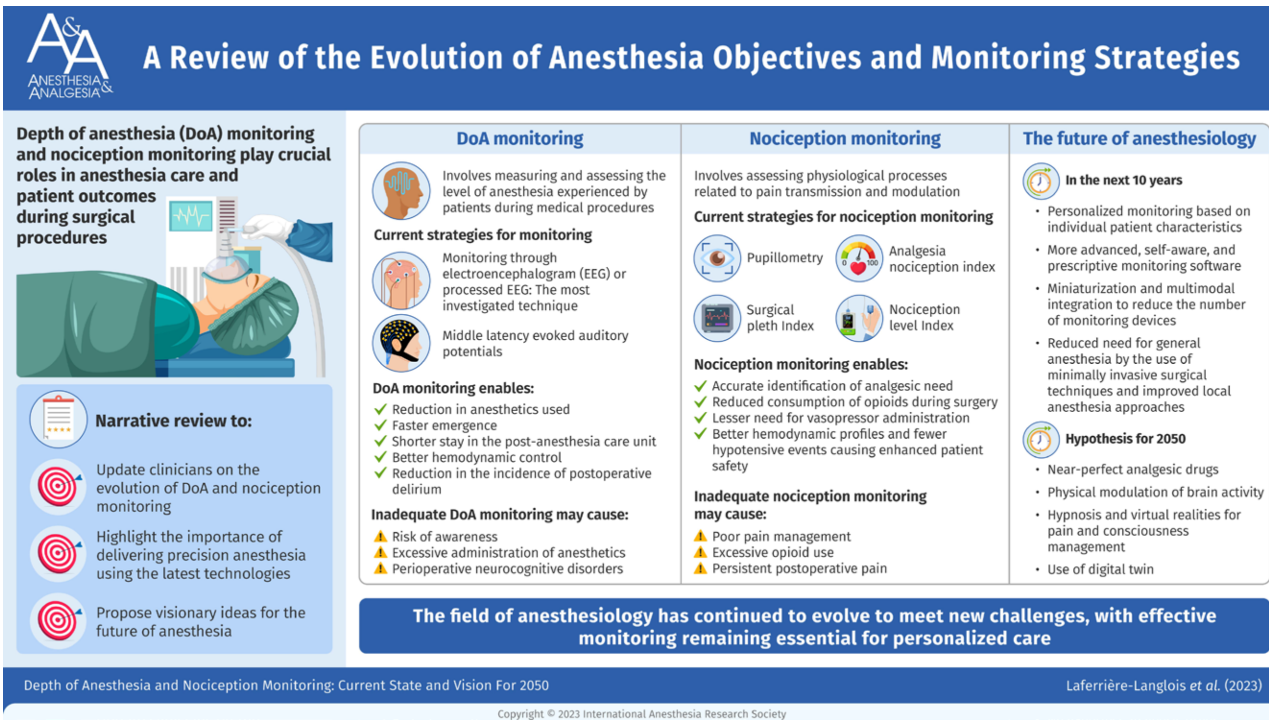
NARRATIVE REVIEW ARTICLE

Depth of Anesthesia and Nociception Monitoring: Current State and Vision For 2050

Pascal Laferrière-Langlois, MD, MSc, FRCPC,*† Louis Morisson, MD, MSc, DESAR,† Sean Jeffries, MSc,‡ Catherine Duclos, PhD,† Fabien Espitalier, MD, PhD, DESAR,§ and Philippe Richebé, MD, PhD, DESAR*†

See Article, page 233



Anesthesia objectives have evolved into combining hypnosis, amnesia, analgesia, paralysis, and suppression of the sympathetic autonomic nervous system. Technological improvements have led to new monitoring strategies, aimed at translating a qualitative physiological state into quantitative metrics, but the optimal strategies for depth of anesthesia (DoA) and analgesia monitoring continue to stimulate debate. Historically, DoA monitoring used patient's movement as a surrogate of awareness. Pharmacokinetic models and metrics, including minimum alveolar concentration for inhaled anesthetics and target-controlled infusion models for intravenous anesthesia, provided further insights to clinicians, but electroencephalography and its derivatives (processed EEG; pEEG) offer the potential for personalization of anesthesia care. Current studies appear to affirm that pEEG monitoring decreases the quantity of anesthetics administered, diminishes postanesthesia care unit duration, and may reduce the occurrence of postoperative delirium (notwithstanding the difficulties of defining this condition). Major trials are underway to further elucidate the impact on postoperative cognitive dysfunction. In this manuscript, we discuss the Bispectral (BIS) index, Narcotrend monitor, Patient State Index, entropy-based monitoring, and Neurosense monitor, as well as middle latency evoked auditory potential, before exploring how these technologies could evolve in the upcoming years. In contrast to developments in pEEG monitors, nociception monitors remain by comparison underdeveloped and underutilized. Just as with anesthetic agents, excessive analgesia can lead to harmful side effects, whereas inadequate analgesia is associated with increased stress response, poorer hemodynamic conditions

From the *Maisonneuve-Rosemont Research Center, CIUSSS de l'Est de L'Ile de Montréal, Montreal, Quebec, Canada; †Department of Anesthesiology and Pain Medicine, Montreal University, Montreal, Quebec, Canada; ‡Department of Experimental Surgery, McGill University, Montreal, Quebec, Canada; and §Department of Anesthesia and Intensive Care, University Hospitals of Tours, Tours, France.

DOI: 10.1213/ANE.0000000000006860

Accepted for publication October 25, 2023.

Funding: P.L-L. is a clinician researcher supported with a salary grant by the *Fond de recherche du Québec en Santé* (FRQS), no. 322164.

Conflicts of Interest: See Disclosures at the end of the article.

Reprints will not be available from the authors.

Address correspondence to Dr Pascal Laferrière-Langlois, MD, MSc, FRCPC, 5415 Boulevard de l'Assomption, Montréal, Québec H1T 2M4, Canada. Address e-mail to pascal.laferriere-langlois@umontreal.ca.

and coagulation, metabolic, and immune system dysregulation. Broadly, 3 distinct monitoring strategies have emerged: motor reflex, central nervous system, and autonomic nervous system monitoring. Generally, nociceptive monitors outperform basic clinical vital sign monitoring in reducing perioperative opioid use. This manuscript describes pupillometry, surgical pleth index, analgesia nociception index, and nociception level index, and suggest how future developments could impact their use. The final section of this review explores the profound implications of future monitoring technologies on anesthesiology practice and envisages 3 transformative scenarios: helping in creation of an optimal analgesic drug, the advent of bidirectional neuron-microelectronic interfaces, and the synergistic combination of hypnosis and virtual reality. (Anesth Analg 2024;138:295–307)

In this article, we will briefly provide an update on the evolution of depth of anesthesia (DoA) and nociception monitoring, we will emphasize the importance of using state-of-the-art monitoring strategies to deliver precision anesthesia, and finally, we will propose an imaginative vision for the future of anesthesia.

A fundamental question for any monitoring device is: "What do we want to monitor to provide information on the patient's status?." To monitor the degree of paralysis, it is accepted that a nerve stimulator provides appropriate information. However, to borrow a phrase from a previous editorial: "What should we properly monitor when we monitor the brain for anesthesia?."[1]

From first principles which have been explored in previous literature,[1,2] the optimal monitor must include several characteristics. Amongst these are the "hardware" properties of: 1) a high refreshment rate with low latency, to ensure that the displayed values reflect the current state of the patient; 2) the ease of use and interpretation; and 3) the economically viability. More challengingly, the monitor must have 4) high sensitivity and specificity to be tailored to the individual patient's state and condition. Hitherto, the success in developing effective monitors is constrained by a circular dilemma: the definition being used to characterize consciousness and pain themselves determine the sensitivity and specificity. Moreover, it is now becoming apparent that consciousness/unconsciousness are not simple binary states, but that several states of unconsciousness exist and can suitable for surgery. Some of these states can permit both recall by the patient and responsiveness during anesthesia, as revealed by studies using the isolated forearm technique. These "in-between" states are variously termed "connected awareness,"[3] "dysanesthesia"[4] or "cognitive unbinding."[5]

