Epilepsy & Behavior 27 (2013) 461–469

Contents lists available at SciVerse ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Atypical neuropsychological profiles and cognitive outcome in mesial temporal lobe epilepsy

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ARTICLE INFO

Article history:
Received 23 January 2013
Revised 25 February 2013
Accepted 6 March 2013
Available online 21 April 2013

Keywords:
Memory
Neuropsychological assessment
Epilepsy
Temporal lobe epilepsy
Hippocampal sclerosis
Epilepsy surgery

ABSTRACT

Patients with left mesial temporal lobe epilepsy (MTLE) have deficits in verbal memory processes, while patients with right MTLE have visuospatial memory impairment. However, atypical cognitive phenotypes among patients with MTLE may occur. In this study, we analyzed preoperative memory deficits in a cohort of 426 right-handed patients with unilateral MTLE. We also evaluated the cognitive outcome after anterior temporal lobectomy (ATL) of patients with atypical profiles in comparison with those with typical memory profile. We found that 25% of our patients had a typical cognitive profile, with verbal memory deficits associated with left side hippocampal sclerosis (HS) and visuospatial memory deficits associated with right side HS. However, 75% of our patients had atypical memory profiles. Despite these atypical profiles, patients submitted to right ATL had no significant cognitive deficit after surgery. In patients submitted to left ATL, the higher the presurgical scores on verbal memory and naming tests, the higher the cognitive decline after surgery.

1. Introduction

Anterior temporal lobectomy (ATL) is the most common surgical procedure used to treat mesial temporal lobe epilepsy associated with hippocampal sclerosis (MTLE-HS), the most common epilepsy syndrome surgically treated in adolescents and adults [1]. The rate of seizure freedom is 60–70%, and the prevalence of neurological complications is low and mostly mild or transient [1]. It has been shown that unilateral resection of mesial temporal structures can result in reduced memory function in patients with MTLE-HS. A recent systematic review reported that 16 to 80% of patients submitted to left ATL may have significant additional verbal memory deficits after surgery. On the other hand, patients submitted to right ATL have a 3 to 42% risk of significant visual memory loss [2]. Most studies reporting cognitive outcome in patients with MTLE-HS group all patients together. However, even patients with a relatively uniform epilepsy syndrome, such as unilateral MTLE-HS, may have differences on cognitive performance before surgery. For example, studies have shown that patients with unilateral left MTLE-HS may have normal memory scores before surgery, which could significantly impact on cognitive outcome after surgery [3]. In addition, few studies have reported cognitive outcome in patients with discordant or bilateral neuropsychological findings. As the presurgical evaluation team needs to discuss the risk of cognitive deficits with their patients, studies are needed to identify those with a higher risk of memory loss according to specific neuropsychological profiles.

Here, we analyzed the neuropsychological profile of 426 right-handed patients with unilateral MTLE-HS. Four groups of patients with MTLE-HS with atypical memory profiles were identified. These "atypical" memory profiles were as follows: (1) bilateral memory deficits despite unilateral MTLE, (2) normal memory performance, (3) memory deficit contralateral to the side of MTLE-HS, and (4) severe memory impairment associated with low IQ. We also report the cognitive outcome in each memory profile subgroup and compared with those with a typical memory profile.

2. Patients and methods

2.1. Patient selection

The study was conducted at the Ribeirao Preto Epilepsy Center, University of São Paulo, Brazil. We retrospectively reviewed charts of 984 patients submitted to epilepsy surgery from 1996 to 2010. Patients satisfying the following inclusion criteria were selected to participate: (1) have drug-refractory TLE with unilateral MTLE-HS and

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1525-5050
http://dx.doi.org/10.1016/j.yebeh.2013.03.002

were submitted to anterior temporal lobectomy; (2) aged 18 years or older at evaluation; (3) have IQ scores higher than 60; (4) have histopathological evidence of hippocampal sclerosis, with neuronal loss in CA1, CA3, and prosubiculum and relative sparing of CA2; (5) right-handed according to the laterality questionnaire [4]; and (6) were submitted to both presurgical neuropsychological assessment and postsurgical neuropsychological assessment (Fig. 1). We excluded patients with temporal or extratemporal lesions other than HS and those patients with bilateral HS based on the review of preoperative MRIs by experienced radiologists.

2.2. Neuropsychological assessment

The neuropsychological evaluation in our center comprises a standard battery of psychometric tests that assesses various cognitive functions, such as attention, executive functions, memory, visuospatial processing, language, and intellectual abilities. For the purposes of this study, we specifically selected the ones that are described below. For IQ evaluation, we used the Wechsler Adult Intelligence Scale Revised (WAIS-R) [5] or the 3rd edition (WAIS-III) [6,7]. For the assessment of cognitive functions mediated by the dominant temporal lobe, we chose the Logical Memory Delayed Recall (LM-DR) from Wechsler Memory Scale Revised (WMS-R) [8] and the Rey Auditory Verbal Learning Test Delayed Recall (RAVLT-DR) [8–10] to assess verbal memory; and the Boston Naming Test (BNT) from Boston Diagnostic Aphasia Examination [8,10,11] to assess naming abilities. For the assessment of cognitive functions mediated by the non-dominant temporal lobe, we chose the Visual Reproduction Delayed Recall (VR-DR) from WMS-R [8], the Rey Visual Design Learning Test Delayed Recall (RVDLT-DR) [9,10], and Delayed Recall of Rey–Osterrieth Complex Figure (RF-DR) [12–14].

2.3. Classification of atypical neuropsychological profiles

Typically, patients with TLE on the dominant hemisphere have verbal memory and language (naming) impairment [15–17], while patients with TLE on the non-dominant hemisphere have visual memory impairment [18]. We focused on verbal memory tests (LM-DR and RAVLT-DR) for the dominant hemisphere and visual memory tests (VR-DR and RF-DR) for the non-dominant hemisphere as representative of temporal lobe functions [10,19].

