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Effect of Wada Memory Stimulus Type in Discriminating Lateralized Temporal Lobe Impairment

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Summary: *Purpose:* To examine the effects of memory stimulus type on Wada memory performance.
Method: Ninety-six patients (left, 47; right, 49) from four epilepsy centers who were candidates for anterior temporal lobectomy (ATL) and who have subsequently undergone surgery were studied. Patients with atypical cerebral language lateralization or with evidence on magnetic resonance imaging (MRI) to suggest a lesion other than hippocampal sclerosis were excluded. Wada memory performance was obtained by using both real objects and line drawings as memory stimuli.
Results: Wada memory laterality scores with either real objects or line drawings as memory stimuli discriminated left from right-ATL groups. However, objects were superior to line drawings in making this differentiation. Further, objects were superior to line drawings in individual patient classification of candidates for left ATL, with no difference in the classification rates using either objects or line drawings in candidates for right ATL.
Conclusions: Type of memory stimuli is an important factor affecting memory results during the Wada test. **Key Words:** Wada test—Amobarbital—Temporal lobectomy—Epilepsy—Memory.

The Wada test is a standard component of the presurgical evaluation for anterior temporal lobectomy (ATL) (1). It was initially developed to determine cerebral language representation (2) but was soon modified to include assessment of memory function (3). Wada memory testing provides a reversible technique for modeling the potential effects of surgery on recent memory. Amobarbital is injected into the internal carotid artery, and patients are then presented with a variety of stimulus items during hemispheric anesthesia. If a patient fails to remember material presented after injection ipsilateral to the proposed surgery after the medication effects have worn off, the patient may be considered at risk for postsurgical amnesia. Depending on the specific surgical protocol used, patients performing poorly on Wada memory testing may undergo either repeated Wada testing or a selective posterior cerebral artery Wada test. If poor memory performance is obtained again, the patient may be denied surgery or may undergo a limited resection in which the hippocampus is spared. Wada memory asymmetries provide evidence of lateralized temporal lobe dysfunction and serve a complementary role to EEG and radiologic data in the preoperative evaluation for ATL (4,5) and may help to decrease the need for invasive EEG monitoring (i.e., depth or subdural electrodes).

The ability of Wada memory asymmetries to predict lateralized temporal lobe dysfunction has been variable among epilepsy surgery centers; consequently, some centers rely heavily on these data, whereas others treat these data as secondary in the preoperative surgical evaluation (6). Because the Wada test is not standardized and protocols differ in important ways, including type of material presented for memory testing, determining to what degree method variance is contributing to the differences in the reported results is difficult. Our approach to Wada memory testing developed at the Medical College of Georgia has relied on the presentation of real objects (as opposed to line drawings) for memory testing. Performance asymmetries by using objects have been related to hippocampal volume asymmetries (7), seizure-onset laterality (4,5), postoperative verbal memory decline (8), and the likelihood of being seizure free after

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ATL (9). However, other protocols that do not rely exclusively on real objects as stimulus items are similarly related to structure, function, and outcome (10–12).

This is a collaborative multicenter study designed to examine procedural effects of stimulus type on Wada memory results. If these procedural differences have no effects, then a standardized approach to Wada memory assessment across centers may be unnecessary to produce equivalent results. More practically, real-object memory stimuli could be replaced with less cumbersome and easier to manage line drawings. In this study, we compared the ability of real objects with line drawings to discriminate lateralized temporal lobe dysfunction in ATL candidates. We hypothesized that real-object recognition would be superior to recognition of line drawings, given the greater stimulus salience associated with objects.

