Neuromonitoring and Sedation; Is There a Role?

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Introduction: The History

Neuromonitoring serves as a tool for measuring the depth of anesthesia (DOA) and sedation. These monitors are primarily based on processed electroencephalogram (EEG). The usefulness of EEG when applied during anesthesia was first suggested by Gibbs and Lenox in 1937 [1, 2]. Changes in the EEG during inhalational and intravenous anaesthesia were further defined in 1950; however cost and complexity of information restricted further use. The discovery of tubocurarine led to light anesthesia with muscle relaxation becoming popular in the mid-1970s also known as the "Liverpool technique." This resulted in incidences of the patient being both conscious and unresponsive to surgical stimuli following neuromuscular blockade. The first study of awareness under anesthesia quoting an incidence of 1.2% was published in 1960 [3]. There were however still no practical means of measuring DOA as processed EEG, used to develop cerebral function monitor in 1979 (to detect global ischemia), was found to be unreliable for measuring anesthetic depth. The isolated forearm technique has also been used to detect awareness under anesthesia with muscle relaxation, in children aged over 5 years. Although respond to command with this technique in up to 20% with halothane and more recently 1% with isoflurane has been quoted, there has been no incidence of recall of events in both studies [4, 5]. Brice et al. introduced a structured interview to facilitate detection of awareness [6] which is still popular and used in research and clinical practice.

Recent large multicenter studies in North America and the United Kingdom and Ireland have highlighted the incidence of awareness in children and adults [7–9]. Several DOA monitors have been introduced to the market over the past decade with the intent to decrease risk of intraoperative awareness. This chapter will review the literature with regard to awareness under anesthesia and deep sedation in children, discuss available guidelines to measure the DOA, and apply the current knowledge to sedation practice. The limitations of neuromonitors will be considered. The future in monitoring the depth of anesthesia and sedation lies in understanding consciousness and the comprising neural connections. Current research with functional MRI (fMRI) has improved our understanding of the role of the brain stem and the corticothalamic connections.

Awareness Under Anesthesia and Neuromonitors

Studies have demonstrated the incidence of accidental awareness under general anesthesia (AAGA) in children ranging from 0.06% to 2.7% [8–11]. Davidson's reported incidence of 0.74% is a combination of data from studies which used a direct Brice-type questionnaire [12]. The recent NAP5 (National Audit Project) from the United Kingdom and Ireland published in 2014 looked at the incidence of AAGA over a period of 4 years in adults and children (defined as less than 16 years) [13]. It has been the largest and most comprehensive study of AAGA and its risk factors. It included general anaesthesia and monitored anesthesia care. Some of these could be considered deep sedation with intravenous medications. The findings included every public hospital, baseline survey of anesthetist's knowledge of reports of AAGA, and baseline data of practice of anesthesia followed by prospectively acquired patient's reports of their experiences and concluded with a multidisciplinary structured analysis. NAP5 estimated an incidence of approximately 0.002% (1 in 60,000) from 488,500 general anesthetic in children less than 16 years [13]. This incidence was lower than the 0.74% incidence cited by studies using Brice-type questionnaires. Brice methodology has limitations: false positives can occur from repeated questioning and could result in both amplification of prior memory and false memory formation. Brice can also promote an unconscious bias

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[12]. Future studies are needed, targeted specifically to pediatrics, to evaluate awareness.

The discrepancy between higher incidence of adult AAGA (0.1–0.2%) and that of children has been attributed to differences in pharmacology of drugs, anesthetic technique, level of consciousness monitoring, type of surgery, use of neuromuscular blockers (NMB), childhood experiences and perceptions, parental attitude, and memory formation in children.

There were two important findings of NAP5: few children reported AAGA and even when reported could be after a delay of several years.

The majority of recalled experiences were tactile (79%) and auditory (55%) with some describing being scared or in pain. Dreaming, though commonly reported, usually did not evoke distress, although some cases did report long-term psychological effects. NAP5 concludes that although serious long-term psychological harm and anxiety states are rare, they do occur after AAGA, and children's reports can be as reliable as those of adults.

With respect to neurobehavioral adverse events associated with exposure to anesthesia, the important GAS (general anesthesia vs spinal) and PANDA (Pediatric Anesthesia Neurodevelopment Assessment) studies suggest that a single brief exposure to anesthesia is not associated with neurobehavioral adverse events. Multiple exposures, prolonged sedation, and anesthesia in fetus and infants with congenital cardiac or with complex neonatal surgical conditions still need to be assessed [14, 15]. The Food and Drug Administration (FDA) issued a warning in December 2016 that "repeated or lengthy use of general anesthetic and sedation drugs during surgeries or procedures in children younger than 3 years or in pregnant women during their third trimester may affect the development of children's brains" [16].

Currently, clinical indicators of heart rate, blood pressure, end tidal anesthetic concentration, and estimated plasma concentrations, combined with the application of validated scales such as Observer's Assessment of Alertness and Sedation (OAA/S), Modified Maintenance of Wakefulness Test (MMWT), Ramsay, and University of Michigan Sedation Scale (UMSS), are widely used as monitors of depth of sedation [17, 18]. These scales are not a continuous method of monitoring sedation, and some require patient stimulation to assess depth.

There has been new interest in the use of electroencephalogram (EEG) as a tool to measure depth of sedation. In theory, EEG-based monitoring could be used to monitor the neurological response to sedatives. The B-aware trial in adult demonstrated that awareness with recall was reduced with use of BIS, especially in patients undergoing total intravenous anaesthesia (TIVA). Importantly, in this trial the incidence of awareness was not zero [19, 20]. The incidence of awareness in another study with bispectral index (BIS)-guided (40–60) volatile anesthesia delivery (0.7–1.3 MAC) was found to be similar [20].

Several methods of acquiring EEG and processing EEG have both been developed and approved for clinical use. The most commonly used monitor based on processed EEG is the bispectral index (BIS), widely used in adult and pediatric practice. BIS is based on frequency domain analysis. Other monitors include patient state index (PSI), which is derived from EEG power, frequency, and phase information. M-Entropy is another monitor which measures the amount of disorder in the EEG (state entropy) together with frontalis electromyogram (response entropy) and auditory evoked potential (AEP) which measures latency of cortical response to auditory stimulation. Recently, transcranial magnetic stimulation is being studied as a means to measure fractal dimension as a measure of states of consciousness [21, 22]. All current monitors have limitations, and thus far the threshold and type of EEG changes that would indicate awareness remain unknown. A very low incidence (0.5%) of children surveyed in NAP5 had processed EEG monitoring.

Awareness does not appear to be of significant concern for pediatric Anesthetists. A survey of pediatric anesthetists across the United Kingdom and France demonstrated that although nearly two thirds of the anesthetists surveyed recognized awareness to be an issue, less than 10% discuss the risks with the parents preoperatively or actively look for signs. BIS monitoring was routinely used by 10% [17]. Another survey revealed that 50% of surveyed anesthetists reported an incidence of awareness in their practice and rated awareness as a moderate problem [18]. Anesthetists report a greater likelihood to use DOA monitoring if it could be shown to prevent most cases of awareness.

A Global Review of Published Guidelines on Depth of Anesthesia Monitoring

Although most major international societies recommend monitoring level of consciousness with anesthesia and sedation, thus far there is no uniform consensus.

The National Institute of Clinical Excellence (NICE) UK guidance is based on technology report findings as well as consensus opinion and promotes clinically innovative and cost-effective technologies based on potential to improve care. Current NICE guidelines recommend EEG-based neuromonitoring for any general anesthesia in patients at higher risk of unintended awareness. These would include patients at higher risk of excessively deep anesthesia and in those receiving total intravenous anaesthesia (TIVA). Although NICE recommends BIS, recognizing greater uncertainty of clinical benefit with the E-Entropy and Narcotrend-Compact M depth of anesthesia monitors, the committee concludes

that all monitors are broadly equivalent [23]. NICE refers to a "low probability of awareness" with output reading of both BIS and E-Entropy of 40. The relationship between monitor output probability is unclear as is the variability of DOA monitor between inhalation agents and between isoflurane and propofol [24–27].

