

## **Factors associated with somnolence during brain function mapping in awake craniotomy**

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## **Abstract**

Somnolence during brain function mapping is one of the factors that inhibit the accomplishment of the goals of awake craniotomy. We examined the effect of anesthesia depth measured by bispectral index (BIS) during pre-awake phase on somnolence during brain function mapping and also explored the factors associated with somnolence. We examined the association between BIS values during pre-awake phase and somnolence during the first 30 minutes of brain function mapping in 55 patients who underwent awake craniotomy at Kyoto University Hospital from 2015 to 2018. The pre-awake BIS value was defined as the mean BIS value for 60 minutes before the removal of the airway. Somnolence during brain function mapping was the primary outcome, defined as either of the following conditions: inability to follow up, disorientation, or inability to assess speech function. Additionally, we compared patient or perioperative variables between patients with/without somnolence. Somnolence occurred in 14 patients (25.5%), of which 6 patients (10.9%) were unable to complete brain function mapping. There was no significant difference in the pre-awake BIS value between patients with/without somnolence (median: 46 vs. 49,  $P = 0.192$ ). Somnolence was not significantly associated with age, gender, and the number of preoperative anticonvulsive drugs, but patients with somnolence had a significantly lower preoperative Western Aphasia Battery (WAB) aphasia quotient score (median 93.8 vs. 98.6,  $P = 0.011$ ). We did not find an association between pre-awake BIS value and somnolence during brain function mapping. Somnolence likely occurs in patients with a low preoperative WAB aphasia quotient score.

**Key words:** awake craniotomy, somnolence, bispectral index, Western Aphasia Battery

## 1. Introduction

Somnolence during brain function mapping is one of the serious problems that inhibit the identification of the specific location of the eloquent cortex to minimize an iatrogenic neurological deficit, which is the goal of awake craniotomy. However, there is limited data on the incidence of and risk factors for somnolence during brain function mapping in awake craniotomy.

During pre-awake phase in awake craniotomy, propofol has been widely used to maintain general anesthesia; however, its pharmacokinetics may be altered by various factors including age, gender, weight, preexisting disease, and concomitant medication [1–4], and therefore the amount of propofol required to maintain general anesthesia may differ widely among individuals. To overcome these individual differences in the pharmacokinetics of propofol, bispectral index (BIS®; Aspect Medical System, Norwood, MA) monitoring has been used as an index for monitoring the electrical activity of the cerebral cortex and the sedative ingredients of anesthesia [5,6]. It has been reported that the use of BIS monitoring reduced anesthetic use [7] and the BIS-guided anesthesia could improve postoperative recovery from anesthesia [8].

We hypothesized that the depth of anesthesia during pre-awake phase was associated with somnolence during brain function mapping in awake craniotomy and examined the relationship between the BIS values during pre-awake phase and somnolence during brain function mapping. Moreover, we explored the factors associated with somnolence during brain function mapping.

## 2. Methods

### 2.1. Patient population

This single-center retrospective study was approved by the ethics committee of Kyoto University Hospital (approval number: R1653-1; February 8, 2020); the requirement for informed consent was waived. This manuscript adheres to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [9]. We included patients who underwent awake craniotomy at Kyoto University Hospital, a 1121-bed teaching hospital in Japan, from May 2015 to August 2018. We excluded patients whose record of the verbal assessment during brain function mapping or pre-wake BIS values were not available.

### 2.2. Anesthetic management for awake craniotomy

As reported previously, anesthesia during the pre-awake phase was conducted based on a standardized institutional protocol [10]. None of the patients received premedication. Anesthesia is induced and maintained by continuous infusion of propofol and remifentanyl, combined with infiltration anesthesia with local anesthetics and scalp nerve blocks. A supraglottic airway device (LMA ProSeal™ [The Laryngeal Mask Company, Ltd, Wooburn Green Bucks, UK] or i-gel™ [Intersurgical, Wokingham, UK]) was used to secure the airway during craniotomy. After the general anesthesia was induced and airway secured, the BIS monitor was attached across the nasal bridge. The standard BIS uses a bifrontal montage, but the location of the BIS monitor may be too close to the surgical field or may interfere with Mayfield pin insertion with this approach. Therefore, the approach of attaching a BIS monitor across the nasal bridge was selected, which has been validated in the previous study [11].