METHOD

Subjects

Ninety-six patients undergoing preoperative evaluation for ATL served as subjects (L, 47; R, 49). Patients were studied at the Medical College of Georgia (MCG; n = 47), University of Tennessee/Baptist Memorial Hospital in Memphis (BMH; n = 21), New York University/Hospital for Joint Diseases (HJD-NYU; n = 16), and the University of Texas Medical School at Houston (UTMS; n = 12). Patients were excluded if they were not left cerebral language dominant or if they had evidence to suggest a structural lesion other than hippocampal sclerosis on magnetic resonance imaging (MRI). Equivalent numbers of left/right seizure onset and of each sex were included (seizure laterality: MCG: L, 23, R, 24; BMH: L, 9, R, 12; HJD-NYU: L, 9, R, 12; UTMS: L, 6, R, 6; Sex: MCG: M, 21, F, 26; BMH: M, 9, F, 12; HJD-NYU: M, 8, F, 8; UTMS: M, 5, F, 7). All patients have subsequently undergone ATL at their institutions.

Wada protocol

Slight institutional differences existed in the protocol for drug administration. At all centers, amobarbital was administered after a transfemoral approach into the internal carotid artery. The goal was to administer a 100-mg injection, although this was occasionally adjusted because of low body weight. Incremental injections were administered at two institutions if marked hemiparesis was not induced. The average left hemisphere dose was 101.7 mg (SD = 11.0) and the mean right hemisphere dose was 102.0 mg (SD = 10.6).

At NYU-HJD, amobarbital was delivered by machine (1 ml/s). The remaining centers delivered the amobarbital by hand over a 4- to 5-s interval. The side of the suspected seizure focus was injected first at the BMH and NYU-HJD. At the MCG, the order of amobarbital administration was sequentially alternated across subjects. The UTMS used both approaches, with some patients tested first on the side ipsilateral to the presumed seizure focus and others tested with the order determined randomly. All centers performed both left and right evaluations on the same day with a minimum of 30 min separating the two studies.

Memory presentation

After assessment of eye-gaze deviation and simple comprehension, which took ~30–45 s, four common objects were presented during the period of unilateral hemiplegia. Objects were presented in the central visual field and in the visual field ipsilateral to the injection for ~4–8 s each, and the names of the objects were repeated twice to the patient. The objects included a combination of ordinary household items (e.g., fork), small toys (e.g., troll doll), and plastic food (e.g., pizza). At times, because of patient confusion, inattention, or nonresponsiveness, holding the patient's eyes open was necessary. Four black-and-white line drawings (e.g., cat, key) were then presented in the same fashion as the objects, followed by presentation of four additional objects. This consistent order of stimulus presentation was chosen to minimize deviation from the clinical Wada protocol that has been previously validated (4,7).

Wada memory assessment

Memory was assessed after return to baseline as demonstrated by 5/5 strength, normal language, and absence of pronator drift and asterixis. A minimum of 10 min after amobarbital injection also was required before memory testing. Object recall was tested by using a recognition format, with the eight objects interspersed with 16 foils. Objects were presented in a randomized sequence, and patients indicated whether each object had been presented earlier during the test. If a patient was unsure if an item had been presented, forced-choice recognition was obtained. Line-drawing recognition was assessed similarly, with four targets randomly interspersed with eight foils. However, the line-drawing presentation order did not differ across patients. For the primary analyses, a correction of half the number of false-positive responses was subtracted from the number of stimuli correctly recognized for both real objects and line drawings to correct for possible response bias and guessing.

RESULTS

Wada asymmetry scores/corrected data

Interhemispheric Wada memory asymmetry scores (i.e., left injection − right injection) derived from corrected memory performances were computed separately for both objects and line drawings; positive scores represent left temporal lobe dysfunction, and negative scores suggest right temporal lobe impairment. Both object and line-drawing performances were transformed into percentages to facilitate comparison of stimulus types.

The mean object asymmetry score for left ATL was +20% (SD = 0.37) and for right ATL was −48% (SD = 0.35). The mean line-drawing asymmetry score for left ATL was +2% (SD = .50) and for right ATL was −43% (SD = 0.36). Left–right asymmetry scores were subjected to a two-way mixed-design analysis of variance (ANOVA), with seizure focus (left vs. right) as the between-subject factor and stimulus type (object vs. line drawing) as the within-subject factor. A statistically significant seizure focus-by-stimulus type interaction was obtained ($F_{1,\ 94} = 12.4$; $p < 0.0007$). A significant main effect of seizure focus ($F_{1,\ 94} = 58.9$; $p < 0.00001$) was present with a trend for stimulus type ($F_{1,\ 94} = 3.7$; $p < 0.06$).

