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Grammar tests increase the ability to lateralize language function in the Wada test

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Summary
Introduction: Grammar is a core component of the language system, yet it is rarely assessed during the Wada (intracarotid amobarbital) test. It is hypothesized that adding grammar tests to the recovery phase of the Wada test will increase our ability to lateralize language function.
Method: Sixteen individuals (nine females, fifteen right-handed, mean age 38.4 years, SD = 10.7) with medically refractory temporal lobe epilepsy participated in the study. On EEG ten patients had seizures originating in the left hemisphere (LH), five in the right hemisphere (RH), and one was insufficiently lateralized. We included only patients who were LH-dominant on the standard test in the encoding phase of the Wada test. In the recovery phase of Wada testing the participants underwent evaluation with a standard language and a new test of grammar, the CYCLE-N. Ten patients underwent bilateral injections, six unilateral (one RH, five LH).
Results: As expected, injection in the LH decreased language performance to a greater extent than injection to the RH on both tests. However, the CYCLE-N produced more profound language deficits in the injected LH compared to the RH ($p = 0.01$), whereas the standard tests did not cause such pronounced differences ($p = 0.2$).

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Conclusion: The results suggest that the standard tests did not significantly differentiate the effects of the injections and the CYCLE-N, for the most part, did. Our results are of particular relevance to patients who are too obtunded to speak in the encoding phase. In sum, the CYCLE-N may be helpful in assessing hemispheric dominance for language.

Introduction

Resection of the epileptogenic region offers a seizure free outcome rate of up to 80% for individuals with medically refractory temporal lobe epilepsy (TLE) (Quirico-Santos et al., 2013). Since resection of cortex essential for language function may result in aphasia (Hader et al., 2013), knowing the localization and lateralization of language dominance is essential in surgical planning of epilepsy. The resection of the temporal lobe in the language dominant side may be more limited than in the non-dominant side (Rosazza et al., 2013).

Individuals with epilepsy are more likely to have altered language representation within the left hemisphere (LH) (intrahemispheric reorganization) or atypical hemispheric dominance (interhemispheric reorganization) compared to the healthy population (Dijkstra and Ferrier, 2013; Enatsu et al., 2013). Left TLE is associated with more symmetrical language activity on functional Magnetic Resonance Imaging (fMRI) accompanied by more prominent right hemisphere (RH) and reduced LH structural connections (Rosenberger et al., 2009). Right TLE patients tend to have their language functions lateralized to the left, similar to healthy controls (Powell et al., 2007). However, Rosazza et al. (2013) recently showed that decreased left lateralization occurs both in left and right TLE. The most common predictors of atypical language dominance in epilepsy include: early age of onset (Federico, 2011; Korman et al., 2010); left-handedness (Janszky et al., 2003; Rasmussen and Milner, 1977); lesion location (Helmstaedter et al., 1997); pathology such as hippocampal sclerosis (Rathore et al., 2009), and left-sided interictal activity (Janszky et al., 2006).

The Wada (intracarotid amobarbital) test is considered the gold standard assessment of risk to language and memory function post surgery (Whitman et al., 2012). In this procedure the capacity of the hemisphere contralateral to the epileptogenic lesion to support language and memory is evaluated while the pathological hemisphere is anesthetized. Various epilepsy centers use different Wada protocols. At our center we use a modified Montreal protocol. The Wada procedure begins with a bolus injection of sodium amytal in saline and, for clinical purposes, is followed by the first part of standard evaluation that we will refer to as the ''Encoding Phase''. This is considered a period of ''full anesthetization''. Anesthetization is judged by a neurologist on the basis of distal grip strength (scale 0—5, where 0 is full anesthesia and 5 is baseline), clear hemispheric EEG slowing, and where relevant, speech/language disturbance. The primary goal of the encoding phase is to perform memory encoding and assess basic language functions. Typically, based on results from this phase, dominance for memory and language is determined. Wada protocols also differ significantly across epilepsy centers in terms of timing, number, or types of presented stimuli (Sharan et al., 2011). As in many Wada protocols, the Montreal protocol assesses lexical-semantic aspects of language (''meaning'') through object naming, i.e., labeling pictures, and understanding of verbal instructions conducted in the encoding phase. This phase is usually completed within 60—90 s and marks the beginning of the ''Recovery Phase'', during which language is tested more extensively. In our protocol, the recovery phase evaluates auditory responsive naming, i.e., naming a described item (e.g., *a tall pink bird*), repetition, and understanding of simple *yes-no* questions (Wang et al., 2012).

