Neuropsychological outcome following frontal lobectomy for pharmacoresistant epilepsy in adults

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ABSTRACT

Objective: This retrospective cohort study characterized cognitive and motor outcomes in a large sample of adults who underwent frontal lobe resections for treatment of pharmacoresistant epilepsy.

Methods: Ninety patients who underwent unilateral frontal lobe resection for epilepsy (42 language-dominant hemisphere/48 nondominant hemisphere) between 1989 and 2014 completed comprehensive preoperative and postoperative neuropsychological evaluations that included measures of verbal and nonverbal intellectual functioning, attention/working memory, processing speed, language, executive functioning, verbal and visual memory, and motor functioning. Objective methods were used to assess meaningful change across a wide range of abilities and to identify factors associated with neuropsychological decline following frontal lobectomy. Detailed postoperative neuroimaging analysis was conducted to characterize region, extent, and volume of resection.

Results: Forty-eight percent of patients did not demonstrate meaningful postoperative declines in cognition and an additional 42% demonstrated decline in 1 or 2 cognitive domains. When cognitive decline was observed, it usually occurred on measures of intelligence, visuomotor processing speed, or executive functioning. Side and site of resection were unrelated to cognitive outcome, but played a role in decline of contralateral manual dexterity following supplementary motor area resection. Higher preoperative ability, older age at surgery, absence of a malformation of cortical development on MRI, and poor seizure outcome were related to cognitive decline on some measures, but had poor sensitivity in identifying at-risk patients.

Conclusions: The vast majority of patients who undergo frontal lobectomy for treatment of pharmacoresistant epilepsy demonstrate good cognitive and motor outcomes. *Neurology*® 2017;88:692–700

GLOSSARY

ANOVA = analysis of variance; **LF** = lateral frontal; **MF** = medial frontal; **OF** = orbital frontal; **RCI** = reliable change index; **ROI** = region of interest; **SMA** = supplementary motor area.

Frontal lobectomy is the second most common type of surgery used to treat pharmacoresistant epilepsy.¹ However, little is known about neuropsychological outcome following frontal resection. Early studies from the Montreal Neurologic Institute documented declines in motor skills, concept formation, problem-solving, fluency, and recency/frequency judgments following frontal lobe resections in adults with medically intractable epilepsy.^{2–6} More recent studies have demonstrated postoperative deficits in speed/attention, motor sequencing/coordination, language, verbal reasoning, and executive functioning.^{7–10} However, existing studies have been conducted on small samples, ranging from 11 to 36 patients, with limited cognitive batteries. As a result, conclusions regarding effects of surgical resection site and extent on a wide range of cognitive tasks have been limited. Further, we are unaware of any studies that have identified clinically meaningful neuropsychological change following frontal resection in adults using epilepsy-specific methods that account for test reliability and practice effects. Thus, goals of

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the current study were to (1) characterize cognitive and motor outcomes in a large sample of adult patients who underwent frontal lobe resections for treatment of pharmacoresistant epilepsy by using epilepsy-specific reliable change indices (RCIs)^{11–13} and (2) identify factors associated with cognitive and motor decline following frontal lobe resection.

METHODS **Standard protocol approvals, registrations, and patient consents.** Data for this retrospective, observational study were obtained from an institutional review board–approved neuropsychology registry containing demographic, cognitive, seizure-related, and surgical variables for patients 16 years or older who underwent epilepsy surgery for the treatment of pharmacoresistant epilepsy.

Participants. All patients underwent unilateral frontal lobe resection between 1989 and 2014 and completed both preoperative and postoperative neuropsychological evaluations. Patients with a history of prior neurosurgery were excluded. Ninety patients were identified (51% male) ranging in age from 16 to 59 years (mean 29.4, SD 10.5). Mean age at seizure onset was 13.4 years (SD 10.0) and mean epilepsy duration was 16 years (SD 11.0). Seventy percent of patients had an Engel class I outcome (free of disabling seizures) at the time of their postoperative evaluation.¹⁴ The individuals included in this study were not significantly different in demographic or disease characteristics than patients who were lost to follow-up.

