellas son de causa desconocida (Waalder *et al.*, 2000). Solo del 25% al 45% de la epilepsia se ha atribuido a factores etiológicos específicos. La mayoría de los estudios que han examinado los factores perinatales, especialmente aquellos relacionados con hipoxia en el parto, no han encontrado asociaciones significativas con el riesgo de epilepsia (Hauser *et al.*, 1996; Roberti *et al.*, 2022). Los factores que han sido consistentemente asociados con un mayor riesgo de epilepsia en niños incluyen: malformaciones congénitas y trastornos metabólicos, convulsiones febriles, convulsiones en los primeros 28 días de vida (convulsiones neonatales), traumatismos craneoencefálicos moderados o graves, infecciones del sistema nervioso central y antecedentes familiares de epilepsia.

La presencia de epilepsia en la familia es un factor determinante en la asociación del riesgo de aparición de epilepsia en un menor (Pitkänen y Immonen, 2014). El riesgo es mayor en los hijos de madres con epilepsia que en los hijos de padres con esta condición (Kobow y Blümcke, 2018). Se ha demostrado que un

historial materno de epilepsia o convulsiones febriles aumenta las probabilidades tanto de epilepsia focal como de epilepsia generalizada (Nascimento *et al.*, 2023). Se ha supuesto desde hace mucho tiempo que los factores genéticos juegan un papel en la epilepsia, aunque los modos exactos de herencia de estas condiciones siguen siendo poco claros en la mayoría de los casos (Kundu *et al.*, 2018).

El traumatismo craneoencefálico (TCE) y las infecciones del sistema nervioso central son causas importantes de epilepsia secundaria derivada de daño cerebral adquirido en niños. El porcentaje de epilepsia atribuida al TCE oscila entre aproximadamente el 4% (Annegers *et al.*, 1996) y casi el 10% (Fordington y Manford, 2020). El traumatismo es una de las etiologías que mayor porcentaje de epilepsia secundaria causa entre los niños mayores de 5 años que entre los más pequeños (Hauser *et al.*, 1996). Por otro lado, las infecciones del sistema nervioso central se establecen con una incidencia del 3% (Waalder *et al.*, 2000) al 4% (Lucke-Wold *et al.*, 2015), y a veces hasta el 6% (Sirven, 2015) de los casos de epilepsia. En general, en aquellos que sobreviven a la infección, el riesgo de episodios de epilepsia se incrementa 3 veces. La magnitud y la duración de la epilepsia después de la infección del sistema nervioso central varían considerablemente según el tipo de infección (Annegers *et al.*, 1996). Por ejemplo, la encefalitis se asocia con un aumento en la magnitud que puede tardar en controlarse o estabilizarse hasta 15 años después de la infección. Con respecto a la meningitis bacteriana no se observan alteraciones tan graves como en el caso de la encefalitis, puesto que el aumento del riesgo se limita a los primeros 5 años después de la infección.

Varios estudios han examinado las posibles asociaciones de factores prenatales y perinatales con el riesgo de aparición de episodios de epilepsia (Joensen, 1986; Pakdaman *et al.*, 2021). Estos factores incluyeron complicaciones del embarazo como toxemia o hemorragia, anomalías placentarias, líquido amniótico teñido de meconio, uso de fórceps, restricción del crecimiento intrauterino, cordón umbilical nual, parto de nalgas entre otros (Ding *et al.*, 2018). Ninguno de estos factores, incluidas las medidas de asfixia perinatal, se ha indicado como un factor que aumente significativamente el riesgo de aparición de epilepsia en niños (Banerjee *et al.*, 2009). Estos resultados parecerían sugerir que los factores pre y perinatales no influyen en el riesgo de epilepsia en la infancia. Sin embargo, puede ser que los estudios empleen metodologías o instrumentos de medición que no permitan registrar correctamente las exposiciones del feto a estos factores de riesgo.

Además de ello, el amplio espectro de casos clínicos y la heterogeneidad en los procedimientos y en las diferencias individuales de cada paciente impidan que se obtengan resultados significativos que permitan una generalización adecuada (Pellinen, 2022).

1.2.1. Características lingüísticas

El manual para la clasificación operativa de los tipos de convulsiones por la Liga Internacional Contra la Epilepsia (ILAE; Fisher *et al.*, 2014) describe la epilepsia como una condición que provoca alteraciones en el lenguaje. La epilepsia suele cursar con síntomas afásicos con dificultades que radican, sobre todo, en el apartado del lenguaje expresivo, aunque también se pueden encontrar déficit en la comprensión (Cano-Villagrasa *et al.*, 2023). Otras características comunes del patrón conductual asociado al lenguaje en la epilepsia comprenden los automatismos (vocalización, habla, problemas sociales) y síntomas motores como la disartria (Scheffer *et al.*, 2017).

En general, las personas con epilepsia se caracterizan por un mal uso para organizar, procesar y conectar pensamientos lingüísticos, provocando, además, una comunicación social deteriorada (Plioplys *et al.*, 2007). Los niños que tienen un desarrollo normotípico adquieren la capacidad de organizar su pensamiento y proporcionar al oyente las funciones lingüísticas necesarias para desarrollar adecuadamente su lenguaje expresivo y receptivo desde la infancia hasta la adolescencia (Caplan, 2019). En contraposición, la población infantil con epilepsia suele presentar dificultades para organizar, planificar y estructurar sus pensamientos e ideas, lo que conlleva a que el resto de los interlocutores tengan problemas para comprender o seguir una conversación extensa. Asimismo, sus competencias morfosintácticas se describen como inconexas, con agramatismos, dificultades en la cohesión de oraciones y una narración incoherente en los momentos más tardíos de la conversación (Bailey y Im-Bolter, 2021). También cometen errores en la monitorización de la información lingüística que emiten, tratando de llevar a cabo circunloquios para poder expresar las ideas que quieren transmitir, además de perder el hilo conductor de los mensajes producidos (Smith *et al.*, 2015).

Este tipo de alteraciones han sido descritas de forma empírica en la literatura científica. Un estudio compuesto por 182 niños con epilepsia crónica, 104 con epilepsia focal y 78 con epilepsia generalizada, obtuvo resultados significativamente peores que 102 sujetos de control sanos en pruebas de habilidades lingüísticas básicas (Hammill y Newcomer, 2002). Además de ello, su discurso carecía tanto de coherencia como de cohesión. Durante una tarea de contar historias, abusaron del razonamiento deficiente (pensamiento ilógico), usaron menos pronombres, demostrativos, así como artículo definido y comparativos para referirse a personas u objetos.

A pesar del diseño transversal de estos estudios, sus hallazgos deben entenderse desde la perspectiva del desarrollo. Las regiones cerebrales en desarrollo son sensibles a los efectos de los episodios de epilepsia (Casanova *et al.*, 2012). Si no se controlan los focos o episodios epilépticos, la maduración de las regiones cerebrales relacionadas con el lenguaje durante la infancia y la adolescencia (Caplan *et al.*, 2009; Giedd *et al.*, 2015) las hace particularmente vulnerables provocando alteraciones significativas en las dimensiones del lenguaje (fonología, semántica, morfosintaxis y pragmática). Por ejemplo, la predominancia de la actividad epiléptica en la región frontal (Carney *et al.*, 2012) y en el lóbulo temporal (Giedd *et al.*, 2015) en los pacientes con epilepsia podría contribuir a la aparición de problemas de acceso al léxico, denominación de imágenes, comprensión de instrucciones complejas, así como en la velocidad de procesamiento auditivo de la información registrada.

1.2.2. Características cognitivas

Las alteraciones cognitivas pueden observarse antes del diagnóstico o hacerse evidente después de la detección de la epilepsia. Las dificultades cognitivas en niños con epilepsia deben ser adecuadamente evaluada, diagnosticada y tratada porque puede afectar el rendimiento académico y la calidad de vida de los pacientes y sus familias (Thompson *et al.*, 2020). Un adecuado nivel cognitivo en la persona con epilepsia es un factor importante para el correcto desempeño académico, pero no es el único, ya que las dificultades académicas son más frecuentes que en la población general y podrían observarse en niños con un cociente intelectual dentro del rango normotípico (Nickels *et al.*, 2016).

Varios factores contribuyen a la aparición de dificultades cognitivas en niños con epilepsia. En una primera instancia, la etiología subyacente es el principal factor que influye en la función cognitiva (Kaur *et al.*, 2022). Esto es más evidente cuando existen trastornos severos del desarrollo cortical, como la lisencefalia, o un trastorno cromosómico, como la trisomía del cromosoma 21 (Addis *et al.*, 2013). Sin embargo, es más complicado determinar cuando no hay evidencia de una etiología subyacente, lo que provoca que las alteraciones cognitivas sean significativas en las condiciones comórbidas relativas a síndromes de origen genético (Simmatís *et al.*, 2020).

Otro factor de riesgo es la discapacidad intelectual (DI), ya que es relativamente común en niños con epilepsia. Los estudios epidemiológicos y de casos han ayudado a identificar los factores de riesgo para el deterioro cognitivo (Stefanski *et al.*, 2021). La edad de inicio de la epilepsia es un aspecto fundamental que puede influir en la gravedad de la discapacidad intelectual (Winterhalder *et al.*, 2022). En el estudio de Camelo *et al.* (2023) utilizaron datos de evaluación prequirúrgica de niños con epilepsia del lóbulo temporal, y en el que se pudo observar una correlación significativa entre la edad de inicio y el CI, lo que sugiere que el momento en el que aparece la epilepsia y su impacto en el desarrollo del sistema nervioso central es más importante que la duración de la enfermedad. Asimismo, cuando la edad de inicio de la epilepsia se sitúa antes del primer año se observó un mayor déficit cognitivo, así como una mayor discapacidad intelectual. Por el contrario, cuando los primeros síntomas de epilepsia se localizan después de los 5 años, se apreció un menor riesgo de disfunción intelectual.

Un análisis multivariado realizado por van Ool *et al.* (2016), compuesto por un grupo muestral que incluyó participantes en el momento del diagnóstico inicial de la epilepsia, permitió la identificación de factores significativamente asociados con la participación de la función cognitiva. Estos factores incluyen el inicio de la epilepsia antes de los 5 años, la etiología sintomática de la epilepsia, el control de los episodios epilépticos y su localización. Los niños con un CI dentro del rango normal representaron el 59,1% cuando el inicio de la epilepsia fue antes de los 5 años, y el 85,3% cuando el inicio se situó en edades comprendidas entre los 5 y 9 años (Branford *et al.*, 2023). Se llevó a cabo otro estudio prospectivo (Operto *et al.*, 2023) configurado por participantes en edad infantil en el momento del diagnóstico de epilepsia (dentro de los 3 meses del primer ataque) y sus hermanos con un

desarrollo normotípico, en los cuales se valoraron varios dominios cognitivos: lenguaje, velocidad de procesamiento, memoria verbal y aprendizaje, y atención/habilidad constructiva ejecutiva. Los resultados obtenidos reflejaron que las puntuaciones obtenidas en los instrumentos de medición (en las dimensiones cognitivas evaluadas) de las competencias cognitivas de los niños que presentaron epilepsia eran menores en comparación con sus hermanos.

1.2.3. Comorbilidades

Varios estudios han examinado la comorbilidad en personas con epilepsia, describiendo la existencia de una amplia heterogeneidad de cuadros diagnósticos que se pueden observar de forma conjunta a la epilepsia (Guekht, 2017; Keezer *et al.*, 2016; Mula *et al.*, 2022). Muchas de las asociaciones entre epilepsia y las condiciones comórbidas tienen una vinculación común, ya que la epilepsia suele aparecer como una condición secundaria a esta, como por ejemplo en las neoplasias del sistema nervioso central, los accidentes cerebrovasculares o los TCEs en la edad infantil (Yuen *et al.*, 2018). Además de ello, se ha observado que ciertos fármacos antiepilépticos pueden conllevar problemas cardíacos, lo que puede provocar la aparición de riesgo vascular, arritmias o insuficiencias cardíacas en los casos más graves (Kubota *et al.*, 2022). Asimismo, también se ha observado una relación entre el sistema endocrino y la epilepsia, ya que esta puede estar asociada a la aparición de diabetes tipo 1 debido a la presencia de anticuerpos contra la decarboxilasa del ácido glutámico (GAD), y están presentes en hasta un 6% de las personas con epilepsia (Shlobin y Sander, 2020). En la misma línea, se ha sugerido que las alergias son el resultado de medicamentos antiepilépticos específicos en algunas personas, y el asma podría ocurrir como resultado de condiciones ambientales y de vida relacionadas indirectamente con la epilepsia (Beghi *et al.*, 2015).

Por último, algunos estudios longitudinales llevados a cabo en la actualidad han reportado una estrecha relación entre la epilepsia y varios trastornos psiquiátricos y del neurodesarrollo, incluyendo depresión, ansiedad, esquizofrenia, TEA, TDAH, Trastornos de la Comunicación, parálisis cerebral infantil, entre otros. Sin embargo, la evidencia empírica actual no permite hacer una relación directa de que la epilepsia sea la causa o la consecuencia de estos trastornos mencionados, por lo que se necesita más investigación para poder determinar si la

epilepsia actúa como causante o consecuente de estas condiciones (Manni y Terzaghi, 2010; Steriade *et al.*, 2021; Tao y Wang, 2016; Wang *et al.*, 2023).

1.3. EL TRASTORNO DEL ESPECTRO AUTISTA Y LA EPILEPSIA

La población infantil con TEA tiene un mayor riesgo de presentar epilepsia (Kanner, 1943; Spence y Schneider, 2009), y, a su vez, los niños con epilepsia tienen un mayor riesgo de ser diagnosticados con TEA (Spence y Schneider, 2009; Sundelin *et al.*, 2016). Se ha entendido generalmente que la sintomatología del TEA contribuye específicamente a un mayor riesgo de epilepsia. Como resultado de esta comprensión, ha habido y sigue habiendo un considerable trabajo en el área de la biomedicina, particularmente en genética, para comprender cómo se relacionan la epilepsia y el TEA, con la esperanza de avanzar en la comprensión de estos mecanismos con el fin de diseñar intervenciones más específicas y efectivas en la población que presenta esta comorbilidad (Frye *et al.*, 2013; Frye *et al.*, 2016).

Desde que Kanner describió por primera vez a un paciente con TEA y epilepsia (Kanner, 1943), muchos autores han argumentado que existe una fuerte asociación entre el autismo y la epilepsia (Frye *et al.*, 2011; Hughes y Melyn, 2005; Kang & Barnes, 2013). Aunque existe consenso sobre la alta tasa de comorbilidad entre el TEA y la epilepsia, la estimación de la prevalencia e incidencia de la epilepsia en pacientes con TEA varía de entre un 29% y un 33% según diferentes estudios (Lee *et al.*, 2015). En la práctica clínica, los episodios de epilepsia son un punto de evaluación y diagnóstico frecuente en pacientes con TEA. Sin embargo, el diagnóstico de epilepsia en pacientes con TEA es complejo debido a las limitaciones en las preguntas utilizadas en las entrevistas clínicas, las dificultades para realizar registros EEG en esta población y la alta frecuencia de anomalías en los EEG (Vasa *et al.*, 2016).

De hecho, los EEG suelen ser anormales en la población con TEA, lo que conduce a un razonamiento clínico complejo, ya que la detección de estas anomalías se suele camuflar con las dificultades propias de este trastorno, retrasando el diagnóstico de epilepsia en este colectivo (Kang y Barnes, 2013). Además, los pacientes con TEA tienen un mayor riesgo de desarrollar epilepsia en comparación con la población general, y con frecuencia se someten a registros EEG.

En la mayoría de los casos, se encuentran anomalías epileptiformes sin convulsiones (Frye *et al.*, 2016). En algunos análisis, las anomalías en el EEG se han correlacionado con características clínicas, como la regresión o el riesgo de ocurrencia de convulsiones (Chez *et al.*, 2006). En otros estudios, estas anomalías no parecen estar correlacionadas con ningún evento clínico relevante (Sansa *et al.*, 2011).

La epilepsia es una comorbilidad común en niños con TEA, con una prevalencia del 32% (Clarke *et al.*, 2005). Esta prevalencia es mucho más alta que en niños con desarrollo típico, en quienes la epilepsia se informa en aproximadamente 3.2 a 5.1 por cada 1000 (Camfield y Camfield, 2015). El 60% de los niños con TEA muestran una actividad epileptiforme anormal en su EEG; sin embargo, no se encontrarían convulsiones clínicas significativas (Chez *et al.*, 2006). Se ha observado que el porcentaje de niños con epilepsia resistente a fármacos y TEA es del 33.9% (Sansa *et al.*, 2011). Una revisión retrospectiva de los TEA en candidatos a cirugía de epilepsia infantil informó que, en 19 niños con TEA, los niños con regresión autista e inicio muy temprano de la epilepsia, aquellos con lesiones de origen embrionario y/o lesiones en el lóbulo temporal derecho deberían ser referidos para considerar el tratamiento quirúrgico de la epilepsia (Taylor *et al.*, 1999).

Al igual que en niños sin TEA, las opciones quirúrgicas disponibles para niños con farmacorresistencia incluyen cirugía resectiva (ya sea con o sin una lesión demostrada en neuroimagen), callosotomía del cuerpo calloso o colocación de un estimulador del nervio vago (ENV). Los niños con epilepsia refractaria que son candidatos para la cirugía de epilepsia resectiva pueden tener excelentes resultados. Se han informado resultados sin convulsiones en hasta el 70% de los sujetos con epilepsia lesional y el 45% de los sujetos con epilepsia no lesional (Téllez-Zenteno *et al.*, 2010; Teutonico *et al.*, 2013). Los niños con epilepsia que no responden al tratamiento y que no son candidatos adecuados para resección pueden experimentar hasta un 50% de reducción de las convulsiones con un ENV (Elliott *et al.*, 2011). En una revisión sistemática de pacientes pediátricos que se sometieron a callosotomía del cuerpo calloso, el 88% reportó convulsiones atónicas raras o nulas después de una callosotomía completa, y otro informe que tenía un período de seguimiento más largo mostró que el 65% estaba libre o casi libres de convulsiones atónicas (Graham *et al.*, 2016).

1.3.1. Perfil cognitivo-lingüístico

El perfil cognitivo de la persona con TEA y epilepsia se caracteriza por alteraciones severas en su funcionamiento y en la mayoría de los procesos relacionados con la cognición y el funcionamiento ejecutivo. La discapacidad intelectual (DI) está presente en aproximadamente el 38% de los niños con TEA (Baio, 2018). Las personas con DI tienen un mayor riesgo de epilepsia (McGrother *et al.*, 2006), además del TEA. La DI es independientemente un factor de riesgo para la epilepsia; este es aproximadamente 10 veces mayor en individuos con DI (Brown, 2008), con un rango de estimaciones que se superponen al rango de prevalencia de epilepsia en TEA. Entre el 20% al 30% de los niños con epilepsia tienen DI (Besag, 2002). El estudio de mayor envergadura sobre epilepsia y TEA hasta la fecha es el de Viscidi *et al.* (2013), en el que participaron un total de 5,815 participantes y concluyó que el CI y la edad fueron los únicos predictores dentro de sus cohortes de TEA que moderaron el riesgo de epilepsia. Aunque Viscidi *et al.* (2013) no examinaron una cohorte no TEA y, por lo tanto, no pudieron desambiguar el papel independiente del CI versus la interacción TEA-CI, este hallazgo cuestiona si existe una asociación única entre TEA y epilepsia, o si el aumento del riesgo de epilepsia en TEA se debe únicamente al aumento del riesgo de DI en TEA. De hecho, la presencia de un aumento del riesgo de TEA de epilepsia dentro de muestras de niños que no tienen TEA con DI concomitante parecería argumentar en contra de que el riesgo de epilepsia en TEA sea exclusivamente moderado por DI (Amiet *et al.*, 2008).

La gravedad del TEA también puede caracterizarse por la magnitud de los síntomas diagnósticos principales: síntomas sociales-comunicativos y comportamientos restringidos/repetitivos específicos del TEA y no de otros diagnósticos del desarrollo (APA, 2022). Además de los déficits de comunicación específicos del TEA, algunos niños con TEA también muestran limitaciones en aspectos más básicos del lenguaje. Los déficits en estas capacidades de lenguaje basal sugieren que el rendimiento del lenguaje en TEA puede explicar su relación con la epilepsia (Tuchman y Rapin, 2002).

En la práctica, existen limitaciones para separar los síntomas de los diagnósticos: los déficits del lenguaje proposicional pueden ser una consecuencia de la DI; los déficits de comunicación específicos del TEA se pueden ver

incrementados por la aparición de la epilepsia (Bishop, 2010; Williams *et al.*, 2008); incluso dando lugar a déficits y síndromes específicos y propios de la epilepsia. Por ejemplo, el Síndrome de Landau-Kleffner (SLK) involucra de manera similar la regresión de habilidades de desarrollo seguida por la presencia de un fenotipo social-comunicativo similar al TEA, aunque en el SLK, la regresión ocurre más comúnmente alrededor de los 5 años de edad, en su mayoría, pero no todos los niños afectados también tienen convulsiones (Shao & Stafstrom, 2016). El SLK se caracteriza por la aparición de descargas epilépticas en todo el EEG con privación de sueño que se entiende que afectan el procesamiento cognitivo mientras está despierto. Lo más importante es que el SLK es potencialmente tratable (van den Munckhof *et al.*, 2018), y el fenotipo social-comunicativo característico del TEA puede ser intervenido con un tratamiento interdisciplinar con una amplia tasa de éxito.

En contraste, el mecanismo por el cual ocurre la regresión del desarrollo en el TEA es desconocido, y generalmente no hay una terapia molecular (análoga a los medicamentos antiepilépticos en el SLK) que sea tan impactante para los síntomas principales del TEA idiopático. La relación entre la regresión y la epilepsia en el TEA ha sido de interés durante mucho tiempo debido a la esperanza de que alguna regresión del desarrollo en el TEA idiopático, incluso en casos fuera del espectro del SLK, ya que este podría ser causado por la epilepsia y, en consecuencia, ser tratado mediante terapias farmacológicas antiepilépticas (Leyfer *et al.*, 2008).

1.4. LA EVALUACIÓN DE LA POBLACIÓN INFANTIL CON TEA Y EPILEPSIA

1.4.1. Evaluación del Trastorno del Espectro Autista

En la actualidad, existen numerosos protocolos de diagnóstico y evaluación del TEA. Todo ello es debido al aumento de la prevalencia de este trastorno y la necesidad de desarrollar tratamientos eficaces que aborden las necesidades de la población infantil con esta condición. En la Tabla 3, se recogen los principales instrumentos de evaluación del TEA.

Tabla 3. Instrumentos de evaluación y diagnóstico del TEA

Prueba	Descripción
<i>ADI-R. Entrevista Diagnóstica del Autismo-Revisada (Lord et al., 1999)</i>	Una entrevista semiestructurada para padres y cuidadores diseñada para evaluar el desarrollo y el comportamiento de los individuos con TEA. Se centra en áreas como la comunicación, la socialización, los intereses y el comportamiento estereotipado. Es útil para el diagnóstico diferencial y la evaluación del nivel de funcionamiento.
<i>CARS. Escala de Evaluación del Autismo en Niños (Schopler et al., 1988)</i>	Una escala utilizada para evaluar la gravedad del autismo en niños, adolescentes y adultos. Se basa en observaciones clínicas y proporciona una puntuación global que indica la gravedad del TEA. Es útil para el diagnóstico inicial y el seguimiento del progreso durante el tratamiento.
<i>M-CHAT. Cuestionario de detección del autismo en niños pequeños (Robins et al., 2009)</i>	Un cuestionario breve de 23 ítems para padres y cuidadores diseñado para identificar signos tempranos de TEA en niños pequeños. Es una herramienta de detección rápida y fácil de usar que puede ayudar a identificar a los niños que pueden necesitar una evaluación más completa para el diagnóstico de TEA.
<i>Vineland-II. Escala de Valoración del Comportamiento de Vineland-II (Sparrow et al., 2016)</i>	Una entrevista estructurada o un cuestionario utilizado para evaluar la conducta adaptativa en individuos con TEA y otros trastornos del desarrollo. Se centra en áreas como la comunicación, la vida diaria, las habilidades sociales y la autonomía personal. Proporciona una medida integral del funcionamiento adaptativo y puede ayudar en la planificación del tratamiento y la intervención.
<i>SCQ. Cuestionario de Comunicación Social (Rutter et al., 2003)</i>	Un cuestionario diseñado para evaluar los comportamientos asociados con el TEA, como dificultades en la comunicación social, comportamientos estereotipados y restricciones en los intereses. Es una herramienta de detección útil para identificar posibles casos de TEA y determinar si se necesita una evaluación más exhaustiva.
<i>GARS - 2. Escala de Clasificación del Autismo de Gilliam (Gilliam, 2006)</i>	Una escala diseñada para evaluar el comportamiento autista en niños y adolescentes. Se basa en la observación del comportamiento en diferentes situaciones y proporciona una puntuación global de la gravedad de los

	síntomas del TEA. Es útil para el diagnóstico diferencial y para evaluar el progreso en el tratamiento del TEA.
<i>ADOS-2. Escala de Observación del Autismo (Lord et al., 2012)</i>	Una entrevista semiestructurada y una serie de actividades diseñadas para evaluar el comportamiento social y comunicativo en individuos con TEA. Se utiliza principalmente para diagnosticar el TEA y diferenciarlo de otros trastornos del desarrollo.
<i>SRS. Escala de Respuesta Social (Constantino y Gruber, 2012).</i>	Un cuestionario diseñado para evaluar las habilidades sociales y el comportamiento asociado con el TEA. Los padres, maestros o cuidadores completan el cuestionario, que aborda áreas como la comunicación social, el comportamiento estereotipado y las dificultades en las interacciones sociales. Proporciona una medida cuantitativa de la gravedad de los síntomas del TEA y es útil para el diagnóstico y la evaluación del tratamiento.

Los profesionales sanitarios de atención primaria tienen la tarea de identificar a todos los niños que se beneficiarían de una intervención temprana, no solo a los niños en riesgo de TEA (Guthrie *et al.*, 2013). Es importante identificar todas las alteraciones clínicamente significativas en la población pediátrica y derivarlos para una evaluación diagnóstica e intervención adecuadas. Sin embargo, el TEA cobra una importancia destacada en los últimos años, debido a la complejidad de su diagnóstico y al cambio de los criterios recogidos en el DSM-5 TR (APA, 2022), lo que provoca la necesidad de que los profesionales sanitarios tengan una amplia experiencia y formación en la evaluación de este colectivo vulnerable, haciendo hincapié en el desarrollo madurativo y en las disfunciones que comúnmente se describen en el TEA. No obstante, aún con la preparación que debe presentar el profesional que realiza la evaluación, existen ciertos inconvenientes en el uso de los protocolos de evaluación anteriormente mencionados (Duvall *et al.*, 2022).

Una revisión sistemática concluyó que las herramientas de detección existentes no demostraban una especificidad suficiente para justificar la detección universal del TEA (Kamp-Becker *et al.*, 2020). Los autores señalaron que ningún estudio ha examinado directamente si los niños con TEA detectados mediante detección temprana tienen mejores resultados que aquellos detectados por otros

medios. Sin embargo, dicho estudio requeriría la asignación aleatoria de grandes muestras representativas a nivel internacional, con seguimiento de resultados a largo plazo. Asimismo, se concluyó que se necesita más investigación para evaluar las edades y poblaciones apropiadas de niños con TEA y que se deberían desarrollar medidas más precisas y culturalmente sensibles. Se recomienda, por tanto, la creación de protocolos estandarizados a nivel universal con el fin de llevar a cabo una detección independientemente del lugar o localidad de procedencia del menor con sospecha de TEA, aunque esta labor es altamente compleja (Randall *et al.*, 2016).

La estabilidad diagnóstica suele ser alta en niños que son diagnosticados de TEA en edades comprendidas entre los 18 y 36 meses de edad (van Niekirk *et al.*, 2011). La detección temprana no identifica a muchos niños con síntomas más leves y habilidades cognitivas típicas en riesgo de TEA; por lo tanto, la evaluación continua y prolongada sigue siendo necesaria. En la actualidad, para niños mayores de 48 meses, hay pocas herramientas de detección validadas y disponibles para su uso en la práctica pediátrica, así como recomendaciones actualizadas por parte de la literatura científica para la detección de TEA en ese grupo de edad (Ahlers *et al.*, 2019).

Los niños con síntomas más leves y/o inteligencia promedio o superior pueden no ser identificados con un cuadro semiológico propio del TEA hasta la edad escolar, cuando las diferencias en el lenguaje social o las rigideces personales afectan la función (Wieckowski *et al.*, 2021). Prueba de ello es que muchos niños presentan alteraciones en las habilidades relativas al lenguaje, la lectura o las matemáticas y, no es hasta que las demandas sociales de la escuela son superiores a sus capacidades, que los síntomas relacionados con la comunicación social se manifiestan (Millikovsky-Ayalon *et al.*, 2012).

Por último, la evaluación y diagnóstico del TEA representan un proceso complejo y multifacético que requiere una comprensión profunda de las características individuales de cada persona. Aunque existen varias herramientas de evaluación disponibles, la naturaleza heterogénea del TEA puede presentar dificultades y limitaciones para su diagnóstico preciso. Una de las principales dificultades radica en la variabilidad de los síntomas y su manifestación en contextos diferentes (Xu *et al.*, 2024). Esto puede hacer que la evaluación sea desafiante, ya que los síntomas pueden ser sutiles o estar enmascarados por otros

factores, lo que dificulta la identificación del TEA en algunas personas. Por esto, la evaluación interdisciplinaria emerge como una estrategia crucial para abordar estas dificultades (Frenette *et al.*, 2013). La colaboración entre profesionales de diferentes disciplinas, como psicólogos, psiquiatras, terapeutas del habla y ocupacionales, permite una evaluación más completa y holística de las necesidades de la persona con TEA. Esta aproximación integral ayuda a identificar no solo los déficits, sino también las fortalezas y habilidades únicas de cada individuo (Daniels *et al.*, 2011).

La participación de la familia también desempeña un papel fundamental en el proceso de evaluación y diagnóstico. Los padres y cuidadores poseen una perspectiva invaluable sobre el comportamiento y el desarrollo de su hijo, lo que puede enriquecer la evaluación clínica (Karst y Van Hecke, 2012). Además, el apoyo y la colaboración de la familia son esenciales para el diseño y la implementación de intervenciones efectivas (Losada-Puente *et al.*, 2022). En el contexto actual, es crucial reconocer los avances en la comprensión y evaluación del TEA, así como las áreas que requieren mayor investigación y desarrollo (Cohen *et al.*, 2023). La detección temprana y la intervención precoz continúan siendo prioridades, y se han desarrollado herramientas de detección más sensibles para identificar signos de TEA en etapas tempranas de la infancia (Bonis, 2016). Además, se están explorando nuevas tecnologías y enfoques innovadores para mejorar la precisión y eficacia de la evaluación y diagnóstico del TEA.

Por tanto, la evaluación diagnóstica del TEA es un proceso integral que implica la recopilación de información de múltiples fuentes, incluidas las observaciones clínicas, los informes de los cuidadores y maestros, y las pruebas estandarizadas de desarrollo cognitivo, lenguaje, habilidades adaptativas y funcionamiento social y emocional. La evaluación también puede implicar pruebas adicionales, como pruebas genéticas o metabólicas, para descartar otras condiciones médicas que pueden imitar el TEA. Un diagnóstico preciso es fundamental para guiar el tratamiento y la intervención temprana para niños con TEA.

1.4.2. Evaluación de la epilepsia

El diagnóstico de la epilepsia en edades tempranas presenta múltiples complejidades, entre los que se encuentran la variabilidad en la presentación clínica y la dificultad para distinguir las convulsiones de otros eventos paroxísticos comunes en la infancia. Esta situación se ve agravada por la falta de recursos especializados en muchos entornos clínicos, lo que dificulta aún más la evaluación adecuada de los niños con sospecha de epilepsia. Además, la incapacidad para comunicarse verbalmente en los pacientes más jóvenes puede dificultar la identificación de los síntomas y la obtención de una historia clínica detallada, lo que a su vez complica el proceso diagnóstico.

En este contexto, la importancia de la tecnología de imagenología se vuelve cada vez más relevante. Las técnicas de neuroimagen en la epilepsia cumplen diferentes propósitos como el diagnóstico de la tipología, la localización y la extensión del foco epiléptico. En emergencias, la neuroimagen temprana es crucial cuando una convulsión puede ocurrir como una manifestación secundaria acompañante, por ejemplo, de déficits neurológicos focales, alteraciones cognitivas, dolor de cabeza o fiebre (Beghi *et al.*, 2015). Los episodios epilépticos también pueden ocurrir como primera manifestación de tumores intracraneales, orientando al paciente hacia un camino diagnóstico y tratamiento oncológico en lugar de predominantemente epileptológico (Nascimento *et al.*, 2023). La neuroimagen se realiza en la etapa temprana de la evaluación diagnóstica de la epilepsia para establecer un diagnóstico sindrómico y determinar la etiología subyacente de la epilepsia. Sin embargo, en general, la imagen revela una lesión epileptogénica en solo alrededor del 20% de los pacientes con epilepsia de inicio reciente (Guerreiro, 2016).

En pacientes con epilepsia de inicio focal, este porcentaje alcanza aproximadamente el 50%, pero depende del nivel de sofisticación tecnológica y de la técnica de neuroimagen empleada (Zupanc, 2009). En general, los pacientes con epilepsia sin una lesión identificable en la resonancia magnética (es decir, con causas distintas a las lesiones estructurales) tienen un mejor pronóstico para el control de las convulsiones con medicamentos anticonvulsivos (Rowan, 1983). En pacientes con epilepsias focales farmacorresistentes, la neuroimagen estructural juega un papel esencial en la planificación de grabaciones invasivas y cirugía de

epilepsia. La presencia de una lesión epileptogénica es un predictor significativo de una cirugía de epilepsia exitosa, aunque la lesionectomía completa de la lesión estructural por sí sola no siempre es suficiente para lograr la libertad de convulsiones a largo plazo (Peter y Camfield, 2013). Por el contrario, los pacientes no lesionales representan un subgrupo especialmente desafiante con resultados de convulsiones postquirúrgicas comparativamente limitados (Eschbach *et al.*, 2018).

El Grupo de Trabajo de Neuroimagen de ILAE ha recomendado recientemente el *protocolo de resonancia magnética HARNESS* (Secuencias Estructurales de Neuroimagen Armonizadas para Epilepsia, según sus siglas en inglés), que permite la detección de la gama completa de lesiones epileptogénicas, mientras limita el tiempo de escaneo requerido (Kishk *et al.*, 2023). Este protocolo incluye tres secuencias obligatorias y dos opcionales. HARNESS aprovecha las ventajas de la adquisición de resonancia magnética (MRI) 3D isotrópica sin brecha entre cortes para permitir el rebanado flexible. Se sugiere una alta resolución de 1 mm o mejor para reducir los efectos de volumen parcial. Para la inspección del hipocampo, se sugiere una serie 2D T2 ponderada angulada perpendicularmente al eje largo del hipocampo con una resolución intra-rebanada aumentada (Larivière *et al.*, 2021). Dos series opcionales proporcionan sensibilidad adicional en casos específicos: T1 3D con gadolinio mejorado para evaluar tumores, malformaciones vasculares y procesos infecciosos, y SWI/T2 ponderada con susceptibilidad, que es sensible a depósitos de hierro, productos sanguíneos y calcificaciones.

El protocolo se recomienda para campos magnéticos de 3 T, sin embargo, las secuencias también se pueden obtener con 1,5 T. Incluso cuando se adquiere con un protocolo HARNESS óptimo, la interpretación de la MRI debe considerar el contexto de los hallazgos del EEG, la semiología y otra información clínica. La experiencia del examinador también es fundamental, y una resonancia magnética informada como normal podría albergar realmente una anomalía estructural sutil no identificada inicialmente por el intérprete, en particular las displasias corticales focales (Abdelsamad *et al.*, 2023). La inspección visual de resonancias magnéticas 3D almacenadas digitalmente (generalmente en formato DICOM), adquiridas con el tamaño de vóxel isotrópico más pequeño posible, debe realizarse utilizando una plataforma que permita el reformateo multiaxial. Hay varias opciones de visualizadores DICOM fáciles de usar que se ejecutan en la mayoría de las

computadoras de escritorio y pueden incorporarse a la rutina de los neurólogos especialistas en epilepsia (Lapalme-Remis y Nguyen, 2022).

En pacientes con lesiones sutiles, el análisis visual de la resonancia magnética puede no ser suficiente. Las técnicas de procesamiento posterior pueden ofrecer soluciones al analizar computacionalmente características morfológicas de la resonancia magnética, como la profundidad de las cisuras, el contraste de la unión gris-blanca, los volúmenes y el grosor cortical, entre otros. Una comparación con controles sanos proporciona métricas objetivas de alteraciones estructurales que potencialmente brindan evidencia de una lesión sutil (Bernasconi *et al.*, 2019). El uso de enfoques de inteligencia artificial en paralelo con los análisis visuales puede mejorar aún más la detección de epilepsias focales muy sutiles en resonancias magnéticas previamente negativas (Decker *et al.*, 2021). A continuación, en la Tabla 4, se describen los diferentes métodos más empleados para el diagnóstico de la epilepsia.

Tabla 4. Tipos de pruebas de neuroimagen para el diagnóstico de la epilepsia

Tipo de Evaluación	Descripción
<i>Neuroimagen Estructural</i>	La resonancia magnética (MRI) y la tomografía computarizada (CT) son técnicas utilizadas para evaluar la estructura cerebral en pacientes con epilepsia. Se recomienda la MRI en pacientes con epilepsia focal debido a su mejor diferenciación de tejidos cerebrales. En situaciones especiales, la CT puede ser útil. El procesamiento posterior de MRI y el análisis computacional pueden detectar características morfológicas sutiles.
<i>PET y SPECT</i>	El PET y el SPECT, utilizados principalmente en evaluaciones presquirúrgicas, proporcionan información adicional sobre la localización de la actividad metabólica y el flujo sanguíneo cerebral, respectivamente. El PET interictal puede revelar un metabolismo glucídico disminuido, mientras que el SPECT puede localizar la zona de inicio de la convulsión durante un episodio. La sustracción SPECT interictal-ictal co-registrada con MRI (SISCOM) mejora la especificidad.

<i>Imagen Funcional</i>	La resonancia magnética funcional (fMRI) y la magnetoencefalografía (MEG) ofrecen información sobre la actividad cerebral relacionada con funciones específicas, como el lenguaje y el movimiento. Ayudan a evaluar la viabilidad de la terapia quirúrgica y la planificación de la resección al considerar la reorganización funcional y la distribución de la corteza cerebral. La imagen multimodal funcional mejora la detección de lesiones sutiles.
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Una vez que se considera un diagnóstico de epilepsia focal, el EEG puede usarse para confirmar o refutar sospechas clínicas y, en algunos casos, establecer un diagnóstico neurológico: un diagnóstico clínico respaldado por EEG. Sin embargo, varios factores limitan el uso del EEG como prueba auxiliar en el diagnóstico de la epilepsia focal (Fernandez-Baca Vaca y Park, 2020).

En primer lugar, el EEG es una señal biológica de baja amplitud, continua y dinámica que requiere considerable experiencia para su interpretación. La señal de EEG registrada en el cuero cabelludo refleja los potenciales sumados generados en un área relativamente grande (≥ 6 -10 cm²) de la corteza en la convexidad cerebral y, por lo tanto, representa solo una pequeña porción de la actividad cerebral de interés clínico. Múltiples fuentes no cerebrales reducen aún más la relación señal-ruido (SNR). Este bajo SNR es en parte responsable de la alta variabilidad entre observadores (Gooley *et al.*, 2022). Además, existe el riesgo de interpretar en exceso o en defecto los hallazgos del EEG. El primero constituye la interpretación errónea de variantes normales, artefactos u otros transitorios clínicamente irrelevantes como epileptiformes. El segundo constituye el descartar una anomalía epileptiforme sutil pero verdadera. Incluso los lectores experimentados de EEG pueden tener un estilo de práctica de interpretación con "alta sensibilidad" o con "alta especificidad" (Sánchez Fernández y Loddenkemper, 2012). Se ha recomendado una lectura de EEG "conservadora" para lograr una alta especificidad y evitar la sobrelectura con el consiguiente error de diagnóstico de epilepsia (Goldberg *et al.*, 2022).

En segundo lugar, las anomalías epileptiformes pueden ocurrir en el EEG de hasta el 4% de los niños en edad escolar en ausencia de epilepsia, es decir, en promedio, 1 niño en cada salón de clases de 30 niños si todos se sometieran a un

EEG sin indicación. En la práctica clínica, por lo tanto, el rendimiento diagnóstico de un EEG depende de la probabilidad previa (Andrade-Machado *et al.*, 2021). En este sentido, la evidencia y la información se presentan de manera secuencial, no todas a la vez. Por ejemplo, un niño neurológicamente sano con un episodio de ausencia breve y un EEG con una descarga epileptiforme focal puede seguir sin tener epilepsia (Janković *et al.*, 2021). Sin embargo, el mismo EEG podría apoyar el diagnóstico de epilepsia cuando la probabilidad previa es mayor: ocurre un nuevo evento o un testigo proporciona una historia más detallada en el mismo paciente. El EEG tiene limitaciones importantes y los resultados deben interpretarse dentro del contexto clínico apropiado del paciente (von Ellenrieder *et al.*, 2022).

El rendimiento diagnóstico del EEG puede mejorarse de varias maneras. Si el primer EEG de rutina es normal, considere obtener un EEG de rutina repetido que capture el sueño y, idealmente, se grabe después de la privación de sueño. El EEG ambulatorio es una buena herramienta para capturar "episodios" importantes, pero puede no revelar eventos breves y sutiles (Morales-Chacon *et al.*, 2015). Además, la calidad de las grabaciones de EEG ambulatorio puede deteriorarse con el tiempo, lo que puede evitar la evaluación de los hallazgos interictales. Los niños, los pacientes no cooperativos y las grabaciones prolongadas pueden ser susceptibles al artefacto, lo que oscurece la interpretación significativa. La monitorización de video-EEG de larga duración en una unidad dedicada de monitorización de epilepsia es el estándar de oro para diagnosticar, clasificar, cuantificar y caracterizar a los pacientes referidos por convulsiones no controladas cuando se captura el evento de interés. La evaluación prolongada de alta calidad tanto del fondo como de los patrones interictales proporciona información de apoyo junto con el EEG ictal (Cerminara *et al.*, 2013).

El EEG interictal también tiene un papel importante en el diagnóstico de la epilepsia (Andrade, 2013). Cuando las convulsiones son altamente sospechosas desde un punto de vista clínico, el diagnóstico de epilepsia es clínico y puede realizarse independientemente de la presencia o ausencia de un EEG epileptiforme. En estos casos, sin embargo, el EEG puede ser útil para clasificar la epilepsia, focal, generalizada, o combinada generalizada y focal, o desconocida, con las respectivas implicaciones de tratamiento (Jefferys *et al.*, 1995). Si los episodios tienen una sospecha clínica moderada de convulsiones epilépticas, la presencia de

anormalidades epileptiformes interictales en EEG establece el diagnóstico de epilepsia.

1.5. LA INTERVENCIÓN DE LA POBLACIÓN INFANTIL CON TEA Y EPILEPSIA

1.5.1. Intervención farmacológica

El tratamiento farmacológico en las personas con TEA y epilepsia se establece como un pilar fundamental en el pronóstico del trastorno, y su combinación con la intervención cognitivo-conductual conforman el tratamiento idóneo que permite aumentar la eficacia de la intervención y la calidad de vida de la persona y de su entorno (O'Dwyer *et al.*, 2023).

Los tratamientos de primera línea para el control de las alteraciones conductuales en la persona diagnosticada de TEA y epilepsia se corresponden con dos fármacos: la risperidona y el aripiprazol (Manford, 2017). Estos fármacos, que tienen efectos antagonistas dopaminérgicos y serotoninérgicos, están actualmente aprobados por la Agencia Española de Medicamentos y Productos Sanitarios de España para la irritabilidad y la agresión en pacientes con esta comorbilidad. Aunque su eficacia está respaldada por varios metaanálisis de ensayos clínicos aleatorizados, los medicamentos tienen efectos adversos que incluyen hiperglucemia, dislipidemia y aumento de peso (Ali, 2018; Auvin, 2019; Guerrini *et al.*, 2021).

Por ejemplo, en un metaanálisis (Hon *et al.*, 2018) de 4 ensayos clínicos que incluyeron a 97 participantes con TEA, en comparación con el placebo, el metilfenidato tuvo un tamaño de efecto de 0,6 (IC del 95%, 0,2-1,0) para los síntomas de hiperactividad, y en un metaanálisis de 4 ensayos clínicos que incluyeron a 204 personas con TEA, en comparación con el placebo, la atomoxetina tuvo un tamaño de efecto de 0.5 (IC del 95%, 0,2-0,8) para los síntomas de hiperactividad. En otro ensayo clínico aleatorizado de 62 personas con TEA (Sultana *et al.*, 2021), en comparación con el grupo placebo, la guanfacina de liberación prolongada tuvo un tamaño de efecto de 1.2 (IC del 95%, 0,7-1,8) para los síntomas totales de agresividad e hiperactividad. Sin embargo, las personas con

TEA y epilepsia tienen más probabilidades de experimentar activación conductual, que consiste en inquietud y desinhibición, con psicoestimulantes en comparación con individuos sin epilepsia.

Para los trastornos del sueño, el fármaco por excelencia en estas condiciones es la melatonina. En un ensayo clínico (Cortese *et al.*, 2020) aleatorizado de 125 niños y adolescentes en el que el 97% de los participantes tenía TEA, la melatonina de liberación prolongada, en comparación con el placebo, aumentó la duración del sueño en 32 minutos ($P = .03$; tamaño del efecto, 0.4) y redujo la latencia del inicio del sueño en 25 minutos ($P = .01$; tamaño del efecto, 0.5).

Por último, para los comportamientos obsesivos-compulsivos, los Inhibidores Selectivos de la Recaptación de Serotonina (ISRS) como la fluoxetina, puede ayudar a mejorar la sintomatología característica de esta condición (Kim *et al.*, 2023). No obstante, los estudios actuales que han medido su efecto en personas con TEA sin epilepsia no son esperanzadores, ya que indican que no se encontraron mejorías significativas en comparación con el grupo control. De manera similar, en un metaanálisis (Yang *et al.*, 2021) de 7 ensayos clínicos aleatorizados que incluyeron a 519 personas, los ISRS en general no estuvieron asociados con una reducción de los comportamientos restrictivos y repetitivos en el TEA.

Debido a la falta de farmacoterapias efectivas para el TEA, las familias a menudo están interesadas en enfoques complementarios y alternativos. Algunos suplementos, como la N-acetilcisteína y el sulforafano, han sido estudiados en ensayos clínicos aleatorizados y han demostrado eficacia para los síntomas emocionales y conductuales (James *et al.*, 2020). Sin embargo, la evidencia actual no respalda ningún suplemento para los síntomas del TEA, relacionada con el retraso en el lenguaje, la pobre interacción social o los comportamientos restringidos o repetitivos. En un ensayo clínico (Hollocks *et al.*, 2019) aleatorizado de 150 niños y adolescentes con TEA, que comparó el uso del cannabidiol con tetrahidrocannabinol administrado en una proporción de 20:1 (extracto de cannabis de planta entera), cannabinoides purificados que contienen cannabidiol y tetrahidrocannabinol administrados en una proporción de 1:1 (cannabinoides puros) y placebo, se observó que no hubo cambios significativos a nivel conductual en los participantes de los 3 grupos. Actualmente, no se encuentran estudios relacionados con el tratamiento farmacológico realizados en población pediátrica con TEA y epilepsia de forma comórbida, por lo que no se puede inferir que este tipo de

medicación tendría un efecto similar al encontrado en los estudios configurados con menores con diagnóstico de TEA, siendo necesaria una mayor evidencia empírica y publicaciones que aborden esta comorbilidad.

1.5.2. Intervención cognitivo-conductual

La intervención temprana basada en el análisis de la conducta ha estado principalmente dirigida a niños con edades comprendidas entre los 3 y los 6 años, pero puede aplicarse a personas de todas las edades para ayudarles a adquirir habilidades específicas y enfrentar dificultades a lo largo de la vida (Han *et al.*, 2022). Estos principios buscan generar un cambio en el comportamiento a través de la comprensión y la manipulación de condiciones ambientales predisponentes o eventos que refuercen comportamientos específicos una vez que hayan ocurrido. En general, las terapias muestran mayor efectividad en la mejora de síntomas asociados con el TEA, como el uso efectivo del lenguaje, en comparación con características del TEA como el deterioro en la comunicación social y los patrones repetitivos y restringidos de comportamiento (Dawson *et al.*, 2010). Las intervenciones conductuales del desarrollo naturalístico implican la aplicación de principios de aprendizaje analítico del comportamiento con un enfoque en enseñar habilidades apropiadas para el desarrollo en entornos naturales, como el juego y las actividades rutinarias. Estas intervenciones han demostrado mejorar el lenguaje, el juego y la comunicación social de los niños en un metaanálisis que incluyó 16, 7 y 17 ensayos clínicos aleatorizados, con tamaños de efecto de 0.2 (IC del 95%, 0.1-0.4), 0.3 (IC del 95%, 0.1-0.5) y 0.4 (IC del 95%, 0.2-0.6), respectivamente. Se recomienda al menos 25 horas por semana de estas intervenciones para obtener resultados óptimos en el desarrollo (Lukito *et al.*, 2020).

La intervención mediada por padres, que incluye terapia de atención conjunta, terapia de comunicación social y terapia conductual, impartida por padres capacitados y entrenados por profesionales de la salud (Rumball *et al.*, 2021). En un metaanálisis, estas intervenciones dirigidas por padres mostraron una mejoría significativa, aunque relativamente modesta, en la gravedad de los síntomas del TEA y de la epilepsia, así como en la socialización y la cognición (Koshiba *et al.*, 2016).

Los niños en edad escolar diagnosticados con TEA y epilepsia generalmente tienen acceso a terapias conductuales, del habla, ocupacionales y físicas en el entorno escolar. La inclusión de estos niños en aulas de educación general se realiza con estrategias de apoyo visual para fomentar comportamientos adaptativos (Yu *et al.*, 2024). Un programa educativo bien establecido para este fin es el Tratamiento y Educación de Niños Autistas y con Trastornos de la Comunicación Relacionados (Saban-Bezalel *et al.*, 2022), caracterizado por rutinas de trabajo altamente estructuradas y la presentación visual de información para facilitar la consecución de objetivos de aprendizaje. Estos objetivos se establecen a partir de horarios individualizados que se adaptan a las características de aprendizaje, habilidades y fortalezas de cada individuo.

La ansiedad y la depresión suelen estar presentes en el TEA y la epilepsia, con un 20% y 14% respectivamente. La terapia cognitivo-conductual (TCC) es la primera opción de tratamiento para estas condiciones en individuos con TEA. Sin embargo, hay pocos ensayos clínicos aleatorizados que hayan investigado la eficacia de la TCC para tratar la depresión en personas con TEA (Rosello *et al.*, 2023). En niños con TEA y epilepsia, especialmente aquellos sin o con un leve deterioro cognitivo, los déficits sociales y la calidad de las relaciones de amistad tienden a empeorar durante la adolescencia. Por ello, llevar a cabo una intervención en habilidades sociales en grupos para personas con TEA y epilepsia se asocia con mejoras en la competencia social, por lo que se necesitan terapias efectivas para apoyar el éxito en la educación postsecundaria y en el ámbito laboral de las personas con esta comorbilidad (Bradbury *et al.*, 2022).

Las intervenciones conductuales para el TEA y la epilepsia tienen como objetivo aumentar la autonomía y la funcionalidad en las actividades de la vida diaria. Estas intervenciones están estrechamente relacionadas con el Análisis Conductual Aplicado (ABA). El método ABA analiza cómo el entorno influye en el comportamiento y desarrolla intervenciones basadas en estos hallazgos (Leaf *et al.*, 2022). Utilizando el condicionamiento operante, busca evaluar y cambiar el comportamiento desafiante mientras promueve comportamientos adaptativos mediante refuerzos sistemáticos. Mientras que los métodos basados en ABA pueden dirigirse a comportamientos específicos, las intervenciones integrales basadas en ABA comienzan en la infancia temprana (preferiblemente entre los 3 y 4 años), son intensivas (20 a 40 horas por semana), personalizadas para cada niño,

y abordan múltiples habilidades simultáneamente (Choueiri y Zimmerman, 2017). Además, estas intervenciones se realizan de forma individual, gradualmente incorporando actividades grupales y se adaptan a entornos naturales, involucrando activamente a los padres (Yu *et al.*, 2020). Un ejemplo de ello son las Intervenciones Conductuales Intensivas Tempranas (EIBI). Sin embargo, algunas de estas intervenciones, aunque no se las denomine EIBI, también siguen este enfoque, como el enfoque de Conducta Verbal (ABA-VB).

Del mismo modo, otra metodología que tiene una gran relevancia y eficacia probada es la referente al Tratamiento y Educación de Niños Autistas y con Deficiencias Relacionadas con la Comunicación (*Treatment and Education of Autistic and related Communication Handicapped Children*; TEACCH en inglés) TEACCH. Una encuesta multinacional completada por padres de niños con autismo indicó que más del 30% de las familias actualmente utilizan o han utilizado el programa TEACCH (Green *et al.*, 2006). De manera similar, una encuesta epidemiológica realizada en Finlandia indicó que más del 40% de los niños con autismo estaban recibiendo servicios basados en TEACCH (Kielinen *et al.*, 2002). Además, TEACCH se utiliza frecuentemente como un servicio educativo especializado en escuelas (Hess *et al.*, 2008).

El programa TEACCH (a) enfatiza una estrecha relación de trabajo entre padres y profesionales, (b) adapta la intervención a las características particulares del cliente individual, y (c) hace uso de experiencias de enseñanza estructuradas (Van Bourgondien & Schopler, 1996). En una intervención típica de TEACCH, las habilidades de los individuos son evaluadas a través de pruebas estandarizadas (por ejemplo, Perfil Psicoeducativo). Los resultados de la evaluación proporcionarán la base para el desarrollo de un plan de estudios que sea consistente con las necesidades individuales del cliente (Mesibov, 1997). El especialista de TEACCH utilizaría procedimientos de enseñanza estructurados para facilitar la adquisición de los objetivos de aprendizaje que componen el plan de estudios individual del individuo. El componente de enseñanza estructurada requiere que el entorno y las actividades del individuo se organicen de manera que optimicen el aprendizaje y eviten la frustración. Se reporta que tres factores son esenciales en este sentido: (a) organización del entorno físico de una manera que sea consistente con las necesidades del niño (por ejemplo, minimizando posibles distracciones), (b) disposición de las actividades de manera predecible (por

ejemplo, uso de horarios visuales de rutinas diarias), y (c) organización de los materiales y tareas para promover la independencia de las direcciones / indicaciones de los adultos (por ejemplo, uso de materiales visuales si el estudiante se beneficia más de ellos).

Los estudios que se han realizado sobre TEACCH varían en el conjunto de componentes de TEACCH utilizados, la intensidad y duración de la intervención, las características de los participantes (edad, diagnóstico, funcionamiento previo a la intervención), los métodos de evaluación utilizados y el diseño del estudio (pre-post, entre grupos) (Eikeseth, 2009; Ospina *et al.*, 2008; Simpson *et al.*, 2005). Tal variabilidad impide una apreciación directa de la efectividad del tratamiento. Aunque existen síntesis en la literatura, no cumplen con los estándares de una revisión sistemática o un metaanálisis (Probst *et al.*, 2010; Simpson *et al.*, 2005) y no utilizan métodos estándar para extraer y combinar datos (Moher *et al.*, 2009). Este escenario aumenta aún más la complejidad para evaluar la magnitud y calidad de la evidencia empírica asociada con el programa TEACCH. Una apreciación más clara de la evidencia a favor del programa TEACCH podría lograrse a través de un metaanálisis. Solo recientemente, se ha publicado un número suficiente de estudios siguiendo una metodología relativamente consistente para permitir un metaanálisis con suficiente poder. El programa TEACCH es uno de los pocos enfoques no farmacológicos que cumple con este umbral (Virués-Ortega, 2010).

Mientras que las intervenciones conductuales se centran en promover comportamientos adaptativos, otras intervenciones, llamadas Intervenciones Conductuales del Desarrollo Natural (NDBI), aplican métodos conductuales y estrategias basadas en el desarrollo en entornos naturalistas, derivando objetivos de aprendizaje individuales de secuencias de desarrollo (Rogers *et al.*, 2022). Un ejemplo destacado de NDBI es el Modelo de Denver de Inicio Temprano (ESDM), que ha demostrado eficacia en metaanálisis recientes. Aunque las intervenciones integrales basadas en ABA son ampliamente utilizadas en América del Norte, su aplicación en Europa es limitada debido a la percepción de una falta de base de evidencia, en parte debido a limitaciones metodológicas en los estudios publicados hasta el momento. La discusión sobre la ética y la eficacia de estos enfoques también es relevante. A pesar de las críticas, las intervenciones integrales basadas en ABA proporcionan una base teórica sólida (Vibert *et al.*, 2020).

Aunque varios metaanálisis han encontrado que las intervenciones integrales basadas en ABA son más efectivas que la atención estándar para el TEA y la epilepsia (Eckes *et al.*, 2023; Rae y Ramey, 2020), existen problemas metodológicos en estos estudios que afectan la interpretación de los resultados. Los moduladores principales del impacto de estas intervenciones en el desarrollo incluyen el funcionamiento intelectual, las habilidades lingüísticas, el comportamiento adaptativo, la psicopatología inicial, la edad, la intensidad y duración del tratamiento, y la participación de los padres (Kohli *et al.*, 2022). Sin embargo, los hallazgos en este campo siguen siendo inconclusos debido a la heterogeneidad de los resultados y las limitaciones metodológicas en el estudio de la comorbilidad entre el TEA y la epilepsia.

1.5.3. Intervención del lenguaje

La intervención en el lenguaje no verbal para niños pequeños se enfoca principalmente en el período de uno a tres años de edad. Sin embargo, también es relevante para niños mayores con TEA severo que aún no han desarrollado expresión oral (Cui *et al.*, 2023). Durante las etapas iniciales, los niños con autismo muestran similitudes en la expresión del lenguaje con aquellos que tienen retraso en el desarrollo del lenguaje y trastornos del lenguaje, lo cual respalda la predicción de la "hipótesis de consenso multidimensional" (Chan y Leung, 2022). La "hipótesis de consenso multidimensional" postula que, durante las etapas tempranas del desarrollo del lenguaje, los niños con autismo comparten similitudes en su expresión lingüística con aquellos que experimentan retraso en el desarrollo del lenguaje y trastornos específicos del lenguaje. Esta teoría sugiere que las características lingüísticas observadas en niños con TEA, como la ausencia de lenguaje oral o el uso limitado de palabras, pueden reflejar patrones similares a los presentes en otros trastornos del lenguaje (Friedman y Sterling, 2019). En este sentido, la identificación precoz y la intervención adecuada se vuelven cruciales para comprender las necesidades individuales de los niños y proporcionarles el apoyo lingüístico necesario. Asimismo, resalta la importancia de considerar diversos factores, como los contextos sociales, cognitivos y emocionales, en la evaluación del desarrollo del lenguaje en niños con TEA (Hampton y Kaiser, 2016).

