

# NeuroSENSE<sup>®</sup> Monitor with WAV<sub>CNS</sub> Cortical Quantifier:

## *A Deterministic Approach to EEG Analysis*

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**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<sup>®</sup>, a bilateral hemisphere monitor of patient's brain activity for the anesthesia specialty. The NeuroSENSE incorporates the WAV<sub>CNS</sub> technology for automated EEG quantification.

The WAV<sub>CNS</sub> (Wavelet-based Anesthetic Value for Central Nervous System) utilizes wavelet analysis of the 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<sub>CNS</sub> method employs a deterministic algorithm, which yields a delay-free, linear and time-invariant quantifier of cortical activity. The WAV<sub>CNS</sub> algorithm has been fully disclosed in [7].

This white paper provides interested readers with more information about the WAV<sub>CNS</sub> technology, the NeuroSENSE monitor and its use.

**W**ith 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, due to a simplistic burst suppression detection mechanism, 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 regimen 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 (i.e., the offset of the sine wave from a reference point in time). 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<sup>1</sup> thus 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.

The commercialization of the first brain function monitor for anesthesia in the late 1990's yielded a realization that monitoring the brain may provide a number of advantages directly related to patient outcome. In essence, brain function monitoring used as a supplement provides additional information to help deliver adequate levels of anesthesia. This, in turn, may help reduce the risks of intra-operative awareness, post-operative nausea and vomiting, delayed emergence and recovery, and prolonged stay in post-anesthesia care units. While still a matter of debate, it has been shown that maintaining patients at too deep anesthetic levels can be associated with an increased 1-year post-operative mortality rate. In fact, brain monitoring provides anesthesiologists with an additional, more direct means for assessing drug effect and adjusting titration accordingly. Such technologies are

hence a step towards the customization of anesthetic administration according to the patient specific needs.

### **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 EEG 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

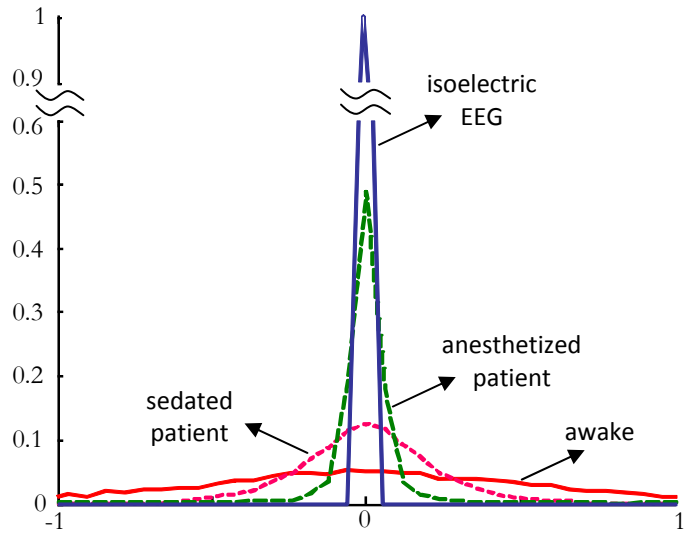
<sup>1</sup> Bispectral Index is a trademark of Aspect Medical Systems, Inc.

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.

### The WAV<sub>CNS</sub> 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 [12] describing the new Wavelet-based Anesthetic Value (WAV). This early publication was followed by a comprehensive manuscript in 2006 [7], where the algorithm was fully disclosed.

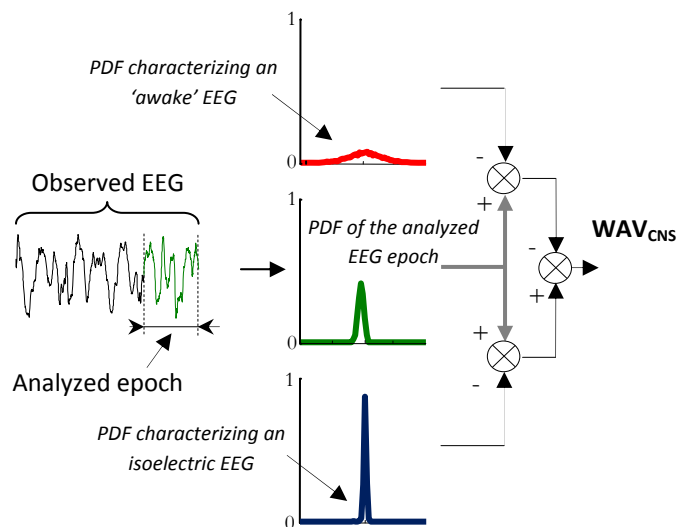
The major finding of the UBC group was that the wavelet information associated with the EEG gamma<sup>2</sup> frequencies (32-64 Hz) can be statistically represented in a form of a Probability Density Function (PDF), which shape evolves from a flat and wide envelope to a sharp and narrow spike, see Fig. 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



