NeuroSENSE® Monitor with WAV$_{CNS}$ Cortical Quantifier:

A Deterministic Approach to EEG Analysis

NeuroWave Systems Inc., Beachwood, OH, USA

ABSTRACT – Brain function monitoring has been shown to provide additional insight for the assessment and optimization of the anesthetic drugs administration.

Since 2003, NeuroWave Systems Inc. has been developing the NeuroSENSE®, a bilateral monitor of patient's brain activity for the anesthesia specialty. The NeuroSENSE incorporates the WAV$_{CNS}$ technology for automated EEG quantification.

The WAV$_{CNS}$ (Wavelet-based Anesthetic Value for Central Nervous System) utilizes wavelet analysis of the normalized EEG signal in the gamma frequency band. This EEG quantifier was intentionally developed for future use in closed-loop anesthesia delivery systems. As such, the WAV$_{CNS}$ method employs a deterministic algorithm, which yields a delay-free, linear and time-invariant quantifier of cortical activity. The WAV$_{CNS}$ algorithm has been fully disclosed in [24].

This white paper provides interested readers with more information about the WAV$_{CNS}$ technology, the NeuroSENSE monitor and its use.

With the discovery of the effect of cyclopropane on brainwaves in the late 1930's came the realization that electroencephalogram (EEG) signals could be used effectively to monitor the effect of anesthetic drugs. Since then, unlocking the hidden message behind the EEG waveforms has been the subject of intense research.

Progress in the use of EEG to quantify anesthetic drug effect happened rapidly, with the first EEG-based closed-loop delivery system developed and tested in the early 1950's by Bickford and his colleagues. Yet, powered by a simplistic burst suppression detection algorithm, the burgeoning technology did not expand beyond the Mayo Clinic and remained a technological curiosity.

For the following 20 years, researchers used different time series analysis techniques to determine anesthetic depth. But none of these techniques could be used reliably across patients and anesthetic drug regimens to provide a viable quantifier.

In the mid-1970's, progress in computing science enabled researchers to use the spectral analysis in order to extract frequency information from the EEG signal. This opened a new era for the use of EEG in anesthesia, which culminated with the development of the Spectral Edge Frequency and Median Edge Frequency indexes. Yet, once again, repeatability of these measures was limited between patients and across anesthetic regimens.

It is only in the early 1990's that changes in both time and frequency content of the EEG signals were found to be complementary. For instance, with increasing drug concentration, certain EEG frequency components tend to synchronize by shifting their phase. Larger and more obvious changes in the EEG amplitude occur only at higher concentrations. This observation led to the use of bispectral analysis to capture these early phase shifts. The bispectral variables best able to discriminate between different sedation levels were supplemented by traditional power spectral measures. These features were further combined using multivariate statistical modeling to form a single, composite index bounded between 0 and 100. The Bispectral Index[1] provides an interpretation of the EEG waveform based on a learn-and-test approach using a training database of EEG segments and associated clinically derived sedation levels.

[1] The Bispectral Index is a trademark of a Medtronic company.

Clinical Utility

Since the commercialization of the first brain function monitor for anesthesia in the late 1990's, mounting evidence has demonstrated the clinical utility of such monitors. When used as a supplement to the standard of care, brain function monitoring provides greater insight into drug effect and sedation levels, thus helping the clinician to deliver adequate anesthesia tailored to the specific needs of the patient and the procedure, and in turn achieve improved clinical outcomes.

Anesthetic underdosing can result in intra-operative awareness and memory formation, which leads to anxiety, sleep disturbance and a high risk of developing PTSD. Intra-operative awareness is often cited as one of the top medical errors and remains a concern to patients undergoing surgical procedures [31]. Clinical evidence [11] has shown that the incidence of intra-operative awareness can be reduced by a factor of 5 when brain function monitoring is employed.

Using such monitors to help avoid this complication, particularly in paralyzed patients, is considered to be an important factor for patient safety. This has led several practice advisories to revise and update their clinical guidelines related to anesthesia management.

For example, as of September 2021, the Association of Anaesthetists [4] published updated guidelines for standards of monitoring during anesthesia and recovery, advising that '*processed electroencephalogram (pEEG) monitoring should be used when total intravenous anesthesia (TIVA) is administered together with a neuromuscular blocking (NMB) drug*' and that it '*should be considered during other anesthetic techniques including inhalation anaesthesia and for the high-risk patient*'.

In February 2022, the Anesthesia Patient Safety Foundation (APSF), advised [2] that '*whenever a NMB agent is administered during inhalational anesthesia, if 0.7 MAC cannot be maintained, an EEG-based monitor of anesthetic depth should be used and an inadequate anesthetic depth alarm limit set if available*.' Furthermore, the APSF explicitly states that '*an EEG-based monitor for unconsciousness (depth of anesthesia monitor) is required to reduce the likelihood of awareness whenever total intravenous anesthesia is combined with the administration of NMB agents*.'

Updated guidelines from the Neurocritical Care Society published in July 2022 [1] advise that '*all sedated patients (paralyzed or nonparalyzed) unfit for clinical evaluation would benefit from depth-of-sedation (DOS) monitoring (strong consensus) after a specific training program has been performed by the ICU staff*.'

