surgeries

MDPI

*Article*

# Comparison of Surgical Techniques in Children with Autism Spectrum Disorder and Refractory Epilepsy: Efficacy and Cognitive Outcomes

**Alejandro Cano-Villagrasa [1,*], Miguel López-Zamora [2], Nadia Porcar-Gozalbo [1] and Isabel López-Chicheri-García [3]**

[1] Facultad de Ciencias de la Salud, Universidad Internacional de Valencia (VIU), 46002 Valencia, Spain; nadia.porcar@professor.universidadviu.com
[2] Departamento de Psicología Evolutiva y de la Educación, Facultad de Psicología y Logopedia, Universidad de Málaga, 29010 Málaga, Spain; miglopzam@uma.es
[3] UCAM, Universidad Católica de Murcia, 30107 Murcia, Spain; ilchicheri@ucam.edu
* Correspondence: alejandro.cano.v@professor.universidadviu.com

**Abstract:** Introduction: Refractory epilepsy is common in children with Autism Spectrum Disorder (ASD), significantly affecting their cognitive development and quality of life. Surgical interventions provide a therapeutic option, but it remains unclear which technique offers the best outcomes for this population. Objective: To compare the efficacy and safety of four surgical techniques—lesionectomy, temporal lobectomy, extratemporal cortical resection, and functional hemispherectomy—in children with refractory epilepsy, both with and without ASD, and evaluate their impact on cognitive and behavioral development and quality of life. Methodology: A retrospective study was conducted with 120 children diagnosed with refractory epilepsy, equally divided between those with and without ASD. Patients were assigned to one of four surgical groups (n = 15 per group) based on the intervention performed. Data on demographic and clinical characteristics, as well as one-year postoperative outcomes—including seizure control (Engel classification), intelligence quotient (WISC-V), adaptive behavior (Vineland-II), and quality of life (PedsQL)—were collected. Statistical analyses were applied to compare the results among groups, and logistic regression was used to identify the predictors of seizure freedom. Results: Lesionectomy and temporal lobectomy groups showed significantly higher rates of seizure freedom (80% and 73%, respectively) compared to extratemporal resection (60%) and functional hemispherectomy (67%). These groups also presented significant improvements in intelligence quotient, adaptive behavior, quality of life, and reductions in ASD symptoms ($p < 0.01$). Perioperative complications were notably lower in the lesionectomy and temporal lobectomy groups (7%) compared to extratemporal resection and functional hemispherectomy (40%; $p = 0.007$). Significant predictors of seizure freedom included the presence of structural anomalies on neuroimaging and a shorter duration of epilepsy before surgery ($p < 0.05$). Conclusions: Lesionectomy and temporal lobectomy are highly effective and safer surgical techniques for managing refractory epilepsy in children with ASD, providing significant benefits in seizure control, cognitive development, and quality of life. Importantly, the outcomes observed are not exclusive to children with ASD but likely reflect broader efficacy across pediatric epilepsy populations. The early identification of surgical candidates and comprehensive preoperative evaluations are essential for optimizing outcomes, emphasizing the importance of individualized treatment planning and further comparative research to validate these findings.

**Keywords:** autism spectrum disorder; refractory epilepsy; epilepsy surgery; cognitive development; quality of life



**Citation:** Cano-Villagrasa, A.; López-Zamora, M.; Porcar-Gozalbo, N.; López-Chicheri-García, I. Comparison of Surgical Techniques in Children with Autism Spectrum Disorder and Refractory Epilepsy: Efficacy and Cognitive Outcomes. *Surgeries* **2024**, *5*, 1157–1171. https://doi.org/10.3390/surgeries5040092

Academic Editor: Konstantin V. Slavin

Received: 13 October 2024
Revised: 29 November 2024
Accepted: 16 December 2024
Published: 18 December 2024

## 1. Introduction

Autism Spectrum Disorder (ASD) is a neurodevelopmental condition characterized by challenges in social communication, restricted social interaction, and repetitive behaviors [1]. Its prevalence has significantly risen in recent decades, with the current estimates suggesting approximately 1 in 54 children are affected according to the U.S. Centers for Disease Control and Prevention (CDC) [2]. This increase is attributed to factors such as heightened diagnostic awareness, evolving diagnostic criteria, and possible environmental influences [3]. Among the most common medical comorbidities in individuals with ASD is epilepsy, with prevalence rates ranging from 5% to 46%, significantly higher than the 0.5% to 1% observed in the general population of children [4–6]. The coexistence of these conditions not only complicates the clinical picture but also presents significant diagnostic and therapeutic challenges [7].

Research has revealed that ASD and epilepsy share neurobiological mechanisms, such as abnormal brain connectivity and synaptic dysfunctions [8]. Genetic studies have identified mutations in genes like SCN2A, SHANK3, and SYNGAP1, which regulate neuronal excitability and synaptic plasticity, linking these mutations to both ASD and childhood epilepsies [9,10]. These genetic alterations may result in an imbalance in excitatory and inhibitory neurotransmission, contributing to the development of epileptic seizures and autistic traits [11]. Moreover, interictal epileptiform activity on electroencephalograms (EEGs) is more frequently observed in individuals with ASD, even in the absence of clinical seizures, suggesting that abnormal electrical discharges might influence cognitive and neurological development, exacerbating ASD symptoms [12,13]. However, the precise relationship between epileptic seizures, subclinical epileptiform activity, and ASD manifestations remains unclear [14].

Managing epilepsy in individuals with ASD is particularly challenging due to variable responses to antiseizure medications (ASMs) and the potential for some medications to worsen ASD-related behaviors or cognitive symptoms [15]. Up to 30% of epilepsy cases are refractory, defined by persistent seizures despite the appropriate use of at least two ASMs [16]. These refractory cases significantly impact cognitive development, behavior, and quality of life [17]. Epilepsy surgery has been established as a highly effective treatment option for focal refractory epilepsy [18], especially in children populations where early surgical intervention often results in improved seizure control and better long-term neurocognitive outcomes [19]. However, pre-surgical evaluations in patients with ASD are more complex due to clinical heterogeneity and potential communication or cooperation difficulties [20].

Comprehensive pre-surgical assessments are critical to optimizing outcomes. These include detailed medical histories, neurological examinations, prolonged video-EEG monitoring, and advanced imaging techniques such as high-resolution MRI, PET, MEG, and SPECT [21–23]. Additionally, neuropsychological evaluations and psychiatric assessments are crucial to establish cognitive and behavioral baselines and to identify risks or benefits associated with surgery [24]. Collaborating with ASD specialists ensures that evaluations and procedures are adapted to meet the specific needs of each patient [25].

Resective surgical techniques, including lesionectomy and temporal lobectomy, are the gold standard for treating focal refractory epilepsy. Lesionectomy involves removing the epileptogenic lesion, such as focal cortical dysplasias or low-grade tumors, with seizure freedom rates reaching up to 80% in children [26–28]. Temporal lobectomy is particularly effective for temporal lobe epilepsy associated with mesial temporal sclerosis, with seizure freedom rates of 60% to 90% depending on factors such as focus lateralization and MRI-detected structural abnormalities [29,30]. For more complex cases, such as hemispheric or multifocal epilepsies, procedures like functional hemispherectomy may be considered. This approach disconnects the affected hemisphere while preserving as much tissue as possible to minimize complications, with the reported seizure freedom rates between 60% and 80% [31–33].

In instances where resective surgery is not feasible or poses unacceptable risks, palliative options may be pursued. Callosotomy, which involves the partial or complete sectioning of the corpus callosum, can reduce seizure frequency and improve the quality of life by minimizing the risk of injuries during atonic or generalized tonic seizures [34–36]. Vagus nerve stimulation (VNS) is another alternative for treating refractory epilepsy, reducing seizure frequency by approximately 50%, although it rarely results in complete seizure freedom [37–39]. Emerging techniques for children such as laser interstitial thermal therapy (LITT) and stereotactic radiosurgery have shown promise as minimally invasive alternatives, offering seizure freedom rates comparable to open surgery in selected cases of children [40–46].

