NINDEX

TECHNOLOGY REVIEW

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Monitoring of electrical activity of the brain during surgery has been goal off research and development in the field of automatic electroencephalogram (EEG) analysis for decades. Controles S.A. and Dr. D. Cibils have developed a processed EEG parameter called "NINDEX" (from Narcosis INDEX), to quantify and express in a simple index the hypnosis state of the brain induced by the effects of hypnotic agent and other pharmacological agents.

Introduction

Clinical assessment of the effect of hypnotic agents (level of hipnosis) is usually performed by heart rate and blood pressure (hemodynamic variables). Hemodynamic variables are relative measures of the level of hypnosis, used by comparison with a baseline value.

The use of hemodynamic variables to assess the level of hypnosis has limitations, which may lead to overdosing or underdosing of anesthetic agents. In order to overcome these limitations, research efforts have turned to look for objective real time measures of the level of hypnosis, independent of the patient and independent of the type of hypnotic agent. At present, the best approximation to such measure is the visual assessment of the EEG. This technique allows a specialist to assess the level of hypnosis among 6 possible levels by using visual scales.

The assessment of the level of hypnosis by visual assessment of the EEG is not routinely used due to the difficulty of interpreting the EEG and due to the considerable cost that should be involved in the presence of a specialist exclusively to assess the level of hypnosis. However, this technique has led to the development of measures of the level of hypnosis by automatic EEG analysis. This document describes the development of one of such measures, NINDEX.

EEG changes with level of hypnosis

The EEG is a graphic record of the electrical activity of the brain. Although it's a stochastic process, decades of empirical observation have shown that certain statistical features of the EEG represent the state of the brain when subjected to the effect of hypnotic agents.

The assessment of the level of hypnosis by the EEG has been developed on the general principle that an awaken patient has a low-amplitude, high-frequency EEG signal while a deeply anesthetized patient has a high-amplitude, low-frequency EEG signal. The ideal overall pattern of EEG changes with increased hypnosis level is shown in Figure 1.

