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# Verbal Memory Localized in Non-language-dominant Hemisphere: Atypical Lateralization Revealed by Material-specific Memory Evaluation Using Super-selective Wada Test

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## Abstract

**Hippocampectomy is effective for drug-resistant mesial temporal lobe epilepsy with hippocampal sclerosis. However, multiple studies have reported high risks associated with hippocampectomy in patients with mesial temporal lobe epilepsy without hippocampal sclerosis on magnetic resonance imaging and in those with preserved memory function. Verbal memory and language functions are believed to coexist in the same hemisphere. We present a case of left mesial temporal lobe epilepsy with atypical memory function lateralization revealed by super-selective infusion of propofol to the intracranial artery (super-selective Wada test). A 24-year-old right-handed man with drug-resistant focal impaired awareness seizures was diagnosed with left mesial temporal lobe epilepsy without hippocampal sclerosis, but he showed preserved verbal intelligence quotient and memory, suggesting a high risk of severe memory decline after hippocampectomy. We performed super-selective Wada test to the posterior cerebral artery to assess the lateralization of verbal and visual memory separately, and to the middle cerebral artery to assess language function. The results revealed right-sided dominance for both verbal and visual memory, although the language was left-dominant. Hippocampectomy was performed and resulted in freedom from seizures. Memory assessments 1 year postoperatively showed no decline in all subtests. In patients with drug-resistant epilepsy exhibiting atypical neuropsychological profiles, the memory-dominant, and language-dominant hemispheres may not align; detailed evaluations of function lateralization are necessary for tailored treatment.**

Keywords: verbal memory, memory lateralization, hippocampus, super-selective infusion, epilepsy surgery

## Introduction

Epilepsy affects approximately 1% of the global population. While many patients with epilepsy achieve a seizure-free status with medication, approximately 30% of them do not respond effectively to drug treatment.[1)] Surgical treatment is a viable option for drug-resistant cases of mesial temporal lobe epilepsy (MTLE), a condition characterized by an epileptic focus in the ipsilateral hippocampus.[2)] However, the risk of memory decline after hippocampal resection must be considered. When the language-dominant hemisphere is ipsilateral to the epileptic focus, hippocampectomy is associated with a decline in verbal memory.[3,4)] In contrast, hippocampectomy on the contralateral side of the language-dominant hemisphere is associated with visual memory decline,[5)] albeit with less distinct lateralization compared to verbal memory decline in left hippocampectomy.[6)] Predictive factors of postoperative verbal memory

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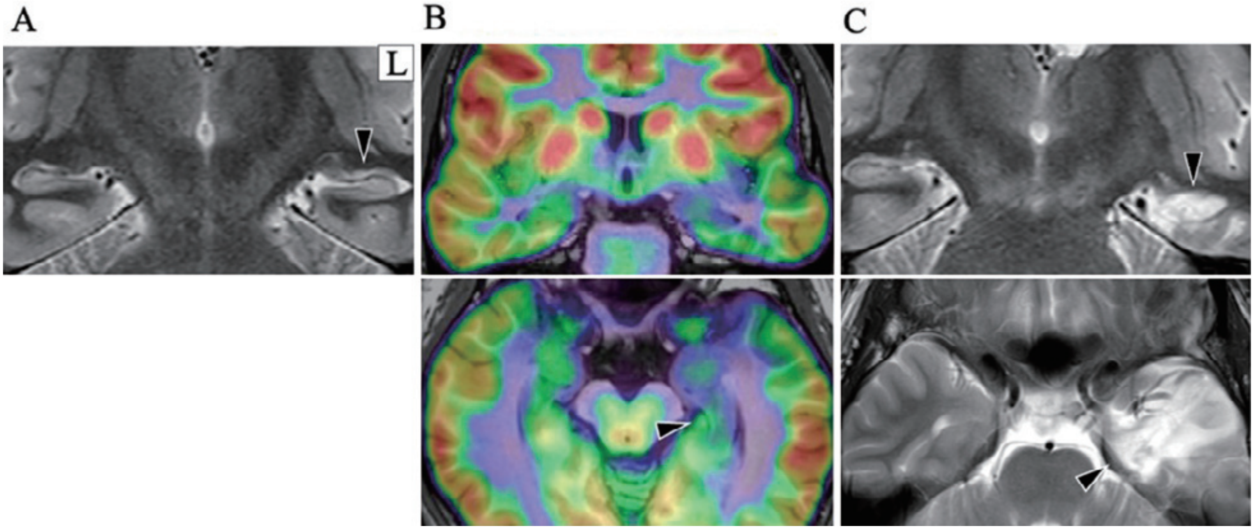


