ANESTHESIOLOGY

# Midazolam Sedation Induces Upper Limb Coordination Deficits That Are Reversed by Flumazenil in Patients with Eloquent Area Gliomas

Nan Lin, M.D., Ph.D., Ruquan Han, M.D., Ph.D., Xuan Hui, M.D., Sc.M., Kaiying Zhang, M.D., Adrian W. Gelb, M.B.Ch.B.

*ANESTHESIOLOGY 2019; 131:36–45*


## ABSTRACT

**Background:** Midazolam has been found to exacerbate or unmask limb motor dysfunction in patients with brain tumors. This study aimed to determine whether the exacerbated upper limb motor-sensory deficits are mediated through benzodiazepine sites by demonstrating reversibility by flumazenil in patients with gliomas in eloquent areas.

**Methods:** This was an interventional, parallel assignment, nonrandomized trial. Study subjects were admitted in the operating room. Patients with supratentorial eloquent area gliomas and volunteers of similar age without neurologic disease were sedated with midazolam, but still responsive and cooperative. Motor and sensory functions for upper extremities were evaluated by the Nine-Hole Peg Test before and after midazolam, as well as after flumazenil reversal.

**Results:** Thirty-two cases were included: 15 in the glioma group and 17 in the control group. The total dose of midazolam and flumazenil were comparable between the groups. In the glioma group, the times to task completion after midazolam in the contralateral hand ($P = 0.001$) and ipsilateral hand ($P = 0.002$) were 26.5 (95% CI, 11.3 to 41.7) and 13.7 (95% CI, 5.0 to 22.4) seconds slower than baseline, respectively. After flumazenil reversal, the contralateral hand ($P = 0.99$) and ipsilateral hand ($P = 0.187$) performed 1.2 (95% CI, −3.3 to 5.8) and 1.5 (95% CI, −0.5 to 3.5) seconds slower than baseline, respectively. In the control group, the dominant ($P < 0.001$) and nondominant hand ($P = 0.006$) were 2.9 (95% CI, 1.4 to 4.3) and 1.7 (95% CI, 0.5 to 2.9) seconds slower than baseline, respectively. After flumazenil, the dominant hand ($P = 0.99$) and nondominant hand ($P = 0.019$) performed 0.2 (95% CI, −0.7 to 1.0) and 1.3 (95% CI, −0.2 to 2.4) seconds faster than baseline, respectively.

**Conclusions:** In patients with eloquent area gliomas, mild sedation with midazolam induced motor coordination deficits in upper limbs. This deficit was almost completely reversed by the benzodiazepine antagonist flumazenil, suggesting that this is a reversible abnormality linked to occupation of the receptor by midazolam.

(ANESTHESIOLOGY 2019; 131:36–45)


## EDITOR'S PERSPECTIVE

### What We Already Know about This Topic

- Sedation is known to unmask focal neurologic deficits in patients with supratentorial brain tumors but the mechanism is unclear

### What This Article Tells Us That Is New

- When induced with midazolam, these deficits can be reversed by flumazenil, suggesting a γ-aminobutyric acid–mediated mechanism

Sedation in the operating room, the postanesthesia care unit, and the intensive care unit is common and often necessary for patients with intracranial brain tumors. Repeated neurologic function assessments are needed, especially in patients with tumors in or near eloquent regions. This is to monitor neurologic performance to determine if there are alterations that require treatment.[1] Some slowly infiltrative low-grade gliomas near eloquent regions do not show any clinically detectable neurologic deficits, perhaps from neuronal reorganization.[2,3] However, with sedation by some γ-aminobutyric acid–mediated (GABAergic) sedatives neurologic deficits may manifest or worsen,[4] resulting in delayed surgery or altered clinical care while further assessments are carried out. This may be especially problematic in patients undergoing awake craniotomy for tumors in eloquent regions.[5]

In our previous study, we found that midazolam sedation profoundly exacerbates or unmasks motor deficits in patients with supratentorial mass lesions. These deficits primarily involved limb motor function or ataxia as assessed using the National Institutes of Health Stroke Scale[6]; however, neither the mechanism nor the reversibility of effects

This article is featured in "This Month in Anesthesiology," page 1A. This article is accompanied by an editorial on p. 5. This article has a related Infographic on p. 17A. This article has an audio podcast. This article has a visual abstract available in the online version. This work was presented in a poster session at the Society for Neuroscience in Anesthesiology and Critical Care 45th annual meeting in Boston, Massachusetts, on October 20, 2017.

Submitted for publication on September 20, 2018. Accepted for publication on February 22, 2019. From the Department of Anesthesiology, Beijing Tiantan Hospital, Capital Medical University, Fengtai District, Beijing, China (N.L., R.H., K.Z.); the Department of Public Health Sciences, University of Chicago, Chicago, Illinois (X.H.); the Department of Anesthesiology, University of Texas Health Science Center at Houston, Houston, Texas (K.Z.); and the Department of Anesthesia and Perioperative Care, University of California San Francisco, San Francisco, California (A.W.G.).

 Anesthesiology 2019; 131:36–45. DOI: 10.1097/ALN.0000000000002726

were investigated. The aim of the current study was to (1) more precisely document the worsening of motor coordination induced by midazolam; (2) determine whether the neuronal deficits are mediated specifically through benzodiazepine sites by demonstrating reversibility with flumazenil; and (3) investigate how specific patient populations with gliomas in eloquent area react to mild midazolam sedation. We hypothesized that mild sedation by midazolam can unmask or exacerbate upper limb motor incoordination in patients with eloquent area gliomas but not in nonneurosurgical patients, and that the neurologic deficits induced by midazolam can be reversed by the antagonist flumazenil.

## Materials and Methods

This was an interventional, parallel assignment, nonrandomized trial and was approved by the Institutional Review Board of Beijing Tiantan Hospital, Capital Medical University (approval number: KY2014-040-03). This study was registered in ClinicalTrials.gov (registration number: NCT02439164).