Propofol infusion was discontinued after making the dural incision. Simultaneously, remifentanyl infusion was discontinued or reduced, which was decided at the discretion of the attending anesthesiologist. After confirmation of spontaneous breathing and awakening of the patient (becoming responsive to stimuli), the supraglottic airway device was removed.

### *2.3. Data collection*

The following patient and perioperative variables were obtained from the anesthesia information management system and the electronic medical record system: age, gender, body mass index, the American Society of Anesthesiologists physical status (ASA-PS), preoperative test results, etiology of brain lesion (brain tumor/epilepsy), operation site, the number of preoperative anticonvulsive drugs, amount and timing of drugs used intraoperatively, propofol target concentration and remifentanyl infusion rate during pre-awake phase, operation time, blood loss, and duration of pre-awake/awake phases.

### *2.4. Exposure*

The primary exposure was BIS values for 60 minutes before awakening (BIS<sub>60</sub>), defined as mean of all BIS values recorded in the 60 minutes prior cessation of propofol infusion. BIS values with a signal quality index below 50% were removed from the data analysis. Secondary exposures were BIS values for 30 minutes before awakening (BIS<sub>30</sub>; mean of all BIS values recorded in the 60 minutes prior cessation of propofol infusion) and BIS values during pre-awake phase (BIS<sub>pre</sub>; mean of all BIS values recorded from insertion of airway device to cessation of propofol infusion).

### 2.5. Outcomes

Somnolence was the primary outcome during brain function mapping, which was defined as either of the following conditions endured for more than 30 minutes after removal of the airway securing device: 1) inability to follow up, 2) disorientation, or 3) inability to assess speech function. Record of the verbal assessment determines the presence or absence of somnolence.

### 2.6. Statistical analyses

Continuous variables were presented as medians (interquartile range) and compared using the Mann–Whitney U test. Categorical variables were presented as numbers (percentage) and compared using the Pearson chi-square test or Fisher exact test, as appropriate.

The association between BIS values before awakening and somnolence during brain function mapping was examined by comparing BIS<sub>60</sub> in patients with/without somnolence. Additionally, patients were divided into three groups according to BIS<sub>60</sub> values ( $\text{BIS}_{60} < 45$ ,  $45 \leq \text{BIS}_{60} < 55$ , and  $\text{BIS}_{60} \geq 55$ ), and the incidences of somnolence among the three groups were compared.

As exploratory analyses, we investigated patient and surgical factors associated with somnolence during brain function mapping. In these exploratory analyses, we included patients with missing pre-awake BIS values. In addition to patient and perioperative variables, preoperative score on the Japanese version of Western Aphasia Battery (WAB) aphasia quotient, preoperative neuropsychological performance assessed based on the Japanese version of Wechsler Adult Intelligence Scale–Third edition (verbal, performance, and full-scale intelligence quotient), and preoperative memory function

assessed based on the Japanese version of Wechsler Memory Scale–Revised (verbal memory, visual memory, general memory, attention/concentration, and delayed recall) were compared in patients with/without somnolence. We performed receiver operating characteristic (ROC) curve analysis to evaluate the ability of a continuous variable to predict somnolence during brain function mapping. By maximizing the Youden index (sensitivity + specificity - 1), the optimal cutoff point was determined.

All statistical tests were two tailed, and  $P < 0.05$  was considered statistically significant. All statistical analyses were performed using Stata version 16.0 (StataCorp, College Station, Texas, USA).

### **3. Results**

Seventy-one awake craniotomies were performed during the study period. After excluding three patients for whom the record of the verbal assessment during brain function mapping was not available and 13 patients for whom pre-wake BIS values were not available, 55 patients were included in the study.