Simple main-effect analysis of seizure focus showed that left- and right-ATL asymmetry scores differed significantly when scores were based either on objects ($F_{1,\ 94} = 87.8$; $p < 0.00001$) or when they were based on line drawings ($F_{1,\ 94} = 25.38$; $p < 0.00001$). However, the greater effect size for objects as reflected in the magnitude of the *F* statistic suggests greater sensitivity of objects to memory asymmetry differences between groups.

The greater sensitivity of objects to right-ATL versus left-ATL differences is the result of a disparity of object and line-drawing asymmetry scores in the left-ATL group. Simple main-effect analyses of stimulus type showed that object and line-drawing asymmetry scores were similar in the right-ATL group ($F_{1,\ 48} = 1.6$; $p = 0.2$) but differed significantly in the left-ATL group ($F_{1,\ 47} = 11.95$; $p < 0.001$).

Single-injection performances

Memory performances after left- and right-hemisphere injection are presented in Table 1. These data were analyzed by using 2 (seizure focus: left vs. right) by 2 (hemisphere injected: left vs. right) ANOVAs. A significant effect for hemisphere injected was present for object memory ($F_{1,\ 94} = 14.6$; $p < 0.0002$) in addition to a significant seizure focus–by–hemisphere injected interaction ($F_{1,\ 94} = 87.7$; $p < 0.00001$). For line-drawing recognition, both the hemisphere injected ($F_{1,\ 94} = 21.7$; $p < 0.00001$) and the focus-by-hemisphere injected interaction ($F_{1,\ 94} = 25.2$; $p < 0.00001$) were also significant. However, the magnitude of the focus-by-hemisphere interaction, as reflected by the *F* statistics, is much greater for objects than with line drawings.

Simple main-effect analyses revealed significant ipsilateral versus contralateral performance differences on object memory in both left ATL ($F_{1,\ 46} = 14.5$; $p < 0.0004$) and in right ATL ($F_{1,\ 47} = 92.4$; $p < 0.00001$). Although ipsilateral versus contralateral line-drawing performance differences were present in patients with right ATL ($F_{1,\ 47} = 72.0$; $p < 0.00001$), equivalent ipsilateral versus contralateral performance was present in patients with left ATL ($F_{1,\ 46} = 0.05$; $p = 0.8$). This indicates that the failure of line-drawing memory asymmetries to be a sensitive measure of left temporal lobe impairment in patients with left ATL results from the absence of a differential ipsilateral versus contralateral performance difference.

TABLE 1. *Mean corrected Wada memory performances (standard deviations) after unilateral hemispheric injection (n = 96)*

	Left ATL (%)	Right ATL (%)
Objects		
Left injection	66 (0.27)	27 (0.29)
Right injection	46 (0.37)	75 (0.27)
Line drawings		
Left injection	34 (0.38)	13 (0.23)
Right injection	32 (0.38)	56 (0.33)

ATL, anterior temporal lobectomy.

Stimulus-timing effects

Because the line drawings were always presented between two sets of objects, possible differential drug effects on task performance as a function of time creates a potential confound. To explore stimulus-timing effects, we performed secondary analyses on the subset of patients for whom separate performance for the first and second object sets was available. All patients in this subsample were from MCG because it was the only center to record performance for the first four and second four object sets separately.

Because the two object sets were not associated with unique sets of foils (i.e., a single object-recognition assessment was performed with eight target items and 24 foils), corrected scores could not be calculated for the first and second object sets independently. Consequently, we analyzed uncorrected memory scores. However, we first performed group analyses to ensure that we would not introduce systematic error into our results by employing uncorrected data.