Resections were classified as dominant ($n = 42$) or nondominant ($n = 48$) based on side of surgical resection and results of language lateralization procedures (Wada or fMRI). Of those who completed a language lateralization procedure ($n = 64$), 51 showed typical language lateralization, 10 showed atypical lateralization, and 3 had bilateral language representation with evidence for predominance on one side. In cases where lateralization procedures were not conducted ($n = 26$; all right-handed), left-sided resections were coded as dominant and right-sided resections were coded as nondominant. Patients who underwent dominant frontal resections demonstrated lower preoperative performance on measures of verbal intelligence and working memory than those with nondominant resections. The groups were similar on demographic or seizure variables (table 1).

Neuropsychological measures. As part of standard of care, all patients completed a comprehensive neuropsychological evaluation before and 8 ± 7 months after surgery. The assessment included measures of cognitive ability (intelligence, attention/working memory, visuomotor processing speed, language, executive functioning, and memory) and motor functioning. The neuropsychological battery changed several times over the course of the 25 years covered by this study; therefore, not all patients had complete data on all measures. The specific measures and sample sizes are provided in table e-1 at Neurology.org and the figure.

Neuroimaging analyses. Anatomic localization. Postoperative MRIs were available for most patients ($n = 78$) and were used to identify the resection locations within the frontal lobe: medial frontal (MF), lateral frontal (LF), orbital frontal (OF), and supplementary motor area (SMA). A 3D tool was employed to visualize the images in 3 orthogonal planes and facilitate anatomical localization. All images were coded by a neuroradiology fellow (S.M.) under the supervision of a board-certified neuroradiologist (S.J.). A third rater (D.P.F.) reviewed images for a small subset of patients with discrepant ratings relative to those published previously in

a subsample of these patients.⁹ In cases where lesion location was questionable due to neuroanatomical anomalies or reduced image quality ($n = 10$), final determination was made by a neuroradiologist (S.J.) who was blinded to results of prior coding.

Resection cavity volume. Seventy-three patients had postoperative images of sufficient quality to characterize resection cavity volume. Regions of interest (ROIs) corresponding to the resection cavity were drawn on coronal T1 magnetization-prepared rapid gradient echo images or coronal T1-weighted spin echo images. Total resection volume was calculated by summing ROI volumes for each slice, accounting for slice thickness. These volumes were calculated by the same neuroradiology fellow (S.M.) under the supervision of a neuroradiologist (S.J.).

Statistical analyses. Neuropsychological change. RCIs (90% confidence interval), developed from nonsurgical epilepsy patients tested twice (without surgery or other intervention) and corrected for practice effects, were used to characterize clinically meaningful change following epilepsy surgery (i.e., improve, no change, decline).^{11–13} For measures without published RCIs in epilepsy (i.e., Processing Speed Index, Ruff Figural Fluency Test), 1 SD change (i.e., ± 15 standard score points or ± 10 t score points) was used to categorize outcome. Chi-square analyses were used to determine whether the base rate of neuropsychological change following frontal lobe resection was greater than expected by chance alone using a 90% confidence interval (i.e., 5% of patients improve, 5% of patients decline).

To better understand cognitive morbidity for individual patients, the number of cognitive domains within which each patient declined following surgery was calculated. Analyses of variance (ANOVAs) and χ^2 analyses were then conducted to determine if there were differences in demographic or seizure variables between patients who showed postoperative cognitive decline and those who did not.

To identify patients at risk for cognitive or motor decline, improve and no change groups were combined into a no decline group and compared to the decline group for all remaining analyses. Furthermore, subsequent analyses were conducted only for measures on which patients demonstrated greater than expected postoperative decline.

