Epilepsia Open® The Open Access Journal of the International League Against Epilepsy

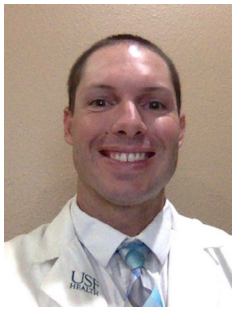
Open Access

FULL-LENGTH ORIGINAL RESEARCH

Wada asymmetry in patients with drug-resistant mesial temporal lobe epilepsy: Implications for postoperative neuropsychological outcomes

*†Ryan W. Sever, *Andrew C. Vivas, *Fernando L. Vale , and *‡Mike R. Schoenberg

Epilepsia Open, 3(3):399–408, 2018
doi: 10.1002/epi4.12250



Ryan W. Sever is a research coordinator with the University of South Florida, Department of Neurosurgery.

Summary

Objective: This study reports neuropsychological outcomes based on preoperative Wada testing in patients with drug-resistant mesial temporal lobe epilepsy (mTLE).

Methods: Patient records were retrospectively reviewed as part of a larger database. Patients with a diagnosis of TLE based on seizure semiology and long-term surface video–electroencephalography (EEG) were identified. These patients underwent preoperative and postoperative testing including advanced imaging (magnetic resonance imaging [MRI]), Wada testing, and neuropsychological assessment. Decrements in neuropsychological function were noted in comparison of pre- and postoperative studies. Patients had regular follow-up in the multidisciplinary epilepsy clinic to assess seizure outcomes. All participants had Engel class I/II outcome following selective amygdalohippocampectomy (AH) via the inferior temporal gyrus (ITG) approach.

Results: Forty-eight patients with electrographic and clinical semiology consistent with unilateral mTLE were identified. Left mTLE was identified in 28 patients (58.3%), whereas 20 patients (41.7%) had right mTLE. Language-dominant hemisphere resections were performed on 23 patients (47.9%) (all left-sided surgery), whereas 25 (52.1%) had language nondominant resection (all right-sided and five left-sided surgery). Twenty-two participants (45.8%) showed no Wada memory asymmetry (No-WMA), whereas 26 (54.2%) exhibited Wada memory asymmetry (WMA). Postoperatively, analysis of variance (ANOVA) found that the No-WMA group exhibited a decline in verbal memory, but average scores on measures of nonverbal reasoning, general intelligence, and mood improved. Alternatively, patients with WMA did not show declines in memory postoperatively, and also exhibited improved nonverbal reasoning and general intelligence. Neither group exhibited reliable decline in verbal fluency or visual confrontation naming.

Significance: Wada procedures for predicting surgical outcome from elective temporal surgery have been criticized and remain an area of active debate. However, decades of data across multiple epilepsy centers have demonstrated the value of Wada for reducing unanticipated neuropsychological adverse effects of surgical treatment. These data show that no Wada memory asymmetry increases the risk for neuropsychological decline following ITG approach for selective AH for drug-resistant mTLE.

KEY WORDS: Wada, Asymmetry, Neuropsychological outcomes, Inferior temporal gyrus.

Accepted June 20, 2018.

*Department of Neurosurgery and Brain Repair, Morsani College of Medicine, University of South Florida, Tampa, Florida, U.S.A.; †Florida School of Professional Psychology, Argosy University, Tampa, Florida, U.S.A.; and ‡Department of Neurology, Morsani College of Medicine, University of South Florida, Tampa, Florida, U.S.A.

Address correspondence to Mike R. Schoenberg, Department of Neurosurgery and Brain Repair, University of South Florida, Tampa, FL, U.S.A. E-mail: mschoenb@health.usf.edu

Key Points

- Participants with Wada memory asymmetry did not exhibit a significant decline in memory or language function in neuropsychological tests
- Patients with no Wada memory asymmetry showed a great decline in verbal memory
- Decline in verbal memory in patients with no Wada asymmetry was found only in patients who underwent dominant-side resection

Surgery for drug-resistant epilepsy (DRE) entails a risk of neuropsychological decline. The intracarotid methohexital procedure (Wada test) was developed to determine hemispheric language lateralization preoperatively and to reduce the potential for language loss after surgery. A memory assessment was added later to explore memory capacity and laterality. The Wada procedure has long been considered the gold standard for the preoperative assessment of language and memory.[1] Despite this, there remains debate regarding the utility of the Wada procedure to predict outcome from elective epilepsy surgery.[2,3] Recently, functional magnetic resonance imaging (fMRI) has gained acceptance as a noninvasive means for evaluating for lateralization of language and memory. However, the specificity for predicting memory outcome remains variable and differs across fMRI procedures used and centers.[4] Specifically, fMRI can yield an abundance of bilateral hemispheric activation, which makes postoperative prediction challenging.[5]

Lateralization of language and memory are crucial aspects of surgical planning for patients undergoing procedures for mesial temporal lobe epilepsy (mTLE). Material-specific memory deficits are a frequent adverse event following anterior temporal lobectomy (ATL), and patients undergoing language-dominant ATL are at an increased risk for postoperative decrements in memory and language.[6–9] Changes in intelligence have also been observed,[10–12] with dominant resections showing worse verbal IQ outcomes.[10–13] Because of the risk for iatrogenic neurocognitive injury, surgeons often treat drug-resistant TLE via a selective amygdalohippocampectomy (AH). This allows resection of presumed seizure foci within the mesial structures (amygdala, hippocampus, entorhinal cortex, parahippocampal gyrus), while preserving the anterior temporal neocortex. Several procedures to the mesial temporal lobe have been described including the transsylvian, subtemporal, middle temporal gyrus, and inferior temporal gyrus (ITG) approaches.

The difference between hemispheric short-term memory, or Wada memory asymmetry (WMA) scores, has predicted verbal memory decline in patients undergoing dominant ATL.[6–8,14] Studies have reported that WMA scores with worse performance ipsilateral to the seizure side portends a lower risk for postoperative neuropsychological deficits.[15] Other studies have found little value in WMA scores, reporting that neuropsychological outcomes are based on the functional integrity of the ipsilateral temporal lobe.[16]

The purpose of this study was to evaluate postoperative neuropsychological outcomes in patients with preoperative WMA who underwent AH via ITG for TLE. Our group hypothesized that the presence of WMA would add value to predicting change in postoperative neuropsychological functioning to include verbal and visual memory, language, and mood.

