Reprinted from the German Journal of Psychiatry · http://www.gjpsy.uni-goettingen.de · ISSN 1433-1055

A Decision Support System of Evoked Potentials for the Classification of Patients with First-Episode Schizophrenia

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Abstract

Background: Recently it has been shown that the second-pass parsing process of information processing, as indexed by the P600 component of event-related potentials (ERPs), elicited during a working memory (WM) test, is impaired in first episode schizophrenic (FES) patients.
Objective: The purpose of this study is to develop a decision support system – based on artificial neural networks (ANN) technology – for the classification of patients experiencing FES compared to healthy controls, utilizing the P600.
Method: We examined 14 FES patients and 23 healthy controls, matched for age, sex and educational level. The proposed system comprises two levels: the feature extraction level and the classification level. The former is based on the implementation of an autoregression model to estimate the corresponding coefficients, which form the input vector for the later level. The classification level consists of a multi-layer neural network.
Results: The performance of the system in terms of classification rate has been tested for a total of 15 abductions of each subject and for a specific order of the autoregression model according to the modified Schwarz criterion. The best classification rate, up to 100% has been achieved for the (C4-T6)/2 abduction compared to the other abductions and for all the subjects. Furthermore, the performance of the classifier for this abduction is consistent against the other adductions and for all the specific orders of the autoregression model implemented.
Conclusions: The findings indicate that activities related to the P600 component during a WM task and explored by the proposed system may be involved in FES. Additionally, the findings also indicate that this approach may significantly facilitate the computer-aided analysis of ERPs (German J Psychiatry 2002; 5: 78-84).

Keywords: event-related potentials, first-episode schizophrenia, feature extraction, autoregression model, classification, neural network

Received: 15.05.2002
Published: 12.09.2002

Introduction

The evolution of medical data processing has been given the opportunity to develop various diagnostic support systems for the classification of biosignals, including electroencephalograms (EEGs) and Event Related Potentials (ERPs) (Chabat et al., 2000).

In a previous study, an attempt to differentiate normal subjects and subjects diagnosed as suffering from severe obsessive-compulsive disorder (OCD) and from severe schizophrenia had been proposed (Tsoi et al., 1994). By recording one channel of EEG, they estimated the autoregressive model coefficients, as feature vector, and by using a multilayer neural network classifier, they correctly classified all normal cases, while missing one each of the obsessive compulsive and schizophrenia cases. In a similar approach, the use of scalar and multivariate autoregressive models to extract features from the EEG related to mental tasks had been explored (Anderson et al., 1998). These features were then classified with a standard feedforward neural network trained via the error backpropagation algorithm, resulting an average classification accuracy of 91.4% on novel EEG signals.

Furthermore, a new scheme for the identification of problems in neurological intensive care units has been proposed by identifying different EEG patterns present in the recording and providing their chronological distribution (Agarwal et al., 1998). According to this study, an automated-analysis of segmented EEG methods was proposed which relies on the segmentation of EEG into short stationary segments, the feature extraction of the EEG segments with relevant features, the classification of EEG segments into clusters based on the previous parameterisation, and the display of the different patterns of the EEGs as well as representative segments of each pattern type present in the recording. A modification of this method had also been presented by comparing the EEG from different parts of the brain (Agarwal et al., 2001).

Event Related Potentials (ERPs) provide a valuable means of studying brain-behaviour relations (Fabiani et al., 2000). Psychophysiological research postulated that the P600 component of ERPs (elicited between 500 and 800 ms or later after warning stimuli) indexes the completion of any synchronized operation immediately following target detection (Friederici et al., 1999). Recently, we have shown that second-pass parsing process of information processing, as indexed by P600 component of ERP, elicited during a working memory (WM) test, is impaired in first-episode schizophrenic (FES) patients (Papageorgiou et al., 2001). Schizophrenic patients as compared to controls, using conventional aspects of the P600 component, namely amplitude and latency, showed reduced P600 amplitude on left temporoparietal region and increased P600 amplitude on left occipital region. With regard to the latency, the patients exhibited significant prolongation on right temporoparietal region. The pattern of differences obtained classified 89.20 % of the cases correctly.

These findings are extended throughout this study by applying a decision support system, based on Artificial Neural Network methodology, for the classification of FES patients as compared to healthy controls, utilizing the P600 waveform.