Durante el período no verbal del desarrollo, la mayoría de los niños, a medida que crecen, experimentan la ausencia de habla o incluso pueden experimentar la regresión del lenguaje. En esta etapa, los principales objetivos para los niños incluyen establecer una conciencia básica de la comunicación, mejorar su actitud hacia la misma y fomentar la pronunciación (Thomas *et al.*, 2023). En este sentido, es beneficioso recurrir a métodos de evaluación e intervención diseñados para abordar el retraso en el desarrollo del lenguaje. Estas estrategias pueden ayudar a proporcionar el apoyo necesario para facilitar el progreso en la adquisición del lenguaje y la comunicación durante esta etapa crítica del desarrollo infantil (Neuhaus *et al.*, 2022).

La NDBI es una combinación de intervenciones diseñadas para ser implementadas en entornos naturales, aprovechando situaciones cotidianas y utilizando una variedad de estrategias conductuales. Su objetivo es ayudar a los niños con autismo a desarrollar habilidades de supervivencia apropiadas y esenciales (Volkmar *et al.*, 2014). La NDBI se lleva a cabo de manera natural en la vida diaria, aprovechando las interacciones sociales y las actividades cotidianas de los niños, que suelen tener lugar en el entorno familiar. Dado que los principales déficits en los niños con TEA involucran el comportamiento social y la comunicación, los cuidadores tienen numerosas oportunidades para implementar estrategias de NDBI y fomentar el desarrollo de sus hijos en su entorno habitual. Esto no solo promueve el progreso de los niños, sino que también ayuda a mitigar el impacto de posibles interrupciones en el entrenamiento durante un evento de desregulación conductual (Crank *et al.*, 2021).

Los niños con TEA y epilepsia suelen experimentar trastornos del habla, siendo la dispraxia verbal más común que las malformaciones orofaciales. Las intervenciones para estos trastornos se centran principalmente en el entrenamiento de la capacidad de imitación de los niños (Yankowitz *et al.*, 2019). Este proceso puede comenzar con la imitación de movimientos gruesos y progresar hacia movimientos orales y finos, con un enfoque en la expansión desde la imitación de "sonidos" hasta "palabras" y "oraciones cortas", utilizando diversos métodos de aprendizaje. La imitación de la articulación evoluciona de imitaciones silenciosas a la producción de sonidos, iniciando con sílabas fáciles de articular y avanzando gradualmente hacia palabras y oraciones completas (MacFarlane *et al.*, 2022). Durante este proceso, se pueden emplear juegos intuitivos para captar el interés de

los niños, así como ofrecer respuestas exageradas para proporcionar retroalimentación inmediata y recompensas, facilitando así la transición a la etapa de producción verbal y promoviendo su desarrollo del lenguaje (McDaniel *et al.*, 2018).

Por otro lado, la capacidad de comprensión es un prerrequisito importante para el desarrollo de habilidades de comunicación del lenguaje. En la actualidad, se sabe que los pacientes con TEA y epilepsia están claramente limitados en la capacidad de compartir, empatía, atención conjunta, comprensión de los deseos de los demás y comportamiento cooperativo (Macdonald *et al.*, 2022). Estas deficiencias dificultan la comprensión de los pacientes sobre el propósito, la intención, la sugerencia, la creencia, el deseo, la broma, el engaño, la comparación, la "duplicidad" y otras actividades psicológicas del comportamiento de la otra parte. En consecuencia, los pacientes con TEA y epilepsia no pueden entender reglas sociales no instauradas explícitamente o el humor. Esta falta de comprensión es perjudicial dificultando la elaboración y ejecución de planes o acciones sociales (Boucher, 2012).

Para mejorar la capacidad de comunicación social, es importante instaurar un sistema aumentativo de comunicación que permita llevar a cabo intercambios comunicativos eficaces con el resto de las personas de su entorno (Flippin *et al.*, 2010). El sistema de comunicación por intercambio de imágenes (PECS) es un método de entrenamiento de rehabilitación con muchas aplicaciones clínicas. Al utilizar el intercambio de imágenes como una forma auxiliar de comunicarse con los niños, PECS puede mejorar el seguimiento visual y la comprensión de los niños a través de la enseñanza estructurada y el análisis del comportamiento (Frolli *et al.*, 2022). El método PECS estimula la mejora de las habilidades de comunicación y lenguaje de los niños. Un estudio ha encontrado que PECS causa cierta mejora en la comunicación y la expresión, pero la mejora en el nivel de desarrollo no ha alcanzado las expectativas clínicas (Ganz *et al.*, 2012). De esta manera, la persona con TEA y epilepsia mejora significativamente su capacidad de comunicación y le permite ganar autonomía en el desarrollo de la comunicación y la interacción social.

1.6. RESUMEN DE LAS IDEAS CLAVE

El TEA es un trastorno del neurodesarrollo caracterizado por déficits en la comunicación social y comportamientos repetitivos e intereses restringidos. Los criterios diagnósticos del DSM-5 TR para el TEA incluyen deficiencias persistentes en la reciprocidad socioemocional, en las conductas comunicativas no verbales, y en el desarrollo, mantenimiento y comprensión de las relaciones. Además, se requieren patrones restrictivos y repetitivos de comportamiento, que se manifiestan en movimientos estereotipados, insistencia en la monotonía, intereses muy restringidos y una reactividad sensorial atípica.

Este trastorno se presenta desde las primeras fases del desarrollo y causa un deterioro clínicamente significativo en diversas áreas del funcionamiento. No debe explicarse mejor por otros trastornos del desarrollo intelectual. El DSM-5 TR clasifica la gravedad del TEA en tres grados, basados en el nivel de apoyo necesario para la comunicación social y los comportamientos repetitivos. La etiología del TEA involucra factores genéticos y ambientales. Los estudios neuropatológicos han revelado diferencias en la estructura y conectividad cerebelosa, anomalías en el sistema límbico y alteraciones corticales. La genética juega un papel crucial, con más de 700 genes identificados como asociados al TEA. Los factores ambientales prenatales, perinatales y postnatales también modulan el riesgo, incluyendo la exposición a ciertos medicamentos y las condiciones de salud materna. La prevalencia del TEA varía globalmente, estimada por la OMS en 0.76% y por los CDC en 1.68% en Estados Unidos. Los estudios indican una mayor prevalencia en hombres, aunque las mujeres podrían estar subdiagnosticadas debido a diferencias en la manifestación de síntomas.

En cuanto a las características lingüísticas, las personas con TEA muestran una gran diversidad en el desarrollo del lenguaje, con dificultades que van desde habilidades lingüísticas deterioradas hasta competencias excepcionales. Las alteraciones incluyen problemas en la pragmática del lenguaje, la fonología y la morfosintaxis. La ecolalia es común y puede ser una estrategia de comunicación. Las características cognitivas del TEA incluyen déficits en funciones ejecutivas como el control inhibitorio, la flexibilidad cognitiva y la memoria de trabajo. Los estudios han encontrado inconsistencias en estos hallazgos, posiblemente debido a la heterogeneidad de los participantes y a la variedad de métodos utilizados para

medir estas funciones. Por último, el TEA presenta una alta comorbilidad con otros trastornos médicos, psiquiátricos y neurológicos, lo que aumenta la discapacidad y la demanda de cuidados, siendo la epilepsia uno de los trastornos más prevalentes en esta condición.

La epilepsia es una enfermedad neurológica caracterizada por su impacto significativo en el correcto funcionamiento cerebral, con manifestaciones que comúnmente se agrupan en síndromes epilépticos. Estos síndromes se definen por un conjunto de signos y síntomas específicos, y se clasifican según tipos de convulsiones, contexto clínico, neurofisiología y localización del foco epiléptico, identificado mediante técnicas de neuroimagen. Se divide en dos categorías: generalizada y focal (parcial). La epilepsia generalizada implica convulsiones y anomalías en el EEG que no son específicas de una zona cortical, mientras que la focal sugiere un inicio focal específico tanto en manifestaciones clínicas como en el EEG. Las epilepsias pueden ser idiopáticas, de etiología desconocida, pero con una predisposición genética compleja, o sintomáticas, resultado de lesiones cerebrales no necesariamente detectables por neuroimagen.

A nivel global, se estima que 10.5 millones de niños menores de 15 años tienen epilepsia activa, representando aproximadamente el 25% de la población mundial con epilepsia. De los 3.5 millones de nuevos casos anuales, el 40% son niños menores de 15 años, con más del 80% viviendo en países en desarrollo. La incidencia de epilepsia infantil varía significativamente entre regiones desarrolladas y en desarrollo, con tasas de incidencia anual de 61-124 por 100,000 en países desarrollados y 41-50 por 100,000 en países en desarrollo. Aproximadamente del 55% al 75% de las epilepsias infantiles son de causa desconocida, con solo el 25%-45% atribuibles a factores etiológicos específicos. Los factores de riesgo incluyen malformaciones congénitas, trastornos metabólicos, convulsiones febriles, traumatismos craneoencefálicos, infecciones del sistema nervioso central y antecedentes familiares de epilepsia. Los estudios sobre factores perinatales no han encontrado asociaciones significativas con el riesgo de epilepsia, aunque pueden existir limitaciones metodológicas y variabilidad en los procedimientos y diferencias individuales que afectan los resultados.

La epilepsia puede afectar el lenguaje, causando síntomas afásicos, dificultades en el lenguaje expresivo y problemas de comprensión. También se observan automatismos y disartria. Los niños con epilepsia a menudo presentan

dificultades para organizar y estructurar pensamientos, lo que lleva a problemas en la comunicación social, narrativas incoherentes y errores en la monitorización de la información emitida. Las alteraciones cognitivas en niños con epilepsia pueden aparecer antes del diagnóstico o hacerse evidentes después, afectando significativamente el rendimiento académico y la calidad de vida. La etiología subyacente, la edad de inicio y el control de los episodios epilépticos son factores cruciales que influyen en la función cognitiva. Esta condición se asocia con una amplia variedad de comorbilidades, incluyendo trastornos cardíacos, diabetes tipo 1, alergias, asma y trastornos psiquiátricos y del neurodesarrollo como depresión, ansiedad, esquizofrenia, TEA, TDAH y parálisis cerebral infantil. La relación exacta entre epilepsia y el TEA sigue siendo investigada, sin poder determinarse si la causa o consecuencia de estos trastornos.

La población infantil con TEA presenta un mayor riesgo de desarrollar epilepsia, y viceversa. Esta relación ha impulsado numerosas investigaciones biomédicas, especialmente en genética, para entender y diseñar intervenciones específicas para esta comorbilidad. Desde los primeros estudios, se ha establecido una fuerte asociación entre el TEA y la epilepsia, con una prevalencia estimada de epilepsia en pacientes con TEA que varía entre el 29% y el 33%. En la práctica clínica, diagnosticar epilepsia en niños con TEA es complejo debido a las limitaciones en las entrevistas clínicas y las dificultades para realizar registros EEG precisos, que a menudo muestran anomalías incluso sin convulsiones. La epilepsia es común en niños con TEA, con una prevalencia significativamente mayor que en niños con desarrollo típico. Aproximadamente el 60% de los niños con TEA tienen actividad epileptiforme anormal en sus EEGs sin convulsiones clínicas significativas. Los niños con epilepsia farmacorresistente y TEA a menudo requieren opciones quirúrgicas, como la cirugía resectiva, callosotomía del cuerpo calloso o la colocación de un estimulador del nervio vago, que han mostrado resultados positivos en la reducción o eliminación de convulsiones. El perfil cognitivo-lingüístico de los niños con TEA y epilepsia se caracteriza por alteraciones severas en la cognición y el funcionamiento ejecutivo. La discapacidad intelectual (DI) está presente en un alto porcentaje de estos niños, aumentando aún más el riesgo de epilepsia. La gravedad del TEA puede evaluarse por los síntomas sociales-comunicativos y los comportamientos repetitivos. Algunos niños con TEA también muestran limitaciones en el lenguaje, lo que puede estar relacionado con

la epilepsia. Existen diagnósticos específicos, como el Síndrome de Landau-Kleffner (SLK), que presentan síntomas similares al TEA y son tratables, sugiriendo que algunas regresiones del desarrollo en TEA podrían ser manejadas con terapias antiepilépticas. Sin embargo, es necesario llevar a cabo una correcta evaluación para poder detectar y mejorar el pronóstico de estos perfiles.

La evaluación TEA es crucial debido a su creciente prevalencia y la necesidad de tratamientos efectivos. Se dispone de una variedad de herramientas de evaluación, como ADI-R, CARS, M-CHAT, Vineland-II, SCQ, GARS - 2, ADOS-2 y SRS, diseñadas para evaluar diferentes aspectos del desarrollo y el comportamiento de los individuos con TEA. Estas herramientas son útiles para el diagnóstico diferencial, la evaluación del nivel de funcionamiento y la planificación del tratamiento. A pesar de la importancia de la detección temprana, las herramientas actuales de detección no siempre son lo suficientemente específicas, lo que plantea desafíos en la identificación precisa del TEA en etapas tempranas. La estabilidad diagnóstica es alta entre los 18 y 36 meses de edad, pero muchos niños con síntomas leves pueden no ser identificados hasta la edad escolar. Por lo tanto, se necesita una evaluación continua y prolongada para captar a todos los niños que podrían beneficiarse de intervenciones tempranas. La evaluación interdisciplinaria, que involucra a profesionales de diferentes disciplinas, junto con la participación activa de la familia, es crucial en la evaluación del TEA. Esta aproximación holística permite una comprensión más completa de las necesidades individuales de cada persona con TEA y facilita la identificación tanto de déficits como de fortalezas.

En cuanto a la epilepsia, el diagnóstico en la infancia es complejo debido a la variedad de presentaciones clínicas y la dificultad para diferenciar las convulsiones de otros eventos paroxísticos comunes en la infancia. La tecnología de imagenología, como la MRI y la CT, juega un papel fundamental en la evaluación de la estructura cerebral y la detección de lesiones epileptogénicas. Aunque la MRI revela lesiones epileptogénicas en aproximadamente el 20% de los pacientes con epilepsia reciente, en muchos casos no se identifican lesiones estructurales. En este contexto, el EEG es una herramienta complementaria valiosa que puede ayudar a confirmar el diagnóstico de epilepsia y clasificar los tipos de epilepsia. Sin embargo, la interpretación del EEG puede ser compleja y requiere experiencia debido a factores como la baja amplitud de la señal y la presencia de artefactos. Además, el EEG interictal puede ser útil para clasificar la epilepsia, pero sus hallazgos deben

interpretarse dentro del contexto clínico del paciente. La monitorización de video-EEG de larga duración es esencial para capturar y caracterizar eventos epilépticos en pacientes con convulsiones no controladas.

Con respecto al tratamiento de las personas con TEA y epilepsia, el tratamiento farmacológico es fundamental en el manejo de esta comorbilidad. Para el control de las alteraciones conductuales en personas con TEA y epilepsia, se utilizan fármacos como la risperidona y el aripiprazol, que tienen efectos antagonistas dopaminérgicos y serotoninérgicos. Estos medicamentos están aprobados para el tratamiento de la irritabilidad y la agresión en pacientes con esta comorbilidad. Sin embargo, hay que tener presente que pueden provocar efectos adversos como hiperglucemia, dislipidemia y aumento de peso. Para los trastornos del sueño, la melatonina es el fármaco por excelencia. Estudios han demostrado que la melatonina de liberación prolongada puede aumentar la duración del sueño y reducir la latencia del inicio del sueño en niños y adolescentes con TEA. En cuanto a los comportamientos obsesivos-compulsivos, los Inhibidores Selectivos de la Recaptación de Serotonina (ISRS) como la fluoxetina pueden ayudar a mejorar la sintomatología, aunque los estudios actuales sobre su efectividad en personas con TEA sin epilepsia no son concluyentes. Debido a la falta de opciones farmacológicas efectivas para el TEA, muchas familias buscan enfoques complementarios y alternativos. Algunos suplementos, como la N-acetilcisteína y el sulforafano, han demostrado eficacia para los síntomas emocionales y conductuales, pero la evidencia actual no respalda ningún suplemento específico para los síntomas del TEA relacionados con el lenguaje, la interacción social o los comportamientos repetitivos.

En cuanto a la intervención cognitivo-conductual, se ha demostrado que las terapias conductuales son efectivas para mejorar síntomas asociados con el TEA, como el uso del lenguaje. Las intervenciones conductuales del desarrollo natural, que se centran en enseñar habilidades apropiadas para el desarrollo en entornos naturales como el juego, han mostrado mejoras significativas en el lenguaje, el juego y la comunicación social en niños con TEA. La intervención mediada por padres, que incluye aproximaciones como la terapia de atención conjunta, terapia de comunicación social y conductual impartida por padres capacitados, ha mejorado significativamente la gravedad de los síntomas del TEA y de la epilepsia, y en la socialización y la cognición. Además, las intervenciones basadas en ABA y

TEACCH son ampliamente utilizadas para enseñar habilidades y mejorar la funcionalidad en las actividades de la vida diaria en niños con TEA y epilepsia. Estas intervenciones se adaptan a las necesidades individuales de cada niño y se centran en promover la autonomía y el desarrollo del lenguaje. Por último, en lo relativo a la intervención del lenguaje, se enfoca en mejorar la comunicación tanto verbal como no verbal en niños con TEA y epilepsia. Se utilizan diferentes enfoques, como el entrenamiento de la imitación y el uso de sistemas aumentativos de comunicación como el PECS, para mejorar la comprensión y expresión del lenguaje y fomentar la interacción social.

II – JUSTIFICACIÓN

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La justificación de esta tesis doctoral se erige sobre un escenario de imperativa necesidad: la comprensión y la atención de las personas con TEA y epilepsia, dos condiciones neurológicas complejas que afectan a una proporción significativa de la población mundial. Este trabajo doctoral no solo aspira a profundizar en el conocimiento de estas condiciones de manera individual, sino que también se centra en la exploración de su comorbilidad y las implicaciones que ello conlleva.

En primer lugar, es necesario subrayar la complejidad del TEA y la epilepsia. El TEA abarca una amplia gama de perfiles clínicos, que van desde formas leves hasta severas, y se caracteriza por dificultades en la comunicación, la interacción social y patrones de comportamiento repetitivos y restringidos. Por otro lado, la epilepsia, una condición neurológica definida por la presencia de convulsiones recurrentes, también presenta una variabilidad significativa en cuanto a la frecuencia, la gravedad y los desencadenantes de las convulsiones. La coexistencia de ambos trastornos añade una capa adicional de complejidad a este escenario. Varios estudios han sugerido que hasta un tercio de las personas con TEA pueden desarrollar epilepsia en algún momento de sus vidas, y la prevalencia de TEA en individuos con epilepsia también parece ser significativamente mayor que en la población general. Esta interacción entre TEA y epilepsia plantea una necesidad en términos de diagnóstico diferencial, manejo clínico y pronóstico, ya que las características clínicas de ambas condiciones pueden superponerse e influirse negativamente de forma conjunta.

Otro aspecto que justifica esta investigación es la necesidad de desarrollar intervenciones y servicios de atención específicamente adaptados a las necesidades de las personas con TEA y epilepsia. A pesar de los avances en el desarrollo de intervenciones para cada trastorno por separado, existe una falta de enfoque integrado en el manejo de esta comorbilidad. Es crucial desarrollar protocolos de evaluación y tratamiento que aborden de manera holística las necesidades cognitivas, emocionales y físicas de esta población, reconociendo la complejidad de su presentación clínica y la interacción entre ambas condiciones.

Además, la investigación en el TEA y epilepsia tiene importantes implicaciones en términos de salud pública y políticas sociales. El aumento en la prevalencia de ambos trastornos en las últimas décadas ha generado una demanda creciente en los servicios de salud y educación especializados, así como un aumento en la conciencia pública y la sensibilización sobre estas condiciones. Sin embargo, aún persisten limitaciones significativas en términos de acceso equitativo a servicios de calidad, capacitación de profesionales de la salud y apoyo a las familias y cuidadores de personas con TEA y epilepsia.

En este contexto, la presente tesis doctoral se justifica como una contribución significativa al campo de la salud mental y neurológica, al abordar una brecha crítica en la investigación y práctica clínica relacionada con el TEA y la epilepsia. Al profundizar en la comprensión de la trayectoria evolutiva, las características clínicas y las necesidades de intervención de las personas con esta comorbilidad, esta investigación tiene el potencial de mejorar la calidad de vida y el bienestar de un número significativo de personas y familias que se encuentran en esta situación. Por tanto, la justificación de esta tesis doctoral radica en la necesidad apremiante de comprender y abordar los TEA y la epilepsia desde una perspectiva integral e interdisciplinar.

III – OBJETIVOS

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La presente tesis doctoral tuvo el objetivo general de analizar y explorar las características clínicas y los protocolos de evaluación e intervención existentes en las personas diagnosticadas con TEA y epilepsia desde una perspectiva bio-psico-social.

Asimismo, se establecieron los siguientes objetivos específicos:

- Revisar la literatura científica actual y comparar la relación de la epilepsia en el desarrollo de habilidades cognitivas y lingüísticas de niños con TEA.
- Analizar la relación entre el TEA, la epilepsia y los trastornos del sueño, explorando las disfunciones neurobiológicas y alteraciones cognitivas.
- Evaluar y comparar el funcionamiento ejecutivo y las habilidades lingüísticas entre una población infantil diagnosticada de TEA, otra diagnosticada de epilepsia y otra con un diagnóstico de TEA y epilepsia.
- Explorar las diferencias en el patrón conductual, emocional y de funcionamiento ejecutivo en personas con diagnóstico de TEA, epilepsia y TEA con epilepsia.
- Evaluar y comparar la comprensión auditiva de estructuras gramaticales en personas con TEA, epilepsia y TEA con epilepsia.
- Diseñar un protocolo de evaluación para población infantil con un diagnóstico de TEA y epilepsia, valorando su perfil lingüístico, cognitivo y sensorial.
- Discutir y actualizar los tratamientos farmacológicos primarios para la atención de la población pediátrica diagnosticada de TEA y epilepsia.
- Analizar y explorar los protocolos actuales sobre la intervención en los procesos de lenguaje y comunicación funcional en la población infantil con diagnóstico de TEA y epilepsia.

IV - MATERIAL Y MÉTODO

IV -MATERIAL Y MÉTODO

4.1. PARTICIPANTES

Para la realización de la presente tesis doctoral, se ha seleccionado a un total de 170 participantes con edades comprendidas entre los 7 y los 9 años, los cuales se han dividido en los tres grupos descritos a continuación:

- **Primer Grupo (G1):** 57 participantes con diagnóstico de Trastorno del Espectro del Autismo con Grado 1 (36 niños y 21 niñas ($M_{\text{edad}} = 8.1$; $DT = 0.9$)) según los criterios establecidos en el DSM-5 (APA, 2013).
- **Segundo Grupo (G2):** 60 participantes con diagnóstico de epilepsia generalizada (41 niños y 19 niñas ($M_{\text{edad}} = 8.6$; $DT = 0.4$)).
- **Tercer Grupo (G3):** 53 participantes con diagnóstico de Trastorno del Espectro del Autismo con Grado 1 y epilepsia generalizada (27 niños y 26 niñas ($M_{\text{edad}} = 7.8$; $DT = 0.8$)) según los criterios establecidos en el DSM-5 (APA, 2013).

Todos los participantes que fueron diagnosticados de TEA o epilepsia han sido evaluados en la Unidad de Salud Mental y servicio de Neurología Pediátrica anexa a su centro médico de referencia, por parte del equipo profesional multidisciplinar de esta unidad. En estos centros, se llevaron a cabo una evaluación de cribaje diagnóstico a través de la administración del cuestionario M-CHAT-R (Robins *et al.*, 2004). Aquellos niños que presentaron puntuaciones que indicaban una posible sospecha de alarma, se procedió al empleo de los protocolos ADOS-2 (Lord *et al.*, 2008) y ADI-R (Rutter *et al.*, 2006), con el objetivo de confirmar la sospecha diagnóstica de TEA. Asimismo, los participantes tuvieron una evaluación por parte del equipo de neuropediatría, llevando a cabo una evaluación neurológica a través de la exploración con el uso de Resonancia Magnética, Electroencefalograma con privación de sueño y pruebas genéticas que ayudaron a confirmar el diagnóstico.

En la Tabla 5, se recogen las principales características de los participantes que conformaron el grupo muestral de este estudio:

Tabla 5. *Características de los participantes incluidos en el estudio*

Caracterización de los participantes				
		N	Porcentaje	X ²
Sexo	Varón	104	61.2	1.02
	Mujer	66	38.2	
Edad	7 años	47	27.6	2.15
	8 años	61	35.9	
	9 años	62	36.5	
Diagnóstico	TEA	57	33.5	5.52
	TEA+Epilepsia	53	31.2	
	Epilepsia	60	35.3	
Años de tratamiento	2 años	34	20.0	5.75
	3 años	73	42.9	
	4 años	63	37.1	
Grado de discapacidad	Menos de 33%	52	29.1	6.49
	Entre 33% y 66%	74	40.0	
	Más de 66%	44	30.9	
Apoyos en la escuela	Maestro de Audición y Lenguaje	41	30.6	6.49
	Maestro de Audición y Lenguaje y Pedagogía Terapéutica	87	51.2	
	Maestro de Audición y Lenguaje, Pedagogía Terapéutica y Educador	42	24.7	
Semanas de gestación	30 – 35	52	30.6	2.11
	35 – 40	87	51.2	
	Más de 40	31	18.2	
Apgar	Con riesgo	77	45.3	0.58
	Intermedia	63	37.1	
	Normal	30	17.6	
	No presencia	123	72.4	

Discapacidad Intelectual	Leve	47	27.6	34.58*
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Nota: * $p < .05$

Finalmente, se establecieron los siguientes criterios de inclusión y exclusión. Por un lado, los criterios de inclusión fueron: (I) tener entre 7 y 9 años de edad, (II) presentar un diagnóstico de TEA emitido por un hospital o centro de salud público, y (III) someterse a tratamiento de rehabilitación en la clínica de rehabilitación. Por otro lado, los criterios de exclusión fueron: (I) presentar alguna enfermedad o trastorno motor o sensorial que dificulte o impida el correcto desempeño del estudio, (II) no presentar ninguna comunicación o lenguaje a los 5 años de edad, y (III) presentar discapacidad intelectual moderada, grave o profunda.

4.2. INSTRUMENTOS Y MATERIALES

4.2.1. Evaluación Clínica de Fundamentos del Lenguaje 5

La Evaluación Clínica de Fundamentos del Lenguaje - 5 (CELF-5; Wiig *et al.*, 2013) es un instrumento clínico de aplicación individual diseñado para identificar, diagnosticar y hacer seguimiento de trastornos del lenguaje y la comunicación en niños y adolescentes de 5 a 15 años de edad. Este instrumento, mediante una aplicación individual, tiene como objetivo evaluar las fortalezas y debilidades del usuario en los diferentes aspectos y dimensiones del lenguaje. Todas estas escalas se puntúan con 0-1 puntos, siendo 0 la ausencia de la habilidad y 1 la presencia de esta; excepto por el cuestionario del perfil lingüístico, que consta de una respuesta estructurada en una escala tipo Likert de 0-4, donde la puntuación 0 está relacionada con "nunca" y 4 con "siempre".

4.2.2. CEG. Test de Comprensión de Estructuras Gramaticales

La prueba CEG. Test de Comprensión de Estructuras Gramaticales (CEG; Mendoza *et al.*, 2005) es un instrumento de evaluación que mide la comprensión de

enunciados y oraciones en sus diferentes formas. Está baremado para población española de entre 4 y 12 años. Este test se compone de 80 elementos o ítems de elección múltiple (cuatro alternativas de respuesta), distribuidos en 20 bloques de cuatro elementos cada uno, que constituyen las estructuras gramaticales más representativas en la lengua española. La consistencia interna de la prueba se ha estudiado mediante el coeficiente α de Cronbach, y se ha obtenido un índice de fiabilidad de 0.9096. La fiabilidad obtenida para cada grupo de edad ha sido: 4 años: 0.825; 5 años: 0.779; 6 años: 0.866; 7 años: 0.797; 8 años: 0.828; 9 años: 0.807; 10 años: 0.794; y 11 años: 0.842.

4.2.3. BRIEF-2 de Evaluación Conductual de la Función Ejecutiva

El Cuestionario BRIEF-2 de Evaluación Conductual de la Función Ejecutiva (BRIEF-2; Gioia *et al.*, 2003; adaptación de Bausela-Herreras y Luque-Cuenca, 2017) es un instrumento que proporciona una evaluación de las funciones ejecutivas de niños con edades comprendidas entre los 5 y los 18 años. Permite medir los diferentes aspectos del funcionamiento ejecutivo de una manera más precisa que otras pruebas e instrumentos existentes en la actualidad. El BRIEF-2 obedece a la necesidad prominente de encontrar un método ecológicamente válido para realizar evaluaciones de las dimensiones y aspectos molares, conductuales y del ámbito cotidiano de las funciones ejecutivas de los niños (Donders, 2002). Por ende, con dicho objetivo, el BRIEF-2 consiste en un cuestionario compuesto por 63 ítems con estructura de respuesta tipo Likert de frecuencia: nunca, a veces y frecuentemente. Se realiza en un tiempo estimado de 10 minutos. Cuenta con dos versiones de un mismo cuestionario, uno que rellena la familia del niño/adolescente y otro que lo completa el profesor tutor del centro educativo al cual está escolarizado el menor.

4.2.4. ENFEN, Evaluación Neuropsicológica de las Funciones Ejecutivas en Niños

El ENFEN, Evaluación Neuropsicológica de las Funciones Ejecutivas en Niños (ENFEN; Portellano *et al.*, 2009) evalúa el rendimiento cognitivo en

actividades relacionadas con las funciones ejecutivas en niños y su nivel de madurez, mediante cuatro pruebas (resistencia a la interferencia, construcción de senderos, fluidez verbal y construcción con anillas). Respecto a sus propiedades psicométricas, Rodríguez et al. (2018), realizaron una medición de estas y previamente al análisis factorial, desarrollaron una matriz de correlaciones entre las subescalas del instrumento y cuyos valores superaban el 0,3. A partir de esa correlación ejecutaron el índice de adecuación Kaiser-Meyer-Olkin, (KMO) el cual presentó un valor de 0,87.

4.2.5. Wechsler Intelligence Scale for Children - Fourth Edition

La Wechsler Intelligence Scale for Children - Fourth Edition (WISC-IV; Wechsler, 2010). Es un instrumento clínico integral administrado individualmente para evaluar la capacidad cognitiva/inteligencia de niños de 6 años 0 meses a 16 años 11 meses (6:0 - 16:11). La WISC-IV proporciona puntuaciones compuestas y de subpruebas que representan el funcionamiento intelectual en dominios cognitivos específicos, así como una puntuación compuesta que representa la capacidad intelectual general. Se compone de 16 subpruebas que se pueden agrupar en dos categorías generales: primarias o secundarias. Esta prueba permite determinar el cociente intelectual. Con respecto a su valor psicométrico, el alfa de Cronbach es de 0.89.

4.2.6. Cuestionario SENA, sistema de evaluación de niños y adolescentes

El cuestionario SENA, sistema de evaluación de niños y adolescentes (SENA; Fernández *et al.*, 2015) está compuesto por un total de 9 cuestionarios dirigidos a tres niveles de edad: Infantil (3-6 años), Primaria (6-12 años) y Secundaria (12-18 años). Incluye cuestionarios específicos para recabar información de diferentes informadores atendiendo a los principales contextos en los que se desenvuelve el niño (cuestionarios para familia y para la escuela), además de tres modelos de autoinforme según la edad de la persona evaluada que se aplican a partir de los 6 años. En cada uno de ellos los informadores deben valorar la

frecuencia de aparición de la conducta descrita mediante una escala de cinco puntos (Nunca o casi nunca a Siempre o casi siempre) salvo en el autoinforme para los 6-8 años, que incluye una escala de tres opciones: Sí, No y A veces.

4.2.7. BASC-3, sistema de evaluación de la conducta de niños y adolescentes - 3

El BASC-3, sistema de evaluación de la conducta de niños y adolescentes – 3 (BASC-3; González *et al.*, 2004) es un instrumento que se utiliza para evaluar de manera clínica las emociones y las conductas de los niños y adolescentes detectando trastornos desadaptativos en el contexto familiar y escolar. El BASC-3 consta de un autoinforme para el paciente y dos cuestionarios dirigidos a padres (P) y para profesores/tutores (T).

4.2.8. PROLEC-R. Batería de Evaluación de los Procesos Lectores Revisada

La Batería de Evaluación de los Procesos Lectores Revisada (PROLEC-R; Cuetos *et al.*, 2007) es un instrumento ampliamente reconocido en el ámbito de la evaluación de las habilidades lectoras. Este test está diseñado para proporcionar una valoración exhaustiva y detallada de cada uno de los módulos involucrados en el procesamiento de la lectura, como la decodificación, la comprensión y la fluidez lectora, entre otros. Además, la fiabilidad del instrumento es sólida, como lo indica un alfa de Cronbach de 0.86, lo que garantiza la consistencia interna de las medidas que se obtienen a través de esta batería.

4.3. PROCEDIMIENTO

4.3.1. Procedimiento de recolección de datos

El procedimiento de recolección de los datos de los participantes que se incluyeron en la presente tesis doctoral se divide en tres fases de actuación diferenciadas.

En primer lugar, la primera fase consistió en el diseño del plan de investigación y propuesta de investigación a la Universidad Católica San Antonio de Murcia (UCAM) para su aceptación en el programa de doctorado al cual está adscrito la presente tesis doctoral (véase *Anexo 1*). Asimismo, se envió la solicitud para la aprobación del proyecto de investigación por parte del Comité de ética de esta misma universidad.

A continuación, en segundo lugar, la segunda fase se correspondió a la selección del grupo muestral de los participantes que se incluirían en este estudio siguiendo los criterios de inclusión y exclusión previamente descritos. Todos los familiares de los participantes firmaron un consentimiento informado de forma voluntaria y admitiendo su aceptación para la participación en el presente estudio (véase *Anexo 2*). Una vez establecido los tres grupos de participantes, se llevaron a cabo las evaluaciones aplicando los instrumentos de evaluación y medición empleados en la presente tesis doctoral. La evaluación fue llevada a cabo por un profesional de la logopedia y de la psicología, experto en trastornos del neurodesarrollo y atención temprana. Las sesiones de evaluación se establecieron de lunes a viernes en horario vespertino con una duración máxima de una hora y media, con dos descansos de diez minutos dentro de las mismas para cada uno de los participantes que conformaban el grupo muestral de esta investigación.

Por último, en tercer lugar, la tercera fase consistió en alojar en una base de datos usando el paquete estadístico SPSS en su versión 26.0 para MAC-OS X, los datos obtenidos de las evaluaciones de los participantes en la presente tesis doctoral. Asimismo, se depuró la base de datos y se procedió a la realización de los supuestos estadísticos pertinentes para la comprobación de los objetivos específicos establecidos en las investigaciones recopiladas en esta tesis doctoral.

4.3.2. Procedimiento para la aprobación del comité de ética

Los estudios comprendidos en la presente tesis doctoral fueron aprobados por el comité ético de la Universidad Católica San Antonio de Murcia (UCAM) el día 27 de mayo de 2022 con el código: CE052206.

4.4. DISEÑO Y ANÁLISIS DE DATOS

Los estudios empíricos que componen el compendio de artículos de la presente tesis doctoral se establecieron como estudios descriptivos-comparativos, con un diseño transversal con un solo momento de evaluación en cada uno de ellos. En primer lugar, se utilizó la prueba de Kolmogorov-Smirnoff para examinar la normalidad de la distribución de las variables dependientes que componen el estudio. A continuación, se usó el análisis de la covarianza multivariada (MANCOVA) para observar la relación entre las variables relativas al lenguaje, el funcionamiento ejecutivo, la cognición, los aspectos emocionales y de conducta exteriorizados e interiorizados, así como los problemas de conducta. De esta manera, se explorará las diferencias entre los grupos que componen la muestra. La variable discapacidad intelectual se determinó como covariable. Posteriormente, se llevó a cabo pruebas de análisis de la covarianza (ANCOVA) con el objetivo de observar las diferencias individuales de cada una de las variables en los tres grupos. Finalmente, para controlar el error tipo I, se realizó la corrección de Holm-Bonferroni (Holm, 1979).

V – COMPENDIO DE ARTÍCULOS

V - COMPENDIO DE ARTÍCULOS

5.1. ARTÍCULO 1

Cano-Villagrasa, A., Moya-Faz, F. J., & López-Zamora, M. (2023). Relationship of epilepsy on the linguistic-cognitive profile of children with ASD: A systematic review of the literature. *Frontiers in psychology*, 14, 1101535. <https://doi.org/10.3389/fpsyg.2023.1101535>



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Relationship of epilepsy on the linguistic-cognitive profile of children with ASD: A systematic review of the literature

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Universidad de Málaga, Málaga, Spain**Introduction:** The prevalence of comorbidity between epilepsy and Autism Spectrum Disorder (ASD) in the pediatric age increased significantly in recent years. The onset of epilepsy negatively influences the abilities of the user with ASD. Thus, epilepsy will be a disabling factor that will reduce the cognitive-linguistic skills of users with ASD. The main objective of this work is to review the current scientific literature and to compare the relationship of epilepsy on the development of cognitive and linguistic skills of children with ASD.**Methods:** In this regard, a systematic search was carried out in the main sources (Medline, PubMed, WOS, ResearchGate and Google Scholar). 481 articles were identified, from which, after meeting the different inclusion and exclusion criteria, a total of 18 studies of relevance to the objectives of this work were selected.**Results:** The results reflect that, at a global level, epilepsy significantly influences the performance of cognitive-linguistic skills in people with ASD.**Discussion:** In conclusion, epilepsy in the ASD population leads to a reduction in cognitive and linguistic abilities, which respond to the different types of epilepsy and their location, significantly impacting the quality of life and basic activities of daily living of the user with ASD.

KEYWORDS

autism spectrum disorder, epilepsy, cognition, language, comparison

Introduction

The study of comorbidity between epilepsy and Autism Spectrum Disorder (ASD) has acquired importance in recent years due to a significant increase in the prevalence found in the profiles of users with these two comorbid pathologies (Spence and Schneider, 2009; Mannion and Leader, 2014; Strasser et al., 2018). On the one hand, epilepsy is defined as a brain alteration characterized by a permanent predisposition to generate seizures and by the neurobiological, cognitive, psychological, and social consequences derived from this condition (Pastorino et al., 2021). Its diagnosis is possible after the user experiences an isolated seizure which is not caused by any external factor (Muñoz Yunta et al., 2006). Epilepsy encompasses a series of signs and symptoms of various etiologies that are grouped according to the type of seizures, electroencephalogram (EEG) alterations, age of symptom onset, the existence of precipitating factors, cause, prognosis, response to treatment, and anatomical location of the initial focus of the seizures (Ewen et al., 2019). On the other hand, ASD is classified within neurodevelopmental disorders.

The most plausible hypothesis with the most scientific support places its origin in a complex and multifactorial genetic predisposition that produces neuronal abnormalities due to alterations in early synaptic plasticity during development (Poduri and Lowenstein, 2011; Tuchman and Cuccaro, 2011). These children could have common mechanisms due to neurobehavioral phenotypes that, interacting with environmental factors, would produce significant deficits in expressive and receptive language dimensions (Miranda et al., 2022). Without considering the etiological variability of these disorders, their different development according to age and the modification of the evolutionary course of the patient that these disorders impose separately, when both disorders appear in an individual, the impact produced is difficult to detect and quantify. Consequently, this comorbidity is significantly changing the way in which ASD is evaluated and intervened.

In this regard, an increase in the incidence of clinical epilepsy and/or epileptiform activity on EEG in children with ASD is being observed, possibly due to the sensitization of clinical protocols to this comorbidity. However, studies are far from homogeneous, so the association between these two disorders can be estimated at a percentage ranging from 7 to 42% depending on the research (Ghacibeh and Fields, 2015). This variability may occur due to the clinical differences of both disorders and their evolutionary course. For example, in ASD, seizures can begin at any age; however, a higher rate of occurrence of these episodes is observed in early childhood and early adolescence. In addition to this, it is estimated that 23% of children with this comorbidity also have hyperactivity, so other symptoms that could be present and complicate the differential diagnosis must be added. Another reason could be due to differences in the distribution of the manifestations of ASD in current studies, where unequal importance is given to the individual characteristics of the users, together with the form of onset and typology of epilepsy (Besag, 2015; Dunn et al., 2016).

The study of comorbidity between ASD and epilepsy is not recent. In the first clinical descriptions of ASD, Kanner (1943) indicated that, in patients with autism, episodes of epileptic seizures were already observed. According to him, these episodes could have repercussions on a worse acquisition of linguistic and social competences in children with both disorders (Rutter, 1978). Nowadays, neurologists specializing in childhood epilepsy carry out an extensive evaluation to determine the existence of this comorbidity, since early detection is a good prognostic factor for the development of cognitive-linguistic and social skills of users with epilepsy and ASD, especially if the disease manifests itself in early childhood (Muñoz-Yunta et al., 2008). This way, it is common to incorporate families in the evaluation process so that they are the ones who detect the possible existence of epileptic seizure episodes (Auvin, 2021).

It should be highlighted that, in clinical practice, there are difficulties in making a differential diagnosis of ASD and epilepsy in relation to other diseases. Generally, the involution in the maturational processes of the child is taken as a reference, in addition to alterations in EEG patterns, but these symptoms are common to other pathologies that may interfere with the diagnosis of ASD. Among them, Landau-Kleffner Syndrome (LKS), also known as epileptic aphasia, stands out. During the early stages of this syndrome, prolonged spike-wave activity during

sleep is common, which may cause a conflict in establishing an accurate diagnosis (Pablo et al., 2002). EEG changes in the infantile population with LKS are characterized, as a rule, by pronounced paroxysmal activity. Likewise, spike-wave complexes and multiple sharp waves with prevalence in the temporal regions with a unilateral or bilateral profile and generally asymmetrical are detected. Thus, in most cases cognitive and linguistic disturbances develop. However, in studies such as that of Berkvens et al. (2015), the anomalous epileptiform activity is localized in temporal areas (30%), central areas (28%), frontal areas (23%) and occipital areas (8%). It is also common in LKS for there to be a rapid deterioration in expressive language comprehension (Matthews et al., 2012; El Achkar and Spence, 2015) due to the involvement of the respective brain areas, which can be confused with the regression of language and cognitive skills that occurs in childhood in children with ASD.

Regarding the influence of epilepsy during the critical periods of childhood development and how it can affect its differential diagnosis, the need for an exhaustive and early analysis is highlighted, since this disorder has a direct impact on the development of higher cognitive skills, including language (Junior et al., 2021). This can cause epilepsy to be confused with other pathologies. This is because brain regions mature earlier than others in chronological order. Therefore, if this development is disrupted by the onset of epilepsy in key areas for cognition and language, such as the Sylvian fissure, the temporal area, and the insula, all this will negatively affect the development of these processes (Bitton et al., 2015; Trauner, 2015). In fact, seizure episodes may occur without the patient presenting any clinical symptomatology, which may affect the overall maturation process, but further hindering the diagnosis (Karrasch et al., 2017). In summary, these symptoms can interfere with the correct diagnosis of epilepsy.

Regarding the comorbidity of both disorders, it has been reported that between 10 and 15% of children with ASD experience a regression in acquired behaviors after the initial stage of maturational development, especially in language skills, social interaction, and symbolic play (Matthews et al., 2012). In the last two decades, studies related to neurodevelopmental disorders have questioned whether epilepsy would play a role in the onset of cognitive and language disorders (Bitton et al., 2015). Currently, it is considered that epilepsy can mainly influence cognition and behavior at a very early age, even in cases where there are no clinically visible seizures (Tuchman et al., 2013; Galán-López et al., 2017). This has led to an increase in research to find evidence of subclinical epilepsy in children with developmental problems (Smith, 2016), one of the most relevant being ASD due to its prevalence and clinical interest. On the other hand, epilepsy is also related to language disorders. In the process of language development (both expressive and receptive), epilepsy can negatively condition its acquisition, as well as favor its degradation. When language has been acquired in a normal chronological order, neurodevelopmental disorders such as ASD that co-occur with epilepsy may present significant language impairment or delay (Berg, 2016). In these cases, the influence of epilepsy on ASD symptoms should be considered, since the development of higher psychological processes is related to communication and language. Therefore, continued exposure to epileptic seizures could impair

aspects such as empathy and activities where expressive language takes on greater weight, hindering the child's communication with the surrounding environment (Braakman et al., 2012).

Within this framework, the main objective of this systematic review of the literature is to analyze the co-existence and relationship of epilepsy in the deterioration of cognitive-linguistic skills of those users who present an ASD in childhood. Likewise, this work establishes a series of specific objectives: (I) to analyze the general symptomatology of children presenting an ASD with epilepsy, and (II) to explore the existing differences between both sexes in ASD children with epilepsy.

Materials and methods

In the present article, a systematic review of the literature regarding ASD and epilepsy is presented. To ensure the accuracy of the study's question, we specified the criteria related to users with ASD and epilepsy, comparing the symptoms and the results of their respective diagnostic evaluations (Liberati et al., 2009). The question to be answered is what relationship epilepsy has on the development of cognitive-linguistic skills of users with ASD, following the criteria of the following PICO model: (P) People diagnosed with ASD and epilepsy. (I) Does not apply. (C) Does not apply. (O) Decrease in cognitive-linguistic skills. On the other hand, this literature review has followed the guidelines and recommendations established in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (PRISMA; Yepes-Núñez et al., 2021).

Search strategy

An electronic search was carried out between November 2021 and June 2022 in the following databases: Medline, Pubmed, PsycINFO, Web of Science and Google Scholar. The search was restricted to peer-reviewed articles published in journals and/or available online and written in Spanish or English. To ensure that the included articles were current, the search was restricted to the last 11 years. In the study search, the following terms were considered in the article title, abstract and key words: epilepsy, ASD, and linguistic-cognitive development.

As for the search strategy, the following terms were used, combined with Boolean operators: "(epilepsy relationship) and (children with ASD) and (linguistic development)" "(epilepsy comorbidity) and (children with ASD) and (cognitive development)" "(epilepsy co-existence) and (children with ASD)" "(cognitive and linguistic development) and (children with ASD and epilepsy)" "(epilepsy) and (ASD) and (linguistic and cognitive skills)."

Study selection process

To obtain highly relevant published studies based on the study's objectives and the PRISMA guidelines (Page et al., 2021), inclusion and exclusion criteria were established prior to the systematic search. To improve the quality of the search, a peer

review was carried out using the standardized Peer Review of Electronic Search Strategies (PRESS) instrument (Sampson et al., 2009). In this manner, in the first study pre-selection stage, based on the information provided in the title and abstract, the following inclusion criteria were considered for the selection of articles of relevance: (I) the samples of the studies reflect the existences between the comorbidities of the two studied conditions (epilepsy-ASD and cognitive competence or language competence); (II) these conditions have been specifically assessed; and (III) the assessments have been carried out by professionals in psychology or medicine. Regarding exclusion criteria, the following were considered: (I) single case-reports, without a methodological design; (II) the study of epilepsy unrelated to ASD or vice versa; and (III) review papers, editorials, or abstracts of studies presented at congresses.

In the second stage of study selection, the complete analysis of the articles that met the indicated inclusion criteria was performed. In this process, the following inclusion criteria were considered: (I) the study participants had an official diagnosis of ASD; (II) the article precisely described the parameters of the assessment performed in the participants; and (III) the individual characteristics of the linguistic or cognitive performance of the study participants were specified.

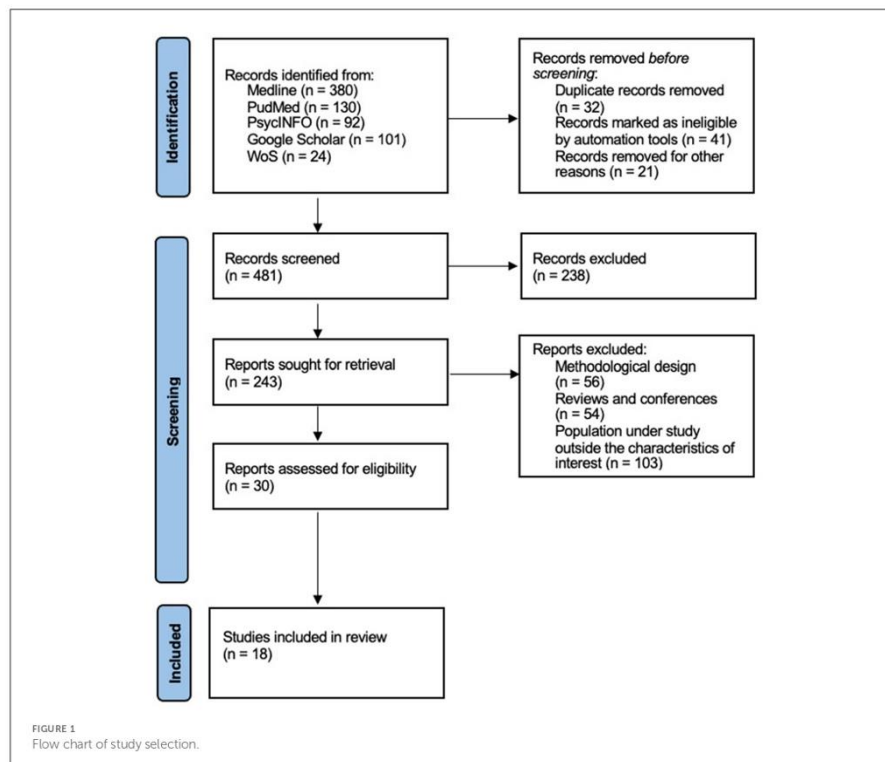
The selection process of the studies included in this systematic review was carried out by two researchers and consisted of 4 phases: In the first phase, we proceeded to review the scientific literature in the main databases in the field of psychology and medicine. In the second phase, each of the researchers checked the title and abstract of each eligible article, according to the previously established inclusion and exclusion criteria. In the third phase, the articles that met the inclusion and exclusion criteria were analyzed in detail by full-text screening. Finally, in the fourth phase, we concluded with the scrutiny and discarding of the articles that did not address the topic of interest of this systematic review, evaluating the main information of the selected articles.

Final study selection

During the initial search for studies, a total of 481 articles that were potentially eligible were found, which were distributed as follows: 134 from Medline, 130 from Pubmed, 92 from PsycINFO, 101 from Google Scholar (through a manual bibliographic search) and 24 from Web of Science. Figure 1 shows a flow chart illustrating the study selection process, considering the PRISMA statement (Moher et al., 2009). From this total, 238 duplicated references were discarded.

Thus, based on the information contained in the title and abstract sections of the manuscript, 243 articles were identified as potentially eligible for review. From the 243 eligible articles, 213 were discarded because they did not meet the previously established inclusion and exclusion criteria: (I) 103 did not include children with ASD or epilepsy, (II) 56 articles were single case reports without an adequate methodological design, and (III) 54 were reviews and papers presented at research congresses.

Of the remaining 30 articles, a detailed assessment of each was carried out, of which 12 were rejected because they did not meet the



previously established selection criteria, leaving a total of 18 articles that were finally included in this systematic review.

Study description

The methodological characteristics of the selected articles are summarized in Table 1. The sample size of the selected articles ranged from 20 to 85,248 participants ($M = 5422$). The studies used different community services, health systems or a combination of other processes to select their final sample. Regarding the ages of the subjects in the studies, it is observed that this was between 2 and 18 years old.

Lastly, with regards to the type of methodological design of the selected studies, quasi-experimental studies were conducted with evaluations at a single point in time, in a cross-sectional intra-group and inter-group manner, to assess the differences.

Results

The selection of articles reviewed below follow the previously established inclusion and exclusion criteria, in addition to being the most recent articles, with the greatest relevance and sample of participants published to date. These are reported in thematic blocks according to the proposed objectives.

The clinical characteristics of the user with ASD and epilepsy

An overview of the clinical characteristics and comorbidities of persons aged 5–15 years with epilepsy who, in turn, meet the diagnostic criteria for ASD is presented in the article by Reilly et al. (2015). In this investigation, 61% of users with epilepsy and ASD had a conduct disorder; a level similar to that of the general population with ASD. In those participants who met DSM-5 diagnostic criteria, 33% had hyperactive behavior and another

TABLE 1 Description of study selected.

Authors (year)	Title	Objective	Results	Conclusions	N	Age (SD)	Journal (IF)
Characteristics and general symptomatology							
Reilly et al. (2015)	Features of autism spectrum disorder (ASD) in childhood epilepsy: a population-based study.	To describe neurobehavioral comorbidity in children with both epilepsy and ASD, to identify the distribution of features of ASD in children with epilepsy, and to assess the utility of the ASSQ as a screening tool for ASD in children with epilepsy.	Parents reported significantly ($P < 0.05$) more features of ASD on the ASSQ compared with teachers. Factors significantly associated with responses on the ASSQ included respondent (parents reported more features), school placement (more features in specialized settings), and respondent by school placement interaction.	Effective screening for ASD in children with epilepsy will need a consideration of the impact of informant and school placement on ratings.	117	5–15 (2.16)	Epilepsy Behav (2.96)
Berg et al. (2011)	Risk and correlates of autism spectrum disorder in children with epilepsy: a community-based study.	To estimate the prevalence of ASD in a representative, prospectively identified, community-based cohort of children with epilepsy and provide information about the main factors associated with ASD in this context.	West syndrome (prevalence ratio = 4.53, $P = 0.002$), and intellectual impairment (prevalence ratio = 4.34, $P = 0.002$), were independently associated with autism spectrum disorder. Absent West syndrome, male gender was associated with autism spectrum disorder (prevalence ratio = 3.71, $P = 0.02$).	The most important determinants of autism spectrum disorder in the general population (intellectual impairment and male sex) are also important in young people with epilepsy.	613	3.5–10 (6.72)	Journal of child neurology (2.36)
Sahyabama (2019)	Clinical characteristics and demographic profile of children with Autism Spectrum Disorder (ASD) at child development clinic (CDC), Penang Hospital, Malaysia.	To explore socio-demographics and clinical characteristics of children with Autism Spectrum Disorder (ASD) at Child Development Clinic (CDC), Penang Hospital.	History of speech regression was noted in 14.8%, epilepsy and genetic disorders in 9.4% and 5.7% respectively. Sleep problems was reported in 29.3%, dietary issues 22.1%, challenging behavior 24.2% and ADHD 14.2%. Mean age of the father and mother at birth was 33.6 and 31.6 years respectively.	Report a higher male to female ratio and mean age at referral with some similar rates of neurodevelopmental and medical comorbidities and relatively younger parental age with higher parental education levels.	331	5.6 (3.6)	The Medical journal of Malaysia (0.53)
Jokiranta et al. (2014)	Epilepsy among children and adolescents with autism spectrum disorders: a population-based study.	To examine associations between epilepsy and autism spectrum disorders (ASD).	Epilepsy was associated with ASD regardless of the subgroup after adjusting for covariates. The associations were stronger among cases with intellectual disability, especially among females.	Their findings emphasize the importance of examining neurodevelopmental pathways in ASDs, epilepsy, and intellectual disability.	4,705	5.5–9.3 (3.3)	Journal of autism and developmental disorders (4.34)
Sharma et al. (2021)	Epilepsy and EEG Abnormalities in Children with Autism Spectrum Disorders.	To evaluate the prevalence of epilepsy and electroencephalographic abnormalities in children with autism spectrum disorders (ASD) and determine their risk factors.	Epilepsy was reported in 23% and subclinical electroencephalographic abnormalities were documented in 8%. The most common seizure types were generalized-onset tonic-clonic (48%), focal-onset with impaired awareness (17%), and focal to bilateral tonic-clonic seizures (17%). In children with subclinical epileptiform discharges, focal abnormalities were most common (75%) and were maximally seen over the temporal region (50%). Subnormal intellect (88.6%) and abnormal global developmental score (82%) were noted in the majority of children.	Epilepsy is seen in up to one-fourth children with ASD. Female gender and adverse perinatal events are independent risk factors for epilepsy. Subclinical or isolated EEG abnormalities are associated with abnormal neurological examination.	100	3–14 (5.6)	Indian Journal Pediatric (5.31)

(Continued)

TABLE 1 (Continued)

Authors (year)	Title	Objective	Results	Conclusions	N	Age (SD)	Journal (IF)
Norredgen et al. (2013)	Children with autism spectrum disorder who do not develop phrase speech in the preschool years.	To examine this ratio in a population-based community sample of children.	The proportion of children who met the criteria for non-verbal, minimally verbal, and phrase speech were 15, 10, and 75%, respectively.	The single most important factor linked to expressive language was the child's cognitive level, and all children classified as being non-verbal or minimally verbal had intellectual disability.	165	4-6 (2)	Autism (5.68)
Celik et al. (2021)	Evaluation of the clinical characteristics of children with autism spectrum disorder and epilepsy, demonstrate the perception of their parents on quality of life.	To examine the clinical conditions that mediate this comorbidity, compare parental quality of life in isolated ASD and ASD with epilepsy, demonstrate the relationships between clinical and EEG findings obtained in diagnostic evaluation, and examine the results in light of the literature.	Mean (SD) total scores in the Quality of Life in Autism Questionnaire were 131.84 (10.68) among mothers of children with ASD-epilepsy and 148.33 (14.03) among mothers of children with ASD alone ($P < 0.001$).	Many psychiatric and medical conditions can co-occur with ASD. Determining the prognostic criteria for ASD is of great importance in coordinating lifelong autism rehabilitation. Improving autism-specific symptoms will benefit children with ASD as well as help mitigate parental anxiety.	154	3.5–16.3 (3.16)	Epilepsy research (2.75)
Gender differences							
Amiet et al. (2013)	Does epilepsy in multiplex autism pedigrees define a different subgroup in terms of clinical characteristics and genetic risk?	The aim of this study was to assess: 1. The prevalence of epilepsy in multiplex autism and its association with genetic and non-genetic risk factors of major effect, intellectual disability and gender. 2. Whether autism and epilepsy co-segregate within multiplex autism families	The prevalence of epilepsy was 12.8% in cases with ASD and 2.2% in siblings without ASD ($P < 0.05$). With each RCPM or VABS measure, the risk of epilepsy in multiplex autism was significantly associated with intellectual disability, but not with gender. Identified risk factors (genetic or non-genetic) of autism tended to be significantly associated with epilepsy ($P = 0.052$). When children with prematurity, pre- or perinatal insult, or cerebral palsy were excluded, a genetic risk factor was reported for 6/59 (10.2%) of children with epilepsy and 12/395 (3.0%) of children without epilepsy ($P = 0.002$).	Epilepsy in multiplex autism may define a different subgroup in terms of clinical characteristics and genetic risk.	664	9.2 (5.02)	Molecular autism (6.26)
Thomas et al. (2017)	Brief Report: Prevalence of Co-occurring Epilepsy and Autism Spectrum Disorder: The U.S. National Survey of Children's Health 2011-2012.	To quantify the co-occurrence of epilepsy and ASD in a large nationally representative sample of the US.	In the overall analytic sample of 85,248 children ages 2-17, there were 1,694 children with ASD (prevalence of 1.8 %) and 1,083 children with epilepsy (prevalence of 1.2 %). Epilepsy was reported to co-occur in 8.6 % of ASD cases.	In children with ASD, the co-occurrence of epilepsy was associated with increasing child age, female gender, intellectual disability, speech problems and lower socioeconomic status.	85,248	2-17 (2.23)	Journal of autism and developmental disorders (5.25)
Viscidi et al. (2013)	Clinical characteristics of children with autism spectrum disorder and co-occurring epilepsy.	To estimate the prevalence of epilepsy in children with Autism Spectrum Disorder (ASD) and to determine the demographic and clinical characteristics of children with ASD and epilepsy in a large patient population.	The average prevalence of epilepsy in children with ASD 2-17 years was 12.5% among children aged 13 years and older, 26% had epilepsy. Epilepsy was associated with older age, lower cognitive ability, poorer adaptive and language functioning, a history of developmental regression and more severe ASD symptoms	This is among the largest studies to date of patients with ASD and co-occurring epilepsy. Based on a representative sample of children with ASD, the average prevalence of epilepsy is approximately 12% and reaches 26% by adolescence. Independent associations were found between epilepsy and older age and lower cognitive ability.	5,815	13-17 (3.12)	PLoS ONE (3.75)

(Continued)

TABLE 1 (Continued)

Authors (year)	Title	Objective	Results	Conclusions	N	Age (SD)	Journal (IF)
Linguistic profile in participants with ASD and epilepsy							
Saxe-Ridebow et al. (2016)	The development of pragmatic skills in children after hemispherectomy: contribution from left and right hemispheres.	To analyze whether any correlation exists with age at surgery and side of surgery on pragmatic skills following H.	The whole group had significant deficits in all three measures. We demonstrated a statistically significant crossed interaction between the side of H and the age of H with pragmatic language impairments $F(1,36) = 17.48$, $P = 0.0002$ and discourse impairments $F(1,36) = 5.80$, $P = 0.021$ in left early H and in right late H patients.	These results emphasize for the first time that hemispherotomized children have pragmatic language impairments that are independent of receptive language.	39	12.8 (2, 6)	Epilepsy Behav (2.96)
Howlin et al. (2014)	Cognitive and language skills in adults with autism: a 40-year follow-up.	To assess cognitive and language change in a cohort of individuals first diagnosed as children and followed up to mid-late adulthood.	For the majority of participants ($N = 45$; 75%), who were testable both as children and adults, IQ remained very stable and language also improved over time.	For most individuals with autism who had an IQ in the average range (i.e. ≥ 70) as children, childhood IQ proved a reliable predictor of cognitive functioning well into mid- to late adulthood.	60	2–13 (6)	Journal Child Psychol Psychiatry (2.21)
Hoglund Carlsson et al. (2013)	Coexisting disorders and problems in preschool children with autism spectrum disorders.	To analyze cooccurring disorders and problems in a representative group of 198 preschool children with autism spectrum disorders (ASD) who had had interventions at a specialized habilitation center.	Children with autism had a mean of 3.2 coexisting disorders or problems, the ALC/Asperger group had a mean of 1.6, and children with autistic traits had a mean of 1.6. The most common disorder/problems in the total group pertained to language problems (78%), intellectual disability (ID) (49%), below average motor function (37%), and severe hyperactivity/ADHD (33%).	The results accord with the concept of early symptomatic syndromes eliciting neurodevelopmental clinical examination (ESSENCE) and highlight the need of considering ASD in a broad perspective taking also other cooccurring developmental disorders into account.	198	4, 5–6, 5 (2)	Scientific World Journal (2.10)
Cognitive profile in participants with ASD and epilepsy							
Villeneuve et al. (2014)	Cognitive and adaptive evaluation of 21 consecutive patients with Dravet syndrome.	To assess the cognitive and adaptive profiles of school-aged patients with Dravet syndrome (DS), we proposed to evaluate the intelligence and adaptive scores in twenty-one 6- to 10-year-old patients with DS followed in our institution between 1997 and 2013.	They did not find any significant correlation between the IQ or developmental quotient assessed between 6 and 10 years of age and the quantitative and qualitative parameters of epilepsy during the first 2 years of life in this small group of patients.	Despite an overall moderate cognitive deficit in this group of patients, the Vineland Adaptive Behavioral Scales described an adaptive/behavioral profile with low communication and autonomy capacities, whereas the socialization skills were more preserved.	21	6–10 (2.3)	Epilepsy Behav (2.96)
Ewen et al. (2019)	Epilepsy and Autism Severity: A Study of 6,975 Children.	To examine the extent to which ID, language dysfunction, and core autism symptoms mediate the relationship between ASD and epilepsy, and to assess a specific link between developmental regression and epilepsy in children with ASD.	They found that each severity factor—presence of intellectual disability, presence of language atypicalities, ASD-specific symptoms severity, and presence of motor issues—individually predicted a small increased risk for epilepsy, countering the argument that IQ alone is a risk factor.	Although severe epilepsy syndromes such as Landau-Kleffner syndrome are known to cause autistic-like symptoms following developmental regression, there is controversy about whether other forms of epilepsy are associated with the more common developmental regression seen in many young children with epilepsy.	6,975	6–17.9 (3.21)	Autism research (4.63)

(Continued)

TABLE 1 (Continued)

Authors (year)	Title	Objective	Results	Conclusions	N	Age (SD)	Journal (IF)
Eon et al. (2014)	Routine developmental, autism, behavioral, and psychological screening in epilepsy care settings.	To assess the value of this screening and its validity for determining previously unidentified ("actionable") problems in children with epilepsy.	Positive findings by test were 82% (ASQ), 54% (mCHAT), 15% (SQQ), and 58% (SDQ). Findings were actionable in 46 children (20%); 18% of findings in children with established epilepsy and 23% of findings in patients with new-onset epilepsy. Of the 46 children for whom further referrals were made, the parents of 28 (61%) have pursued further evaluations.	Children with existing and new-onset diagnoses of epilepsy had actionable screening findings. These findings support the development of systematic screening of comorbidities for children with epilepsy.	236	4–6 (1)	Developmental Medicine and Child Neurology (2.77)

33% had linguistic and cognitive disturbances. The remaining third had no relevant data. It should be noted that hyperactivity features are common in children with ASD, especially in preschool children. Therefore, although there is a high rate of behavioral and psychiatric comorbidity in users with epilepsy and ASD, no significant difference was observed with the group of people with ASD without epilepsy compared with the group of children with ASD and epilepsy. These data follow the same trend as those obtained by functional neuroimaging techniques. For example, the research by [Sharma et al. \(2021\)](#) demonstrated the presence of specific EEG alterations in children with epilepsy and ASD, and further confirmed that these techniques allowed the identification of almost one fifth of children with ASD.

