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CEREBRAL LANGUAGE LATERALIZATION: EVIDENCE FROM INTRACAROTID AMOBARBITAL TESTING

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Abstract—Cerebral language lateralization was investigated in 103 patients undergoing intracarotid amobarbital testing as part of their diagnostic work-up for epilepsy surgery. Inclusion criteria included adequate bilateral intracarotid amobarbital studies and no radiologic lesion in areas other than the temporal lobe. Language was evaluated with respect to strict presence or absence of language representation, in which a patient was considered to have bilateral language despite potentially having asymmetric language representation, and with respect to forced relative hemispheric dominance, in which a single side could be considered dominant despite bilateral language representation. Seventy-nine patients displayed exclusive left hemisphere language representation, two patients showed exclusive right hemisphere language representation, and 22 patients had language represented in each hemisphere. In the 22 patients with bilateral language, an asymmetry was present in 17 cases (13 L > R, 4 R > L). These data indicate that language restricted only to the right hemisphere is rare, and that in the absence of purely left hemisphere language, most patients exhibit bilateral representation. Previously reported incidence of exclusive right hemisphere language may be an artifact of dichotomizing a continuous variable.

INTRODUCTION

The dominance of the left cerebral hemisphere for language function is well established. Although estimates vary, between 92 and 99% of dextral individuals are believed to be left-hemisphere dominant for language [1, 3, 7]. However, the pattern of cerebral language asymmetry is less clear in non-dextral (i.e. left- or mixed-handed) patients. Summarizing the incidence of aphasia with unilateral hemispheric lesions in previous reports, Benson [2] calculated that 60% of dextral patients with damage to the left hemisphere developed aphasia, whereas only 32% of non-dextral patients with left hemispheric damage become language impaired. Similarly, only 2% of dextral patients sustaining injury to the right hemisphere become aphasic. In contrast, 24% of non-dextral patients are aphasic following right hemisphere injury. These data indicate that a sizeable number of non-dextral patients display left-hemisphere language. However, the degree of bilateral language representation cannot be determined based upon unilateral lesions.

The first use of local anesthesia to identify cerebral language areas was described by Gardner [5]. Procaine hydrochloride was injected directly into the cortex thought to potentially subserve language. In contrast to the unilateral method of Gardner, the intracarotid amobarbital procedure, developed by Wada [20] affords the opportunity to assess each hemisphere's contribution to language function independently. In the largest and most commonly cited patient series, Rasmussen and Milner [14] reported that 96% of dextral patients without evidence of early damage to the left hemisphere were left hemisphere dominant for language, with all remaining patients being right hemisphere language dominant. In contrast, language in left- or mixed-handed patients without early injury exhibited less laterality to the left, with only 70% displaying left language dominance. The remaining patients were equally divided between bilateral representation and right cerebral dominance (15% each). Across their entire series of patients without respect to handedness or age of probable brain injury, approximately twice as many patients displayed right hemisphere language (19.7%) as mixed speech dominance (9.6%). These data suggest that if language is not under exclusive left hemisphere control, language is more likely to be under exclusive right hemisphere control compared to bilateral representation by a 2:1 ratio.

Several authors have reported greater bilateral language representation than the Montreal series. Hommes and Panhuysen [8] observed language disturbance following right amobarbital injections in 9/11 depressed patients assessed, although the deficit was much less than that following left hemisphere injections. Oxbury and Oxbury [12] described aphasic errors following both left and right hemisphere injections in 14/23 patients, and right hemisphere speech in only a single patient. Powell *et al.* [13] reported mixed cerebral dominance in 6/27 patients (22%) and right hemisphere speech in only 4 patients (15%). Although Rey *et al.* [16] described greater right than bilateral language representation in their patient sample of 73 [17 (23%) right dominant vs 11 (15%) mixed dominant], 15 patients were presented with a right sided hemiparesis. Patients with right hemiparesis would be expected to have a greater likelihood of exclusive right hemisphere speech given greater left cerebral dysfunction associated with hemiparesis.