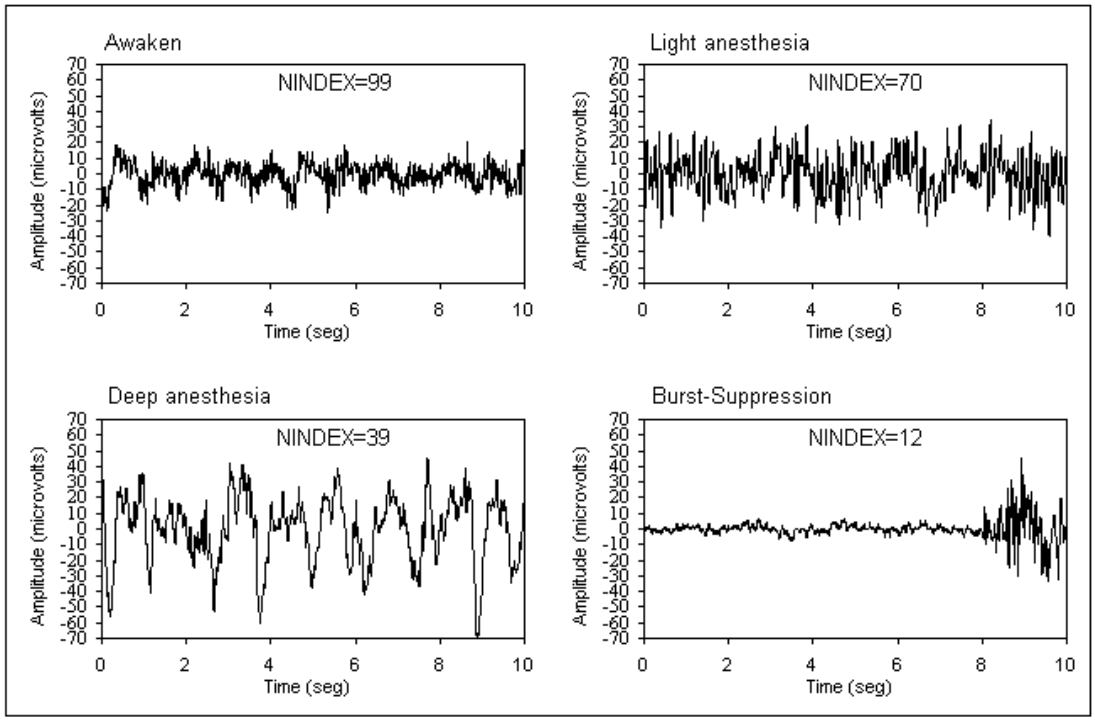

Figure 1: Ideal overall pattern of EEG changes with level of hypnosis

The EEG changes with the level of hypnosis may be analyzed by means of the frequency bands in Table 1.

Frequency band	**Frecuency range (Hz)**
Very low frequencies (Delta)	0-3.5 Hz
Low frequencies (Theta)	4-7.5 Hz
Medium frequencies (Alfa)	8-13 Hz
High frequencies (Beta)	14-30 Hz

Table 1: EEG frequency bands

In awake state, muscle activity or electromyogram (EMG) extends across all frequency bands including above 30Hz, and EEG activity is characterized by "alpha" and "beta" frequencies. After delivering a hypnotic agent to achieve loss of consciousness, the amplitude at low frequencies increases and overall amplitude of the EEG increases. At deeper levels of hypnosis, high frequency activity disappears and EEG overall amplitude continues increasing. At very high hypnotic doses the EEG develops a pattern known as "burst-suppression", which alternates intervals of normal amplitude activity and intervals of very low-voltage activity, including isoelectric activity. At even higher doses all activity disappears and the EEG becomes isoelectric.

Different EEG scales are available to visually assess the level of hypnosis. One of the most widespread is the Kugler scale, which establishes 6 levels of hypnosis according to Figure 2. These levels are referenced as “A”, “B”, “C”, “D”, “E” and “F”.

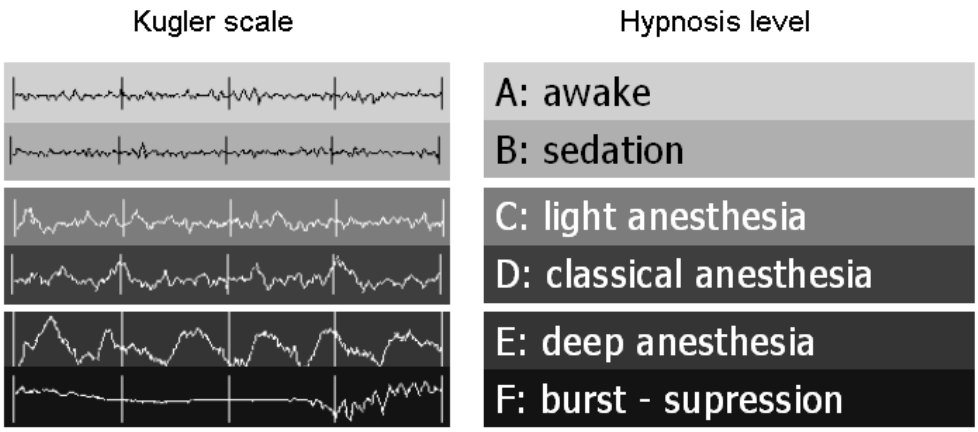

Figure 2: Kugler hipnosis levels

The statistical features of the assessment of the level of hypnosis by visual EEG scales have allowed the development of measures of the level of hypnosis by automatic EEG analysis. These automatic measures assess the level of hypnosis in the same way as would be done by visual assessment of the EEG, and then express the level of hypnosis by a number.

One such measures, developed from visual assessment by Kugler scale, is NINDEX. The correspondence between NINDEX values and Kugler scale is shown in Figure 3.

