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Density-modulated t's array, a new technique of processed electroencephalogram, for monitoring the effects of midazolam and nitrous oxide during spinal anesthesia

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Abstract: We have investigated the utility of a new electroencephalogram (EEG) processing system, density-modulated t's array (DTA), which we have installed in a laptop personal computer together with density-modulated spectral array (DSA) for clinical monitoring. Ten patients scheduled for orthopedic operations on the lower extremities were anesthetized with 0.5% bupivacaine intrathecally, 50% nitrous oxide in oxygen by mask, and midazolam at a dose of 0.1 mg/kg intravenously. Immediately following the administration of the drugs, the power at the frequencies between 15 and 20 Hz increased. However, the power at these higher frequencies disappeared gradually and the power in the delta band and the smaller one in the alpha band became predominant. This pattern of dominant-band shift on the DSA and DTA was observed in all the patients. In three of the patients, the sedation level remained stable as judged by the absence of body movement, quiet, regular breathing and stable hemodynamics as well as steady EEG frequency distribution throughout the operations. They awoke from anesthesia rapidly on withdrawal of nitrous oxide, with return of the power at the higher frequencies. In the other seven patients, the power at the higher frequencies suddenly reappeared on the DSA and DTA during operation and slight movements of the head and upper limbs were observed with rises in blood pressure and heart rate. In three of these seven patients, the EEG change notably preceded the physiological activities by a few minutes. On the DTA, the occurrence of any significant clinical phenomenon was displayed in a color representing a t value greater than ± 3. The DTA, testing power changes in the EEG at each 1-Hz interval for significant difference, permits the visual and quantitative assessment of EEG changes.

Key words: EEG—Processed EEG—DSA—DTA—Brain monitoring—Sedation

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Introduction

The usefulness of the electroencephalogram (EEG) as a tool for intraoperative monitoring of brain function has been explored since the 1950s. Although the definitive advantages are the ease with which EEG can be obtained and the non-invasiveness of the procedure, the complexity of the information contained in the raw EEG defies meaningful interpretation. Recent technical developments in processed EEG, such as frequency analysis by fast Fourier transformation (FFT) and compressed spectral array (CSA) display, have made it more amenable for clinical use.

We have achieved further refinements in processing and display techniques in density-modulated spectral array (DSA) and density-modulated t's array (DTA), which may incorporate such parameters as spectral edge frequency and mean frequency. We have applied these techniques in a clinical setting and sought to establish a method of monitoring brain function during anesthesia and possibly to facilitate an early detection of brain complications.

Methods

Instrumentation

EEGs were recorded monopolarly with the disk electrodes positioned at F3 and F4 according to the international 10–20 electrode system. The derived EEG, as shown in the block diagram in Fig. 1, was fed to an amplifier (MEG-2100, Nihon Kohden, Tokyo, Japan) for amplification and filtering (0.5–30 Hz), and inputted via a handmade main amplifier (± 5 V) and an analog-to-digital converter (CANOPUS, Analog-Pro II, Kobe, Japan) into a lap-top personal computer [PC-9801NC (CPU: 386SX, 20 MHz), NEC, Tokyo, Japan] interfaced with a digital signal processor (Flash 16, CANO-