The most recent guidelines come from the European Society of Anaesthesiology in February 2024 [36], stating that *'We suggest Index-based EEG monitoring depth of anaesthesia guidance to decrease the risk of POD'* and *'We suggest multiparameter, intraoperative EEG monitoring (burst suppression, density spectral array, DSA) during anaesthesia to decrease the risk of POD.'*

Conversely, maintaining patients at very deep anesthetic levels has been shown to result in post-operative nausea and vomiting, delayed recovery and lengthier stays in post-anesthesia care units, as well as a higher 1-year post-operative mortality rate. Besides having a substantial impact on the quality of life, these adverse events can directly impact healthcare costs for clinical institutions.

More importantly, overdosing may also negatively impact overall brain health, as it has been correlated with a greater occurrence of post-operative delirium (POD) and long-term post-operative cognitive decline (POCD). While subjective clinical tests like the RASS (Richmond Agitation Sedation Scale) have been shown to miss overdosing and suppression that were detected by an EEG-based monitor to which the clinicians were blinded [30], studies of brain function monitoring support the hypothesis that pEEG use can help promote optimal brain health by decreasing post-operative delirium. Independent studies by Chan *et al.* [19] and Radtke *et al.* [18] showed in 2013 that EEG-guided anesthesia significantly decreases postoperative delirium. These findings were echoed in 2019, by a large 1600-patient study [6] exploring the ability to predict POD with combined NeuroSENSE and near-infrared spectroscopy monitoring during cardiac interventions. The authors reported that having experienced high magnitudes of EEG suppression was significantly associated with increased risk of POD. A more recent large multicenter randomized clinical trial [3] also revealed that maintaining patients purposely at a deep anesthetic level results in a significant increase in incidence of both POD and long-term POCD. In 2023 a retrospective study of 7318 procedures found that using interoperative pEEG significantly reduced incidence of POD in the ≥75 years population from 5.1% to 1.56%, the population most likely to experience POD [32].

On the contrary, in February 2019, JAMA published the results of the ENGAGES randomized clinical trial [8] on the effects of EEG-guided anesthetic administration on POD among older adults undergoing major surgery. In this study, EEG-guided anesthetic administration, compared with usual care, did not decrease the incidence of postoperative delirium. However, many members of the anesthesia community have since voiced their concerns about the trial, citing insufficient POD screening, ineffective EEG guidance and misappropriate presentation of results [33],[34],[35]. The value of pEEG in reducing POD remains a subject of clinical research and debate.

In conclusion, the latest research and the backing by international advisory boards make a strong case for the use of brain function monitoring in anesthesia to mitigate

adverse events and improve patient safety. When used in conjunction with the usual standard of care, these technologies can serve as a welcomed tool in the armamentarium of the anesthesiologist, providing an additional, more direct means for assessing drug effect and patient state. With this greater insight, the clinicians have a better ability to customize anesthetic drug delivery according to the patient's unique needs and thus achieve optimal clinical outcomes.

The Need and Motivation for a Deterministic Approach to Cortical Activity Quantification

In 2001, a research group at the University of British Columbia (UBC - Vancouver, Canada) was formed to introduce the benefits of industrial process control technologies to the anesthesia practice. The research team was composed of experts and scientists in process control, anesthesia, pharmacology and therapeutics. One of the main goals of the group was to assess the feasibility of a reliable closed-loop anesthesia drug delivery system and to establish the path for its future development.

The success of any closed-loop system is intimately linked to the performance of the feedback sensor used to measure the controlled output. In the case of anesthesia delivery, an EEG-based monitor that quantifies the physiological effect of the administered drug can be used as a sensor. However, the industrial process control theory shows that interpretative feedback sensors are difficult to use reliably since they often introduce discontinuities, variable time delays, and other non-linearities. For an EEG-based monitor, this can result in an inaccurate and/or delayed interpretation during sudden changes in cortical activity due to, e.g., a sudden change in drug administration or change in surgical stimulation. As a result, when regulating the patient's cortical state, the control action (i.e., adjustments in anesthetic delivery) needs to be slowed down in order to account for the limitations in the sensing technology. Consequently, the overall regulation of anesthetic delivery would be less than optimal. A non-linear sensor further implies that the stability of the control system cannot be evaluated mathematically and hence, a large effort in empirical tuning, testing and validation is required. Thus, future evolutions of automated anesthesia drug delivery systems are limited without first improving the feedback technology used for sensing, i.e., the EEG-based monitor that quantifies the physiological effect of the administered drug.

In addition, the limitations of interpretative indexes for the future closed-loop systems may also affect their clinical performance when used as a guide for titration of anesthetics, or to assess the patient's anesthetic state. The UBC group thus concluded that a better suited cortical quantifier should be based on a deterministic, instead of interpretative, approach to EEG analysis, where multiple features and their combination into a composite index should be avoided. In this context, a deterministic approach refers to a method of computation that always produces the same result for a given EEG segment. Therefore, for a given EEG segment, the output of a deterministic computation method is fully predictable.

