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Impact of resective surgery for pediatric drug-resistant epilepsy on emotional functioning

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ABSTRACT

Objective: The objective of the study was to evaluate emotional functioning following surgical and medical treatment in children with drug-resistant epilepsy (DRE; i.e., uncontrolled seizures despite treatment with ≥2 antiepileptic drugs [AED]).
Method: This prospective, longitudinal, multicenter study involved 128 children and adolescents (8–18 years) with DRE who were assessed for surgical candidacy; 48 went on to have surgery and 80 continued medical treatment. Participants completed child-validated self-report measures of anxiety and depression at baseline, 6, and 12 month follow-up. Standardized z-scores were calculated with higher scores indicative of greater symptoms.
Results: At baseline, 16% and 22% of all patients reported elevated symptoms of depression and anxiety, respectively (i.e., z ≥ 1.00). Seizure freedom was higher in the surgical, compared with the medical, group at 6 (64 vs. 11%) and 12 month (77 vs. 24%) follow-up. Linear mixed effects models controlling for age found a main effect of time for both depression and anxiety; scores decreased over time for all patients. A main effect of seizure outcome was found for depression, but not anxiety; seizure freedom was associated with lower scores overall. There were no main effects of treatment or significant interactions. Multiple regression analyses found baseline mood predicted outcomes at 6 and 12 month follow-up; higher anxiety and depression scores at baseline were associated with higher scores at follow-up. Older age and greater number of AEDs at baseline was associated with higher depression scores at 12 month follow-up.
Conclusion: Overall, patients reported a reduction in anxiety and depressive symptoms over the first 12 months, irrespective of treatment, and baseline level of functioning was the best predictor of outcome. Despite more children achieving seizure freedom with surgery compared with medical treatment, surgery was not associated with better outcomes over time. It may be that changes in anxiety and depression require a longer time to emerge postsurgery; however, being seizure-free is associated with fewer depressive symptoms, irrespective of treatment type.

1. Introduction

Children with epilepsy experience significantly higher rates of anxiety and depression (i.e., 15–36% and 8–35%, respectively) compared with the general pediatric population (i.e., 4–7% and 1–3%, respectively) [1], placing them at risk of lifelong disability (including the development of serious psychiatric illness) and poor quality of life [2,3] well into adulthood. Internalizing problems, including anxiety and depression, are more prevalent in children with persistent seizures and with greater seizure severity [4–6]. Consequently, children with drug-resistant epilepsy (DRE), which is characterized by poor seizure control despite medical treatment on at least two antiepileptic drug (AED) schedules [7], are at increased risk of psychiatric comorbidities [5]. Resective surgery improves seizure control in up to 90% of children and adults with DRE [8,9], and the benefits may extend to improvements in emotional functioning. Yet, few studies have examined psychological outcomes of epilepsy surgery in children with DRE [10].

According to a recent systematic review, emotional–behavioral outcomes after surgery are mixed [10], with postsurgical improvements in internalizing (i.e., internal processes such as anxiety and depression) problems found in some [11,12], but not all [13–17] studies involving children with DRE. Better outcome has been shown to be associated

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with the degree of seizure control, independent of treatment, in the long-term (i.e., 4–11 years) [18,19], rather than short-term (i.e., 1–2 years) [13,16] follow-up studies. That is, patients who were seizure-free at long-term follow-up had significantly fewer depressive symptoms and reported being less withdrawn compared with those with continued seizures, irrespective of whether patients had received surgery or medical treatment [18,19]. Nevertheless, these two studies comprised the same sample of children, and rates of seizure freedom at follow-up were comparable across treatment groups, which may explain the lack of group difference (i.e., surgical vs. control) in internalizing symptoms at follow-up [18,19]. Site and side of surgical resection may influence outcome, with one study demonstrating significantly greater improvement in anhedonia, social anxiety, and withdrawn/depressed symptoms in children who underwent left frontal compared with left temporal surgery, while no differences were found between those who underwent right frontal versus right temporal surgeries [11]. In contrast, two other studies failed to find an association between site or side of resection and internalizing behavior [16] or psychosocial outcome [13] following surgery. There is some evidence that greater number of AEDs, but not other clinical factors (i.e., age at seizure onset, age at surgery, intelligence etc.), is associated with poorer internalizing problems, including withdrawn/depressed symptoms, and poorer psychosocial functioning at follow-up [16,19]. Baseline functioning has been shown to predict change over time in at least one study, with higher (worse) scores associated with greater improvement in psychosocial functioning after surgery [13].

The limited number of studies and heterogeneous study designs, however, make it difficult to draw conclusions regarding emotional functioning outcome following surgery. Studies have involved variable follow-up periods [18,19], small sample sizes [12,14,15,17], largely cross-sectional study designs [18,19], or lack of control groups [11,15], making it difficult to differentiate the impact of surgery on change in emotional functioning over time, from other factors such as developmental maturation, seizure progression, and test–retest effects. Moreover, most studies primarily relied on parent report of children's emotional functioning [12–17]. However, high levels of disagreement between parent proxy- and child self-report of behavior are common [20], especially for internalizing, relative to externalizing (i.e., external behaviors such as acting out, antisocial behavior, hostility, aggression), problems [21,22]. In general, children report significantly more behavioral problems, including internalizing problems, than their parents, and agreement is particularly low for anxiety symptoms. Yet, research indicates that children may be better predictors of their internalizing experiences than their parents as indicated by higher correlations between child self-reported anxiety (compared with parent report) and physiological response (e.g., heart rate, sweat gland activity as measured by galvanic skin response) to fear stimuli [23,24]. Parent–child disagreement extends to populations with epilepsy such that children with epilepsy report significantly more symptoms of anxiety overall [3,18], as well as higher rates of obsessive–compulsive disorder, panic, and generalized anxiety disorder, compared with their parents [3]. In addition, parental emotional factors, including anxiety and depression, associated with caring for a child with chronic illness has been shown to be related to parent reporting of child internalizing psychopathology [25–27], questioning the precision of parent report in assessing internalizing problems following surgery.