Elective neurosurgery patients with supratentorial (frontotemporal–parietal) eloquent area gliomas diagnosed by magnetic resonance imaging were eligible for this study. All subjects provided written informed consent before participating in the study. The inclusion criteria were age between 18 and 60 with American Society of Anesthesiology status I and II. The control group included volunteers of the same age, but without neurologic diseases. Exclusion was based on screening the hospital record. Patients excluded: (1) were unable to comprehend and cooperate with the neurologic examination; (2) had impaired mental status or took sedative drugs by any route in the past 24 h; (3) received any type of pain reliever in the past 24 h; (4) had a history of drug and/or alcohol abuse; (5) currently pregnant and/or lactating; (6) had a history of recurrent glioma or multiple gliomas; (7) currently undergoing radiotherapy or chemotherapy; and (8) had complications such as intracranial trauma, vascular diseases, grand mal epilepsy, neuromuscular diseases, and cutaneous paresthesia.

Demographic characteristics, clinical manifestations, and past history were obtained before the study. On the day of study, subjects were admitted into the operating room in the supine position with the head up at 60 degrees. Nasal cannula was used for providing oxygen. Vital signs including blood pressure, heart rate, and pulse oximetry ($Spo_2$) were monitored and recorded during the study. Observer Assessment of Alertness and Sedation was evaluated and recorded before and after drug administration. Observer Assessment of Alertness and Sedation is scored from 1 to 5, indicating deep unresponsive sleep to fully alert (5 equals alert, 4 equals lethargic, 3 equals aroused by voice, 2 equals aroused by shaking, 1 equals unresponsive). The Nine-Hole Peg Test (Rolyan A851-5, United Kingdom) was used to evaluate motor function in each hand after midazolam sedation and flumazenil reversal. After obtaining the baseline vital signs and the Nine-Hole Peg Test data, a small dose of midazolam (0.02 mg/kg as initial dose), was given intravenously with the aim to get an Observer Assessment of Alertness and Sedation score of 4, *i.e.,* sedated, but arousable and fully cooperative. If the sedation level was not achieved, additional doses of 0.01 mg/kg were given, waiting 3 to 5 min to allow peak effect to be reached. After Observer Assessment of Alertness and Sedation score of 4 was reached, the Nine-Hole Peg Test was repeated. After the evaluation, the specific benzodiazepine receptor antagonist, 4 μg/kg flumazenil, was given intravenously to reverse midazolam's sedation as assessed by achieving Observer Assessment of Alertness and Sedation score of 5. Thereafter, the Nine-Hole Peg Test was repeated to test motor function (fig. 1). Any other drugs used, *e.g.,* atropine for bradycardia, were also recorded. Detailed descriptions of the lesion on magnetic resonance imaging were obtained. The lesions' pathologic diagnosis was obtained 2 weeks after the tumor removal.

The interventions were stopped if any of the following occurred: systolic blood pressure less than 90 mmHg or more than 180 mmHg after administration of the drugs; heart rate less than 50 beats/min after 0.5 mg atropine; $Spo_2$ less than 90%; Observer Assessment of Alertness and Sedation score equal to or less than 3, indicating oversedation; or occurrence of any drug-related side effect, such as respiratory depression, unstable hemodynamic, or agitation, among others.

The Nine-Hole Peg Test[7] was used for upper extremity evaluation in this study. It tests motor coordination, eye–hand coordination and the ability to follow simple directions, and it requires brain sensorimotor integration. The testing board is a square board with nine holes that are spaced 1.25 inches apart in a 3×3 array. Each hole is 0.5 inches deep and each peg is 1.25 inches long and 0.25 inches in diameter. The pegboard

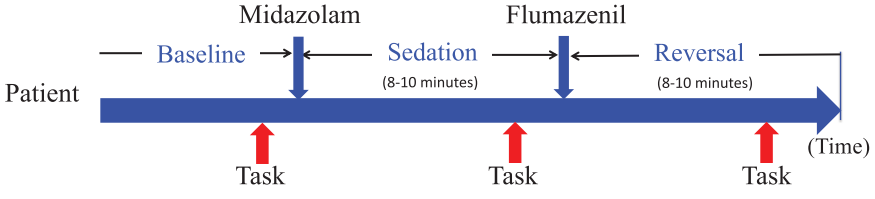


**Fig. 1.** The study flow diagram. "Task" indicates the Nine-hole Peg Test. The level of sedation was assessed by Observer Assessment of Alertness/Sedation (OAA/S) score = 4 during the sedation phase and OAA/S score = 5 at baseline and reversal.

was centered in front of the subject with the container holding the pegs placed at the hand being tested. Instruction was provided while the demonstration was given. Subjects were instructed to pick up the pegs one at a time using the testing hand and put them into the holes in any order as quickly as they could, until all holes were filled and then remove the pegs one at a time and return them to the container at the full speed. The nontested hand was used to stabilize the peg board. After the subjects performed the two practice trials, they performed the actual test. The outcome measure was the length of time from the first peg subject touched to the last peg placed in the container. The ipsilateral hand was tested first in the glioma patient group and the dominant hand was tested first in the control group. After testing the ipsilateral limb, the container was placed on the opposite side of the pegboard, and testing repeated with the contralateral hand in the glioma group and with nondominant hand in the control group. Time was recorded in seconds with a stopwatch by the same nurse during the whole study period. Neither the patients nor the doctors performing the study were informed of the times taken until the trial was completed. This test was performed before the administration of midazolam at baseline, after midazolam administration, and after flumazenil administration in each patient. Patients were allowed to wear corrective lenses. Motor arm function was concurrently evaluated before and after interventions using the four levels in the standard National Institutes of Health Stroke Scale[8]: 0 equals no drift; 1 equals drift; 2 equals against gravity; 3 equals no effort against gravity; 4 equals no movement when the patient was asked to hold the upper limb horizontally for 10 s. Due to the nature of the interventions, the study was nonblinded.

The primary outcomes were the changes in task performance time after midazolam sedation and flumazenil reversal, as compared to the normal control group. The secondary outcomes were the differences in performance time among baseline, midazolam sedation, and flumazenil reversal, as well as the differences in time changes between low-grade glioma and high-grade glioma.

### Sample Size Justification

Based on a previous study,[7] the length of the Nine-hole Peg Test performance in patient and control groups after sedation was 49 s (13.11) and 31.2 s (7.4) , respectively, with a two-sided alpha level of 0.05. The minimum number of cases was 15 per group to achieve 99% power to detect a possible statistical difference between the two groups. Allowing for a 20% rate of drop-out, we increased the case number to 18 for each group, as 1:1 assignment in the glioma group and the control group. We aimed to enroll at least 36 subjects in total. Sample size was calculated by PASS11.0.2 (NCSS Statistical Software, USA).