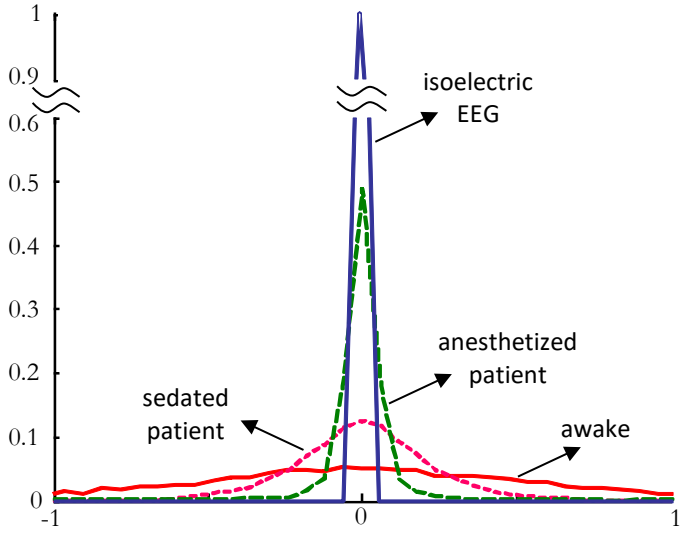

Fig. 1 – Probability Density Functions (PDFs) of EEG waveforms obtained from patients at different levels of anesthetic-induced cortical depression. Note how the shape of the function changes in a predictable fashion as the anesthetic drug effect changes, from flat and wide to sharp and narrow.

The WAV_{CNS} Cortical Quantifier

In the late 1990's, a new signal processing approach that could simultaneously track changes in both time and frequency was developed and made practical for real-time implementation: Wavelet analysis. Since then, this methodology has been applied to a wide variety of biomedical applications and has proven to be particularly well suited for the analysis of spontaneous EEG activity. In October 2001, the UBC group published a first conference paper [29] describing the new Wavelet-based Anesthetic Value (WAV). This early publication was followed by a comprehensive manuscript in 2006 [24], where the algorithm was fully disclosed.

The major finding of the UBC group was that the wavelet information associated with the gamma[2] frequencies (32-64 Hz) of the normalized[3] EEG signal can be statistically represented in a form of a Probability Density Function

[2] In fact, recent research has associated EEG gamma frequencies with mechanisms of conscious awareness.

[3] Normalization of EEG signal removes the influence of amplitude from signal analysis, and also incorporates other non-gamma frequency components into the analysis.

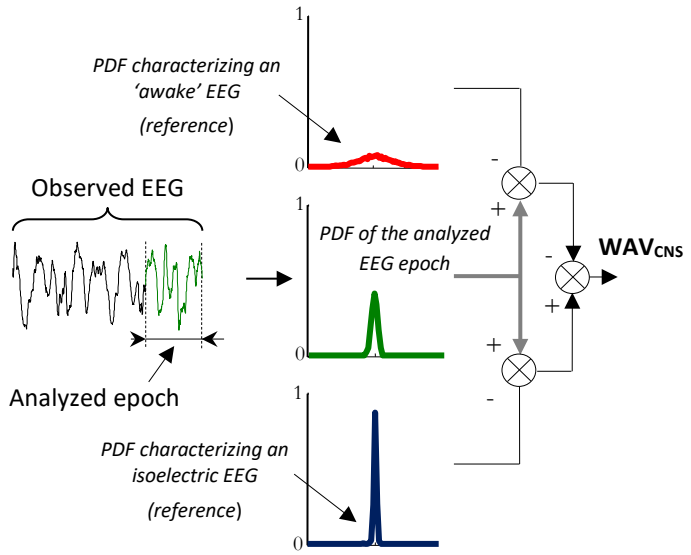

Fig. 2 – Overview of the WAV_{CNS} algorithm.

(PDF), whose shape evolves from a flat and wide envelope to a sharp and narrow spike, see **Fig. 1**.

The flat and wide envelope is typical for EEG signals acquired from fully conscious and awake subjects, while the sharp and narrow spike represents an isoelectric EEG signal (i.e., when all cortical activity is fully suppressed). Furthermore, the evolution between these two shapes is consistent with an increasing anesthetic drug effect on the cortical state and is fully reversible when the drug plasma concentration decreases. In order to quantify the cortical state based on a given EEG segment, its corresponding PDF is compared with the two reference PDFs: awake and isoelectric, see **Fig. 2**.

A convenient characteristic of PDFs is that the area under the curve is always equal to 1. Thus, the comparison between the observed PDF and the two reference PDFs yields a bounded and dimensionless index, the WAV_{CNS}, which expresses how far the observed EEG has evolved from either reference endpoint.

One of the important advantages of the WAV_{CNS} method is that it can easily be implemented in real time, based on very short EEG segments. The ability of the wavelet analysis to characterize changes in both time and frequency enables the WAV_{CNS} quantifier to rapidly capture fast changes in cortical activity, which more traditional spectral analyses are typically unable to track timely. The current algorithm uses a 1-second EEG epoch resulting in a per-second actualization rate of the WAV_{CNS} quantifier that instantly responds to the changes in patient state. A post-analysis trending filter is further applied to the WAV_{CNS} in order to attenuate the measurement noise and extract the trend. An advanced trending filter was designed to provide a high frequency noise rejection superior to averaging filters, resulting in a smoother trend.

The WAV_{CNS} index is further scaled into the 100-0 range familiar to clinicians, where 100 denotes a brain state consistent with an awake patient, and 0 denotes the total and prolonged absence of cortical activity.

The WAV_{CNS} Scale

Initial clinical data suggested that the WAV_{CNS} scale is similar to that of the BIS index (trademark of a Medtronic company) [24],[62]. For instance, a 2002 clinical study involving 25 knee surgery cases, which aimed at comparing the WAV_{CNS} and BIS technologies, revealed that the WAV_{CNS} scale closely agrees to that of BIS (v.3.4), see for example **Fig. 3**. The correlation coefficient across all patients included in the study was 0.969 [24]. The Bland-Altman analysis performed on steady state data points [62] further suggested the equivalence of the two scales. The bias between the two indexes was 1.4, and the 95% confidence intervals were [-9.8; +12.5].