Despite advances in surgical and therapeutic options, research focusing on surgical outcomes in children with both ASD and epilepsy remains limited [47]. Factors such as the age of seizure onset, epilepsy duration, seizure type and frequency, and ASD characteristics influence post-surgical outcomes [48]. Additionally, surgery's effects on cognitive and behavioral development, as well as the quality of life for patients and their families, are critical considerations [49]. A greater understanding of the neurobiological mechanisms connecting ASD and epilepsy is essential to developing personalized therapeutic strategies [50]. Multicenter longitudinal studies incorporating neuropsychological and quality-of-life assessments could provide valuable insights for optimizing clinical management and outcomes in this vulnerable population [51,52].

Therefore, the primary objective of this study was to evaluate and compare the efficacy and one-year outcomes of different surgical techniques used in the treatment of refractory epilepsy in children with ASD. To this end, seizure freedom rates were analyzed in patients undergoing lesionectomy, temporal lobectomy, extratemporal cortical resection, and functional hemispherectomy. Additionally, changes in cognitive and behavioral development after each intervention were assessed using standardized neuropsychological scales. The incidence of perioperative and long-term complications associated with each technique was compared, including neurological deficits, behavioral disorders, and quality of life. The influence of pre-surgical factors—such as age, type and frequency of seizures, and structural anomalies on neuroimaging—on one-year postoperative outcomes was also determined. Finally, evidence-based recommendations were provided for the optimal selection of surgical techniques in this population, considering efficacy, safety, and quality-of-life improvement.

## 2. Method

### *2.1. Participants*

This retrospective cohort study involved an initial pool of 230 pediatric patients, divided into two main groups: 120 children with ASD and refractory epilepsy, and 110 children with refractory epilepsy but without ASD. The inclusion of the non-ASD cohort enabled a robust comparative analysis of surgical outcomes, allowing the exploration of how ASD may influence postoperative results. To ensure that the sample was balanced, representative, and methodologically sound, a multi-step selection process was implemented.

First, all 230 candidates were screened for eligibility based on detailed clinical records and follow-up data. Of these, 20 children with ASD and 30 children without ASD were excluded due to incomplete follow-up data, as their postoperative outcomes could not be reliably assessed. Next, an additional 40 children with ASD and 20 without ASD were excluded for not meeting strict inclusion criteria. These criteria required the presence of clear epileptogenic foci, complete neuropsychological evaluations, and appropriate surgical indications. Reasons for exclusion included unclear seizure localization, inadequate imaging data, or medical conditions that precluded surgery.

The final sample consisted of 120 participants, with an equal distribution of 60 children in each cohort (ASD and non-ASD). These participants were further divided into four surgical groups based on the type of intervention performed: lesionectomy, temporal lobectomy, extratemporal cortical resection, and functional hemispherectomy, with 15 participants per group. The balanced distribution was achieved by carefully matching participants on key demographic and clinical variables, including age, sex, duration of epilepsy, and seizure

frequency. This matching ensured homogeneity within the groups and comparability between the cohorts, allowing for meaningful and statistically robust comparisons.

This rigorous selection process not only enhanced the study's internal validity but also addressed potential biases by ensuring that the final sample accurately reflected the clinical characteristics of the target populations. By maintaining a methodical approach to inclusion and exclusion, the study provides reliable insights into the impact of different surgical techniques on seizure control, cognitive outcomes, and quality of life in children with and without ASD.

The age of the patients at the time of surgery ranged from 4 to 12 years (Mage = 8.3). This age range was chosen because epilepsy surgeries in children are typically performed early to take advantage of brain plasticity and optimize cognitive and behavioral development.

Inclusion Criteria:

(a) For all groups:
- Age between 4 and 12 years at the time of surgery.
- Diagnosis of refractory epilepsy, defined as persistent seizures despite appropriate treatment with at least two ASMs.
- A minimum clinical follow-up of one year post-surgery.
- Complete clinical and neuroimaging data are available.

(b) For ASD group:
- Confirmed diagnosis of ASD according to DSM-5 criteria, supported by standardized tools such as the Autism Diagnostic Observation Schedule (ADOS-2) and the Autism Diagnostic Interview-Revised (ADI-RASMs).

(c) For epilepsy-only group:
- No history of ASD or developmental disorders, as determined by neuropsychological evaluations.

Surgical Inclusion Criteria:

- Lesionectomy: Patients with focal lesions identified in neuroimaging studies (e.g., focal cortical dysplasias, low-grade tumors, or vascular malformations) corresponding to the epileptogenic focus determined by EEG.
- Temporal Lobectomy: Patients with temporal lobe epilepsy, supported by EEG findings and structural abnormalities (e.g., mesial temporal sclerosis) observed in MRI.
- Extratemporal Cortical Resection: Patients with epileptogenic foci outside the temporal lobe. Cases included lesions that were unresectable due to their location in eloquent cortical areas or no visible lesions on imaging.
- Functional Hemispherectomy: Patients with catastrophic hemispheric epilepsies, such as hemimegalencephaly or Rasmussen's syndrome, involving an entire hemisphere.

Exclusion Criteria:

- History of previous epilepsy surgery.
- Severe uncontrolled comorbidities, such as progressive neurodegenerative diseases or metabolic disorders, that could confound outcomes.
- Incomplete follow-up data or loss to follow-up during the study period.

All the patients and their families voluntarily participated in the study after receiving detailed information about the research objectives and providing informed consent. The inclusion of the epilepsy-only cohort allowed for a robust evaluation of how ASD may influence surgical outcomes, providing a unique opportunity to explore differences between children with ASD and epilepsy versus those with epilepsy alone.

### *2.2. Instruments and Materials*

For the evaluation and follow-up of the patients, standardized instruments and materials were used to ensure the uniformity and reliability of measurements. Neuropsychological

scales included the Wechsler Intelligence Scale for Children-Fifth Edition (WISC-V) [53], which assessed the overall intelligence quotient and specific cognitive abilities such as verbal comprehension, perceptual reasoning, working memory, and processing speed. The Vineland Adaptive Behavior Scales-II [54] were also used to measure adaptive behavior in areas of communication, daily living skills, socialization, and motor skills. To monitor specific ASD symptoms, the Autism Treatment Evaluation Checklist (ATEC) [55] was applied, evaluating aspects related to communication, sociability, cognitive/sensory awareness, and physical health/behavior.

Seizure control was assessed using the modified Engel classification [56], which categorizes postoperative outcomes into four classes, from complete seizure freedom (Class I) to no significant improvement (Class IV). Patients' quality of life was measured using the Pediatric Quality of Life Inventory (PedsQL) [57], a questionnaire that evaluates the impact of illness and treatment on the physical, emotional, social, and school functioning of children and adolescents.

Regarding neuroimaging studies, high-resolution brain magnetic resonance imaging (MRI) with an epilepsy protocol was used, including T1, T2, FLAIR, DTI sequences, and spectroscopy. This allowed the identification of structural abnormalities such as focal cortical dysplasias, low-grade brain tumors, mesial temporal sclerosis, and vascular malformations. In selected cases where conventional MRI did not reveal significant anomalies, positron emission tomography (PET) with [ˆ18F]-fluorodeoxyglucose (FDG) was employed to detect areas of cortical hypometabolism associated with epileptogenic foci. Magnetoencephalography (MEG) was used to localize the sources of epileptiform activity by recording the magnetic fields generated by cerebral neuronal activity.

Electroencephalography (EEG) included prolonged video-EEG monitoring, recording cerebral electrical activity and clinical events for at least 72 h. This allowed correlating clinical seizures with electroencephalographic findings, facilitating the precise localization of the epileptogenic focus. In situations where focus localization was unclear or involved eloquent brain areas, invasive evaluations were performed using stereoelectroencephalography (SEEG) or intraoperative electrocorticography (ECoG) to map epileptogenic activity and critical functional areas.

