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Intraoperative Awareness

From Neurobiology to Clinical Practice

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ABSTRACT

Intraoperative awareness is defined by both consciousness and explicit memory of surgical events. Although electroencephalographic techniques to detect and prevent awareness are being investigated, no method has proven uniformly reliable. The lack of a standard intraoperative monitor for the brain likely reflects our insufficient understanding of consciousness and memory. In this review, the authors discuss the neurobiology of consciousness and memory, as well as the incidence, risk factors, sequelae, and prevention of intraoperative awareness.

UNINTENDED intraoperative awareness is a dreaded complication of anesthetic practice that is associated with a high rate of posttraumatic stress disorder (PTSD).[1] As a frightening iatrogenic complication, awareness has a high public profile, increases patients' apprehension of surgery, and affects the medical-legal risks associated with anesthesia.[2] Unlike the connotation of "awareness" in cognitive science, the meaning of this term in a clinical context generally refers to both consciousness *and* explicit recall of intraoperative events. As such, our use of the term "awareness" in this article implies explicit recall. In this review, we will first discuss the underlying neurobiology of intraoperative awareness, with a focus on mechanisms of arousal, experience, and memory. We will then discuss the clinical aspects of intraoperative awareness in adult patients, including incidence, risk factors, sequelae, and prevention.

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Neurobiology of Awareness

The current inability to distinguish reliably between the anesthetized and the awake patient is a fundamental shortcoming of our clinical practice. The brain is the major target organ of general anesthesia, yet we do not have a standard monitor for drug action on brain function. Indeed, standard intraoperative monitors assess the side effects, rather than the primary effects, of general anesthesia. The lack of a standard cerebral function monitor likely reflects our incomplete understanding of anesthetic effects on the brain and how best to measure them. To improve our intraoperative monitoring capabilities, we must better understand the underlying neurobiology of intraoperative awareness: arousal and experience (which together constitute consciousness), as well as explicit recall.

Mechanisms of Arousal

A description of mechanisms of general anesthesia typically begins with a discussion at the molecular level; however, mechanisms of consciousness cannot be reduced easily to simple molecular targets. Thus, we begin by focusing on the organizing framework of sleep–wake neurobiology to explain how the cortex normally is aroused and how general anesthetics modulate this process. The hypothesis that anesthetics act preferentially through subcortical sleep centers was proposed in the mid-1990s[3] and has gained significant traction in the literature[4] and empirical support.[5,6] Although sleep and anesthesia are clearly distinct states, they share phenotypic traits and underlying mechanisms.

A number of nuclei located in the pons, midbrain, hypothalamus, and basal forebrain regulate normal sleep–wake cycles.[7] Some arousal centers are active primarily during

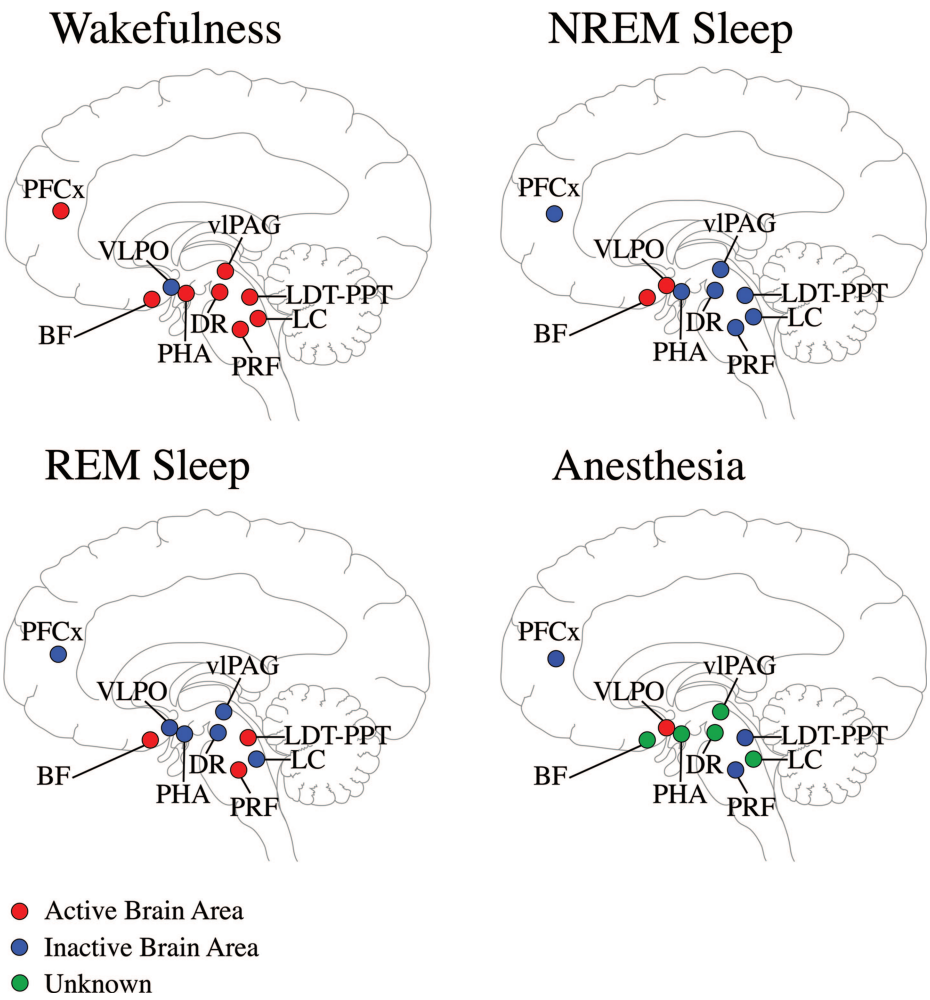


Fig. 1. Brain activity patterns of wake- and sleep-promoting nuclei during states of wakefulness, sleep, and general anesthesia. BF = basal forebrain; DR = dorsal raphe nucleus; LC = locus coeruleus; LDT-PPT = laterodorsal and pedunculopontine tegmental nucleus; NREM = nonrapid eye movement sleep; PFCx = prefrontal cortex; PHA = posterior hypothalamic area; PRF = pontine reticular formation; REM = rapid eye movement sleep; vlPAG = ventrolateral periaqueductal gray; VLPO = ventrolateral preoptic area. Adapted with permission from Vanini G, Baghdoyan HA, Lydic R: Relevance of sleep neurobiology for cognitive neuroscience and anesthesiology, Consciousness, Awareness, and Anesthesia. Edited by Mashour GA, Cambridge University Press, 2010.

wakefulness, with cholinergic nuclei also active during rapid eye movement sleep (fig. 1). Other centers, such as the ventrolateral preoptic nucleus, are active during sleep (fig. 1). These wake-ON/sleep-OFF and sleep-ON/wake-OFF nuclei are thought to inhibit one another reciprocally, which has led to the hypothesis of a "flip-flop" mechanism of sleep–wake cycles.[8–10] For example, the noradrenergic locus coeruleus in the pons and the histaminergic tuberomamillary nucleus in the posterior hypothalamus are active during waking, whereas the γ-aminobutyric acid–transmitting (GABAergic) ventrolateral preoptic nucleus is inhibited. As the homeostatic pressure for sleep builds, the ventrolateral preoptic nucleus becomes active in association with sleep and then inhibits the activity of the arousal-promoting locus coeruleus and tuberomamillary nuclei.