Taking into account the limitations of previous research, this study examined child self-reported changes in emotional functioning (i.e., anxiety and depression) following resective epilepsy surgery in children with DRE, compared with control children with DRE who did not undergo surgery (i.e., continued medical treatment on AEDs). Given that resective surgery results in improved seizure control [8,9] and children who achieve seizure control exhibit fewer internalizing symptoms [4–6], we hypothesized that children undergoing surgery would demonstrate greater improvement (i.e., reduction of symptoms) in anxiety and depression, compared with children undergoing medical treatment, from baseline to follow-up (6 and 12 months). Based on previous studies, it was also expected that baseline characteristics (demographic, seizure-related, mood) would predict anxiety and depression at follow-up.

2. Material and methods

2.1. Participants

Participants were 128 children with DRE who had undergone multidisciplinary evaluation to determine candidacy for resective epilepsy surgery (from 2013 to 2018). Data were obtained from the Impact of Paediatric Epilepsy Surgery on Health Related Quality of Life Study (PEPSQOL), a larger, ongoing, prospective, longitudinal, multicenter cohort study involving children aged 4 to 18 years [28,29]. Participants were recruited from nine hospitals across Canada: The Hospital for Sick Children, Toronto; McMaster Children's Hospital, Hamilton; London Health Sciences Centre, London; Alberta Children's Hospital, Calgary; British Columbia Children's Hospital, Vancouver; The Children's Hospital of Winnipeg, Winnipeg; CHU *Sainte-Justine*, Montreal; Royal University Hospital, Saskatoon; IWK Children's Hospital, Halifax.

Only those participants who (i) were aged ≥8 years old (due to available normative data on outcomes measures) and (ii) had data at baseline and follow-up (6 and/or 12 months) on self-report measures were included in this study. Exclusion criteria included (i) previous neurosurgical procedure or vagal nerve stimulator placement, (ii) neurometabolic disorders, neurodegenerative disorders, and genetic epilepsy syndromes, and (iii) primary generalized epilepsy and epileptic encephalopathies.

Patients with localization-related epilepsy (assessed by clinical semiology and/or electroencephalography) who underwent resective surgery comprised the surgical group ($n = 48$). Those who did not undergo resective surgery because of ineligibility (e.g., unilateral seizure focus could not be identified) or other reasons (e.g., epileptogenic zone involved eloquent cortex) but continued with medical treatment (i.e., AEDs) served as the control group ($n = 80$). There was, however, a small proportion of patients in the control group who were still being investigated for surgical candidacy during the study period who eventually went on to have surgery ($n = 9$, 11.25%).

2.2. Measures

2.2.1. Depressive and anxiety symptoms

Because of the age of participants included in the larger cohort study (i.e., 4 to 18 years) and the lack of available measures spanning the entire age range, children and adolescents completed different, but comparable, measures of depression and anxiety, all of which included items corresponding to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) diagnostic criteria for major depressive disorder and generalized anxiety disorder [30]. Consequently, scores from measures of anxiety and depression were standardized using normative data and converted to z-scores for comparative purposes. Higher z-scores indicate greater anxiety or depressive symptomology.

In children aged 8 to 11 years, the Major Depressive Disorder and Generalized Anxiety Disorder subscales of the Revised Children's Anxiety and Depression Scale (RCADS) [31,32] was used to examine depressive and anxiety symptoms, respectively. The RCADS is a 47-item standardized child self-report measure with responses rated on a 4-point Likert scale from 0 (never) to 3 (always). The Major Depression subscale is comprised of 10 items with a total raw score of 0 to 30 while the Generalized Anxiety Disorder subscale is comprised of 6 items with scores ranging from 0 to 18. The RCADS Major Depression and Generalized Anxiety Disorder subscales have demonstrated good internal consistency (Cronbach's $\alpha = 0.82$–0.87) [32,33], adequate test–retest reliability ($r = 0.64$–0.85) [31] as well as convergent validity with the Child Depression Inventory ($r = 0.70$) and Revised Children's

Manifest Anxiety Scale ($r = 0.65$), respectively [32]. The RCADS has been validated for use in children as young as 6 years old; however, normative data are only available for Grade 3 and above [31]. We initially calculated *T*-scores (i.e., [*M*] = 50, standard deviation [*SD*] = 10) using the RCADS normative data [34] based on the child's sex and grade level. *T*-scores were then converted to standardized z-scores (i.e., $M = 0.00$, $SD = 1.00$).

In adolescents aged 12 to 18 years, the total score from the Quick Inventory of Depressive Symptomology, Self-Report (QIDS-SR_{16}) [35] was used to assess depression. The QIDS-SR_{16} is a 16-item questionnaire with responses rated on a 4-point Likert scale from 0 to 3 and a total score of 0 to 27. The QIDS-SR_{16} has been shown to be a valid measure of depressive symptomology with adequate psychometric properties [36]. Moderate to high correlations with other measures of depressive symptomology ($r = 0.68$–0.95) [35,36] and good internal consistency (Cronbach's $\alpha = 0.86$–0.81) [37,38] have been found. The QIDS-SR_{16} has been validated for use in adolescent outpatients aged 12 years and over [37], as well as in adolescents from the general population [38]. Raw scores from the QIDS-SR_{16} were converted to standardized z-scores using data obtained from adolescents in the general population ($N = 342$, $M = 1.73$, $SD = 8.14$) [38].

