Effect of invasive EEG monitoring on cognitive outcome after left temporal lobe epilepsy surgery

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ABSTRACT

Objectives: The objective of this cohort study was to compare neuropsychological outcomes following left temporal lobe resection (TLR) in patients with epilepsy who had or had not undergone prior invasive monitoring.

Methods: Data were obtained from an institutional review board-approved, neuropsychology registry for patients who underwent epilepsy surgery at Cleveland Clinic between 1997 and 2013. A total of 176 patients (45 with and 131 without invasive EEG) met inclusion criteria. Primary outcome measures were verbal memory and language scores. Other cognitive outcomes were also examined. Outcomes were assessed using difference in scores from before to after surgery and by presence/absence of clinically meaningful decline using reliable change indices (RCIs). Effect of invasive EEG on cognitive outcomes was estimated using weighting and propensity score adjustment to account for differences in baseline characteristics. Linear and logistic regression models compared surgical groups on all cognitive outcomes.

Results: Patients with invasive monitoring showed greater declines in confrontation naming; however, when RCIs were used to assess *clinically meaningful* change, there was no significant treatment effect on naming performance. No difference in verbal memory was observed, regardless of how the outcome was measured. In secondary outcomes, patients with invasive monitoring showed greater declines in working memory, which were no longer apparent using RCIs to define change. There were no outcome differences on other cognitive measures.

Conclusions: Results suggest that invasive EEG monitoring conducted prior to left TLR is not associated with greater cognitive morbidity than left TLR alone. This information is important when counseling patients regarding cognitive risks associated with this elective surgery.

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GLOSSARY

CI = confidence interval; **OR** = odds ratio; **RCI** = reliable change index; **SEEG** = stereotactic EEG; **TLR** = temporal lobe resection.

Temporal lobe epilepsy is the most frequent type of epilepsy encountered in surgical centers,¹ and resective surgery is an effective treatment option for patients with drug-resistant seizures.² Often, temporal lobe seizures are localized using scalp EEG, allowing direct progression to temporal lobe resection (TLR). However, invasive EEG monitoring is sometimes needed in patients with poorly localized, multifocal, or discordant scalp EEG ictal patterns to map seizure onset or in those whose epileptogenic zone is in close proximity to functional cortex to minimize functional deficits following resection.³⁻⁸ These EEG techniques invade the brain parenchyma along the trajectories of multiple depth electrodes (stereotactic EEG [SEEG]) and/or cover the cortex with a “foreign body” (subdural grids) and often extend beyond the eventual resection area. Furthermore, greater histopathologic changes are evident in the resected tissue of patients who have undergone invasive EEG monitoring as compared to those who undergo surgical resection without prior monitoring.⁹ It is well established that patients who undergo dominant TLR are at risk of declines in naming and verbal memory.^{10,11} However, it remains unclear

Supplemental data
at Neurology.org

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whether invasive monitoring infers additional cognitive risk. The primary objective of this investigation was to compare neuropsychological outcomes following TLR in patients who underwent invasive EEG monitoring prior to resection to patients who did not to determine whether invasive monitoring is associated with greater cognitive morbidity. We used propensity weighting to account for potential exposure selection bias given the expected differences between these 2 patient populations (with or without invasive EEG).

METHODS **Standard protocol approvals, registrations, and patient consents.** Data for this retrospective cohort study were obtained from an institutional review board–approved, neuropsychology data registry containing demographic, cognitive, seizure-related, and surgical variables for patients who underwent epilepsy surgery for the treatment of pharmacoresistant seizures at Cleveland Clinic between 1997 and 2013.

Participants. Individuals were included if they met the following criteria: (1) age 16 years or older at the time of preoperative neuropsychological evaluation, (2) underwent a left TLR that included removal of mesial temporal structures, (3) no evidence

of right hemispheric language dominance on functional MRI or Wada testing, (4) no prior brain surgery, and (5) completed pre- and postoperative comprehensive neuropsychological assessments that included the outcomes studied here. The goal was to identify a relatively homogeneous cohort of patients at high risk of postoperative cognitive decline. Patients were only included if they had complete data on all relevant covariates and outcomes of interest, which excluded patients who completed neuropsychological testing with alternate cognitive measures or who were unable to return for postoperative follow-up. A total of 176 patients met all inclusion criteria (figure 1). Of these, 131 had left TLRs without any invasive monitoring, while the remaining 45 patients underwent invasive monitoring (7 SEEG, 8 grids only, 6 depths only, and 24 both grids and depths) to better characterize their seizures prior to left TLR. Surgical complications following invasive monitoring alone were rare ($n = 5$) and transient without any lasting sequelae. On average, patients were 37 years old (range 16–65) with 13 years of education (range 8–20). Mean age at seizure onset was just under 18 years, and mean duration of epilepsy was 19 years.