Without focusing deeply on the biological theories, it has been well established that neuronal excitability, whether increased or inhibited, is a key element contributing to the conscious state.[6,7] Three mechanisms exist to reduce this excitability: hyperpolarization of the cell resting potential, increasing the threshold for action potential generation, or reducing the amplitude and propagation speed of the action potential once it has fired.[6] In example, most GABAergic drugs will act with the first mechanism, while other agents can act on one or a combination of these mechanisms. The addition of these mechanisms on the neurons will evolve into a global network phenomenon within the brain, which will produce distinct signatures on an EEG for each agent.[8]

This mainstay of modern DoA monitoring is processed electroencephalogram (pEEG), in which the proprietary algorithms are used to create a dimensionless scale ranging from 0 to 100 to describe the result (eg, BIS or entropy values). EEG is transformed into a 3-dimensional power spectral density by plotting the power per wave frequency over time,[9] which can also be represented by color to reflect the power of the waves, creating the density spectral array (DSA).[10] However, these algorithms were developed based on different populations than those encountered during surgery. Concomitant use of psychoactive and antidepressant medications has risen in recent years, along with aging, which brings with it a higher prevalence of neurocognitive disorders. Finally, a combination of agents is used during anesthesia and all these factors can exert an influence on the EEG signal.[11]

The limitations of pEEG reflect back onto the discussion above, wherein consciousness and responsiveness are appreciated as different.[3] With ketamine, the patient can undergo satisfactory surgery, despite maintaining high pEEG scores that with other agents would indicate conscious awareness. The patient experiences a form of consciousness in the form of dissociation.

The use of DoA monitoring and analysis by individual research groups, in ways unconstrained by proprietary algorithms, has provided valuable insights into the distinct pEEG and DSA signatures observed with different anesthetic drugs. Even though we may struggle to clinically differentiate the states of unconsciousness induced by propofol, etomidate, and benzodiazepines administered at therapeutic doses, and especially in the presence of neuromuscular blockade, the variations in their signatures reflect their differing and respectively unique effects on the brain.[8]

Currently, clinicians primarily rely on the pharmacokinetics and side effect profiles of these drugs to guide their selection. However, future investigations may explore whether specific DSA signatures have an impact on clinical outcomes, thereby introducing a new dimension to DoA monitoring.

The main outcome that DoA monitoring seek to prevent is accidental awareness during general anesthesia (AAGA).[12]The incidence of AAGA is as high as 1 in 600[13]if patients are directly questioned postoperatively (the Brice interview) but is about 1 in 19,000 (1 in 8000 with neuromuscular blockade) if studies rely on self-reporting of patients[14] and may be higher in patients with poor cardiac reserve or when undergoing cardiac or in obstetric c-section surgery.[15] Total intravenous anesthesia (TIVA) is particularly associated with the risk of awareness compared to volatile anesthesia as there is no direct real-time measure of plasma concentration, unlike end-expiratory concentrations for volatile agents. Despite encouraging results from earlier studies, recent randomized controlled trials (RCTs) evaluating DoA monitoring *versus* ETAG monitoring using minimum alveolar concentration (MAC), reported no significant difference in the risk of AAGA between groups.[16,17] These results were further confirmed by a meta-analysis.[18] To date, only 1 study investigated the use of DoA monitoring during propofol anesthesia. The authors found that the risk of awareness was significantly lower in the DoA monitoring group.[19]

However, DoA monitoring has allowed clinicians to reduce the amount of anesthetics administered.[20,21] Prevention of excessively deep anesthesia offers better intraoperative hemodynamic control and is associated with faster emergence and shorter stay in PACU (postanesthesia care unit).[21] Moreover, it may reduce the development of perioperative neurocognitive disorders such as postoperative delirium (POD).[22] Several studies[23–25] showed that monitoring DoA was associated with a marked reduction in the incidence of POD.[26] Recently, a substudy of the BALANCED study compared light anesthesia (BIS index readings target of 50) versus deep anesthesia (BIS index readings of 35) on the incidence of postoperative delirium,[27] with POD being reduced in the light anesthesia group. However, these conclusions have been questioned on statistical grounds[28] and the ENGAGES trial failed to find reduction in POD with BIS-guided anesthesia compared to routine care.[29]

Therefore, the current state of knowledge is that there is no robust evidence that pEEG monitors reduce the incidence of AAGA, nor that they reduce POD, although there is hope that they might do so in future.

Processed EEG

There are several specific pEEG monitors that we briefly summarize here. The BIS index[30,31] is a combination of time domain (burst suppression ratio), frequency domain (relative beta ratio) and higher order spectral subparameters (bispectrum). A nonlinear function combines these parameters to produce a 0-100 index.

The Narcotrend monitor automatically classifies the resting EEG into stages defined by Kugler[32]from awake state (stage A) to isoelectric EEG (stage F) using 14 distinct graduations. From EEG signal, time and frequency domain parameters are extracted and a subset of features is selected based on their ability to discriminate between the different determined EEG substages.

The Patient State Index (PSI) is also 0-100 index[33,34] based on quantitative EEG features extracted from a bilateral forehead probe. The EEG signals are passed into a series of artifact detection and burst suppression detection algorithms and finally transformed in the frequency domain. A subset of features (mostly related to absolute and relative powers of different sub bands from 0.5 to 50Hz) that contribute most to the variance related to the hypnotic state are normalized, log-transformed and combined in a discriminant (proprietary) algorithm. The final PSI algorithm is modulated by 2 functions sensitive to suppression ratio and to abrupt changes in the level of sedation.

The entropy monitor relies on the observation that in the awake patient, the EEG waveform is not a simple sum of sine waves. Instead, the signal exhibits nonlinear or chaotic behaviors. As the depth of anesthesia increases, the EEG shifts from this chaotic pattern to a more organized one. The measure associated with chaos is called entropy and was first proposed as a thermodynamic principle. There appears to be a correlation between the entropy of the EEG signal and the depth of anesthesia. There are numerous ways to compute entropy. In the commercially available entropy module of Datex-Ohmeda, the entropy is calculated in the frequency domain and is called spectral entropy. In fact, 2 spectral entropies are computed.[35,36] The State entropy (SE) is computed over the frequency range from 0.8Hz to 32Hz. It includes the EEG-dominant part of the spectrum. The response entropy (RE) is computed over a frequency range from 0.8Hz to 47Hz. It includes both the EEG-dominant (0.8 to 32Hz) and electromyography dominant (32 to 47Hz) part of the spectrum. Both have their own informative purpose. The time windows for SE range from 60s to 15s to compute entropy over low frequencies. It is believed to be a stable indicator of the effect of anesthetics on the brain. On the other hand, the time windows of RE range from 15.36s to 1.92s. RE reacts faster to changes and will first rise together with muscle contractions during arousal.

The Neurosense was developed on the assumption that the BIS analysis technique induces large time delays and is therefore not appropriate for closed-loop anesthesia. The new index, the WAV_{CNS}, is especially suited to dynamic situations.[37] The overall technique is based on wavelet transformation of the EEG signal.[38] It is a common technique used in signal processing when both time and frequency information are of interest. The researchers found that the wavelet information associated with the gamma frequencies (32 to 64 Hz) can be statistically represented as a probability density function (PDF). Its shape evolves from a flat and wide envelope (awake patient) to a sharp and narrow pike (isoelectric state). The evolution between these 2 states (ie fully awake to totally suppressed cortical activity) characterize the DoA of the patient and correspond to the probability of being in one of these to states. The advantage of WAV_{CNS} method is that it can easily be implemented in real time (1 sec EEG epoch is required). It theoretically captures changes in cortical activity faster than spectral analysis. Like the BIS, the WAS_{CNS} is a 0-100 index. The correlation coefficient between BIS and WAV_{CNS} is 0.969.