Yet, it should be noted that differences in the way the BIS and WAV_{CNS} algorithms handle burst suppression can result in lower BIS values compared to WAV_{CNS} [12]. Specifically, suppression ratios between 5 and 40 typically result in a BIS value between 30 and 35, see **Fig 4**. This relationship was first identified by Bruhn and his colleagues in 2000. The authors concluded that an increase in anesthetic drug effect resulting in an increase in suppression up to 40% was not adequately reflected by the BIS. In contrast, the WAV_{CNS} relationship with SR exhibits a more desirable, monotonously decreasing characteristic, thereby better capturing the deepening of the drug effect in cases of low suppression [46].

The WAV_{CNS} clinical guidelines were derived on additional clinical data [45] and are presented in **Fig. 5**. WAV_{CNS} values under 60 are associated with an extremely low probability of consciousness. Values between 40-60 are additionally associated with a very low probability of burst suppression, whereas values under 40 are associated with an increasing probability of significant suppression levels.

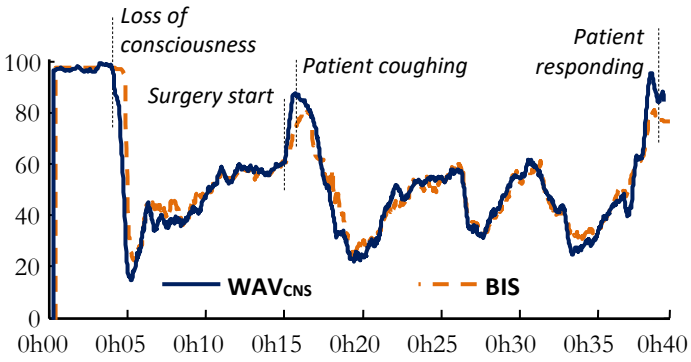

Fig. 3 – Example of the WAV_{CNS} and BIS (v.3.4) time courses in an arthroscopy case (adapted from [62]).

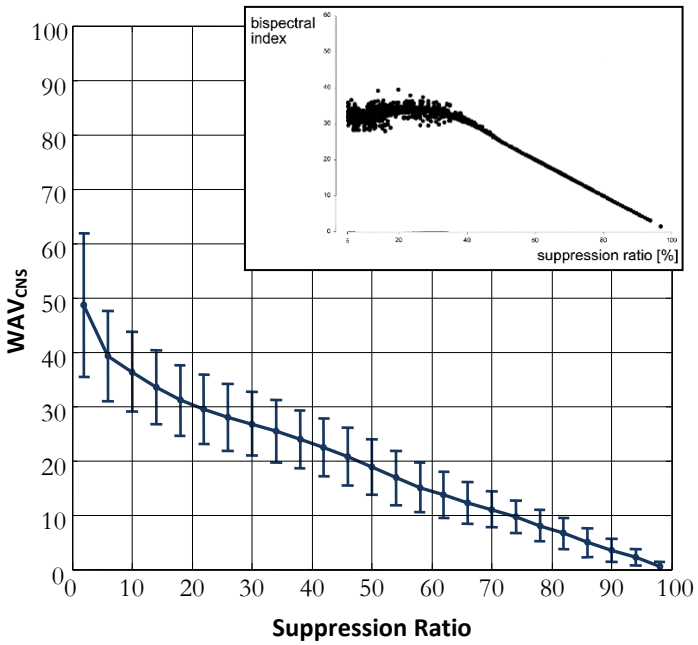

Fig. 4 – Effect of suppression on the WAV_{CNS} (mean index value ± standard deviation) (adapted from [46]). The linearly decreasing relationship comes in contrast to the BIS vs. SR relationship derived by Bruhn and colleagues (adapted from Bruhn et al., "Bispectral index (BIS) and burst suppression: revealing a part of the BIS algorithm", in J. Clin. Monitoring & Control, 2000). Increasing anesthetic effect resulting in an increase in burst suppression in the 5-40% range is not adequately reflected by the BIS.

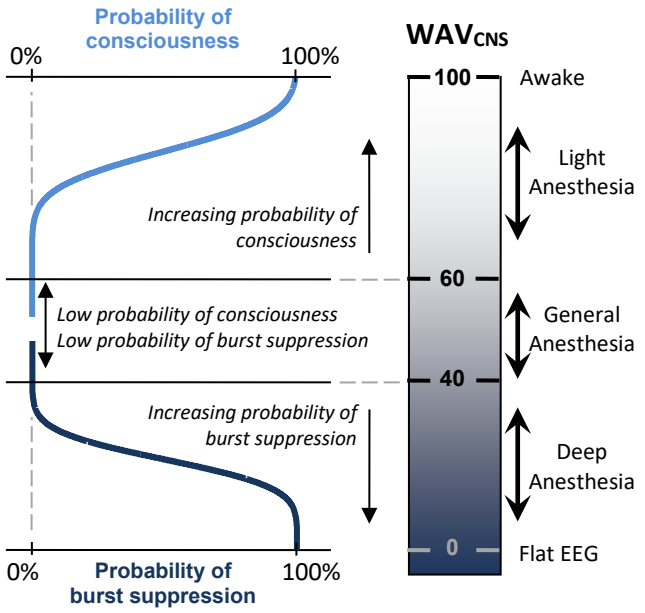

Fig. 5 – WAV_{CNS} Scale. An appropriate WAV_{CNS} range for general anesthesia is between 40 and 60 as within this range there is a very low probability of a patient being either awake or in deep anesthetic state as characterized by the presence of significant burst suppression (adapted from [45]).