Measures. Given that verbal memory and confrontation naming are the cognitive domains most likely to be affected by left (dominant) TLR,¹¹ these were the primary cognitive outcomes in this study. Secondary cognitive outcomes included intellectual functioning, attention/working memory, visuospatial processing speed, executive function, visuospatial skills, and visual memory. Table 1 lists the specific neuropsychological measures used to assess these cognitive domains. All patients completed a

Figure 1 Flowchart summarizing patient selection based on inclusion/exclusion criteria

Table 1 Cognitive outcome measures

Cognitive measures	Score type
Intelligence	
WAIS-III Full Scale IQ	Standard
Attention/working memory	
WMS-III Working Memory Index	Standard
Processing speed	
WAIS-III Processing Speed Index	Standard
Trail Making Test-Part A	Raw (seconds to completion)
Language	
WAIS-III Verbal Comprehension Index	Standard
Boston Naming Test (total score)	Raw (total raw score)
Executive function	
Controlled Oral Word Association Test	Raw (total raw score)
Trail Making Test-Part B	Raw (seconds to completion)
Visuospatial skills	
WAIS-III Perceptual Organization Index	
Memory	
WMS-III Auditory Immediate and Delayed Memory Indices	Standard
WMS-III Visual Immediate and Delayed Memory Indices	Standard

Abbreviations: WAIS-III = Wechsler Adult Intelligence Scale-Third Edition; WMS-III = Wechsler Memory Scale-Third Edition.

Standard score mean = 100 and SD = 15.

comprehensive neuropsychological assessment before surgery and a follow-up assessment a median of 6 months postsurgery. There was no significant difference in length to postoperative neuropsychological follow-up between patients who underwent invasive monitoring and those who did not ($t_{175} = 1.02$, $p = 0.31$).

Analyses. Cognitive outcome for each measure was evaluated using 2 different methods: (1) postoperative minus preoperative score difference (change scores), and (2) whether the patient met established thresholds for *clinically meaningful* decline using cutoffs from published reliable change indices (RCIs) developed from patients with epilepsy tested twice without intervening surgery.^{12–14} Clinical investigators specializing in epilepsy (neurology, neuropsychology, and neurosurgery) identified 17 covariates believed to be important contributors to the likelihood of performing invasive monitoring and/or to decline in cognitive outcome following TLR (table 2). We considered including results of PET and SPECT studies; however, a large subset of patients did not complete these tests preoperatively. Specifically, 154 of 176 patients completed preoperative PET studies and only 25 of 176 completed preoperative SPECT studies. Given the missing data, these variables were excluded from our analyses. Of note, examination of existing PET data indicated that the majority of patients (84%) had unilateral, left-sided hypometabolism with involvement of the left temporal lobe. Furthermore, there was no significant difference between the 2 surgical groups in the proportion of patients who showed left-sided hypometabolism on PET (invasive = 81%, noninvasive = 85%, $\chi^2_1 = 0.412$, $p = 0.521$). This provides some reassurance that omission of PET data from our analyses is unlikely to have affected the results. Our propensity score model estimates the probability of invasive monitoring for each patient, using the covariates in table 2. The resulting propensity score captures

the covariate information regarding selection of patients from this sample for invasive monitoring. We then employed weighting and regression adjustment using the propensity score (referred to as a double robust approach¹²) to account for differences in baseline characteristics between the 2 surgical groups.

Linear and logistic regression models (for continuous and binary cognitive outcome measures, respectively) were then used to compare the surgical groups, accounting for the propensity to be in the invasive monitoring group. Similar analyses were also conducted to examine differences in seizure outcome (Engel class I vs classes II–IV¹³) between the 2 surgical groups at postoperative neuropsychological testing. These seizure outcome analyses also accounted for the propensity to be in the invasive monitoring group.

Supplemental exploratory analyses examined differences in cognitive outcome by invasive type, combining the very small SEEG and depth-only groups and comparing these to patients who were evaluated using subdural grids (with or without depths).

RESULTS Primary cognitive outcomes: Confrontation naming and verbal memory. Propensity score weighting using the double robust approach improved covariate balance between the 2 surgical groups (table 2, figure 2). After weighting and adjustment for the propensity score, the estimate for treatment effects indicated greater declines in confrontation naming among patients who had invasive monitoring compared to those who directly underwent TLR without invasive EEG recordings (Boston Naming Test raw score difference = -4.50 ; 95% confidence interval [CI] -8.50 , -0.50). However, when RCIs were used to assess *clinically meaningful* cognitive change on this naming measure, there was no significant treatment effect (Boston Naming Test odds ratio [OR] = 1.94, 95% CI 0.77, 4.91). There were no differences between the 2 surgical groups on verbal memory measures, regardless of how outcome was assessed (i.e., change scores or RCIs). A summary of the unadjusted and adjusted estimates using change scores and RCI cutoffs to assess cognitive outcome is provided in table e-1 on the *Neurology*[®] Web site at Neurology.org and depicted in figure 3, A and B, respectively.