Resection location and extent. Chi-square analyses were used to determine if outcomes (decline/no decline) differed as a function of resection side (dominant/nondominant) among the entire sample as well as separately by lesion location. Separate χ^2 examined differences in outcome (decline/no decline) as a function of surgical resection (resected/spared) for each frontal region coded on postoperative MRI (MF, LF, OF, SMA). These analyses were also repeated separately by side of surgery (dominant/nondominant). Then, frequencies were calculated to determine the prevalence of decline based on extent of resection (combinations of all regions involved). Finally, a series of ANOVAs was conducted to determine if there were differences in resection volume between patients who declined following surgery and those who did not.

Predictors of cognitive decline. Using t tests or χ^2 analyses, we examined the association between postoperative cognitive or motor decline and a series of patient and disease variables including age at time of surgery, age at seizure onset, preoperative test performance, presence/absence of malformation of cortical development on preoperative MRI, reduction/no reduction in number of antiepileptic drugs following surgery, postoperative test interval, and good (Engel I/II)/poor (Engel III/IV) seizure outcome at time of postoperative assessment. These variables were selected as they have been associated with postoperative cognitive outcome following epilepsy surgery in other studies (see summaries in references 15 and 16). Given the high correlation between age at seizure onset and duration

Table 1 Demographic, baseline cognitive/motor ability, and seizure data for study patients by surgical side

	Dominant (n = 42) ^a	Nondominant (n = 48) ^a	t/F	χ^2	p	d/ ϕ
Age, y, mean (SD)	30.7 (9.3)	28.2 (11.4)	1.13		0.26	0.24
Education, y, mean (SD)	12.8 (2.0)	12.4 (2.1)	0.91		0.36	0.20
Age at seizure onset, y, mean (SD)	12.5 (9.1)	14.1 (10.8)	−0.78		0.44	−0.16
Duration of epilepsy, y, mean (SD)	18.2 (10.5)	14.1 (11.1)	1.82		0.07	0.38
Preoperative AEDs, mean (SD)	2.3 (0.9)	2.2 (0.9)	0.46		0.65	0.09
Postoperative AEDs, mean (SD)	1.9 (0.8)	1.9 (0.9)	0.01		0.99	0.84
Intelligence, mean (SD)						
Verbal IQ	85.6 (11.7)	91.4 (12.6)	4.57		0.04	−0.48
Performance IQ	89.3 (14.0)	91.8 (13.9)	0.66		0.42	−0.18
Attention/working memory, mean (SD)						
Working Memory Index	77.7 (12.2)	86.8 (12.2)	7.23		0.01	−0.75
Processing speed, mean (SD)						
Processing Speed Index	84.6 (12.4)	86.6 (13.1)	0.40		0.53	−0.16
Trail-Making Test, part A (raw)	33.9 (13.2)	41.3 (23.0)	3.07		0.08	−0.39
Language, mean (SD)						
Boston Naming Test (raw)	46.5 (7.8)	48.7 (7.9)	1.78		0.19	−0.28
Executive functioning, mean (SD)						
COWAT (raw)	24.8 (9.7)	26.3 (10.1)	0.50		0.48	−0.15
WCST, categories (raw)	4.0 (2.3)	4.6 (2.1)	1.67		0.20	−0.27
WCST, perseverative errors	85.9 (20.1)	93.4 (22.2)	2.46		0.12	−0.35
Trail-Making Test, part B (raw)	100.5 (54.1)	112.6 (68.5)	0.77		0.38	−0.20
Ruff Figural Fluency Test (t score)	39.0 (8.7)	38.5 (8.9)	0.06		0.80	0.06
Memory, mean (SD)						
Auditory Immediate Memory Index	87.1 (15.2)	89.4 (17.9)	0.28		0.60	−0.14
Auditory Delayed Memory Index	88.6 (13.4)	90.0 (17.8)	0.10		0.75	−0.09
Auditory Delayed Recognition Index	91.7 (17.5)	92.1 (19.2)	0.01		0.94	−0.02
Visual Immediate Memory Index	87.7 (13.0)	87.2 (13.7)	0.01		0.91	0.04
Visual Delayed Memory Index	87.5 (13.6)	87.7 (13.4)	0.00		0.96	−0.01
Sex, n (%)						
Male	22 (52)	24 (50)		0.05	0.82	0.02
Female	20 (48)	24 (50)				
Race, n (%)						
White	41 (98)	42 (88)		3.96	0.14	0.21
Black	0 (0)	4 (8)				
Other	1 (2)	2 (4)				
Postoperative AED change, n (%)						
AED reduction	14 (36)	16 (35)		0.01	0.92	0.01
No AED reduction	25 (64)	30 (65)				
Seizure outcome, n (%)						
Engel I/II	28 (67)	35 (73)		0.42	0.51	−0.07
Engel III/IV	14 (33)	13 (27)				