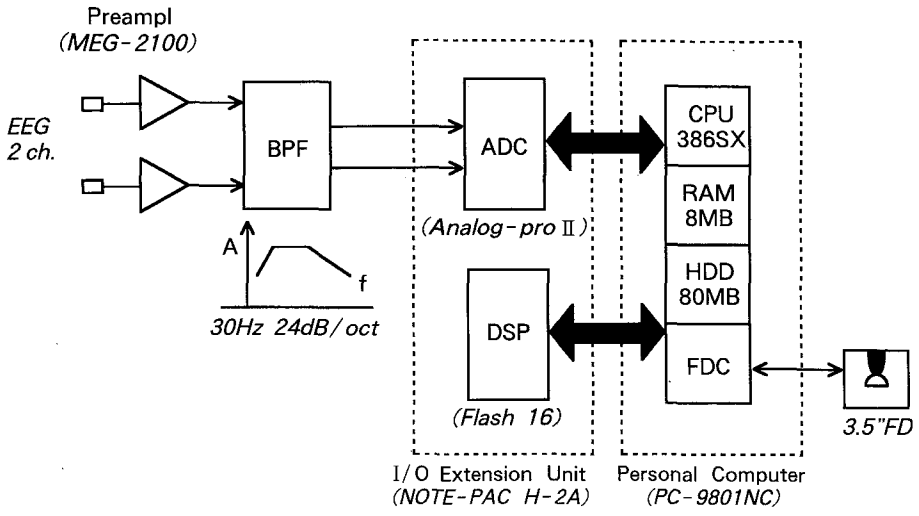

Fig. 1. System block diagram. *Preampl*, preamplifier; *EEG*, electroencephalogram; *BPF*, band-pass filter; *ADC*, analog-to-digital converter; *DSP*, digital signal processor

PUS, Kobe, Japan) housed in an interface extension unit (NOTE-PAC H-2A, Contec, Tokyo, Japan).

The FFT technique used for frequency analysis in DSA is described below. Because the sampling interval was set at 10 ms, the maximum frequency was 50 Hz, but the analysis was displayed up to 25 Hz on the screen. Also, as the sample number was 512, one epoch (data length) was 5.12 s, and the frequency resolution was 0.2 Hz. A longer epoch may be undesirable because of increased spectrum errors which are large enough in FFT technique. A spectrum of longer durations through any number (n) of 5.12-s epochs was obtained by smoothing out using ensemble averaging without increasing the errors. In other words, each line in DSA is the mean spectrum for n × 5.12 s. The program was written in C language.

Our DSA display converts the magnitude of power to 8 colors, i.e., white, red, pink, yellow, green, light blue, blue, and black in decreasing sequence of power, and may be regarded as a flattened image of CSA. The colors are not equally assigned in proportion to the magnitudes of power but more preferentially to the smaller magnitudes so that minute changes in lower power can change the color readily.

Comparing two power spectra obtained by frequency analysis, it is possible to obtain the t profile [1] by Student's paired *t*-test to see whether there is a significant difference between the pair of powers in the same 1-Hz interval consisting of five spectral data. One of the 12 colors in Fig. 2 is assigned to each t value and these colored 1-Hz segments make up a t profile. The latter in turn is drawn on top of the other sequentially to compose our DTA (Fig. 3). In other words, if the difference between a pair of spectral data is designated as d_i (i = 1, 2, . . . N), the mean of the d_i, i.e., $\bar{d}$, is given as:

$$\bar{d} = (1/N) \sum_{i=1}^{N} d_i$$

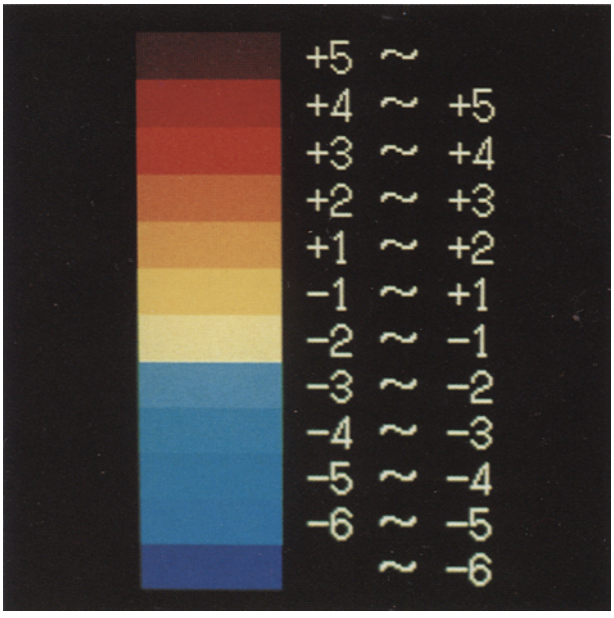

Fig. 2. Twelve colors representing t values in density-modulated t's array (DTA). Reddish colors signify an increase in power and bluish colors signify a decrease