### Statistical Analysis

Shapiro–Wilk test was used for evaluating the normality of continuous variables. The normally distributed data was described as mean ± SD, the nonnormally distributed data is presented as median [interquartile range]. For categorical variables, numbers or percentage are described, and the chi-square or Fisher exact test was used to evaluate the differences between groups. Two-way repeated ANOVA was used to test the interaction effect of hands and Nine-hole Peg Test time points (baseline, sedation, reversal). To analyze the time to completion of the Nine-hole Peg Test before and after drug administration, a general linear model for repeated measures ANOVA was used. Kruskal–Wallis test was used to analyze the performance difference among handedness and education levels. Spearman correlation was used to test the correlation between hand dominance and task completion length. Paired *t* test was used to compare the performance between dominant and nondominant hands. The statistical tests were two-tailed and significance was defined as $P < 0.05$. Analyses were conducted using SPSS, version 17.0 (USA).

## Results

Thirty-six eligible cases were included in the study. One patient in the control group was excluded because he reported a history of carotid disease after the task testing. In the glioma group, two patients were excluded because one had metastases and one tumor was diagnosed as a meningioma. Fifteen in the glioma group and 17 in the control group completed the study and were included in the analysis. There are no missing subjects and/or data.

### Demographics and Characteristics

Patients' characteristics are shown in table 1. The age of the glioma patients was 46 (9) yr old, and 35 (7) yr old in the control group ($P < 0.001$). Hemodynamic parameters were comparable between the two groups during the whole procedure. $Spo_2$ was above 96% in all patients through the study. The total titrated doses of midazolam and flumazenil were comparable between the groups. The pathologic diagnosis of gliomas with World Health Organization grade and the type of surgery in the control cases are also shown in table 1. Forty percent of patients (6 of 15) in the glioma group had low-grade glioma and 60% (9 of 15) had high-grade glioma. Three patients had history of epilepsy, with two on sodium valproate and one on oxcarbazepine as antiepileptic treatments.

The size of the tumor in the glioma patients was 52.0 (12.4) mm. Tumors involved one or multiple areas in the frontoparietal–temporal region, including primary motor cortex (n = 7), supplemental motor area (n = 5), somatosensory cortex (n = 3), Broca area (n = 3), insular lobe (n = 6), internal capsule (n = 3), corpus callosum (n = 3), cingulate gyrus (n = 3), basal ganglion (n = 2), and occipital lobe (n = 1; tumor was primarily in M1 and corpus callosum, and extended partly to occipital area). There were 9 cases that had midline shift, 13 cases presented peritumoral edema. No case experienced intracranial or parenchymal hemorrhage.

**Table 1.** Demographics and Characteristics

| | Glioma Group (N = 15) | Control Group (N = 17) | *P* Value |
|---|---|---|---|
| Age, yr | 46 ± 9 | 35 ± 7 | < 0.001* |
| Sex, male (n) | 7 | 7 | 0.517 |
| Height, cm | 166.3 ± 8.1 | 168.8 ± 6.7 | 0.348 |
| Weight, kg | 64.9 ± 14.0 | 71.0 [56.0, 84.5] | 0.205 |
| Midazolam, mg | 1.7 [1.2, 2.0] | 1.4 [1.15, 1.7] | 0.296 |
| Flumazenil, mg | 0.3 ± 0.1 | 0.3 [0.24, 0.34] | 0.555 |
| MAP, mmHg | | | |
| Baseline | 96.5 ± 13.5 | 95.7 ± 14.7 | 0.881 |
| Sedation | 96.2 ± 9.5 | 91.2 ± 12.2 | 0.296 |
| Reversal | 95.4 ± 13.6 | 88.2 ± 14.1 | 0.660 |
| HR, bpm | | | |
| Baseline | 78.1 ± 15.6 | 79.0 ± 9.1 | 0.835 |
| Sedation | 84.3 ± 14.3 | 79.0 ± 9.4 | 0.359 |
| Reversal | 81.5 ± 17.7 | 71.5 ± 8.9 | 0.042* |
| Education, N | | | 0.05 |
| Primary school | 2 | 3 | |
| Middle school | 2 | 2 | |
| High school | 8 | 2 | |
| College | 3 | 10 | |
| Smoking, N | | | 0.603 |
| Nonsmoking | 14 | 14 | |
| Regular | 1 | 3 | |
| Type of glioma/surgery, N | | | |
| Glioma group | | | |
| Oligodendroglioma | 1 (LGG) | | |
| Oligoastrocytoma | 1 (LGG) | | |
| Astrocytoma | 4 (LGG) | | |
| Anaplastic oligoastrocytoma | 1 (HGG) | | |
| Anaplastic astrocytoma | 1 (HGG) | | |
| Glioblastoma | 7 (HGG) | | |
| Control group | | | |
| Cholecystectomy surgery | | 2 | |
| Ureteric surgery | | 1 | |
| Anal fistula surgery | | 2 | |
| Thyroid surgery | | 5 | |
| Spleen surgery | | 1 | |
| Breast surgery | | 2 | |
| Gynecological surgery | | 4 | |

Mann–Whitney U, chi-square, fisher exact, or t test was used to compare the difference between the glioma and control group. Normally distributed data are presented as mean ± SD and non-normally distributed data are presented as median [IQR]. Grade of malignancy is classified based on World Health Organization glioma grade: grade 1 to 2 indicates low-grade glioma and grade 3 to 4 indicates high-grade glioma.

*$P < 0.05$ indicates statistical significance.

HGG, high-grade glioma; HR, heart rate; IQR, interquartile range; LGG, low-grade glioma; MAP, mean arterial pressure; N, number of case.

## Task Performance Changes after Midazolam Sedation and Flumazenil Reversal

One patient with a low-grade glioma experienced contralateral motor arm function that worsened from normal to drift after sedation; other patients did not have motor arm function deterioration. None of the patients experienced seizures induced by flumazenil. Four types of hands were defined in this study: contralateral hand in the glioma group; ipsilateral hand in the glioma group; nondominant hand in the control group; and dominant hand in the control group.

