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Structured Cueing on a Semantic Fluency Task Differentiates Patients with Temporal Versus Frontal Lobe Seizure Onset

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Abstract

Patients with frontal lobe dysfunction (e.g., Huntington's Disease) reportedly benefit more from cueing on measures of semantic fluency than do patients with damage to temporal lobe structures (e.g., Alzheimer's disease). This differential benefit from cueing suggests that different neurocognitive functions are impaired in these two groups. Patients with frontal lobe dysfunction are presumed to have difficulty with the executive aspects of this generative fluency task while patients with temporal lobe impairment are limited by deficits in semantic memory. We studied the performance of patients with complex partial seizures of frontal or temporal lobe onset as determined by video-EEG monitoring on standard and cued measures of semantic fluency administered in a counterbalanced sequence across groups. These groups did not differ significantly in terms of age, education, gender, age of seizure onset, total number of antiepileptic drugs, or IQ, and all patients subsequently underwent surgery for intractable epilepsy. FL patients performed significantly worse than TL patients on the standard semantic fluency paradigm (TL $M = 18.4$, $SD = 4.7$; FL $M = 11.1$, $SD = 5.3$), $t(27) = -3.75$, $p < .001$. Nevertheless, results of an ANCOVA demonstrated that the FL patients showed significantly greater performance improvement than the TL patients when provided with a cued semantic fluency format even after controlling for baseline differences in ability on the standard semantic fluency task (TL $M = 0.45$, $SD = 3.8$; FL $M = 9.4$, $SD = 5.1$), $F(1, 29) = 12.37$, $p = .002$. These findings support previous research suggesting that frontal and temporal structures contribute uniquely to semantic generative fluency and suggest that using a combination of standard and cued semantic fluency tasks may help confirm localization of seizure onset in partial epilepsy by localizing the associated cognitive dysfunction

Keywords

semantic fluency; frontal and temporal lobe epilepsy; localization of seizures

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Recent studies suggest that benefits obtained from semantic cueing are greater for patient groups experiencing frontal system dysfunction than they are for patients whose cerebral impairment is concentrated in more posterior regions. For example, patients with Huntington's or Parkinson's disease, subcortical conditions that are often associated with frontal system dysfunction, were shown to benefit from a cued semantic fluency task more than Alzheimer's patients (1). It has been posited that the mechanism of impairment underlying limitations in semantic fluency differs on the basis of anterior versus posterior cerebral damage. Restricted semantic fluency among patients with frontal system impairment is thought to have several potential causes, including a retrieval problem resulting from deficits in the executive aspects of searching one's own semantic memory stores or deficits involving initiation of action or self-monitoring (1–4). In contrast, similar semantic fluency limitations observed among patients with more posterior lesions, particularly those involving the temporal lobes, are thought to be attributable to deficits in semantic memory (3,5).

Growing evidence points to the complementary roles of storage and retrieval respectively played by temporal and frontal regions in the performance of semantic fluency tasks. Lesions in either of these areas have been shown to result in decreased semantic fluency performance (6,7). In addition, functional neuroimaging studies have demonstrated the importance of these regions in both healthy control subjects and patient groups (8–10). For example, numerous studies using functional magnetic resonance imaging (fMRI) have demonstrated activation of the left inferior frontal gyrus during the generation of semantic exemplars (11–13). Frith and colleagues (8), using PET technology to study cerebral blood flow during a semantic fluency task, found primary activation of the left dorsolateral prefrontal cortex and a bilateral decrease in the temporal cortices. These findings were interpreted as showing an inhibitory modulation of temporal regions by the prefrontal cortex as the basis of word generation. Finally, there are also a number of functional neuroimaging studies that suggest that semantic knowledge may be represented in distributed neural sites in the temporal lobes (14,15). Taken together, these lesion and functional neuroimaging studies have led to a semantic network model involved with word generation that involves distributed systems involving both the frontal and temporal lobes (16).

Given that epilepsy patients with frontal or temporal lobe seizure onset have been shown to be impaired on semantic fluency tasks (6), these groups appear to be natural target populations for examining this differential phenomena. The performance of patients with frontal lobe (FL) seizure onset would be expected to improve when provided with a cued semantic paradigm that gives them additional organizational structure, while the performance of temporal lobe (TL) epilepsy patients would not be expected to show the same benefit. Should this dissociation hold up between these patient groups, standard versus cued semantic fluency performance could be of use in confirming localization of seizure onset. Likewise, with the difficulty involved in developing measures that reliably capture the “control” features of executive processing (17), this differential pattern of semantic fluency performance could also add to the available tools in this seemingly elusive domain of neuropsychological assessment. In the present report, we examined the performance of patients with complex partial seizures of frontal or temporal lobe onset as determined by video-EEG monitoring to determine the robustness of previous findings using a different patient population.

