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Prediction of Neuroleptic On-Drug Response in Schizophrenic In-Patients by EEG*

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Summary. The subjects were 34 acutely ill in-patients who met the RDC criteria of schizophrenic psychosis, and 4 EEGs were recorded from each patient before, 2 h and 24 h after oral intake of a single dose of 150 mg perazine, and on the 28th day of the neuroleptic treatment period. As a criterion of clinical response a decrease of at least 66% in the schizophrenia-specific sum score of the Brief Psychiatric Rating Scale on day 28 relative to the baseline value was decided upon. The EEGs were assessed using a newly developed procedure which takes into consideration 4 derivations simultaneously. As we tried to search out EEG variables with predictive value the statistical data analysis underlying our findings should largely by regarded as exploratory. Independent of day, responders (R) showed a tendency towards more low voltage desynchronized epochs (non-A stage) than non-responders (NR). Thus, R exhibited a higher degree of dynamic variability or a broader range of control of the spontaneous vigilance fluctuation (dynamic lability) than NR (dynamic rigidity). Furthermore, R and NR differed with respect to their time-dependent changes of non-A epoch frequencies before medication. While R showed a monotonous increase which is typical for normals, NR did not. Because of considerable inter-individual variability these group differences could not be used for individual prediction of the therapy response. By means of a qualitative data analysis R could be distinguished from NR with regard to various test dose-induced changes of the topographical distribution of absolute alpha power. All the group differentiating variables showed a time course of the same kind: R showed a prompt and ample deflection and the same recovery of baseline; NR, in contrast, showed no significant deflections at all. These findings are in line with the results concerning the dynamics of vigilance and certain claims of earlier authors according to which EEG changeability should be decisive for therapeutic outcome. The prediction power could be enhanced considerably by means of a classification procedure for qualitative data, which allows a combination of two variables. Allowing the three qualities increase, decrease and no change a combination of two variables rendered $3^2 = 9$ possible answer patterns, the individual patient showing only one of these patterns, of course. A correct classification of 26 out of the 34 patients (76.5%) was achieved by 12 different 2-fold combinations of variables. Eventually, we tried to base an individual prediction upon a multitude of selected, clearly response predicting answer patterns. We were governed by the idea that a patient who shows the total number of the response predicting answer patterns, can be regarded as R with much higher probability than a patient who shows only half the number or even none of them.

Key words: EEG – Schizophrenia – Neuroleptic treatment

Introduction

Itil (1980) stated that one of the major goals in schizophrenia research was the prediction of the therapeutic

* This investigation is dedicated to the late Prof. Dr. H. Selbach who followed its proceeding with vivid interest

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outcome based on objective criteria: "Based on the test dose procedures using computer-analysed EEG, it may be possible to tailor the type of the drug treatment and the dosage for each individual patient."

The first step toward this goal consists of the definition of EEG features with potentially predictive power. As Bente (1961) stressed, quantification of isolated parameters like frequencies and amplitudes could not be expected to succeed. Spatio-temporally defined patterns of higher complexity ("höhere Strukturmerkmale"), should rather be considered. Such a demand is based on the assumption that the EEG reflects the neuronal bioelectric mass action as well as its dynamic states of order (levels of vigilance sensu Head 1923), and furthermore that psychotropic agents effect a complex modification of brain electrical organization. Consequently an operationalization is required, both of the different states of order eo ipso (level of vigilance) and of their time-dependent variability (dynamics of vigilance).