Secondary cognitive outcomes: Other cognitive domains. After weighting and propensity score adjustment, the estimate for treatment effects suggested greater declines in working memory among patients who had invasive monitoring (Working Memory standard score difference = -6.32 , 95% CI -11.66 , -0.98). However, there was no significant treatment effect when outcome was measured using RCIs (Working Memory OR = 1.32, 95% CI 0.13, 14.10). Outcomes on other cognitive measures were similar across the 2 surgical groups (see table e-1).

Seizure outcome. Eighty-five percent of patients were seizure free at the time of their postoperative neuropsychological evaluation. There was no significant difference in seizure outcome between the 2 surgical groups (OR = 2.62, 95% CI 0.82, 8.38).

Table 2 Baseline characteristics of surgery groups before and after propensity score weighting and adjustment

	Before propensity weighting		After propensity weighting	
	Invasive (n = 45)	Noninvasive (n = 131)	Invasive (n = 45)	Noninvasive (n = 131)
Demographic variables				
Age at time of surgery, y	35.5 (11.4)	37.3 (12.8)	35.5 (11.4)	35.9 (13.0)
Education, y	12.9 (2.0)	13.3 (2.2)	12.9 (2.0)	13.0 (1.8)
Sex, male, %	47	40	47	52
Epilepsy-related variables				
Age at seizure onset, y	18.1 (14.0)	17.4 (13.8)	18.1 (13.9)	19.3 (13.6)
Duration of epilepsy, y	16.7 (12.9)	19.9 (13.9)	16.7 (12.9)	16.0 (13.2)
Baseline seizure frequency (no. per month)	21.3 (46.8)	18.2 (55.9)	21.3 (46.8)	20.0 (64.4)
No. of antiepileptic drugs	2.2 (0.7)	2.0 (0.7)	2.2 (0.7)	2.2 (0.7)
Bilateral ictal scalp EEG abnormalities, %	11	5	11	14
Bilateral interictal scalp EEG abnormalities, %	16	15	16	23
Neuroimaging (MRI) variables, %				
Temporal abnormality^a				
None	44	10	44	50
Mesial temporal sclerosis	31	73	31	30
Cortical dysplasia	13	6	13	10
Other	11	12	11	13
Extratemporal abnormality	9	5	9	10
Contralateral temporal abnormality	9	9	9	9
Contralateral extratemporal abnormality	2	3	2	1
Cognitive variables				
Full Scale IQ (standard score)	91.7 (11.0)	90.4 (13.3)	91.7 (11.0)	90.6 (11.2)
Boston Naming Test (raw score)	44.7 (7.9)	44.9 (9.2)	44.7 (7.9)	43.7 (10.5)
Auditory Immediate Memory Index (standard score)	89.7 (14.3)	85.9 (15.0)	89.7 (14.3)	87.8 (15.0)
Auditory Delayed Memory Index (standard score)	88.6 (14.7)	84.4 (15.9)	88.6 (14.7)	87.8 (15.0)

^a Before weighting, the 2 surgical groups were significantly different in MRI temporal abnormality rates. No other significant group differences were observed before weighting.

Data represent mean (SD) unless otherwise indicated.

Supplemental analyses: Effects of invasive type. Patients who underwent subdural grid evaluations demonstrated greater declines in Auditory Immediate Memory (mean = −13.90, 95% CI −18.53, −9.27) and Auditory Delayed Memory (mean = −13.42, 95% CI −18.59, −8.25) than those who underwent invasive monitoring with depth electrodes only (mean = −5.50, 95% CI −10.54, −0.46 and mean = −4.00, 95% CI −10.68, 2.68, respectively). Similar results were observed when using RCI cutoffs to define meaningful cognitive change after surgery. Specifically, a larger proportion of patients who underwent evaluation with subdural grids demonstrated declines on measures of Auditory Immediate Memory (45%) and Auditory Delayed Memory (23%) than those who underwent monitoring with SEEG or depth electrodes (21% and 7%, respectively). In addition, there was a larger proportion of

subdural patients who declined on the Verbal Comprehension Index of the Wechsler Adult Intelligence Scale–Third Edition (42% vs 21%). See table e-2 for a summary of the proportion of patients who showed clinically meaningful cognitive declines as a function of invasive type. However, it should be noted that patients who had subdural grids also had somewhat higher preoperative Auditory Immediate (M = 92.2, SD = 13.4) and Delayed (M = 91.9, SD = 13.4) Memory scores on the Wechsler Memory Scale–Third Edition than those who underwent monitoring with depth electrodes (Immediate M = 84.1, SD = 15.2; Delayed M = 81.1, SD = 15.0), which may account for these findings.