The total score from the Generalized Anxiety Disorder 7-item (GAD-7) scale [39] was used to examine anxiety symptoms in adolescents. The GAD-7 is a 7-item questionnaire comprising a 4-point Likert scale with scores ranging from 0 to 21. The GAD-7 has demonstrated strong reliability, including good to excellent internal consistency (Cronbach's $\alpha = 0.92$) [39,40] and good test–retest reliability (intraclass correlation = 0.82) [39]. Convergent validity has also been shown to be adequate ($r = 0.72$–0.74) [39]. The GAD-7 has been validated in adolescent clinical (i.e., adolescents with generalized anxiety disorder) [41] and community samples [40]. Data from adolescent community samples ($N = 5036$, $M = 2.95$, $SD = 4.00$) [40] were used to convert raw scores from the GAD-7 to standardized z-scores.

2.3. Procedure

Research ethics board approvals were obtained at each site. Parents and/or patients provided informed written consent or assent as appropriate. Paper-based or online questionnaires were completed by patients individually, or with assistance from parents or researchers if required, at baseline and again at 6- and 12-month follow-up. For those requiring assistance, parents/researchers simply read the questions to the child and had the child select the appropriate response. Parents only assisted in response selection for a small portion of participants ($n = 4$; 3.13%); in these cases, either the parent felt the questions were too sensitive for the child to answer or the child had developmental delay. Parents were prompted to read the questions without any indications of positive or negative answers in order to avoid assistance affecting the ratings.

Data were collected, managed, and stored using the REDCap (Research Electronic Data Capture) tool, which is a secure web-based application designed to support data capture for research studies [42].

2.4. Analyses

Data were analyzed using IBM Statistical Package for Social Sciences (SPSS Statistics 23). Between-group differences (surgical vs. medical) on demographic and seizure-related variables, baseline anxiety and depression scores (z-scores and proportion of patients in the borderline to clinical range i.e., $z \geq 1.00$), as well as seizure outcome (seizure-free vs. continued seizures) at 6 and 12 month, were analyzed using independent samples *t*-tests for continuous variable or chi-square (χ^2) tests for categorical variables. The magnitude of effect sizes was interpreted as follows: for χ^2 tests, phi (ϕ) was considered small ($\phi = 0.01$), medium ($\phi = 0.03$), and large ($\phi = 0.05$); and for independent samples *t*-tests, Cohen's d (*d*) was considered very small ($d = 0.01$), small ($d = 0.20$), medium ($d = 0.50$), large ($d = 0.80$), and very large ($d = 1.20$) [43,44].

Linear mixed effects modeling examined the change in self-reported depression and anxiety for the surgical and medical group over time. Group (surgical vs. medical) and Time (baseline, 6-month follow-up, and 12-month follow-up) were entered as fixed factors. Seizure outcome (seizure-free vs. continued seizures) and age (in years) were entered as time-variant covariates. A model with a random intercept (patients and hospital site) and slope (time) was compared with a repeated measures model (with different covariance matrices) for fit according to Akaike's information criterion. While patients and hospital site were initially entered as random effects, no clustering effect of hospital site was found. Hospital site was removed from the model. A repeated measures model provided the best model fit. As such, time was specified as a repeated measure using an unstructured covariance matrix. All analyses were conducted using residual maximum likelihood estimation. Two-way (Group by Time, Seizure Outcome by Time, Seizure Outcome by Group) and three-way (Group by Time by Seizure Outcome) interactions were included in the model; however, interactions that did not reach significance ($p > .05$) were removed from the model sequentially starting with higher order interactions (i.e., backward selection method). Simple effects analysis and pairwise comparisons with Sidak correction for multiple comparisons were planned in the event of significant main effects and interactions.

Clinically important change at the individual level was also examined. We calculated the proportion of patients who improved (i.e., scored within the borderline–clinical range at baseline, but within the normal range at follow-up) or deteriorated (i.e., scored within the normal range at baseline, but within the borderline–clinical range at follow-up) from baseline to 6- and 12-month follow-up. Between-group differences (treatment: surgical vs. medical; seizure outcome: seizure-free vs. continued seizures) in clinical change on anxiety and depression measures were then examined using χ^2 or Fisher's exact tests where appropriate.

Linear multiple regression examined baseline predictors of anxiety and depression at 6 and 12 month follow-up. First, a series of univariable linear regressions were conducted to identify relevant variables predictive of outcome (i.e., anxiety and depression scores); baseline demographic (age, sex, full scale intelligence quotient [FSIQ]) and seizure-related variables (age at seizure onset, duration of epilepsy, site [unilobar—temporal, unilobar—extratemporal, multilobar] and side [left, right, bilateral] of seizures, number of AEDs at baseline, and baseline seizure frequency [low, high]), as well as baseline depression and anxiety scores. Variables found to be significant predictors (i.e., $p < .05$) in the univariable regression were included in multivariable regression.

3. Results

3.1. Demographic and clinical characteristics

Demographic, seizure/surgical-related variables, and baseline anxiety and depression scores for the total sample and by treatment group are shown in Table 1. There were no significant differences in baseline demographic or seizure/surgical-related variables between children who underwent surgery and those that received medical treatment, with the exception of seizure laterality, $\chi^2_{(2)} = 6.84$, $p = .033$, $\phi = 0.24$. Post hoc tests using the adjusted residual method found that the treatment (medical vs. surgical) groups differed with respect to the proportion of patients in each group who had bilateral (12.9% vs. 0.0%; $z = 2.56$, $\chi^2_{(1)} = 6.55$, $p = .010$), but not left (47.1% vs. 48.9%; $z = 1.18$, $\chi^2_{(1)} = 1.39$, $p = .238$) or right (40.0% vs. 51.1%; $z = 0.19$, $\chi^2_{(1)} = 0.04$, $p = .849$) side of seizure focus. This was due to no patients in the surgical group experiencing bilateral seizures, which was expected as it is a contraindication for surgery.

At follow-up, a larger proportion of patients in the surgery group were seizure-free compared with those in the medical group (6 months, $\chi^2_{(1)} = 36.32, p < .001, \phi = 0.56$; 12 months, $\chi^2_{(1)} = 26.11, p < .001, \phi = 0.53$). There were no group differences in the number of AEDs at baseline, 6, or 12 month follow-up.