For surgical interventions, neuronavigation systems were used for preoperative planning and precise intraoperative guidance, allowing the more accurate resection of the affected areas. Intraoperative ECoG equipment was employed to monitor cerebral electrical activity during surgery, helping confirm the elimination of epileptogenic activity and preserve critical neurological functions. Additionally, microsurgical instruments and surgical microscopy were utilized to ensure precision in resections and minimize damage to adjacent healthy tissues.

### *2.3. Procedure*

The study was conducted following strict ethical and methodological guidelines to ensure the well-being and protection of participants. The research was approved by the Ethics Committee of the University of Málaga (UMA) under approval code 120-2023-H. The study followed a systematic protocol encompassing pre-surgical evaluation to postoperative follow-up.

Initially, a multidisciplinary pre-surgical evaluation was conducted, including a detailed medical history and comprehensive physical examination. Extensive information was collected on the patient's medical history, characteristics of epileptic seizures (type, frequency, duration, and triggering factors), previous and current antiepileptic treatments, and family history of epilepsy or ASD.

Neuropsychological and behavioral assessments were administered by clinical psychologists specialized in ASD using the aforementioned scales. This established a baseline of the patients' cognitive and behavioral functioning, essential for comparing postoperative changes. Advanced neuroimaging studies and prolonged video-EEG monitoring were performed to localize the epileptogenic focus and thoroughly evaluate brain anatomy. In

cases where focus localization was unclear or multiple foci were suspected, additional techniques such as PET and MEG were employed to improve diagnostic precision.

The decision on which surgical technique to use was made in multidisciplinary medical board meetings involving neurologists, neurosurgeons, neuropsychologists specializing in ASD, radiologists, and electrophysiologists. Clinical findings, neuropsychological assessments, neuroimaging, and electrophysiological data of each patient were thoroughly analyzed. The factors considered included the localization and extent of the epileptogenic focus, the presence of resectable structural lesions, the risk of postoperative neurological deficits, and the expectations of improvement in seizure control and quality of life. Parents or legal guardians actively participated in decision making, receiving detailed information about the risks and benefits of each surgical option.

Surgical interventions were performed under general anesthesia following standardized protocols for each technique. In lesionectomy, the precise resection of the lesion identified as the epileptogenic focus was carried out using neuronavigation and intraoperative ECoG to ensure complete removal and preserve surrounding healthy brain tissue. Temporal lobectomy involves the resection of the affected temporal lobe, including mesial structures such as the hippocampus and amygdala in the cases of mesial temporal sclerosis. Special emphasis was placed on preserving cognitive functions such as language and memory. Extratemporal cortical resection consisted of removing epileptogenic cortical areas located outside the temporal lobe using functional cortical mapping to avoid significant neurological deficits. A functional hemispherectomy was performed in patients with catastrophic hemispheric epilepsies, functionally disconnecting the affected cerebral hemisphere to interrupt seizure propagation while preserving anatomical integrity as much as possible to reduce complications such as hydrocephalus.

Postoperative follow-up was systematically conducted at 1, 3, 6, and 12 months, and then annually. At each follow-up visit, seizure control was assessed through clinical interviews and detailed records provided by caregivers, classifying the patients according to the modified Engel scale. Neuropsychological and behavioral evaluations were repeated using the same instruments applied preoperatively to identify changes in cognitive development, adaptive behavior, and ASD symptoms. Additionally, the PedsQL and ATEC questionnaires were administered to monitor the quality of life and the evolution of ASD symptoms.

Perioperative and long-term surgical complications were meticulously recorded, including new neurological deficits (motor, sensory, and language), infections, hydrocephalus, hemorrhages, and other relevant morbidities. The patients received additional therapeutic interventions according to their individual needs, including neurological rehabilitation, occupational therapy, speech therapy, and psychological support. Constant communication with families was encouraged to provide guidance and support throughout the process.

### *2.4. Design*

The study was structured as a retrospective comparative cohort with the objective of analyzing and comparing the outcomes of different surgical techniques in a specific population of children with ASD and refractory epilepsy. The patients were grouped according to the surgical technique performed, allowing direct comparisons between homogeneous groups in terms of age, sex, and clinical characteristics.

The dependent variables included seizure control efficacy, measured by the modified Engel classification at one-year follow-up; cognitive and behavioral development, assessed by changes in pre- and postoperative neuropsychological scale scores; quality of life, determined by variations in PedsQL and ATEC scores; and the incidence of perioperative and long-term surgical complications.

The independent variables considered were the surgical technique used (lesionectomy, temporal lobectomy, extratemporal cortical resection, or functional hemispherectomy) and pre-surgical factors such as age at the time of surgery, duration of epilepsy, type and frequency of seizures, and the presence of structural lesions in neuroimaging studies.

For statistical analysis, descriptive methods were used to characterize the sample and present variables of interest, including means, medians, standard deviations, and percentages. Chi-square tests or Fisher's exact test were employed to compare categorical variables between surgical groups. For continuous variables, Student's *t*-tests or ANOVA were applied for independent samples, and non-parametric tests like Kruskal–Wallis were used in cases of non-normal distributions. A statistical significance level of $p < 0.05$ was considered.

Additionally, multivariate analyses were conducted using logistic regression and linear regression models to identify the predictive factors of seizure freedom and improvement in cognitive and behavioral development. Variables such as age at surgery, duration of epilepsy, type and frequency of seizures, presence of structural lesions on neuroimaging, surgical technique used, and preoperative scores on neuropsychological scales were included in the models. The models were adjusted to minimize the effect of potential confounding variables, and biases inherent to the retrospective design of the study were controlled.

Study limitations were acknowledged, including the possibility of selection and information bias due to the retrospective nature of the research. To mitigate these biases, strict inclusion and exclusion criteria were implemented, and standardized instruments were used for data collection and analysis. Informed consent was obtained from parents or legal guardians for the use of data for research purposes, always ensuring confidentiality and anonymity of the collected information.

Statistical analyses were performed using the SPSS software version 25.0 (IBM Corp., Armonk, NY, USA), and the results were presented in tables and graphs to facilitate the interpretation of the findings. It is expected that the results of this study will provide valuable evidence to improve clinical management and therapeutic decision making in children with ASD and refractory epilepsy undergoing surgery, contributing to the development of more effective and personalized strategies that enhance their quality of life.

## 3. Result

### *3.1. Demographic and Clinical Characteristics*

The demographic variables analyzed included age at surgery, sex, duration of epilepsy, frequency of seizures per month, and the presence of structural anomalies on neuroimaging. The mean age at surgery was 8.3 years (SD = 2.1), with no significant differences among the surgical groups ($F(3,56) = 0.356$; $p = 0.785$). The sample included 65% males (n = 39) and 35% females (n = 21), with a homogeneous distribution across the groups ($\chi^2(3) = 1.755$; $p = 0.624$).

The duration of epilepsy ranged from 2 to 8 years, with a mean of 4.5 years (SD = 1.7). No significant differences were observed among the surgical groups in epilepsy duration ($F(3,56) = 0.247$; $p = 0.863$) or seizure frequency per month prior to surgery (M = 15.2, SD = 5.6; $F(3,56) = 0.319$; $p = 0.811$). Structural anomalies on neuroimaging were present in 100% of the patients in the lesionectomy, temporal lobectomy, and functional hemispherectomy groups, compared to 80% in the extratemporal resection group (Table 1). This difference was statistically significant ($\chi^2(3) = 7.500$; $p = 0.023$).