Most Wada protocols assess aspects of grammar (or ''form'') only minimally. Yet meaning and form have (at least partially) separate neural and temporal representations (Yamada and Neville, 2007; Dapretto and Bookheimer, 1999). Moreover, grammatical functions are more lateralized than semantic functions (Menenti et al., 2011; Bornkessel et al., 2005; Dronkers et al., 2004).

Although it is rarely evaluated during the Wada procedure, grammar plays *the* central role in the human language system. Grammar constitutes the abstract structural principles that govern what can be a language and the principles that govern how sounds may be combined into syllables, what a possible syllable is in a given language, how complex words can be formed from simple words, how words can be combined into larger units such as phrases and sentences, and how clauses (sentences) may be combined. The components of grammar that we are concerned with in this study are (1) syntax—the principles governing how words may be combined into phrases and sentences, and (2) morphology—-how complex words may be formed, e.g., by compounding, in this study, by affixing inflections to word stems, e.g., *walk-walked*. ''Bound'' morphemes are units that combine with word stems to carry a grammatical function or meaning (e.g., plural markers, tense markers, case markers). Lesions can selectively impair the ability to form morphological inflections (e.g., *grilled*, *grills*) while the ability to use simple word forms (e.g., *grill*) is preserved (Miozzo et al., 2010). Regular inflections (e.g., regular past tense) recruit the dominant LH, especially the left inferior frontal areas (Ullman, 2001).

Grammar must be accessed in a rapid and simultaneous fashion during language processing. The rules and constraints of syntax and morphology are implicitly processed by mechanisms outside conscious awareness (Pulvermüller and Assadollahi, 2007; Pulvermüller et al., 2008; Batterink and Neville, 2013). Critically, damage to the left perisylvian network causes both syntactic and morphological deficits in comprehension and production for which the RH cannot compensate (Thompson et al., 2013; Wright et al., 2012).

Gutbrod et al. (2012) pointed out that syntax was the one main language component that was not evaluated in any studies comparing the Wada method with fMRI. Moreover,

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there are no data evaluating whether aspects of grammar are lateralized in the same way as lexical semantics, or whether they may dissociate in some patients. The Montreal protocol as used at our center contains only one item assessing morphology and two evaluating syntax. Our aim was to investigate the ability of more comprehensive grammar tests to lateralize language function in the recovery phase. Based on our clinical experience, some patients are too obtunded in the encoding phase to adequately evaluate language. In such cases, it is only during recovery that one can measure their language performance. In order to obtain language lateralization in this phase of the Wada test, we need to do so with language stimuli known to be strongly lateralized in the language dominant hemisphere. We hypothesize that introducing grammar tests to the recovery phase of the Wada test will increase our ability to assess language dominance in surgical candidates. If currently used tests conducted in both phases of the Wada tests do not accurately lateralize language function, especially crucial language functions, such as how to make or comprehend a sentence, patients may have their language abilities unexpectedly compromised in subsequent surgical procedures.

Methods

Participants

Sixteen subjects (nine females) with TLE participated in our study. The patients' mean age was 38.4 (SD = 10.7) years. Fifteen participants were right-handed, one was left-handed. On EEG ten patients had seizures originating in the LH, five in the RH, and one was insufficiently lateralized. We included only patients who had LH-dominance for language in the encoding phase of the Wada test. Patients' demographic information is summarized in Table 1. All the participants provided written informed consent following the UCLA IRB-approved procedure.

