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Language Lateralization in Temporal Lobe Epilepsy: A Behavioral Screening Tool for Surgical Planning

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Abstract

Objective: Temporal lobe epilepsy can disturb eloquent areas, affecting language. We applied a visually-mediated task to measure lateralization of language recognition in drug resistant temporal lobe epilepsy. ***Method***: Patients with left (n=26), right (n=28) temporal lobe epilepsy, and controls (n=30) were administered the translingual lexical decision task. We performed repeated measures ANOVAs, with visual half-field as intra-subject factor, and group as inter-subject factor. ***Results:*** A main effect of visual half-field was found, showing right visual-field (left hemisphere) advantage for both accuracy and response time. A main effect of group was found in accuracy, showing that both epilepsy groups performed less accurately than controls, and left temporal lobe epilepsy performed less accurately than right temporal lobe epilepsy. Also, the group by visual half-field interaction was significant. Post hoc t-tests indicated the controls and right temporal lobe epilepsy performed better in the right visual-field than in the left visual-field whereas no visual half-field effect was found in left temporal lobe epilepsy. For response times, the interaction was also significant. Post hoc t-tests showed a significant right visual-field advantage for controls (two tailed), and for the right temporal lobe epilepsy (one-tailed). Right visual-field advantage was absent in left temporal lobe epilepsy. ***Conclusions:*** The translingual lexical decision task can efficiently distinguish between left and right temporal lobe epilepsy. Compared to right temporal lobe epilepsy and controls, language lateralization is diminished in left temporal lobe epilepsy. The potential use of translingual lexical decision task as an effective non-invasive presurgical language lateralization screening tool is highlighted.

Key Points

Question: How effective is a visual field task for assessing language lateralization in patients with temporal epilepsy? Findings: Results obtained through the translingual lexical decision task corroborate the known leftward asymmetry for language processing in controls and right temporal lobe epilepsy patients, and also showed decreased language lateralization left temporal lobe epilepsy patients. Significance: The applied task has a potential use as a screening tool for brain surgery planning. Next steps: Future research efforts should directly compare results from the lexical decision task with gold standards presurgical assessment tools.

Keywords: dominance, resection, refractory epilepsy, reorganization, lexicon

Supplemental materials: https://doi.org/10.1037/neu0000962.supp

Introduction

Brain Mapping of Language Functions in Epilepsy

Temporal lobe epilepsy (TLE) is the most common type of drug-resistant epilepsy in young adults which can be treated with focal resection of the epileptogenic foci (Querol Pascual, 2007). Although anti-seizure medications are the most effective treatment in most cases (Shinnar & Berg, 1996), TLE frequently becomes resistant to medication and, the gold standard treatment under those circumstances is resective surgery. Determination of the location of the epileptogenic zone becomes crucial to delimit the surgical target.

In healthy controls (CTRL), syntactic, semantic, lexical, and phonetic components of language are predominantly processed in the left cerebral hemisphere (Hickok, 2022). Based on this understanding, the present study focuses on the orthographic lexicon input through the visual channel, that is, on words that are visually perceived (Price, 2000) and processed by the left hemisphere. It is worth noting that the initial stages of language comprehension, from sensory input to semantic processing, are of particular interest, as these stages are highly susceptible to and affected by temporal lobe epilepsy (Hamberger, 2015).

The brain determines whether a string of letters form a word before analyzing their phonological component and meaning. The middle fusiform gyrus (BA 37) has been identified as a critical region associated with this function (Purcell et al., 2014), and is considered an integral part of the basal temporal language area (Middlebrooks et al., 2017), which comprises a set of areas fundamental to linguistic processing. The basal temporal language area has been extensively studied in the classical literature by Penfield (1957) in numerous articles and is currently considered one of the main studied brain node in cases of resective surgery for epilepsy

(Enatsu et al., 2017). Once a string of letters is identified as a word, the naming process is carried out by the superior temporal gyrus and the pars triangularis of the dominant (typically left) hemisphere (Binding et al., 2022; Sone et al., 2022). Since left TLE (LTLE) frequently affects the aforementioned areas of language subfunctions, individuals with LTLE often exhibit atypical lateralization of language (Brázdil et al., 2003; Möddel et al., 2009). This atypical representation of language can be observed in preoperative assessments aiming to localize eloquent areas (Hickok, 2022).