**Fig. 1** – Probability Density Functions (PDFs) of EEG waveforms obtained from patients at different level 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.

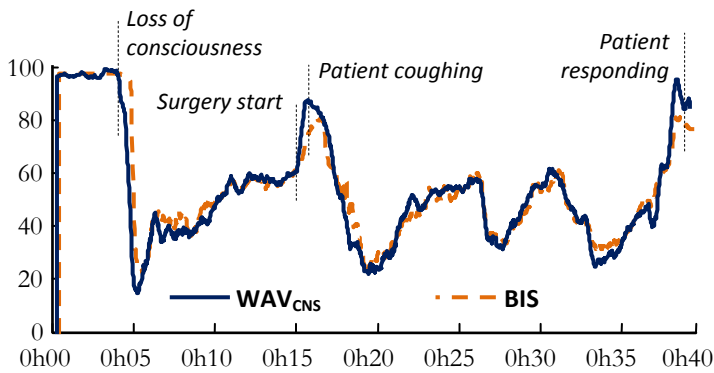
always equal to 1. Thus, the comparison between the observed PDF and the two reference PDFs yields a bounded and dimensionless index, the WAV<sub>CNS</sub>, which expresses how far the observed EEG has evolved from either reference endpoint.

One of the important advantages of the WAV<sub>CNS</sub> method is that it can easily be implemented in real time, based on very short EEG segments. The ability of the wavelet



**Fig. 2** – Overview of the WAV<sub>CNS</sub> algorithm.

<sup>2</sup> In fact, recent research has associated EEG gamma frequencies with mechanisms of conscious awareness.



**Fig. 3** – Example of the WAV<sub>CNS</sub> and BIS (v.3.4.) time courses in an arthroscopy case (adapted from [26]).

analysis to characterize changes in both time and frequency enables the WAV<sub>CNS</sub> 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<sub>CNS</sub> quantifier that instantly responds to the changes in patient state. A post-analysis trending filter is further applied to the WAV<sub>CNS</sub> 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, which results in a smoother trend.

The WAV<sub>CNS</sub> 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<sub>CNS</sub> Scale

Preliminary clinical data suggests that the WAV<sub>CNS</sub> scale is similar to that of the BIS index (trademark of Aspect Medical Systems, Inc.) [7],[26]. For instance, a 2002 clinical study involving 25 knee surgery cases, which aimed at

comparing the WAV<sub>CNS</sub> and BIS technologies, revealed that the WAV<sub>CNS</sub> 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 [7]. The Bland-Altman analysis performed on steady state data points [26] 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].

These results suggest that the WAV<sub>CNS</sub> quantifier may be used as an aid to guide anesthetic administration similar to BIS. While the appropriate cortical depth target is always a function of the patient, the requirements of the surgery, and the intensity of the next surgical stimulus, the similarities between the WAV<sub>CNS</sub> and BIS scales further suggest that the optimal range for anesthesia maintenance is between 40 and 60. Any level below 40 may be an indication that the patient is too deep, while levels above 60 may indicate increased chances for intra-operative awareness.

Further studies are needed to validate the equivalence of the WAV<sub>CNS</sub> and the BIS scales.

### A Delay-Free Response

An important distinguishing factor of the WAV<sub>CNS</sub> 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<sub>CNS</sub> within 1 second of the change onset. As such, the algorithm does not introduce any delay in the quantification of the patient's cortical state.

