

Impact of epilepsy surgery on development of preschool children: identification of a cohort likely to benefit from early intervention

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OBJECT Outcomes of focal resection in young children with early-onset epilepsy are varied in the literature due to study differences. In this paper, the authors sought to define the effect of focal resection in a small homogeneous sample of children who were otherwise cognitively intact, but who required early surgical treatment. Preservation of and age-appropriate development of intelligence following focal resection was hypothesized.

METHODS Cognitive outcome after focal resection was retrospectively reviewed for 15 cognitively intact children who were operated on at the ages of 2–6 years for lesion-related, early-onset epilepsy. Intelligence was tested prior to and after surgery. Effect sizes and confidence intervals for means and standard deviations were used to infer changes and differences in intelligence between 1) groups (pre vs post), 2) left versus right hemisphere resections, and 3) short versus long duration of seizures prior to resection.

RESULTS No group changes from baseline occurred in Full Scale, verbal, or nonverbal IQ. No change from baseline intelligence occurred in children who underwent left or right hemisphere surgery, including no group effect on verbal scores following surgery in the dominant hemisphere. Patients with seizure durations of less than 6 months prior to resection showed improvement from their presurgical baseline in contrast to those with seizure duration of greater than 6 months prior to surgery, particularly in Wechsler Full Scale IQ and nonverbal intelligence.

CONCLUSIONS This study suggests that surgical treatment of focal seizures in cognitively intact preschool children is likely to result in seizure remediation, antiepileptic drug discontinuation, and no significant decrement in intelligence. The latter finding is particularly significant in light of the long-standing concern associated with performing resections in the language-dominant hemisphere. Importantly, shorter seizure duration prior to resection can result in improved cognitive outcome, suggesting that surgery for this population should occur sooner to help improve intelligence outcomes.

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KEY WORDS pediatric epilepsy; surgery; outcome

EARLY-ONSET epilepsy is a risk factor for cognitive impairment,^{3,17,27} and evidence suggests that morbidity is evident even very early in new-onset epilepsy.¹⁵ Risk of mental retardation is significantly increased in infants less than 24 months of age with onset of intractable epilepsy,³⁶ and even children with later-onset epilepsy and nonintractable epilepsy are at increased risk for behav-

ioral and cognitive deficits.^{5,11,15,24} Further, cognitive decline may occur with short duration epilepsy in pediatric patients,²⁷ and ongoing seizures may further compromise cognition and may be associated with alterations in brain morphometry, particularly reduced white matter volume, especially in the frontal lobes.¹⁰

At the same time, resection for the remediation of

ABBREVIATIONS AED = antiepileptic drug; DNET = dysembryoplastic neuroepithelial tumor; FSIQ = Wechsler Full Scale IQ; MTS = mesial temporal sclerosis.

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epilepsy is well accepted.^{19,23,33} However, literature evaluating cognitive outcome in young children to date has yielded contradictory and confusing results, perhaps stemming from methodological confounds. Outcome studies have yielded such varied results as 1) improved cognitive outcomes;^{3,8,19,34} 2) slight improvement in cognition being more likely than decline, with significant declines in some children;³⁷ 3) reversible decline in at least some children, especially following left temporal lobectomy;⁷ 4) lack of improved outcome, with some cognitive recovery being a “bonus”;²⁸ 5) “stabilized developmental velocity”;⁶ 6) no improvement in outcome postsurgery,^{2,30} with this lack of improvement theorized to be associated with an abnormal neural substrate versus seizures per se;³⁰ and 7) no improvement, with the possibility of decline in some cases.¹

Although methodological issues are beginning to be addressed in adolescents and adults,⁴ they have not been addressed to the same extent in children, particularly very young children. Generally, the pediatric surgical outcome literature has been muddled by heterogeneous samples, combining many factors, including 1) markedly different surgical therapies, from focal resections to hemispherectomies;^{3,26,28} 2) broad age inclusion criteria, at different developmental levels, from 6 to 17 or 18 years^{30,37} or 1 to 15 years¹ or “all children”;² 3) variable levels of functioning prior to resection;³⁰ 4) wide ranges of presurgical seizure duration;²⁸ and 5) variable pathologies.^{2,28}

Because many pediatric studies have focused on different age ranges, some studies have attempted to narrow the developmental scope, but their methods have still varied from each other, making them difficult to compare. Age range samples include patients less than 6 or 7 years at surgery,^{19,28} 3 to 7 years,⁶ 8 to 159 months,³⁴ less than 3 years,^{20,26} or 3 to 36 months.³

A number of studies^{7,21,22,29,32,37} have focused on temporal lobectomies and have provided important information regarding outcome following this procedure, with some variable findings. Yet, these studies, so far, have wide surgical age ranges, crossing developmental stages, as well as lengthy presurgical seizure durations, lasting many years, and do not differentiate between outcome following short versus long presurgical seizure duration. Smith and associates³¹ have furthered the literature by reporting on long-term outcome (mean 8.5 years postresection), but their findings may be compromised by particularly long seizure durations (mean seizure onset and mean surgery ages differ by about 10 years) prior to resection as well as the mixture of focal resections and pathologies with multilobar resections and more generalized disease.