**Fig. 1 Preoperative and postoperative neuroimaging. A: Presurgical MRI showing no evidence of hippocampal atrophy. B: Presurgical FDG-PET fusion images showing reduced accumulation in the anterior basal portion of the left temporal lobe. C: Postsurgical MRI of hippocampectomy.**
**FDG-PET: fluorodeoxyglucose positron-emission tomography; MRI: magnetic resonance imaging**

decline following temporal lobectomy include age at surgery, age of onset, duration of illness, etiology of epilepsy, side of surgery, Wada test results, remaining hippocampal volume, and preoperative cognitive functions.[7,8] Patients with preserved memory function, especially in verbal memory, have been reported to have a higher risk of memory decline after left hippocampectomy than those with impaired verbal memory functions.[9] A tailored risk assessment aids in rational decision-making regarding the suitability of surgery.

Herein, we present a case of left MTLE with preserved memory function in both verbal and visual materials. The patient was right-handed and had language dominance in the left hemisphere; therefore, left hippocampectomy could have posed a high risk of postoperative memory decline. Given that preserved memory suggests atypical lateralization, we performed a super-selective Wada test (ssWada), a detailed memory function assessment through a selective infusion of an anesthetic agent to the posterior cerebral artery (PCA) with a precise neurocognitive test.

## Case Reports

A 24-year-old right-handed man with 16 years of education, employed at the city office, was referred to our institution for epilepsy surgery. He had a history of febrile seizures from ages 2 to 5 years. At the age of 16 years, he developed monthly focal impaired awareness seizure (FIAS), characterized by altered consciousness and oral automatism. He exhibited aphasic symptoms of FIAS, occasionally followed by focal-to-bilateral tonic-clonic seizures. His seizures occurred every 2-3 months and were drug-resistant, prompting referral to the comprehensive epilepsy center.

Long-term video-electroencephalography (EEG) monitoring revealed ictal EEG changes in the left temporal region. Magnetoencephalography revealed equivalent current dipoles of interictal epileptiform discharges clustered in the left medial temporal lobe. Magnetic resonance imaging (MRI) showed no evidence of hippocampal sclerosis (HS) (Fig. 1A); however, fluorodeoxyglucose positron-emission tomography (FDG-PET) revealed reduced accumulation in the mesial structure of the left anterior temporal lobe, including the hippocampus, parahippocampal gyrus, and fusiform gyrus (Fig. 1B). These results supported the presurgical diagnosis of left MTLE without HS.

Neurological examinations revealed no abnormalities. Neuropsychological assessment results, including the Wechsler Adult Intelligence Scale III (WAIS-III) verbal intelligence quotient (VIQ): 122 and Performance IQ: 91, and the Wechsler Memory Scale-Revised (WMS-R) Verbal Memory: 94 and Visual Memory: 106, indicated normal cognitive function (Supplementary Table 1). Aphasia during seizure semiology suggested an epileptic focus in the language-dominant hemisphere. Cortical activation with language tasks on functional MRI (fMRI) indicated that the language-dominant hemisphere was the left hemisphere.

We predicted a high risk of memory decline after hippocampectomy for the patient based on the VIQ score and preserved verbal memory. To evaluate the functional risk in detail and consider the potential impacts on employment or other social activities, we performed ssWada.