The mean uncorrected object-difference score for left ATL was +24% (SD = 0.43) and for right ATL was −43% (SD = 0.34). The mean line-drawing difference score for left ATL was +2% (SD = 0.54) and for right ATL was −42% (SD = 0.39). Uncorrected left–right difference scores were subjected to separate repeated measure ANOVAs for both object and line-drawing stimuli. A significant difference for stimulus type was present in left-ATL candidates ($F_{1,22} = 6.2$; $p < 0.02$). Stimulus type did not differ in right-ATL candidates ($F_{1,\ 23} = 0.2$; $p < 0.9$). Similar corrected and uncorrected mean performances with the same statistical results show comparable results by using either corrected or uncorrected data.

Mean uncorrected memory performances are pre-

TABLE 2. *Mean uncorrected Wada memory performances (standard deviations) after unilateral hemispheric injection (patient subsample, n = 47)*

	Left ATL (%)	Right ATL (%)
Left injection		
1st objects	63 (0.33)	23 (0.31)
Line drawings	29 (0.36)	9 (0.15)
2nd objects	69 (0.32)	31 (0.31)
Right injection		
1st objects	44 (0.41)	68 (0.29)
Line drawings	26 (0.34)	47 (0.39)
2nd objects	43 (0.42)	72 (0.31)

ATL, anterior temporal lobectomy.

sented in Table 2. Pairwise analyses comparing line-drawing recognition with recognition memory of either the first or second object set and comparing memory for first object series with that of the second object set yielded the same pattern of results for all four conditions (left and right hemisphere injection in both left- and right-ATL candidates; $\leq p < 0.05$). Line-drawing recognition was significantly poorer than object recognition for either the first or second object set. In contrast, recognition of the first object series did not differ from that of the second object series. Because the first set of objects was always presented before the line drawings, when amobarbital effects would be greater, and because recognition performance of the first object set was superior to line-drawing recognition, fixed-order effects alone cannot be the sole explanation of superior memory performance with objects.

Individual patient classification

Chi-square analysis

Patient-classification rates for the entire patient sample were examined based on frequency of correct lateralization by using Wada memory-asymmetry scores. A patient was considered to have lateralized Wada memory asymmetries if an interhemispheric asymmetry score (ipsilateral − contralateral) of ≥25% was present (Tables 3 and 4). The classification rates for left and right ATL were compared for each stimulus set independently. For both object (χ^2 = 9.6, *df* = 2; p = 0.008) and line-drawing stimuli (χ^2 = 17.4, *df* = 2; p = 0.0002), there was a significant difference in classification rates for candidates for left and right ATL. This indicates a greater correct classification rate for candidates for right ATL, regardless of whether object or line-drawing stimuli are used. However, the size of this difference for left versus right classification, as reflected in the size of the χ^2 statistic, is greater for line-drawing stimuli. This shows a greater left-ATL versus right-ATL discrepancy when using line-drawing stimuli to classify patients.

TABLE 3. *Classification rates with object memory asymmetry scores of at least 25%*

	Correct	Indeterminate	Incorrect
L ATL (n = 47)	21 (45%)	21 (45%)	5 (11%)
R ATL (n = 49)	37 (76%)	10 (20%)	2 (4%)
Total (n = 96)	58 (60%)	31 (32%)	7 (7%)

Percentages reflect row totals, and do not always sum to 100% because of rounding.
ATL, anterior temporal lobectomy; R, right; L, left.

TABLE 4. *Classification rates with line drawing memory asymmetry scores of at least 25% (n = 96)*

	Correct	Indeterminate	Incorrect
L ATL (n = 47)	17 (36%)	14 (30%)	16 (34%)
R ATL (n = 49)	37 (76%)	9 (18%)	3 (6%)
Total (n = 96)	54 (56%)	23 (24%)	19 (20%)

Percentages reflect row totals.
ATL, anterior temporal lobectomy; L, left; R, right.

As with the parametric analysis, type of stimulus material was compared for candidates for left and right ATL independently. A significantly different classification rate for the objects versus line drawings was present in the candidates for left ATL (χ^2 = 7.6, *df* = 2; p = 0.02, with poorer classification by using line drawings. In contrast, no significant classification-rate difference by using objects or line drawings was present in candidates for right ATL (χ^2 = 0.3, *df* = 2; p = 0.9).