While the above studies have provided crucial first steps in our attempts to better define pediatric epilepsy and the efficacy of resection, all of the above factors make pediatric outcome studies, particularly of young children, difficult to compare. There is a clear need to better define and study more homogeneous groups of children despite the challenges of power inherent in narrowing groups. In addition, because resection can be undertaken too late to avoid irreversible disability⁴ and because early cessation of epileptogenic spread from a focal onset can be crucial for the return to normal developmental trajectories,²⁸ it is

essential to identify well-defined patient groups who may particularly benefit from early surgical therapy.

We sought to narrow the scope of our evaluation to 1) focal resections; 2) a specific and narrow age range and developmental level, 2–6 years, similar to at least 1 prior study⁶ and corresponding with a specific developmental period previously identified by Piaget (preoperational stage, 2–6 or 7 years); and 3) patients who were not yet showing clear global cognitive deficits at the time of resection. Additionally, we examined the impact of duration of seizures prior to surgery.

Methods

Participants

This study was approved by the institutional review board at Seattle Children’s Hospital. We retrospectively identified Seattle Children’s Hospital patients who had epilepsy surgery between April 2000 and July 2012, were 2–6 years old at surgery, did not present with developmental delays or cognitive impairment, and had focal resective epilepsy surgery and pre- and postsurgical neuropsychological evaluations. These patients were selected from a larger and more heterogeneous sample of patients who did not have lesion-related epilepsy, were not functioning within average cognitive limits, and/or needed larger resections. Patients with presurgical Wechsler Full Scale IQ (FSIQ) scores of less than 80, large (e.g., multilobar or hemispherectomy) resections, and/or dual pathology were excluded. Two patients with no presurgery IQ testing were included in this study because developmental screening showed average functioning, but these patients were excluded only from pre/post comparisons due to the lack of presurgical Wechsler scores. Patients with Vineland-structured interviews were excluded from statistical analyses.

Pathology and surgical information for the 15 patients included by our protocol is summarized in Table 1. All patients had focal resections, 6 right and 9 left hemisphere. Postsurgical MRI scans were independently reviewed to confirm areas resected. Pathology included the following: 2 DNETs (dysembryoplastic neuroepithelial tumors); 4 gangliogliomas; 2 oligodendrogiomas; 1 gliosis; 2 vascular malformations (cavernomas); 2 mesial temporal sclerosis (MTS); and 2 focal cortical dysplasias (Taylor Type IIA).

Data Collection and Analysis

Seizure duration prior to resection was identified in months for each patient via chart review of existing medical records, and postsurgical seizure outcome was determined by using Engel’s criteria.³⁸ Because there is no precedence for measuring presurgical seizure duration in young children, we arbitrarily assigned 6 months as “short” duration and anything longer as “long” duration, and in our sample the latter meant children with 18 or more months of seizure activity prior to surgery. Presurgically, all patients had seizures associated with identified lesions and were treated with at least 1 antiepileptic drug (AED), except for 1 patient who had only 1 seizure and was not on medication. The exception was included because she was expected to have continued seizures associated with her

TABLE 1. Surgical details, postsurgical pathology, and postsurgical seizure classification

Case No.	Side	Age at Op (yr, mo)	Sz Prior to Op			Resection	Pathology	Postop			
			Lobe	Duration (mo)	Characterization			Mos	Engel Class		
1	Rt	4, 3	Temporal	5	Controlled on 1 AED	Anterior temporal lobectomy	DNET	93	IA		
2	Rt	6, 5	Temporal	5	Sz on 1 AED	Selective temporal lesionectomy	Oligodendrogioma	19	IA		
3	Lt	5, 7	Frontal	5	Intractable	Inferior frontal gyrus (triangular gyrus & insula)	Cavernoma	47	IA		
4	Rt	2, 1	Temporal	19	Sz on 1 AED	Anterior temporal lobectomy	Ganglioglioma	47	IA		
5	Lt	6, 6	Temporal	32	Intractable	Anterior temporal lobectomy	Gliosis	8	IA		
6	Lt	6, 3	Temporal	23	Intractable	Anterior temporal lobectomy	MTS	131	ID		
7	Lt	6, 2	Temporal	62	Intractable	Selective temporal lobectomy (mesial resection)	MTS	24	IA		
8	Rt	4, 0	Frontal	2	Intractable	Frontal lesionectomy (inferior orbital & medial gyrus)	Oligodendrogioma	88	IC		
9	Lt	6, 9	Frontal	0	1 Sz, no AED	Frontal lesionectomy (medial frontal gyrus)	Cavernoma	41	IC		
10	Rt	6, 0	Frontal	35	Intractable	Frontal lesionectomy (superior frontal gyrus)	DNET	68	IIA		
11	Lt	2, 8	Temporal	2	Sz on 1 AED	Selective temporal lobectomy (mesial resection)	Ganglioglioma	40	IA		
12	Lt	6, 5	Frontal	24	Intractable	Middle & superior frontal gyrus	Dysplasia, Taylor Type IIB	36	IA		
13	Lt	3, 1	Temporal	5	Intractable	Selective temporal lobectomy (tumor & hippocampus)	Ganglioglioma	82	IA*		
14	Rt	1, 11	Temporal	18	Sz on 1 AED	Selective temporal lesionectomy	Ganglioglioma	78	IA		
15	Lt	5, 4	Frontal	3	Intractable	Superior & middle frontal gyrus	Dysplasia, Taylor Type IIB	25	IA		