Methodology

Subjects

This study included 29 patients with intractable epilepsy of either unilateral frontal or temporal lobe origin. All epilepsy patients included in this study were right-handed and left-hemisphere dominant for language. Handedness was determined with the Benton Handedness Inventory

(18) and language dominance was evaluated using intracarotid amobarbital (Wada) assessment (19). Patients were excluded if they had evidence of a structural lesion other than mesial temporal sclerosis. Site and laterality of seizure onset was determined through the use of multiple scalp/sphenoidal ictal recordings with simultaneous audio-video recording of behavioral phenomena. Results from MRI, neuropsychological examination including Wada testing, and where available, ictal and interictal SPECT scanning, were also considered in order to determine the focus of seizure onset. Frontal lobe seizure onset was observed in 9 of the epilepsy patients (4 left frontal/5 right frontal), while temporal lobe onset was observed in the remaining 20 epilepsy patients (10 left temporal/10 right temporal). These groups did not differ significantly in terms of age, education, gender, age of seizure onset, laterality of seizure onset, number of antiepileptic drugs taken, or IQ, and all patients ultimately underwent surgery for intractable epilepsy. Demographic data, seizure-related variables, and relevant neurocognitive scores are provided in Table 1.

Procedures

All subjects were administered a standard and a cued version of a semantic fluency task developed by Randolph et al. (1). The standard semantic task consisted of naming as many exemplars of a category as possible during a 60-second time interval. Categories included “animals” and “supermarket items.” The cued semantic task also lasted for a total duration of 60 seconds. However, it was broken into four 15 second-blocks that were each preceded by a cued retrieval aid. Semantic cues consisted of specific descriptive criteria from the two general categories used during the standard administration. The animal category cues were (a) animals that people keep in their home as pets, (b) animals that are found on a farm, (c) animals that live in the jungle, and (d) animals that live in the water. The supermarket category cues included (a) fruits and vegetables, (b) meat and seafood, (c) things people drink, and (d) household cleaning products. Category types (“animal” versus “supermarket items”) and administration procedure (standard versus cued) were counterbalanced across patients to control for differences in category difficulty and possible practice effects. Each patient received a different semantic category type for the standard and cued administrations.

The FL and TL groups were compared using appropriate parametric tests (e.g., *t* statistic, ANCOVA) using version 12.0 of SPSS for Windows (20). As performance on the semantic fluency paradigm used in the current study appears to be normally distributed, we did not feel compelled to use nonparametric statistics. Although errors variance differed between the FL and TL groups for some of the semantic fluency scores analyzed, SPSS provides an alternative *t* value that corrects for this unequal variance (20). As we did not include a control group in the current study, we compared each individual’s uncued semantic fluency performance to available normative data to evaluate the degree of actual impairment in these two groups (21). We considered a patient to be impaired if they performed greater than 1 standard deviation below the mean as compared to individuals of their age and education.

Results

We first calculated a cued-uncued difference score (change score) for each patient, as we felt that this represented a good way to capture the relative benefit that each group received from the provision of cueing on our semantic fluency paradigm. The FL group improved by an average of 9.4 exemplars generated ($SD = 5.1$), while the TL group improved by an average of only 0.45 items ($SD = 3.8$), $t(27) = 5.30$, $p < .001$. While this change score clearly differed between the FL and TL groups, this comparison is not the best way to statistically demonstrate group differences as change scores tend to be vulnerable to the impact of regression to the mean. In addition, this simple comparison also fails to consider baseline differences in uncued performance. In fact, a comparison of the two group’s uncued semantic fluency performance

demonstrated that the FL group was more impaired than the TL group on the uncued (baseline) task, $t(27) = -3.75, p = .001$. Therefore, one would have to consider the possibility that the TL group experienced less improvement with cueing simply because they were less impaired on the standard task. Group means for the standard and cued semantic fluency performances and the change score are provided in Table 2.