A number of anesthetic and sedative agents have been shown to modulate the activity of these structures. For example, the hypnotic effects of dexmedetomidine likely are mediated by the activation of α_2-adrenergic receptors and inhibition of noradrenergic projections from the locus coeruleus.[11] The presence of electroencephalographic sleep spindles during halothane anesthesia is associated with a reduction of cholinergic transmission from the pedunculopontine and laterodorsal tegmentum.[12] Several agents, such as propofol, isoflurane, and the commonly used drug diphenhydramine, may cause hypnosis by inhibiting or interrupting histaminergic transmission from the tuberomamillary nucleus.[13,14] The arousal-promoting orexinergic neurons in the hypothalamus are thought to play an essential role in emergence from sevoflurane and isoflurane anesthesia[15] but not during emergence from halothane anesthesia.[16] This variability suggests that the effects of general anesthetics on sleep–wake centers are specific to individual agents. Agent-specific effects have also been demonstrated for the ventro-

lateral preoptic nucleus, the inhibitory center that is activated by GABAergic drugs such as propofol but not by the *N*-methyl-D-aspartate glutamate receptor antagonist ketamine.[14,17] It is also becoming clear on the behavioral level that different anesthetic agents have differential effects on the pathways regulating sleep.[18]

Mechanisms of Experience

In the previous section, we discussed the subcortical structures thought to mediate arousal states in the brain. However, consciousness implies not simply brain arousal but also subjective experience. Persistent vegetative states and somnambulism demonstrate that brain arousal is not necessarily associated with the experiential contents of consciousness. Thus, we must also consider the mechanisms by which information processing acquires a subjective dimension. Neuroscientific investigation in this area has focused on identifying various "neural correlates" of consciousness, which can be defined as the minimal neuronal mechanisms that are jointly sufficient for any one specific conscious percept.[19,20] In recent years, general anesthetics have proven to be useful tools for assessing proposed neural correlates.[21] Unlike the neural correlates of arousal, which are found primarily in the subcortical areas, the neural correlates of subjective experience are thought to be generally related to the cortical or thalamocortical system.

Feedback or Reentrant Neural Activity. It is well known that visual processing follows a "feed-forward" direction from the primary visual cortex to either the temporal lobe (ventral stream) or the frontal lobe (dorsal stream).[22] However, evoked activity in the primary visual cortex and subsequent feed-forward processing are not sufficient to generate conscious experience; what is referred to as a "feedback," "recurrent," or "reentrant" pathway is also thought to be required.[22–26] There is now strong evidence from both animal models and humans to suggest that anesthetic-induced unconsciousness is associated with the selective inhibition of anterior-to-posterior feedback activity. By measuring the transfer entropy of visual evoked potentials in a rodent model, Imas *et al.*[27] found that the conscious state was associated with a balance of feed-forward activity (occipital → parietal → frontal) and feedback activity (frontal → parietal → occipital). After induction of general anesthesia with isoflurane, feed-forward activity persisted, but feedback activity was suppressed selectively. These data were supported by an analysis of anterior-posterior phase synchronization.[28] In a follow-up study in humans, Lee *et al.*[29] studied the directionality of frontoparietal activity during consciousness, propofol anesthesia, and recovery. In contrast to the results obtained with rats, the baseline conscious state of humans was associated with more feedback than feed-forward activity, which may reflect the predominance of feedback fibers in the human brain.[30] However, consistent with the results from animal studies, feedback connectivity was suppressed selectively during anesthesia and spiked upon the return of consciousness (fig. 2). In summary, both inhalational and intravenous general anesthetics appear to selectively suppress reentrant or feedback activity in the cortex, which may be one mechanism for loss of consciousness. The recovery of feedback connectivity after anesthesia has not yet been carefully studied.

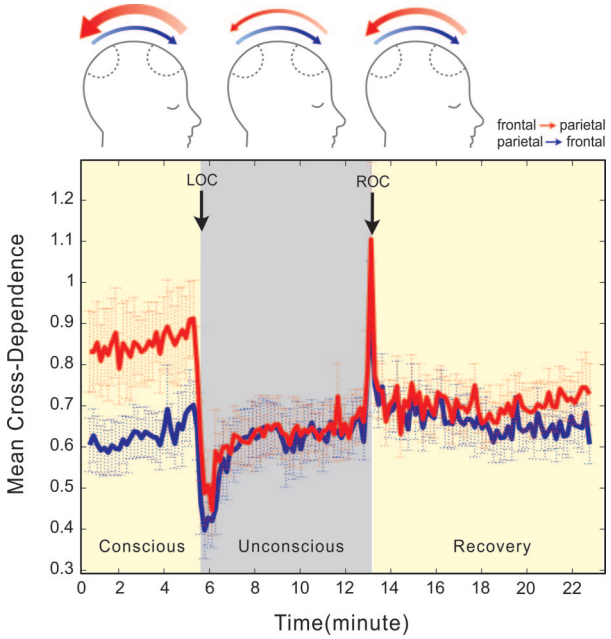


Fig. 2. Selective inhibition of frontoparietal feedback activity after induction of general anesthesia with propofol in humans. LOC = loss of consciousness; ROC = return of consciousness. Adapted with permission from Lee U, Kim S, Noh G-J, Choi B-M, Hwang E, Mashour GA: The directionality and functional organization of frontoparietal connectivity during consciousness and anesthesia in humans. Conscious Cogn 2009; 18:1069–78.

The suggestion that consciousness appears to be mediated not by the primary sensory cortices but rather by the coordinated activity of higher-order areas[27,31] has implications for the timing of conscious *versus* unconscious events. In one study, subliminal processing of visual information in humans occurred in less than 250 ms, whereas conscious activity was associated with activation of a distributed fronto-parieto-temporal network that occurred at times greater than 270 ms.[32] These data are relevant to mechanisms of anesthetic-induced unconsciousness. In a rodent model, Hudetz *et al.*[33] found that desflurane had no effect on early flash-induced visual evoked potentials (which likely reflected primary processing) but caused a dose-dependent reduction of late potentials. A study of the effects of general anesthesia on the auditory system has yielded consistent conclusions with respect to primary and higher-order processing, with the latter being affected preferentially.[31]

Collectively, these data suggest that mechanisms of consciousness do not necessarily relate to activation of primary sensory cortices but to later, higher-order processes. Consequently, mechanisms of anesthetic-induced unconsciousness

likely relate to the interruption of higher-order processes rather than alterations of primary sensory processing.[21,34–36] Both of these phenomena may reflect the importance of integration of neural information.