In his sample of 61 patients from the Montreal Neurological Institute, most of whom were unilateral temporal lobe epilepsy patients, Zatorre [21] reported only 35 (57%) were left hemisphere dominant for speech, whereas 22 (36%) were considered bilateral and 4 (7%) were right hemisphere speech dominant. These more recent figures from Montreal provide different estimates of language laterality from the original reports suggesting a natural evolution of criteria based upon experience along with minor procedural improvements. Thus, the consensus across multiple centers is that unless there is evidence of significant neurologic dysfunction, mixed language dominance is more frequently observed than right hemisphere language dominance. In an international survey of epilepsy surgery centers, Snyder *et al.* [18] reported that the incidence of bilateral speech varied from 0% (11/47 centers) to 60% (1 center), with bilateral speech between 15–20% in 11 centers. The differences in language bilaterality suggest that patient inclusion criteria, a relatively low base-rate occurrence of mixed- and right-hemisphere language dominance, and variations in language assessment techniques may be contributing to inconsistencies in reported language representation.

In the present study, we describe hemispheric language representation in 103 patients undergoing intracarotid amobarbital evaluation who had adequate bilateral studies. Further, all patients with radiologic evidence of a structural lesion outside of the temporal lobes were excluded. In contrast to previous reports, we explicitly differentiated between patients with bilateral language representation who had greater linguistic impairment following a single injection and those who displayed deficits following a single hemisphere injection on one side only. The former patients may be considered to be language dominant in a single hemisphere using relative language asymmetry as a criterion of dominance, or to have bilateral language representation if the presence of language deficits following unilateral injection is considered.

METHOD

Subjects

We evaluated data from 143 consecutive patients undergoing intracarotid amobarbital evaluation as candidates for epilepsy surgery between January 1985 and June 1989. All patients received standard neurological evaluation, EEG, angiography, CT and/or MR scans, and neuropsychological assessment. From the original patient pool, 40 subjects were excluded due to absence of adequate bilateral intracarotid amobarbital studies, presence of a structural lesion in an area other than the temporal lobe, and/or significant crossflow or abnormal vascular circulation by angiography. Patients with non-temporal lobe lesions were excluded to obtain as homogeneous a sample as possible. Laterality of typical seizure onset was determined by either scalp/sphenoidal or scalp depth recording of ictal EEG (left = 36, right = 39; bilateral or non-localized = 28). One hundred and three patients were included in the study. Handedness was determined on the basis of the Benton Handedness Inventory [4].

Intracarotid amobarbital protocol

Intracarotid amobarbital assessment was conducted with the patient supine immediately following angiography. At the onset of testing, patients held both hands straight up with palms turned rostrally and fingers spread. Patients began counting repeatedly from 1–20. An initial injection of 75–100 mg sodium amytal (5% solution) was administered over a 4 sec interval via catheter placed using a transfemoral approach into the internal carotid artery. Incremental injections of 25–50 mg up to a maximum of 250 mg total were delivered as necessary to produce transient contralateral hemiplegia (mean left intracarotid amobarbital dosage = 123 mg, mean right intracarotid amobarbital dosage = 122 mg). Left and right intracarotid amobarbital evaluations and angiograms were performed on the same day and the order of injection was sequentially alternated. Patients were retested prior to the second injection to ensure return to baseline. Sessions were videotaped for subsequent review.

Language rating

Language rating was based upon performance on four linguistic tasks (*viz.* counting disruption, comprehension, naming, and repetition). The expressive language score (0–4) was based upon disruption of counting ability (0 = normal, slowed, or brief pause ≤ 20 sec; 1 = counting perseveration with normal sequencing; 2 = sequencing errors; 3 = single number or word perseveration; 4 = arrest > 20 sec). Comprehension was assessed by a modified token test in which four geometric shapes of different colors were presented vertically to the subject's ipsilateral visual field. Commands of decreasing complexity were administered: 1. "point to the red circle after the green square", 2. "point to the red circle and then point to the green square", 3. "point to the red triangle". A score of 0 was awarded for completion of the complex two-stage command with inverted syntax, a score of 1 reflected successful simple two-stage command, 2 was scored for the one-stage commands, and 3 if the subject could not perform any commands. Minimal return of receptive language (e.g. "stick out your tongue") was required prior to additional testing. After demonstration of minimal return of receptive language, two real objects were presented and the subject was asked to name them. Following object naming, the patient repeated a nursery rhyme, and the repetition was graded on a 0–3 rating scale. In all four categories, a score of 0 reflected normal function.