Each psychometric test described above was analyzed according to its normative data. As indicative of impairment on dominant temporal function, it was required that a patient had to have a score of two standard deviations below the norm in one test or one standard deviation below the norm in both tests (LM-DR and RAVLT-DR). To indicate impairment on non-dominant temporal function, it was required that a patient had to have a score of two standard deviations below the norm in one test or one standard deviation below the norm in both tests (VR-DR and RF-DR).

2.4. Group classification

Considering that we included only right-handed patients, the results obtained on neuropsychological evaluation before surgery, and the operated side (left-dominant hemisphere or right-non-dominant hemisphere), the groups were divided as follows: IPSILATERAL (cognitive deficits compatible with the side of HS), NORMAL (without functional deficits despite the unilateral HS), BITEMPORAL (involvement of dominant and non-dominant hemispheres, regardless of the side of unilateral HS), Global Cognitive Impairment — GCI (severe involvement of dominant and non-dominant memory functions associated with an IQ lower than 70), and CONTRALATERAL (cognitive deficits contralateral to the side of EH).

To assess cognitive outcome after surgery, we performed another neuropsychological evaluation one year after surgery, with the same battery performed before the surgery. All patients were interviewed regarding any events that could affect cognition between surgery and the neuropsychological examination.

2.5. Presurgical evaluation protocol

2.5.1. Video-EEG monitoring

At least two events similar to the patients' habitual seizures were recorded. If no seizure was registered in the first 24 h, antiepileptic drugs (AEDs) were progressively tapered until seizures were recorded. The laterality of ictal onset zone was independently assessed on ictal video-EEG by two investigators [20,21].

2.5.2. Neuroimaging

Most patients were scanned in a 1.5-T magnet (Magnetom Vision; Siemens AG, Erlangen, Germany) MRI machine, with 25-mT gradient coils of circular polarization. Since 2007, patients underwent high-resolution MRI in a 3-T scanner eight-channel head coil with a similar acquisition protocol. The sequences performed were a gradient echo 3D T1-weighted, axial T2, coronal and axial FLAIR (fluid attenuation

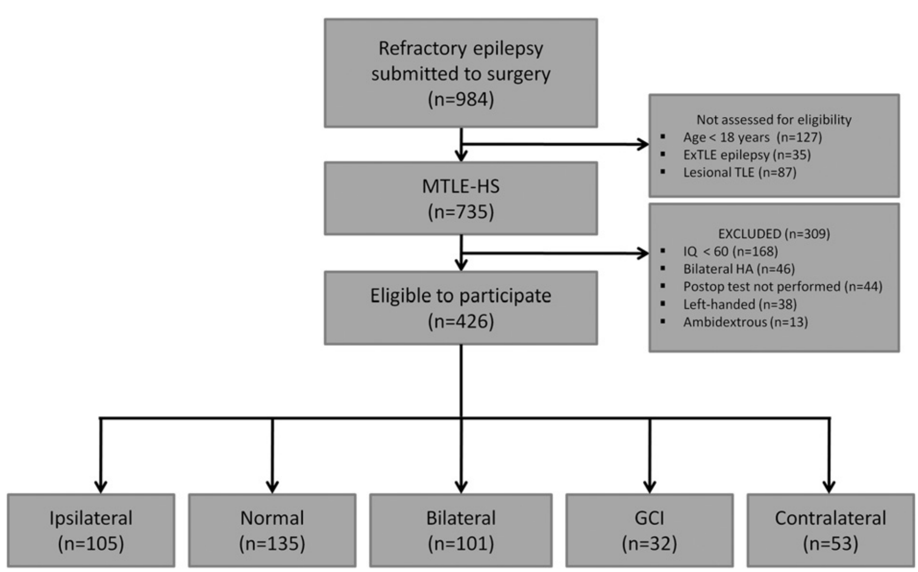

Fig. 1. The flow diagram shows the process of recruiting study participants.

inversion recovery) and T1-weighted inversion recovery. The images were reformatted to the coronal plane by using a multiplanar reformatting protocol in coronal, sagittal, and axial 5-mm slices, without interslice gaps, perpendicular to the main axis of the temporal lobe and hippocampus. For the ictal SPECT, ethylcysteinate dimmer labeled with 3 GBq of 99mTc was injected immediately after the clinical or EEG seizure onset at a maximum dose of 1295 MBq (35 mCi).

2.6. Temporal resection

Patients were included in the study if they had unilateral TLE. Therefore, we included only patients with unilateral ictal EEG. Patients with bilateral ictal EEGs were submitted to surgery only if it was invasively or semi-invasively confirmed that the seizure onset zone was unilateral. All patients were submitted to a standard anterior temporal resection with amygdalohippocampectomy (ATL). One of two neurosurgeons experienced in surgery for epilepsy resected a maximum of 5.0 to 6.0 cm of the anterior lateral non-dominant temporal lobe or 3.5 to 4.5 cm of the dominant temporal lobe. The mesial resection included the amygdala and, at a minimum, the anterior 1.0 to 3.0 cm of the hippocampus.

2.7. Statistical analysis

The statistical analysis was performed using the software PASW Statistics 18 (Release 18.0.0, July 30, 2009).

2.7.1. Univariate analysis

To evaluate differences between categorical variables among groups, we used the chi-square test. To obtain an accurate significance level in tables with 0 cell counts or tables with more than 20% of cells with counts lower than 5, we used an exact test. Numerical variables were evaluated using the Kruskal–Wallis test for non-normally distributed variables. To evaluate postsurgical cognitive outcome, we performed the paired sample *t*-tests.

To evaluate the magnitude of effect size of numerical variables between groups, we calculated Cohen's d, the difference between the means, divided by standard deviation, of either group. Values > or = 0.8 indicate a larger effect size, =0.5 a medium effect size, and =0.2 a small effect size. To evaluate the association between categorical variables between groups, we calculated Phi, a chi-square-based measure of association ranging between 0 and 1, with 0 indicating no association and values close to 1 indicating a high degree of association.