Abbreviations: AED = antiepileptic drug; COWAT = Controlled Oral Word Association Test; WCST = Wisconsin Card Sorting Test.

Neuropsychological test scores are reported as standard scores unless otherwise indicated.

^aNot all patients completed all cognitive measures (due to changes in test battery over time). Actual sample sizes for cognitive measures are provided in table e-1.

Figure Cognitive and motor outcomes after frontal resection for epilepsy

Percentage of patients demonstrating meaningful postoperative neuropsychological change (90% confidence interval) following frontal lobe resection. Numbers in parentheses after the test name represent the number of patients in the study who completed that particular measure. ^a $p < 0.0001$; ^b $p < 0.01$; ^c $p < 0.05$. Auditory Delayed = Auditory Delayed Memory Index; Auditory Immediate = Auditory Immediate Memory Index; Auditory Recog = Auditory Recognition Delayed Memory Index; GPT = Grooved Pegboard Test; PE = perseverative errors; Visual Delayed = Visual Delayed Memory Index; Visual Immediate = Visual Immediate Memory Index; WCST = Wisconsin Card Sorting Test.

of epilepsy ($r = -0.503$, $p < 0.001$), duration of epilepsy was not included as an independent predictor. Factors found to be most associated with cognitive or motor decline were used as predictor variables in a series of binary logistic regression analyses.

RESULTS Neuropsychological change. A significantly larger proportion of patients demonstrated change (in either direction) following frontal lobectomy than expected by chance alone on most neuropsychological

measures. Frequency distributions revealed a larger than expected proportion of patients demonstrated decline on select measures of nonverbal intellectual abilities (Performance IQ), processing speed (Trail-Making Test, part A), verbal fluency (Controlled Oral Word Association Test), novel problem-solving (Wisconsin Card Sorting Test, perseverative errors), and fine manual dexterity bilaterally (Grooved Pegboard Test with ipsilateral and contralateral hands). In contrast,

a larger than expected proportion of patients demonstrated postoperative improvement on measures of confrontation naming (Boston Naming Test) and verbal and visual memory (Wechsler Memory Scale Indices). On measures of verbal intellectual function (Verbal IQ) and nonverbal memory (Visual Delayed Memory Index), patients demonstrated greater than expected cognitive changes in both directions. Few patients demonstrated clinically meaningful change (in either direction) on measures of attention/working memory (Working Memory Index), visuomotor processing speed (Processing Speed Index), and most measures of executive functioning (Wisconsin Card Sorting Test categories; Trail-Making Test, part B; and Ruff Figural Fluency Test, unique designs) (figure and table e-1).

Forty-eight percent of the sample did not show decline on any of the 16 cognitive measures examined in this study. Forty-two showed decline on measures in 1 or 2 cognitive domains. In contrast, 10% of the sample showed declines in 3 or more cognitive domains. Examination of demographic and seizure variables did not reveal any significant differences between patients with and without postoperative cognitive decline or between patients with limited cognitive decline (2 or fewer domains) and those with more widespread cognitive decline (3 or more measures).

Resection location/extent. Side of resection. There were no differences in cognitive or motor outcome as a function of resection side on any measure when the sample was analyzed together or separately by lesion location.

Region of resection. Thirty-one percent of patients who had resections involving the SMA demonstrated clinically meaningful declines in contralateral manual dexterity (Grooved Pegboard Test) following surgery as compared to only 10% of patients who had frontal resections that spared the SMA ($\chi^2[1] = 5.59, p < 0.05, \phi = 0.275$). There were no differences in cognitive outcome or ipsilateral manual dexterity as a function of resection region.