Methods

Subjects

Fourteen never medicated first-episode schizophrenic patients (7 men and 7 women) with mean age 28.87 (±6.88) years were matched for age and sex to 23 healthy controls (12 men and 11 women) with mean age 29.73 (±6.09) years. The mean educational level was 11.2 (±3.0) and 13.3 (±0.5) years of schooling, for the patients and controls (p=0.02), respectively. All patients met DSM-IV criteria (American Psychiatric Association 1994) for schizophrenic disorder, paranoid type. The diagnosis was verified independently by two psychiatrists. Age at onset was defined as the earliest age at which medical advice was sought for psychiatric reasons or at which there was subjective distress or impairment of functioning (McGuffin et al., 1991). The controls were recruited from hospital staff and local volunteer groups. They were free of psychiatric and physical illness. All participants had no history of any neurological or hearing problems. All participants were right-handed as assessed by the Edinburg Inventory (Oldfield, 1971). Written informed consent was obtained from both patients and controls.

Stimuli and Procedure

Patients and controls were evaluated by a computerized version of the digit span Wechsler Test (Papageorgiou et al., 2001; Wechsler, 1955). The subjects sat in an anatomical chair placed inside an electromagnetically shielded room (an outline of the procedure is provided in Figure 1). A single sound of either high (3000 Hz) or low frequency (500 Hz) was presented to the subjects who were asked to memorize the numbers that followed.

Before any ERP recording, a pre-process was performed in order for the two sounds to be differentiated by the

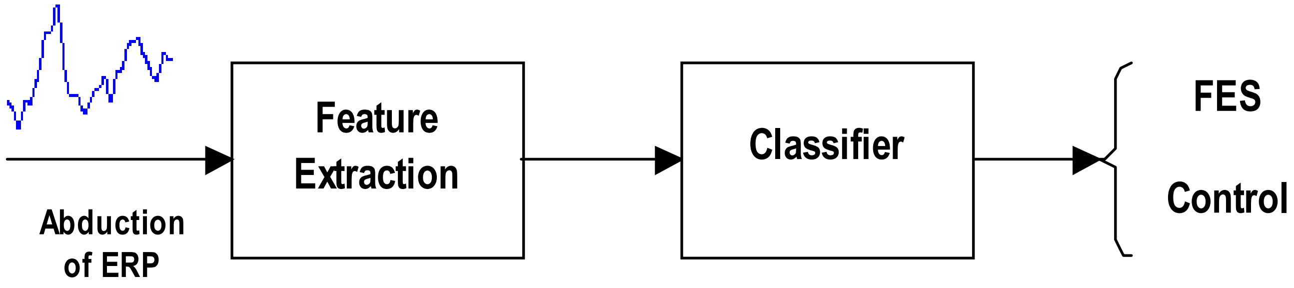
Figure 1: Outline of the Experimental Procedure

A B C D E F

↓ ↓ ↓ ↓ ↓ ↓

Time period	*Action*
AB (100 msec)	Administration of warning stimulus (500 or 3000 Hz, 65dB).
BC (1 sec)	Recording of ERPs.
CD (not in scale)	Computerized administration of the set of numbers of the Wechsler Direct Auditory Memory Test.
DE (100 msec)	Repetition of the warning stimulus
EF (not in scale)	Recording of the memory recall performance according to the accuracy of responses

Figure 2: Block Diagram of the proposed decision support system for the classification of the ERPs into two classes: FES and healthy controls



subjects. According to this process, various trials took place until each subject understood both the different tonalities and the requirements of the test, concerning the storage and retrieval of presented numbers. After the completion of the above-mentioned process, a rest period of five minutes was allowed, before the recording of the ERPs. The warning stimulus lasted 100msec. A 1-sec interval followed and then the numbers to be memorized were presented. At the end of the number sequence presentation, the signal tone was repeated and subjects were asked to recall the administered numbers as quickly as possible. The numbers were recalled in the same (low frequency tone) or in the opposite order (high frequency tone) to that presented to the subject.