Despite the established general rule of left hemisphere dominance for language, there is evidence of non-dominant lateralization of lexical function in some cases of epilepsy, as previously reported by Springer et al (1999). This study found a more symmetrical dominance pattern (with 16% more cases) in patients with TLE compared to CTRL. This brain reorganization phenomenon is known as neuroplasticity, in which the brain modifies its neural connections to maintain activity levels during the performance of cognitive tasks (Huttenlocher, 2009). This phenomenon serves as an illustration of the brain´s inherent ability to undergo changes, both in its structural composition and functional processes (Scharfman, 2002). In the context of epilepsy, neuroplasticity can arise as a consequence of recurrent seizures (Issa et al., 2023). Neuroplasticity in patients with LTLE could preserve cognitive functions through the recruitment of non-putative areas. Neuroplasticity in TLE may trigger right laterality or bilaterality for language processing (i.e., less interhemispheric asymmetry and greater participation of both hemispheres) (Enatsu et al., 2017; Hamberger, 2015; Hamberger & Cole, 2011; Janszky, 2003; Lüders et al., 1991; Middlebrooks et al., 2017; Möddel et al., 2009; Pataraia et al., 2004; Price, 2000; Rice et al., 2018; Sone et al., 2022).

Möddel et al. (2009) found evidence of inter- and intrahemispheric reorganization of language in a study that included 445 TLE patients evaluated with the Wada test. The authors observed that 46% of patients with early onset of epilepsy – prior to 5 years of age – had a right language dominance while 37% with later onset had a more bilateral representation. However, there are other studies that have reached contradictory conclusions regarding the reorganization of language functions. Several papers by Hamberger & colleagues (2015, 2011) claim that earlier onset of epilepsy is associated with a higher incidence of intra-hemispheric rather than inter-hemispheric reorganization of language. Nevertheless, it is likely that these findings reflect the existence of multiple language support systems that come online once the main system in the language-dominant left hemisphere is disrupted (Saur, 2006).

Another study showed that frequent chronic interictal epileptic activity can induce language reorganization (Janszky, 2003). This functional magnetic resonance imaging (fMRI) study showed that LTLE patients had a higher incidence of atypical language representation than right TLE (RTLE) patients, demonstrating the presence of interictal abnormalities and a shift of language from left to right.

Pataraia et al. (2004) conducted a study using magnetoencephalography to examine brain activation induced by speech perception in patients with LTLE. Using the formula *"(R-L)/(R+L)"* the authors calculated a language laterality index based on the number of activity sources on each hemisphere. They observed a higher incidence of atypical language lateralization among patients with mesiotemporal sclerosis than among more widespread lesions (43% vs. 13%). A study by Rice et al. (2018) addressed the laterality of semantic processing in patients with postsurgical LTLE by comparing them with CTRLs. This research used fMRI to examine brain reorganization of semantic associations represented in words and images. During semantic associations, patients showed increased activation in the prefrontal cortex of the unaffected (right) hemisphere in comparison to controls, and this was interpreted as a compensatory mechanism. In other words, activations in patients with LTLE showed increased right prefrontal and temporal lobe activity.

Taken together, these studies provide evidence that TLE activity can induce changes in language representation in the brain, resulting in atypical language lateralization. Neuroplasticity allows the brain to adapt and reorganize its language networks in response to epileptic activity. In the context of epilepsy, brain reorganization of cognitive functions is not merely the result of a single seizure but rather it is due to the chronicity of recurrent seizures. Factors such as epilepsy age of onset, genetics, severity of sclerosis, illness duration, and medication treatment, among others, may influence brain reorganization (Helmstaedter et al., 1997).

Furthermore, to further understand the neuroplasticity of the language network in TLE, it is crucial to identify subtypes of language components, such as semantic, syntactic, and pragmatic representation. However, it is particularly important to focus on the fundamental level of language, which is the semantic-morphological aspect. This approach is useful for the planning of surgical interventions while preserving language functions in TLE patients.

Studying the Lexical Function

Assessing language lateralization can provide critical information when considering surgical resection of epileptogenic foci within the dominant temporal lobe. There are several techniques used to determine language lateralization in patients, including the Wada test, transcranial doppler ultrasound, and fMRI. Each of these techniques has sought to surpass their predecessors in terms of reliability and, to be less invasive, accessible, more applicable to clinicians and patients undergoing treatment. For example, currently, the use of fMRI has gained popularity and has been widely recommended in the determination of language lateralization (Bradshaw et al., 2017) given its effectiveness in mapping the brain areas involved in language function. However, it is worth mentioning that fMRI also has inherent limitations in its methodology and clinical application. The high costs and infrastructure requirements limit its accessibility. Additionally, the use of diverse tasks and scanning parameters to assess language with fMRI has partially prevented replication of results, limiting the robustness of the technique. Despite technological advances and improvements in language lateralization assessment techniques, a comprehensive evaluation using a combination of different methods can help to obtain more accurate and reliable results. For this reason, a behavioral technique called the Visual Half Field (VHF) paradigm (Hunter & Brysbaert, 2008) has been developed to assess language lateralization in a simple, inexpensive, and non-invasive way.