Methods

Patient characteristics and study design

This is a retrospective review of patients who were prospectively enrolled in an epilepsy surgery database at a tertiary care center between 2010 and 2015. All patients were evaluated by a multidisciplinary epilepsy team that included epileptology, neurosurgery, neuroradiology, and neuropsychology. A standard presurgical evaluation was used to assess surgical candidacy including the following: (1) history/physical including seizure semiology, (2) prolonged video-electroencephalography (v-EEG), (3) a high-resolution 3T MRI study with thin cuts through temporal lobes, (4) fluorodeoxyglucose (FDG)–positron emission tomography (PET) study of brain, (5) Wada testing to assess language dominance/lateralized memory deficits, and (6) a comprehensive neuropsychological evaluation. Lateralization and localization of seizure onset was determined using long-term v-EEG. Surface v-EEG long-term monitoring (International 10–20 system) was conducted using the XLTEK EEG monitoring system (XLTEK, Oakville, ON, Canada). Bilateral basilar-temporal placements such as T1/T2 electrodes were used. Sphenoidal electrodes were not used. All patients underwent a selective AH through the ITG approach with at least 2 years of documented seizure outcome. In addition, postsurgical imaging was reviewed to confirm satisfactory resection of mesial temporal lobe structures.

Successful surgical outcome was defined using the Engel classification system,[17] with class I or II being considered satisfactory for this study population. Engel class III/IV were excluded from further analyses as lack of seizure control is recognized to adversely affect neuropsychological results.[18,19,20] Furthermore, patients with Engel class I or II are expected to have had a diagnostic work-up that was accurate with regard to seizure localization and surgical treatment that adequately resected the epileptic zone.[19] In addition, postsurgical imaging was reviewed to confirm satisfactory resection of mesial temporal lobe structures.

This study was approved by the local institutional review board and all participants signed informed consent.

Neuropsychological measures

The standard neuropsychological battery incorporated NINDS (National Institute of Neurological Disorders and Stroke) common data elements for epilepsy.[21] Neuropsychological study included 13 measures with scores assessing processing speed, attention/executive, verbal and visual memory, language (naming, verbal fluency), and visuospatial/constructional functions. Specifically, the Boston Naming Test[22] was used to assess confrontation naming. Controlled Oral Word Association Test (COWAT)[23] phonemic (letters F, A, & S) and semantic (animal) naming was used to assess verbal fluency. The Rey Auditory Verbal Learning Test (RAVLT) and Wechsler Memory Scale-IV[24] (WMS-IV) Logical Memory subtests were used as measures of verbal memory. WMS-IV[24] Visual Reproduction subtests and the Rey Osterrieth Complex Figure Test[25] (ROCFT) assessed visual memory. Mood was assessed using the Beck Depression Inventory-II[26] (BDI-II). The Wechsler Adult Intelligence Scale-4th Edition (WAIS-IV)[27] was administered as a measure of general cognitive function. Raw scores were used for all assessments, with the exception of the WAIS-IV in which a prorated full-scale IQ (PFSIQ) score was used for analyses. To evaluate change intra-individual and between-person, raw scores were treated as continuous variables in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[28] WAIS-IV PFSIQ, verbal comprehension index (VCI), and prorated perceptual reasoning index (PPRI) index scores (mean = 100, standard deviation = 15) were derived from the test manual. All neuropsychological studies were completed by a board-certified neuropsychologist who was blinded to the patient allotment for the study. Neuropsychological study results were determined prior to epilepsy case conferences with the integrated healthcare team.

Wada procedure

Wada testing was performed in accordance with the protocol of Loring et al.[29] with a methohexital adaptation. Both hemispheres were tested on the same day. An initial 3 mg dose of methohexital was injected into the internal carotid artery via hand push at a rate of 5–8 s. Additional 2 mg doses of methohexital were administered until hemiparesis was established and EEG demonstrated delta slowing in the ipsilateral hemisphere. Language and memory testing were then conducted. Language was assessed by the quality of spontaneous speech, the ability to comprehend simple commands, object naming, repetition of simple phrases, and comprehension of single-step midline commands. Each memory procedure included 8 targets and 16 foils. Memory score was the total correct recognition score out of 8 minus 0.5 points for any false positive error among the 16 foils (possible score range from 8 to −8). Language lateralization and recognition memory scores were recorded for each hemisphere. A recognition memory asymmetry >3/8 was considered lateralized for memory.[30] Participants with a difference >3 between left and right Wada memory recognition scores (ranging from 8 to −8) were allocated to the Wada memory asymmetry group.

Surgical technique

Details of the technique have been described.[31] Utilizing a small linear skin incision and performing a temporal craniotomy flush with the middle fossa floor (zygomatic root as a landmark),[32] access is gained to the mesial temporal lobe by a limited corticectomy of the inferior temporal gyrus (ITG) (access corridor). Subpial dissection is guided by intraoperative anatomic landmarks to allow identification of the collateral sulcus and access to the temporal horn. The hippocampus, amygdala, and surrounding mesial structures are identified and resected.

Statistical analysis

Statistical analyses were performed with Statistical Package for Social Science (SPSS) version 24 (SPSS Inc., Chicago, IL, U.S.A.). Demographic variables between groups were analyzed via chi-square and analysis of variance (ANOVA) to ensure no significant differences. Preoperative and postoperative neuropsychological functioning was compared at the group level using a repeated-measures ANOVA. Disease variables such as Wada asymmetry and language dominance were analyzed to compare neuropsychological outcomes following surgery at the individual level. Alpha was set at $p < 0.05$ for all analyses.

Results

Patients who underwent AH via the ITG approach for unilateral mTLE between April 2010 and September 2015 were considered for the study. Initially, 104 patients were evaluated for the study. Thirty-five participants were removed due to not having selective temporal surgery or epilepsy surgery due to other causes such as congenital abnormalities or benign tumors. Six patients with poor seizure outcome (Engel class III/IV) were also excluded. Another 15 individuals were removed because they did not complete the full work-up or records of studies were incomplete. A total of 48 patients met the inclusion criteria and were considered for the study.

