Anesthesia for functional neurosurgery: the role of dexmedetomidine
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Purpose of review
The purpose of this review is to summarize current approaches to the anesthetic management of functional neurosurgery and to describe the application of an \( \alpha \)-2-adrenergic agonist dexmedetomidine in the anesthetic management of functional neurosurgical procedures.

Recent findings
Dexmedetomidine, an \( \alpha \)-2-adrenergic agonist, causes a unique kind of sedation, acting on the subcortical areas, which resembles natural sleep without respiratory depression. Experimental data demonstrate both cerebral vasoconstriction and vasodilatation, depending on the model and dose studied. At the clinically relevant doses, dexmedetomidine decreases cerebral blood flow and cerebral metabolic rate of oxygen in healthy volunteers. Clinical experience of dexmedetomidine use in functional neurosurgery is limited to small case-series. Nevertheless, these reports indicate that use of dexmedetomidine does not interfere with electrophysiologic monitoring, thus allowing brain mapping during awake craniotomy and microelectrode recording during implantation of deep-brain stimulators.

Summary
Dexmedetomidine has been demonstrated to provide a successful sedation without impairment of electrophysiologic monitoring in functional neurosurgery. Prospective randomized studies are warranted to delineate an optimal regimen of dexmedetomidine sedation and any dose-related influence on neurophysiologic function.

Keywords
awake craniotomy, dexmedetomidine, implantation of deep brain stimulator

Introduction
‘Functional neurosurgery’ is a broad term applied to a variety of neurosurgical procedures in which monitoring of brain function during the procedure is crucial for localization of the area of surgical interest and successful outcome. Anesthetic management for these procedures is challenging because intraoperative monitoring requires fully preserved brain function. This is a direct contradiction of the essential goal of anesthesiology, which is to provide the patient with sedation, analgesia, and anesthesia.

Dexmedetomidine, an \( \alpha \)-2-adrenergic agonist, acting at the subcortical areas of the brain and not involving the \( \gamma \)-amino-butyric acid (GABA) receptors, provides a sedation, which resembles natural sleep, without respiratory depression. These unique properties of dexmedetomidine make it a potentially advantageous sedative agent for functional neurosurgery.

The review discusses the challenges and current approaches of anesthetic management, including clinical applications of dexmedetomidine, for the two most popular functional neurosurgical procedures requiring an awake cooperative patient and fully preserved cerebral electrophysiology: ‘awake’ craniotomy requiring brain mapping, and implantation of deep brain stimulators for movement disorders.

General principles of anesthetic management of functional neurosurgery
Ideal perioperative management for functional neurosurgery should satisfy multiple anesthetic and surgical goals simultaneously. These objectives include patient comfort and analgesia, patient immobility throughout the procedure (often for a long duration), adequate oxygenation and ventilation, hemodynamic stability, optimal brain conditions, prevention of brain swelling, and full

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patient cooperation with intact electrophysiologic monitoring. Obviously, the above-mentioned conditions often contradict each other, making ‘anesthetic’ management for awake neurosurgical procedures one of the most challenging in anesthesia practice.

The kind of neurologic monitoring required for functional neurosurgery depends on the procedure and the area of interest in the brain. An assessment of cognitive function, speech, vision, and motor function is required in surgery for resection of brain tumors or epileptic focus located close to the eloquent cortex (Broca’s and Wernicke’s speech areas in the dominant frontal and temporal lobe, motor strip, and visual cortex). During implantation of a deep brain stimulator (DBS) for a patient with movement disorder, an assessment of changes in tremor or spasticity/rigidity in a fully awake patient is mandatory. Intraoperative electrophysiologic testing for tumor and epilepsy surgery includes electroencephalography (EEG) and electrocorticography (ECoG) for cortical brain mapping. The microelectrode recording (MER) of impulses of subcortical areas, including subthalamic nucleus, is used during DBS implantation.

Patient positioning for functional neurosurgery makes access to the patient’s airway difficult, further complicating anesthesia management (Fig. 1).