Middle Latency Evoked Auditory Potentials

In auditory evoked potentials (AEP)[39] the response of the brain to an auditory stimulus can be separated into 3 phases. Early components of the AEP are mainly generated in the brainstem. Middle latency AEPs occur 10-100ms after stimulus and originate mainly from the primary auditory cortex. Finally, late latency AEPs reflect neural activity of the association cortex and are influenced by cognitive analysis. Early components are not specifically affected by anesthesia and late components are not present during anesthesia. On the other hand, middle latency AEPs are affected in a dose-dependent way under general anesthesia. Latency increases and amplitude decreases with increasing doses of anesthetics for both volatile and intravenous anesthesia. The Alaris AEP monitor generates an Alaris AEP index to estimate DoA.[40] The latter is believed to be best at distinguishing the transition from unconsciousness to consciousness compared to BIS, spectral edge frequency and median frequency.[41,42]

Pain and Nociception Monitors

Historically, attempts were made in vain to combine different clinical parameters into a composite score.[43] More specific and more sensitive indexes have since been developed, validated, and proposed to the clinician to perform personalized anesthesia and precision medicine perioperatively.[44–48] These monitors and their related indexes will also allow researchers to precisely study the real impact of anesthetic[49] or analgesic[47] drugs to block the transmission of noxious stimuli to allow for an optimal balance between nociception and antinociception. Only monitors used to assess intraoperative nociception under general anesthesia in an adult population will be discussed in this section.

The general principle of nociception monitoring relies on the neurophysiology of pain pathways as originating in a peripheral stimulus, transduced into electrical impulses, and traveling along the peripheral unmyelinated C fibers or the myelinated A delta fibers to the dorsal horn of the spinal cord, where a synapse exists between this peripheral first-order neuron and the second-order neuron. The latter will travel the spinal cord in the anterolateral quadrant up to the thalamus, from which the impulse will be relayed to the somatosensory cortex, the frontal cortex, and the limbic system.[50] Each of these relays can be monitored, which explains the 3 broad categories of nociception monitors: motor reflex monitoring, CNS-based monitoring, and autonomic nervous system (ANS)-based monitoring.

Motor reflex monitoring, discussed below, is similar to the isolated forearm technique to monitor depth of anesthesia. The core principle is that if the patient is too lightly anesthetized, they will react to noxious stimuli, with movement. However, paralyzing agents automatically blunts this monitoring approach, and in an unparalyzed patient, it is questionable whether this specific monitoring adds anything to clinical observation of patient movement. Finally, it is a curious property of the isolated forearm responses that patients do not respond with movement to surgically induced pain, but they do respond to a verbal command to move.[51,52] Thus it is possible that patients may not respond to painful stimulus in the monitoring of motor responses.

CNS-based monitoring is closely related to current state-of-the-art DoA monitoring.[53] By identifying and monitoring the brain regions triggered by pain and influenced by the administration of analgesic agents to brain tissue, the monitor aims to extract specific electrical activity, which in turn would be interpreted as nociception.

ANS-based is a distinct monitoring approach and exploits the sympathetic response associated with nociceptive stimuli, and its numerous external physiological manifestations. High frequency pupillometry can assess the pupillary dilation associated with sympathetic stimulus[54,55]; skin conductance assesses the sudation[56,57]; plethysmography assesses the heartbeat variations. To improve clinical interpretation, these monitors analyze values with proprietary algorithms and offer a summarized interface to the clinician, in conjunction with a scale from 0 to 100 as we see with DoA monitoring.

The 4 most commonly commercially available monitors include: 1) the Analgesia Nociception Index (ANI, Mdoloris Medical System); 2) Surgical Pleth Index (SPI, GE Healthcare); 3) pupillometry (AlgiScan/ Neurolight, IDMed); and 4) the Nociception Level index (NOL, Medasense)].

Pupillometry measures the pupillary diameter and its variations in response to nociceptive stimuli, thus studying the sympathetic activity of the ANS (eg, the Algiscan; Figure 1A). However, ocular lesions, head access during surgery, and artifacts due to bright environmental lighting limit use, and pupillary diameter cannot be measured continuously.

The SPI, formerly named Stress Surgical Index, reflects the sympathetic activity of the ANS. The information given by the microvascular wave impulse signal of a finger photoplethysmograph, is used to calculate the 2 parameters: the heart rate variability and the pulse of the photopletysmographic amplitude (PPGA)(Figure 1B). This dimensionless continuous numerical index (from 0 to 100, with 0= no stress and 100= high intensity stress) was previously developed to give a numeric measure of the surgical stress in patients under general anesthesia. The manufacturer recommends a SPI <50 during surgery. Limits in the use of SPI are cardiac arrhythmia, cardiac pacing and peripheric vasoconstriction.

The Analgesia Nociception Index (ANI) is based on the heart rate variability. This technology continuously analyzes the impact of respiratory sinusal arrhythmia on heart rate, leading to a measure of the parasympathetic tone (Figure 1C). Each R spike in the electrocardiogram (ECG) signal is used to measure the time variation of the R-R interval. This signal is normalized and filtered between 0.15 and 0.4 Hz. Only the parasympathetic variations are used in the calculation of the index, which are mainly influenced by the respiratory cycle. The ANI is a dimensionless index from 0 to 100, where 0 is the sign of high ANS response to stress, and 100 is a low ANS response to stress and possibly less nociception. Limits in the use of ANI are cardiac arrhythmia and cardiac pacing.

Figure 1. Four most commonly commercially available nociception monitors.

The NOL index is a multiparametric index using the combination of 5 parameters to measure nociception: the heart rate, the PPGA, the skin conductance and temperature and the time derivative of these parameters. These parameters, collected from a finger probe (PMD Medasense Biometrics Ltd, Ramat Yishai, Israel), are analyzed using a nonlinear regression of Forest, giving a dimensionless number from 0 to 100, where 0 is no nociception and 100 is very high nociception (Figure 1D). Limits in the use of NOL are cardiac arrhythmia, cardiac pacing.

To summarize most of the indexes that reached the market for clinical daily use were based on 1 or 2 single parameters: pupil diameter, heart rate variability (HRV, with the ANI index), skin conductance, plethysmography (with the SPI), skin conductance, or more recently, a combination of more than 2 parameters such as the NOL index (for Nociception Level Index, based on heart rate, HRV, skin conductance, skin temperature, plethysmography). Most of these indexes (ANI, SPI, pupil, NOL) were compared to the classically used clinical parameters of heart rate and blood pressure.[44–48,58–65] Literature indicates that these indexes are more precise to detect intraoperative nociception under general anesthesia.[66]One even more recent study using secondary analysis of 1 study published in 2021[67] demonstrated that some index (here the NOL index) was also able to identify the analgesic effect of intraoperatively administered opioids more precisely than heart rate and blood pressure which suggests it allows for better administration of the opioids during surgery.[68]Finally, the concomitant intraoperative use of nociception monitors (NOL index) with EEG monitors (BIS index) improves the time for emergence from anesthesia and PACU recovery.[20]

Their use was also able to help identifying whether regional techniques used intraoperatively offered proper antinociception during major surgery.[69] Many clinical studies reported a strong reduction of intraoperative opioids in the groups for whom opioids were given based on this index versus based on heart rate and blood pressure.[61,67,70–73] That said, there is no universal agreement, and 1 systematic review did not support the conclusion of reduced opioids use.[74] Arguably, this review did not include the most recent publications and retrieved only 12 studies with small sample sizes. Finally, nociception monitors could also yield better hemodynamic intraoperative profiles,.[70,73]

The beneficial effects described above also translates into lower postoperative pain scores and opioid consumption for several hours after surgery when these monitors are used. This was consistent when using the pupil diameter monitoring in gynecological surgery,[61,75] when ANI was used during general anesthesia for spine surgery,[71] and when NOL index was used in major abdominal surgery[74] or gynecological surgery.[67]

Regarding the impact of nociception monitoring during general anesthesia on long-term outcomes such as persistent postsurgical pain or opioid use disorders after major surgery, very few studies evaluated these outcomes and were not robust enough to answer this specific question.[61] Future research endeavors should encompass more targeted studies that specifically address this question. Postoperative acute or chronic outcomes are outcomes that can be regarded as patient-centered outcomes (pain levels, quality of recovery, quality of life…) which are of major importance nowadays in research and for the clinical relevance of the trials.