There was a statistically significant interaction between the effects of hand type and testing time point (baseline, midazolam sedation, flumazenil reversal) based on two-way repeated ANOVA, $F(1.8, 25.4) = 13.696$, $P < 0.001$. There was a statistically significant simple main effect of testing time point, $F(1.1, 15.4) = 37.653$, $P < 0.001$; as well as simple main effect of hand-type, $F(1.2, 17.4) = 10.892$, $P < 0.001$. Both interaction and simple main effects had violated sphericity and were corrected using Greenhouse–Geisser.

The subsequent *post hoc* test with Bonferroni adjustment showed statistical difference of task completion time among testing time points for all type of hands (table 2). For glioma patients, compared to baseline, the task completion time in the contralateral hand was 26.5 s (95% CI, 11.3 to 41.7) slower after midazolam sedation ($P = 0.001$) and only 1.2 s (95% CI, −3.3 to 5.8) slower after flumazenil reversal ($P = 0.99$). The performance in the sedation phase was 25.3 s (95% CI, 11.5 to 39.0) slower than in the flumazenil phase ($P = 0.001$). The performance of the ipsilateral hand was 13.7 s (95% CI, 5.0 to 22.4) slower after sedation ($P = 0.002$) and 1.5 s (95% CI, −0.5 to 3.5) slower after flumazenil ($P = 0.187$) than at baseline; in the sedation phase it was 12.2 s (95% CI, 4.7 to 19.8) slower than in the flumazenil phase ($P = 0.002$). In the control group, the task completion time in the dominant hand was 2.9 s (95% CI, 1.4 to 4.3) slower after sedation ($P < 0.001$) and 0.2 s (95% CI, −0.7 to 1.0) faster after flumazenil ($P = 0.99$) than at baseline; in the sedation phase it was 3.1 s (95% CI, 1.7 to 4.4) slower than in the flumazenil phase ($P < 0.001$). For the nondominant hand in the control group, the performance was 1.7 s (95% CI, 0.5 to 2.9) slower after sedation ($P = 0.006$) and 1.3 s (95% CI, −0.2 to 2.4) faster after flumazenil ($P = 0.019$) than at baseline; in the sedation phase it was 3.0 s (95% CI, 2.2 to 3.9) slower than in the flumazenil phase ($P < 0.001$).

There were statistical differences in task completion time among four types of hand (contralateral and ipsilateral hands in the glioma group, dominant and nondominant hands in the control group) for baseline ($F = 3.771$; $P = 0.015$), midazolam sedation phase ($F = 12.134$; $P < 0.001$), and flumazenil reversal phase ($F = 5.043$; $P = 0.004$). *Post hoc* tests using the Bonferroni correction revealed that differences existed between contralateral and dominant hands at baseline ($P = 0.011$). After sedation, the contralateral hand was slower, in terms of statistical significance, than the dominant hand ($P < 0.001$), nondominant hands ($P < 0.001$), and ipsilateral hand ($P = 0.031$); the ipsilateral hand was slower in the control group, although not statistically different; and after flumazenil reversal, the contralateral hand remained slower than the dominant ($P = 0.004$) and nondominant ($P = 0.018$) hands (fig. 2). The results of pairwise comparisons were shown in table 3.

## Effects of Hand Dominance on Task Performance

In the control group, the dominant and nondominant hands were statistically different at baseline (paired $t$ [16] = 4.401; $P < 0.001$), midazolam sedation (paired $t$ [16] = 2.998;

**Table 2.** Time to Complete Nine-hole Peg Test in the Glioma and Control Groups

| | Time to Complete Nine-hole Peg Test (s) | | | Repeated ANOVA | |
|---|---|---|---|---|---|
| | Baseline | Midazolam Sedation | Flumazenil Reversal | *F* | *P* Value |
| Glioma (N = 15) | | | | | |
| Contralateral hand | | | | 22.435† | < 0.001* |
| Median [IQR] | 24.3 [18.7–30.0] | 50.7 [30.6–68.6] | 24.0 [19.3–31.8] | | |
| Min-max | 12.0–79.5 | 15.6–120.0 | 13.8–71.6 | | |
| 95% CI | 19.0 to 30.0 | 30.6 to 68.6 | 19.3 to 31.8 | | |
| Ipsilateral hand | | | | 18.414§ | 0.001* |
| Median [IQR] | 20.5 [16.7–24.5] | 28.9 [25.0–41.9] | 20.9 [19.6–24.3] | | |
| Min-max | 12.9–42.9 | 18.8–82.5 | 16.4–49.1 | | |
| 95% CI | 16.7 to 24.5 | 25.0 to 41.9 | 19.6 to 24.3 | | |
| Control (N = 17) | | | | | |
| Dominant hand | | | | 28.091 | < 0.001* |
| Mean ± SD | 17.8 ± 2.6 | 20.6 ± 3.8 | 17.6 ± 2.6 | | |
| Min-max | 12.6–22.8 | 15.1–31.0 | 13.5–23.5 | | |
| 95% CI | 16.0–18.9 | 18.4–22.7 | 16.1–19.1 | | |
| Nondominant hand | | | | 28.099 | < 0.001* |
| Mean ± SD | 20.4 ± 3.2 | 22.1 ± 2.9 | 19.1 ± 3.0 | | |
| Min-max | 15.3–26.0 | 17.8–28.0 | 13.7–24.2 | | |
| 95% CI | 18.5–22.2 | 20.4–23.7 | 17.3–20.7 | | |

Adjustment for multiple comparisons: Bonferroni. Shapiro-Wilk was used for normality assumption.
*$P < 0.05$ indicates statistical significance. †Mauchly Test of Sphericity was violated; Greenhouse–Geisser was used as the correction.
IQR, interquartile range; Min-max, minimum and maximum value.

$P = 0.009$), and flumazenil reversal (paired $t$ [16] = 5.375; $P < 0.001$). In the glioma group, the contralateral hand can be either the dominant (N = 9) or nondominant hand (N = 6), as well as for the ipsilateral hands. In all contralateral limbs in the glioma group, hand dominance and task completion length had a weak correlation that was not statistically significant (baseline: correlation coefficient = 0.079, $P = 0.780$; midazolam: correlation coefficient = 0.126, $P = 0.654$; flumazenil: correlation coefficient = 0.126, $P = 0.655$), and similar correlation was observed in ipsilateral limbs (baseline: correlation coefficient = −0.315, $P = 0.253$; midazolam: correlation coefficient = −0.473, $P = 0.075$; flumazenil: correlation coefficient = −0.284, $P = 0.305$).