Information Integration. The information integration theory of consciousness is currently a commonly discussed framework.[21,37] The central tenet is that the global integration of many functionally specialized cognitive modules *is* consciousness.[37,38] The thalamocortical system is proposed as a strong candidate for such a system in the brain, and computational modeling predicts that the capacity for information integration, often denoted as ϕ, would decrease in states of nonrapid eye movement sleep, as well as during seizures.[39,40] In this model, consciousness is a graded event, unlike the binary flip-flop mechanisms hypothesized for sleep and wakefulness.[9]

In addition to the data described in the previous section, several lines of evidence suggest that general anesthesia may induce unconsciousness through the disruption of information synthesis in the cortex. First, there is a loss of functional connectivity of the thalamocortical system during general anesthesia,[41] which is consistent with the "thalamocortical switch" hypothesis of the general anesthetic mechanism.[42] It is clear that the centromedian thalamus can play a modulatory role in the recovery from anesthesia.[43,44] However, the importance of thalamic inhibition in the induction of general anesthesia is not yet clear.[45] The observed suppression of the thalamus during general anesthesia may be the cause of cortical inhibition (in which the thalamus functions as a "switch"), but it might also be the effect of cortical inhibition (in which the thalamus functions as a "readout" for cortical activity). Recently, the induction of general anesthesia with midazolam was shown to be associated with a loss of cortical effective connectivity,[46] a finding paralleled by studies of nonrapid eye movement sleep.[47] Other studies have demonstrated the loss of corticocortical functional connectivity during general anesthesia.[48,49] Furthermore, Lee *et al.*[50] approximated ϕ in humans from electroencephalographic data and demonstrated its decrease in several bandwidths after induction of anesthesia with propofol. Additional study of information integration and its interruption in the anesthetized state may be a future line of investigation for more sophisticated intraoperative monitoring.

Mechanisms of Explicit Recall

Taxonomy of Memory. Intraoperative awareness requires not only consciousness, but also memory. Although the terms "learning" and "memory" are often considered synonymous, they are not the same process. Learning has been defined as the process of acquiring new information, whereas memory refers to the persistence of learning in a state that can be recalled at a later time.[51] Current research is aimed at understanding the mechanisms underlying the effects of anesthetics on learning and memory processes. The goal is to develop strategies to prevent intraoperative awareness and possible memory deficits in the postoperative period. In turn, much like in consciousness research, anesthetics can be used as powerful probes to gain fundamental insights into the biology and neuronal substrates of memory.

Learning and memory take several distinct forms.[52] *Explicit* (or *declarative*) memory refers to memories that can be verified as fact and are accessible to the conscious state. *Implicit* (or *nondeclarative*) memory accounts for changes in behavior (skills, habits, simple forms of conditioning) that result from experience without the person or animal being consciously aware that learning has caused the change in behavior.[53] For example, implicit memory in humans could result in faster reaction times in response to a stimulus or improved motor skill. Explicit memory has been subclassified into *episodic* memory, which refers to long-term memory of personal events associated with a specific place and context, and *semantic* memory, which refers to the recall of known facts about the world, such as the names of objects. Implicit memory has been subdivided into *procedural* memory, such as improvements in the ability to ride a bike, and *priming*, which occurs when a response interval is reduced by previous exposure to a familiar stimulus. Most studies of intraoperative awareness address *explicit episodic memory*.[54]

One of the most potent actions of general anesthetics is memory blockade. Intravenous and inhalation anesthetics cause memory blockade at doses considerably lower than those required for loss of consciousness and immobility.[55,56] In human volunteers, the concentration of isoflurane that suppresses learning and memory of verbal cues was approximately one quarter of the dose required for immobilization.[57] In animal studies, subanesthetic concentrations of isoflurane (0.25–0.5 minimum alveolar concentration [MAC]) caused dose-dependent suppression of fear-associated learning and memory.[58] Interestingly, the relationship between the sedative and amnesic doses differs for different classes of neurodepressant drugs. For example, in human patients, propofol and midazolam caused greater memory blockade than did thiopental or fentanyl at equisedative doses.[59] The potency of anesthetics for memory blockade also depends on the type of learning. For example, suppression of fear-conditioned memory in response to an auditory tone[60] required twice the concentration of isoflurane (half-effective concentration [EC_{50}], 0.47 MAC) that was required to suppress fear-conditioning memory to the environmental context (EC_{50} 0.25 MAC).[61] The relative resistance of memory for auditory events to inhaled anesthetics is of particular interest, as patients who experience intraoperative awareness frequently describe auditory perceptions, such as hearing sounds or voices.[62]

The relative potencies of the commonly used inhaled anesthetics were compared in rats using a Pavlovian conditioning paradigm known as inhibitory avoidance.[63] In this conditioning paradigm, the animal learns to suppress the natural tendency to enter the darkened compartment of a maze because entry is associated with a noxious stimulus (a foot

shock). In the study by Alkire and Gorski, this type of learning was impaired by low concentrations of most inhaled anesthetics (0.15% halothane, 0.3% sevoflurane, 1% desflurane) but, surprisingly, was not impaired by isoflurane or nitrous oxide. In contrast, retention of memory (studied after 24 h) was impaired by all anesthetics at relatively low concentrations (0.2% isoflurane, 0.3% sevoflurane, 0.3% halothane, 0.44% desflurane, 20% nitrous oxide).[63] Finally, most anesthetics cause *antegrade amnesia* (loss of memory for a period after administration of the drug) but not *retrograde amnesia* (loss of memory for events preceding administration of the drug).[58] Intravenous anesthetics, including propofol and etomidate,[64] cause antegrade amnesia and can also interfere with memory consolidation, which refers to the stabilization of memories after the initial acquisition.[65]

Neurobiology of Memory. The key molecular targets of anesthetics are thought to be the ion channels and neurotransmitter receptors that regulate synaptic transmission and neuronal excitability.[66–68] In particular γ-aminobutyric acid receptor type A ($GABA_A$) receptors are allosterically modulated by most inhaled and intravenous anesthetics, such as etomidate, propofol, barbiturates, many benzodiazepines, ethanol, and neurosteroid-based anesthetics.[69–72] The $GABA_A$ receptors are composed of multiple subunits. At least 19 mammalian genes encode for the various subunits (α_{1-6}, β_{1-3}, γ_{1-3}, δ, ε, θ, π, and ρ_{1-3}).[71,72] The subunit composition of a given $GABA_A$ receptor critically determines its cellular expression pattern and pharmacologic properties. For example, $GABA_A$ receptors generate two major forms of inhibition: *synaptic inhibition*, which is mediated by postsynaptic receptors containing an α_{1-3} subunit, $\beta_{2,3}$ subunits, and a γ subunit, and a *persistent or tonic inhibition* that is generated predominantly by $\alpha_{4-6}\beta_{1-3}\delta$, and $\alpha_5\beta_{2,3}\gamma_2$ receptors.[73,74] The receptors that generate tonic inhibition are localized predominantly to the extrasynaptic region of the neurons.

Of particular relevance to the memory-blocking properties of anesthetics is a tonic inhibitory conductance generated by α_5 subunit-containing $GABA_A$ receptors.[75] These receptors have a restricted pattern of distribution, being expressed predominantly in the hippocampus, where they represent 20% of all $GABA_A$ receptors.[76] The α_5GABA_A receptors have been strongly implicated in learning and memory processes because compounds that selectively inhibit their activity (specifically, inverse agonists) and genetic manipulations that reduce receptor expression have been associated with improved memory performance in animals.[77–80] In humans, an inverse agonist for α_5GABA_A receptors also improved word recall after ethanol-induced memory impairment.[81] A variety of anesthetics, including propofol,[82,83] isoflurane,[84] and etomidate,[64] enhance the activity of α_5GABA_A receptors *in vitro*. *In vivo* behavioral studies showed that a low, clinically relevant dose of etomidate impaired performance for memory tasks in wild-type but not null mutant mice lacking the α_5 subunit ($\alpha_5-/-$ mice).[64,85] Etomidate produced similar impairment of motor coordination, loss of righting reflex, and anxiolysis in wild-type and $\alpha_5-/-$ mice,[64] which indicated that α_5GABA_A receptors are involved in the memory-impairing effects of general anesthetics but not sedation or hypnosis.