Almost 20% of AAGA reports occurred in patients at time of emergence and in whom neuromuscular blockade (NMB) had been inadequately reversed. Based on the NICE guidance and following the NAP5 report, the Association of Anesthetists of Great Britain and Ireland (AAGBI) recommend DOA monitoring for patients in whom NMB are used together with TIVA. The guidelines state that although the data may provide an additional source of information, the literature on the "efficacy of these devices in correctly predicting AAGA or correctly predicting adequate level of anaesthesia remains inconsistent and debated." If neuromonitoring is used, the AAGBI recommend that monitoring starts from induction and remains till completion of surgical or anesthetic intervention including transfer. They also recognize that portability and continuity of monitoring could be an issue with the device as they are not powered by battery and need to be plugged into mains to work [24].

Most of the international societies such as the American Society of Anesthesiologists (ASA), the Association of Anesthetists of Great Britain and Ireland, the European Society of Anaesthesiology, and the Australian and New Zealand College of Anesthetists recommend the assessment of the depth of sedation through sedation scales and scores such as the ASA Continuum of Depth of Sedation, the Modified Observer's Assessment of Alertness/Sedation (MOAA/S) scale, and the Ramsay Sedation Scale (RSS) [28] (Table 7.1).

It is recommended that the depth of sedation is assessed periodically by using one of these scales or by assessing responsiveness to verbal and tactile stimulation [28]. The OAA/S scale has been found to have limitations during deep levels of sedation in pediatric setting [29]. The UMSS is a simple scale and has been found to be a valid and reliable scale in children undergoing sedation for non-painful procedures [30].

The Practice Guidelines by ASA for Sedation and Analgesia by Non-Anesthesiologists recommend that response to verbal command should be routinely used as a guide to level of consciousness in all cases involving moderate sedation unless the patient is unable to respond appropriately or where movement could be harmful. Where a verbal response is not possible, (upper esophageal endoscopy), a sign such as "thumbs up" is recommended. For deep sedation, a more profound stimulus is recommended. A reflex withdrawal to painful stimulus could indicate a state of general anesthesia. The ASA guideline states that although the literature does not support the use of neuromonitoring as a means to improve outcome, the consensus is that neuromonitoring could prevent complications associated with moderate and deep sedation [31].

Table 7.1 Sedation scores used in both clinical practice and research

ASA continuum of sedation [11]	Modified Observer's Assessment of Alertness/Sedation Scale [12]	Modified Ramsay Sedation Scale [13]
Minimal sedation/ anxiolysis: a drug-induced state during which patients respond normally to verbal commands	5—Responds readily to name spoken in normal tone	1—Awake and alert, minimal or no cognitive impairment
Moderate sedation/ analgesia ("conscious sedation"): a drug-induced depression of consciousness during which patients respond purposefully* to verbal commands, either alone or accompanied by light tactile stimulation	4—Lethargic response to name spoken in normal tone	2—Awake but tranquil, purposeful responses to verbal commands at a conversational level
	3—Responds after name called loudly or repeatedly or both	3—Appears asleep, purposeful response to verbal commands at a conversational level
	2—Responds only after mild prodding or mild shaking	4—Appears asleep, purposeful responses to commands but at a louder than conversational level, requiring light glabellar tap or both
Deep sedation/ analgesia—purposeful* response after repeated or painful stimulation	1—Responds only to painful stimulation	5—Asleep, sluggish purposeful responses only to loud verbal commands, strong glabellar tap, or both
		6—Asleep, sluggish purposeful responses only to painful stimuli
General anaesthesia—a drug-induced loss of consciousness during which patients are not arousable, even by painful stimulation	0—No response to painful stimulation	7—Asleep, reflex withdrawal to painful stimuli only
		8—Unresponsive to external stimuli, including pain
Note: *Reflex withdrawal from a painful stimulus is not considered a purposeful response	Note: MOASS is the responsiveness component of the Observer's Assessment of Alertness/Sedation Scale [12]	Original Ramsay Sedation Scale is a 6-item scale developed to assess ICU sedation [14]

*Common scales used and how they relate to each other

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The American Academy of Pediatrics (AAP) recently published an updated report which is a combination of guidance published by both the AAP and the American Academy of Pediatric Dentistry (AAPD) for monitoring and management of pediatric patients during and after procedural sedation [32]. They recommend close observation and documentation of loss of consciousness (LOC) and responsiveness with the aid of various scoring systems. There is no mention of neuromonitors.

The African Society Guidelines emphasize monitoring the LOC with the UMSS scale. Neuromonitoring is not included in the recommendations [33].

In summary, most international societies concur on the need for monitoring DOA and sedation to decrease the probability of awareness. To date there is no ideal neuromonitor available or recommended by most societies.

The Range of Neuromonitors: The Science, Practice, and Function

Several monitors based on processed EEG have been marketed in the last two decades. Table 7.2 lists the currently available [34].

BIS

Bispectral index (BIS) monitoring is linked to brain cellular activity and based on processed electroencephalogram (EEG). The link between degree of sedation and depression of brain cellular activity and BIS was first investigated by Alkire [35].

BIS is derived from both power spectral analysis and bispectral analysis. It is determined by three factors which include EEG wave frequency, synchronization of high- and low-frequency information, and time spent in burst suppression. BIS is a scale from 0 to 100 with zero correlating to complete cortical suppression and electrical silence while 100 representing EEG found in an awake person.

Figure 7.1 describes BIS used for sedation in intensive care setting [36].

Gugino and colleagues showed the changes in the EEG that occur with propofol or sevoflurane anesthesia in healthy adult paid volunteers as they move from awake and relaxed state to a deepened state. Alpha waves predominate in the relaxed state followed by beta waves during light anesthesia, and as the state of deep anesthesia is reached, thalamo-hippocampal-septal generators take control, and there is a

Table 7.2 The technology of processed electroencephalogram monitoring devices for assessment of depth of anesthesia

Monitor	Features
AEP Monitor/2 (Danmeter A/S. Odense. Denmark)	The AEP index, the AAI, is an index relying on MLAEP and EEG signals. Bilateral click stimuli are delivered through headphones. The EEG signals after the stimuli are discerned from the background EEG noise and processed for MLAEPs, reflecting neural activity within the thalamus and primary auditory cortex. When the AEP signals are low in quality, the AAI is derived mainly from EEG-based spectral parameters. Burst suppression ratio and EMG data are also displayed. Two index scales: 0–60 and 0–100 [9].
BIS Monitor (Medtronic. Minneapolis. MN)	It utilizes an algorithm based on power spectral analysis, bispectral analysis, and burst suppression data. The derivation of the BIS index is achieved through a weighted sum of relevant subparameters. The BIS index scale is from 0 to 100. In addition to a single-channel EEG, it also offers a bilateral sensor for assessment of asymmetry. Density spectral arrays and spectral edge frequencies can be displayed as well as EMG activity and burst suppression information.[3]
Cerebral State Monitor (Danmeter A/S, Odense, Denmark)	The algorithm for the cerebral state index utilizes frequency domain analysis and burst suppression ratio processed with fuzzy logic methodology for inference of the index. It uses a single-channel EEG with an index scale of 0 to 100. In addition to the index, it also provides measures of burst suppression percentage and EMG activity [10].
Entropy Module (GE Health care Technologies, Helsinki, Finland)	The algorithm uses spectral analysis to produce two main parameters for overall assessment of depth of anesthesia: the SE, for depth of hypnosis (index scale. 0–100), and RE, for indirect assessment of noniception/responsiveness to stimuli (derived from the frontal EMG: index scale. 0–91). A widening difference between SE and RE is deemed a likely indicator of inadequate anesthesia. In addition to the waveform display of SE and RE, a burst suppression ratio is also displayed. It uses a single-channel EEG [7].
Index of consciousness monitor (Morpheus Medical, Barcelona, Spain)	The index of consciousness is derived via symbolic dynamics, a time domain method that divides the EEG signals into partitions and labels each partition with symbols of 1 and 0, depending on mathematical determination. It is conceptually similar to entropy. This approach can detect nonlinear EEG characteristics and assess levels of signal complexity. The algorithm also includes frequency domain methods and burst suppression analysis. A fuzzy logic inference system is used in index derivation. Burst suppression and EMG information are also displayed. Single-channel EEG with an index scale of 0 to 99 [11].
Narcotrend Monitor (MonitorTechnik, Bad Bramstedt, Germany)	The Narcotrend index is derived from a system developed for the visual classification of the EEG patterns associated with stages of natural sleep. It uses burst suppression, time, and frequency domain analysis to extract the relevant EEG parameters, which are then classified through plausibility testing into a total of 14 possible substages: A (awake) to F (deep) with further subdivisions. The most recent version also provides an index from 0 to 100. Uses 1- or 2-channel EEG. Also displays EMG information [12].
NeuroSENSE Monitor (NeuroWave Systems Inc. Cleveland Heights, OH)	The WAVcns index is calculated via wavelet analysis of the EEG signals in the gamma frequency band, using a deterministic approach (a method that always produces the same output for a given EEG interval). This monitor was purposefully developed for use in anesthesia closed-loop delivery systems. It uses bilateral brain monitoring for derivation of index with a scale of 1 to 100 [15].