ERPs were recorded during the 1-sec interval between the warning stimulus and the first administered number at a sampling rate of 500 Hz. The electrophysiological signals were recorded through Ag/AgCl electrodes. Electrode resistance was kept constantly below 5 kΩ. EEG activity was recorded from 15 scalp electrodes based on the International 10-20 system (Jasper et al., 1958), referred to both earlobes. An electrode placed on the forehead served as ground. The bandwidth of the amplifiers was set at 1-35Hz. During the administration of stimuli, the subjects had their eyes closed in order to minimise eye movements and blinks. Eye movements were recorded by EOG and recordings with EOG > 75μV were rejected. Warning stimuli as well as learning material, i.e. numbers to recall, were presented binaurally via earphones at an intensity of 65 dB sound pressure level. The evoked biopotential signal was submitted to an analogue digital converter and was averaged by a computerized system. Each recording session consisted of 26 repetitions of the trial.

Since the warning stimuli were of two different frequencies, one high and one low, it was not clear whether they could generate the same P600 - although the P600 component is included in the array of late-endogenous ERP components, which normally are not modality specific (Fabiani et al., 2000). We therefore conducted an analysis of both sounds in each group (13 high and 13 low frequencies) in order to ensure that there were not differences in the P600 waveforms caused by frequency modalities. As expected, there were no differences in the P600 waveform by frequency in each group.

The parameters calculated were ERPs for each subject as well as for each of the abductions Fp1, Fp2, F3, F4, Fz, C3, C4, Cz, C3-T5/2, C4-T6/2, P3, P4, Pz, O1, O2, resulting from the 26-test repetition. In this context, it should be noted that the positions C3-T5/2 and C4-T6/2 are used as electrode leads, because these positions correspond to brain areas serving verbal memory and language (Binder et al., 1997).

System Description

The proposed decision support system consists of two basic levels: the feature extraction and the classification levels, as shown in Figure 2. The input to the first level is the 500-800 ms time interval of the ERP signal for all subjects. The appropriate features are extracted and processed by the extraction level, and then fed to the classification level. The output of the system is one of two classes: patients experiencing first episode schizophrenia (FES) and normal subjects.

Feature Extraction Level

The feature extraction sub-system comprises the implementation of the autoregressive model (Wright et al., 1990). Let assume that the ERP input signal $x(t)$ can be defined as $\{x(n)\}_{n=0}^{N-1}$ which is a time domain representation of $x(t)$ sampled at latencies $t_n=nT_5$ where T_5 is the sampling period. This signal is termed as an autoregressive model if the following equation is satisfied:

$$x(n) = -\sum_{k=1}^{p} a_k x(n-k) + w(n) \qquad (1)$$

where p is the order of the model a_k(k=1,...,p) are the autoregression coefficients and $w(n)$ is the white noise with $(E\{w(n)\}=0)$ and $\mathrm{var}\{w(n)\}=\sigma^2_w$. In this case, the $\{x(n)\}$ is called an autoregressive process of order p and is denoted by $AR(p)$.

The calculation of the parameters a_k(k=1,...,p) can be obtained as follows: by multiplying both of the parts of the

Equation (1) by the factor $x(n\text{-}k)$ and by taking expectation $E\{\bullet\}$ yields that:

$$E\{x(n-k)x(n)\} = -\sum_{i=1}^{p} a_i E\{x(n-i)x(n-k)\} + E\{w(n)x(n-k)\}$$

(2)

Considering that $r_{xx}(k)=E(x(n\text{-}k)\ x\ (n))$ where $r_{xx}(k)$ shows the autocorrelation function and $E\{w(n)\ x\ (n\text{-}k)\}=\sigma^2_w\delta(k)$, where $\delta(k)$ is the impulse response, Equation (2) becomes:

$$r_{xx}(k) = -\sum_{i=1}^{p} a_i r_{xx}(k-i) + \sigma_w^2 \qquad (3)$$

and in matrix form:

$$\begin{bmatrix} r_{xx}(0) & r_{xx}(1) & \dots & r_{xx}(p-1) \\ r_{xx}(1) & r_{xx}(0) & \dots & r_{xx}(p-2) \\ \vdots & \vdots & \ddots & \vdots \\ r_{xx}(p-1) & r_{xx}(p-2) & \dots & r_{xx}(0) \end{bmatrix} \begin{bmatrix} a_1 \\ a_2 \\ \vdots \\ a_p \end{bmatrix} = - \begin{bmatrix} r_{xx}(1) \\ r_{xx}(2) \\ \vdots \\ r_{xx}(p) \end{bmatrix}$$