Sz = seizure.

* Except for 1 event with a very high fever.

lesion had surgical intervention not occurred. Specifically, 9 patients had seizures that were considered intractable (i.e., at least 2 AEDs had failed to control their seizures); 4 children were continuing to have seizures while on 1 AED; 1 child's seizures were controlled with 1 AED, but her parents were concerned about the cognitive effects of long-term medical treatment; and 1 patient who had 1 seizure and was not being treated with any AED required surgery for removal of a cavernoma.

The clinical protocol in the Seattle Children's Hospital Epilepsy Surgery Program specifies that children being considered for epilepsy surgery are to undergo presurgical neuropsychological evaluations, whenever possible, during the presurgical workup and, if surgery occurs, they should be evaluated at 6 months, 18 months, and 5 years postsurgery, although the actual follow-up time varies. The neuropsychological tests include a broad range of measures, even for young children, including intelligence, lateral dominance, sensory-motor, visual-spatial, language, memory, attention/executive functions, and behavioral/psychosocial/mood functions. For the purposes of our focused study, only intelligence test scores were retrospectively evaluated, as intelligence is frequently used as an outcome measure and as the heterogeneous nature of specific lesion locations precluded using other single tests.

Wechsler intelligence tests were administered to all patients, with the majority of the patients having been given the Wechsler Preschool and Primary Scale of Intel-

ligence–III and the Wechsler Intelligence Scale for Children–IV, depending upon the age of the child at the time of pre- or postoperative testing. One patient had the Wechsler Abbreviated Scale of Intelligence prior to resection, and 1 patient had the Wechsler Preschool and Primary Scale of Intelligence–Revised and the Wechsler Intelligence Scale for Children–III. Because the different Wechsler scales have different nonverbal scale names (i.e., Performance IQ versus Perceptual Reasoning Index), the label “nonverbal” was assigned, and the “verbal” label was also assigned due to different verbal scale names.

Fourteen of 15 patients completed presurgical testing between 0 and 7 months prior to resection. Twelve patients completed the Wechsler FSIQ test, with a mean score of 100 (SD 13.1). Two patients did not complete Wechsler IQ testing (due to 1 being just shy of her second birthday and 1 being too distracted in the Telemetry Unit environment), but had Vineland-structured parent interviews, with overall scores of 88 and 99; they were excluded from statistical analyses to ensure that score comparisons were all done using the same test type, but were included for descriptive purposes because they met all other enrollment conditions. Two patients did not have any testing prior to surgery, but were considered to be developmentally average.

Initial postsurgical testing occurred for 14 of 15 patients between 5 and 27 months postsurgery (11 had both pre- and postsurgical intelligence testing). Of the 15 who had postsurgical testing, 11 of those patients had testing

within 7 months or less from surgery. One patient did not have early postsurgical testing at all, and because he was first tested at 47 months postsurgery, he was included only in the “late” postsurgery group. Three patients did not have longer-term follow-up.

Our analysis looked at 2 primary contrasts: 1) postsurgical outcomes for all patients as compared with presurgical baseline and 2) postsurgical outcomes by groupings based on a) seizure duration prior to surgery and b) surgery hemisphere, with 9 patients’ resections occurring on the left side and 6 on the right side. Some patients did not have second follow-up evaluations; for those patients, we used their first (and only) follow-up score as their “post-surgery” score values. For all others, we used the scores from the second testing period.