Table 7.2 (continued)

Monitor	Features
SEDline Monitor (Masimo, Irvine, CA)	The patient state index is calculated by a 4-channel EEG with an algorithm incorporating high heterogeneity of variance at different levels of sedation/hypnosis, taking into account anterior-posterior relationships in the brain and coherence between bilateral brain regions. Burst suppression data and plausibility analysis are applied for final index derivation. It also displays bilateral density spectral arrays, and bilateral 4 channels of raw EEG waveforms. Scale consists of 0–100 with optimal depth between 25 and 50 (in contrast to other monitors with similar scale and recommended anesthetic depth between 40 and 60) [14].
SNAPII Monitor (Stryker, Inc. Kalamazoo, MI)	The SNAP index is based on calculations involving power spectral analysis in the 0 to 18 and 80 to 420 Hz frequency ranges, called the low-frequency index and high-frequency index, respectively, for the derivation of the single index. It claims an algorithm that minimizes artifacts and a shorter lag time to detect patient awakening. It uses a single-channel EEG and an index scale of 0 to 99 [15].
qCON 2000 monitor (Quantium Medical, Barcelona, Spain)	The qCON index is derived from spectral analysis and burst suppression rate and processed through an artificial neural network and fuzzy logic system. Conceptually, it has similarities to the entropy approach. The qCON index is a measure of hypnosis, whereas the qNOX index is a measure of noniception, each similarly derived through different frequencies. Both indexes range from 0 to 99. The qNOX reference scale was derived through EEG signals in patients moving in response to nailbed pressure. Single-channel EEG. Also displays EMG and burst suppression data [10].

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This list is not intended to be all-inclusive
Abbreviations: *AEP* auditory evoked potential, *EEG* electroencephalogram, *EMG* eleclromyograni, *MLAER* middle-latency AEP, *RE* response entropy, *SE* state entropy

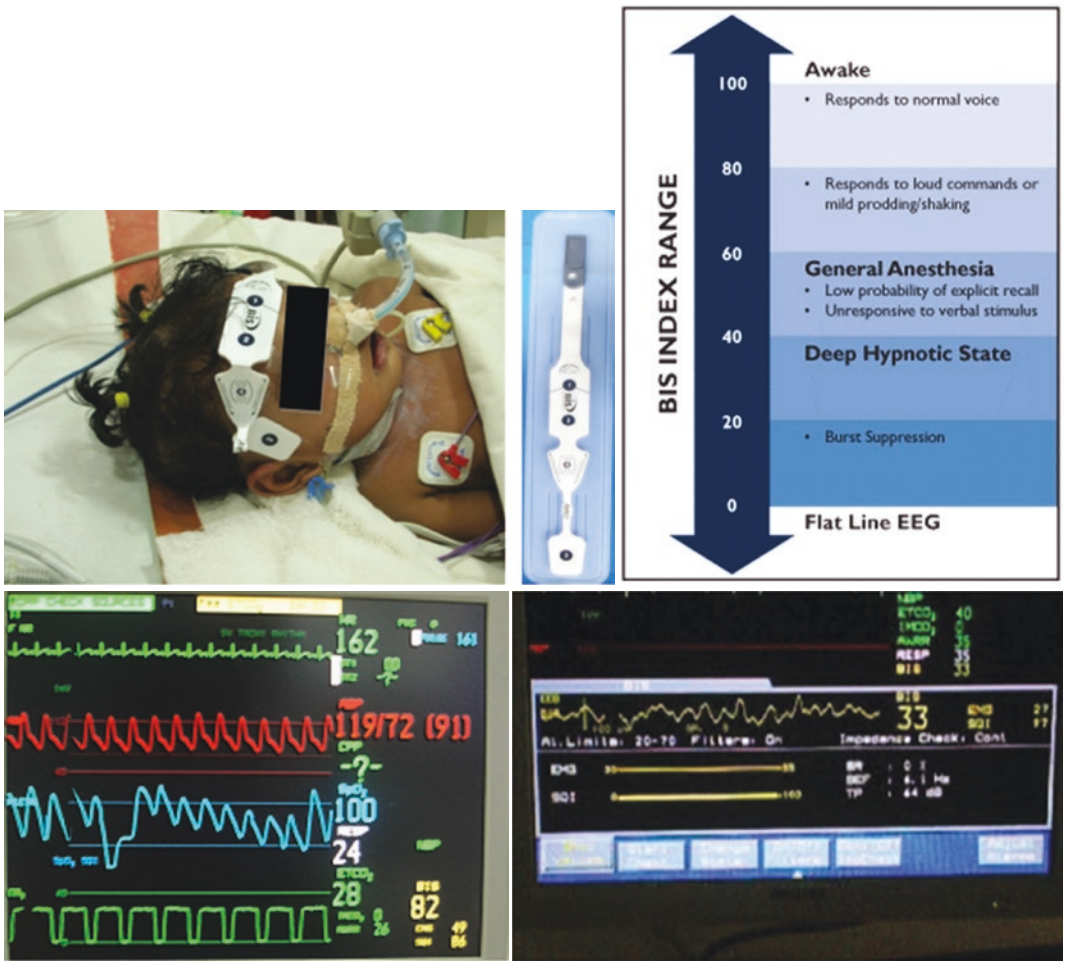

Fig. 7.1 The BIS pediatric sensor and monitor. The BIS monitor displays a single processed EEG number from 0 to 100, as well as the raw EEG waveform, and signal strength indicator. The BIS algorithm is displayed with the corresponding sedation depth. (Reproduced from Doshi et al. [36] with permission from Pediatric Oncall Journal. Originally licensed under a Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License. https://creativecommons.org/licenses/by-nc-sa/4.0/)

predominance of delta and theta waves. With return of consciousness (ROC), all these changes are reversed in the same order [37].

The relation between cortical suppression by sedatives and measurement of this EEG activity was conceptualized as far back as 1937. Recent advances in technology and computer analysis enable EEG data to be processed into different derivatives which include power spectral edge, median frequency, and zero crossing frequency. The initial studies of BIS were published in 1971and FDA approval obtained in 1996. In 2004 BIS received a FDA approved indication for reducing the incidence of intraoperative awareness. The BIS algorithm has evolved over the last two decades to the current v4 and v4.1 [38] (Table 7.3) (Fig. 7.2a–c) [38].

(a) Quattro Sensor for BIS has four self-prepping silver/silver chloride electrodes placed on the forehead. Lead 4 is the ground electrode and measures electromyography activity of the frontalis muscle below the sensor. Sensor placement requires skin preparation with alcohol, mild debridement with gauze, and 2–5-second application of digital pressure over sensor lead.