Procedure

We use a modified Montreal protocol for Wada testing at our center, which we will henceforth refer to as the standard Wada protocol. Prior to Wada testing all the participants underwent baseline testing with both standard language items and the Curtiss-Yamada Comprehensive Language Evaluation, Neurosurgery (CYCLE-N). Stimuli that were incorrect at baseline were excluded from Wada testing. Moreover, only 14 items from the CYCLE-N were administered per injection due to the severe time constraints of the WADA procedure. Injection of sodium amytal in saline was followed by the encoding phase during which the participants performed memory encoding and two standard language tests (object naming and verbal instructions). If there was initial speech arrest, we waited until the patient was able to respond to basic questions (e.g., *What is your name?*) before proceeding. We then completed the recovery phase presenting items from both the standard language testing and the CYCLE-N, but with the order of presentation randomized and counterbalanced across subjects. Given the limited amount of time available between memory encoding, the two standard language tests, and full recovery (complete motor and EEG recovery), we could only perform a subset of CYCLE-N items. We defined the recovery phase as the moment the patient showed improvement in motor skills and/or there was reduced slowing noted on EEG. As such a complete testing session always included the encoding phase first, and was followed by both language assessments presented sequentially. The entire procedure was recorded on audiotape for further analysis of language performance. Standard testing was administered by a neuropsychologist who was one of the authors (PW, SB or CB); the CYCLE-N was administered by PW or MP. The final phase (memory assessment) occurred following full recovery and is not discussed in this paper.

Materials

Standard testing

This included tasks evaluating language performance in the recovery phase. We then separately analyzed language production (object naming and repetition) and language comprehension (understanding verbal instructions, comprehending *yes-no* questions, auditory responsive naming; comprehension of ''complex'' grammatical questions). Object naming included up to six real objects (e.g. *a hammer, a toothbrush*) (average number in our sample = 5.8; only five items were presented in rare cases in which patients recovered early). Verbal instructions included up to two stimuli (average $n = 1.9$). The first two tasks were conducted during the encoding phase. The remaining tasks were carried out during the recovery phase: simple comprehension included up to eight complex ideation *yes-no* questions; e.g., *Does a stone sink in water?* (average $n = 3.9$), auditory responsive naming included up to five stimuli e.g., *What do you call a place of worship?* (average $n = 2.4$), repetition stimuli included up to seven sentences, e.g., *Pry the tin lid off*. (average $n = 3.5$). Two syntactic items followed by questions about them were also presented (e.g., *The lion was fatally attacked by the tiger. Which animal died?*) (average $n = 1.6$) as well as one morphological item testing comprehension of the possessive marker (*The sister of your husband's brother: Is that a boy or girl?*) (average $n = 0.8$). Baseline in each domain was considered to have been established when all items in that domain were answered correctly.

CYCLE-N

The test was conducted in the recovery phase. The CYCLE-N included a set of 14 trials testing syntax (up to 10 trials, average number in our sample = 9.81) and morphology (up to four trials, average $n = 3.9$). Eight trials focused on comprehension, six on production. Sample trials are shown in Table 2. Each trial was presented once and included a pair of drawings presented on a card with accompanying sentences or sentence frames to be completed (Fig. 1). Different stimulus sets were used for LH and RH injections (randomized across patients). Presentation of the set took approximately 5 min. Only stimuli that the patients had answered correctly at baseline were included. We thus excluded a total of seven stimuli from the Wada test out of a total of 375 CYCLE-N stimuli used at this study.

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Table 1 Demographic information. *Abbreviatoins*: L = left; R = right; TL = temporal lobe; CPS = complex partial seizure; GTC = generalized tonic clonic seizure (all GTSs were secondarily generalized because all the patients had presumed focal inset seizures); ILAE = International League against Epilepsy; MTS = mesial temporal sclerosis.