### ssWada

All procedures were performed by endovascular neurosurgeons and behavioral neurologists in an endovascular

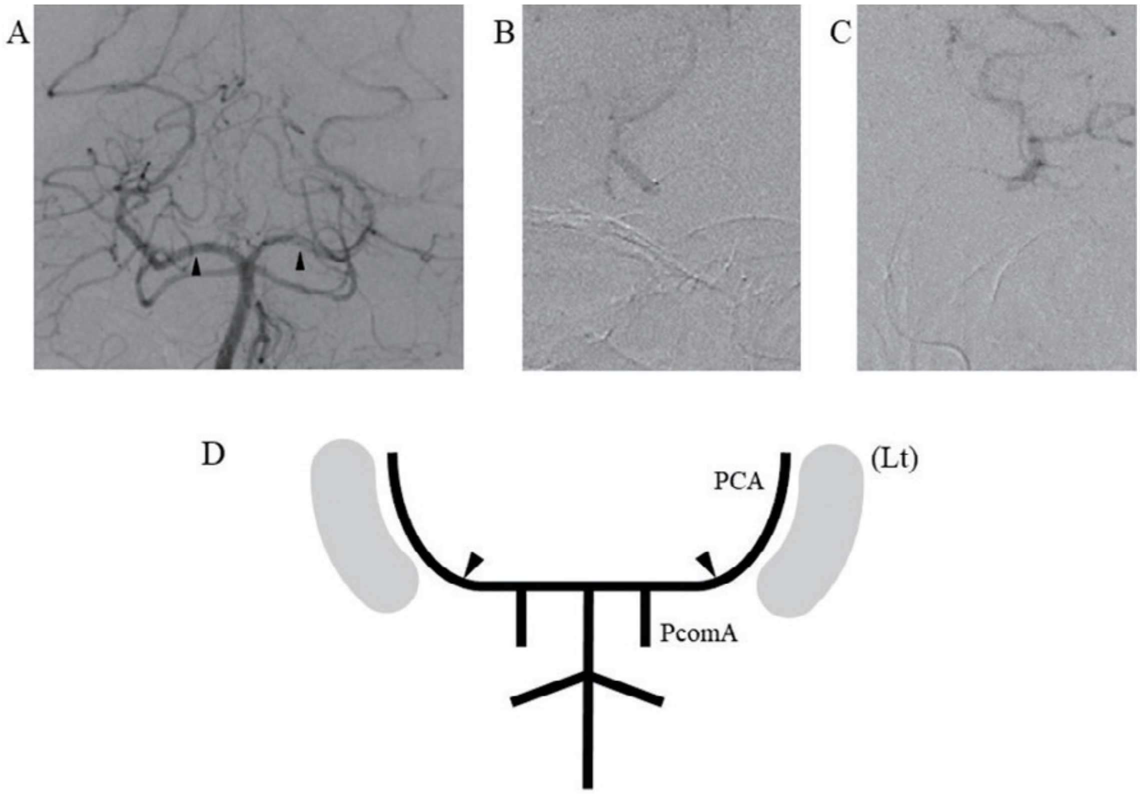


**Fig. 2 Angiography and schematic of vascular anatomy. A: Angiography of the vertebrobasilar artery territory. Arrowheads indicate P1-P2 junctions, which connect the PcomA with the PCA. B, C: Super-selective angiography of right and left P2, respectively. D: Schematic of vascular anatomy, hippocampal formation (filled gray), and infusion site of propofol (filled arrowhead).**
**PCA: posterior cerebral artery; PcomA: posterior communicating artery**

neurosurgical suite, as previously reported.[10] After confirmation of the perfusion area with super-selective angiography, propofol (1 mg/mL) was infused at 1 mL/s after baseline evaluation of the neurological findings (Fig. 2).