With regard to the dynamics of vigilance there were early hints that a lack of a clear-cut EEG effect after intake of a neuroleptic drug usually indicates that no therapeutic effect upon schizophrenic symptomatology could be expected (Borenstein and Dabbah 1961; Schneider 1961). This view was confirmed and extended later by a number of authors. Igert and Lairy (1962), for example, stated that patients with poor therapeutic response (essentially those with a chronic course of illness) were characterized by "hypersynchronous" continuous occipital alpha activity in their baseline EEGs. Patients with good response, on the other hand (essentially those with a recidivating course of illness), showed scanty and discontinuous alpha activity. Bente (1963) stated: "In those cases in which a low voltage baseline EEG with poor alpha activity is replaced by a well-marked continuous alpha activity under neuroleptic medication, an excellent therapeutic effect upon paranoid-hallucinatory phenomena can be expected with high probability". This statement has been repeatedly confirmed (e.g. Feigenberg 1964; Helmchen and Künkel 1964; Itil et al. 1966, 1975). Furthermore, Itil et al. (1969) reported that pharmacological transformation of hypersynchronous alpha EEG, for example by LSD, to a desynchronized low voltage EEG significantly increases therapeutic responsiveness to subsequent neuroleptic treatment.

When investigating drug-induced changes of the dynamics of vigilance it does not seem to be necessary to take into consideration the total range of states of order since we are only interested in group discriminating initial effects. Neuroleptics typically cause certain modifications within the subvigilant stage A (Bente 1979). Furthermore, a change of the proportion of stages A and B can be expected. Our procedure of analysing the resting EEG (Ulrich and Frick 1986) permits automatic differentiation of epochs representing stage A from the total of all non-A epochs. The time course of non-A epochs – physiologically a steady increase, beginning with minutes 4 to 6 of the recording period, can be expected (Ulrich et al. 1986, 1987) – is a measure of the dynamics of vigilance.

Drug-induced changes of the mean vigilance level can be inferred from the topographical distribution, i.e. from the anterior-posterior ratio of alpha activity according to the definition of subvigilant stages A_1 to A_3 which was given by Bente (1964, 1979). Bente (1984) also showed that stage B, which has been characterized by Roth (1961) by shortage of alpha activity (stage B_1) and/or a prevalance of theta (stage B_2) or delta activity (stage B_3), exhibits an anterior shifting of the (more or less sparse) alpha activity. Assuming that this concept is valid, an approximate estimation of the mean vigilance level (across the recording period) can be derived from the anterior-posterior ratio of alpha activity. Naturally this only applies to EEGs which show at least a certain amount of alpha activity.

Whereas, supported by numerous psychopharmacological studies (e.g. Bente 1961, 1963, 1981) the importance of the anterior-posterior ratio in evaluating EEG vigilance should be undisputable, the left-right ratio has hardly been paid attention to until now. We share the opinion put forward by Matoušek et al. (1981) that lateralization of alpha activity is also vigilance dependent (Ulrich and Frick 1985).

As can be seen from the literature, EEG topography increasingly gains in interest in various fields of investigation (Goldstein and Stolzfus 1973; Giannitrapani and Kayton 1974; d'Elia et al. 1977; Etevenon et al. 1979; Matoušek et al. 1981; Shagass et al. 1982; Künkel 1982; Tucker 1983; Gruzelier 1983; Laurian et al. 1981, 1983; Etevenon 1984; Merrin et al. 1986). While the importance of topography is generally agreed upon, no reasonable conceptual frame-work exists. A quotation by Gruzelier (1983) directly refers to the aim of our study: "It is perhaps not too far fetched to posit that an alteration of lateral balance underlies in part the therapeutic efficacy of drug treatment."

Thus, there are two methodologically different approaches for dealing with EEG prediction. Relating to earlier observations, the first part of our investigation deals exclusively with whether, and how far, predictions may be based on the dynamics of vigilance. In the second part this question will be followed up with respect to the topographical distribution of alpha activity.

Subjects and Design

This EEG study was part of a more comprehensive investigation in which, based on the so-called test dose model (May et al. 1976; Gaebel et al. 1986), the predictive power of various neuroleptic initial effects (psychopathology, subjective response, hand writing, plasma level of mother compound and metabolites, prolactin, etc.) was studied.