Among the 55 patients, 14 patients (25.5%) had somnolence during brain function mapping, of which six patients (10.9%) were unable to complete brain function mapping. Table 1 presented the patient characteristics and perioperative variables stratified by the presence or absence of somnolence. Except for a tendency for a slightly longer time between discontinuation of propofol infusion and removal of the airway device in patients with somnolence, no significant patient or perioperative factors associated with somnolence were found.

The median BIS<sub>60</sub> for the study participants was 49 (interquartile range: 43–57). BIS<sub>60</sub> was similar between patients with/without somnolence (46 vs. 49,  $P = 0.192$ ). Similarly,

BIS<sub>30</sub> and BIS<sub>pre</sub> did not differ significantly between the groups (BIS<sub>30</sub>: 47 vs. 51,  $P = 0.164$ ; BIS<sub>pre</sub>: 45 vs. 50,  $P = 0.132$ ). However, when we divided study participants into three groups according to BIS<sub>60</sub> values (BIS<sub>60</sub> < 45,  $45 \leq \text{BIS}_{60} < 55$ , and  $\text{BIS}_{60} \geq 55$ ), more patients with a BIS<sub>60</sub> value of < 45 tended to have somnolence (Fig. 1).

Thereafter, we explored the factors associated with somnolence. Factors such as age, gender, and the number of preoperative anticonvulsive drugs could not be found to be associated with somnolence, but the preoperative WAB aphasia quotient score was significantly lower in patients with somnolence (median: 93.8 vs. 98.6,  $P = 0.011$ ; Table 2). The area under the ROC curve of the WAB aphasia quotient score was 0.744 and the cutoff value for the maximum Youden index was 95 (Fig. 2). Of the 51 patients for whom a WAB aphasia quotient score was available, 11 (21.6%) had a WAB aphasia quotient score less than 95; the incidences of somnolence were 63.6% and 12.5% in patients with a WAB aphasia quotient score of < 95 and  $\geq 95$ , respectively ( $P < 0.001$ ; Fig.3).

#### 4. Discussion

In the present study, the relationship between the pre-awake BIS value and somnolence during brain function mapping was examined, but a significant association between pre-awake BIS values and somnolence was not found. In an exploratory analysis, the preoperative WAB aphasia quotient score was significantly associated with somnolence, and an optimal cutoff point of 95 was determined.

In a study by Nossek et al. [12] that analyzed 477 cases of awake craniotomy, 37 patients (7.8%) experienced awake craniotomy failure (conversion to general anesthesia

was required or adequate mapping/monitoring could not have been achieved), and the leading cause of awake craniotomy failure was communication difficulties. In our study, somnolence occurred in about a quarter of the cases, and brain function mapping could not be performed throughout the awake phase in nearly half of them. These data suggest that obtaining an arousal that is good enough for brain function mapping in awake craniotomy remains a challenge.

We examined the association between anesthesia depth during pre-awake phase and somnolence during brain function mapping by comparing pre-awake BIS values between patients with/without somnolence; however, a significant association was not found. One possible explanation for the lack of association is that somnolence during brain function mapping is not simply due to residual anesthetics but is multifactorial. In our study, age and gender, which are known to be associated with propofol pharmacokinetics [2,3], were not significantly associated with somnolence, indicating that factors other than residual anesthetics may be involved in somnolence during brain function mapping.

Nevertheless, in an analysis in which patients were divided into three groups according to their BIS<sub>60</sub> values, the patients with a BIS<sub>60</sub> of < 45 tended to have more somnolence during brain function mapping. Given that the recommended range of BIS is between 40 to 60 during maintenance of anesthesia [13,14] and 55 to 70 at 15 minutes prior to the end of surgery [15], a BIS<sub>60</sub> of < 45 may reflect the fact that propofol is being administered more than required for maintenance of general anesthesia. Although it should be confirmed in a larger study, our data suggest that a very low BIS value (e.g., < 45) during pre-awake phase might be associated with somnolence during brain function mapping.