Low (amnesic) concentrations of anesthetics also target extrasynaptic $\alpha_4\delta$ subunit-containing $GABA_A$ receptors, which generate a tonic conductance in the hippocampus[74] and thalamus.[86,87] Interestingly, the potency of isoflurane in inhibiting fear memory was reduced in α_4 subunit knockout mice, whereas the hypnotic and immobilizing effects of isoflurane were unchanged.[88] The α_1 subunit-containing $GABA_A$ receptor is abundantly expressed at synapses in the cortex, thalamus, and hippocampus.[89] Knockin mice that expressed an isoflurane-resistant α_1GABA_A receptor displayed normal sensitivity to the amnesic effect of isoflurane.[90] This result is consistent with the notion that a tonic inhibitory conductance generated by extrasynaptic $GABA_A$ receptors regulates memory blockade by anesthetics. Furthermore, the amnesic effects of anesthetics can be dissociated from other behavioral components of the anesthetic state such as sedation or immobility.

The regions of the brain that contribute to explicit episodic memory (memory for facts and events) have been revealed through examination of human patients such as "HM," who had areas of his temporal lobe surgically resected bilaterally.[91] Such studies on patients or animal models have shown that the medial temporal lobe, which includes the hippocampus, amygdala, and perirhinal, entorhinal, and parahippocampal cortices, plays a critical role in spatial memory, recognition of novelty, and contextual fear.[53] There is a division of function within the medial temporal lobe, and lesions of the hippocampus prevent the acquisition of episodic memory in humans.[91] Memory for emotionally charged content, such as fear, involves the amygdala and the anterior cingulate cortex.[92] The amygdala appears to be particularly important for anesthetic blockade of emotionally charged memory. Lesions of the basolateral nucleus of the amygdala in rats attenuated the amnesic effect of low doses of sevoflurane and propofol for fear-associated aversive learning.[93,94] In addition, infusion of a $GABA_A$ receptor antagonist into the basolateral amygdala of rats blocked propofol-induced amnesia, as well as the loss of activity-regulated cytoskeleton-associated protein, which is induced by synaptic plasticity in the hippocampus.[95] Emotional memory in humans can also be blocked by subanesthetic concentrations of sevoflurane (0.25%).[96] In addition, neuroimaging studies involving positron emission tomography in human volunteers showed that 0.25% sevoflurane impaired the functional connectivity between the amygdala and the hippocampus.[96] Brain regions involved in implicit, explicit, and traumatic memory are depicted in figure 3.

At the level of the hippocampus, the mechanism for long-term storage of memories is thought to be an enhancement of excitatory synaptic transmission, referred to as long-term potentiation (LTP).[97] LTP results from functional and structural changes at excitatory synapses, including enhanced ac-

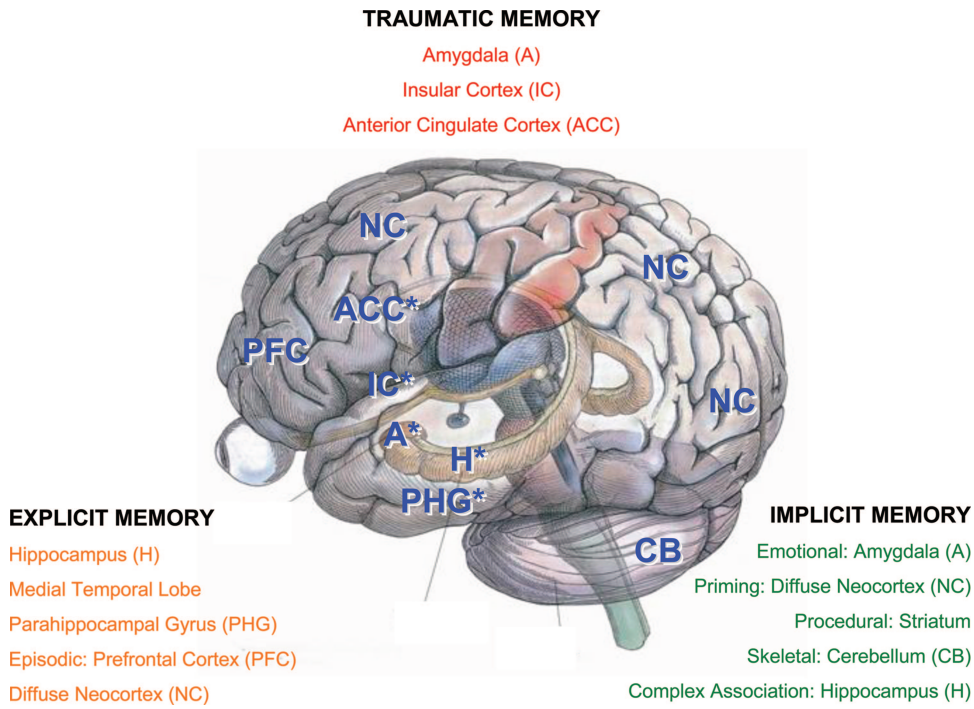


Fig. 3. Neuroanatomical regions associated with implicit, explicit, and traumatic memory formation. Some of the nonoverlapping brain regions provide a conceptual framework for understanding why these various processes may be dissociable from one another. Given the complexity of memory systems, only primary areas of importance are demonstrated. * = a more medial structure.

tivity of AMPA-subtype glutamate receptors, insertion of new AMPA receptors into the postsynaptic membrane,[98] activation of transcription factors, and synthesis of memory-related proteins.[99] Memory-blocking concentrations of several anesthetics impair LTP[64,100] and the production of memory-related proteins.[101] Various lines of evidence have demonstrated a strong correlation between blockade of LTP by neurodepressive drugs (including anesthetics) and memory impairment. Of particular interest are $GABA_A$ receptor subtypes that generate a tonic inhibitory conductance in the hippocampus and cortex. An increase in tonic inhibitory conductance by low (amnesic) concentrations of etomidate strongly impaired LTP in hippocampal slices from wild-type but not $\alpha_5-/-$ mice.[80] Interestingly, LTP was first described in animals anesthetized by chloralose and urethane, which suggests that during anesthesia, memory storage can still occur under some conditions.[102]

At the forefront of memory-related anesthesia research are studies aimed at understanding how the coordinated activity of neuronal networks in memory structures, including the hippocampus, forms the substrate for memory behavior. A prominent oscillatory pattern in the θ frequency range (4–12 Hz) has been extensively linked to exploratory behavior and memory processes in primates and nonprimates.[103] The θ rhythm is synchronized or phase-locked in subfields of the hippocampus, neighboring structures (including the amygdala), and subcortical nuclei. Reversible disruption of the θ rhythm by a variety of anesthetics has been associated with memory impairment. A nonimmobilizing compound that causes amnesia[104] without causing immobility or sedation at low doses, 1,2-dichlorohexafluorocyclobutane (also referred to as F6 or 2N), reduces the power but not the frequency of θ oscillations *in vivo*.[105] Furthermore, isoflurane slows θ frequency and increases power.[105] A key outstanding question is whether slowing of θ oscillations causes anesthetic memory blockade or is simply an epiphenomenon. Many additional outstanding questions exist. For example, there is a need to understand the mechanisms underlying persistent memory deficits in the postanesthesia period[106,107] and whether the disruption of neurogenesis (the production of new neurons) in the hippocampus contributes to memory blockade.[107]