Intraoperative ‘anesthetic’ management of awake craniotomy has changed during the last two decades. Anesthesia medications with rapid onset of action and short half-lives such as propofol and remifentanil replaced previously used neuroleptanalgesia with fentanyl and droperidol. Multiple anesthetic techniques are used for awake craniotomies: monitored anesthesia care, conscious sedation, the ‘asleep–awake’ and ‘asleep–awake–asleep’ techniques [1**]. The ‘asleep–awake–asleep’ technique is currently considered as the most popular one [1**]. The first ‘asleep’ stage is provided with heavy sedation or even general anesthesia in the beginning of the surgery during a patient’s positioning, fixation of the head with pins, craniotomy or burr holes, and final exposure of the brain. Skin infiltration with local anesthetic at pin insertion sites and the skin incision, or performance of a scalp nerve block, are essential for pain relief and reducing opiates-related complications [2]. A variety of different medications and combinations of medications has been reported to be successfully used: propofol, remifentanil, fentanyl, midzolam [1**,3,4]. For airway management, oral or nasopharyngeal airways, oral and nasal endotracheal tubes, laryngeal mask (LMA) as well as unprotected airway have all been used with different degrees of success [1**]. For the next awake stage, the patient must be brought to full consciousness. In this awake phase, mapping of the brain with electrocorticography during cognitive testing is performed to delineate the area to be resected. The transition from the ‘asleep’ to the ‘awake’ phase is the most challenging task in the anesthetic management because of potential complications during the awakening and manipulation of the airway, while the brain is exposed. Coughing, Valsalva maneuver, vomiting and movement during extubation of the airway may lead to disastrous complications such as bleeding, brain swelling, venous air embolism, and potentially death. Consequently, many anesthesiologists

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**Figure 1 Positioning of patient for functional neurosurgery**

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<table>
<thead>
<tr>
<th>Positioning</th>
<th>Head fixation</th>
<th>Body positioning</th>
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<tbody>
<tr>
<td>Pins</td>
<td>Head position</td>
<td>Supine</td>
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<tr>
<td>Mayfield frame</td>
<td>Neutral</td>
<td>Lateral</td>
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<td>Stereotactic frame</td>
<td>Flexion</td>
<td>Sitting</td>
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<td>Hoarshoe gelpad</td>
<td>Extension</td>
<td>OR Table</td>
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<td>OR Table</td>
<td>Lateral flexion</td>
<td>90°</td>
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<td>180°</td>
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OR, operating room.
try to avoid airway instrumentation. When mapping is completed, either sedation or analgesia or both may be provided again for the ‘asleep’ phase. Airway instrumentation when the patient’s head is in pins and covered by the surgical drapes may be difficult, especially if emergency intubation of the trachea is required.

In implantations of DBS, the first ‘asleep’ phase usually requires less time than the first ‘asleep’ phase in awake craniotomy. DBS implantation does not require wide exposure of the brain. Only burr holes are needed, which can be performed under local infiltration of the scalp. Although the use of various sedative techniques, including propofol infusion, fentanyl, remifentanil, and inhalational anesthetics have been reported [5, 6*], many surgeons prefer to avoid any sedation because of the extreme sensitivity of subcortical areas to the GABA-ergic medications, which may completely abolish MER recording and tremor. When localization of the DBS electrode is finalized, the patient’s head is disengaged from the frame, and the patient may then be anesthetized for the implantation of the generator into the chest wall.

Table 1. Potential risks and complications expected in awake functional neurosurgery

<table>
<thead>
<tr>
<th>Undersedation</th>
<th>Oversedation</th>
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<tbody>
<tr>
<td>General</td>
<td>General</td>
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<tr>
<td>Pain</td>
<td>Drowsiness</td>
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<tr>
<td>Discomfort</td>
<td>Restlessness</td>
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<tr>
<td>Restlessness</td>
<td>Impaired cognition, lack of cooperation, inability to perform mapping</td>
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<tr>
<td>Anxiety</td>
<td>Respiratory</td>
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<tr>
<td>Inability to stay still</td>
<td>Airway obstruction</td>
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<tr>
<td>Voluntary movements</td>
<td>Respiratory depression</td>
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<td></td>
<td>Hypoventilation</td>
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<td></td>
<td>Hypercarbia</td>
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<tr>
<td>Respiratory</td>
<td>Oxygen desaturation</td>
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<td>Inability to clear secretions (PD)</td>
<td>Apnea</td>
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<tr>
<td>Coughing</td>
<td>Need for airway manipulations and for providing an emergency airway</td>
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<tr>
<td>Dyspnea—hyperventilation</td>
<td>Coughing and Valsalva during transition from ‘asleep’ to ‘awake’ stage</td>
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<td>Neurological</td>
<td>Neurological</td>
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<td>Seizures</td>
<td>Brain swelling</td>
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<td>Brain swelling</td>
<td>Seizures</td>
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<td>Bleeding</td>
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<td>Hemodynamic</td>
<td>Hemodynamic</td>
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<td>Arterial hypertension</td>
<td>Arterial hypertension</td>
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<tr>
<td>Tachycardia, arrhythmia</td>
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<tr>
<td>Gastrointestinal</td>
<td>Gastrointestinal</td>
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<tr>
<td>Nausea, vomiting</td>
<td>Nausea, vomiting</td>
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<td></td>
<td>Aspiration of gastric contents</td>
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<td></td>
<td>Involutary movements</td>
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<td>Shivering</td>
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<td>Sedative-induced dyskinesias</td>
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<td></td>
<td>Arterial hypotension</td>
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PD, Parkinson’s disease.