Subject	Sex	Handedness	Age	Age of onset	Duration of epilepsy[a]	Seizure per month	Ictal zone[b]	Lesion (MRI, PET, SPECT)	Type of seizures
S1	F	R	56	36	20	6	R TL	R temporal hypometabolism, decrease in the size of R hippocampus with an increased FLAIR signal	CPS, CPS > GTC
S2	M	R	39	15	10	1.5	L TL (mesial)	Low grade astrocytoma in L temporal lobe, left hippocampal sclerosis	CPS
S3	F	R	51	32	19	12	L TL	L hippocampal sclerosis	CPS, GTC
S4	F	R	32	28	4	4	L TL	L cavernous angioma in the middle and superior temporal gyri	CPS
S5	M	R	55	36	19	3	L TL (mesial)	L PCA infarct extending to hippocampus, small fusiform gyrus infarction	CPS, GTC
S6	M	R	23	19	4	2	R TL	Possible diffuse right temporal cortical dysplasia versus low grade glioma	CPS, GTC
S7	M	R	42	15	27	6	R TL	L anterior temporal pilotic astrocytoma WHO grade I	CPS, GTC
S8	M	R	37	34	3	0.5	L TL	L MTS	CPS, GTC
S9	F	R	32	11	4	1.5	R TL	L temporal cystic low grade neoplasm in the amygdala, cortical dysplasia in L temporal lobe, PET showed decreased activity in L medial temporal lobe	CPS
S10	F	R	49	5	24	3	Independent R and L TL (R > L)	R focal cortical dysplasia, ILAE Type Ic	CPS, GTC
S11	M	L	38	16	21	2.5	L & R TL	L temporal astrocytoma grade II/IV (Daumas-Duport)	GTC
S12	F	R	23	20	3	22	L TL	L amygdalar lesion	CPS
S13	M	R	39	16	23	4	R TL	R focal cortical dysplasia, ILAE type Ic	CPS, GTC
S14	F	R	21	15	6	30	L TL	L temporal pole cavernous malformation, possible L MTS	CPS
S15	F	R	33	13	20	6	L TL	L focal cortical dysplasia, ILAE 1c	CPS, GTC
S16	F	R	36	15	21	4	L TL	Possible subtle L MTS and focal cortical dysplasia, ILAE type III	CPS

[a] Seizure duration excludes seizure free periods.
[b] Ictal zone determined by EEG/EEG as available.

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Table 2 A set of CYCLE-N stimuli administered during one injection. A parallel form was used for the contralateral hemisphere, and the set used was randomized.

Grammatical structure	Syntax or morphology	Comprehension: instruction: which picture matches the sentence?	Production: instruction: finish my sentence
Active Voice	Syntax	The girl is pulling the boy	*Here* the boy is chasing the dog but *here*:::
Passive Voice	Syntax	The boy is being chased by the dog. (Fig. 1)	*Here* the boy is kicking the girl but *here the boy*:::
Relativized subjects	Syntax	The clown who is hugging the girl is wearing yellow	One of these girls is painting a picture, one of these girls is opening a present. This is the girl:::
Relativized objects	Syntax	The boy who the girl is kicking is wearing purple	The *boy* is holding *one* ball. The *girl* is holding *another* ball. *This* is the ball:::
Regular Past Tense Formation	Morphology	The girl opened the present	Here the boy is *about* to wash his face but here he *already*:::
Irregular Past Tense Formation	Morphology	The boy ate his dinner	Here the girl is *about* to light the candle but here she *already*:::
Subject questions	Syntax	Which person is the man pushing? (Figure)	-
Object questions	Syntax	Which animal is the cat chasing?	-