In an exploratory analysis, the preoperative WAB aphasia quotient score was significantly associated with somnolence. Predicting somnolence or communication difficulties could help in patient selection for awake craniotomy but patient or perioperative factors associated with somnolence or communication difficulties are not known, except for a report that preoperative mixed dysphasia and treatment with phenytoin were related to awake craniotomy failure due to lack of communication [16]. Our analysis showing that even a small decrease in WAB aphasia quotient score (e.g., 90 to <95) is associated with somnolence suggests that WAB aphasia quotient score might be a promising predictor of somnolence during brain function mapping. Future studies are needed to confirm the association between the preoperative WAB aphasia quotient score and somnolence and to find the optimal cutoff value.

This study has limitations which are as follows. This was a single-center study, which may reduce the generalizability of our results. The results of this observational study examined an association which does not imply a causal relationship. To avoid interfering with surgical manipulation or Mayfield pin insertion, we used the approach of attaching a BIS monitor across the nasal bridge instead of the standard approach (bifrontal montage). However, our approach has been validated in the previous study [11]. Finally, our sample size was small and type II error (incorrectly retaining the null hypothesis) cannot be excluded.

## **5. Conclusions**

We did not find any association between pre-wake BIS values and somnolence during brain function mapping. It was suggested that patients with a low preoperative WAB

aphasia quotient score were more likely to be less cooperative during brain function mapping in the first 30 minutes after laryngeal mask removal.

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### **Declaration of competing interest**

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Tables

Table 1. Patient characteristics and perioperative variables stratified by the presence or absence of somnolence

|                                                        | All patients (n = 55) | With somnolence<br>(n = 14) | Without somnolence<br>(n= 41) | P value |
|--------------------------------------------------------|-----------------------|-----------------------------|-------------------------------|---------|
| Age (years)                                            | 39 [29–50]            | 44 [36–59]                  | 38 [26–50]                    | 0.344   |
| Female                                                 | 30 (54.5%)            | 9 (64.3%)                   | 21 (51.2%)                    | 0.397   |
| Body mass index (kg/m <sup>2</sup> )                   | 21.9 [19.5–24.5]      | 21.3 [18.2–24.8]            | 22.3 [19.6–24.5]              | 0.524   |
| ASA-PS (I/II/III)                                      | 14/39/2               | 4/9/1                       | 10/30/1                       | 0.663   |
| Preoperative total bilirubin (mg/dL)                   | 0.5 [0.4–0.8]         | 0.5 [0.4–0.9]               | 0.5 [0.4–0.8]                 | 0.945   |
| Preoperative creatinine (mg/dL)                        | 0.7 [0.6–0.8]         | 0.6 [0.5–0.9]               | 0.7 [0.6–0.8]                 | 0.493   |
| Number of preoperative anticonvulsive drugs (0/1/2/≥3) | 4/29/9/13             | 2/6/3/3                     | 2/23/6/10                     | 0.583   |
| Site of the lesion                                     |                       |                             |                               | 0.453   |
| Frontal lobe                                           | 22 (40.0%)            | 7 (50.0%)                   | 15 (36.6%)                    |         |
| Temporal lobe                                          | 17 (30.9%)            | 5 (35.7%)                   | 12 (29.3%)                    |         |