Potential risks involved in anesthetic management for awake neurosurgical procedures are summarized in Table 1. Unfortunately, the actual incidence of complications and therefore the optimal anesthetic management are largely unknown due to the lack of prospective randomized studies. Currently available data are inconclusive because the studies differ in: anesthetic management, criteria applied for definitions of complications, and study design. The largest retrospective chart review of awake craniotomy by Skucas and Artru [3] reported that airway problems occurred in 2% out of 332 cases of asleep–awake–asleep technique using only propofol infusion in patients with unsecured airway undergoing epilepsy surgery. Manninen et al. [4] prospectively randomized 50 patients undergoing tumor surgery with brain mapping to receive sedation with propofol and remifentanil infusion, or propofol and fentanyl, and observed an incidence of respiratory complications as high as 18% in this cohort, without any difference between the two groups. Respiratory complications were defined as any of following: a decrease in respiratory rate, oxygen desaturation, or airway obstruction. Because the majority of surgeons request the avoidance of any sedation, the most significant challenge in DBS implantations is the maintenance of hemodynamic stability and the prevention/treatment of intraoperative hypertension, a known risk factor for developing intracerebral hemorrhage. In the prospective study involving 128 patients receiving DBS implantations for Parkinson’s disease with intermittent infusion of propofol, about 60% of patients developed intraoperative hypertension [7]. Intracerebral hemorrhage is considered to be the most severe complication, with an incidence of 3.3–6% reported in the prospective studies [8–10]. The incidence of respiratory complications in DBS implantations is unknown.

Benzodiazepines, barbiturates, and opioids may deliver patient comfort and hemodynamic stability, but they may also depress electrophysiologic activity of the brain, interfere with mapping, and cause respiratory depression and airway compromise. To achieve a balance between uneventful awakening and avoidance of respiratory complications, the pharmacokinetic-guided titration of propofol and remifentanil using the target control infusion device has been advocated in patients with Parkinson’s disease [11] and for awake cranietomies [12]. These devices are not yet approved for use in the United States.

In addition to obesity [3] and age [6*], which were suggested by the retrospective chart reviews as risk factors, other patient-related risk factors are less clear. Previously, obstructive sleep apnea was considered as a potential risk factor for perioperative respiratory complications [1*]. However, there are no data to support this. There is also a paucity of data to predict who would be an ideal candidate for awake functional neurosurgery. According to the
current data, in most instances, only the lack of patient cooperation will preclude awake neurosurgery. However, factors including abnormal anatomy of the airway, presence of gastroesophageal reflux and obesity should be considered as potential risk factors.

**Dexmedetomidine: a unique sedative agent**

Dexmedetomidine is a selective agonist of α2-adrenergic receptors (α2-ARs) with high affinity to α2-ARS (α2α1 effect ratio of 1620:1), which is eight times higher than with clonidine. Dexmedetomidine has a rapid onset of action. It undergoes biotransformation in the liver, and the kidneys excrete about 95% of its metabolites. Its distribution half-life is 6 min, and a clearance half-life is 2 h.