The WAV_{CNS} range of 40-60 thus appears to be adequate for general anesthesia.

A randomized clinical trial sponsored by NeuroWave confirmed the above findings and demonstrated that the WAV_{CNS} is an effective monitor of the hypnotic effect of anesthetic drugs, such as propofol and inhaled anesthetics [5].

The index discriminates effectively between clinical endpoints such as loss and return of consciousness, when anesthetic agents such as propofol or desflurane are used. Values under 60 are strongly associated with unconsciousness during both the induction and emergence time periods. The WAV_{CNS} further correlates with inhaled anesthetic dosing. The study shows that the WAV_{CNS} decreases with increasing desflurane dosing, in the MAC range under 1.2. At higher MAC values, the WAV_{CNS} vs. MAC slope flattens, which limits its utility to titrate such concentrations of inhaled anesthetic. Note, however, that at such dosing, the index is well below the WAV_{CNS} range of 40-60. Also, a similar plateau effect has been reported with inhaled agents using other legally marketed devices.

While clinical data support the WAV_{CNS} range of 40-60 to be adequate for general anesthesia, it is important to note that the appropriate cortical depth target is always a function of the patient, the requirements of the surgery and the intensity of the surgical stimuli.

A Delay-Free Response

An important distinguishing factor of the WAV_{CNS} quantifier is the deterministic approach used in its derivation. The main innovation is the wavelet-based quantification of the cortical activity where each segment of EEG is processed using a unique method of computation that does not depend on the current or past values of the patient state. This approach inherently avoids any interpretation of the EEG signal via expert-type systems, such as neural network classifier, weight-based discriminant analysis, fuzzy logic, etc. Consequently, regardless the current status of the patient state, any rapid cortical change will start to be reflected by the WAV_{CNS} within 1 second of the change onset. As such, the algorithm does not introduce delay in the quantification of the patient's cortical state.

Clinically, the instantaneous response of the WAV_{CNS} can be easily observed, e.g., during anesthesia induction, where the patient's cortical state evolves rapidly from conscious state to a level suitable for airway management, see **Fig. 6**. The UBC group has further shown that the WAV_{CNS} quantifier leads the BIS (v.3.4) index during both loss and

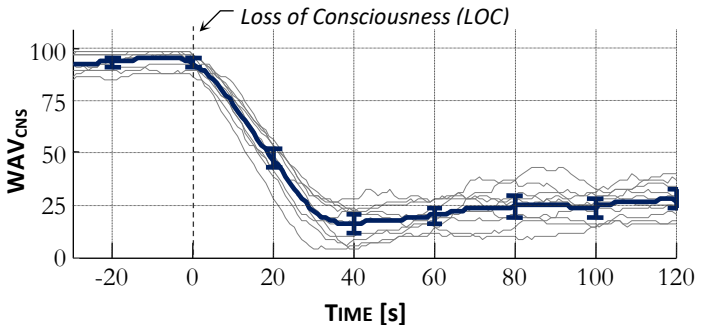

Fig. 6 – WAV_{CNS} time courses during induction (adapted from [24]).

return of consciousness by a significant margin of 15 and 30 seconds on average respectively, see **Fig. 7**. This result is a direct consequence of a delay-free per-second quantification of the cortical state.

With an aim to further explore the rapid quantification of the cortical state during induction, the UBC group conducted a study designed to assess the performance of the WAV_{CNS} for determining whether a patient has lost consciousness after a standard bolus-based propofol induction. It was found that 95% of patients had lost consciousness under a WAV_{CNS} level of 72 [56]. The PK prediction probabilities were 0.975 for the WAV_{CNS}, and 0.890 for the BIS (v.3.4). The difference in performance between the two systems was further evaluated through a standard sensitivity/specificity analysis, see **Fig. 8**.

The limited performance of the BIS, assessed by the comparison of the ROC curves, could be explained by its

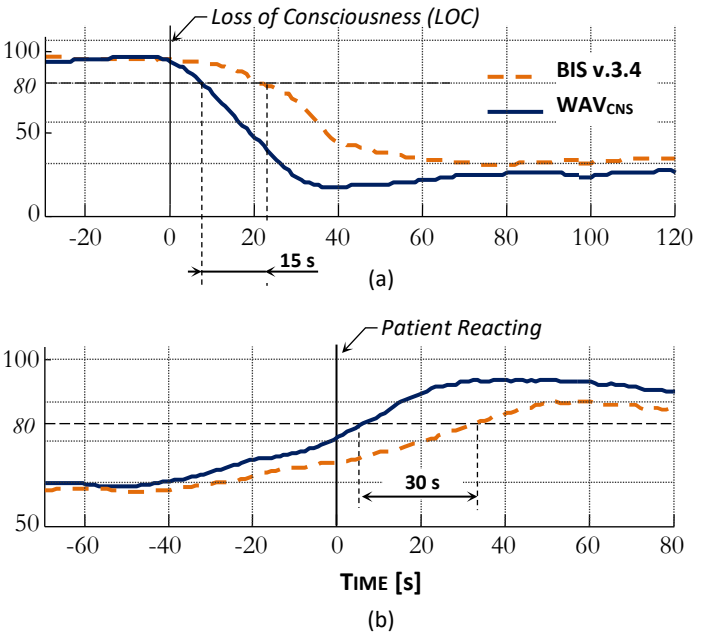

Fig. 7 – Comparison between WAV_{CNS} and BIS during (a) induction and (b) emergence. Individual time courses were synchronized based on the loss of consciousness and the patient reacting event (adapted from [24]).