2.7.2. Controlling for multiple comparisons

To control for multiple comparisons, we used the false discovery rate (FDR) Benjamini–Hochberg procedure [22]. For this procedure, the *p*-values were sorted by size. The smallest *p*-value must then be compared with the Bonferroni limit — the selected FDR level, divided by the number of hypotheses. The second smallest *p*-value must be compared with the level multiplied by 2, divided by the number of hypotheses. The third smallest *p*-value must be compared with the level multiplied by 3, divided by the number of hypotheses, etc. This procedure allows for the rejection of all null hypotheses with a *p*-value smaller than the largest *p*-value divided by the n number of hypotheses.

2.7.3. Missing variables

For some patients, one subtest of verbal or nonverbal memory was not performed due to the patient's distress or lack of cooperation, resulting in missing data for these scores. However, missing data analysis revealed that these events occurred completely at random and did not result in any bias (Little's MCAR test: chi-square = 7.749, df = 8, $p = 0.458$).

3. Results

3.1. Clinical characteristics of the cohort

From the 426 patients eligible to participate, 105 patients (25%) had temporal cognitive deficits ipsilateral to the side of hippocampal sclerosis and were classified as IPSILATERAL, 135 patients had a normal cognitive profile and were classified as NORMAL (32%), 101 patients had bitemporal cognitive deficits and were classified as BITEMPORAL (24%), 32 patients had global cognitive impairment (beyond temporal deficits) and were classified as GCI (7%), and 53 patients had temporal cognitive deficits contralateral to the side of hippocampal sclerosis and were classified as CONTRALATERAL (12%) (Fig. 1). Table 1 shows the demographical characteristics of the cohort.

Fifty-four percent of our sample was female. The mean (±SD) age at seizure onset was 9.1 (8.1) years, the age at evaluation was 36.8 (9.3) years, and the epilepsy duration was 26.9 (10.8) years. There was no difference between groups regarding gender, age at seizure onset, age at evaluation, and epilepsy duration. The mean (±SD) number of years of education was 6.9 (4.2) years and differed between groups ($p < 0.001$, ANOVA test). The NORMAL group had a higher number of years of education when compared with the other groups ($p = 0.019$ to $p < 0.001$, Games–Howell post hoc test, Cohen's d = 1.2). The GCI group had a lower number of years of education when compared with all other groups ($p < 0.001$, Games–Howell post hoc test, Cohen's d = 1.2). The mean (±SD) intelligence quotient (IQ) was 83.8 (10.9) and was significantly higher in the NORMAL group when compared with all the other groups ($p < 0.001$, Games–Howell post hoc test, Cohen's d = 2.1). In addition, the IQ in the GCI group was lower than that in all other groups ($p < 0.001$, Games–Howell post hoc test, Cohen's d = 2.1). The BITEMPORAL group had a lower IQ when compared with the IPSILATERAL, NORMAL, and CONTRALATERAL groups and a higher IQ when compared with the GCI group ($p < 0.001$, Games–Howell post hoc test, Cohen's d = 2.1) (see Table 1 for details).

There was also an association between the side of hippocampal sclerosis and cognitive profile. Patients from the BITEMPORAL group had more frequent left hippocampal sclerosis, while patients from the NORMAL group had more frequent right hippocampal sclerosis ($p = 0.001$, chi-square test, Phi = 0.214). There was no association between employment status, laterality of interictal EEG and ictal EEG, and cognitive profiles ($p = 0.325$ and $p = 0.638$, chi-square test).

A total of 336 out of the 426 patients (79%) became seizure-free after surgery. The mean (±SD) follow-up duration regarding seizure outcome was 9.4 (4.0) years. There was no difference in the percentage of seizure-free patients between groups ($p = 0.478$, chi-square test).

Table 2 shows the mean results of neuropsychological tests for each group, separated by the side of hippocampal sclerosis (left HS and right HS). For both sides, patients from the NORMAL group had significantly higher scores when compared with those from the IPSILATERAL group, except for one test in left HS (RF-DR, $p = 0.862$). In left HS, patients from the GCI group had scores significantly lower when compared with those from the IPSILATERAL group. In right HS, patients from the GCI group had lower LM-DR e VR-DR scores when compared with those from the IPSILATERAL group ($p = 0.003$ and $p < 0.001$). Patients from the BITEMPORAL group with left side hippocampal sclerosis (left HS) had similar scores for verbal neuropsychological tests (LM-DR and RAVLT-DR) when compared with those from the IPSILATERAL group but lower scores for the visual tests (RF-DR and VR-DR). This relationship was inversed on patients with right hippocampal sclerosis (right HS). The visual tests from the BITEMPORAL group were similar to the IPSILATERAL group, but the verbal scores were significantly lower. Finally, patients from the CONTRALATERAL group with left HS had lower visual scores and higher verbal scores when compared with those from the IPSILATERAL group. Those with right HS had lower LM-DR scores

Table 1
Characteristics of study participants in total and divided by group.

