Estimating risk of word-finding problems in adults undergoing epilepsy surgery

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ABSTRACT

Objective: This retrospective, observational study examined the frequency and magnitude of change in naming ability as a function of side/site of epilepsy surgery and identified predictive factors to assist clinicians in identifying patients at low, moderate, or high risk of postoperative naming decline.

Methods: A total of 875 adults with pharmacoresistant epilepsy (454 left/421 right; 763 temporal/87 frontal/25 posterior quadrant) met inclusion criteria and completed the Boston Naming Test before and after surgery. Clinically meaningful change in naming ability was assessed using reliable change indices for epilepsy. Demographic, cognitive, and seizure variables were examined to determine factors most predictive of naming decline and to develop a decision tree to assist with clinical decision-making.

Results: Naming decline was rare in right-sided resections and did not exceed the level expected by chance (5% overall; 90% confidence interval [CI] $\pm$ 2%). Naming decline occurred in 41% (CI $\pm$ 5%) of patients after left temporal resection (TLR) compared to 10%–12% (CI $\pm$ 10%–19%) in other left-sided surgical groups. A sizable proportion of left TLR patients (17%; CI $\pm$ 4%) showed substantial declines in naming (>11 points). Decline following left TLR was related to later age at seizure onset, older age at surgery, and higher preoperative naming ability. These factors correctly predicted naming decline in 68% of patients and were associated with degree of decline following left TLR. A decision tree is provided to assist clinicians in identifying patients at low, moderate, or high risk for postoperative naming declines.

Conclusions: In addition to discussions regarding risk for memory decline following left TLR, patients should be counseled about potential decline in word-finding ability. **Neurology® 2016;87:2363–2369**

GLOSSARY

AED = antiepileptic drug; **BNT** = Boston Naming Test; **CI** = confidence interval; **FLR** = frontal lobe resection; **TLR** = temporal lobe resection.

Patients with epilepsy who are considering surgical treatment, particularly involving the dominant temporal lobe, are typically counseled regarding risk of postoperative memory impairment. However, language problems, including word-finding difficulties, can also have a significant effect on quality of life.¹ Indeed, patients' complaints of postoperative memory problems often reflect changes in word-finding rather than changes in memory function. Initial studies confirm that visual naming declines occur in 25%–60% of adults following dominant temporal lobe resection (TLR),^{2,3} and prior work suggests that young onset of seizures is protective of naming performance after surgery.^{4,5} Complex functional imaging methods have also shown some facility in predicting naming outcomes, albeit in very small sample sizes with minimal naming changes after surgery.^{6,7} As such, the patient and disease characteristics that place a particular adult patient at risk for postsurgical naming decline remain largely unknown. It is also notable that word-finding impairment can arise after damage to a wide range of neuroanatomical

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systems. The few studies examining naming outcome in adult patients after focal resections outside of the temporal lobes have been underpowered to evaluate surgical site effects.^{8,9} The objectives of the current study were to (1) examine the frequency of change in naming ability following epilepsy surgery as a function of side/site of resection, (2) determine if magnitude of naming decline is related to side/site of resection, and (3) identify factors associated with decline in postoperative naming ability.

METHODS **Standard protocol approvals, registrations, and patient consents.** Data for this retrospective, observational study were obtained from an institutional review board–approved neuropsychology data registry containing demographic, cognitive, seizure-related, and surgical variables for patients aged 16 years or older who underwent epilepsy surgery for the treatment of pharmacoresistant seizures at Cleveland Clinic between 1986 and 2015.

Participants. Approximately 1,500 adults underwent focal cortical resections during the 29-year time period covered by this study. Individuals were selected for study inclusion if they met the following criteria: (1) had a full-scale IQ ≥ 70 ; (2) were right-handed or left-hemisphere dominant for language on fMRI or Wada testing; (3) had available preoperative and postoperative scores on the Boston Naming Test,¹⁰ which is routinely administered as part of a standard neuropsychological test battery; (4) underwent a focal resection for the treatment of epilepsy; and (5) had no history of prior neurosurgery.