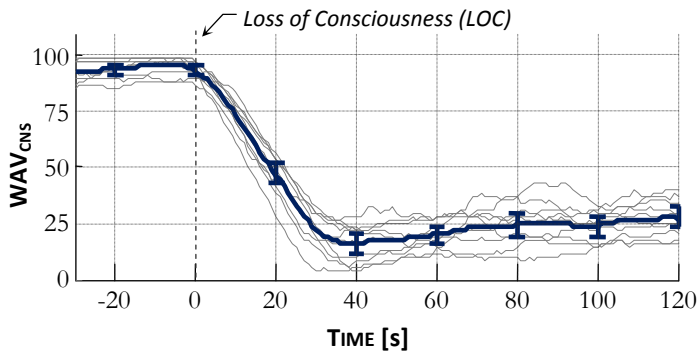


Fig. 4 – WAV<sub>CNS</sub> time courses during induction (adapted from [7]).

Clinically, the instantaneous response of the WAV<sub>CNS</sub> 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. 4. The UBC group has further shown that the WAV<sub>CNS</sub> quantifier leads the BIS (v.3.4) index during both loss and return of consciousness by a significant margin of 15 to 30 seconds, see Fig. 5. This result is a direct consequence of a delay-free per-second quantification of the cortical state.

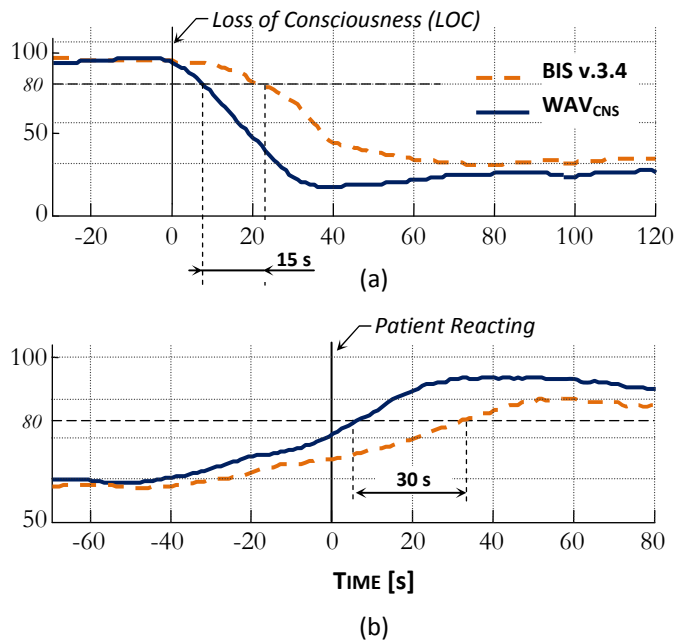


Fig. 5 – Comparison between WAV<sub>CNS</sub> and BIS during (a) induction and (b) emergence. Individual time courses were synchronized based on the loss of consciousness and the patient reacting event. Crossing the 80 level was considered to be a significant event for both loss and return of consciousness (adapted from [7]).

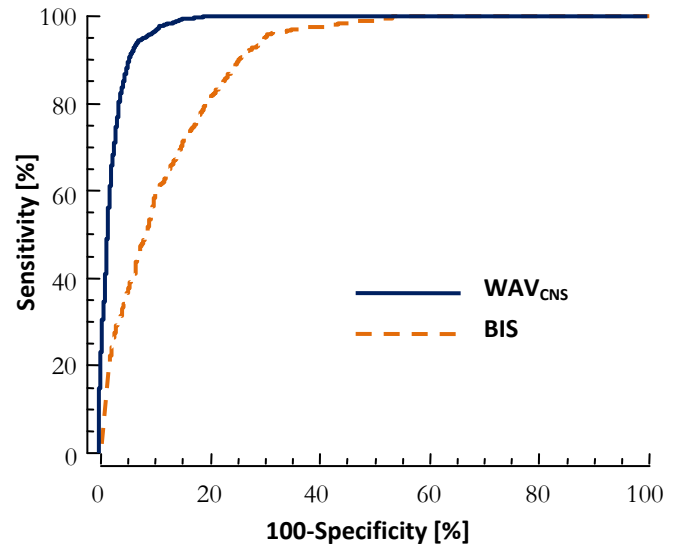


Fig. 6 – Performance comparison of the WAV<sub>CNS</sub> and BIS during propofol induction (data from 54 patients and 2 channels). The ROC curves show the superior performance of WAV<sub>CNS</sub> in discriminating between conscious and unconscious state (adapted from [20]).

