Epilepsy & Behavior 27 (2013) 326–329

Contents lists available at SciVerse ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Predictors of decline in verbal fluency after frontal lobe epilepsy surgery

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ARTICLE INFO

Article history:
Received 22 November 2012
Revised 14 February 2013
Accepted 16 February 2013
Available online 23 March 2013

Keywords:
Epilepsy
Epilepsy surgery
Frontal lobe epilepsy
Surgical outcome
Verbal fluency

ABSTRACT

Few studies have focused on language changes following frontal lobe epilepsy (FLE) surgery. The aim of the current study is to quantify the role of resection location and size in verbal fluency decline after FLE surgery and to examine its predictors. A retrospective chart review identified 36 adult patients who underwent FLE surgery. Verbal fluency was assessed using the Controlled Oral Word Association Test (COWAT). Nine (25%) of the patients had significant decline. Binary logistic regression incorporating side of resection and preoperative COWAT score significantly predicted decline and accounted for 25% of the variance. A trend was also noted for decliners to have higher postoperative seizure recurrence ($p = 0.067$). There was no effect of size of resection. Patients undergoing FLE surgery are at risk of verbal fluency decline, especially if they have a high presurgical verbal fluency score, undergo a frontal lobe resection in the language dominant hemisphere, and have poor seizure outcome.

1. Introduction

Patients who undergo epilepsy surgery, particularly within the language dominant hemisphere, often complain of language difficulties, which adversely affect quality of life [1]. Earlier studies looking at language performance in patients with frontal lobe lesions showed evidence for a decrease in verbal fluency after damage to the left frontal lobe [2–5]. However, few studies have examined outcomes following frontal lobe resection for treatment of intractable epilepsy [3,6–8].

Tests of verbal fluency are frequently used in the preoperative and postoperative neuropsychological assessments of patients with epilepsy. These tasks measure executive functions involving word retrieval/recall, monitoring of prior responses, self-initiation, and inhibition of alternate responses [9]. Phonemic fluency, in particular, is related to frontal lobe functioning [10], and impaired phonemic fluency is often found in patients with various types of frontal pathology [11].

Of the studies examining changes in cognitive function following frontal lobe epilepsy surgery, only one study found a significant decline in verbal fluency following resection [7]. However, examination of the data in other reported studies showed similar trends with respectable effect sizes [6,8], suggesting that verbal fluency was likely impacted by the surgery.

Examination of the role of resection location has suggested that fluency decline is most apparent following resection of left SMA regions [6] or left lateral/dorsolateral frontal cortex [7]. However, given the prevalence of atypical language dominance in patients with FLE [12], it is unclear how this may have influenced the lesion location findings.

The goal of the current study was to quantify the role of resection location and size in verbal fluency decline after frontal lobe surgery to treat epilepsy and to identify the demographic and seizure factors most predictive of this decline.

2. Methods

2.1. Participants

A retrospective chart review of adult patients undergoing epilepsy surgery between 1991 and 2010 at the Cleveland Clinic Epilepsy Center was performed. Patients were included if they had: 1) undergone a unilateral frontal cortical resection, 2) completed the Controlled Oral Word Association Test [COWAT [13]; part of routine battery] prior to and following (mean of 8 ± 4.4 months) surgical resection, 3) a standard score of ≥ 70 on the Reading subtest of the Wide Range Achievement Test — Fourth Edition, 4) available postoperative neuroimaging, 5) no prior neurosurgery, and 6) no evidence for bilateral language representation on Wada or fMRI. The study was approved by the Cleveland Clinic IRB committee.

Out of 94 patients who underwent frontal lobe surgery during the study period, 39 patients met the first 5 inclusion criteria. Three additional patients were excluded due to bilateral language dominance. The remaining 36 patients (89% Caucasian) were divided into two groups based on presence or absence of significant postoperative COWAT decline as determined using standardized regression-based change scores

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http://dx.doi.org/10.1016/j.yebeh.2013.02.015

[14] with a z-score cutoff of 1.25 (representing 90 percentile). Importantly, the mean test/retest interval was 8 months which is similar to the interval used to establish standardized regression-based change scores [14]. See Table 1 for demographic and seizure variables. A subset of patients (maximum n = 14) has previously been described by Suchy et al. [8].

Performance on part A of the Trail Making Test was also examined for each patient to determine whether change in COWAT performance was an artifact of impaired processing speed.

2.2. Postoperative imaging

All patients had a postoperative MRI or CT performed 1–24 months (median = 6.25 months) after surgery. The area of resection was determined by reviewing postoperative MRI (3-Tesla T1 axial sequences in 28 patients, 1.5-Tesla T2 FLAIR sequence in 2 patients) or CT scans (6 patients). Resection extent was reconstructed on a standard whole-brain template of 12 AC–PC aligned axial slices (Talairach Z coordinates = −25, −18, −10, −3, 5, 13, 21, 29, 37, 45, 53, and 61) using MRICron [15] by two of the authors (RS & DF). Reconstructions based on CT or limited MRI acquisitions were confirmed by a neuroradiologist (PR) and used to produce lesion density maps.

Lesions were coded based on presence or absence of resection in 4 frontal regions: superior medial (SM; involving Z > 0), inferior medial (IM), orbitofrontal (OF), and lateral frontal (LF).