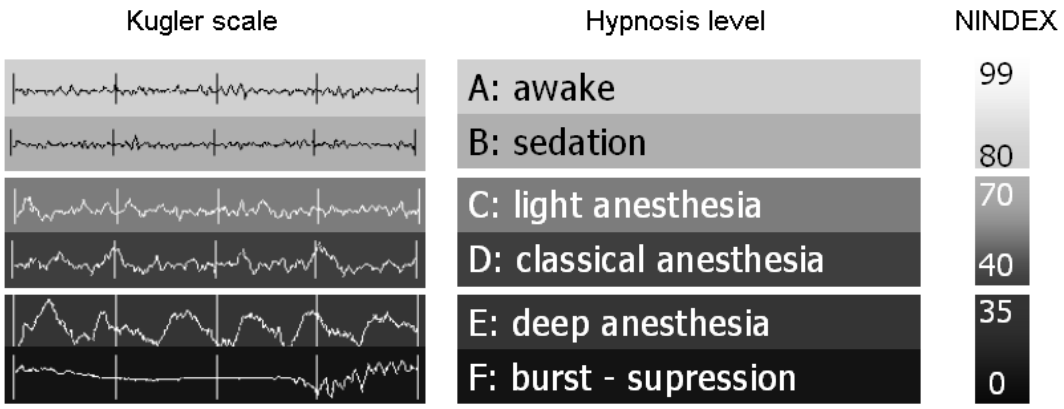

Figure 3: Correspondence between NINDEX values and Kugler scale.

Development of NINDEX

The development database

The development of a measure of the level of hypnosis by automatic EEG processing poses two main difficulties:

- The statistical nature of the visual assessment of the level of hypnosis by the EEG
- The large amount of artifacts that corrupt the EEG in a surgical block.

Therefore, development of such measure requires a statistical approach based on a development database which comes from hundreds of continuous EEG records of patients without known neurological disease and without treatment with psychoactive drugs, undergoing several different anesthetics (including isofluorane, sevoflurane, propofol, thiopental, etc.).

Two development databases are implemented for the development of NINDEX:

- EEG database (EEGDB): thousand of artifact-free EEG frames visually classified by Kugler scale
- Artifact database (ARTDB): thousand of EEG frames corrupted by artifacts, classified by artifact type.

Description of the NINDEX algorithm

Starting from the analysis of EEGDB, the most appropriate EEG features to asses the level of hypnosis are selected. These features are used to the development of an EEG classifier that automatically assesses the level of hypnosis in the same way as would be done by visual assessment of the EEG using the Kugler scale.

Starting from the analysis of ARTDB, a set of artifact detection algorithms are developed for detection and eventual correction of artifacts.

Starting from the EEG classifier and the artifact detection algorithms, NINDEX is determined in 3 steps according to Figure 4:

1) Artifact detection: starting from raw EEG, it returns a preprocessed artifact free EEG
2) EEG classification: starting from preprocessed EEG, it assesses the level of hypnosis according to Kugler scale
3) NINDEX calculation: starting from the level of hypnosis it returns the NINDEX value.

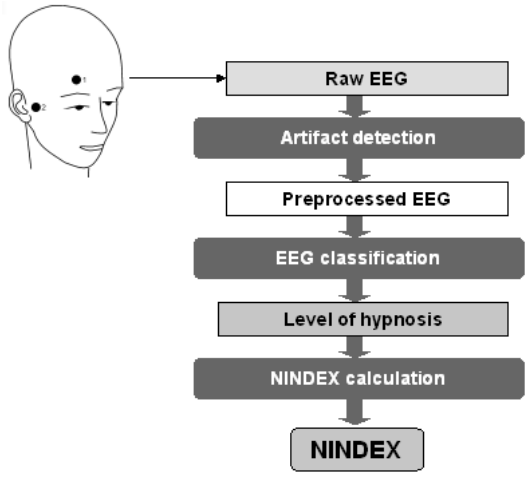

Figure 4: NINDEX algorithm

Continuous improvement

The NINDEX algorithm is of statistical nature. It was designed to evolve from ever more complete development databases, in a continuous improvement process of 3 steps:

1) Collection of EEG records
2) Classification of EEG frames and adding into the development database
3) Development of a new version of NINDEX algorithm.

NINDEX algorithm verification

The verification of each version of the NINDEX algorithm has three parts:

1) Verification of the EEG classifier algorithm
2) Verification of artifact detection algorithms
3) Verification of the NINDEX algorithm in real time.