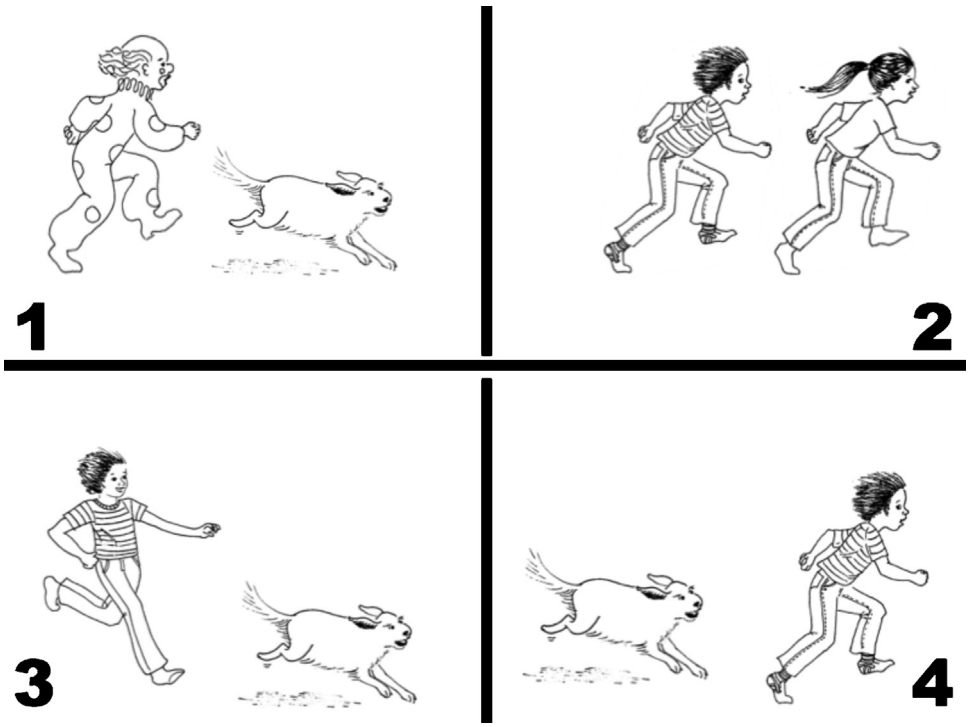

Fig. 1 Sample CYCLE-N stimulus for the Wada test. The stimulus evaluates comprehension of passive voice sentences (syntax). The patient hears a sentence *The boy is being chased by the dog* and is asked to point to a picture that matches the sentence.

Analysis

For the 12 RH and 15 LH injections we calculated the number of correct responses for each hemisphere separately: (1) the standard test versus the CYCLE-N, (2) language production and comprehension for the standard tests versus the CYCLE-N, and (3) each language aspect (e.g., repetition, syntax) for the standard test and the CYCLE-N. For the standard evaluation raw data from the encoding phase included 88 correct out of 209 items. Raw data from the recovery phase included 171 correct out of 221 items for the standard test and 163 correct of 375 items for the CYCLE-N. The correct responses from the recovery phase were averaged according to language production and comprehension, as well as

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Table 3 Median percentage of correct responses for the standard and CYCLE-N tests separately for LH versus RH function.

Test[a]	RH function (LH injection)		LH function (RH injection)			p[b]
	Median		Median		Statistic	
Standard (comprehension and production)	75.2		85.3		175	0.2
	Min.	Max.	Min.	Max.		
	43.7	100	60	100		
Standard comprehension	72.5		84.6		78.5	0.3
	Min.	Max.	Min.	Max.		
	37.5	100	40	100		
Standard production	79.1		79.9		66.5	1
	Min.	Max.	Min.	Max.		
	0	37.5	50	100		
CYCLE-N (comprehension and production)	41.2		72.2		200	0.01
	Min.	Max.	Min.	Max.		
	0	92.8	42.8	92.8		
CYCLE-N comprehension	46.9		67		179.5	0.1
	Min.	Max.	Min.	Max.		
	0	100	37.5	100		
CYCLE-N production	35.5		78.7		205.5	0.006
	Min.	Max.	Min.	Max.		
	0	100	50	100		