Variable	Total N = 426	Ipsilateral N = 105 (25%)	Normal N = 135 (32%)	Bitemporal N = 101 (24%)	GCI N = 32 (7%)	Contralateral N = 53 (12%)	p-Value	Measure of association
Gender — N (% female)	231 (54%)	53 (50%)	79 (58%)	49 (55%)	16 (59%)	24 (45%)	$p = 0.447$ [a]	0.093 [f]
Age at seizure onset	9.1 (8.1)	8.85 (7.5)	10.3 (9.3)	8.5 (7.7)	7.6 (6.6)	8.4 (7.2)	$p = 0.308$ [b]	0.2204 [g]
Age at evaluation	36.8 (9.3)	37.3 (9.6)	37.2 (9.4)	36.6 (8.6)	35.3 (9.6)	36.5 (9.4)	$p = 0.785$ [b]	0.1538 [g]
Epilepsy duration	26.9 (10.8)	25.8 (11.7)	26.6 (11.2)	27.5 (10.1)	27.8 (10.2)	27.9 (9.5)	$p = 0.715$ [b]	0.1507 [g]
Years of education	6.9 (4.2)	6.5 (4.0)	9.2 (4.2) [c]	5.6 (3.6)	2.4 (2.1) [c]	7.2 (3.5)	**$p < 0.001$** [b]	1.1734 [g]
IQ	83.8 (10.9)	83.7 (8.5)	90.5 (10.3) [d]	80.5 (6.1) [d]	63.8 (5.3) [d]	85.1 (8.7)	**$p < 0.001$** [b]	2.1378 [g]
Employment status (% active)	202 (47%)	47 (45%)	73 (54%)	43 (42%)	9 (28%)	30 (56%)	$p = 0.056$ [a]	0.093 [f]
HS side — N (% left)	225 (53%)	50 (48%)	55 (41%) [e]	64 (63%) [e]	22 (69%)	34 (64%)	**$p = 0.001$** [a]	0.214 [f]
EEG ictal (% unilateral)	396 (93%)	94 (90%)	129 (96%)	94 (93%)	30 (94%)	49 (92%)	$p = 0.638$ [a]	0.077 [f]
EEG interictal								
% normal	9 (2%)	4 (4%)	2 (1%)	0 (0%)	1 (3%)	2 (4%)		
% unilateral	328 (77%)	75 (71%)	112 (83%)	76 (75%)	24 (75%)	41 (77%)	$p = 0.325$ [a]	0.147 [f]
% bilateral	89 (21%)	26 (25%)	21 (16%)	25 (25%)	7 (22%)	10 (19%)		
Outcome (% Engel I)	336 (79%)	87 (83%)	108 (80%)	77 (76%)	22 (69%)	42 (79%)	$p = 0.478$ [a]	0.091 [f]

Numerical variables are mean (SD); GCI is global cognitive impairment, IQ intelligence quotient, HS hippocampal sclerosis.
[a] Chi-square test.
[b] ANOVA.
[c] The NORMAL group had significantly higher and the GCI group had significantly lower years of education than all other groups (Games–Howell post hoc test).
[d] The NORMAL group had significantly higher and the GCI group had significantly lower IQ scores than all other groups (Games–Howell post hoc test). The BITEMPORAL group had IQ scores lower than the IPSILATERAL, NORMAL, and CONTRALATERAL groups, but higher IQ scores when compared with the GCI group.
[e] The NORMAL group had a significantly higher proportion of patients with right HS and the BITEMPORAL group a higher proportion of left HS.
[f] Phi, a chi-square-based measure of association ranging between 0 and 1, with 0 indicating no association and values close to 1 indicating a high degree of association.
[g] Cohen's d effect size. Values > or =0.8 indicate a larger effect size, =0.5 a medium effect size, and = 0.2 a small effect size.

and higher visual scores (RF-DR and VR-DR) when compared with those from the IPSILATERAL group. These results support our group classification as atypical, provided that these confirm the presence of groups of (i) patients with unilateral HS but a normal cognitive profile (NORMAL group), (ii) patients with unilateral HS but bitemporal memory deficits (BITEMPORAL group), (iii) patients with unilateral HS but a global cognitive impairment (GCI group), and (iv) patients with left HS but predominantly visual memory deficits and patients with right HS but predominantly verbal memory deficits (CONTRALATERAL group).

3.2. Cognitive outcome and its relationship with atypical memory profiles

3.2.1. Left side temporal lobectomy

Patients submitted to left temporal lobectomy had significant postoperative declines in verbal neuropsychological scores. Patients from the IPSILATERAL group had a lower Boston Naming Test (BNT) postoperative score ($p < 0.0001$; Cohen's d = 0.45) and no significant change in memory scores. The NORMAL group had significant declines in verbal memory scores (LM-DR, $p < 0.0001$, Cohen's d = 0.77 and RAVLT-DR, $p < 0.0001$, Cohen's d = 0.83), naming scores (BNT, $p < 0.0001$, Cohen's d = 0.59), and visual memory scores (VR-DR, $p = 0.001$, Cohen's d = 0.59) after surgery. The BITEMPORAL group had a lower naming postoperative score (BNT, $p < 0.0001$, Cohen's d = 0.45) and an improvement on visual memory test (RF-DR, $p = 0.003$, Cohen's d = −0.47). The GCI group had no significant change in memory or BNT scores. Finally, the CONTRALATERAL group had a significant decline in verbal memory scores (LM-DR, $p = 0.001$, Cohen's d = 0.73 and RAVLT-DR, $p < 0.0001$, Cohen's d = 0.70) and a significant improvement on a visual memory test score (VR-DR, $p = 0.003$, Cohen's d = −0.82) (see Table 3 and Fig. 2A for details).

3.2.2. Right side temporal lobectomy

Patients submitted to right temporal lobectomy had no significant decline in any of the neuropsychological tests. In fact, for some groups, there was an improvement on test scores. The IPSILATERAL, NORMAL, and GCI groups had a slightly higher postoperative BNT score ($p = 0.004$, Cohen's d = −0.25, $p = 0.001$, Cohen's d = −0.12, and $p = 0.004$, Cohen's d = −0.32, respectively). The IPSILATERAL group had a significant improvement on a visual memory score (RF-DR, $p = 0.009$, Cohen's d = −0.47). Finally, the BITEMPORAL group also had a significant improvement on LM-DR and RAVLT-DR scores ($p < 0.0001$,

Table 2
Side of hippocampal sclerosis and neuropsychological tests.