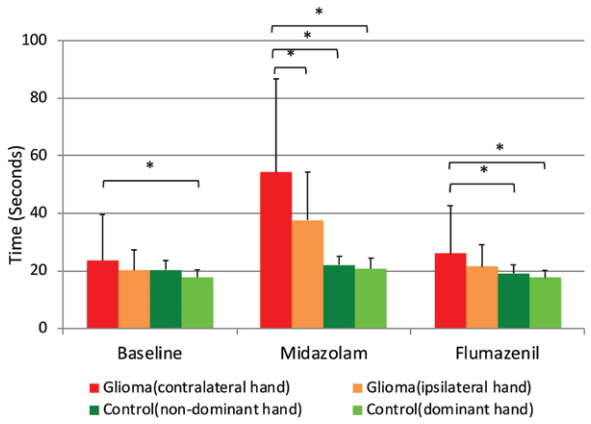


**Fig. 2.** The Nine-hole Peg Test completion time (in seconds) in the phase of baseline, midazolam sedation, and flumazenil reversal. Midazolam sedation reached the Observer Assessment of Alertness/Sedation (OAA/S) score = 4, and flumazenil reversal was at OAA/S score = 5. *$P < 0.05$ in Bonferroni correction indicated statistical significance.

## Effect of Education Level on Task Performance

The performance in each type of hand did not show a statistically significant difference among education levels (primary, middle school, high school, and college), based on Kruskal–Wallis test. For the dominant hands in the control group, the time to complete the test was same in each period, regardless of education (baseline: $P = 0.885$; midazolam: $P = 0.686$, flumazenil: $P = 0.570$), as well as for the nondominant hands (baseline: $P = 0.816$; midazolam: $P = 0.706$, flumazenil: $P = 0.710$). Patients with four education levels in the glioma group were also comparable for both contralateral (baseline: $P = 0.146$; midazolam: $P = 0.347$, flumazenil: $P = 0.643$) and ipsilateral (baseline: $P = 0.990$; midazolam: $P = 0.753$, flumazenil: $P = 0.725$) hands.

## Effect of Glioma Grade on Task Performance

In the glioma group, patients were further divided into low-grade glioma and high-grade glioma indicating less malignant and more malignant glioma, respectively. Hence, six hand conditions were generated: low-grade glioma–ipsilateral hand, low-grade glioma–contralateral hand, high-grade glioma–ipsilateral hand, high-grade glioma–contralateral

**Table 3.** Pairwise Comparisons between Type of Hands at Different Testing Phase (Baseline, Midazolam Sedation, and Flumazenil Reversal)

| Task Completion Time Difference between Hands | Baseline | | Midazolam | | Flumazenil | |
|---|---|---|---|---|---|---|
| | Mean, s (95% CI) | *P* Value | Mean, s (95% CI) | *P* Value | Mean, s (95% CI) | *P* Value |
| Contralateral–Ipsilateral | 6.1 (–2.6 to 14.7) | 0.363 | 18.8 (1.1 to 36.6) | 0.031* | 5.8 (–3.2 to 14.8) | 0.511 |
| Contralateral–Dominant | 10.1 (1.7 to 18.5) | 0.011* | 33.7 (16.5 to 50.8) | < 0.001* | 11.5 (2.7 to 20.2) | 0.004* |
| Contralateral–Nondominant | 7.4 (–1.0 to 15.8) | 0.116 | 32.2 (15.0 to 49.3) | < 0.001* | 9.9 (1.2 to 18.7) | 0.018* |
| Ipsilateral–Dominant | 4.0 (–4.4 to 12.4) | 1.000 | 14.8 (–2.3 to 32.0) | 0.131 | 5.7 (–3.1 to 14.4) | 0.495 |
| Ipsilateral–Nondominant | 1.3 (–7.1 to 9.7) | 1.000 | 13.4 (–3.8 to 30.5) | 0.228 | 4.1 (–4.6 to 12.9) | 1.000 |
| Nondominant–Dominant | 2.7 (–5.5 to 10.8) | 1.000 | 1.5 (–15.2 to 18.1) | 1.000 | 1.5 (–7.0 to 10.0) | 1.000 |

Adjustment for multiple comparisons: Bonferroni.
*$P < 0.05$ indicates statistical significance.

hand, control-dominant hand, control-nondominant hand.There was a statistically significant interaction between the effects of hand condition and testing time point for task completion time based on two-way repeated ANOVA ($F$[1.8, 8.9] = 9.967; $P$ = 0.006; the interaction effect violated sphericity and was corrected using Greenhouse–Geisser). There was a statistically significant simple main effect of hand condition ($F$[5, 25] = 6.144; $P$ = 0.001), as well as a simple main effect of testing time point ($F$[2, 10]=38.291; $P < 0.001$) (fig. 3). After midazolam sedation, patients with high-grade glioma performed 38.6 s (95% CI, 8.1 to 69.1) more slowly than those with low-grade glioma (t[13]=2.732; $P$ = 0.017). Even after flumazenil reversal, the performance in patients with high-grade glioma was still 35.6 s (95% CI, 8.7 to 62.6) slower than with low-grade glioma (t[16]=2.809; $P$ = 0.013).