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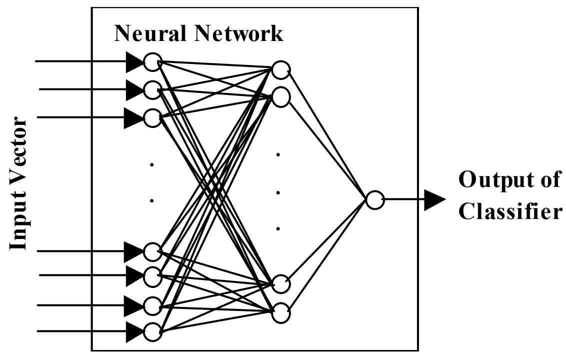
$$\sigma_w^2 = r_{xx}(0) + \sum_{i=1}^{p} a_i r_{xx}(i) \qquad (4)$$

Equations (4) are termed as Yule-Walker equations (Karagiannis et al.). Solution of the Equations (4) for the unknown AR parameters $a_1 \dots a_p$ can be obtained recursively using the Levinson-Durbin Method (Karagiannis et al.) which reduces the computational complexity of the solution.

Classification Level

The second level of the proposed system is a classifier, implemented with neural networks (NNs) (Masters, 1993). In this system, the classifier consists of a single NN with three layers (see Figure 3).

Figure 3: Architecture of the Classifier



The input layer consists of a number of neurons equal to the number of the selected features. The hidden layer has a variable number of neurons. The output layer consists of one neuron, encoding the two classes of the subjects: FES and normal (0=FES and 1=normal). The back-propagation algorithm with adaptive learning rate and momentum has been used in order to train the NN (Haykin, 1999). The initial weights of the neurons have been randomly selected in the range [−1.0, +1.0]. The log-sigmoid and tan-sigmoid activation functions have been used for the hidden and the output layer, respectively. The appropriate number of hidden neurons, and the values of the learning rate and the momentum have been estimated using a process of trial-and-error until no further improvement in classification could be obtained.

In order to avoid overtraining and achieve an accepted generalization in the classification, three data sets have been selected: training set, validation set, and testing set. The NN is trained using the training set and the training phase stops when the performance in the validation set is maximized. The generalization ability is tested using the testing set, which contains samples that have not been used previously.

Results

According to the description of the proposed system in Figure 2, the input of the system consists of the 500-800 ms time interval of an ERP abduction signal of the subjects. For each abduction, the autoregression coefficients are firstly calculated, forming the feature vector, which is then fed as an input to the classifier. The dimensionality of the feature vector coincides with the order *p* of the autoregression model implemented. Thus, for each input signal, the performance of the system, in terms of classification rate, may depend on the order of the autoregression model implemented. Extensive trials with different orders are the ideal solution to obtain the optimum order of the model for the specific application. However, this process is rather computationally extensive. In order to limit the search space for the order of the model, we adopted the modified Schwarz criterion according to which specific orders of the autoregression model are finally obtained which result an optimal representation of the input signal; thus narrowing the search process (Kay, 1988). This criterion has been applied to each abduction and for each patient providing order of the model in the range [3, 8] in order to be used in the classification process. In Tables 1 and 2, the specific orders of the autoregression model, obtained using the modified Schwarz criterion, and for each abduction, are presented for all FES and normal subjects, respectively.

Table 1. Optimum orders of the autoregression model according to the Modified Schwarz Criterion for each abduction and for all FES patients