[a] Median percentage values of correct responses are presented for all tests.
[b] p-Values reported are from Wilcoxon two-sample test

each language aspect (e.g., repetition, syntax). Finally, we compared the laterality index (LI) calculation of the object naming task alone — as the most commonly used task across epilepsy centers — with the LI of the standard tests and the CYCLE-N. We applied the LI formula $(L-R)/(L+R)$ where 1 reflects complete LH dominance and −1 reflects complete RH dominance.

Statistical analysis

First, language performance with each hemisphere (left versus right) was compared using nonparametric Wilcoxon tests by analyzing the standard and CYCLE-N language trials together. Since our sample size was small ($n=16$), we used median values. We compared accuracy for (a) the standard tests and the CYCLE-N in the recovery phase, (b) language production and language comprehension in the standard test and the CYCLE-N in the recovery phase, and (c) more specific language aspects: from the standard tests in the encoding phase we evaluated object naming, verbal instructions (the only language aspect for which we reported the Fisher's exact test p-value), and from the recovery phase we assessed *yes-no* questions, auditory responsive naming, and repetition. The analyses were conducted to determine which tests better lateralized language functions. We combined syntax and morphology items from the standard tests ($n=3$) and the CYCLE-N test ($n=14$). A significance level of 0.05 was adopted for all inferences.

Results

Ten patients had bilateral injections and six had unilateral injections (one RH and five LH). As shown in Table 3 the CYCLE-N produced more profound language deficits in the injected LH (RH function) compared to the injected RH (LH function) ($p=0.01$). In contrast, the standard tests conducted in the recovery phase did not cause such pronounced differences in performance between the hemispheres ($p=0.3$). Language production in the CYCLE-N significantly lateralized language function to the LH ($p=0.006$), whereas language comprehension did not ($p=0.1$). Neither language production ($p=1$), or comprehension ($p=0.3$) significantly lateralized language function in the standard test carried out in the recovery phase.

As expected, the two initial language tasks presented during the encoding phase significantly lateralized language function to the LH (object naming: $p=0.0002$, verbal instructions: $p=0.004$). We assured that all the participants received the two tasks before they started to recover. Despite that fact that, by definition, all subjects had strong LH laterality based on object naming (all LIs = 1), laterality during the recovery phase differed based on language protocol (Table 4).

Results from individual tasks within the standard and CYLE-N language batteries are summarized in Table 5. Among language tasks presented during the recovery phase (data combined) that significantly lateralized language function to the LH were the *yes-no* question task from the standard tests ($p=0.03$), and syntax production ($p=0.003$), syntax comprehension ($p=0.006$), and morphology production (0.008) from the CYCLE-N.

Discussion

Our study showed that language testing focused on grammar was more effective than a battery of typically assessed language abilities in lateralizing language function in the

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Table 4 Laterality index calculation for the standard and CYCLE-N testing from the recovery phase in 10 patients with bilateral injections who were LH-dominant on the object naming task in the encoding phase (LI = 1).

Order	Standard test					CYCLE-N				
Subject	S10	S5	S3	S9	S15	S4	S12	S13	S14	S16
Laterality index	0	-1	0.1	0	0.3	0	0	0	0.1	0
	1	1	0.6	0	0.2	0.2	0	0.5	0.3	0.8

Table 5 Median percentage of correct responses for language tasks, standard and CYCLE-N together, for LH versus RH function.