Because of the small sample size, we used 90% bias-corrected and accelerated, bootstrapped confidence intervals on means and standard deviations using 10,000 replications. The p values were obtained via exact permutation tests.^{12,14} For effect size comparisons, we calculated the absolute difference between means (IDI), the nonparametric Vargha-Delaney *A* measure of stochastic superiority,³⁵ and the variance ratio. While calculating IDI is a common way to provide information on group-level responses, the *A* measure is a recent advance that allows for comparisons at the individual level for any measurement at or above an ordinal scale; it is defined as the probability that a patient sampled randomly from 1 group will have a higher score than 1 patient sampled randomly from the other group. In effect, it can be thought of as the percentage of individuals in 1 group who might show improvement over those in the contrasting group. *A* values of 0.50 represent no grouping effect, 0.71 is considered the lower threshold for an important effect, and 1.0 represents perfect distinction between individual outcomes in each group. Confidence intervals are not included for effect sizes so as to preclude interpretations that all values in the interval are equally likely.¹⁶ All analyses were carried out using R-3.0.2; p values were obtained using the coin package;¹³ and *A* values were obtained using the orddom package.

Results

Good seizure outcome was observed in all patients at an average postsurgical follow-up duration of 55.1 months (SD 33.8) (see Table 1). Engel Class I seizure freedom occurred in 14 of 15 patients, with 11 patients meeting criteria for Engel Class IA, 2 patients meeting criteria for class IC, and 1 patient meeting criteria for class ID. One patient met Engel Class IIA.

Decreased need for AEDs was observed in all but 3 patients. Fourteen of 15 patients were being treated with AEDs prior to surgery, and 5 patients were receiving polytherapy. All patients, except for 1, were on AEDs at the time of the initial postsurgical testing, with 3 patients receiving polytherapy. Only 4 of 12 patients were being treated with AEDs at the time of the last postsurgical testing, with each of those 4 patients being treated with monotherapy only, and with 2 of those 4 having been on polytherapy prior to resection. The patient who had 1 seizure prior to resection did not have her AED treatment initiated

until after surgery, and she was still on that medication at the last postsurgical testing despite having only 1 seizure presurgery and 1 postsurgery.

The mean presurgical Wechsler FSIQ was 100 (SD 13.1); see Table 2 for a summary of test results referenced here and in subsequent paragraphs. Initial postsurgery testing resulted in a mean FSIQ of 100 (SD 15.9). When the 3 patients who did not have postsurgical follow-up within 7 months after surgery were excluded, the remaining 12 patients in this initial test group had a mean FSIQ of 99.1 (SD 16.4). Additional testing (Table 2) occurred further out after surgery, at a mean of 41.3 (SD 23.3) months and resulted in a mean FSIQ of 106 (SD 17.7) for the 12 patients tested.

An important result is that surgical treatment did not result in intellectual decline. On average, patients did not lose cognitive abilities, with no single patient losing more than 12 IQ points, meaning that patients showed age-appropriate cognitive development. Most IQs fell within the average range or above, although several patients had low average scores, and the only patient to have a borderline FSIQ at the first postoperative testing had a low average FSIQ at the later follow-up. Following surgery, patients showed a slight improvement in mean FSIQ, verbal, and nonverbal scores when contrasting their presurgery results with their last test results, although the improvements were not statistically (FSIQ p = 0.46, verbal p = 0.50, and nonverbal p = 0.95) or practically significant (Fig. 1A and B, Table 3). In addition, there was a fair amount of individual variability (Fig. 1A), though individuals tended to have postsurgery results similar to where they started, i.e., those with higher scores before surgery tended to have relatively higher scores afterward and vice versa. There was also no practical change in group variability for any of the 3 scores either before or after surgery.

An additional important result is that left and right hemisphere surgery location groups were not significantly different, statistically (FSIQ p = 0.96, verbal p = 0.73, and nonverbal p = 0.54) or practically (Fig. 2, Table 3); on average, both groups improved, but the confidence limits suggest that the results are consistent with no change. Changes between groups were minuscule, with the largest change occurring between verbal scores, with the left hemisphere group scoring on average 5 points higher. Variation was essentially identical, suggesting no difference in the variability of outcomes based on surgery hemisphere; left and right verbal confidence intervals on the standard deviation of the difference also share considerable overlap.

The duration from the onset of seizures to surgery appears to have an important effect on outcomes. Patients who had surgery within 6 months of onset generally had better outcomes (Fig. 3, Table 3) compared with patients who had longer duration from the onset of seizures prior to resection. While we did not detect statistically significant differences (FSIQ p = 0.06, verbal p = 0.44, and nonverbal p = 0.05), when patients with seizure duration of less than 6 months (“short duration”) prior to surgery were compared with those having a duration greater than 6 months prior to surgery (“long duration”), the balance of evidence suggests that important differences were observed between the 2 groups. Specifically, clinically important im-