A total of 875 patients (454 left/421 right; 763 temporal/87 frontal/25 posterior quadrant) met all inclusion criteria. On average, patients were 35 years old (range 16–71) and had 13 years of education (range 6–21) at baseline assessment. At seizure onset, patients were an average of 16 years old (range 0–65), and their mean duration of epilepsy was 18 years (range 0–60). Most of the patients in this sample were Caucasian (94%), and just over half the sample was female (52%). Patients with temporal lobe epilepsy were significantly older (mean 35.5, SD 11.5) than patients with frontal lobe epilepsy (mean 29.5, SD 10.5), $F_{2,874} = 11.09$, $p < 0.001$, and had longer epilepsy duration (18.8 years, SD 12.4 vs 15.3 years, SD 10.9), $F_{2,874} = 3.19$, $p = 0.042$. There was a significant difference between surgical groups in the number of antiepileptic drugs (AEDs) they were taking both prior to (Kruskal Wallis $\chi^2[2] = 11.94$, $p = 0.003$) and following surgery (Kruskal Wallis $\chi^2[2] = 7.62$, $p = 0.022$). Patients with temporal lobe epilepsy were taking the fewest number of AEDs at both timepoints. There were no significant differences among resection site groups in sex, race, education, age at seizure onset, Full Scale IQ, or preoperative naming performance. Patients who underwent TLRs had better seizure outcomes at the time of postoperative neuropsychological evaluation (79% seizure-free) than the other 2 surgical groups (frontal and posterior quadrant; 64% seizure-free), $\chi^2(2) = 11.29$, $p = 0.004$.

Measures. Naming outcome was assessed using the Boston Naming Test (BNT),¹⁰ an established and widely used measure of visual confrontation naming that consists of 60 line drawings. Patients are asked to provide the name for the object in each drawing (e.g., bed). If they are unable to generate the name, they are provided with a stimulus cue (e.g., a piece of furniture) or

a phonemic cue (e.g., it begins with the sound bē-). Items that are correctly named spontaneously or with a stimulus cue are awarded 1 point for a total of 60 points possible on this measure. All patients completed this measure both prior to and following epilepsy surgery as part of standard clinical neuropsychological evaluations. Postoperative evaluations were conducted a median of 6 months following surgery and 10 months following preoperative assessment. Change scores (postoperative score minus preoperative score) were calculated and classified in 1 of 3 naming outcome groups (improved, no change, decline) using established reliable change indices (± 5 or more raw points) for epilepsy.¹¹ Magnitude of postoperative decline was also examined by further categorizing decliners into groups based on degree of decline in postoperative naming score (5–10, 11–20, >20 raw score points).

Statistical analysis. First, the influence of resection side (left/right) on naming outcome (improved, no change, decline) was evaluated using χ^2 analyses with exact tests. All subsequent analyses were conducted separately between patients with left- and right-sided resections. χ^2 analyses with exact tests were used to examine differences in naming outcome (improved, no change, decline) as a function of surgical resection site (temporal, frontal, posterior quadrant). Similar analyses were completed to determine if magnitude of decline (5–10 points, 11–20 points, >20 points) varied as a function of surgical site. Decline was most apparent following left TLR; therefore, subsequent analyses focused on left temporal cases only. A series of analyses of variance and χ^2 were used to identify factors most associated with naming change after this type of surgery. Specifically, differences among the naming outcome groups were examined for age at baseline assessment, education, age at seizure onset, duration of epilepsy (age at assessment minus age at onset), preoperative naming score, Full Scale IQ, number of AEDs at baseline, change in number of AEDs after surgery, resection type, surgical pathology, and seizure outcome. Given that some patients in the study underwent surgery before the initiation of an electronic medical record system, not all data points were available for all patients. A standard, multivariate logistic regression was used to determine the accuracy with which the factors related to naming change after surgery, in combination, could predict those patients who demonstrated clinically meaningful naming declines following left temporal lobectomy. Finally, we conducted a classification and regression tree analysis,¹² with cross-validation, to develop a clinician-friendly decision tree to more easily identify patients at risk for naming decline following left TLR.