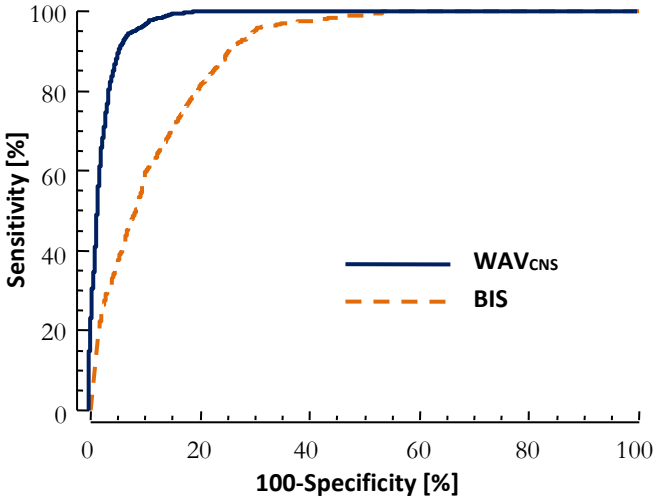

Fig. 8 – Performance comparison of the WAV_{CNS} and BIS during propofol induction (data from 54 patients and 2 channels). The ROC curves show the superior performance of WAV_{CNS} in discriminating between conscious and unconscious state (adapted from [56]).

lag at induction. This result illustrates the potential of the WAV_{CNS} to help detect instances of consciousness during anesthesia procedures.

A Known Transient Behavior

Another important advantage of the WAV_{CNS} quantifier lies in its consistent and well-defined transient behavior during cortical changes. The WAV_{CNS} always exhibits the same, delay-free response to changes in cortical activity, regardless of the anesthetic level or the amplitude of change. The only dynamic difference between the physiological effect and its quantification through the WAV_{CNS} algorithm is due to the post-analysis trending filter, which is well-defined, linear and time-invariant.

This characteristic can be captured through a simple test. A signal composed of random EEG segments obtained from patients at different anesthetic levels (awake, sedated, anesthetized, deep, and isoelectric) is used as input to the WAV_{CNS} quantifier. The resulting WAV_{CNS} levels are then used to identify a model describing its transient behavior, see **Fig. 9**. In case of the WAV_{CNS}, there exists a linear time-invariant function that adequately predicts the evolution of the index [50].

In contrast, **Fig. 9** also illustrates the limited fit obtained with the BIS index. Its apparent non-linearity and time-variance may pose limitations for its use in, e.g., pharmacodynamic (PD) modeling or closed-loop anesthesia delivery.

Conversely, the existence of a reliable mathematical function relating a physiological change in drug effect and its corresponding quantification by the WAV_{CNS} entitles researchers to derive PD drug models independent of the

monitor used to observe the effect. This essentially means that the effect of the monitoring technology can be mathematically removed from the model. Therefore, these models can be identified in such a way that they describe the real physiological effect of the administered drugs.

In that respect, the UBC group developed a new PD modeling approach based on the WAV_{CNS} quantifier [52]. They have shown that, by using only data obtained during induction, they could adequately model propofol pharmacodynamics [51]. They have further shown that, contrary to published models, the effect rate constant k_{e0} is significantly higher when the transient behavior introduced by the cortical monitor is removed from the identification data. This suggests that the equilibration time constant between the plasma concentration of propofol and the physiological effect is much faster than initially anticipated [58].

In addition to PD modeling, the WAV_{CNS} quantifier is also a good candidate for use within a closed-loop framework. The fact that its dynamic behavior is linear and time-invariant (unlike other depth-of-anesthesia monitors such as BIS and M-Entropy [21]) allows for development of reliable control designs with optimal performance [17],[15]. This further allows for the characterization of the uncertainty due to inter-patient variability in drug sensitivity [22],[23], and for the design of a stable closed-loop control system,