In another study carried out by [Berg et al. \(2011\)](#) a more specific range of ages of onset of diagnosis was included, specifically between 5 and 9 years. The results showed that 3.71% of the infantile population presented ASD and epilepsy in a comorbid manner. The study highlights that adolescents with childhood-onset epilepsy frequently have other disorders, such as hyperactivity, disruptive behavior, or cognitive or language difficulties. However, it is worth mentioning that no information was provided on the nature of the epilepsy in the participants and the characteristics that distinguished users with ASD from those without. Another interesting study regarding autism, epilepsy and age is the one performed by [Viscidi et al. \(2013\)](#). In it the authors state that in people with ASD two major peaks of epilepsy prevalence appear according to age. The first occurs in childhood, which corresponds to what was mentioned above. However, these authors state that there is another large peak around 12–14 years of age, since adolescents with the potential to develop epilepsy have more time to develop during their evolutionary course, something that is corroborated by studies such as that of [Tuchman and Cuccaro \(2011\)](#).

Age is a primary factor in the diagnosis of epilepsy, as there are works, such as that of [Sathyabama \(2019\)](#), showing that early recognition and initiation of early intervention result in better prevalence and improvement of symptoms. This study analyzed the clinical and symptomatologic characteristics of the ASD population in a sample aged 6 to 9 years. The results showed that 46.1% of the children with ASD had a comorbid psychological or medical diagnosis while 10.1% of them had epilepsy. The frequency of comorbid hyperactivity symptoms was 14.2%, while medical disorders were 15.1%, making a total of 29.3%. It was also indicated that children with ASD with less severity in their symptoms are diagnosed at relatively late ages, between 7 and 10 years, something that is also corroborated by other studies such as [Mannion and Leader \(2014b\)](#).

Other interesting results related to the general characteristics of the user with ASD and epilepsy are those of the study by [Jokiranta et al. \(2014\)](#), where three main findings stand out. Firstly, epilepsy was significantly associated with ASD and showed ten times higher odds of appearing together with ASD. Within this association, intellectual disability (ID) appeared as a predictor of altered cognitive functioning in children with ASD and epilepsy. This is because the presence of ID produces a linguistic and cognitive performance well below what is expected for their age. Secondly, effective treatment of comorbidity between ASD and epilepsy requires a thorough evaluation and screening to establish

a differential diagnosis matched with correct pharmacological treatment. This is because in the study by [Jokiranta et al. \(2014\)](#), the authors confirm that all epileptic syndromes present a very similar concurrence with ASD, i.e., there is none that appears more frequently. Consequently, all syndromes must be considered when identifying them. This can make differential diagnosis very difficult, since it is easy for symptoms such as stereotyped behaviors or repetitive movements associated with ASD to be confused with epileptic symptoms, or *vice versa*. Thirdly, although the data indicate that the greatest risk of epilepsy occurs in early childhood, before the age of 3 years, the age of onset of epilepsy was not a distinguishing variable between users with and without ASD.

An interesting clinical feature in these disorders is the presence of disruptive behaviors. Research conducted by [Norrelgen et al. \(2015\)](#) showed that, in people with ASD and epilepsy, there was a higher prevalence of this type of behavior in the home environment than in the academic environment due to language and communication difficulties. A priori, it could be assumed that a greater number of cases and severity would be found in ASD residing in institutions or special education centers where children with greater linguistic and cognitive compromises go to school. However, significant differences were found in favor of the student assessment scores obtained by parents and teachers in regular schools, as opposed to those recorded by teachers in special education schools. According to [Norrelgen et al. \(2015\)](#), this is because in the context of the special education school, the child with ASD lives with other students with disorders or pathologies of equal or greater severity and, therefore, the characteristics of this may go more unnoticed or are addressed more efficiently. On the other hand, in the home context, parents may perceive more and worse disruptive behaviors or have more problems to address them.

Finally, regarding quality of life, in [Celik et al. \(2021\)](#) study on quality of life in ASD, the records of 154 patients were retrospectively analyzed to investigate the effect of the epilepsy diagnosis and factors related to how they perceived their life and the consequences of their children's diagnosis using the Quality of Life in Autism Questionnaire ([Eapen et al., 2014](#)). When an analysis of differences in quality of life among the participants in this study was conducted, a significant difference was appreciated between the mothers of 19 children with ASD-epilepsy and those of 30 children with ASD. Mothers of children with a combination of epilepsy and autism had a lower overall perceived quality of life and greater autism-specific difficulties compared to mothers of children with autism alone.

Comparison between users with ASD and epilepsy with different sexes

The first included study referring to the sex of the patients was that of [Amiet et al. \(2013\)](#). In this work it was found that the prevalence of epilepsy was 41.2% in individuals with autism and intellectual disability vs. 11.1% in individuals with autism and normal intelligence, and that the worse the level of adaptive behavior the higher the prevalence of epilepsy. With regards to sex, the authors found that, in general, the prevalence of ASD was higher in males, but when the factors of epilepsy

and intelligence quotient (IQ) are introduced, female sex appears as a significant variable. That is, the risk of epilepsy in people with ASD was significantly associated with intellectual disability in women, and that these differences are independent of IQ. For these authors, there are two risk and severity factors for epilepsy in autism: intellectual disability and female sex. In another study by [Sharma et al. \(2021\)](#), similar results were found, showing that the proportion of epilepsy in girls (24%) with ASD was higher than in boys (11%). In addition, these authors observed language and cognitive difficulties (82%) and a lower-than-normal IQ (88.6%) in most of the girls with ASD, which led them to state that this greater intellectual and motor disability in girls could be a consequence of the comorbidity between epilepsy and ASD.

A third study by [Thomas et al. \(2017\)](#), again, found significant differences in demographic and clinical characteristics in users with ASD and epilepsy with regards to sex. Overall, it was observed that there was a sevenfold increased risk of epilepsy in ASD compared to the general population without this disorder (8.6 vs. 1.2%). A higher prevalence of ASD was found in boys than in girls, but the latter had a higher risk of comorbidity with epilepsy, corroborating the data of [Bolton et al. \(2011\)](#). A higher prevalence of comorbid epilepsy was also seen in the population up to 17 years of age, as well as higher rates of intellectual disability and concurrent speech problems. Finally, epilepsy was more common in children with ASD with lower family income, consistent with what has been observed in the general population without ASD.

Finally, it is worth mentioning the work of [Viscidi et al. \(2013\)](#), whose results, once again, seem to confirm that there is a higher proportion of girls with ASD who have a low cognitive profile, together with an intellectual disability, which correlates with the presence of epilepsy. Another interesting finding, with respect to prevalence, is the existence of a greater number of children with ASD with epilepsy between the ages of 3 and 6 years, since the manifestations of epilepsy did not become evident until that age. This clinical profile was similar in both boys and girls, so no significant differences were found according to sex.

The linguistic profile of the user with ASD and epilepsy

In the study by [Norrelgen et al. \(2015\)](#), a sample of 4- and 5-year-old children with a diagnosis of ASD or ASD and epilepsy who had not developed sentence utterance and structuring was selected. The data showed that approximately one in four children with ASD did not exhibit verbal language and that children who exhibited correct sentence production had a higher mean age than the group that did not exhibit non-verbal language. The observed age differences, according to the authors, could indicate that children with ASD acquire sentence production during the later preschool years before starting the primary school cycle. However, children with ASD and epilepsy would not acquire oral language production until later years, approximately after the age of 4 and 5 years, and may not even present oral language during the entire infantile stage. The results also showed that children with ASD and epilepsy present a greater delay in the acquisition of oral communication, compared to those children who do not have epilepsy.

Regarding the linguistic abilities of these users, the study by [Save-Pédebois et al. \(2016\)](#), analyzed the role of the left and right hemispheres in pragmatic skills in people with ASD and epilepsy. In this work, they show how children with right hemisphere damage develop an altered cognitive-linguistic profile from the early language stage, characterized by normal verbal reasoning, but with limitations in phonological, grammatical, and syntactic skills. Along with these alterations, the authors found a significant reduction in their pragmatics, with the way children use language to relate to their immediate environment being significantly affected. These data have been corroborated by [Howlin et al. \(2014\)](#), who studied comorbidity with language disorders in childhood patients with ASD and epilepsy. The rate of occurrence of language problems in these patients was very high (88.8%), although language and communication impairments may vary depending on the different degrees of ASD or type of epilepsy. For these authors, the imbalance in language development in children with ASD is the main symptom indicating a greater degradation of the individual's maturational development.

Finally, it is worth mentioning the work of [Höglund Carlsson et al. \(2013\)](#), which not only shows a high prevalence (56%) of language disorders in children with ASD and epilepsy, but also that this comorbidity correlates significantly with other areas, such as learning or physical development. For these authors, language impairment will negatively influence cognitive development and the degree of autonomy, needs and support of the person with ASD and epilepsy.

The cognitive profile of the user with ASD and epilepsy

Regarding the cognitive profile of ASD children with and without epilepsy, in the study by [Villeneuve et al. \(2014\)](#), an analysis of the cognitive performance of individuals with ASD between 6 and 10 years of age was carried out to assess a global cognitive evaluation using the WISC-V ([Wechsler, 2015](#)). The highest rate of comorbidity was established with language alterations at 78%, followed by cognitive alterations at 44%. The authors did not find severe cognitive alterations at early ages, which they justified could be due to the fact that in that age range the requirements of the environment do not yet condition the appearance of this type of limitations. For them, it is in the school stage, which is much more demanding, where this gap in the acquisition of basic concepts and learning appears in comparison with the normative group of the same age. This could be one reason why children with ASD often do not see a neurologist until later ages, which in turn can lead to biases, delays, and errors in diagnosis, even more so when there are frequent comorbidities with ASD or intellectual disability (ID). In fact, it is essential to establish as soon as possible what the patient's symptoms are, since as the research by [Viscidi et al. \(2013\)](#) highlights, ID and ASD symptoms contribute independently to the risk of epilepsy in children with ASD. In this regard, the risk of epilepsy in children with ASD is not comprehensively explained by ID, which can complicate making an accurate differential diagnosis.

On the other hand, a factor that greatly affects the cognitive development and autonomy of people with ASD and epilepsy are

disruptive behaviors, as they affect all the patient's contexts, impair their adaptability to the environment and negatively impact all activities of daily living. Studies such as [Norrelgen et al. \(2015\)](#) or [Ewen et al. \(2019\)](#) show that DI is directly associated with the presence of epilepsy, increased ASD symptoms and disruptive behaviors, and that children with ASD and epilepsy are at risk of presenting disruptive behaviors more frequently due to the higher probability of having a low IQ.

Finally, it is important to mention the study by [Eom et al. \(2014\)](#), which shows the enormous difficulty in making a correct assessment and diagnosis of ASD and epilepsy and their cognitive competencies, since it requires a detailed exploration and interpretation of the neurological and developmental status of the child. However, this work shows that the protocols of routine and screening evaluations of these users that are carried out in primary care centers are sensitive for the detection of cognitive alterations. However, to acquire greater reliability and validity in the assessment of the cognitive profile of these users, it is necessary to perform the examinations throughout the maturational process. For these authors, the use of tests of longer duration and complexity are not as useful as screening tests, either because of problems such as the time that can be dedicated to the patient, the context in which they are applied or the individual and evolutionary characteristics of the child.

For all these reasons, this review once again emphasizes the importance of an accurate differential diagnosis, in which all the clinical, cognitive-linguistic, and contextual characteristics of subjects with ASD and epilepsy are considered, emphasizing the need for an exhaustive evaluation of the characteristics of this population.

Discussion

The main objective of this systematic review was to analyze the available evidence on the co-existence and relationship of epilepsy in the deterioration of cognitive-linguistic skills of those users who present an ASD in infancy. Likewise, the specific objectives were to analyze the general symptomatology of children with an ASD and epilepsy, and to explore the existing differences between both sexes in children with this comorbidity.

Regarding the general symptomatology of these comorbid disorders, the scientific literature has shown that, in neurological conditions in the pediatric setting, the impact on cognition and language exceeds the expectations of focal epilepsy and affects the function of multiple areas ([Ortiz et al., 2009](#); [Olmos-Hernández et al., 2013](#); [Acquesta et al., 2018](#)). However, research in this field is very limited due, in part, to the scarcity of studies, the small number of homogeneous samples, the variability of the manifestations of neurological alterations in clinical variables and their etiology; making studies inconclusive ([Braakman et al., 2015](#); [van Ijzerson et al., 2015](#); [Specchio and Curatolo, 2021](#)). So far, although changes in child development are an important factor which negatively influences the prognosis of children with epilepsy, none of the selected studies have specifically analyzed the effects of epilepsy and ASD comorbidity, their overall development, and their relationship with cognitive-linguistic competencies in the infantile population and gender in this population.

Regarding the differences with regards to age and sex, the reviewed articles show that if we observe the age of the participants in the studies, we will find that late diagnoses are milder precisely because the symptoms are less limiting. Therefore, many profiles with this comorbidity go unnoticed until later ages, when the demands of the environment will be more demanding and, therefore, will show the limitations of people with ASD and epilepsy. Likewise, in the female sex there was a higher prevalence than in the male sex with regards to the comorbidity of ASD and epilepsy. In addition, girls with this comorbidity show worse intellectual performance, presenting with ID in a high percentage of participants in the selected studies (Amiet et al., 2013; Thomas et al., 2017; Sharma et al., 2021). However, girls with ASD and epilepsy exhibit greater deficits in the language and cognition section (Thomas et al., 2017). It can be concluded that this symptomatologic profile could be due to the development of epilepsy, which is more pronounced in girls than in boys, especially at early ages, and that it causes minors to present a significant alteration in intellectual capacity which negatively affects quality of life and overall child development (Viscidi et al., 2013).

Regarding cognitive changes in pediatric epilepsy, it should be noted that they are part of the current definition of this comorbidity and have a significant impact on the adaptation of children to the environment, on the relationship with peers and on cognitive-linguistic development. Thus, they determine a poor prognosis and a poor quality of life for both the user and the entire family environment around him/her. In the last decade, the negative impact of early epilepsy on cognitive ability has been confirmed, establishing itself as a powerful predictor of difficulties in the development of these functions in children with ASD (Karrasch et al., 2017) and causing all areas of language and cognition to show a reduced performance. When their impact is analyzed in relation to other clinical variables such as duration, frequency, or time of development, the early onset of this disorder is the variable that presents the greatest predictive weight in the production of these alterations. This may be due to the fact that, in childhood, the mechanisms of neuronal plasticity are at their peak, trying to consolidate the mechanisms of learning and memory through excitatory processes (Jensen, 2011). However, an excess of neuronal activation due to epileptic episodes can have a cascading effect that impairs the entire subsequent cognitive development of children. Previous studies have also shown that all these factors correlate negatively with IQ (Lee et al., 2014) and cognition (Riva et al., 2005; Campiglia et al., 2014). Seizures in the first year of life are associated with greater impairment in intelligence level (Campiglia et al., 2014), and may cause metabolic or structural abnormalities, which may later affect cognitive development (Braakman et al., 2012; Lee et al., 2014). In ASD, cognitive conditions are particularly sensitive to the early onset of epilepsy (Malcher-Lopes, 2014), which supports the early vulnerability hypothesis stating that seizures in the first year of life are associated with greater impairment in intelligence level (Campiglia et al., 2014). This hypothesis alludes to the period in which a minor presents a high risk of developing alterations in their evolutionary milestones that would imply a considerable deterioration in their motor, adaptive,

communicative, cognitive, or social abilities. In this regard, it has been shown that the age span of up to 3 years old could be the most vulnerable critical point, especially in terms of memory and cognitive flexibility (Anderson et al., 2010).

Regarding language skills, the performance of children with ASD and epilepsy appears to be lower than that found in children with ASD alone (Höglund Carlsson et al., 2013; Sharma et al., 2021). This may indicate that, in the case of epilepsy, the language skills assessed may be significantly impaired (MacAllister and Schaffer, 2007); mainly those dealing with oral language utterances. This could be explained by the alteration of different functional areas in charge of language production, highlighting pragmatics as the most notorious dimension. However, other aspects such as semantics, morphosyntax and phonology can also exhibit slight difficulties (Braakman et al., 2015). Syntactic structure is also altered, since children with ASD and epilepsy produce errors when organizing the elements of a sentence with a correct grammatical structure (Save-Pédebos et al., 2016). Regarding the location of the alterations, functional neuroimaging studies with EEG have shown that the activation of the multimodal cortex during semantic processing is supported by the ventral network connecting the frontal lobe and temporal lobe through the inferior occipital frontal lobe. This implies that people with ASD and epilepsy show alterations in lexical acquisition, as well as in the production of oral discourse in accordance with their maturational age (Friederici and Gierhan, 2013). Furthermore, the proposed results may explain the lack of significant differences between the left and right hemispheres, especially in language skills. This is due to differences with adults, as the left hemisphere language neural network of children is not as significantly lateralized. All this shows that activation contrasts with the contralateral cortex during the process of oral communication (Save-Pédebos et al., 2016).

Finally, it should be noted that there is a lack of scientific literature that addresses this issue directly and obtains significant data. At present, only a few studies address the linguistic and cognitive characteristics of children with ASD and epilepsy, so this systematic review has only been able to select a total of 18 articles that meet the required quality criteria. In this sense, there is no research in the current scientific literature that shows a comparison between cognitive and linguistic skills in children with comorbidity between ASD and epilepsy. All this leads us to conclude that the present systematic review has a useful value for the field of research with ASD, being a novel study that provides accurate and precise information on a current problem. This may open the door to new lines of research that relate the linguistic-cognitive aspects of users with ASD and epilepsy, which highlights the need to focus on this topic. This is imperative, since in the coming years a considerable increase in profiles with these characteristics and conditions is expected due, in part, to poor nutrition, exposure to narcotic substances during gestation, obesity, existence of a psychiatric disorder, advanced age or autoimmune diseases, stress, and infections of the mother (Arroyo, 2022). Therefore, relevant information should be provided to the professionals who will oversee the enhancement of the skills of this population, as well as improving their quality of life.

Cano-Villagrasa et al.

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Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Author contributions

AC-V, ML-Z, and FM-F conceptualized the study. AC-V wrote the review protocol and original draft of this manuscript, which was reviewed by ML-Z and FM-F. AC-V and ML-Z conducted the database search. AC-V and FM-F screened the studies and extracted the data. FM-F acted as a third reviewer and resolving disagreements. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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5.2. ARTÍCULO 2

López-Zamora, M., Cano-Villagrasa, A., Cortés-Ramos, A., & Porcar-Gozalbo, N. (2023). The Influence of Sleep Disorders on Neurobiological Structures and Cognitive Processes in Pediatric Population with ASD and Epilepsy: A Systematic Review. *European journal of investigation in health, psychology and education*, 13(11), 2358–2372. <https://doi.org/10.3390/ejihpe13110166>



Systematic Review

The Influence of Sleep Disorders on Neurobiological Structures and Cognitive Processes in Pediatric Population with ASD and Epilepsy: A Systematic Review

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Abstract: Autism Spectrum Disorder (ASD) and epilepsy are increasingly prevalent comorbidities in our society. These two disorders are often accompanied by other comorbidities, such as sleep disorders, significantly impacting the quality of life of individuals with ASD and epilepsy. To date, clinical approaches have primarily been descriptive in nature. Therefore, this study aimed to analyze the relationship between ASD, epilepsy, and sleep disorders, exploring neurobiological dysfunctions and cognitive alterations. A total of 22 scientific articles were selected using a systematic literature review following the criteria established using the PRISMA model. The selected articles were gathered from major databases: Medline, PubMed, PsycINFO, Google Scholar, and Web of Science. Inclusion criteria specified that study participants had an official diagnosis of ASD, the article precisely described the evaluation parameters used in the study participants, and individual characteristics of the sleep disorders of the study participants were specified. The results indicate, firstly, that the primary cause of sleep disorders in this population is directly linked to abnormal serotonin behaviors. Secondly, significant alterations in memory, attention, and hyperactivity were observed. In conclusion, sleep disorders negatively impact the quality of life and neurocognitive development of the pediatric population with ASD and epilepsy.

Keywords: childhood; ASD; epilepsy; sleep disorders; systematic review



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1. Introduction

Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder that typically begins in the first 30 months of life and affects the normal development of the brain in terms of social and communication skills [1]. Common characteristics of ASD encompass a wide and heterogeneous range of symptoms, including impaired social relationships [2], difficulties in verbal and non-verbal communication [3], problems processing sensory information [4], as well as restricted and repetitive patterns of behavior [5].

Between 5–40% of children with ASD develop epilepsy during their developmental course [6]. This high incidence appears to follow a bimodal distribution, with an initial peak between 1–5 years of age and a second peak during prepuberty and adolescence [7]. There is a significant difference in the rates of epilepsy in children with ASD without comorbid conditions compared to those who exhibit neurological disorders, such as intellectual disability, hypotonic syndrome, or cerebral palsy, which exhibit epilepsy. In this second group, epilepsy rates are higher, affecting more than 60% of patients [8].

Among the comorbid disorders in the pediatric population with ASD, sleep disorders (SD) stand out, primarily manifesting as difficulties in sleep onset, maintenance, nighttime awakenings, and sleep apnea [9]. Generally, individuals with ASD have a multifactorial etiology, tend to be chronic, and have negative consequences on the patient and/or the family environment, both in their progression and quality of life [10]. Sleep disorders (SD) are reported in 6–25% of the pediatric population, but this figure rises to between 50–95% in children with ASD and epilepsy [11]. SD in the population with ASD and epilepsy can be similar to those seen in the general pediatric population, with the most prevalent being onset insomnia, nighttime awakenings, and reduced total sleep time [12].

SD should hold a prominent place in the diagnostic and therapeutic stage for individuals with ASD and epilepsy. The pediatric population with ASD and epilepsy has proven effects on cognition and behavior, which become even more evident in patients with this comorbidity. These effects can be specific to certain genetic conditions and may, therefore, require a specific clinical approach and intervention [13]. The pathophysiology of SD in children with ASD and epilepsy is multifactorial, with some patients having a direct relationship with their specific genetic diagnosis or phenotype. SD in this population is often associated with common causes of sleep problems in the general pediatric population [14]. These factors are related to neurobiochemistry, seizures and epileptic syndromes, and specific cognitive impairments seen in this population. Regarding the neurobiochemistry of SD, various neurobiological anomalies have been described in ASD and epilepsy, highlighting alterations in neurotransmitters and hormones involved in sleep regulation [15]. On one hand, serotonin, through its modulation of cholinergic neurons in the brainstem, plays a critical role in suppressing REM sleep and promoting wakefulness [16]. However, a decrease in serotonin synthesis has been observed in children with ASD compared to those who do not have it [17]. On the other hand, melatonin, produced by the pineal gland, is a key regulator of circadian rhythms, and a decrease in melatonin during sleep has been reported in children [18] and young adults [19] with ASD and epilepsy. Therefore, due to the neurobiological alterations in children with ASD, sleep can be affected by this disorder. Additionally, it is observed that individuals with ASD who have epilepsy have a direct relationship with sleep disorders.

Epileptic syndromes, particularly those affecting the frontal lobe, are characterized by seizures that occur exclusively or predominantly during non-rapid eye movement sleep (NREM) [20]. Interictal epileptiform discharges (IEDs) are sharp waves or spikes that occur on an electroencephalogram (EEG) between seizures. IEDs refer to abnormal electrical brain activity between seizures in individuals with epilepsy. Chronic sleep deprivation can lower the seizure threshold, making it more likely for IEDs to trigger actual seizures. This connection underscores the importance of maintaining good sleep habits and managing sleep disorders in epilepsy patients to reduce the risk of seizures. Like seizures, IEDs are activated during NREM sleep and suppressed during REM sleep [21]. Chronic sleep deprivation can be caused by sleep disorders that disrupt and interfere with sleep, such as obstructive sleep apnea (OSA). In OSA, breathing pauses awaken the patient from sleep due to a protective response, resulting in fragmented sleep. A study on the treatment of OSA in children with ASD and epilepsy has shown an improvement in seizure control [22]. Other sleep disorders, such as insomnia, can also lead to sleep deprivation and worsen seizure control [23]. Therefore, paying attention to sleep in children with ASD and seizures and implementing appropriate treatment strategies can result in better seizure control.

Epileptic seizures themselves can impact sleep, and this influence is not limited to the moment of seizure onset. Complex partial seizures of the temporal lobe decrease REM sleep, especially when they occur during sleep but also when they happen the day before sleep onset [24]. These changes may result from disruption in circadian rhythms or hormonal influences resulting from seizures.

Regarding the cognitive impairments that seizures related to sleep and IEDs produce in learning, memory, and daytime behavior, these are still largely unknown and represent a rapidly expanding area of research [25]. Sleep-related problems have been shown to

disrupt daytime behavior and academic performance [26]. Sleep-related problems are significantly more common in children with ASD and epilepsy. Researchers have attempted to establish a correlation between behavioral problems identified in epilepsy patients and various sleep indices. In Zwaigenbaum et al.'s study [27], it was found that rapid eye movement latency, apnea duration, and periodic leg movements in children with epilepsy correlated with depression, inattention, hyperactivity, and/or oppositional defiant disorder. Therefore, sleep disorders in the pediatric population with ASD and epilepsy constitute a comorbidity that negatively influences overall developmental progress, impairing the acquisition of skills such as communication, attention, emotional control, and the quality of life of this group.

Based on this, the aim of this systematic literature review was to compile relevant data from research on the relationship between sleep disorders and the pediatric population with ASD and epilepsy. Furthermore, the specific objectives were to analyze the neurobiological alterations related to sleep disorders and describe the cognitive performance related to the pediatric population diagnosed with ASD and epilepsy. The hypotheses of this systematic review were as follows: (I) It is expected that the neurobiological and neurochemical alterations described in children with ASD and epilepsy will disrupt brain activity and give rise to various sleep disorders, and (II) it is expected that sleep disorders in this population will limit cognitive competencies and alterations in basic and higher-order cognitive processes will be observed.

2. Materials and Methods

This work presents a systematic literature review on ASD and epilepsy and how sleep disorders are affected in this population. The question to be addressed is the relationship between sleep disorders, cognitive impairments, and emotional disturbances in family members in the pediatric population with ASD and epilepsy, following the criteria of the following PICO (Patient, Intervention, Comparison, Outcomes) model: (P) Individuals diagnosed with ASD and epilepsy. (I) Not applicable. (C) Not applicable. (O) Sleep disorders. To ensure the precision of the research question, criteria related to individuals with ASD and epilepsy were specified, comparing their symptoms and the results of their respective diagnostic assessments [28]. Furthermore, this literature review adhered to the guidelines and recommendations established in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [29].

2.1. Search Strategy

An electronic search was conducted between March 2023 and July 2023 in the following databases: Medline, PubMed, PsycINFO, Web of Science, and Google Scholar. The search was limited to peer-reviewed articles published in journals and/or available online and written in Spanish or English. To ensure that the included articles were current, the search was limited to the last 20 years. The following terms in the article title, abstract, and keywords were considered in the study's search: epilepsy, ASD, and sleep disorders.

Regarding the search strategy, the following terms were used, combined with Boolean operators: "(epilepsy) AND (ASD) AND (sleep disorders)", "(epilepsy comorbidity) AND (ASD) AND (cognitive impairments)", "(causes of sleep disorders) AND (ASD and epilepsy)".

2.2. Study Selection Process

To obtain highly relevant published studies based on the study's objectives and PRISMA guidelines [30], inclusion and exclusion criteria were established before the systematic review. To improve the search's quality, a peer review was conducted using the standardized Peer Review of Electronic Search Strategies (PRESS) tool [31]. In this way, in the initial stage of study pre-selection, based on the information provided in the title and abstract, the following inclusion criteria were considered for the selection of relevant articles: (I) study samples reflect the comorbidities of the two conditions under study

(epilepsy-ASD and sleep disorders); (II) these conditions have been specifically evaluated; and (III) evaluations have been conducted by professionals in psychology or medicine. As for exclusion criteria, the following were considered: (I) individual case reports without a methodological design; (II) studies of epilepsy unrelated to ASD or vice versa; and (III) reviews, editorials, or abstracts of studies presented at conferences.

In the second stage of study selection, a comprehensive analysis of articles meeting the specified inclusion criteria was carried out. In this process, the following inclusion criteria were considered: (I) study participants had an official diagnosis of ASD; (II) the article accurately described the parameters of the evaluation conducted on the participants; and (III) individual characteristics of sleep disorders in study participants were specified.

The process of selecting studies included in this systematic review was conducted by two researchers and consisted of four phases. In the first phase, scientific literature in the fields of psychology and medicine was reviewed in major databases. In the second phase, each researcher reviewed the title and abstract of each eligible article in accordance with the pre-established inclusion and exclusion criteria. In the third phase, articles meeting the inclusion and exclusion criteria underwent a detailed analysis using a thorough reading of the full text. Finally, in the fourth phase, the examination and exclusion of articles that did not address the topic of interest in this systematic review were completed, evaluating the main information from the selected articles.

2.3. Final Study Selection

During the initial search for studies, a total of 632 potentially eligible articles were found, distributed as follows: 175 from Medline, 183 from PubMed, 167 from PsycINFO, 93 from Google Scholar (via manual bibliographic search), and 32 from Web of Science. Figure 1 presents a flowchart illustrating the study selection process, following the PRISMA statement [32]. Out of this total, 322 duplicate references were discarded. Finally, a total of 22 articles have been selected and included in this systematic review (Table 1).

Lastly, regarding the methodological design of the selected studies, quasi-experimental studies with assessments at one or multiple points in time, both cross-sectional and intra-group and inter-group longitudinal assessments to evaluate differences, were conducted.

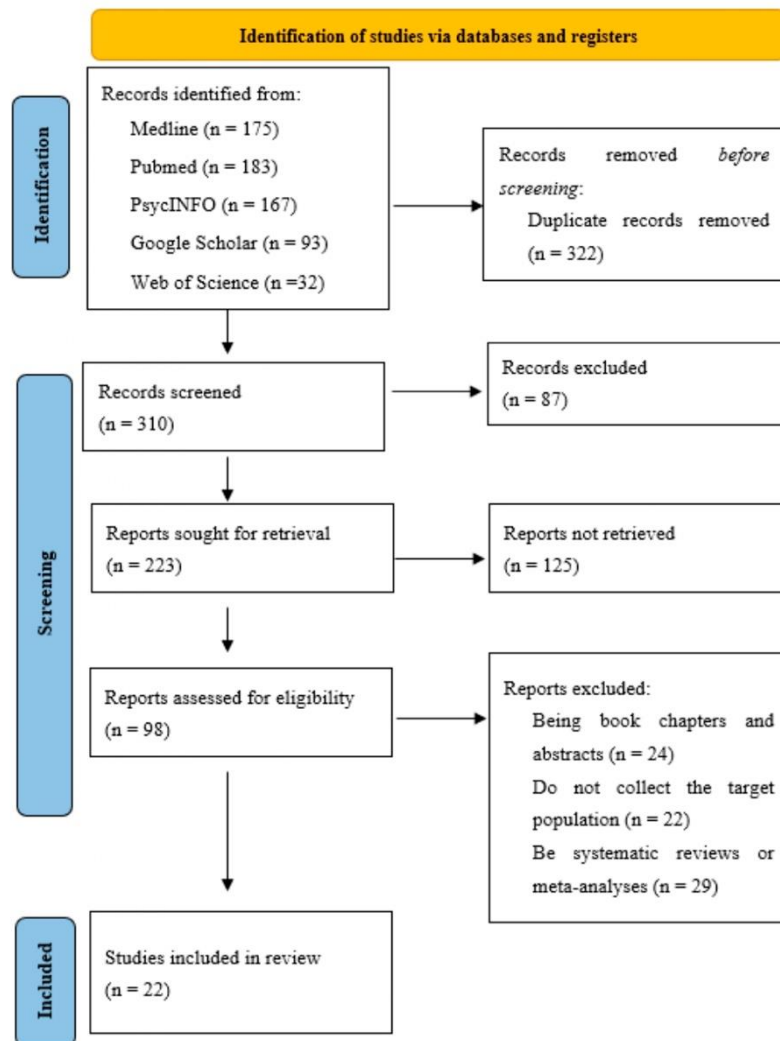


Figure 1. Modified PRISMA Diagram with the Studies Included in the Systematic Review.

Table 1. Summary of selected articles.

Authors	Year	N	Age (Years)	Objective	Abstract	Journal	Impact Factor (2022)
Neurobiological alterations of Sleep Disorders in children with ASD and epilepsy							
Saravanapandian et al. [33]	2021	27	6	To analyze abnormal sleep physiology in children with ASD and other related disorders.	Abnormal sleep physiology in children with ASD was investigated, and altered patterns of sleep and wakefulness were found.	Molecular autism	6.8
McCauley et al. [34]	2004	123	8	To map the linkage imbalance in the GABA(A) subunit cluster of the 15q12 receptor of children with ASD and epilepsy and its association with sleep disorders	A map of linkage imbalance in the GABA(A) receptor 15q12 was performed in people with ASD and epilepsy and was related to sleep disorders.	American journal of medical genetics. Part B, Neuropsychiatric genetics	3.0
Chen et al. [35]	2017	133	12	Use blood serotonin as an endophenotype to identify rare variants involved in ASD and epilepsy.	Blood serotonin was used as an endophenotype to identify genetic variants associated with ASD and epilepsy.	Molecular autism	6.8
Hranilović et al. [36]	2008	63	6	To examine hyperserotonism in ASD and epilepsy and its relationship to serotonin-related gene variants.	Hyperserotonism in ASD is comorbid with epilepsy, and its relationship with serotonin-related gene variants was investigated.	Collegium antropologicum	N/D
Prasad et al. [37]	2009	5	5	To study the enhanced activity of human serotonin transporter variants associated with ASD.	The enhanced activity of human serotonin transporter variants associated with ASD was studied.	Philosophical Transactions of the Royal Society of London. Series B, Biological sciences	6.0
Verma et al. [38]	2014	422	4–17	To investigate the dimorphic sexual effect on the genetic association of monoamine oxidase A (MAOA) markers with ASD and epilepsy.	We investigated the dimorphic sexual effect on the genetic association of MAOA markers with ASD and epilepsy.	Progress in neuro-psychopharmacology and biological psychiatry	4.2
Goldman et al. [39]	2014	24	7	Characterize melatonin in children with ASD in relation to sleep.	Melatonin was characterized in children with ASD in relation to sleep, finding differences in endogenous production and pharmacokinetics.	Journal of autism and developmental disorders	3.8

Table 1. Cont.

Authors	Year	N	Age (Years)	Objective	Abstract	Journal	Impact Factor (2022)
Goldman et al. [40]	2017	28	13	Characterize sleep in children with ASD.	Sleep was characterized in children with ASD, observing differences in sleep duration and quality.	Journal of autism and developmental disorders	3.8
Braam et al. [41]	2018	60	5–17	To investigate the low level of maternal melatonin and its relationship with the risk of epilepsy and ASD in children.	Low maternal melatonin levels and their relationship to the risk of ASD and epilepsy in children were investigated.	Research in developmental disabilities	2.2
Jonsson et al. [42]	2014	1771	7	Acetylserotonin O-methyltransferase (ASMT) associated with ASD traits in children from a Swedish cohort.	An association between ASMT and ASD traits was found in children from a Swedish cohort.	Psychiatric genetics	2.2
Veatch et al. [43]	2015	15	3–15	To examine genetic variation in melatonin pathway enzymes in children with ASD and epilepsy and delayed sleep onset.	We examined genetic variation in melatonin pathway enzymes in children with ASD and epilepsy and delayed sleep onset.	Journal of autism and developmental disorders	3.8
Gunes et al. [44]	2019	112	2–18	To assess sleep problems in children with ASD and their correlation with attention deficit hyperactivity disorder.	Sleep problems in children with ASD and their correlation with ADHD were evaluated, finding differences in sleep patterns.	Neuropsychiatric disease and treatment	3.2
Cognitive alterations of Sleep Disorders in children with ASD and epilepsy							
Qin et al. [45]	2022	54	2–6	Analyze brain networks in preschool children with ASD.	Brain networks were investigated in preschool children with ASD, and differences in functional connectivity were found.	Frontiers in psychiatry	3.5
Miner et al. [46]	2023	24	6–12	To evaluate the relationship between sleep disorders and the severity and common behaviors in ASD.	The relationship between sleep disorders and the severity of behaviors in ASD was evaluated, finding associations between sleep patterns and behaviors.	Research square	2.3
Fadini et al. [47]	2015	101	4–18	Investigate the influence of sleep disorders on the behavior of individuals with ASD.	The influence of sleep disorders on the behavior of individuals with ASD was investigated, finding correlations between sleep disorders and behavior.	Frontiers in Human Neuroscience	3.6

Table 1. *Cont.*

Authors	Year	N	Age (Years)	Objective	Abstract	Journal	Impact Factor (2022)
Sikora et al. [48]	2012	3452	4–10	To examine the relationship between sleep problems and daytime behavior in children of different ages with ASD.	The relationship between sleep problems and daytime behavior in children with ASD of different ages was examined, finding correlations between both.	Pediatrics	6.6
Park et al. [49]	2012	166	4–15	To investigate sleep problems and their relationship with comorbid psychopathology in children with ASD.	Sleep problems and their relationship with psychopathology in children with ASD were investigated, finding associations between sleep problems and comorbidity.	Research in Autism Spectrum Disorders	2.4
da Silva Cruz-Machado et al. [50]	2021	40	6–8	To study disrupted nocturnal melatonin in ASD and its relationship with tumor necrosis factor and sleep disorders.	Disrupted nocturnal melatonin was studied in ASD and its relationship with tumor necrosis factor and sleep disorders.	Journal of Pineal Research	14.7
Bin Eid et al. [51]	2022	29	6–16	To analyze the alterations in cortisol profiles in mothers of children with ASD related to the poor quality of sleep in children.	Alterations in cortisol profiles in mothers of children with ASD related to the children's sleep quality were analyzed.	Healthcare (Basel, Switzerland)	2.3
Page et al. [52]	2020	13	2.5	To investigate the relationship between non-rapid eye movement sleep and the risk of autism spectrum disorder in early development.	The relationship between non-rapid eye movement sleep and ASD risk in early development was investigated, finding differences in EEG topography.	Brain and behavior	2.5
DeVincent et al. [53]	2007	112	3–5	To evaluate sleep disorders and their relationship with psychiatric symptoms in preschoolers with ASD and community controls.	Sleep disorders and their relationship with psychiatric symptoms were evaluated in preschoolers with ASD and controls, finding associations.	Journal of Child Neurology	2.0
Goldman et al. [54]	2009	58	4–10	Define the sleep phenotype in children with ASD.	The sleep phenotype in children with ASD was defined, highlighting differences in sleep latency and nocturnal disturbances.	Developmental neuropsychology	2.0

3. Results

The selection of the reviewed articles below follows the previously established inclusion and exclusion criteria, as well as being the most recent articles with the highest relevance and participant samples published to date. These are reported in thematic blocks in accordance with the proposed objectives.

3.1. Neurobiological Alterations of Sleep Disorders in the Pediatric Population with ASD and Epilepsy

Neurobiological alterations related to ASD and epilepsy lead to a dysregulation of the sleep-wake cycle in individuals with this comorbidity, primarily manifested via altered functioning of the neurotransmitters gamma-aminobutyric acid (GABA) and serotonin, as well as the neurohormone melatonin [33,34].

GABA, an inhibitory neurotransmitter of the central nervous system, acts as a sleep inducer by inhibiting the activity of neurons in the brainstem that are active during wakefulness [33]. Children with ASD and epilepsy exhibit dysregulation in GABA interneurons, which can be explained by the presence of mutations in chromosome 15q in some patients, which is related to the storage of GABA-related genes [34]. The identification of a susceptibility region for ASD and epilepsy with genes related to GABA suggests that changes in gene expression in this area could disrupt GABA's inhibitory function, leading to hyperactivity and, consequently, insomnia in individuals.

The other neurotransmitter, serotonin, also plays a significant role in sleep cycles, as it promotes wakefulness and inhibits REM sleep, making it a key factor in studying sleep disorders in this population. Hyperserotonemia is present in more than 25% of children with this comorbidity and in many of their first-degree relatives. Research on the pediatric population with ASD and epilepsy has also suggested genetic variations related to serotonin transport and degradation [35]. Therefore, abnormal serotonergic activity will impair sleep due to its impact on melatonin [36]. It has been proposed that elevated levels of serotonin in blood could be used as the first biomarker to identify patients with ASD and epilepsy [37].

Finally, melatonin, a hormone produced by the pineal gland, plays a critical role in regulating sleep-wake rhythms [38]. Its release is suppressed in the presence of bright light and increases in response to darkness [39]. Melatonin is synthesized from serotonin using the enzyme acetylserotonin O-methyltransferase (ASMT). Despite this population having low levels of melatonin and high levels of serotonin, research attention is focused on the gene that controls ASMT production [40]. Mutations or polymorphisms in this gene are associated with low melatonin levels in individuals with ASD and epilepsy, as well as certain autism-related traits like language impairments or social behavior in the general population [41,42]. Genetic variation in ASMT and another enzyme in the melatonin pathway, cytochrome P450 1A2 (CYP1A2), were identified in children with ASD and epilepsy and comorbid sleep onset delay [43,44]. Therefore, differences in sleep architecture based on genetic abnormalities provide further evidence of the neurobiological basis of sleep disorders in individuals with ASD and epilepsy.

3.2. Cognitive Impairments Caused by Sleep Problems in Individuals with ASD and Epilepsy

In the pediatric population diagnosed with ASD and epilepsy, it is crucial to analyze the relationship between sleep disorders and cognitive impairments. Sleep problems can exacerbate neurocognitive dysfunction in areas such as behavior, attention, or memory. Children with ASD and epilepsy often exhibit various behavioral problems, including disruptive behaviors, tantrums, aggression, self-injury, hyperactivity, impulsivity, and non-compliance with rules [45]. Behaviors such as aggression, impulsivity, and non-compliance with rules increase their stress levels and have a negative impact on the quality of life of individuals with ASD and epilepsy [46]. Some studies have indicated that sleep disorders can worsen behavioral problems in individuals with ASD and epilepsy. For example, Fadini et al. [47], when examining the relationship between sleep and behavior in a sample of

45 children with ASD and epilepsy, concluded that sleep disorders were linked to thinking and behavioral problems. Similarly, Sikora et al. [48], in a sample of 1193 children with ASD, found that children with ASD and epilepsy who had a sleep disorder exhibited more internalizing and externalizing behavior problems, as well as poorer adaptive skill development compared to children with ASD and epilepsy without sleep problems. Park et al. [49] analyzed sleep disorders, their correlates, and psychopathological comorbidities in 166 children with ASD and epilepsy compared to 111 siblings without pathology. They found that children with sleep disorders were more likely to display aggressive behaviors, internalizing and externalizing problems, and behavior problems compared to those without sleep problems.

On the other hand, children with ASD and epilepsy who experience sleep disorders exhibit symptoms of hyperactivity, inattention, and memory problems, with around 30% of them reporting cognitive issues encompassing one or more of these functions [49,50]. Various studies have found that children with ASD and epilepsy experience a high degree of sleep problems, including variable sleep patterns, delayed sleep onset, insomnia, and, consequently, daytime sleepiness [50–52]. Consistent with these findings, it has been noted that epilepsy symptoms can exacerbate sleep disorders in individuals with ASD. For example, a high degree of hyperactivity could delay sleep onset and, over time, lead to insomnia [52]. Therefore, the presence of sleep disorders at an early age negatively influences the development of attention and memory processes. DeVincent et al. [53], when exploring the relationship between sleep problems and cognitive symptoms, found that children with ASD, epilepsy, and sleep difficulties also had higher rates of hyperactivity and cognitive dysfunction compared to children without sleep problems. Similarly, Goldman et al. [54], when assessing the potential effect of sleep disorders in a cohort of children with ASD and epilepsy, identified that those with disrupted sleep patterns exhibited more inattention, hyperactivity, and restricted/repetitive behaviors. In the following table (Table 2), sleep disorders, their affected neurotransmitters, behavioral characteristics, and their treatment are reflected.

Table 2. Characteristics related to sleep disorders in the pediatric population with ASD and epilepsy.

Sleep Disorder	Affected Neurotransmitters	Characteristic Behavior	Common Treatment
Insomnia	Serotonin	Difficulty falling asleep, frequent awakenings during the night.	Cognitive-Behavioral Therapy for Insomnia (CBT-I), medications under medical supervision.
Nightmares	Norepinephrine	Sudden awakenings with fear or anxiety.	Nightmare Desensitization Therapy, cognitive-behavioral therapy.
Night Terrors	GABA	Loud screams or extreme agitation during sleep without fully waking up.	Education about the disorder, sleep environment adjustments, and cognitive-behavioral therapy.
Sleep Apnea	N/A	Loud snoring, breathing pauses during sleep.	CPAP (Continuous Positive Airway Pressure), lifestyle changes.

These findings support the notion that improving sleep in the pediatric population aims to reduce behavioral problems, which, in turn, helps alleviate stress in individuals with ASD and epilepsy and enhances family functioning. A recent report proposing a practical approach to the identification, assessment, and management of insomnia in children and adolescents with ASD suggests that pharmacological therapy (such as melatonin) may be recommended in certain cases, especially in those individuals who experience epileptic seizures during sleep phases [50]. Behavioral interventions, such as sleep hygiene, have been shown to be effective in addressing sleep difficulties in children with ASD and epilepsy [51]. In this regard, parents of children with ASD, epilepsy, and sleep disorders can benefit from tools to manage these challenges. Treatment approaches for sleep disorders in the population with both ASD and epilepsy often involve a combination of behavioral

interventions, environmental adjustments, and, in some cases, pharmacological options. Behavioral interventions encompass strategies like establishing consistent bedtime routines, improving sleep hygiene, and utilizing relaxation techniques. Environmental adjustments may include creating a comfortable and sensory-friendly sleep environment. In certain instances, pharmacological therapies, such as melatonin supplementation, may be considered, especially for individuals prone to seizures during sleep phases. The choice of treatment depends on the specific sleep disorder, its underlying causes, and individual needs, underscoring the importance of a personalized and multidisciplinary approach to address the complex interplay of these conditions.

4. Discussion

The primary objective of this systematic review was to analyze the available evidence regarding the relationship between sleep disorders and neurobiological and cognitive alterations in the pediatric population with ASD. Additionally, the specific objectives were to examine the neurobiological alterations that occur due to sleep disorders and to describe the dysfunctions in cognitive processes in children diagnosed with ASD and epilepsy.

Regarding the neurobiological alterations present in individuals with these comorbid disorders, scientific literature has demonstrated that, in pediatric neurological conditions, the impact of sleep disorders involves dysregulation of a significant portion of the nervous system. This, in turn, signifies dysfunction in the GABAergic and serotonergic systems, implying a disruption of the hormonal system, specifically the one responsible for melatonin regulation [55–57]. However, research in this field is very limited due, in part, to the scarcity of studies, the small number of homogeneous samples, and the variability in the manifestations of neurological alterations in clinical variables and their etiology, making the studies inconclusive [58,59]. Nevertheless, this dysregulation of different neurological systems negatively impacts the developmental maturation of individuals with ASD and epilepsy, as it affects the learning processes [60], causing the symptoms of ASD itself to be more pronounced with greater disruptions in communication and language or in social behavior [61].

Regarding the cognitive changes due to sleep disorders (SD), it is noteworthy that they are part of the current definition of this comorbidity and have a significant impact on children with ASD and epilepsy adaptation to their environment, their relationships with peers, and cognitive development. In the past decade, the negative impact of early epilepsy on cognitive capacity has been confirmed, establishing it as a predictor of difficulties in the development of these functions in children with ASD and epilepsy [62]. All of this results in cognitive processes such as attention or memory showing reduced performance compared to the ASD population without epilepsy. This may be because, in childhood, neuronal plasticity mechanisms are at their peak, trying to consolidate attention and memory mechanisms via the assimilation of environmental stimuli [63]. However, the existence of an SD will have a negative effect and reduce the ability to integrate knowledge from acquired context stimuli, as it will reduce cognitive alertness, preventing proper attentional focus, limiting the information captured by the child's sensory system from being recorded and stored in memory [64].

The strengths and limitations of this study should be considered. A limitation of this study is that it relied on a review of existing literature, so the availability and quality of the included studies may have influenced the results. Since no original research was conducted and no new data were collected, there is a possibility that some relevant studies were omitted or that the results are influenced by publication bias. Additionally, the quality and methodology of the studies included in the review may vary, which could affect the reliability of the findings. Therefore, the results should be interpreted with caution and take into account the inherent limitations of the literature review. However, a strength of this study is that it considered recent and relevant research, providing an updated insight into the neurobiological causes of sleep disorders, cognitive impairments, and emotional disturbances in families with children with ASD and epilepsy. By including previous

high-quality studies, a solid foundation was established for understanding the phenomena studied, and a broader coverage of the existing literature was achieved. Furthermore, by reviewing both international and national studies, a global perspective of research in the field was obtained, increasing the generalizability of the results. Another strength of this study is that it addressed multiple aspects related to sleep disorders, cognitive impairments, and emotional disturbances in the studied population. By examining the neurobiological causes and potential relationships between these phenomena, a more comprehensive and holistic understanding of the issue was achieved. This allows for the identification of key areas for intervention and the development of more effective therapeutic strategies.

The results of this study have important implications both in the clinical and research domains. In the clinical realm, it highlights the importance of assessing and addressing sleep disorders and neurological and cognitive impairments in individuals with ASD and epilepsy. Healthcare professionals should consider these areas and adopt a comprehensive approach to improve the quality of life for affected individuals and their families. Regarding future research, there is a suggestion to delve deeper into the understanding of the underlying neurobiological causes of sleep disorders in this population. It is necessary to review the action of neurotransmitters such as serotonin, GABA, and other substances like dopamine, which play a crucial role in sleep behavior disorders. In addition, studies exploring specific therapeutic interventions aimed at improving the quality of sleep patterns in individuals with ASD and epilepsy are needed. Furthermore, protocols for assessing cognitive processes affected by sleep disorders, such as memory, attention, or executive functions, should be established. Longitudinal studies could also be conducted to better comprehend the evolution of sleep disorders and cognitive impairments over time in individuals with ASD and epilepsy, comparing cognitive impairments and neurobiological activity based on types of sleep disorders. These investigations would allow for the assessment of the long-term effectiveness of different intervention approaches and provide insights into how these phenomena develop and change over time.

In conclusion, this review underscores the importance of understanding the neurobiological causes of sleep disorders and neurobiological and cognitive impairments in individuals with ASD and epilepsy. The results support the existence of relationships between these phenomena and emphasize the need for a comprehensive approach to the assessment and treatment of these conditions. Further research is required to deepen our understanding and develop more effective interventions that comprehensively address sleep disorders and neurobiological and cognitive impairments in individuals with ASD and epilepsy.

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5.3. ARTÍCULO 3

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Article

Executive Functioning and Language in a Pediatric Population with Autism Spectrum Disorders and Epilepsy: A Comparative Study

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Abstract: In recent years, there has been an increase in the prevalence of comorbidity between ASD and epilepsy in the pediatric population. Children with ASD and epilepsy often exhibit greater impairments in executive functions such as cognitive flexibility, planning, inhibition, and emotional control, as well as in language dimensions such as phonology, semantics, morphosyntax, and pragmatics. These impairments can significantly impact their maturation and development. The aim of this study was to assess and compare the executive functioning and language skills of 150 participants, divided into three groups: one with ASD only, another with epilepsy only, and the third group with both ASD and epilepsy. The study utilized the Behavior Rating Inventory of Executive Function (BRIEF-2) and Neuropsychological Evaluation of Executive Functions in Children (ENFEN) to assess executive functions, and Clinical Evaluation of Language Fundamentals 5 (CELF-5) to evaluate language skills. The results indicated that participants with this comorbidity had lower scores in both executive functioning and language skills compared to children with only ASD or epilepsy. The presence of epilepsy significantly limits the executive and linguistic performance of children with ASD, negatively affecting language acquisition, functionality, and the ability to carry out basic life activities independently.

Keywords: autism; childhood; language; executive functions; epilepsy



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1. Introduction

The study of the comorbidity between Autism Spectrum Disorder (ASD) and epilepsy is a rapidly growing field of research due to its increasing prevalence and the limitations imposed on the affected pediatric population, which go beyond those caused by the two disorders separately [1]. ASD is characterized by limitations in social interaction and repeated and stereotyped behaviors [2]. It presents a variety of symptoms and developmental alterations, including deficiencies in cognitive and language dimensions. Difficulties in expressive language, such as pragmatics and understanding writing are found [3]. Intelligence, executive functions, memory, and attention may also be affected [4].

Research on epilepsy in ASD is not new. As early as 1943, Leo Kanner observed that the presence of epileptic seizures in children with autism could negatively impact the acquisition of their language and social skills [5]. Currently, routine screening protocols have been established by epilepsy specialist neurologists to detect this comorbidity early, as early detection is a good prognostic factor for the development of cognitive-linguistic and social skills in children with epilepsy and ASD, especially if both disorders manifest in the early preschool years [6]. Additionally, families often participate in the evaluation process, as they can detect the possible occurrence of epileptic episodes [7,8].

ASD has a significant prevalence, with data from the Centers for Disease Control and Prevention (CDC) in the United States estimating that approximately 1 in 44 children are affected by this condition [8,9]. Globally, the World Health Organization (WHO) reports an average prevalence of around 1% for ASD [7–10]. On the other hand, epilepsy, a disease with prevalence variations depending on the region and age, affects approximately 50 million people worldwide, with rates ranging from 0.5% to 1% of the general population, according to the WHO [9–12]. The coexistence of ASD and epilepsy presents specific rates that can vary depending on the studied population and the methodology used in the research, reporting that between 5% and 38% of individuals with ASD also experience epilepsy, according to various studies [8–11].