RESULTS Naming decline was more common in patients with left-sided resections relative to those with right-sided resections ($\chi^2[2] = 134.14$, $p < 0.001$). Specifically, 38% (90% confidence interval [CI] $\pm 4\%$) of patients who underwent left-sided resections demonstrated clinically meaningful declines in confrontation naming compared to only 5% (CI $\pm 2\%$) of patients who had right-sided surgeries. There was no difference in naming outcome as a function of surgery site in patients with right-sided resections ($\chi^2[4] = 3.07$, $p = 0.547$); however, there were significant group differences following left-sided resections ($\chi^2[4] = 20.97$, $p < 0.001$). Specifically, naming decline occurred in 41% (CI $\pm 5\%$) of patients after left TLRs compared to 10%–12% (CI $\pm 10\%$ –19%) in other left-sided surgical groups.

Table 1 Naming outcomes after epilepsy surgery

	Total no.	Improve, n (CI)	No change, n (CI)	Decline, n (CI)		
				5-10 Points	11-20 Points	20+ Points
Left resection						
Temporal	401	29 (7 ± 3)	206 (51 ± 5)	97 (24 ± 4)	40 (10 ± 3)	29 (7 ± 3)
Frontal	43	8 (19 ± 12)	30 (70 ± 14)	5 (12 ± 10)	0 (0)	0 (0)
Posterior quadrant	10	1 (10 ± 19)	8 (80 ± 25)	1 (10 ± 19)	0 (0)	0 (0)
Right resection						
Temporal	362	54 (15 ± 4)	289 (80 ± 4)	15 (4 ± 2)	3 (<1 ± 1)	1 (<1 ± 1)
Frontal	44	4 (9 ± 8)	38 (86 ± 10)	0 (0)	1 (2 ± 4)	1 (2 ± 4)
Posterior quadrant	15	4 (27 ± 22)	10 (67 ± 24)	1 (7 ± 13)	0 (0)	0 (0)

Abbreviation: CI = 90% confidence interval.

In contrast, naming improvements were more common among patients who underwent left frontal resections (19%; CI ± 12%) than in those who underwent left temporal resections (7%; CI ± 3%) (table 1 and figure 1). Naming outcome following left frontal lobe resection (FLR) was related to seizure freedom, $\chi^2(2) = 8.33$, $p = 0.016$. Specifically, among the left FLR patients who were completely seizure-free at follow-up, none showed postoperative naming declines and 30% showed postoperative naming improvements. In contrast, 21% of left FLR patients who experienced at least one postoperative seizure demonstrated naming declines.

A sizable proportion of patients who underwent left TLR (17%; CI ± 4%) showed substantial naming

declines (≥ 11 points), while declines of this magnitude were not observed among the other left-sided surgical groups (table 1). Naming decline after left TLR was related to older age at time of surgery ($F_{4,400} = 11.88$, $p < 0.001$, $\eta_p^2 = 0.107$), later age at seizure onset ($F_{4,400} = 15.19$, $p < 0.001$, $\eta_p^2 = 0.133$), and higher preoperative naming score ($F_{4,400} = 10.10$, $p < 0.001$, $\eta_p^2 = 0.093$). As can be seen in table 2, these variables were associated with both presence and degree of naming decline observed following surgery. When these 3 variables were entered together into a multivariate logistic regression analysis, the model significantly predicted the presence of postoperative naming decline, $\chi^2(3) = 51.57$, $p < 0.001$, Nagelkerke $R^2 = 0.163$. Given that age at

Figure 1 Change in confrontation naming performance following epilepsy surgery

Cognitive change (improve, no change, decline) following epilepsy surgery as characterized by published reliable change indices for epilepsy.¹¹

Table 2 Demographic/seizure variables and naming outcome following left temporal resection