Subjects were acutely ill in-patients who fulfilled the RDC criteria (Spitzer et al. 1978) of a schizophrenic psychosis and who were kept drug-free for at least 3 days. A further criterion for inclusion was the existence of 4 EEGs, as provided for by the design of the study, which had to be essentially free of artefacts. Our sample consisted of 34 patients: 20 males and 14 females with a mean age of 32.4 ± 12.1 (18 to 63) years and a mean age of illness onset of 25 ± 9.3 (15 to 36) years.

The 4 EEGs were recorded before medication (day 0, 8.00 a.m.), 2 h after oral intake of a single dose of 150 mg perazine (day 1, 10.00 a.m.), 24 h after intake of the test dose (day 2, 8.00 a.m.) and after 4 weeks of drug treatment (day 28, 8.00 a.m.). Due to former hospitalizations all patients (except 2) were well-acquainted with the recording procedure. Immediately before recording the on-drug EEG, blood was obtained for determination of the perazine plasma level. After recording the 3rd EEG (day 2), patients were treated with flexible dosage perazine, the daily mean dose being 454 ± 190 mg.

Psychopathology was assessed by the Brief Psychiatric Rating Scale (BPRS, Overall and Gorham 1961). As a criterion of clinical response a decrease of at least 66% in the schizophrenia-specific sum score (using thought disturbances, activation and hostility/suspiciousness) on day 28 relative to the baseline value was settled upon.

EEG Recording Technique

A total of 13 min of EEG under resting conditions (eyes closed, semi-recumbent position, free floating attention) was simultaneously recorded on paper chart and stored on FM analogue tape. The Ag/AgCl electrodes were fixed by collodium according to the 10–20 system in parasagittal montage referenced to the ipsilateral ear. Electrode skin impedance which did not exceed 5 kΩ was checked before each recording. We used a low pass filter of 70 Hz and a time constant of 0.3 s. The size of the signal was calibrated by applying 70 μV (≙ 1 cm) DC steps to the amplifier in order to allow visual control of filter and time constant.

EEG Data Analysis

Since the procedure has been described in detail elsewhere (Ulrich and Frick 1986), only a condensed summary will be presented here. This procedure is an attempt to quantitatively reconstruct visually defined patterns of EEG vigilance. Beginning with minute 4 of the recording, 10 min of the EEG, were subjected to quantitative analysis. The leads F3/A1, F4/A2, O1/A1 and O2/A2 were analysed. After consecutive segmentation into 300 2-s epochs and A/D conversion (sampling frequency of 64 Hz, anti-aliasing filter) the absolute power spectrum was estimated for each epoch applying Fast Fourier Transform (spectral resolution: 0.5 Hz, frequency range: 0 to 32 Hz). The resulting sequences of 300 periodograms represented the data base for the subsequent operations. For each epoch and for each lead the percentage of alpha power (7.5 to 13 Hz) relative to the total power (0 to 32 Hz) was calculated. This step was a prerequisite for automatic differentiation of epochs considered to be stage A from all other epochs. A non-A stage was present if no single lead showed a definite alpha rhythm. The criterion for definite alpha rhythm was a minimum of 50% alpha power related to the total power. To record the increase in non-A epochs expected along with physiologically declining vigilance in the time course the rate of non-A epochs was determined separately for each minute of the 10 min recording period.

Because this was an essentially exploratory study we strived for a description of all potentially predictive topographical relationships between the 4 leads as comprehensively as possible. Taking into account only those epochs which had previously been determined to represent stage A, the following mean values were calculated for each individual EEG:

- absolute alpha power (7.5 to 13 Hz) of the leads F3/A1, F4/A2, O1/A1, O2/A2,
- using the absolute power two quotients of anteriorization, a left and a right one,

$$\left(AQ_l = \frac{F3/A1}{F3/A1 + O1/A1},\right.$$

$$\left.AQ_r = \frac{F4/A2}{F4/A2 + O2/A2}\right)$$

and two quotients of lateralization

$$\left(LQ_{anterior} = \frac{F3/A1}{F3/A1 + F4/A2},\right.$$

$$\left.LQ_{posterior} = \frac{O1/A1}{O1/A1 + O2/A2}\right),$$

– percentage of absolute alpha power of each of the 4 leads (PF3, PF4, PO1 and PO2) relative to the sum of the alpha power of all 4 leads combined.