1.1. Cognitive-Linguistic Profile of Epilepsy

In terms of executive functions, epilepsy influences various neural components. Inhibition, crucial for impulse control and concentration on specific tasks, may experience disruptions, manifesting in challenges to restrain inappropriate behaviors or disruptive conduct [12–14]. Cognitive flexibility, one of the fundamental factors for adapting to changes is presented as a potentially vulnerable area, affecting the ability to transition smoothly between different tasks or situations [13–15]. Emotional control, essential for emotional regulation, may be affected, contributing to variations in mood [12]. In terms of planning, the ability to organize sequences of actions and establish goals may experience difficulties [13]. The organization and supervision of material, crucial elements in the management of daily tasks, also present alterations, with implications for autonomy and efficiency in everyday activities [16,17].

An analysis of the linguistic profile of these populations reveals the existence of linguistic difficulties associated with pediatric epilepsy, encompassing phonology, semantics, morphosyntax, pragmatics, and oral comprehension [13]. In the phonological domain, there is the possibility of alterations in speech sound production, leading to complications in articulation and auditory discrimination, phenomena directly linked to the variability in the frequency and severity of seizures [11–13]. Semantically, the acquisition and organization of word meanings seem disrupted, directly affecting the understanding of abstract concepts [10]. Morphosyntactic difficulties indicate variations in grammatical expression, while in the pragmatic domain, crucial for social communication, children affected by epilepsy may manifest obstacles in using language appropriately in social contexts, significantly affecting the quality of interactions [14]. Regarding comprehension, the interpretation of verbal instructions and text comprehension may be compromised, generating additional challenges in both academic and social environments [15].

1.2. Cognitive-Linguistic Profile of ASD

Regarding executive functions, ASD implies additional challenges. Problems in inhibition, necessary for impulse control and maintaining focus on specific tasks, have been found, resulting in difficulties in stopping unwanted behaviors [11–14]. Cognitive flexibility may also be altered, affecting the ability to transition smoothly from one task to another [8–11]. The presence of difficulties in emotional control has also been studied, contributing to mood variability and emotional expression [14–16]. Lastly, in terms of planning, the ability to organize sequences of actions and establish goals may be compromised [15–18], affecting the organization and supervision of materials, the pillars of task management [17].

The linguistic profile of individuals with ASD can be complex and varied, with similarities and differences compared to epilepsy. Although both disorders share certain aspects, ASD presents specific symptoms that require detailed analysis. For example, in the phonological domain, they face challenges such as articulatory difficulties and auditory discrimination, which can affect both comprehension and verbal expression [10]. In the semantic domain, alterations in the acquisition and organization of word meanings are observed, influencing the understanding of abstract concepts [13–18]. Additionally, at the morphosyntactic level, they may exhibit variations in grammatical expression. These

difficulties are reflected in the pragmatics of language, where individuals with ASD may struggle to use language appropriately in social contexts, affecting their social interactions and the comprehension of verbal instructions and texts [12–17]. Although some characteristics may be shared with other disorders such as epilepsy, ASD is distinguished by its unevenness in the linguistic profile, with more pronounced weaknesses in pragmatics and strengths in phonological development. Understanding these differences is essential to provide appropriate interventions and support for individuals with ASD, recognizing that not all experience the same difficulties.

1.3. Cognitive-Linguistic Profile of ASD with Epilepsy

As for deficiencies in executive functions in participants with ASD and epilepsy, 50% experience delays in learning due to various factors such as syndrome type, etiology, age of onset, frequency and duration of seizures, family history, psychiatric comorbidity, and treatment-related factors [18–21]. These alterations are directly related to basic executive functions such as cognitive flexibility, planning, emotional control, monitoring, flexibility, working memory, and material organization [22–24]. On one hand, children with ASD and epilepsy may face difficulties with cognitive flexibility, planning, and organization when initiating or completing tasks. They may also struggle to organize their belongings and study materials, leading to frustration due to the inability to perform these activities independently [25,26].

On the other hand, deficits in working memory may be observed when completing activities, following instructions, and remembering recent information, important details, and information necessary to correctly complete an activity or task [27]. Research such as that by Papazian et al. [28] and Diamond [29] indicates that children with ASD and epilepsy experience difficulties in inhibition, manifested in impulsive reactions without thought, initiating activities without considering factors to achieve goals or speaking without waiting for their turn. Additionally, emotional control and regulation have been identified as one of the main areas affected in individuals with comorbid ASD and epilepsy. This population may experience difficulties in self-regulation, impulse management, problem recognition, and interpretation of emotions [30,31]. Difficulties in emotional regulation can lead to increased stress in response to new situations, sensory stimuli, or mood changes, resulting in irritability, lack of anger control, tantrums, and self-injurious behaviors [32]. Therefore, establishing daily routines with a structured environment for each activity is crucial to support individuals with this comorbidity [33].

An area significantly affected by the presence of comorbidity between ASD and epilepsy is language. However, research on linguistic competence in this population is limited. A study by Kuczynski [34] on children with ASD and focal epilepsy found a high incidence of language impairment, especially in the areas of semantics, morphosyntax, and pragmatics. Similarly, a study by Requero and Bermejo [35] showed that early-onset focal epilepsy in childhood has a negative impact on the development of expressive and receptive language due to cortical structural alterations in ventral and temporal pathways. This indicates that children with this comorbidity may have poor performance in language skills [36]. Ruggieri [37] attributes this to a higher prevalence of left hemisphere involvement in children with right dominance and early-onset epileptic episodes.

1.4. Comparison of Executive Functioning and Language in the Population with Epilepsy, ASD, and ASD with Epilepsy

A detailed comparison of executive functioning and language skills among populations with epilepsy, ASD, and ASD with epilepsy reveals distinctive nuances that underscore the complexities associated with each group. In the case of epilepsy, challenges in executive functioning are observed, especially after seizure episodes, with notable impacts on working memory and selective attention [33–36]. Linguistically, variability in the frequency and severity of seizures can influence difficulties in language comprehension and expression. On the other hand, ASD presents a unique profile with specific challenges in

inhibition, cognitive flexibility, and emotional control, affecting adaptability and emotional regulation [38].

Language difficulties in ASD encompass challenges in social communication, organization, and expression of meaning, with notable pragmatic alterations and a tendency towards literal language interpretation. When examining the population with ASD and epilepsy, the intersection of both conditions generates a combination of challenges in both executive functioning and language skills [36–38]. Executive difficulties, such as inhibition, cognitive flexibility, and emotional control, may experience intensification, affecting adaptability and emotional regulation more profoundly. Linguistically, the coexistence of ASD and epilepsy could lead to a combination of challenges in social communication and language processing capacity, exacerbating pragmatic alterations and literal language interpretations [39].

1.5. Justification of the Research

This research arises from the need to explore and compare the inherent complexities in explaining difficulties in executive and linguistic functioning in the population with ASD and epilepsy. As described earlier, current scientific literature indicates that the comorbid condition of ASD and epilepsy complicates the linguistic and executive functioning profiles of children with these two conditions, significantly limiting maturation, learning, and integration into the environments and contexts where individuals with ASD and epilepsy live. However, it is important to note that there is a limited number of published studies about linguistic and executive functioning in this population. Additionally, there are no articles comparing language and executive functioning among these three clinical profiles, except for the recently published article by Cano-Villagrasa et al. [40], which only measures executive functioning and compares individuals with epilepsy, ASD, or ASD and epilepsy. Findings suggest that participants diagnosed with epilepsy demonstrate better performance in tasks related to executive functions compared to individuals with ASD and ASD with epilepsy.

However, other comparative studies attempt to describe the profiles of linguistic and executive functioning in these populations without directly comparing them. For example, studies conducted by Barboza Ubarnes et al. [41], Pisón et al. [25], del Busto [42], Campos-Castelló and Campos-Soler [36], Zambarbieri [43], Dioses Chocano et al. [44], Juillerat et al. [45], Muñoz-Yunta et al. [6], Norrelgen et al. [46], and Rotta [47] provide an exposition of expressive and receptive language characteristics, as well as cognitive and executive competencies in individuals with epilepsy, ASD, or ASD with epilepsy, describing existing alterations in these populations. From these studies, it can be inferred that the profiles of children with epilepsy will show better performance in tasks related to language and executive functioning compared to children diagnosed with ASD or ASD comorbid with epilepsy. Therefore, this research emphasizes that, due to the absence of recent investigations, the importance of our work is increased, as it provides a valuable contribution to understanding the difficulties in executive and linguistic functioning in this specific group of children.

2. Objectives and Research Hypothesis

Consequently, the main objective of this study is to assess and compare deviations in executive functioning and language within three distinct groups: children diagnosed with ASD, children diagnosed with epilepsy, and children diagnosed with both ASD and epilepsy. Currently, there is a scarcity of research systematically contrasting linguistic competence and executive functioning in children facing this comorbidity. Within this framework, regarding the comparison between these three groups, the general hypothesis posited that children with epilepsy would demonstrate better cognitive and linguistic performance than groups composed of children diagnosed with ASD or ASD and epilepsy. Thus, the first hypothesis proposed for this study is that executive functioning skills will be superior in the group of children with epilepsy compared to the group of individuals

with ASD, followed by the group of ASD with epilepsy [20,40,41,43–46]. Similarly, the second research hypothesis posited that performance in language dimensions is higher in the group of children with epilepsy compared to the group of children with ASD and the group of children with ASD with epilepsy [14,17,18,22,47–50].

3. Materials and Methods

3.1. Participants

The study involved 150 children aged 6 to 8 years, categorized into three groups: ASD ($n = 50$), epilepsy ($n = 50$), and ASD with epilepsy ($n = 50$). Within the ASD group (G1), there were 24 boys and 26 girls (Mean Age = 6.8; SD = 0.9) diagnosed with ASD levels 2 and 3 according to DSM-5 criteria (63% and 37%, respectively). The epilepsy group (G2) comprised 28 boys and 22 girls (Mean Age = 7.4; SD = 0.6). Lastly, the ASD with epilepsy group (G3) included 31 boys and 19 girls (Mean Age = 7.2; SD = 0.8) diagnosed with ASD level 3 based on DSM-5 criteria. This age range was selected because the assessment tools used in the study are suitable for children aged 6 and above, and it represents a stage where diagnoses are typically established. All participants in the G2 and G3 groups received a diagnosis of generalized epilepsy. To ensure homogeneity in the number of participants between groups, each group was configured with a total of 50 participants. This process involved refining the database that recorded the participants' scores and standardizing the number of subjects to 50 per group.

All participants in this study were diagnosed with ASD or epilepsy in the Mental Health Units or Neuropediatrics services of reference hospitals in their respective cities. The diagnosis of ASD and/or epilepsy was conducted by an interdisciplinary team composed of a psychiatrist, a pediatrician, a neurologist, and a psychologist at the hospital in their locality. On one hand, the diagnosis of ASD was made using the M-CHAT-R instrument [51]. Children with scores indicating suspected ASD underwent additional assessment using the ADOS-2. Autism Diagnostic Observation Schedule—2 [52] and ADI-R. Autism Diagnostic Interview—Revised [53] protocols to confirm ASD diagnosis. The diagnostic criteria established in DSM-5 for ASD and the level of needs presented by the participants in this study were also followed. Furthermore, individuals displaying symptoms of epilepsy underwent neurological assessments, including nuclear magnetic resonance, private sleep electroencephalogram, and genetic testing to confirm the diagnosis. The participants in this study exhibited a level of disability characterized by limitations or obstacles hindering their full participation in society in a functional capacity. Lastly, all participants underwent evaluation using the Wechsler Intelligence Scale for Children-IV (WISC-IV) [54], with exclusion criteria based on an IQ below 60 (Table 1).

Specific inclusion and exclusion criteria were defined. Inclusions covered individuals within the age range of 6 to 8 years, along with a confirmed diagnosis of ASD or epilepsy. Conversely, exclusions encompassed individuals meeting any of the following conditions: (I) presenting a motor or sensory ailment that hindered or obstructed the precise execution of the study; (II) lacking any form of communication or language competence before the age of 5 and (III) all those participants who scored below 60 on the WISC-IV assessment test, indicating a level of intellectual disability categorized as moderate, severe, or profound. Finally, sample selection was carried out by identifying participants with a diagnosis of ASD, epilepsy, or ASD with epilepsy. A total of 232 participants were obtained, of which 82 were excluded for not meeting the inclusion and exclusion criteria. Therefore, a sample of 150 participants was configured and divided into three groups of 50 subjects each, forming the study's sample group.

Table 1. Characteristics of the study participants.

	Epilepsy Group (n = 50)	ASD Group (n = 50)		ASD with Epilepsy Group (n = 50)	Chi-Square (p)
Gender					1.025 (0.599)
Men (%)	28 (56%)	25 (50%)		30 (60%)	
Female (%)	22 (44%)	25 (50%)		20 (40%)	
Treatment Duration					5.529 (0.237)
2 years (%)	16 (32%)	16 (32%)	18 (36%)		
3 years (%)	16 (32%)	17 (34%)	17 (34%)		
4 years (%)	18 (36%)	17 (34%)	15 (30%)		
Grade of Disability					5.756 (0.218)
Less than 33%	17 (34%)	17 (34%)	16 (32%)		
Between 33% and 66%		15 (30%)		16 (32%)	17 (34%)
More than 66%	18 (36%)	17 (34%)	17 (34%)		
Educational supports at school					6.492 (0.165)
Speech and Language Teacher (%)	15 (30%)	15 (30%)	20 (40%)		
Speech and Language Teacher + Special Education Teacher (%)	17 (34%)	17 (34%)	16 (32%)		
Speech and Language Teacher + Special Education Teacher + Educator (%)	18 (36%)	18 (36%)	14 (28%)		
Gestation Weeks					2.114 (0.715)
30–35 weeks (%)	18 (36%)	17 (34%)	15 (30%)		
35–40 weeks (%)	16 (32%)	16 (32%)	18 (36%)		
>40 weeks (%)	16 (32%)	17 (34%)	17 (34%)		
Apgar Score					0.584 (0.965)
At risk (%)	16 (32%)	17 (34%)	14 (28%)		
Intermediate (%)	17 (34%)	16 (32%)	17 (34%)		
Normal (%)	17 (34%)	17 (34%)	19 (38%)		
Medication					7.447 (0.281)
No presence (%)	16 (32%)	17 (34%)	17 (34%)		
Valproate (%)	17 (34%)	16 (32%)	17 (34%)		
Risperidone (%)	17 (34%)	18 (36%)	15 (30%)		
Clonazepam (%)	17 (34%)	16 (32%)	18 (36%)		
Intellectual disability					34.584 (0.001)
Non-presence	50 (41%)	45 (37%)	28 (22%)		
Mild intellectual disability	0 (0%)	5 (18%)	22 (82%)		
Total mean IQ (Mean)	91.4	87.2	78.1		

3.2. Instruments and Materials

3.2.1. Behavior Rating Inventory of Executive Function

Behavior Rating Inventory of Executive Function (BRIEF-2) [55] is an instrument that provides an assessment of executive functions in participants aged 5 to 18. It measures different aspects of executive functioning more precisely than other available tests and instruments. BRIEF-2 responds to the highlighted need for an ecologically valid method to evaluate the molar, behavioral, and everyday dimensions and aspects of executive functions in participants. It is completed in an estimated time of 10 min. There are two versions of the questionnaire, one completed by the primary caregivers and the other by the tutor at the educational center the child attends. The Cronbach's alpha value is 0.82. In this study, the dependent variables included for data analysis were: Inhibition, Flexibility, Emotional Control, Working Memory, Planning, Organization of Materials, and Monitoring.

3.2.2. ENFEN—Neuropsychological Evaluation of Executive Functions in Children

The ENFEN Neuropsychological Evaluation of Executive Functions in Children tool, translated as Neuropsychological Evaluation of Executive Functions in Children [56],

assesses cognitive performance in activities related to executive functions in children and their level of maturity through four tests (interference resistance, path construction, verbal fluency, and ring construction). Regarding its psychometric properties, Rodríguez et al. [57] conducted a measurement of these factors. The Cronbach's alpha value is 0.81. In this study, the dependent variables included for data analysis were: Verbal Fluency, Path Construction, Ring Construction, and Interference Resistance.

3.2.3. Clinical Evaluation of Language Fundamentals 5

Clinical Evaluation of Language Fundamentals 5 (CELF-5) [58] is an individual clinical assessment tool designed to identify, diagnose, and monitor language and communication disorders in children and adolescents aged 5 to 15 years. This instrument aims to evaluate the strengths and weaknesses of the participant in different aspects and dimensions of language. It is an assessment test that demonstrates high reliability and effectiveness in evaluating the linguistic profile of child and adolescent populations. All these scales are scored on a scale from 0 to 1, where 0 represents the absence of the skill and 1 represents the presence of the skill, except for the linguistic profile questionnaire, which consists of a structured response on a Likert scale from 0 to 4, where 0 is related to never and 4 to always. The Cronbach's alpha value is 0.89. In this study, the dependent variables included for data analysis were only those listed below, using the raw direct scores of each: Sentence Comprehension, Linguistic Concepts, Word Structure, Semantic Relationships, Following Directions, Formulated Sentences, Recalling Sentences, Understanding Spoken Paragraphs, Word Definitions, Sentence Assembly, and Pragmatics Profile.

3.3. Procedure

This research was approved by the ethics committee of the Universidad Católica San Antonio de Murcia (UCAM) with the code CE052206 on 27 May 2022. The study protocol involved an initial evaluation of participants according to the previously established inclusion and exclusion criteria. Subsequently, the sample was divided into three groups: ASD without epilepsy, Epilepsy, and ASD with epilepsy. Participant data were recorded in two assessment sessions, each lasting approximately 60 min. In the first session, participants' main data were collected through an initial interview, and the ENFEN test was administered to the children, while the BRIEF-2 test was given to the parents. In the second session, the CELF-5 test was administered to the participants. The assessment was conducted by two specialized professionals: a speech and language therapist for language evaluation and a neuropsychologist for executive functioning assessment. All data were recorded in a protected database, with the aim of organizing the data and conducting relevant statistical analyses. Finally, a report with the participants' assessment results was sent to the parents.

3.4. Data Analysis

The analyses in this quasi-experimental cross-sectional study were conducted using the statistical package SPSS (version 25). Firstly, the normality of the distributions of the continuous dependent variables was examined using the Chi-Square test to observe the differences in each of the sociodemographic variables characterizing the sample group. After analyzing the homogeneity of variances, homoscedasticity was found among the sociodemographic variables of the participants. Secondly, multivariate analysis of covariance (MANCOVA) analyses were performed to compare language skills and variables related to executive functioning among the groups to observe differences using the intellectual disability variable as a covariate, due to significant differences in the distribution of this variable in the sample of the present study ($n = 27$; participants with intellectual disability scoring between 60 and 70 on the IQ scale). The IQ is distributed as follows in the different study groups; ASD group [$M = 89.2$; $SD = 6.23$]; Epilepsy group [$M = 91.4$; $SD = 3.54$] and ASD with Epilepsy [$M = 78.1$; $SD = 13.57$; $G3 < G1, G2$]. To control the probability of a Type I error, a correction factor for adjusted critical p -values was introduced when

conducting multiple comparisons, employing a reduction method: the Holm–Bonferroni correction [59].

4. Results

4.1. Difference in Executive Functioning between the Tested Groups

The MANCOVA was conducted to examine variations in executive functioning skills across the ASD, Epilepsy, and combined ASD and epilepsy groups. The analysis revealed significant differences, supported by statistically significant results (Wilks' Lambda = 0.023, $F(14) = 113.195$, $p < 0.001$, $\eta^2_p = 0.849$). As depicted in Table 2, the variables showing noteworthy distinctions included inhibition, flexibility, emotional control, working memory, planning, organization of materials, and monitoring. The detailed outcomes of the MANCOVAs regarding executive functioning are outlined in Table 2.

Table 2. Comparative analysis among groups: ASD (G1), Epilepsy (G2), and ASD and epilepsy (G3) in executive functioning measures assessed in the BRIEF-2 test.

	ASD (<i>n</i> = 50)		Epilepsy (<i>n</i> = 50)		ASD and Epilepsy (<i>n</i> = 50)		$F_{(2,147)}$	η^2_p	Difference between Groups
	M	SD	M	SD	M	SD			
Inhibition	14.86	3.60	23.58	3.74	4.50	2.97	382.16 *	0.839	G3 < G1 < G2
Flexibility	13.42	3.74	23.92	3.70	4.72	2.90	382.53 *	0.839	G3 < G1 < G2
Emocional control	13.20	3.06	24.16	3.54	4.50	2.95	475.18 *	0.866	G3 < G1 < G2
Work memory	14.00	3.85	23.98	4.06	4.58	2.95	351.65 *	0.827	G3 < G1 < G2
Planning	14.12	3.79	23.60	3.54	4.10	2.83	406.85 *	0.847	G3 < G1 < G2
Organization of materials	13.80	3.79	23.36	3.83	4.48	3.07	347.30 *	0.825	G3 < G1 < G2
Monitoring	13.90	3.53	24.66	3.52	4.52	2.94	453.46 *	0.861	G3 < G1 < G2

* $p < 0.05$.

The results from Table 2 indicate significant differences in executive functioning measures among the three groups: ASD (G1), Epilepsy (G2), and ASD with epilepsy (G3), as obtained in the BRIEF-2 test. For the Inhibition domain, G3 ($M = 4.50$, $SD = 2.97$) showed lower scores compared to G1 ($M = 14.86$, $SD = 3.60$) and G2 ($M = 23.58$, $SD = 3.74$), with a statistically significant difference ($F = 382.16$, $p < 0.05$, $\eta^2_p = 0.839$), indicating that G3 exhibited the least inhibitory control. Similar patterns were observed in the Flexibility, Emotional Control, Work Memory, Planning, Organization of Materials, and Monitoring domains, with G3 consistently showing lower scores than G1 and G2. These differences were statistically significant for all domains ($p < 0.05$), with large effect sizes (η^2_p ranging from 0.825 to 0.866). The general trend suggests that the executive functioning of children with both ASD and epilepsy (G3) is poorer compared to those with ASD alone (G1) and epilepsy alone (G2), highlighting the potential additive impact of the coexistence of these conditions on various aspects of executive functioning.

Post-hoc analyses revealed significant differences among the ASD, epilepsy, and ASD with epilepsy groups in the variables assessed by the BRIEF-2 test ($p < 0.001$). Across all variables, the epilepsy group showed higher scores in executive functioning subscales compared to the ASD group, followed by the ASD and epilepsy group, which exhibited the most pronounced alterations.

Similarly, a MANCOVA was performed to examine variations in executive functioning skills, as measured by the ENFEN instrument, among the ASD, epilepsy, and combined ASD and epilepsy groups. The analysis revealed significant differences (Wilks' Lambda = 0.083, $F(8) = 87.304$, $p < 0.001$, $\eta^2_p = 0.708$). As delineated in Table 3, notable differences were observed in variables such as Verbal Fluency, Trail Construction, Ring Construction, and In-

terference Resistance. Detailed results of the MANCOVAs concerning executive functioning are provided in Table 3.

Table 3. Comparative analysis among groups: ASD (G1), epilepsy (G2), and ASD and epilepsy (G3) in executive functioning measures assessed in the ENFEN test.

	ASD (<i>n</i> = 50)		Epilepsy (<i>n</i> = 50)		ASD and Epilepsy (<i>n</i> = 50)		<i>F</i> (2,147)	η^2_p	Difference between Groups
	M	SD	M	SD	M	SD			
Verbal fluency	16.82	3.37	23.84	5.25	9.40	3.37	155.27 *	0.679	G3 < G1 < G2
Trail construction	18.26	3.48	23.74	5.11	8.26	3.16	191.16 *	0.722	G3 < G1 < G2
Ring construction	17.48	3.88	24.46	5.05	8.06	3.01	204.40 *	0.736	G3 < G1 < G2
Interference resistance	18.22	3.77	24.12	5.39	8.20	2.99	185.84 *	0.717	G3 < G1 < G2

* $p < 0.05$.

The results of Table 3 indicate significant differences in executive functioning measures among the three groups: ASD (G1), Epilepsy (G2), and ASD with epilepsy (G3). In verbal fluency, G3 ($M = 9.40$, $SD = 3.37$) showed lower scores compared to G1 ($M = 16.82$, $SD = 3.37$) and G2 ($M = 23.84$, $SD = 5.25$), with a statistically significant difference ($F = 155.27$, $p < 0.05$, $\eta^2_p = 0.679$), indicating that G3 exhibited less fluent verbal performance. In trail and ring constructions, G3 also demonstrated lower scores than G1 and G2, with significant differences in all three cases ($F = 191.16$, $F = 204.40$, $p < 0.05$, $\eta^2_p = 0.722$, 0.736 , respectively), indicating difficulties in visuospatial planning and fine motor skills in G3. In interference resistance, G3 ($M = 8.20$, $SD = 2.99$) showed inferior performance compared to G1 ($M = 18.22$, $SD = 3.77$) and G2 ($M = 24.12$, $SD = 5.39$), with a statistically significant difference ($F = 185.84$, $p < 0.05$, $\eta^2_p = 0.717$), indicating challenges in suppressing interference and maintaining selective attention in G3. These findings support the notion that the coexistence of Autism Spectrum Disorder and epilepsy (G3) is associated with specific deficiencies in various facets of executive functioning compared to the individual groups G1 and G2.

Post-hoc tests showed statistically significant differences between ASD, epilepsy, and ASD with epilepsy groups in the variables comprising the ENFEN test ($p < 0.001$). In all variables, the scores in the subscales measuring executive functioning of the epilepsy group were higher than those obtained in the ASD group, followed by the ASD and epilepsy group. The latter was the one in which greater alterations were observed.

4.2. Language Differences between the Tested Groups

The MANCOVA analysis conducted to examine variations in language proficiency measures among ASD, epilepsy, and ASD with epilepsy groups revealed notable distinctions (Wilks' Lambda = 0.020, $F(18) = 94.530$, $p < 0.001$, $\eta^2_p = 0.860$). As depicted in Table 4, significant differences were observed in Sentence Comprehension, Linguistic Concepts, Word Structure, Semantic Relationships, Following Directions, Formulated Sentences, Recalling Sentences, Understanding Spoken Paragraphs, Word Definitions, Sentence Assembly, and Pragmatics Profile. The outcomes of the MANCOVAs regarding linguistic abilities are outlined in Table 4 below.

The analysis reveals significant differences among the ASD (G1), Epilepsy (G2), and ASD with epilepsy (G3) groups. In terms of Sentence Comprehension, the G3 group exhibits notably lower mean scores ($M = 4.44$, $SD = 2.908$) compared to both G1 ($M = 14.92$, $SD = 3.680$) and G2 ($M = 25.06$, $SD = 4.133$), indicating pronounced challenges in comprehending complex linguistic structures within G3 ($F = 408.05$, $p < 0.05$, $\eta^2_p = 0.847$). Similarly, in Linguistic Concepts, G3 ($M = 4.40$, $SD = 3.117$) demonstrates inferior performance relative to both G1 ($M = 15.84$, $SD = 3.776$) and G2 ($M = 24.40$, $SD = 3.860$), with a significant difference ($F = 388.55$, $p < 0.05$, $\eta^2_p = 0.841$), suggesting difficulties in grasping abstract concepts. Word Structure also presents challenges for G3 ($M = 4.12$, $SD = 3.055$), which

scores lower than both G1 ($M = 16.36$, $SD = 4.355$) and G2 ($M = 23.50$, $SD = 3.477$) with a significant difference ($F = 356.72$, $p < 0.05$, $\eta^2_p = 0.829$), indicating difficulties in understanding grammatical structure and syntax. Furthermore, G3 exhibits inferior performance in Semantic Relationships ($M = 4.72$, $SD = 2.865$) compared to G1 ($M = 16.58$, $SD = 3.866$) and G2 ($M = 24.18$, $SD = 4.183$), with a significant difference ($F = 354.96$, $p < 0.05$, $\eta^2_p = 0.828$), suggesting additional challenges in word and concept association.

Table 4. Comparative analysis among ASD (G1), epilepsy (G2), and ASD with epilepsy (G3) groups based on language measures derived from the CELF-5 assessment.

	ASD ($n = 50$)		Epilepsy ($n = 50$)		ASD and Epilepsy ($n = 50$)		$F_{(2,147)}$	η^2_p	Difference between Groups
	M	SD	M	SD	M	SD			
Sentence Comprehension	14.92	3.680	25.06	4.133	4.44	2.908	408.05 *	0.847	G3 < G1 < G2
Linguistic Concepts	15.84	3.776	24.40	3.860	4.40	3.117	388.55 *	0.841	G3 < G1 < G2
Word Structure	16.36	4.355	23.50	3.477	4.12	3.055	356.72 *	0.829	G3 < G1 < G2
Semantic Relationships	16.58	3.866	24.18	4.183	4.72	2.865	354.96 *	0.828	G3 < G1 < G2
Following Directions	15.60	3.725	25.36	4.070	4.48	2.936	419.14 *	0.851	G3 < G1 < G2
Formulated Sentences	16.06	3.909	23.54	3.945	4.54	2.943	347.85 *	0.826	G3 < G1 < G2
Recalling Sentences	15.72	4.010	24.78	4.674	3.72	2.872	362.51 *	0.831	G3 < G1 < G2
Understanding Spoken Paragraphs	16.26	3.942	23.70	3.955	4.44	2.786	363.31 *	0.832	G3 < G1 < G2
Word Definitions	15.94	3.582	25.45	4.476	4.23	2.954	395.64 *	0.864	G3 < G1 < G2
Sentence Assembly	16.02	3.877	24.49	4.258	4.73	2.621	357.45 *	0.851	G3 < G1 < G2
Pragmatics Profile	16.90	4.414	23.80	3.725	4.44	2.830	349.14 *	0.826	G3 < G1 < G2

* $p < 0.05$.

Additionally, G3 demonstrates lower performance in Following Directions compared to both G1 and G2, with a significant difference ($F = 419.14$, $p < 0.05$, $\eta^2_p = 0.851$). Formulated Sentences also present challenges for G3 ($M = 4.54$, $SD = 2.943$) compared to G1 ($M = 16.06$, $SD = 3.909$) and G2 ($M = 23.54$, $SD = 3.945$), with a significant difference ($F = 347.85$, $p < 0.05$, $\eta^2_p = 0.826$), indicating difficulties in constructing coherent sentences. Likewise, Recalling Sentences reveals lower performance in G3 ($M = 3.72$, $SD = 2.872$) compared to G1 ($M = 15.72$, $SD = 4.010$) and G2 ($M = 24.78$, $SD = 4.674$), with a significant difference ($F = 362.51$, $p < 0.05$, $\eta^2_p = 0.831$), suggesting challenges in recalling and reproducing sentences accurately. Furthermore, Understanding Spoken Paragraphs shows G3 ($M = 4.44$, $SD = 2.786$) with inferior performance relative to G1 ($M = 16.26$, $SD = 3.942$) and G2 ($M = 23.70$, $SD = 3.955$), with a significant difference ($F = 363.31$, $p < 0.05$, $\eta^2_p = 0.832$), indicating difficulties in comprehending longer verbal passages. Word Definitions also present challenges for G3 ($M = 4.23$, $SD = 2.954$) compared to G1 ($M = 15.94$, $SD = 3.582$) and G2 ($M = 25.45$, $SD = 4.476$), with a significant difference ($F = 395.64$, $p < 0.05$, $\eta^2_p = 0.864$), suggesting limitations in defining and understanding word meanings. Additionally, Sentence Assembly reveals G3 ($M = 4.73$, $SD = 2.621$) with lower performance compared to G1 ($M = 16.02$, $SD = 3.877$) and G2 ($M = 24.49$, $SD = 4.258$), with a significant difference ($F = 357.45$, $p < 0.05$, $\eta^2_p = 0.851$), indicating challenges in assembling sentences logically. Lastly, the Pragmatics Profile demonstrates G3 ($M = 4.44$, $SD = 2.830$) with inferior performance relative to G1 ($M = 16.90$, $SD = 4.414$) and G2 ($M = 23.80$, $SD = 3.725$), with a significant difference ($F = 349.14$, $p < 0.05$, $\eta^2_p = 0.826$), suggesting difficulties in using language appropriately in social contexts. These findings underscore the heightened dif-

difficulties in various aspects of language observed within the G3 group in contrast to the individual groups G1 and G2.

5. Discussion

The objective of this research was to examine and contrast potential variations in both language and executive functioning across three distinct groups: individuals diagnosed solely with ASD, those diagnosed solely with epilepsy, and those diagnosed with the comorbidity of ASD and epilepsy during childhood. The primary hypothesis posited that individuals diagnosed with epilepsy would demonstrate superior scores on assessments of executive functioning in comparison to those with ASD or the comorbid condition of ASD and epilepsy. The secondary hypothesis suggested that individuals with epilepsy would display enhanced performance and higher scores across language dimensions relative to individuals with ASD or the comorbid condition of ASD and epilepsy.

Below, discussions of the results regarding executive functioning and language skills obtained by the three groups of participants in the present study are carried out.

5.1. Discussion of Results Regarding Participants' Executive Functioning

In terms of executive functioning abilities, the findings indicated that the epilepsy group outperformed both the ASD group and the group with comorbid ASD and epilepsy. Moreover, the epilepsy group demonstrated superior skills in executive functioning, including planning, organization, working memory, inhibition, and emotional control, among others. These competencies enable them to carry out daily tasks more effectively compared to children with ASD and epilepsy. Consequently, individuals with epilepsy but without ASD generally exhibit better performance in executive functioning processes, leading to an enhanced development of daily life activities and autonomy in various settings such as home or school. It is suggested that the presence of ASD may impede the proper development of certain executive functioning processes, like cognitive flexibility, planning, organization, inhibition, or emotional control, which significantly affects the execution of basic daily activities across different contexts. However, when ASD and epilepsy coexist in children, challenges in executive functioning become more pronounced due to impairments in specific brain regions, such as the prefrontal and temporal lobes.

The current study identified a notable pattern indicating that individuals with ASD and epilepsy exhibit compromised executive functions in comparison to other participants. This suggests that ASD has a detrimental effect on these executive skills, consequently impeding autonomy, learning, and integration across various daily life contexts. This observation is corroborated by studies such as Pisón et al. [25], which demonstrate that children diagnosed with both ASD and epilepsy display more pronounced cognitive impairment and poorer executive functioning when compared to those with ASD alone.

Regarding tasks such as information processing, emotional control, attention, and working memory, the study by Pisón et al. [25] also indicates that this population usually experiences severe difficulties in all these areas. These results are similar to those of Barboza Ubarnes et al. [41], where it is demonstrated that children with ASD and epilepsy often exhibit a symptomatic pattern highlighting difficulties in executive functioning, specifically in working memory, verbal information processing, and emotional control. This is attributed to focal damage in brain areas related to executive functions, such as the frontal lobe. However, these studies do not conduct a comparative analysis between language and executive functioning competencies but offer a general view of the alterations presented by these profiles without establishing a relationship between the two competencies. Therefore, executive functioning skills might be more pronounced in children with ASD who also have epilepsy, potentially reducing their abilities in cognitive flexibility, planning, organization, working memory, inhibition, or emotional control [60–62].

5.2. Discussion of Results Regarding Participants' Language Skills

Regarding language skills, the results obtained in the present study confirm the previously established research hypothesis. This is because participants who had epilepsy as the primary diagnosis demonstrated better performance in communicative and linguistic abilities, showing a linguistic profile characterized by better performance in tasks related to Sentence Comprehension, Linguistic Concepts, Word Structure, Semantic Relationships, Following Directions, Formulated Sentences, Recalling Sentences, Understanding Spoken Paragraphs, Word Definitions, Sentence Assembly, and Pragmatics Profile, compared to children diagnosed with ASD or ASD with epilepsy. Additionally, the results indicate that the presence of ASD alongside epilepsy leads to limitations in language, communication, and speech performance. The pediatric population with ASD exhibits atypical development in terms of language aspects and dimensions, where alterations in speech sound articulation and its phonological and phonetic processing, acquisition of functional vocabulary and its integration into their lexical-semantic store, grammatical coherence, and cohesion with morphosyntactic structures adjusted to their chronological age, and the interaction and use of language through gestures, communicative intention, or narrative related to pragmatics can be observed [60]. It seems that epilepsy located in the major areas of expressive and receptive language causes a delay in acquiring linguistic competencies in this pediatric population with ASD during the early stages of maturation. This is manifested in the lack of proper theory of mind, difficulties in relating to peers, as well as expressing desires or needs [61–63].

Similarly, in the present study, alterations are observed in grammatical processes, sentence repetition, elaboration of morphosyntactic structures, and difficulties in lexical access and vocabulary. All of this leads participants with ASD and epilepsy to show limited performance in linguistic processes, both in their expressive and receptive dimensions, thus limiting their interaction with the environment and exacerbating linguistic characteristics already observed in epilepsy as the primary diagnosis. These results align with current research, such as that conducted by del Busto [42] and Campos-Castelló and Campos-Soler [36], which indicate that the pediatric population with ASD and epilepsy often presents alterations in lexical access processes, as well as in the pragmatic dimension of language.

Communication difficulties in children with epilepsy have been noted in studies such as Zambarbieri [43], which highlight the vulnerability of areas such as the temporal and frontal lobes to epileptic foci. Consequently, deficits in semantic memory and language, including reduced verbal fluency and anomia are frequently reported. When epilepsy coexists with ASD, these linguistic challenges appear to be more pronounced [40]. This suggests that individuals with ASD and epilepsy face heightened limitations in communication and language, necessitating specialized care, as emphasized in this study. Support for this notion is evident in research by Diones-Chocano et al. [44], Juillerat et al. [45], Norrelgen et al. [46], and Rotta [47], which examine language skills in pediatric populations with ASD or ASD with epilepsy. These studies consistently indicate greater language impairments in children with ASD and epilepsy compared to those without this comorbidity. Furthermore, it is suggested that this population experiences difficulties in acquiring first words, mastering grammatical and syntactic language forms, and engaging in functional conversation with their surroundings. Consequently, the present study underscores that children meeting this profile often exhibit delays in sentence production prior to entering primary school. Therefore, compelling evidence from this study suggests that children diagnosed with both ASD and epilepsy tend to experience more pronounced delays in acquiring oral communication skills compared to their peers without epilepsy [64].

5.3. Discussion of the Results from the Perspective of Educational Neuroscience

Adverse outcomes in children's cognitive and linguistic development can be attributed to the ongoing interaction of toxic stressors impacting the brain both during pregnancy and the child's first 1000 days of life. These stressors may include environmental expo-

tures such as air pollution, household or community toxin exposure, prenatal stress, and inadequate nutrition, among others. Exposure to these stressors during critical periods of brain development can have significant and lasting consequences on brain structure and function, which in turn, can negatively affect the child's cognitive and linguistic development. In this context, it is emphasized how decisions made by the school team in collaboration with families can be crucial in designing individualized educational plans that accommodate each child's strengths and weaknesses. These plans include specific interventions to address areas of development affected by identified stressors, such as early intervention programs, speech and language therapy, and emotional and psychological support. However, to further enrich this educational strategy, it would be beneficial to establish close collaboration with healthcare professionals. These professionals offer valuable diagnostic insights based on the origins of language and cognitive-related educational challenges, considering both endogenous and exogenous stressors, such as interactions between genes and the environment. For example, a pediatrician may identify and address underlying health issues contributing to the child's developmental challenges, while a pediatric neurologist can assess and treat specific neurological disorders affecting cognitive and linguistic development. Additionally, an interdisciplinary perspective spanning neuroscience, psychology, education, and medicine provides a more comprehensive understanding of factors influencing children's cognitive and linguistic development and allows for a more holistic approach to intervention and treatment. This interdisciplinary collaboration would include regular meetings among educators, physicians, and other healthcare professionals to review the child's progress, share relevant information, and coordinate interventions to ensure comprehensive, child-centered care.

Furthermore, it would be valuable to examine how these recent research findings relate to the findings of the present study and how they can inform our interpretations and recommendations. For example, considering the healthcare disparities highlighted by Scher [65], we could reflect on how these disparities may affect access to early intervention services and specialized healthcare for children at risk of cognitive and linguistic challenges. This could include a lack of access to specialized assessments and treatments, which could, in turn, delay identification and early intervention in children with specific needs, directly influencing their long-term cognitive and linguistic development. Similarly, by exploring the role of the neuronal exposome in childhood development according to Scher [66], we could reflect on how environmental exposures and stressors may interact with biological processes to influence brain development and ultimately cognitive and linguistic skills in children with ASD and epilepsy. This could involve considering how environmental pollution, prenatal stress, and other environmental factors may negatively impact brain development and cognitive function in this population, which could have significant consequences for their ability to acquire and develop language and other cognitive skills. These reflections may lead to recommendations for policies and practices that address healthcare inequities and promote healthy and safe environments for child development. For example, policies could be suggested to increase equitable access to healthcare and education services, as well as community interventions aimed at reducing exposure to environmental stressors and promoting healthy parenting environments. Ultimately, a deeper understanding of these issues can lead to more effective strategies to support optimal cognitive and linguistic development in children and address disparities in child health and well-being.

6. Conclusions

In summary, individuals with ASD and epilepsy demonstrate heightened deficits in executive functions such as inhibition, flexibility, emotional control, working memory, planning, organization, and monitoring, along with challenges in language areas including phonology, semantics, morphosyntax, and pragmatics, when compared to those with ASD alone. It is evident that children affected by these conditions encounter obstacles in both ex-

ecutive functioning and expression as well as receptive language abilities. These challenges stem from disruptions in cognitive-linguistic capabilities, impacting overall functioning.

However, this study faces limitations related to the choice of instruments, which are objective and not reliant on self-reports. The BRIEF-2 is employed to assess executive functions, utilizing a questionnaire completed by family members based on their observations and experiences within the child's developmental environment. While offering considerable ecological validity, the BRIEF-2 could benefit from the inclusion of additional tests administered directly to participants by examiners. However, the ENFEN test was indeed administered by a neuropsychologist, allowing for the control of potential bias found in the self-administration of the BRIEF-2 questionnaire by the family members and teachers of the participants comprising the sample group in this study. Moreover, it is important to acknowledge the variability in clinical and symptomatic profiles among individuals diagnosed with epilepsy, ASD, or both. A thorough analysis of alterations based on the severity of ASD within these populations is warranted. Additionally, an evaluation within an academic setting is proposed to enable comparisons between assessment scores, parental reports, and feedback from teachers.

Despite these limitations, this work paves the way for future research to address these deficiencies. Furthermore, other subtypes of ASD should be evaluated for a more profound comparison of this disorder. Different types of epilepsy should also be compared, as well as conducting neuroimaging studies to allow comparisons based on the location of the epileptic focus in the pediatric population with this condition. Along the same lines, a research avenue is proposed to describe emotional alterations or the quality of life of the family nucleus. The information collected in the parental references of the selected populations in this study would help determine the linguistic and cognitive maturation of these three groups of individuals. Additionally, it is essential to carry out additional assessments of other factors, such as motor skills and sensory profiles, which are crucial in the ASD population. Lastly, future research could incorporate the examination of social skills and their development across various forms of ASD, comparing them with other comorbid disorders.

In summary, the rising prevalence of coexisting ASD and epilepsy highlights the importance of identifying and monitoring various factors and characteristics for early intervention in the cognitive-linguistic impairments associated with this dual condition. The concurrent presence of ASD and epilepsy may hinder the optimal development of affected children, impacting their executive and language skills. As a result, these limitations could impede the smooth execution of daily activities, reducing the efficiency and autonomy of individuals with ASD with epilepsy.

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5.4. ARTÍCULO 4

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The Comprehension of Grammatical Structures in a Pediatric Population with ASD and Epilepsy: A Comparative Study

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Abstract

Autism Spectrum Disorder (ASD) and epilepsy represent a comorbidity that negatively influences the proper development of linguistic competencies, particularly in receptive language, in the pediatric population. This group displays impairments in the auditory comprehension of both simple and complex grammatical structures, significantly limiting their performance in language-related activities, hampering their integration into social contexts, and affecting their quality of life. The main objective of this study was to assess auditory comprehension of grammatical structures in individuals with ASD and epilepsy and compare the results among the three groups. A non-experimental cross-sectional study was designed, including a total of 170 participants aged between 7 and 9 years, divided into three groups: a group with ASD, a group with epilepsy, and a comorbid group with both ASD and epilepsy (ASDEP). The comprehension of grammatical structures was assessed using the CEG and CELF-5 instruments. Statistical analyses included MANOVA and ANOVA to compare scores between groups to verify associations between study variables. The results indicate that the group with ASD and epilepsy performed worse compared to the ASD and epilepsy-only groups, respectively. Additionally, a significant and directly proportional association was observed among all variables within the measures of grammatical structure comprehension. The neurological damage caused by epilepsy in the pediatric population with ASD leads to difficulties in understanding oral language. This level of functioning significantly limits the linguistic performance of these children, negatively impacting their quality of life and the development of core language skills.

Keywords ASD · Epilepsy · Childhood · Auditory comprehension · Morphosyntax

Introduction

The pediatric population with Autism Spectrum Disorder (ASD) and comorbid neurological conditions such as epilepsy exhibits a highly heterogeneous linguistic profile (Wiklund & Laakso, 2021). Deficits in language skills represent one of the most relevant factors determining the clinical severity of children with ASD (Hirota & King, 2023). However, when an individual with ASD also presents with epilepsy, competencies in expressive and receptive language manifest greater difficulty compared to when only one of these two disorders is present (Braconnier & Siper, 2021). Linguistic alterations in children with ASD and epilepsy can be described as a highly variable continuum, where on one hand, there are minimally verbal children (Tuchman et al., 2010) or those who do not acquire verbal language (in variable percentages of up to 50% according to different studies), and on the other hand, there are children with a level of linguistic form development that can be

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considered appropriate (Duffy et al., 2013), but pragmatically inadequate (Roberts et al., 2008). Within this spectrum, highly variable profiles of linguistic development can be found (Mukherjee, 2017), with children exhibiting mild language delay (Davidson & Weismer, 2017), children with severe language disorders (Eigsti et al., 2015), and those who, despite reaching their early development milestones, such as first word production or usage between 12 and 18 months, subsequently experience stagnation or regression in their language development (Ricketts, 2011).

Although communication and language in children with ASD have been extensively researched (Davidson et al., 2018; Naigles, 2013; Torrens & Ruiz, 2021), when this disorder is accompanied by epilepsy, the nature and characteristics of language deficits become an evident issue that requires further investigation (Cano-Villagrasa et al., 2023). For instance, according to the DSM-5 (APA, 2013), ASD exhibits significant alterations in the pragmatic-social dimension of expressive language. Its diagnostic criteria emphasize difficulties in establishing functional conversations and interacting with the environment, particularly in contexts where linguistic demands on the individual with ASD are higher. However, the DSM-5 diagnostic criteria do not provide a detailed description of the linguistic alterations that a child with a diagnosis of both ASD and epilepsy might present. Some authors consider ASD and epilepsy as potentially comorbid conditions (Ali, 2018; Ricketts, 2011; Tran et al., 2020) and suggest that these clinical profiles are associated with more pronounced disruptions in expressive language development (Eigsti et al., 2015). These disruptions include difficulties in phonological, semantic, morphosyntactic, and pragmatic functioning, in addition to receptive language impairments involving comprehension and following complex instructions with multiple elements (Saban-Bezael & Mashal, 2019).

Delving into linguistic competencies related to language comprehension, most published studies report that in ASD and epilepsy, receptive language is more affected than expressive language (Asberg, 2010; Henry & Solari, 2020). However, this finding has not been fully confirmed (Roemer et al., 2019). Furthermore, the question of the discrepancy between receptive and expressive competencies is still unclear in terms of whether it should be considered a potential marker of ASD (Saban-Bezael & Mashal, 2015) or if both receptive and expressive language difficulties are comorbid with ASD and epilepsy (Cano-Villagrasa et al., 2023).

Difficulties in language comprehension in children with ASD and epilepsy are part of a broad and complex spectrum characterized by pragmatic deficits (Eberhardt & Nadig, 2018) and executive functioning impairments that can affect verbal comprehension (Asberg et al., 2010).

According to Tager-Flusberg et al. (2009), language comprehension problems in the presence of this comorbidity are particularly evident in everyday situations rather than during single-word comprehension tasks. Children with ASD and epilepsy have impairments in their ability to decode relevant contextual cues and deficits in social attention (Svindt & Surányi, 2021), while typically developing children can identify or select salient sensory and social stimuli relevant for both comprehension and communication from an early age (Boucher, 2012).

Grammatical comprehension, as a specific receptive language skill required to decode verbal messages in interactions (Naigles & Tovar, 2012), represents a crucial research target in the field of ASD and epilepsy (Kalandadze et al., 2022). However, it is worth noting that few studies assess the comprehension of individuals with ASD and epilepsy through specific tasks that evaluate differences in their grammatical comprehension skills.

Several research findings suggest that syntactic deficits are apparent across individuals on the spectrum, including among older adolescents with ASD and epilepsy who have average or above-average cognitive abilities (Eigsti & Bennetto, 2007; Gonzalez-Barrero & Nadig, 2019; Loukusa et al., 2014). However, syntactic deficits tend to be localized rather than global and vary among individuals with ASD and epilepsy. For instance, some children with these two disorders display deficiencies in the comprehension of past tense verbs (Kelley et al., 2006), while others exhibit alterations in morpheme comprehension (Tovar et al., 2015). Similar to the semantic component, research suggests variability in syntactic language skills exhibited by individuals with ASD and epilepsy (Eigsti & Bennetto, 2007).

Some authors hypothesize that this variability can be explained by cognitive abilities and the severity of symptoms in ASD and epilepsy, as individuals with these conditions show deficits in syntactic language (Roberts et al., 2010; Shulman & Guberman, 2007). However, other authors have found that even among individuals with ASD and epilepsy who have better cognitive abilities, most still demonstrate specific syntactic deficits, such as the use of simplified phrases, limitations in the comprehension of complex grammatical structures, and challenges with verb tense conjugation and inflection (Eigsti & Bennetto, 2007; Kelley et al., 2006).

The discrepancy in findings likely reflects the interplay between ASD and epilepsy, as several studies have reported that this population experiences difficulties in comprehending grammatical structures related to passive voice or those with a high degree of inferential content (Roberts et al., 2010; Shulman & Guberman, 2007). Given the limited literature examining the comprehension of morphosyntactic structures in the pediatric population with ASD and

epilepsy, along with methodological limitations in research in this area, there is a need to expand research in this domain to gain a better understanding of syntactic language in these disorders and the influence of syntactic language skills on other aspects of psychosocial functioning for children with ASD and epilepsy.

Therefore, the assessment of receptive skills in children with ASD and epilepsy is of crucial clinical importance for defining their language profile more clearly (Ge et al., 2023). It is considered a fundamental prognostic marker for the development of linguistic competencies (Garrido et al., 2015). In fact, children with ASD and epilepsy who have minimal ability to emit verbal information and communication exhibit greater severity of autistic symptoms and overall worse clinical outcomes (Baixauli et al., 2020) than those with only one of the two disorders, for whom the outcome might be more satisfactory (Venker et al., 2016).

For these reasons, the main objective of this study was to evaluate competencies in the comprehension of grammatical structures in the Spanish language in a group of minors diagnosed with ASD and epilepsy. Additionally, a series of specific objectives were established, including: (I) comparing performance in grammatical structure comprehension tasks, and (II) examining the relationship between the subscales of grammatical structure comprehension among the three participant groups. Based on the empirical evidence in the scientific literature, it was hypothesized in this study that participants diagnosed with both ASD and epilepsy would perform worse in comprehension tasks compared to the group diagnosed with ASD, followed by the group composed of individuals diagnosed with epilepsy.

Method

Participants

All participants diagnosed with ASD or epilepsy underwent evaluation in the Mental Health Unit and Pediatric Neurology service attached to their medical reference center by a multidisciplinary professional team. In these centers, a diagnostic screening assessment was conducted using the M-CHAT-R questionnaire (Robins et al., 2004). Children who scored in a way that raised suspicion underwent the ADOS-2 (Lord et al., 2008) and ADI-R (Rutter et al., 2006) protocols to confirm the diagnostic suspicion of ASD. Additionally, participants received a neurological evaluation from the neuropsychiatric team, which included a neurological assessment using Magnetic Resonance Imaging, sleep-deprived Electroencephalogram, and genetic tests to help confirm the diagnosis.

Finally, the following inclusion and exclusion criteria were established. Inclusion criteria were: (I) being between 7 and 9 years old, (II) having a diagnosis of ASD issued by a public hospital or health center, and (III) undergoing rehabilitation treatment at the rehabilitation clinic. Exclusion criteria were: (I) having any motor or sensory disease or disorder that hinders or prevents proper study performance, (II) not exhibiting any communication or language by 5 years of age, and (III) having mild, moderate, severe, or profound intellectual disability or an IQ score below 75 as measured by the WISC-V test (Wechsler, 2015).

Instruments and Materials

"CEG. Test de Comprensión de Estructuras Gramaticales"

The *CEG. Test de Comprensión de Estructuras Gramaticales* (CEG; Mendoza et al., 2005) is an assessment instrument that measures the comprehension of statements and sentences with varying levels of morphosyntactic complexity in the Spanish language. It is standardized for the Spanish population between the ages of 4 and 12. This test consists of 80 multiple-choice items (four answer alternatives) distributed across 20 blocks of four items each, representing the most representative grammatical structures in the Spanish language. The internal consistency of the test has been studied using Cronbach's alpha coefficient, and a reliability index of 0.9096 has been obtained. The reliability obtained for each age group was as follows: 4 years: 0.825; 5 years: 0.779; 6 years: 0.866; 7 years: 0.797; 8 years: 0.828; 9 years: 0.807; 10 years: 0.794; and 11 years: 0.842.

CELF-5. Clinical Evaluation of Language Fundamentals – 5

The Clinical Evaluation of Language Fundamentals – 5 (CELF-5; Wiig et al., 2013) is an individual clinical assessment instrument designed to identify, diagnose, and monitor language and communication disorders in children and adolescents aged 5 to 15 years. This individual application instrument aims to evaluate the user's strengths and weaknesses in different aspects and dimensions of language in Spanish. This instrument consists of 14 subscales, but only two were used in this research: Sentence comprehension and Execution of instructions. These two scales are scored with 0–1 points, with 0 indicating the absence of the skill and 1 indicating its presence, except for the linguistic profile questionnaire, which consists of a structured response on a Likert-type scale of 0–4, where a score of 0 is associated with "never" and 4 with "always." The internal consistency of the CELF-5 obtained by Cronbach's alpha coefficient is 0.901. According to the study by Denman et al. (2017), the reliability of the test is between 72.4 and 66.7, which makes

it an instrument with good psychometric quality evidence and its use is recommended.

Procedure

For the completion of this study, first, approval was obtained from the Ethics Committee of the Universidad Católica San Antonio de Murcia (UCAM), with the code: CE052206. Next, the participant groups were configured, following the inclusion and exclusion criteria previously established for this study, and they were grouped into three experimental groups. In this way, an evaluation of the participants included two 60-minute sessions. The data from the measurement instruments were stored in protected databases, which were later analyzed by the research group members, checking the fulfillment of the research hypotheses.

Design and Data Analysis

The statistical analysis of this non-experimental cross-sectional study was conducted using the Statistical Package for the Social Sciences (SPSS) software, version 23.0 for Windows, developed by IBM, for statistical analysis in this

study. Two different statistical designs were used to carry out the analyses. First, the Kolmogorov-Smirnoff test was used to examine the normality of the distribution of the variables that make up the study, which was found to meet the normality assumption. Next, multivariate analysis of variance (MANOVA) was used to observe the relationship between the variables related to the comprehension of different types of grammatical structures in Spanish. This allowed for exploring the differences among the groups that make up the sample. Subsequently, analysis of variance (ANOVA) tests was performed to observe individual differences in each of the variables in the three groups. Finally, to control for Type I error, the Holm-Bonferroni correction (Holm, 1979) was applied to the statistical analyses conducted. Subsequently, post hoc analyses for multiple comparisons between the three groups (ASD, Epilepsy, and ASD and epilepsy) were performed using Bonferroni's method (Bonferroni, 1936).