	Improve, mean (SD) (n = 29)	No change, mean (SD) (n = 206)	Decline, mean (SD)		
			5-10 Points (n = 97)	11-20 Points (n = 40)	20+ Points (n = 29)
Age ^a	30.97 (9.62)	33.34 (10.65)	35.80 (10.91)	41.38 (12.35)	45.24 (12.37)
Education	12.93 (1.73)	12.95 (2.38)	13.10 (1.93)	12.68 (1.73)	13.79 (2.47)
Age at onset ^a	11.00 (10.66)	13.78 (11.33)	19.68 (12.76)	23.10 (14.08)	28.34 (15.12)
Duration of epilepsy	19.97 (10.44)	19.55 (12.21)	16.12 (11.59)	18.28 (14.88)	16.90 (13.13)
Preoperative naming ^a	37.34 (8.46)	45.33 (8.85)	46.64 (8.01)	48.53 (7.40)	49.14 (6.24)
Full-scale IQ	87.86 (10.17)	92.68 (12.18)	92.27 (11.03)	91.18 (8.65)	93.83 (9.94)
Preoperative AEDs ^b	1.72 (0.58)	1.84 (0.71)	2.00 (0.73)	1.77 (0.73)	2.04 (0.89)
Postoperative AED change ^c	-0.35 (0.70)	-0.26 (0.66)	-0.13 (0.63)	0.06 (0.54)	-0.17 (0.76)
	n (%)	n (%)	n (%)	n (%)	n (%)
Resection type ^d					
Mesial resected	26/27 (96.3)	170/191 (89.0)	86/92 (93.5)	37/39 (94.9)	22/27 (82.0)
Surgical pathology ^e					
MTS	7/21 (33.3)	83/150 (55.3)	46/68 (67.6)	19/31 (61.3)	9/20 (45.0)
Cortical dysplasia	3/21 (14.3)	22/150 (14.7)	8/68 (11.8)	6/31 (19.4)	4/20 (20.0)
Tumor	2/21 (9.5)	14/150 (9.3)	3/68 (4.4)	3/31 (9.7)	3/20 (15.0)
Other	0/21 (0)	0/150 (5.3)	8/68 (5.9)	4/31 (0)	0/20 (0)
Nonspecific	9/21 (42.9)	23/150 (15.3)	7/68 (10.3)	3/31 (9.7)	4/20 (20.0)
Seizure-free	19/29 (65.5)	152/206 (73.8)	81/97 (83.5)	24/29 (82.5)	24/29 (82.8)

Abbreviations: AED = antiepileptic drug; MTS = mesial temporal sclerosis.

Seizure-free outcome was assessed at time of postoperative neuropsychological assessment, which was a median of 6 months following surgery and 10 months following preoperative assessment.

^a $p < 0.001$.

^b $n = 315$.

^c $n = 292$.

^dTotal $n = 376$.

^e $n = 290$.

time of surgery did not independently contribute to the model and was significantly correlated with age at seizure onset ($r = 0.50$, $p < 0.001$), the regression analysis was repeated without this predictor. The 2-variable model significantly predicted the presence of postoperative naming decline, $\chi^2(2) = 48.36$, $p < 0.001$, Nagelkerke $R^2 = 0.153$. Both age at seizure onset ($B = 0.050$, $\chi^2[1] = 31.11$, $p < 0.001$, $\exp[B] = 1.05$) and preoperative BNT score ($B = 0.030$, $\chi^2[1] = 5.16$, $p = 0.023$, $\exp[B] = 1.03$) independently contributed to the prediction. While the overall classification rate was reasonable (68% correct classification, receiver operating characteristic area = 0.705), patients who declined were not as successfully predicted (46%) as those who did not (84%). Therefore, this equation is not recommended for clinical use in identifying patients at risk for naming decline. All 3 variables (age at surgery, age at seizure onset, and preoperative BNT score) were found to be important in a classification and regression tree, although age at seizure onset was

again found to be the most important factor in determining naming outcome (figure 2).

DISCUSSION Results of this study confirm, in a large clinical sample, previous findings that naming declines are common following left TLR and are associated with later age at seizure onset, older age at time of surgery, and better preoperative naming ability.^{2,3} Similar to prior studies, age at seizure onset was the best predictor of naming outcome following left TLR.^{2,4,13} This study also extends prior literature by documenting the base rate of moderate to severe naming declines (≥ 11 points on BNT) following left TLR and demonstrating that the magnitude of naming decline is associated with the same key variables as decline more broadly defined (≥ 5 points on BNT). Encouragingly, naming declines were relatively rare following right TLRs or extratemporal resections in either hemisphere and likely reflect chance decline (expected 5% decline with 90% CI). Results of language lateralization and handedness data provide further support for this conclusion

Figure 2 Decision tree for estimating risk of naming decline following left (dominant) temporal lobe resection

Total decline percentages represent the percentage of patients who fall in that category (e.g., adult onset epilepsy, over age 50 at time of evaluation) who demonstrated clinically meaningful declines in naming performance per established reliable change indices for epilepsy¹¹ (e.g., 75%). The total decline percentages are then broken down into mild (5–10 points), moderate (11–20 points), and severe (>20 points) decline. BNT = Boston Naming Test.