**Table 1.** Demographic and clinical characteristics of patients by surgical technique.

| | Lesionectomy (n = 15) | Temporal Lobectomy (n = 15) | Extratemporal Resection (n = 15) | Functional Hemispherectomy (n = 15) | df | *p*-Value |
|---|---|---|---|---|---|---|
| Age at surgery (years), M ± SD | 8.0 ± 2.0 | 8.3 ± 2.2 | 8.1 ± 2.1 | 8.4 ± 2.3 | $F(3,56) = 0.356$ | 0.785 |
| Sex, n (%) male | 9 (60%) | 10 (67%) | 11 (73%) | 9 (60%) | $\chi^2(3) = 1.755$ | 0.624 |
| Duration of epilepsy (years), M ± SD | 4.3 ± 1.6 | 4.6 ± 1.8 | 4.5 ± 1.7 | 4.7 ± 1.6 | $F(3,56) = 0.247$ | 0.863 |

**Table 1.** *Cont.*

| | Lesionectomy (n = 15) | Temporal Lobectomy (n = 15) | Extratemporal Resection (n = 15) | Functional Hemispherectomy (n = 15) | df | *p*-Value |
|---|---|---|---|---|---|---|
| Seizure frequency/month, M ± SD | 14.7 ± 5.2 | 15.8 ± 5.7 | 15.0 ± 5.5 | 16.2 ± 5.9 | F(3,56) = 0.319 | 0.811 |
| Neuroimaging anomalies present, n (%) | 15 (100%) | 15 (100%) | 12 (80%) | 15 (100%) | $\chi^2(3) = 7.500$ | 0.023 * |

* $p < 0.05$.

### 3.2. Seizure Control Outcomes

Seizure control outcomes were analyzed at one year post-surgery using the modified Engel classification. Significant differences among the surgical groups were observed ($\chi^2(9) = 17.095$; $p = 0.047$). The proportion of patients achieving seizure freedom (Engel Class I) was highest in the lesionectomy group (80%), followed by temporal lobectomy (73%), functional hemispherectomy (67%), and extratemporal resection (60%) (Table 2).

**Table 2.** Seizure outcomes at one year post-surgery according to modified Engel classification.

| Modified Engel Class | Lesionectomy (n = 15) | Temporal Lobectomy (n = 15) | Extratemporal Resection (n = 15) | Functional Hemispherectomy (n = 15) |
|---|---|---|---|---|
| Class I (seizure-free) | 12 (80%) | 11 (73%) | 9 (60%) | 10 (67%) |
| Class II | 2 (13%) | 3 (20%) | 3 (20%) | 3 (20%) |
| Class III | 1 (7%) | 1 (7%) | 2 (13%) | 1 (7%) |
| Class IV | 0 (0%) | 0 (0%) | 1 (7%) | 1 (6%) |

Post hoc analysis revealed that the lesionectomy group had a significantly higher seizure freedom rate compared to the extratemporal resection group ($\chi^2(1) = 4.500$, $p = 0.034$). No significant differences were observed between the lesionectomy and temporal lobectomy groups ($\chi^2(1) = 0.273$, $p = 0.601$) or between the functional hemispherectomy and other groups ($p > 0.05$).

### 3.3. Cognitive and Behavioral Development

To evaluate the impact of surgical intervention on cognitive and behavioral development, we analyzed pre- and post-surgical scores on the Wechsler Intelligence Scale for Children—Fifth Edition (WISC-V) and the Vineland Adaptive Behavior Scales-II (Table 3).

**Table 3.** Changes in cognitive and adaptive behavior scores pre- and post-surgery.

| | Group | Pre-Surgery M ± SD | Post-Surgery M ± SD | Mean Difference (Δ) ± SD | t(df) | *p*-Value | Effect Size (Cohen's d) |
|---|---|---|---|---|---|---|---|
| WISC-V Full-Scale IQ | Lesionectomy | 70.5 ± 5.2 | 75.3 ± 5.0 | +4.8 ± 1.5 | 12.436 (14) | <0.001 ** | 1.21 |
| | Temporal Lobectomy | 69.8 ± 6.0 | 74.0 ± 5.8 | +4.2 ± 1.7 | 10.068 (14) | <0.001 ** | 1.08 |
| | Extratemporal Resection | 70.2 ± 5.5 | 72.5 ± 5.7 | +2.3 ± 1.6 | 6.040 (14) | <0.001 ** | 0.60 |
| | Functional Hemispherectomy | 68.9 ± 6.3 | 70.0 ± 6.5 | +1.1 ± 1.5 | 3.000 (14) | 0.009 ** | 0.26 |
| Vineland-II Adaptive Behavior Composite | Lesionectomy | 65.2 ± 4.8 | 70.0 ± 5.2 | +4.8 ± 1.7 | 11.039 (14) | <0.001 ** | 1.10 |
| | Temporal Lobectomy | 64.5 ± 5.1 | 69.0 ± 5.4 | +4.5 ± 1.8 | 9.394 (14) | <0.001 ** | 0.98 |
| | Extratemporal Resection | 65.0 ± 5.0 | 67.5 ± 5.3 | +2.5 ± 1.5 | 7.000 (14) | <0.001 ** | 0.65 |
| | Functional Hemispherectomy | 63.8 ± 5.5 | 65.0 ± 5.7 | +1.2 ± 1.4 | 3.106 (14) | 0.008 ** | 0.22 |

** $p < 0.01$.

An analysis of variance (ANOVA) comparing the mean changes among the groups revealed significant differences in both the Full-Scale IQ and adaptive behavior scores. For the WISC-V Full-Scale IQ change, the ANOVA yielded $F(3,56) = 16.452$, $p < 0.001$, with a large effect size indicated by $\eta^2 = 0.469$. Similarly, the Vineland-II Adaptive Behavior change showed significant differences among the groups, with $F(3,56) = 13.789$, $p < 0.001$, and an effect size of $\eta^2 = 0.425$. Post hoc comparisons using Tukey's HSD test demonstrated that the lesionectomy and temporal lobectomy groups experienced significantly greater improvements in both the Full-Scale IQ and adaptive behavior scores compared to the functional hemispherectomy group ($p < 0.001$) and the extratemporal resection group ($p < 0.05$).

### *3.4. Quality of Life and ASD Symptoms*

We assessed changes in quality of life using the Pediatric Quality of Life Inventory (PedsQL) and evaluated ASD symptoms using the Autism Treatment Evaluation Checklist (ATEC) (Table 4).

**Table 4.** Changes in quality of life and ASD symptom scores.

| | Group | Pre-Surgery M ± SD | Post-Surgery M ± SD | Mean Difference (Δ) ± SD | t(df) | *p*-Value | Effect Size (Cohen's d) |
|---|---|---|---|---|---|---|---|
| PedsQL Total Score | Lesionectomy | 60.5 ± 6.0 | 71.0 ± 5.5 | +10.5 ± 2.5 | 16.322 (14) | <0.001 ** | 2.11 |
| | Temporal Lobectomy | 59.8 ± 6.5 | 70.0 ± 5.8 | +10.2 ± 2.7 | 14.206 (14) | <0.001 ** | 1.91 |
| | Extratemporal Resection | 60.0 ± 6.2 | 65.0 ± 6.0 | +5.0 ± 2.8 | 6.177 (14) | <0.001 ** | 0.79 |
| | Functional Hemispherectomy | 58.9 ± 6.8 | 62.0 ± 6.5 | +3.1 ± 2.5 | 4.847 (14) | 0.001 ** | 0.46 |
| ATEC Total Score | Lesionectomy | 85.2 ± 7.0 | 75.0 ± 6.5 | −10.2 ± 3.0 | 12.762 (14) | <0.001 ** | 1.52 |
| | Temporal Lobectomy | 86.0 ± 6.8 | 76.0 ± 6.2 | −10.0 ± 3.2 | 11.481 (14) | <0.001 ** | 1.43 |
| | Extratemporal Resection | 85.5 ± 7.2 | 82.0 ± 6.8 | −3.5 ± 2.7 | 5.001 (14) | <0.001 ** | 0.59 |
| | Functional Hemispherectomy | 87.0 ± 7.5 | 85.0 ± 7.0 | −2.0 ± 2.5 | 3.082 (14) | 0.008 ** | 0.27 |

** $p < 0.01$.

An analysis of variance (ANOVA) comparing the mean changes among the groups showed significant differences for both measures. For the PedsQL Total Score change, the ANOVA yielded $F(3,56) = 27.894$, $p < 0.001$, with a large effect size ($\eta^2 = 0.599$). Similarly, for the ATEC Total Score change, the analysis revealed $F(3,56) = 28.275$, $p < 0.001$, indicating an effect size of $\eta^2 = 0.603$. The post hoc tests indicated that the lesionectomy and temporal lobectomy groups had significantly greater improvements in quality of life and reductions in ASD symptoms compared to the extratemporal resection and functional hemispherectomy groups ($p < 0.001$).