Table 2 summarizes the observed declines by extent of resection. Across neuropsychological measures, declines were most prevalent following large resections involving LF/MF/OF regions, with and without inclusion of the SMA. It is important to note that these were also the most common resection types. Sample sizes were too small to draw conclusions regarding cognitive outcome for some of the less frequent, more limited resection types.

Volume of resection. Patients who demonstrated declines in verbal intellectual abilities following surgery had significantly larger resection volumes than those who did not (Verbal IQ $F_{1,64} = 4.9, p < 0.05, \eta_p^2 = 0.07$). No differences in resection volume were

found between decliners and nondecliners on any of the other measures examined.

Predictors of cognitive decline. Baseline test performance was associated with postoperative outcome on measures of nonverbal intellectual ability (Performance IQ) and verbal fluency (Controlled Oral Word Association Test). Specifically, patients who demonstrated postoperative declines on these measures had higher preoperative performance on these tasks than those who did not. Absence of malformation of cortical development on MRI was related to worsened nonverbal intelligence (Performance IQ) and nonverbal memory (Visual Delayed Memory). Older age at time of surgery was associated with poorer cognitive outcome on measures of speeded visuomotor sequencing (Trail-Making Test, part A) and contralateral manual dexterity (Grooved Pegboard Test). Finally, good seizure outcome was related to better outcome on measures of nonverbal intelligence (Performance IQ) and nonverbal memory (Visual Delayed Memory) (table 3). The other demographic and seizure variables examined were not related to cognitive decline.

Because seizure outcome is unknown prior to surgery, only age at seizure onset, preoperative test performance, and presence/absence of malformation of cortical development on preoperative MRI were included in binary logistic regression analyses. While these 3 variables significantly predicted postoperative cognitive outcome on measures of Performance IQ ($\chi^2[3] = 15.7, p < 0.01$, Nagelkerke $R^2 = 0.28$), Trail-Making Test, part A ($\chi^2[3] = 10.9, p < 0.05$, Nagelkerke $R^2 = 0.21$), and Grooved Pegboard, contralateral hand ($\chi^2[3] = 9.4, p < 0.05$, Nagelkerke $R^2 = 0.17$) with excellent specificity (0.96–0.99), sensitivity was very poor (0.15–0.20).

DISCUSSION Results of this study suggest that most patients who undergo frontal lobe resections for treatment of pharmacoresistant epilepsy have good cognitive outcomes. Forty-eight percent of patients in this study did not demonstrate any postoperative declines in cognition and an additional 42% demonstrated decline in 1 or 2 cognitive domains. Interestingly, there was a subset of patients who demonstrated clinically meaningful improvements in confrontation naming (15% of sample), verbal intellectual function (11%), or memory (10%–17%) following frontal lobectomy. When postoperative declines were present, they occurred most frequently on measures of intellectual functioning (verbal and nonverbal), visuomotor processing speed, aspects of executive functioning (verbal fluency, perseverative errors), and fine manual dexterity (particularly with the hand contralateral to surgical resection). These findings are consistent with previous studies that have reported declines on

Table 2 Cognitive and motor decline following frontal lobectomy by region of resection