There were no significant differences in baseline anxiety or depression between the surgical and medical group. The proportion of patients at risk of major depressive disorder and generalized anxiety disorder (i.e., z-score ≥ 1.00) at baseline was 15.7% and 22.0%, respectively.

3.2. Change in emotional functioning over time: group change

Results of linear mixed effects models are presented in Table 2. The model predicting depressive symptoms found that age was a significant predictor ($F_{(1, 119.56)} = 37.29, p < .001$), such that younger age was associated with fewer depressive symptoms. There was a significant main effect of time ($F_{(1, 120.65)} = 7.10, p = .009$), indicating a reduction in depressive symptoms over the 12-month period for the entire sample. There was also a significant main effect of seizure outcome ($F_{(1, 212.38)}$

Table 1
Demographic and seizure/surgical characteristics.

Characteristic	Total ($N = 128$)	Medical ($n = 80$)	Surgical ($n = 48$)	Between-group difference
Sex, *n* (%)				$\chi^2_{(1)} = 2.47, p = .116, \phi = 0.14$
Male	74 (57.8)	42 (52.5)	32 (66.7)	
Female	54 (42.2)	38 (47.5)	16 (33.3)	
Age at baseline (years)				$t_{(126)} = 1.57, p = .119, d = 0.28$
Mean (SD)	13.09 (2.66)	12.80 (2.54)	13.56 (2.81)	
Age at seizure onset (years)				$t_{(125)} = 0.16, p = .872, d = 0.03$
Mean (SD)	7.60 (4.09)	7.55 (4.21)	7.67 (3.50)	
Duration of epilepsy (years)				$t_{(125)} = 0.77, p = .443, d = 0.14$
Mean (SD)	5.47 (4.17)	5.25 (4.00)	5.84 (4.46)	
Percent of life with epilepsy				$t_{(125)} = 0.17, p = .866, d = 0.03$
Mean (SD)	58.64 (29.39)	58.31 (30.65)	59.22 (27.43)	
Age at surgery (years)				–
Mean (SD)	–	–	13.72 (2.83)	
Full-scale intelligence quotient				$t_{(110)} = 0.97, p = .333, d = 0.19$
Mean (SD)	87.76 (17.89)	86.49 (18.71)	89.88 (16.41)	
Range	44–125	44–125	45–120	
Seizure frequency at baseline[a], *n* (%)				$\chi^2_{(1)} = 0.85, p = .356, \phi = 0.08$
High: daily–weekly	73 (57.0)	42 (57.5)	31 (66.0)	
Low: monthly–yearly	47 (36.7)	31 (42.5)	16 (34.0)	
Site of seizure focus[b], *n* (%)				$\chi^2_{(2)} = 2.80, p = .247, \phi = 0.16$
Unilobar: temporal	43 (37.7)	23 (34.3)	20 (42.6)	
Unilobar: extratemporal	48 (42.1)	27 (40.3)	21 (44.7)	
Multilobar	23 (20.2)	17 (25.4)	6 (12.8)	
Laterality of seizure focus[c], *n* (%)				$\chi^2_{(2)} = 6.84, p = .033, \phi = 0.24$
Left	56 (47.9)	33 (47.1)	23 (48.9)	
Right	52 (44.4)	28 (40.0)	24 (51.1)	
Bilateral	9 (7.7)	9 (12.9)	0 (0.0)	
Pathology[d], *n* (%)				
Focal cortical dysplasia	–	–	13 (27.1)	–
Subpial/mild gliosis	–	–	11 (22.9)	–
Tumor	–	–	8 (16.7)	–
Chronic gliosis from previous infarct or hemorrhage	–	–	4 (8.3)	–
Hippocampus sclerosis	–	–	4 (8.3)	–
Tuberous sclerosis	–	–	1 (2.1)	–
Cavernoma	–	–	1 (2.1)	–
Other/no data	–	–	10 (20.8)	–
Number of AEDs, Mean (SD)				
Baseline	1.88 (0.83)	1.84 (0.86)	1.96 (0.77)	$t_{(126)} = 0.80, p = .427, d = 0.15$
6 months	1.95 (0.93)	1.69 (0.81)	2.11 (1.01)	$t_{(113)} = 1.74, p = .085, d = 0.32$
12 months	1.85 (0.96)	1.73 (0.91)	2.03 (1.02)	$t_{(96)} = 1.54, p = .126, d = 0.32$
Seizure status/outcome, *n* (%)				
6 months[e]				$\chi^2_{(1)} = 36.32, p < .001, \phi = 0.56$
Seizure-free	36 (30.5)	8 (10.8)	28 (63.6)	
Continued seizures	82 (69.5)	66 (89.2)	16 (36.4)	
12 months[f]				$\chi^2_{(1)} = 26.11, p < .001, \phi = 0.53$
Seizure-free	43 (45.7)	13 (23.6)	30 (76.9)	
Continued seizures	51 (54.3)	42 (76.4)	9 (23.1)	
Baseline anxiety symptoms				
z-Scores, Mean (SD)	0.16 (1.50)	0.24 (1.56)	0.03 (1.40)	$t_{(125)} = 0.74, p = .459, d = 0.14$
Borderline–clinical range[g], *n* (%)	28 (22.0)	19 (24.1)	9 (18.8)	$\chi^2_{(1)} = 0.49, p = .485, \phi = 0.06$
Baseline depressive symptoms				
z-Scores, Mean (SD)	0.36 (0.85)	0.42 (0.92)	0.27 (0.71)	$t_{(125)} = 0.92, p = .362, d = 0.18$
Borderline–clinical range[g], *n* (%)	20 (15.7)	15 (19.0)	5 (10.4)	$\chi^2_{(1)} = 1.65, p = .199, \phi = 0.11$

Note. AED = antiepileptic drugs.
[a] Data unavailable for 1 patient (1 surgical, 0 nonsurgical), and 7 patients reportedly had no seizures in the previous year (0 surgical, 7 nonsurgical).
[b] Data unavailable for 2 patients (1 surgical, 1 nonsurgical) and site of seizure focus unable to be located in 12 patients (0 surgical, 12 nonsurgical).
[c] Data unavailable for 11 patients (1 surgical [not reported], 10 nonsurgical [2 not reported, 8 unable to locate]).
[d] More than one type of pathology reported in 4 surgical cases.
[e] Data based on $n = 118$.
[f] Data based on $n = 94$.
[g] Borderline–clinical range classified as ≥1 standard deviation above the mean (i.e., z ≥ 1.0); data unavailable for 1 patient (anxiety score, nonsurgical) and 1 patient (depression score, nonsurgical).