To account for temporal variability we additionally calculated – now taking into consideration the total of 300 2-s epochs – the coefficients of variation (CV) of the parameters mentioned.

Results

Dynamics of Vigilance

Compared were 20 clinically defined on-drug responders (R) and 14 non-responders (NR). The groups did not differ with respect to age, gender, age of illness onset or baseline psychopathology (schizophrenia-specific BPRS score: 17.4 ± 8.5 vs 19.1 ± 6.8).

Individual Frequencies of Non-A Epochs. With individual numbers of non-A epochs during a total recording time of 10 min as an independent variable, a two-way repeated measure ANOVA was performed. Independent variables were groups G (R, NR) and days D (0, 1, 2, 28).

According to the main effect G ($F_{1,32} = 3.54$, $p = 0.07$), R ($\bar{x}$: 143) showed a tendency towards more non-A epochs than NR ($\bar{x}$: 82). The main effect D ($F_{3,96} = 3.07$, $p = 0.04$), which was indicative of the drug effect, underscored the sensitivity of the procedure to drug effects. There was no significant interaction G × D ($F_{3,86} = 0.36$, NS).

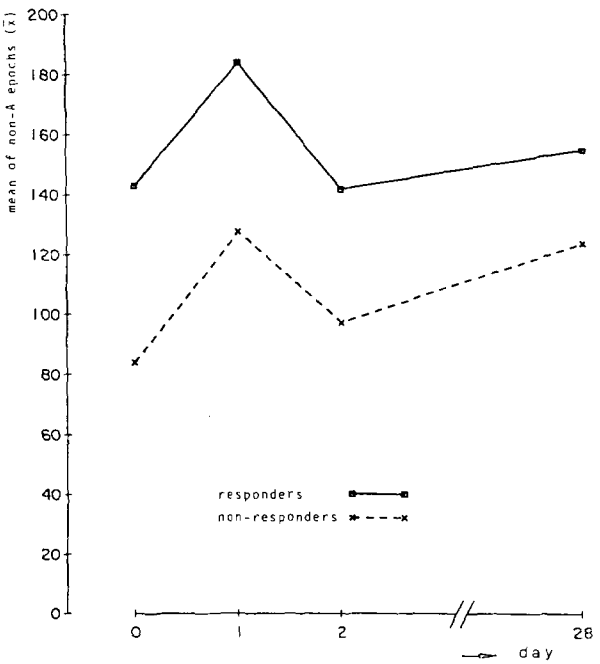


Fig. 1. Mean number of non-A epochs for a total recording period of 10 min

An eyeball evaluation of all paper charts showed that the quantitatively ascertained non-A epochs overwhelmingly corresponded to low voltage activity, more or less with a certain amount of interspersed fast beta activity. The paper chart samples (Fig. 2) can be regarded as representative of R and NR, respectively. This pattern matches the definition of a subvigilant stage B_1, as given by Roth (1961). Epochs with prevailing irregular theta (stage B_2) or delta activity (stage B_3) were comparatively rare. Because of considerable inter-individual variability prediction of the individual therapy response could not be based on the variable frequency of non-A epochs. Since the obtained group differences related to global frequencies (Fig. 1) they permitted only indirect conclusions regarding the dynamics of vigilance. Therefore, in a second step the frequency of non-A epochs as a function of the time course of the individual recording period were analysed.

Non-A Epochs in the Time Course. Table 1 gives the group mean values of the non-A frequency during each individual minute of the recording period.

