Epilepsy is one of the most common neurological disorders; its prevalence is 0.5%–1% in the adult population. Of the many different types of epilepsy, temporal lobe epilepsy (TLE) is the most common, and it is often intractable despite treatment with antiepileptic drugs. In the first randomized trial to investigate the effectiveness of surgery versus optimum drug treatment in patients with TLE, researchers found a 7-fold increase in the likelihood of freedom from seizures in patients treated surgically. In a recent meta-analysis reported significantly improved seizure control in about 60%–70% of patients treated surgically. Despite seizure-free outcomes, however, a certain number of patients suffer significant decline in verbal memory after hippocampectomy. To prevent this disabling complication, a reliable test for predicting postoperative memory decline is greatly desired. Therefore, the authors assessed the value of electrical stimulation of the parahippocampal gyrus (PHG) as a provocation test of verbal memory decline after hippocampectomy on the dominant side.

OBJECTIVE
Epilepsy surgery is of known benefit for drug-resistant temporal lobe epilepsy (TLE); however, a certain number of patients suffer significant decline in verbal memory after hippocampectomy. To prevent this disabling complication, a reliable test for predicting postoperative memory decline is greatly desired. Therefore, the authors assessed the value of electrical stimulation of the parahippocampal gyrus (PHG) as a provocation test of verbal memory decline after hippocampectomy on the dominant side.

METHODS
Eleven right-handed, Japanese-speaking patients with medically intractable left TLE participated in the study. Before surgery, they underwent provocative testing via electrical stimulation of the left PHG during a verbal encoding task. Their pre- and posthippocampectomy memory function was evaluated according to the Wechsler Memory Scale-Revised (WMS-R) and/or Mini-Mental State Examination (MMSE) before and 6 months after surgery. The relationship between postsurgical memory decline and results of the provocative test was evaluated.

RESULTS
Left hippocampectomy was performed in 7 of the 11 patients. In 3 patients with a positive provocative recognition test, verbal memory function, as assessed by the WMS-R, decreased after hippocampectomy, whereas in 4 patients with a negative provocative recognition test, verbal memory function, as assessed by the WMS-R or MMSE, was preserved.

CONCLUSIONS
Results of the present study suggest that electrical stimulation of the PHG is a reliable provocative test to predict posthippocampectomy verbal memory decline.

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KEY WORDS
temporal lobe epilepsy; verbal memory function; depth electrodes; hippocampus; entorhinal cortex; functional neurosurgery
ever, a certain number of patients suffer considerable decline in memory function, especially verbal memory function, after surgery.\textsuperscript{11,16}

Verbal memory function is of particular concern in patients with relatively high preoperative verbal memory performance who will undergo hippocampectomy on the language-dominant side; these patients have an increased risk of postoperative decline in verbal memory function.\textsuperscript{14} Currently, the severity of hippocampal sclerosis, as assessed by left hippocampal volume loss, is considered one of the predictors of memory outcome, with mild or no hippocampal sclerosis posing an increased risk of postoperative memory decline.\textsuperscript{15} Older age at the time of surgery, late onset of seizures, and male sex are also risk factors for memory decline after left anterior temporal lobectomy.\textsuperscript{10,17} Patients at high risk for postoperative memory decline may undergo the intracarotid amytal procedure (Wada test).\textsuperscript{19,25} This procedure provides a reasonable index of the risk for developing amnesia, but its predictive value for the degree of verbal memory decline remains controversial.\textsuperscript{19,25}

Together, concerns about postoperative memory decline and limitations in predicting it play a pivotal role in keeping patients away from potentially seizure-curing surgery. Thus, a reliable means of predicting, and thus circumventing, disabling postoperative memory complications is eagerly awaited. Direct electrical stimulation of functional cortical regions, such as the motor and language areas, is performed in patients scheduled for epilepsy or glioma surgery.\textsuperscript{1,4,18} Its utility for identifying the essential language cortex has been demonstrated in a large number of patients,\textsuperscript{27} and it is considered the gold standard for predicting postoperative functional impairment. Implanted electrodes are also used for ictal recordings before surgery in patients with intractable epilepsy.\textsuperscript{23} Direct electrical stimulation of the hippocampus during memory encoding in humans has been shown to disrupt subsequent recognition memory.\textsuperscript{9,22}

Herein we describe our preliminary experience with parahippocampal electrical stimulation (PES) during a memory encoding task in a series of patients who had depth electrodes already implanted for presurgical identification of the seizure focus. This is the first reported attempt to evaluate this technique as a provocation test for the prediction of verbal memory decline after hippocampectomy on the dominant side.