Table 7.3 Bispectral index algorithm development [38]

BIS version	Release date	Clinical endpoint	Comment
1.0	1992	MAC/ hemodynamic	Agent-specific, modified by analgesic dose
2.0	1994	Hypnosis/ awareness	Reformulation of index, agent-independent
2.5	1995		"Awake" artifact recognition/ removal
3.0	1995[a]		Sedation performance enhanced
3.1	1996		EEG burst suppression detection enhanced
3.2	1997		EMG and "near" suppression handling improved
3.3	1998		EMG detection/removal improved
3.4	1999		15 seconds smoothing, less susceptible to "arousal delta" patterns on emergence
4.0 (XP)	2001		Resistant to electrocautery, improved performance in sedation range and handling of near-suppression states, lead 4 sensor, upgraded DSC, advanced error handling 2nd bipolar EEG rejects eye movement artifact+
4.1	2004[b]		Improved performance in sedation range

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MAC minimum alveolar concentration suppressing movement to surgical incision by 50%, *EEG* electroencephalogram, *EMG* electromyogram
[a] FDA (510k) granted 10/96 for monitoring anesthetic effect.
[b] FDA (510k) granted 10/03 for decreasing incidence of recall during general anesthesia in adults.

(b) Bispectral index XP monitor (Aspect Medical Systems, Inc., Natick, MA). Raw EEG data is converted by the digital signal processing cable or DSC.
(c) The trend screen can be reconfigured to review other stored EEG or quality control parameters or to review cases over the last 48 h. The monitor also has long-term memory that can store events over the last 60 days for review of critical incidents.

Suppression ratio (SR) represents the cumulative percent of cortical silence over the last 65 seconds. Data reliability may be assessed by evaluating the bar graphs for signal quality index (SQI; global parameter incorporating electrode impedance and artifact detection) and electromyographic activity (EMG) of the frontalis muscle in the 70–110 Hz band (dB).

Adult databases have been used to develop BIS with majority of the studies been done in adults, and good correlation found between BIS and the Observer's Assessment of Awareness and Sedation (OAA/S) scale with midazolam, isoflurane, propofol, alfentanil, and sevoflurane [27, 39, 40].

Validity of BIS Scores with Sedation Scales and Depth of Sedation in Infants and Children

BIS scores have found significant correlation with both UMSS and OAA/S and Ramsay scales in children >1 year with non-dissociative sedatives and sevoflurane [41–46]. The correlation between BIS and UMSS, especially in non-invasive procedures, has not been supported as in "nearly 25% of the time a UMSS of 3 (deeply sedated) correlated with a BIS of >80 and in 33% a BIS of >70" [47]. Although BIS monitor is effective in delineating mild from deep sedation, it is not able to consistently differentiate moderate and deep sedation [42, 48].

Although brain maturation does not occur till puberty, formation of new synapses with changes in the EEG continues after birth and "in the first year of life the EEG is characterized by appearance and disappearance of special patterns and by an increasing synchronization between hemispheres" [49]. Several studies have found BIS to correlate with EEG in children over 1 year of age [50–52] and in older children [53, 54]. However, BIS scores have not correlated well with DOA in younger children less than 2 [55] and specifically in infants [42, 56–58].

In another study, children <6 months–12 years received invasive and non-invasive procedures with a range of sedatives. Significant correlation was found between BIS and UMSS. Although the correlation was significant in children <6 months, this study was not blinded with only 6 of 86 children in this age group [43].

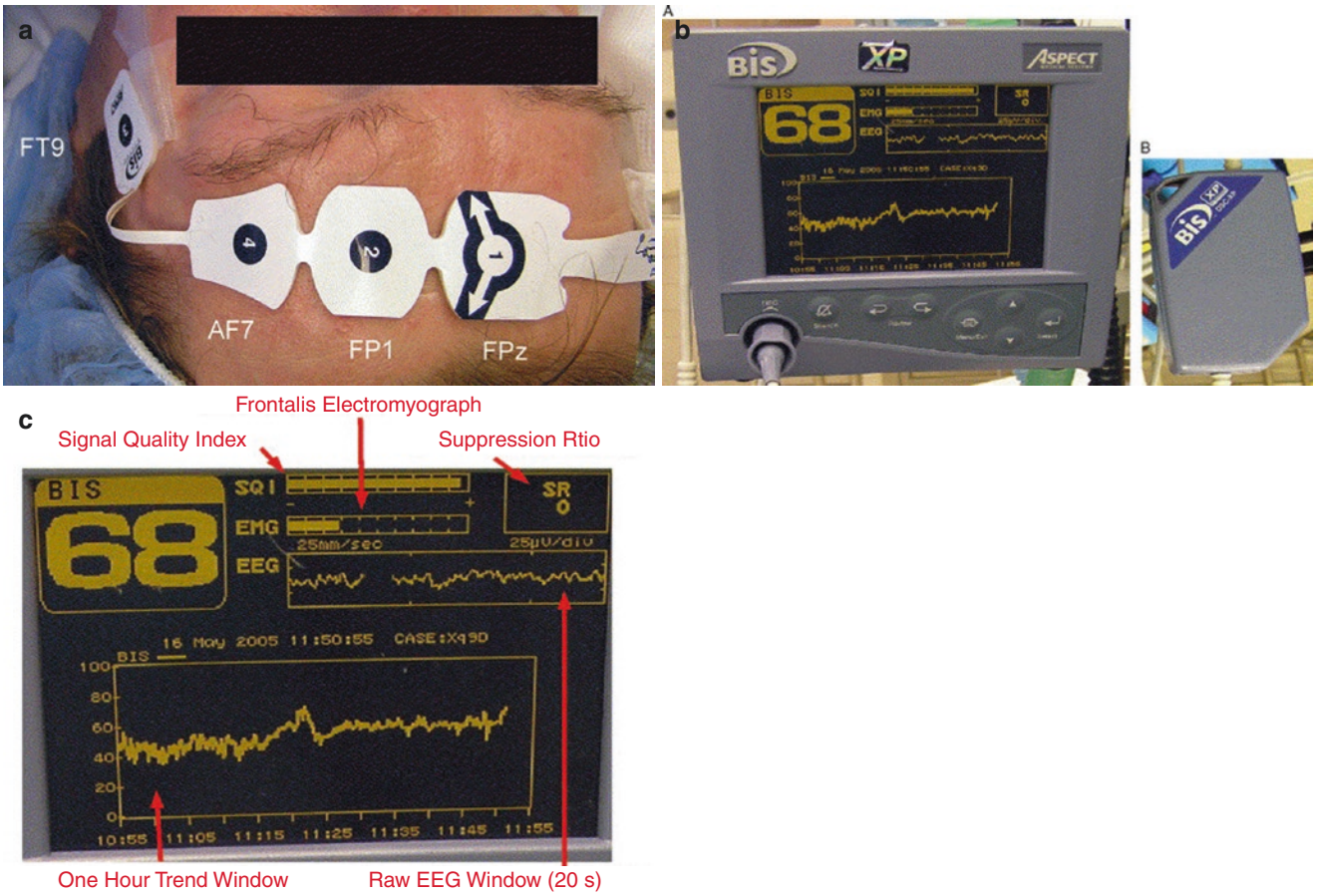

Fig. 7.2 (**a**) Quattro Sensor for BIS has four self-prepping silver/silver chloride electrodes placed on the forehead. Lead 4 is the ground electrode and measures electromyography activity of the frontalis muscle below the sensor. Sensor placement requires skin preparation with alcohol, mild debridement with gauze, and 2–5-second application of digital pressure over sensor lead. (**b**) Bispectral index XP monitor (Aspect Medical Systems Inc., Natick, MA). Raw EEG data is converted by the digital signal processing cable or DSC. (**c**) The trend screen can be reconfigured to review other stored EEG or quality control parameters or to review cases over the last 48 h. The monitor also has long-term memory that can store events over the last 60 days for review of critical incidents. (Reproduced from Johansen [38] with permission from Elsevier)

The use and value of BIS remain controversial. Dahaba states that "the BIS cannot be considered a true reflection of the depth of anesthesia nor an independent measure of electroencephalographic (EEG) cerebral function" and compares the "BIS monitor to a 'black box' headset and the value being merely a reflection of a 'head-related' biosignal that correlates with changes in certain hypnotic drug effects" [59].