|                                                    |                  |                  |                  |       |
|----------------------------------------------------|------------------|------------------|------------------|-------|
| Parietal lobe                                      | 5 (9.1%)         | 0 (0.0%)         | 5 (12.2%)        |       |
| Multiple lobes/other                               | 11 (20.0%)       | 2 (14.3%)        | 9 (21.9%)        |       |
| Brain tumor/epilepsy                               | 43/12            | 11/3             | 32/9             | 0.967 |
| Use of anticonvulsive drugs during pre-awake phase | 37 (67.3%)       | 11 (78.6%)       | 26 (63.4%)       | 0.297 |
| Use of droperidol during pre-awake phase           | 1 (1.8%)         | 1 (7.1%)         | 0 (0.0%)         | 0.084 |
| Mean of propofol target concentration (µg/mL)      |                  |                  |                  |       |
| During pre-awake phase                             | 2.9 [2.5–3.2]    | 2.7 [2.4–3.0]    | 3.0 [2.7–3.2]    | 0.097 |
| 30 minutes before awakening                        | 2.6 [2.3–3.0]    | 2.4 [2.2–2.7]    | 2.9 [2.4–3.0]    | 0.107 |
| 60 minutes before awakening                        | 2.7 [2.3–3.0]    | 2.4 [2.2–2.7]    | 2.7 [2.5–3.0]    | 0.083 |
| Mean of remifentanil infusion rate (µg/kg/min)     |                  |                  |                  |       |
| During pre-awake phase                             | 0.17 [0.13–0.22] | 0.17 [0.11–0.20] | 0.17 [0.13–0.22] | 0.643 |
| 30 minutes before awakening                        | 0.15 [0.10–0.20] | 0.14 [0.10–0.20] | 0.15 [0.11–0.20] | 0.442 |
| 60 minutes before awakening                        | 0.16 [0.10–0.21] | 0.15 [0.10–0.20] | 0.16 [0.12–0.21] | 0.421 |

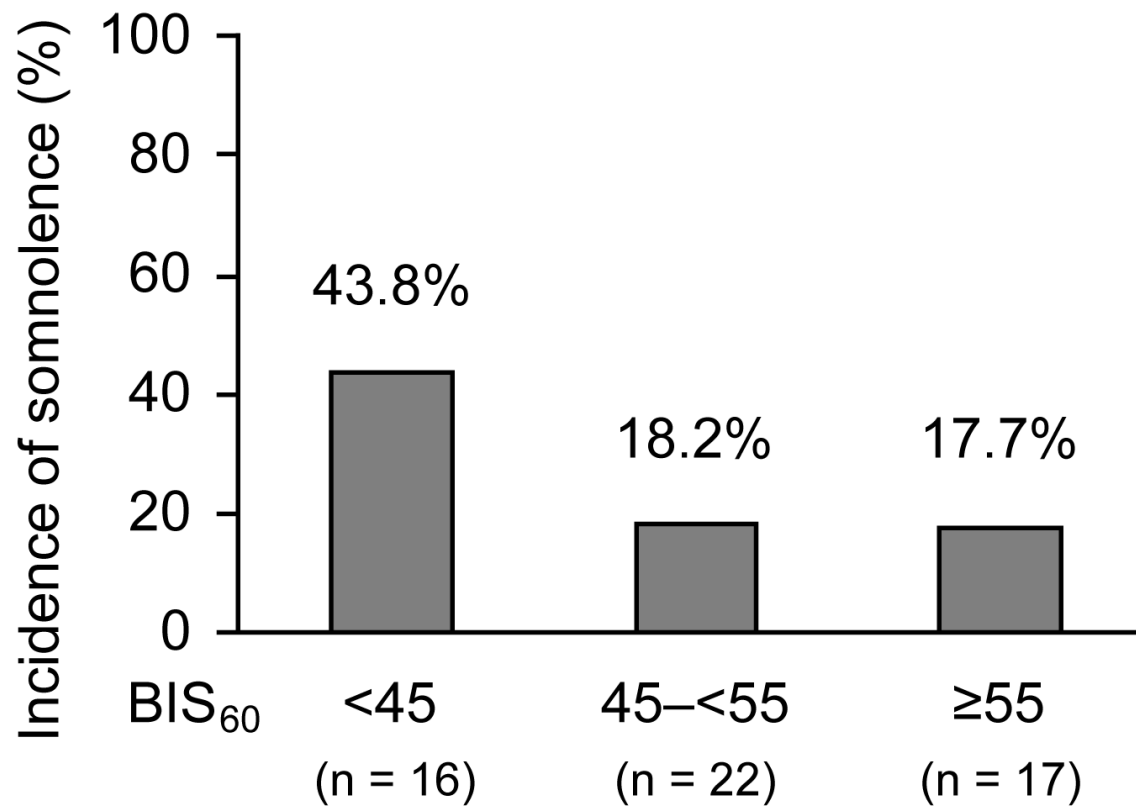
|                                                               |               |               |               |       |
|---------------------------------------------------------------|---------------|---------------|---------------|-------|
| Cessation of propofol infusion to airway device removal (min) | 18 [12–27]    | 23 [15–34]    | 17 [12–23]    | 0.077 |
| Convulsive episodes during awake phase                        | 3 (5.5%)      | 0 (0.0%)      | 3 (7.3%)      | 0.329 |
| Use of anticonvulsive drugs during awake phase                | 7 (12.7%)     | 0 (0.0%)      | 7 (17.1%)     | 0.098 |
| Use of droperidol during awake phase                          | 2 (3.6%)      | 1 (7.1%)      | 1 (2.4%)      | 0.417 |
| Duration of pre-awake phase (min)                             | 216 [169–282] | 240 [170–300] | 215 [167–256] | 0.481 |
| Duration of awake phase (min)                                 | 231 [111–293] | 242 [180–300] | 228 [101–295] | 0.292 |
| Duration of surgery (min)                                     | 481 [381–572] | 468 [235–542] | 481 [392–583] | 0.486 |
| Blood loss (mL)                                               | 195 [100–335] | 220 [110–520] | 180 [88–305]  | 0.250 |