TABLE 2. Presurgical and postsurgical test scores

Case No.	Sz Duration (mos)*	Presurgical Testing				1st Postsurgical Testing				Last Postsurgical Testing								
		Mos Before Opt†	Rx at Testing	FSIQ	Verbal Score	Mos After Opt‡	Rx at Testing	FSIQ	Verbal Score	Non-verbal Score	Mos After Op§	Rx at Testing	FSIQ	Verbal Score				
		Sz duration <6 mos preop												Non-verbal Score				
1	5	2	Tegretol	118	129	103	5	Trileptal	117	133	101	80	None	140	146	115		
2	5	1	Keppra	116	138	115	7	None	124	136	117	19	None	120	126	115		
3	5	3	Topamax Tegretol	101	100	6	6	Topamax	89	93	88	20	None	112	110	104		
8	2	0	Zonegran, Tegretol	94	97	90	7	Keppra, Zonegran	104	98	112	19	Keppra	104	100	110		
9	0	NA	NA			16		Trileptal	109	106	108	33	Trileptal	99	96	100		
11	2	1	Topamax	99¶		27		Lamictal	84	86	85	40	Lamictal	89	100	83		
13	5	0	Tegretol	112	120	100	5	Trileptal	115	113	114	51	None	132	134	133		
15	3	0	Depakote, Keppra, Phenobarbitol	91	102	79	7	Keppra	107	128	100	24	None	96	110	86		
Overall**																		
Mean	3	1		105	114	98	10		106	112	103	36		112	115	106		
SD	1.9	1.2		11.6	17.1	12.2	7.7		13.7	19.1	11.9	21.3		18.0	18.1	16.4		
Sz duration >6 mos preop																		
4	19	NA	NA															
5	32	4	Depakote	115	102	123	7	Depakote, Lamictal	105	95	112	Not done		47	None	108	104	106
6	23	5	Topamax, Depakote, Dilantin	89	82	101	5	Dilantin	91	79	111	83	None	105	98	110		
7	62	4	Trileptal	87	90	93	5	Trileptal	80	80	93	Not done						
10	35	0	Trileptal	94	86	98	7	Trileptal	83	83	93	Not done						
12	24	7	Keppra, Topamax	82	88	86	7	Keppra	75	85	75	18	Keppra	87	99	86		
14	18	0	Tegretol	88¶		26		Tegretol	82	83	90	57	None	82	89	88		
Overall††																		
Mean	30	3		93	90	100	10		86	84	96	51		96	98	98		
SD	15.3	2.8		12.8	7.5	14.0	8.1		10.7	5.7	14.0	26.9		12.9	6.2	12.3		
Summary for the entire cohort (Wechsler scores only)																		
Rx																		
13/13 on AEDs																		
Mean	16	2		100	103	99	10	13/14 on AEDs	98	100	100	41		106	109	103		
SD	17.2	2.3		13.1	18.3	12.4	7.6		15.9	20.2	12.9	23.3		17.7	17.2	15.1		

NA = not applicable; Rx = antiepileptic medication.

* Prior to resection.

† Between presurgical testing and surgery.

‡ Structured parent interview (Vineland Adaptive Behavior Scales) summary (Adaptive Behavior Composite) score.

** Summary for the short seizure duration (< 6 months) prior to surgery group (Wechsler scores only).

†† Summary for the long seizure duration (> 6 months) prior to surgery group (Wechsler scores only).

TABLE 3. Descriptive results and effect sizes for all patients

Characteristic	FSIQ (90% CI)	Verbal (90% CI)	Nonverbal (90% CI)
Op groups*			
Mean			
Pre	100 (94–106)	103 (96–113)	99 (93–105)
Post	103 (96–111)	105 (98–113)	102 (97–108)
SD			
Pre	13.1 (11.2–15.9)	18.3 (13.7–23.9)	12.4 (8.9–17.2)
Post	17.9 (13.8–23.5)	18.3 (13.2–24.6)	14.1 (11.1–19.2)
Range			
Pre	82 to 118	82 to 138	79 to 123
Post	80 to 140	80 to 146	83 to 133
Percentage w/ same or improved score (n = 11)	0.73	0.64	0.82
Absolute difference btwn means D †	3	2	3
Mean individual improvement (n = 11)	6	4	6
Vargha-Delaney A	0.52	0.53	0.57
Variance ratio	1.9	1.0	1.3
Changes according to side‡			
Mean change			
Lt	6 (-1 to 12)	6 (-1 to 11)	6 (0–16)
Rt	6 (-6 to 15)	1 (-8 to 9)	7 (-3 to 14)
SD			
Lt	11.2 (8.7–14.5)	10.2 (7.5–12.7)	13.6 (6.2–19.9)
Rt	13.7 (7.5–19.1)	12.2 (6.2–16.7)	11.4 (7.2–14.4)
Range			
Lt	-10 to 20	-10 to 16	-11 to 33
Rt	-11 to 22	-12 to 17	-5 to 20
Percent w/ same or improved score			
Lt	0.71	0.71	0.86
Rt	0.75	0.50	0.75
Absolute difference btwn means D †	1	5	1
Vargha-Delaney A	0.54	0.61	0.54
Variance ratio	1.5	1.4	1.4
Changes according to duration§			
Mean change			
Short	12 (8–17)	7 (-2 to 11)	13 (6–22)
Long	-1 (-9 to 7)	1 (-6 to 9)	-1 (-7 to 3)
SD			
Short	7.5 (5.8–9.3)	10.4 (4.5–14.6)	12.1 (7.2–16.7)
Long	11.6 (6.8–14.8)	11.5 (9.2–14.2)	7.4 (4.7–10.2)
Range			
Short	4 to 22	-12 to 17	0 to 33
Long	-11 to 16	-10 to 16	-11 to 9
Percent w/ same or improved score			
Short	1.00	0.83	1.00
Long	0.40	0.40	0.60
Absolute difference btwn means D †	13	5	14
Vargha-Delaney A	0.82	0.60	0.87
Variance ratio	2.4	0.8	2.7