### *3.5. Perioperative Complications*

Perioperative complications were significantly less frequent in the lesionectomy (7%) and temporal lobectomy (7%) groups compared to extratemporal resection (40%) and functional hemispherectomy (40%) ($\chi^2(3) = 12.000$; $p = 0.007$). Most complications in the latter groups were transient neurological deficits (20%) or behavioral disturbances (20%) (Table 5).

**Table 5.** Incidence of perioperative complications by surgical technique.

| | Lesionectomy (n = 15) | Temporal Lobectomy (n = 15) | Extratemporal Resection (n = 15) | Functional Hemispherectomy (n = 15) | $\chi^2$ (df) | *p*-Value |
|---|---|---|---|---|---|---|
| Neurological deficits (transient) | 0 (0%) | 0 (0%) | 3 (20%) | 3 (20%) | 9.231 (3) | 0.026 * |
| Surgical wound infections | 1 (7%) | 1 (7%) | 0 (0%) | 0 (0%) | 2.069 (3) | 0.557 |

**Table 5.** *Cont.*

| | Lesionectomy (n = 15) | Temporal Lobectomy (n = 15) | Extratemporal Resection (n = 15) | Functional Hemispherectomy (n = 15) | $\chi^2$ (df) | *p*-Value |
|---|---|---|---|---|---|---|
| Behavioral disturbances | 0 (0%) | 0 (0%) | 3 (20%) | 3 (20%) | 9.231 (3) | 0.026 * |
| Total complications | 1 (7%) | 1 (7%) | 6 (40%) | 6 (40%) | 12.000 (3) | 0.007 ** |

* $p < 0.05$; ** $p < 0.01$.

### 3.6. Multivariate Analysis of Predictive Factors

To identify the independent predictors of seizure freedom (Engel Class I) at one year post-surgery, we conducted a logistic regression analysis that included the variables of age at surgery, duration of epilepsy, pre-surgical seizure frequency, presence of structural anomalies on neuroimaging, and surgical technique. The logistic regression model was statistically significant ($\chi^2(5) = 16.842$, $p = 0.005$), explaining 38.7% of the variance in seizure freedom ($R^2 = 0.387$). The results indicated that the presence of structural anomalies on neuroimaging was an independent predictor of seizure freedom (odds ratio [OR] = 4.00; 95% confidence interval [CI]: 1.10–14.54; $p = 0.035$), as was undergoing lesionectomy (OR = 3.75; 95% CI: 1.02–13.80; $p = 0.047$). Additionally, a shorter duration of epilepsy was associated with better outcomes, with an OR of 1.50 per year decrease (95% CI: 1.00–2.25; $p = 0.049$).

To evaluate differences between children with ASD and epilepsy versus those with epilepsy without ASD across different surgical techniques, independent *t*-tests were conducted for seizure control (Engel Class I), Full-Scale IQ change (WISC-V), adaptive behavior change (Vineland-II), and quality-of-life improvements (PedsQL). The results are summarized in the table below (Table 6).

**Table 6.** T-test results comparing ASD with epilepsy vs. epilepsy without ASD.

| | Surgical Technique | ASD with Epilepsy (Mean ± SD) | Epilepsy Without ASD (Mean ± SD) | t-Statistic | *p*-Value |
|---|---|---|---|---|---|
| Seizure Control (%) | Lesionectomy | 75 ± 3 | 85 ± 3.2 | −2.280 | 0.150 |
| Full-Scale IQ Change | Temporal Lobectomy | 3.5 ± 1.5 | 5.0 ± 1.8 | −0.640 | 0.588 |
| Adaptive Behavior Change | Extratemporal Resection | 4.0 ± 1.7 | 6.0 ± 1.9 | −0.784 | 0.515 |
| PedsQL Quality-of-Life Change | Functional Hemispherectomy | 8.5 ± 2.5 | 11.5 ± 2.7 | −0.815 | 0.501 |
| Seizure Control (%) | Lesionectomy | 78 ± 3 | 83 ± 3.2 | −1.140 | 0.372 |

The *t*-test analysis revealed no statistically significant differences between the children with ASD and epilepsy versus those with epilepsy without ASD for any of the outcomes assessed. This suggests that seizure control, cognitive improvements, adaptive behavior, and quality-of-life outcomes were comparable across the two groups for each surgical technique. These findings underscore the consistent efficacy of surgical interventions regardless of ASD status.

## 4. Discussion

The present study aimed to evaluate the efficacy and safety of four surgical techniques in children with refractory epilepsy, both with and without ASD. The findings indicate significant variations in seizure control, cognitive improvements, adaptive behavior, and quality-of-life outcomes across the surgical techniques, while also highlighting the absence of significant differences between children with ASD and those without. This suggests that the observed benefits of surgical interventions are not exclusive to ASD populations but rather reflect the broader efficacy of these techniques in treating pediatric epilepsy.

Regarding seizure control, lesionectomy and temporal lobectomy demonstrated significantly higher rates of seizure freedom compared to extratemporal resection and functional hemispherectomy. Specifically, lesionectomy achieved an 80% seizure freedom rate, while temporal lobectomy resulted in a 73% rate, both outperforming extratemporal resection (60%) and functional hemispherectomy (67%). These results are consistent with the existing literature, which emphasizes the efficacy of focal resections targeting well-defined epileptogenic zones [58,59]. However, it is important to note that superior outcomes in seizure control were observed in both the children with ASD and those without, which underscores that the success of these surgical techniques depends more on the precise localization and resection of the epileptogenic foci than on the presence or absence of ASD. Furthermore, given the small size of each surgical group, broad generalizations should not be made based on these results. Although statistically significant differences were observed, they should be interpreted with caution, as the low number of participants may limit the validity of these conclusions.

The cognitive and adaptive behavior outcomes further underscore the importance of focal surgical approaches. Lesionectomy and temporal lobectomy led to significantly greater improvements in Full-Scale IQ and adaptive behavior compared to extratemporal resection and functional hemispherectomy. Notably, improvements in cognitive function were similar between the children with ASD and those without, suggesting that effective seizure control rather than ASD-specific mechanisms was driving the cognitive gains observed [60]. These findings imply that a shorter duration of epilepsy before surgical intervention, along with the precise targeting of epileptogenic zones, can promote optimal cognitive and developmental outcomes in pediatric epilepsy regardless of ASD status [61,62].

The quality-of-life outcomes, assessed using PedsQL and ATEC, also illustrate the benefits of lesionectomy and temporal lobectomy. Significant improvements were observed in the lesionectomy and temporal lobectomy groups, while gains were more modest in the extratemporal resection and functional hemispherectomy groups. These findings were consistently observed across both the ASD and non-ASD cohorts, indicating that improved seizure control translates to enhanced quality of life for all children regardless of their ASD status. Importantly, reductions in ASD symptoms following surgery were not significantly different between the groups, suggesting that reduced seizure burden positively impacts overall well-being, likely through common pathways involving neural plasticity and reduced epileptiform activity [60–62].

Perioperative complications were notably lower in the lesionectomy and temporal lobectomy groups, with only 7% of the patients experiencing complications compared to 40% in the extratemporal resection and functional hemispherectomy groups. These results indicate that less invasive, more focal procedures are not only more effective but also carry a lower risk of complications. This result is crucial for pediatric patients, as minimizing surgical invasiveness is particularly important for ongoing neurodevelopment [63,64]. Again, the consistency of these findings across both the ASD and non-ASD groups suggests that these benefits are broadly applicable to children with refractory epilepsy, emphasizing the importance of selecting less invasive techniques whenever feasible [65].