Incidence of Awareness

Given the discussion above, the incidence of intraoperative awareness can be regarded as the incidence of a failure to suppress arousal, experience, and explicit episodic memory. Although the first study of the incidence of intraoperative awareness was reported by Hutchinson in 1960,[108] Brice *et al.* initiated the current era of its investigation by describing an instrument to detect awareness.[109] Using a modification of this interview, there have been large, prospective, multicenter studies of awareness in the United States and Europe. The study by Sandin *et al.* reported 19 awareness events in 11,785 cases (0.16%),[110] whereas the study by Sebel *et al.* at seven centers in the United States reported 25 awareness events in 19,575 cases (0.13%).[111] Collectively, these studies suggest that the incidence of anesthesia awareness is approx-

Table 1. Michigan Awareness Classification Instrument

Class 0: No awareness
Class 1: Isolated auditory perceptions
Class 2: Tactile perceptions (*e.g.*, surgical manipulation or endotracheal tube)
Class 3: Pain
Class 4: Paralysis (*e.g.*, feeling one cannot move, speak, or breathe)
Class 5: Paralysis and pain
An additional designation of "D" for distress is included for patient reports of fear, anxiety, suffocation, sense of doom, sense of impending death, *etc.*

imately 1 or 2 cases in 1,000 in the general population, with high-risk cases 10 times more common (1 case in 100). A subsequent large observational study by Pollard *et al.* (2007) using quality control data from a regional medical center reported a much lower frequency of intraoperative awareness with an incidence of approximately 1 in 14,000 patients.[112] Several reasons have been suggested for the discrepancy in awareness incidence seen between the prospective studies and that found with the data of Pollard *et al.* Some have argued that the instrument used by Pollard's group to assess awareness omitted the critical question used in the Brice interviews, that directly asks about explicit recall.[113] Others have suggested that retrospective approaches based on quality control data are insufficient for studying the incidence of intraoperative awareness.[114] However, it is also possible that the discrepancy may not relate to methodological issues. Rather, the standardized anesthetic protocol used in the cases studied by Pollard *et al.* might have been superior in minimizing intraoperative awareness events. Clearly, different practices will generate different results, as suggested by studies of Errando *et al.*[115] and Xu *et al.*[116] In both of these studies, the incidence of awareness (1 in 100 and 1 in 250, respectively) was higher than would be expected based on the studies of Sandin *et al.*[110] and Sebel *et al.*[111]

One limitation of comparing the incidence reported in different studies is variation in the content of the awareness experiences. To address the qualitative aspect of awareness events, a framework was developed to classify the features of intraoperative awareness reports (table 1).[117] This framework, known as the Michigan Awareness Classification Instrument, has an excellent interrater reliability and may (1) allow at least nominal statistical analysis on the qualitative aspects of awareness reports, (2) facilitate the study of more subtle effects of interventions to prevent awareness, and (3) aid in the prediction of postawareness sequelae such as PTSD. This instrument is being used by investigators working with data in the American Society of Anesthesiologists Anesthesia Awareness Registry and in several large, prospective, randomized controlled trials on preventing awareness.[118,119]

Risk Factors for Awareness

Given that intraoperative awareness is rare, our understanding of its risk is imprecise. Attempts to characterize risk factors are based on disparate studies, reported over many decades.[120] There have been numerous changes in anesthetic practice and monitoring techniques. Therefore, it is likely that both the incidence and risk factors for awareness have changed. Increased risk for awareness has been attributed to patient-related and surgical factors. Broadly speaking, these factors have been conceptualized as patients with genetic or acquired resistance to anesthetic agents, patients who are unable to tolerate high-dose anesthetic agents because of poor cardiac reserve, and surgeries in which the anesthetic dose has typically been low, such as cardiac surgery and cesarean section with general anesthesia.[120–123] The most important risk factor is underdosing of anesthesia relative to a specific patient's requirements. Underdosing typically occurs for the following reasons: (1) it is judged unsafe to administer sufficient anesthesia, (2) there is a mistake or failure in the delivery of anesthesia, (3) the anesthetic technique results in inadequate anesthesia, or (4) the particular patient's needs are underappreciated. The risk of awareness probably is compounded by pharmacologic paralysis, which prevents patients from moving and signaling distress. The results from two recent large prospective trials suggest that the use of modern anesthetic agents, the ability to monitor the concentration of exhaled anesthetic and set alarms for low MAC, and the use of sufficient anesthetic dosing and appropriate vigilance have decreased significantly the incidence of awareness in patients historically considered to be at high risk for this problem.[123,124]

It is conceivable that some patients may be physiologically resistant to the amnesic or hypnotic effects of anesthetic agents.[125] Resistance could be attributable to pharmacokinetic factors, such as accelerated metabolism of anesthetic drugs, or to pharmacodynamic factors, such as an altered affinity of the target receptors for anesthetic drugs. Patients who use benzodiazepines and opiates frequently can develop tolerance to drugs in these and similar classes. Many anesthetic drugs are metabolized in the liver by one of the cytochrome P450 hemoproteins, which can be induced by alcohol. Thus, people who habitually drink alcohol may require increased doses of anesthetics. Many benzodiazepines and opioids are metabolized by proteins in the cytochrome P450 3A family, which may be induced by numerous drugs, including efavirenz, nevirapine, barbiturates, carbamazepine, glucocorticoids, phenytoin, rifampicin, and St. John's wort.§ Patients who regularly take these agents may therefore require increased opioid doses for adequate analgesia. In addition, patients with mutations of the melanocortin-1 receptor gene, which is associated with the red hair phenotype, have greater requirements for inhalation anesthesia than do those without such mutations.[126] It is likely that several other, heretofore uncharacterized mutations result in resistance to various anesthetic agents. Patients with a history of aware-

§ Flockhart D: Drug Interactions: Cytochrome P450 Drug Interaction Table. Available at: http://medicine.iupui.edu/clinpharm/ddis/table.asp. Indiana University School of Medicine 2007. Accessed December 12, 2010.

ness are thought to be at higher risk for subsequent episodes,[120] which may be related to genetic factors.

Drug-induced paralysis may be an important factor contributing to the incidence and severity of awareness.[120] In a large, prospective, observational study, the incidence of awareness was 0.18% when muscle relaxants were used and 0.10% when they were not.[110] In another study, all patients who had awareness had received muscle relaxants as part of the anesthetic regimen.[115] Many of the patients who were disturbed by their experiences described feelings of helplessness and an inability to move.[115] Thus, the use of muscle relaxants may modify the experience of awareness and increase the likelihood of PTSD.[120] Patients whose airways are difficult to intubate are also at increased risk for awareness,[120] probably because insufficient attention is paid to ensuring adequate anesthesia during prolonged intubation attempts. Total intravenous anesthesia appears to carry a greater risk for awareness than does present-day inhalation anesthesia,[115,116] perhaps because practitioners using current technology can routinely monitor exhaled anesthetic gas and alarms can be set for low concentrations, whereas neither of those practices is possible with the use of intravenous drugs. In addition, with total intravenous anesthesia, concentrations of anesthetic in the blood are not measured in real time, and infiltration of intravenous catheters or dosage miscalculations may result in inadequate anesthesia. Beyond the risk factors mentioned, human error and equipment malfunction also may lead to awareness.