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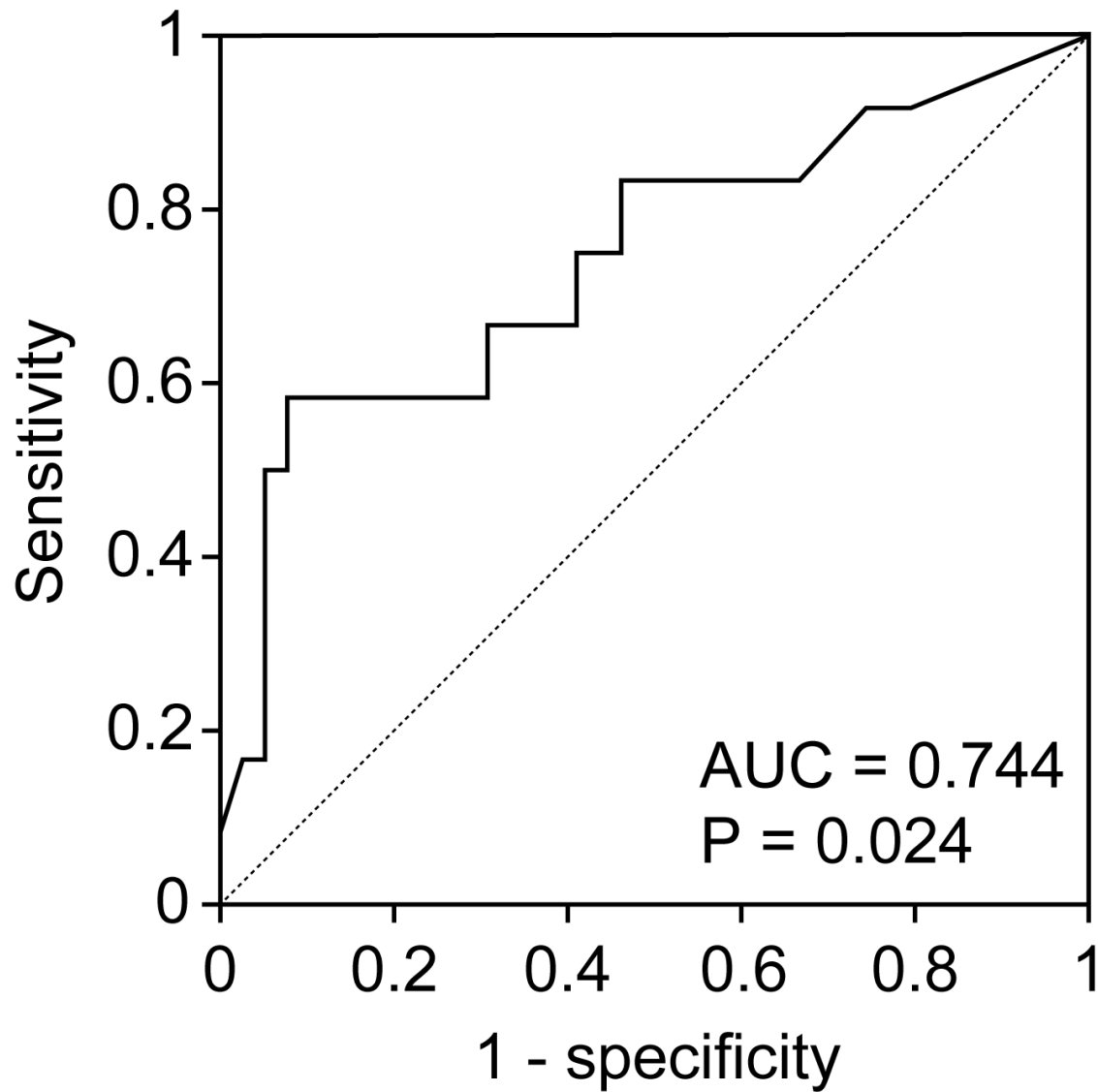
Table 2. Preoperative aphasia, neuropsychological performance, and memory function by the presence or absence of somnolence