The VHF tasks is a validated and standardized behavioral technique, and a study by Hunter and Brysbaert (2008) tested a VHF paradigm in an fMRI setting. They aimed to determine the optimal parameters for measuring language dominance in VHF experiments by comparing the laterality indices obtained from a behavioral task with a word generation task in fMRI in a repeated measures design. The results revealed a direct correlation between VHF response times (RT) and the fMRI task, demonstrating paradigm robustness. RT in individuals with left hemisphere dominance differ from those with right hemisphere dominance, suggesting that VHF tests can be used as a reliable predictor of cerebral language dominance.

In VHF tasks, it is assumed that stimuli presented to each visual hemifield are initially received and processed in the contralateral cerebral hemisphere (Beaumont, 1983). The nasal retinal fibers decussate at the optic chiasm and project towards the visual cortex of the opposite hemisphere, causing the information obtained from the RVF to be processed quickly by the left hemisphere and vice versa (Hunter & Brysbaert, 2008). Thus, any effect on RT between the VHF can be considered a reflection of early differences in hemispheric functioning. As a result, an advantage for stimuli presented in the RVF would be expected, indicating a superiority of the left hemisphere in language processing. The RVF advantage is reflected in higher accuracy and shorter RT. This methodology offers a relatively simple and non-invasive avenue to examine lateralization, which can be easily implemented, requiring only the basic equipment (i.e., a computer with stimuli presentation software and a chin rest) to perform these tasks (see Vingerhoets et al., 2023, for methodological recommendations on the VHF task).

Studies conducted by Van der Haegen and colleagues (Van der Haegen et al., 2011, 2013; Van der Haegen & Brysbaert, 2018) aimed to further explore the application of VHF for laterality research. Van der Haegen (2013) investigated the relationship between ear dominance, handedness, and language dominance measured with fMRI, finding that left-handed individuals with atypical cerebral dominance for language in fMRI also showed a left ear advantage (right hemisphere dominance) in the VHF task. Another study by Van der Haegen (2018) found some significant correlations between lateralized language tasks (speech production, reading, and speech perception) and measures of laterality (dexterity with hands, feet, ear, and eyes dominance), in self-reported left handers. These correlations allowed to classify them as typical, bilateral or atypical participants. In the study conducted by Van der Haegen (2011), language lateralization was measured in a group of healthy left-handers with VHF tasks. The researchers calculated laterality indices on the participants' RT. These laterality indices were compared with brain activity measured in a silent word generation fMRI task. Results confirmed that none of the left-handers with clear right visual field (RVF) advantages showed right hemisphere dominance in the scanner. Moreover, participants with a left visual field (LVF) advantage had atypical right brain dominance in the fMRI task.

In the present study, we administered the Translingual Lexical Decision Task (TLDT) to assess language dominance. The TLDT is a well-established VHF task for assessing language lateralization (Willemin et al., 2016) and it can be used with a variety languages. A recent study (Hausmann et al., 2019) used the TLDT to investigate language lateralization in mono- and bilingual participants speaking European languages that use the Latin alphabet. As expected, responses to words presented in the RVF were faster and more accurate than those presented in the LVF, indicating left hemisphere's dominance in language processing. However, the study concluded that the TLDT is a reliable measure of language lateralization across different languages.

The present work aimed to extend the application of TLDT to patients with medication resistant TLE. Our main objective is to assess the clinical utility of a mid-visual field behavioral task as a first screening tool for language lateralization assessment, particularly for lexical processing, in patients candidates for brain surgery. We hypothesized that individuals with RTLE and CTRL groups will exhibit typical left hemisphere language lateralization as shown by increased accuracy and faster RT in RVF compared to LVF. In contrast, we expect that patients with LTLE will have similar accuracy and RT for both VHF, indicating a more bilateral language performance compared to RTLE and CTRL.

Methods

Participants

Patients with Left and Right Temporal Lobe Epilepsy.