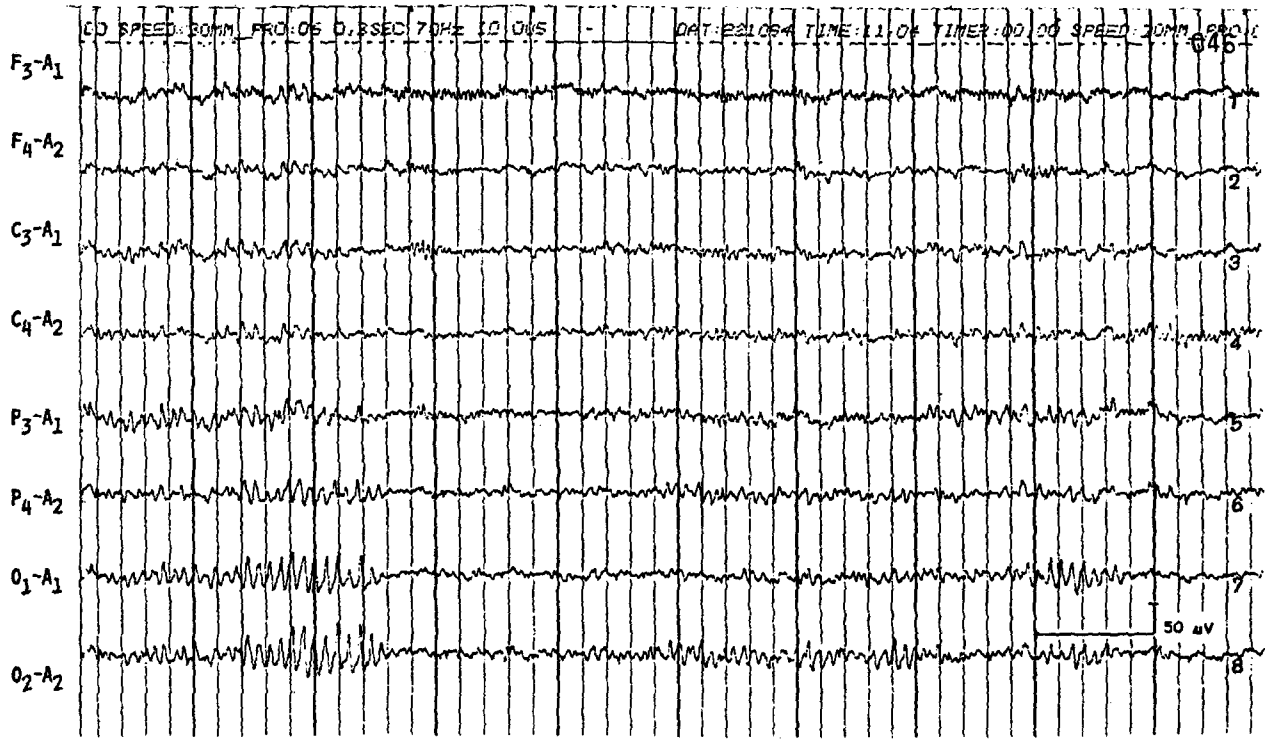
Two-way repeated measure ANOVAs, factors being group G (R, NR) and recording time T (minutes 1 to 10), were performed. Regarding the central question, namely whether R and NR can be distinguished by their dynamics of EEG vigilance, only interaction effects were of interest. An interaction was found only for the baseline (day 0) EEG (G × T: $F_{9,288} = 1.94$, $p = 0.04$). According to the trend test by Moore and Wallis which was applied in the descriptive sense only, there was a monotonic increase for R but not for NR (R: $U = 2.36$, $p < 0.01$; NR: $U = 0.03$, NS). Because of considerable inter-individual variability prediction of the individual therapy response could not be based on the variable frequency of non-A epochs.

Power Spectra

A supplementary analysis, done separately for the 4 leads, showed that R and NR could not be differentiated before test medication (day 0) by means of conventional power spectra averaged over the groups. We also found that the alpha peak frequencies or their drug-induced changes could not be differentiated.