A related question is whether pain may be predicable. ANI values at the end of the surgery, before extubation, when anesthesia was based on a combination of sevoflurane and remifentanil, were predictive of the immediate level of postoperative pain in PACU.[76] Similar results were reported for SPI.[77,78] More recently, the NOL index values recorded during surgery and more precisely NOL values after skin incision were correlated with the level of pain in postanesthesia care unit.[79]One more recent ancillary analysis of the NOLGYN study[67] evaluated the ability of new machine-learning algorithms to predict moderate to severe acute postoperative pain based on intraoperative NOL values.[80]

What Might the Future Hold?

Bill Gates said: “We always overestimate the change that will occur in the next 2 years and underestimate the changes that will occur in the next 10.” We expect both the software and the hardware to change dramatically and help individualize the indices of the monitors to the patient’s specific conditions, including age, relevant comorbidities, chronic intake of psychoactive medications (antidepressants, sleeping drugs), as well as the anesthetic strategy used. By knowing the patient’s age and extracting the DSA signature from the EEG, the monitors will recognize specifically which anesthetic agent is administered, whether intravenous or inhaled, and will specifically select the algorithm associated with this anesthetic strategy to display a personalized index value. Target-controlled infusion (TCI) pumps use distinct pharmacokinetic models based on the drug (propofol) and patient’s demographic, and a similar approach will become a standard for all these monitors currently “blind” to the patient’s characteristics.

Software will become self-aware of its own limitations and might have embedded alternate algorithms to compensate this limitation. For example, a NOL index monitor might itself suggest omitting the RR interval variability if the patient has a pacemaker, detected as the absence of any variability for a prolonged period, and use an alternate integrated algorithm using PPGA, skin impedance, and their time derivatives.

Monitors will become more prescriptive than solely descriptive. Closed-loop systems will continuously modulate the administration rate of the anesthetic medication based on the DoA and nociception monitors. The optimal range will either be established by the physician or suggested from an integrated decision support system (DSS) which preemptively extracts the digital signature from the patient's electronic health record. Discrepancies between the expected evolution of the patient's state and the one monitored, will trigger a new set of alarms suggesting contextualized complications, ranging from a situation as simple as the loss of our intravenous access, to something as complex as suggesting undiagnosed carotid stenosis with brain anoxia. With the increasing number of monitors, clinicians will be able to focus on optimizing the patient's homoeostasis based on the medical situation, instead of continuously and manually modulating infusion rates to maintain the mean arterial pressure and NOL index inside the selected range.

Regarding the hardware components, we will witness a miniaturization of monitors, the elimination or reduction of the number of wires, and we will use wearable technologies to continuously monitor the patient during pre-and postoperative settings. As the commercial landscape evolves with the merger and demerger of companies, we will witness the integration of currently distinct hardware systems, allowing the monitoring of more parameters with fewer devices applied to patients. Both qNOX and qCON are novel indexes extracted from the same frontal electrodes but providing simultaneous information on both nociception and DoA.[81] We will witness a combination of peripheral autonomic system monitor, with oxygen saturation and potentially some cardiac output analysis, as well as the integration of neuromuscular monitoring with frontal electrodes for DoA.

Anesthesia services will continue to be impacted by the modification surgical techniques, which progressively favor minimally invasive approaches with reduced recovery time. Whether we think about transapical valve replacement in cardiac surgery, about endovascular aortic prosthesis instead of open abdominal surgery, or about cryogenic obliteration of renal neoplasia, we have witnessed how new minimally invasive procedures reduce our requirements for general anesthesia. In parallel, our increased understanding of nerve anatomy combined with the improvements of ultrasound technologies democratized the sole use of regional anesthesia for perioperative anesthesia, which shows clear benefits over general anesthesia and improves postoperative pain managements.[82] A striking example is how mastectomies are now performed under paravertebral blocks and sedation, allowing faster hospital discharge, less postoperative nausea, and almost twice as many patients operated per day by reducing turnover time.[82] We will probably see a shift away from general anesthesia for many surgeries, and the anesthesiologist's expertise and monitoring tools might evolve accordingly. Current DoA and nociception monitoring strategies are studied on patients under general anesthesia, but they will have to adapt their use to the state of sedation, implying more noise (eg the impact of emotions on the autonomous nervous system used to monitor nociception), and thorough analysis of intermediate states (ie BIS index between 60 and 80).

During the writing of this article, the large language model *Generative Pretrained Transformers 4* (GPT4) was released to the greater public. After training on the World Wide Web, this algorithm offered a chat-based interface capable of answering any questions asked by the end users, whether it is to write a poem, to summarize an article, or tackle more abstract conceptual question. GPT4 now scores at or above the 90th percentile on certain bar exams, is competitive in mathematical competitions, and has even acquired respectable credentials as a wine steward, passing the introductory Sommelier examination. Similar performance can be seen throughout exams in biology, economics, and history. While this algorithm still produces error 20% of the time by inventing facts, a behavior called "hallucinations," its strength resides in its ability to learn from massive amount of information, condense it into short relevant answers.

By 2050, we suggest that these technologies will have been exposed not only to the scientific medical literature, but also to the raw data of the electronic health records across the globe. The ethical barriers surrounding accessibility of this sensitive data will have been addressed by different strategies, for example by using federated machine learning in which the algorithm travels instead of the data and can thus be exposed to medical data within the protected firewalls without risking being compromised. By standardizing the way that medical data is reported across the globe, we will be able to quickly cross-train numerous algorithms, which will allow the development of new biotechnologies, and the development of new drugs. We will be able to personalize the anesthetic treatment and monitoring to the genome of the patients, or to their connectome, the mapping of the brain's synapses (Figure 2). DoA and nociception monitoring could be achieved by installing high density EEG on the patients by using a quick interface, which could be a helmet, and continuously assessing the true behavior of the brain. From this, artificial intelligence algorithms, previously exposed to the connectome of millions of patients across the globe, will be able to monitor and cross-control the reactivity of the brain to the medication. This could extend to presurgical assessment, in which digital twin would be created to tests virtual events before their occurrence[83] (Figure 3). To illustrate further, we outline 3 creative scenarios.

Groundbreaking Analgesic Drugs

We argue that improved and more accurate nociception monitoring will itself feedback into our frameworks for how we understand the pain pathway, and in turn this could help design better analgesic drugs using molecular engineering, the increase of computational power, and the development of interfacing between living cells and electronics (Figure 4). The ideal drug would offer predictable pain control without the side effects of respiratory depression, alteration of consciousness, nausea, pruritus, etc. For many surgeries, the patient could remain awake and be administered only mild anxiolysis. This medication could also be used at home and increase the possibilities for ambulatory surgery.

Moreover, this drug could also be targeted to the specific source of postsurgical pain whilst leaving intact the ability to feel other sources of pain. For example, a burn on the hand would still be felt. Magnetic guidance could be used to achieve concentrating the drug close to the magnet.[84,85] An alternate strategy would be to synthetically design both the agonist and the receptors, and to integrate or genomically express the receptors only in the targeted cells to be able to provide the agonist via other administration routes afterwards.

Physical Manipulation of the Brain Cells' Depolarization

By increasing our ability to interface microelectronic systems with biological processes, we might become able to physically control, or at least modify, neuronal depolarization and so mimic the cell membrane potential changes created by hypnotic or analgesic drugs, and control nociception or consciousness at