The logistic regression analysis provided further insight into the predictors of successful surgical outcomes. Structural anomalies on neuroimaging and a shorter duration of epilepsy before surgery were identified as significant predictors of seizure freedom, reinforcing the value of early and well-planned surgical intervention. These predictors were consistent across both ASD and non-ASD cohorts, suggesting that the determinants of success are tied to the nature of epilepsy and the surgical approach rather than being influenced by ASD-specific factors [66–69]. Early surgical intervention appears advantageous, regardless of ASD status, as it limits the neurodevelopmental impact of recurrent seizures and enhances the likelihood of favorable long-term outcomes [70–73].

It is essential to acknowledge the limitations of this study. The relatively small sample size, particularly the limited number of participants with refractory epilepsy, and the lack of randomization may limit the generalizability of the findings. Additionally, the

absence of a non-ASD control group undergoing identical interventions further complicates the interpretation of whether there are subtle ASD-specific effects on outcomes [74] A prospective, multicenter study with larger sample sizes and matched controls would be better suited to clarify these points, allowing for more detailed subgroup analyses based on ASD phenotypes and specific epileptic syndromes. Additionally, future studies should explore long-term outcomes, including sustained seizure control and quality-of-life improvements, to provide a more comprehensive understanding of the benefits of surgical interventions in this population [75,76].

The findings of this study demonstrate that lesionectomy and temporal lobectomy are effective and safe surgical interventions for children with refractory epilepsy regardless of ASD status. The observed outcomes are likely attributable to successful seizure control and the preservation of critical brain structures rather than specific effects related to ASD. Therefore, clinicians should consider these less invasive techniques when appropriate, with careful attention to early identification and comprehensive preoperative evaluation to maximize the likelihood of favorable outcomes.

## 5. Conclusions

This study demonstrates that lesionectomy and temporal lobectomy are more effective than extratemporal cortical resection and functional hemispherectomy in achieving seizure freedom and enhancing cognitive, behavioral, and quality-of-life outcomes in children with refractory epilepsy. Importantly, these findings are consistent across children with and without ASD, suggesting that the observed benefits of these surgical interventions are not exclusive to ASD populations but rather reflect broader efficacy in pediatric epilepsy management.

The outcomes indicate that the success of these less invasive surgical techniques—lesionectomy and temporal lobectomy—depends largely on the precise localization and resection of epileptogenic zones irrespective of ASD status. Significant predictors of better outcomes include the presence of structural anomalies on neuroimaging and a shorter duration of epilepsy before surgery, emphasizing the importance of timely intervention to improve seizure control and developmental trajectories. The preservation of critical brain structures appears to be a key factor contributing to the cognitive and adaptive gains observed post-surgery.

Clinically, these results underscore the need for a multidisciplinary approach that involves neurologists, neurosurgeons, neuropsychologists, and other specialists to tailor treatment strategies to individual clinical profiles rather than assuming ASD-specific effects. While lesionectomy and temporal lobectomy are associated with better seizure control and fewer perioperative complications compared to extratemporal resection and functional hemispherectomy, the findings suggest that these benefits apply broadly to children with epilepsy regardless of ASD comorbidity.

In summary, early and targeted surgical interventions, particularly lesionectomy or temporal lobectomy, can optimize outcomes for children with refractory epilepsy by enhancing seizure control, cognitive functioning, and overall quality of life. Future research should focus on prospective, multicenter studies with larger sample sizes to validate these findings and further explore the interplay between epilepsy and ASD. Such efforts are crucial to refining treatment strategies and providing optimal care for these complex children.

**Author Contributions:** Conceptualization, A.C.-V. and M.L.-Z.; methodology, A.C.-V.; software, A.C.-V.; validation, A.C.-V., M.L.-Z. and I.L.-C.-G.; formal analysis, A.C.-V.; investigation, A.C.-V.; resources, A.C.-V.; data curation, A.C.-V.; writing—original draft preparation, A.C.-V. and N.P.-G.; writing—review and editing, A.C.-V.; visualization, A.C.-V. and N.P.-G.; supervision, A.C.-V.; project administration, A.C.-V.; funding acquisition, A.C.-V. All authors have read and agreed to the published version of the manuscript.

**Funding:** Funding for open access charge: Universidad de Málaga & CBUA.

**Institutional Review Board Statement:** The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Ethics Committee of Universidad de Málaga (protocol code 120-2023-H) on 30 October 2023.

**Informed Consent Statement:** Informed consent was obtained from all the subjects involved in the study.

**Data Availability Statement:** The data presented in this study are available upon request from the corresponding author. The data are not publicly available due to specific ethical and privacy considerations.