We next employed a 2 (seizure focus: TL vs. FL) X 2 (seizure laterality: dominant hemisphere vs. non-dominant hemisphere) mixed design analysis of covariance (ANCOVA) in order to examine the main effects of seizure focus and seizure laterality and their interaction on cued semantic fluency performance while controlling for any potential baseline differences in performance. We used the cued score as the dependent variable in this analysis while using each group's performance on the standard semantic fluency task as a covariate. This method again demonstrates that the main effect for seizure focus remains significant even when controlling for baseline differences on the uncued task, $F(1, 29) = 12.37, p = .002, \eta^2 = 0.34$. There was also a trend for laterality, $F(1, 29) = 2.99, p = .09, \eta^2 = 0.11$, which should be re-examined with a larger sample size. Epilepsy patients with dominant hemisphere seizure onset tended to benefit slightly less from cueing ($M = 1.9, SD = 3.5$) than did patients with non-dominant hemisphere seizure onset ($M = 4.5, SD = 7.0$). The interaction of seizure laterality and seizure focus was not significant.

We next compared each patient's uncued semantic fluency performance to available normative data to evaluate the relative level of impairment experienced by each of the two groups. Seven of nine (77.8%) FL patients and seven of twenty (35.0%) TL patients were impaired on their respective uncued semantic fluency performance. This rate of baseline impairment proved significantly worse for the FL group using a chi square analysis, $\chi^2(1, 14) = 4.55, p = .03$. We also compared failure rates across groups after dividing them by both seizure focus (FL/TL) and seizure laterality (left hemisphere/right hemisphere). The FL group continued to exhibit worse performance on the uncued semantic fluency task than did the TL group regardless of seizure laterality (percent impaired: right FL = 80%; left FL = 75%; right TL = 30%; Left TL = 40%). Once again, consideration of laterality of seizure onset did not appear to add anything beyond our initial examination of seizure focus. However, it does highlight the fact that a significant proportion of TL and FL epilepsy patients demonstrate impaired semantic fluency performance regardless of seizure laterality.

Finally, as another check of our statistical analysis above regarding the significant difference between groups on the change score, we examined the change score of only those patients who were impaired on the uncued task. Using a t test comparison, even when considering only the patients who were impaired on this task at baseline, the FL patients exhibited significantly greater improvement on this measure than did the TL patients (FL $M = 9.0, SD = 4.6$; TL $M = 1.4, SD = 4.4, t(12) = 3.1, p = .008$). Moreover, all seven of the FL patients who performed in the impaired range showed an improvement of at least five exemplars when provided with cueing (range = 5 to 18). In contrast, only one of the TL patients who performed in the impaired range improved by as much as five exemplars (range = -5 to 10), with four of the seven declining with cueing or staying the same.

Discussion

These findings indicate that frontal and temporal lobe structures contribute uniquely to semantic generative fluency (1,3) and indicate that intact frontal systems functioning is required for optimal task performance on such measures. As reported by prior studies (1,4), it appears that frontal systems dysfunction contributes to poor word retrieval, as FL epilepsy patients showed significant improvement in the generation of category exemplars when provided with structured cueing. This suggests that such patients have not experienced a

primary degradation of semantic memory. Instead, this pattern of performance seems more consistent with a model of retrieval dysfunction based upon poor search strategies of more broadly distributed semantic memory networks.

In our sample, impaired performance on a baseline uncued semantic fluency task was more prevalent among patients with FL seizure onset (77.8%), although such deficits were observed in a significant number of patients with TL seizure onset as well (35%). Impaired performance was observed for both groups at a similar rate regardless of the laterality of seizure onset. These findings are consistent with prior behavioral studies (1,3,22,23), which have demonstrated that standard semantic fluency tasks can be impacted by dysfunction in a wide range of brain regions. Such findings have led researchers to propose that semantic fluency is a complex cognitive task requiring the interaction of distributed neural networks, encompassing aspects of language functioning, executive control processes, attention, and semantic memory.

There was a trend for patients with left (dominant)¹ hemisphere dysfunction to perform worse than those with right (non-dominant) hemisphere dysfunction although this finding did not reach significance and produced a rather small effect size. Sample size limitations precluded any further statistical analysis of these differences. It would be worthwhile to explore this trend in future studies.

As some of the newer antiepileptic drugs (AEDs) appear to negatively impact verbal fluency in general (e.g., topiramate, zonisamide) (24,25), differences in AED usage across patient groups represents a potential confound for all verbal fluency studies conducted with epilepsy patients. In the current study, there were no significant differences across groups in the number of total AEDs administered. In addition, only two patients were taking either topiramate or zonisamide, and neither demonstrated impaired performance on the semantic fluency task. While we cannot completely rule-out the impact of AEDs on semantic fluency performance, it does not appear to represent a significant factor in the differential performance between FL and TL groups in the current study.