Language classification was determined by performance on each of the four language categories assessed, i.e. counting disruption, aural comprehension, naming, and repetition. Because there were considerable differences in reaction to the medication and in duration of the anaesthetic effects, we adopted a conservative classification for language representation. For language impairment to be inferred, as distinct from confusion or abulia, one of two error configurations had to be detected. In the first, impairments (scores > 0) had to be present in at least two categories, with one of the scores greater than 1. In the second pattern, language representation was inferred if at least 3/4 language categories were only mildly impaired (e.g. scores of 1).

Two language classifications were employed. The first considered the presence or absence of linguistic errors using the above criteria following injection of each hemisphere independently. Language impairment following both injections was classified as bilateral language representation regardless of relative asymmetry of language impairment. Language deficits following a single injection only were classified as unilateral cerebral dominance (i.e. exclusive language representation).

The second classification examined forced relative language dominance. In this categorization, language dominance was based upon relative language impairment. A patient who displayed bilateral language impairment, but with a greater deficit following a single injection, was classified as language dominant for the hemisphere with greater linguistic failure. Patients were classified as having bilateral language only when a side of greater representation could not be established. To determine language asymmetry, the sum of language ratings was calculated for each side, and laterality ratios were computed (i.e. $L - R/L + R$). For example, patients with errors following left hemisphere injection *only* received scores of $+1.0$, and patients with errors *only* following right hemisphere injection scores of -1.0. Subjects with laterality ratios greater than 0.15 or less than -0.15 were classified as having either left or right language dominance, whereas patients with laterality scores between 0.15 and -0.15 were classified as bilateral language with no asymmetry. Thus, a patient displaying bilateral but asymmetrical language representation was classified according to the side of greater language disruption (e.g. $L > R$

classified as L). Ratings on the language tasks were based upon consensus from two raters. The intracarotid amobarbital videotape was reviewed, when necessary, to resolve disagreements in language ratings.

Functional cortical mapping

In patients who underwent ablative procedures on a hemisphere in which language representation was present, intraoperative functional mapping of sensorimotor, and frontal and temporal language areas was performed. Stimulation was provided by a Grass constant current generator and a Codman bipolar stimulator with the tip separated approx 4 mm. The stimulus was a 60 Hz, balanced square wave pulse of 0.5–1.0 msec per phase, and 0.5–1.0 msec between phases. Stimulation varied from 1.0–5.0 mA/phase.

The inferior sensorimotor area was mapped initially, and the threshold necessary for physiologic response was established. For mapping of the posterior frontal lobe including Broca's area, patients counted repeatedly from 1–20. Language representation was inferred if there was a reproducible interruption in counting, sequencing was altered, paraphasic substitution occurred, or cadence was disrupted. The behavior change had to be reproducible with repeated stimulation, but it was not necessary to be observed with every stimulation. Temporal lobe mapping was performed while the patients repeatedly recited a nursery rhyme (e.g. "Mary had a little lamb"). Language errors were inferred if there was recitation cessation, change of cadence, paraphasic substitution, and/or sequencing errors. Mapping was conducted on all exposed lateral temporal cortex, usually including cortex of the first, second, and third convolutions and extending as far posteriorly as 8 cm from the temporal tip.

RESULTS

Seventy-nine patients had exclusive left hemisphere language representation, two patients had exclusive right hemisphere language representation, and 22 patients had language represented in each hemisphere. Language was confirmed at the time of surgery with functional cortical mapping in patients undergoing temporal lobe resection in a language hemisphere. Three patterns of language representation were observed in patients with bilateral language representation: 17/22 (77%) displayed asymmetric representation (13 L > R, 4 R > L); no relative dominance was present in the remaining five patients. These data are contrasted with previous intracarotid amobarbital reports with samples sizes greater than 60 in Table 1. Table 2 presents the results of hemispheric language representation as a function of handedness. Eighty per cent of the dextral patients displayed exclusive left hemisphere language; 19% had bilateral language, and one patient had language impairment following right hemisphere injection only. Of the 12 non-dextral patients, 6 had exclusive LH language, 1 had exclusive RH language, and 5 displayed bilateral language. Based upon forced relative language dominance, 91% of the dextral patients were LH dominant, 4% RH dominant, and 4% mixed dominant (one each in the latter two categories). Of the 12 non-dextral patients, 9 were LH dominant, 2 were RH dominant, and 1 mixed cerebral dominant.