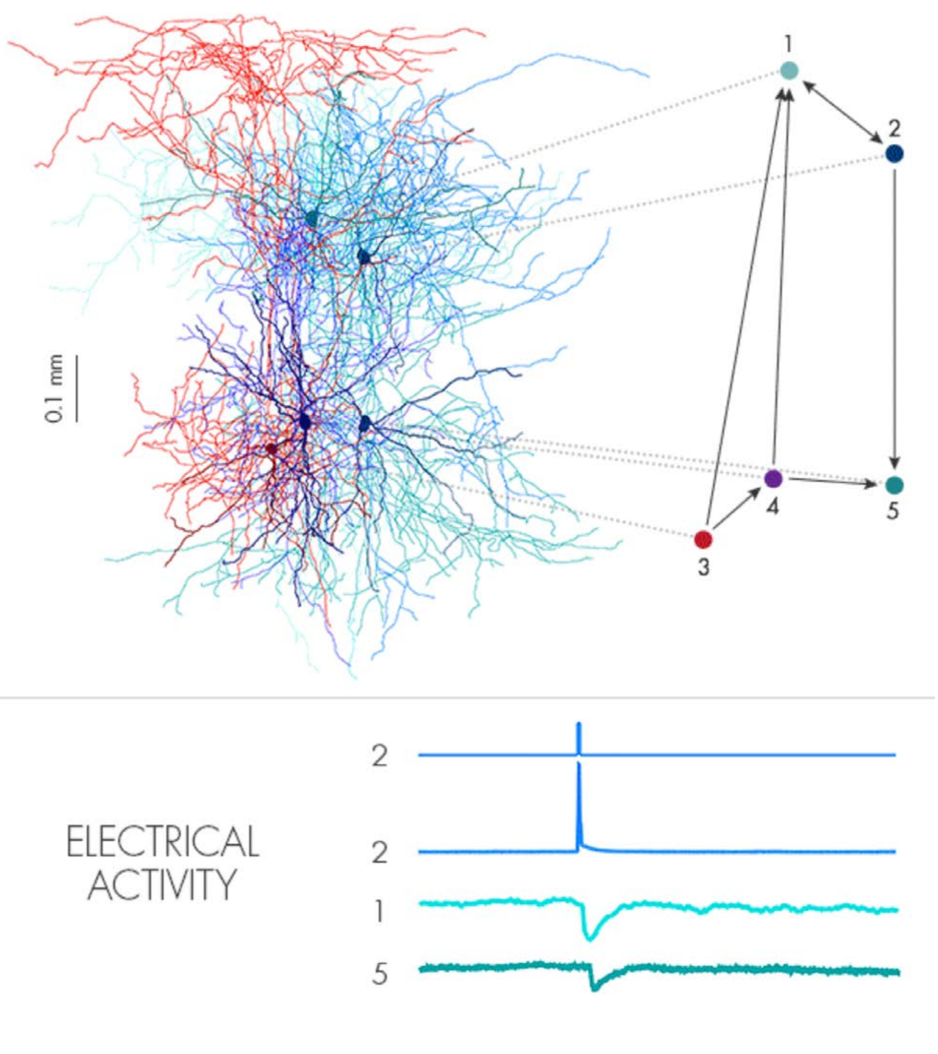


Figure 2. Visual depiction of the connectome, mapping the central nervous system connections and electrical interactions.

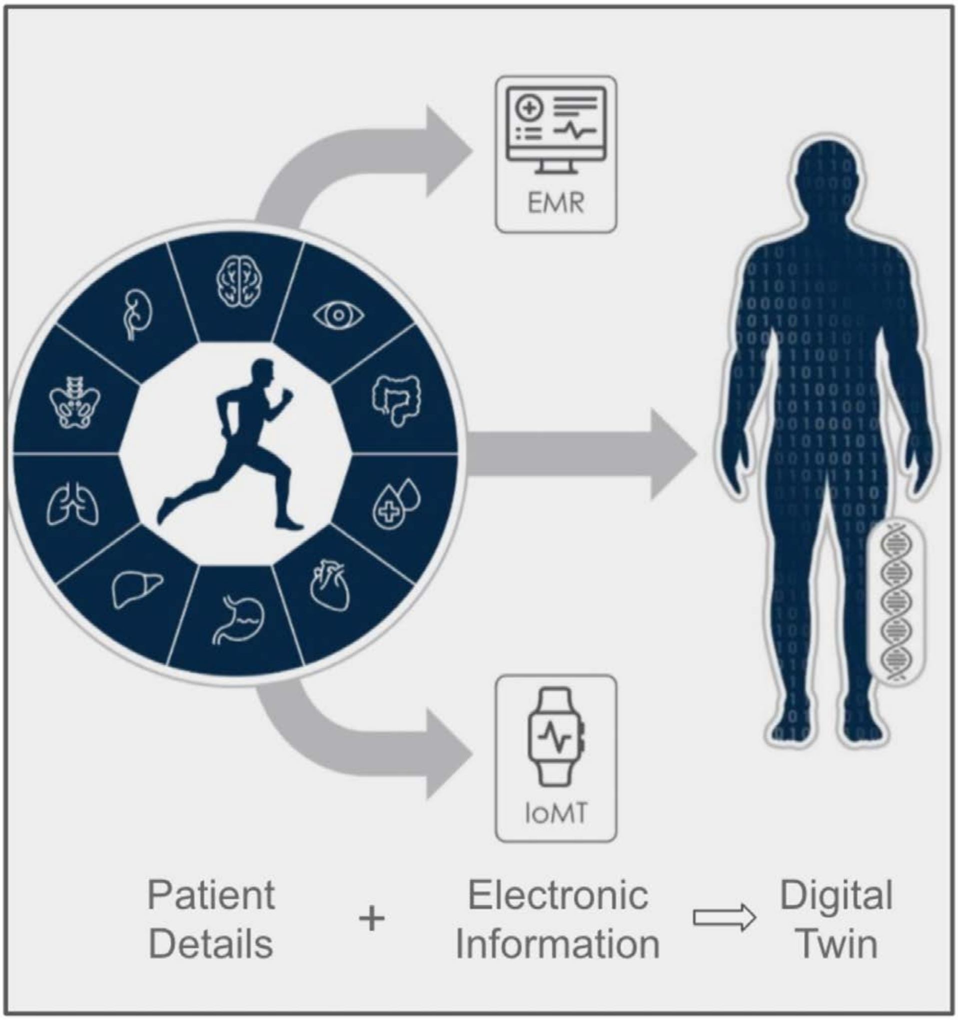


Figure 3. Concept of digital twin for continuous personalized simulation. EMR indicates electronic medical records; IoMT, internet of medical things. Image inspired from Lonsdale et al.[83]

the cellular level. Emerging companies are currently working on a digital neocortex, which would interface with the human cortex to improve connectivity with the digital world. This technology currently uses a vast network of tiny ramifications, like limbs, with sensors recording the electrical activity and relaying it to the relaying capsule (see Figure 5). While the demonstrations made so far are mostly focused on "reading" the brain activity to manipulate external devices like robotic limbs, a natural evolution of the technology is also to "write" on the neocortex, and thus transmit new information to the brain. This creates a whole new set of ethical considerations, but also brings a whole new set of possibilities. Addressing this question is inevitable if we want to interface the digital world with the human brain.

We could create an interface controlling consciousness and nociception by hyperpolarizing neurons or

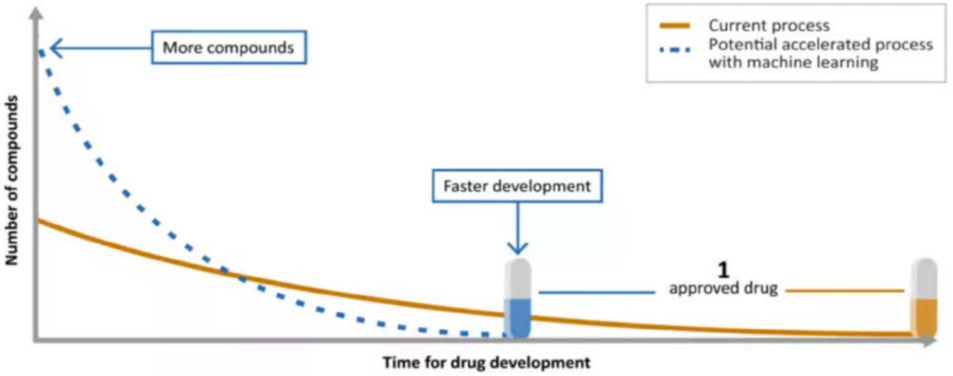


Figure 4. Graphical representation of the impact of machine learning on drug engineering and time for development. Source: https://www.gao.gov/blog/could-ai-help-create-new-medicines.