## Discussion

The main findings of this study are consistent with our hypothesis that patients with supratentorial eloquent area gliomas had temporary midazolam-induced upper limb

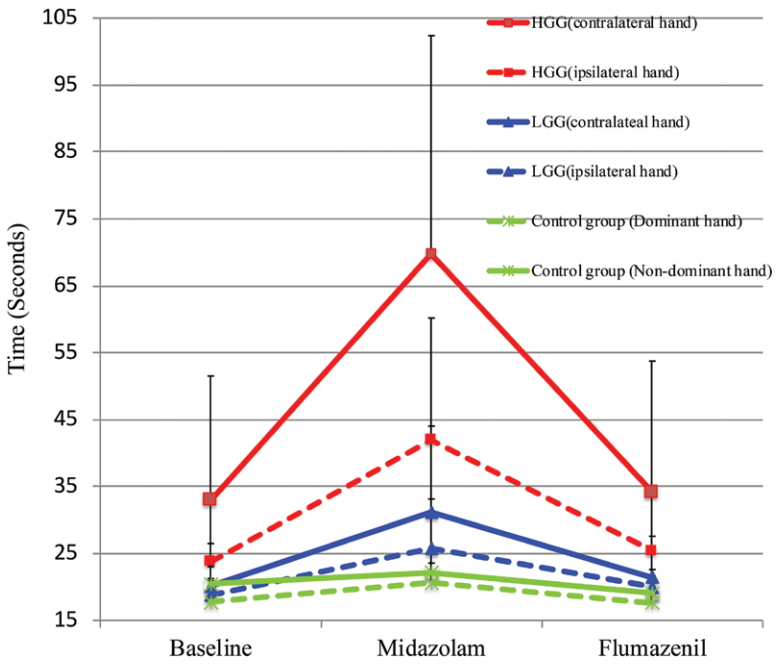


**Fig. 3.** The Nine-hole Peg Test performing time (in seconds) for six types of hands in different phases. Grade of malignancy is classified based on World Health Organization glioma grade; grade 1 or 2 indicates low-grade glioma and grade 3 or 4 indicates high-grade glioma. LGG, low-grade glioma; HGG, high-grade glioma.

motor coordination deficits and these were reversed by the specific antagonist flumazenil. Further, neurologic deficits were unmasked in both contralateral and ipsilateral hands, and patients with high-grade gliomas were more greatly affected than those with low-grade gliomas.

We targeted patients who had a pathologic diagnosis of glioma. These tumors diffusely infiltrate brain and damage the functional structure that may be compensated by dynamic circuit reorganization. Brain compensation for neurologic dysfunction makes clinical symptoms appear less severe than the patient's matching imaging would suggest for the location.[2] The patients may thus experience functional recovery following damage.[2,9] Large numbers of patients with gliomas in eloquent area do not show obvious sensory or motor deficits based on motor-scale evaluation, but the patients may note and complain of fine motor dysfunction. These deficits involve motor–sensory function that—to some extent—reflect brain connection integration in the cortical and subcortical structures. Therefore, we selected those who had cortical and/or subcortical eloquent area gliomas to observe potential motor–sensory function compensation that we believe may be most susceptible to disruption by medications.

In our previous investigation, we found motor function and limb ataxia were the most affected.[6] In order to more accurately detect and quantify this deficit, the Nine-hole Peg Test has good reliability for testing upper limb dexterity, motor coordination, and hand–eye coordination, as well as patient ability to follow simple directions.[7,10] It therefore goes beyond assessing a single neurologic function confined to the tumor and its surroundings, but also assesses multiple functions reflecting the network connections between cortical and subcortical regions. The Nine-hole Peg Test has also been successfully used to detect GABAergic re-induced neurologic deficits in stroke patients.[7] Quantification of hand performance using the Nine-hole Peg Test task revealed obvious fine motor dysfunction while the five-scale motor clinical assessment showed no change in the same patient. This indicated that the network disturbance is more widely spread, especially with our evidence that both contralateral and ipsilateral limbs were affected during sedation.

We speculated in our previous investigation that mild sedation–induced focal neurologic function worsening in patients with supratentorial intracranial lesions was likely transient and would return to baseline once the medications were no longer present on relevant receptors.[6] The sedative we used in this study is a specific benzodiazepine agonist: midazolam. It is a GABAergic agent that we previously found to most impair neurologic function, compared with other agents that have other pharmacologic mechanisms.[6] The benzodiazepine-specific antagonist flumazenil reversed the midazolam-induced deterioration in motor coordination, as evidenced by our findings that the task performance returned to baseline after flumazenil. This confirms that the induced neurologic functional deficits were transient and related to the specific GABAergic receptors.

The mechanism by which sedatives induce neurologic deficits in patients with glioma is unclear. Our previous study, in which four different agents producing the same level of sedation, resulted in very different degrees of neurologic impairment. This indicates that the mechanism is not a nonspecific sedative effect. A possible explanation is that the brain reorganization that compensates for injured areas are disrupted by sedatives through the alteration of regional metabolism, synaptic connections, or receptor sensitivity.[11,12] It is conceivable that midazolam exerted its effects by influencing regional blood flow. Ogawa *et al.* found that moderate sedation with midazolam in healthy volunteers reduced cerebral blood flow velocity that was not reversible by flumazenil.[13] This suggests that the reversible neurologic dysfunction in our study is not primarily related to an alternation of cerebral hemodynamics.

Gliomas are more than a simple focal disruption in local brain parenchyma and have been shown to result in functional neurocognitive decline associated with remotely located brain regions.[14,15] Studies using functional magnetic resonance imaging have shown that, compared to healthy subjects, supratentorial brain gliomas decrease long-distance connectivity,[16] and alter cross-hemispheric connections,[14,17] which indicates that the functional connectivity alterations in these patients is a whole brain phenomenon. A single lesion may therefore lead to more than one localized neurologic function deficit, and these more extensive functional changes cannot be explained by a local anatomical injury alone, but must also alter the dynamic interconnected networks. The increasingly used connectome analysis of glioma patients demonstrates both the regional and long-range connection loss in complex network connectivity.[18,19]

These findings serve to confirm the notion that purely local effects of the tumor may not explain the sedative related neurologic deficits unmasked on the uninjured side. In our study, the ipsilateral "noneffected" limb performance changed after sedation in glioma patients and was 3.7 times longer than the dominant hands in the control group. This indicates neurologic function changes despite the tumor being unilateral with no imaging evidence of metastases. The technique of imaging connectomics currently describes a number of possible adaptive and maladaptive processes associated with brain injury.[18] The most likely of those mechanism in our study is diaschisis,[20] a term coined by Von Monakow,[21] which means a lesion site in the brain that results in functional impairments in undamaged distant regions.[18] This is a maladaptive brain network response to the damage. Such maladaptive processes have been reported in patients with intracranial tumors.[22–24] Instead of being confined to a single area, the pathologic perturbations from the tumor influence brain across many regions, illustrating complex neural architecture and interconnections. In our study, the phenomenon of diaschisis was hidden in our patients because of adaptive compensation processes, but it was unmasked by midazolam sedation and then hidden again after sedation reversal. The unmasked/induced "covert"

diaschisis may help to locate interconnections, predict the consequences of lesion growth, and explain the emergence deficits from GABAergic sedation in circumstances of awake craniotomy and recovery from anesthesia and intensive care unit sedation, and guide the clinical sedatives used in patients with gliomas in other circumstances. Such pharmacologic intervention may also help with translational studies investigating the mechanism of functional connectivity.