The amount of infused propofol was 5.0 mg in the P2 segment of the PCA and 10 mg in the M1 segment of the middle cerebral artery (MCA), the established standard dose according to our previous reports.[10,11] Scalp EEG was monitored to confirm the electrophysiological changes during drug infusion. Behavioral neurologists evaluated all neurological symptoms pre- and post-infusion as the baseline and anesthetic conditions, respectively. To assess language impairment, language tasks included sequential speech, oral comprehension, repetition, naming, reading aloud, reading comprehension, and writing. The memory tasks comprised sets of 8 words as verbal items and 8 pictures and 5 figures as nonverbal items. The number of stimuli that were successfully recognized after the disappearance of the anesthetic effect was recorded. The memory score was calculated by subtracting the number of stimuli recognized during anesthesia from the number of those during the baseline tasks, indicating the extent of decline from baseline. The patient was asked to recall and recognize words, pictures, and figures. If the memory score was ≥2, the infusion area was considered to have contributed to the memory function. To rule out residual effects from the previous infusion, the interval was adjusted to 3 times the symptom duration before the next infusion. To account for infusion order and fatigue effects, we verified baseline scores at each trial to compare them with scores under anesthesia.

The infusion site at the P2 segment of the left and that on the right PCA were selected to induce memory symptoms, including the hippocampal formation and basal temporal structures. The M1 segment of the MCA was selected to induce language symptoms in the language areas of the cortex. Anesthetic effects were confirmed by neurological changes, such as hemianopia at the P2 and upper limb paresis at M1. EEG changes were also confirmed within seconds of infusion.

The test results are presented in Fig. 3. No language symptoms or consciousness disturbances were induced by the infusion into the left or right PCA (Supplementary Table 2). In the memory task, infusion into the left PCA induced no decline in recognition tasks for words and pictures, with only a 1-point decrease for figures (Fig. 3A). However, infusion into the right PCA resulted in more than 2 decreased recognition task scores for both words

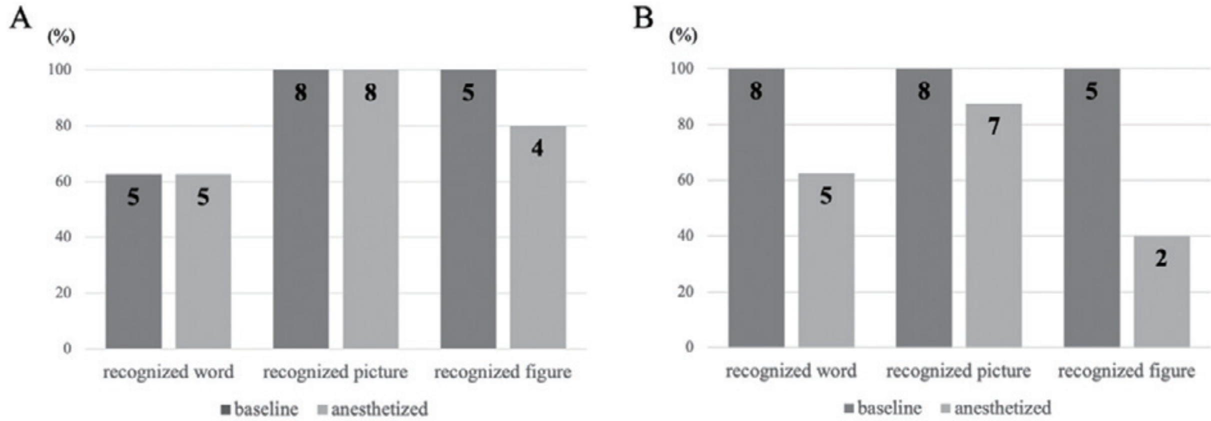


**Fig. 3 Percentage of correct answers in each task: recognized words, pictures, and figures for the left PCA (A) and right PCA (B). Note that the scores for all items declined with the infusion into the right PCA, while scores were maintained with the infusion into the left PCA.**
**PCA: posterior cerebral artery**

and figures (Fig. 3B). During left M1 infusion to assess language lateralization, the patient presented with global aphasia, including both speech and comprehension deficits, without any disturbance in consciousness. This confirms that the left hemisphere was dominant in terms of language.

In summary, we expected a lower functional risk after left hippocampectomy than previously estimated based on the results of the comprehensive epilepsy evaluation. The ssWada estimated that there was less memory function in the left PCA territory and the functional reserve of the right PCA territory for memory function in both verbal and visual materials.