Receiver operating characteristic curves

Receiver operating characteristic (ROC) curves were used to evaluate patient classification for both object (Fig. 1) and line-drawing asymmetries (Fig. 2). ROC analyses characterize diagnostic test efficacy by using empirically derived values rather than a priori asymmetry scores (i.e., 25%) for classification (13). Each patient-

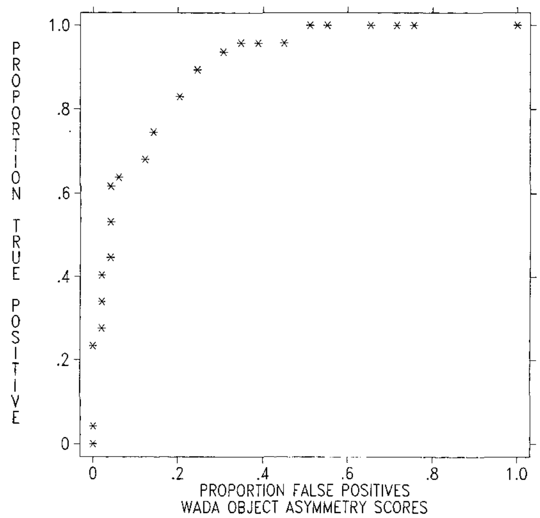

FIG. 1. Receiver operating characteristic (ROC) curve for real object Wada asymmetry scores. Each plotted point represents a specific cut-point present in the sample. Because multiple patients may have obtained the same Wada asymmetry scores, the number of points plotted is less than the total sample size of 96.

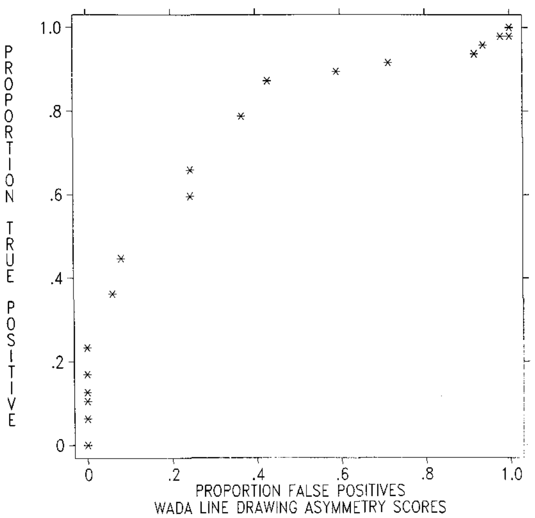

FIG. 2. Receiver operating characteristic (ROC) curve for line drawing Wada asymmetry scores.

asymmetry score is treated as a separate cutoff score, and the numbers of candidates for left and right ATL correctly classified with that asymmetry score are calculated. The proportion of correct classifications (true positive) is plotted against the proportion of incorrect classifications (false positives) to obtain an ROC curve. The area under the ROC curve provides a quantitative metric with which to compare classification rates. In our sample, the area under the curve for object asymmetries is 0.91, and the area under the curve for drawing asymmetries is 0.77.

DISCUSSION

Our report illustrates the superiority of using real objects to line drawings as stimuli for the Wada procedure in reflecting lateralized temporal lobe impairment. This superiority is seen regardless of whether group or individual classification data are analyzed and derives primarily from a greater tendency for candidates for left ATL to recognize objects after left-hemisphere injection. Further, line-drawing asymmetries incorrectly lateralized temporal lobe impairment in candidates for left ATL at 2.7 times the frequency compared with asymmetries based on object recognition. Real objects and line drawings were equivalent in candidates for right ATL for both group performance and patient-classification accuracy.

The object and line-drawing stimulus sets differed in number (eight objects vs. four line drawings), and we used a fixed sequence of stimulus-type presentation (object/line drawing/object). This approach to stimulus presentation was used to minimize deviation from the clinical Wada protocol by initiating the Wada object presentation at the same time after injection as with our previously validated procedure and to allow adequate time for language assessment. However, this method also introduces several potential limitations.