Participants with LTLE (n=26, aged between 18 and 48 years) and RTLE (n=28, aged between 18 and 57 years) were recruited from Hospital “El Cruce Nestor Kirchner” in Florencio Varela, Province of Buenos Aires, Argentina. The group was formed by patients with drug resistant temporal lobe epilepsy (non-responders to antiseizure medication therapy) focal unilateral (for more information, see supplementary material). Inclusion criteria consisted of at least one characteristic clinical event documented by the presence of ictal abnormalities confirmed by video EEG, and diagnosed according to the International League Against Epilepsy nomenclature (Berg & Cross, 2010; Scheffer et al., 2016). For the diagnostic process, all patients were hospitalized during 4 to 5 days to undergo a video EEG, and every recorded seizure was examined 3 to 4 times by two trained experts in order to identify semiological signs and ictal activity. To define laterality motor behavior as well as EEG channel sources showing abnormal activity were considered in agreement with ILAE. All selected patients were candidates for resective brain surgery, and those whose epileptogenic zone could not be localized were excluded. All patients underwent a volumetric T1 sequence of high field MRI scan to check for brain abnormalities. Ictal and interictal activity, and structural MRI findings were coincident regarding laterality (either left or right) and localization to temporal lobe. Patients with psychosis, bipolar disorders, progressive neurological condition (dementia, higher-grade brain tumors, encephalopathies) or previous surgery for epilepsy were excluded. Other exclusion criteria consisted in failure to complete all diagnostic steps not to sign informed consent or had IQ equal to or less than 70 on the Wechsler IQ Test (Wechsler, 2002). All participants reported to have normal vision. A t-test was conducted to compare the epilepsy age of onset between LTLE and RTLE patients.

Control Group

Thirty healthy subjects aged 18 to 75 years without history of neurological or psychiatric diseases and with normal or corrected-to-normal vision were included. A brief survey collecting demographic data (see Table 1) and screening for visual impairments, such as myopia or astigmatism, were administered to all participants. Only those with no visual impairments were included in the study. After completing the TLDT, a neuropsychological battery was administered to all participants (see Table 1).

Ethical Considerations.

All participants signed an informed consent attesting that they were participating voluntarily and were aware they could leave the experiment at any time. Also, the study has the approval of the Bioethics Commission of Hospital “El Cruce”, based on the Declaration of Helsinki. No part of the study procedures and analyses was preregistered prior to the research being conducted.

Materials and Procedure

Demographic Data and Manual Dominance.

Initially, demographic data such as age, education, and occupation were collected through interviews with the participants. Patients were also asked to report their age of epilepsy onset and current medication (see Supplementary material). Each participant completed both the Edinburgh Handedness Inventory (Oldfield, 1971) and the Waterloo Footedness Questionnaire (Elias et al., 1998). Patient groups data on epilepsy age of onset are shown in Table 1. All participants had Spanish as their native language and were not exposed to a second language until schooling.

Psychometric assessment. All subjects were assessed with the Digit Span task (Wechsler, 2002) to measure their short term and working memory. Subjects were also evaluated with the Word Accentuation Test (Burin et al., 2000) to estimate pre-morbid verbal IQ, where significant differences between the CTRL, the RTLE, and LTLE groups were found (Table 1).

The patients completed a battery of neuropsychological tests to assess language and executive functions. Specifically, the Boston Naming Test (Allegri et al., 1997) was used to evaluate naming ability, and verbal fluency tests were used to assess word generation ability. The verbal fluency tasks (Labos et al., 2013) included semantic fluency (animals and fruits) and phonemic fluency (letters F, A, and S) tasks. The tasks were administered in Spanish-speaking and were scored according to standard procedures (Strauss et al., 2006). Patient groups data on verbal IQ and verbal fluency are shown in Table 1.

Table 1. *Demographic data and neuropsychological results.*

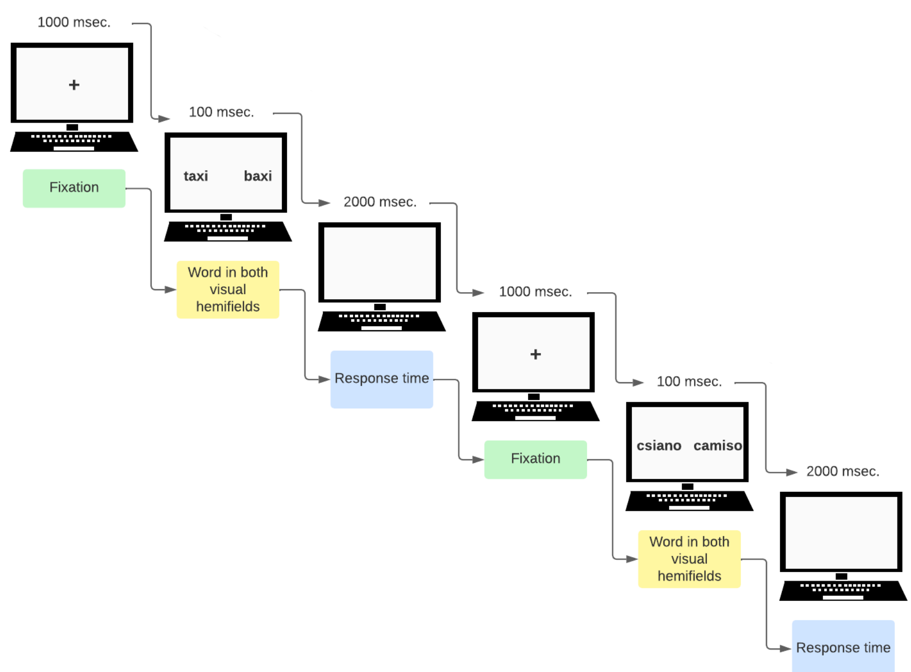
	LTLE	RTLE	CTRL	*p*
Number of subjects	26	28	30	
Sex (F/M)	(15/11)	(15/13)	(19/11)	
	M (SD)	*M (SD)*	*M (SD)*	
Age	30.65 (9.10)	32.25 (10.92)	26.80 (12.97)	*.169*
Years of Education	12.19 (2.53)	12.71 (2.94)	15.20 (1.71)	*.000***
Onset of Epilepsy	12.89 (9.02)	12.96 (11.16)	-	*.307*
Edinburgh	64.56% (63.51)	86.70% (37.43)	84.56% (31.63)	*.171*
Waterloo	6.54 (10.03)	11.45 (7.44)	9.08 (3.18)	*.105*
Digit Span	6.92 (2.75)	7.60 (2.97)	5.88 (2.05)	*.115*
Word Accentuation Test	10.95 (4.56)	9.59 (4.60)	5.94 (2.18)	*.001**
Boston Naming Test	-2.59 (2.22)	-2.20 (2.92)	-	*.865*
Phonemic Fluency Tasks	-.83 (.76)	-.60 (1.12)	-	*.216*
Semantic Fluency Task	-1.21 (.97)	-1.08 (.96)	-	*.459*