Table 1 summarize demographics and there was no difference between groups in terms of age, education, ethnicity, gender, and dexterity ($p > 0.05$). There was no significant difference in age at first seizure or disease duration. There was no differences in postoperative follow-up time between the No-WMA group (mean 16.3, standard deviation [SD] 12.5 months, min5.6, max 47.7) and the WMA group (mean 19.0, SD 12.8 months; $p > 0.05$, min 6.3, max 48.4). There was no significant difference between groups with regard to the amount of medication changes following surgery, and the average medication change was a

Table 1. Postoperative demographics according to seizure group

Demographic	No Wada asymmetry (n = 22)	Wada asymmetry (n = 26)	F/X^2	*P*-value
Age	32.82 (11.39)	35.65 (11.55)	0.727	0.398
Education (years)	13.23 (2.79)	13.31 (2.59)	0.011	0.918
Gender			1.242	0.265
Female	12 (54.5%)	10 (38.5%)		
Male	10 (45.5%)	16 (61.5%)		
Ethnicity			6.274	0.099
Caucasian	21 (95.5%)	18 (69.2%)		
African American	0 (0.0%)	5 (19.2%)		
Hispanic	1 (4.5%)	2 (7.7%		
Other	0 (0.0%)	1 (3.8%)		
Dexterity			0.173	0.731
Left	4 (18.2%)	6 (23.1%)		
Right	18 (81.8%)	20 (76.9%)		
Employment			7.224	0.677
Semiskilled	2 (9.1%)	5 (19.2%)		
Unemployed	5 (22.7%)	5 (19.2%)		
Student	5 (22.7%)	3 (11.5%)		
Technical	0 (0.0%)	2 (7.7%)		
Professional	7 (31.8%)	3 (11.5%)		
Disabled	2 (9.1%)	4 (15.4%)		
Part-time	0 (0.0%)	1 (3.8%		
Unskilled	1 (4.3%)	2 (7.7%)		
Age at first seizure	19.77 (13.94)	15.60 (12.13)	1.207	0.278
Years since first seizure	12.61 (11.94)	20.07 (13.57)	3.905	0.054
Follow-up time			0.363	0.552
Mean (SD)	16.3 (12.5)	19.0 (12.8)		
Median	10.6	13.3		
Range	42.1	42.0		

Means (SD) or frequencies (%) are reported for each variable; SD, standard deviation.

decline of 0.44 (mode = decline of 1) antiepileptic medications from presurgical neuropsychological evaluation to postsurgical neuropsychological evaluation.

Clinical semiology and v-EEG indicated that 28 patients (58.3%) had left TLE and 20 patients (41.7%) had right TLE. Twenty-two participants (45.8%) showed no asymmetry on Wada testing, whereas 26 (54.2%) exhibited memory asymmetry. Of the 28 patients with left mTLE, 12 patients were found to have WMA, whereas 16 patients showed No-WMA. In the group of right mTLE patients, 14 were found to have WMA and 6 showed No-WMA. Wada testing confirmed that 5 participants with left mTLE were found to be right-side dominant for language (and were considered to have nondominant resections for purposes of all analyses). Dominant hemisphere for language and memory asymmetry was based on Wada testing. Dominant hemisphere resections were performed on 23 patients (47.9%) (all left-sided surgery), whereas nondominant hemisphere surgery was done on 25 (52.1%). Specifically, 15 participants with dominant resection had No-WMA, whereas 8 participants were found to have WMA. Conversely, 7 participants who underwent nondominant resection had No-WMA, whereas 18 participants had WMA.

Effects of WMA were assessed using ANOVA, with presence of WMA as the between-subject factor and neuropsychological outcome as within-subject factors. The main effect of WMA presence showed significant differences between groups in immediate verbal recall (RAVLT immediate delay [p = 0.012] and mood BDI [p = 0.032]). Although statistically significant, the small change can likely be attributed to known practice effects rather than presence of WMA.

Mean group differences on neuropsychological tests

Wada memory asymmetry

Neuropsychological outcomes significantly differed between the WMA group and the No-WMA group (see Table 2). ANOVA comparing presurgical and postsurgical neuropsychological functioning found that the No-WMA patients exhibited a significant decline in verbal memory (RAVLT immediate delay [p = 0.006 and RAVLT 30-min delay [p = 0.045]) scores. Alternatively, the No-WMA group exhibited a significant improvement in prorated nonverbal reasoning scores (WAIS-IV PPRI, p = 0.035) and general intelligence scores (WAIS-IV PFSIQ, p = 0.029). The No-WMA group also exhibited a significant improvement in mood (BDI-II, p = 0.002). Patients with WMA did not show significant declines in memory scores postoperatively (all p's > 0.05). There was also significant improvement in prorated nonverbal reasoning scores (WAIS-IV PPRI, p = 0.025) and general intelligence scores (WAIS-IV

Table 2. Neuropsychological results comparing Wada asymmetry (WMA) versus no-Wada asymmetry (No-WMA) scores