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<sub>CNS</sub> 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<sub>CNS</sub> level of 72 [20]. The PK prediction probabilities were 0.975 for the WAV<sub>CNS</sub>, and 0.890 for the BIS (v.3.4). The difference in performance between the two systems was further demonstrated through a standard sensitivity/specificity analysis, see Fig. 6. The limited performance of the BIS, assessed by the comparison of the ROC curves, could be explained by its lag at induction. We also believe that this result illustrates the potential of the WAV<sub>CNS</sub> to help detect instances of consciousness during anesthesia procedures.

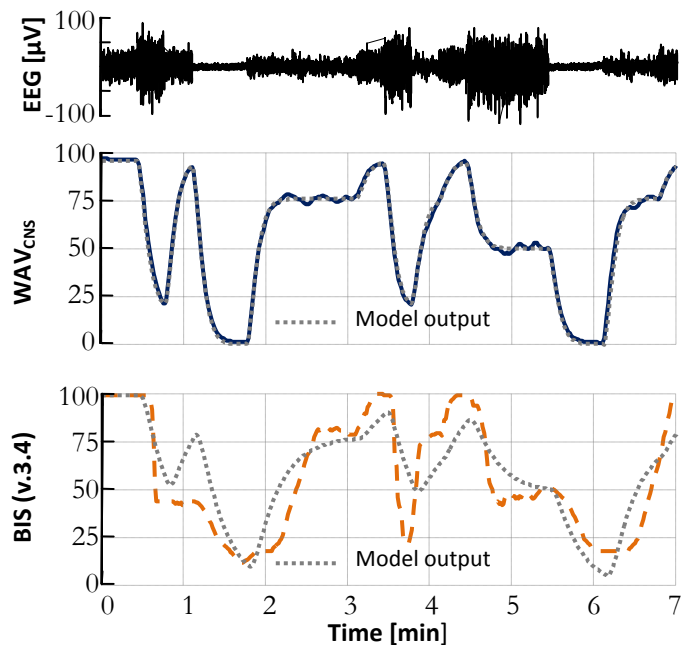
### A Known Transient Behavior

A particularly important advantage of the WAV<sub>CNS</sub> quantifier lies in its consistent and well-defined transient behavior during cortical changes. The WAV<sub>CNS</sub> 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<sub>CNS</sub> 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<sub>CNS</sub> quantifier. The resulting WAV<sub>CNS</sub> levels are then used to identify a model describing its transient behavior, see **Fig. 7**. In case of the WAV<sub>CNS</sub>, there exists a linear time-invariant function that adequately predicts the evolution of the index [14].

In contrast, **Fig. 7** also illustrates the limited fit obtained with the BIS index. We believe that its apparent non-linearity and time-variance may pose limitations for its use in, e.g., pharmacodynamic (PD) modeling or closed-loop anesthesia delivery.



**Fig. 7** – Transitory behavior of the WAV<sub>CNS</sub> 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 [14]).

Conversely, the existence of a reliable mathematical function relating a physiological change in drug effect and its corresponding quantification by the WAV<sub>CNS</sub> entitles researchers to derive PD drug models that are 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.

In that respect, the UBC group developed a new PD modeling approach based on the WAV<sub>CNS</sub> quantifier [16]. They have shown that, by using only data obtained during induction, they could adequately model propofol pharmacodynamics [15]. 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 [22].

In addition to PD modeling, the WAV<sub>CNS</sub> quantifier is also a good candidate for use within a closed-loop framework. The fact that its transient behavior is linear and time-invariant allows for a more aggressive control design, and therefore optimized performance.

### 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 2003, NeuroWave has been actively working on the development of the NeuroSENSE monitor (see **Fig. 8**), which integrates the WAV<sub>CNS</sub> technology and is dedicated to cortical monitoring during anesthesia/sedation.