CTRL, healthy Controls; LTLE, left temporal lobe epilepsy; RTLE, right temporal lobe epilepsy; M, mean; SD, standard deviation; Edinburgh, Manual dominance cut off was -40 for left handers and +40 for right handers. Participants with results between -40 and +40 were considered mixed handers; Waterloo, Footedness Questionnaire; WAT, Word Accentuation Test (number of errors); ns, not significant. Groups were compared by One-Way ANOVA and three t tests within the epilepsy groups. Difference between the RTLE and LTLE with the CTRL, group was significant (One-Way ANOVA test, DMS corrected). $^{*}p<.01$. $^{**}p<.001$.

Translingual Lexical Decision Task

The technique has been validated by Hausmann and colleges (Hausmann et al., 2019) in different European countries and is identical to the task used in this research, including the word stimuli. Stimuli were selected based on frequency use and finally 16 lowercase words were retained: agenda, alibi, aura, casino, film, gala, garage, jazz, jury, menu, radio, piano, snob, studio, taxi, virus (Willemin et al., 2016).

Figure 1. The TLDT (Translingual Lexical Decision Task) lasted between 15 to 20 minutes, including a break of 5 minutes approximately.



Note. The task begins with fixation cross displayed for 1000 milliseconds. Next, a pair made of a word and a pseudoword (one on the left and other on the right visual hemifield) or a baseline trial (both pseudowords) were shown for 100 ms. The side of word and pseudoword was counterbalanced. Participants have 2000 ms to respond on which side the word was presented by pressing a button (right or left). For baseline trials, participants pressed a third button.

Translingual Lexical Decision Task Procedure

During the task, two stimuli were presented simultaneously, either words or non-words, in the RVF and LVF of a computer screen with a white background. The stimuli were presented in lowercase, in 12-point Courier New font, and in black color. Each trial began with a fixation cross for 1000ms, followed by a brief presentation of the two stimuli for 100ms. This brief bilateral presentation of the stimuli ensured adequate control of eye movements in previous experiments with verbal stimuli (Beaumont, 1982).

Participants had 2000 milliseconds to decide whether a meaningful word was presented in the LVF or RVF before the next trial began. Participants were instructed to indicate by button press on a keyboard whether they saw a meaningful word on the left ("respond with left index finger on a left-sided button"), on the right ("respond side with right index finger on a right-sided button"') or if they did not see a meaningful word on each side ("press space bar with both thumbs"). Each combination of letter strings was presented four times in random order: word/non-word (16 pairs), non-word/word (16 pairs), and 32 pairs of non-word/non-word (the original 16 pairs of non-word/non-word were also shown in reverse order).

Statistical Analysis

Two repeated measures ANOVAs (Accuracy and Response Times) were carried out, with the visual half field as the intra-subject factor (LVF and RVF), and Group as an inter-subject factor (CTRL, RTLE and LTLE). As detailed in sections 3.1 and 3.2, post-hoc tests were used to explore and confirm the findings. The interactions found in the main ANOVA were further explored by Bonferroni-Holm corrected for multiple comparisons paired sample *t* test. We ensured that all necessary assumptions for using mixed model ANOVAs were met, including normal distribution of the data, independence of cases, and consistent variances. In a preliminary analysis, handedness was included as a covariate, but as it did not have any effect on the analysis, it was finally excluded. This negative finding is in line with previous research (Hausmann et al., 2019). The IBM SPSS program was used for all statistical analyses.