Presynaptic and postsynaptic α2-ARs are distributed over vital organs (heart, pancreas, kidneys), blood vessels and the central and the peripheral nervous system. Stimulation of postsynaptic α2-ARs leads to hyperpolarization of neuronal membrane, whereas stimulation of presynaptic α2-ARs reduces the release of norepinephrine. In the spinal cord, α2-ARs are predominantly postsynaptic, and located in the dorsal horn. Activation of spinal α2-ARs inhibits nociception, which most likely explains the analgetic properties of dexmedetomidine. Both presynaptic and postsynaptic α2-ARs are widely distributed in the brain, particularly in the pons and medulla. The major site of noradrenergic innervation in the brain with the highest concentration of presynaptic α2-ARs is the locus ceruleus, which is responsible for arousal, sleep, anxiety, and withdrawal symptoms from drug addiction. As a result, the central effect of dexmedetomidine, which is manifested by anxiolysis and sedation, is noncortical and subcortical in origin. It does not involve the GABA system and consequently does not cause cognitive impairment or disinhibition, differentiating dexmedetomidine from all GABA-mimetic sedatives and anesthetics.

The mechanisms of anesthetic-induced effects on unconsciousness and amnesia are not clear. Recently, both cortex [13] and thalamus [14] have been suggested to be primarily responsible for the anesthetic-induced unconsciousness. The unusual subcortical form of dexmedetomidine-induced sedation is characterized by an easy and quick arousal, resembling natural sleep.

The neuroprotective properties of dexmedetomidine have been demonstrated in various animal models of cerebral ischemia [15–17]. There are recent experimental data suggesting that in addition to α2-ARs, the neuroprotective effect of dexmedetomidine may include other pathways in the brain, independent of α2-ARs, and most probably involve α2-imidazoline receptors in the brainstem and hippocampus [18]. Further in-vivo studies are required to support this suggestion and to elucidate mechanisms of dexmedetomidine-induced neuroprotection.

Postsynaptic α2-ARs are widely presented in smooth muscles of conductance and resistance vessels. Both vasodilatating [19–21] and vasoconstricting [21–24] effects of dexmedetomidine on cerebral and spinal arteries and venules have been reported in animal studies. These contradictory results may be explained by the differences between models, animal species, and the dose of dexmedetomidine, as well as experimental conditions and background anesthesia, all of which can potentially modify vascular reactivity to the drug. Current data suggest that dexmedetomidine-induced cerebral vasoconstriction has a direct nonendothelium-dependent mechanism, whereas dexmedetomidine-induced vasodilation may be endothelium dependent and involve nitric oxide pathways. However, the exact mechanisms of dexmedetomidine’s effect on the cerebral vasculature have not been completely elucidated yet.

Regardless of the mechanisms involved, current human studies on healthy volunteers clearly demonstrate that dexmedetomidine decreases cerebral blood flow (CBF) [25,26**]. Using a PET-scan in awake healthy volunteers, Prielipp et al. [25] demonstrated a decrease in global CBF by about 30% with intravenous infusion of dexmedetomidine of only 0.2 μg/kg/hour for 30 min. Prielipp et al. [25] suggested cerebral vasoconstriction as an underlying mechanism of decreased CBF, which is in agreement with the previous in-vitro data and one in-vivo study in dogs [27]; however, a recent study by Drummond et al. [26**] demonstrated a simultaneous decrease of CBF and CMRO2 with dexmedetomidine in healthy volunteers. In this study [26**] CBF was estimated by measuring blood flow velocity in the middle cerebral arteries (Vmca) using Transcranial Doppler Ultrasonography (TCD) and CMRO2 was calculated by measuring oxygen saturation in the jugular bulb. In healthy volunteers, dexmedetomidine also preserves cerebral autoregulation but slightly decreases carbon dioxide reactivity (A.M. Lam, personal communication).

Although both anticonvulsant and proconvulsant effects of dexmedetomidine have been shown in animal studies [28–31], there are no data supporting proconvulsant effects of dexmedetomidine in humans; however, α-2 agonists may produce epileptiform activity in some patients with epilepsy. The underlying mechanism of this phenomenon was suggested to resemble the epileptiform activity during sleep deprivation, as α-2 agonists modulate pathways of natural sleep [32].

The effect of dexmedetomidine on ventilation is minimal. Initially, administration of dexmedetomidine increases arterial carbon dioxide (PaCO2), but it also leads to
Clinical application of dexmedetomidine to functional neurosurgery

The first successful use of dexmedetomidine in functional neurosurgery was published in 2001 by Bekker et al. [34], who reported sedation with dexmedetomidine in a patient requiring language mapping for tumor resection. It was followed by the discouraging report of the inability to perform neurocognitive testing with dexmedetomidine by Bustillo et al. [35]. This most probably occurred because of concomitant use of fentanyl and midazolam. A number of recent case series clearly demonstrate that dexmedetomidine may be successfully used in functional neurosurgery [6,36,37,38,39].