FES Patients	Fp1	F3	(C3-T5)/2	C3	Fp2	F4	(C4-T6)/2	C4	O1	O2	P4	P3	Pz	Cz	Fz
FES-1	5	5	5	4	5	5	**3**	5	4	4	4	4	4	5	5
FES-2	5	5	5	5	5	5	**5**	3	5	6	5	5	5	5	5
FES-3	4	5	5	5	4	5	**3**	5	6	4	4	6	6	5	4
FES-4	5	4	4	5	4	4	**8**	4	3	4	5	4	3	4	4
FES-5	4	4	4	4	5	4	**5**	4	5	4	4	5	5	4	4
FES-6	5	5	5	3	4	6	**8**	4	4	4	4	4	4	5	6
FES-7	8	4	7	5	4	4	**5**	4	5	5	5	4	4	5	4
FES-8	4	4	4	3	4	4	**5**	5	4	3	4	3	4	3	3
FES-9	3	3	3	3	4	4	**5**	3	3	4	3	3	3	3	3
FES-10	4	4	4	4	4	4	**5**	4	4	4	4	4	4	4	4
FES-11	4	6	3	4	3	5	**6**	3	5	4	3	4	3	4	4
FES-12	5	4	4	4	5	5	**5**	5	5	7	6	5	4	5	5
FES-13	4	4	4	4	4	4	**5**	4	4	4	4	4	4	4	4
FES-14	4	5	6	5	4	5	**8**	5	3	5	5	4	5	5	5

In this study, a total of 37 subjects, comprising 14 FES and 23 normal have been used for the training procedure of the classification level. From the 37 samples, 23 have been used in the training set, 7 in the validation set, and 7 in the testing set. As shown in Table 3, the different classes are represented with 62% in the training set, 19% in the validation set and 19% in the testing set.

In Table 4, the classification rates of the proposed system for different abductions and for specific orders, according to the modified Schwarz criterion, are presented. 85% classification rate corresponds to one misclassified subject, 71% to two, 57% to three misclassified subjects and 100% to a correct classification for all subjects.

It can be observed that the best classification rate has been achieved for the (C4-T6)/2 abduction compared to the others. Also, the performance of the classifier for this abduction is consistent for the rest of the adductions and for all the specific orders of the autoregression model, according to the modified Schwarz criterion, achieving a classification rate of up to 100%. Specifically, the classification rate drops to 85% for the (C4-T6)/2 abduction for order 6 of the autoregression model (thus corresponding to misclassification of one subject), but it still remains the best rate compared to the rates of the other abductions.

Table 3. Distribution of the Two Classes in the Training, Validation and Testing Set

Class	Training Set	Validation Set	Testing Set
Normal (23)	15	4	4
FES (14)	8	3	3
Total	23	7	7

Table 2. Optimum orders of the autoregression model according to the Modified Schwarz Criterion for each abduction and for all healthy controls

Healthy Controls	Fp1	F3	(C3-T5)/2	C3	Fp2	F4	(C4-T6)/2	C4	O1	O2	P4	P3	Pz	Cz	Fz
HC-1	4	4	4	4	4	4	**4**	4	4	4	4	5	4	5	4
HC-2	6	5	5	5	5	5	**5**	5	5	4	5	5	5	5	5
HC-3	6	5	5	5	5	5	**6**	5	5	3	5	5	5	5	5
HC-4	4	4	4	4	4	4	**4**	4	4	4	4	4	4	4	4
HC-5	4	3	5	4	5	4	**4**	4	4	4	5	5	4	5	4
HC-6	5	5	3	5	5	5	**5**	5	5	5	5	3	5	5	5
HC-7	5	4	4	5	4	4	**3**	3	5	6	3	5	4	3	4
HC-8	3	3	4	5	5	5	**4**	5	4	4	5	5	4	5	5
HC-9	4	4	4	3	4	3	**3**	4	3	4	4	3	3	5	4
HC-10	5	4	4	5	4	5	**4**	5	5	5	5	4	5	5	5
HC-11	5	5	3	4	5	5	**5**	5	4	5	5	5	5	5	5
HC-12	3	3	3	5	3	4	**5**	5	4	5	5	5	5	5	4
HC-13	5	5	5	3	4	5	**3**	3	4	5	3	4	3	3	5
HC-14	4	5	3	3	5	5	**4**	4	4	5	5	3	5	5	5
HC-15	3	4	4	5	3	3	**3**	3	5	4	4	4	5	3	4
HC-16	4	4	4	4	4	4	**4**	4	4	4	4	4	4	4	4
HC-17	5	4	4	5	4	4	**4**	4	4	6	4	4	4	4	3
HC-18	3	5	5	5	4	4	**4**	3	3	3	3	3	3	3	5
HC-19	5	6	3	4	5	3	**3**	4	3	3	3	3	3	3	8
HC-20	5	5	5	5	5	5	**3**	4	4	6	3	5	5	5	5
HC-21	4	3	4	3	3	3	**3**	3	4	5	4	3	4	5	3
HC-22	4	4	5	4	6	4	**4**	4	5	4	4	5	4	4	4
HC-23	3	4	3	3	3	7	**3**	5	4	3	3	3	3	3	7

