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Short Communication

Sex differences in lateralization of semantic verbal fluency in temporal lobe epilepsy

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ABSTRACT

When differences exist, women tend to outperform men on measures of verbal fluency, possibly due to greater bilateral language representation. Patients with temporal lobe epilepsy (TLE) have a higher rate of atypical cortical language representation than the general population, making them a population of interest for the study of language. For the current study, 78 TLE patients (51% male, 51% left temporal focus) underwent pre-surgical neuropsychological evaluations. Retrospective data analyses investigated the impact of seizure laterality and sex on letter and semantic verbal fluency. Results indicated an interaction between sex and laterality for semantic, but not letter, verbal fluency. Males with left TLE exhibited significantly worse semantic fluency than males with right TLE, whereas females' semantic fluency did not differ by seizure focus. These data indicate that females with TLE may indeed engage in more bilateral hemispheric processing of semantic verbal fluency, whereas males may be more reliant on left temporal cortical function for this task.

1. Introduction

The extent of potential sex differences in cerebral organization of language remains incompletely explored. Although studies have demonstrated language processing to be typically left hemisphere dominant in both sexes (e.g., Halpern, 2000; Kimura, 1992, 2004), some research have found a tendency for women to outperform men on neuropsychological language tasks (Clements et al., 2006; Gauthier, Duyme, Zanca, & Capron, 2009; Sommer, Aleman, Bouma, & Kahn, 2004). However, other studies have refuted a trend for female superiority in language skills, arguing that such findings are of too small of an effect size to be clinically relevant (see Hyde & Linn, 1988; Wallentin, 2009 for reviews). One hypothesis for the purported sex differences in language performance suggests the left lateralization of language may be stronger in men, whereas women may benefit from a more bilateral pattern of cerebral involvement in language functions (Kansaku & Kitazawa, 2001; Shaywitz et al., 1995; Strauss, Wada, & Goldwater, 1992; Weiss et al., 2006).

1.1. Potential sex differences in cerebral organization of language

Early support for the theory of increased bilateral representation of language function in women arose from a study by McGlone (1977) that evaluated aphasia symptoms following acquired unilateral brain lesions. McGlone argued that most early research pertaining to cerebral language organization in humans was conducted using samples comprised almost entirely of men, which may not generalize to women based on her finding that females were less likely to develop aphasia following left hemisphere lesions, but were more likely than males to develop expressive language deficits following right hemisphere lesions. Subsequent neuropsychological studies have found verbal fluency tasks tend to show the greatest degree of sex variance with females often performing better than males, with sex differences in behavioral approaches for task completion (e.g., Kimura, 1992; Weiss et al., 2006). Supporting these behavioral clinical findings, neuroimaging research using several different methods have found a tendency for females to exhibit more bilateral cortical activity

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during language tasks than males. For instance, Schlosser et al. (1998) found increased fMRI bilateral cortical activity among women during a silent verbal fluency task. Baxter et al. (2003) found both interhemispheric and intrahemispheric differences in fMRI cortical activation patterns between sexes in a semantic verbal processing task. Using functional near-infrared spectroscopy (fNIRS), Heinzel et al. (2013) found females showed greater bilateral activation of the inferior frontal junction during letter fluency tasks, and the extent of bilateral activation was correlated with better verbal performances in females but not males. Yu et al. (2014) also support sex differences in language cortical activity based on magnetoencephalography in which male children displayed more prominent left hemisphere lateralization in frontal and temporal areas, whereas females showed more bilateral activity when performing a verb generation task. Similarly, other fMRI studies have observed increased interhemispheric activity in females for verbal comprehension (Kansaku, Yamaura, & Kitazawa, 2000), and phonological processing (Clements et al., 2006). Together, these data support the hypothesis that increased bilateral cerebral activity can improve verbal fluency performance, particularly among women.

1.2. Cerebral organization of verbal fluency

Letter fluency is thought to rely predominantly on strategic search strategies mediated by the frontal lobes, whereas semantic/category fluency relies more heavily on semantic knowledge mediated by the temporal lobes (Baldo, Schwartz, Wilkins, & Dronkers, 2006; Giovagnoli & Bell, 2011; Gleissner & Elger, 2001; Tupak et al., 2012). However, previous verbal fluency studies with epilepsy patients status pre- and post-anterior temporal lobectomy have exhibited impairment in both letter and semantic verbal fluency tests, suggesting both types of fluency can be negatively impacted by temporal lobe pathology (Loring, Meador, & Lee, 1994; Martin, Loring, Meador, & Lee, 1990; Saykin et al., 1992).