Topographical Distribution of Alpha Activity

Absolute Alpha Power. Non-parametrical statistics were used to investigate group differentiating initial



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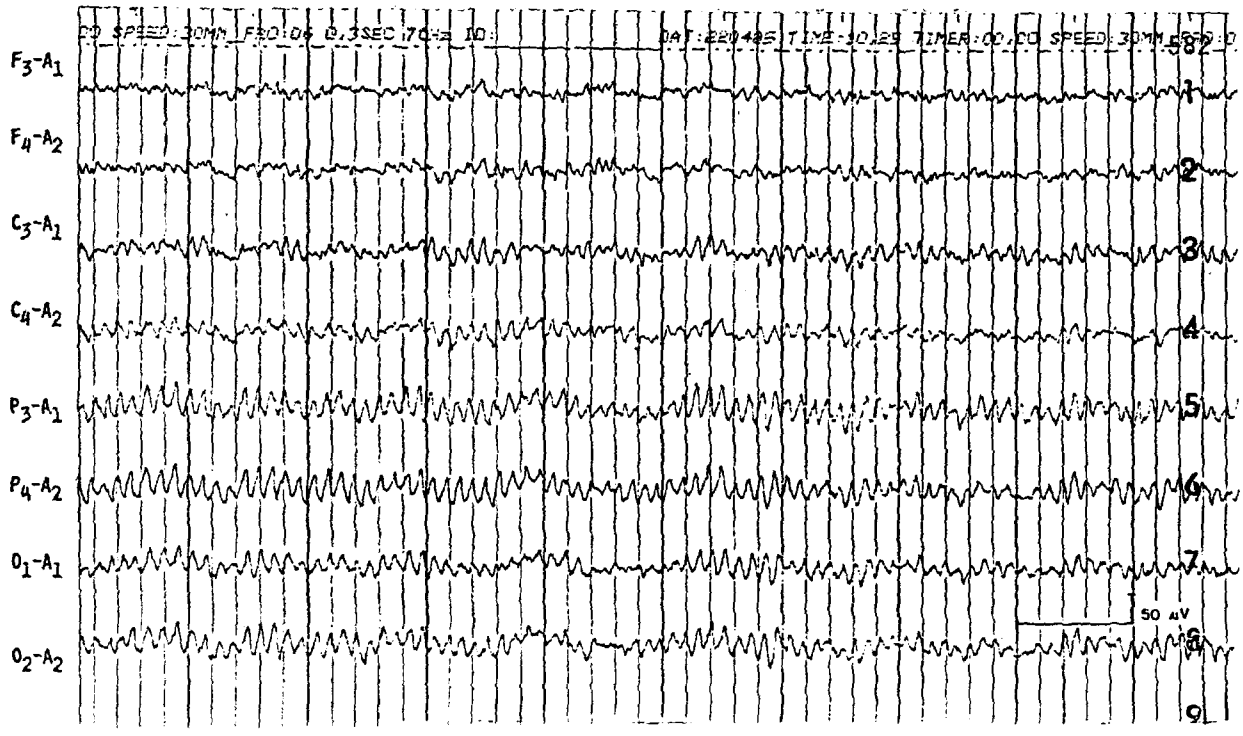

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Fig. 2. **a** Typical R EEG, patient R. K., ♀, 36 years, ICD No. 295.3; day 0: 192 non-A 2-s epochs within a recording time of 600 s. **b** Typical NR EEG, patient M. S., ♂, 38 years, ICD No. 295.3, day 0: 26 non-A 2-s epochs within a recording time of 600 s

Table 1. Mean frequency of non-A epochs during each individual minute of the recording period – R = responders, NR = non-responders