= 4.27, $p = .040$), suggesting that fewer depressive symptoms were reported among seizure-free patients ($M = 0.13$, 95% confidence interval CI [−0.06, 0.31], standard error [SE] = 0.10), relative to those with continued seizures ($M = 0.34$, 95% CI [0.22, 0.46], $SE = 0.06$). There was no main effect of group ($F_{(1, 128.90)} = 0.78$, $p = .377$). Two- and three-way interactions were not included in the final model as no significant interactions were found (i.e., all $p > .05$).

With respect to anxiety, age was again found to be a significant predictor ($F_{(1, 132.21)} = 30.98$, $p < .001$), indicating that younger age was associated with fewer symptoms of anxiety. A main effect of time was found ($F_{(1, 131.87)} = 4.79$, $p = .030$) indicating a reduction in anxiety over time. There was no main effect of group ($F_{(1, 140.23)} = 0.55$, $p = .459$) or seizure outcome ($F_{(1, 166.29)} = 0.46$, $p = .500$). No significant interactions were found and as such were removed from the model.

3.3. Change in emotional functioning over time: individual clinical change

The proportion of patients in each group (surgical vs. medical and seizure-free vs. continued seizures) that reported clinically meaningful change from baseline to 6 and 12 month follow-up is shown in Fig. 1. There were no significant group differences in the proportion of patients who reported improvement or deterioration when comparing treatment groups or seizure outcome (i.e., $p > .05$). Most patients reported no clinically meaningful change, and of these, a small portion remained in the borderline to clinical range for anxiety (6 months: surgical 9% vs. medical 13%, and continued seizures 14% vs. seizure-free 6%; 12 months: surgical 14% vs. medical 11%, and continued seizures 19% vs. seizure-free 6%) or depression (6 months: surgical 6% vs. medical 7%, and continued seizures 4% vs. seizure-free 3%; 12 months: surgical 3% vs. medical 4%, and continued seizures 2% vs. seizure-free 3%).

3.4. Predictors of outcome in emotional functioning at follow-up for the entire sample (surgical and medical)

A series of exploratory linear bivariable regressions identified older age ($\beta = 0.35$, $p < .001$), female sex ($\beta = 0.23$, $p = .009$), older age at seizure onset ($\beta = 0.25$, $p = .006$), higher baseline anxiety ($\beta = 0.55$, $p < .001$), and higher baseline depression ($\beta = 0.41$, $p < .001$) scores as individual predictors of higher anxiety scores at 6 month follow-up. No other significant predictors (demographic or seizure-related) were found. As such, these five variables were entered into the multivariable regression model predicting anxiety at 6 months. After removal of three multivariable outliers, the model was significant ($R^2 = 0.43$, $F_{(5,114)} = 18.49$, $p < .001$) accounting for 43% of the variance in anxiety scores. Only baseline anxiety ($\beta = 0.49$, $p < .001$) remained as a significant predictor; higher baseline anxiety scores were associated with higher anxiety scores at 6 month follow-up (Table 3).

Results of linear bivariable regressions predicting anxiety at 12 month follow-up identified older age ($\beta = 0.42$, $p < .001$), greater number of AEDs ($\beta = 0.21$, $p = .044$), higher baseline anxiety ($\beta = 0.64$, $p < .001$), and higher baseline depression ($\beta = 0.61$, $p < .001$) scores as significant individual predictors. When these variables were entered into the multivariable regression, only baseline anxiety ($\beta = 0.44$, $p < .001$) and baseline depression ($\beta = 0.26$, $p < .001$), but not age or number of AEDs, remained significant. Baseline anxiety emerged as the strongest predictor of anxiety at 12 month follow-up. The model accounted for 61% of the variance ($R^2 = 0.61$, $F_{(4,83)} = 32.46$, $p < .001$).

Older age ($\beta = 0.40$, $p < .001$), female sex ($\beta = 0.21$, $p = .019$), higher baseline depression ($\beta = 0.52$, $p < .001$), and higher baseline anxiety ($\beta = 0.47$, $p = .021$) scores were all identified as individual predictors of higher depressive symptoms at 6 month follow-up. Results of the multivariable regression revealed that age ($\beta = 0.18$, $p = .032$) and baseline depression ($\beta = 0.35$, $p = .001$) remained significant, with baseline depression identified as the strongest predictor of depression at 6 month follow-up. The model accounted for 36% of the variance ($R^2 = 0.36$, $F_{(4,118)} = 16.58$, $p < .001$).

When depressive symptoms were examined at 12 month follow-up, older age ($\beta = 0.52$, $p < .001$), greater number of AEDs ($\beta = 0.32$, $p = .002$), baseline depression ($\beta = 0.58$, $p < .001$), and baseline anxiety ($\beta = 0.53$, $p < .001$) scores were found to significantly predict follow-up depression scores. When these variables were entered into the multivariable regression model, all variables remained significant; age ($\beta = 0.21$, $p = .023$), number of AEDs ($\beta = 0.21$, $p = .007$), baseline anxiety ($\beta = 0.21$, $p = .032$), and baseline depression ($\beta = 0.36$, $p = .001$); baseline depression was found to be the strongest predictor of depression at 12 month follow-up. The total variance explained by the model was 52% ($R^2 = 0.52$, $F_{(4,86)} = 23.60$, $p < .001$).