1.3. Verbal fluency in temporal lobe epilepsy

The study of verbal fluency performance among individuals with temporal lobe epilepsy (TLE) offers an opportunity to assess for sex differences in individuals with known lateralized neurological dysfunction. Individuals with TLE have a higher rate of atypical cortical language representation than healthy counterparts (Goldmann & Golby, 2005), and evaluation of sex differences in language organization has practical implications for predicting neurosurgical outcomes and planning rehabilitation interventions (Janszky et al., 2003). In general, individuals with language dominant (left) hemisphere TLE exhibit greater deficits in verbal fluency than patients with right TLE (RTLE) (Martin et al., 1990; Metternich, Buschmann, Wagner, Schulze-Bonhage, & Kriston, 2014; Troyer, Moscovitch, Winocur, Alexander, & Stuss, 1998; Tröster et al., 1995). However, a minority of studies has failed to find the greater fluency deficit commonly reported for patients with left TLE (LTLE) (e.g., Saykin et al., 1992; Vilkki & Holst, 1994). Further, letter fluency deficits have been shown to be dissociated from semantic verbal fluency in patients with TLE, such that RTLE and LTLE groups exhibited no difference in letter fluency, but LTLE performed worse than RTLE on semantic fluency. These data raise the question if sex differences in language organization may moderate verbal fluency patterns found among patients with TLE. The sex difference in extent of bilateral language representation may be a confound to the general finding of impaired language function among patients with language dominant TLE (Koepp, 2011).

The purpose of this study was to examine whether sex differences in verbal fluency performances occur among individuals with TLE by hemisphere of seizure onset. We hypothesized females would show less difference in verbal fluency performances between LTLE and RTLE compared to males. We also hypothesized difference in verbal fluency performances between sexes would be more apparent for the semantic fluency task (vs. letter fluency) given its supposed greater dependence on temporal lobe functioning.

2. Results

Demographic and clinical information for the groups are presented in Table 1. Males and females did not differ in terms of age ($F(1, 76) = .11$, $p = 0.77$), education ($F(1, 76) = 2.17$, $p = 0.15$), epilepsy duration ($F(1, 73) = .54$, $p = 0.46$), Beck Depression Inventory (BDI-II; Beck, Steer, & Brown, 1996) scores ($F(1, 76) < .01$, $p = 0.99$), or general verbal abilities defined as VIQ/VCI standardized index scores from the WAIS-III/WAIS-IV ($F(1, 69) = 1.50$, $p = 0.23$). For males, LTLE and RTLE groups did not differ between age ($F(1, 38) = .02$, $p = 0.90$), education ($F(1, 38) = 3.26$, $p = 0.08$), epilepsy duration ($F(1, 38) = .28$, $p = 0.60$), or BDI-II scores ($F(1, 38) = .35$, $p = 0.56$); however, males with RTLE had significantly better general verbal abilities than their LTLE counterparts, with $F(1, 36) = 5.03$, $p = 0.03$, $\eta_p^2 = 12$. For females, no differences between LTLE and RTLE groups were observed in terms of age ($F(1, 36) = .95$, $p = 0.34$), education ($F(1, 36) = .02$, $p = 0.89$), epilepsy duration ($F(1, 33) = .63$, $p = 0.43$), BDI-II scores ($F(1, 38) = .05$, $p = 0.82$), or general verbal abilities ($F(1, 31) = .59$, $p = 0.45$).

Letter fluency performances failed to show a main effect based on seizure laterality group after using VCI/VIQ scores as a covariate ($F(4, 64) = .05$, $p = .82$), nor were there significant difference in performance based on sex ($F(4, 64) = .46$, $p = .50$). No seizure laterality by sex interaction was observed ($F(4, 64) = .002$, $p = .96$) (Fig. 1). In contrast, there was a significant sex by seizure laterality interaction for semantic fluency scores ($F(4, 66) = 4.71$, $p < .05$, $\eta_p^2 = .07$) in which males with RTLE performed better than males on semantic verbal fluency with LTLE, whereas females' scores did not differ. A main effect for seizure laterality also was detected ($F(4, 66) = 4.52$, $p < .05$, $\eta_p^2 = .06$) (Fig. 2).