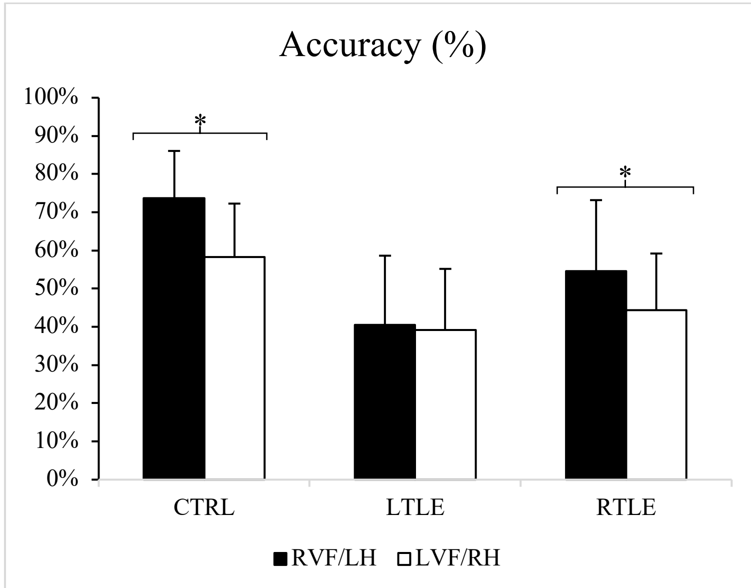
Results

Accuracy

A main effect of VHF was significant, $F(1,81)=22.84$, $p<.001$, indicating the expected RVF advantage (M=57.05, SD=21.27) (i.e., left-hemisphere language lateralization) over LVF (M=47.78, SD=16.81). The main effect of group was also significant, $F(2,81)=28.44$, $p<.001$. Bonferroni corrected pairwise comparisons revealed that the LTLE (M=40.32, SD=14.53) and RTLE group (M=49.47, SD=14.23) differed significantly from healthy CTRL (M=66.01, SD=10.42). Moreover, RTLE performed significantly better than LTLE (all p's<.05). The interaction between VHF and group was also significant, $F(2,81)=28.44$, $p<.001$. Bonferroni-Holm corrected for multiple comparisons post hoc *t*-tests showed that for CTRLs, RVF (M=73.70, SD=12.37) accuracy was higher than LVF (M=58.34, SD=13.94), [$t(29)=-5.216$,$p<.001$,$d=.95$]. In RTLE, RVF (M=54.53, SD=18.66) accuracy was higher than LVF (M=44.42, SD=14.79) [$t(27)=-2.916$,$p<.05$,$d=.55$]. In LTLE, RVF (M=40.57, SD=18.07) did not differ significantly from LVF (M=39.24, SD=15.95), [$t(25)=-.404$, $p=.690$,$d=.08$].

Figure 2.

Accuracy in Visual Half Fields for Each Group.



Note. CTRL, healthy Controls; LTLE, left temporal lobe epilepsy; RTLE, right temporal lobe epilepsy; RVF, right visual field; LVF left visual field. *Difference between the RVF and LVF was significant at p<.05 (Post hoc t-tests).