Variables	Total	IPSILATERAL	NORMAL	BITEMPORAL	GCI	CONTRALATERAL	p-Value [a]	Cohen's d
Left HS								
LM-DR (N = 225)	10.30 (7.90)	6.2 (4.67)	19.91 (5.45) [b]	5.33 (4.11)	2.68 (3.03) [b]	15.06 (3.84) [b]	**$p < 0.001$**	2.9196
RAVLT-DR (N = 224)	8.00 (3.66)	7.36 (3.20)	10.93 (2.63) [b]	6.46 (3.17)	4.41 (3.74) [b]	9.41 (2.50) [b]	**$p < 0.001$**	1.5043
RF-DR (N = 221)	11.01 (6.12)	14.56 (4.84)	15.54 (5.29)	7.16 (4.17) [b]	5.42 (5.10) [b]	9.06 (4.27) [b]	**$p < 0.001$**	1.7045
VR-DR (N = 224)	20.66 (10.62)	27.31 (6.52)	30.87 (6.30) [b]	14.11 (7.67) [b]	7.77 (5.72) [b]	15.24 (6.16) [b]	**$p < 0.001$**	2.5839
Right HS								
LM-DR (N = 200)	14.34 (8.45)	16.38 (6.08)	20.00 (6.61) [b]	6.49 (5.00) [b]	2.00 (2.49) [b]	6.63 (2.85) [b]	**$p < 0.001$**	2.3434
RAVLT-DR (N = 199)	10.09 (3.36)	10.39 (2.40)	11.90 (2.34) [b]	7.39 (3.43) [b]	6.80 (3.65)	8.42 (3.78)	**$p < 0.001$**	1.2362
RF-DR (N = 198)	10.75 (6.27)	7.12 (3.57)	14.95 (5.12) [b]	6.93 (6.24)	3.81 (3.05)	14.10 (3.97) [b]	**$p < 0.001$**	1.8155
VR-DR (N = 199)	20.61 (10.71)	15.45 (8.70)	28.60 (6.77) [b]	12.65 (8.15)	5.50 (5.08) [b]	26.21 (6.85) [b]	**$p < 0.001$**	2.2805

Numerical variables are mean (±SD); GCI is global cognitive impairment, BNT — Boston Naming Test, LM-DR — Logical Memory Delayed Recall (WMS-R), RAVLT-DR — Rey Auditory Verbal Learning Test Delayed Recall, RF-DR — Rey Complex Figure Delayed Recall, VR-DR — Visual Reproduction Delayed Recall (WMS-R), RVDLT-DR — Rey Visual Design Learning Test Delayed Recall.
[a] Kruskal–Wallis test.
[b] Significant differences between the IPSILATERAL group and other groups (Games–Howell post hoc test for unequal variances).

Table 3
Paired comparisons between preoperative scores and postoperative scores separated by groups in patients submitted to left temporal lobectomy.

Group	Tests	Pre	Post	p-Value[a]	Cohen's d[b]
IPSILATERAL	BNT	39.18 (10.21)	34.58 (10.12)	$\mathbf{p < 0.0001}$	0.4525
	LM-DR	6.20 (4.67)	5.68 (6.05)	$p = 0.745$	0.0962
	RAVLT-DR	7.35 (3.23)	6.12 (3.71)	$p = 0.023$	0.3536
	RF-DR	14.64 (4.86)	14.34 (6.16)	$p = 0.709$	0.0540
	VR-DR	27.31 (6.52)	24.71 (11.44)	$p = 0.047$	0.2792
	RVDLT-DR	6.21 (2.90)	6.62 (3.86)	$p = 0.384$	−0.1200
NORMAL	BNT	47.42 (7.38)	42.76 (8.33)	$\mathbf{p < 0.0001}$	0.5922
	LM-DR	19.91 (5.46)	14.42 (8.51)	$\mathbf{p < 0.0001}$	0.7678
	RAVLT-DR	10.85 (2.60)	8.43 (3.17)	$\mathbf{p < 0.0001}$	0.8347
	RF-DR	15.59 (5.32)	16.39 (8.21)	$p = 0.434$	−0.1156
	VR-DR	30.87 (6.30)	26.36 (8.77)	$\mathbf{p = 0.001}$	0.5906
	RVDLT-DR	8.81 (3.30)	9.69 (3.85)	$p = 0.093$	−0.2454
BITEMPORAL	BNT	37.97 (8.01)	34.31 (8.19)	$\mathbf{p < 0.0001}$	0.4518
	LM-DR	5.21 (4.03)	5.79 (4.92)	$p = 0.331$	0.1290
	RAVLT-DR	6.46 (3.16)	5.51 (3.41)	$p = 0.028$	0.2890
	RF-DR	7.13 (4.19)	9.30 (5.08)	$\mathbf{p = 0.003}$	−0.4660
	VR-DR	14.11 (7.67)	15.39 (10.67)	$p = 0.379$	0.1378
	RVDLT-DR	5.19 (2.64)	5.78 (3.43)	$p = 0.218$	0.1928
GCI	BNT	27.14 (10.13)	26.33 (9.33)	$p = 0.341$	0.0831
	LM-DR	2.81 (3.04)	3.43 (4.35)	$p = 0.487$	−0.1652
	RAVLT-DR	4.41 (3.73)	5.27 (4.15)	$p = 0.428$	−0.2179
	RF-DR	5.97 (5.08)	8.44 (5.17)	$p = 0.097$	−0.4819
	VR-DR	7.77 (5.72)	11.45 (7.03)	$p = 0.056$	−0.5742
	RVDLT-DR	3.46 (1.90)	4.15 (2.15)	$p = 0.273$	−0.3400
CONTRALATERAL	BNT	42.41 (9.15)	39.06 (11.64)	$p = 0.027$	0.3199
	LM-DR	15.06 (3.84)	11.38 (6.01)	$\mathbf{p = 0.001}$	0.7297
	RAVLT-DR	9.41 (2.49)	7.44 (3.13)	$\mathbf{p < 0.0001}$	0.6965
	RF-DR	19.06 (4.27)	10.36 (5.48)	$p = 0.085$	−0.2646
	VR-DR	15.24 (6.16)	21.91 (9.68)	$\mathbf{p = 0.003}$	−0.8221
	RVDLT-DR	5.95 (2.55)	6.11 (3.11)	$p = 0.754$	−0.0562

[a] Paired sample *t*-test.
[b] Cohen's d effect size. Values > or = 0.8 indicate a larger effect size, = 0.5 a medium effect size, and = 0.2 a small effect size.