For verification of the EEG classifier algorithm, the EEGDB is divided into two independent subsets: a verification subset with 75% of the data and a validation subset with 25% of the data. The EEG classifier algorithm is developed by an iterative semiautomatic process using exclusively the data of the verification subset. The following conditions must be met for EEG classifier algorithm verification:

- Error probability shall be less than 20% with respect to the visual classification in each of the 2 data subsets
- Error probability of discrimination between level A and levels C, D, E and F shall be less than 2% with respect to the visual classification in each of the 2 subsets of data.

For verification of the artifact detection algorithms, the error probability of detection of each type of artifact shall be less than 2% in ARTDB.

For verification of the NINDEX algorithm in real time, numeric values are assigned to the different levels of the Kugler scale, according to Table 2. The verification of the NINDEX algorithm consists of qualitative and quantitative assessment of hundreds of complete records of surgeries classified by Kugler scale. For each record, NINDEX trend chart is compared with the chart of numeric values assigned to visual assessment (according to Table 2). Along all EEG records, any difference between the NINDEX value and the visually assessed value greater than 15 shall be explained by artifacts.

Kugler level	Value
A	99
B	85
C	70
D	50
E	35

Table 2: Correspondence between Kugler levels and NINDEX values for verification of NINDEX algorithm.

Correspondence between NINDEX values and level of hipnosis

Figure 5 shows the distribution of NINDEX values for each level of Kugler scale, on approximately 4000 data from 100 EEG records. For each level of hipnosis, the average and the standard deviation of NINDEX are shown.

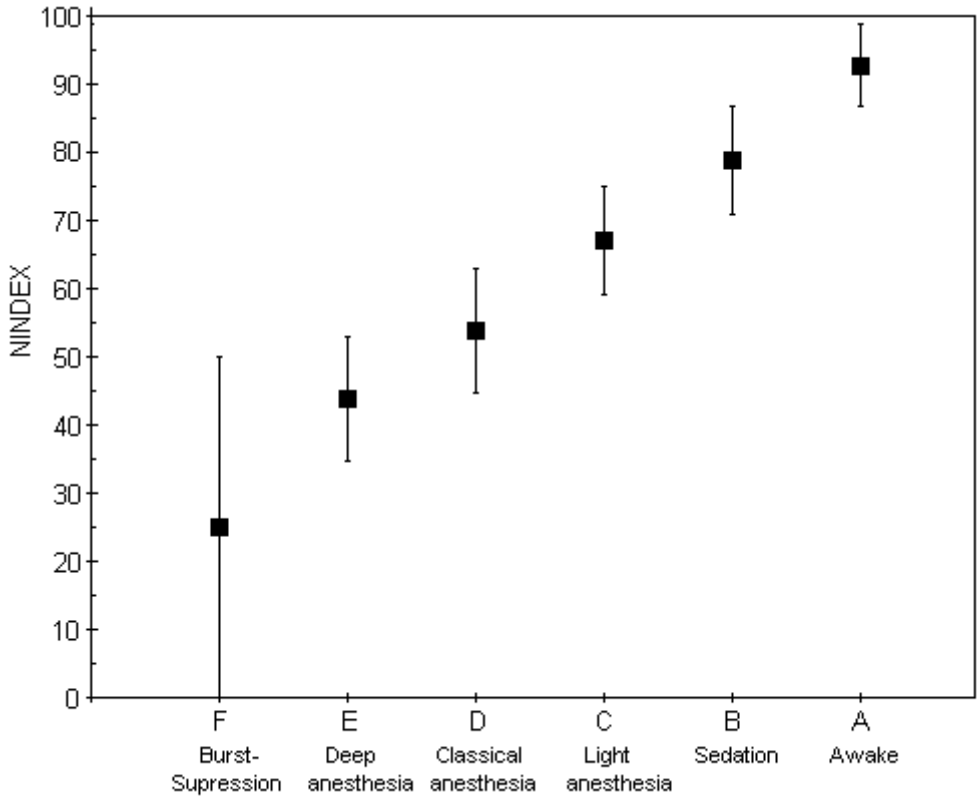

Figure 5: NINDEX values for each hypnosis level of Kugler scale.