Entropy is blind to nitrous oxide. Can we see why?


The word ‘entropy’ tends to cause cessation of rational thought in the reader, reflecting the difficulty we have in understanding this concept. It is therefore risky to base an editorial on the critical examination of why change in the spectral entropy of the EEG may be a useful indicator of consciousness.

In this issue of the journal, Anderson and Jakobsson demonstrate that the administration of incremental doses of propofol, to the point of loss-of-responsiveness, causes a concomitant decrease in the Spectral Entropy of the EEG compared with alert, baseline values. In contrast, the administration of nitrous oxide to the same endpoint results in no change in this entropy. In other words, the monitor seems to be blind to the effect of nitrous oxide. Although the experimental designs vary slightly, these results are virtually identical to those obtained by a number of different workers when using the Bispectral Index to quantify anaesthetic effect. Both the Spectral Entropy and the Bispectral Index quantify the loss of high frequency activity in the EEG signal that occurs in the patient on induction of anaesthesia. The assumption underpinning both the devices is that a change in the state of consciousness of the subject reliably causes a detectable change in the measured electrical activity in the frontal cortex.

Is the patient unconscious? Are they forming memories? Will they respond to stimulation? These are questions we would like answered by a putative depth-of-anaesthesia monitor. Electrical evidence of each of these three facets of cerebral function can be measured, but the measurement techniques are fundamentally flawed. The flaws lie not so much in the technology itself, but in our basic lack of understanding of how both the brain and general anaesthetic agents work. A parallel can be drawn with early astronomers studying the path of planets moving in the night sky. The assumption was that the planets circled around the earth. Plotting out the path of the planets around the earth showed that they followed a smooth arc, interrupted by occasional tight loops or epicycles. How do you make a planet do a tight loop? The initial assumption was at fault. The sun, not the earth, is the centre of the solar system. Similarly, it is wrong to assume that anaesthesia is a single state reflected by the electrical behaviour of the cerebral cortex. In 1993, Kissin wrote an article with the challenging title ‘General anesthetic action: an obsolete notion’. In it he stressed that anaesthesia represented a conglomeration of different endpoints. An interesting twist to this story is added by the knowledge that MAC, an anaesthetic endpoint and our classic indicator of general anaesthetic agent potency, is dependent largely on an agent’s effect on the spinal cord, not on the cortex. It is therefore obvious that an EEG monitor cannot measure depth-of-anaesthesia as defined by MAC. Another commonly used endpoint is the loss-of-response to verbal command. In the setting of general anaesthesia, this is taken as an indicator of loss-of-consciousness. This latter transition is a subjective or internal phenomenon, and we cannot measure it directly. During emergence from anaesthesia, auditory awareness may return before response to verbal command. Despite this we must rely on patients’ behaviour—that is the transition from responsiveness to non-responsiveness—to indicate when they become unconscious.

What aspects of cerebral function are essential to allow consciousness? Is there some invariant property of the EEG that reliably indicates the transition between consciousness and unconsciousness, independent of the class of drug used for anaesthesia? The idea of Spectral Entropy of the EEG has some intuitive appeal in this regard. The electrical activity of cortical neurones is reflected in the EEG. It is reasonable to assume that the conscious state is dependent on the electrical activity of cortical neurones. A complex, low-voltage waveform like the ‘awake’ EEG implies that individual neurones, or small groups of neurones, can interact accurately and quickly, without constraint. To put this in the parlance of entropy, the neurones are free to exist in a large number of different microstates. Imagine a single channel ‘awake’ EEG vs a 3 Hz sine wave. A Fourier transformation of these two waveforms would yield different power spectra. The awake EEG would demonstrate a flat band of power across the whole frequency range (typically 2–30 Hz), whereas the sine wave would be represented by a
single peak at 3 Hz, and no power at other frequencies. The Spectral Entropy of the ‘awake’ EEG approaches one (scaled to 100 by the Datex-Ohmeda monitor), whereas the Spectral Entropy of a perfect sine wave is zero. Unlike the ‘awake’ EEG, a 3 Hz sine wave, if seen on an EEG, would imply that the electrical behaviour of the cortical neurones was extremely constrained and synchronized across the cortex. This slow sine wave is a crude approximation of delta wave activity, the dominant wave seen on EEG during deep anaesthesia and stage 4 sleep.