Table 4. Classification rates (%) for the optimum orders according to the Modified Schwarz Criterion for each abduction (best classification rates obtained presented in bold)

Abduction	Order 3	Order 4	Order 5	Order 6	Order 7	Order 8	Order 9	Order 10
Fp1	57	71	71	71	71	71	71	71
F3	71	57	57	57	57	57	57	57
(C3-T5)/2	85	57	71	71	71	71	57	57
C3	71	57	57	57	57	71	71	71
Fp2	57	71	71	71	71	71	57	57
F4	71	85	85	85	85	75	71	71
(C4-T6)/2	**100**	**100**	**100**	**85**	**100**	**100**	**100**	**100**
C4	57	57	85	85	85	71	71	71
O1	57	57	57	57	57	57	57	57
O2	57	57	71	71	57	71	57	71
P4	57	57	71	71	71	57	57	57
P3	71	71	57	57	57	57	57	57
Pz	57	57	57	71	71	57	57	57
Cz	57	57	71	71	57	57	71	71
Fz	71	71	57	57	57	57	57	57

Discussion

In this study, a decision support system for the classification of subjects with first–episode schizophrenia and normal has been presented, utilizing the P600 ERP component elicited during a working memory test. The system consists of two levels: the feature extraction and the classification level. The first level calculates a feature vector based on the calculation of the autoregression coefficients, whereas the second level is a classifier, implemented with feed-forward NN's. The feature extraction methodology is a linear-based approach according to which the signal's autoregression coefficients are estimated for a specific order. These coefficients can reproduce the input signal if the number of the initial values of the signal, equal to the order of the model, is known. Based on these parameters, a classification rate up to 100% has been obtained for the (C4-T6)/2 abduction and for most of the tested orders.

Taking into account, the obtained classification results based on the particular method and the classified differences achieved with the use of conventional exploratory analysis of differences e.g. t-tests and logistic regression models (Papageorgiou et al., 2001), it is obvious that the certain methodology is prevailing.

Although in this study we focus on methodological issues, we briefly discuss physiological implications of the present results. As mentioned, the current technique provides an optimal classification result that was localized to the right temporoparietal area, a brain region involved in the emotional aspects and the prosody of information processing. As a corollary, these findings are similar to those reported both in patients with chronic schizophrenia (Niznikiewicz et al., 2000) and in patients with FES (Hirayasu et al., 2000) presenting abnormal angular gyrus asymmetry using MRI methodology and suggesting that such abnormalities are specific in schizophrenia. Moreover, considering the fact that delusions and auditory hallucinations in schizophrenia are mostly derogatory and hostile in content, then the engagement of the right temporoparietal region in schizophrenia, as emergent from our results, might represent processing of the prosody (George et al., 1996) as well as an emotional response to its content (Canli et al., 1998).

This paper, as a more technical one, deals with the application of a multi-layer network analysis methodology of the P600 component elicited during a WM test in never medicated patients suffering from FES and normal controls in order to enhance automation of the classification, between the two groups. The proposed methodology correctly classified the groups compared, for the right temporoparietal abduction, indicating that activities signalised by P600 during a WM task and explored by such designed techniques may be involved in patients with FES. Additionally, these findings also indicate that this approach may considerably facilitate the computer-aided analysis of ERPs.

Moreover, ERP interpretation requires considerable training and it is currently restricted to personnel experienced and trained to read them. Within the proposed architecture, classification between patients suffering from FES and normal ones can be achieved via automatic computer methods, such as the proposed decision system providing a classification rate of up to 100% for specific abduction. Currently, the feature extraction level of the system has been based on the use of a linear-based approach; this methodology must be seen as an initial attempt towards the parameterisation of the ERPs. In the near future, the feature extraction level of the proposed system could be enhanced in order to co-operate features extracted from non-linear methods, since many EEG activities can be described as non-linear stochastic processes (van Putten et al., 2001). Furthermore, the classification level of the system could also be expanded to a multi-output neural network, thus classifying different categories of neurocognitive abnormalities.

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