|                                                 | All patients     | With somnolence  | Without somnolence | P value |
|-------------------------------------------------|------------------|------------------|--------------------|---------|
| Western Aphasia Battery aphasia quotient score  | 97.8 [95.0–99.6] | 93.8 [89.7–98.2] | 98.6 [95.9–99.9]   | 0.011   |
| Wechsler Adult Intelligence Scale–Third edition |                  |                  |                    |         |
| Verbal IQ                                       | 91 [72–101]      | 86 [61–103]      | 93 [73–101]        | 0.514   |
| Performance IQ                                  | 92 [72–99]       | 85 [64–101]      | 92 [75–101]        | 0.569   |
| Full-scale IQ                                   | 90 [70–99]       | 90 [60–102]      | 91 [74–99]         | 0.514   |
| Wechsler Memory Scale–Revised                   |                  |                  |                    |         |
| Verbal memory                                   | 87 [72–98]       | 85 [67–99]       | 88 [73–98]         | 0.574   |
| Visual memory                                   | 97 [87–111]      | 96 [89–106]      | 97 [85–111]        | 0.851   |
| General memory                                  | 86 [73–102]      | 83 [73–102]      | 87 [73–102]        | 0.731   |
| Attention/concentration                         | 95 [81–103]      | 96 [73–103]      | 95 [81–103]        | 0.934   |
| Delayed recall                                  | 85 [76–99]       | 80 [73–96]       | 89 [76–103]        | 0.429   |

Data on Western Aphasia Battery score were available in 51 patients (12 with somnolence and 39 without somnolence), Wechsler Adult Intelligence Scale–Third edition in 51 patients (10 with somnolence and 41 without somnolence), and Wechsler Memory Scale–Revised in 54 patients (12 with somnolence and 42 without somnolence).

**Figure captions****Fig. 1.** Incidences of somnolence during brain function mapping stratified by BIS<sub>60</sub>

**Fig. 2.** Receiver operating characteristic (ROC) curve for the prediction of somnolence during brain function mapping using preoperative WAB score. AUC, area under the ROC curve, with 95% confidence interval given in parentheses



**Fig. 3.** Incidences of somnolence during brain function mapping stratified by WAB

score