**Surgical treatment and outcomes**

Based on our interpretation, surgery was deemed reasonable. Anterior temporal lobectomy with amygdalohippocampectomy was performed (Fig. 1C). The seizure outcome was Engel's Ia at 24 months after surgery. Postoperative histopathological examination revealed HS International League Against Epilepsy (ILAE) type 1.

Postoperative neuropsychological testing, conducted 12 months after surgery revealed no cognitive decline; WMS-R scores were 98 for verbal memory and 121 for visual memory. All the WMS-R and WAIS-III subtests showed maintenance of function and improvement (Supplementary Table 1). There were no subjective complaints of decreased function. He returned to his job and subsequently remained seizure-free.

## Discussion

We reported the case of a patient with left temporal epilepsy who demonstrated the dominance of both verbal and visual memories in the non-language-dominant right hemisphere, as confirmed by ssWada. This result significantly influenced the surgical indication. After the hippocampectomy, the patient had a good seizure outcome with preserved memory function, indicating the reliability of the test results.

Fatoorechi et al.[12] reported that left hippocampectomy caused postoperative verbal memory decline in 69% of temporal lobe epilepsy (TLE) patients with left hemisphere language dominance, compared to only 5% in those with atypical language lateralization. Helmstaedter et al.[13] also reported that TLE patients with right-hemisphere language dominance showed better postoperative verbal memory than patients with left or bilateral language dominance. Additionally, we reported a case of right TLE with right language dominance and left verbal memory dominance.[14] These findings suggest a parallel reorganization of TLE patients' verbal memory and language functions.

In this case, we confirmed global aphasia resulted from the left M1 injection, demonstrating the language-dominant hemisphere to be on the left side. Global aphasia following M1 injection typically indicates ipsilateral language dominance.[11]

Several fMRI studies in patients with left MTLE have reported increased blood oxygen level-dependent (BOLD) signals in the hippocampus contralateral to the language-dominant hemisphere during verbal memory tasks compared to those in normal controls, suggesting the reorganization of memory function from the dominant to the non-dominant hemisphere.[15,16] Powell et al.[16] demonstrated that greater activation of BOLD signal in the damaged left hippocampus correlated with better verbal memory test performance in left TLE patients with HS, indicating that reorganizing memory function from the affected side to the contralateral side does not equate to compensatory function.

Another study using FDG-PET reported that postoperative memory decline correlated with reduced accumulation in preoperative FDG-PET.[17] Reduced glucose metabolism reflected lower neuronal activity in the region, suggesting a comparatively lower risk of functional decline after cortical resection than regions with normal glucose metabolism.

In this case, the ssWada results indicated that the patient had a low level of memory function in the left hippocampus and a high level of functional reserve in the contralateral hippocampus for both verbal and visual memories. Although it is not clear whether the atypical memory lateralization in this patient was congenital or acquired due to epileptic lesions, we emphasize the importance of considering that both verbal and visual memory functions can be lateralized in the language nondominant hemisphere.

The Wada test, traditionally a gold standard for assessing language and memory lateralization, is being supplanted by fMRI due to its noninvasive nature.[18] The Wada test remains effective for atypical lateralization[19] but has several limitations in assessing memory lateralization. First, perfusion to the hippocampus is minimal during the infusion of anesthetics into the internal carotid artery (ICA).[20] Second, there are potential impacts of aphasia and disturbance of consciousness on the performance of memory tasks, especially verbal memory, during anesthesia.[21,22] Previous studies have identified language hemispheric dominance as a confounding factor in the interpretation of memory scores of the Wada test.[23] Third, scores for verbal memory and visual memory are usually combined into a single memory score, without assessing the laterality of verbal memory and visual memory separately in ICA-Wada.[18] Reports on the PCA Wada test have been presented to address the first and second issues, especially in cases where ICA-Wada assessment is difficult.[24-26] Most of the mesial temporal lobe, including the hippocampus, is supplied by the PCA; therefore, super-selective infusion from the PCA can be superior to that from the ICA in assessing hippocampal function independently. Regarding the third limitation, most studies on the PCA Wada test have not examined verbal and nonverbal memory separately.[24,25] Yen et al.[26] separately scored verbal and nonverbal memory for PCA infusion but only assessed the affected side without evaluating contralateral memory function.