	WMA (n = 26)			No-WMA (n = 22)		
Test	Preoperative	Postoperative	(*d*)	Preoperative	Postoperative	(*d*)
Language						
BNT total (raw score)	46.0 (11.5) Min: 14 Max: 58	47.4 (12.4) Min: 11 Max: 58	0.12	47.2 (7.7) Min: 31 Max: 59	47.3 (7.6) Min: 22 Max: 56	0.01
FAS total (raw score)	33.3 (10.8) Min: 10 Max: 56	33.1 (11.1) Min: 11 Max: 58	−0.02	33.2 (12.3) Min: 6 Max: 59	32.7 (11.7) Min: 16 Max: 64	−0.04
Semantic/Animal (raw score)	16.2 (5.0) Min: 8 Max: 26	16.6 (5.3) Min: 7 Max: 25	0.09	18.0 (5.0) Min: 6 Max: 29	18.4 (5.4) Min: 11 Max: 32	0.08
Memory						
RAVLT (raw score)						
Imm. Delay	7.8 (3.6) Min: 1 Max: 15	8.4 (4.4) Min: 0 Max: 15	0.16	9.1 (3.4) Min: 3 Max: 13	6.4 (3.8)* Min: 1 Max: 15	−0.75
Delayed recall	7.3 (4.1) Min: 0 Max: 14	6.9 (4.9) Min: 0 Max: 15	−0.08	7.6 (4.5) Min: 0 Max: 13	5.7 (4.7)* Min: 0 Max: 15	−0.42
WMS-IV (raw score)						
Logical memory I	22.9 (6.8) Min: 8 Max: 36	23.5 (6.4) Min: 8 Max: 37	0.09	21.3 (9.5) Min: 6 Max: 36	20.2 (6.9) Min: 4 Max: 38	−0.13
Logical memory II	18.2 (6.9) Min: 4 Max: 33	18.5 (8.3) Min: 6 Max: 37	0.04	16.6 (9.1) Min: 1 Max: 30	16.9 (7.7) Min: 0 Max: 31	0.04
Visual reproduction I	31.2 (6.3) Min: 19 Max: 41	31.7 (10.2) Min: 3 Max: 42	0.06	32.0 (7.1) Min: 17 Max: 42	32.5 (6.8) Min: 16 Max: 41	0.07
Visual reproduction II	16.9 (9.3) Min: 0 Max: 32	17.6 (10.8) Min: 0 Max: 35	0.07	20.8 (10.6) Min: 0 Max: 37	21.5 (7.2) Min: 8 Max: 31	0.08
RCFT 30-min delay (raw score)	9.4 (5.6) Min: 1 Max: 23	10.0 (6.0) Min: 0 Max: 19	0.10	12.2 (6.2) Min: 0 Max: 21.5	12.3 (4.9) Min: 1.5 Max: 20.5	0.02
General Cognitive/IQ						
WAIS-IV Prorated FSIQ	86.6 (13.3) Min: 59 Max: 112	90.2 (14.9)* Min: 63 Max: 122	0.26	88.8 (14.3) Min: 64 Max: 110	91.7 (13.1)* Min: 62 Max: 110	0.21
WAIS-IV prorated VCI	88.4 (14.4) Min: 58 Max: 116	89.0 (15.0) Min: 63 Max: 122	0.04	88.1 (11.8) Min: 70 Max: 110	86.5 (11.7) Min: 70 Max: 114	−0.14
WAIS-IV Prorated PRI	87.2 (11.5) Min: 69 Max: 105	90.7 (14.1)* Min: 69 Max: 123	0.28	93.1 (14.2) Min: 71 Max:117	98.7 (12.7)* Min: 71 Max: 121	0.42
Affect/Mood						
BDI (raw score)	12.3 (11.0) Min: 0 Max: 40	12.7 (10.7) Min: 0 Max: 37	0.04	14.0 (8.8) Min: 0 Max: 32	8.0 (6.8)* Min: 0 Max: 23	−0.76

Mean and standard deviation (SD) are provided for each variable; *$p < 0.05$.

PFSIQ, $p = 0.010$) in both groups. There was no significant postoperative change in verbal fluency of visual confrontation naming observed in either group (all p's > 0.05).

Wada results and language dominance

Table 3 summarizes results from an ANOVA comparing language dominance AH within the WMA and No-WMA groups. Patients with No-WMA who underwent language dominant AH significantly declined in verbal memory (RAVLT immediate delay [$p = 0.000$] and RAVLT 30-min delay [$p = 0.001$]) scores. Patients with No-WMA who underwent dominant side AH also showed significantly improved mood (BDI-II, $p = 0.006$). No significant changes were observed in the group of patients with No-

Table 3. Sub-analyses by asymmetry and language dominance change scores

	WMA		No-WMA	
Test	Non-dominant (n = 18)	Dominant (n = 8)	Non-dominant (n = 7)	Dominant (n = 15)
Language				
BNT total (raw score)	2.5 (3.8)*	2.0 (8.8)	2.4 (3.3)	−2.8 (7.9)
FAS Total (raw score)	−0.6 (7.2)	4.4 (11.7)	1.6 (10.5)	2.8 (9.6)
Semantic/animal (raw score)	−0.2 (4.0)	2.3 (5.5)	1.6 (4.2)	−0.2 (7.2)
Memory				
RAVLT (raw score)				
Imm. delay	−0.4 (3.4)	1.7 (3.9)	0.29 (3.3)	−4.0 (2.6)*
Delayed recall	−1.7 (3.9)	1.7 (3.7)	2.3 (2.7)	−4.1 (3.0)*
WMS-IV (raw score)				
Logical memory I	1.7 (7.2)	0.4 (9.5)	4.6 (4.9)	−5.2 (7.8)
Logical memory II	1.8 (7.4)	0.3 (7.8)	5.4 (7.8)	−3.2 (7.1)
Visual reproduction I	−2.8 (11.0)	10.4 (8.8)*	1.0 (8.2)	−0.5 (6.5)
Visual reproduction II	−2.1 (11.2)	5.0 (8.9)	3.7 (10.2)	−0.7 (10.5)
ROCFT 30-min delay (raw score)	−0.1 (5.4)	1.7 (7.5)	3.1 (4.2)	−1.3 (7.5)
General cognitive/IQ				
WAIS-IV prorated FSIQ	3.0 (7.8)	9.6 (14.2)	4.8 (7.4)	−1.4 (13.7)
WAIS-IV Prorated VCI	−1.5 (9.0)	5.9 (11.5)	−1.6 (4.3)	−4.5 (12.0)
WAIS-IV prorated PRI	2.2 (6.0)	7.1 (13.9)	4.8 (10.3)	6.7 (15.0)
Affect/mood				
BDI (raw score)	0.1 (12.0)	1.4 (7.3)	−2.6 (6.6)	−8.5 (8.7)*

Mean and standard deviation (SD) are provided for each variable; negative BDI change score indicates improvement in depressive symptoms; *$p < 0.05$.

WMA who underwent nondominant AH (all $p > 0.05$). Alternatively, participants with WMA significantly improved visual confrontation naming after undergoing language nondominant AH (BNT, $p = 0.021$). Patients with WMA who underwent language dominant AH showed significant improvement in immediate visual memory (WMS-IV Visual Reproduction I, $p = 0.010$).