Measure	All regions (n = 19)	LF/MF/OF (n = 20)	LF/MF/SMA (n = 10)	LF/MF (n = 8)	MF/SMA (n = 3)	LF only (n = 12)
Verbal IQ						
No. decline (total ^a)	4 (16)	2 (17)	1 (8)	0 (8)	1 (3)	2 (11)
% of decliners	40	20	10	—	10	20
% of resection type	25	12	13	—	33	18
Performance IQ						
No. decline (total ^a)	3 (17)	3 (19)	1 (9)	0 (8)	1 (3)	4 (11)
% of decliners	25	25	8	—	8	33
% of resection type	18	16	11	—	33	36
COWAT						
No. decline (total ^a)	2 (19)	5 (20)	2 (10)	1 (7)	0 (3)	1 (12)
% of decliners	18	46	18	9	—	9
% of resection type	11	25	20	14	—	8
WCST perseverative errors						
No. decline (total ^a)	5 (17)	3 (20)	0 (10)	0 (7)	0 (1)	2 (11)
% of decliners	50	30	—	—	—	20
% of resection type	29	15	—	—	—	18
Trail-Making Test, part A						
No. decline (total ^a)	3 (18)	4 (19)	1 (10)	0 (7)	0 (1)	2 (11)
% of decliners	30	40	10	—	—	20
% of resection type	17	21	10	—	—	18
Visual Delayed Memory						
No. decline (total ^a)	1 (13)	2 (18)	0 (6)	0 (5)	0 (1)	3 (10)
% of decliners	17	33	—	—	—	50
% of resection type	8	11	—	—	—	30
GPT, ipsilateral hand						
No. decline (total ^a)	3 (18)	1 (20)	2 (9)	2 (7)	1 (3)	1 (11)
% of decliners	30	10	20	20	10	10
% of resection type	17	5	22	29	33	9
GPT, contralateral hand						
No. decline (total ^a)	5 (18)	2 (20)	4 (9)	1 (8)	(1)	1 (10)
% of decliners	38	15	31	8	—	8
% of resection type	28	10	44	13	—	10

Abbreviations: COWAT = Controlled Oral Word Association Test (FAS, verbal fluency); GPT = Grooved Pegboard Test; LF = lateral frontal; MF = medial frontal; OF = orbitofrontal; SMA = supplementary motor area; WCST = Wisconsin Card Sorting Test.

Resection types with very small sample sizes were omitted from this table (i.e., LF/OF = 1, LF/SMA = 1, MF only = 2, SMA only = 2) as no declines were observed.

^aTotal number of patients with that resection type who completed the cognitive measure.

measures of executive functioning, including verbal fluency,^{2,7–9,17} aspects of problem-solving,^{2,8,17} processing speed,⁷ and motor functioning.⁷ Existing studies that have examined change in intellectual functioning following frontal lobe surgery have had mixed results, with some studies reporting no change on intelligence measures⁸ and others reporting apparent improvements.¹⁸ These discrepant findings are related, at least in part, to the fact that prior studies did not make use of epilepsy-specific RCIs to

assess cognitive outcome. Further, examination of subtest scores from the Wechsler Adult Intelligence Scale IQ indices suggests that measures of working memory (i.e., letter number sequencing and arithmetic) contributed the most to declines in Verbal IQ and a measure of visual reasoning (i.e., matrix reasoning) contributed the most to declines in Performance IQ. The frontal lobes are known to play a role in working memory and reasoning functions.^{19,20} Thus, our findings appear to reflect declines in these

Table 3 Factors associated with cognitive and motor decline following frontal lobe resection