* Presurgery (n = 11) versus postsurgery (n = 15).

† Values may not match the difference between the means above them due to rounding.

‡ Left (n = 7) versus right (n = 4) hemisphere resection groups.

§ Short (n = 6) versus long (n = 5) seizure duration groups.

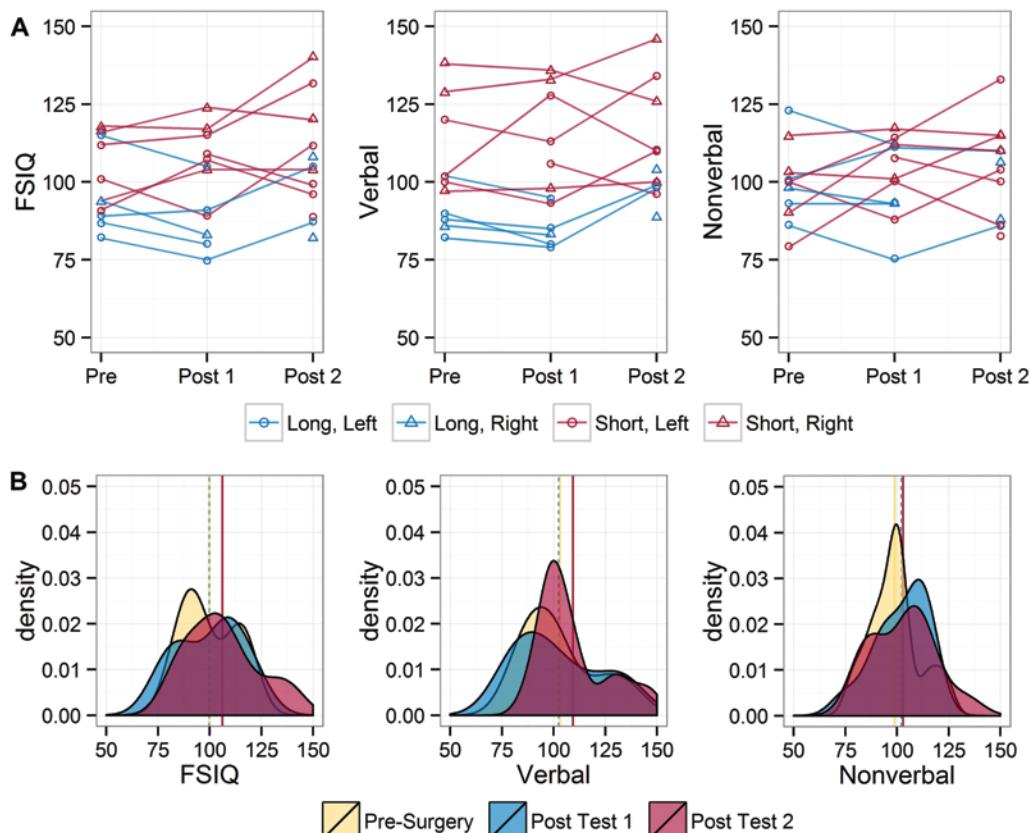


FIG. 1. Individual and group changes in FSIQ, verbal, and nonverbal intelligence test scores after surgery. **A:** Parallel coordinates plots detail individual-level changes in test scores before (Pre) and after (Post 1, Post 2) surgery. Circles represent patients in the left-hemisphere surgery group, triangles represent those in the right-hemisphere group, red represents having surgery within 6 months of diagnosis (Short), and blue represents having surgery 18 months or more after diagnosis (Long). **B:** Density histograms summarize individual responses by time for each test grouping, where vertical solid lines correspond to the mean score for each time step. The vertical dashed lines represent the Post 1 time step to help distinguish it from presurgery and later postsurgery mean results.

provements for the short duration group occurred in both FSIQ and nonverbal scores; FSIQ and nonverbal scores improved by 13 and 14 points on average, respectively. The Vargha-Delaney A results for these 2 improvements suggest that patients who undergo surgery within 6 months will show improved FSIQ and nonverbal scores about 82% and 87% of the time, respectively, as compared with waiting 18 months or more for surgery after seizure onset. There was indication of a slight difference between the short and long duration groups in verbal scores, although interpretation of confidence intervals and A value for this comparison suggests that this result is also consistent with no difference. The group variances for all 3 scores were also not different given the sample size; variance ratios of 3 or more are needed before one can suspect that differences in variability are a result of treatment.