**Methods**

**Study Patients**

The study group comprised 11 consecutive right-handed, Japanese-speaking patients with medically intractable left TLE who had undergone implantation of electrodes in the left temporal lobe for the purpose of localizing the epileptogenic focus. These patients, described in Table 1, were all treated at Osaka University Hospital. Patients ranged in age from 16 to 66 years (mean 37.4 years), and the average duration of complex partial seizures was 17.4 years. Preoperative diagnostics consisted of high-resolution MRI, surface ictal and interictal electroencephalography (EEG), interictal magnetoencephalography (MEG), seizure semiology, and neuropsychological examination.

Upon MRI, radiologists blinded to the other evaluations reported hippocampal atrophy in 4 patients (Cases 1, 3, 5, and 6). No other abnormality was noted except in the patient in Case 4, who had a left middle cranial arachnoid cyst. Interictal fluordeoxyglucose positron emission tomography (FDG-PET) hypometabolism was seen in the ipsilateral mesial temporal lobe in all but 2 patients (Cases 3 and 10).

All 11 patients underwent the intracarotid amytal procedure (Wada test) for determination of hemispheric language and memory dominance. For language, 10 patients were judged to have left-side dominance and 1 patient to have bilateral dominance. For verbal memory, 6 patients were judged to have left-side dominance (i.e., preserved asymmetry; memory better after right-side injection than after left-side injection), and 5 patients were judged to have bilateral dominance (symmetry).

The study protocol was approved by the Ethics Committee of Osaka University Hospital.

**Neuropsychological Tests for Memory Function Before and After Surgery**

All but 1 patient underwent neuropsychological examination for memory function before and 6 months after surgery by means of both the Wechsler Memory Scale-Revised (WMS-R) and the Mini-Mental State Examination (MMSE); the patient in Case 3 was assessed using only the MMSE. A total of 5 domains were scored: verbal memory, visual memory, general memory, attention/concentration, and delayed recall. An increase or decrease of more than 10% in the WMS-R score after surgery was defined as a significant improvement or decline.

**Provocative Memory Testing by PES**

Presurgical provocative memory testing was performed using the electrodes implanted for localizing the epileptogenic focus. Intracerebral depth electrodes and surface strip and sheet electrodes had been implanted in the left temporal lobe in all 11 patients (implantation was bilateral in 2 patients). The location and number of electrodes depended on the potential area of the epileptogenic zone. The depth electrodes were implanted in the target area with the aid of an MRI-guided stereotactic system (Leksell Coordinate Frame G, Elekta Instrument AB; Fisher ZD stereotactic frame, Stryker Leibinger; or VarioGuide, BrainLAB) and planning software (iPlan, BrainLAB AG; or iNtellect Cranial Navigation System, Stryker Leibinger). The electrode locations were confirmed by postimplantation MRI (Fig. 1) or CT. The depth electrode bundles consisted of 6 cylindrical 1-mm-long platinum contacts spaced 5 mm apart (Unique Medical Co., Ltd.).