Cohen's d = −0.65 and $p = 0.002$, Cohen's d = −0.50) (see Table 4 and Fig. 2B for details).

4. Discussion

The material-specific theory for memory holds that, generally, right-handed patients with left mesial temporal lesions have impairment on verbal memory and patients with right mesial temporal lesions have impairment on visuospatial memory [16–18]. In this study, we analyzed preoperative memory deficits and postoperative memory deficits in a cohort of the 426 right-handed patients with unilateral HS submitted to temporal lobectomy. We found that 25% of our patients had a typical cognitive profile, with verbal memory deficits associated with left side HS and visuospatial memory deficits associated with right side HS. However, 75% of our patients had atypical memory profiles: (1) patients with normal memory profile (32%), (2) patients with bilateral memory deficits (24%), (3) patients with severe bilateral memory deficits associated with low IQ (7%), and (4) patients with memory deficits contralateral to the side of HS (12%). This is in line with previous studies showing that a sizable proportion of patients with TLE have atypical neuropsychological examinations [23,24]. We also found that these preoperative memory profiles predicted memory outcome after surgery. In patients submitted to left temporal lobectomy, only those from the NORMAL and CONTRALATERAL groups had significant memory declines after surgery. Patients submitted to right temporal lobectomy had most improvement on memory scores.

4.1. Why do some patients have atypical cognitive profile?

One important question that emerges from our findings is why patients with unilateral MTLE may disclose BITEMPORAL, NORMAL, CONTRALATERAL, or GCI profiles. We do not believe that patients with atypical profiles have unidentified lesions, provided that the percentage of patients who became seizure-free after surgery was similar to that between typical and atypical groups ($p = 0.478$). Therefore, there has to be another explanation for atypical profiles.

In relation to the BITEMPORAL group, it is well known from neuroimaging studies that patients with unilateral HS may reveal contralateral hippocampal volume loss [25], as well as contralateral reduction of N-acetylaspartate (NAA) [26]. This is in line with neuropathological studies showing that MTLE is mostly a bilateral asymmetric disease, which could be associated with bilateral memory deficits [27].

In relation to the group with NORMAL memory profile, studies using fMRI have shown reorganization of memory function to the contralateral temporal lobe (TL). One study showed right TL activation for word encoding in patients with left MTLE and left TL activation for the nonverbal encoding tasks in patients with right MTLE [28]. Finally, patients with normal cognitive profile had a higher IQ and school years when compared with those with ipsilateral memory profile (97 versus 87 and 10 versus 8 years, respectively, $p < 0.001$, Kruskal–Wallis test). This result is in line with others showing that IQ, although more strongly correlated with verbal and figural learning, is correlated with verbal memory scores [29]. However, another explanation could be that patients with higher IQs could develop mechanisms to attain good performance during memory tests, while patients with intellectual impairment (low IQ) could not.

Regarding the CONTRALATERAL group, the logical explanation for contralateral memory deficits might be an atypical language lateralization. In fact, it is well recognized that the incidence of atypical language lateralization is increased in patients with left MTLE [30]. In addition, two other factors may explain this finding [31]. First, visual memory tests are not sensitive to identify visual memory deficits related to hippocampal atrophy. Second, visual memory may have a more diffuse or bilateral brain representation. Finally, both factors may be combined and contribute for an atypical language lateralization.

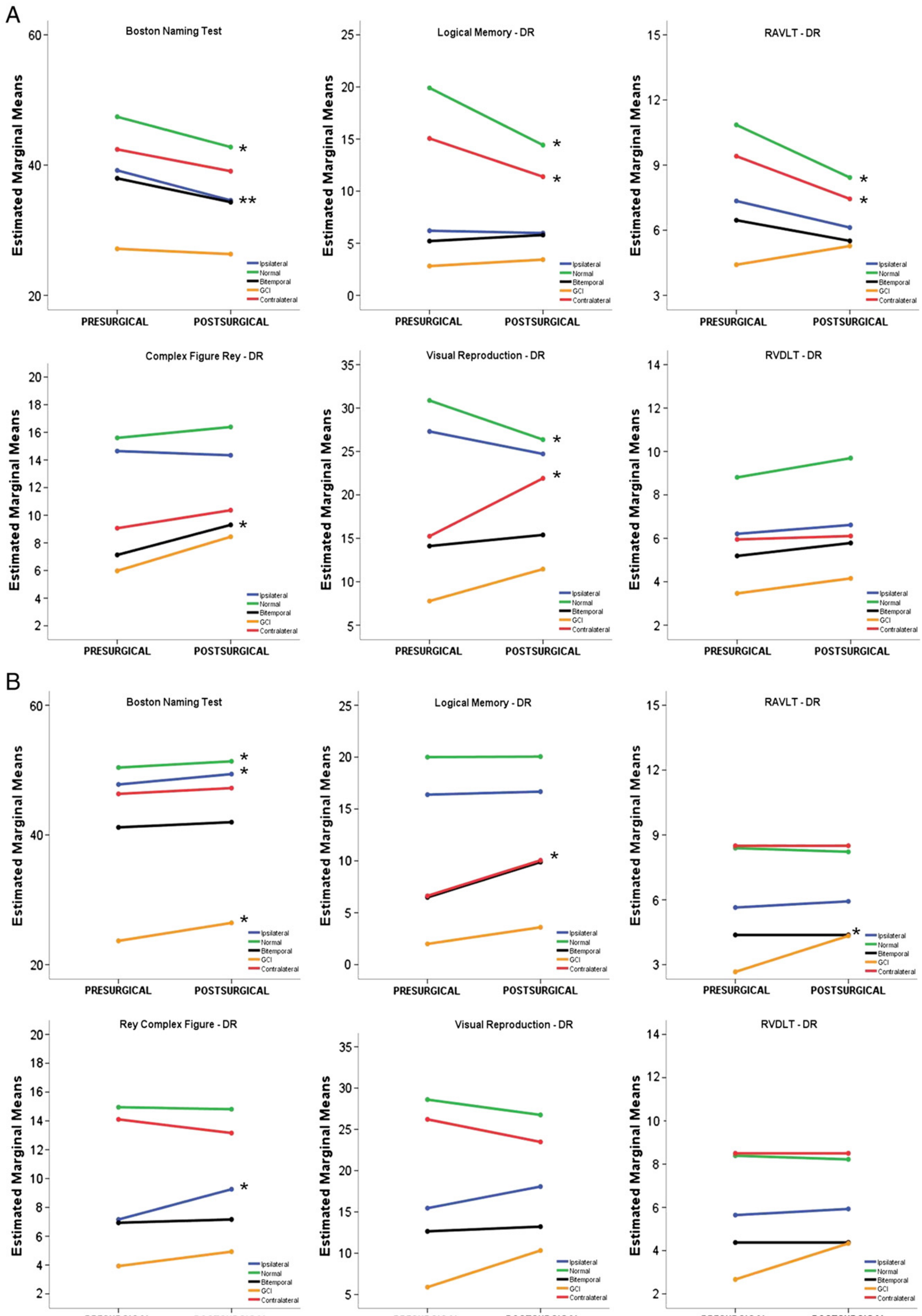
A
Boston Naming Test
Logical Memory - DR
RAVLT - DR
Complex Figure Rey - DR
Visual Reproduction - DR
RVDLT - DR
B
Boston Naming Test
Logical Memory - DR
RAVLT - DR
Rey Complex Figure - DR
Visual Reproduction - DR
RVDLT - DR
Estimated Marginal Means
PRESURGICAL
POSTSURGICAL
Ipsilateral
Normal
Bitemporal
GCI
Contralateral
*
**