Wada results and side of seizure onset

Given the literature establishing that patients with language-dominant (left) TLE tend to experience greater risk for decline in memory and confrontation naming,[33] we completed sub-analyses of Wada asymmetry, sub-classifying WMA by those having left or right TLE (see Table 4). ANOVA comparing side of seizure onset within the WMA and No-WMA groups found patients with left mTLE who showed No-WMA significantly declined in immediate (RAVLT immediate delay, $p = 0.001$) and delayed (RAVLT 30-min delay, $p = 0.001$) verbal recall, but exhibited an improvement in perceptual reasoning (WAIS-IV PRI, $p = 0.035$) and depressive symptoms (BDI-II, $p = 0.004$). Alternatively, the left mTLE participants with WMA exhibited an significant increase in immediate visual memory (WMS-IV Visual Reproduction I, $p = 0.010$) and general intellectual functioning (WAIS-IV prorated full-scale IQ [FSIQ], $p = 0.027$) scores. In the group with left mTLE, no significant postoperative changes were found in verbal fluency, confrontation naming, semantic memory, delayed visual recall, or verbal intelligence. The group of participants with right mTLE and WMA showed significant improvement in confrontation naming (BNT, $p = 0.035$) postoperatively. No significant postoperative changes were found for participants with right-sided seizure onset and No-WMA. In the group with right mTLE, no significant postoperative changes were found in verbal fluency, visual or verbal memory, general cognition, or mood.

Prediction of neuropsychological outcome

Wada memory lateralization was also analyzed as a continuous variable to evaluate the extent to which Wada memory difference scores can predict neuropsychological outcome. Differences between left and right Wada memory scores were recorded as absolute values. Linear regression using Wada memory asymmetry scores was found to be a significant predictor of RAVLT immediate delay scores accounting for 14.8% of variance (F [1, 43] = 7.46, $p = 0.009$). Upon further examination, only Wada memory asymmetry scores in left-sided resection patients was a significant predictor of RAVLT immediate delay scores accounting for 27.0% of variance (F [1, 24] = 8.86, $p = 0.007$). The other 12 algorithms to predict each of the postoperative neuropsychological test scores were not significant ($p > 0.05$).

Reliable change analyses for intra-individual analyses

To compare neuropsychological change at the individual level, reliable change index (RCI) scores[34] corrected for practice effects[35] were used. Cut-off values have been published for patients with drug-resistant epilepsy.[35,36] In neuropsychological practice, reliable change can be inferred for

Table 4. Sub-analyses by asymmetry and seizure-onset change scores

	Left		Right	
Test	No-WMA (n = 16)	WMA (n = 12)	No-WMA (n = 6)	WMA (n = 14)
Language				
BNT total (raw score)	−2.5 (7.6)	3.3 (7.7)	2.5 (3.6)	1.6 (3.1)*
FAS total (raw score)	1.9 (9.7)	4.4 (10.0)	3.2 (10.5)	−2.3 (6.7)
Semantic/animal (raw score)	−0.1 (6.8)	2.3 (5.1)	1.7 (4.6)	−0.8 (3.7)
Memory				
RAVLT (raw score)				
Imm. delay	−3.7 (2.8)*	0.05 (4.0)	0.2 (3.5)	0.0 (3.4)
Delayed recall	−3.7 (3.1)*	−0.6 (4.8)	2.5 (2.9)	−0.7 (3.6)
WMS-IV (raw score)				
Logical memory I	−4.0 (8.7)	2.3 (8.8)	3.5 (4.3)	0.4 (7.2)
Logical memory II	−2.0 (8.1)	3.0 (8.1)	4.2 (7.7)	−0.2 (6.7)
Visual reproduction I	− 0.2 (6.3)	8.3 (8.2)*	0.6 (9.1)	−4.8 (11.2)
Visual reproduction II	−0.8 (10.0)	3.9 (6.9)	4.6 (11.1)	−3.1 (11.8)
ROCFT 30-min delay (raw score)	−1.1 (7.2)	1.8 (7.2)	3.3 (4.5)	−0.7 (4.7)
General cognitive/IQ				
WAIS-IV prorated FSIQ	−0.7 (13.4)	10.2 (11.6)*	4.0 (7.9)	0.6 (6.5)
WAIS-IV prorated VCI	−4.9 (11.6)	3.2 (11.7)	0.3 (1.3)	−1.3 (8.6)
WAIS-IV prorated PRI	7.8 (15.0)*	5.7 (12.7)	0.5 (4.1)	2.0 (4.2)
Affect/mood				
BDI (raw score)	−8.1 (8.4)*	−0.1 (7.0)	−2.3 (7.2)	1.0 (13.4)

Mean and standard deviation (SD) are provided for each variable; negative BDI change score indicates improvement in depressive symptoms; *$p < 0.05$.

those patients who obtain pre/post difference scores that meet or exceed the 90% confidence interval for each assessment.[35,36] A change score greater than the 90% confidence interval (CI) can be attributed to a change in neuropsychological functioning rather than variations in scores that can occur due to measurement error. For the Boston Naming Test, the 90% RCI cutoff was ±5 raw points.[35] The 90% RCI cutoff was −7 and +5 for the RAVLT trial 6 short-delay and −7 and +6 for the RAVLT trial 7 long-delay.[34] The ROCFT 90% CI with practice was −7 or +10 points.[36]

Reliable change scores were calculated for neuropsychological measures that were observed to significantly change postoperatively for each participant. Table 5 summarizes the proportion of participants in each group exceeding the 90% CI RCI score for a reliable change in neuropsychological score following surgery. The majority of patients did not experience a reliable decline in neuropsychological test scores known to be negatively affected by temporal lobectomy procedures.[37,38] Delayed verbal memory was most affected in patients with No-WMA who underwent language dominant AH (see Table 5). Of the patients with No-WMA who underwent language dominant AH, 26.7% showed a reliable decline in verbal naming and delayed verbal recall. Twenty-five percent of patients with WMA who underwent language-dominant AH showed reliable improvement in immediate verbal memory. For the entire sample, a greater proportion of patients exhibited a reliable increase in visual confrontation naming (n = 8) and verbal immediate recall (n = 5) than patients exhibiting a reliable decline in visual confrontation naming (n = 5) and verbal immediate recall (n = 4).