Psychologic Sequelae of Awareness

Intraoperative awareness may lead to catastrophic psychologic sequelae such as PTSD.[127] This often-devastating consequence for patients is the major motivation for anesthesiologists to prevent awareness. The most recent study of postawareness PTSD[1] followed up patients who had experienced awareness during the B-Aware trial, which compared Bispectral Index™ (BIS™; Covidien, Boulder, CO) monitoring with routine care for the prevention of awareness.[121] Of the seven patients available for further evaluation, five or 71% met the criteria for PTSD. Notably, a proportion of those who experienced PTSD did not report any psychologic symptoms during the 30-day follow-up assessment. Thus, initial assurance by the patient that he or she is not experiencing any psychologic consequences does not obviate the need for careful psychiatric follow-up. Risk factors for the development of postawareness PTSD include initial emotional distress[128] and the experience of paralysis.[120] As with the incidence of awareness itself, the incidence of postawareness PTSD has been a matter of controversy. Because of the rarity of the primary event, studying the secondary event of postawareness PTSD has proven difficult. As such, various methodologies have been employed, including referral, advertising, analysis of closed claims, consecutive enrollment of patients reporting previous episodes of awareness, and secondary outcomes of primary awareness studies.[62,128–133] These methods have been associated with disparate results.[134]

Prevention of Awareness

Target Adequate Dose

In principle, intraoperative awareness can be prevented by ensuring that individual patients receive more than a sufficient dose of the intravenous or inhalation anesthetic throughout the period that general anesthesia is desired. This assumes adequate cardiovascular reserve, which is compromised in some high-risk patients. In general, anesthesia practitioners could use a gas analyzer to titrate the concentration of volatile anesthetic beyond a threshold that would ensure lack of awareness with explicit recall. This threshold probably lies between the concentration of anesthetic gas at which 50% of patients do not move upon surgical incision (MAC) and the concentration of anesthetic gas at which 50% of patients regain responsiveness from anesthesia, or MAC_{awake}, which is typically approximately 0.3–0.5 MAC.[135] Gas monitors with audible alarms may help in alerting practitioners to suboptimal concentrations of exhaled anesthetic. Unfortunately, there are no fail-safe methods for determining what constitutes a sufficient dose of anesthetic for an individual patient, especially in the context of varying surgical stimulation. Furthermore, numerous factors, such as age,[135,136] temperature,[135] and opioid administration[137] alter an individual patient's requirement for inhalation anesthesia. The ability of a gas analyzer to predict depth of anesthesia is severely curtailed when intravenous hypnotic drugs, such as opioids and ketamine, are part of the anesthetic regimen.[138]

Assess Purposeful Movement

It can be argued that we are not routinely exploiting what may be the best manifestation of awareness available: voluntary movement. Minimizing or avoiding the administration of muscle relaxants might help to prevent a prolonged, traumatic episode of awareness. The experience of intraoperative events may be inferred when a patient responds appropriately to a specific command.[139,140] However, failure to respond to a command does not guarantee unconsciousness. Furthermore, suppression of movement during anesthesia is primarily mediated in the spinal cord, as opposed to the brain.[141,142] Nonetheless, patients who are distressed or in pain can be expected to register their discomfort with movement, unless they are paralyzed. When pharmacologic paralysis is used, a "safety cushion" in anesthetic dosing is advisable; light anesthesia coupled with muscle relaxation generally is inappropriate.

Monitor the Brain

The difficulty of assessing the presence of consciousness in paralyzed patients has motivated the use of electroencephalography as an aid in preventing intraoperative awareness. One of the many available brain monitors, including units that generate an

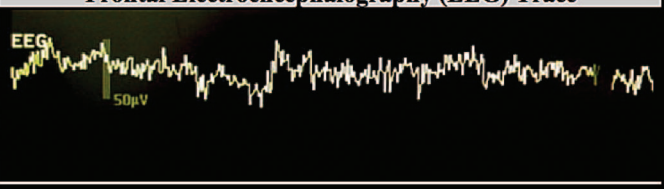
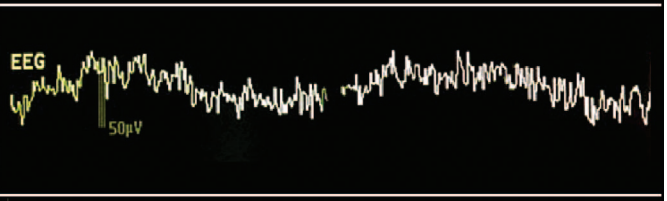
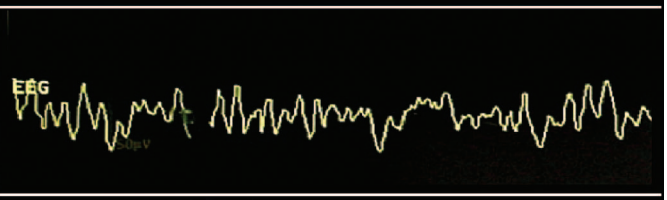
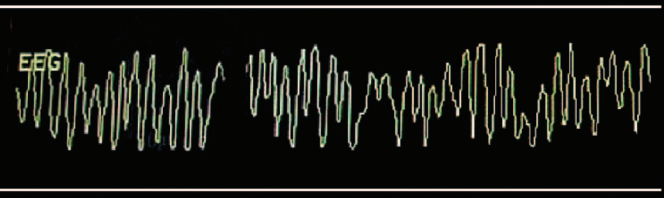
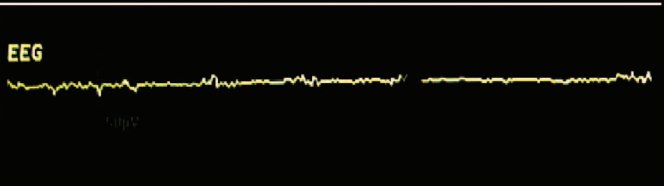
Patient State	Device	Features	Reading	Frontal Electroencephalography (EEG) Trace
Wakeful	EEG	↑*f*, ↓Amp, blinks	↑γ,β,α↓θ,δ	
	SEF_{95}	Twenties	26 Hz.	
	BIS	High β ratio	96	
	Entropy	High entropy	97	
	AAI	↓lat, ↑Δamp	81	
	NI	EEG *f* band analysis	A	
	ETAG	Age-adjusted MAC	0 MAC	
Sedated	EEG	α oscillations	↓γ,β, ↑α,θ,δ	
	SEF_{95}	High teens	19 Hz.	
	BIS	Low β ratio	78	
	Entropy	High entropy	85	
	AAI	↑ing lat, ↓ing ΔAmp	45	
	NI	EEG *f* band analysis	B / C	
	ETAG	Age-adjusted MAC	0.4 MAC	
Unresponsive	EEG	Spindles, K, ↓*f*	↑α,θ,δ	
	SEF_{95}	Low teens	14 Hz.	
	BIS	Bispectral coherence	52	
	Entropy	Entropy drop	43	
	AAI	↑ing lat, ↓ing ΔAmp	30	
	NI	EEG *f* band analysis	D	
	ETAG	Age-adjusted MAC	0.8 MAC	
Surgically Anesthetized	EEG	Slow δ waves, ↓*f*	δ dominance	
	SEF_{95}	< 12 Hz.	10 Hz.	
	BIS	Bispectral coherence	42	
	Entropy	Low entropy	38	
	AAI	↑ing lat, ↓ing ΔAmp	22	
	NI	EEG *f* band analysis	E	
	ETAG	Age-adjusted MAC	1.3 MAC	
Deeply Anesthetized	EEG	BS, isoelectricity	Bursts & flat	
	SEF_{95}	< 2 Hz. (BS corrected)	2 Hz.	
	BIS	High BSR	9	
	Entropy	Burst suppression	8	
	AAI	↑latency, ↓Δamp	11	
	NI	EEG *f* band analysis	F	
	ETAG	Age-adjusted MAC	2 MAC	