and the unbiased variance of d_i, i.e., V, as:

$$V = \{1/(N-1)\} \sum_{i=1}^{N} (d_i - \bar{d})^2$$

and t is calculated as

$$t = \bar{d}/SQR(V/N).$$

The t value is displayed with color for each 1-Hz interval. Furthermore, to improve the accuracy of the technique, spectral data in 1-Hz intervals on both sides of the target interval were added together to make up 15 for N instead of 5. Three kinds of DTA can be made

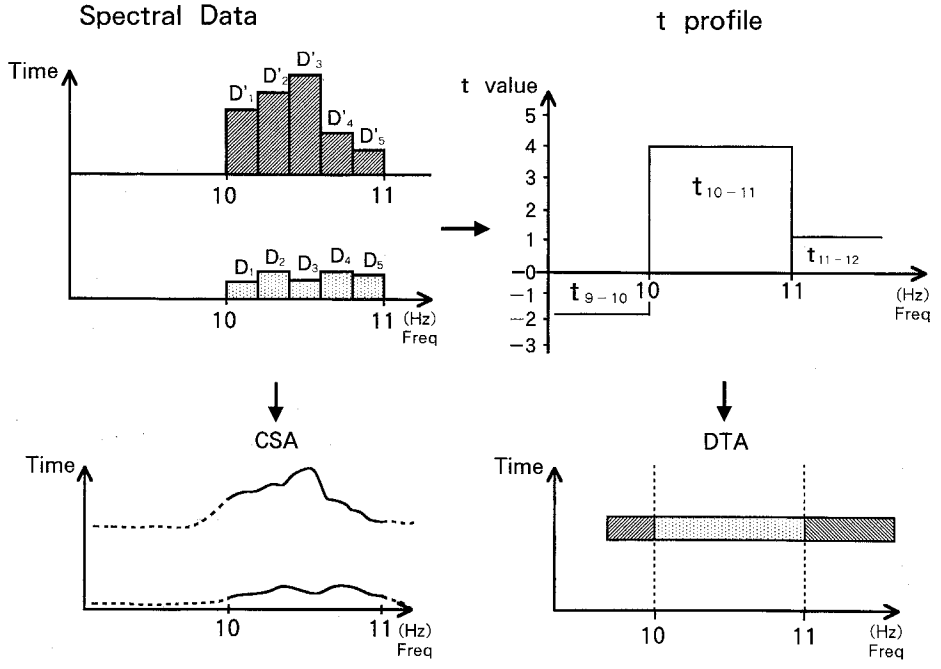

Fig. 3. Production chart of DTA made from spectral analysis and Student's *t*-test. *CSA*, compressed spectral array

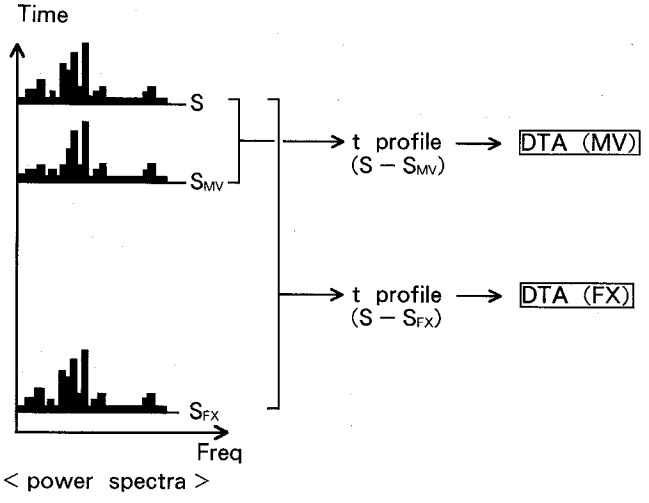

Fig. 4. Two types of DTA. *DTA(FX)* compares each spectrum with the fixed spectrum. *DTA(MV)* compares each spectrum with the spectrum preceded by five spectra. (*S*) each spectrum, (S_{FX}) the fixed spectrum, (S_{MV}) the spectrum preceded by five spectra