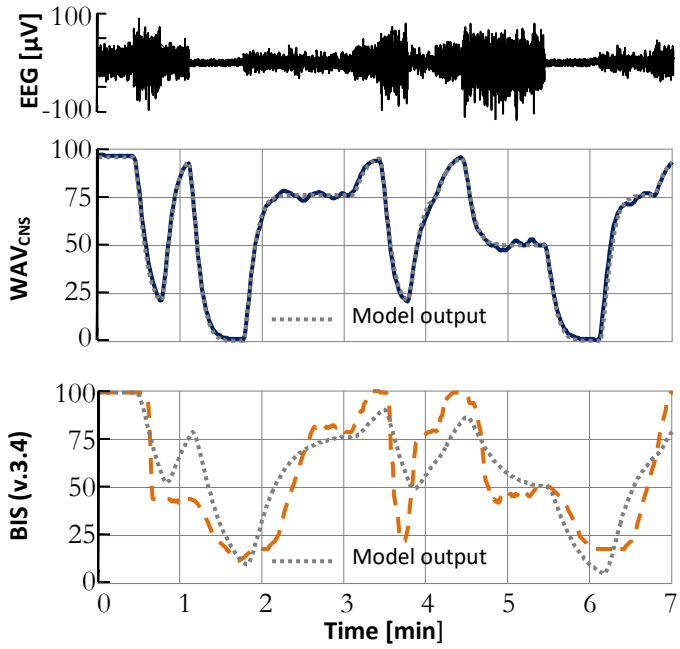

Fig. 9 – Transitory behavior of the WAV_{CNS} and BIS for large and rapid cortical changes. A linear time-invariant model was identified for the two indexes. The large difference between the model output and the BIS index indicates that the BIS index cannot be adequately described by a linear time-invariant function (adapted from [50]).

necessary for wide acceptance by clinicians and regulatory authorities.

The NeuroSENSE® Monitor

In 2003, the UBC technology was licensed to the NeuroWave Division of Cleveland Medical Devices Inc. (Cleveland, OH, USA), a medical device manufacturer specializing in portable electrophysiological monitors. In 2007, the Division was incorporated into NeuroWave Systems Inc., a company dedicated to advanced EEG signal acquisition and processing for neuromonitoring applications.

Since its inception, NeuroWave has been actively working on the development of the NeuroSENSE monitor (see **Fig. 10)**, which integrates the WAV_{CNS} technology.

The NeuroSENSE is equipped with an external EEG Module that acquires and processes 2 frontal EEG signals. The module presents itself as a small low-profile box integrated directly at the level of the patient cable. The module provides signal amplification and digitization, patient isolation, cardiac defibrillation protection, electro-surgical interference detection and filtering, and continuous impedance check of the electrode-skin contacts. It also embeds a processor running the WAV_{CNS} algorithms. Its analog front-end was engineered to have a very low noise profile (< 0.25 μV_{rms} between 0.125-100 Hz) for accurate detection of electro-cortical silence, and a high common mode rejection (> 110 dB) for effective extraneous noise cancellation. Its wide bandwidth (0.125 – 200 Hz) makes it suitable for acquisition of signals containing EEG, EOG and EMG information. The EEG Module acquires data from 2 fronto/fronto-temporal channels at a sampling rate of 896 samples/second.

In addition to the advantages provided by the WAV_{CNS} technology (i.e., delay-free, linear and time-invariant response to cortical changes), the NeuroSENSE monitor offers clinicians and researchers several beneficial features:

- **Bilateral monitoring**: the NeuroSENSE acquires 2 frontal, bilateral EEG channels corresponding to the left and right temple areas that are referenced to the F_{pz} electrode location. The WAV_{CNS} is calculated, trended and displayed for both channels.

  The left and right channels are in general very similar during anesthesia. However, some differences are to be expected. In the absence of unilateral brain pathology and with good signal quality, the level of agreement between the WAV_{CNS} indexes for the left and right cerebral hemispheres is typically within ±8 units with a negligible bias [47], in comparison to ±15 units for the BIS index. Furthermore, if we consider only sustained differences in

Fig. 10 – NeuroSENSE Monitor (model NS-901) and its EEG Module.

anesthetic depth (at least 30s in duration), only 2.22% of WAV_{CNS} readings suggested different depths as compared to 8.03% for BIS.

In [57], we have assessed the bilateral reproducibility of the WAV_{CNS} and BIS (v.3.4) specifically during anesthesia induction in 57 patients. The 95% limits of agreement, as defined by a standard Bland-Altman analysis, were [-12; +11] for the WAV_{CNS}, and [-18; +19] for the BIS. Hemispheric discrepancy where channels diverged for more than 10 units (20 units) occurred in 9% (<1%) of the time for the WAV_{CNS} *vs.* 19% (6%) of the time for the BIS.

In addition, discrepancies may be expected as a result of, e.g., an underlying neurological pathology, or due to a focal disruption in blood flow and/or oxygenation (e.g., during cardio-vascular procedures, see for instance **Fig. 11**). Significant differences between bilateral WAV_{CNS} values may be able to serve as early indicators of underlying discrepancies in the neuropathways, signifying the onset of neurological trauma. For instance, Momeni et al. [13] have reported two cases where asymmetry in the WAV_{CNS} and suppression ratio were found during cardiopulmonary bypass, and preceded changes in cerebral oximetry. In both cases, the patients suffered a hemispheric stroke. The authors concluded that the use of bilateral processed EEG could be helpful to detect an ongoing neurotrauma and provide physicians additional time to prevent severe side effects.

Differences between channels may also arise when one channel is strongly perturbed by environmental noise. This situation is typically resolved by improving the electrode impedances, and/or moving away potential sources of electromagnetic interferences (e.g., warmers).

Finally, in our experience, sudden differences between the two channels may also be related to a marked increase in EMG activity in the channel with the higher WAV_{CNS} value.

As compared to unilateral monitoring, bilateral monitoring provides a more comprehensive insight into the patient's state. We further believe that neuromonitoring during anesthesia should not ignore any one hemisphere. Further research needs to be conducted to establish the benefits of bilateral monitoring.