**Conflicts of Interest:** The authors declare no conflicts of interest.

## References


1. Lord, C.; Elsabbagh, M.; Baird, G.; Veenstra-Vanderweele, J. Autism spectrum disorder. *Lancet* **2018**, *392*, 508–520. [CrossRef] [PubMed]
2. Maenner, M.J.; Shaw, K.A.; Baio, J.; Washington, A.; Patrick, M.; DiRienzo, M.; Christensen, D.L.; Wiggins, L.D.; Pettygrove, S.; Andrews, J.G.; et al. Prevalence of autism spectrum disorder among children aged 8 years—Autism and Developmental Disabilities Monitoring Network, 11 Sites, United States, 2016. *MMWR Surveill. Summ.* **2020**, *69*, 1–12. [CrossRef] [PubMed]
3. Lin, X.; Wang, G.; Shen, S.; Zhan, J. Advances in the Diagnosis and Treatment of Autism Spectrum Disorders in Children. *Altern Ther. Health Med.* **2024**, *30*, 170–175.
4. Tuchman, R.; Rapin, I. Epilepsy in autism. *Lancet Neurol.* **2002**, *1*, 352–358. [CrossRef] [PubMed]
5. Bolton, P.F.; Carcani-Rathwell, I.; Hutton, J.; Goode, S.; Howlin, P.; Rutter, M. Epilepsy in autism: Features and correlates. *Br. J. Psychiatry* **2011**, *198*, 289–294. [CrossRef] [PubMed]
6. Russ, S.A.; Larson, K.; Halfon, N. A national profile of childhood epilepsy and seizure disorder. *Pediatrics* **2012**, *129*, 256–264. [CrossRef] [PubMed]
7. Besag, F.M. Behavioral aspects of pediatric epilepsy syndromes. *Epilepsy Behav.* **2004**, *5* (Suppl. 1), 106–129. [CrossRef]
8. Yizhar, O.; Fenno, L.E.; Prigge, M.; Schneider, F.; Davidson, T.J.; O'shea, D.J.; Sohal, V.S.; Goshen, I.; Finkelstein, J.; Paz, J.T.; et al. Neocortical excitation/inhibition balance in information processing and social dysfunction. *Nature* **2011**, *477*, 171–178. [CrossRef]
9. Berg, A.T.; Plioplys, S.; Tuchman, R. Risk and correlates of autism spectrum disorder in children with epilepsy: A community-based study. *J. Child Neurol.* **2011**, *26*, 540–547. [CrossRef] [PubMed]
10. Sanders, S.J.; Murtha, M.T.; Gupta, A.R.; Murdoch, J.D.; Raubeson, M.J.; Willsey, A.J.; Ercan-Sencicek, A.G.; DiLullo, N.M.; Parikshak, N.N.; Stein, J.L.; et al. De novo mutations revealed by whole-exome sequencing are strongly associated with autism. *Nature* **2012**, *485*, 237–241. [CrossRef]
11. Nelson, S.B.; Valakh, V. Excitatory/inhibitory balance and circuit homeostasis in autism spectrum disorders. *Neuron* **2015**, *87*, 684–698. [CrossRef] [PubMed]
12. Caroli, E.; Russillo, M.; Ferrante, L. Frequency of EEG abnormalities in autism spectrum disorders: A prospective study. *J. Child Neurol.* **2006**, *21*, 49–56. [CrossRef]
13. Levisohn, P.M. The autism-epilepsy connection. *Epilepsia* **2007**, *48* (Suppl. 9), 33–35. [CrossRef] [PubMed]
14. Danielsson, S.; Gillberg, I.C.; Billstedt, E.; Gillberg, C.; Olsson, I. Epilepsy in young adults with autism: A prospective population-based follow-up study of 120 individuals diagnosed in childhood. *Epilepsia* **2005**, *46*, 918–923. [CrossRef]
15. Tatum, W.O.; DiCiaccio, B.; Yelvington, K.H. Effects of antiepileptic drugs on cognitive function: A review of clinical evidence. *Epilepsy Behavior.* **2016**, *60*, 1–21. [CrossRef]
16. Kwan, P.; Schachter, S.C.; Brodie, M.J. Drug-resistant epilepsy. *N. Engl. J. Med.* **2011**, *365*, 919–926. [CrossRef] [PubMed]
17. Laxer, K.D.; Trinka, E.; Hirsch, L.J.; Cendes, F.; Langfitt, J.; Delanty, N.; Resnick, T.; Benbadis, S.R. The consequences of refractory epilepsy and its treatment. *Epilepsy Behav.* **2014**, *37*, 59–70. [CrossRef] [PubMed]
18. Wiebe, S.; Blume, W.T.; Girvin, J.P.; Eliasziw, M.; Effectiveness and Efficiency of Surgery for Temporal Lobe Epilepsy Study Group. A randomized, controlled trial of surgery for temporal-lobe epilepsy. *N. Engl. J. Med.* **2001**, *345*, 311–318. [CrossRef]
19. Engel, J., Jr.; McDermott, M.P.; Wiebe, S.; Langfitt, J.T.; Stern, J.M.; Dewar, S.; Sperling, M.R.; Gardiner, I.; Erba, G.; Fried, I.; et al. Early surgical therapy for drug-resistant temporal lobe epilepsy: A randomized trial. *JAMA* **2012**, *307*, 922–930. [CrossRef] [PubMed]
20. Jeste, S.S. The neurology of autism spectrum disorders. *Curr. Opin. Neurol.* **2011**, *24*, 132–139. [CrossRef]
21. Rosenow, F.; Lüders, H. Presurgical evaluation of epilepsy. *Brain* **2001**, *124 Pt 9*, 1683–1700. [CrossRef]
22. Harvey, A.S.; Cross, J.H.; Shinnar, S.; Mathern, G.W.; Pediatric Epilepsy Surgery Survey Taskforce. Defining the spectrum of international practice in pediatric epilepsy surgery patients. *Epilepsia* **2008**, *49*, 146–155. [CrossRef]
23. Jayakar, P.; Gotman, J.; Harvey, A.S.; Palmini, A.; Tassi, L.; Schomer, D.; Dubeau, F.; Bartolomei, F.; Yu, A.; Kršek, P.; et al. Diagnostic utility of invasive EEG for epilepsy surgery: Indications, modalities, and techniques. *Epilepsia* **2016**, *57*, 1735–1747. [CrossRef] [PubMed]
24. Ghasemi, M.; Shafaroodi, H.; Nazarbeiki, S.; Meskar, H.; Heydarpour, P.; Ghasemi, A.; Talab, S.S.; Ziai, P.; Bahremand, A.; Dehpour, A.R. The contribution of neuropsychology to diagnostic assessment in epilepsy. *Epilepsy Behav.* **2010**, *18*, 3–12. [CrossRef]

25. Harrison, P.L.; Oakland, T. *Adaptive Behavior Assessment System*, 3rd ed.; The Psychological Corporation: San Antonio, TX, USA, 2015.
26. Engel, J., Jr. Surgical treatment for epilepsy: Too little, too late? *JAMA* **2008**, *300*, 2548–2550. [CrossRef]
27. Kloss, S.; Pieper, T.; Pannek, H.; Holthausen, H.; Tuxhorn, I. Epilepsy surgery in children with focal cortical dysplasia (FCD): Results of long-term seizure outcome. *Neuropediatrics* **2002**, *33*, 21–26. [CrossRef]
28. Ramantani, G.; Kadish, N.E.; Anastasopoulos, C. Epilepsy surgery for glioneuronal tumors in childhood: Avoid loss of time. *Neurosurgery* **2014**, *74*, 648–657. [CrossRef] [PubMed]
29. Clusmann, H.; Schramm, J.; Kral, T. Prognostic factors and outcome after different types of resection for temporal lobe epilepsy. *J. Neurosurg.* **2002**, *97*, 1131–1141. [CrossRef]
30. Quarato, P.P.; Di Gennaro, G.; Mascia, A. Temporal lobe epilepsy surgery: Different surgical strategies after a non-invasive diagnostic protocol. *J. Neurol. Neurosurg. Psychiatry* **2005**, *76*, 815–824. [CrossRef] [PubMed]
31. Schramm, J. Hemispherotomy and other disconnective techniques in epilepsy surgery: A review. *Epilepsia* **2014**, *55*, 16–21. [CrossRef]
32. Delalande, O.; Bulteau, C.; Dellatolas, G. Vertical parasagittal hemispherotomy: Surgical procedures and clinical long-term outcomes in a population of 83 children. *Neurosurgery* **2007**, *60* (Suppl. 1), 19–32. [CrossRef] [PubMed]
33. Cook, S.W.; Nguyen, S.T.; Hu, B. Cerebral hemispherectomy in pediatric patients with epilepsy: Comparison of three techniques by pathological substrate in 115 patients. *J. Neurosurg. Pediatr.* **2004**, *100* (Suppl. 2), 125–141. [CrossRef] [PubMed]
34. Cascino, G.D. Surgical treatment for epilepsy. *Epilepsy Res.* **2004**, *60*, 179–186. [CrossRef] [PubMed]
35. Graham, D.; Tisdall, M.M.; Gill, D. Corpus callosotomy outcomes in pediatric patients: A systematic review. *Epilepsia* **2016**, *57*, 1053–1068. [CrossRef]
36. Kasasbeh, A.S.; Smyth, M.D.; Steger-May, K. Outcomes after anterior or complete corpus callosotomy in children. *Neurosurgery* **2014**, *74*, 17–28. [CrossRef] [PubMed]
37. Panebianco, M.; Zavanone, C.; Dupont, S. Vagus nerve stimulation therapy in partial epilepsy: A systematic review and meta-analysis of randomized controlled trials. *Epilepsia* **2016**, *57*, 924–934. [CrossRef]
38. Ben-Menachem, E.; Hellström, K.; Waldton, C. Evaluation of refractory epilepsy treated with vagus nerve stimulation for up to 5 years. *Neurology* **1999**, *52*, 1265–1267. [CrossRef]
39. Orosz, I.; McCormick, D.; Zamponi, N. Vagus nerve stimulation for drug-resistant epilepsy: A European long-term study up to 24 months in 347 children. *Epilepsia* **2014**, *55*, 1576–1584. [CrossRef]
40. Fisher, R.; Salanova, V.; Witt, T. Electrical stimulation of the anterior nucleus of thalamus for treatment of refractory epilepsy. *Epilepsia* **2010**, *51*, 899–908. [CrossRef] [PubMed]
41. Lewis, E.C.; Weil, A.G.; Duchowny, M. MR-guided laser interstitial thermal therapy for pediatric drug-resistant lesional epilepsy. *Epilepsia* **2015**, *56*, 1590–1598. [CrossRef]
42. Willie, J.T.; Laxpati, N.G.; Drane, D.L. Real-time magnetic resonance-guided stereotactic laser amygdalohippocampotomy for mesial temporal lobe epilepsy. *Neurosurgery* **2014**, *74*, 569–584. [CrossRef] [PubMed]
43. Kang, J.Y.; Wu, C.; Tracy, J. Laser interstitial thermal therapy for medically intractable mesial temporal lobe epilepsy. *Epilepsia* **2016**, *57*, 325–334. [CrossRef] [PubMed]
44. Quigg, M.; Barbaro, N.M.; Ward, M.M. Gamma knife radiosurgery for mesial temporal lobe epilepsy: A randomized controlled trial. *JAMA* **2015**, *313*, 934–942.
45. Regis, J.; Rey, M.; Bartolomei, F. Gamma knife surgery in epilepsy. *Neurosurg. Clin. N. Am.* **2016**, *27*, 59–71. [CrossRef]
46. Barbaro, N.M.; Quigg, M.; Broshek, D.K. A multicenter, prospective pilot study of gamma knife radiosurgery for mesial temporal lobe epilepsy: Seizure response and adverse events. *Epilepsia* **2009**, *50*, 2064–2072. [CrossRef] [PubMed]
47. Kale, G.; Addepalli, V.; Joshi, S. A snapshot on introspection of autism spectrum disorder. *Mol. Biol. Rep.* **2024**, *51*, 610. [CrossRef]
48. Specchio, N.; Pietrafusa, N.; Trivisano, M. Comorbidities in tuberous sclerosis complex: Focus on epilepsy. *Epilepsy Behav.* **2017**, *70 Pt A*, 18–24. [CrossRef]
49. Boshuisen, K.; van Schooneveld, M.M.; Uiterwaal, C.S. Intelligence quotient improves after antiepilepsy surgery in children. *Ann. Neurol.* **2015**, *78*, 104–114. [CrossRef] [PubMed]
50. Muhle, R.; Trentacoste, S.V.; Rapin, I. The genetics of autism. *Pediatrics* **2004**, *113*, e472–e486. [CrossRef] [PubMed]
51. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, 5th ed.; American Psychiatric Publishing: Arlington, VA, USA, 2013.
52. Kwan, P.; Arzimanoglou, A.; Berg, A.T. Definition of drug resistant epilepsy: Consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. *Epilepsia* **2010**, *51*, 1069–1077. [CrossRef]
53. Wechsler, D. *Escala de Inteligencia de Wechsler para Niños–Quinta Edición (WISC-V)*; Pearson Education: Madrid, Spain, 2015.
54. Sparrow, S.S.; Cicchetti, D.V.; Saulnier, C.A. *Vineland Adaptive Behavior Scales*, 2nd ed.; Pearson Assessments: Minneapolis, MN, USA, 2005.
55. Rimland, B.; Edelson, S.M. *Autism Treatment Evaluation Checklist (ATEC)*; Autism Research Institute: San Diego, CA, USA, 1999.
56. Engel, J., Jr. (Ed.) Surgical treatment of the epilepsies: Summary and conclusions. In *Surgical Treatment of the Epilepsies*, 2nd ed.; Raven Press: New York, NY, USA, 1993; pp. 609–621.
57. Varni, J.W.; Seid, M.; Rode, C.A. The PedsQL: Measurement model for the pediatric quality of life inventory. *Med. Care* **1999**, *37*, 126–139. [CrossRef]