Table 4
Paired comparisons between preoperative scores and postoperative scores separated by groups in patients submitted to right temporal lobectomy.

Group	Tests	Pre	Post	p-Value[a]	Cohen's d[b]
IPSILATERAL	BNT	47.78 (6.43)	49.38 (6.38)	$\mathbf{p = 0.004}$	−0.2498
	LM-DR	16.38 (6.09)	16.67 (7.57)	$p = 0.770$	−0.0422
	RAVLT-DR	10.39 (2.40)	10.48 (2.96)	$p = 0.815$	−0.0334
	RF-DR	7.16 (3.59)	9.26 (5.22)	$\mathbf{p = 0.009}$	−0.4687
	VR-DR	15.45 (8.70)	18.07 (8.93)	$p = 0.026$	−0.2971
	RVDLT-DR	5.64 (2.35)	5.93 (2.91)	$p = 0.509$	−0.1096
NORMAL	BNT	50.39 (8.18)	51.35 (7.57)	$\mathbf{p = 0.001}$	−0.1218
	LM-DR	20.00 (6.61)	20.05 (6.95)	$p = 0.930$	−0.0073
	RAVLT-DR	11.86 (2.33)	12.11 (2.36)	$p = 0.234$	−0.1066
	RF-DR	14.95 (5.16)	14.81 (5.47)	$p = 0.812$	0.0263
	VR-DR	28.60 (6.76)	26.74 (9.35)	$p = 0.048$	0.2279
	RVDLT-DR	8.39 (3.49)	8.22 (3.62)	$p = 0.613$	0.0478
BITEMPORAL	BNT	41.17 (7.83)	41.97 (7.94)	$p = 0.284$	−0.1014
	LM-DR	6.49 (5.00)	9.89 (5.52)	$\mathbf{p < 0.0001}$	−0.6455
	RAVLT-DR	7.39 (3.43)	8.94 (2.91)	$\mathbf{p = 0.002}$	−0.4873
	RF-DR	6.93 (6.24)	7.10 (4.52)	$p = 0.844$	−0.0312
	VR-DR	12.65 (8.15)	13.22 (8.26)	$p = 0.629$	−0.0694
	RVDLT-DR	4.38 (1.54)	4.38 (2.03)	$p = 1.000$	0
GCI	BNT	23.67 (8.37)	26.44 (8.88)	$\mathbf{p = 0.004}$	−0.3210
	LM-DR	2.00 (2.49)	3.60 (3.37)	$p = 0.226$	−0.5400
	RAVLT-DR	6.80 (3.65)	7.20 (2.77)	$p = 0.753$	−0.1234
	RF-DR	3.93 (3.27)	4.93 (3.43)	$p = 0.292$	−0.2984
	VR-DR	5.89 (5.23)	10.33 (7.00)	$p = 0.092$	0.7185
	RVDLT-DR	2.67 (1.16)	4.33 (2.52)	$p = 0.199$	−0.8462
CONTRALATERAL	BNT	46.33 (9.11)	47.22 (7.68)	$p = 0.215$	−0.1056
	LM-DR	6.63 (2.85)	10.05 (7.68)	$p = 0.071$	−0.5904
	RAVLT-DR	8.42 (3.78)	9.89 (3.41)	$p = 0.018$	−0.4083
	RF-DR	14.11 (3.97)	13.16 (4.67)	$p = 0.545$	0.2194
	VR-DR	26.21 (6.85)	23.47 (10.11)	$p = 0.249$	0.3173
	RVDLT-DR	8.50 (3.54)	8.50 (3.47)	$p = 1.000$	0

[a] Paired sample *t*-test.
[b] Cohen's d effect size. Values > or =0.8 indicate a larger effect size, =0.5 a medium effect size, and = 0.2 a small effect size.