Validation of BIS with Inhalational Agents and Sedatives

Nitrous Oxide

The actions of nitrous oxide (N_2O) in the dorsal horn are probably responsible for the BIS values either not being affected by nitrous oxide as shown in an adult study [60] or resulting in a paradoxical decrease upon withdrawal of N_2O [61, 62].

Nitrous oxide (N_2O) has a weak cortical action as its main analgesic effect follows a release of norepinephrine in the dorsal horn of the spinal cord [63].

In two small studies of 22 children and 40 children, BIS was unaffected with 40–60% N_2O [64, 65].

Chloral Hydrate (CHO)

There is conflicting evidence on the relationship between BIS and UMSS scales with chloral hydrate (CHO) sedation in children [43, 47, 66]. In a study of 38 children (mean age of 5.8 years) sedated for non-invasive and invasive procedures with chloral hydrate, midazolam, meperidine, or pentobarbitone, BIS and UMSS matched in only 36%, and BIS tended to underestimate the clinical level of sedation.

Ketamine

Ketamine causes an increase in beta activity with a reduction in delta in the EEG.

Studies have not demonstrated a correlation between BIS and ketamine for DOA. In adults, ketamine has been shown to cause inconsistent effects on BIS and spectral entropy when used alone or with inhalation anesthetics, propofol, or remifentanil [67, 68].

Propofol

The use of BIS has been shown to be both useful in titrating effect site concentration of propofol and superior when compared to other depth monitors such as frontal electromyography (SEMG), EEG spectral edge frequency (SEF95%), median frequency (MF), and relative delta power (RDELTA) in adult patients sedated with propofol TCI [69, 70].

A good correlation has been found for BIS-guided propofol for total intravenous anaesthesia (TIVA) and target-controlled infusion (TCI) model in children over 1 year [42, 43, 48, 71].

The need for pharmacodynamic feedback during propofol anesthesia has been highlighted in a prospective randomized study in 66 children between ages of 4 and 14 years. Propofol consumption was calculated in four groups with titration using clinical signs and BIS in two TIVA groups and BIS alone in two TCI groups using either TCI (Kataria) or TCI (Schnider) model. No difference was found between the groups. For propofol TIVA and TCI, BIS may be a useful adjunct to tailor depth of sedation [72].

In the past decade, a number of studies have focused on both delivery methods and accurate and effective delivery (pK-pD and closed-loop) of propofol with some limited studies including BIS for estimation [71, 73–79].

Studies using pharmacodynamic modelling have shown that BIS relates to cortical EEG changes in children similar to adults. Propofol requirement was higher in children to reach similar levels of hypnosis (same BIS point) to that seen in adults demonstrated via Emax curve (dose needed for 50% response) [50] (Fig. 7.3).

Nonverbal/noncommunicative children with CP required significantly less propofol than normal children with BIS values at 35–45 [80].

Dexmedetomidine

Dexmedetomidine at 0.5 and 1 mcg/kg doses given to 225 adult patients in a randomized double-blind placebo-controlled trial, sedated with propofol at 0, 1, 2, 3, and 4 mcg/ml, seems to enhance but not significantly influence prediction probability of BIS values for LOC. This is in contrast to the study by Kasuya. In a 2-day cross-over study with both drugs being used separately, Kasuya's study found BIS values to be less with dexmedetomidine versus propofol at comparable OAA/S scores and cutoff value for LOC [81, 82].

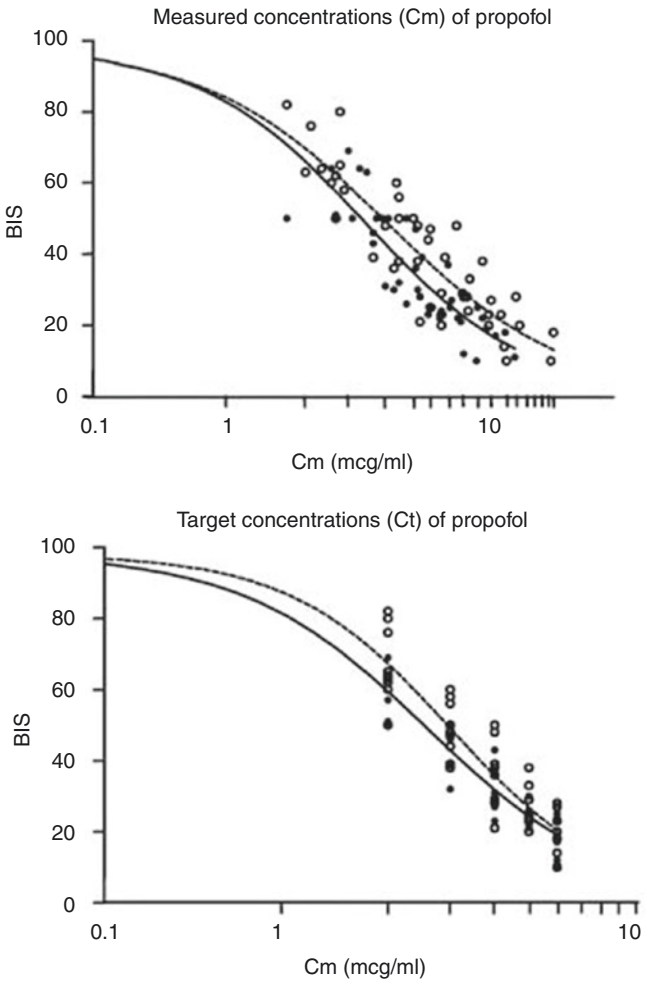

Fig. 7.3 Nonlinear regression curve [50]. Nonlinear regression curves (E_{max} model) between bispectral index (BIS) values and measured concentrations (Cm) of propofol or target concentrations (Ct) of propofol in children (open circles and dotted line) and adults (solid circles and full line). The differences between children and adults were statistically significant. (Reproduced from Rigouzzo et al. [50] with permission from Wolters Kluwer Heatlh, Inc.)

Eighty adult patients, in a single center prospective double-blind, two-arm trial for elective major laparoscopic/robotic surgery, were randomly allocated to receive TIVA with propofol closed-loop anesthesia delivery system (CLADS) with or without dexmedetomidine. The closed-loop delivery system automatically controlled the administration of propofol by using BIS as the variable targeted at 50. The study found use of dexmedetomidine during induction and maintenance of propofol TIVA with CLAD significantly reduced (29%) total propofol requirements while producing consistent depth-of-anesthesia state. Also despite significant hemodynamic effects in the dexmedetomidine group and early postop sedative effects, there was no delay in the time to eye opening or extubation [83].

In a prospective randomized study of 54 children anesthetized with sevoflurane, dexmedetomidine infusion resulted in significant decrease in both end tidal sevoflurane concentration and BIS number [84].

Sedation has also been compared using BIS and standard scales in a prospective randomized trial with either midazolam (0.1 mg/kg/h) or two different doses of dexmedetomidine (0.25 and 0.5 mcg/kg/h) and intermittent morphine boluses as required in 30 infants and children. BIS correlated well with clinical scores used to assess the effectiveness of sedation [85].