Discussion

In contrast to some prior research that has shown resection in young children to be associated with subnormal intelligence, our study identified a cadre of cognitively intact young children with focal seizures and lesions on MRI who benefitted from surgical treatment. Our study group was cognitively intact at the time of resection and

remained so at the time of the last follow-up, and, in addition, our patients experienced significant reduction in, and in most cases cessation of, seizure activity, with a concomitant discontinuation of AED in most cases.

Our sample represents a significantly different group as compared with prior studies for several reasons. First, because we chose a developmental group that excluded infants and toddlers, our group did not include patients in the first year of life, who are likely to have more severe disease.²⁸ Second, resection was undertaken prior to potential cognitive decline and involved only limited focal resections. In addition, patients who needed more extensive resections, such as multilobar surgeries or hemispherectomies, and patients who were already functioning below average prior to referral for presurgical workup, were not included in this study. These latter patients likely also have worse disease, with potentially more widespread pathology of cerebral organization. To define a homogeneous group, we purposefully chose this very select sample with lesion-related seizures, precluding a more heterogeneous group that would likely include more medically intractable and non-lesion-related epilepsy. Duration from seizure onset to resection appeared to impact outcome, with the shorter duration group data suggesting more normal cog-

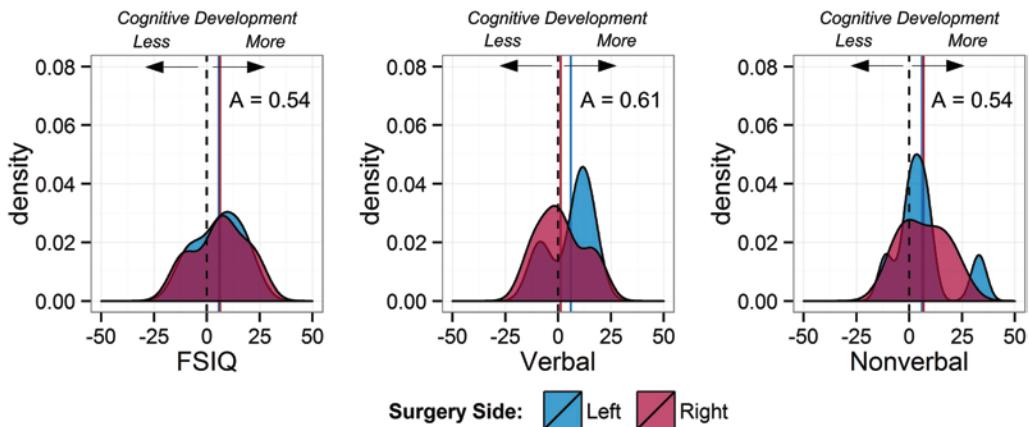


FIG. 2. Comparison of density histograms for pre- and postsurgery responses shows no cognitive difference in any intelligence test score grouping based on the hemisphere of surgery. A is the nonparametric Vargha-Delaney effect size measure and represents the probability that a patient sampled randomly from one group will have a higher score than one patient sampled randomly from the other group. Values greater than 0.71 suggest an important effect, while values near 0.50 suggest no effect. The vertical solid lines represent the mean change in test score for each group while the vertical dashed lines represent no change from baseline for comparison.

nitive expectations than the longer duration group. This finding is consistent with the literature that shows that ongoing refractory seizures are associated with poorer cognitive outcome.^{5,9,24} In contrast, the patients with short duration of seizures prior to resection had better outcomes, with more postsurgical improvement. These findings argue for earlier resection in the context of lesion-associated seizures to preserve cognitive functions.

Side of surgery, whether the left or right hemisphere, did not appear to have a differential effect on postsurgical verbal intelligence, consistent with prior findings following temporal lobectomies.²² More specifically, left hemisphere resections did not result in verbal intelligence declines and did not result in lower verbal intelligence, as compared with right hemisphere resections. This finding is particularly significant in light of the longstanding concern associated with performing resections in the lan-

guage dominant hemisphere in older individuals. Though we did not report verbal memory scores, it is important to note that sustained verbal intelligence reflects normal cognitive development, including normal verbal learning or acquisition of verbal knowledge. Additional research will be important to further improve our understanding of outcome expectations, particularly within specific domains beyond intelligence.