For the provocative test, electrical stimulation was performed in the left parahippocampal gyrus (PHG) during a verbal encoding task. The patient was first asked to memorize 3 target words, each presented for 5 seconds, while his or her left PHG was stimulated. For some patients, depending on the results of the preexamination, only 1 or 2 words were presented. The PHG was stimulated by a pair of adjacent electrodes under the conditions described below, after which the patient was distracted for 60 sec-
ons by a simple calculation task. The patient was then instructed to retrieve the target words, either by recall or by recognition (recall: the patient must answer the question “What are the words presented a little while ago?” without being given a clue; recognition: the patient is presented with 2 to 6 words—target and nontarget words—and must respond with a “yes” or “no” as to whether or not he or she recognizes the target words; Fig. 2). The test result was considered positive when 1 or more answers were incorrect. Positivity was confirmed by comparing the patient’s memory function with and without electrical stimulation. When at least 1 pair of electrodes produced a positive response, the test was judged positive.

Stimulation Conditions

Stimulation was current regulated and charge balanced, with biphasic rectangular pulses set below the afterdischarge threshold. The patients were unaware of the stimulation conditions, and no patient reported noticing any effect. Electrode contacts were stimulated through an interface with an electric stimulator (NS101, Unique Medical Co., Ltd.). Stimulation was bipolar at a frequency of 50 Hz and a pulse width of 200 μsec. The surface area of each electrode was 1.77 cm², and the impedance was < 10 kΩ. The limit for stimulation was a current of up to 6.0 mA (0.68 μC/cm²/phase), which is considered safe and is well tolerated in patients with epilepsy who have depth electrodes in the temporal lobe. During stimulation, EEG responses, especially afterdischarges, were recorded by the electrodes not used for stimulation by means of a 128-channel digital EEG system (EEG 2000, Nihon Kohden Corporation).

Surgical Procedures

Ictal EEG recordings obtained via the intracranial electrodes revealed that the epileptic focus was located in the left medial temporal lobe in 6 patients, in the left lateral temporal lobe in 2 patients, in both the left medial and lateral temporal lobes in 1 patient, and in the left and right temporal lobes in 2 patients. Locations of the epileptic foci are shown in Table 2 along with the types of surgeries performed. Of the 6 patients diagnosed with left medial TLE, 1 (Case 4) underwent anterior temporal lobectomy (ATL) combined with hippocampectomy, 4 (Cases 2 and 5–7) underwent selective amygdalohippocampectomy (SAH), and 1 (Case 8) underwent only electrode removal. Of the 2 patients diagnosed with left lateral TLE, 1 (Case 1) underwent ATL, and 1 (Case 9) underwent focal resection within the left lateral temporal lobe without hippocampectomy. The patient (Case 3) diagnosed with left medial and lateral TLE underwent left ATL. A total of 7 patients with left TLE underwent resection of the left hippocampus. Six of these 7 patients were seizure free after surgery (Engel Class I), and 1 (Case 3) showed substantial seizure reduction (Engel Class IIIA). Two patients diagnosed with bilateral TLE underwent only electrode removal (Cases 10 and 11).

Results

Provocative Test Results

PES during memory encoding was performed in all 11 patients. Verbal memory was assessed by means of recognition in all patients; recall was not used for assessment in 2 patients (Cases 6 and 11) because they were not able to give an appropriate response even under normal conditions without the electrical stimulation.

Eight of the 11 patients showed transient verbal memory decline with PES (a positive test). These 8 patients are listed in Table 3. In 7 of the 8 patients, the positive result was observed with stimulation of the anterior part of the PHG, including the entorhinal cortex. An MR image of electrode positions in a representative case (Case 9) is shown in Fig. 1. In this patient, verbal memory disturbance was provoked with electrical stimulation at 6 mA via the depth electrode implanted in the entorhinal cortex, which served as the cathode. In 2 (Cases 8 and 11) of the 7 patients, verbal memory was disturbed with stimulation of the anterior and posterior parahippocampal cortex. In 1 patient (Case 3), the verbal memory decline was induced with stimulation of the posterior PHG but not the anterior PHG.
Pre- and postsurgical WMS-R scores are summarized in Table 4. Seven (Cases 1–3 and 8–11) of the 11 patients had a positive recognition test result. Three (Cases 1–3) of these 7 patients underwent left hippocampal resection, and their WMS-R verbal memory, general memory, and delayed recall scores decreased after surgery. The visual memory score increased in 2 of these 3 patients. The other 4 patients (Cases 8–11) underwent surgical procedures that preserved the left hippocampus. Upon PES, 3 (Cases 5–7) of the 11 patients showed no verbal memory disturbance (a negative test). These 3 patients underwent left hippocampal resection, and their WMS-R verbal memory
scores, attention/concentration scores, and delayed recall scores increased to some extent after surgery (Fig. 3). The patient in Case 4, who had a negative recognition test and positive recall test, underwent left hippocampal resection and showed no change in his MMSE score after surgery.

