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

Accepted September 13, 1996.
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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 = 0.34) and for right ATL was −43% (SD = 0.36). Left–right asymmetry scores were sub-
jected to a two-way mixed-design analysis of variance
(ANOVA), with seizure focus (left vs. right) as the be-
tween-subject factor and stimulus type (object vs. line
drawing) as the within-subject factor. A statistically sig-
nificant seizure focus–by-stimulus type interaction was
obtained (F1, 94 = 12.4; p < 0.0007). A significant main
effect of seizure focus (F1, 94 = 58.9; p < 0.000001) was
present with a trend for stimulus type (F1, 94 = 3.7; p < 0.06).

Simple main-effect analysis of seizure focus showed that left- and right-ATL asymmetry scores differed sig-
nificantly when scores were based either on objects (F1,
94 = 87.8; p < 0.000001) or when they were based on line
drawings (F1, 94 = 25.38; p < 0.000001). However, the
greater effect size for objects as reflected in the magni-
tude of the F statistic suggests greater sensitivity of ob-
jects 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 (F1, 48 = 1.6; p = 0.2) but differed significantly in the left-ATL group (F1,
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 ana-
lyzed by using 2 (seizure focus: left vs. right) by 2 (hem-
sphere injected: left vs. right) ANOVAs. A significant
effect for hemisphere injected was present for object
memory (F1, 94 = 14.6; p < 0.0002) in addition to a sig-
nificant seizure focus–by–hemisphere injected inter-
action (F1, 94 = 87.7; p < 0.000001). For line-drawing
recognition, both the hemisphere injected (F1, 94 = 21.7;
p < 0.000001) and the focus-by-hemisphere injected in-
teraction (F1, 94 = 25.2; p < 0.000001) were also sig-
nificant. 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 ipsi-
lateral versus contralateral performance differences on
object memory in both left ATL (F1, 46 = 14.5; p < 0.0004) and in right ATL (F1, 47 = 92.4; p < 0.000001).
Although ipsilateral versus contralateral line-drawing
performance differences were present in patients with
right ATL (F1, 47 = 72.0; p < 0.000001), equivalent ip-
silateral versus contralateral performance was present
in patients with left ATL (F1, 46 = 0.05; p = 0.8). This
indicates that the failure of line-drawing memory asym-
metries 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.

**Stimulus-timing effects**

Because the line drawings were always presented be-
tween two sets of objects, possible differential drug ef-
fects 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 pa-
tients for whom separate performance for the first and
second object sets was available. All patients in this sub-
sample 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 as-
essment 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 em-
ploying 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 (F1,22 = 6.2; p < 0.02).
Stimulus type did not differ in right-ATL candidates (F1,
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 uncor-
rected data.

Mean uncorrected memory performances are pre-

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

<table>
<thead>
<tr>
<th></th>
<th>Left ATL (%)</th>
<th>Right ATL (%)</th>
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</thead>
<tbody>
<tr>
<td><strong>Objects</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left injection</td>
<td>66 (0.27)</td>
<td>27 (0.29)</td>
</tr>
<tr>
<td>Right injection</td>
<td>46 (0.37)</td>
<td>75 (0.27)</td>
</tr>
<tr>
<td><strong>Line drawings</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left injection</td>
<td>34 (0.38)</td>
<td>13 (0.23)</td>
</tr>
<tr>
<td>Right injection</td>
<td>32 (0.38)</td>
<td>56 (0.33)</td>
</tr>
</tbody>
</table>

ATL, anterior temporal lobectomy.
sent in Table 2. Pairwise analyses comparing line-drawing recognition with recognition memory of either the first or second object set and comparing memory for the first or second object set and comparing memory for drawing recognition with recognition memory of either presented in Table 2. Pairwise analyses comparing line-
yielded the same pattern of results for all four conditions.
right-ATL candidates; Gp
jectons was always presented before the line drawings,
ition was significantly poorer than object recognition
(right hemisphere injection in both left- and
recognition performance of the first object set was supe-
of the second object series. Because the first set of ob-
ior to line-drawing recognition, fixed-order effects alone
cannot be the sole explanation of superior memory per-
formance 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 (χ² = 9.6, df = 2; p = 0.008) and line-drawing stimuli (χ² = 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 χ² 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.

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 (χ² = 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 (χ² = 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-

![Figure 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.](image-url)
asymmetry score is treated as a separate cutoff score, and
the numbers of candidates for left and right ATL cor-
correctly classified with that asymmetry score are calcu-
lated. The proportion of correct classifications (true posi-
tive) is plotted against the proportion of incorrect clas-
sifications (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 asym-
metries is 0.77.

DISCUSSION

Our report illustrates the superiority of using real ob-
jects to line drawings as stimuli for the Wada procedure
in reflecting lateralized temporal lobe impairment. This
superiority is seen regardless of whether group or indi-
vidual classification data are analyzed and derives pri-
marily 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 draw-
ings 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 (ob-
ject/line drawing/object). This approach to stimulus pre-
sentation was used to minimize deviation from the clini-
cal Wada protocol by initiating the Wada object presen-
tation 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 be-
cause the scores will be less reliable performance mea-
sures. For individual patient classification, this will result
in a higher number of patients being classified as inde-
terminate. However, because patients were more likely
to be incorrectly classified rather than classified as inde-
terminate by using line drawings as compared with ob-
jects, set-size differences cannot account for our find-
ings.

Examination of order effects suggests that timing of
stimulus presentation also cannot account for these re-
sults. Decomposing the order effects suggests that timing of
stimulus 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
time for language assessment. However, this method also
several minutes into the procedure (16).

Although the line drawings were presented in the
middle third of the presentation, superior object perfor-
many centers classify successful performance as recog-
nition of ≥67% of the stimuli present, our line-drawings
score after ipsilateral injection may appear dispropor-
tionately 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 dura-
tion 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 lateral-
ized asymmetry for consistency with previous reports.
Any fixed criterion can be criticized as being arbitrary,
with concern raised that different results could poten-
tially be observed if different cut-points were used. How-

ever, 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 design and to be equivalent between hemispheres (18). Because a material-specific memory asymmetry was present, with greater impairment of words after left-hemisphere 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.

REFERENCES