Test[a]	Comprehension or production	Wada phase	RH function (LH injection)		LH function (RH injection)		p[b]
Object naming	Production	Encoding	3.6		74.2		0.0002
			Min.	Max.	Min.	Max.	
			0	50	16.6	100	
Verbal instructions[a]	Comprehension	Encoding	28.6		71.4		0.004
Yes-no questions	Comprehension	Recovery	78.3		93.9		0.03
			Min.	Max.	Min.	Max.	
			20	100	33.3	100	
Auditory responsive naming	Comprehension	Recovery	87.2		100		0.1
			Min.	Max.	Min.	Max.	
			50	100	100	100	
Repetition	Production	Recovery	64.7		77.3		0.3
			Min.	Max.	Min.	Max.	
			0	100	50	100	
Syntax	Production	Recovery	25		66.6		0.003
			Min.	Max.	Min.	Max.	
			0	100	40	100	
	Comprehension	Recovery	33.3		75		0.006
			Min.	Max.	Min.	Max.	
			0	100	50	100	
Morphology	Production	Recovery	50		100		0.008
			Min.	Max.	Min.	Max.	
			0	100	0	100	
	Comprehension	Recovery	50		100		0.5
			Min.	Max.	Min.	Max.	
			0	100	50	100	

[a] Median percentage values of correct responses are presented for all tasks except Verbal instructions, for which percentage of subjects scoring all correct are given.
[b] p-Values reported are from Wilcoxon two-sample test except for verbal instructions, where Fisher's exact test p-value is reported.

recovery phase of Wada testing in patients undergoing a resective epilepsy surgery workup. A more detailed analysis of different language aspects from each test showed that syntax (both comprehension and production) and morphology (production) from the CYCLE-N, as well as *yes-no* questions from the standard tests significantly lateralized language function in the recovery phase. Therefore, adding the CYCLE-N to the standard testing provided a more thorough and therefore more accurate prognosis of postoperative deficits.

When we compared the standard test and the CYCLE-N, only the latter test produced significant differences in language performance between the injected hemispheres (see Table 3) following the initial period of speech arrest. LH language function was significantly more impaired than the RH language function in all confirmed LH dominance cases, and the LI calculation for the CYCLE-N matched the object naming LI values closer than the standard test LI values from the recovery phase. This may be indicative of the fact that, overall, the CYCLE-N test targets more left-lateralized linguistic functions than the standard test; thus we suggest this is a more adequate tool to assess language dominance. Our results are consistent with the notion that grammar is more strongly left lateralized than other aspects of language, including lexical semantics and repetition (Menenti et al., 2011, 2012; Wright et al., 2012) and underscore the need to focus on grammar when determining language laterality during the recovery phase of the Wada test.

Language function was significantly lateralized to the LH on the CYCLE-N production test (see Table 3). This result correlates with the object naming task from the encoding phase that also evaluates language production. The object naming task revealed strong LH lateralization in all our subjects. However, we did not see a significant difference on

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language performance between the hemispheres on production tasks in the standard battery, including repetition and auditory responsive naming, suggesting that even within the domain of production, grammatical complexity is more consistently left-lateralized. We also did not observe significant differences for language comprehension stimuli either on the standard test or the CYCLE-N. Menenti et al. (2011) showed that the RH was recruited equally in production and comprehension for semantic processing but not for syntax. However, our results for comprehension of the grammar stimuli (syntax and morphology) were similar after injection to each hemisphere, which may suggest that grammar production might be more left-lateralized and grammar comprehension might be more bilaterally distributed. This explanation would support a claim that production in general is supported by the LH to a greater extent than comprehension (Humphreys and Gennari, 2014; Federmeier, 2007).