3. Discussion

Results support our hypotheses by demonstrating a sex by laterality interaction for semantic fluency in which males with LTLE performed significantly worse than those with RTLE, whereas females performed similarly regardless of hemisphere of seizure onset. A reasonable explanation for these findings is the possibility that females may exhibit greater bilateral language organization than males. However, it remains unknown from these findings whether females with TLE exhibit more bilateral involvement for verbal fluency tasks premorbidly, or whether they may be more adept at compensating for epilepsy-related left temporal dysfunction by subsequently adapting to incorporate the use of the right temporal lobes to augment verbal functioning. Alternatively, the difference in performances may be due to differing behavioral approaches to the tasks. For example, Lanting, Haugrud, and Crossley (2009) found females tend to employ more switching techniques (i.e., oscillating between subcategories) when performing verbal fluency tasks, whereas males rely more on a clustering approach (i.e., generating multiple words within a single subcategory). Switching techniques have been shown to require more frontal lobe involvement in contrast to clustering that is more dependent on temporal lobe functioning (Troyer et al., 1998). Accordingly, the sex differences in performance observed in our study may be due, at least in part, to differing behavioral strategies, with males potentially exhibiting more of a lateralizing effect

Table 1
Demographics and clinical characteristics for participant groups.

Variable	LTLE Males $n = 22$	RTLE Males $n = 18$	LTLE Females $n = 18$	RTLE Females $n = 20$
Ethnicity n (%)				
Caucasian	15 (68.2%)	15 (83.3%)	16 (88.9%)	14 (70.0%)
African American	2 (9.1%)	2 (11.1%)	2 (11.1%)	5 (25.0%)
Other	5 (22.7%)	1 (5.6%)	0	1 (5.0%)
Years of age	40.50 (12.20)	41.00 (13.50)	41.72 (10.19)	38.15 (12.22)
Years of education	12.59 (2.72)	14.11 (2.56)	14.22 (2.16)	14.10 (2.94)
Years of epilepsy duration	18.16 (14.83)	20.44 (12.21)	18.91 (15.14)	15.05 (13.64)
WAIS-III/IV VIQ/VCI (combined)	85.48 (11.28)	95.06 (15.05)	91.73 (13.49)	96.06 (18.03)
Beck depression inventory, 2nd edition raw score	11.64 (7.61)	10.22 (7.53)	11.33 (8.01)	10.75 (7.58)

Note. Data are means (SD), except where noted; LTLE = left temporal lobe epilepsy; RTLE = right temporal lobe epilepsy; WAIS = Wechsler Adult Intelligence Scale; VCI = Verbal Comprehension Index; VIQ = Verbal Intellectual Quotient.

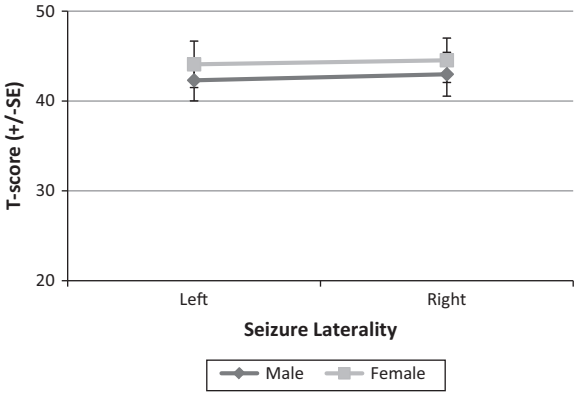

Fig. 1. Letter fluency by sex and laterality. Note: Values plotted are adjusted to the WAIS-III VIQ/WAIS-IV VCI value of 92.64.

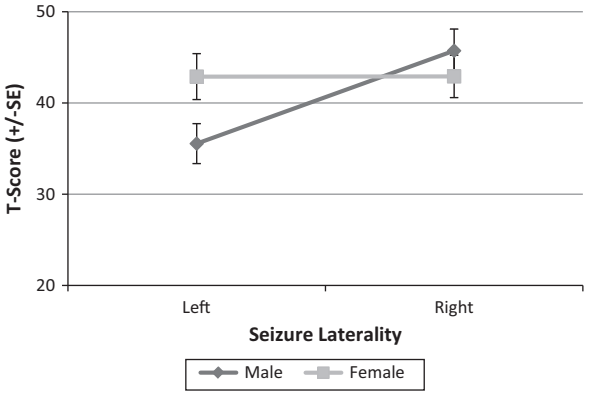

Fig. 2. Semantic fluency by sex and laterality. Note: Values plotted are adjusted to the WAIS-III VIQ/WAIS-IV VCI value of 91.77.

secondary to behavioral strategies that require greater left temporal lobe involvement.

Several study limitations are important. The sample was reduced within each right and left TLE group; larger sample sizes using implanted electrodes for more defined seizure onset regions may provide further information about potential compensatory changes across ages and sexes. Furthermore, our study included a predominantly Caucasian participant sample. As such, findings may not necessarily generalize across ethnicities, and further research is needed to assess performances among more ethnically diverse samples. Analyses of potential sex by seizure laterality interactions on other neuropsychological measures of verbal functioning would also be of interest. Given that our sample was comprised of preoperative epilepsy patients, future research should also examine potential sex differences in verbal fluency performance among postoperative epilepsy samples to assess for potential gender differences in neuropsychological outcomes of temporal resections. Follow-up studies could also use diffusion tensor imaging (DTI) maps of white matter tracts such as the arcuate fasiculus to better assess potential sex differences in language functioning among temporal lobe epilepsy patients. Finally, further evaluation of functional neuroanatomical organization of expressive language using fMRI between males and females with established left and right TLE would be of interest.