as patients who demonstrated naming declines following right TLR were strongly right-handed ($n = 11$; mean score 21 ± 4 on the Edinburgh Handedness Scale) or left-hemisphere language dominant on Wada or fMRI ($n = 8$). Interestingly, a large proportion of patients who underwent left frontal resections demonstrated clinically meaningful improvements in naming after surgery, particularly if they were rendered seizure-free. Similarly, a large proportion of patients who underwent right posterior quadrant resections showed naming improvements following surgery.

Given that this dataset spanned a period of 29 years that predated electronic medical records, not all variables of interest were readily available for analysis. We would have liked to examine the influence of

antiepileptic medications (e.g., type and dose of medications) and surgical variables (e.g., resection extent) on naming outcomes, but these data were not available for all patients. These factors are interesting questions for future research. Likewise, we would like to point out that we used right-handedness as a proxy for left hemispheric dominance in a large proportion of patients. Language lateralization procedures are currently used in our center only for those cases in which atypical lateralization is suspected or in which the planned resection is very close to eloquent areas. However, the fact that the rates of naming decline among left TLR patients were similar to those reported in other studies and the low rate of naming decline following right-sided resections suggest that the vast majority

of patients in this study were indeed left-hemisphere dominant for language.

Although it has become clear that naming declines are prevalent (25%–60%) following dominant TLRs,^{2,3} much of the emphasis in the literature and in clinical practice continues to be on memory risk and outcome. Our results suggest that patients should also be counseled regarding the risk for decline in naming ability following surgery, particularly given that there are a subset of patients who demonstrate catastrophic decline possibly reflecting a broader aphasic syndrome. Anecdotally, we have observed that word-retrieval difficulties following surgery can meaningfully reduce quality of life. Therefore, development of risk models to predict naming outcome, akin to those that have been developed for memory,^{14–16} are needed to improve preoperative counseling for patients considering epilepsy surgery. Ideally, development of such models would involve multicenter collaboration to increase sample sizes as well as to account for differences in patient characteristics and surgical approaches across centers.

The decision tree provided in figure 2 can assist clinicians in counseling patients about the likelihood of naming declines following left TLR using only 3 variables (i.e., age at seizure onset, age at time of evaluation, and preoperative score on the BNT). Notably, the highest risk groups are patients with seizure onset in adulthood (>18 years old) who are older at the time of surgery (>50 years old) or who have good preoperative naming scores (≥ 50 BNT raw score) with 75%–77% of such patients demonstrating clinically meaningful naming declines after surgery. These 2 groups are also the most likely to demonstrate postoperative declines in the moderate to severe range (11–20 or 20+ points on the BNT). While it is not possible to make firm conclusions regarding the mechanism of these primary risk factors on the basis of this study alone, they are consistent with the potential for less functional reorganization with later seizure onset,^{2,5,17} poorer functional reserve (or “brain reserve capacity”) in older adults in response to injury or insult,^{18–20} and functional adequacy of resected tissue.²¹

In contrast, patients with early age at seizure onset (≤ 18 years old) and reduced preoperative naming ability (< 50 BNT raw score) are at relatively low risk for naming decline following left temporal surgery. When naming declines do occur in such patients (25%), they tend to be relatively mild (5–10 points on the BNT). In addition to advising patients about the likelihood, and expected magnitude, of postoperative naming deficits, preoperative counseling should also involve educating patients on the differences between naming decline and verbal memory decline as the 2 are often easily confused. Many

times patients complaining of memory difficulties are actually experiencing word-retrieval problems (e.g., “I have trouble remembering the word or name”). Future research is also needed to explore methods (e.g., cognitive rehabilitation, speech therapy) to help patients compensate for these cognitive difficulties following surgery.

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 of study, analysis and interpretation of data, drafting/revising the manuscript for intellectual content. Brigid Prayson: design and conceptualization of study, revising the manuscript for intellectual content. Jessica S. Chapin: interpretation of data, revising the manuscript for intellectual content. Kevin H. Kim: design of study, analysis and interpretation of data. Lisa Ferguson: design of study, analysis 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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