Table 7.4 BIS_{50} values and corresponding C_e dexmedetomidine for five levels of the MOAA/S score for subjects exposed to and deprived from ambient operating room noise

	Ambient operating room noise cohort		Silent cohort	
	C_e (ng ml^{-1})	BIS_{50}	C_e (ng ml^{-1})	BIS_{50}
Loss of MOAA/S 5	0.29	87	0.43	83
Loss of MOAA/S 4	0.54	80	0.79	74
Loss of MOAA/S 3	0.91	72	1.34	64
Loss of MOAA/S 2	4.10	38	5.99	29
Loss of MOAA/S 1	9.88	20	14.4	15

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BIS monitoring and MOAA/S have been used to explore the pK-pD modelling and co-variate analysis in a two-period randomized study in 18 healthy adult volunteers sedated with TCI dexmedetomidine using Dyck model with stepwise increasing targets of 1, 2, 3, 4, 6, and 8 ng/ml. Volunteers were randomly allocated to groups that were either exposed to pre-recorded operating room background noise or not exposed to noise. Stimulation of patients for evaluation of MOAA/S scores exhibited increased BIS scores and dexmedetomidine requirement. Volunteers exposed to the background noise were sensitive to the sedative effects of dexmedetomidine and achieved similar BIS values at effect site concentration (Ce) that were on an average 32% lower. Those who were exposed to background noise exhibited lower BIS and lower dexmedetomidine requirements. The reason for decreased dexmedetomidine with exposure to ambient noise remains unclear and may reflect a relaxing "white noise" effect of ambient noise [86] (Table 7.4) (Fig. 7.4).

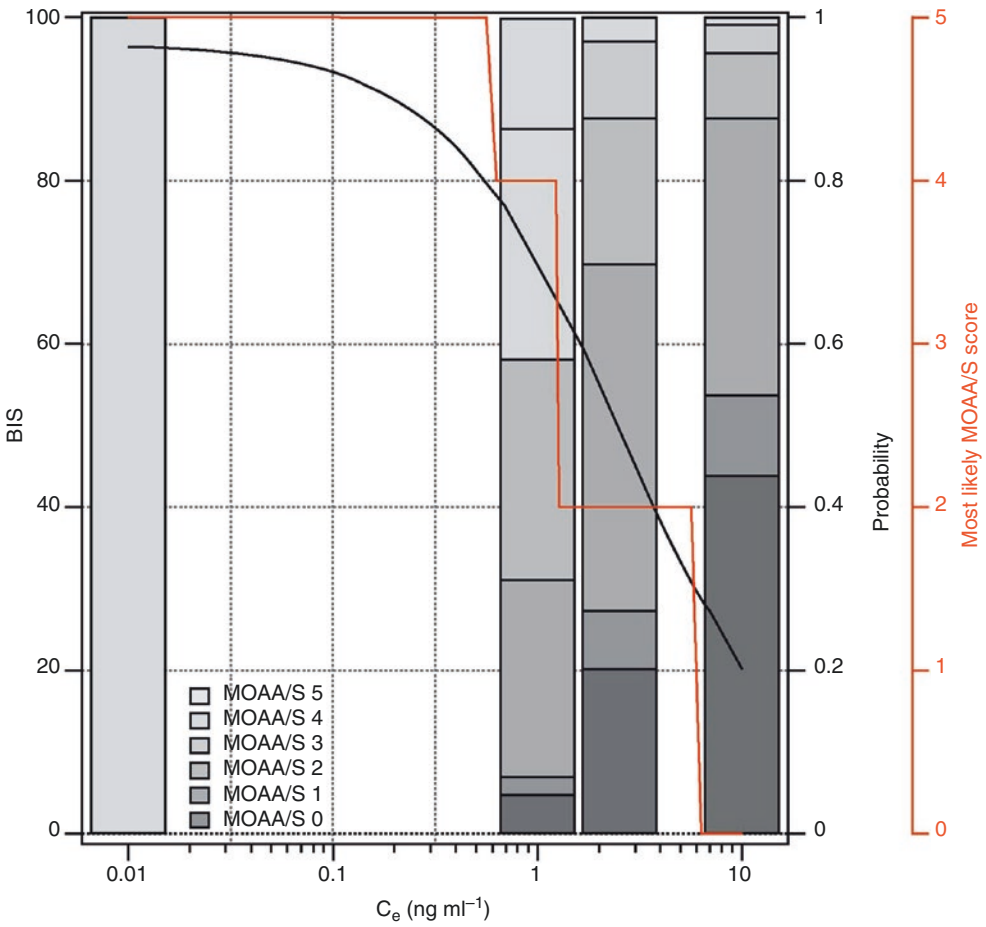

Fig. 7.4 Relationship between effect site concentration and BIS and MOAA/S. The continuous black line is predicted BIS, continuous red line is MOAA/S with highest predictability. *X*-axis is effect site concentrations with stacked bar plots illustrating the distribution of MOAA/S predictability corresponding to predicted BIS values on *Y*-axis. (Reproduced from Colin et al. [86] with permission from Elsevier)

Midazolam

No significant difference was seen with premedication with 0.5 mg/kg of midazolam on BIS during sevoflurane/N_2O anesthesia in 52 children aged between 1 and 10 years [87].

The same authors in another similar prospective randomized study in patients aged between 10 and 18 years found pre-induction BIS to be lower in those sedated with 20 mg midazolam versus placebo, still lower in the patients who demonstrated clinically detectable sedation and significantly correlated with simultaneous OAA/S scores. There was however no difference in the intraoperative BIS values between the two groups [88].

Narcotrend

Narcotrend uses power spectral analysis and automated pattern recognition and unlike other monitors also incorporates age-related changes into its algorithm. The calculation of NI is still proprietary (Table 7.5).

Narcotrend has been found limited accuracy in detecting changes in sedation level [89, 90].

Weber and colleagues have found NI useful for time to discharge readiness from operating room and recovery with propofol TCI and remifentanil for endoscopy [91].

M-Entropy

Entropy quantifies nonlinear dynamics in a mathematical manner. This consists of state entropy or SE (based upon the amount of disorder in the EEG signal) and response entropy or RE (irregularities of the frontalis electromyogram (FEMG)). The RE scale ranges from 0 (no brain activity) to 100 (fully awake), and the SE scale ranges from 0 (no brain activity) to 91 (fully awake). RE has a fast response time and uses a higher-frequency range, and SE uses lower frequencies, provides a more stable value, but has a slow response time. The clinically relevant target range for entropy values is 40–60. RE and SE values near 40 indicate a low probability of consciousness. If the response entropy diverges from the state entropy by more than 10 points, it may imply the analgesic component of the anesthesia is inadequate as the response entropy reflects the analgesic adequacy.

BIS and entropy values correlated in children ≥1 year but were less defined in infants with sevoflurane [92–94].

Table 7.5 Narcotrend index with EEG/waves and clinical characteristic

Narcotrend index	Predominant EEG characteristics	Clinical description
100–95	α-waves	Awake
94–90	↓	Sedation
89–85	β-waves	↓
84–80	↓	
79–75		Light anesthesia
74–70	θ-waves	↓
69–65	↓	
64–57		General anesthesia
56–47		↓
46–37		
36–27		General anesthesia with deep hypnosis
26–20	δ-waves	↓
19–13	↓	
12–5	Burst suppression	Very deep general anesthesia
4–0	Isoelectric EEG	

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Auditory Evoked Potential (AEP)

The evoked response is generated by synapse during passage of signal from the cochlea to the cortex and extracted from the EEG by averaging. Mid-latency auditory evoked potential (MLEAP) is got from EEG within 10–100 ms following an auditory signal and is the earliest cortical response to stimulus from acoustic. MLAEP amplitudes and latencies are influenced by anesthetics and surgical stimuli.

AAI-1.6 derived from AEP/2 monitor combines passive EEG and AEP into a single index used to assess level of anaesthesia in infants and children. Recent developments of autoregressive method help in faster generation of AEP. MLEAP waves do not show wave suppression with larger doses of anesthetic.

Consumption of propofol and time for emergence were outcome measures in a study of 22 children (3–11 years) for strabismus surgery under TIVA randomly allocated for continuous propofol infusion with conventional practice or guided with composite auditory evoked potential (CAAI) 25–35 as derived from AEP monitor. All children received an infusion of remifentanil at 0.3 mcg/kg/min. CAAI guidance led to a 34% reduction in propofol and a significantly shortened time for anesthetic emergence and return to consciousness [95].