Unfortunately, we did not perform a WADA test or language fMRI studies in all patients to confirm language lateralization, a limitation of our study.

4.2. Atypical memory profiles and cognitive outcome

It has been shown that 16–80% of the patients submitted to left ATL may have significant additional verbal memory deficits after surgery. Also, patients submitted to right ATL have a 3 to 42% risk of significant visual memory loss [2]. However, fewer studies have reported cognitive outcome separated by presurgical memory profiles. In relation to patients submitted to right ATL, we found that most patients had an improvement on verbal memory and naming scores. Our results are in line with previous studies showing that right ATL is not associated with significant cognitive deficits after surgery [31–33].

In relation to patients submitted to left ATL, only the NORMAL and CONTRALATERAL groups had a significant decline in verbal memory after surgery. This is in line with a recent systematic review showing that 44% of the patients submitted to left ATL are at risk for verbal memory decline [2]. Patients from the NORMAL group, which had higher preoperative verbal memory scores, had the worst verbal memory decline. This could suggest that the sclerotic hippocampus had retained memory function or that other areas in mesial TL might be involved on mnestic process for verbal encoding [3]. The same rationale holds for the CONTRALATERAL group, who had preserved preoperative verbal memory scores and also had significant memory decline after surgery. The memory decline in patients with already impaired memory scores was less severe in the IPSILATERAL and BITEMPORAL groups and absent in the GCI group in agreement with other studies [34]. In relation to naming abilities, only patients submitted to left ATL from the IPSILATERAL, NORMAL, and BITEMPORAL groups had a significant decline, in agreement with previous studies [35,36].

In summary, our findings support the notion that patients submitted to left ATL are in risk for cognitive decline, particularly in the presence of higher preoperative memory scores, as in our patients from the NORMAL and CONTRALATERAL groups. In addition, patients submitted to right ATL generally improve verbal memory and naming scores in agreement with previous studies [37,38].

4.3. Who needs a WADA test?

The WADA test (intracarotid amobarbital procedure or IAP) has been used to identify the dominant language hemisphere and to predict memory deficits after ATL. However, the IAP is an invasive procedure with small but serious risks of significant morbidity. A recent survey found that, although 12% of epilepsy surgery centers indicated that all TLE surgical candidates should undergo an IAP, the majority of centers no longer advocate the IAP for all TLE surgical candidates [39]. This suggests that the decision to perform an IAP should be determined on an individual basis. Based on our observations that right-handed patients with unilateral HS submitted to right ATL actually improve on verbal memory scores, the IAP should not be performed

Fig. 2. A. Memory profiles for patients submitted to left anterior temporal lobectomy (ATL). Patients from the NORMAL, BITEMPORAL, and IPSILATERAL groups had significant declines in postsurgical Boston Naming Test. A significant decline was also observed in Logical Memory Delayed Recall scores of patients from the CONTRALATERAL and NORMAL groups. Postsurgical Rey Auditory Verbal Learning Test Delayed Recall (RAVLT-DR) scores were significantly lower in patients from the NORMAL and CONTRALATERAL groups. B. Memory profiles for patients submitted to right anterior temporal lobectomy (ATL). There was no significant decline in memory and naming scores in patients submitted to right ATL. The IPSILATERAL, NORMAL, and GCI groups had a slightly higher postoperative Boston Naming Test score. The BITEMPORAL group had improvement on Logical Memory Delayed Recall and Rey Auditory Verbal Learning Test Delayed Recall (RAVLT-DR) scores.

on this subgroup of patients. In relation to patients submitted to left ATL, we found that patients with higher verbal memory scores before surgery (NORMAL and CONTRALATERAL groups) have a higher risk of developing memory decline after surgery. This could pressure physicians to perform IAP due to defensive medicine linked to the possibility of malpractice lawsuits. However, it has been shown that IAP does not add value in the prediction of postoperative memory outcome in left ATL when the results of comprehensive neuropsychological evaluation and MRI data are known [40]. Therefore, we do not perform IAP in patients from the NORMAL and CONTRALATERAL groups if the hippocampal atrophy is unilateral. They are informed about the risk of memory decline because of their higher scores before surgery. Nowadays, we perform IAP in left MTLE only in those patients with normal MRI and bilateral hippocampal atrophy.

4.4. Atypical memory profiles and postsurgical seizure outcome

In our study, there was no association between atypical memory profiles and seizure outcome after surgery. At least theoretically, patients from the BITEMPORAL, GCI, and CONTRALATERAL groups, by reflecting bilateral or global or contralateral temporomesial dysfunction, should have worse postsurgical seizure outcome when compared with those from the IPSILATERAL group. In fact, 69% of our patients with global cognitive impairment (GCI group) were seizure-free after surgery compared with 83% of the patients with ipsilateral memory deficits (IPSILATERAL group). However, as the sample size of the GCI group was small, this difference was not statistically significant ($p = 0.091$).

4.5. Strengths and weaknesses

The reader should be aware of the limitations of our study. As stressed before, we did not perform WADA tests or fMRI studies to confirm language lateralization. Although we included only right-handed patients, atypical language localization might explain some of our results, especially the contralateral memory deficits. Finally, we included only patients with hippocampal sclerosis. Therefore, our data apply only to patients with refractory MTLE-HS.

In conclusion, we found that discordant or atypical presurgical memory and cognitive profiles confer different odds of cognitive decline after surgery when compared with those with test results that are more prototypic of the hypothesized ipsilateral deficit pattern.

Ethics approval

Ethics approval was obtained by the Ethics Committee of our institution (CEP HCFMRP-USP — Process # 13485/2006).

Conflicts of interest

All authors declare no actual or potential conflict of interest including any financial, personal, or other relationships with people or organizations that could inappropriately influence our work.

Funding

This study was fully supported by Brazilian research governmental grants (FAPESP/CINAPCE Project #04/14004-9 and CNPq). MM Bianchin is further supported by FAPERGS/PRONEM.

Ethical publication

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.

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