according to our selection. One is DTA denoting the difference between two spectra of EEGs from two leads (F3 and F4); and the others are DTA(FX) and DTA(MV) which compare each spectrum with the control spectrum in one lead (F3 or F4), as shown in Fig. 4. DTA(FX) was defined as the DTA whose control spectrum was fixed previously by us, and DTA(MV) was defined as the DTA whose control spectrum preceded by five spectra and moved in turn one by one. DTA(FX) and DTA(MV) were provided in this study because the main purpose was to detect EEG changes over time after administration of drugs rather than brain ischemia. If the sedation level varies very slowly, it may be easier to get hold of such variations with DTA(FX). The t values ranging from −2 to +2 were displayed in three colors of the yellow color group, and those of +2 and more in four colors of the red color group, meaning an increase in power. The t values of −2 and less were displayed in five colors of the blue group, meaning a decrease in power. With N = 15, there were 14 degrees of freedom, so that differences were taken as significant when $t > +3$ and $t < -3$ ($P < 0.05$). In short, DTA shows in color the frequency at which the change has occurred on the EEG and how great the change is, that is, whether it is statistically significant.

Patients and anesthetic management

Chosen as subjects were 10 ASA-1 patients (four men and six women) aged between 17 and 50 years who had no past history of brain diseases and who were scheduled for knee or ankle surgery without use of electric surgical unit. The patients had been informed of the objective and the procedures of the study, and their consents had been obtained. The study design had also been approved by the Ethics Committee of Tokai University Hospital.

The patients had been premedicated orally with pentobarbital, 50 mg 90 min before, and injected intramuscularly with pethidine 35 or 50 mg, and atropine 0.5 mg 30 min before arrival in the operating room. Spinal anesthesia was performed with 0.5% bupivacaine hydrochloride by puncture at a site between L3

and L4. The analgesic region required for each operation was ensured 15 min after the injection of bupivacaine. Inhalation of 50% nitrous oxide in oxygen by mask was begun 10 min after the beginning of EEG derivation, and a fivefold dilution of midazolam in distilled water for injection was administered intravenously at a dose of 0.1 mg/kg in 1 min. In addition to the EEG monitoring, blood pressure, heart rate, respiratory rate, body movement, and eyelash reflex were examined at 5-min intervals to monitor the sedation level. If sedation was judged to be too light according to the parameters other than the EEG, midazolam was additionally administered at a dose of 0.05 mg/kg. Nitrous oxide was withdrawn on completion of the operation. If a patient did not awake sufficiently 5 min after withdrawal of nitrous oxide, flumazenil, a specific benzodiazepine antagonist, was administered intravenously at a dose of 0.2 mg.

Results

Immediately following the administration of the drugs, the power at the frequencies between 15 and 20 Hz increased. However, the power at these higher frequencies disappeared gradually and the power in the delta band and the smaller one in the alpha band became predominant. This pattern of dominant-band shift on the DSA and DTA was observed in all the patients. In three of the patients, the sedation level remained stable as judged by the absence of body movement, quiet, regular breathing, and stable hemodynamics as well as steady EEG frequency distribution throughout the operations. They awoke from anesthesia rapidly on withdrawal of nitrous oxide, with return of the power at the higher frequencies. An example of the DSA and DTA from a 26-year-old male patient is shown in Fig. 5.