To some extent, a positive provocative test result corresponded to left-side dominance on the Wada memory test. Five of 6 patients showing left-side dominance on the Wada memory test had a positive provocative test, and 3 of 5 patients showing symmetry on the Wada memory test had a negative provocative test. A patient (Case 6) showing left-side dominance on the Wada memory test and a negative provocative test underwent left SAH, and memory function improved after surgery. Of the 2 patients (Cases 2 and 8) who showed symmetry on the Wada memory test and had a positive provocative test, 1 (Case 2) underwent left SAH, and memory function declined after surgery. The other patient (Case 8) underwent only electrode removal.

For 1 patient (Case 6), the provocative test was postponed because a secondarily generalized seizure following a complex partial seizure was induced by PES. This seizure was considered a habitual seizure induced by stimulation of the epileptogenic zone.

**Discussion**

We found that the provocative test conducted using depth electrodes placed in the PHG can provide reliable complementary information for estimating the verbal memory decline that can be expected after resection of the left hippocampus. In all 4 patients with a negative provocative test for recognition, verbal memory function did not deteriorate after left hippocampal resection. In contrast, verbal memory function declined after left hippocampal resection in 3 patients with a positive provocative test for recognition.

One of the most impressive results of our study was the apparently strong positive association between a negative provocative test result and the preservation of verbal memory function after hippocampectomy. Thus, a negative provocative test for recognition appeared to be a clinically important indicator of a favorable prognosis. To the contrary, a positive provocative test for recognition was related to a poor functional outcome.

Good preoperative memory performance and the absence of hippocampal sclerosis have been reported as risk factors for postoperative memory decline. In support of this, we found that among our patients who underwent hippocampal resection, the postoperative verbal memory score decreased in those whose preoperative verbal memory scores were 75, 79, and 102, whereas postoperative scores surpassed preoperative scores in those whose preoperative scores were 72, 75, and 79. Postoperative memory decline was seen in 2 of our 4 patients with

**TABLE 2. Location of the epileptic focus and type of surgery performed in each patient**

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Epileptic Focus</th>
<th>Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Lt lateral TL</td>
<td>Lt ATL</td>
</tr>
<tr>
<td>2</td>
<td>Lt medial TL</td>
<td>Lt SAH</td>
</tr>
<tr>
<td>3</td>
<td>Lt medial &amp; lateral TL</td>
<td>Lt ATL</td>
</tr>
<tr>
<td>4</td>
<td>Lt medial TL</td>
<td>Lt ATL</td>
</tr>
<tr>
<td>5</td>
<td>Lt medial TL</td>
<td>Lt SAH</td>
</tr>
<tr>
<td>6</td>
<td>Lt medial TL</td>
<td>Lt SAH</td>
</tr>
<tr>
<td>7</td>
<td>Lt medial TL</td>
<td>Lt SAH</td>
</tr>
<tr>
<td>8</td>
<td>Lt medial TL</td>
<td>Removal of electrodes</td>
</tr>
<tr>
<td>9</td>
<td>Lt lateral TL</td>
<td>Focal resection w/o hippocampectomy</td>
</tr>
<tr>
<td>10</td>
<td>Bilateral TL</td>
<td>Removal of electrodes</td>
</tr>
<tr>
<td>11</td>
<td>Bilateral TL</td>
<td>Removal of electrodes</td>
</tr>
</tbody>
</table>