DISCUSSION Results suggest that invasive EEG monitoring conducted prior to left (dominant) TLR is not associated with greater cognitive morbidity

Figure 2 Love plot displaying absolute standardized differences for baseline covariates

Love plot displays absolute standardized differences for baseline covariates for patients who underwent invasive monitoring prior to temporal lobe resection and those who did not, before and after propensity score weighting and adjustment. AED = antiepileptic drug; MTS = mesial temporal sclerosis.

than left TLR alone. While change scores revealed greater decrements in naming and working memory among patients who underwent invasive monitoring, these score changes did not exceed the recommended cutoffs for identifying *clinically meaningful* cognitive change using RCIs.^{14–16} RCIs are a preferred method for assessing cognitive change after epilepsy surgery, because they adjust for methodologic artifacts (e.g., imperfect test reliability, measurement error, practice effects) that simple change scores do not take into account. As such, these methods have become commonplace for assessing cognitive change among adults who undergo epilepsy surgery.¹¹

It is well established that dominant TLR for treatment of epilepsy results in clinically meaningful declines in verbal memory and/or naming in more than a third of patients,¹¹ and preoperative neuropsychological testing is routinely conducted to counsel patients about the likely risk of cognitive change if they elect to proceed with surgery. Until now, we have not had any information to provide patients regarding the cognitive risks of invasive EEG monitoring. Results of the current study provide preliminary data to suggest that invasive EEG monitoring is unlikely to confer additional cognitive risk, beyond that already associated with TLR. This is an encouraging finding, particularly given that the purpose of invasive monitoring, in at least a subset of patients at

high risk of cognitive decline, is to better localize the seizures within the temporal lobe in an attempt to limit the resection site and reduce cognitive morbidity.

The lack of literature on this topic may be attributable to the fact that patients who undergo invasive EEG monitoring tend to be quite different in many respects than those who proceed directly to resection. The gold standard randomized controlled trial would be unethical in this circumstance, and the second best option, to conduct cognitive assessments of patients before and after monitoring (with or without invasive recordings) but prior to resective surgery, is not feasible in most clinical situations. While the latter design would isolate the impact of monitoring uncomplicated by surgery, it would require a longer test-retest interval in order to avoid acute and recoverable effects and delay surgical resection. Observational research is the only feasible option to investigate this topic. Propensity modeling provides a unique opportunity to statistically equate these seemingly disparate patient groups in order to approximate a randomized controlled trial using observational data. The propensity score weighting and adjustment used in this study resulted in good covariate balance between the 2 surgical groups allowing us to compare cognitive outcomes in groups that have not previously been compared in the literature.

Figure 3 Estimates of invasive EEG effect on memory and language outcomes

As measured by (A) change scores from before to after surgery (change scores). (B) Reliable change indices (odds ratios). * $p < 0.05$, ** $p < 0.01$, [†]age-corrected standard score, ^{††}raw score.

There are a host of factors pertaining to type and method of invasive implantation that may differentially affect cognitive outcome. Our supplemental analyses raise the possibility that outcomes may vary as a function of type of invasive implantation (i.e., depths vs grids); however, the groups were not well matched in terms of their preoperative memory ability precluding any definitive conclusions in this regard. Unfortunately, given small sample sizes, we were unable to use propensity score methods to investigate this further or to examine the role of other potentially important surgical factors (e.g., number and location of electrodes placed). Nevertheless, this study provides preliminary evidence that, despite greater pathologic changes in the resected tissue of patients who undergo invasive EEG monitoring,⁹ these procedures are not associated with greater cognitive risk than left temporal resection alone. Future research will be needed to replicate these findings and to investigate cognitive outcomes in other surgical groups. Inclusion of

other potentially important covariates (e.g., PET, SPECT, ictal semiology) should also be considered in future research.

AUTHOR CONTRIBUTIONS

Design/conceptualization: Busch, Love, Jehi, and Gonzalez-Martinez. Data analysis/interpretation: Busch, Love, Jehi, Ferguson, Yardi, Najm, Bingaman, and Gonzalez-Martinez. Drafting/revising manuscript for intellectual content: Busch, Love, Jehi, Ferguson, Yardi, Najm, Bingaman, and Gonzalez-Martinez.

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DISCLOSURE

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