Results

A total of 170 participants aged between 7 and 9 years were selected and divided into three groups: the ASD group ($n=57$), the ASD and epilepsy group ($n=53$), and the epilepsy-only group ($n=60$). The ASD group (ASD) consisted of 36 boys and 21 girls ($M_{age} = 8.1$; $SD=0.9$) diagnosed with grade 1 ASD. The Epilepsy group (EP) comprised 41 boys and 19 girls ($M_{age} = 8.6$; $SD=0.4$). The ASD and epilepsy group (ASDEP) consisted of 27 boys and 26 girls ($M_{age} = 7.8$; $SD=0.8$) who also had a diagnosis of grade 1 ASD and were evaluated and diagnosed at their medical reference center. All participants were native Spanish speakers. Table 1 summarizes the main characteristics of the participants who comprised the study's sample group:

With respect to the results of the analyses, first, the Kolmogorov-Smirnoff test was performed, and its significance level was found to be greater than 0.05, indicating that there is insufficient empirical evidence to reject the null hypothesis, which suggests that the distribution of the participants' scores follows a normal distribution. In addition, a descriptive analysis was performed to determine the mean scores (M) and standard deviation (SD) for each of the variables included in the study. Finally, the MANOVA conducted to assess differences in measures of grammatical structure comprehension among the ASD, Epilepsy, and ASD with Epilepsy groups revealed the presence of statistically significant differences (Wilks' $\Lambda=0.013$, $F(2,167)=81.031$, $p<0.001$, $\eta^2P=0.888$). As can be seen in Table 2, the variables in which significant differences were obtained included Inferences, Active Structure, Passive Structure, Declaratives, Reflexives, Datives, Interrogative, Exclamatory, Dubitative, Desiderative, Exhortative,

Table 1 Characteristics of the study participants
Characterization of the participants

		N	Percentage
Sex	Male	104	61.2
	Woman	66	38.2
Age	7 years old	47	27.6
	8 years old	61	35.9
	9 years old	62	36.5
Diagnosis	ASD	57	33.5
	ASD + Epilepsy	53	31.2
	Epilepsy	60	35.3
Years of treatment	2 years	34	20.0
	3 years	73	42.9
	4 years	63	37.1
Grade of incapacity	Less than 33%	52	29.1
	Between 33% and 66%	74	40
	More than 66%	44	30.9
Educational supports at school	Hearing and Language Teacher	41	30.6
	Teacher of Hearing and Language and Therapeutic Pedagogy	87	51.2
	Hearing and Language Teacher, Therapeutic Pedagogy and Educator	42	24.7
Gestation weeks	30–35	52	30.6
	35–40	87	51.2
	More than 40	31	18.2
Apgar	With risk	77	45.3
	Intermediate	63	37.1
	Normal	30	17.6
Intellectual disability	No presence	123	72.4
	Mind	47	27.6

Table 2 Differences among the measures of the groups: Autism Spectrum Disorder (ASD), Epilepsy (EP), and ASD with epilepsy (ASDEP) in the comprehension of grammatical structures from CEG and CELF-5 tests

CEG and CELF-5 tests			ASD (n = 57)			EP (n = 60)			ASDEP (n = 53)			F _(3,167)	η^2_p	Differences between groups	
Comprehension grammatical structures			M	SD		M	SD		M	SD					
Variables included in the CEG test															
Inferences			8.53	2.458		13.95	1.926		3.85	1.598		349.697*	0.807	ASDEP* < ASD* < EP*	
Active structure			8.39	2.313		13.73	2.049		3.23	1.728		370.045*	0.816	ASDEP* < ASD* < EP*	
Passive structure			8.32	2.293		14.10	2.121		3.87	1.744		347.017*	0.806	ASDEP* < ASD* < EP*	
Declaratives			8.33	2.030		14.02	2.029		3.32	1.837		416.255*	0.833	ASDEP* < ASD* < EP*	
Reflective			8.42	2.236		13.85	2.057		3.45	1.749		370.252*	0.816	ASDEP* < ASD* < EP*	
Datives			8.46	2.164		14.00	1.957		3.23	1.739		423.763*	0.835	ASDEP* < ASD* < EP*	
Interrogative			8.23	2.053		14.27	1.831		3.38	1.643		490.018*	0.854	ASDEP* < ASD* < EP*	
Exclamative			8.46	2.465		14.00	2.099		3.45	1.716		348.517*	0.807	ASDEP* < ASD* < EP*	
Doubtful			8.98	2.272		13.73	1.840		3.68	1.718		369.841*	0.816	ASDEP* < ASD* < EP*	
Desiderative			8.19	2.560		14.00	2.131		3.74	1.631		324.219*	0.795	ASDEP* < ASD* < EP*	
Exhortative			8.77	2.260		13.75	2.055		3.70	1.917		327.132*	0.797	ASDEP* < ASD* < EP*	
Personal			8.72	2.234		14.23	1.826		3.72	1.634		424.304*	0.836	ASDEP* < ASD* < EP*	
Impersonal			8.60	2.404		14.00	1.957		4.00	1.687		339.093*	0.802	ASDEP* < ASD* < EP*	
Variables included in the CELF-5 test															
Sentence comprehension			8.88	2.398		14.12	2.210		3.81	1.688		329.722*	0.798	ASDEP* < ASD* < EP*	
Execution of instructions			9.11	2.425		14.35	1.921		3.77	1.552		391.354*	0.824	ASDEP* < ASD* < EP*	
$p < 0.05$															

*p < 0.05

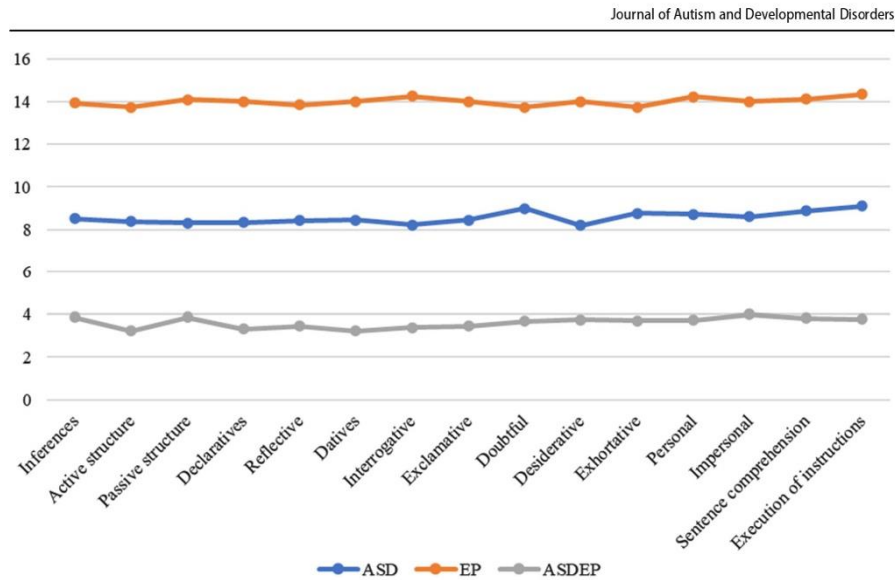


Fig. 1 Comparison of grammatical structures of comprehension between ASD, epilepsy and ASD with epilepsy groups from CEG and CELF-5 tests

Personal, Impersonal, Phrase Comprehension, and Instruction Execution ($p < 0.05$). The results of the ANOVAs related to the performance in the comprehension of grammatical structures are presented in Table 2.

As can be observed in Table 2, Bonferroni post-hoc tests showed statistically significant differences between the ASD, Epilepsy, and ASD with Epilepsy groups in all variables included in the measures of grammatical structure comprehension ($p < 0.001$). Thus, the scores obtained by the Epilepsy group were higher than those of the ASD group, and these were higher compared to the ASD with Epilepsy group.

To provide a visual perspective of the mean scores obtained by the three groups in the study, a graph (Fig. 1) was created, which displays a descriptive comparison of the means obtained in each of the variables related to the comprehension of grammatical structures.

As can be observed in Table 2, the variables included in the measurements of grammatical structure comprehension show a statistically significant association and a directly proportional trend ($p < 0.001$). These results have been established with a 99% confidence interval ($p = 0.001$).

Discussion

As previously described, the main objective of this study was to explore the differences in the performance of grammatical structure comprehension among three groups of participants diagnosed with ASD, epilepsy, and ASD with epilepsy. The research hypothesis posited that the group of participants diagnosed with epilepsy alone would perform better than the group of participants with ASD, followed by those with the comorbidity of ASD and epilepsy.

The results obtained in our study indicate that participants with epilepsy demonstrate better performance than the other two groups of participants, confirming what was initially proposed in the research hypothesis for this study. Significant differences in grammatical structure comprehension skills exist between the groups. These data cannot be confirmed by other research because there are no studies that compare performance in grammatical structure comprehension in these three disorders. However, these results can be corroborated with other studies conducted with these groups independently (Asberg, 2010; Baixeli et al., 2020; Eigsti et al., 2007; Eberhardt & Nadig, 2018; Henry & Solari, 2020; Saban-Bezael & Mashal, 2015), which confirm their contribution to the communicative problems presented by

individuals with these three disorders, with varying performance in these skills depending on the specific type of diagnosis.

Regarding the pediatric population with epilepsy, there is no consensus on the specific grammar-related skills that may be affected. Some tasks that have been reported as impaired in some studies (Durrleman et al., 2015; Su et al., 2018) appear preserved in others (Bangert et al., 2019; Maltman et al., 2023). However, there seems to be a higher prevalence of poorer performance in tasks involving syntactic skills, such as completing and producing sentences, understanding ambiguous sentences, sentence-picture matching, and comprehending complex syntactic structures (Bulteau et al., 2015; Skotko et al., 2008). Although previous studies have extensively analyzed comprehension skills related to morphosyntax in these children, there is no significant data that allows for the establishment of a specific linguistic profile (Cohen & Le Normand, 1998; Ménard et al., 2000). In terms of verbal comprehension, they exhibit difficulties in understanding verbal messages, often requiring message repetition, providing correct answers/information, and reformulating messages for optimal retention and comprehension (Teixeira & Santos, 2018). In our study, we observed poor performance in variables related to grammatical structure comprehension, especially those involving or related to executive functioning skills, such as understanding inferences, reflexive statements, and executing instructions. One possible explanation for these difficulties may be attributed to the damage present in this population in areas such as the frontal lobe and the networks connecting this lobe to the temporal lobe, which is the primary area responsible for oral language comprehension (Ballester-Plané et al., 2018). People with epilepsy have slowed processing speed, which also hampers effective comprehension of grammatical statements (Caplan et al., 2009). However, even though this population experiences difficulties in these skills, their performance will be superior to what is observed in other neurodevelopmental disorders such as ASD (Debiais et al., 2007).

In the case of participants diagnosed with ASD, current scientific literature indicates that these clinical profiles are associated with impairments in both language expression and comprehension. For example, Eigsti & Bennetto (2007) observed grammatical disorders in the majority of children with ASD, aged 9–17 years, in grammatical judgment tasks. In our study, the structures that are most challenging for children with ASD are those that do not follow the common structural order, subject-verb-predicate (SVP), such as coordinated sentences or relative clauses, in which all these children failed. Conversely, the easiest structures are those of SVP, with a 60% success rate, followed by attributive structures, with a 30% success rate (Barsotti et al., 2020).

Swensen et al. (2007) also state that children with ASD understand sentences in this SVP order before producing continuous speech. These results demonstrate the difficulties that children with ASD face, limiting their understanding of verbal messages from the main agents in their environment, hindering functional communication, and engaging in more complex conversations beyond their personal interests or motivations. Therefore, difficulties in verbal comprehension have a negative impact on the communicative skills and quality of life of individuals with ASD, severely affecting their inclusion in developmental contexts (Tovar et al., 2015).

Finally, the pediatric population with both ASD and epilepsy displays severe impairments in receptive language skills, including the comprehension of grammatical structures in oral language (Cano-Villagrasa et al., 2023). To date, no research on grammatical structures in Spanish-speaking children with both ASD and epilepsy is available. Therefore, the results indicate that language comprehension, especially grammatical structures, is one of the areas of weakness in both ASD and epilepsy that may contribute to explaining the observed communication deficits. However, there is very little evidence regarding grammatical impairments, and this remains an open area for research (Kanner & Bicchì, 2022). In the present study, the group of participants with both ASD and epilepsy displayed the lowest performance in grammatical structure comprehension tasks among the three groups in this investigation. One of the most plausible explanations for these results is that the presence of epilepsy, in addition to the diagnosis of ASD, leads to increased difficulties in language skills, especially those related to receptive language (Stefanski et al., 2021). With impaired executive functioning, as well as in linguistic dimensions such as lexicon, morphology, and pragmatics, it is logical to assume that verbal comprehension of grammatical structures is also compromised, primarily due to difficulties in following conversations and instructions. This negatively impacts their language skills, resulting in poorer performance in such tasks compared to other profiles, such as those in the epilepsy group and the ASD group (Montouris et al., 2020). Therefore, although studies like Saban-Bezael and Mashal (2015) suggest that the relationship between auditory comprehension and the severity of linguistic symptoms in ASD is not clear, the present study confirms that linguistic comprehension is a predictor of language difficulties in ASD.

The study has certain limitations that should be taken into account. Firstly, the small sample size raises questions about the generalizability of the results to a larger population. Additionally, variability in the ages of the participant groups could introduce elements of uncertainty in the results, as language abilities tend to evolve with age. Heterogeneity in

individual conditions within each group could also influence the observed results. It is noteworthy that external factors, such as linguistic environment and prior education, were not taken into account, which could have had an impact on the participants' performance. Finally, the specific methodology used in the tests may limit comparability with other similar studies. Despite the mentioned limitations, the study has several strengths worth considering. The formulation of a clear and precise hypothesis provided a specific direction for the research. The results obtained represent a significant contribution to the scientific corpus, shedding light on differences in grammatical comprehension in neurological contexts. Detailed analyses of the particular difficulties of each group enrich our understanding of the linguistic challenges they face. The multidisciplinary perspective of the study, considering both neurological conditions and language skills, offers valuable implications for clinical and educational practice, suggesting ways to address these difficulties from multiple areas.

In conclusion, this study highlights the diversity in grammatical structure comprehension among different participant groups: those with epilepsy, ASD, and ASD with epilepsy. The results support the notion of better performance in the epilepsy group, followed by the ASD group, while the group with both conditions exhibited the lowest performance. These discrepancies have significant implications for communication and the quality of life of those affected. Furthermore, they emphasize the need for future research to delve into the comprehension of grammatical impairments in these disorders and their relationship with other cognitive and linguistic aspects. Ultimately, these findings support the importance of developing personalized therapeutic approaches and educational programs to address the specific needs of these groups of children.

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Declarations

Conflict of Interest The authors declare that they have no conflicts of interest that could influence the.

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5.5. ARTÍCULO 5

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Emotional and behavioral alterations and their relationship with executive functioning in the pediatric population with autism spectrum disorder and epilepsy: a comparative study

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Introduction: The pediatric population with Autism Spectrum Disorder (ASD) and epilepsy presents behavioral and emotional alterations that hinder their correct developmental maturation as well as their integration in different contexts such as school, family or social. This population shows atypical behavioral and emotional patterns, with difficulties in emotional regulation, understanding of emotions, aggressiveness, or low frustration tolerance. They also present alterations in executive functions, which significantly influence the emotional and behavioral characteristics of this population. Research suggests that epilepsy worsens the emotional, behavioral, and executive functioning status.

Objective: To explore differences in behavioral, emotional, and executive functioning profile in individuals with a diagnosis of ASD, epilepsy, and ASD with epilepsy.

Method: In this quasi-experimental and cross-sectional study, a total of 170 participants were selected and distributed into three groups: a group of participants with ASD, a group with epilepsy, and a group of participants with ASD and epilepsy. The SENA, BASC-3, and ENFEN tests were administered to verify the behavioral, emotional, and executive functioning profile in the three groups.

Results: The results indicate that individuals diagnosed with ASD and epilepsy present greater emotional, behavioral, and executive functioning alterations compared to those who only present ASD or epilepsy.

Conclusion: Individuals with ASD and epilepsy present significant alterations in emotional, behavioral, and executive functioning processes, which hinder their adaptation to different contexts, as well as decreasing their quality of life and that of their family.

KEYWORDS

ASD, epilepsy, childhood, behavior, emotion

Introduction

Autism Spectrum Disorder (ASD) and epilepsy are two disorders that fall under the category of Neurodevelopmental Disorders (American Psychiatric Association, 2013). On one hand, individuals diagnosed with ASD are characterized by limitations in reciprocal social interaction, communication, and restricted interests that result in repetitive or stereotyped behaviors (Sevilla et al., 2014). On the other hand, those who have epilepsy, in addition to the seizures associated with this disorder, show alterations in linguistic, motor, or sensory competences (Vania and De La Barra, 2013). People with either of these two disorders, in addition to the specific symptomatology of their pathology, often present difficulties in cognitive functioning, learning, attention, and sensory processing (Angulo et al., 2020), negatively affecting the correct developmental maturation and the quality of life of families and individuals diagnosed with them (García-Peñas, 2009). However, the situation is worsened if both disorders are present in the same person. Thus, if a person with ASD also has comorbid epilepsy, this will lead to an increase in the frequency and severity of autism symptoms, causing greater difficulties in areas such as communication, social interaction, learning, behavior, and emotional regulation (Gutiérrez-Ruiz, 2019; Cano-Villagrasa et al., 2023).

Epilepsy and ASD are neurological disorders that affect the brain; however, a comprehensive understanding of their connection and differentiation using brain signals has yet to be fully elucidated. The scholarly article authored by Wadhera (2021) brings to the forefront the development of an automated diagnostic model based on electroencephalography (EEG) with the intention of unraveling the association between epilepsy and ASD. The fundamental objective of this investigation is to acquire a deeper comprehension of the intricate relationship between these two neurological conditions and ascertain their detectability through EEG analysis techniques. The proposed model makes effective use of EEG data acquired from patients diagnosed with epilepsy, patients diagnosed with ASD, and a control group devoid of either condition, ultimately facilitating the construction of an automated classification model. The discernible outcomes of this study reveal marked distinctions in the distinctive characteristics of the brain network between the epilepsy and ASD cohorts. The automated diagnostic model successfully achieves noteworthy accuracy in categorizing patients with epilepsy and those with ASD, as compared to the control group. These consequential findings postulate the existence of a relationship between epilepsy and ASD at the level of brain connectivity, which can be discerned through the utilization of automated EEG analysis techniques. The proposed model harbors the potential to substantially enhance the accuracy of diagnosis and further our understanding of these neurological conditions, thereby engendering noteworthy implications for treatment modalities and early intervention strategies.

In a related vein, the work conducted by Wadhera and Mahmud (2022) delves into the exploration of brain networks in the context of ASD and epilepsy, while simultaneously investigating their interconnectedness. Employing an innovative approach that amalgamates machine learning methodologies with functional magnetic resonance imaging (fMRI) and EEG data, this study endeavors to attain insights into the intricate network patterns within the brains of individuals afflicted by ASD, epilepsy, and control subjects. Machine learning algorithms elucidate compelling disparities

in the salient characteristics of brain networks amongst the ASD, epilepsy, and control groups, effectively unveiling unique and distinctive connectivity patterns intrinsic to each group. Furthermore, this research reveals an inherent relationship between ASD and epilepsy, as evidenced by shared characteristics observed in the brain networks. The utilization of machine learning techniques in this investigatory endeavor yields a powerful toolset, facilitating the comprehensive analysis and comprehension of intricate brain networks implicated in both ASD and epilepsy. This pioneering approach exhibits the potential to significantly enhance the precision of diagnostic processes associated with these neurological conditions, while concurrently augmenting our comprehension of their intricate interplay and interdependencies.

The main characteristics of a person with comorbid ASD and epilepsy include impairments in social interaction and communication skills, as well as the presence of restricted and repetitive interests and behaviors (Málaga et al., 2019). However, individuals with this comorbidity often experience additional physical and mental health conditions, as well as behavior problems that can affect their lives and families, such as aggression, lack of control, emotional dysregulation, among others. Among these, one that stands out for its manifestations at all levels of these patients is the presence of emotional and behavioral problems (Dominick et al., 2007; Hurtig et al., 2009), which include aggression, tantrums, or self-injurious behaviors. Sleep, feeding, and sensory disorders are also common, as well as intellectual disability or learning difficulties, in addition to mental health conditions such as attention deficit hyperactivity disorder, anxiety, obsessive-compulsive disorder, and tic disorders (Dominick et al., 2007).

Regarding the etiology of this comorbidity, authors such as López Rodríguez and Cañadas Pérez (2018) and Ruggieri (2020) suggest the presence of shared underlying mechanisms that may play a role in the existence of anxiety or depression disorders in the child population with ASD and epilepsy. On the one hand, there are social factors that trigger a barrier in the interaction of the person with ASD and epilepsy, leading to communicative limitations with other individuals. This will lead to inefficient emotional management, with a diminished self-perception of the correct execution of social strategies, generating a situation of discomfort and frustration that is related to a state of high anxiety. On the other hand, there will be biological factors that will play a fundamental role in the onset of anxiety or depression in the person with ASD and epilepsy. In these patients, there is identified a hyperactivation of the amygdala, as well as other structures of the central nervous system such as the hippocampus and the brainstem, structures that end up triggering alarm responses in the person with ASD and epilepsy when detecting a threat in social contexts.

In this sense, it is vital to consider the possibility that the child population with the joint comorbidity of ASD and epilepsy shows depressive episodes and an acute state of hyperactivation compared to those children who only have ASD or epilepsy (Vania and De La Barra, 2013). People with ASD and epilepsy are four times more likely to develop depression than the general population, being considered one of the most common mental health conditions among them (Benítez Gort et al., 2010). This can have devastating consequences on quality of life and increase the risk of suicidal thoughts and behaviors in the child population with ASD and epilepsy (Hofvander et al., 2009). Furthermore, it is important to take into account the existence of a possible sex bias when diagnosing depression in ASD and epilepsy,

since females usually have a higher prevalence of depressive episodes than males. According to Vania and De La Barra (2013), this may be due to a later diagnosis, inadequate approaches due to lack of detection, and their own awareness of social difficulties, highlighting the need for improved diagnosis of emotional problems in people with ASD and epilepsy.

Difficulties in regulating emotions seem to characterize both ASD and epilepsy. Individuals with ASD and epilepsy often struggle with regulating negative affect, which is characterized by the existence of aversive emotional states such as nervousness, fear, disgust, guilt, anger, emotional distress, and non-pleasurable engagement (León Rodríguez and Cárdenas, 2020). They also exhibit characteristic emotional responses and self-regulation difficulties, making it harder to calm down once they are upset, compared to typically developing children (Rodríguez-Fernández et al., 2013). Therefore, it is crucial to address emotional needs in individuals with these two disorders, as their own manifestations, alongside behavioral and mental health problems, contribute to significantly higher levels of stress and anxiety observed in families of children with these characteristics (Allik et al., 2006; Lecavalier et al., 2006; Manning et al., 2015).

There is growing awareness of the importance of recognizing emotional and behavioral conditions as part of assessment and diagnosis (Begeer et al., 2008). However, reported rates of behavioral or emotional problems vary considerably from one study to another (Cano-Villagrasa et al., 2023). For instance, rates of anxiety reported by parents in children with ASD and epilepsy range from 22 to 84% (Gadow et al., 2005; Pearson et al., 2006; Simonoff et al., 2008; Kanne et al., 2009; White and Roberson-Nay, 2009; Mattila et al., 2010; MacNeil and Mostofsky, 2012), and stress problems have been identified in 31 to 80% of this population (Couturier et al., 2005; Oyane and Bjorvatn, 2005; Allik et al., 2006; Dominick et al., 2007; Krakowiak et al., 2008; Souders et al., 2009). Leekam et al. (2007) found that adverse sensory reactions occur in at least 90% of individuals with ASD and epilepsy and highlighted that these problems can cause disruptive and aggressive behavior in individuals with low autonomy and language impairments, as well as a low tolerance for frustration and emotional dysregulation. Moreover, in this study, it was observed that sensory reactions contribute to the occurrence of high rates of anxiety, which is also corroborated by the study of Kern et al. (2007). Lastly, in a population-based cohort study in the United Kingdom, Simonoff et al. (2008) investigated behavioral and emotional disorders in a sample of 112 children aged 5–10 years with ASD and epilepsy. The authors identified that 70% met criteria for at least one emotional or behavioral disorder, and 41% had two or more disorders, most commonly social anxiety and hyperactivity. These widely disparate prevalences are observed due to the large individual differences of each person with ASD and epilepsy, as well as the methodology and variables related to the home and school environment as relevant aspects determining emotional and behavioral problems in this population (Espinosa et al., 2018).

In addition to the marked behavioral and emotional profile of individuals with ASD and epilepsy, executive functions (EF) appear to be an area that is frequently affected in this comorbidity. The behavioral and emotional profile of individuals with ASD and epilepsy is significantly related to their executive functioning (López et al., 2016). EFs include a series of neurocognitive processes that enable intentional and goal-directed behavior, such as designing plans, setting goals, selecting appropriate behaviors, and inhibiting incorrect ones, cognitive flexibility, sustained attention, effective

self-monitoring, and task organization (Zelazo and Carlson, 2012; Delgado Mejía and Etchepareborda Simonini, 2013; Schoemaker et al., 2013). In this line, one of the essential processes of EF is inhibitory control, defined as the ability to deliberately inhibit or suppress a dominant response (Diamond, 2013). The importance of inhibitory control lies in the fact that it enables individuals to control inappropriate behaviors in some contexts and to perform adequate responses to meet complex demands and to live adaptively in changing environments, being essential in the prevention of behavioral problems (Goldstein et al., 2007). Another basic process of executive functions is working memory, which, together with cognitive flexibility, facilitates the solution of social conflicts (Ziermans et al., 2012). Damasio and Maurer (1978) were the first researchers to link executive dysfunction in individuals with these disorders, as they share some common manifestations with people who have localized damage in the prefrontal cortex.

Among the most relevant symptomatology of the population with ASD and epilepsy regarding their executive functions are: absence of empathy, presence of stereotyped behaviors, perseverations, routines and restricted interests, compulsive behaviors, inappropriate and sudden emotional reactions, and lack of originality and creativity. The degree of alteration of EF varies depending on the age and level of impairment of this population. Thus, Han and Chan (2017) find significantly poorer performance in low-intelligence ASD children compared to those without intellectual deficits in three dimensions: planning, inhibitory control, and cognitive flexibility. Related to this, Hagberg et al. (2015) state in their study that high competence in verbal intelligence is a predictor of higher performance in inhibition, executive memory, and attention. Van Eylen et al. (2015) also show the existence of a strong association between variables related to age and intelligence quotient with executive functioning: inhibition of automatic responses, cognitive flexibility, spatial working memory, planning, and information processing speed. Finally, Chen et al. (2016) report in their comparative study of children with these disorders of different ages that children aged between 8 and 13 perform worse than the group of children aged between 13 and 18 in the dimensions of planning and working memory.

The previous discussion highlights the need to study EF in this population in order to characterize their functioning and develop research lines based on emotional and behavioral alterations, as well as their relationship with executive functioning in individuals with ASD and epilepsy (Mulas et al., 2001). However, there are problems in interpreting research findings due to the use of different sampling frames, sample sizes, criteria, and classifications in a large number of studies (Cala Hernández et al., 2015; Oviedo et al., 2015; Orduña and Barrio, 2021), making it difficult to obtain a global interpretation of the data. Further studies are needed to identify the precise rates of coexisting conditions and relevant risk and protective factors for planning appropriate services and interventions, and providing family support to minimize frustration and deterioration in children with ASD and epilepsy (Saeteros, 2022). The study conducted by Operto et al. (2021) reveals a significant negative correlation between adaptive behavior and emotional/behavioral problems in children diagnosed with Autism Spectrum Disorder (ASD). This suggests that individuals with higher levels of adaptive functioning tend to experience fewer emotional and behavioral difficulties. Moreover, the study establishes a noteworthy association between parental stress levels and the adaptive behavior as well as emotional/behavioral problems of children with ASD. Parents of children with higher levels of adaptive

behavior tend to experience reduced stress, while those whose children exhibit more emotional and behavioral problems face heightened stress levels. Another study, such as the one conducted by [Pastorino et al. \(2021\)](#), explores the impact of these disorders and epilepsy on social cognition, which involves the ability to comprehend and respond to social and emotional signals from others. The findings demonstrate an impairment in social cognition in both individuals with ASD and epilepsy. People with these conditions encounter challenges in interpreting facial expressions, understanding others' emotions, and engaging in appropriate social interactions. Furthermore, the study emphasizes the significance of considering the relationship between neurodevelopmental disorders and epilepsy in terms of their influence on social cognition. It is suggested that epilepsy may contribute to the observed difficulties in social cognition among individuals with ASD, although further research is required to gain a deeper understanding of this association. These findings underscore the importance of addressing both adaptive behavior and emotional/behavioral problems in children with ASD to enhance their quality of life and alleviate parental stress. Additionally, they emphasize the necessity of providing adequate support and resources for parents who face challenges related to caring for children with ASD ([Volk, 2019](#)).

Therefore, the main objective of the present study is to compare emotional and behavioral problems in three groups: a group of children with ASD, a group of children with epilepsy, and a group of children with ASD and epilepsy. Thus, the first hypothesis proposed for this study is that internalizing problems (depression, anxiety, social anxiety, and somatic complaints) will be more prominent in the group of children diagnosed with ASD and epilepsy than in the ASD and epilepsy groups alone. Likewise, the second research hypothesis is that externalizing problems (attention problems, hyperactivity-impulsivity, anger control problems, aggression, and defiant behavior) will be more pronounced in the group of children with ASD and epilepsy than in the ASD and epilepsy groups alone. Finally, the third research hypothesis proposed for this study is that participants with ASD and

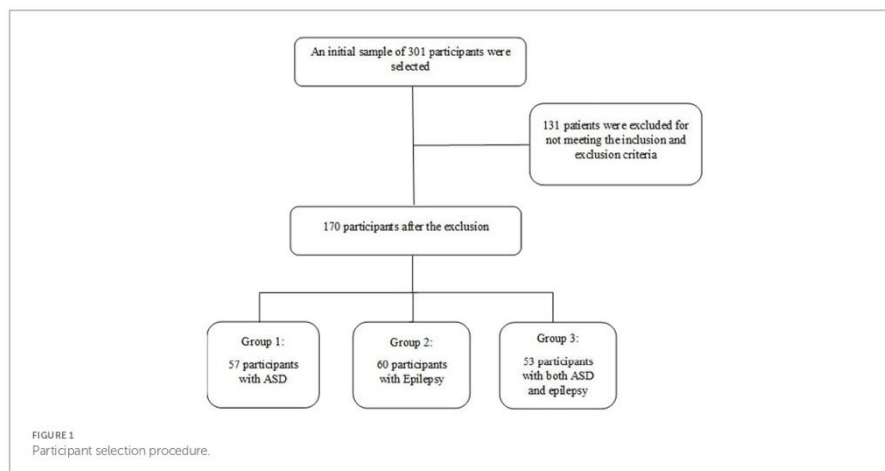
epilepsy will have greater executive functioning impairments than those with ASD or epilepsy alone.

Methods

Participants

An initial sample of 301 subjects diagnosed with ASD, epilepsy, or both disorders was selected and underwent a rigorous screening process ([Figure 1](#)). The inclusion criteria were: being between 7 and 9 years old and having a diagnosis of ASD or epilepsy issued by a public health center. All participants diagnosed with ASD or epilepsy were evaluated at the Child and Adolescent Psychiatry and Pediatric Neurology Unit attached to their reference medical center by the multidisciplinary professional team of this unit. In these centers, a diagnostic screening evaluation was carried out through the administration of the M-CHAT-R questionnaire ([Dereu, 2013](#)). Those children who scored indicating a possible suspicion of alarm proceeded to use the ADOS-2 ([Lord et al., 2008](#)) and ADI-R ([Rutter et al., 2006](#)) protocols to confirm the diagnostic suspicion of ASD. Likewise, participants were evaluated by the neuropsychiatric team, conducting a neurological evaluation through Magnetic Resonance Imaging, Sleep-Deprived Electroencephalogram, and genetic tests that helped confirm both diagnoses. Finally, to control the variable of intellectual disability, all participants were administered the Wechsler Intelligence Scale for Children-IV (WISC-IV, [Wechsler, 2010](#)), excluding those with an IQ below 60.

After the initial selection of 301 subjects, a series of exclusion criteria were established, including having a motor or sensory disorder that would prevent study participation and having a moderate, severe, or profound intellectual disability. After the selection process, 131 subjects were excluded, resulting in a final sample of 170 participants between the ages of 7 and 9, divided into three groups: the ASD group ($n = 57$), the ASD and epilepsy group ($n = 53$), and the epilepsy group



($n=60$). The ASD group (G1) consisted of 36 boys and 21 girls ($M_{age}=8.1$; $SD=0.9$) with a diagnosis of grade 3 ASD. The Epilepsy group (G2) consisted of 41 boys and 19 girls ($M_{age}=8.6$; $SD=0.4$). The ASD and epilepsy group (G3) consisted of 27 boys and 26 girls ($M_{age}=7.8$; $SD=0.8$), who also had a grade 3 ASD diagnosis and were evaluated at their reference medical center. This age range was chosen because assessment tests can be directly administered to study participants at age 6. Additionally, the diagnosis of ASD is established at age 6, and participants have had several years of speech and language therapy and neuropsychological intervention. Table 1 summarizes the main characteristics of the participants who made up the sample group of this study.

Finally, the following inclusion and exclusion criteria were established. On the one hand, the inclusion criteria were: (I) being between 5 and 8 years of age, (II) presenting a diagnosis of ASD or epilepsy issued by a public health agency or center, and (III) undergoing rehabilitation treatment at a rehabilitation clinic. On the other hand, the exclusion criteria were: (I) presenting a motor or sensory disease or disorder that hinders or prevents the correct performance of the study, (II) not presenting any communication or language at 5 years of age, and (III) presenting a moderate, severe or profound intellectual disability.

Instruments

Evaluation system for children and adolescents

The SENA questionnaire, system for the evaluation of children and adolescents (SENA; Fernández et al., 2015) consists of a total of 9 questionnaires aimed at three age levels: Infant (3–6 years), Primary (6–12 years), and Secondary (12–18 years). It includes specific questionnaires to gather information from different informants regarding the main contexts in which the child operates (questionnaires for family and school), as well as three self-report models according to the age of the evaluated person that are applied from 6 years old. In each of them, the informants must assess the frequency of the described behavior using a five-point scale (Never or almost never to Always or almost always), except for the self-report for 6–8 years, which includes a three-option scale: Yes, No, and Sometimes.

Behavior assessment system for children and adolescents-3

The Behavior Assessment System for Children and Adolescents-3rd Edition (BASC-3; González et al., 2004) is an instrument used for clinically evaluating the emotions and behaviors of children and adolescents, detecting maladaptive disorders in the family and school contexts. The BASC-3 consists of a self-report form for the patient and two questionnaires for parents (P) and teachers (T). For the purpose of this research, only the latter two will be taken into account.

Neuropsychological evaluation of executive functions in children

Neuropsychological Evaluation of Executive Functions in Children (ENFEN; Portellano et al., 2009), is an instrument that allows to determine the level of maturity and cognitive performance

TABLE 1 Characteristics of the study participants.

Characterization of the participants			
		N	Percentage
Sex	Male	104	61.2
	Woman	66	38.2
Age	7 years old	47	27.6
	8 years old	61	35.9
	9 years old	62	36.5
Diagnosis	ASD	57	33.5
	ASD+ Epilepsy	53	31.2
	Epilepsy	60	35.3
Years of treatment	2 years	34	20.0
	3 years	73	42.9
	4 years	63	37.1
Grade of incapacity	Less than 33%	52	29.1
	Between 33 and 66%	74	40
	More than 66%	44	30.9
Educational supports at school	Hearing and Language Teacher	41	30.6
	Teacher of Hearing and Language and Therapeutic Pedagogy	87	51.2
	Hearing and Language Teacher, Therapeutic Pedagogy and Educator	42	24.7
Gestation weeks	30–35	52	30.6
	35–40	87	51.2
	More than 40	31	18.2
Apgar	With risk	77	45.3
	Intermediate	63	37.1
	Normal	30	17.6
Intellectual disability	No presence	123	72.4
	Mild	47	27.6
Pharmacological therapy	No presence	52	30.6
	Valproate	41	24.1
	Risperidone	19	11.2
	Clonazepam	58	34.1

in activities related to EF in children aged 6–12 years on an individual basis. The battery consists of four tests (Verbal Fluency, Trail Making, Ring Construction, and Resistance to Interference) that measure different components of EF. The results allow for a deeper diagnosis and guidance for neuropsychological intervention, both in healthy children and in those with developmental delay or cognitive or emotional alterations derived from brain damage or dysfunction.

Procedure

For the present study, participant selection was carried out following the inclusion and exclusion criteria for the sample (see

Table 1; Figure 1), subsequently grouping them into three experimental groups. Participants and their families were evaluated in two 1-h sessions. Data from the measurement instruments were stored in protected databases, which were later analyzed by the research group members, checking the fulfillment of the research hypotheses. Finally, this study was reviewed by the ethics committee of the Universidad Católica San Antonio de Murcia (UCAM), proposing its favorable verdict with the code: CE052206.

Data analysis

The statistical analysis of this quasi-experimental study was carried out using different statistical designs. First, the Kolmogorov-Smirnov test was used to examine the normality of the distribution of the dependent variables that make up the study. However, a graphical position point analysis has been conducted through a plot Q-Q study, whose results indicate that there is a homogeneous distribution among the groups comprising the study. Next, multivariate analysis of covariance (MANCOVA) was used to observe the relationship between variables related to externalizing and internalizing emotional and behavioral problems, conduct problems, and executive functions. The objective of using the MANCOVA statistical analysis is to control for the variable "intellectual disability" in the model of the present study. In this way, differences between the two groups that make up the sample were explored. Subsequently, analysis of covariance (ANCOVA) tests was carried out to observe the individual differences of each of the variables in the two groups. Finally, to control for Type I error, Holm-Bonferroni correction was performed (Holm, 1979).

Results

Difference in internalized problems in the groups

The MANCOVA conducted to evaluate differences in measures of internalizing problems among the ASD, Epilepsy, and ASD with Epilepsy groups revealed the presence of statistically significant differences (Wilks' Lambda = 0.104, $F(6,92) = 328.000$, $p < 0.001$, $\eta^2_p = 0.677$). As can be seen in Table 2, the variables in which significant differences were obtained were depression, anxiety, social anxiety, and somatic complaints. The results of the ANCOVAs related to internalizing problems are presented in Table 2.

Differences in externalized problems in the groups

The MANCOVA conducted to evaluate the differences in measures of externalized problems among the groups of ASD, Epilepsy, and ASD with Epilepsy revealed the presence of statistically significant differences (Wilks' Lambda = 0.093, $F(7,92) = 326.000$, $p < 0.001$, $\eta^2_p = 0.694$). As can be seen in Table 3, the variables in which significant differences were found were attention problems, hyperactivity-impulsivity, anger control problems, aggression, and defiant behavior. On the other hand, the results of the ANCOVAs related to externalized problems are presented in Table 3.

Differences in the behavioral profile in the groups

Finally, the MANCOVA performed to evaluate differences in behavioral profile measures among the groups with ASD, Epilepsy, and ASD with Epilepsy revealed the presence of statistically significant differences (Wilks' Lambda = 0.025, $F(7,92) = 300.000$, $p < 0.001$, $\eta^2_p = 0.840$). As can be seen in Table 4, significant differences were obtained in the variables that make up the questionnaire. On the other hand, the results of the ANCOVAs related to behavioral problems are presented in the following Table 4.

Differences in executive functions in the groups

The MANCOVA performed to evaluate the differences in executive functioning measures among the groups of ASD, Epilepsy, and ASD with Epilepsy revealed the presence of statistically significant differences (Wilks' Lambda = 0.126, $F(4,95) = 328.000$, $p < 0.001$, $\eta^2_p = 0.645$). As can be seen in Table 5, the variables in which significant differences were obtained were verbal fluency, trail making test, block design, and interference control. On the other hand, the results of the ANCOVAs related to executive functioning are presented in Table 5.

Discussion

It has been found that children with a comorbidity of ASD and epilepsy often experience emotional, behavioral, and executive functioning problems (Morgan and Lilienfeld, 2000; Riccio et al., 2011; Schoemaker et al., 2013; López Rodríguez and Cañadas Pérez, 2018; Ruggieri, 2020). However, discrepancies in the prevalence and methodologies of previous studies create a need for further research to better characterize this comorbidity.

Therefore, the main objective of this study was to compare emotional, behavioral, and executive functioning problems in a group of children with ASD, another group of children with ASD who also had epilepsy, and a last group that only had epilepsy. The first research hypothesis was that internalizing problems would be more pronounced in the group of children with ASD and epilepsy compared to those with only ASD and those with only epilepsy. The second research hypothesis was that externalizing problems would be more pronounced in the group of children with ASD and epilepsy compared to those with only ASD and those with only epilepsy. Finally, the third hypothesis was that the group of participants with ASD and epilepsy would present greater executive functioning impairments than those with only ASD and those with only epilepsy.

Overall, the results of this study indicate significant differences between the evaluated participant groups, especially that the group with ASD and the group with epilepsy show lower occurrence of internalizing and externalizing problems compared to the group of participants with comorbid ASD and epilepsy. This is related to the fact that individuals with ASD who do not have epilepsy show lower levels of anxiety or depression and fewer somatic complaints. Additionally, these participants exhibit fewer behavioral and attentional problems, which positively impacts their ability to perform

TABLE 2 Differences between the measures of the groups: ASD (G1), Epilepsy (G2) and ASD with epilepsy (G3) in behavioral and emotional problems internalized in the SENA test.

Internalized problems	G1 (n =57)		G2 (n =60)		G3 (n =53)		$F_{(6,92)}$	η^2_p	Differences between groups
	M	SD	M	SD	M	SD			
Depression	13.38	4.41	6.18	2.22	23.74	3.64	304.182*	0.785	G2 < G1 < G3
Anxiety	13.86	4.33	5.73	2.29	22.18	3.82	245.391*	0.746	G2 < G1 < G3
Social Anxiety	11.42	4.11	6.55	2.10	22.82	4.19	288.063*	0.775	G2 < G1 < G3
Somatic complaints	13.74	4.27	6.30	2.16	23.26	3.87	287.669*	0.775	G2 < G1 < G3

* $p < 0.05$.

M (Mean); SD (Standard Deviation).

TABLE 3 Differences between the measures of the groups: ASD (G1), Epilepsy (G2) and ASD with epilepsy (G3) in the behavioral and emotional problems externalized in the SENA test.

Externalized problems	G1 (n =57)		G2 (n =60)		G3 (n =53)		$F_{(6,92)}$	η^2_p	Differences between groups
	M	SD	M	SD	M	SD			
Attention problems	11.78	3.43	6.08	2.23	24.48	2.88	237.076*	0.740	G2 < G1 < G3
Hyperactivity-impulsivity	13.70	4.44	6.03	2.40	24.04	2.74	227.424*	0.731	G2 < G1 < G3
Anger control problems	12.36	4.35	6.32	2.38	24.12	3.05	289.035*	0.776	G2 < G1 < G3
Aggression	14.90	4.41	6.22	2.17	24.44	2.83	286.645*	0.774	G2 < G1 < G3
Defiant behavior	11.86	4.21	6.37	2.13	22.32	2.91	265.126*	0.760	G2 < G1 < G3

* $p < 0.05$.

M (Mean); SD (Standard Deviation).

TABLE 4 Differences between the measures of the groups: ASD (G1), Epilepsy (G2) and ASD with epilepsy (G3) in the behavioral profile recorded by parents and teachers in the BASC-3.

Behavioral profile	G1 (n =57)		G2 (n =60)		G3 (n =53)		F _(6,92)	η ² _p	Differences between groups
	M	SD	M	SD	M	SD			
Composite, clinical, and adaptive scale scores									
Aggressiveness	23.18	3.70	28.72	2.91	14.00	4.29	280.136*	0.770	G3<G2<G1
Anxiety	22.76	3.78	28.97	3.37	12.76	4.63	187.522*	0.692	G3<G2<G1
Depression	22.06	3.37	28.32	3.44	11.02	2.99	203.063*	0.709	G3<G2<G1
Somatization	21.78	3.74	28.03	2.99	11.62	3.56	247.547*	0.748	G3<G2<G1
Atypicality	20.80	3.48	28.53	2.87	11.14	3.43	200.885*	0.706	G3<G2<G1
Retreat	20.98	3.60	27.83	3.28	11.12	3.07	217.828*	0.723	G3<G2<G1
Attention problems	22.44	3.28	28.12	3.13	11.12	2.88	310.423*	0.788	G3<G2<G1
Adaptability	21.24	3.05	27.78	3.17	11.16	3.25	256.461*	0.754	G3<G2<G1
Social skills	21.84	3.65	28.00	3.10	11.06	2.69	284.131*	0.773	G3<G2<G1
Daily activities	21.06	3.38	28.40	3.44	11.24	3.31	203.021*	0.709	G3<G2<G1
Functional communication	21.86	2.98	28.27	3.08	11.08	3.06	296.367*	0.780	G3<G2<G1
Content scale scores									
Anger control	22.32	3.15	28.13	3.10	10.38	2.98	323.198*	0.795	G3<G2<G1
Bullying	22.04	3.38	27.97	3.00	9.90	3.05	304.054*	0.785	G3<G2<G1
Social development disorders	21.42	3.62	27.72	3.21	11.52	3.33	236.167*	0.739	G3<G2<G1
Emotional self-control	21.32	3.64	27.58	2.90	11.04	2.55	278.836*	0.770	G3<G2<G1
Executive functioning	21.32	3.82	27.87	3.18	10.08	3.02	247.922*	0.748	G3<G2<G1
Negative emotionality	21.28	3.43	27.83	2.96	10.46	3.45	248.719*	0.749	G3<G2<G1
Resilience	22.04	3.31	28.42	3.06	11.12	3.28	264.604*	0.760	G3<G2<G1

* $p < 0.05$.

M (Mean); SD (Standard Deviation).

TABLE 5 Differences between the measures of the groups: ASD (G1), and Epilepsy (G2) and ASD with epilepsy (G3) in the measures of executive functioning in the ENFEN.

Executive functioning	G1 (n = 57)		G2 (n = 53)		G3 (n = 60)		F _(6,92)	η^2_p	Differences between groups
	M	SD	M	SD	M	SD			
Verbal fluency	4.90	1.17	5.40	1.16	2.38	1.48	87.33*	0.511	G3 < G1 < G2
Trail Making test	25.78	3.17	24.83	8.17	36.45	6.91	56.20*	0.402	G1 < G2 < G3
Block design	268.97	84.83	123.58	67.40	303.32	24.27	119.11*	0.588	G2 < G1 < G3
Interference control	39.34	4.48	27.92	3.89	48.76	5.01	122.50*	0.595	G2 < G1 < G3

* $p < 0.05$.

M (Mean); SD (Standard Deviation).

basic activities of daily living and their inclusion in various contexts, compared to children with a diagnosis of comorbid ASD and epilepsy.

Regarding internalizing and externalizing emotional and behavioral problems, the results indicate that the group with ASD and the group with epilepsy obtain lower scores compared to the group with comorbid ASD and epilepsy. When the condition of comorbid ASD and epilepsy is present in the pediatric population, there is an increase in emotional and depressive disorders in these individuals due to genetic, environmental, and etiological factors of the disorder (Maskey et al., 2013). These findings are consistent with studies such as Tseng et al. (2011), which concludes that children with comorbid ASD and epilepsy are more likely to develop emotional and behavioral disorders than other neurodevelopmental disorders. The clinical profile described in that research indicates that individuals with comorbid ASD and epilepsy exhibit higher levels of anxiety and depression and have difficulties in socialization due to social anxiety problems. These findings are consistent with studies such as Canitano (2007), which provides a detailed description of emotional characteristics in children with comorbid ASD and epilepsy, showing how these children manifest significant alterations in emotional regulation, low frustration tolerance, and difficulties in effectively resolving social conflicts.

The present study is in line with the findings of previous scientific literature, as previous studies (Nordin and Gillberg, 1996; Canitano et al., 2005; Tuchman et al., 2010) indicate the general presence of emotional disturbances related to anxiety and depression in children with either ASD, epilepsy, or ASD with epilepsy, but do not compare these conditions in detail. The results of this study indicate that individuals with epilepsy show fewer alterations in the dimensions of depression, anxiety, social anxiety, and somatic complaints, compared to the other two groups (ASD and ASD with epilepsy), whose difficulties are more pronounced. This explains why ASD is a condition that significantly worsens these behavioral and emotional problems, being the determining disorder in the limitation of the anxious and depressive state of this pediatric population. Therefore, the internalized problems related to anxiety and depression in the population with ASD, who also have epilepsy, significantly limit the maturation development, as well as the adaptation to the environment of children with this clinical profile.

Secondly, regarding externalized emotional and behavioral problems, the results of our study reflect that the group with ASD and epilepsy presents higher scores than those presented in the ASD and epilepsy groups. Individuals with ASD and epilepsy show greater difficulties in attention processes, hyperactive or impulsive behavior, difficulty controlling anger, much more pronounced aggressive

episodes, and defiant behavior than in the pediatric population that only presents ASD or epilepsy (Tuchman et al., 2005). The behavioral profile of children who only have ASD or epilepsy corresponds to high limitations in cognitive flexibility, emotional self-regulation (Mira et al., 2019), impulse control (Tárraga-Mínguez et al., 2021), or even the appearance of aggressive behaviors (Serna and Gallegos, 2021), although in those profiles that only present epilepsy, a slight improvement in these symptoms is observed (Muñoz, 2004).

These data suggest that the population with ASD and epilepsy is more limited in their emotional control and tends to exhibit more disruptive behaviors, therefore requiring special considerations in their care. This assertion is supported by studies such as those by del Barrio and Carrasco (2016), Juillerat et al. (2015), and Mena-Chamorro and Caqueo-Urizar (2020), which analyzed the emotional and behavioral problems exhibited by children with ASD or ASD with epilepsy. The results of these studies showed that there is greater emotional and behavioral disturbance exhibited in children with both ASD and epilepsy, as compared to those who do not present this comorbidity.

In ASD, the problem with emotional control and the emergence of social anxiety stems from difficulties in demonstrating empathy or recognizing the emotions of others, which generates difficulties in social relationships and affects the quality of life for both the child and their parents or significant figures. This can also be observed in the first years of life, as it is evident that the child does not present any type of attachment to their parents (Masada Prats, 2013). Furthermore, in these children, emotional and behavioral control, which is responsible for modulating adaptation to different contexts, is affected because they generally do not use emotional or adaptive strategies, which means that reactions tend to be impulsive, irritating, and composed of aggressions, tantrums, or self-injuries, which in turn can be considered challenging. Additionally, empathy is affected, as it is one of the components that allows a person to understand both their own emotions and those of others (Mazefsky, 2015). Therefore, these problems will be magnified in our sample because ASD converges with epilepsy, damaging the main structures of emotion regulation, which implies a greater occurrence of anxiety and depression in these clinical profiles.

Finally, regarding executive functioning, the results of this study reveal that the group with ASD and epilepsy presents greater alterations than those shown by the ASD group and the Epilepsy group. These data can be interpreted to mean that individuals with ASD who also have epilepsy have greater difficulties in accessing functional lexicon, as well as in following an activity with high levels of sustained, selective, and divided attention, with task switching. This

is in line with studies by Artigas (1999), Aparicio and Aguirre-García (2011), and García-Peñas (2009), which describe the behavioral and emotional characteristics of individuals with ASD and epilepsy. These studies indicate that children with this comorbidity show severe alterations in emotional management, as well as difficulties in behavior, significantly affecting skills such as planning and cognitive flexibility. Additionally, children with ASD and epilepsy show alterations in executive functioning, which implies difficulties in emotional and behavioral self-regulation, language, task switching, processing speed, and planning. All of this is consistent with studies by Pisón et al. (2022) and Mulas et al. (2001), which explored executive functions in various neurodevelopmental disorders, including ASD, and describe significant alterations in planning, inhibition, and emotional control, which are further compromised by the coexistence of epilepsy in these clinical profiles. These alterations negatively impact proper emotional management, as well as the application of self-regulation strategies that lead individuals with this disorder to develop aggressive or violent behaviors to resolve conflict situations, in addition to displaying impulsive behavior in environments such as schools and homes.

In summary, the population with ASD and epilepsy presents greater internalized emotional and behavioral problems related to depression, anxiety, social anxiety, and somatic complaints, as well as greater externalized emotional and behavioral problems related to attentional problems, hyperactivity or impulsivity, problems in anger control, aggression, and defiant behavior, compared to children who only have ASD or epilepsy. These disorders are explained by alterations in emotional and behavioral competencies, which compromise overall functioning of the individual.

However, this study has limitations regarding the selection of objective instruments rather than self-reported measures. The SENA questionnaire (Fernández et al., 2015) was administered to evaluate emotional and behavioral problems, which is filled out by family members based on their observations and experiences in different contexts where the child interacts. Although this is a test with a high ecological validity, other tests could be included that are directly administered by examiners to the participants. Despite these limitations, this study opens a line of work for future research and to respond to the needs of children with this profile and their families, who are also one of the most affected by the emotional and behavioral alterations characteristic of TEA, which are further increased by the co-occurrence of epilepsy. Lastly, social skills and the development of these competencies in different types of ASD could be included for future research and compared with other comorbid disorders.

In conclusion, the comorbidity between ASD and epilepsy has a high prevalence that has been increasing in recent years. The diagnosis of children with either of these disorders is becoming more common,

which implies the need to determine and observe different factors and characteristics early and concisely to allow for early intervention in the emotional and behavioral alterations of the individual with this condition. The comorbid appearance of ASD and epilepsy implies a deficit in the proper developmental process of the child, seriously compromising emotional management and behavioral self-regulation. These limitations will significantly impair the proper performance of daily life activities, reducing the effectiveness and autonomy of the population with this comorbidity.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Universidad Católica San Antonio de Murcia. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

AC-V designed the study, analyzed the data and prepared the draft. All the authors reviewed the writing of the manuscript and approved the version finally submitted.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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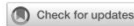
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5.6. ARTÍCULO 6

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Case report: Assessment of linguistic, cognitive, and sensory profile competencies in a child with ASD and epilepsy

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Spain**Introduction:** Autism Spectrum Disorder (ASD) and epilepsy pose significant challenges for early diagnosis during childhood. Current scientific literature does not reflect robust action protocols that allow for a detailed screening of difficulties in this population, especially in areas such as language, cognition, and sensory profile. Additionally, detecting epilepsy before the age of 4 is established as a major current public health challenge in our society.**Objective:** The aim was to evaluate a patient exhibiting symptoms compatible with both ASD and epilepsy, determining the linguistic, cognitive, and sensory profile through a clinical assessment protocol. Furthermore, the objective included establishing a diagnosis of ASD.**Method:** This single-case study ($N = 1$) presents the evaluation of a 7-year-old patient with suspected ASD, experiencing a decline in linguistic and cognitive competencies following a documented epileptic episode. Evaluation was conducted using instruments such as CELF-5, PROLEC-R, WISC-V, ENFEN, PS-2, ADI-R, and ADOS-2.**Results:** Following assessment of language, cognition, sensory aspects, and behaviors associated with ASD, the diagnosis of ASD was confirmed in the patient, along with impairments in expressive and receptive language, executive functioning, and alterations in the sensory profile.**Conclusion:** Diagnosing ASD and epilepsy, as well as their evaluation, is a complex process requiring interdisciplinary assessment involving a detailed exploration of all functional competencies in individuals with this comorbidity. Future studies should focus on creating and improving existing protocols to develop optimal and effective evaluation strategies for assessing this population during childhood.

KEYWORDS

ASD, epilepsy, childhood, language, cognition, sensory profile

Introduction

Autism Spectrum Disorder (ASD) has become the primary neurodevelopmental disorder in the pediatric population of our society (Crowell et al., 2019). This disorder is characterized by significant impairments in the pragmatic dimension of language and social interaction across various environments in which the individual develops (American Psychiatric Association, 2013). ASD imposes considerable limitations on the integration and autonomy of individuals, affecting their maturation and overall quality of life (May et al., 2017).

ASD often coexists with a broad spectrum of neurological, psychosocial, or educational pathologies and disorders (Stefanski et al., 2021). One of the major neurological diseases that frequently co-occurs with ASD is epilepsy (Kwon et al., 2022). Epilepsy is a neurological disorder originating in the central nervous system, specifically in the cerebral cortex, where episodes of bioelectrical discharges cause damage to brain structures. In individuals with ASD, these disruptions are exacerbated by the inherent challenges of the condition (Guo et al., 2023). For example, Cano-Villagrasa et al. (2023) describe significant impairments in linguistic and cognitive competencies in individuals with ASD, including difficulties in phonology (problems in speech sound articulation and phoneme discrimination), semantics (limited lexical repertoire in both expression and comprehension), morphosyntax (difficulties in verb conjugation and gender and number agreement in grammatical structures), and pragmatics (disruptions in event narration, social interaction, social cognition, and theory of mind), along with delayed acquisition of reading processes involving alterations in reading speed and accuracy (Keller et al., 2017).

Concerning cognition, individuals with ASD and epilepsy experience difficulties in attentional and mnemonic processes. Performance in tasks involving selective, sustained, and divided attention is significantly lower compared to their peers (Tuchman, 2013). According to Strasser et al. (2018), these clinical profiles exhibit cognitive immaturity, making them unable to sustain attention for extended periods. Additionally, Liu et al. (2022) note that attentional difficulties lead to memory alterations, as the individual's ability to retain environmental information is directly proportional to their attentional capacity. This means that insufficient attention to surrounding stimuli hinders the creation of a sufficiently strong memory trace, affecting later recall. Finally, Bougeard et al. (2021) state that individuals with ASD and epilepsy also show significant alterations in executive functions related to inhibition, emotional control, and working memory—key functions for the child's proper functional development, especially in processes like learning and behavioral regulation (Accardo and Malow, 2015).

In addition to linguistic-cognitive impairments, current research indicates that individuals with ASD and epilepsy also experience alterations in sensory profiles (Kashefimehr et al., 2018). Studies such as that by Bjork et al. (2022) suggest that comorbidity with epilepsy intensifies sensory peculiarities in individuals with ASD, leading to significant alterations in dimensions of registration, sensitivity, and sensory avoidance, forming a dysfunctional sensory profile. This results in difficulties in adequately registering sensory stimuli from the environment (Kadwa et al., 2019), heightened sensitivity to stimuli (van Campen et al., 2015), and a tendency to avoid these stimuli, causing aversion and emotional dysregulation when exposed to them (van Andel et al., 2022).

All these dysfunctions in the linguistic, cognitive, and sensory profiles of children with ASD and epilepsy have a negative impact on their developmental maturation. Therefore, this symptomatic situation is of great interest to national and international healthcare systems, as the prevalence of this comorbidity has exponentially increased in recent decades (Lee et al., 2015). Europe is one of the global regions with lower prevalence of ASD and epilepsy, with the World Health Organization estimating approximately 6 million affected Europeans across 53 countries, with an average prevalence of 8.2 affected individuals per 1,000 inhabitants (Tuchman et al., 2010), and an annual incidence of around 300,000 new cases diagnosed (Sharma et al., 2022). Regarding prevalence, some epidemiological studies highlight that 80% of individuals with ASD and epilepsy are children under the age of 10, and another 20% are adolescents aged between 12 and 15. However, there is a high likelihood of bias in these data due to limitations in epilepsy evaluations in the pediatric population with ASD, as several studies indicate late diagnosis (Francis et al., 2013).

In this way, the comorbidity between ASD and epilepsy becomes a condition with a relatively high prevalence, challenging diagnosis, and significant impairments affecting fundamental competencies such as language, cognition, and sensory profile (El Achkar and Spence, 2015). All of this negatively impacts child developmental maturation, compromising the quality of life for individuals with this comorbidity and increasing the demand for detection by healthcare professionals (Anukirthiga et al., 2019). The early detection of epilepsy in children with ASD is crucial in our country's neuropsychiatric units, allowing healthcare professionals to design early interventions aimed at significantly improving the child's prognosis (Chen et al., 2022). Furthermore, early detection of epilepsy in this population could reduce setbacks in the development of linguistic, cognitive, and sensory profile skills for this group (Pastorino et al., 2021). International evaluation protocols for this comorbidity (Sharma et al., 2022) include measuring alterations in language and communication, intelligence, learning, as well as conducting neuroimaging tests such as electroencephalograms (EEG) to detect underlying epileptic activity (Wadhwa, 2021). Interdisciplinary collaboration among neurologists, pediatricians, and ASD specialists is essential to ensure accurate diagnosis and the implementation of an appropriate and personalized treatment plan (Ewen et al., 2019; Wadhwa and Mahmud, 2022).

Objective

This case study presents the evaluation of a patient who sought consultation after visiting several healthcare centers without receiving a definitive diagnosis. Following the initial interview, there is suspicion of a diagnosis of ASD with epilepsy, manifesting linguistic, cognitive, and sensory alterations. This work aims to first describe the evaluation of the patient's linguistic, cognitive, and sensory competencies; secondly, verify the clinical characteristics established in previous diagnoses, and finally, thirdly, describe the process that ultimately led to the definitive diagnosis of ASD and epilepsy.

Case history

The patient, MR, 7 years, and 8 months old, is referred to our service by the pediatrician from his community's reference

healthcare center after being assessed by the psycho-pedagogical unit at his educational center, consisting of a psychologist, a pedagogue, and a teacher specializing in hearing and language. Until the date of referral, there was no prior diagnosis, although the educational center suspected a Grade 1 ASD diagnosis, which was never considered due to the child's satisfactory academic performance until the age of 5. However, at 6 years old, during the 1st year of Compulsory Primary Education, the child experienced a significant regression in linguistic and cognitive competencies, raising concerns among the teaching staff. Consequently, he was referred to the psycho-pedagogical assessment unit at the school. This assessment took place over 5 months due to the child's attentional difficulties, making it challenging to record language and cognition competencies. The results of this evaluation are reflected in the following (Tables 1, 2).

After the relevant evaluation, a diversity care plan was initiated at MR's school, consisting of four educational support sessions per week: two sessions of pedagogical re-education and two sessions of language re-education. Four months later, the neuropaediatrician from the Child and Adolescent Mental Health Unit (USMIA, in Spanish) at his reference hospital conducted a general exploration of the patient's physical health.

Firstly, a blood test was performed, and the results did not indicate relevant alterations. Secondly, a sleep-deprived electroencephalogram (EEG) was conducted, revealing that MR had generalized spike-and-wave discharges at three cycles per second, confirming episodes of epilepsy causing absences. The neurology professional highlighted the following information: Upon analyzing the sleep-deprived EEG results, distinctive patterns in brain electrical activity were observed. During normal sleep, a significant increase in delta waves, indicative of deep and restorative sleep, was evident. However, after sleep deprivation, a marked increase in beta waves was noted, suggesting heightened brain activity and a response to wakefulness. Additionally, variability in theta waves was observed, indicating the brain's adaptation to sleep deprivation. This phenomenon may indicate a compensatory response of the central nervous system to maintain a minimum level of cognitive functioning. Moreover, more frequent spikes and sharp waves were recorded after sleep deprivation, suggesting increased neuronal excitability. These changes could be related to heightened neuronal irritability and may have implications for cognitive function and performance. The parents had not previously reported any absence episodes.