	Decline	No decline	t/χ^2	p
Verbal IQ	n = 12	n = 67		
Age at surgery, y	30.9 (10.2)	29.64 (10.9)	-0.37	0.71
Baseline score (standard score)	92.8 (9.6)	87.6 (13.0)	-1.32	0.19
MCD on preoperative MRI	1 (8%)	22 (33.3%)	3.05	0.08
Good seizure outcome (Engel I/II)	6 (50%)	49 (73%)	2.58	0.11
Performance IQ	n = 15	n = 68		
Age at surgery	32.1 (12.3)	29.3 (10.4)	-0.92	0.36
Baseline score (standard score)	100.8 (11.8)	88.4 (13.2)	-3.33 ^a	0.001 ^a
MCD on preoperative MRI	1 (7%)	24 (36%)	4.92 ^a	0.03 ^a
Good seizure outcome (Engel I/II)	7 (47%)	51 (75%)	4.69 ^a	0.03 ^a
Trail-Making Test, part A	n = 13	n = 69		
Age at surgery	36.7 (12.9)	28.3 (9.9)	-2.66 ^a	0.009 ^a
Age at seizure onset	17.4 (13.9)	13.0 (9.3)	-1.44	0.15
Baseline score (raw seconds)	29.2 (7.1)	39.5 (20.5)	1.78	0.08
MCD on preoperative MRI	4 (31%)	23 (33%)	0.03	0.86
Good seizure outcome (Engel I/II)	10 (77%)	50 (73%)	0.11	0.74
Controlled Oral Word Association Test	n = 11	n = 78		
Age at surgery	33.7 (8.9)	28.7 (10.6)	-1.49	0.14
Baseline score (raw score)	32.4 (6.5)	24.6 (10.0)	-2.50 ^a	0.01 ^a
MCD on preoperative MRI	2 (18%)	26 (34%)	1.08	0.30
Good seizure outcome (Engel I/II)	5 (46%)	57 (73%)	3.48	0.06
Wisconsin Card Sorting Test, perseverative errors	n = 12	n = 72		
Age at surgery	29.1 (12.1)	29.6 (10.6)	0.14	0.89
Baseline score (raw score)	16.8 (11.7)	22.0 (17.6)	0.99	0.32
MCD on preoperative MRI	5 (46%)	23 (32%)	0.78	0.38
Good seizure outcome (Engel I/II)	8 (67%)	51 (71%)	0.09	0.77
Visual Delayed Memory	n = 6	n = 53		
Age at surgery	31.2 (11.4)	29.8 (11.6)	-0.27	0.79
Baseline score (standard score)	92.2 (10.4)	87.1 (13.7)	-0.87	0.39
MCD on preoperative MRI	0 (0%)	24 (45%)	4.6 ^a	0.03 ^a
Good seizure outcome (Engel I/II)	2 (33%)	42 (79%)	6.0 ^a	0.01 ^a
Grooved Pegboard, ipsilateral hand	n = 11	n = 74		
Age at surgery	30.0 (11.8)	29.6 (10.6)	-0.12	0.90
Baseline score (raw seconds)	80.4 (23.0)	84.7 (22.8)	0.59	0.56
MCD on preoperative MRI	5 (46%)	22 (30.1%)	1.03	0.31
Good seizure outcome (Engel I/II)	8 (73%)	53 (72%)	0.01	0.94
Grooved Pegboard, contralateral hand	n = 16	n = 70		
Age at surgery	35.6 (13.1)	28.2 (9.5)	-2.60 ^a	0.01 ^a
Baseline score (raw seconds)	91.1 (29.8)	100.8 (52.6)	0.71	0.48
MCD on preoperative MRI	8 (53%)	19 (27%)	3.91	0.05
Good seizure outcome (Engel I/II)	10 (63%)	51 (73%)	0.68	0.41

Abbreviation: MCD = malformation of cortical development.

Not all sample sizes sum to 90 as not all patients completed all cognitive measures (due to changes in test battery over time).

^aSignificant.

more specific domains rather than overall intelligence per se.

Surgical location (side or site) was found to play a role on only one neuropsychological measure—fine manual dexterity. Patients who underwent resection of the SMA were more likely to demonstrate postoperative declines in dexterity on the Grooved Pegboard Test with their contralateral hand than patients in whom this region was spared. Previous research has reported contralateral motor declines following SMA resection that typically resolve within a few months (references 21 and 22; but see reference 23). However, these studies assessed gross motor functioning. The current study suggests that more subtle motor difficulties (i.e., manual dexterity) may persist following surgery. This is consistent with a recent study,²⁴ which found that fine motor functioning recovered much slower than gross motor abilities following SMA resection. Future studies with longer follow-up periods will be needed to determine if dexterity improves back to baseline following a longer time period.