Discussion

The clinical value of the Wada test in the evaluation of candidates for selective AH in the treatment of drug-resistant mTLE remains an area of debate and controversy.[2,3] There is an increasing emphasis of the use of noninvasive methods to lateralize language and memory.[39–41] Proponents of noninvasive alternatives to the Wada test cite the risk of the Wada procedure as an invasive test that includes a risk (albeit low) of infection, stroke, and post-procedural discomfort.[42] A recent comprehensive review by the American Academy of Neurology found data, albeit sometimes controversial, to support the use of fMRI to predict language and postsurgical verbal memory outcomes in patients with mTLE.[4] Some studies have shown an inability to accurately and precisely detect critical language regions as well as an abundance of bilateral hemispheric activation with the noninvasive alternatives.[5] The latter has been improved on largely by the establishment of a lateralization index.[43–45] Studies reviewing the ability of Wada and fMRI to detect language lateralization yield approximately 86% agreement, with 92–94% concordance when left hemisphere language dominance was detected.[46] However, fMRI has not yet been established as an alternative to Wada testing for prediction of global amnesia, so Wada testing continues to offer clinical value to predict surgical outcomes. In addition, WMA scores have been correlated significantly with surgical outcome in those patient with TLE and bilateral features on noninvasive preoperative evaluation.[47]

Physiologically, the importance of WMA in presurgical evaluations lies in the functional reserve capacity of the

Table 5. Proportion of patients exhibiting reliable change in selected neuropsychological tests

	WMA (n = 26)				No-WMA (n = 22)			
	Nondominant (n = 18)		Dominant(n = 8)		Nondominant (n = 7)		Dominant (n = 15)	
Test	Decrease	Increase	Decrease	Increase	Decrease	Increase	Decrease	Increase
Language								
BNT (−5/+5)	0 (0.0%)	4 (22.2%)	1 (12.5%)	1 (12.5%)	0 (0.0%)	2 (28.6%)	4 (26.7%)	1 (6.7%)
Memory								
RAVLT trial 6 (−7/+5)	2 (11.1%)	2 (11.1%)	0 (0.0%)	2 (25.0%)	0 (0.0%)	1 (14.3%)	2 (13.3%)	0 (0.0%)
RAVLT trial 7 (−7/+6)	2 (11.1%)	0 (0.0%)	0 (0.0%)	1 (12.5%)	0 (0.0%)	1 (14.3%)	4 (26.7%)	0 (0.0%)
ROCFT 30 min delay (−7/+10)	2 (11.1%)	0 (0.0%)	1 (12.5%)	1 (12.5%)	0 (0.0%)	0 (0.0%)	3 (20.0%)	1 (6.7%)

Asymmetry, Wada asymmetry; BNT, Boston Naming Test; RAVLT, Rey Auditory Verbal Learning Test; ROCFT, Rey-Osterrieth Complex Figure Test; Reliable Change Index points are raw points of the test with (−/+) indicating decrease or increase in raw score.

spared region.[16] Wada testing allows for real-time assessment of hemispheric functioning to evaluate the likely influence of resection and probable support from the unaffected region. The lateralization technique employed during Wada testing has been shown to accurately predict postoperative memory decline in patients with left temporal lobectomy, specifically when recognition following left injection was superior to recognition following right injection.[48]

The rate of seizure freedom after selective AH via an ITG approach are similar to outcomes after other selective approaches, and not dissimilar to en block ATL.[49–51] Age at seizure onset, mesial temporal sclerosis, and EEG laterality all contribute to operative planning.[38,48,50,51] The variability of neuropsychological outcomes after different procedures can be explained by collateral damage along the approach corridor, variances in the extent of mesial and neocortical resection, and differences in the postoperative neuropsychological evaluation.[38,49–51] One advantage of the ITG approach is preservation of the temporal stem, a region containing association fibers connecting frontal lobe executive functioning to language and memory processing in the temporal lobe. Substantial disruptions of connection fibers can have detrimental negative effects on cognition and language.[52,53]

This study reports a comparison of neuropsychological outcomes based on the presence of WMA in patients undergoing selective AH via ITG for the treatment of drug-resistant mTLE. The results from the present study are largely congruent with the prior literature predicting neuropsychological outcomes based on WMA.[37,38,46,51] Participants with WMA did not exhibit a significant decline in memory or language function on neuropsychological tests that are known to be sensitive to changes following anterior temporal lobectomy. The findings that the WMA group did not decline in memory or language function are not surprising. Wada testing revealed that the resected area was functioning significantly worse than the spared region and that the spared region possessed enough functional reserve to support at least a current level of functioning following ATL. When memory was evaluated at an individual level with reliable change indices, patients with No-WMA had a greater decline in verbal memory. In fact, a proportion of individuals with WMA exhibited improvement in measures of immediate verbal memory. Deficits in visual confrontation naming were unrelated to WMA in this cohort; however, a majority of individuals with WMA who showed improvement in the Boston Naming Test had nondominant resections, implying the expected relation to language laterality.

Contrary to prior research among patients undergoing temporal lobectomies,[51] we found no decline in semantic fluency regardless of dominant or nondominant resection using the selective procedures utilized for these patients. This finding likely reflects sparing of semantic networks within the anterior and lateral neocortex in selective AH via ITG procedure, as compared to more traditional ATL procedures.[36,38] Within the group of patients with No-WMA, there was a decline in immediate and delayed verbal recall compared to their counterparts with WMA. More patients with No-WMA than patients with WMA had a decline in delayed verbal recall.

Additional analysis revealed that of the participants in the No-WMA group who showed reliable decline on verbal tasks, all underwent dominant-side resection. Likewise, a higher proportion of patients with No-WMA had worse visual confrontation naming compared to the group that had WMA. Of interest, 10% of the WMA group showed improvement in visual confrontation naming. Wada asymmetry (e.g., WMA group), when considered in conjunction with language dominance, provided clarity into the risk of decline in neuropsychological function. These data support prior research that indicates that verbal memory and visual confrontation naming are at the most risk of decline for patients with no Wada asymmetry and with a dominant AH,

even in patients with selective ATL procedures to treat pharmacoresistent epilepsy.[8,33] Change in visual memory functioning has been shown to be variable across literature. Contrary to the findings of Kneebone et al., visual memory decline was small, which is consistent with the majority of the literature.[8,38,51]

Unexpectedly, patients with WMA did not exhibit an improvement in mood despite achieving Engle class I or II outcomes (seizure freedom), whereas patients in the No-WMA group did report significantly fewer symptoms of depression after having a dominant-hemisphere selective resection. Intelligence measures of FSIQ and nonverbal intelligence exhibited significant improvement for both the No-WMA and the WMA groups when evaluated at the group level. Sub-analyses within the WMA and No-WMA groups found that the improvement in FSIQ was observed primarily in the WMA group having dominant resections (n = 8).