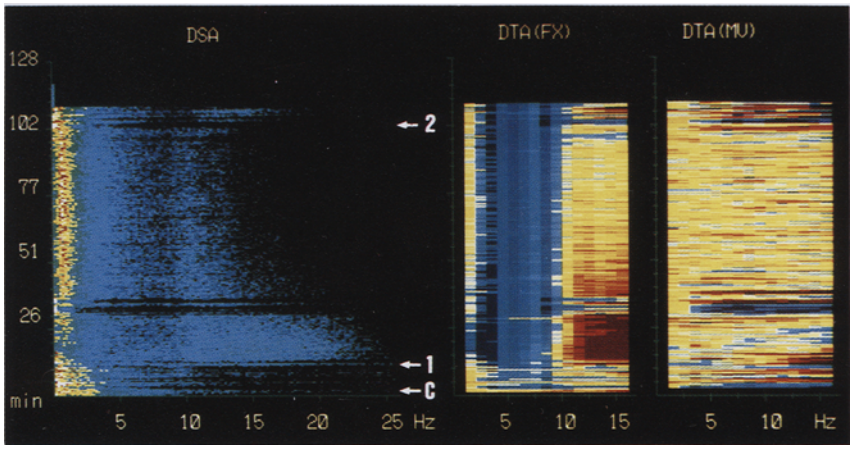

Fig. 5. *DSA* and *DTA* from a 26-year-old male patient. One line expresses 30.72 (5.12 × 6)-s EEG. (*C*) Control spectrum for *DTA(FX)*, (*1*) administration of midazolam and nitrous oxide, (*2*) withdrawal of nitrous oxide

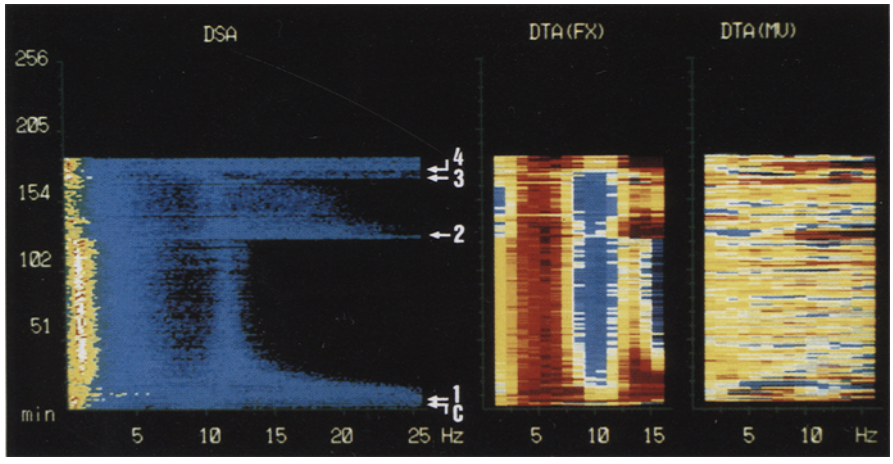

Fig. 6. *DSA* and *DTA* from a 20-year-old female patient. One line expresses 61.44 (5.12 × 12)-s EEG. (*C*) Control spectrum for *DTA(FX)*, (*1*) administration of midazolam and nitrous oxide, (*2*) head move and additional injection of midazolam, (*3*) withdrawal of nitrous oxide, and (*4*) flumazenil injection

On the other hand, in the other seven patients, the power at the higher frequencies suddenly reappeared on the DSA and DTA during surgery, 67 ± 38 min (mean ± SD) after the administration of midazolam, and slight movements of the head and upper limbs were observed with rises in blood pressure and heart rate. In three of these seven patients, the EEG change, i.e., decrease in the power in the alpha band or increase in the power at the higher frequencies, preceded the physiological activities by a few minutes. By additional injection of midazolam, the body movements of these seven patients subsided and the EEG tended to gradually return to the state prior to the event. One of them rapidly awoke upon withdrawal of nitrous oxide. However, the other 6 did not awake even 5 minutes after withdrawal of nitrous oxide, although the fast wave power somewhat increased. Rapidly after they were administered with flumazenil 0.2 mg, they awoke with an increase in the power over a wide area on the processed EEGs. An example of the DSA and DTA from a 20-year-old female patient is shown in Fig. 6.