Finally, the M-CHAT instrument (Dereu, 2013) was administered to the family, and 10 min of joint play were conducted to observe potential signs or features of ASD in the patient. The M-CHAT results reflected elevated suspicions of ASD ($PD > 3$), indicating a possible diagnosis of ASD but without confirmation. Therefore, the professional referred MR to the specialized ASD rehabilitation unit where the present work was conducted for outpatient care and ASD diagnosis.

Diagnostic evaluation

MR attended the unit for a comprehensive evaluation of all linguistic and cognitive competencies. Additionally, an assessment of his intelligence, executive functioning, and sensory profile was conducted for a complete differential diagnosis.

In the initial interview, the family reported that MR's birth was full-term without relevant perinatal or postnatal complications, allergies, or physical illnesses of note. Regarding his developmental milestones, MR acquired oral language (first words) at the age of 3. Until then, his communication was through gestures and signs. His comprehension was within the normal range for his chronological age, and his parents did not express concerns about this. He began walking at 12 months, with appropriate postural control as expected. His feeding followed a normal course, without the appearance of food aversions to textures, temperatures, or flavors. Toilet training was achieved at 3 years and 3 months. Lastly, in terms of schooling, MR attends a public school from 9:00 to 17:00. The educational professionals did not report significant abnormalities. They described MR as a calm student who keeps up with the class pace, integrating into the school adequately with no difficulties in acquiring basic concepts related to semantic fields of numbers, letters, or common vocabulary. He participates lightly in class activities without opposition, although he tries to avoid them to not be the center of attention. He does not engage in conflicts with his peers, nor does he self-aggress. However, they mentioned that the patient is perfectionistic and takes time to complete most activities presented in the classroom context.

During the family interview, it was revealed that until the age of 5, MR displayed apparently normal developmental progress. His parents did not notice any language, cognitive, or sensory competency alterations. However, they described MR as a solitary but affectionate child. He enjoys playing with cars and drawing but does not pay

TABLE 1 Results in the linguistic performance from the initial evaluation by the psycho-pedagogical team at the educational center.

CELF-5	PD	PE	Percentile	PC	Interpretation
Sentence comprehension	13	4	<0.1	47	Altered
Linguistic concept	17	6	0.1	54	Not altered
Morphosyntax	20	8	0.2	55	Not altered
Related words	6	2	<0.1	46	Altered
Execution of instructions	21	12	2	66	Not altered
Preparation of sentences	24	10	0.5	60	Not altered
Phrase repetition	34	10	0.5	60	Not altered
Reading Comprehension	3	2	<0.1	39	Altered
Pragmatic Skills Profile	103	3	<0.1	42	Altered

PD, Direct Score; PE, Scalar score; PC, Composite Score.

TABLE 2 Results in cognitive performance from initial evaluation by the educational center's psychopedagogical team.

WISC-V	Sum of scalar scores	Composite scores	Percentile	Interpretation
Verbal comprehension	23	88	45	Medium-Low
Visuospatial	29	94	55	Medium
Fluid reasoning	18	90	50	Medium
Work memory	21	85	42	Medium-Low
Processing speed	26	86	43	Medium-Low
Total intelligence quotient	39	92	55	Medium

TABLE 3 Evaluation protocol for patient MR.

Assessment of language skills
CELF-5. Clinical Evaluation of Language Fundamentals – 5 (CELF-5; Wiig et al., 2018).
The Revised Reading Processes Assessment Battery (PROLEC-R; Cueto et al., 2007).
Evaluation of cognitive processes and executive functioning
Wechsler Intelligence Scale for Children - Fifth Edition (WISC-V; Wechsler, 2010).
ENFEN. Neuropsychological Evaluation of Executive Functions in Children (ENFEN; Portellano et al., 2009).
Sensory profile evaluation
Sensory Profile-2 (PS-2; Romero-Ayuso et al., 2016).
ASD Diagnosis
The Autism Diagnostic Interview – Revised (ADI-R; Rutter et al., 2006).
Autism Diagnostic Observation Schedule, Second Edition (ADOS-2; Lord et al., 2008).

attention on a single toy. He systematically stacks toys and becomes upset if the arrangement is changed. During play, he does not seek to share with other children, although he occasionally approaches his parents to show them something interesting about an object.

As for family history, none of his relatives has or had a neurodevelopmental disorder or any other relevant alteration. The parenting practices established by the parents appear suitable. The family is permissive and attempts to engage in dialog with MR when he exhibits unwanted or disruptive behavior. The family environment is also competent, and they have support networks for childcare to attend to the child during the parents' working hours (Monday to Thursday) in the evenings.

Therefore, the objective of this evaluation was to determine linguistic and cognitive performance, as well as establish alterations in the sensory profile of patient MR. Similarly, an assessment of ASD traits was conducted to confirm the diagnosis. For this purpose, an evaluation protocol was devised, as described in Table 3.

The choice to use a specific set of tests for the evaluation of children with ASD and epilepsy is based on the need to obtain a comprehensive and detailed understanding of the abilities and challenges that each individual faces. Both conditions, ASD and epilepsy, have a unique complexity that requires a comprehensive evaluation to inform personalized and effective intervention strategies. In the language domain, the use of CELF-5 and PROLEC-R is justified not only for their ability to assess language skills but also for their capacity to reveal potential interferences in reading processes, a crucial aspect for academic development and effective communication in children. The inclusion of WISC-V and ENFEN in the assessment

makes sense when considering the need to understand not only the overall intelligence quotient but also specific cognitive processes and executive functions. Given the high prevalence of cognitive comorbidities in ASD and epilepsy, these tools are essential for identifying areas of strength and weakness that guide intervention strategies tailored to each child's individual skills. The relevance of PS-2 is emphasized when considering the influence of sensory regulation on the daily experiences of the child. Atypical sensory responses can significantly impact the quality of life and participation in everyday activities, and their assessment is crucial to inform therapeutic interventions addressing these specific sensitivities. Regarding the diagnosis of ASD, the inclusion of ADI-R and ADOS-2 is justified due to their recognized validity and reliability in evaluating behaviors and social skills characteristic of the autism spectrum. These tools allow for a structured and observational assessment that facilitates the confirmation or exclusion of the ASD diagnosis.

The next section outlines the methodology employed in the evaluation of patient MR.

Method

Instruments

CELF-5. Clinical evaluation of language fundamentals – 5

An individual clinical instrument designed to identify, diagnose, and monitor language and communication disorders in children and adolescents aged 5 to 15 years. Its Cronbach's alpha is 0.91 (Wiig et al., 2018).

Revised battery for the evaluation of Reading processes

Proposes appropriate tasks for the evaluation of each reading processing module. Its Cronbach's alpha is 0.86 (Cueto et al., 2007).

Wechsler intelligence scale for children – fourth edition

A comprehensive clinical instrument administered individually to assess the cognitive capacity/intelligence of children aged 6 years 0 months to 16 years 11 months (6:0–16:11). The WISC-V provides composite and subtest scores representing intellectual functioning in specific cognitive domains, as well as a composite score representing overall intellectual ability. It consists of 16 subtests that can be grouped into two general categories: primary or secondary. This test allows determining the intelligence quotient. Its Cronbach's alpha is 0.89 (Wechsler, 2010).

ENFEN. Neuropsychological evaluation of executive functions in children

Evaluates cognitive performance in activities related to executive functions in children and their level of maturity through four tests (interference resistance, path construction, verbal fluency, and ring construction). The Cronbach's alpha of this test is 0.87 (Portellano et al., 2009).

Sensory Profile-2

Evaluates a child's sensory processing patterns in the context of daily life, based on the theoretical foundation that differences in children's sensory processing can either help them integrate more into daily activities or manifest difficulties. The age range to assess is from 3 years old to adolescents (14 years and 11 months). Its Cronbach's alpha is 0.72 (Dunn, 2014).

Autism diagnostic interview – revised

A structured interview conducted with the parent or caregiver of a child and an adult with a mental age of at least 2 years, referred for the evaluation of a possible ASD. The interview is divided into five sections: opening questions, communication questions, social development and play questions, repetitive and restricted behavior questions, and questions about general behavior problems. The Cronbach's alpha for this test is 0.79 (Rutter et al., 2006).

Autism diagnostic observation schedule, second edition

A semi-structured set of observations and a series of activities involving the referred individual and a trained examiner. It can be used to evaluate almost anyone suspected of having ASD, from non-verbal 12-month-olds to verbally fluent adults. The Cronbach's alpha for this test is 0.84 (Lord et al., 2008).

Procedure

The assessment of patient MR was conducted in 6 one-hour sessions. These sessions were spaced with this duration interval due to the attentional difficulties presented by the patient and to avoid causing cognitive fatigue and introducing biases during the evaluation. MR's behavior during the assessment was appropriate, as he cooperated adequately. The evaluation process took place in three phases, detailed in Table 4.

TABLE 4 Patient evaluation phases.

Evaluation phase	Session number	Session objective	Tests administered
1	1	Evaluate	CEL-F-5
	2	language and sensory profile	PROLEC-R Sensory Profile-2
2	3	Assess cognitive function	WISC-V
	4		ENFEN
3	5	Assess ASD traits	ADI-R
	6		ADOS-2

In addition, in Figure 1, a timeline detailing the evaluation process after the diagnostic suspicion is presented.

Results

Language and Reading skills

The results of the CELF-5 test indicate that MR shows significant impairments in various aspects of his expressive and receptive language (Table 5). MR's language profile is characterized by difficulties in understanding sentences (PE=5) and oral texts (PE=5), as well as challenges in establishing word relationships (PE=3) and pragmatic language skills (PE=4).

Similarly, the results of the PROLEC-R instrument reflect difficulties in various reading processes for the patient (Table 6). On one hand, in processes such as identifying equal or different words (PD=14), reading words (PD=32), reading pseudowords (PD=30), respecting punctuation marks during reading (PD=8), and oral comprehension (PD=3), patient MR shows slight difficulties compared to his peer group. On the other hand, in processes related to sentence comprehension (PD=13) and text comprehension (PD=5), his difficulties are severe.

Cognitive and executive functioning skills

The results of the WISC-V test indicate that MR had an intelligence quotient within the normative range (IQ=98). However, the ENFEN test reflected that the patient exhibited alterations in executive and cognitive functions (Tables 7, 8). MR's executive functioning scored slightly below the expected level for his age in subtests related to phonological verbal fluency (PD=4), color trail (PD=8), and interference (PD=38). In the rest of the subtests, the patient demonstrates executive functioning within the normotypic range.

Sensory profile status

The results of the Sensory Profile-2 indicate that MR has scores that fall into the "typical" category. The most significant differences are observed in the behavioral section. Differences are also found in the scores related to avoidance (PD=30), sensitivity (PD=60), and registration (PD=49), with scores placing the patient in a more sensory-sensitive sensory profile than other children of his age (Table 9).

Autism Spectrum disorder assessment

Following the evaluation with the ADOS-2 (Table 10) and ADI-R (Table 11) tests, the diagnosis of ASD is confirmed. The results indicate that MR exhibits a set of behaviors consistent with a 299.00 (F84.0) Autism Spectrum Disorder - Level 1, according to the criteria established in the DSM-5 (American Psychiatric Association, 2013), at the time of the assessment.

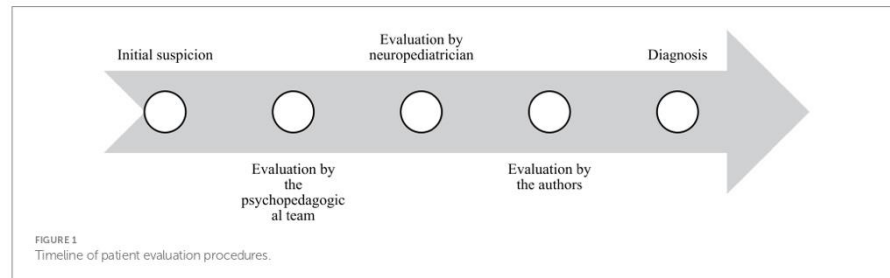


TABLE 5 CELF-5 test results.

	PD	PE	Percentile	PC	Interpretation
Sentence comprehension	18	5	<0.1	49	Altered
Linguistic concept	21	7	0.1	55	Not Altered
Morphosyntax	23	8	0.2	57	Not Altered
Related words	8	3	<0.1	49	Altered
Execution of instructions	24	13	2	68	Not Altered
Preparation of sentences	28	10	0.5	61	Not Altered
Phrase repetition	36	10	0.5	61	Not Altered
Reading Comprehension	6	5	<0.1	49	Altered
Pragmatic Skills Profile	116	4	<0.1	49	Altered

PD, Direct Score; PE, Scalar score; PC, Composite Score.

TABLE 6 PROLEC-R test results.

	PD	Reading performance		
		DD	D	N
Letter name	64			X
Same-Different	14		X	
Lec. Word	32		X	
Lec. Pseudoword	30		X	
Grammar Est.	12			X
Next Score	8		X	
Comp. Prayers	13	X		
Comp. Texts	5	X		
Comp. Oral	3		X	

PD, Direct Score; DD, Severe difficulty; D, Slight Difficulty; N, Normal.

disorders may primarily affect language acquisition and use. The presence of specific ASD characteristics, such as a lack of emotional reciprocity and stereotyped language use, should be evaluated.

- c) ASD and Epilepsy vs. Obsessive-Compulsive Spectrum Disorders (OCD): Repetitive behaviors in ASD may overlap with obsessive-compulsive behaviors. In ASD, these behaviors are linked to restricted interests, while epilepsy could present compulsive behaviors during or after seizures.
- d) ASD and Epilepsy vs. Sleep Disorders: Absence seizures may be misinterpreted as sleep-related events. Exploring the child's sleep history, identifying events during sleep, and evaluating the possible coexistence of sleep disorders that may influence clinical presentation are essential.

Differential diagnosis

- a) ASD and Epilepsy vs. Developmental Delay: ASD is characterized by significant deficits in social communication and repetitive behavior patterns. In contrast, developmental delay may manifest more generally, without necessarily including the specific features of ASD, such as a lack of social reciprocity and restricted interests.
- b) ASD and Epilepsy vs. Language Disorder: In ASD, deficits in social communication are more pronounced, and language

Comorbidity analysis

The comorbidity analysis of patient MR reveals a series of complications that require comprehensive attention. The simultaneous presence of both disorders may increase the risk of mental health issues, such as anxiety and depression. This underscores the need for a thorough mental health assessment to address these concerns and provide appropriate therapeutic interventions. Furthermore, the interaction between ASD and epilepsy can have a significant impact on the child's cognitive and academic development. The complex relationships between both

disorders can influence areas such as attention, learning, and memory. A detailed neuropsychological assessment is essential to understand these areas and design tailored educational strategies. Challenges in communication, inherent to ASD, may be exacerbated by the presence of epilepsy. Epileptic seizures can interfere with effective communication and affect the child's verbal expression. This highlights the importance of addressing the child's communicative skills comprehensively. Similarly, challenges in social skills, common in ASD, may be affected by epilepsy. Epileptic seizures can interfere with social interactions and contribute to peers' perception of strangeness. Specific interventions to improve social skills are essential in this context. Both disorders can also influence the child's sleep patterns. The complexity of comorbidity may lead to additional difficulties in sleep initiation and quality. Moreover, the simultaneous presence of ASD and epilepsy significantly impacts the family dynamics. Emotional burden, daily challenges, and the need for specialized attention can create family stress. Providing guidance and support to the family is crucial to strengthen resilience and improve the quality of life. Given this complexity, there is a highlighted need for comprehensive intervention addressing both medical and psychosocial aspects. Collaboration among mental health professionals, neurology, special education, and social services is essential to design a personalized treatment plan and provide ongoing support. This coordinated and multidisciplinary approach is key to enhancing the child's and the family's quality of life.

Discussion

Patient MR came to our service with a diagnosis of epilepsy and suspicions of Autism Spectrum Disorder (ASD) without a confirmed diagnosis. The patient did not exhibit significant alterations until the age of 6, when the first recorded epileptic

seizure occurred, leading to a decline in linguistic and cognitive abilities, affecting learning and adaptation to daily life contexts. The family reported that during the first 5 years, they did not notice significant difficulties or suspicions of epilepsy or ASD in MR, attributing his isolated and solitary play behaviors to his personality traits. After the epileptic episode and the deterioration of his abilities detected by the educational center, they requested a comprehensive evaluation of linguistic, cognitive, and sensory profile competencies, as well as an evaluation of ASD behaviors that increased in MR.

The assessment had four main objectives. The first was to evaluate language competencies. The second was to assess executive functioning and the possibility of intellectual disability. The third main objective was to determine alterations in the sensory profile. Finally, the fourth objective aimed to confirm the diagnosis of ASD following previous suspicions. The results of the evaluation led to a diagnosis of Grade 1 ASD and epilepsy in patient MR.

This diagnosis was confirmed based on evidence found through the administered instruments. Initially, from the initial family interview and the results of language, reading, executive functioning, and sensory profile tests, it was determined that MR showed linguistic capacity below expectations for his age. Following the epileptic episode, they observed a significant decrease in his vocabulary and comprehension. Additionally, an increase in impulsivity, greater cognitive rigidity, and attention difficulties leading to disruptive behaviors at home were noted. However, they reported that his adaptation to relevant contexts for the child was appropriate, confirming the absence of intellectual disability. Regarding the sensory profile, parents noted that MR tended to avoid certain stimuli and was more sensitive to touch.

After evaluating linguistic, cognitive, and sensory profile competencies related to the ASD diagnosis, MR meets the criteria outlined in the DSM-5 (American Psychiatric Association, 2013). The relevant tests provided evidence of behaviors and conditions sufficient to confirm the diagnosis. The patient exhibited altered linguistic development, with later acquisition of first words (around 3 years old). Furthermore, difficulties in joint play and social relationships were observed. Following this evaluation, contact was made with four specialists in ASD and epilepsy diagnosis, each confirming the diagnosis for MR after reviewing and discussing the assessment results. In summary, behavioral patterns outlined in the DSM-5 (American Psychiatric Association, 2013) for ASD diagnosis in patient MR were confirmed, meeting the following diagnostic criteria: (A) *Persistent deficits in social communication and social interaction across multiple contexts, as manifested by the following, currently or by history; (B) Restricted, repetitive patterns of behavior,*

TABLE 7 ENFEN test results.

		PD	DC	Interpretation
Verbal fluency	Semantics	14	7	High
	Phonological	4	3	Medium-Low
Trails	Gray trail	17	6	Medium
	Color trail	8	4	Medium-Low
Rings		228	5	Medium
Interference		38	4	Medium-Low

PD, Direct Score; DC, Decatype.

TABLE 8 WISC-V test results.

WISC-V	Sum of scalar scores	Composite scores	Percentile	Interpretation
Verbal comprehension	26	89	49	Medium-Low
Visuospatial	31	96	56	Medium
Fluid reasoning	21	93	53	Medium
Work memory	24	87	45	Medium-Low
Processing speed	28	88	46	Medium-Low
Total intelligence quotient	46	98	64	Medium

TABLE 9 Sensory Profile-2 test results.

	PD	Percentile	Interpretation				
			Much less than the others	Less than the others	Like the rest	More than the others	Much more than the others
Search	30	10–82			X		
Avoidance	60	>97					X
Sensitivity	50	84–95				X	
Record	49	87–96				X	
Auditory	22	15–80			X		
Visual	13	8–86			X		
Tactile	17	8–86			X		
Motion	11	6–82			X		
Bodily	10	8–89			X		
Oral	22	6–86			X		
Behavioral	33	>96					X
Socio-emotional	38	88–94				X	
Attention	40	>96					X

TABLE 10 ADOS-2 results.

	PD	Interpretation
Social impact	13	Risk
Restricted and repetitive behaviors	6	Risk
Total score	19	ASD Level 1

PD, Direct Score.

TABLE 11 ADI-R results.

	PD	Cut point
Domino A. Qualitative alterations of reciprocal social interaction	27	CPoint=10 (Risk)
Domain B. Qualitative communication alterations	10	CPoint=8 (Risk)
Domain C. Restricted, repetitive and stereotyped patterns of behavior	5	CPoint=3 (Risk)
Domain D. Developmental alterations evident at 36months or earlier	2	CPoint=1 (Risk)

PD, Puntuación Directa; CPoint, Cut Point.

interests, or activities, as manifested by at least two of the following, currently or by history, (C) Symptoms must be present in the early developmental period (but may not fully manifest until social demands exceed limited capacities, or may be masked by learned strategies in later life), (D) Symptoms cause clinically significant impairment in social, occupational, or other important areas of current functioning, and (E) These disturbances are not better explained by intellectual disability (intellectual developmental disorder) or global developmental delay.

In conclusion, cases like MR's prompt reflect on the difficulty in detecting ASD and epilepsy, establishing an accurate early diagnosis for proper language competency intervention. On one hand, ASD, a

complex developmental disorder, manifests differently in each individual, from difficulties in communication and social interaction to repetitive behavior patterns (Lee et al., 2015). These initial manifestations often go unnoticed or are confused with normal developmental phases, leading to delayed and sometimes incorrect diagnoses (Chen et al., 2022). The general lack of awareness about ASD, both among healthcare professionals and society as a whole, exacerbates this situation, delaying early intervention (El Achkar and Spence, 2015).

On the other hand, epilepsy, a neurological condition characterized by recurrent epileptic seizures, manifests in various forms with a wide range of symptoms, complicating its diagnosis (Keller et al., 2017). Episodes may be misinterpreted as neuropsychiatric disorders, delaying the identification of the true cause and, consequently, the application of effective treatments. This diagnostic delay carries significant risks, such as injury or brain damage (Kwon et al., 2022). Therefore, adopting an interdisciplinary approach involving a wide range of health and education professionals is imperative, with speech therapists playing a crucial role in these teams as linguistic impairments are among the most affected competencies in this population. It is essential for healthcare professionals to screen the linguistic, cognitive, and sensory functions of this population to determine their functional status and issue an early diagnosis, initiating multidisciplinary rehabilitation therapy as soon as possible (Cano-Villagrasa et al., 2023).

Investing in scientific research and the development of more precise diagnostic tools also plays a fundamental role in improving the quality of life for individuals diagnosed with ASD and epilepsy. Future research should continue working in this direction to refine an operational evaluation protocol that can detect the regression of some competencies in the population with ASD and epilepsy, such as language and cognition. In this sense, efforts should continue to improve the quality of life and autonomy of the pediatric population with ASD and epilepsy.

Cano-Villagrasa et al.

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Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Universidad Católica San Antonio de Murcia. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin. Written informed consent was obtained from the minor(s)' legal guardian/next of kin for the publication of any potentially identifiable images or data included in this article. Written informed consent was obtained from the participant/patient(s) for the publication of this case report.

Author contributions

AC-V: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Writing – original draft, Writing – review & editing. NP-G: Conceptualization, Methodology, Project administration, Writing – original draft, Writing – review & editing. IG: Conceptualization, Data curation,

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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5.7. ARTÍCULO 7

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Treatment options in autism with epilepsy

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KEYWORDS

ASD, epilepsy, surgical treatment, children, pharmacotherapy

1 Introduction

Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder characterized by deficits in social communication, repetitive behaviors, and restricted interests (1). ASD is associated with a broad range of concomitant conditions, with epilepsy being one of the most significant and frequent (2, 3). Although ASD and epilepsy exhibit different symptoms and underlying causes (4), there is a strong relationship in their physical and cognitive manifestations (4, 5), as confirmed by the fact that up to 30% of individuals with ASD may have epilepsy (6).

In a recent meta-analysis, a comprehensive exploration of seventy-three studies delved into the point prevalence of active epilepsy, ultimately distilling 67 estimates from 63 unique studies for inclusion in the meta-analysis (6, 7). The resultant synthesis revealed a pooled point prevalence of active epilepsy standing at 6.38 per 1,000 persons (7). Shifting focus to the USA, several population-based studies in the pediatric realm uncovered a notably higher incidence of epilepsy within the first year of life, ranging from 82.1 to 118 per 100,000 person-years, eclipsing the rate observed in older children, which hovered around 46 per 100,000 person-years. An additional prospective study mirrored this trend, recording an incidence of 75 per 100,000 live births before 6 months and 62 per 100,000 between 6 and 12 months—an unprecedented revelation that diverges significantly from previously published estimates (8). Beyond point prevalence, twelve studies contributed insights into the annual prevalence of active epilepsy (9). The pooled outcome showcased an annual prevalence of 2.83 per 1,000 persons, while the median annual prevalence charted at 3.91 per 1,000 persons (10). Nestled within this complex tapestry of prevalence, the pediatric population grappling with both ASD and epilepsy emerges as a multifaceted, multidimensional conundrum. This intricate landscape unfolds against a backdrop of diverse symptoms, genetic foundations, and clinical expressions (11). ASD and epilepsy embark on an evolutionary journey from childhood to adulthood, casting a growing therapeutic demand that resonates not only with patients and their families but reverberates within educational systems and society at large (11, 12).

Delving into the realm of seizures, their classification unfolds into episodes characterized by either motor or non-motor symptoms—a spectrum encompassing generalized tonic-clonic seizures, clonic seizures, tonic seizures, and myoclonic seizures (13–15). Typical absences manifest with a sudden onset, interrupting ongoing activities, featuring a fixed gaze, unresponsiveness to speech, and a duration spanning seconds to half a minute, culminating in a swift recovery (16). Crucially, it's paramount to underscore that the term “absence” doesn't equate to a fixed gaze, as this characteristic

may also manifest in focal onset seizures (17). In contrast, atypical absence displays more pronounced changes in tone compared to typical absence, marked by a non-abrupt onset or termination. Myoclonic absence introduces a sudden, brief (<100 ms), involuntary, non-repetitive, and non-sustained contraction with associated absence. Adding another layer to this intricate spectrum, absence with eyelid myoclonia involves eyelid jerks occurring at a frequency of less than 3 per second, often with eyes deviated upward, typically lasting less than 10 s. This phenomenon is frequently triggered by eye closure and bears a high likelihood of photosensitivity (18).

In 2017, the ILAE Epilepsy Classification unfurled three diagnostic levels (15), enriching our understanding of this intricate landscape. The first level takes root in the seizure type, encompassing an expansive array of concepts—be they focal, generalized, or of unknown onset. This level also introduces two pivotal concepts woven into the diagnostic fabric: comorbidity (associated pathological entities) and etiology. Some patients may find a resting place at this diagnostic level due to investigational limitations, either as a valid endpoint or as the precursor in their diagnostic journey (19). Stepping into the second diagnostic level, the scene unfolds when at least one EEG and brain imaging study graces the diagnostic landscape. Here, the focus shifts to determining the type of epilepsy—focal, generalized, combined (merging both focal and generalized seizures, a common theme in various epileptic syndromes), or of unknown origin. Etiological diagnoses cast their net into structural, genetic, infectious, metabolic, immune, or unknown categories (20). In the intricate dance of medical complexities, a patient may wear more than one etiological hat. For instance, a patient with tuberous sclerosis might proudly display cortical tubers, embodying both a structural and genetic etiology (21). The final frontier, the third diagnostic level, immerses us in the realm of epileptic syndromes—a composite tapestry weaving together common characteristics such as seizure types, specific EEG findings, age-dependent imaging features, onset and remission age, specific triggering factors, daily variations, prognosis nuances, and distinctive intellectual and psychiatric comorbidities. It's a canvas where etiological and treatment implications unfurl their tales (22, 23). This paradigm-shifting classification boldly swaps out the term “benign” for the more apt descriptors “self-limited” or “drug-responsive.” The unfolding

narrative beckons further exploration and inquiry into the ever-evolving lexicon of epilepsy classification.

Regarding ASD, there is significant interindividual clinical variability. Within families, it has been indicated that both genetic and environmental factors influence the phenotypic expression of ASD (12, 13). Many of the core or nuclear symptoms, while reduced to deficits in social communication and interaction and repetitive or stereotyped behaviors, do not manifest their extensive symptomatic expression (10–13).

The neural pathways proposed as the biological basis in ASD associated with epilepsy are related to: (1) imbalance between the glutamatergic (excitatory) and GABAergic (inhibitory) pathways; (2) alteration in the cholinergic pathway; and (3) disruption in synaptic plasticity and oxidative stress (23).

ASD and epilepsy are associated with a high level of psychiatric comorbidity, including anxiety, self or hetero-aggression, depression, hyperactivity, obsessive-compulsive disorder, attention difficulties, tics, eating disorders, executive function impairment, and sleep disorders, which may require pharmacological therapy at some stage of evolution, as well as other relevant symptoms (24), highlighted in the following Table 1:

There are commonly other comorbidities related to severe neurological alterations. A well-studied example of which association between ASD and epilepsy is tuberous sclerosis, in which infantile epileptic spasms appear to be a risk factor for ASD regardless of the location and number of brain tubers (26). All of this is related to the fact that, during the ontogenesis of the nervous system, certain brain areas mature chronologically before others, following a genetically determined program (27). If this maturation process is interfered with by frequent seizures, the consequences can be serious for the consolidation of emerging cognitive functions and the development of the social brain (28). Moreover, epileptiform discharges can occur in the absence of clinical seizures but still impact the brain's maturation process (29). Therefore, tuberous sclerosis represents one of the most attractive etiopathogenic models—genetic, biochemical, structural, and neurophysiological—to understand the bidirectional interaction between ASD and epilepsy (27).

Considering this information, the main objective of this opinion article is to discuss and update the primary pharmacological and surgical treatments for the care of the pediatric population diagnosed with ASD and epilepsy.

2 Pharmacological treatment in the pediatric population with ASD and epilepsy

The pharmacological treatment choice in the pediatric population with ASD and epilepsy is complex and requires an interdisciplinary approach. Specialists in neurology, pediatrics, and psychiatry must design a personalized treatment plan to address the child's needs (28).

As mentioned earlier, the comorbidity of ASD and epilepsy presents a wide range of associated symptoms in individuals (29). The pharmacological care for this population becomes

TABLE 1 Comorbidities associated with ASD or epilepsy condition.

Disorders/Comorbidities	ASD (%)	Epilepsy (%)
Anxiety disorder	10–80	64
Sensory processing disorder	>80	20–35
Sleep disorder	40–80	2.7
Attention deficit Hyperactivity disorder	30–80	4.4
Oppositional defiant disorder	20–80	1.7
Intellectual disability	20–60	1.8–4.1
Obsessive-compulsive disorder	10–40	12
Depression	10–30	2.1
Tics	10–20	-

Adapted from Popow et al. (24) and Boesen et al. (25).

significantly complex. Many experts recommend treatment plan begins with the management of ASD-related symptoms using medications that help reduce or alleviate these symptoms (30). Several studies refer to the administration of drugs such as antipsychotics or antidepressants to address the semiological characteristics that appear in this disorder (31). Table 2 provides a list of the most common alterations in ASD and their pharmacological treatment.

Medications administered for psychiatric symptoms work by reducing or preventing abnormal electrical activity in the brain that leads to seizures. Currently, there are different drugs available, and their selection depends on the type of seizure, the child's age, and comorbid conditions (32–35). In cases where a person with ASD does not experience seizures, the administration of medications to address psychiatric symptoms will focus on addressing behavioral, emotional, or cognitive aspects associated with ASD. These medications may be prescribed to manage issues such as anxiety, hyperactivity, aggression, sleep disorders, or other psychiatric symptoms that may arise in individuals with ASD. The choice of medication will depend on the specific nature of the symptoms and the assessment by the healthcare professional. Medications administered for psychiatric symptoms associated with ASD are often used in combination with other types of medications such as anxiolytics, antipsychotics, and antidepressants, depending on the epileptic symptoms and the severity of the epilepsy episodes the person is experiencing (35). Table 3 details the main drugs for treating epilepsy based on the symptoms presented by individuals with ASD and epilepsy.

Another significant challenge is the high interaction among the drugs described above (26–37). Antipsychotic drugs have significant reactions and drug interactions with anticonvulsants and mood stabilizers, including carbamazepine, though not all of these interactions occur negatively (38, 39). Identifying the consequences of such combinations is highly relevant, as, in some cases, serious adverse reactions may develop. This is exemplified by De León et al.'s (40) of interactions between anti-seizure medicines (ASMs) and second-generation antipsychotics potentially leading to exceptional cases of pancreatitis, agranulocytosis/leukopenia, and heatstroke. Additionally, Hitchings (41), in a review study, suggests that antipsychotics, by

reducing the antiepileptic effect of these drugs, may reduce the efficacy of anti-seizure drugs.

Clozapine, known for reducing the seizure threshold, is linked to dose-dependent electroencephalographic alterations, impacting approximately 3%–6% of patients under clozapine treatment.

Asenjo Lobos et al. (42) highlight favorable outcomes in combined therapy involving antipsychotics for patients exhibiting partial response, as evidenced in several double-blind studies. The combinations encompass olanzapine paired with lithium or valproate, risperidone combined with lithium or valproate, haloperidol alongside lithium or valproate, and quetiapine in conjunction with lithium or valproate.

Similarly, the effectiveness of combined therapy has been demonstrated in open-label studies for patients with both ASD and epilepsy showing partial response. Such studies endorse combinations like olanzapine with lithium, valproate, or carbamazepine; risperidone paired with lithium or valproate, and quetiapine combined with lithium or valproate (43). The simultaneous administration of these medications should be approached with caution due to the potential emergence of toxic symptoms at high doses. Moreover, acute manic symptoms, extrapyramidal effects, physiological disorders, or brain damage could manifest, altering the neurological structure in which the epilepsy focus is located (44–46).

3 Surgical treatment in the pediatric population with ASD and epilepsy

Medical treatments for ASD and epilepsy typically focus on managing the core symptoms of both disorders (ASD and epilepsy), addressing concurrent physical conditions such as sleep disorders, gastrointestinal issues, and sensory difficulties (47). However, unresolved issues persist in understanding the comorbidity between ASD and epilepsy. One fundamental challenge lies in the relationship between seizures and the central social symptoms of ASD. Although there is a high prevalence of epilepsy in individuals with ASD, the exact nature of how seizures contribute to the social aspects of ASD remains an actively researched area. Significant variability in the frequency of seizures also raises questions. While some children with ASD and epilepsy experience recurrent episodes, others may have a

TABLE 2 Pharmacological Treatment of symptoms associated with ASD.

Symptoms	Available medications
Behavioral symptoms, restlessness, self-aggression	Antipsychotics, Anticonvulsants
Socialization problems	Oxytocin, D-cycloserine, Memantine (experimental)
Sleep disorders	Melatonin, Antipsychotics, Antihistamines
Attention deficit hyperactivity disorder (ADHD)	Atomoxetine, Methylphenidate, Amphetamines, Desmethylamphetamines, Guanfacine
Tics	Antipsychotics, $\alpha 2$ agonists, SSRIs
Depression	SSRIs, SNRIs + Antipsychotics
Anxiety and OCD	SSRIs (high doses), Pregabalin
Psychosis	Antipsychotics

Adapted from Popow et al. (24).

TABLE 3 Preferred pharmacological treatment for addressing epilepsy in the pediatric population with ASD.

Drug	Adverse effect	Indicated for epilepsy type
Carbamazepine	Sedation, drowsiness, anxiety, visuomotor incoordination, attention deficit, hyperactivity, behavioral disorders, or learning problems (27–30, 33–36)	Focal and focal to bilateral tonic clonic
Sodium valproate	Drowsiness, irritability, sleep disturbance, or motor incoordination (26–32)	Focal, focal to bilateral tonic clonic, generalized tonic clonic, and myoclonic

single episode in their lifetime. This variability not only complicates the understanding of the relationship between seizures and ASD but also presents challenges in identifying predictive patterns and personalized treatment strategies. Epilepsy itself represents a significant clinical problem, but the decision to resort to surgery must be approached with caution and is reserved for cases of refractory epilepsy with clearly defined cortical abnormalities that require surgical intervention (48). This decision entails the need for an accurate diagnosis and the identification of suitable candidates for surgical procedures, which remains an area in development. The comorbidity between ASD and epilepsy remains an unresolved clinical issue, exacerbated by a substantial lack of data and the complexity of interactions between both disorders (49). Ongoing research is essential to unravel the underlying mechanisms, better understand the variability in clinical presentation, and develop more effective and personalized treatment approaches for those affected by this comorbidity (50).

Upon receiving a referral, it is customary for the patient to undergo a thorough preoperative evaluation with the aim of identifying the epileptogenic zone and evaluating the patient's suitability for surgery (51). This evaluation typically includes a detailed medical history (analyzing clinical semiology, seizure frequency, severity, and prior treatments), video electroencephalography (EEG), magnetic resonance imaging (MRI) using an epilepsy protocol, and neuropsychological testing (52). Depending on the clinical context, additional tests such as positron emission tomography, single-photon emission computed tomography, magnetoencephalography, functional magnetic resonance imaging, and Wada testing may be considered (52, 53). The results of these assessments are then reviewed by a multidisciplinary team, which provides treatment recommendations. In certain cases, supplementary information is gathered through the surgical placement of intracranial electrodes to enhance the localization of the epileptogenic focus and identify critical brain areas for preservation during surgery (53).

For focal-onset seizures that can be localized in a surgically manageable area, available options encompass lesionectomy, temporal lobectomy, or extratemporal cortical resection. These procedures may be executed as a single intervention or in two stages, occasionally preceded by invasive EEG monitoring (54). In more severe epilepsies, alternatives may include functional disconnection (hemispherotomy) or anatomical hemispherectomy (complete removal of a hemisphere) (53, 54). Patients experiencing drop seizures, ineligible for resective options, may be candidates for palliative disconnection through a callosotomy of the corpus callosum. Palliative interventions like vagus nerve stimulation (VNS), and more recent approaches such as responsive neurostimulation (RNS) and deep brain stimulation (DBS), are also viable for patients not suitable for resection (55). Lastly, advancing technologies like laser ablation and gamma knife radiosurgery (GK) are continuously emerging, fostering ongoing exploration of minimally invasive approaches to addressing epileptogenic lesions (55, 56).

3.1 Surgical resective techniques for epilepsy

Lesionectomy stands out as a viable choice for addressing diverse lesions that provoke seizures, including neoplasms (such as gangliogliomas, oligodendrogliomas, astrocytomas, and dysembryonic neuroepithelial tumors) and vascular malformations (cavernomas and arteriovenous malformations) (57–59). In situations where there is alignment among seizure semiology, EEG monitoring findings, and lesion localization on magnetic resonance imaging (MRI), lesionectomy without the need for invasive monitoring is regarded as a favorable option (55–59). While the ultimate objective is complete lesion removal, this can prove challenging in eloquent regions. In many instances, the resection is confined to a portion of the lesion, such as retaining surrounding hemosiderin in the case of cavernomas and arteriovenous malformations (60).

Results after lesionectomy are generally excellent, particularly in pediatric patients. The extent of resection is critical, as total resection has been positively correlated with seizure freedom, reaching approximately 80%, while subtotal resection has a success rate of around 50%. Intraoperative electrocorticography guides resection and often results in the removal of perilesional tissue, with the potential to improve long-term seizure freedom rates (60, 61).

As for temporal lobectomy, one of the most studied surgical options, randomized controlled trials have shown that 58% of patients are seizure-free one year after surgery, compared to only 8% with medical management. The complication rate is relatively low, although side effects such as contralateral upper quadrantanopsia, loss of verbal memory, and, rarely, depression may arise (60–62). The success rate of temporal lobectomy in children is reported to be around 76% (62).

Extratemporal resection typically requires prior implantation of intracranial electrodes to map the epileptogenic focus and preserve eloquent brain areas. Although the effectiveness of extratemporal resection is lower than that of temporal foci, it significantly surpasses continuous medical management, with seizure freedom rates close to 56% in pediatric patients, according to a meta-analysis. Variability in results is associated with seizure duration, the presence of epileptogenic lesions, and/or partial seizures (63).

In extreme cases of catastrophic epilepsy in children and adolescents, such as hemimegalencephaly, hemispherectomy is presented as an option. This intervention aims to functionally disconnect or, in more aggressive cases, physically remove an affected cerebral hemisphere (64). "Hemispherotomy," a less resective variant, has demonstrated similar success rates, with an overall seizure freedom rate of 73.4%. Functional disconnection, known as "disconnective hemispherectomy," reduces intraoperative blood loss and minimizes anatomical resection, albeit with slightly higher risks of hydrocephalus (14%) and superficial hemosiderosis (65). Other less resective modifications have emerged under the term "hemispherotomy." It is emphasized that up to approximately 14 years of age, pediatric and adolescent patients experience greater brain plasticity,

contributing to substantially higher neurological recovery compared to adults undergoing more aggressive surgical interventions (64–66). Systematic studies have reviewed various hemispherectomy techniques in the pediatric/adolescent population, reporting an overall seizure freedom rate of 73.4%, with no significant differences in outcomes based on the type of hemispherectomy. Hemispherotomies, however, are associated with a lower risk of complications compared to other techniques. Additional research supports similar outcomes, highlighting seizure freedom rates of 63% or higher in patients five years post-surgical intervention (67).

3.2 Palliative procedures

Callosotomy is frequently reserved as a surgical intervention for managing medically resistant atonic seizures. Its primary objective is to reduce the occurrence of drop attacks, subsequently minimizing injuries resulting from falls. In contrast to procedures aiming for complete seizure freedom, callosotomy is considered a palliative measure (60–62).

Within this intricate landscape, the decision-making process between opting for a partial callosotomy, involving the anterior two-thirds of the corpus callosum, and a complete callosotomy remains a nuanced endeavor without a definitive consensus. The pursuit of superior seizure control leans decisively towards a complete callosotomy, boasting a remarkable 91% achievement of Engel class I–III, in stark comparison to the relatively lower 75% observed in partial callosotomies (59–61). The inclination towards the latter procedure may stem from a strategic intent to mitigate the occurrence of disconnection syndromes. While transient acute disconnection syndromes find a place in relative commonality, the occurrence of permanent disconnection syndromes is a rare phenomenon. Furthermore, strategic measures such as restricting the extent of callosal transection and orchestrating the procedure at a younger age or in staged interventions appear promising avenues to curtail the risk of disconnection syndromes (64).

On a divergent note, Vagus Nerve Stimulation (VNS), having received FDA approval in 1997, emerges as a compelling alternative for grappling with intractable partial-onset epilepsy, particularly in patients aged 12 and older. Despite the enigma surrounding its mechanism of action, VNS is postulated to exert its effects through thalamocortical projections. While the surgical complications of VNS are notably infrequent, boasting an infection rate of 4%–6%, and accompanied by generally well-tolerated side effects like hoarseness and voice changes, the occurrence of asystole is an exceedingly rare event, reported in less than 0.1% of patients. A recent meta-analysis paints a compelling picture, revealing a 50% reduction rate in seizures for half of the patients undergoing VNS therapy. Notably, this therapeutic avenue extends its benefits to both pediatric and adult populations with generalized epilepsy, despite its off-label application in both cohorts (58, 64).

In tandem with VNS, Responsive Neurostimulation (RNS) emerges as a notable player, securing FDA approval in 2013.

Current indications cast a broad net, encompassing individuals aged 18 or older who grapple with at least three partial-onset seizures monthly, have experienced treatment failures, and have undergone comprehensive diagnostic tests to pinpoint a seizure focus amenable to stimulation (65). While the current approval lends credence to its clinical utility, ongoing research endeavors strive to illuminate its long-term efficacy, particularly in the context of treating medically resistant epilepsies in the pediatric population. A recent multicenter, double-blind, randomized controlled trial involving 191 patients paints an optimistic picture, indicating a median reduction of 44% in seizures at 1 year and an even more encouraging 53% at the 2-year mark within an open-label treatment interval (68). These strides in neuromodulatory therapies underscore a continuously evolving landscape, offering renewed hope and options for patients ensnared by the clutches of treatment-resistant epilepsy.

Finally, the precise mechanism by which Deep Brain Stimulation (DBS) exerts its anticonvulsant effect is not precisely known, but the most widely accepted explanation is that it induces an acute electrical disruption of synchronous activity at its origin, necessary for the propagation of ictal activity (48). It is noteworthy that, in DBS, most efferents of a target can follow action potentials at the stimulation frequency (49, 50). However, the generation of action potentials may be interfered with by the stimulation of afferent fibers towards the dendrites and somas of the target neurons, which can be excitatory or inhibitory, affecting the soma (49, 50). Nevertheless, the palliative option of deep brain stimulation for patients with poorly localized focal or generalized-onset epilepsy has been proposed for analysis, considering it as an emerging treatment in pediatrics, although it lacks FDA approval (49, 61).

3.3 Emerging minimally invasive therapies

In the realm of cutting-edge therapeutic approaches, interstitial laser thermal therapy guided by MRI emerges as a promising, less invasive method for ablating epileptic foci. This innovative procedure involves the meticulous placement of an optical fiber catheter, encased in a cooling sheath, within an identified epileptogenic focus. The subsequent application of laser energy orchestrates thermal ablation in the region of interest, unfolding a novel frontier in epilepsy treatment (67). Executed within the confines of the MRI suite, this procedure leverages real-time thermal imaging to meticulously monitor the treatment's progression, estimating the size and final location of the lesion with unparalleled precision. Currently, the narrative of its application in epilepsy treatment is predominantly woven through the fabric of case reports and small case series (68–70). The roster of treated lesions encompasses periventricular heterotopias, hypothalamic hamartomas, cortical dysplasia, and tubers. A groundbreaking study featuring 268 consecutively treated patients with Magnetic Resonance-guided Laser Interstitial Thermal Therapy (MRgLITT) in the medial temporal lobe has unveiled compelling rates of seizure freedom over time: 55.8% at 1 year, 52.5% at 2 years, and 49.3% at the last follow-up of ≥ 1 year (median of 47 months).

Further bolstering these findings, combined results of Engel I or II showcase encouraging rates of 74.2% at 1 year, 75.0% at 2 years, and 66.0% at the last follow-up. Notably, an independent association has been discerned between preoperative focal to bilateral tonic-clonic seizures and the recurrence of seizures. In a striking turn of events, among patients grappling with seizure recurrence, a significant cohort attained seizure freedom post subsequent surgeries—be it anterior temporal lobectomy (ATL) or a repeat of MRgLITT—underscoring the profound effectiveness of these supplementary approaches in the realm of long-term seizure control (71).

Turning the narrative lens to another groundbreaking frontier, Gamma Knife (GK) radiosurgery has ascended in recent years as a precision-driven, stereotactic powerhouse for delivering focal radiation to intracranial epileptogenic targets, all while sparing surrounding tissues from appreciable radiation damage (72). This sophisticated tool offers a ray of hope in the treatment of epilepsy, presenting the capability to administer targeted radiation doses to specific regions of the affected brain. By elegantly sidestepping the need for whole-brain irradiation, the GK minimizes the collateral damage and toxicity associated with conventional radiotherapy. Its prowess in delivering focused and precise treatments positions it as a valuable asset in the nuanced landscape of epilepsy management, particularly when pharmacological avenues have proven futile. Beyond the realm of epilepsy, this technology currently finds widespread application in focal radiosurgical ablation, ranging from intracranial metastatic diseases and pituitary lesions to acoustic neuromas, refractory trigeminal neuralgia, and various other neurosurgical conditions (73). Its efficacy has been scrutinized in the context of mesial temporal lobe epilepsy, particularly when there is telltale evidence of hippocampal sclerosis in magnetic resonance imaging—a scenario traditionally addressed through selective amygdalohippocampectomy (74). For those navigating the treacherous waters of surgical risks or having faced disappointments in prior surgical interventions for epilepsy, Gamma Knife radiosurgery emerges as a beacon of hope—a non-invasive alternative boasting successful long-term seizure freedom outcomes of 60% or more (75–77). However, the saga continues with an earnest call for further research and clinical studies to meticulously evaluate the effectiveness and potential enduring benefits of stereotactic radiosurgery, notably the kind bestowed by the Gamma Knife, in the expansive tapestry of epilepsy treatment. This quest extends to comparing its outcomes with other therapeutic modalities, charting the course for the future of epilepsy care.

4 Discussion

This opinion article aimed to describe and analyze the most effective pharmacological and surgical treatments for addressing the symptoms in the pediatric population with ASD and epilepsy.

The analysis conducted in this study identified the challenge of treating the clinical picture experienced by individuals with ASD and epilepsy. Approaching this comorbidity from a pharmacological perspective is a complex task. Firstly, pharmacological treatment does not allow for the elimination of the aversive symptoms of

ASD and epilepsy; instead, it focuses on alleviating and reducing the patient's symptoms. Furthermore, the heterogeneity of symptoms in individuals with ASD and epilepsy significantly complicates the selection of combined drugs to reduce behavioral and physiological symptoms of ASD, as well as epilepsy episodes. Additionally, drug interactions contribute to unwanted effects in patients with this comorbidity.

Secondly, medical interventions focus on alleviating symptoms by addressing concurrent physical conditions. For those resistant to pharmacotherapy, surgery, such as temporal resection or functional disconnection, is considered effective, with careful attention to thorough preoperative evaluation. Additionally, palliative procedures like callosotomy and neuromodulatory therapies such as VNS, RNS, and DBS offer promising treatments for patients who are not resection candidates. Emerging therapies, like laser ablation and GK, present minimally invasive approaches. These surgical and therapeutic options constitute comprehensive strategies to address the complexity of the comorbidity between ASD and epilepsy, emphasizing the need to consider approaches beyond conventional medical options to enhance the quality of life for patients.

Current scientific literature does not present significant results that allow determining the most effective treatment choice for the pediatric population with ASD and epilepsy (37–42, 44, 53, 55–57). In this regard, (I) the clinical, genetic, and physiopathological heterogeneity, the multiple possible targets, and the different pathways involved in the pathogenesis; (II) the lack of case-control and cohort follow-up studies from the onset of symptoms in preschoolers (2 years or less) that differentiate between the natural evolution of the condition and the evolution of the condition with intervention; (III) the difficulty in conducting studies with patient and family consent; (IV) the absence of biomarkers that allow grouping similar patients with more homogeneous, evaluable, and reproducible clinical characteristics; (V) the lack of randomized, placebo-controlled, and double-blind studies; (VI) the difficulty in determining the duration of studies, as the evolution of children with ASD and epilepsy undergoes modifications not only attributable to pharmacological interventions but also inherent to development; and (VII) the lack of family adherence to research significantly limit the treatment plan for individuals with this comorbidity (11–14).

In conclusion, the treatment of children with ASD and epilepsy requires an interdisciplinary approach that includes rehabilitation, pharmacology, and ultimately, surgical intervention (23). It is important to mention that these treatments can be costly and may not always be available to all children with ASD and epilepsy (2–5). Accessibility to treatments is a significant concern for parents, caregivers, and healthcare professionals (6), which can greatly influence the choice of the most suitable treatment modality (24). Additionally, pharmacological, and surgical treatments may have side effects, emphasizing the importance of closely monitoring children during treatment to minimize them as much as possible (37). Finally, it is essential to consider the warning signs of ASD and epilepsy to provide early attention to comorbidity, allowing for a differential diagnosis and designing evidence-based personalized interventions to enhance children's development and ensure an improvement in their quality of life (13).

Author contributions

AC-V: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. FM-F: Conceptualization, Supervision, Writing – review & editing. NP-G: Writing – original draft, Writing – review & editing. ML-Z: Conceptualization, Investigation, Methodology, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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5.8. ARTÍCULO 8

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Atención del Trastorno del Espectro Autista y epilepsia a través de Sistemas Aumentativos/Alternativos de Comunicación

Una revisión narrativa

Care of Autism Spectrum Disorder and Epilepsy through Augmentative/Alternative Communication Systems: A Narrative Review

Alejandro Cano Villagrasa
Francisco José Moya Faz
Nadia Porcar Gozalbo
Miguel López Zamora

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Resumen

El incremento de la prevalencia de los perfiles clínicos de personas con TEA y epilepsia en la etapa infantil ha aumentado en los últimos años, describiendo una problemática en su evaluación e intervención en las competencias lingüísticas. Esta población muestra graves alteraciones en el lenguaje expresivo que abarcan diferentes dimensiones de este como la fonología, la semántica, la morfosintaxis, la pragmática y la comprensión auditiva. Todo ello hace que estos usuarios muestren alteraciones significativas en su comunicación y expresión del lenguaje, lo que dificulta significativamente su autonomía y calidad de vida. Por ello, según la literatura científica, uno de los planes de intervención más efectivo que disponemos en la actualidad es el uso de los Sistemas Aumentativos y/o Alternativos de Comunicación (SAAC), los cuales han demostrado en esta población que permiten aumentar su capacidad comunicativa y resolver situaciones lingüísticas con éxito. Es por lo que los profesionales de la salud deben tener un plan de evaluación e intervención adecuado que permita solventar las necesidades comunicativas de las personas con TEA y epilepsia en la etapa infantil. Por ende, este trabajo tuvo el objetivo de reflexionar y proporcionar una revisión de la atención de la población infantil con TEA y epilepsia a través del uso de los SAACs. Para ello, se llevó a cabo una revisión narrativa de la literatura científica publicada hasta el momento, con la lectura de 51 artículos de investigación sobre la atención de la población infantil con TEA y epilepsia. Los resultados indicaron que el protocolo de evaluación para su implementación debe seguir una serie de pasos como son: Recogida de información, Valoración de la persona, Valoración del entorno cercano, Selección del vocabulario, Selección de los reforzadores, Análisis de los sistemas de comunicación, Toma de decisiones y Evaluación de la efectividad del sistema de comunicación. Asimismo, el uso de SAACs en este colectivo mejora de forma significativa la comunicación funcional en diferentes contextos y entornos. En conclusión, se debe llevar a cabo una atención multidisciplinar para mejorar las competencias lingüísticas de las personas con TEA y epilepsia.

Abstract

The increasing prevalence of clinical profiles of individuals with ASD and epilepsy in childhood has grown in recent years, describing a challenge in their assessment and intervention in language competencies. This population exhibits severe impairments in expressive language that encompass various dimensions of language, such as phonology, semantics, morphosyntax, pragmatics, and auditory comprehension. All of this results in these individuals showing significant disruptions in their communication and language expression, significantly impacting their autonomy and quality of life. Therefore, according to scientific literature, one of the most effective intervention plans currently available is the use of Augmentative and Alternative Communication Systems (AAC), which have shown in this population to increase their communicative capacity and successfully address language-related situations. Hence, healthcare professionals should have an appropriate assessment and intervention plan to address the communication needs of children with ASD and epilepsy. Therefore, this work aimed to reflect on and provide a review of the care for children with ASD and epilepsy through the use of AACs. To achieve this, a narrative review of the scientific literature published up to now was conducted, with the reading of 51 research articles on the care of children with ASD and epilepsy. The results indicated that the assessment protocol for its implementation should follow a series of steps, including: Gathering information, Assessing the individual, Assessing the immediate environment, Selecting vocabulary, Choosing reinforcers, Analyzing communication systems, Making decisions, and Evaluating the effectiveness of the communication system. Furthermore, the use of AACs in this group significantly improves functional communication in various contexts and environments. In conclusion, a multidisciplinary approach should be taken to enhance the language competencies of individuals with ASD and epilepsy.

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Atención del Trastorno del Espectro Autista y epilepsia a través de Sistemas Aumentativos/Alternativos de Comunicación

Una revisión narrativa

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Introducción

En la actualidad, el Trastorno del Espectro Autista (TEA) es un trastorno del neurodesarrollo que se caracteriza por cambios y alteraciones en la comunicación, la interacción social y patrones de comportamiento, intereses y actividades restringidos y repetitivos, presentando una gran variación en los grados de intensidad (*Boster y McCarthy, 2018*). Es un trastorno de gran relevancia por su alta prevalencia de aproximadamente el 62% (*Alzayer, 2020*), pero también por su comorbilidad (*Cano-Villagrasa et al., 2023*), puesto que las condiciones que se puedan adjuntar a este trastorno pueden influir negativamente en su desarrollo lingüístico y cognitivo (*Holyfield, 2021*), como podría ser la epilepsia en la población infantil con TEA.

La epilepsia es una alteración neurológica que provoca daños en diferentes localizaciones del sistema nervioso central. En la actualidad, el 72% de las personas con TEA que presentan epilepsia comórbida a esta, su efecto se localiza en el lóbulo frontal, alterando los procesos de funcionamiento ejecutivo y de lenguaje expresivo (*Zhang et al., 2018*). Cuando una persona presenta una epilepsia, el rendimiento del lenguaje y del funcionamiento ejecutivo suele estar deteriorado, sobre todo cuando el diagnóstico es tardío. Sin embargo, este deterioro no es tan pronunciado en comparación con el TEA, puesto que las personas que cursan con este trastorno presentan mayores alteraciones en las dimensiones lingüísticas y cognitivas. No obstante, cuando una persona cursa con TEA comórbido a la epilepsia se observa que ambas competencias se encuentran severamente limitadas, lo que perjudica la calidad conversacional y cognitiva del individuo.



Atención del Trastorno del Espectro Autista y epilepsia a través de Sistemas Aumentativos/Alternativos de Comunicación
Una revisión narrativa

Por lo tanto, un diagnóstico precoz de la epilepsia en la población infantil con TEA es fundamental, ya que permite una intervención temprana, un factor primordial para la mejora de las alteraciones clínicas que mostraría este colectivo, permitiendo logros significativos en el desarrollo del niño y aumentando la posibilidad de desarrollar sus potencialidades y su inclusión social de manera efectiva (Bhat et al., 2022). Sin embargo, se sabe que uno de los mayores problemas en la atención del TEA y de la epilepsia es el diagnóstico y tratamiento tardío (Grzadzinski et al., 2021), lo cual es paradójico sabiendo que, entre los derechos garantizados a la persona con TEA, se encuentra la información para ayudar en el abordaje terapéutico de estos dos trastornos (Manwaring et al., 2017).

Metodología

Este trabajo presenta una revisión sistemática de la literatura sobre el TEA y la epilepsia, y cómo atender las dificultades comunicativas en esta población. La pregunta para abordar es la relación entre el uso de los SAACs, las deficiencias lingüísticas y su comunicación en los diferentes entornos en el cual la persona con estos dos trastornos se desarrolla, siguiendo los criterios del modelo PICO (Paciente, Intervención, Comparación, Resultados) siguiente: (P) Individuos diagnosticados con TEA y epilepsia. (I) SAACs. (C) No aplicable. (O) Dificultades Lingüísticas. Para asegurar la precisión de la pregunta de investigación, se especificaron criterios de inclusión relacionados con individuos con TEA y epilepsia, comparando sus síntomas y los resultados de sus respectivas evaluaciones diagnósticas e intervenciones multidisciplinarias.

Se realizó una búsqueda electrónica entre marzo de 2023 y julio de 2023 en las siguientes bases de datos: Medline, PubMed, PsycINFO, Web of Science y Google Scholar, en la que se seleccionó un total de 51 artículos. La búsqueda se limitó a artículos revisados por pares publicados en revistas y/o disponibles en línea y escritos en español o

Tabla 1
Alteraciones comunes en las personas con TEA y epilepsia

Alteraciones lingüísticas	Alteraciones cognitivas
Errores en la articulación de los fonemas.	Intervalos cortos de atención sostenida.
Conciencia fonológica disminuida.	Comportamientos rígidos, inflexibles y estereotipados.
Léxico pobre tanto en lenguaje expresivo como receptivo.	Disfunción ejecutiva en procesos como la planificación, control inhibitorio y flexibilidad cognitiva.
Problemas en la flexión verbal y adecuación de género y número en frases.	Problemas de memoria a corto y a largo plazo.
Dificultades en la interacción social y pragmática del lenguaje	Baja velocidad de procesamiento de la información.
Alteraciones en la comprensión de instrucciones complejas.	Problemas de memoria de trabajo.

