



19 October, 2010

Cortical Dynamics Poster Presentation at Anesthesiology 2010

BPH Corporate Ltd [ASX: BPH] investee company Cortical Dynamics Ltd ("**Cortical**"), has presented a poster entitled "*Propofol and Remifentanyl Differentially Modulate Frontal Electroencephalographic Activity*" at the 2010 Annual Meeting of the American Society of Anesthesiologists in San Diego today (*please see attached*).

Professor David Liley of Cortical commented that "based on the number of companies exhibiting depth of anaesthesia monitoring solutions and scientific papers evaluating such monitors it is quite clear that brain function monitoring continues to grow in importance for the safe and effective practice of anaesthesia."

The BAR monitoring system utilises a number of innovative developments to better monitor brain function that emerge out of recent advances in our understanding of how the brain's rhythmic electrical activity, the electroencephalogram (**EEG**), is produced. The approach used is fundamentally different from all other devices currently available in the market in that its underlying algorithm produces EEG indexes which are directly related to the physiological state of the patient's brain. Other systems on the market produce EEG measures based on physiologically arbitrary statistical methods that utilise the trial-and-error identification of anaesthetic induced EEG regularities in patients undergoing a variety of operative procedures. The BAR system provides much greater sensitivity to anaesthetic drug effect enabling the monitoring of a wider range of anaesthetic agents, some of which are not properly detected by the competing technologies. The physiological underpinnings of the BAR monitoring system makes it particularly relevant to quantifying changes in brain function that attend the early onset of a range of degenerative neurological illnesses such as Alzheimer's dementia.

BPH has an interest in the medical devices sector and is currently working towards the commercialisation of the BAR monitoring system for the measurement and monitoring of patient brain activity during anaesthesia as well as in conditions of health and disease. Cortical is working towards listing on the Australian Securities Exchange (ASX).

Cortical Dynamics Ltd

ACN 107 557 620

PO box 317, North Perth, WA, 6906

14 View Street, North Perth, Western Australia

T: +61 8 6467 9525 F: +61 8 9328 8733

contact@corticaldynamics.com www.corticaldynamics.com

Propofol and Remifentanil Differentially Modulate Frontal Electroencephalographic Activity

David TJ Liley^{1,2}, Nicholas C Sinclair², Tarmo Lipping³, Bjorn Heyse⁴, Hugo EM Vereecke⁴, Michel MRF Struys^{4,5}

¹ Swinburne University of Technology, Melbourne, Australia ² Cortical Dynamics Ltd, Perth, Australia
³ Tampere University of Technology, Pori, Finland ⁴ Ghent University, Ghent, Belgium
⁵ University of Groningen, Groningen, The Netherlands

Overview

A recently developed, physiologically inspired, electroencephalographic method for monitoring anaesthetic drug action is expected to show superior performance compared to existing heuristic approaches^{1,2,3} (Figure 1).

It is hypothesised that this method is capable of dissociating the effects hypnotic and analgesic agents have on frontally recorded electroencephalographic activity. Such a feature is absent from all other existing processed electroencephalographic depth of anaesthesia monitoring approaches.

In order to test this hypothesis electroencephalogram collected during propofol-remifentanil anaesthesia was evaluated using a physiologically constrained fixed order time series analysis method.

Methods

Forty five ASA I patients were randomly allocated to one of three groups based on target effect site remifentanil concentration (0, 2, 4 ng/ml).

Subsequently all patients received stepwise increased targeted effect site concentrations of propofol until loss of response to all measures of alertness and sedation. At each step change the Observer's Assessment of Alertness/Sedation (OAA/S) score was determined.

Raw electroencephalogram was continuously acquired from a bipolar frontal montage and analysed offline using a fixed order autoregressive moving average model to give derived measures of Cortical State (CS) and Cortical Input (CI).

CS is designed to quantify the response of cortex to arbitrary input whereas CI is designed to quantify the magnitude of actual input to cortex (Figure 2).

Results

CS was found to clearly decrease with decreasing levels of consciousness ($P_k = 0.814$) whereas CI was largely independent of the OAA/S assessed state ($P_k = 0.527$) (Figure 3).

Regression analysis (hierarchical linear modelling) revealed that CS was significantly negatively correlated with predicted effect site propofol concentration but uncorrelated with predicted effect site remifentanil concentration (Figure 4).

In contrast CI was strongly correlated with target effect site concentrations of both propofol and remifentanil.

In particular it was observed that CI decreased with increasing remifentanil concentration.

Conclusion

Because CS responds principally to variations in target effect site propofol concentrations and is strongly correlated with OAA/S assessed levels it may represent an alternative measure of hypnosis to existing indices.

In contrast, because of the clear dependency on target remifentanil concentrations CI may be useful as a measure of analgesic efficacy and the nociceptive – antinociceptive balance. Prospective studies with noxious stimuli will be needed to validate such speculations.