- **Automated artifact detection and removal**: the NeuroSENSE also incorporates advanced algorithms for artifact recognition and removal including ocular activity, epileptic spikes and electro-surgical interference detection [28]. These algorithms also provide signal quality assessment through continuous electrode-skin impedance and electromagnetic interference measurements. The system is fully automated and warns

users if the signal quality and/or artifacts prevent the accurate quantification of the cortical state.

- **User-accessible case data:** all raw EEG signals and processed data are systematically archived for later review. Users can access the data files, which include the full 896 samples/second resolution EEG, directly through the NeuroSENSE user interface. In addition, real-time processed data are available through the Ethernet port for easy integration in advisory and/or closed-loop systems.

Closing the loop in Anesthesia Delivery

The NeuroSENSE monitor has been used in closed-loop clinical studies by the UBC group as part of their iControl platform since 2009. They have demonstrated the technical and clinical feasibility of automatically regulating the infusion rates of propofol and remifentanil to drive and maintain patients at a depth-of-anesthesia level targeted by the anesthesia care provider in both adults [42] and pediatrics [16]. In their paper, West *et al.* [9] have shown that the controller was able of maintaining the WAV_{CNS} value within +/- 10 units of the target 88.2% of the time. A more recent study [37] sponsored by NeuroWave with funding from the US Navy showed that the co-administration of low-dose ketamine did not affect the ability of the controller to reach and maintain its WAV_{CNS} target (it stayed within a +/- 10 units range of the target for 86.5% of the time). However, the full dose of ketamine recommended for postoperative pain management had a significant effect on the WAV_{CNS} this effect should be considered when using the WAV_{CNS} to guide anesthesia dosing [7].

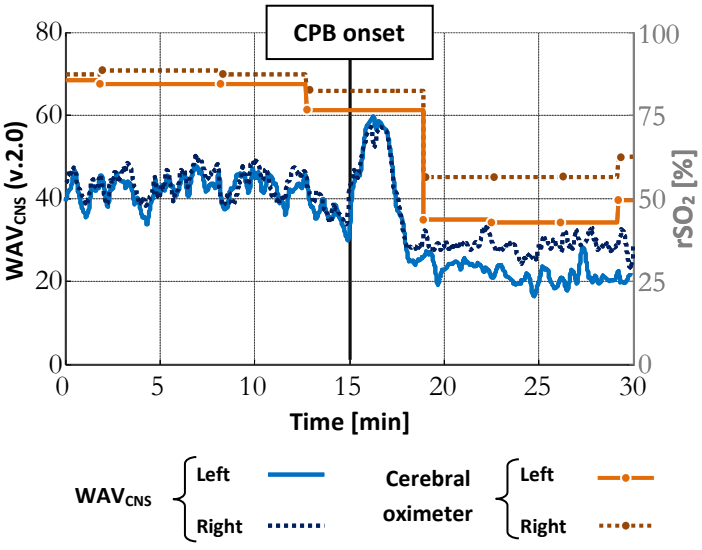

Fig. 11 – Bilateral WAV_{CNS} during onset of cardio-pulmonary bypass. In this case, a significant depression of the cortical state can be observed after the bypass was initiated. A sustained moderate hemispheric asymmetry followed. These observations were confirmed by the INVOS™ cerebral oximeter (adapted from [55]).

NeuroWave Systems has been working diligently on the development of a commercial closed-loop TIVA delivery system in collaboration with the UBC iControl research group, and with the support of the US Department of Defense. In 2018, NeuroWave introduced an advanced prototype, the AutoTIVA™, at the annual meeting of the Society for Technology in Anesthesia (STA). The AutoTIVA is an extension of the NeuroSENSE Monitor, where a dual channel pump module is attached to the right side of the monitor to provide infusion capabilities, see **Fig.12**. The infusion pump technology developed for this application is based on a rotary peristaltic mechanism integrated directly in the disposable administration set. This vertically integrated solution provides brain monitoring, drug infusion, and closed-loop control capabilities in a single compact and easy-to-use platform. We believe the AutoTIVA will act as a force multiplier, bringing together the benefits of TIVA and brain monitoring through automation, and it represents an evolutionary step forward in the practice of anesthesia. The controller adjusts the drug titration continuously, and within the safety margins defined from the drug label dosing guidelines, or by the provider him/herself. Changes in patient's state, surgical stimulation level, or drug metabolism and elimination, are automatically accounted for by the system.

We expect the AutoTIVA will be a factor for improved patient safety and outcome, while reducing the care provider workload and allowing junior providers to perform at the same level as their more senior counterparts. Improvement in anesthesia delivery will lead to higher patient satisfaction and reduction in costs of care.

Fig. 12 – AutoTIVA (model AT-901) closed-loop TIVA delivery system. Advanced prototype and research platform (not for sale).

CONCLUSION

The WAV_{CNS} technology provides a deterministic approach to EEG quantification. Conversely to interpretative indexes, the WAV_{CNS} quantifier is delay-free with respect to its response to cortical changes. It is also characterized by a linear and time-invariant transitory behavior, which allows the WAV_{CNS} to be optimally used in pharmacodynamic studies and closed-loop anesthesia delivery systems.

The NeuroSENSE monitor, which incorporates the WAV_{CNS} technology and bilateral hemispheric monitoring, provides clinicians and researchers with an easy-to-use and robust cortical monitoring platform. Built around the WAV_{CNS} technology, we believe the NeuroSENSE represents a technological step forward in brain function monitoring for anesthesia, as evidenced by its use in closed-loop TIVA delivery.

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