**TABLE 3. Electrode location in the 8 patients with a positive provocative test**

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Electrode Position*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Anterior PHG</td>
</tr>
<tr>
<td>2</td>
<td>Anterior PHG</td>
</tr>
<tr>
<td>3</td>
<td>Posterior PHG</td>
</tr>
<tr>
<td>4</td>
<td>Anterior PHG</td>
</tr>
<tr>
<td>8</td>
<td>Anterior &amp; posterior PHG</td>
</tr>
<tr>
<td>9</td>
<td>Anterior PHG</td>
</tr>
<tr>
<td>10</td>
<td>Anterior PHG</td>
</tr>
<tr>
<td>11</td>
<td>Anterior &amp; posterior PHG</td>
</tr>
</tbody>
</table>

* The location of the electrode was judged by means of postoperative MRI, except in Cases 1 and 4, where it was judged by CT.
hippocampal atrophy and in 1 of our 3 patients without hippocampal atrophy. Our study group was rather small for strict statistical analysis; however, these results suggest that the absence of hippocampal sclerosis is not a perfect predictor of postoperative memory decline. Memory function was preserved if the provocative test was negative, even for those without hippocampal atrophy.

The Wada memory test has been used to predict postoperative memory impairment in patients with left TLE. Early studies that examined memory asymmetry patterns and postoperative memory outcomes in patients with TLE demonstrated poorer memory outcomes in patients with left TLE who showed left-side dominance on the Wada memory test.25,26 Recently, the Wada memory test has been used in the statistical modeling of postoperative memory decline, but the reported studies present conflicting evidence.3,20,26 Our provocative test results were in close agreement with the Wada memory test results. Of the 6 patients who showed preserved asymmetry on the Wada memory test, 5 had a positive provocative test result. However, 1 patient (Case 6) showed left-side dominance on the Wada test and had a negative provocative test result, and his verbal memory improved after left hippocampectomy. Language function will inevitably be impaired for patients in whom verbal memory is being tested on the language-dominant side by the Wada memory test. It is possible that this language disturbance influences the results of the test.3 Additionally, because the hippocampus lies in the watershed zone between the carotid and posterior cerebral arteries,32 the Wada memory test could be sensitive to individual variations in blood flow distribution. Our provocative test can temporarily disturb the specific area being tested and elucidate its function. Our provocative test is potentially more accurate than the

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Wada Memory Test</th>
<th>Provocative Test</th>
<th>Hippocampal Resection</th>
<th>WMS-R (Pre-/Posthippocampectomy)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Recall</td>
<td>Recognition</td>
<td>Verbal Memory</td>
</tr>
<tr>
<td>1</td>
<td>Lt</td>
<td>+</td>
<td>+</td>
<td>Yes</td>
</tr>
<tr>
<td>2</td>
<td>Symmetry</td>
<td>+</td>
<td>+</td>
<td>Yes</td>
</tr>
<tr>
<td>3</td>
<td>Lt</td>
<td>+</td>
<td>+</td>
<td>Yes</td>
</tr>
<tr>
<td>4</td>
<td>Symmetry</td>
<td>+</td>
<td>−</td>
<td>Yes</td>
</tr>
<tr>
<td>5</td>
<td>Symmetry</td>
<td>−</td>
<td>−</td>
<td>Yes</td>
</tr>
<tr>
<td>6</td>
<td>Lt</td>
<td>NA</td>
<td>−</td>
<td>Yes</td>
</tr>
<tr>
<td>7</td>
<td>Symmetry</td>
<td>−</td>
<td>−</td>
<td>Yes</td>
</tr>
<tr>
<td>8</td>
<td>Symmetry</td>
<td>+</td>
<td>+</td>
<td>No</td>
</tr>
<tr>
<td>9</td>
<td>Lt</td>
<td>+</td>
<td>+</td>
<td>No</td>
</tr>
<tr>
<td>10</td>
<td>Lt</td>
<td>NA</td>
<td>+</td>
<td>No</td>
</tr>
</tbody>
</table>

+= positive test result; − = negative test result; NA = not assessed.
Provocative test for verbal memory decline

Wada test in predicting memory decline after left hippocampectomy, and it is quite practical because implantation of the depth electrodes is essential for localizing the epileptic focus.