It was somewhat surprising that side and site of surgical resection were not strongly associated with cognitive outcome. While we observed some score differences in the same direction as reported in existing studies (e.g., reduced verbal fluency following dominant-sided resections), effect sizes were generally small and therefore not reported. Our failure to find effects of surgical side/site likely reflects, at least in part, the more rigorous methodology we used to characterize clinically meaningful cognitive change at the individual level using RCIs that account for test-retest reliability and practice effects. Studies that have tested patients with epilepsy on 2 separate occasions in the absence of any intervention (surgical or otherwise) have demonstrated that some cognitive measures have very low test-retest reliabilities in this population.^{11–13,25} Further, while some measures have rather large, positive practice effects, others actually have negative practice effects, with epilepsy patients demonstrating lower test scores on repeat testing.^{11–13,25} Failure to account for these factors can lead to erroneous assumptions regarding cognitive outcome, particularly when examining differences in group means, rather than individual change. Perhaps more importantly, without adjusting for test reliability and practice effects specific to epilepsy, it is impossible to determine whether a postoperative change in test score is due to effects of epilepsy surgery or the seizure disorder itself.

It is important to note that while most patients had very good cognitive outcomes, there was a small subset (10%) who demonstrated postoperative declines across 3 or more cognitive domains. The sample size ($n = 9$) precluded statistical analysis to identify demographic or seizure variables associated with this widespread cognitive decline. Nevertheless,

there was no clear association with side of resection (56% dominant) or seizure outcome (56% Engel I/II). Extent of resection was also very similar to patients without global decline.

Several factors were related to postoperative decline on individual cognitive measures following frontal lobe surgery (i.e., baseline ability, age at time of surgery, seizure outcome, presence of a malformation of cortical development on MRI), but these variables had low sensitivity in identifying patients at risk for cognitive decline and would be inadequate for clinical use. Further research will be needed to identify variables that better predict decline in specific cognitive domains as well as factors that may assist clinicians in predicting the small subset of patients at risk for more widespread cognitive decline.

There are several limitations to this study that deserve mention. Given the time span of data collection necessary to amass a large study sample, complete data (high-resolution MRI, comprehensive clinical data, current editions of neuropsychological measures) were not available for all patients. In addition, the methods used to characterize language lateralization (i.e., dichotomization of language dominance in patients with atypical/bilateral language representation, use of handedness as a proxy for language lateralization in some patients) are relatively simplistic and may not fully represent actual language distribution in all patients. Finally, we were unable to adequately assess cognitive outcome following focal frontal resections involving discrete regions given that most patients (~80%) had rather large resections that involved 2 or more frontal lobe regions. Despite these limitations, this study provides important insights into cognitive outcome after frontal lobe resection for epilepsy as it includes the largest sample size to date and is the first to make use of RCIs, specific to epilepsy, to characterize clinically meaningful cognitive change following frontal lobectomy.

This study suggests that the vast majority of adults who undergo frontal lobectomy for treatment of pharmacoresistant epilepsy demonstrate good cognitive outcomes. When cognitive declines occur, they are typically restricted to 2 or fewer cognitive domains (90%). Encouragingly, more widespread declines in cognition, across 3 or more cognitive domains, appear to be relatively rare (~10%). Future research will seek to identify factors to assist clinicians in predicting cognitive outcome following frontal lobectomy.

AUTHOR CONTRIBUTIONS

Robyn M. Busch: design and conceptualization of study, analysis and interpretation of data, drafting/revising the manuscript for intellectual content, study supervision and coordination. Darlene P. Floden: design and conceptualization of study, analysis and interpretation of data, drafting/revising the manuscript for intellectual content, study supervision and coordination. Lisa Ferguson: design of study, analysis of data, revising the manuscript for intellectual content. Shamseldeen Mahmoud: analysis and

interpretation of data, drafting/revising the manuscript for intellectual content. Audrina Mullane: analysis and interpretation of data, revising the manuscript for intellectual content. Stephen Jones: conceptualization of study, analysis and interpretation of data, revising the manuscript for intellectual content, supervision. Lara Jehi: interpretation of data, revising the manuscript for intellectual content. William Bingaman: interpretation of data, revising the manuscript for intellectual content. Imad M. Najm: interpretation of data, revising the manuscript for intellectual content.

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DISCLOSURE

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