When using either the Bispectral Index or the Spectral Entropy, the clinician is presented with a number between zero and 100. A number less than 60 implies that the patient is almost certainly unconscious. The data on which this judgement is based has largely been derived from studies using propofol or one of the halogenated ethers. These agents are thought to have a predominantly GABA-ergic effect on neurophysiological function and to cause the cerebral cortex to become less active. The cerebral metabolic rate is depressed and the EEG shifts to low frequencies. In contrast, when nitrous oxide, xenon, or ketamine is used, the level of cortical activity is maintained, even when the patient is anaesthetized. With these latter drugs, high frequency EEG power is relatively unaffected, slow waves are not as enhanced, and isoflurane-induced burst suppression may even be inhibited. The work by Anderson and Jakobsson demonstrates that it is possible for a patient to be unresponsive to mild external stimuli, but to retain a broad-spectrum, active, ‘awake looking’, high Spectral Entropy EEG. This nitrous oxide induced state has many similarities with REM sleep and with ICU delirium. Subjects are unresponsive to their surroundings, and have low-amplitude desynchronized EEG. Their cerebral metabolism is not depressed and their unfocused cognitive activity is associated with dreams and hallucinations. Both the Bispectral Index and the Spectral Entropy may be considered to be primarily indicators of cerebral activity. If depression of that activity is associated with the administration of one of the GABA-ergic agents to the point of loss-ofresponsiveness, then these indices become surrogate, but indirect, measures of consciousness. Conversely, these indices are not surrogate measures of consciousness when the drug induced loss-of responsiveness occurs without cortical depression. How then does nitrous oxide cause unconsciousness? We must speculate that, although cortical activity is present, it lacks the functional integration necessary for consciousness.

Consciousness has been conceptualized as a combination of two essential sub-components, alertness (a non-specific level of basal arousal), and awareness (an ability to focus on and manipulate the information presented). Alertness is the enabling function: ‘the TV is on’, and awareness the ultimate function: ‘the tuner is set and the program is running’. Using this framework, unconsciousness will result when either or both of these components are sufficiently depressed by the action of drugs, disease or the process of natural sleep. Importantly, we now have an expectation that different drugs may produce unconsciousness in fundamentally different ways. A GABA-ergic agent like propofol turns the TV off, whereas nitrous oxide disrupts the tuning. Although being conscious is dependent on cortical function, it may be impossible to find a single change in cortical function that defines the state of unconsciousness or predicts unresponsiveness to verbal command.

What conclusions now can be drawn? Spectral Entropy and Bispectral Index poorly detect the effect of nitrous oxide on the cerebral cortex. These indices of cerebral function may therefore encourage the clinician to deepen the anaesthetic, perhaps unnecessarily, when nitrous oxide is being used along with GABA-ergic agents. It is very doubtful whether this would lead to any significant problems.

Spectral Entropy is a fast, simple, and elegant method of analysis of the EEG. Its use is linked to a basic premise about the electrical behaviour of the cortex when making the transition from consciousness to unconsciousness.

Both Spectral Entropy and Bispectral Index are indicators of cortical activity, rather than level of consciousness, or depth-of-anaesthesia per se. It is unclear whether these two indices differ greatly in performance so we await further critical examination with interest.

Clearly, knowledge of its boundaries and constraints is essential to the safe use of any monitor. It is important to understand that entropy is blind to the effects of nitrous oxide on the state of responsiveness to verbal command. This does not, however, negate the benefit of having a monitor that shows us when the cortex is inactive. One cannot be conscious when the cortex is inactive.

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