Limitations of EEG-Based Monitors

There are a number of limitations of EEG-based technology. The first limitation is in the process of EEG between the various monitors. It is difficult to compare devices as the algorithms used are proprietary and not available to the public [96]. In a study involving 15 children, BIS values during deep sleep were found to be comparable to that found in deep sedation [97]. Signal acquisition can be affected by noise, temperature, humidity, head tissue con-

ductivity and poor use of proper abrasive technique to reduce impedance.

A polyacrylate-based electrode design which doesn't require prior forehead skin preparation has recently been developed [98].

Facial EMG (f-EMG) due to spontaneous facial and temporal muscle activity influences the EEG activity, and in cases where NMB are not used, this factor should be kept in mind. EMG is affected by noxious stimuli and depth of anesthesia, and this would affect the EEG. Entropy might be more resistant to f-EMG artifacts than BIS [99].

Other environmental factors such as high-frequency diathermy, Doppler ultrasound (TOE), pulsatile cardiopulmonary bypass, and pacemakers have been published as case reports. Noise in the operating room has also shown to affect BIS in a linear fashion.

There are, as already detailed in the chapter, different BIS responses and correlations between sedatives and anesthetics: The first is ketamine which has been associated with increase in BIS and entropy especially over prolonged period [67, 68, 100, 101].

N_2O does not affect BIS and state entropy in majority of studies discussed [64, 65, 102].

Noxious stimulation increased BIS values [103].

Opioids have a poor correlation with BIS and AEP [104].

Sevoflurane, propofol, and dexmedetomidine also have shown poor correlation with BIS and entropy due to high interindividual variation in 19–30-year-old [105].

In children BIS has shown a paradoxical response with sevoflurane [106, 107], and in fact epileptiform EEG changes have been observed with deep sevoflurane anesthesia [108].

Conditions that have affected brain perfusion, and children with cerebral palsy, with brain lesions, demonstrate low BIS values at baseline.

The time to generate a signal can get delayed from 30 seconds to 2.5 min. An online time delay estimation (TDE) has been introduced for reference tracking.

Recent Advances and Future Considerations

In 1987, Prys-Roberts compared the "concept of anesthetic depth" to an illusion, and the search for its measure was as evasive as searching for a "Philosopher's stone." He defined anesthesia as "binary" all or none phenomenon, stating that degrees of anaesthesia or variable depths of anaesthesia don't exist [109]. This binary concept is still used to explain return of consciousness with rapid awakening in studies involving infants.

The very definition of anesthesia as a binary phenomenon has been challenged in recent literature, and there have been attempts to redefine anesthesia as a state that results from an action at a spectrum of receptors, with intraoperative awareness reflecting a spectrum of brain states [110, 111].

In a two-part review of clinical electrography, Purdon and his colleagues demonstrate the molecular site of actions of different agents and the neural connectivity to produce the various brain states [112] (Fig. 7.5).

Understanding consciousness and neural connections could offer explanations toward DOA [113].

Studies in fMRI have demonstrated that the brain stem is stimulated first as sedation lightens and the connections are

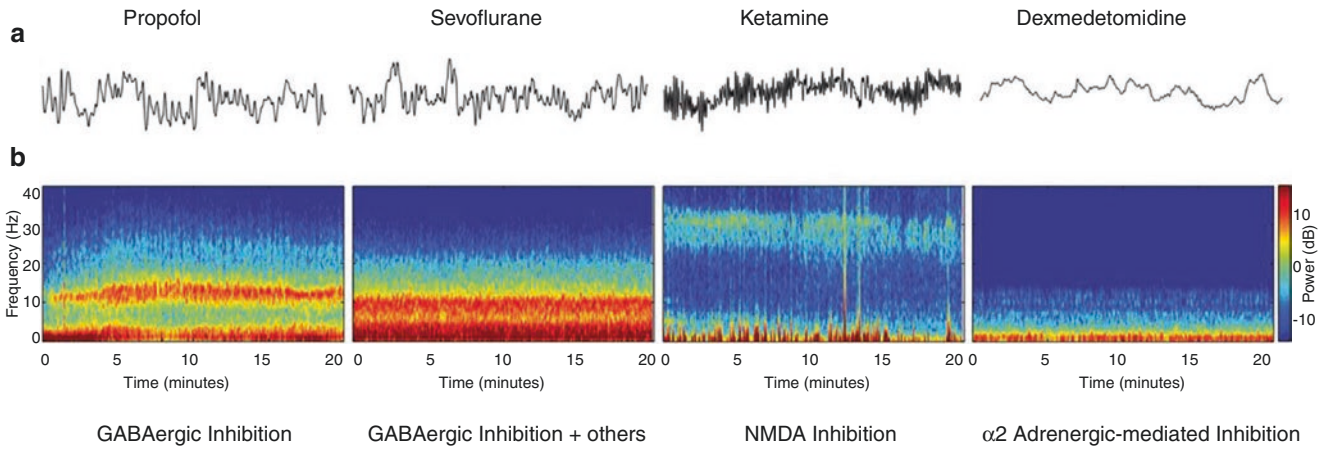

Fig. 7.5 Different anesthetics (propofol, sevoflurane, ketamine, and dexmedetomidine), different electroencephalogram signatures, and different molecular and neural circuit mechanisms. (**a**) Anesthetic-specific differences in the electroencephalogram are difficult to discern in unprocessed electroencephalogram waveforms. (**b**). In the spectrogram, it is clear that different anesthetics produce different electroencephalogram signatures. The dynamics the electroencephalogram signatures can be related to the molecular targets and the neural circuits at which the anesthetics act to create altered states of arousal. (Reproduced from Purdon et al. [112], with permission from Wolters Kluwer Health, Inc.)

established with the cortex. This has led to the brain stem being referred to as the engine of consciousness [114].

Recently the states of consciousness have been researched using fractal dimension. Fractal dimension (FD) is a quantitative parameter used to decipher complex interactions within the corticothalamic system. Theoretically, consciousness requires a balance between integration and differentiation of networks within the corticothalamic system.

These complex systems respond to transcranial magnetic stimulation (TMS). The high-density EEG derived from this has been used to measure FD. A fractal dimension has a numerical value and expresses a visual shape. This method can be used for analysis of even nanoparticles. FDIndex (FDI) is a computation of integration and differentiation FD and can categorize the information structures and information fields. FDI can be used to differentiate between conscious and unconscious states. FDI may be a useful tool to study relationship between consciousness and brain complexity [115] (Fig. 7.6).

Conclusion

As we step into the twenty-first century, the key issues with regard to the use of neuromonitoring for sedation in children include whether this is beneficial and is there an ideal neuromonitor available?