Nota: adaptado de Cano-Villagrasa et al. (2023)

Por un lado, la comunicación y el lenguaje se destacan por sus limitaciones en las dimensiones como la fonología, la semántica, la morfosintaxis, la pragmática y la comprensión auditiva. Según el estudio de (Siyambalapitiya et al., 2022), los niños con TEA y epilepsia presentan dificultades en la discriminación y conciencia fonológica, provocando la aparición de alteración en la identificación de los sonidos del habla, al igual que en la expresión de fonemas de adquisición más tardía como podrían ser los fonemas róticos (/r/) y los grupos silábicos compuestos por ellos. En la misma línea, (Poon et al.,

inglés. Para asegurarse de que los artículos incluidos fueran actuales, la búsqueda se limitó a los últimos 25 años. Se consideraron los siguientes términos en el título del artículo, resumen y palabras clave del estudio: epilepsia, TEA, las dificultades lingüísticas y el uso de los SAACs.

Características de las alteraciones lingüísticas y otras funciones relacionadas con el lenguaje de la población infantil con TEA y epilepsia

Como se refleja en la literatura científica, las personas con TEA y epilepsia muestran alteraciones significativas en los procesos de comunicación y de funcionamiento ejecutivo (Jiménez-Romero et al., 2022). La población infantil con esta comorbilidad experimentará un retroceso significativo en la adquisición del lenguaje, pudiendo no adquirir lenguaje expresivo hasta los 5 o 6 años. Además de ello, los estudios actuales indican que en el 52% de las personas con TEA y epilepsia, se experimenta una regresión en sus hitos de desarrollo madurativo (Cano-Villagrasa et al., 2023). De la misma manera, los procesos cognitivos y de funcionamiento ejecutivo se ven afectados por las limitaciones en el lenguaje (Rossi et al., 2013). Varios estudios demuestran que, al no presentar un lenguaje expresivo adecuado para su edad cronológica, aparecerán alteraciones en el pensamiento lógico, la memorización y problemas de conducta dificultando, así el correcto desarrollo de las funciones cerebrales durante las primeras etapas del crecimiento madurativo (McIntosh et al., 2016; Ibrahimagić et al., 2022). En la Tabla 1, se presenta un resumen de las principales alteraciones cognitivo-lingüísticas de las personas con TEA y epilepsia en la etapa infantil:

2012) indican que esta población cursa con dificultades en la flexión verbal y adecuación de la estructura sintáctica en la conversación. Estos perfiles experimentan limitaciones para la conjugación de verbos irregulares y adecuar la coherencia de la estructura morfosintáctica de frases, con errores para coordinar correctamente el género y el número de los elementos de la oración.

Asimismo, los resultados del estudio de (Cano-Villagrasa et al., 2023) permiten afirmar que la pragmática del lenguaje estará más

Cano Villagrasa, Moya Faz, Porcar Gozalbo & López Zamora

limitada que en las personas que solo dispongan de un diagnóstico de TEA o epilepsia como diagnóstico principal. Todo ello es debido a que esta función se describe en estos perfiles con alteraciones en la interacción social, desconexión del entorno que le rodea, así como dificultades en los aspectos básicos de comunicación social como el contacto ocular, la intención comunicativa o el mantenimiento de la conversación con otro interlocutor. Por último, los procesos de comprensión verbal o auditiva también se encuentran gravemente alterados en la población infantil con TEA y epilepsia. (Fodstad et al., 2009) exponen que este colectivo presenta dificultades para comprender instrucciones simples que contemplen más de dos elementos de acción, así como aquellas estructuras con una composición negativa o con estructura pasiva. De igual manera, (Kang et al., 2020) explican que estos perfiles muestran dificultades en la comprensión de inferencias, siendo incapaces de codificar la información y poder interpretar la realidad con información más abstracta, sin la literalidad de esta.

Aparte de las manifestaciones lingüísticas de esta población, otro conjunto de síntomas relevantes en la población con TEA tiene que ver con sus funciones ejecutivas: ausencia de empatía, presencia de comportamientos estereotipados, perseveraciones, rutinas e intereses restringidos, comportamientos compulsivos, reacciones emocionales inapropiadas y repentinas, y falta de originalidad y creatividad. El grado de alteración de las funciones ejecutivas varía según la edad y el grado de discapacidad de discapacidad de esta población. Así, (Han y Chan, 2017) encuentran un rendimiento significativamente peor en niños con TEA y epilepsia en tres dimensiones: planificación, control inhibitorio y flexibilidad cognitiva, en comparación con aquellos sin epilepsia. En relación con esto, (Hagberg et al., 2015) afirman en su estudio que la competencia verbal alta es un predictor de un mejor desempeño en la inhibición, la memoria ejecutiva y la atención. (Van Eylen et al., 2015) también muestran la existencia de una fuerte asociación entre variables relacionadas con la edad y el cociente intelectual con el funcionamiento ejecutivo: inhibición de respuestas automáticas, flexibilidad cognitiva, memoria de trabajo espacial, planificación y velocidad de procesamiento de la información. Finalmente, (Chen et al., 2016) informan en su estudio comparativo de niños con estos trastornos de diferentes edades que los niños de 8 a 13 años tienen un peor rendimiento que el grupo de niños de 13 a 18 años en las dimensiones de planificación y memoria de trabajo.

Por lo tanto, las limitaciones lingüísticas y ejecutivas que se evidencian en la población con TEA y epilepsia son significativas. Dada la cantidad y heterogeneidad de las alteraciones en las personas con TEA y epilepsia, actualmente existen varios tipos de intervenciones (Muharib et al., 2021). Entre los protocolos más utilizados se encuentra el uso de los Sistemas Aumentativos y/o Alternativos de Comunicación (SAAC), que sirven como herramienta para facilitar la comunicación de las personas que presentan alteraciones en el lenguaje expresivo (Morison et al., 2022). El acceso a este tipo de estrategias permite que las personas con TEA y epilepsia tengan mayor autonomía personal y, por ende, mejore su calidad de vida.

Estrategias de atención a través de sistemas de comunicación en la persona con TEA y epilepsia

Todos los niños con TEA y epilepsia requieren intervenciones, especialmente para abordar las dificultades de comunicación, ya que un alto porcentaje de personas con este trastorno carece de un lenguaje funcional (Finke et al., 2017; Jaber, 2017). Se ha propuesto que los problemas conductuales existente en estos perfiles están relacionados con la incapacidad para comunicarse de manera efectiva a través

del lenguaje expresivo. La investigación ha demostrado una relación directa entre una mayor capacidad comunicativa y comportamientos menos disruptivos (Franchini et al., 2017; Nakamura et al., 2023), resaltando la importancia de las habilidades comunicativas y el funcionamiento social general en el TEA y la epilepsia. Por esta razón se debe llevar a cabo una atención basada en la evidencia científica y en los protocolos de evaluación e intervención para la instauración de un SAAC en esta población, y que están disponibles en la literatura científica internacional (Carter et al., 2020).

Evaluación de la persona con TEA y epilepsia para instaurar un SAAC

En primer lugar, se debe llevar a cabo una evaluación de las competencias lingüísticas de la persona con TEA y epilepsia (Ganz et al., 2012). La evaluación individualizada emerge como un elemento crítico en el proceso de abordar las intrincadas necesidades de comunicación que confrontan los niños que muestran tanto el TEA como la epilepsia (Sievers et al., 2018). Estas dos condiciones, si bien distintas en su origen, manifiestan una variabilidad significativa en su presentación clínica, lo que enfatiza la importancia suprema de la personalización en la evaluación de sus requerimientos comunicativos (Donato et al., 2018). En este contexto, la evaluación debe ser minuciosa, detallada y, sobre todo, centrada en el niño como persona (Clarke y Williams, 2020).

Cada niño con TEA y epilepsia exhibe un perfil único en cuanto a sus fortalezas y desafíos en el ámbito de la comunicación (Gadberry, 2011). Por consiguiente, resulta esencial llevar a cabo una identificación precisa de las habilidades comunicativas existentes y de los obstáculos específicos que afronta cada niño (Wallace y Yerys, 2020). No obstante, es necesario centrar la evaluación en una serie de variables significativas que permitan la recopilación de información, tal y como se muestra en la Figura 1.

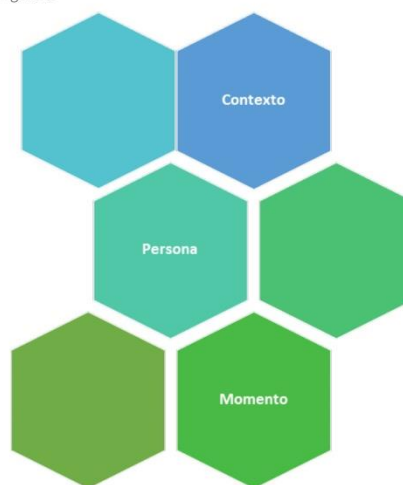


Figura 1
Variables relevantes en la evaluación para implementar un SAAC en la población infantil con TEA y epilepsia

Nota: adaptado de Frolil et al. (2022)

La complejidad de la evaluación de la persona con TEA y epilepsia radica en la recopilación sustancial de factores como: el

Atención del Trastorno del Espectro Autista y epilepsia a través de Sistemas Aumentativos/Alternativos de Comunicación

Una revisión narrativa

contexto (familiar, escolar y entorno social, desde una perspectiva eco-sistémica), la persona y el momento. El contexto implica la evaluación del entorno en el cual el menor interactúa (Sievers et al., 2018). Según (Frolli et al., 2022) se debe realizar una evaluación pormenorizada de localizaciones como la escuela, el domicilio, las sesiones con los profesionales o incluso otros lugares que el niño transite con frecuencia como podría ser el parque. En la misma línea, (Pelphrey et al., 2014) indican que la evaluación de las competencias generales del desarrollo de la persona con TEA y epilepsia resulta fundamental para la aplicación de un SAAC. En este sentido se debe llevar a cabo una evaluación de su comunicación, del funcionamiento ejecutivo, de la sensorialidad, del sueño, de la alimentación, del apartado social y adaptativo del paciente con estas características (Tierney et al., 2014).

Por último, (Ganz et al., 2014) indicaban que el momento en el cual se encontraba el menor con TEA y epilepsia formaría parte de las variables fundamentales para instaurar un SAAC. Aspectos como el estado de la medicación, el trimestre académico, el periodo vacacional o las sesiones de rehabilitación con profesionales, son momentos para tener en cuenta para poder instaurar correctamente un SAAC en la población infantil con TEA y epilepsia (Bhandari et al., 2020).

En resumen, el proceso de evaluación de la población infantil con TEA y epilepsia es complejo, debido a las grandes peculiaridades sintomatológicas que se observan durante todo su desarrollo (Ganz et al., 2008). En la figura 2, se destaca el proceso de evaluación para instaurar un SAAC en este colectivo.

Proceso de evaluación	Recogida de información
	Valoración de la persona
	Valoración del entorno cercano
	Selección del vocabulario
	Selección de los reforzadores
	Análisis de los sistemas de comunicación
	Toma de decisiones
	Evaluación de la efectividad del sistema de comunicación

Figura 2
Protocolo de evaluación para instaurar un SAAC en niños con TEA y epilepsia

Nota: adaptado de Muharib et al. (2021)

Debido a todo lo anterior se entiende que la evaluación de la idoneidad de un SAAC en niños con TEA y epilepsia necesita e implica un seguimiento durante todo su desarrollo madurativo (Muharib et al., 2021). Además, las evaluaciones multidisciplinares se destacan como un enfoque recomendado en este contexto (McCarthy et al., 2018). En lugar de depender exclusivamente de una perspectiva, las evaluaciones multidisciplinares involucran a una variedad de profesionales de la salud, incluyendo fonoaudiólogos/logopedas, psicólogos, neurólogos y otros especialistas, que trabajan conjuntamente (Waynarowski et al., 2017). Esta perspectiva integral permite una evaluación más completa de las habilidades y desafíos de comunicación de un niño (Greene et al., 2018). Es por ello por lo que reconocer la singularidad de cada niño, identificar con precisión sus habilidades y desafíos, y adaptar el enfoque a su nivel de desarrollo son componentes clave para determinar la selección y la aplicación efectiva de un SAAC (Morison et al., 2022).

tiempo para poder instaurar correctamente este tipo de recursos, lo que limita el pronóstico si el programa de intervención no presenta un diseño adecuado (Fortea-Sevilla et al., 2015). Por ello, esta etapa requiere de una exigente toma de decisiones y se debe fundamentar en la evidencia científica con el fin de garantizar que se proporcione el apoyo óptimo a la comunicación de estos niños (Carter et al., 2020).

La elección de un SAAC adecuado depende en gran medida de la evaluación previa y debe ser altamente individualizada (Holyfield, 2021). Cada niño presenta un conjunto único de habilidades y desafíos en el ámbito de la comunicación, y, por lo tanto, no existe un enfoque universal. Primero, es fundamental considerar las habilidades comunicativas preexistentes del niño (Wallace y Yerys, 2020). Algunos niños con TEA y epilepsia pueden tener habilidades verbales limitadas, pero aun así pueden beneficiarse de un SAAC que respalden y amplíen su lenguaje oral (Ganz et al., 2014). En cambio, otros niños pueden ser no verbales o tener habilidades verbales muy limitadas, lo que hace necesario el uso de enfoques de comunicación no verbales. El nivel de desarrollo cognitivo del niño también desempeña un papel crucial en la elección del SAAC más adecuado (Couper et al., 2014).

Intervención de la comunicación en la persona con TEA y epilepsia

Una vez completada la evaluación en niños diagnosticados con TEA y epilepsia, es necesario llevar a cabo un diseño de intervención centrado en la mejora de la comunicación y el lenguaje (Ganz y Simpson, 2004). Una de las herramientas más empleadas para la mejora de estas competencias es la selección de un SAAC que satisfaga las necesidades de comunicación de cada niño (Thirumanickam et al., 2018). El desarrollo de un programa de intervención basado en SAAC es un punto de inflexión en el proceso de atención del menor con TEA y epilepsia, debido a que se necesita de largos periodos de

Los niños con un nivel cognitivo más avanzado pueden ser capaces de utilizar sistemas más complejos, como dispositivos de comunicación con símbolos o aplicaciones de comunicación en tabletas (Tierney et al., 2014). Sin embargo, los niños con un nivel cognitivo más limitado pueden necesitar sistemas más simples y directos, como tarjetas de comunicación o tableros de comunicación visual (Sharma y Rangarajan, 2019). Las preferencias personales y la comodidad de la persona con TEA y epilepsia son factores igualmente

importantes (Morison et al., 2022). Algunos niños pueden sentirse más cómodos con el uso de sistemas táctiles, mientras que otros pueden preferir sistemas de comunicación basados en voz o incluso sistemas híbridos que combinan múltiples modalidades (Yoshikawa et al., 2019).

Sin embargo, se debe tener en cuenta que, dado que algunos niños con TEA y epilepsia experimentan convulsiones, es imperativo considerar cualquier necesidad médica específica al seleccionar un SAAC (Ganz et al., 2008). Es crucial garantizar que el sistema elegido sea seguro y no conlleve un riesgo de desencadenar convulsiones inducidas por la luz, particularmente en el caso de niños con fotosensibilidad epiléptica (Nakamura et al., 2023). El entorno de comunicación del niño también debe ser tenido en cuenta, abarcando la escuela, el hogar y otros lugares frecuentados (Muharib et al., 2021). La consistencia en la implementación de SAAC en múltiples entornos puede ser esencial para lograr el éxito en la comunicación (Jaber, 2017).

La literatura científica y la investigación en el campo de SAAC ofrecen una base sólida para guiar la selección de SAACs adecuados (Franchini et al., 2017; Greene et al., 2018; McCarthy et al., 2018). En la Tabla 2, se ilustran los sistemas de comunicación más empleados para estos perfiles clínicos.

Tabla 2
Ejemplos de SAAC empleados en la población con TEA y epilepsia

Sistema de Comunicación
Sistemas pictográficos
Sistema PECS
Sistema Bliss
Sistema PIC
Sistema SPC
Sistema PICSYS
Sistemas gestuales
Lengua de Señas
Palabra Complementada
Lenguaje Bimodal
Gestos naturales y culturales
Dispositivos de Comunicación y app
Proloquo2Go
TouchChat
Let me Talk
Eneso Verbo
Symbotalk
Pulsadores
CPA – Comunicador Personal Adaptable
Jabtalk
Niki Talk
Speak It

Nota: adaptado de Franchini et al. (2017); Greene et al. (2018); McCarthy et al. (2018)

Discusión

Este estudio tuvo como objetivo principal el revisar la información existente en la actualidad sobre los SAACs y su uso en la atención de la persona con TEA y epilepsia durante su infancia. Este trabajo reflexionó sobre las características cognitivo-lingüísticas de las personas con TEA y epilepsia, con el fin de contextualizar las limitaciones existentes en esta población, desarrollando un planteamiento sobre la atención de la población infantil con TEA y epilepsia a través del uso de los SAACs, detallando una propuesta de evaluación e intervención empleando este tipo de herramientas.

Los resultados del presente estudio presentan una profunda reflexión sobre las dificultades actuales en la mejora de las competencias comunicativas, así como de aquellas relacionadas con esta, como son las funciones ejecutivas, las cuales están gravemente alteradas en la población infantil con TEA y epilepsia (Boster y McCarthy, 2018). Además de indicar protocolos efectivos de actuación para la evaluación e intervención a través de los SAACs que presenta esta comorbilidad. Son numerosas las investigaciones que hacen una revisión sobre esta temática y arrojan resultados que van en la línea de lo presentado en nuestro estudio (Alzayer, 2020; Clarke y Williams, 2020; Franchini et al., 2017; Gadberry, 2011).

Por ejemplo, en el estudio de (Cano-Villagrasa et al., 2023), se exploran las limitaciones que presentan las personas con TEA y epilepsia en lo relativo al lenguaje y al funcionamiento ejecutivo. Los autores exponen que este colectivo muestra graves dificultades en la pragmática del lenguaje, así como en los apartados relacionados con la inhibición, el control emocional y la memoria de trabajo. Estos datos son de gran interés, ya que estas funciones son primordiales para la implementación de un SAAC en la persona con TEA y epilepsia. Debido a esta comorbilidad, los usuarios muestran dificultades en la correcta asimilación de las pautas de uso de los SAAC en los contextos como la escuela o el domicilio (Ganz et al., 2014).

Al presentar alteraciones en el funcionamiento ejecutivo cursaran con problemas para poder instaurar un SAAC adecuadamente, puesto que el apartado cognitivo de la persona con esta comorbilidad mostrará procesos de desatención, despistes u olvidos en el uso del SAAC, lo que limitará el aprendizaje de este y no lo empleará adecuadamente en los contextos fundamentales para su desarrollo (Zhao et al., 2021). Todo ello se corrobora con lo publicado hasta la fecha en la literatura científica. (Brignell et al., 2018) indican que las personas con TEA que muestran graves alteraciones en el funcionamiento ejecutivo tendrán un aprendizaje más lento que aquellas que no presentan estas dificultades. De igual manera, (Hage et al., 2021) demuestran que las personas con epilepsia que no poseen lenguaje oral tienen graves limitaciones para la comprensión del uso de un SAAC, sobre todo en las primeras etapas del desarrollo madurativo. Por último, las dificultades en el lenguaje expresivo y receptivo también impiden el correcto aprendizaje de los SAAC en las personas con TEA y epilepsia (Almurashi et al., 2022).

La falta de interés por comunicarse, el pobre contacto ocular, las limitaciones en la interacción social y las alteraciones en la comprensión oral del lenguaje, son importantes barreras que disminuyen el éxito en la implementación de un SAAC en esta población (Chen et al., 2022). Estudios como el de (White et al., 2021) exponen que los requisitos lingüísticos son un pilar fundamental para la correcta implementación de un SAAC. Los resultados de su investigación indican que previo a la implementación de un SAAC en la población infantil, independientemente del trastorno que curse, se deben mejorar y entrenar los requisitos del lenguaje oral, con el fin de que



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Atención del Trastorno del Espectro Autista y epilepsia a través de Sistemas Aumentativos/Alternativos de Comunicación

Una revisión narrativa

esta herramienta se emplee como una ampliación de este, y mejore las competencias en interacción y uso de la comunicación funcional en personas que presentan un deterioro significativo del lenguaje oral.

Con respecto a la atención de la persona con TEA y epilepsia, las investigaciones revisadas en el presente estudio indican que los protocolos de actuación en la mejora de la comunicación de estos perfiles comprenden grandes retos para el diseño correcto y adecuado para su evaluación e intervención (Brignell et al., 2018). Por un lado, la evaluación se complejiza debido a la condición de la epilepsia en los niños con TEA, ya que, como se ha determinado previamente, las habilidades lingüísticas y cognitivas se encuentran más limitadas en comparación con las personas que solo cursan una de las dos condiciones (Donato et al., 2018). Esto conlleva a que los protocolos de evaluación sean inservibles debido a que no están adaptados a las deficiencias que presentan esta población, por lo que encontraremos sesgos importantes, así como una baja sensibilidad para determinar las habilidades lingüísticas reales de las cuales disponen en el momento en el que se evalúan. En este sentido, (Franchini et al., 2017) permiten hacer una reflexión sobre las dificultades en la evaluación en los perfiles clínicos que experimentan un bajo nivel de lenguaje, indicando que existe un número muy restringido de pruebas que permiten evaluar el lenguaje en perfiles con graves problemas en su lenguaje expresivo. Por ello, el presente estudio hace una revisión de la literatura científica publicada en la actualidad y propone un protocolo de evaluación que permita recoger información no solo de las competencias lingüísticas del menor, sino de su entorno, el cual proporcionará una visión más amplia de las necesidades de la persona con TEA y epilepsia, con el fin de instaurar un SAAC funcional y que le permita responder a las exigencias lingüísticas del medio en el cual se desarrolla (Ganz et al., 2012).

Por otro lado, con respecto a la intervención, también se encuentran limitaciones para poder diseñar un protocolo de intervención eficaz en esta población. La literatura científica en este aspecto no acaba de esclarecer las líneas de intervención eficaces en la intervención del lenguaje (Hage et al., 2021). Sin embargo, todas las investigaciones coinciden en que el uso de los SAAC en la población infantil con TEA y epilepsia tienen una eficacia altamente demostrada, puesto que les permiten obtener una comunicación funcional, conectando con su entorno y complementando el poco lenguaje expresivo que puedan presentar para demandar deseos o necesidades (Pelphrey et al., 2014). En este sentido, es preciso la adaptación del medio con el uso de dispositivos electrónicos, imágenes o apoyo por parte del adulto para que el usuario con estas condiciones de salud pueda llevar a cabo interacciones comunicativas exitosas a través del empleo de un SAAC adaptado a las características lingüísticas y cognitivas del usuario (White et al., 2021).

Conclusión

En conclusión, el uso de los SAACs en la población con TEA y epilepsia pueden tener un gran beneficio para mejorar sus competencias lingüísticas. Este colectivo presenta graves alteraciones en el lenguaje y en la cognición, por lo que la intervención en estas competencias a través de la implantación de un SAAC conllevaría a la mejora de las habilidades comunicativas y cognitivas del paciente con TEA y epilepsia.

De esta manera, se confirma la hipótesis de investigación establecida en este trabajo, puesto que, según los artículos revisados en esta revisión narrativa, estas dificultades en lenguaje expresivo se podrían suplir con el uso de tecnología o herramientas basadas

en SAACs para potenciar las competencias comunicativas de esta población.

No obstante, existe una multitud de limitaciones que implican que la atención de este colectivo se complejice de manera significativa, como por ejemplo los bajos recursos en las instituciones sanitarias a nivel nacional e internacional, lo que conlleva a unos largos intervalos de tiempo de espera para poder acceder al cuerpo clínico de rehabilitación, así como desarrollar protocolos de actuación sanitaria para la atención de la población infantil con TEA y epilepsia.

Por todo ello, la evaluación y la intervención en el lenguaje y comunicación funcional se debe basar en las competencias lingüísticas y cognitivas que presentan estos perfiles para así diseñar un protocolo de evaluación e intervención ajustados a las capacidades del usuario, con el fin de mejorar también su calidad de vida y su participación en los contextos en los cuales habita durante su día a día.

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Atención del Trastorno del Espectro Autista y epilepsia a través de Sistemas Aumentativos/Alternativos de Comunicación

Una revisión narrativa

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VI – RESULTADOS Y DISCUSIÓN

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Las alteraciones en las competencias lingüísticas, cognitivas, emocionales y conductuales en las personas con TEA y epilepsia impactan negativamente en el desarrollo infantil en las primeras etapas. Todo ello influye en las capacidades generales de la persona y provocan un déficit en las áreas relacionadas con su desarrollo madurativo, como podrían ser el apartado social, adaptativo o motor, así como en la calidad de vida y la autonomía del individuo que cursa con esta comorbilidad.

Las personas afectadas por TEA y epilepsia enfrentan desafíos significativos que repercuten en su desarrollo infantil temprano. Las alteraciones en competencias lingüísticas, cognitivas, emocionales y conductuales tienen un impacto negativo sustancial en la vida de estas personas. Estas dificultades no solo comprometen las habilidades generales del individuo, sino que también generan un déficit en áreas críticas para su crecimiento madurativo, como lo son las habilidades sociales, adaptativas y motoras. Además, se observa una repercusión adversa en la calidad de vida y la autonomía de aquellos que enfrentan esta comorbilidad. Abordar estas dificultades de manera integral es imperativo para proporcionar el apoyo necesario y promover un desarrollo óptimo en estas personas.

El objetivo general de esta tesis doctoral fue analizar y explorar las características clínicas y los protocolos de evaluación e intervención existentes en las personas diagnosticadas con TEA y epilepsia desde una perspectiva bio-psico-social. Para ello, se ha evaluado las competencias lingüísticas, cognitivas, emocionales y conductuales de una cohorte de menores con TEA y epilepsia. Además de ello, se ha diseñado y estudiado protocolos de evaluación y de intervención de estos perfiles clínicos.

A continuación, se discuten los resultados obtenidos en cada uno de los objetivos específicos de este estudio.

6.1. RELACIÓN DE LA EPILEPSIA EN LAS ALTERACIONES COGNITIVAS Y LINGÜÍSTICAS DE LAS PERSONAS CON TEA

Los resultados arrojados por la presente tesis doctoral permiten destacar que la epilepsia influye negativamente en el desarrollo de las habilidades cognitivas y lingüísticas de la persona con TEA, puesto que presentan mayores alteraciones en los procesos cognitivos y lingüísticos en comparación con otros colectivos con un diagnóstico diferente de trastornos del neurodesarrollo. Los cambios cognitivos en la epilepsia pediátrica son parte de la definición actual de la enfermedad, y tienen un impacto importante en la adaptación de los niños al entorno, la relación con los compañeros y el rendimiento académico, determinando así un mal pronóstico y una mala calidad de vida tanto para el usuario como para todo el entorno familiar que le rodea. Sin embargo, en la actualidad existen pocos estudios que hayan estudiado estas alteraciones.

La literatura científica ha demostrado que, en las afecciones neurológicas del ámbito pediátrico, el impacto en la cognición excede de las expectativas de la epilepsia focal y afecta la función de múltiples áreas. La escasez de estudios, el escaso número de muestras homogéneas, la variabilidad de las manifestaciones de alteraciones neurológicas en las variables clínicas y su etiología hacen que estos estudios no sean concluyentes (Amiet *et al.*, 2013; Braakman *et al.*, 2015; Perinelli *et al.*, 2023). Hasta el momento, aunque los cambios cognitivos son un factor importante en el mal pronóstico de los niños con epilepsia, ningún estudio ha analizado específicamente los efectos de diversas causas, su ubicación y alcance sobre las características neuropsicológicas de los niños. En comparación con otros estudios, el desempeño de las habilidades académicas de los niños con TEA y epilepsia es una de las debilidades más alteradas en las características cognitivas (Braakman *et al.*, 2011; Braakman *et al.*, 2012; Vaessen *et al.*, 2014). En diferentes estudios se han encontrado que los puntajes aritméticos estaban por debajo del promedio (Lopes *et al.*, 2013; Sharma *et al.*, 2022). La dificultad en el proceso de atención y memoria de trabajo mostrada por estos usuarios puede ser la razón de su pobre rendimiento académico.

Respecto a las competencias lingüísticas, el rendimiento de los niños con TEA y epilepsia es menor que encontrado en aquellos niños TEA que no cursan con esta afectación. Esto indica que, en el caso de la epilepsia, las habilidades lingüísticas evaluadas presentan una afectación significativa, algo que ya se ha encontrado en otros estudios (MacAllister y Schaffer, 2007). La mayor debilidad en el proceso del lenguaje es el registro en tareas que requieren un proceso de emisión del lenguaje oral. Estos resultados pueden explicarse por la conocida participación de diferentes estructuras cerebrales en el proceso de la expresión del lenguaje (Braakman *et al.*, 2011). Sin embargo, también se registran debilidades en tareas que requieren contenidos semánticos, como el acceso al léxico o la comprensión de palabras. Los estudios de neuroimagen funcional han demostrado que la activación de la corteza multimodal durante el procesamiento semántico está respaldada por la red ventral que conecta el lóbulo frontal y el lóbulo temporal a través del lóbulo frontal occipital inferior y el tracto uncinado (Friederici y Gierhan, 2013). Además, estos resultados pueden explicar la falta de diferencias significativas entre el enfoque del hemisferio izquierdo y derecho, incluidas las habilidades del lenguaje, porque a diferencia de los adultos, la red neuronal del lenguaje del hemisferio izquierdo de los niños no está lateralizada de manera tan significativa, lo que demuestra que la activación está en contraste con la corteza contralateral durante el proceso de comunicación oral (Frederici, *et al.*, 2011).

En la última década, ha destacado el impacto negativo de la epilepsia temprana en la capacidad cognitiva como un poderoso predictor de dificultades en el desarrollo de estas funciones en los niños con TEA (Karrasch *et al.*, 2017). La aparición temprana de crisis epilépticas determina que todas las áreas funcionales muestren un peor desempeño. Cuando se analiza el impacto en relación con otras variables clínicas, la aparición temprana es la variable que presenta mayor peso predictivo en la aparición de estas alteraciones. Estudios previos también han demostrado que está relacionado con la CI (Lee *et al.*, 2013) y la cognición (Campiglia *et al.*, 2014; Riva *et al.*, 2005). Las convulsiones en el primer año de vida están asociadas con el mayor deterioro en el nivel de inteligencia (Campiglia *et al.*, 2014). En el TEA, las afecciones cognitivas son particularmente sensibles al inicio temprano de la epilepsia (Lopes *et al.*, 2014), lo que respalda la hipótesis de vulnerabilidad temprana (Campiglia *et al.*, 2014). Algunos estudios han demostrado que la edad de menos de 3 años es el punto crítico más vulnerable,

especialmente en términos de memoria y flexibilidad cognitiva (Anderson *et al.*, 2010). Las convulsiones prematuras pueden causar anomalías metabólicas o estructurales, que pueden afectar el desarrollo cognitivo posterior (Braakman *et al.*, 2013; Lee *et al.*, 2013).

En resumen, la epilepsia es una enfermedad neurológica compleja de múltiples sistemas que implica cambios cognitivos y conductuales, de los cuales las convulsiones son solo un aspecto (Berg, 2016). Si la epilepsia se entiende como conexiones de redes neuronales deterioradas, como lo respaldan las investigaciones actuales, aclarar la disfunción cognitiva asociada con diferentes tipos de epilepsia puede proporcionar marcadores potenciales de redes epilépticas, lo que sugiere la necesidad de evaluaciones neuropsicológicas y logopédicas extensas que den cuenta de todos sus déficits y no de aspectos parciales, aparcando la influencia de la tradición localizacionista de la investigación en adultos en epilepsia (Smith, 2016). Además, se tiene que caracterizar los fenotipos cognitivos y conductuales de los niños con TEA, que puede mejorar el sistema de clasificación de la epilepsia, y la investigación sobre la estructura y función de esta, pudiendo ayudar a profundizar en la comprensión del cerebro (Berg, 2016).

6.2. LOS TRASTORNOS DEL SUEÑO Y SU RELACIÓN CON LA DISFUNCIÓN NEUROBIOLÓGICA Y LAS ALTERACIONES COGNITIVAS EN LA PERSONA CON TEA Y EPILEPSIA

Tras los resultados obtenidos en la presente tesis doctoral, se confirma que los trastornos del sueño (TS) presentan una estrecha vinculación con las disfunciones neurobiológicas y las alteraciones cognitivas propias de las personas con TEA y epilepsia, destacando una desregulación en estos procesos en la población con esta comorbilidad.

Respecto a las alteraciones neurobiológicas presentes en las personas que cursan estos trastornos comórbidos, la literatura científica ha demostrado que, en condiciones neurológicas en el entorno pediátrico, el impacto de los TS implica una desregulación de gran parte del sistema nervioso, mostrando una disfunción en los sistemas gabaérgicos y serotoninérgicos, lo que implica una alteración del sistema hormonal, concretamente el encargado de la regulación de la melatonina (Lalanne

et al., 2021; Martin *et al.*, 2018; Siemann *et al.*, 2020). Sin embargo, la investigación en este campo es muy limitada debido, en parte, a la escasez de estudios, al pequeño número de muestras homogéneas, a la variabilidad de las manifestaciones de las alteraciones neurológicas en las variables clínicas y su etiología; lo que hace que los estudios no sean concluyentes (Dan *et al.*, 2020; Takumi *et al.*, 2020). No obstante, esta desregulación de los diferentes sistemas neurológicos impacta negativamente en el desarrollo madurativo de la persona con TEA y epilepsia, puesto que repercute en los procesos de aprendizaje (Leshem *et al.*, 2021), provocando que la sintomatología del propio trastorno TEA sea más pronunciada con mayores alteraciones en la comunicación y el lenguaje, o en la conducta social (Bhat *et al.*, 2014).

En cuanto a los cambios cognitivos debido a los TS, cabe destacar que forman parte de la definición actual de esta comorbilidad y tienen un impacto significativo en la adaptación de los niños al entorno, en la relación con sus pares y en el desarrollo cognitivo. En la última década, se ha confirmado la presencia negativa de la epilepsia temprana en la capacidad cognitiva, estableciéndose como un predictor de dificultades en el desarrollo de estas funciones en niños con TEA y epilepsia (Karrasch *et al.*, 2017), causando que procesos cognitivos como la atención o la memoria muestren un rendimiento reducido. Esto puede deberse a que, en la infancia, los mecanismos de plasticidad neuronal están en su punto máximo, tratando de consolidar los mecanismos de atención y memoria a través de la asimilación de estímulos del entorno (Bölte *et al.*, 2019). Sin embargo, la existencia de un TS tendrá un efecto negativo y reducirá la capacidad de integrar los conocimientos de los estímulos adquiridos del contexto en el cual desarrolla la persona que presenta TEA y epilepsia, puesto que reducirá el estado de alerta cognitiva, impidiendo que exista una focalización atencional correcta, limitando que la información captada por el sistema sensorial del niño se registre y almacene en la memoria (Cano-Villagrasa *et al.*, 2023).

En resumen, la investigación científica sobre las alteraciones neurobiológicas en personas con TEA y epilepsia, en el entorno pediátrico, ha evidenciado una desregulación significativa del sistema nervioso, afectando los sistemas gabaérgicos y serotoninérgicos, así como la regulación hormonal, particularmente en relación con la melatonina. Sin embargo, la falta de estudios exhaustivos y la diversidad de manifestaciones clínicas y etiológicas dificultan la obtención de

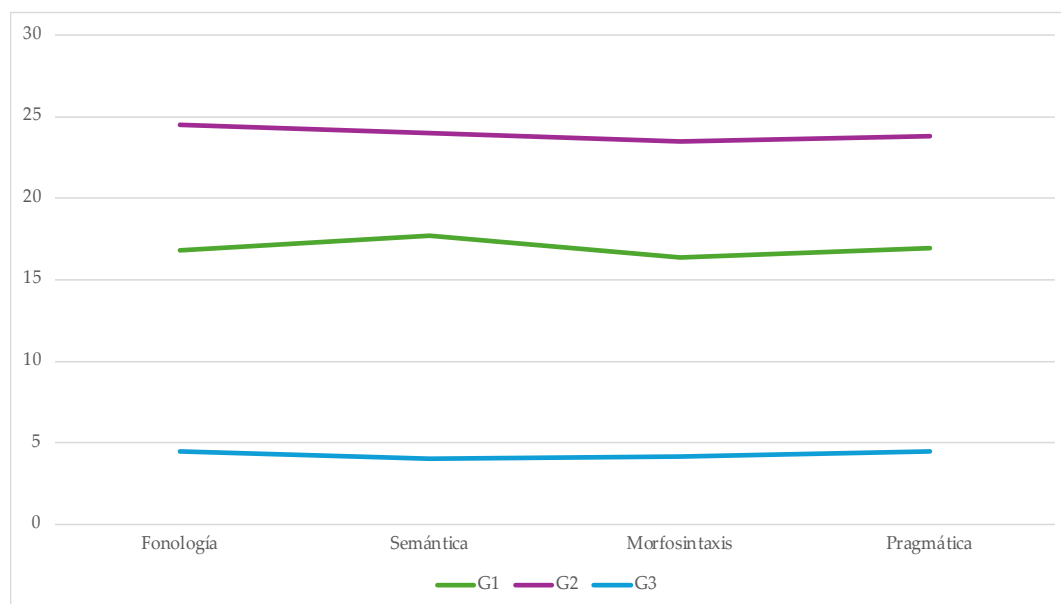
conclusiones definitivas. Esta desregulación neurológica impacta negativamente en el desarrollo madurativo, exacerbando la sintomatología del TEA y la epilepsia. Además, estos trastornos comórbidos influyen en los cambios cognitivos, reduciendo la capacidad de adaptación, las habilidades cognitivas y la integración de estímulos del entorno. La epilepsia temprana se ha identificado como un predictor de dificultades en el desarrollo cognitivo, afectando la atención, la memoria y la capacidad de procesamiento de información, lo que sugiere una interferencia con los mecanismos de plasticidad neuronal que están en su apogeo durante la infancia. Esta interacción compleja entre los sistemas neurológicos y cognitivos destaca la necesidad de una investigación más exhaustiva para comprender mejor las implicaciones clínicas y el manejo de estos trastornos comórbidos.

6.3. COMPARACIÓN DEL RENDIMIENTO EN EL FUNCIONAMIENTO EJECUTIVO Y EL LENGUAJE ENTRE LA POBLACIÓN INFANTIL CON TEA, EPILEPSIA Y TEA CON EPILEPSIA

Los resultados encontrados en la presente tesis doctoral permiten confirmar que existen diferencias significativas entre las cohortes de personas evaluadas que presentaban un diagnóstico de TEA, epilepsia o TEA con epilepsia, mostrando un peor rendimiento en las habilidades lingüísticas y en el funcionamiento ejecutivo en el grupo de personas con TEA y epilepsia. Se destaca que las personas que solo cursan con epilepsia muestran un mejor rendimiento en los actos comunicativos y lingüísticos, pudiendo desarrollar una mejor habla, lenguaje y comunicación frente aquellos que presentan un TEA (Tabla 6 y Figura 1).

Tabla 6. Diferencias entre los grupos: TEA (G1), Epilepsia (G2) y TEA y epilepsia (G3) en las medidas del lenguaje obtenidas en la prueba CELF-5.

Habilidades lingüísticas	G1		G2		G3		F (8)	η²P	Diferencia entre los grupos
	(n = 50)		(n = 50)		(n = 50)				
	M	DT	M	DT	M	DT			
Fonología	16.78	3.43	24.50	3.57	4.48	2.88	464.96*	.864	G2 > G1 > G3
Semántica	17.70	4.44	23.98	3.72	4.04	2.74	379.05*	.838	G2 > G1 > G3
Morfosintaxis	16.36	4.35	23.50	3.47	4.12	3.05	356.72*	.829	G2 > G1 > G3
Pragmática	16.90	4.41	23.80	3.72	4.44	2.83	349.14*	.826	G2 > G1 > G3

* $p < .05$ **Figura 1.** Comparación de las puntuaciones medias entre el grupo TEA (G1), el grupo Epilepsia (G2) y el grupo TEA y epilepsia (G3) en las medidas correspondientes a la prueba CELF-5.

Haciendo un análisis pormenorizado de los resultados, con respecto a las competencias relativas al lenguaje, se encuentra que las personas con diagnóstico

de epilepsia presentan unas puntuaciones muy superiores a las que se reflejan en el TEA o en aquellos con TEA con epilepsia. Estos resultados indican que la condición de TEA asociada a la epilepsia provoca una limitación en el rendimiento del lenguaje, la comunicación y el habla. La población infantil con TEA cursa con un desarrollo atípico en cuanto a los aspectos y dimensiones del lenguaje, en donde se pueden observar alteraciones en la articulación de los sonidos del habla y su procesamiento fonológico y fonético (Bedore y Leonard, 1998; Crissien-Quiroz *et al.*, 2017), la adquisición de vocabulario funcional y la integración de este en su almacén léxico-semántico (Mendoza y Muñoz, 2005; Roberts *et al.*, 1998), la coherencia y cohesión gramatical con estructuras morfosintácticas ajustadas a su edad cronológica (Fortea Sevilla *et al.*, 2013) y la interacción y uso del lenguaje a través de gestos, intención comunicativa o la narración relacionado con la pragmática (Bejarano-Martín *et al.*, 2020; Brinton *et al.*, 1998; Fletcher, 1992). Todos estos aspectos lingüísticos se ven especialmente perjudicados si la persona con TEA cursa, asociado a esta, con epilepsia. Esto podría indicar que la población con TEA y epilepsia esté más limitada en su comunicación y lenguaje, y por tanto exige tener consideraciones especiales en la atención de esta población. Esta afirmación se puede corroborar en estudios como los de Dioses-Chocano *et al.* (2014), Juillerat *et al.* (2015), Muñoz-Yunta *et al.* (2008), Norrelgen *et al.* (2015) y Rotta (2013) en los cuales se realizó un análisis de las competencias lingüísticas en la población infantil con TEA o TEA con epilepsia. Los resultados de estos estudios indicaron que existe una mayor alteración en el lenguaje en los niños con TEA y epilepsia frente a aquellos que no presentan esta comorbilidad. Además de esto, se indica que esta población muestra mayores limitaciones en la adquisición de las primeras palabras, combinar adecuadamente las formas gramaticales y sintácticas de la lengua, así como producir y mantener una conversación funcional con su entorno. Por lo tanto, los resultados del presente estudio mostrarían que los niños con este perfil adquirirían la producción de frases durante los años previos al comienzo del primer ciclo de educación primaria. Por ello, se observa que los niños con TEA y epilepsia presentan un mayor retraso en la adquisición de la comunicación oral frente a aquellos niños que no cursan con epilepsia. Asimismo, también desempeñan un mejor funcionamiento ejecutivo, con mejor planificación, organización, memoria de trabajo, inhibición, control emocional, entre otros, lo que le permite desarrollar las actividades básicas de la vida diaria con mejor

rendimiento en relación con aquellos niños que presentan un diagnóstico de TEA junto a una epilepsia (Tabla 7, Tabla 8 y Figura 2).

Tabla 7. Diferencias entre los grupos: TEA (G1), Epilepsia (G2) y TEA y epilepsia (G3) en las medidas del funcionamiento ejecutivo obtenidas en la prueba BRIEF-2.

Funcionamiento ejecutivo	G1 (n = 50)		G2 (n = 50)		G3 (n = 50)		F (14)	η^2_p	Difference between groups
	M	DT	M	DT	M	DT			
Inhibición	14.86	3.60	23.58	3.74	4.50	2.97	382.16*	.839	G2 > G1 > G3
Flexibilidad	13.42	3.74	23.92	3.70	4.72	2.90	382.53*	.839	G2 > G1 > G3
Control emocional	13.20	3.06	24.16	3.54	4.50	2.95	475.18*	.866	G2 > G1 > G3
Memoria de trabajo	14.00	3.85	23.98	4.06	4.58	2.95	351.65*	.827	G2 > G1 > G3
Planificación	14.12	3.79	23.60	3.54	4.10	2.83	406.85*	.847	G2 > G1 > G3
Organización de materiales	13.80	3.79	23.36	3.83	4.48	3.07	347.30*	.825	G2 > G1 > G3
Monitorización	13.90	3.53	24.66	3.52	4.52	2.94	453.46*	.861	G2 > G1 > G3

* $p < .05$

Figura 2. Comparación de las puntuaciones medias entre el grupo TEA (G1), el grupo Epilepsia (G2) y el grupo TEA y epilepsia (G3) en las medidas correspondientes a la prueba BRIEF-2.

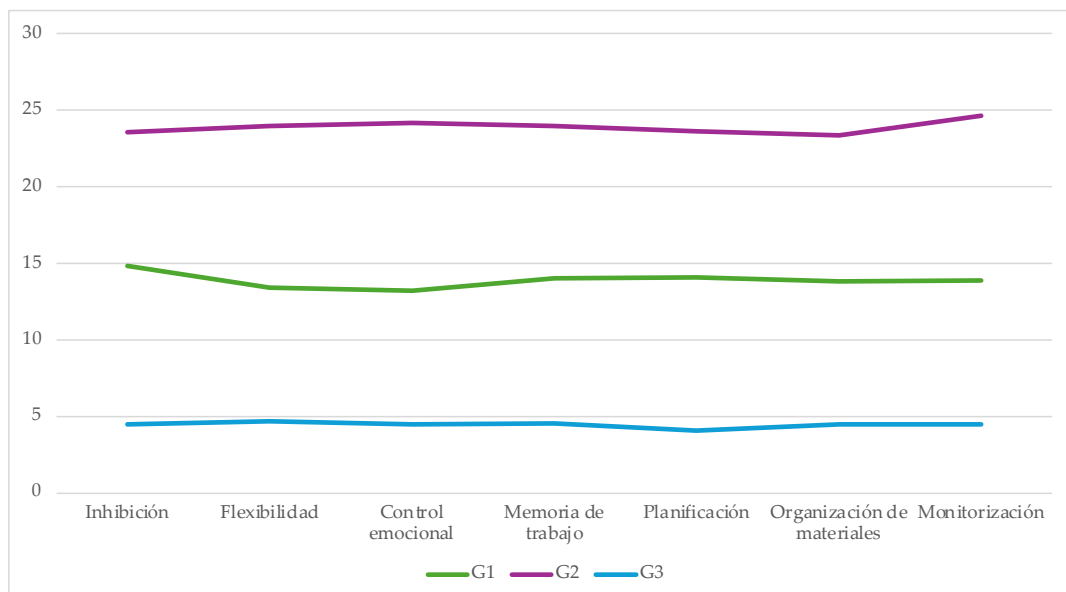
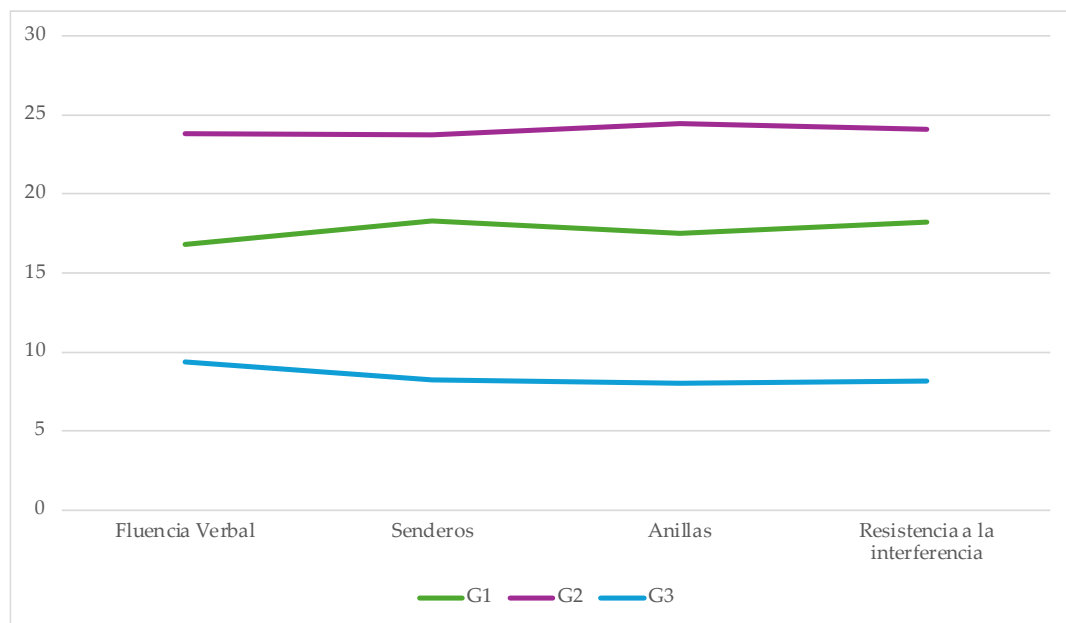


Tabla 8. Diferencias entre los grupos: TEA (G1), Epilepsia (G2) y TEA y epilepsia (G3) en las medidas del funcionamiento ejecutivo obtenidas en la prueba ENFEN.

Funcionamiento ejecutivo	G1 (n = 50)		G2 (n = 50)		G3 (n = 50)		F ₍₈₎	η^2_p	Difference between groups
	M	DT	M	DT	M	DT			
Fluencia Verbal	16.82	3.37	23.84	5.25	9.40	3.37	155.27*	.679	G2 > G1 > G3
Senderos	18.26	3.48	23.74	5.11	8.26	3.16	191.16*	.722	G2 > G1 > G3
Anillas	17.48	3.88	24.46	5.05	8.06	3.01	204.40*	.736	G2 > G1 > G3
Resistencia a la interferencia	18.22	3.77	24.12	5.39	8.20	2.99	185.84*	.717	G2 > G1 > G3

* $p < .05$

Figura 3. Comparación de las puntuaciones medias entre el grupo TEA (G1), el grupo Epilepsia (G2) y el grupo TEA y epilepsia (G3) en las medidas correspondientes a la prueba ENFEN.



Respecto a las competencias en el funcionamiento ejecutivo, los resultados indicaron que las personas con epilepsia presentan puntuaciones superiores en comparación con aquellas que presentan un TEA o un TEA con epilepsia. Todo ello se traduce en que las personas con epilepsia que no cursan con TEA tendrán un mejor rendimiento en los procesos de funcionamiento ejecutivo, permitiendo un mejor desarrollo de las actividades de la vida diaria, así como la autonomía en diferentes contextos como el familiar o el escolar. Es por ende que la condición de diagnóstico de TEA podría ser un factor que perjudique el correcto desarrollo de ciertos procesos del funcionamiento ejecutivo como son la flexibilidad cognitiva, la planificación, la organización, la inhibición o el control emocional entre otros. Estas limitaciones repercuten en el correcto desempeño de las actividades básicas de la vida diaria de diferentes contextos como pueden ser el doméstico, el académico o el social.

No obstante, cuando se presenta de forma comórbida la condición de TEA y epilepsia en la población infantil, las dificultades en el funcionamiento ejecutivo se ven incrementadas debido, principalmente, al daño producido en zonas concretas, como podría ser el lóbulo prefrontal y temporal (Miranda-Casas *et al.*, 2013). Esta afirmación se justifica con investigaciones como la de Pisón *et al.* (2022) en la cual se indica que los niños con un TEA y epilepsia presentan una cognición y funcionamiento ejecutivo más mermado que en aquellas personas con TEA que no presentan esta alteración neurológica. El perfil clínico que describen en su artículo es que esta población suele cursar con graves dificultades para llevar a cabo tareas de procesamiento de la información, control emocional, atención y memoria de trabajo. En la misma línea, el estudio de Barboza Ubarnes *et al.* (2014) muestra que la población infantil con TEA y epilepsia suele tener un patrón sintomatológico en el cual se resaltan dificultades en funcionamiento ejecutivo, concretamente en la memoria de trabajo, el procesamiento de la información verbal y el control emocional. Esto se explica debido a los daños focales en las áreas cerebrales relacionadas con las funciones ejecutivas, es decir, el lóbulo frontal. No obstante, estos trabajos no llevan a cabo un análisis comparativo entre las competencias lingüísticas y de funcionamiento ejecutivo, quedándose en una visión general de las alteraciones que presentan estos perfiles sin aportar datos relacionando ambas competencias. Por lo que las competencias en el funcionamiento ejecutivo podrían ser más pronunciadas en aquellos niños con TEA que tengan, además, asociada una

epilepsia, disminuyendo sus capacidades de flexibilidad cognitiva, planificación, organización, memoria de trabajo, inhibición o control emocional.

En resumen, la población con TEA y epilepsia presenta mayores alteraciones en las funciones ejecutivas relacionadas con la inhibición, la flexibilidad, el control emocional, la memoria de trabajo, la planificación, la organización de materiales y la monitorización, así como en las dimensiones del lenguaje relativas a la fonología, la semántica, la morfosintaxis y la pragmática, con respecto a la población infantil que solo presenta un TEA. Se observa que los niños que cursan con estos tipos de trastornos presentan dificultades en las funciones ejecutivas y en habilidades lingüísticas tanto expresivas como receptivas. Estos desórdenes son explicados a partir de las alteraciones en las competencias cognitivo-lingüísticas, las cuales comprometen el funcionamiento global de la persona.

6.4. COMPARACIÓN DEL PATRÓN EMOCIONAL, CONDUCTUAL Y DE FUNCIONAMIENTO EJECUTIVO ENTRE LA POBLACIÓN INFANTIL CON TEA, EPILEPSIA Y TEA CON EPILEPSIA

Los resultados encontrados en la presente tesis doctoral indicaron que existen diferencias significativas entre las personas con TEA, epilepsia y TEA con epilepsia, destacando un peor rendimiento en tareas relacionadas con el funcionamiento ejecutivo y mayores alteraciones en el patrón emocional y conductual en la población infantil con diagnóstico comórbido entre el TEA y la epilepsia. Todo ello se relaciona con que los menores con TEA que no presentan episodios de epilepsia muestran un menor estado de ansiedad o depresión, y con menos quejas somáticas. Además, estos participantes reportan menos problemas conductuales y atencionales, lo que influye en la correcta realización de las actividades básicas de la vida diaria y una mejor inclusión en los diferentes contextos en donde se desarrollan, en comparación con aquellos niños que presentan un diagnóstico de TEA comórbido a una epilepsia (Tabla 9, Tabla 10 y Tabla 11; y Figura 4 y Figura 5).

Tabla 9. Diferencias entre las medidas de los grupos: TEA (G1), Epilepsia (G2) y TEA con epilepsia (G3) en los problemas conductuales y emocionales interiorizados en la prueba SENA.

Problemas interiorizados	G1 (n = 57)		G2 (n = 60)		G3 (n = 53)		F _(6,92)	η^2_p	Diferencias entre grupos
	M	DT	M	DT	M	DT			
Depresión	13.38	4.41	6.18	2.22	23.74	3.64	304.182*	.785	G2<G1<G3
Ansiedad	13.86	4.33	5.73	2.29	22.18	3.82	245.391*	.746	G2<G1<G3
Ansiedad social	11.42	4.11	6.55	2.10	22.82	4.19	288.063*	.775	G2<G1<G3
Quejas somáticas	13.74	4.27	6.30	2.16	23.26	3.87	287.669*	.775	G2<G1<G3

* $p < .05$

Figura 4. Comparación de las puntuaciones medias entre el grupo TEA (G1), el grupo Epilepsia (G2) y el grupo TEA y epilepsia (G3) en los problemas conductuales y emocionales interiorizados en la prueba SENA.

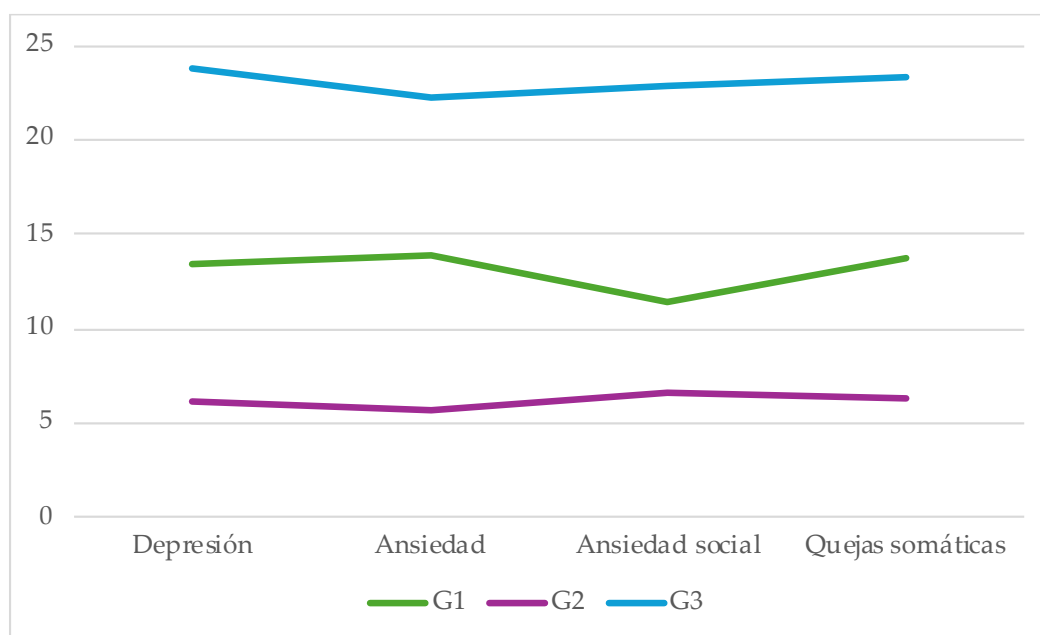


Tabla 10. Diferencias entre las medidas de los grupos: TEA (G1), Epilepsia (G2) y TEA con epilepsia (G3) en los problemas conductuales y emocionales exteriorizados en la prueba SENA.

Problemas exteriorizados	G1 (n = 57)		G2 (n = 60)		G3 (n = 53)		F _(6,92)	η^2_p	Diferencias entre grupos
	M	DT	M	DT	M	DT			
Problemas de atención	11.78	3.43	6.08	2.23	24.48	2.88	237.076*	.740	G2<G1<G3
Hiperactividad-impulsividad	13.70	4.44	6.03	2.40	24.04	2.74	227.424*	.731	G2<G1<G3
Problemas de control de la ira	12.36	4.35	6.32	2.38	24.12	3.05	289.035*	.776	G2<G1<G3
Agresión	14.90	4.41	6.22	2.17	24.44	2.83	286.645*	.774	G2<G1<G3
Conducta desafiante	11.86	4.21	6.37	2.13	22.32	2.91	265.126*	.760	G2<G1<G3

* $p < .05$

Figura 5. Comparación de las puntuaciones medias entre el grupo TEA (G1), el grupo Epilepsia (G2) y el grupo TEA y epilepsia (G3) en los problemas conductuales y emocionales exteriorizados en la prueba SENA.