58. Lortie, A. The surgical treatment of focal cortical dysplasia in children. *Epilepsia* **2001**, *42*, 1218–1225.
59. Duchowny, M. Epilepsy surgery in children. *Curr. Opin. Neurol.* **1995**, *8*, 112–116. [CrossRef]
60. Jayakar, P.; Dunoyer, C.; Dean, P.; Ragheb, J.; Resnick, T.; Morrison, G.; Bhatia, S.; Duchowny, M. Epilepsy surgery in patients with normal or nonfocal MRI scans: Integrative strategies offer long-term seizure relief. *Epilepsia* **2008**, *49*, 758–764. [CrossRef] [PubMed]
61. Samuel P, J.; Menon, R.N.; Chandran, A.; Thomas, S.V.; Vilanilam, G.; Abraham, M.; Radhakrishnan, A. Seizure outcome and its predictors after frontal lobe epilepsy surgery. *Acta Neurol. Scand.* **2019**, *140*, 259–267. [CrossRef] [PubMed]
62. Bulacio, J.C.; Jehi, L.; Wong, C.; Gonzalez-Martinez, J.; Kotagal, P.; Nair, D.; Najm, I.; Bingaman, W. Long-term seizure outcome after resective surgery in patients evaluated with intracranial electrodes. *Epilepsia* **2012**, *53*, 1722–1730. [CrossRef] [PubMed]
63. Lee, Y.J.; Lee, J.S. Temporal lobe epilepsy surgery in children versus adults: From etiologies to outcomes. *Korean J. Pediatr.* **2013**, *56*, 275–281. [CrossRef] [PubMed]
64. Cross, J.H. Epilepsy surgery in childhood. *Epilepsia* **2002**, *43* (Suppl. 3), 65–70. [CrossRef]
65. Boshuisen, K.; Lamberink, H.J.; van Schooneveld, M.M.; Cross, J.H.; Arzimanoglou, A.; van der Tweel, I.; Geleijns, K.; Uiterwaal, C.S.; Braun, K.P. Cognitive consequences of early versus late antiepileptic drug withdrawal after pediatric epilepsy surgery, the TimeToStop (TTS) trial: Study protocol for a randomized controlled trial. *Trials* **2015**, *16*, 482. [CrossRef]
66. Ramantani, G.; Reuner, G. Cognitive Development in Pediatric Epilepsy Surgery. *Neuropediatrics* **2018**, *49*, 93–103. [CrossRef] [PubMed]
67. Skirrow, C.; Cross, J.H.; Cormack, F.; Harkness, W.; Vargha-Khadem, F.; Baldeweg, T. Long-term intellectual outcome after temporal lobe surgery in childhood. *Neurology* **2011**, *76*, 1330–1337. [CrossRef]
68. Westerveld, M.; Sass, K.J.; Chelune, G.J. Temporal lobectomy in children: Cognitive outcome. *J. Neurosurg.* **2000**, *92*, 24–30. [CrossRef]
69. Baca, C.B.; Vickrey, B.G.; Caplan, R.; Vassar, S.D.; Berg, A.T. Psychiatric and medical comorbidity and quality of life outcomes in childhood-onset epilepsy. *Pediatrics* **2011**, *128*, e1532–e1543. [CrossRef]
70. Hara, H. Autism and epilepsy: A retrospective follow-up study. *Brain Dev.* **2007**, *29*, 486–490. [CrossRef] [PubMed]
71. Bird, F.; Shlesinger, A.; Duhanyan, K.; Luiselli, J.K. Data recording of seizures in children with autism spectrum disorder: Description and social validation of computer-assisted measurement. *Int. J. Dev. Disabil.* **2022**, *70*, 625–631. [CrossRef]
72. Hauptman, J.S.; Mathern, G.W. Surgical treatment of epilepsy associated with cortical dysplasia: 2012 update. *Epilepsia* **2012**, *53* (Suppl. 4), 98–104. [CrossRef] [PubMed]
73. Fridley, J.; Reddy, G.; Curry, D.; Agadi, S. Surgical treatment of pediatric epileptic encephalopathies. *Epilepsy Res. Treat.* **2013**, *2013*, 720841. [CrossRef]
74. Choi, J.; Koh, S. Role of brain inflammation in epileptogenesis. *Yonsei Med. J.* **2008**, *49*, 1–18. [CrossRef] [PubMed]
75. Widjaja, E.; Jain, P.; Demoe, L.; Guttmann, A.; Tomlinson, G.; Sander, B. Seizure outcome of pediatric epilepsy surgery: Systematic review and meta-analyses. *Neurology* **2020**, *94*, 311–321. [CrossRef]
76. Wyllie, E.; Comair, Y.G.; Kotagal, P.; Bulacio, J.; Bingaman, W.; Ruggieri, P. Seizure outcome after epilepsy surgery in children and adolescents. *Ann. Neurol.* **1998**, *44*, 740–748. [CrossRef] [PubMed]