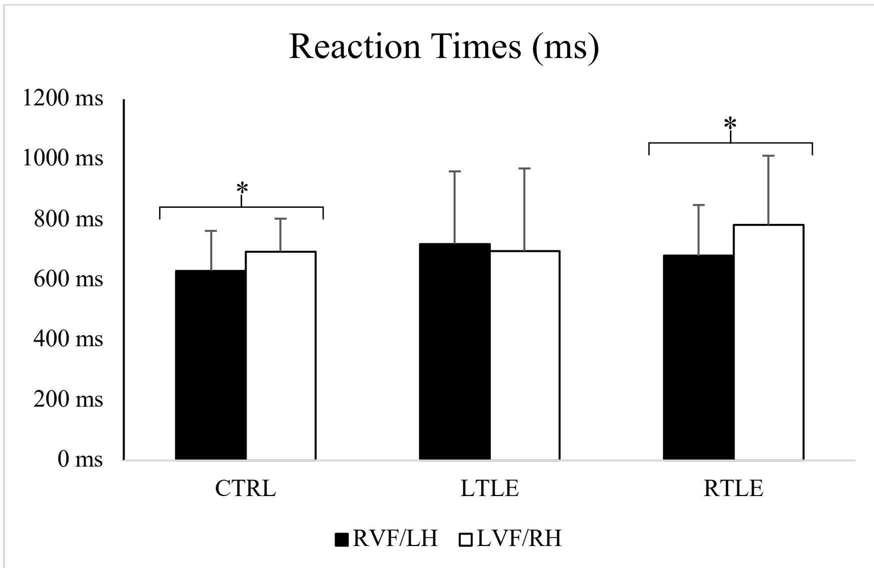
Response times

A main effect of VHF was found $F(1,81) = 12.94$, $p < .005$. As expected, stimuli in the RVF, corresponding to the left hemisphere, (M=674, SD=199) were processed faster than in the LVF (M=724, SD=201). We did not find a main effect of group, $F(2,81)=1.00$,$p=.372$. The interaction between VHF and Group was significant, $F(2,81)=7.06$, $p<.001$. Bonferroni-Holm corrected for multiple comparisons post hoc t-tests showed that CTRL revealed faster responses in the RVF (M=630, SD=132) compared to LVF responses (M=694, SD=109), [$t(29)=3.69$, $p=.001$,$d=.67$]. In RTLE, there was a trend showing faster responses in the RVF (M=679, SD=169) than LVF (M=783, SD=229) but this effect did not reach significance,

[$t(27)$=4.50,p=.0001,d=.85]. In LTLE, RT did not differ between RVF (M=695, SD=241) and LVF responses (M=719, SD=274), [$t(25)$=-.80,p=.428,d=.15].

Figure 3.

Reaction Times in Half Fields for Each Group.



Note. CTRL, healthy Controls; LTLE, left temporal lobe epilepsy; RTLE, right temporal lobe epilepsy; RVF, right visual field; LVF, left visual field; ms, milliseconds. *Difference between the RVF and LVF was significant at p<.001 (Post hoc t-tests)

Discussion

The present study aimed to investigate language lateralization in candidates for focal resection TLE patients, testing the potential use of the VHF technique as a screening tool for surgical planning. The results revealed that LTLE patients did not show the typical RVF advantage in lexical processing, indicating reduced language lateralization. Reduced language lateralization might reflect compensatory neural mechanisms to overcome the aberrant functioning of the putative language-dominant left hemisphere. These findings have significant implications for pre-surgical evaluation protocols, as the lateralized TLDT could potentially identify patients with atypical lateralization. The results suggest that TLDT is an accessible screening tool easy to apply in neuropsychological evaluation and it could potentially contribute to screen out candidates for brain surgery.

Use of the Task in a Spanish-Speaking Sample

The VHF methodology used in the TLDT allows for the evaluation of language lateralization across several languages that use the Latin alphabet. Results obtained from the CTRL group demonstrate that the TLDT was a useful and reliable tool for assessing language lateralization in healthy Spanish-speaking individuals, with results similar to those reported by Hausmann et. al (2019). In the aforementioned work, Hausmann and colleagues (2019) evaluated VHF in native speakers of different European languages, such as Dutch, English, French, German, Italian, and Norwegian, and found a consistent RVF/left hemisphere advantage in both accuracy and RT in all language groups with the same stimuli set. The present study extends these results of Hausmann et al. (2019) and revealed that the TLDT can also be administered to Spanish-speaking participants, and it is suitable for evaluating clinical populations as described here.

The aim of TLDT is to provide information about language lateralization by assessing lexical access, it does not measure all language proficiency or skills *per se* but is a relative measure of language lateralization, comparing left and right hemispheric functioning. Beyond that, the assessment of language capacity as well as other higher cognitive functions should be performed and completed by a neuropsychological evaluation. It is important to note that the lexical function evaluated in this study represents a very basic form of language processing and cannot be directly compared to other neuropsychological tests, such as those evaluating naming –

e.g., Boston Naming Test (Kaplan et al., 2001) – or verbal fluency – e.g., FAS (Strauss et al., 2006).

The novelty of the TLDT is that it allows to obtain a behavioral marker of language lateralization by measuring accuracy and RT in the task. This feature makes the TLDT a more accessible tool than fMRI, as it is cost and time efficient, and can help clinicians to identify lateralization of language and ultimately aid in treatment planning for patients with neurological disorders.

Atypical Lateralization of Language in Left Temporal Lobe Epilepsy

The brain has a dynamic capacity for reorganization (Ius et al., 2011), and this ability can be reflected both in normal conditions (e.g., learning), and as a result of pathological events (e.g., epilepsy). It has previously been shown that language function can be reorganized in eloquent areas, as evidenced in other studies (Hamberger & Cole, 2011; Szaflarski et al., 2001). The present study evaluated language lateralization in patients who may have undergone reorganization of language function due to epilepsy.