4. Discussion

The primary aim of this study was to evaluate changes in child self-reported emotional functioning, specifically anxiety and depression, across the first 12 months following surgery, compared with medical treatment only, in pediatric DRE. We found no effect of surgery on emotional functioning relative to medical treatment only. Instead, patients in both groups (surgical and medical) improved over time as indicated by a reduction in self-reported depressive and anxiety symptoms from baseline to follow-up. Moreover, seizure freedom at follow-up was associated with better functioning, with patients who were seizure-free reporting fewer depressive (but not anxiety) symptoms overall, compared with those who experienced continued seizures. The secondary aim was to examine baseline predictors of functioning at follow-up in order to identify child factors associated with better outcome. The strongest and most consistent predictor of depressive and anxiety symptoms at follow-up was baseline depression and anxiety scores, respectively; patients who reported fewer symptoms at baseline also reported fewer symptoms at 6 and 12 month follow-up. Few demographic or seizure-related variables were associated with

Table 2
Results of linear mixed effects models examining change in anxiety and depression over time for the surgical and medical treatment groups.

Parameter	Depression			Anxiety		
	B	[95% CI]	p	B	[95% CI]	p
Intercept	−1.32**	[−1.91, −0.73]	<.001	−2.81**	[−3.91, −1.70]	<.001
Age[a]	0.12**	[0.08, 0.17]	<.001	0.21**	[0.14, 0.29]	<.001
Group	0.10	[−0.13, 0.34]	.377	0.17	[−0.27, 0.60]	.459
Time	−0.23**	[−0.40, −0.06]	.009	−0.36*	[−0.69, −0.03]	.030
Seizure status/outcome[a]	−0.21*	[−0.42, −0.01]	.040	0.13	[−0.24, 0.49]	.500

Note. 2-way (Group * Time, Seizure * Time, Group * Seizure) and 3-way (Group * Time * Seizure) interaction effects were removed from the model as $p > .05$. All analyses based on residual maximum likelihood estimation.

[a] Age (years) and seizure status/outcome (0 = seizure-free, 1 = continued seizures) entered as time-variant predictors.

* $p < .05$.

** $p < .01$.

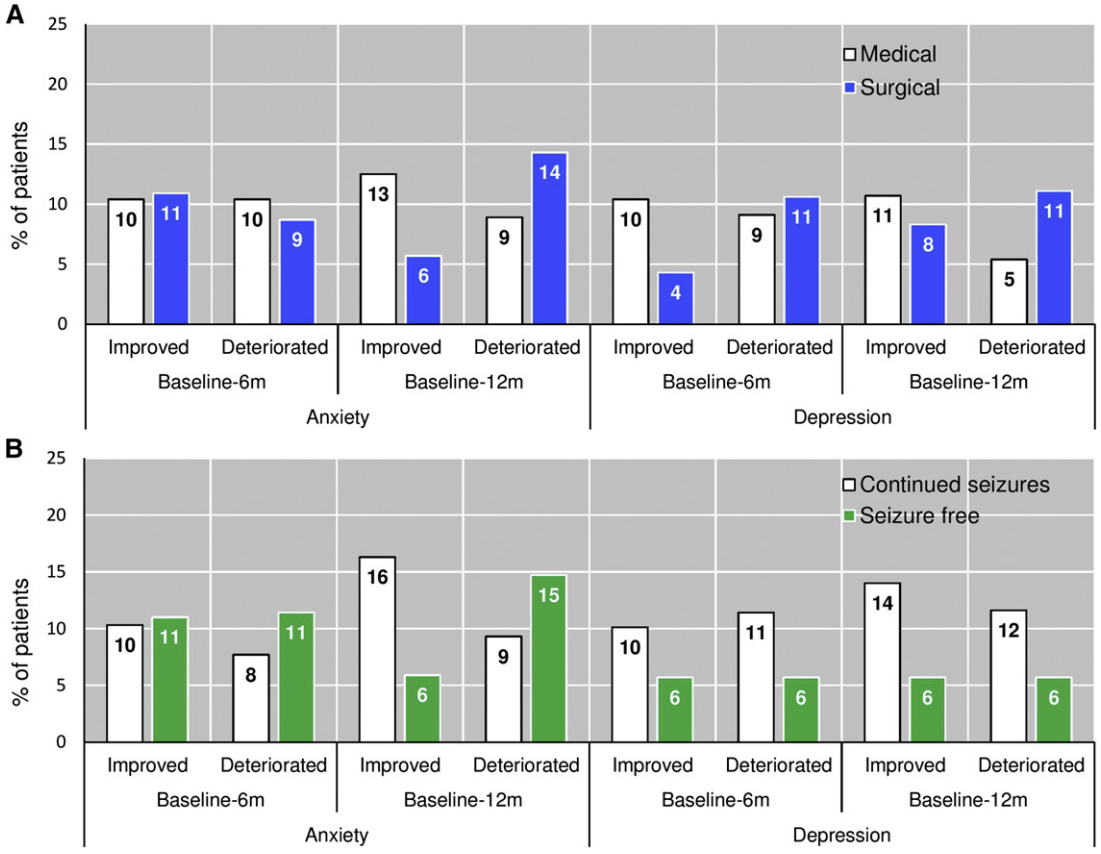

Fig. 1. Proportion (%) of patients who demonstrated clinically meaningful improvement (borderline-clinical range at baseline [z ≥ 1.00], but normal range at follow-up [z < 1.00]) or deterioration (normal range at baseline [z < 1.00]), but borderline-clinical range at follow-up [z ≥ 1.00]) in anxiety and depressive symptoms from baseline to 6 and 12 month follow-up stratified by A) treatment group, and B) seizure outcome. There were no significant group differences found (all $p > .05$). The proportion of patients who did not demonstrate clinically meaningful change is not shown.

outcome, except for age and number of AEDs; younger patients and those taking fewer AEDs reported fewer depressive (but not anxiety) symptoms at follow-up.