A smaller number of memory items will decrease the likelihood of obtaining Wada asymmetries simply because the scores will be less reliable performance measures. For individual patient classification, this will result in a higher number of patients being classified as indeterminate. However, because patients were more likely to be incorrectly classified rather than classified as indeterminate by using line drawings as compared with objects, set-size differences cannot account for our findings.

Examination of order effects suggests that timing of stimulus presentation also cannot account for these results. Decomposing the object sets into separate groups of four stimuli and repeating the analyses shows poorer performance on line-drawing recognition than either the first or second object series in candidates for left ATL after left-hemisphere injection. Performance on the first four objects was superior to performance on the line drawings in all conditions despite being presented earlier in the sequence when greater anesthetic effects would be expected more greatly to interfere with memory acquisition.

Although the line drawings were presented in the middle third of the presentation, superior object performance is not the result of primacy and recency effects, in which the initial and ending portions of a learning trial are more easily recalled. The terms *primacy* and *recency* are derived relative to when the memory assessment is performed relative to the acquisition trials (14). Because memory testing was performed $\geq$10 min after injection and ~7 min after memory items presentation, this differentiation is not applicable to our stimulus sets. Further, primacy and recency effects have been described only for free recall rather than for recognition memory tasks, which we used for our Wada memory task.

Line drawings compose part of the Wada memory stimuli employed in other Wada protocols. Because many centers classify successful performance as recognition of $\geq$67% of the stimuli present, our line-drawings score after ipsilateral injection may appear disproportionately low (i.e., L injection = 34%; right injection = 56%). However, the duration of stimulus presentation also differs. For example, in one recent report of using line drawings (15), stimuli were presented for 10–15 s each, which is approximately twice as long as the duration of our stimulus presentation (4–8 s each). In other approaches, the memory stimuli are not presented until several minutes into the procedure (16).

We used a 25%-asymmetry criterion to infer lateralized asymmetry for consistency with previous reports. Any fixed criterion can be criticized as being arbitrary, with concern raised that different results could potentially be observed if different cut-points were used. However, similar results were obtained with ROC analysis, which classifies patients empirically based on cumulative percentages by using all cut-points. Thus classification differences between stimulus types cannot be attributed to our decision to use a 25%-asymmetry criterion.

Responses to quasi-random strobe-light flashes are more greatly impaired after left intracarotid injection, suggesting a greater disruptive effect of left hemisphere injection on certain types of attention (17). With our data, we believe that the differential effect of stimulus type may be attributed to this greater disruptive effect of left hemisphere injection on attention. Real objects are easier to see and encode than are line drawings, which may be an important factor given the acute disruptive amobarbital effects on normal brain function. Further, the line drawings are black and white in two dimensions only, decreasing the likelihood of encoding by multiple-stimulus attributes. Real objects have been shown to be recognized better than either words or designs and to be equivalent between hemispheres (18). Because a material-specific memory asymmetry was present, with greater impairment of words after left-hemipshere injection and greater impairment of designs after right-hemisphere injection, the absence of a left/right difference for objects suggests that objects are dually encoded. In our study, comparison of left ipsilateral injection in left ATL with right ipsilateral injection in right ATL yields a difference of only 9% for object memory. This same comparison for line drawings is 22%, further indicating greater disruptive effects after left-hemisphere injection on line-drawing memory performance. Because line drawings were more difficult to recognize than the objects (see Table 2), nonspecific attentional effects would be expected more adversely to affect line-drawing recognition.

We conclude that differences in stimulus type contribute to differences in the reported utility of Wada memory performance in the preoperative evaluation for ATL. Thus what appears to be minor variation in protocols may have significant effects on Wada results. The presence of incorrect lateralization has the potential for a more negative impact on patient management than does failing to demonstrate an asymmetry (i.e., indeterminate classification) because strongly discordant data may prompt more invasive monitoring before surgery, restrict the size of the resection, or even be the cause of denying surgery at some centers. These results also highlight that what is called Wada testing consists of many different approaches to assessment that vary in their methodologic characteristics. This procedural heterogeneity will affect Wada test results, which will increase the likelihood of nonreplication and lack of consensus among centers and has the potential to affect patient care adversely.

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