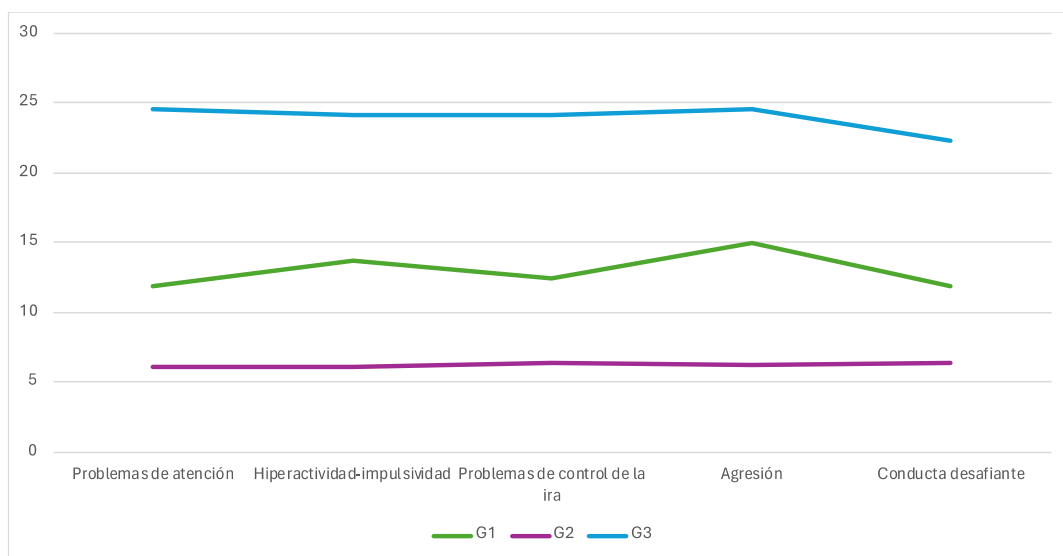


Tabla 11. Diferencias entre las medidas de los grupos: TEA (G1), Epilepsia (G2) y TEA con epilepsia (G3) en el perfil conductual registrados por los padres y los profesores en el BASC-3.

Problemas exteriorizados	G1 (n = 57)		G2 (n = 60)		G3 (n = 53)		F _(6,92)	η ² P	Diferencias entre grupos
	M	DT	M	DT	M	DT			
Puntuaciones de las escalas compuestas, clínicas y adaptativas									
Agresividad	23.18	3.70	28.72	2.91	14.00	4.29	280.136*	.770	G3<G1<G2
Ansiedad	22.76	3.78	28.97	3.37	12.76	4.63	187.522*	.692	G3<G1<G2
Depresión	22.06	3.37	28.32	3.44	11.02	2.99	203.063*	.709	G3<G1<G2
Somatización	21.78	3.74	28.03	2.99	11.62	3.56	247.547*	.748	G3<G1<G2
Atipicidad	20.80	3.48	28.53	2.87	11.14	3.43	200.885*	.706	G3<G1<G2
Retraimiento	20.98	3.60	27.83	3.28	11.12	3.07	217.828*	.723	G3<G1<G2
Problemas de atención	22.44	3.28	28.12	3.13	11.12	2.88	310.423*	.788	G3<G1<G2
Adaptabilidad	21.24	3.05	27.78	3.17	11.16	3.25	256.461*	.754	G3<G1<G2
Habilidades sociales	21.84	3.65	28.00	3.10	11.06	2.69	284.131*	.773	G3<G1<G2
Actividades cotidianas	21.06	3.38	28.40	3.44	11.24	3.31	203.021*	.709	G3<G1<G2
Comunicación funcional	21.86	2.98	28.27	3.08	11.08	3.06	296.367*	.780	G3<G1<G2
Agresividad	23.18	3.70	28.13	3.10	14.00	4.29	210.144*	.795	G3<G1<G2
Ansiedad	22.76	3.78	27.97	3.00	12.76	4.63	187.112*	.785	G3<G1<G2
Depresión	22.06	3.37	27.72	3.21	11.02	2.99	202.123*	.739	G3<G1<G2
Puntuaciones de las escalas de contenido									

<i>Control de la ira</i>	22.32	3.15	28.13	3.10	10.38	2.98	323.198*	.795	G3<G1<G2
<i>Acoso escolar</i>	22.04	3.38	27.97	3.00	9.90	3.05	304.054*	.785	G3<G1<G2
<i>Trastornos del desarrollo social</i>	21.42	3.62	27.72	3.21	11.52	3.33	236.167*	.739	G3<G1<G2
<i>Autocontrol emocional</i>	21.32	3.64	27.58	2.90	11.04	2.55	278.836*	.770	G3<G1<G2
<i>Funcionamiento ejecutivo</i>	21.32	3.82	27.87	3.18	10.08	3.02	247.922*	.748	G3<G1<G2
<i>Emocionalidad negativa</i>	21.28	3.43	27.83	2.96	10.46	3.45	248.719*	.749	G3<G1<G2
<i>Resiliencia</i>	22.04	3.31	28.42	3.06	11.12	3.28	264.604*	.760	G3<G1<G2

* $p < .05$

En una primera instancia, en lo relativo a los problemas emocionales y conductuales interiorizados, los resultados indicaron que en el TEA y en la epilepsia se obtienen medidas inferiores en comparación con el TEA con epilepsia. Cuando se presenta de forma comórbida la condición de TEA y epilepsia en la población infantil, se observa un incremento de las alteraciones emocionales y de estado depresivo en este tipo de perfiles debido a factores genéticos, ambientales y de la propia etiología del trastorno (Maskey *et al.*, 2013). Estos datos se pueden corroborar con estudios publicados como el de Tseng *et al.* (2011) en el cual se concluye que los niños con TEA y epilepsia son más propensos a desarrollar trastornos emocionales y de conducta que otros trastornos del neurodesarrollo. El perfil clínico que se describe en esa investigación nos informa que las personas con TEA y epilepsia presentan un mayor estado de ansiedad y de depresión, con dificultades en la socialización debido a problemas de ansiedad social. En la misma línea podemos mencionar el trabajo de Canitano (2007), en el que se realiza una descripción pormenorizada de las características emocionales que presentan los niños que presentan un TEA junto a una epilepsia. En él se describe que los niños que presentan estos trastornos muestran graves alteraciones en la regulación de sus emociones, baja tolerancia a la frustración, así como dificultades en la resolución de conflictos sociales de manera efectiva.

El presente estudio va en la línea de lo encontrado en la literatura científica, puesto que en varios artículos de investigación (Canitano *et al.*, 2005; Nordin y Gillberg, 1996; Tuchman *et al.*, 2010) se señala la presencia de manera general de alteraciones emocionales relacionadas con ansiedad y depresión en los niños que presentan un solo un TEA, epilepsia o TEA con epilepsia, pero no se llega a comparar ambas condiciones de forma pormenorizada. Los resultados de esta investigación indican que las personas con epilepsia muestran ligeras alteraciones en las dimensiones de depresión, ansiedad, ansiedad social y quejas somáticas, con respecto a los otros dos grupos de personas (TEA y TEA con epilepsia), cuyas dificultades son más notorias. Todo ello explica que el TEA sea una condición que implica un empeoramiento significativo en estos problemas conductuales y emocionales, siendo el trastorno determinante en la limitación del estado ansioso y depresivo de esta población infantil. Por ende, los problemas interiorizados relacionados con la ansiedad y la depresión en la población con TEA que además presente epilepsia limitan significativamente el desarrollo madurativo, así como la adaptación al entorno del menor con este perfil clínico.

En una segunda instancia, en lo referente a los problemas emocionales y conductuales exteriorizados, los resultados de la presente tesis doctoral reflejan que el TEA con epilepsia presenta unas puntuaciones superiores a las que se presentan en el TEA y en la epilepsia. Las personas con TEA y epilepsia muestran mayores dificultades en los procesos de atención, conducta hiperactiva o impulsiva, dificultades para controlar la ira, episodios de agresividad y conducta desafiante mucho más pronunciadas que en aquella población infantil que solo presenta un TEA o una epilepsia (Tuchman, 2002). El perfil conductual de los niños que cursan solo con un TEA o una epilepsia se corresponde con altas limitaciones en la flexibilidad cognitiva, la autorregulación emocional (Mira *et al.*, 2019), el control de los impulsos (Tárraga-Mínguez *et al.*, 2021), o incluso, la aparición de conductas de agresivas (Serna y Gallegos, 2021), aunque en aquellos perfiles que solo cursan con epilepsia se observa una ligera mejoría en estos síntomas.

Estos datos dan a entender que la población con TEA y epilepsia esté más limitada en su control emocional y suele presentar más conductas disruptivas y, por tanto, exige tener consideraciones especiales en la atención de esta población. Esta afirmación se puede corroborar en estudios como los de del Barrio y Carrasco (2016), Juillerat *et al.* (2015) y Mena-Chamorro y Caqueo-Úrizar (2020) en los cuales

se realizó un análisis de los problemas emocionales y conductuales exteriorizados en la población infantil con TEA o TEA con epilepsia. Los resultados de estos estudios indicaron que existe una mayor alteración emocional y conductual exteriorizada en los niños con TEA y epilepsia frente a aquellos que no presentan esta comorbilidad. En TEA, el problema en el control emocional y aparición de ansiedad social radica en la dificultad para demostrar empatía, o reconocer las emociones del otros, lo que genera dificultades en los vínculos sociales, afectación en la calidad de vida tanto para el niño como para las figuras parentales o significativas, eso además puede observarse en los primeros años de vida, al evidenciarse que el niño no presenta ningún tipo de apego con los padres (Maseda, 2013). Asimismo, el control emocional y conductual, en el TEA, el cual promueve una adaptación a los comportamientos, se ve afectado porque los niños generalmente no utilizan estrategias emocionales o de adaptación, lo que quiere decir, que las reacciones generalmente tienden a ser impulsivas, irritantes, compuesta por agresiones, berrinches o autolesiones, que a su vez pueden considerarse como desafiantes. Además, la empatía se ve afectada, debido que es uno de los componentes que permite que la persona entiende tanto sus propias emociones como las demás (Mazefsky *et al.*, 2013). El presente estudio profundiza en las limitaciones emocionales y conductuales en la población infantil con TEA y epilepsia, llevando a cabo un análisis pormenorizado de estas alteraciones y describiendo un perfil sintomatológico en comparación con aquellos niños que no presentan este trastorno combinado con la epilepsia.

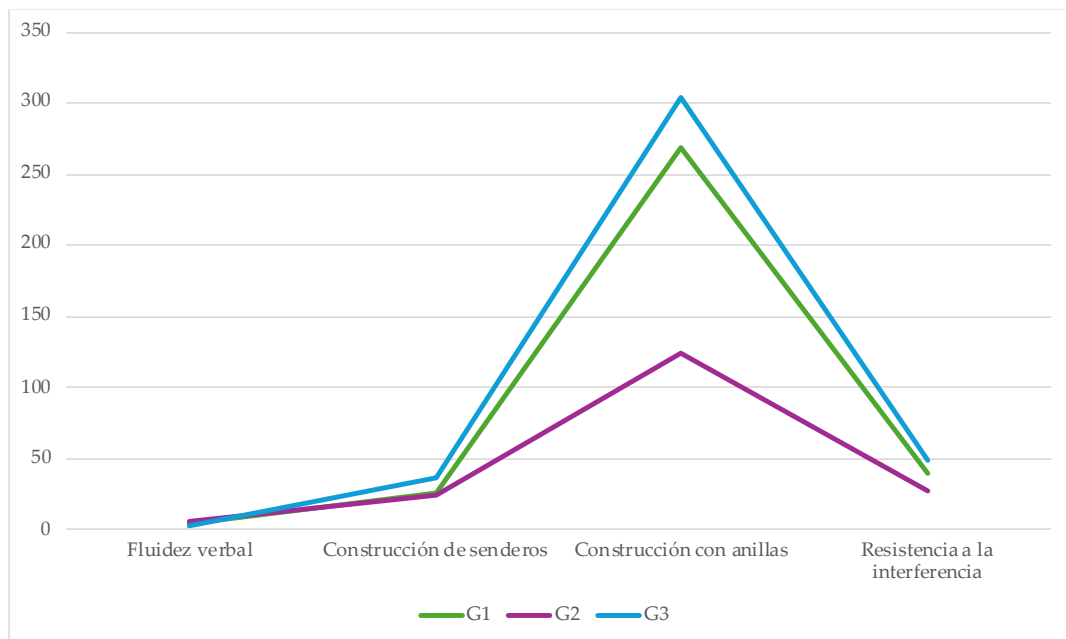
Por último, en lo relativo al funcionamiento ejecutivo, los resultados del presente estudio revelan que las personas con diagnóstico de TEA con epilepsia presentan mayores alteraciones a las mostradas en el TEA y en la epilepsia (Tabla 12 y Figura 6). Estos datos se pueden interpretar en que las personas con TEA que cursan con epilepsia tienen mayores dificultades en el acceso al léxico funcional, así como en el seguimiento de una actividad con altos niveles de atención sostenida, selectiva y dividida, con alternancia de tareas.

Tabla 12. Diferencias entre las medidas los grupos: TEA (G1), y Epilepsia (G2) y TEA con epilepsia (G3) en las medidas de funcionamiento ejecutivo en el ENFEN.

Funcionamiento ejecutivo	G1 (n = 57)		G2 (n = 53)		G3 (n = 60)		F _(6,92)	η^2_p	Diferencias entre grupos
	M	DT	M	DT	M	DT			
Fluidez verbal	4.90	1.17	5.40	1.16	2.38	1.48	87.33*	.511	G3<G1<G2
Construcción de senderos	25.78	3.17	24.83	8.17	36.45	6.91	56.20*	.402	G1,G2<G3
Construcción con anillas	268.97	84.83	123.58	67.40	303.32	24.27	119.11*	.588	G2<G1<G3
Resistencia a la interferencia	39.34	4.48	27.92	3.89	48.76	5.01	122.50*	.595	G2<G1<G3

* $p < .05$

Figura 6. Comparación de las puntuaciones medias entre el grupo TEA (G1), el grupo Epilepsia (G2) y el grupo TEA y epilepsia (G3) en las medidas de funcionamiento ejecutivo en el ENFEN.



Dichos resultados van en consonancia con los estudios de Artigas (1999), Aparicio y Aguirre-García (2011) y García-Peñas (2009), en los cuales se describen las características conductuales y emocionales de las personas que cursan TEA y epilepsia. En ellos se indica que la población infantil con esta comorbilidad muestra severas alteraciones en la gestión emocional, así como dificultades en la conductuales, lo que afecta significativamente a algunas habilidades como la capacidad de planificación y la flexibilidad cognitiva. Asimismo, la población infantil con TEA y epilepsia muestra alteraciones en el funcionamiento ejecutivo, lo que implica una aparición de dificultades en la autorregulación emocional y conductual, el lenguaje, la alternancia de tareas, la velocidad de procesamiento y la planificación. Todo ello va en la misma línea que los estudios realizados por Pison et al. (2022) y Mulas et al. (2001). En estos trabajos se han explorado las funciones ejecutivas en varios trastornos del neurodesarrollo, entre ellos el TEA, y se describen alteraciones significativas en la planificación, inhibición y control emocional, que se ven mermadas por la coexistencia de la epilepsia en estos perfiles clínicos. Estas alteraciones repercuten negativamente en la correcta gestión de las emociones, así como en la aplicación de estrategias de autorregulación que incitan a la persona con este trastorno al desarrollo de conductas agresivas o violentas para solventar situaciones de conflicto, además de mostrar una conducta impulsiva en los entornos en donde se desarrolla como el ámbito escolar y doméstico.

En resumen, la población con TEA y epilepsia presenta mayores problemas emocionales y conductuales interiorizados relacionados con la depresión, la ansiedad, ansiedad social y quejas somáticas, así como mayores problemas emocionales y conductuales exteriorizados relativos a problemas atencionales, hiperactividad o impulsividad, problemas en el control de la ira, agresividad y conducta desafiante, con respecto a la población infantil que solo presenta un TEA o una epilepsia. Estos desórdenes son explicados a partir de las alteraciones en las competencias emocionales y conductuales, las cuales comprometen el funcionamiento global de la persona.

6.5. COMPARACIÓN DEL PROCESAMIENTO Y LA COMPRENSIÓN AUDITIVA ENTRE LA POBLACIÓN INFANTIL CON TEA, EPILEPSIA Y TEA CON EPILEPSIA

En la presente tesis doctoral, los resultados obtenidos indican que las personas con epilepsia muestran un mejor rendimiento que los otros dos colectivos (Tabla 13 y Figura 7).

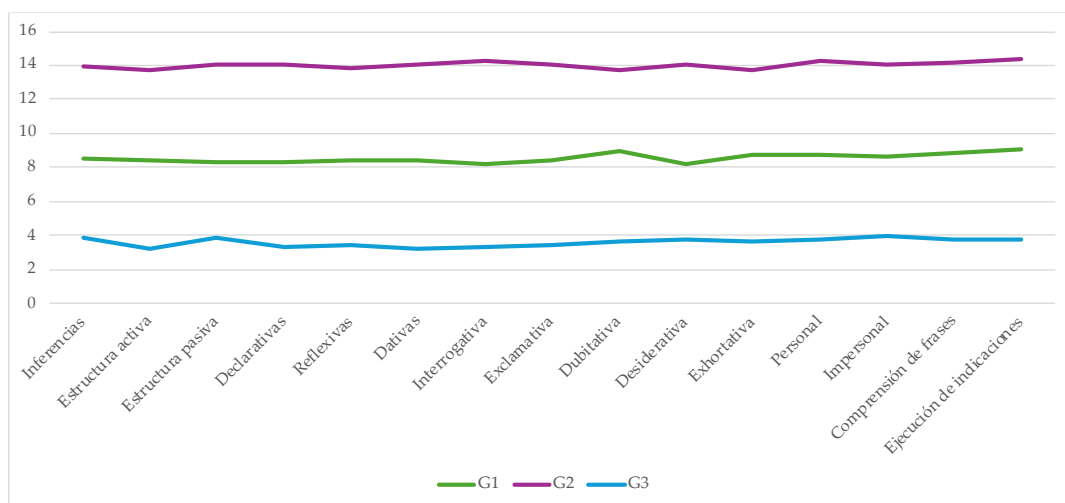
Tabla 13. *Diferencias entre las medidas de los grupos: TEA (G1), Epilepsia (G2) y TEA con epilepsia (G3) en la comprensión de estructuras gramaticales de las pruebas CEG y CELF-5.*

Comprensión de estructuras gramaticales	G1 (n = 57)		G2 (n = 60)		G3 (n = 53)		F _(2,167)	η ² _p	Diferencias entre grupos
	M	DT	M	DT	M	DT			
	Variables comprendidas en la prueba CEG								
<i>Inferencias</i>	8.53	2.458	13.95	1.926	3.85	1.598	349.697*	.807	G2<G1<G3
<i>Estructura activa</i>	8.39	2.313	13.73	2.049	3.23	1.728	370.045*	.816	G2<G1<G3
<i>Estructura pasiva</i>	8.32	2.293	14.10	2.121	3.87	1.744	347.017*	.806	G2<G1<G3
<i>Declarativas</i>	8.33	2.030	14.02	2.029	3.32	1.837	416.255*	.833	G2<G1<G3
<i>Reflexivas</i>	8.42	2.236	13.85	2.057	3.45	1.749	370.252*	.816	G2<G1<G3
<i>Dativas</i>	8.46	2.164	14.00	1.957	3.23	1.739	423.763*	.835	G2<G1<G3
<i>Interrogativa</i>	8.23	2.053	14.27	1.831	3.38	1.643	490.018*	.854	G2<G1<G3
<i>Exclamativa</i>	8.46	2.465	14.00	2.099	3.45	1.716	348.517*	.807	G2<G1<G3
<i>Dubitativa</i>	8.98	2.272	13.73	1.840	3.68	1.718	369.841*	.816	G2<G1<G3
<i>Desiderativa</i>	8.19	2.560	14.00	2.131	3.74	1.631	324.219*	.795	G2<G1<G3
<i>Exhortativa</i>	8.77	2.260	13.75	2.055	3.70	1.917	327.132*	.797	G2<G1<G3
<i>Personal</i>	8.72	2.234	14.23	1.826	3.72	1.634	424.304*	.836	G2<G1<G3
<i>Impersonal</i>	8.60	2.404	14.00	1.957	4.00	1.687	339.093*	.802	G2<G1<G3

Variables comprendidas en la prueba CELF-5									
Comprensión de frases	8.88	2.398	14.12	2.210	3.81	1.688	329.722*	.798	G2<G1<G3
Ejecución de indicaciones	9.11	2.425	14.35	1.921	3.77	1.552	391.354*	.824	G2<G1<G3

* $p < .05$

Figura 7. Comparación de las puntuaciones medias entre el grupo TEA (G1), el grupo Epilepsia (G2) y el grupo TEA y epilepsia (G3) en la comprensión de estructuras gramaticales de las pruebas CEG y CELF-5.



En las habilidades de la comprensión de estructuras gramaticales se encuentran diferencias significativas entre las tres condiciones: TEA, epilepsia y TEA con epilepsia. Estos datos no se pueden confirmar con otras investigaciones debido a que no existen estudios en los cuales se compare el rendimiento en la comprensión de estructuras gramaticales en estos tres condiciones, pero, sí que se puede confirmar estos resultados con otros trabajos realizados con estos grupos de forma independiente (Asberg, 2010; Baixauli *et al.*, 2020; Eigsti *et al.*, 2007; Eberhardt y Nadig, 2018; Henry y Solari, 2020; Saban-Bezael y Mashal, 2015) y que confirman su contribución a los problemas comunicativos que presentan estos tres trastornos, con diferentes rendimientos en estas habilidades en función de este.

En cuanto a la población infantil con epilepsia, en el ámbito de la comprensión de estructuras gramaticales no existe consenso respecto a las habilidades alteradas, ya que algunas tareas presentadas como deterioradas en algunos estudios, aparecen como preservadas en otros. Sin embargo, parece haber un mayor predominio de un peor desempeño en tareas que involucran habilidades sintácticas, como completar y producir oraciones, comprensión de oraciones ambiguas, asociación de oración e imagen y comprensión de estructuras sintácticas complejas (Bulteau *et al.*, 2015; Skotko *et al.*, 2008). Si bien estudios previos han analizado ampliamente las habilidades de comprensión de este tipo de estructuras con respecto a la dimensión de la comprensión morfosintácticas de estos niños, no se observan datos significativos que permitan establecer un perfil lingüístico concreto (Cohen y Le Normand, 1998; Ménard *et al.*, 2000). A nivel de comprensión verbal, muestran problemas en cuanto a la comprensión de mensajes verbales, teniendo que solicitar la repetición de la información, proporcionar respuestas/información correcta y reformular mensajes para que la capacidad de retención y comprensión sea óptima (Teixeira y Santos, 2018). En nuestro estudio, se observa un rendimiento deficiente en las variables relativas a la comprensión de estructuras gramaticales, sobre todo en aquellas que implican o se relacionan con habilidades de funcionamiento ejecutivo como son la comprensión de inferencias, enunciados reflexivos y la ejecución de indicaciones. Todo ello se explica debido a los daños que presenta esta población en zonas como el lóbulo frontal y las redes que conectan este lóbulo con el temporal, principal zona encargada de la comprensión del lenguaje oral (Ballester-Plané *et al.*, 2018). Así pues, las personas con epilepsia cuentan con una velocidad de procesamiento enlentecida que también dificulta la comprensión efectiva de los enunciados gramaticales (Caplan *et al.*, 2009). No obstante, aunque esta población presenta dificultades en estas habilidades, su rendimiento será superior a los que se observan en otros trastornos del neurodesarrollo como en el caso del TEA (Debiais *et al.*, 2007).

Con respecto a las personas diagnosticadas de TEA, la literatura científica actual indica que estos perfiles clínicos cursan con alteraciones tanto en la expresión como en la comprensión del lenguaje. Por ejemplo, Eigsti y Bennetto (2007) observan trastornos gramaticales en la mayoría de los niños con TEA, entre 9-17 años, en tareas de juicio gramatical. En nuestro estudio, las estructuras que resultan más difíciles para los niños con TEA son las que no siguen el orden estructural

común, sujeto-verbo-predicado (SVP), como las oraciones coordinadas o las de relativo, en las que todos estos niños fallan. Por el contrario, las estructuras más fáciles son las de SVP, con aciertos del 60%, seguidas de las atributivas, con un 30% de aciertos (Barsotti *et al.*, 2020). Swensen *et al.* (2007) también afirman que los niños con TEA comprenden frases en este orden, SVP, antes de producir habla continua. Estos resultados demuestran las dificultades que presentan los niños con TEA, limitándoles la comprensión de los mensajes verbales de los principales agentes de su entorno, lo que les impide llevar a cabo una comunicación funcional y poder entablar una conversación más compleja, más allá de sus intereses o motivaciones personales. Por ello, las dificultades en la comprensión verbal influyen negativamente en las habilidades comunicativas de la persona con TEA, así como en la calidad de vida, lo que perjudica gravemente su inclusión en los contextos de desarrollo de esta población (Tovar *et al.*, 2015).

Por último, la población infantil con TEA y epilepsia muestra graves alteraciones en las competencias del lenguaje receptivo, entre las que se encuentra la comprensión de las estructuras gramaticales del lenguaje oral (Cano-Villagrasa *et al.*, 2023). Hasta la fecha, no se dispone de ningún trabajo sobre estructuras gramaticales del español en población infantil con TEA y epilepsia. Los resultados, por tanto, muestran que la comprensión del lenguaje –y especialmente las estructuras gramaticales– es una de las áreas de debilidad en TEA y epilepsia que puede contribuir a explicar los déficits comunicativos encontrados. Debido a que existe muy poca evidencia sobre las alteraciones gramaticales, algunos autores consideran que esta área de investigación es una de las que más potencial de exploración tiene a corto plazo (Kanner y Bicchi, 2022). En el presente estudio, el grupo de participantes que cursan con TEA y epilepsia muestran el peor rendimiento en tareas de comprensión de estructuras gramaticales de los tres grupos que conforman esta investigación. Una de las explicaciones más plausibles que permitirían describir la obtención de estos resultados sería que la condición de epilepsia, añadida al diagnóstico de TEA supone un incremento de las dificultades en las competencias lingüísticas, sobre todo en las relacionadas con el lenguaje receptivo (Stefanski *et al.*, 2021). Al existir un compromiso en el funcionamiento ejecutivo en dimensiones lingüísticas como el léxico, la morfología y la pragmática, es lógico pensar que la comprensión verbal de estructuras gramaticales también está comprometida, principalmente por los problemas existentes en el seguimiento

de las conversaciones y de instrucciones, lo que influye negativamente en sus habilidades lingüísticas (Montouris *et al.*, 2020).

En resumen, los resultados respaldan la noción de un mejor desempeño en las personas con epilepsia, seguido por el TEA, mientras que en aquellas personas con ambas condiciones se evidenció el rendimiento más bajo. Estas discrepancias tienen implicaciones notables para la comunicación y la calidad de vida de las personas afectadas. Además, subrayan la necesidad de futuras investigaciones que profundicen en la comprensión de las alteraciones gramaticales en estos trastornos y su relación con otros aspectos cognitivos y lingüísticos. En última instancia, estos hallazgos respaldan la importancia de desarrollar enfoques terapéuticos y programas educativos personalizados para abordar las necesidades específicas de estos grupos de niños.

6.6. PROTOCOLO PARA LA EVALUACIÓN DEL LENGUAJE, LA COGNICIÓN Y EL PERFIL SENSORIAL DE LA PERSONA CON TEA Y EPILEPSIA

En la presente tesis doctoral, se propone un protocolo de evaluación de las competencias lingüísticas, cognitivas y del perfil sensorial en las personas con TEA y epilepsia. Este protocolo comprende instrumentos de medida como el CELF-5, el ENFEN, el PROLEC-R, la WISC-V y el SP-2 (Tabla 14).

Tabla 14. *Protocolo de evaluación de las competencias lingüísticas, cognitivas y de perfil sensorial de la persona con TEA y epilepsia.*

Evaluación de las competencias de lenguaje
CELF-5. Evaluación Clínica de los Fundamentos del Lenguaje – 5 (CELF-5; Wiig <i>et al.</i> , 2019)
La Batería de Evaluación de los Procesos Escritores Revisada (PROESC-R; Cuetos <i>et al.</i> , 2018)
Evaluación de los procesos cognitivos y el funcionamiento ejecutivo
Wechsler Intelligence Scale for Children - Fifth Edition (WISC-V; Wechsler, 2016).
ENFEN. Evaluación Neuropsicológica de las Funciones Ejecutivas en Niños (ENFEN; Portellano <i>et al.</i> , 2009)

Evaluación del perfil sensorial

Sensory Profile-2 (PS-2; Romero-Ayuso *et al.*, 2016)

La selección de instrumentos de evaluación para personas con TEA y epilepsia se fundamenta en la necesidad de comprender las complejidades de sus perfiles lingüísticos, cognitivos y sensoriales. Estos instrumentos son escogidos por su capacidad para proporcionar una evaluación integral y precisa de las habilidades y necesidades de estas personas, permitiendo así una intervención adecuada y centrada en cada individuo.

La selección de instrumentos de evaluación para personas con TEA y epilepsia es esencial para comprender en profundidad sus perfiles lingüísticos, cognitivos y sensoriales. Entre estos instrumentos se encuentra el CELF-5, diseñada para identificar y diagnosticar trastornos del lenguaje y la comunicación en niños y adolescentes. Su enfoque individualizado permite una evaluación detallada de la comprensión y expresión del lenguaje, aspectos cruciales para esta población. Asimismo, la Batería de Evaluación de los Procesos Lectores Revisada (PROLEC-R) es crucial para evaluar los procesos relacionados con la lectura, comunes en individuos con TEA y epilepsia. Esta batería proporciona una evaluación exhaustiva de diferentes aspectos de la lectura, lo que permite una comprensión completa de las habilidades lectoras de cada individuo y guía la planificación de intervenciones específicas.

Otro instrumento relevante es la WISC-IV, utilizada para evaluar la capacidad cognitiva e inteligencia en niños y adolescentes. Dado que estas personas pueden presentar una variedad de perfiles cognitivos, el WISC-IV ofrece una evaluación detallada de diferentes áreas cognitivas, lo que permite una comprensión profunda de su funcionamiento cognitivo. Además, el ENFEN se enfoca en evaluar el rendimiento cognitivo en actividades relacionadas con las funciones ejecutivas, aspectos cruciales para el funcionamiento adaptativo en la vida diaria.

Finalmente, el Sensory Profile-2 (PS-2) es una herramienta valiosa para evaluar los patrones de procesamiento sensorial en niños y adolescentes con TEA y epilepsia. Dado que estas personas pueden presentar sensibilidades sensoriales atípicas, el PS-2 proporciona una evaluación detallada de cómo estas diferencias

sensoriales pueden afectar su participación en actividades cotidianas. En conjunto, estos instrumentos permiten una evaluación integral y precisa de las habilidades y necesidades de las personas con TEA y epilepsia, lo que contribuye a mejorar su calidad de vida y su funcionamiento en la vida diaria.

En la actualidad, no existen protocolos actualizados y específicos para la evaluación de los procesos lingüísticos, cognitivos y sensoriales en las personas con TEA y epilepsia. La literatura científica actual no establece un protocolo eficaz y probado empíricamente, puesto que hay una escasa evidencia de investigaciones publicadas que abarquen esta condición. Todas estas disfunciones en el perfil lingüístico, cognitivo y sensorial de la población infantil con TEA y epilepsia repercuten negativamente en el desarrollo madurativo del menor. Por lo que esta situación sintomatológica es de gran interés para los sistemas de salud nacionales e internacionales, puesto que la prevalencia de esta comorbilidad ha aumentado de manera exponencial en las últimas décadas (Lee *et al.*, 2015). Europa es una de las regiones mundiales con menor prevalencia de TEA y epilepsia, por lo que la Organización Mundial de la Salud estima que hay aproximadamente 6 millones de europeos afectados a lo largo de 53 países con una prevalencia media de 8,2 afectados por cada 1.000 habitantes (Tuchman *et al.*, 2010), y una incidencia de alrededor de 300.000 nuevos casos diagnosticados cada año (Sharma *et al.*, 2022). En cuanto a prevalencia se refiere, algunos estudios epidemiológicos destacan que el 80% de las personas que presentan TEA con epilepsia son niños menores de 10 años y otro 20% son adolescentes de edades comprendidas entre los 12 y los 15 años. Sin embargo, existe una alta probabilidad de sesgo en estos datos debido a las limitaciones en las evaluaciones de la epilepsia en la población infantil con TEA, puesto que, según varios estudios, el diagnóstico se realiza de forma tardía (Francis *et al.*, 2013).

De esta manera, la comorbilidad entre el TEA y la epilepsia se convierte en una condición con una prevalencia relativamente alta, con un difícil diagnóstico y que cursa con alteraciones significativas que merman competencias fundamentales como el lenguaje, la cognición y el perfil sensorial (El Achkar *et al.*, 2015). Todo ello repercute negativamente en el desarrollo madurativo infantil, perjudicando la calidad de vida de las personas con esta comorbilidad y aumentando la exigencia de la detección de los profesionales del ámbito sanitario (Anukirthiga *et al.*, 2019). La detección precoz de la epilepsia en niños con TEA se conforma como un aspecto

fundamental en las unidades de neuropediatría de nuestro país, ya que permite que los profesionales de la salud puedan diseñar una intervención temprana con el objetivo de mejorar significativamente el pronóstico del niño (Chen *et al.*, 2022). Además de ello, la detección temprana de la epilepsia en esta población permitiría reducir el retroceso en el desarrollo de las habilidades lingüísticas, cognitivas y de perfil sensorial de este colectivo (Pastorino *et al.*, 2021). Los protocolos de evaluación internacional de esta comorbilidad (Sharma *et al.*, 2022) incluyen en el proceso de diagnóstico la medición de alteraciones en el lenguaje y la comunicación, la inteligencia, el aprendizaje, así como la realización de pruebas de neuroimagen como electroencefalogramas (EEG) para detectar actividad epiléptica subyacente. La colaboración interdisciplinaria entre neurólogos, pediatras y especialistas en TEA es esencial para garantizar un diagnóstico preciso y la implementación de un plan de tratamiento adecuado y personalizado (Ewen *et al.*, 2019).

6.7. EL TRATAMIENTO FARMACOLÓGICO EN LAS PERSONAS CON TEA Y EPILEPSIA

En la presente tesis doctoral, se destacan una serie de fármacos que han resultado efectivos para la población pediátrica con TEA y epilepsia. Actualmente, los avances en nuestra comprensión de la biología molecular del TEA y de la epilepsia ahora permiten conceptualizar estrategias de intervención que pueden cambiar positivamente la trayectoria del desarrollo tanto del TEA como de la epilepsia. Un enfoque emergente para dirigirse más específicamente al fenotipo TEA-epilepsia se basa en la comprensión de que las anomalías de la estructura y función sinápticas son centrales en la base cerebral del TEA y de la epilepsia.

El tratamiento farmacológico de elección en la población pediátrica con TEA y epilepsia es complejo y requiere un enfoque interdisciplinario para su manejo. Especialistas en neurología, pediatría y psiquiatría deben diseñar un plan de tratamiento personalizado para abordar las necesidades del niño (Berg *et al.*, 2010).

Sin embargo, como se mencionó anteriormente, la comorbilidad de TEA y epilepsia presenta una amplia gama de síntomas asociados en individuos con este diagnóstico (Rubio *et al.*, 2016). Por lo tanto, el cuidado farmacológico para esta

población se vuelve significativamente complejo. Según varias revisiones sistemáticas de la literatura, el plan de tratamiento comienza con el manejo de los síntomas relacionados con el TEA mediante medicamentos que ayudan a reducir o aliviar estos síntomas (Volpe, 1989). Varios estudios hacen referencia a la administración de fármacos como antipsicóticos o antidepresivos para abordar las características semiológicas que aparecen en este trastorno (Liu *et al.*, 2022; Mizrahi y Kellaway, 1987). La Tabla 15 proporciona una lista de las alteraciones más comunes en el TEA y su tratamiento farmacológico.

Tabla 15. *Tratamiento farmacológico de síntomas asociados con el TEA*

Síntomas	Medicamentos Disponibles
Síntomas de comportamiento, inquietud, autoagresión	Antipsicóticos, Anticonvulsivantes
Problemas de socialización	Oxitocina, D-cicloserina, Memantina (experimental)
Trastornos del sueño	Melatonina, Antipsicóticos, Antihistamínicos
Trastorno por déficit de atención e hiperactividad (TDAH)	Atomoxetina, Metilfenidato, Anfetaminas, Desmetilamfetaminas, Guanfacina
Tics	Antipsicóticos, Agonistas de α_2 , Inhibidores selectivos de la recaptación de serotonina (ISRS)
Depresión	Inhibidores selectivos de la recaptación de serotonina (ISRS), Inhibidores selectivos de la recaptación de serotonina y noradrenalina (ISRSN) + Antipsicóticos
Ansiedad y Trastorno Obsesivo Compulsivo (TOC)	Inhibidores selectivos de la recaptación de serotonina (ISRS) (dosis altas), Pregabalina
Psicosis	Antipsicóticos

Del mismo modo, el foco central de varias investigaciones detalla que los síntomas típicos de la epilepsia en esta población también deben abordarse (Liu *et*

al., 2022; Popow *et al.*, 2021). Estos medicamentos funcionan reduciendo o previniendo la actividad eléctrica anormal en el cerebro que conduce a convulsiones (Boesen *et al.*, 2023). Actualmente, hay diferentes medicamentos disponibles, y su selección depende del tipo de convulsión, la edad del niño y la salud general (Rapin y Tuchman, 2008). Estos medicamentos a menudo se usan en combinación con otros tipos de medicamentos como ansiolíticos, antipsicóticos y antidepresivos, según los síntomas epilépticos y la gravedad de los episodios de epilepsia que experimenta la persona (Orlova y Crino, 2010). La Tabla 16 detalla los principales medicamentos para tratar episodios epilépticos basados en los síntomas presentados por individuos con TEA y epilepsia.

Tabla 16. Tratamiento farmacológico preferido para abordar la epilepsia en la población pediátrica con TEA

Medicamento	Efecto Adverso
Fenobarbital	Somnolencia, sedación, astenia, apatía e incoordinación visuomotora. Alteraciones de memoria y atención
Primidona	Somnolencia, sedación, astenia, apatía e incoordinación visuomotora. Alteraciones de memoria y atención
Fenitoína	Somnolencia, confusión, descompensación paradójica de la epilepsia, déficit de atención, hiperactividad, trastornos del comportamiento o problemas de aprendizaje
Etosuximida	Somnolencia, pensamiento lento, síndrome de confusión o psicosis aguda
Carbamazepina	Sedación, somnolencia, ansiedad, incoordinación visuomotora, déficit de atención, hiperactividad, trastornos del comportamiento o problemas de aprendizaje
Valproato de Sodio	Somnolencia, irritabilidad, trastornos del sueño o incoordinación motora
Benzodiacepinas, clonazepam, clobazam	Somnolencia, lentitud mental, incoordinación visuomotora, hipercinesia, impulsividad, insomnio, delirios, deterioro cognitivo crónico en la atención, memoria y concentración
Lamotrigina	Somnolencia, astenia o insomnio. Alteraciones cognitivas

Gabapentina	Irritabilidad, hipercinesia, agitación, agresión e insomnio
Pregabalina	Somnolencia e incoordinación visuomotora. Sin alteraciones cognitivas
Oxycarbazepina	Somnolencia e incoordinación visuomotora. Sin alteraciones cognitivas
Levetiracetam	Comportamiento disruptivo, hiperactividad, impulsividad y agresión
Lacosamida	Fallas en la coordinación visuomotora
Estiripentol	Somnolencia, incoordinación visuomotora, irritabilidad e insomnio
Acetato de Eslicarbazepina	Somnolencia e incoordinación visuomotora. Sin alteraciones cognitivas
Perampanel	Somnolencia e incoordinación visuomotora

Además de establecer la dosis correcta y la administración efectiva de medicamentos en la población pediátrica con TEA y epilepsia, otro desafío significativo enfrentado por los profesionales de la salud es la alta interacción entre los medicamentos descritos anteriormente (Kanner y Bicchi, 2022; Weichhart, 2012). Considerando los hallazgos de varios estudios, que demuestran que los medicamentos antipsicóticos tienen reacciones significativas e interacciones medicamentosas con otros medicamentos psiquiátricos (Gözükızıl *et al.*, 2022), como anticonvulsivantes y estabilizadores del ánimo, incluyendo principalmente la carbamazepina, es importante reconocer que no todas estas interacciones ocurren de manera negativa (Cameron *et al.*, 2018). Identificar las consecuencias de tales combinaciones es muy relevante, ya que, en algunos casos, pueden desarrollarse reacciones adversas graves. Esto se ejemplifica con la descripción de De León *et al.* (2012) de las interacciones entre antiepilépticos y antipsicóticos de segunda generación que pueden llevar a casos excepcionales de pancreatitis, agranulocitosis/leucopenia y golpe de calor. Además, Hitchings (2016), en un estudio de revisión, sugiere que los antipsicóticos, al reducir el efecto antiepiléptico de estos fármacos, pueden inducir el desarrollo de convulsiones.

Además, se considera que la clozapina disminuye el umbral de convulsiones y está asociada con alteraciones electroencefalográficas dependientes de la dosis, afectando las convulsiones en un 3-6% de los pacientes tratados con clozapina. Sin embargo, se percibe la necesidad de ampliar el alcance de la investigación sobre este tema. No obstante, autores como Asenjo Lobos *et al.* (2010) describen resultados favorables en la terapia combinada con el uso de antipsicóticos en pacientes con respuesta parcial, según lo informado en algunos estudios de doble ciego. Estas combinaciones incluyen olanzapina más litio o valproato, risperidona más litio o valproato, haloperidol más litio o valproato y quetiapina más litio o valproato. Del mismo modo, la terapia combinada en pacientes con TEA y epilepsia con respuesta parcial ha demostrado ser efectiva en algunos estudios abiertos, como olanzapina y litio, valproato o carbamazepina; risperidona más litio o valproato y quetiapina más litio o valproato (Tuchman, 2017). Sin embargo, se aconseja la administración simultánea de estos medicamentos con precaución, ya que pueden aparecer síntomas tóxicos a dosis altas, o síntomas maníacos agudos, efectos extrapiramidales, trastornos fisiológicos o daño cerebral (Kokoszka *et al.*, 2017; Zahra *et al.*, 2022).

6.8. LA INTERVENCIÓN DEL LENGUAJE Y LA COMUNICACIÓN EN LAS PERSONAS CON TEA Y EPILEPSIA

Los hallazgos de este estudio proporcionan una profunda reflexión sobre las dificultades actuales en el mejoramiento de las habilidades comunicativas, así como de aquellas asociadas, como las funciones ejecutivas, las cuales muestran una grave alteración en la población infantil con TEA y epilepsia (Boster y McCarthy, 2018). Además, se señalan protocolos de acción efectivos para la evaluación e intervención a través de Sistemas Alternativos y Aumentativos de Comunicación (SAACs) en esta comorbilidad (Tabla 17).

Tabla 17. *Protocolos de intervención en los procesos de comunicación a través de Sistemas Aumentativos de Comunicación en la persona con TEA y epilepsia.*

Sistema de Comunicación
Sistemas pictográficos
Sistema PECS
Sistema Bliss
Sistema PIC
Sistema SPC
Sistema PICSYMS
Sistemas gestuales
Lengua de Signos
Palabra Complementada
Lenguaje Bimodal
Gestos naturales y culturales
Dispositivos de Comunicación y app
Proloquo2Go
TouchChat
Let me Talk
Eneso Verbo
Symbotalk
Pulsadores
CPA- Comunicador Personal Adaptable
Jabtalk
Niki Talk
Speack It

Numerosas investigaciones previas también han revisado este tema y han llegado a resultados que respaldan lo presentado en nuestro estudio (Alzrayer, 2020; Clarke y Williams, 2020; Franchini *et al.*, 2017; Gadberry, 2011).

Por ejemplo, en el estudio realizado por Cano-Villagrasa et al. (2023), se examinan las limitaciones que enfrentan las personas con TEA y epilepsia en lo que respecta al lenguaje y al funcionamiento ejecutivo. Los autores señalan que este grupo muestra serias dificultades en la pragmática del lenguaje, así como en aspectos relacionados con la inhibición, el control emocional y la memoria de trabajo. Estos hallazgos son de gran relevancia, dado que estas habilidades son fundamentales para la utilización efectiva de un SAAC por parte de personas con TEA y epilepsia. Debido a esta comorbilidad, los usuarios encuentran obstáculos para comprender y aplicar adecuadamente las directrices para el uso de SAAC en entornos como la escuela o el hogar (Ganz *et al.*, 2014).

Las alteraciones en el funcionamiento ejecutivo resultan en dificultades para establecer un SAAC de manera efectiva, ya que el componente cognitivo de las personas con esta comorbilidad exhibe déficits de atención, distracciones u olvidos en el uso del SAAC, lo que limita su aprendizaje y su aplicación apropiada en contextos esenciales para su desarrollo (Zhao *et al.*, 2021). Estas observaciones son consistentes con la literatura científica existente. Brignell et al. (2018) señalan que las personas con TEA que presentan graves alteraciones en el funcionamiento ejecutivo tienen un proceso de aprendizaje más lento en comparación con aquellos que no tienen estas dificultades. Del mismo modo, Hage et al. (2021) demuestran que las personas con epilepsia que carecen de lenguaje oral enfrentan limitaciones significativas para comprender el uso de un SAAC, especialmente en las primeras etapas del desarrollo. Por último, las dificultades en el lenguaje expresivo y receptivo también obstaculizan el aprendizaje efectivo de los SAAC en personas con TEA y epilepsia (Almurashi *et al.*, 2022).

La falta de interés en la comunicación, la escasa participación visual, las dificultades en la interacción social y los problemas de comprensión del lenguaje oral representan obstáculos significativos que afectan negativamente la efectividad de la implementación de SAAC en individuos con TEA y epilepsia (Chen *et al.*, 2022). Investigaciones como las realizadas por White et al. (2021) destacan la importancia de los conocimientos lingüísticos previos como requisito fundamental para una implementación adecuada de SAAC. Según los hallazgos de estos estudios, antes de introducir SAAC en la población infantil, independientemente del trastorno, es necesario mejorar y fortalecer los fundamentos del lenguaje oral para que esta herramienta complemente y mejore las habilidades de interacción y

comunicación funcional en individuos con deficiencias significativas en el lenguaje hablado.

En cuanto a la atención de las personas con TEA y epilepsia, los estudios revisados indican que los protocolos para mejorar la comunicación en estos perfiles enfrentan importantes desafíos en cuanto al diseño correcto y adecuado para su evaluación e intervención (Brignell *et al.*, 2018). La evaluación se ve comprometida por la presencia de epilepsia en niños con TEA, ya que, como se ha señalado previamente, las habilidades lingüísticas y cognitivas están más restringidas en comparación con aquellos que presentan solo una de estas condiciones (Donato *et al.*, 2018). Esto conduce a que los protocolos de evaluación sean ineficaces debido a su falta de adaptación a las dificultades específicas de esta población, lo que resulta en sesgos importantes y una baja sensibilidad para determinar con precisión las habilidades lingüísticas reales de los individuos en el momento de la evaluación. Por lo tanto, estudios como el realizado por Franchini *et al.* (2017) resaltan las dificultades en la evaluación de perfiles clínicos con un bajo nivel de lenguaje, evidenciando la escasez de pruebas adecuadas para evaluar el lenguaje en individuos con graves problemas en su expresión verbal. En este contexto, el presente estudio revisa la literatura científica actual y propone un protocolo de evaluación que no solo evalúa las competencias lingüísticas del individuo, sino también su entorno, proporcionando una visión integral de las necesidades de las personas con TEA y epilepsia con el objetivo de establecer un SAAC funcional que satisfaga las demandas lingüísticas del entorno en el que se desenvuelven (Ganz *et al.*, 2012).

Por otro lado, en lo que respecta a la intervención, también se enfrentan limitaciones para desarrollar un protocolo de intervención efectivo en esta población. La literatura científica aún no ha logrado aclarar las estrategias de intervención más eficaces en el ámbito del lenguaje (Hage *et al.*, 2021). No obstante, todas las investigaciones coinciden en que el uso de SAAC en la población infantil con TEA y epilepsia ha demostrado ser altamente eficaz, ya que les permite establecer una comunicación funcional, conectarse con su entorno y compensar la escasez de lenguaje expresivo para expresar deseos o necesidades (Pelphrey *et al.*, 2014). En este contexto, es fundamental adaptar el entorno mediante el uso de dispositivos electrónicos, imágenes o la asistencia de un adulto para que el individuo con esta comorbilidad pueda participar en interacciones comunicativas

exitosas utilizando un SAAC adaptado a sus características lingüísticas y cognitivas (White *et al.*, 2021).

VII – CONCLUSIONES

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En base a los objetivos planteados en la presente tesis doctoral se puede concluir, de acuerdo con los resultados obtenidos, que la población infantil con TEA y epilepsia presentan numerosas alteraciones que abarcan procesos desde lo más cognitivo a lo más funcional, lo que limita su calidad de vida y su autonomía.

De los resultados obtenidos en este estudio, se pueden concluir lo siguiente:

- La coexistencia de epilepsia en las personas con diagnóstico de TEA influye negativamente en el desarrollo de las competencias lingüísticas y cognitivas durante los primeros años de vida. En los menores que cursan con esta comorbilidad muestran alteraciones en el funcionamiento ejecutivo, memoria, atención, discapacidad intelectual y en las dimensiones del lenguaje como la fonología, la semántica, la morfosintaxis y la pragmática.
- Los niveles de serotonina y melatonina son muy bajos en las personas con TEA y epilepsia, lo que causan trastornos del sueño. El trastorno del sueño más prevalente en esta población es el insomnio. Este tipo de alteraciones del sueño causan disfunciones significativas en el funcionamiento ejecutivo, mermando las habilidades como la memoria de trabajo, la planificación, la inhibición y la flexibilidad cognitiva.
- La comorbilidad entre el TEA y la epilepsia causan alteraciones significativas en las funciones del lenguaje y la cognición. Se ha observado que la población infantil con este tipo de comorbilidades presenta un peor rendimiento en estas funciones en comparación con aquellas personas que solo presentan una de estas dos condiciones: TEA o epilepsia como diagnóstico principal.
- Las alteraciones conductuales y emocionales propias del TEA se ven gravemente incentivadas por la presencia de la epilepsia en la población infantil. Estas alteraciones se han relacionado

significativamente con un peor rendimiento en el funcionamiento ejecutivo en las personas con TEA y epilepsia.

- El procesamiento y la comprensión auditiva son habilidades que están significativamente alteradas en los menores con TEA y epilepsia en comparación con otros colectivos como aquellos que presentan solamente TEA o epilepsia. Las dificultades encontradas se localizan en el procesamiento auditivo de información compleja como frases subordinadas, yuxtapuestas o con varios elementos.
- En la actualidad, no existen protocolos específicos de evaluación de los procesos de lenguaje, comunicación, cognición y perfil sensorial de las personas con TEA y epilepsia. Esta investigación propuso que los instrumentos adecuados para la evaluación de estas competencias fueron: CELF-5, PROLEC-R, ENFEN, WISC-IV y Sensory Profile-2. Estas pruebas con una alta fiabilidad y validez permiten evaluar las competencias básicas de la persona con TEA y epilepsia y establecer una línea base para una posterior intervención.
- El fármaco con mayores índices de efectividad en la reducción de los episodios epilépticos en las personas con TEA es la Carbamazepina.
- Las alteraciones en el lenguaje y la comunicación en las personas con TEA y epilepsia son muy severas. Para su intervención se recomienda el uso de los SAACs para potenciar su funcionalidad y poder desarrollar su interacción con las personas de su alrededor.

VIII - LIMITACIONES Y FUTURAS LÍNEAS DE INVESTIGACIÓN

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Como todas las investigaciones, la presente tesis doctoral tuvo una serie de limitaciones que se deben considerar. En primer lugar, es necesario destacar las dificultades para homogeneizar las características de los participantes que conformaron el grupo muestral de esta investigación. La comorbilidad existente en las personas con TEA y con epilepsia resulta compleja y con una prevalencia menor que la de los otros dos trastornos, lo que ha impedido que el número de participantes en los estudios que conforman el compendio de artículos de esta tesis doctoral sea mayor.

Asimismo, en segundo lugar, se ha de mencionar que el uso de la prueba CELF-5 para la evaluación de la pragmática puede conllevar una serie de sesgos ya que la evaluación de esta dimensión lingüística se realiza por el propio examinador en el contexto de evaluación clínica y no en entornos naturales, en los cuales se podría obtener más información.

Por último, en tercer lugar, es necesario resaltar las limitaciones en la obtención de bibliografía científica actual que aborden las temáticas recogidas en la presente tesis doctoral. Existe un número ínfimo de artículos de investigación que recojan las dimensiones lingüísticas y cognitivas de las personas con TEA y epilepsia, así como su evaluación e intervención interdisciplinar.

Sin embargo, a pesar de estas limitaciones, la presente tesis doctoral permite discernir varias líneas de futuro en un marco de investigación interesante para esta población vulnerable. El continuo avance en la comprensión y atención de las personas con TEA y la epilepsia ha marcado un hito significativo en la investigación y práctica clínica actual. Sin embargo, para consolidar y ampliar este progreso, es importante establecer líneas de investigación que aborden tanto las necesidades actuales como las perspectivas futuras en este campo interdisciplinar. Una línea esencial hacia este fin implica la implementación de estudios longitudinales exhaustivos que permitan examinar la trayectoria evolutiva de las características lingüísticas y cognitivas desde las etapas iniciales del desarrollo hasta la adolescencia en individuos con TEA y epilepsia. Estos estudios ofrecerán una

visión integral de cómo se manifiestan y evolucionan estas características a lo largo del tiempo, proporcionando una base crucial para la comprensión de la interacción entre ambas condiciones y su impacto en el desarrollo.

En paralelo, se requiere un enfoque orientado al desarrollo de protocolos específicos de evaluación e intervención diseñados para abordar las necesidades particulares de las personas con TEA y epilepsia. Estos protocolos deben ser sensibles a las complejidades inherentes a estas condiciones duales, ofreciendo herramientas efectivas para evaluar tanto los aspectos cognitivos como los lingüísticos y adaptando estrategias de intervención en consecuencia.

Asimismo, es fundamental continuar profundizando en la exploración de las características cognitivas, físicas y emocionales que definen a las personas con TEA y epilepsia. Estas investigaciones deben abarcar tanto el ámbito individual como el colectivo, buscando identificar patrones comunes y variaciones significativas que puedan informar sobre la diversidad y heterogeneidad de estos perfiles.

Por último, es imprescindible atender a las comorbilidades clínicas que pueden presentar estos perfiles, reconociendo la complejidad y la interconexión de múltiples condiciones médicas que pueden coexistir con TEA y epilepsia. Esto implica un enfoque integral que abarque no solo los aspectos médicos, sino también los psicológicos y sociales, garantizando una atención holística que aborde las necesidades de cada persona.

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X – ANEXOS

X - ANEXOS

ANEXO 1. Aceptación del Comité de Ética de la UCAM



UCAM ETHICS COMMITTEE

PROJECT DATA

Title:	"The influence of epilepsy on the linguistic-cognitive performance of people with Autism Spectrum Disorder"	
Principle Researcher	Name	Email
PhD.	Francisco José Moya Faz	moyafaz@ucam.edu

COMITTEE REPORT

Date	27/05/2022	Code	CE052206
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Type of Experimentation

Experimental clinical research involving human subjects	
Non-clinical experimental research with humans	
Using human tissues from patients, healthy people, embryonic or fetal tissue	
Using human tissues, embryonic or fetal tissue from banks or tissue samples	
Observational research with humans or use of personal data, genetic information, etc.	X
Animal studies	
Use of biological agents of risk to human health, animal or plant	
Use of genetically modified organisms (GMOs)	

Comments regarding the type of experimentation
No comments

Comments regarding the methodology of experimentation
No comments



ANEXO 2. Consentimiento informado



ANNEX II
INFORMED CONSENT

Me,, with DNI:.....

Parent or legal guardian of,

I DECLARE:

To have been informed of the study and research procedures of the Project titled: The influence of epilepsy on the linguistic-cognitive performance of people with Autism Spectrum Disorder.

The researchers who will access our personal data and the test results are: Alejandro Cano Villagrasa, Miguel López Zamora and Francisco José Moya y Faz.

Likewise, I have been able to ask questions about the study, understanding that my son/daughter or ward is voluntarily participating in it and that they can leave it at any time without harming them in any way.

I CONSENT:

1.-) To undergo the following tests: The Clinical Assessment of Language Fundamentals - 5 (CELF-5), The Reynell III Expressive and Receptive Language Development Scale, The BRIEF-2 Questionnaire for Behavioral Assessment of Function, and The Reviewed Reading Process Assessment Battery (PROLEC-R).

2.-) The use of the data obtained as indicated in the following paragraph:
In compliance with Regulation (EU) 2016/679 of the European Parliament and of the Council, of April 27, 2016 and Organic Law 3/2018, of December 5, on the Protection of Personal Data and Guarantee of Digital Rights, we inform you that The information you have provided and that obtained as a result of the tests to which you are going to submit will become part of the INVESALUD automated file, whose owner is the SAN ANTONIO UNIVERSITY FOUNDATION, for the purpose of RESEARCH AND TEACHING IN THE AREAS OF KNOWLEDGE EXPERIMENTAL SCIENCES AND HEALTH SCIENCES. You have the right to access this information and cancel or rectify it, by contacting the entity's address, at Avda. de los Jerónimos de Guadalupe 30107 (Murcia). This entity guarantees the adoption of the appropriate measures to ensure the confidential treatment of said data.

In Valencia to ofof 202

Father/mother/legal guardian,

The researcher

Sign.:.....

Sign.:.....

ANEXO 3. Renuncia de los coautores no doctores

**RENUNCIA DE LOS COAUTORES NO DOCTORES**

Dña. Nadia Porcar Gozalbo como coautora de los trabajos y publicaciones científicas que se detallan en la presente informe, renuncian a que los mismos formen parte de otra Tesis Doctoral diferente a la realizada por D. Alejandro Cano Villagrasa en el Departamento de Ciencias de la Salud de la Universidad Católica San Antonio de Murcia

Firmado por NADIA
PORCAR GOZALBO -
NIF:***1317** el
día 01/10/2024
con un
certificado

Fdo.: Nadia Porcar Gozalbo

ANEXO 4. Aceptación de los coautores**ACEPTACIÓN DE LOS COAUTORES**

D/D^a Isabel López Chicheri García, D/D^a Nadia Porcar Gozalbo, y D/D^a Antonio Cortés, como coautores de los trabajos y publicaciones científicas que se detallan en el presente informe, aceptan que formen parte de la Tesis Doctoral realizada por D. Alejandro Cano Villagrasa en el Departamento de Ciencias de la Salud de la Universidad Católica San Antonio de Murcia.

Fdo.:

Firmado por
NADIA PORCAR
GOZALBO -
NIF:***1317** el
día 01/10/2024
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ANEXO 5. Declaración jurada de originalidad del trabajo



DECLARACIÓN JURADA DE ORIGINALIDAD DEL TRABAJO

Yo, Alejandro Cano Villagrasa, con DNI/Pasaporte 45898034Q, alumno inscrito en la Escuela Internacional de Doctorado, perteneciente a la Universidad Católica San Antonio de Murcia,

DECLARO

Ser el único autor del texto entregado para obtener el título académico de Doctor, y que tal texto no ha sido entregado ni total ni parcialmente para obtención de un título académico en ninguna otra universidad o instituto, ni ha sido publicado anteriormente para cualquier otro fin.

Así mismo, declaro no haber trasgredido ninguna norma universitaria con respecto al plagio ni a las leyes establecidas que protegen la propiedad intelectual.

Declaro, además, que el archivo PDF corresponde exactamente al texto impreso que presento junto al mismo.

Por último, declaro que soy conocedor de las sanciones penales en caso de infringir las leyes del plagio y de falsa declaración, y que firmo la presente con pleno uso de mis facultades y asumiendo todas las responsabilidades de ella derivada.

Firma

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VILLAGRASA -
NIF:45898034Q el

En Murcia, a 3 de septiembre de 2024