The extent of resection was determined by adding the area of resection at each axial slice and then dividing it over the total brain area at these slices.

2.3. Language lateralization

Preoperatively, 23 patients completed Wada testing and another 5 had fMRI data to determine language lateralization. Of the 20 right-handed patients who had available lateralization data, 2 had right-sided language dominance. Three of five left-handed patients had right-sided dominance. All 3 ambidextrous patients were left hemisphere dominant. Eight patients did not undergo preoperative language lateralization procedures; all were right-handed and had right-sided resections.

As reported above, three patients were excluded from the series due to bilateral language dominance on Wada or fMRI. Of note, they all underwent a right-sided resection and did not decline on verbal fluency measures.

Table 1
Patients' characteristics as a function of verbal fluency decline.

	Decliners (n = 9)	Nondecliners (n = 27)	p
Mean age at seizure onset in years (±SD)	10.1 (±5.4)	11.6 (±9.8)	0.575
Mean duration of epilepsy in years (±SD)	22.9.6 (±7.2)	19.0 (±11.1)	0.238
Mean age at surgery in years (±SD)	33.0 (±8.6)	30.6 (±11.2)	0.513
Mean education in years (±SD)	12.9 (±1.5)	12.6 (±2.1)	0.641
Full-scale IQ (±SD)	95.6 (±13.6)	93.3 (±12.3)	0.669
Preoperative COWAT score*	30.8 (±9.7)	24.6 (±8.5)	0.078
Postoperative COWAT score*	18.0 (±6.5)	27.8 (±10.9)	0.015
Surgery of dominant hemisphere*	6 (67%)	3 (11%)	0.008
Handedness			0.310
Right handed	8 (89%)	20 (74%)	
Left handed	1 (11%)	4 (15%)	
Ambidextrous	0 (0%)	3 (10%)	
Females	4 (44%)	12 (44%)	1.00
Pathology			.566
MCD	4 (44%)	15 (56%)	
Gliosis	4 (44%)	7 (26%)	
Tumor	1 (11%)	5 (18%)	
Percentage resection area of the whole brain	7.36% (±5.0)	7.9% (±4.1)	0.753
Seizure free ~6 months postoperatively*	4 (44%)	22 (82%)	0.067

SD = standard deviation, MCD = malformation of cortical development.
* $p < 0.10$.

2.4. Statistical analyses

Chi-Square analyses were conducted to determine whether verbal fluency decline differed as a function of resection side (dominant, nondominant) and location (SM, IM, OF, LF). T-Tests and chi-square analyses were then conducted to examine group differences between decliners and nondecliners on demographic and seizure variables. Finally, binary logistic regression was conducted, using the variables identified as most important in discriminating decliners and nondecliners in prior analyses, to determine their utility in predicting verbal fluency decline. Relaxed conditional input criteria ($p = .1$) were adopted due to the exploratory nature of the analysis.

3. Results

Using regression-based change scores [14] to identify change in verbal fluency scores following frontal lobe resection, 9 patients exhibited a decline in performance while 27 patients did not show a verbal fluency decline. Of the nondecliners, three patients demonstrated significant postoperative improvements in verbal fluency performance. Evidence of cognitive improvement after surgery is of significant clinical interest and deserves further study, but the small sample here precludes analysis.

3.1. Demographic and seizure variables

There were no significant differences between decliners and nondecliners as a function of sex, education, IQ, handedness, age at surgery, age at seizure onset, duration of epilepsy, or pathology (Table 1). Decliners were more likely to have undergone dominant resections and showed trends toward higher postoperative seizure recurrence and higher preoperative verbal fluency scores. While this latter trend was not statistically significant, the effect size was rather large ($d = .679$), suggesting this is an important factor that may have been obscured by limited power.

Three decliners had a nondominant frontal resection. Of these, one patient had a left-sided surgery but was found to be right-side dominant on Wada. The other two had right-sided resections; one demonstrated left-sided language dominance on Wada and the other did not complete preoperative Wada testing.

3.2. Influence of processing speed

All patients in the current study had pre- and post-operative neuropsychological data available on the Trail Making Test (TMT). There was no significant correlation between preoperative scores on verbal fluency and TMT − part A ($r = .203$, $p = .242$). There was also no difference in processing speed between fluency decliners and nondecliners prior to [$t(34) = -.608$, $p = .547$] or following [$t(34) = .747$, $p = .460$] surgery.

3.3. Influence of medications

Fluency decliners and nondecliners did not differ in the number of antiepileptic medications either before [$t(34) = -.506$, $p = .616$] or after [$t(33) = .023$, $p = .982$] surgery. To rule out influence of particular medications with frequent cognitive side effects, we also conducted separate analyses of patients taking zonisamide (ZNS) and topiramate (TPX). However, there was no difference in the proportion of decliners versus nondecliners taking TPX or ZNS either prior to [TPX pre − χ^2 (1) = .267, p = .606; ZNS pre − χ^2 (1) = .655, p = .418] or following [TPX post − χ^2 (1) = .598, p = .439; ZNS post − χ^2 (1) = .604, p = .437] epilepsy surgery.