Two additional patient groupings were formed, each of which attempted to minimize the effects of early injury on cerebral language lateralization. Eighty patients without evidence of brain injury prior to age two are presented in Table 3. This more restricted grouping did not appreciably alter the reported percentages for dextrals. The remaining non-dextral sample size was insufficient to make any inferences. Subjects with evidence of early injury prior to age 6 were then excluded, and the frequency of language and hand dominance was recomputed. Although this grouping creates even smaller sample sizes, the results are also presented in Table 3 for descriptive purposes.

We compared the frequency of non-dextral patients with left hemisphere language (6/79) to the frequency of non-dextrals with mixed and exclusive right hemisphere language (6/24). The difference in frequency was statistically significant ($\chi^2 = 38.3$, d.f. = 1, $P < 0.0001$). Thus, there was a higher proportion of non-dextrals when language was not exclusively represented in the left hemisphere.

Table 1. Incidence of language dominance in several series of intacarotid amobarbital reports. Note that some values have been recombined from the original articles to facilitate cross comparison across reports. Data are from entire series without respect to age of probable CNS damage or to hand preference

	N	Left	Bilateral	Right
Loring *et al.* (1990)	103			
Exclusive language representation		79 (76.7%)	22 (21.4%)	2 (1.9%)
Forced relative dominance		92 (89.3%)	5 (4.9%)	6 (5.8%)
Rey *et al.* (1988)	73	45 (61.6%)	11 (15.1%)	17 (23.3%)
Rausch and Walsh (1984)	62	53 (85.5%)	4 (6.4%)	5 (8.1%)
Mateer and Dodrill (1983)	90	75 (83.3%)	6 (6.7%)	9 (10.0%)
Strauss and Wada (1983)	78	63 (80.8%)	5 (6.4%)	10 (12.8%)
Rasmussen and Milner (1977)	396	280 (70.7%)	38 (9.6%)	78 (19.7%)
Zatorre (1989)	61	35 (57.4%)	22 (36.1%)	4 (6.5%)

Table 2. Incidence of language representation as a function of handedness without regard to early injury

			Language representation		
	Handedness	N	Left	Bilateral	Right
Exclusive language representation	R	91	73 (80.2%)	17 (18.7%)	1 (1.1%)
	L or Mixed	12	6 (50.0%)	5 (41.7%)	1 (8.3%)
Forced relative dominance	R	91	83 (91.2%)	4 (4.4%)	4 (4.4%)
	L or Mixed	12	9 (75.0%)	1 (8.3%)	2 (16.7%)

DISCUSSION

Our data suggest that the presence of exclusive right hemisphere language dominance, with no left hemisphere language representation, is rare. In our patients without evidence of early injury, a single dextral patient displayed exclusive right hemisphere language representation. Similarly, in our non-dextral group, only one patient displayed exclusive right hemisphere language, and his seizures began at age 3 years suggesting the possibility of early brain injury. Across the entire patient series, 21.4% displayed varying degrees of language impairment following both left and right hemisphere injections, with only 1.9% having language restricted only to the right hemisphere.

We believe the higher incidence of bilateral language in our study may result from assessing several language functions during the evaluation. In addition, by sampling different aspects of language function, our results cannot be attributed solely to sedation effects since we required impairment in multiple language domains to infer language representation. In the present series, we excluded all patients with evidence of early injury as well as patients

Table 3. Incidence of language representation without evidence of early injury as a function of handedness