Among language tests conducted during the recovery phase, the following language aspects produced statistically significant performance differences between the hemispheres: syntax production, syntax comprehension and morphology production from the CYCLE-N, and the yes-no question task from the standard test. These results are in line with neuroimaging, lesion, and developmental research. Syntax is strongly left-lateralized in most individuals. As an example, successful syntactic performance has consistently been correlated with the intact LH network, in particular, various subregions of the left inferior frontal gyrus (each of which may have its own contribution to different aspects of syntax) and the left posterior superior and middle temporal gyrus (Magnusdottir et al., 2013; Friederici et al., 2011). Morphology is disrupted after damage to the LH perisylvian region (Thompson et al., 2013), which was confirmed by our results for morphology production. However, we did not observe significant differences between the LH and RH for morphology comprehension. A possible explanation here is that two of three morphology comprehension items were presented on cards with only two pictures. Thus our participants had a 50% chance of success for choosing the correct answer. Such a high potential success rate could have distorted our lateralization results. On the other hand, the success rate in the CYCLE-N comprehension items evaluating syntax had a potential success rate of only 25%. Yet even with this rate we still achieved robust differences between the injected hemispheres. Finally, we are limited in power by the number of items and the probability of chance, and given the short window of time, each task or structure could not be studied in sufficient detail. As a consequence, there might be laterality differences that would have proved significant given more items. This possibility is strengthened, we believe, by the fact that in almost all of the clinical and experimental literature to date on both comprehension and production of specific linguistic/grammatical structures, LH dominance is reported, such that even where the RH may play a role in linguistic processing, only the LH is both necessary and sufficient in processing any given grammatical structure.

On the basis of the results obtained here it appears that repetition and auditory responsive naming from the standard test are of little clinical value because they did not lateralize language function. Language performance on the auditory responsive task after injection to each hemisphere was high. Repetition affected each injected hemisphere to a similar extent. According to neuroimaging studies, the task recruits bilateral fronto-parietal networks that enable maintenance and reproduction of verbal sequences (Majerus, 2013). We suggest, therefore, that repetition and auditory responsive naming not be considered crucial tasks in assessing language laterality in the recovery phase.

Our results here show that adding grammar tests to the recovery phase of the Wada tests increased our ability to lateralize language function. Typically, speech arrest and inability to follow instructions during the encoding phase is sufficient to lateralize language. In this study we used only patients with clear LH dominance based on speech arrest. However, patients react differently to amytal, and some become too obtunded to speak or follow directions at this stage of testing making it unclear whether speech arrest is due to a true aphasia, obtundation or anesthetization of brain areas, e.g., ventral pre- and post-central gyri, that are not considered essential or located in close proximity to language regions (Bouchard et al., 2013). In cases like these, it is the recovery phase that is most likely to show linguistic deficits during testing and determine language dominance.

This study, of course, has limitations. First, the number of study participants was relatively low; thus our results should be treated with caution. Second, the major difficulty of this study is the varying recovery speed among patients, a factor that is challenging to control. Randomizing language stimuli presented in the recovery phase helped us solve this issue to some extent, yet including more participants should further validate the data. To ensure we could make a clear comparison with known language dominance, we focused exclusively on patients with unmistakable LH language as determined during the encoding state. This procedure needs to be validated in a mixed population of left, right and mixed dominance cases and in those who become obtunded after injection. Our statistical analysis was complicated by the fact that our two comparison groups were a mixture of repeated measures and independent observations. We decided to use the Wilcoxon rank sum test rather than the Wilcoxon signed rank test in order to not lose any subjects where we did not have both LH and RH injections. Given the small number of subjects who underwent bilateral injections ($n = 10$), we were unable to perform a robust statistical analysis of potential right-left differences between the CYCLE-N and standard tests. Conducting a direct comparison between the two measures will be an important goal in future research. Finally, using only two pictures for our two morphology comprehension stimuli might have distorted our results for this aspect of language because we gave our participants a 50% chance of success in providing a correct answer.

Conclusions

Despite the limitations of our study, we feel that our findings contribute to the understanding of grammar localization in the epileptic population as well as have clinical implications. Ours is the first study to introduce comprehensive grammar assessment to the Wada procedure. These results confirm previous findings from neuroimaging, lesion and

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developmental studies on different clinical populations as well as healthy participants that grammar is strongly left-lateralized. Our results suggest that the standard tests did not significantly differentiate the effects of left versus right hemisphere injections and the grammatical tests, for the most part, did.

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