When any of the above-mentioned, clinically significant phenomena occurred, a color representing a t value greater than either plus or minus 3 was displayed on the DTA without fail.

Discussion

As EEG is noninvasive, can be continuously monitored, is easy to record, and is inexpensive, it is a clinically important brain monitor [2]. Although, on the raw EEG, the appearance of extremely slow waves or of differences between the right and left patterns as acute responses plays an important role as an alarm of brain ischemia, we have been researching a processing system for using the EEG in monitoring not only brain ischemia but also anesthetic depth. CSA [3] and the aperiodic conversion technique [4,5] display the background rhythm of EEG; there have been reports on the clinical use of the apparatus using these techniques [6–9]. CSA, condensing EEG information, makes EEG changes easy to visually grasp, while it is disadvantageous in that when a large power has appeared, the subsequent spectra are illegible for some time. This is particularly prominent in case of intermixture of an artifact. EEG is most likely to be affected by noise, and is often intermixed with the noise originating in body movement, electrocautery, a heart-lung machine, and an external pacemaker. On CSA, therefore, the spectrum displaying an artifact masks the following spectra, making them illegible. DSA, reported by Fleming and Smith [10,11], displaying the magnitude of power as the grade of gray scale, minimizes the above-mentioned drawback of CSA and has been used for monitoring EEG changes during carotid endarterectomy [12] and during hypothermia [13]. However, it is difficult to grasp power changes only by the grade of gray scale. For this reason, we made the changes very easy to visualize by displaying the power on DSA with 8 colors assigned to its magnitude.

On the other hand, there have been reports on spectral edge frequency, median frequency and the like as a parameter for objectively assessing EEG changes [14–19]. However, each of them is not always the best parameter for monitoring EEG changes. That is because it is occasionally difficult with these parameters to assess the similarity, or rather dissimilarity between power spectra on a real-time basis. For example, the spectral edge frequency which is very popular as a parameter may not be altered even if the dominant power shifts as shown in Fig. 7. The spectral edge frequency is an indicator of changes in power in the whole frequency band, while DTA is a compressed image of the t profiles that compare the power spectra by means of statistical processing to analyze the similarity of back-

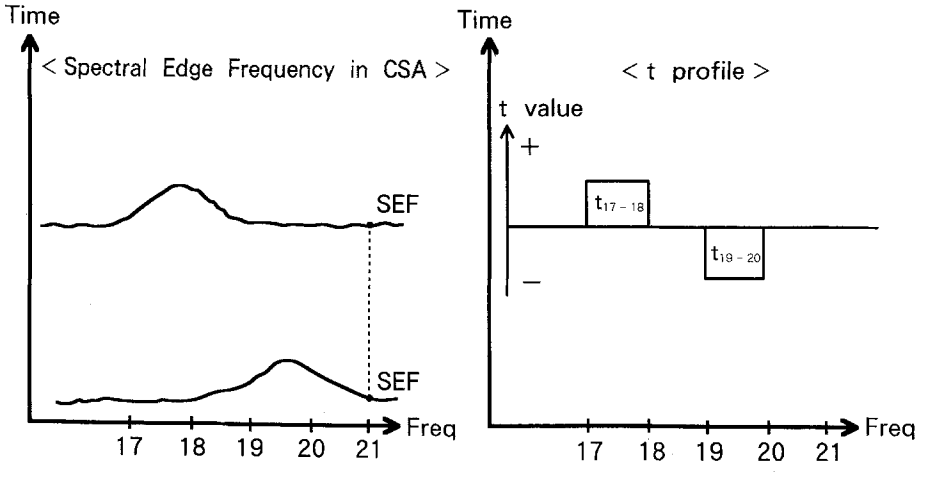

Fig. 7. Exemplified difference between spectral edge frequency (*SEF*) and t profile. *Left*, spectral edge frequency may not change as a parameter. *Right*, t profile manifests degree of EEG change at each 1-Hz interval without fail