Patients with high-grade gliomas performed much worse than those with low-grade gliomas. This is consistent with our previous findings and indicates that the aggressive lesion is more sensitive to sedation, perhaps reflecting the fact that the more aggressive tumor is more destructive and results in less compensation across regions. Our study was not designed to address this finding, and a paradigm that includes the combined examination of gliomas patients with structural, functional imaging, and topology will be more valuable to explore the mechanism of the interaction between sedatives, brain tumor grade, and function.

## Limitations

The age in the two groups was not balanced in that the control group was younger (in the glioma group: 46 [9] yr old, in the control group 35 [7] yr old). This was a consequence of our primary concern for inclusion to the control group of patients with "healthy" brains. Primary brain tumors are mostly diagnosed between 55 and 74 yr of age, according to the Central Brain Tumor Registry of the United States Statistical Report in 2015,[25] indicating that the age of patients in the glioma group was consistent with the real-world prevalence. However, age matched controls may be a better choice.

The population in our study was confined to patients with supratentorial gliomas in the frontotemporal–parietal area. Patients who have had stroke or intracranial vascular disease may also have similar functional compensation and diaschisis. We cannot, however, extend our conclusion to other types of intracranial injury. We did not evaluate patients' anxiety, depression, or reticular activating system functions, such as sleep–awake cycles, which may possibly be cofactors impairing the performance. Three patients were on antiepileptic medication that could possibly interact with benzodiazepines, but such a small number precludes statistical analysis.

Handedness was found to be a confounding factor when comparing affected hands in glioma patients and controls. All the patients in this study were right-handed. The right hand, as expected, performed faster than the left hand in the control group at baseline, but this phenomenon was less obvious in glioma patients whose limbs were affected by tumor. Although the statistical analysis confirmed that hand dominance in this study does not interact with the primary outcome in the glioma group, the limited number of dominant or nondominant hands in both contralateral and ipsilateral groups limits the analysis for the contribution of hand dominance. Interestingly, perhaps due to learning effect, both hands in the control group performed faster than at baseline after flumazenil and the left hand was even faster than right. However, the difference of about 1 s between the two hands does not have clinical significance.

Although we found that midazolam-induced neurologic deficits were transient and reversible, we are unable to extrapolate whether the same reversibility applies after general anesthesia or prolonged postoperative midazolam sedation, because postoperative neurologic function is affected by the surgical intervention, the length of using GABAergic agents, and interaction among anesthetic and/or sedative agents. In addition, we do not know whether flumazenil improves motor deficits in patients who have not received midazolam, and whether simply waiting for recovery from midazolam would result in a different recovery profile. However, given our findings, it may be prudent to avoid or limit midazolam use in patients with gliomas, especially high grade, and if used, to consider a judicious use of flumazenil when there are unanticipated neurologic findings. In these patients dexmedetomidine may be a better choice.[26]

## Conclusions

In summary, this interventional nonrandomized trial found that in patients with supratentorial gliomas in eloquent areas of the brain, the upper limb motor coordination that was comparable with normal subjects at baseline became severely worse after mild sedation with midazolam, and the functional deficits could be reversed by the specific antagonist flumazenil. Midazolam-induced motor incoordination in the ipsilateral upper limbs was also unmasked suggesting diaschisis, with interruption in functional connectivities to remote undamaged areas. It emphasizes that "normal-appearing" brain areas are not necessarily functionally normal and that in some circumstances, such as midazolam administration, the abnormal connectivity is exposed. Future study is needed to explore the mechanism of interactions between specific pharmacologic interventions and functional adaption and maladaptation in patients with brain tumors.

## Acknowledgments

The authors thank the neurosurgical team at Beijing Titan Hospital, Capital Medical University (Beijing, China) led by Yanhui Sun, M.D., Song Lin, M.D., and Zhixian Gao, M.D., for helping to identify the glioma patients and providing unconditional support in allowing consistent access to their patients, and Aidong Wang, M.D., and Mrs. Shirong Peng (nurse-in-charge) for their help in coordinating the study and the operative procedures.

## Research Support

This work was funded by the National Natural Science Foundation of China (Beijing, China; grant No. 81701038);

the Beijing Municipal Administration of Hospitals' Youth Program (Beijing, China; grant No. QML20160503), the Ascent Plan (grant No. DFL20180502), and was also supported by the Beijing Municipal Administration of Hospitals' Clinical Medicine Development of Special Funding (Beijing, China; grant No. ZYLX201708).

## Competing Interests

The authors declare no competing interests.

## Reproducible Science

Full protocol available at: linnan127@gmail.com. Raw data available at: linnan127@gmail.com.

## Correspondence

Address correspondence to Dr. Gelb: Department of Anesthesia and Perioperative Care, University of California San Francisco, 500 Parnassus Ave, MUE 404, San Francisco, California 94143. Adrian.gelb@ucsf.edu. This article may be accessed for personal use at no charge through the Journal Web site, www.anesthesiology.org.