The NeuroSENSE acquires and processes 2 frontal EEG signals. The device was specifically designed for operating in electrically hostile environments, such as the Operating Room (OR). The EEG acquisition module, referred to as Patient Module, integrates cardiac defibrillation protection, electro-surgical interference detection and filtering, and continuous impedance check of the electrode-skin contact. It was also designed with a low noise profile ( $< 0.3 \mu\text{V}_{\text{rms}}$ ) for accurate detection of electro-cortical silence, and a large bandwidth (0.125 to 300 Hz) for improved artifact detection. The Patient Module acquires EEG data from 2 frontal channels at a sampling rate of 900 samples/second and resolution of 16 bits. It is designed to be attached to an IV pole and positioned close to the patient's head in order to minimize motion artifacts and ensure data integrity and reliability. A data cable links the Patient Module to the NeuroSENSE Display Module, which displays high-resolution EEG tracings, hosts the touch screen user interface and the data archive of cases.

In addition to the advantages provided by the  $\text{WAV}_{\text{CNS}}$  technology (i.e., delay-free, linear and time-invariant response to cortical changes), the NeuroSENSE monitor

offers clinicians and researchers a number of beneficial features:

- **Bilateral monitoring:** the NeuroSENSE acquires 2 frontal EEG channels corresponding to the left and right temple areas that are referenced to the  $\text{F}_{\text{pz}}$  electrode location. The  $\text{WAV}_{\text{CNS}}$  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 [21], we have assessed the bilateral reproducibility of the  $\text{WAV}_{\text{CNS}}$  and BIS (v.3.4) during anesthesia induction in 57 patients. The 95% limits of agreement, as defined by a standard Bland-Altman analysis, were [-12 ; +11] for the  $\text{WAV}_{\text{CNS}}$ , 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  $\text{WAV}_{\text{CNS}}$  vs. 19% (6%) of the time for BIS [21].

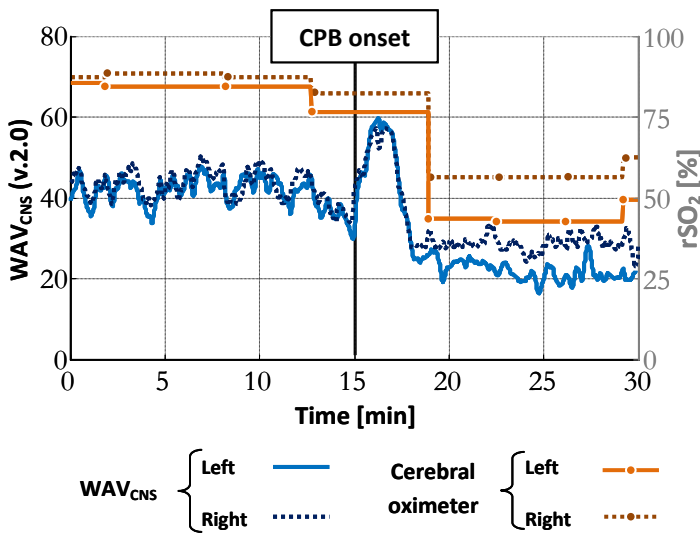
In addition, discrepancies may be expected as a result of, e.g., an underlying neurological pathology, or due to a focal disruption in blood flow and/or oxygenation (e.g., during cardio-vascular procedures, see for instance Fig. 9).

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  $\text{WAV}_{\text{CNS}}$  value.



Fig. 8 NeuroSENSE Monitor (model NS-701).



**Fig. 9** – Bilateral WAV<sub>CNS</sub> 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 [19]).

At this moment, the underlying neurophysiology of the differences between the two hemispheres during anesthesia is not fully understood. Yet, compared to unilateral monitoring, we believe that 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 [3],[4]. 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 900 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.

## CONCLUSION

The WAV<sub>CNS</sub> technology provides a deterministic approach to EEG quantification. Conversely to interpretative indexes, the WAV<sub>CNS</sub> 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<sub>CNS</sub> to be optimally used in pharmacodynamic studies and closed-loop systems.

The NeuroSENSE monitor, which incorporates the WAV<sub>CNS</sub> technology and bilateral hemisphere monitoring, provides clinicians and researchers with an easy-to-use and robust cortical monitoring platform. Built around the WAV<sub>CNS</sub> technology, we believe that the NeuroSENSE represents a technological step forward in brain function monitoring during anesthesia.

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