Pathology underlying refractory seizures can significantly impact outcome,²² and we, therefore, excluded patients with dual structural pathology and attempted to include only focal and benign pathologies, including DNETs, gangliogliomas, oligodysplasias, and cavernomas. Cortical dysplasias vary, and we included only Type IIb dysplasias because previous work by Krsek and associates has shown that the Type IIb cortical dysplasias involve more focal pathology and usually have better postsurgical outcome, as

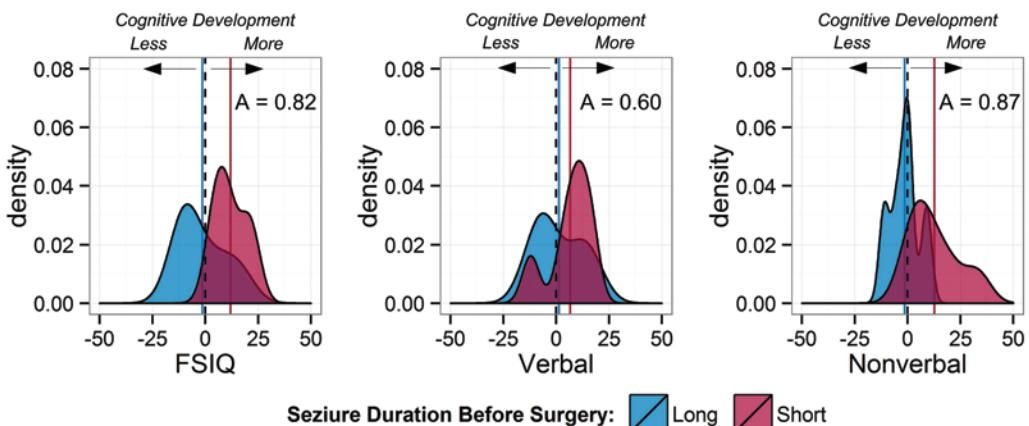


FIG. 3. Comparison of density histograms for pre- and postsurgery responses show a potential cognitive benefit in FSIQ and nonverbal intelligence test scores for subjects in the group that received surgery within 6 months of initial diagnosis (short group) as compared with those who received it more than 18 months after diagnosis (long group). A is the nonparametric Vargha-Delaney effect size measure, and represents the probability that a patient sampled randomly from one group will have a higher score than one patient sampled randomly from the other group. Values greater than 0.71 suggest an important effect, while values near 0.50 suggest no effect. The vertical solid lines represent the mean change in test score for each group while the vertical dashed lines represent no change from baseline for comparison.

contrasted with Type I, which involves more widespread disease.¹⁸ Two patients in our sample had MTS, and it could be argued that these cases should not have been included as MTS might not be as “focal” as once thought, given Kaaden and Helmstaedter’s findings that earlier onset temporal lobe epilepsy may be associated with abnormalities or dysfunction beyond the MTS.¹⁷ Given their findings, it is possible that some MTS patients have “overlooked” focal cortical dysplasias, particularly Type I, and thus our 2 MTS patients might represent worse disease and have worse outcomes over time. Despite this potential concern relative to our 2 MTS patients, our longer-term follow-up data are consistent with previous literature⁷ showing that recovery and improvement in functioning can be appreciated at longer-term follow-up after surgical treatment, at least with follow-ups greater than 1 year postsurgery. Our diverse sample of pathology did not allow for conclusions based on lesion type.

This study is limited by the small number of patients, by not addressing AED effects, and by the lack of long-term outcome measurement. Because of the small sample size, results with high p values cannot be interpreted as “no effect”; at best, we can say that there is either no statistically significant effect or that if there is a statistically significant effect, the study was not powerful enough to detect it. Given the large practical effect sizes detected in this study, this is an important point to realize for future research, especially given how difficult it is to find large numbers of subjects that meet this set of criteria. In addition, also due in part to our small number of included patients, we were not able to adequately parse out specific medication effects, which is important because AEDs can have deleterious cognitive effects particularly in children.²⁵ This issue should certainly be addressed in future studies to explore the specific impacts of AEDs on cognitive outcomes associated with surgeries. We intend to address the issues of very long-term outcomes and medication effects in the future.

Conclusions

This study suggests that early resective epilepsy surgery for seizure remediation in very young, cognitively intact patients can result in seizure reduction/control with AED discontinuation and also preservation of cognitive abilities across verbal and nonverbal domains. Earlier age at resection, intact cognitive functioning prior to resection, short seizure duration prior to resection, focal ictal onset, and focal findings on MRI suggesting lower likelihood of diffuse cerebral pathology are all factors that may be essential for optimal outcome. Although the sample size is small, our study suggests that surgical treatment for refractory epilepsy in this young group is optimal earlier—with in 6 months from diagnosis—than has previously been the norm. At the same time, longer-term follow-up of these children will be important to document whether these advantages persist beyond childhood.

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Supplemental Information

Previous Presentation

A portion of this work was presented in poster form at the American Epilepsy Society Annual Meeting on December 2–6, 2011, Baltimore, MD.

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