			Language representation		
No early injury <2 years	Handedness	N	Left	Bilateral	Right
Exclusive language representation	R	77	63 (81.8%)	13 (16.9%)	1 (1.3%)
	L or Mixed	9	6 (66.7%)	2 (22.2%)	1 (11.1%)
Forced relative dominance	R	77	72 (93.5%)	2 (2.6%)	3 (3.9%)
	L or Mixed	9	7 (77.8%)	0 (0.0%)	2 (22.2%)
			Language representation		
No early injury <6 years	Handedness	N	Left	Bilateral	Right
Exclusive language representation	R	66	56 (84.8%)	9 (13.6%)	1 (1.5%)
	L or Mixed	3	1 (33.3%)	2 (66.7%)	0 (0.0%)
Forced relative dominance	R	66	61 (92.4%)	3 (4.5%)	2 (3.0%)
	L or Mixed	3	2 (66.7%)	0 (0.0%)	1 (33.3%)

with radiologic evidence of structural abnormality in areas other than the temporal lobe, thereby creating a more homogeneous sample.

Although the intracarotid amobarbital technique remains primarily validated on patients whose seizures originate from the left cerebral hemisphere, two patients in whom bilateral language representation was suggested by intracarotid amobarbital testing in the present series (1 L>R, 1 R>L) underwent subsequent right temporal lobectomy. During the intracarotid amobarbital procedure, both patients demonstrated disruption of counting/sequencing, impaired comprehension, and/or produced paraphasic errors with right intracarotid amobarbital injection. Functional cortical mapping in these patients revealed a combination of either posterior frontal and/or perisylvian regions that, when stimulated, produced speech arrest or paraphasic substitution during speech recitation. Formal language assessment was conducted during the initial week following surgery on the patient with greater right than left language representation, and significant paraphasic responses were present during assessment of all core linguistic functions (i.e. naming, repetition, generative fluency, comprehension, reading, writing). Thus, we have converging behavioral evidence of right hemisphere language representation in this patient [9]. In addition, speech representation was observed during cortical mapping of all exclusive left hemisphere and mixed cerebral language dominant patients in whom left temporal lobectomy was performed.

The importance of multiple language measures during intracarotid amobarbital assessment is illustrated by one patient who displayed speech arrest lasting approx 25 sec following right hemisphere injection. Despite this apparent speech arrest, all remaining language functions were normal. Because we were uncertain whether speech cessation reflected language, functional cortical mapping for language was carried out prior to right temporal lobectomy. Despite sufficient threshold for sensorimotor mapping, no language impairment was present during electrical stimulation of either frontal or temporal regions. Further, no impairments were present during language testing conduced during the first post-operative week. These data support our decision to require impairment in multiple language categories prior to inferring language representation. Other authors [12] have similarly noted that patients occasionally will develop speech arrest following injection of the non-language-dominant hemisphere.

Our data agree with that of others suggesting that left- and mixed-hand preference is a marker of mixed cerebral dominance [2]. Among non-dextral patients, right-hemisphere language has been estimated as high as 40% [17]. GLONING [6] examined the incidence of aphasia in patients with structural lesions who eventually came to autopsy. Eighty per cent of the dextral patients with left hemisphere lesions were aphasic, whereas no dextral patients with right hemisphere lesions displayed impaired language function. In contrast, the presence of aphasia was approx 80% in non-dextral patients regardless of hemispheric involvement side. These data suggest significant language bilaterality in non-dextral patients. Bilaterality of language is also suggested by reports of more complete recovery from aphasia in non-dextral individuals than dextral patients [10]. In the present patient series, the proportion of non-dextrals was significantly higher in the mixed and right hemisphere language dominant patients than in the exclusive left hemisphere language representation group.

A continuum from left hemisphere language dominance to right hemisphere language dominance should be expected on the basis of the handedness literature. Patients are frequently rated in their degree of handedness, ranging from strongly dextral, moderately dextral, mixed, to moderately sinistral and strongly sinistral. To the degree that there is a relationship between handedness and cerebral language dominance, one should expect similar degrees of mixed dominance. That is, one should *not* expect language laterality to be primarily discrete when handedness is a continuous variable. Consequently, the previously reported incidence of right hemisphere language dominance likely reflects dichotomizing a continuous variable. Results of the present study suggest that when language functioning is not solely under left hemisphere control for whatever reasons (i.e. handedness and/or early injury), some degree of bilateral language representation can be expected.

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