Limitations

Several limitations of this study are notable. First, the study sample was limited. Evaluation of specific subgroups resulted in small sample sizes, which severely restrict the ability to use parametric statistical analyses. In addition, the study did not evaluate the impact of additional variables such as epilepsy duration or medication adherence during pre- and postoperative evaluations. There were no reversed WMA participants who met criteria for the current study and thus no comparison can be made between WMA and reversed WMA neuropsychological outcomes. Some evidence suggests that seizure freedom following surgery can significantly impact neurocognitive functioning.[54] Because successful surgical outcome was used as inclusion criteria, the effects of seizure outcome cannot be assessed in this study. There are multiple variations of the Wada testing performed currently such as alternative anesthetic agents and different memory stimuli. The current study examines the neuropsychological outcomes from only one such approach to Wada testing and may not be translatable to other studies.

Conclusion

WMA was found to be significantly related to verbal memory outcome. Individuals without WMA were more likely to have a decline in verbal memory compared to subjects with WMA. Mood was also found to significantly improve following surgery in patients without WMA. WMA was not associated with change in postoperative general intelligence or visual memory scores following selective anterior-mesial temporal lobe surgery, with the exception of the WMA group with language-dominant AH who significantly improved in immediate visual memory. Future research is needed to make distinctions between WMA and reversed WMA and draw conclusions regarding neuropsychological outcomes accordingly. In addition, forthcoming studies can determine how the presence of WMA is predictive of neuropsychological outcome in patients with Engel class III or IV outcomes (unsuccessful surgery).

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study, or the findings specified in this paper. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

References

1. Rutten GJ, Ramsey NF. The role of functional magnetic resonance imaging in brain surgery. *Neurosurg Focus* 2010;28:e4.
2. Baxendale S, Thompson PJ, Duncan JS. The role of the Wada test in the surgical treatment of temporal lobe epilepsy: an international survey. *Epilepsia* 2008;49:715–720.
3. Binder JR. Functional MRI is a valid noninvasive alternative to Wada testing. *Epilepsy Behav* 2011;20:214–222.
4. Szaflarski JP, Gloss D, Binder JR, et al. Practice guideline summary: use of fMRI in the presurgical evaluation of patients with epilepsy Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. *Neurology* 2017;88:395–402.
5. Bauer PR, Reitsma JB, Houweling BM, et al. Can fMRI safely replace the Wada test for preoperative assessment of language lateralisation? A meta-analysis and systematic review. *J Neurol Neurosurg Psychiatry* 2014;85:581–588.
6. Kneebone AC, Chelune GJ, Naugle RI, et al. Intracarotid amobarbital procedure as a predictor of material specific memory change after anterior temporal lobectomy. *Epilepsia* 1995;36:857–865.
7. Wyllie E, Naugel R, Awad I, et al. Intracarotid amobarbital procedure: i. prediction of decreased modality- specific memory scores after temporal lobectomy. *Epilepsia* 1991;32:857–864.
8. Loring DW, Meador KJ, Lee GP, et al. Wada memory asymmetries predict verbal memory decline after anterior temporal lobectomy. *Neurology* 1995;45:1329–1333.
9. Baxendale S, Thompson P, Harkness W, et al. Predicting memory decline following epilepsy surgery: a multivariate approach. *Epilepsia* 2006;47:1887–1894.
10. Blakemore CB, Falconer MA. Long-term effects of anterior temporal lobectomy on certain cognitive functions. *J Neurol Neurosurg Psychiatry* 1967;30:364.
11. Selwa LM, Berent S, Giordani B, et al. Serial cognitive testing in temporal lobe epilepsy: longitudinal changes with medical and surgical therapies. *Epilepsia* 1994;35:743–749.
12. Alpherts WC, Vermeulen J, Hendriks MP, et al. Long-term effects of temporal lobectomy on intelligence. *Neurology* 2004;62:607–611.
13. Engman E, Andersson-Roswall L, Samuelsson H, et al. Serial cognitive change patterns across time after temporal lobe resection for epilepsy. *Epilepsy Behav* 2006;8:765–772.
14. Rausch R, Babb TL, Engel J, et al. Memory following intracarotid amobarbital injection contralateral to hippocampal damage. *Arch Neurol* 1989;46:783–788.
15. Loring DW, Bowden SC, Lee GP, et al. Diagnostic utility of Wada Memory Asymmetries: sensitivity, specificity, and likelihood ratio characterization. *Neuropsychology* 2009;23:687.
16. Chelune GJ. Hippocampal adequacy versus functional reserve: predicting memory functions following temporal lobectomy. *Arch Clin Neuropsychol* 1995;10:413–432.
17. Engel Jr JV. Outcome with respect to epileptic seizures. *Surg Treat Epilepsy* 1993:609–621.
18. Tanriverdi T, Dudley RW, Hasan A, et al. Memory outcome after temporal lobe epilepsy surgery: corticoamygdalohippocampectomy versus