## References

1. Fàbregas N, Bruder N: Recovery and neurological evaluation. Best Pract Res Clin Anaesthesiol 2007; 21:431–47
2. Duffau H: The huge plastic potential of adult brain and the role of connectomics: New insights provided by serial mappings in glioma surgery. Cortex 2014; 58:325–37
3. Bryszewski B, Tybor K, Ormezowska EA, Jaskólski DJ, Majos A: Rearrangement of motor centers and its relationship to the neurological status of low-grade glioma examined on pre- and postoperative fMRI. Clin Neurol Neurosurg 2013; 115:2464–70
4. Thal GD, Szabo MD, Lopez-Bresnahan M, Crosby G: Exacerbation or unmasking of focal neurologic deficits by sedatives. Anesthesiology 1996; 85:21–5; discussion 29A–30A
5. Ott C, Kerscher C, Luerding R, Doenitz C, Hoehne J, Zech N, Seemann M, Schlaier J, Brawanski A: The impact of sedation on brain mapping: A prospective, interdisciplinary, clinical trial. Neurosurgery 2014; 75:117–23; discussion 123; quiz 123
6. Lin N, Han R, Zhou J, Gelb AW: Mild sedation exacerbates or unmasks focal neurologic dysfunction in neurosurgical patients with supratentorial brain mass lesions in a drug-specific manner. Anesthesiology 2016; 124:598–607
7. Lazar RM, Berman MF, Festa JR, Geller AE, Matejovsky TG, Marshall RS: GABAergic but not anti-cholinergic agents re-induce clinical deficits after stroke. J Neurol Sci 2010; 292:72–6
8. Cheung RT, Lyden PD, Tsoi TH, Huang Y, Liu M, Hon SF, Raman R, Liu L: Production and validation of Putonghua- and Cantonese-Chinese language National Institutes of Health Stroke Scale training and certification videos. International Journal of Stroke 2010; 5:6
9. Conway N, Wildschuetz N, Moser T, Bulubas L, Sollmann N, Tanigawa N, Meyer B, Krieg SM: Cortical plasticity of motor-eloquent areas measured by navigated transcranial magnetic stimulation in patients with glioma. J Neurosurg 2017: 1–11
10. Oxford Grice K, Vogel KA, Le V, Mitchell A, Muniz S, Vollmer MA: Adult norms for a commercially available Nine Hole Peg Test for finger dexterity. Am J Occup Ther 2003; 57:570–3
11. Shulga A, Rivera C: Interplay between thyroxin, BDNF and GABA in injured neurons. Neuroscience 2013; 239:241–52
12. Saari TI, Uusi-Oukari M, Ahonen J, Olkkola KT: Enhancement of GABAergic activity: Neuropharmacological effects of benzodiazepines and therapeutic use in anesthesiology. Pharmacol Rev 2011; 63:243–67
13. Ogawa Y, Iwasaki K, Aoki K, Yanagida R, Ueda K, Kato J, Ogawa S: The effects of flumazenil after midazolam sedation on cerebral blood flow and dynamic cerebral autoregulation in healthy young males. J Neurosurg Anesthesiol 2015; 27:275–81
14. Maesawa S, Bagarinao E, Fujii M, Futamura M, Motomura K, Watanabe H, Mori D, Sobue G, Wakabayashi T: Evaluation of resting state networks in patients with gliomas: Connectivity changes in the unaffected side and its relation to cognitive function. PLoS One 2015; 10:e0118072
15. Bosma I, Douw L, Bartolomei F, Heimans JJ, van Dijk BW, Postma TJ, Stam CJ, Reijneveld JC, Klein M: Synchronized brain activity and neurocognitive function in patients with low-grade glioma: A magnetoencephalography study. Neuro Oncol 2008; 10:734–44
16. Park JE, Kim HS, Kim SJ, Kim JH, Shim WH: Alteration of long-distance functional connectivity and network topology in patients with supratentorial gliomas. Neuroradiology 2016; 58:311–20
17. Zhang H, Shi Y, Yao C, Tang W, Yao D, Zhang C, Wang M, Wu J, Song Z: Alteration of the intra- and cross-hemisphere posterior default mode network in frontal lobe glioma patients. Sci Rep 2016; 6:26972
18. Fornito A, Zalesky A, Breakspear M: The connectomics of brain disorders. Nat Rev Neurosci 2015; 16:159–72
19. Hart MG, Price SJ, Suckling J: Connectome analysis for pre-operative brain mapping in neurosurgery. Br J Neurosurg 2016; 30:506–17
20. Carrera E, Tononi G: Diaschisis: Past, present, future. Brain 2014; 137(Pt 9):2408–22

21. Finger S, Koehler PJ, Jagella C: The Monakow concept of diaschisis: Origins and perspectives. Arch Neurol 2004; 61:283–8
22. Segtnan EA, Grupe P, Jarden JO, Gerke O, Ivanidze J, Christlieb SB, Constantinescu C, Pedersen JE, Houshmand S, Hess S, Zarei M, Gjedde A, Alavi A, Høilund-Carlsen PF: Prognostic implications of total hemispheric glucose metabolism ratio in cerebrocerebellar diaschisis. J Nucl Med 2017; 58:768–73
23. Kamble RB, Venkataramana NK, Shetty RV, Naik AL, Rao S, Diwakar N: Cerebral high grade glioma with crossed cerebellar metastases. A report of three cases. Neuroradiol J 2010; 23:429–32
24. Newberg AB, Alavi A, Alavi J: Contralateral cortical diaschisis in a patient with cerebellar astrocytoma after radiation therapy. Clin Nucl Med 2000; 25:431–3
25. Ostrom QT, Gittleman H, Fulop J, Liu M, Blanda R, Kromer C, Wolinsky Y, Kruchko C, Barnholtz-Sloan JS: CBTRUS Statistical Report: primary brain and central nervous system rumors diagnosed in the United States in 2008–2012. Neuro Oncol 2015; 17 Suppl 4: iv1–iv62
26. Lin N, Vutskits L, Bebawy JF, Gelb AW: Perspectives on dexmedetomidine use for neurosurgical patients. J Neurosurg Anesthesiol 2018, DOI:10.1097/ANA.0000000000000554

## ANESTHESIOLOGY REFLECTIONS FROM THE WOOD LIBRARY-MUSEUM

# Airs and Affairs: Adulteration and Adultery around Dr. Oliver Walcott Hall


After earning his D.D.S. in 1879 from the Pennsylvania College of Dental Surgery, Oliver Walcott Hall made anesthesia history on Boston's Tremont Street as an early advocate of "Vitalized Air" (*above*), which, in this case, was nitrous oxide adulterated with alcohol and chloroform. After his wife had passed away, a stunned Dr. Hall stumbled across evidence of adultery and made legal history by filing an "alienation of affection" case against his late wife's lover. (Copyright © the American Society of Anesthesiologists' Wood Library-Museum of Anesthesiology.)

*George S. Bause, M.D., M.P.H., Honorary Curator and Laureate of the History of Anesthesia, Wood Library-Museum of Anesthesiology, Schaumburg, Illinois, and Clinical Associate Professor, Case Western Reserve University, Cleveland, Ohio. UJYC@aol.com.*