Fig. 4. Patient states, candidate depth of anesthesia devices or approaches, key features of different monitoring approaches, and possible readings at different depths of anesthesia. The readings shown represent examples of possible readings that may be seen in conjunction with each frontal electroencephalography trace. The electroencephalography traces show 3-s epochs (x-axis), and the scale (y-axis) is 50 μV. AAI = A-Line Autoregressive Index (a proprietary method of extracting the mid-latency auditory evoked potential from the electroencephalogram); Amp = amplitude of an EEG wave; BIS = bispectral index; Blinks = eye blink artifacts; BS = burst suppression; BSR = burst suppression ratio; EEG = electroencephalography; ETAG = end-tidal anesthetic gas concentration; *f* = frequency; γ, β, α, θ, δ = EEG waves in decreasing frequencies (γ, more than 30 hertz [Hz]; β, 12–30 Hz; α, 8–12 Hz; θ, 4–8 Hz; δ, 0–4 Hz); K = K complexes; Lat = latency between an auditory stimulus and an evoked EEG waveform response; MAC = minimum alveolar concentration; NI = Narcotrend index; SEF_{95} = spectral edge frequency below which 95% of the EEG frequencies reside; Spindles = sleep spindles.

unprocessed electroencephalography trace, may provide compelling evidence for hypnosis.[143] Attempts to assess depth of anesthesia by monitoring the brain generally have focused on indices based on spontaneous electroencephalographic recordings or monitoring of evoked potentials. Characteristic changes occur in the electroencephalogram with administration of γ-aminobutyric acid agonist anesthetics[144]: with deepening anesthesia, there is a decrease in high-frequency, low-amplitude waves and a concomitant increase in low-frequency, high-amplitude waves.[145,146] These changes are somewhat variable and are not specific to general anesthesia.[146] Nonetheless, the electroencephalogram may provide valuable information, and anesthesiologists can easily learn to recognize the electroencephalographic patterns associated with general anesthesia.[144] Simplified indices based on proprietary processed electroencephalographic algorithms also have been developed.[147] These algorithms convert the information supplied by the electroencephalogram or derived signals into a simple index intended to reflect the depth of anesthesia (fig. 4).[147]

Two auditory evoked potentials are frequently used to assess the effects of general anesthetics on the brain: the midlatency auditory evoked response and the 40-Hz auditory steady-state response.[148–150] General anesthesia is associated with characteristic alterations in the latencies, amplitudes, and high-frequency components of auditory evoked potentials.[149,151,152]

Many indices have been tested for their precision in discriminating between responsiveness and unresponsiveness by means of the prediction probability metric P_K.[153] The value of P_K, the probability of an index correctly detecting the anesthetic state, ranges between 1, which indicates perfect

discriminatory ability, and 0.5, which indicates performance no better than chance.[153] Techniques such as evoked potentials, BIS, permutation entropy, Hilbert-Huang spectral entropy, bicoherence, weighted spectral median frequency, and combination techniques all are reasonably accurate, with P_K values ranging from approximately 0.75 to 0.9.[154–159] Nevertheless, no technique is completely reliable, and any index may incorrectly indicate unconsciousness when the patient remains awake. In other words, the current technology is not 100% sensitive in ruling out that a patient is awake during general anesthesia.

Utility of Brain Monitors. Two distinct indications have been proposed for brain monitors: to serve as an alert and to guide titration of anesthesia. All currently available brain-monitoring indices have a nonlinear dose–response relationship between the electroencephalography-derived index and increasing concentrations of anesthetic agents, with a plateau in dosing response over the clinically relevant dose range.[160–169] Because of this plateau, the titration of anesthesia according to these devices may not be reliable.[160–170] Moreover, if there is a narrow range of drug concentrations over which the brain undergoes transitions in state (*e.g.*, from unconscious to wakefulness),[171,172] it follows that titrating the anesthetic dose downward for as long as the brain monitor suggests unconsciousness is potentially hazardous. In this scenario, it is possible that the monitor will not have time to register a signal of imminent transition in phase or state, being able to indicate the transition only after it has occurred. Conversely, if brain monitors are used not to help practitioners minimize the anesthetic dose, but rather as an additional alarm to indicate possible insufficient anesthesia, it is very likely that some cases of awareness would be prevented. The extent to which brain monitors contribute to decreasing awareness relative to current best practice without brain monitors is a matter of controversy. In the B-Aware trial, awareness events associated with a BIS-guided protocol in high-risk patients occurred substantially less frequently than did awareness events in the control group.[121] In contrast, in the B-Unaware trial, there was no difference in awareness between high-risk patients treated with the BIS-guided protocol and the control group, which also received protocol-based care, including audible alarms for low concentrations of anesthetic gas.[123] In both of these trials, the estimates of the incidence of awareness had wide confidence intervals, and their discrepant findings highlight the need for additional research. It is anticipated that the results of the ongoing Michigan Awareness Control Study and BAG-RECALL clinical trials will address many of these outstanding controversies.[118,119]

Limitations of Brain Monitors. The most important limitation of brain monitoring is the assumption that uniform changes in electroencephalographic waveforms occur in all patients who receive anesthetic agents. However, the electroencephalogram is affected by multiple factors, many of which also alter MAC. Furthermore, electrical activity, such as surgical cautery, electrocardiography, and muscle depolarization, may introduce artifacts into the electroencephalographic waveform and interfere with its interpretation.[173] Because processed electroencephalographic indices are derived from unprocessed waveforms, it is unsurprising that factors altering the raw waveform may profoundly affect the processed indices. A case in point is the patient's age. An assessment of loss of responsiveness with propofol in younger patients (less than 40 yr) and older patients (more than 65 yr) revealed that the median values for BIS, state entropy, and response entropy were significantly higher for the older patients at the point of loss of responsiveness.[174] If a monitor is calibrated with a specific population (*e.g.*, healthier or younger people), its validity cannot necessarily be extrapolated to other patient populations (*e.g.*, people who are very young or very old; pregnant women; patients with dementia, seizures, or sepsis).[173]

The risk of postoperative recall appears to be low if patients arouse only briefly but increases if patients are awake for more than approximately 30 s.[175] Some of the popular brain monitors, including the BIS™ monitor, the Narcotrend™ monitor (MonitorTechnik, Bad Bramstedt, Germany), and the Cerebral State Index™ monitor (Danmeter, Odense, Denmark), have delays of between 30 s and 2 min before they will indicate a change in the level of anesthesia.[176] Such a delay might not trigger a sufficiently rapid intervention to prevent the encoding of explicit, traumatic memories. Current brain monitors are also limited by their calibration range beyond the point of loss of responsiveness, their inability to discriminate reliably between awareness and unawareness, the interpatient variability in their dose–response curves, their limited intrapatient reproducibility, and their relative insensitivity to opioids and *N*-methyl-D-aspartate glutamate receptor antagonists.[173,177,178]

A general checklist for strategies to prevent intraoperative awareness can be found in table 2.