Contrary to expectations, children who underwent surgery did not exhibit greater improvements in anxiety or depression, compared with those continuing on medical treatment, despite more than three-

Table 3
Multivariable regression predicting anxiety and depressive symptoms at 6 and 12 month follow-up.

Predictors	Anxiety									
	6 months					12 months				
	R^2	*B*	[95% CI]	β	*p*	R^2	*B*	[95% CI]	β	*p*
	0.43**					0.61**				
Age		0.05	[−0.04, 0.13]	0.09	.257		0.03	[−0.16, 0.12]	0.06	.485
Sex		0.26	[−0.14, 0.66]	0.10	.202		–	–	–	–
Age at seizure onset		0.04	[−0.01, 0.08]	0.11	.152		–	–	–	–
Number of AEDs		–	–	–	–		0.22	[−0.12, 0.45]	0.13	.066
Baseline anxiety		0.44	[0.27, 0.61]	0.49**	<.001		0.40	[0.24, 0.56]	0.44**	<.001
Baseline depression		0.13	[−0.18, 0.45]	0.08	.396		0.63	[0.29, 0.96]	0.26**	<.001
Predictors	Depression									
	6 months					12 months				
	R^2	*B*	[95% CI]	β	*p*	R^2	*B*	[95% CI]	β	*p*
	0.36**					0.52**				
Age		0.06	[0.01, 0.11]	0.18*	.032		0.07	[0.01, 0.12]	0.21*	.023
Sex		0.13	[−0.11, 0.38]	0.08	.286		–	–	–	–
Number of AEDs		–	–	–	–		0.21	[0.06, 0.36]	0.21**	.007
Baseline anxiety		0.09	[−0.02, 0.20]	0.16	.107		0.12	[0.01, 0.22]	0.21*	.032
Baseline depression		0.35	[0.15, 0.54]	0.35**	.001		0.38	[0.16, 0.60]	0.36**	.001

Note. AED = antiepileptic drug; Age = age at baseline in years; Sex (1 = male, 2 = female); higher anxiety and depression scores represent greater symptoms/problems;
* $p < .05$.
** $p < .01$.

quarters of patients achieving seizure freedom following surgery compared with only one-quarter achieving seizure freedom with medical treatment. This lack of improvement in internalizing symptoms in the surgical group, relative to the medical group, is somewhat consistent with several prior longitudinal studies that also included an appropriate control group, but assessed mood via parent proxy-report; however, these previous studies did not demonstrate improvement over time in either group [13,14,16]. One possible explanation for this discrepancy could be due to differences in parent–child perceptions of outcome after surgery. For example, Elliott, Lach, and Smith [45] found that most adolescents reported positive changes and few reported negative changes after surgery (i.e., changes in physical, affect, social, cognitive, family relations), compared with their parents who were more likely to report both positive and negative changes. Nevertheless, taken together, the results of the current study and that of previous studies suggest that (i) both parents and children report changes in internalizing symptoms following surgery that are no different than medical treatment, at least in the short term i.e., (≤12 months) and (ii) improvements found following surgery in earlier studies lacking a control group [11] may have been due to factors other than surgery, including developmental maturation, test–retest effects, etc.

Achieving seizure freedom was associated with fewer depressive symptoms across time but was not associated with improvement in anxiety symptoms. It may be that anxiety symptoms persist in the absence of seizures because of the unpredictability of seizures and the associated worry regarding seizure recurrence [18,46]. This interpretation is consistent with prior research demonstrating high rates of worry regarding seizure recurrence in patients with epilepsy who are in remission [47]. Seizure recurrence remains a likely concern for patients in our sample given the relatively short follow-up period of 12 months in which patients and families are still engaged in regular hospital and medical follow-up appointments after surgery. In adults, adjustment to seizure freedom or improvement in the 2 years following surgery has been associated with initial increased participation in activities and elevated mood, followed by subsequent increased levels of depression and anxiety associated with the "burden of normality" (i.e., adjusting to life after a chronic illness) [48,49]. Hence, patients and their families may need more time to adjust and distance themselves from worry associated with seizure recurrence [14], which is likely to impact their overall level of anxiety. In addition, parental mood, including stress and/or anxiety, may have influenced child anxiety given that parental stress and/or anxiety is common in parents caring for a child with epilepsy [50], has been shown to persist after child epilepsy surgery [51], and is related to poorer functioning (e.g., emotional–behavioral functioning and quality of life) in children with epilepsy [50,52].

Alternatively, it may be that certain mood symptoms/disorders (especially generalized anxiety) persist after surgery, even in patients who achieve seizure control, because of an abnormal neural substrate associated with the underlying brain disorder or neurodevelopmental vulnerability that is independent of seizure activity. Brain regions and networks that mediate anxiety, such as the amygdala, are frequently involved in epilepsy [53,54]. For example, children with epilepsy and comorbid anxiety have been shown to exhibit enlarged left amygdala volumes and cortical thinning in the prefrontal cortex, including the left medial orbitofrontal, right lateral orbitofrontal, and right frontal pole, compared with children with epilepsy who do not have anxiety [54]. Moreover, there is a bidirectional relationship between epilepsy and anxiety, with as many as 33% of children meeting criteria for an anxiety disorder prior to seizure onset [55,56]. Anxiety symptoms and disorders have an earlier age of onset than depression, and more often precede the development of comorbid depressive symptoms, rather than the other way around [57,58]. Hence, depressive symptoms may be more likely to resolve prior to anxiety symptoms, which may require more than 12 months postsurgery to improve.