Souter et al. [37] were the first to report the use of dexmedetomidine not just for sedation at the first ‘asleep’ phase in awake craniotomy but during language mapping and electrocorticography (ECoG) recording. It was successfully used in six patients with seizure disorders, with three of them receiving dexmedetomidine only. All three patients received continuous infusion of dexmedetomidine at 0.3–0.7 μg/kg/hour, which was titrated to maintain sedation, guided by modified OAA/S score. One patient developed a subclinical seizure detected by EEG while being sedated with dexmedetomidine, thus allowing the investigators to conclude that dexmedetomidine does not suppress epileptiform activity and can be used in patients with seizure disorders requiring brain mapping [37]. To prove this, Talke et al. [39] prospectively observed EEGs in five patients with intractable seizures who received 0.5 μg/kg/hour of dexmedetomidine, followed by a bolus of 0.5 μg/kg, and found that there was no decrease in epileptiform activity. Moreover, in some foci an increase in epileptiform activity was observed. Oda et al. [40] evaluated the influence of dexmedetomidine on the ECoG recording in 11 patients with temporal lobe epilepsy, anesthetized with 2.5% of sevoflurane and hyperventilated to PaCO2 of 30 mmHg, and demonstrated that the median frequency of ECoG recording did not change at a plasma level of dexmedetomidine of 0.5 ng/ml, but decreased at 1.5 ng/ml. However, there was no change in spike activity. It is possible that concomitant use of sevoflurane and hyperventilation could potentially affect anticonvulsant or proconvulsant activity of dexmedetomidine. To verify the dose-dependent anticonvulsant versus proconvulsant effect of dexmedetomidine, and its effect on the seizure activity when other anesthetics are used concomitantly, prospective randomized trials are required.

As mentioned above, most neurosurgeons are reluctant to use any kind of sedation for DBS implantations when MERs are utilized for the positioning of the DBS electrode because of the profound suppressive effect of GABA-ergic medications on the basal ganglia. At first, dexmedetomidine had been reported to provide adequate sedation without impairment of MER recordings in a series of 11 patients undergoing DBS implantations for Parkinson’s disease [38], when dexmedetomidine was titrated to maintain sedation and guided by the modified OAA/S score. When this cohort of patients was compared with the historical control cases, dexmedetomidine provided better hemodynamic stability and patient satisfaction [38]. Recently, Elias et al. [41] demonstrated the depression of MER recording with moderate/heavy sedation with dexmedetomidine, defined as sleepy and unarousable state, with a bispectral index less than 80. On the contrary, in lightly sedated patients with a bispectral index higher than 80, no depression of MER recording has been observed. This was associated with the dexmedetomidine infusion of 0.1–0.4 μg/kg/hour [41]. Although dexmedetomidine has theoretical advantages over GABA-ergic medications such as lack of respiratory depression, hemodynamic stability, and possible ability to suppress GABA-ergic drugs-induced dyskinesias [42], the optimal sedative dose of dexmedetomidine, the incidence of complications as well as benefits of dexmedetomidine use in DBS implantations remain unknown and should be investigated prospectively.

Conclusion

Current data on the anesthetic techniques for functional neurosurgery is provided by the retrospective chart reviews and small prospective case series. With conventional sedation for the awake craniotomy and implantation of DBS, the patient is potentially at risk for respiratory depression, discomfort and arterial hypertension.

Dexmedetomidine is a unique sedative agent, which does not cause respiratory depression. It has been shown to be safe in both awake craniotomy and DBS implan-
tations in small retrospective case series. The optimal dose regimen of dexmedetomidine for functional neurosurgery is unknown.

Prospective randomized trials are necessary to elucidate: an optimal anesthetic technique for awake craniotomy and DBS implantation; incidence of complications, including respiratory complications and hemodynamic stability; safety and usefulness of combinations of different anesthetics; dose–response of dexmedetomidine on the electrocorticography and MER recording.

Acknowledgement

The author is grateful to Professor AM Lam for providing his data on the influence of sedation and opioids on electrocorticography and MER recording.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

• of special interest

•• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 684).


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