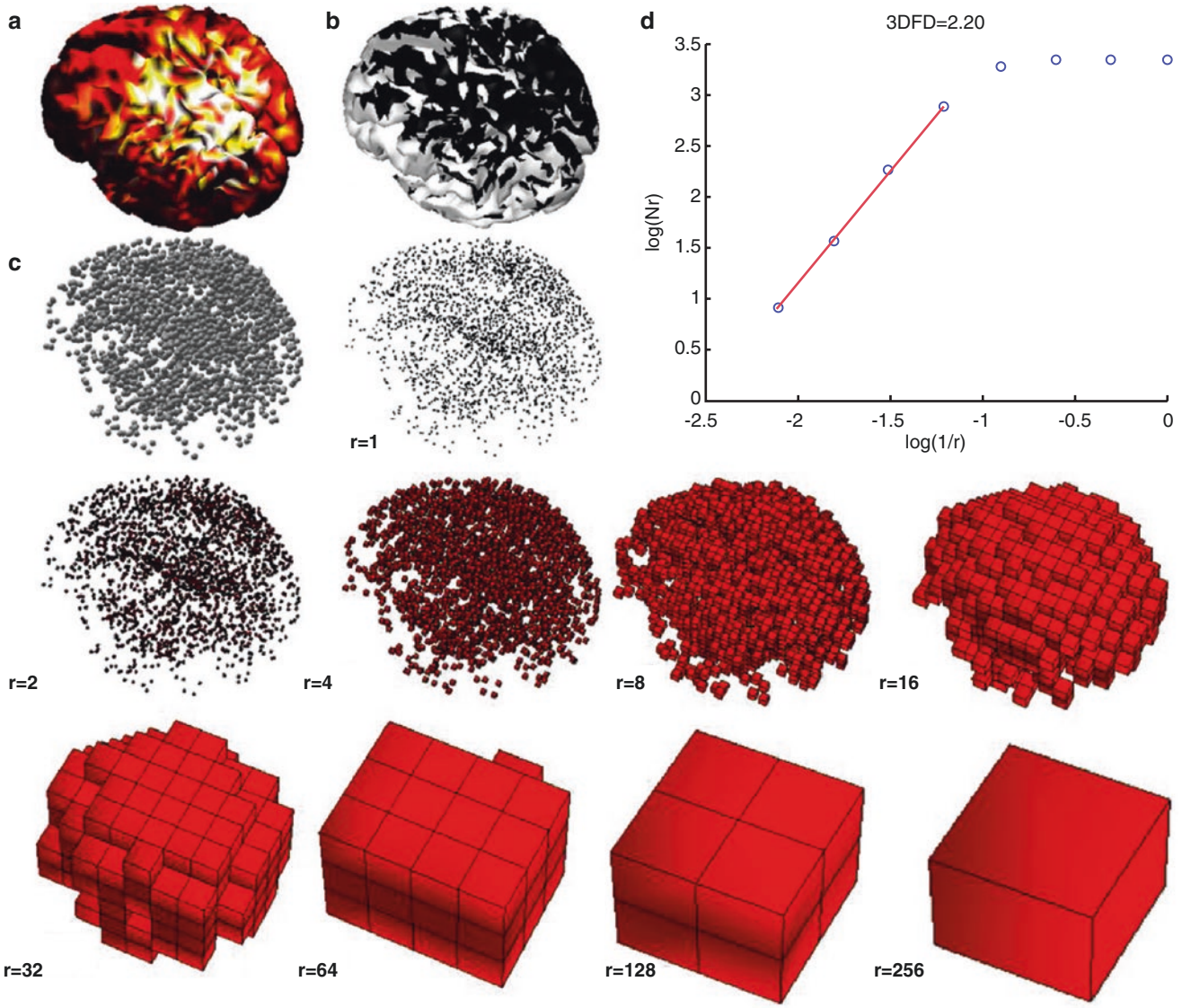

Fig. 7.6 Fractal dimension. (**a**) Significant source activity at the time sample 40 ms after TMS for a subject awake. (**b**) Binarized sources at that time. (**c**) Point cloud defined by binarized sources. (**d**) Log-log plot of number of boxes (*Nr*) vs. 1/*r* for voxelizations of the point cloud with box sizes ranging from $r = 1$ to $r = 256$. 3DFD value (2.20) is computed as the slope of the *linear regression* considering the range of sizes from $r = 16$ to $r = 128$. (Reproduced from Ruiz de Miras et al. [115] with permission from Elsevier)

Recent NAP5 studies on awareness have highlighted the importance of monitoring depth of anesthesia in both adults and children. The use of NMB in anesthesia has been identified as risk factor for awareness, and DOA monitors have been suggested as helpful especially with use of TIVA [116]. The B-aware trial in adult demonstrated that risk of awareness with recall was reduced with use of BIS especially in patients undergoing TIVA. There is as yet no universal consensus on which monitoring is better. The multiple scales used for describing depth of consciousness are still popular but have the disadvantage of being discontinuous and at times requiring patient stimulation to assign a score.

Most of the currently available neuromonitors are based on processed EEG and evoked electrical activity (evoked potential). BIS, the most commonly used, was designed from adult data. EEG waves change, becoming faster with smaller amplitude, from infancy to adulthood. Hence, interpretation of EEG data in pediatric population <1 year needs to be interpreted with caution. A BIS value of 40–60 is indicated as suitable for surgical anesthesia, and as per NICE guidelines, a value of 40 (or 40–60) for BIS and entropy equates to a "low" probability of awareness. Similar to adults, BIS monitoring in pediatrics may decrease drug usage [117]. BIS and other neuromonitors may have a place in sedation practice to avoid deep sedation [118, 119]. The BIS monitor has undergone a number of revisions from when it was first introduced. Moreover, there are new neuromonitors being introduced to the market which use different technology. In summary, this author suggests that neuromonitors have a role in some pediatric sedation practice and, as technology improves, may find more use to monitor and judge depth of sedation and risk of awareness.

Case 1

A child aged 4 years is on the emergency list for nail bed repair following trauma by crushing it accidently in the door shut by older sibling. The child is otherwise healthy, not on any medications, and appropriately fasted and has no allergies. The plastic surgeon said they attempted this in the Emergency Department (ED), but the child was too anxious and would not tolerate local alone and the procedure could be lengthy in duration. As ED is short of staff, the surgeons request the case to be done in the OR under sedation.

As the child is anxious, she has been premedicated with oral midazolam and an intravenous cannula established.

Considerations

This is a short procedure overall and usually done with ring block under local anaesthesia.

The sedation could include intravenous propofol as intravenous canula has already been placed. The sedation could be reduced once the ring block has been achieved. BIS would be helpful to monitor depth of sedation. BIS monitor should ideally be placed before sedation and monitoring continued throughout. In this case it could be challenging and placed immediately after sedation is established. BIS level may need to be 40–60 during the local ring blockade and then may be maintained closer to 60 during the remainder of the propofol infusion.

Case 2

A 6-year-old 20 kg child has provisional diagnosis of celiac disease and has been scheduled for upper endoscopy for biopsies by the gastroenterologists. She is otherwise fit and healthy with no allergies and appropriately fasted. She understands the procedure as she had the same few months ago and would not like to go to sleep with the mask. She did not have BIS monitoring the last time, and the resident explains this to her in detail. BIS monitors would be placed on her forehead before the start of the case as most monitoring is done. After ensuring there is strong contact with her skin as this could affect the reading, the sedation would proceed as normal. The parent of the child would like more information about BIS monitor and how it is used to monitor depth of sedation.

Considerations

Endoscopies are done in darkened rooms and usually under deep sedation with patient breathing spontaneously with nasal specs for added oxygen. With upper endoscopy the airway is shared, and hence the management more challenging. The child is usually in a lateral decubitus position. It is important to ensure all monitoring is attached and working appropriately before the room is darkened. BIS monitor requires the contact points (4 in total) to be displaying a high number for SQI (signal quality index which indicates artifacts and impedance data) more than 50. The procedure itself is not lengthy and not painful but could be stimulating. BIS values of around 45–50 are sought, and intravenous infusion of propofol adjusted accordingly to ensure spontaneous ventilation throughout. Other monitors including capnography, pulse oximetry, ECG, and non-invasive blood pressure are monitored throughout.

Case 3

A 5-year, 20 kg boy for incision and drainage of a large abscess on his left thigh under sedation. He is otherwise fit and healthy ASA1 child and appropriately fasted.

The sedation plan is to use intravenous ketamine and midazolam. He has prepared 10 mg of ketamine and 2 mg of midazolam.

The parents request nitrous oxide and neuromonitoring to "avoid cognitive problems" from ketamine and midazolam.

Considerations

Nitrous oxide to help place the intravenous cannula as per parents' request is acceptable. As the abscess is large, a higher dose of ketamine (up to 0.75 mg/kg) may be required.

BIS monitoring has not been found to correlate with ketamine use and would not offer a benefit. Ketamine causes an increase in beta activity and a reduction in delta in the electroencephalogram. Its use has been associated with paradoxical increases in BIS. The lack of data to support long-term neurocognitive effects of ketamine and midazolam for short procedures should be explained to the family. BIS monitoring would offer no value in this sedation plan.

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