Corroborating group results, the analysis of individual clinical change in depression and anxiety symptoms found no difference in the proportion of patents who reported clinically meaningful change (improvement or deterioration) between those that underwent surgery and those that continued medical treatment. Similarly, there was no difference in the proportion of patients who reported clinically significant change between those patients that were seizure-free and those that experienced continued seizures. These results should be treated with caution given the relatively low number of patients in each group. As such, we were unable to compare the proportion of patients who reported clinically meaningful improvement or deterioration by seizure outcome within each treatment group (i.e., surgical seizure-free, surgical continued seizures, medical seizure-free, medical continued seizures) or whether baseline factors were predictive of clinically meaningful improvement or deterioration, which may differ by group. Nevertheless, in our sample, approximately 4–11% of children reported clinically significant improvement and approximately 9–14% of children reported clinically significant deterioration in mood (depression and anxiety) following epilepsy surgery. These rates are relatively consistent with prior studies [13,18] and suggest that on the whole, children do not get worse after surgery. However, it is important to acknowledge that some children do report continuing symptoms or more symptoms of anxiety and depression after surgery potentially placing them at risk of psychiatric problems into adulthood. Indeed, a small portion of children do go on to develop a psychiatric disorder following pediatric epilepsy surgery [10]. Possible explanations have included increased awareness of emotional symptoms that may have been previously masked by seizures, difficulties adjusting to life after epilepsy (as mentioned earlier), or developmental reasons for the emergence of new emotional disorders as children get older [10]. Whatever the reason, these results highlight the importance of postsurgical clinical follow-up and subsequent screening of mood disorders in children with DRE.

Consistent with prior research examining internalizing [13] and externalizing [59] symptoms after epilepsy surgery, baseline level of functioning was the best predictor of outcome. In fact, children who reported a greater number of mood symptoms in general (i.e., anxiety and depression) were more likely to report greater symptoms at follow-up. That is, both anxiety and depression symptoms predicted depression at 12 month follow-up and both anxiety and depression symptoms predicted anxiety at 12 month follow-up. These findings suggest that children who present with mood disorders at initial evaluation for surgical candidacy are at significant risk of persistent mood problems 12 months later, regardless of whether they undergo surgery or not. While no demographic or seizure-related variables were associated with anxiety symptoms at follow-up, older age was associated with greater depressive symptoms at follow-up. The only clinical variable associated with depressive symptoms was AEDs; greater number of AEDs at baseline was associated with greater symptoms at 12, but not 6 month follow-up. Clinically, these results provide an opportunity for early treatment planning and intervention beyond surgical or medical treatment that involves the multidisciplinary treatment team and referral to appropriate services (including psychologists and outpatient mental health services) for these at-risk children and their families.

While a strength of this study was the use of child self-report, future research should involve multiinformant procedures including parent, child, and teacher reports where appropriate. In addition, while the measures used in this study were based on symptoms consistent with international classification systems (i.e., DSM-IV), structured clinical interviews could also be utilized as a more reliable diagnostic tool; however, clinical interviews are not always practical, and dichotomous categorization of symptoms (i.e., diagnosis vs. no diagnosis) is less likely to be sensitive to change, compared with questionnaires with continuous outcome scores. Incorporating qualitative interviews could shed more light on patient experiences and adjustment after surgery.

Assistance provided by parents and/or researchers to complete the questionnaires, while minimal, may have affected the ratings and resulted in underreporting of symptoms. Further, the validity and reliability of self-report in those children with intellectual impairment,

whether assisted in their completion of the questionnaires by parents/researchers or not, may have confounded our results. Nevertheless, re-examination of the primary analyses involving only those children who had a FSIQ of 70 or more was commensurate with our initial findings.

The current research specifically assessed generalized anxiety disorder symptoms, but children with epilepsy also experience symptoms of social anxiety, separation anxiety, etc. [1], which should be assessed in future research. There is also a link between parental mood (i.e., stress, anxiety, and depression) and child emotional functioning [10], which may have influenced results and could be accounted for in future studies. Changes in anxiety and depression may have been influenced by other factors not accounted for in the current study, such as cognitive outcome following surgery, which is a potential area for future investigation. We examined the number of AEDs rather than changes in AED regimens because of the large and heterogeneous combinations of AEDs in our sample, which limited the ability to analyze group differences. As such, changes in AED regimens may have influenced mood outcomes in our study; however, of the limited number of participants in our study that reported clinically meaningful change, few had changes to their AED regimens that involved AEDs known to affect mood. It is also possible that improvements in anxiety and depression found over time in the current study may have been the result of test–retest effects or regression toward the mean, rather than real improvement over time. Additional data, such as results of brain imaging (i.e., magnetic resonance imaging) were not collected, which could have influenced the likelihood of seizure freedom after surgery. Similarly, groups were not individually matched on the side of hemispheric dysfunction, especially given the inclusion of participants with bilateral seizures in the medical group. The groups were, however, representative of the patients undergoing evaluation for surgical candidacy.

4.1. Conclusions

The current study suggests that while surgery results in higher rates of seizure freedom, compared with continued medical treatment, surgery was not associated with better outcomes with respect to emotional functioning in children with epilepsy. Seizure freedom, whether obtained through surgery or by continued medication management, was a more influential variable, albeit only for depression and not for anxiety. These results provide important clinical information for health professionals involved in presurgical evaluation and planning. Such information includes (i) establishing and managing treatment expectations for patients and families so that they can make an informed decision regarding the risks and benefits of surgery and (ii) the opportunity for treatment planning and implementation of early psychological interventions (e.g., psychoeducation, cognitive behavioral therapy etc.) for children undergoing multidisciplinary assessment of surgical candidacy. Early and targeted intervention is especially important for children with elevated levels of anxiety and/or depression at assessment, irrespective of whether they go on to have surgery or not. Our future research will continue to follow-up these children longer term to determine whether changes in mood associated with seizure outcome require more time to emerge postsurgery.

Declaration of competing interest

The authors declare no conflicts of interest.

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Appendix A. Supplementary data

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