We provoked memory impairment with electrical stimulation of the left PHG, especially in the left entorhinal area (anterior PHG). Decades of research and clinical observation have established that declarative memory—the ability to remember facts and events—depends on the hippocampus and associated structures in the medial temporal lobe, including the entorhinal, perirhinal, and parahippocampal cortices. Coleshill et al. demonstrated that transient unilateral subthreshold electrical stimulation in the left medial temporal area during encoding could produce impairment of subsequent delayed yes–no recognition memory. They stimulated the left hippocampus and adjacent area via electrodes under stimulus parameters similar to ours, i.e., similar stimulus frequency and charge density. The entorhinal cortex receives about two-thirds of its cortical input from the perirhinal and parahippocampal cortices, and it is the major source of cortical projections to the hippocampus.

Kunii et al. reported observing high-frequency oscillation (HFO) during the verbal memory task with subdural electrodes placed on the PHG in 3 of 6 epileptic patients with a normal left hippocampus. In line with their findings, we speculate that the electrical stimulation in our study may affect HFO in the PHG, resulting in impaired recall and recognition function. Subthreshold electrical stimulation is known to act as a transient lesion near the stimulating electrodes and to simulate brain function after electrode removal. By selectively disrupting functions of the memory system, including the entorhinal cortex, that contribute to memory information processing, PES can be used more effectively than the Wada test to assess the specific effect of hippocampal resection on verbal memory.

Studies have suggested that functional MRI (fMRI) may help predict memory decline following anterior temporal lobe resection. Verbal memory encoding activity that is greater in the left hippocampus than in the right hippocampus has been related to the extent of verbal memory decline following left anterior temporal lobe resection. Recently, fMRI-based mapping was shown by multiple regression analysis to have strong predictive power for postoperative memory decline. Our provocative test is more straightforward than fMRI for predicting posthippocampectomy memory decline in patients who have already had depth electrodes implanted for the purpose of presurgical seizure localization. Our method does not require us to set a threshold for the prediction of memory decline, and it takes less than 1 hour to obtain a definitive result. Thus, PES seems to be a clinically valuable provocative test for predicting postoperative memory decline in surgical candidates with medial TLE involving the language-dominant hemisphere and depth electrodes implanted in the PHG. Because verbal memory decline is a serious postoperative complication, it is essential to improve prediction. In terms of mimicking posthippocampectomy, our method is quite different from conventional methods. Our study was limited by the small patient group, and statistical analysis would not have been informative. A logical next step would be to include our provocative testing method in a multiple regression analysis to weigh its utility for predicting postoperative memory decline.

To the best of our knowledge, this is the first reported study to demonstrate the applicability of provocative verbal memory testing via depth electrodes before epilepsy surgery.

Conclusions

Our study showed that provocative memory testing performed via depth electrodes is a reliable technique that can be used to avoid postoperative verbal memory decline in patients with TLE. Such testing could be an important adjunct in clinical practice and might be of substantial assistance in determining indications for surgery. Further studies in a larger series of patients are needed to confirm the reliability of this diagnostic procedure.

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References


**Disclosures**

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

**Author Contributions**

Conception and design: Kishima, Kato. Acquisition of data: Kishima, Tani, Khoo, Yanagisawa, Oshino, Maruo, Hosomi, Hirata, Kazui, Nomura, Aly. Analysis and interpretation of data: Kishima, Tani, Kazui, Nomura, Aly. Drafting the article: Tani, Maruo. Critically revising the article: Kishima, Khoo, Yanagisawa, Oshino. Reviewed submitted version of manuscript: Kishima, Tani, Khoo, Yanagisawa, Oshino, Maruo, Hosomi, Hirata, Aly, Kato, Yoshimine. Approved the final version of the manuscript on behalf of all authors: Kishima. Study supervision: Yoshimine.

**Supplemental Information**

**Previous Presentations**

Portions of this work were presented in poster form at the 29th International Epilepsy Congress held in Rome, Italy, on August 31, 2011.

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