To address these shortcomings, we developed a more sophisticated method, called the ssWada. This approach enabled the elucidation of memory lateralization with minimal effects on consciousness or language. We also evaluated verbal and visual memory separately using memory scores and compared them quantitatively. In this case, comparing the left and right PCA memory scores from the ssWada test revealed an unusual memory lateralization, with the right hemisphere dominant for both verbal and visual memory. Due to clinical priorities for minimizing invasiveness, we could not directly compare ICA-Wada and ssWada results. In a previous report, we acknowledged and discussed the limitations of our ICA-Wada experience and earlier ICA-Wada studies. We now apply the ssWada in cases where noninvasive evaluation suggests potential atypical lateralization.[10] In our case, the absence of verbal memory decline and lack of hippocampal abnormalities on MRI were considered indicative of atypical lateralization. Although histopathology ultimately revealed HS, surgical indications must be carefully evaluated in cases where no structural abnormalities are identified on preoperative MRI.[27]

Tani et al.[28] demonstrated the efficacy of electrical stimulation from an intracranial depth electrode positioned in the parahippocampal gyrus during verbal memory tasks in predicting postsurgical verbal memory function in a patient with left TLE. It is comparable with our methodology in the point that direct electrical stimulation offers more targeted intervention and precise delineation of affected areas. On the contrary, we consider ssWada to have several advantages over intracranial electrode stimulation. One major advantage is its minimally invasive nature. The ssWada enables bilateral hippocampal assessment as presurgical evaluation without requiring an intracranial procedure. Recent advancements in devices and techniques in endovascular procedures have contributed to safety and efficacy. Another advantage of ssWada is its flexibility of affected brain volume and time, enabling to assess both memory and language functions in a single session with several minutes.[10]

In this case, the fact that neither verbal nor visual memories were lateralized on the affected side supported the decision for surgery despite previous studies suggesting a high risk of memory decline.[9] The preserved memory function indicates that the prediction from the ssWada results was accurate in this case. This methodology provides valuable insights for assessing surgical candidacy in patients with an elevated risk of cognitive deterioration.

The ssWada methodology for PCA has several limitations. One limitation is the potential variability in the perfusion area of the hippocampal formations. Anastomotic collaterals exist between the PCA branch and the anterior choroidal artery,[29] but these anastomoses are difficult to visualize on conventional cerebral angiography. Anatomical variations must be considered, as they can impact cognitive scores. Further anatomical insights and accumulation of case data are needed. Also, drug distribution to the thalamus via the thalamoperforating artery or thalamogeniculate artery may influence consciousness level during PCA infusion.[29] We reported the result of PCA infusion at P2 segment, that the incidence of consciousness disturbances was notably low, with 97% of participants able to report subjective symptoms and 91% capable of performing memory tasks.[10] These findings support the validity of our methodology.

In conclusion, we presented a case of left MTLE with left-sided language and right-sided memory dominance in both verbal and visual memory. This lateralization pattern deviated from conventional theory, but was clearly indicated by the ssWada. The development of techniques for evaluating material-specific memory lateralization will lead to more sophisticated predictions for functional outcomes and logical surgical indications.

## Supplementary Material

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## Ethical Statement

This study was approved by the ethics committee of Tohoku University Hospital (2020-1-083) and was conducted in accordance with the 1964 Declaration of Helsinki and its later amendments. We obtained permission and informed consent for publishing information and images with anonymization.

## Disclaimer

Author Nobukazu Nakasato is one of the Editorial Board members of the Journal. This author was not involved in the peer-review or decision-making process for this paper.

## Conflicts of Interest Disclosure

All authors have no conflict of interest.

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