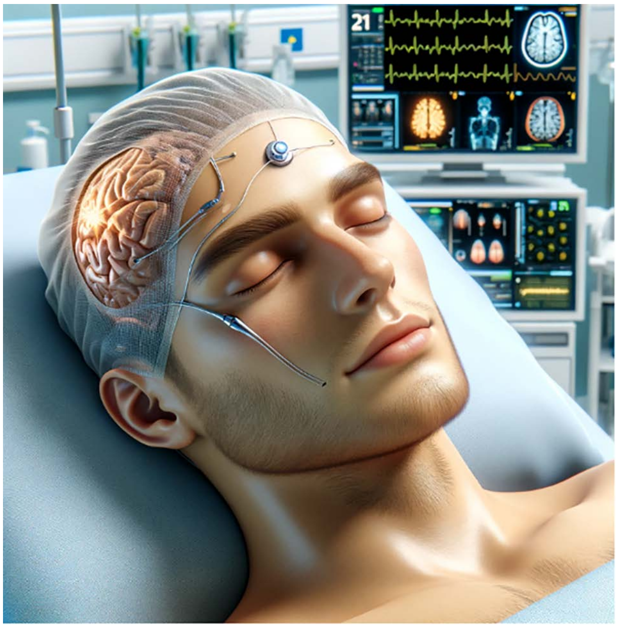


Figure 5. Representation of a digital neocortex with microelectronics and biological interface. Source: Synchron's flagship technology, the Stentrode.

triggering action potentials. A thorough understanding of the patient connectome will be required, and future DoA and pain monitoring might be achieved by controlling the parameters of this interface, or by mapping the regions of the brain that we want to become inactive to avoid relaying nociception. In this scenario, the idea of anesthesia, whether general or regional, could be an electronically controlled static state during which we perform the surgery, and during which the anesthesiologist focuses on organ function. In this scenario, DoA and pain monitors would become therapeutic and prescriptive, creating this static state, and monitoring the steadiness of this static state. Depending on the level of complexity of this new task, a new expert might have to be trained to overview the integrity of this new anesthesia, while the anesthesiologists, as we know them, solely focuses on reanimation and maintaining organ functions.

Figure 6. Tentative representation of a patient under hypnosis and immerged in virtual reality during "anesthesia induction" before a surgical intervention. Image generated by using Midjourney, an image generating software.

Hypnosis and Alternate Realities

In our last transformative scenario, we could transiently bring consciousness into alternate realities while we perform procedures on the physical body. This is the far end of a spectrum currently investigated with hypnosis and virtual reality (VR). Use of VR is already an established distraction strategy to reduce pain anxiety, notably in pediatrics.[86,87] Its use currently remains limited to minor procedures, including venous access, dental, burn, oncological care, and during regional anesthesia[87,88] but could be extended to more procedures, including those currently requiring general anesthesia (Figure 6). Depth of anesthesia could evolve towards a "level of immersion" in these alternate realities. In this hypothetical scenario, pain monitors would be simultaneously used to avoid extracting the patients from the alternate realities due to excessive stimuli from the "real world."

Although we have made significant progress in administering safer anesthetic practices to a majority of patients, the future now holds boundless possibilities for us to explore and embrace.

DISCLOSURES

Name: Pascal Laferrière-Langlois, MD, MSc, FRCPC.
Contribution: This author helped design the article, extract and review the relevant publications, draft the article, manage the coauthors, and edit the article.
Conflicts of Interest: P. Laferrière-Langlois has ownership interest in Divocco Medical (Montreal, Canada) and Divocco AI (Montreal, Canada).
Name: Louis Morisson, MD, MSc, DESAR.
Contribution: This author helped extract and review the relevant publications, draft the article, and critically review the article.
Conflicts of Interest: None.
Name: Sean Jeffries, MSc.
Contribution: This author helped extract and review the relevant publications, critically review the article, and create the figures.
Conflicts of Interest: None.
Name: Catherine Duclos, PhD.
Contribution: This author helped design the article, and critically review the article.
Conflicts of Interest: None.
Name: Fabien Espitalier, MD, PhD, DESAR.
Contribution: This author helped extract the relevant publications, draft the article, and critically review the article.
Conflicts of Interest: None.
Name: Philippe Richebé, MD, PhD, DESAR.
Contribution: This author helped extract and review the relevant publications, draft part of the article, and critically review the article.
Conflicts of Interest: P. Richebé has ownership interest in Divocco AI and received honoraria from several companies to

give educational lectures in the last 5 years (Medtronic Canada, Avirpharma, Merck Canada, Medasense Ltd).

This manuscript was handled by: Thomas M. Hemmerling, MSc, MD, DEAA.

REFERENCES

1. Pandit JJ. Monitoring (un)consciousness: the implications of a new definition of "anaesthesia". *Anaesthesia*. 2014;69:801–807.
2. Mukamel EA, Pirondini E, Babadi B, et al. A transition in brain state during propofol-induced unconsciousness. *J Neurosci*. 2014;34:839–845.
3. Sanders RD, Tononi G, Laureys S, Sleigh JW. Unresponsiveness not equal unconsciousness. *Anesthesiology*. 2012;116:946–959.
4. Pandit JJ. Isolated forearm - or isolated brain? Interpreting responses during anaesthesia - or "dysanaesthesia". *Anaesthesia*. 2013;68:995–1000.
5. Pandit JJ. Acceptably aware during general anaesthesia: "dysanaesthesia"--the uncoupling of perception from sensory inputs. *Conscious Cogn*. 2014;27:194–212.
6. MacIver MB, Kendig JJ. Anesthetic effects on resting membrane potential are voltage-dependent and agent-specific. *Anesthesiology*. 1991;74:83–88.
7. Nicoll RA, Madison DV. General anesthetics hyperpolarize neurons in the vertebrate central nervous system. *Science*. 1982;217:1055–1057.
8. Choi BM. Characteristics of electroencephalogram signatures in sedated patients induced by various anesthetic agents. *J Dent Anesth Pain Med*. 2017;17:241–251.
9. Bickford RG, Fleming N, Billinger T. Compression of EEG data. *Trans Am Neurol Assoc*. 1971;96:118–122.
10. Fleming RA, Smith NT. An inexpensive device for analyzing and monitoring the electroencephalogram. *Anesthesiology*. 1979;50:456–460.
11. Purdon PL, Sampson A, Pavone KJ, Brown EN. Clinical electroencephalography for anesthesiologists: Part I: background and basic signatures. *Anesthesiology*. 2015;123:937–960.
12. American Society of Anesthesiologists Task Force on Intraoperative A. Practice advisory for intraoperative awareness and brain function monitoring: a report by the american society of anesthesiologists task force on intraoperative awareness. *Anesthesiology*. 2006;104:847–864.
13. Sebel PS, Bowdle TA, Ghoneim MM, et al. The incidence of awareness during anesthesia: a multicenter United States study. *Anesth Analg*. 2004;99:833–839.
14. Pandit JJ, Cook TM, Jonker WR, O'Sullivan E; 5th National Audit Project (NAP5) of the Royal College of Anaesthetists and the Association of Anaesthetists of Great Britain and Ireland. A national survey of anaesthetists (NAP5 Baseline) to estimate an annual incidence of accidental awareness during general anaesthesia in the UK. *Anaesthesia*. 2013;68:343–353.
15. Odor PM, Bampoe S, Lucas DN, Moonesinghe SR, Andrade J, Pandit JJ; Pan-London Peri-operative Audit and Research Network (PLAN), for the DREAMY Investigators Group. Incidence of accidental awareness during general anaesthesia in obstetrics: a multicentre, prospective cohort study. *Anaesthesia*. 2021;76:759–776.
16. Avidan MS, Jacobsohn E, Glick D, et al. Prevention of intraoperative awareness in a high-risk surgical population. *N Engl J Med*. 2011;365:591–600.
17. Mashour GA, Shanks A, Tremper KK, et al. Prevention of intraoperative awareness with explicit recall in an unselected surgical population: a randomized comparative effectiveness trial. *Anesthesiology*. 2012;117:717–725.
18. Messina AG, Wang M, Ward MJ, et al. Anaesthetic interventions for prevention of awareness during surgery. *Cochrane Database Syst Rev*. 2016;10:CD007272.
19. Zhang C, Xu L, Ma YQ, et al. Bispectral index monitoring prevent awareness during total intravenous anesthesia: a prospective, randomized, double-blinded, multi-center controlled trial. *Chin Med J (Engl)*. 2011;124:3664–3669.
20. Renaud-Roy E, Morisson L, Brulotte V, et al. Effect of combined intraoperative use of the Nociception Level (NOL) and bispectral (BIS) indexes on desflurane administration. *Anaesth Crit Care Pain Med*. 2022;41:101081.
21. Lewis SR, Pritchard MW, Fawcett LJ, Punjasawadwong Y. Bispectral index for improving intraoperative awareness and early postoperative recovery in adults. *Cochrane Database Syst Rev*. 2019;9:CD003843.
22. Evered L, Silbert B, Knopman DS, et al; Nomenclature Consensus Working Group. Recommendations for the nomenclature of cognitive change associated with anaesthesia and surgery-2018. *Br J Anaesth*. 2018;121:1005–1012.
23. Chan MT, Cheng BC, Lee TM, Gin T, Group CT. BIS-guided anesthesia decreases postoperative delirium and cognitive decline. *J Neurosurg Anesthesiol*. 2013;25:33–42.
24. Radtke FM, Franck M, Lendner J, Kruger S, Wernecke KD, Spies CD. Monitoring depth of anaesthesia in a randomized trial decreases the rate of postoperative delirium but not postoperative cognitive dysfunction. *Br J Anaesth*. 2013;110(Suppl 1):i98–i105.
25. Sieber FE, Zakriya KJ, Gottschalk A, et al. Sedation depth during spinal anesthesia and the development of postoperative delirium in elderly patients undergoing hip fracture repair. *Mayo Clin Proc*. 2010;85:18–26.
26. Chan MTV, Hedrick TL, Egan TD, et al. American society for enhanced recovery and perioperative quality initiative joint consensus statement on the role of neuromonitoring in perioperative outcomes: electroencephalography. *Anesth Analg*. 2020;130:1278–1291.
27. Evered LA, Chan MTV, Han R, et al. Anaesthetic depth and delirium after major surgery: a randomised clinical trial. *Br J Anaesth*. 2021;127:704–712.
28. Whitlock EL, Gross ER, King CR, Avidan MS. Anaesthetic depth and delirium: a challenging balancing act. *Br J Anaesth*. 2021;127:667–671.
29. Wildes TS, Mickle AM, Ben Abdallah A, et al; ENGAGES Research Group. Effect of electroencephalography-guided anesthetic administration on postoperative delirium among older adults undergoing major surgery: the ENGAGES randomized clinical trial. *JAMA*. 2019;321:473–483.
30. Rampil IJ. A primer for EEG signal processing in anesthesia. *Anesthesiology*. 1998;89:980–1002.
31. Sebel PS, Lang E, Rampil IJ, et al. A multicenter study of bispectral electroencephalogram analysis for monitoring anesthetic effect. *Anesth Analg*. 1997;84:891–899.
32. Schultz B, Grouven U, Schultz A. Automatic classification algorithms of the EEG monitor narcotrend for routinely recorded EEG data from general anaesthesia: a validation study. *Biomed Tech (Berl)*. 2002;47:9–13.
33. Drover DR, Lemmens HJ, Pierce ET, et al. Patient state index: titration of delivery and recovery from propofol, alfentanil, and nitrous oxide anesthesia. *Anesthesiology*. 2002;97:82–89.
34. Prichep LS, Gugino LD, John ER, et al. The patient state index as an indicator of the level of hypnosis under general anaesthesia. *Br J Anaesth*. 2004;92:393–399.
35. Bruhn J, Ropcke H, Hoeft A. Approximate entropy as an electroencephalographic measure of anesthetic drug effect during desflurane anesthesia. *Anesthesiology*. 2000;92:715–726.