selective amygdalohippocampectomy. *J Neurosurg* 2010;113:1164–1175.
19. Wyllie E, Lüders H, Morris HH, et al. Clinical outcome after complete or partial cortical resection for intractable epilepsy. *Neurology* 1987;37:1634.
20. Breuer LEM, Boon P, Bergmans JWM, et al. Cognitive deterioration in adult epilepsy: does accelerated cognitive ageing exist? *Neurosci Biobehav Rev* 2016;64:1–11.
21. Loring DW, Lowenstein DH, Barbaro NM, et al. Common data elements in epilepsy research: development and implementation of the NINDS epilepsy CDE project. *Epilepsia* 2011;52:1186–1191.
22. Kaplan E, Goodglass H, Weintraub S. *Boston naming test*. Pro-ed; 2001.
23. Benton AL, Hamsher K. *Multilingual aphasia examination*. Iowa City: AJA Associates; 1976.
24. Wechsler D. *Wechsler memory scale*. 4th Ed. San Antonio, TX: Pearson; 2009.
25. Rey A. L'examen psychologique dans les cas d'encéphalopathie traumatique (Les problems). *Arch Psychol* 1941;28:286–340.
26. Beck AT, Steer RA, Brown GK. *Beck depression inventory-II*. San Antonio, TX: Psychological Corporation; 1996;78:490-8.
27. Wechsler D. *Wechsler adult intelligence scale-fourth edition: technical and interpretive manual*. 4th Ed. San Antonio, TX: Pearson Assessment; 2008.
28. Vandenbroucke JP, Von Elm E, Altman DG, et al. Strobe Initiative. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. *PLoS Med* 2007;4:297.
29. Loring DW, Lee GP, Meador KJ, et al. The intracarotid amobarbital procedure as a predictor of memory failure following unilateral temporal lobectomy. *Neurology* 1990;40:605–610.
30. Sabsevitz DS, Swanson SJ, Morris GL, et al. Memory outcome after left anterior temporal lobectomy in patients with expected and reversed Wada memory asymmetry scores. *Epilepsia* 2001;42:1408–1415.
31. Duckworth EA, Vale FL. Trephine epilepsy surgery: the inferior temporal gyrus approach. *Oper Neurosurg* 2008;63:156–161.
32. Beckman JM, Vale FL. Using the zygomatic root as a reference point in temporal lobe surgery. *Acta Neurochir* 2013;155:2287–2291.
33. Schoenberg MR, Clifton WE, Sever RW, et al. Neuropsychology outcomes following trephine epilepsy surgery: the inferior temporal gyrus approach for amygdalohippocampectomy in medically refractory mesial temporal lobe epilepsy. *Neurosurgery* 2017;82:833–841.
34. Jacobson NS, Truax P. Clinical significance: a statistical approach to defining meaningful change in psychotherapy research. *J Consult Clin Psychol* 1991;59:12.
35. Sawrie SM, Chelune GJ, Naugle RI, et al. Empirical methods for assessing meaningful neuropsychological change following epilepsy surgery. *J Int Neuropsychol Soc* 1996;2:556–564.
36. Nakhutina L, Pramataris P, Morrison C, et al. Reliable change indices and regression-based measures for the Rey-Osterreith Complex Figure test in partial epilepsy patients. *Clin Neuropsychol* 2010;24:38–44.
37. Stroup E, Langfitt J, Berg M, et al. Predicting verbal memory decline following anterior temporal lobectomy (ATL). *Neurology* 2003;60:1266–1273.
38. Sherman E, Wiebe S, Fay-McClymont TB, et al. Neuropsychological outcomes after epilepsy surgery: systematic review and pooled estimates. *Epilepsia* 2011;52:857–869.
39. Medina LS, Aguirre E, Bernal B, et al. Functional MR imaging versus Wada test for evaluation of language lateralization: cost analysis. *Radiology* 2004;230:49–54.
40. Medina LS, Bernal B, Dunoyer C, et al. Seizure disorders: functional MR imaging for diagnostic evaluation and surgical treatment—prospective study. *Radiology* 2005;236:247–253.
41. Fernández G, de Greiff A, von Oertzen J, et al. Language mapping in less than 15 minutes: real-time functional MRI during routine clinical investigation. *NeuroImage* 2001;14:585–594.
42. Loddenkemper T, Morris HH, Möddel G. Complications during the Wada test. *Epilepsy Behav* 2008;13:551–553.
43. Binder JR, Sabsevitz DS, Swanson SJ, et al. Use of preoperative functional MRI to predict verbal memory decline after temporal lobe epilepsy surgery. *Epilepsia* 2008;49:1377–1394.
44. Binder JR, Swanson SJ, Sabsevitz DS, et al. A comparison of two fMRI methods for predicting verbal memory decline after left temporal lobectomy: language lateralization versus hippocampal activation asymmetry. *Epilepsia* 2010;51:618–626.
45. Desmond JE, Sum JM, Wagner AD, et al. Functional MRI measurement of language lateralization in Wada-tested patients. *Brain* 1995;118:1411–1419.
46. Janecek JK, Swanson SJ, Sabsevitz DS, et al. Language lateralization by fMRI and Wada testing in 229 patients with epilepsy: rates and predictors of discordance. *Epilepsia* 2013;54:314–322.
47. Waseem H, Osborn KE, Schoenberg MR, et al. Predictors of surgical outcome in medically-resistant temporal lobe epilepsy with bilateral features on pre-operative evaluation. *Clin Neurol Neurosurg* 2015;139:199–205.
48. Loring DW, Murro AM, Meador KJ, et al. Wada memory testing and hippocampal volume measurements in the evaluation for temporal lobectomy. *Neurology* 1993;43:1789.
49. Hu WH, Zhang C, Zhang K, et al. Selective amygdalohippocampectomy versus anterior temporal lobectomy in the management of mesial temporal lobe epilepsy: a meta-analysis of comparative studies. *J Neurosurg* 2013;119:1089–1097.
50. Josephson CB, Dykeman J, Fiest KM, et al. Systematic review and meta-analysis of standard vs selective temporal lobe epilepsy surgery. *Neurology* 2013;80:1669–1676.
51. von Rhein B, Nelles M, Urbach H, et al. Neuropsychological outcome after selective amygdalohippocampectomy: subtemporal versus transsylvian approach. *J Neurol Neurosurg Psychiatry* 2012;83:887–893.
52. Hori T, Tabuchi S, Kurosaki M, et al. Subtemporal amygdalohippocampectomy for treating medically intractable temporal lobe epilepsy. *Neurosurgery* 1993;33:50–56.
53. Takaya S, Mikuni N, Mitsueda T, et al. Improved cerebral function in mesial temporal lobe epilepsy after subtemporal amygdalohippocampectomy. *Brain* 2009;132:185–194.
54. Leonard G. Temporal lobe surgery for epilepsy: neuropsychological variables related to surgical outcome. *Can J Neurol Sci* 1991;18:593–597.