Future Directions: From Neurobiology to Clinical Practice

In this review we have independently discussed the neurobiologic and clinical aspects of intraoperative awareness. To advance the study of intraoperative awareness, it is critical that we bridge the gap between the underlying neurobiology and our clinical practice. This involves identifying key neuroscientific questions that, if answered, can inform our clinical management. One such question relates to anesthetic state transitions. Understanding the dynamic organization of anesthesia induction and, just as importantly, emergence, will inform the clinical detection of an intraoperative return of consciousness. Frameworks such as the information integration theory of consciousness might predict a return to consciousness that is graded, rather than discrete.[21,37–40] Thus, monitoring based on information integration principles would relate to the real-time measurement of ϕ, with a focus on detecting critical increases associated with awareness. This assumes the requisite spatial resolution of neurophysiologic data to generate the information complexes that

Table 2. Checklist for Preventing Awareness

√ Check all equipment, drugs, and dosages; ensure that drugs are clearly labeled and that infusions are running into veins.
√ Consider administering an amnesic premedication.
√ Avoid or minimize the administration of muscle relaxants. Use a peripheral nerve stimulator to guide minimal required dose.
√ Consider using the isolated forearm technique if intense paralysis is indicated.
√ Choose potent inhalation agents rather than total intravenous anesthesia, if possible.
√ Administer at least 0.5 to 0.7 minimum alveolar concentration (MAC) of the inhalation agent.
√ Set an alarm for a low anesthetic gas concentration.
√ Monitor anesthetic gas concentration during cardiopulmonary bypass from the bypass machine.
√ Consider alternative treatments for hypotension other than decreasing anesthetic concentration.
√ If it is thought that sufficient anesthesia cannot be administered because of concern about hemodynamic compromise, consider the administration of benzodiazepines or scopolamine for amnesia.
√ Supplement hypnotic agents with analgesic agents such as opioids or local anesthetics, which may help decrease the experience of pain in the event of awareness.
√ Consider using a brain monitor, such as a raw or processed electroencephalogram but do not try to minimize the anesthetic dose based on the brain monitor because there currently is insufficient evidence to support this practice.
√ Monitor the brain routinely if using total intravenous anesthesia.
√ Evaluate known risk factors for awareness, and if specific risk factors are identified consider increasing administered anesthetic concentration.
√ Redose intravenous anesthesia when delivery of inhalation anesthesia is difficult, such as during a long intubation attempt or during rigid bronchoscopy.

can be measured, as well as a time frame for computation that is meaningful in the clinical setting. Frameworks such as the flip-flop theory of binary sleep–wake transitions would predict a discrete shift from unconsciousness to consciousness.[8,9,17] Monitoring based on this principle would have to rely heavily on the study of sleep–wake transitions to identify cortical markers of an impending state change to wakefulness. This assumes that anesthetic states follow the same organization as that during sleep, which may not be the case.[18] Nonlinear analysis of anesthesia emergence has suggested yet another alternative of multiple and discrete phase transitions leading to consciousness.[171] Monitoring based on these principles would aim to identify when a shift from linear to nonlinear organization had occurred as a stage toward emergence. As we develop monitoring modalities, we must explicitly consider these neuroscientific frameworks—as well as the evidence and assumptions behind them—to generate algorithms that are based on the neurobiology of consciousness and anesthesia.

According to Steyn-Ross *et al.*, when the anesthetic concentration is gradually increased or decreased, the equilibrium solution of the model suddenly jumps from one stable branch to another, and this can cause sudden transition between awareness and unconsciousness or *vice versa*. Because phase transitions make a hysteresis path, emergence and induction phases of anesthesia occur at different drug concentrations.[179] In addition, the discontinuous step change in cortical entropy suggests that the cortical phase transition is analogous to a first-order thermodynamic transition in which the comatose-quiescent (unaware) state is strongly ordered, while the active cortical (aware) state is relatively disordered.[172] Experimental support for the hysteresis hypothesis was provided by Kelz *et al.*, who showed in a narcoleptic murine model that the endogenous orexin system affects emergence from, but not entry into, the anesthetized state. In doing so, they suggested that induction of anesthesia and emergence from anesthesia are not simply mirror-image processes.[15] Neural inertia refers to a tendency of the brain to resist state transitions between conscious and unconscious states. Additional experimental corroboration for neural inertia and hysteresis recently was provided in experiments in mice and fruit flies.[180] By using a fruit fly model, it was demonstrated convincingly that the hysteresis phenomenon cannot simply be attributed to pharmacokinetic confound.[180] There would be important clinical implications if theories surrounding neural inertia prove correct and if a hysteresis between MAC-awake and MAC-asleep exists, such that the anesthetic concentration at the effect site required for loss of consciousness were higher than the concentration at which awakening occurred. On the upside, there would be a margin of safety in that patients would not awaken despite anesthesia dropping below MAC-asleep. On the downside, when patients did awaken, a high increment of anesthesia (analogous to a large amount of energy) would be required to overcome the neural inertia of wakefulness and to increase the anesthetic concentration at the effect site to achieve MAC-asleep. Furthermore, patients with reduced neural inertia could be more prone to awareness. Our further understanding of anesthetic state transitions may one day critically inform the prevention of intraoperative awareness, both in terms of monitoring and anesthetic delivery.

Conclusions

Intraoperative awareness is defined by both consciousness and explicit memory of surgical events. It occurs in 1 or 2 of every 1,000 surgical cases, but incidence varies with the patient population, methodology used to study awareness, and time frame of the study. Risk factors include compromise of cardiovascular function as well as acquired or inherited resistance to the sedative or amnesic effects of anesthesia. Electroencephalographic techniques to detect and prevent aware-

ness are being investigated, but no method has proven uniformly reliable. The lack of a standard intraoperative monitor for the brain probably reflects the complexities inherent in understanding the neural correlates of consciousness and memory. Consciousness can be subdivided into the dissociable components of brain arousal, which is mediated primarily at the subcortical level, and subjective experience, which is likely mediated by the thalamocortical system. Memory can be subdivided into implicit (unconscious) and explicit (conscious) subtypes, the latter being mediated by structures in the medial temporal lobe. As the scientific investigation of the underlying neurobiology of intraoperative awareness advances, we will be in a better position to understand and monitor the effects of anesthesia on these neural processes. It is hoped that these improvements will one day lead to a reliable method of preventing what can be a feared and psychologically devastating complication of perioperative care.

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