36. Viertio-Oja H, Maja V, Sarkela M, et al. Description of the entropy algorithm as applied in the datex-ohmeda S/5 entropy module. *Acta Anaesthesiol Scand*. 2004;48:154–161.
37. Gorges M, West NC, Cooke EM, et al. Evaluating NeuroSENSE for assessing depth of hypnosis during desflurane anesthesia: an adaptive, randomized-controlled trial. *Can J Anaesth*. 2020;67:324–335. Une evaluation du moniteur NeuroSENSE pour mesurer la profondeur de l'hypnose pendant une anesthesie au desflurane: une etude randomisee controlee adaptable.
38. Zikov T, Bibian S, Dumont GA, Huzmezan M, Ries CR. Quantifying cortical activity during general anesthesia using wavelet analysis. *IEEE Trans Biomed Eng*. 2006;53:617–632.
39. Heneghan CP, Thornton C, Navaratnarajah M, Jones JG. Effect of isoflurane on the auditory evoked response in man. *Br J Anaesth*. 1987;59:277–282.
40. Schwender D, Conzen P, Klasing S, Finsterer U, Poppel E, Peter K. The effects of anesthesia with increasing end-expiratory concentrations of sevoflurane on midlatency auditory evoked potentials. *Anesth Analg*. 1995;81:817–822.
41. Kreuer S, Bruhn J, Larsen R, Hoepstein M, Wilhelm W. Comparison of alaris AEP index and bispectral index during propofol-remifentanil anaesthesia. *Br J Anaesth*. 2003;91:336–340.
42. Gajraj RJ, Doi M, Mantzaridis H, Kenny GN. Analysis of the EEG bispectrum, auditory evoked potentials and the EEG power spectrum during repeated transitions from consciousness to unconsciousness. *Br J Anaesth*. 1998;80:46–52.
43. Hemmerling TM, Salhab E, Aoun G, Charabati S, Mathieu PA. The 'Analgoscore': a novel score to monitor intraoperative pain and its use for remifentanil closed-loop application. 2007 IEEE International Conference on Systems, Man and Cybernetics, Montreal, QC, Canada, 2007, pp 1494-1499, doi: 10.1109/ICSMC.2007.4414030
44. Edry R, Recea V, Dikust Y, Sessler DI. Preliminary intraoperative validation of the nociception level index: a noninvasive nociception monitor. *Anesthesiology*. 2016;125:193–203.
45. Logier R, Jeanne M, Tavernier B, De Jonckheere J. Pain/analgesia evaluation using heart rate variability analysis. *Conf Proc IEEE Eng Med Biol Soc*. 2006;2006:4303–4306.
46. Martini CH, Boon M, Broens SJ, et al. Ability of the nociception level, a multiparameter composite of autonomic signals, to detect noxious stimuli during propofol-remifentanil anesthesia. *Anesthesiology*. 2015;123:524–534.
47. Renaud-Roy E, Stockle PA, Maximos S, et al. Correlation between incremental remifentanil doses and the Nociception Level (NOL) index response after intraoperative noxious stimuli. *Can J Anaesth*. 2019;66:1049–1061. Correlation entre des doses croissantes de remifentanil et la reponse de l'indice de nociception NOL apres des stimuli peroperatoires douloureux.
48. Stockle PA, Julien M, Issa R, et al. Validation of the PMD100 and its NOL index to detect nociception at different infusion regimen of remifentanil in patients under general anesthesia. *Minerva Anestesiol*. 2018;84:1160–1168.
49. Coulombe MA, Decary E, Maximos S, et al. Assessing the antinociceptive effect of nitrous oxide to tetanic stimulation in anaesthetised patients with new intra-operative nociception monitors: an observational study. *Eur J Anaesthesiol*. 2021;38:512–523.
50. Martinez-Vazquez P, Jensen EW. Different perspectives for monitoring nociception during general anesthesia. *Korean J Anesthesiol*. 2022;75:112–123.
51. Pandit JJ. An observational study of the "isolated forearm technique" in unparalysed, spontaneously breathing patients. *Anaesthesia*. 2015;70:1369–1374.
52. Pandit JJ, Russell IF, Wang M. Interpretations of responses using the isolated forearm technique in general anaesthesia: a debate. *Br J Anaesth*. 2015;115:i32–i45.
53. Jensen EW, Valencia JF, Lopez A, et al. Monitoring hypnotic effect and nociception with two EEG-derived indices, qCON and qNOX, during general anaesthesia. *Acta Anaesthesiol Scand*. 2014;58:933–941.
54. Charier D, Vogler MC, Zantour D, et al. Assessing pain in the postoperative period: analgesia nociception index(TM) versus pupillometry. *Br J Anaesth*. 2019;123:e322–e327.
55. Vinclair M, Roudaud F, Francony G, Payen JF. Quantitative pupillometry to assess nociception in a sedated patient with hemispheric cerebral infarction. *Eur J Anaesthesiol*. 2017;34:316–318.
56. Fratino S, Peluso L, Talamonti M, et al. Evaluation of nociception using quantitative pupillometry and skin conductance in critically ill unconscious patients: a pilot study. *Brain Sci*. 2021;11:109.
57. Ledowski T, Pascoe E, Ang B, et al. Monitoring of intraoperative nociception: skin conductance and surgical stress index versus stress hormone plasma levels. *Anaesthesia*. 2010;65:1001–1006.
58. Roquet F, Guezouli L, Wachowska B, et al. Comparison of three stimulation sites on the pupillary dilation reflex amplitude evoked by a standardized noxious test. *Anaesth Crit Care Pain Med*. 2017;36:365–369.
59. Larson MD, Kurz A, Sessler DI, Dechert M, Bjorksten AR, Tayefeh F. Alfentanil blocks reflex pupillary dilation in response to noxious stimulation but does not diminish the light reflex. *Anesthesiology*. 1997;87:849–855.
60. Larson MD, Sessler DI, Ozaki M, McGuire J, Schroeder M. Pupillary assessment of sensory block level during combined epidural/general anesthesia. *Anesthesiology*. 1993;79:42–48.
61. Sabourdin N, Barrois J, Louvet N, et al. Pupillometry-guided intraoperative remifentanil administration versus standard practice influences opioid use: a randomized study. *Anesthesiology*. 2017;127:284–292.
62. Barvais L, Engelman E, Eba JM, Coussaert E, Cantraine F, Kenny GN. Effect site concentrations of remifentanil and pupil response to noxious stimulation. *Br J Anaesth*. 2003;91:347–352.
63. Bourgeois E, Sabourdin N, Louvet N, Donette FX, Guye ML, Constant I. Minimal alveolar concentration of sevoflurane inhibiting the reflex pupillary dilatation after noxious stimulation in children and young adults. *Br J Anaesth*. 2012;108:648–654.
64. Constant I, Nghe MC, Boudet L, et al. Reflex pupillary dilatation in response to skin incision and alfentanil in children anaesthetized with sevoflurane: a more sensitive measure of noxious stimulation than the commonly used variables. *Br J Anaesth*. 2006;96:614–619.
65. Isnardon S, Vinclair M, Genty C, Hebrard A, Albaladejo P, Payen JF. Pupillometry to detect pain response during general anaesthesia following unilateral popliteal sciatic nerve block: a prospective, observational study. *Eur J Anaesthesiol*. 2013;30:429–434.
66. Ruetzler K, Montalvo M, Rotem OM, et al. Generalizability of nociception level as a measure of intraoperative nociceptive stimulation: a retrospective analysis. *Acta Anaesthesiol Scand*. 2023;67:1187–1193.
67. Espitalier F, Idrissi M, Fortier A, et al. Impact of Nociception Level (NOL) index intraoperative guidance of fentanyl administration on opioid consumption, postoperative pain scores and recovery in patients undergoing gynecological laparoscopic surgery a randomized controlled trial. *J Clin Anesth*. 2021;75:110497.