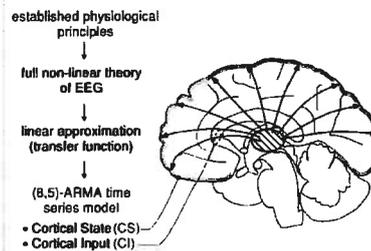


Figure 1: Schematic outline of the physiologically inspired electroencephalographic analysis method. Theory³ suggests that the electroencephalogram (EEG) can be modelled as the result of the cortex acting as a linear filter on its (pseudorandom) input. This allows the derivation of measures of the responsive state of the cortex (Cortical State) and the magnitude of the input to cortex (Cortical Input). ARMA = autoregressive moving average.

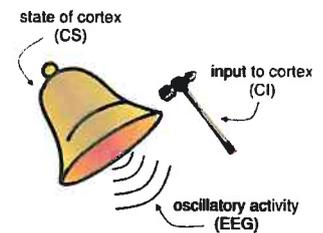


Figure 2: The general concept of the measures of Cortical State (CS) and Cortical Input (CI) can be illustrated using the highly simplified analogy of a bell being struck by a hammer. The sound of the bell ringing is dependent on both the resonant frequency of the bell and how hard it is struck. Analogously, the electroencephalogram (EEG), when modelled as the output of a linear filter, is dependent on both the resonant state of the cortex (CS) and the magnitude of the input to cortex (CI).

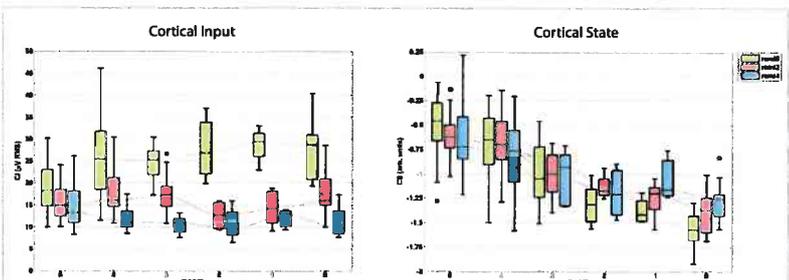


Figure 3: Box and whisker plots for derived electroencephalographic measures as a function of the Observer's Assessment of Alertness/Sedation (OAA/S) level for no remifentanil (remi0), 2 ng/ml remifentanil (remi2) and 4 ng/ml remifentanil (remi4) treatment groups. Boxes represent inter-quartile ranges, lines enclosed within boxes (and connected lines) median values, whiskers the largest (smallest) non-outlier and circles outliers (defined as values extending a further 1.5 times the inter-quartile range – equivalent to approximately 3 standard deviations for normally distributed data).

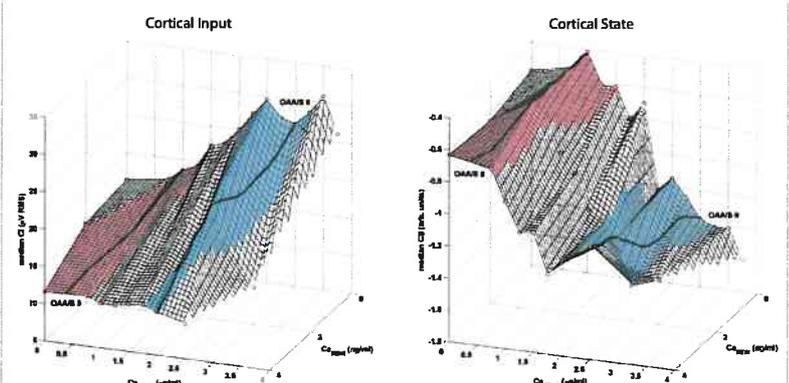


Figure 4: Linearly interpolated surface plots for derived electroencephalographic measures as a function of target remifentanil (C_{remf}) and propofol (C_{prop}) concentrations. Mesh represents the linearly interpolated surface through data (red circles). Inter-quartile (25th – 75th percentile) ranges of target propofol concentration for a given Observer's Assessment of Alertness/Sedation (OAA/S) level and remifentanil level are shown as shaded (OAA/S 5 = red, OAA/S 0 = blue) patches on the interpolated surface. Median values correspond to the respective solid black line.



- [1] Liley DT, Leslie K, Sinclair NC, Feckie M: Dissociating the effects of nitrous oxide on brain electrical activity using fixed order time series modelling. *Comput Biol Med* 2008; 38: 1121-30
- [2] Liley DT, Sinclair NC, Lipping T, Heyse B, Vereecke HE, Struys MM: Propofol and remifentanil differentially modulate frontal electroencephalographic activity. *Anesthesiology*, accepted April 2010. Article in press
- [3] Liley DT, Cadusch PJ, Gray M, Nathan PJ: Drug-induced modification of the system properties associated with spontaneous human electroencephalographic activity. *Phys Rev E Stat Nonlin Soft Matter Phys* 2003; 68: 051906