The current results are consistent with the view that idiopathic seizure activity can contribute to cerebral dysfunction that can be measured with standard neurocognitive tests, and that such information can often be helpful for confirming the localization of seizure onset. While such an approach has been of use with temporal lobe epilepsy (e.g., material specific memory deficits are associated with the laterality of onset of TLE)(26,27), frontal systems impairment has been less reliably measured. These data suggest that using a combination of standard and cued semantic fluency tasks may therefore improve localization of cognitive dysfunction associated with seizure onset in partial epilepsy. In contrast, given that lesions in a large number of brain regions can lead to impaired semantic fluency performance, the total number of exemplars generated on a standard semantic fluency task appears to be of questionable diagnostic utility when examined in isolation.

The use of standard and cued semantic fluency tasks for clinical purposes remains premature at this point. Further research is required with healthy subjects to insure that these semantic categories are equivalent in difficulty and to establish normative data for clinical comparison. On a positive note, the original article using this cued and uncued semantic fluency paradigm demonstrated similar results for both categories of objects in a small, healthy control sample (1). Ideally, for clinical purposes, it would probably be best to develop uncued and cued paradigms that are based on the same category of object (e.g., uncued and cued versions of the animal fluency task administered to each patient). It would also be helpful to develop such

¹We are using laterality (left/right hemisphere) and language dominance (dominant/non-dominant) interchangeably here, as all patients included in this study exhibited left hemisphere language dominance on the basis of Wada evaluations.

paradigms for multiple categories of objects, as the semantic memory literature suggests that different categories themselves may be mediated by different neural regions (28,29). These issues were avoided in the current study by using a counterbalanced administration. However, while this is an effective way to control for differential category difficulty in group studies, this method would be difficult to apply at the level of an individual patient. Nevertheless, the current study suggests that the development of appropriate cued and uncued semantic fluency paradigms would prove helpful for the localization of seizure onset, and would offer another potential means of assessing frontal systems functioning in general.

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Table 1

Demographic and Seizure-Related Variables and Relevant Neurocognitive Scores of Epilepsy Patients With Either Frontal Lobe (FL) or Temporal Lobe (TLE) Seizure Onset

	Frontal Lobe (n = 9)		Temporal Lobe (n= 20)			
	M	(SD)	M	(SD)	U	p
Age (years)	34.4	8.3	31.7	9.0	74.0	.45
Education	10.9	2.9	12.6	2.7	56.0	.10
WAIS-R Full Scale IQ	87.13	6.2	89.3	15.8	60.0	.81
WAIS-R Verbal IQ	84.1	5.6	89.1	15.4	58.0	.71
Digit Span (SS)	8.9	2.6	9.6	3.8	66.5	.93
Age of Seizure Onset	20.6	13.9	19.9	13.7	40.0	.95
Number of AEDs	2.0	0.7	1.9	0.9	77.0	.51
Gender (% females)	33.0%		30.0%		χ^2	p
Seizure Laterality (% left hemisphere onset)	44.4%		50.0%		0.03	.86
					0.08	.78

Note. M = mean; SD = standard deviation; WAIS-R = Wechsler Adult Intelligence Scale Revised; n.s. = non-significant; SS = Scaled Score; AEDs = Antiepileptic drugs. Frontal and temporal lobe patients were shown not to significantly differ on any of the included variables when compared using either a Mann-Whitney U (continuous variables) or chi square analysis (categorical variables).

Table 2
Performance of Epilepsy Patients With Either Frontal Lobe (FL) or Temporal Lobe (TLE) Seizure Onset On Standard and Cued Semantic Fluency Measures

	Frontal Lobe (<i>n</i> = 9)		Temporal Lobe (<i>n</i> =20)		<i>t</i>	<i>p</i>
	<i>M</i>	(<i>SD</i>)	<i>M</i>	(<i>SD</i>)		
Total Exemplars (standard format)	11.1	5.3	18.4	4.7	-3.75	.001
Total Exemplars (cued format)	20.2	6.9	18.9	5.1	0.60	.55
Change Score	9.4	5.1	0.45	3.8	5.30	<.001

Note. n.s. = non-significant; *M* = mean; *SD* = standard deviation.