68. Ghiyasinasab M, Morisson L, Laferriere-Langlois P, et al. Identification of the intraoperative antinociceptive effect of intravenous fentanyl using the Nociception Level (NOL) index versus clinical parameters in patients undergoing gynecological laparoscopic surgery: a secondary analysis of the NOLGYN study. *Anaesth Crit Care Pain Med*. 2022;41:101102.
69. Bollag L, Jelacic S, Delgado Upegui C, Wu C, Richebe P. The nociception level index (NOL) response to intubation and incision in patients undergoing video-assisted thoracoscopic surgery (VATS) with and without thoracic epidural analgesia a pilot study. *F1000Res*. 2018;7:875.
70. Meijer FS, Martini CH, Broens S, et al. Nociception-guided versus standard care during remifentanil-propofol anesthesia: a randomized controlled trial. *Anesthesiology*. 2019;130:745–755.
71. Upton HD, Ludbrook GL, Wing A, Sleigh JW. Intraoperative "analgesia nociception index"-guided fentanyl administration during sevoflurane anesthesia in lumbar discectomy and laminectomy: a randomized clinical trial. *Anesth Analg*. 2017;125:81–90.
72. Bergmann I, Gohner A, Crozier TA, et al. Surgical pleth index-guided remifentanil administration reduces remifentanil and propofol consumption and shortens recovery times in outpatient anaesthesia. *Br J Anaesth*. 2013;110:622–628.
73. Chen X, Thee C, Gruenewald M, et al. Comparison of surgical stress index-guided analgesia with standard clinical practice during routine general anesthesia: a pilot study. *Anesthesiology*. 2010;112:1175–1183.
74. Meijer FS, Niesters M, van Velzen M, et al. Does nociception monitor-guided anesthesia affect opioid consumption? A systematic review of randomized controlled trials. *J Clin Monit Comput*. 2020;34:629–641.
75. Abad Torrent A, Rodriguez Bustamante V, Carrasco Fons N, Roca Tutusaus FJ, Blanco Vargas D, Gonzalez Garcia C. The use of pupillometry as monitoring of intraoperative analgesia in the consumption of analgesics during the first 12 hours after surgery. *Rev Esp Anestesiol Reanim*. 2016;63:253–260.
76. Boselli E, Bouvet L, Begou G, et al. Prediction of immediate postoperative pain using the analgesia/nociception index: a prospective observational study. *Br J Anaesth*. 2014;112:715–721.
77. Ledowski T, Burke J, Hruby J. Surgical pleth index: prediction of postoperative pain and influence of arousal. *Br J Anaesth*. 2016;117:371–374.
78. Ledowski T, Schneider M, Gruenewald M, Goyal RK, Teo SR, Hruby J. Surgical pleth index: prospective validation of the score to predict moderate-to-severe postoperative pain. *Br J Anaesth*. 2019;123:e328–e332.
79. Ledowski T, Schlueter P, Hall N. Nociception level index: do intra-operative values allow the prediction of acute postoperative pain? *J Clin Monit Comput*. 2022;36:349–354.
80. Morisson L, Nadeau-Vallee M, Espitalier F, et al. Prediction of acute postoperative pain based on intraoperative nociception level (NOL) index values: the impact of machine learning-based analysis. *J Clin Monit Comput*. 2023;37:337–344.
81. Kang J, Fang C, Li Y, et al. Effects of qCON and qNOX-guided general anaesthesia management on patient opioid use and prognosis: a study protocol. *BMJ Open*. 2023;13:e069134.
82. Clairoux A, Soucy-Proulx M, Pretto F, et al. Intrapandemic regional anesthesia as practice: a historical cohort study in patients undergoing breast cancer surgery. *Can J Anaesth*. 2022;69:485–493. L'anesthesie regionale en tant que pratique intrapandemique: une etude de cohorte historique chez des patientes beneficiant d'une chirurgie de cancer du sein.
83. Lonsdale H, Gray GM, Ahumada LM, Yates HM, Varughese A, Rehman MA. The perioperative human digital twin. *Anesth Analg*. 2022;134:885–892.
84. Farzin A, Etesami SA, Quint J, Memic A, Tamayol A. Magnetic nanoparticles in cancer therapy and diagnosis. *Adv Healthc Mater*. 2020;9:e1901058.
85. Nan X, Zhang X, Liu Y, Zhou M, Chen X, Zhang X. Dual-targeted multifunctional nanoparticles for magnetic resonance imaging guided cancer diagnosis and therapy. *ACS Appl Mater Interfaces*. 2017;9:9986–9995.
86. Tas FQ, van Eijk CAM, Staals LM, Legerstee JS, Dierckx B. Virtual reality in pediatrics, effects on pain and anxiety: a systematic review and meta-analysis update. *Paediatr Anaesth*. 2022;32:1292–1304.
87. Eijlers R, Utens E, Staals LM, et al. Systematic review and meta-analysis of virtual reality in pediatrics: effects on pain and anxiety. *Anesth Analg*. 2019;129:1344–1353.
88. Alaterre C, Duceau B, Sung Tsai E, et al. Virtual Reality for PEripheral Regional Anesthesia (VR-PERLA Study). *J Clin Med*. 2020;9:215.