4. Methods

4.1. Participants

Participants were 78 adults with diagnosis of localization-related pharmacoresistent epilepsy referred for pre-surgical neuropsychological evaluation as a component of a pre-surgical workup at a large, university-affiliated comprehensive epilepsy center. This study was a retrospective chart review of an archival database approved by the University of South Florida Institutional Review Board (IRB). All participants provided written informed consent for research participation.

Inclusion criteria included the following: at least 18 years of age; fluency in English; diagnosis of localization-related pharmacoresistant TLE; completion of structural MRI brain study, video-electroencephalogram (v-EEG); and no evidence of severe depression on a self-report mood inventory. Participants also underwent the intracarotid methohexital (Wada) procedure if the patient had risk factors for atypical cerebral language organization (e.g., left-handedness, a strong family history of left-handedness, seizure onset prior to age six or perinatal stroke of left hemisphere). Among those included in the study, 24 had Wada study results confirming left hemisphere language dominance. Three participants were excluded from study participation due to atypical cerebral language organization, including two individuals who were right hemisphere dominant for language, as well as one individual with bilateral language representation. In total, 40 males and 38 females met inclusion criteria. A majority of the sample was Caucasian (75% of the males and 78.9% of the females), and all spoke English as their primary or only language. Of the males, 22 were diagnosed with LTLE and 18 were diagnosed with RTLE. Of the females, 18 were diagnosed with LTLE and 20 with RTLE. A neurologist board certified in neurophysiology performed v-EEG and interpreted seizure semiology to confirm seizure lateralization and localization. Seizure presentation was interpreted as unilateral for cases in which at least 80% of EEG ictal activity lateralized to a

particular temporal lobe. A board certified neuroradiologist interpreted presence or absence of mesial temporal sclerosis (MTS) using high quality 3 Tesla T1 and T2 MRI images. MRI studies concluded MTS ipsilateral to seizure focus was present in six males with LTLE, two males with RTLE, four females with LTLE, and one female with RTLE. No participants exhibited contralateral MTS.

4.2. Measures

Each participant was administered a comprehensive neuropsychological evaluation as part of a multidisciplinary medical assessment of surgical candidacy for treatment of localization-related TLE. Severity of mood symptoms was evaluated using the BDI-II, with a cutoff score of 28 indicating severe clinical symptomatology, per BDI-II interpretive guidelines. Given higher rates of depression among individuals with epilepsy (Gilliam et al., 2004), the high BDI-II cutoff was warranted in order to avoid reducing generalizability of the study by unduly excluding participants with a commonly occurring comorbidity. Each participant's general verbal abilities were assessed using either a Wechsler Adult Intelligence Scale, Third Edition, Verbal Intelligence Quotient (WAIS-III VIQ; Wechsler, 1997) or Wechsler Adult Intelligence Scale, Fourth Edition, Verbal Comprehension Index (WAIS-IV VCI; Wechsler, 2008) standard score. Letter fluency was assessed using the Controlled Oral Word Association Test (COWAT), and semantic verbal fluency was assessed using "Animals" category fluency, with both measures using standardized instructions including a 60 s time limit for each trial (as described in Strauss, Sherman, & Spreen, 2006). Raw scores were converted to demographically-adjusted (i.e., age, education, and ethnicity) *t*-scores according to the Heaton, Miller, Taylor, and Grant (2004) revised normative data.

4.3. Data analysis

Analyses of Variance (ANOVAs) were used to assess for potential demographic and clinical differences between sexes for the following variables: age in years, education in years, epilepsy duration in years, and general verbal abilities via WAIS-III VIQ/WAIS-IV VCI standard scores. The dataset was also split by sex, and ANOVAs were run on the same variables to assess for potential differences between LTLE and RTLE participants within each sex-specific TLE group. Finally, with the combined dataset, a 2×2 between-subjects Analysis of Covariance (ANCOVA) was used to assess the effects of sex and seizure laterality on verbal fluency. The ANCOVA was run separately for letter and semantic fluency measures. WAIS-III VIQ/WAIS-IV VCI standard scores were combined into a single variable and used as covariates in order to control for differences in general verbal ability. An alpha level of $p < 0.05$ was used for all analyses.

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