ground rhythms of EEG. DTA is a very sensitive monitoring technique that makes it possible to objectively find how large a power change has occurred and at what frequency it has occurred. Because DTA is a kind of compressed image like DSA, it certainly minimizes the effect of artifacts carried by the raw EEG. As power in 1-Hz intervals is a little affected by those in the adjacent intervals, spectral data on both sides were considered in the t test of each interval to improve the accuracy of DTA. As this technique did not fail to display a color corresponding to a t value when a clinically significant change occurred, setting a limit for t values on DTA may be used as a criteria like other parameters in monitoring EEG.

Under spinal or epidural anesthesia, benzodiazepines are often used for sedation. Among others, midazolam is recently favored because of its short plasma elimination half-life (1.2–3.8 hours) [20]. However, when using intravenous anesthetics (or sedatives) it is difficult to determine the optimal initial dose, the timing of additional administration, and the optimal additional dose; therefore, the potential for intraoperative awareness cannot be completely ruled out when they are administered. It has been reported that midazolam is associated with the occurrence of severe anterograde amnesia [21]; none of the patients entered in this study had intraoperative memory, but amnesia may be brought incompletely in some cases, depending on the dose and on the passage of time. Nitrous oxide is also frequently used, but it has been reported that this agent is associated with the onset of acute tolerance to sleep [22]; and it also involves the risk of the patient regaining consciousness during the operation.

A 1%–3% incidence of awareness during general anesthesia has been reported [23,24]; and the incidence has been reported to be even higher especially under balanced anesthesia [24–27]. It is usually prevented by assessing the anesthetic depth chiefly as changes in hemodynamics, but these changes are not, in reality, intimately correlated with the anesthetic depth [3,18,27]. This study was therefore intended to investigate how the sedation level could be monitored on the processed EEG that we have developed.

EEG changes with administration of nitrous oxide have been reported to include an increase in fast wave components in the early stage of loss of consciousness [28]; and that fast wave components generally decrease, and slow wave components increase [29]. EEG changes reported with administration of midazolam include increases in fast wave components [30]. What we observed in this study is the combined effects of nitrous oxide and midazolam in the later phase toward awakening when dominant slow waves are replaced with fast waves. As shown in our study, there are a few patients who can recover physical activities and EEG changes simultaneously. Sudden awakening may not be predicted in those cases even with our monitoring technique. However, processed EEG provides a means of monitoring the sedation level and indicating when and how much additional sedatives are to be given to keep the anesthesia stable. Every patient who moved had a coincident change in frequency distribution in this series. On the other hand, movement cannot be an indicator of anesthetic depth during general anesthesia with the use of a muscle relaxant. An immobilized patient may be aware. Recognition, if not prevention, of this situation may be facilitated by monitoring the processed-EEG pattern for the anesthetic agent used. In cases of delayed awakening, it is also a useful means to observe EEG changes with time; and especially with the use of antagonists, e.g., naloxone hydrochloride and flumazenil, it may be an indicator of re-sedation.

In conclusion, DTA could be performed on a laptop personal computer, and proved to be a versatile monitoring technique. DTA, testing power changes at each 1-Hz interval for significant difference, facilitates the visual and quantitative assessment of EEG changes, and is of high clinical utility in combination with the raw EEG, CSA or DSA. It is intended chiefly for the prevention of intraoperative awareness, the observation of lag of awaking, and the observation of re-sedation in the use of antagonists. Furthermore, this processed EEG may prove useful as an alarm technique for detecting brain ischemia in extracorporeal circulation, carotid endarterectomy, induced hypotension, and anesthesia in patients with cerebral disease.

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