Although our CTRL and RTLE participants obtained similar accuracy and RT in each VHF compared to those reported previously (Hausmann et al., 2019) the LTLE group did not show differences in accuracy between VHFs. A plausible interpretation of this finding is that LTLE patients did not exhibit a clear left hemisphere language dominance, as observed in RTLE and CTRL participants. Similarly the comparison of RT for VHFs showed that participants with LTLE did not obtain faster responses for the RVF, which again suggests a more bilateral distribution of language processing in this group. This reduced asymmetry may be attributed to specific functional alterations in the left temporal lobe and their impact on language lateralization and visual functions.

All patients included in the present study had focal refractory epilepsy, which is characterized by early onset and long evolution of the disease, making them more prone to functional reorganization. In addition, TLE patients in the present study have been exposed to various groups of antiepileptic drugs, which may have contributed to functional reorganization (Selai et al., 2005). Long lasting epileptogenic discharges, frequent in this type of pathology, propagating though interhemispheric connectivity (Gazzaniga, 2000), seem to trigger functional reorganization to contralateral homologous areas, including word detection.

A previous study of our laboratory with a similar sample under comparable clinical, cognitive, and sociodemographic variables (e.g., diagnosis types, number of participants, sex, IQ, age of epilepsy onset), found evidence of emotional prosody reorganization as measured by fMRI (Elizalde Acevedo et al., 2022). Specifically, contralateral areas mirroring the right superior temporal gyrus were activated in patients with RTLE. In the present study, the findings on lexical processing offer similar evidence of reorganization in the epileptic brain.

The atypical language lateralization in LTLE may be triggered by three white matter tracts: the inferior longitudinal fasciculus, the corpus callosum, and the anterior commissure. Firstly, the left inferior longitudinal fasciculus transmit visual information to associative areas, through an intra-hemispheric pathway involved in word reading, and semantic processing (Binding et al., 2022). This fasciculus connects anterior temporal areas with the occipital pole intra-hemispherically. Additionally, there are inter-hemispheric connections via corpus callosum and anterior commissure, that link left hemisphere language nodes to their homologous areas on the right hemisphere (e.g., the right superior temporal gyrus). Perhaps, in the presence of a unilateral lesion, the right hemisphere is expected to compensate for domains putative to the dominant hemisphere (Herbet et al., 2018) using these intra and inter-hemispheric pathways.

Limitations and Future Lines

Although we present a laterality index that gives hints on language laterality at the individual level (see supplemental material), cut-ff points for the clinical context would be highly desirable to use this tool with clinical purposes, but such use was not in the scope of the current study. The development of TLDT as a clinical tool for the individual would require more patients of different clinical groups, and a direct comparison to other gold standard tools such as neuroimaging. It is important to consider that TLDT is recommended for patients with an IQ above 70, as those with a lower IQ or more compromised functions may have difficulties performing the task adequately. We recommend that future studies match control samples with patients with epilepsy according to their educational level. According to the literature, it is assumed that educational attainment can enhance general cognitive performance. Although the LTLE group had lower educational attainment, their performance was significantly above the chance level for both VHF. It is unlikely that differences in educational attainment affected language laterality as measured with TLDT. Word (e.g., taxi, film, radio) vs non-word (e.g., taia, fitz, rapoo) decisions are cognitively not very demanding. Additionally, our research question focused on language lateralization specifically. Therefore, we are inclined to believe that the overall performance differences are less critical in the present study. On the other hand, in cases where cognitive functions are still preserved along with a normal IQ, TLDT can be a valuable screening tool prior to surgery. Preserving the patient's cognitive functions is crucial and relies on an exhaustive exploration of functional organization. The TLDT might be used to discharge those patients in which surgery is safe (resective zone contralateral to language dominance).

When TLDT results are not as clear, a complementary fMRI study may be needed. In addition, applying TLDT in fMRI (pre- and post- focal resection) might allow for the study of the temporal dynamics of intrahemispheric reorganization of lexical processing, as well as the neuroplasticity caused by surgery.

Conclusion

The present study conducted an evaluation of the TLDT —a non-invasive, inexpensive, visually-mediated task—to determine language lateralization in neurologically health controls as well as participants with drug resistant TLE who were candidates for resective surgery. We have showed that the TLDT can be used to assess language lateralization in a Spanish-speaking sample of neurologically healthy CTRL and patients with TLE. RLTE patients revealed a clear left-dominant language lateralization which did not differ from neurologically healthy CTRL. However, patients with LTLE did not exhibit the typical left-dominant language lateralization but instead showed a more bilateral pattern of language processing. The findings suggest that cerebral reorganization can occur when the lexical processing network overlaps with the epileptogenic zone. Further research is necessary to enhance our understanding of the compensatory cerebral mechanisms of the lexicon in epilepsy. Specifically, additional studies are required to explore the reorganization of the lexicon in the same sample using fMRI.

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