	Day		Minute of the recording period									
			1	2	3	4	5	6	7	8	9	10
R	0	$\bar{x}$	11.1	13.3	13.6	14.4	14.4	15.1	15.3	14.5	14.6	16.7
		SD	11.1	12.3	12.0	12.6	12.4	12.0	12.1	12.4	11.5	11.3
	1	$\bar{x}$	15.9	17.6	17.8	17.9	18.3	20.5	20.7	16.9	18.4	19.6
		SD	10.2	10.0	10.0	10.4	8.7	9.0	7.2	8.3	10.4	9.2
	2	$\bar{x}$	12.8	13.9	14.5	14.4	14.2	13.2	16.1	14.9	14.8	12.7
		SD	10.7	10.7	10.5	10.2	10.3	9.5	10.1	9.3	10.4	9.7
	28	$\bar{x}$	12.8	13.9	13.8	15.3	15.9	16.7	15.7	16.2	17.0	17.0
		SD	10.9	11.2	11.3	10.3	10.9	9.6	10.0	8.6	9.2	9.4
NR	0	$\bar{x}$	8.8	8.6	8.5	7.6	9.7	8.7	6.4	8.0	9.6	7.8
		SD	10.3	7.9	8.7	7.9	8.5	8.9	8.9	8.5	8.3	8.6
	1	$\bar{x}$	12.2	11.2	11.0	11.4	10.4	12.4	13.2	13.6	15.6	16.3
		SD	11.2	9.9	10.0	9.5	10.1	9.7	9.0	10.7	9.8	9.8
	2	$\bar{x}$	7.6	7.4	9.6	10.4	10.9	9.0	9.3	9.4	11.4	11.9
		SD	8.8	9.8	10.6	10.5	11.0	8.7	9.1	9.3	8.8	8.0
	28	$\bar{x}$	11.1	9.4	11.9	11.1	13.0	13.5	13.5	13.2	13.2	13.3
		SD	10.2	9.4	10.4	10.6	9.7	9.0	10.5	10.8	10.2	10.1

Table 2. Numbers of patients (R, NR) with an increase (↑), decrease (↓) or no change (=) of the absolute alpha power (lg power, 7.5 to 13 Hz) of the leads F3/A1 (AF3), F4/A2 (AF4), O1/A1 (AO1) and O2/A2 (AO2) when comparing days 0, 1 and 2. To account for random fluctuations, as a criterion for change a value ≥ 0.05 was used – G index of Holley and Guilford, *P* two-tailed

		Days					
		0→1		0→2		1→2	
		R	NR	R	NR	R	NR
AF3	↑	15	8	7	10	**3**	**5**
	↓	3	3	6	2	**13**	**5**
	=	(2)	(3)	(7)	(2)	(4)	(4)
		G = 0.24		G = 0.28		G = 0.38	
		NS		NS		$P = 0.05$	
AF4	↑	13	8	9	10	6	5
	↓	2	1	7	2	9	3
	=	(5)	(5)	(4)	(2)	(5)	(6)
		G = 0.17		G = 0.21		G = 0.22	
		NS		NS		NS	
AO1	↑	10	5	12	6	8	8
	↓	7	4	6	2	6	4
	=	(3)	(5)	(2)	(6)	(6)	(2)
		G = 0.08		G = 0.08		G = 0.08	
		NS		NS		NS	
AO2	↑	7	5	7	5	9	6
	↓	11	6	10	4	7	6
	=	(2)	(3)	(3)	(5)	(4)	(2)
		G = 0.10		G = 0.15		G = 0.07	
		NS		NS		NS	

Table 3. Numbers of patients (R, NR) with an increase (↑), decrease (↓) or no change (=) of the quotients AQ_l, AQ_r, $LQ_{anterior}$ and $LQ_{posterior}$ (mean values × 100) when comparing days 0, 1 and 2. To account for random fluctuations, as a criterion for change a value ≥ 2 was used – G index, *P* two-tailed

		Days					
		0→1		0→2		1→2	
		R	NR	R	NR	R	NR
AQ_l	↑	10	6	6	6	**3**	**6**
	↓	6	6	11	3	**13**	**4**
	=	(4)	(2)	(3)	(5)	(4)	(4)
		G = 0.14		G = 0.31		G = 0.46	
		NS		NS		$P < 0.02$	
AQ_r	↑	**15**	**7**	11	7	7	5
	↓	**2**	**5**	4	5	13	6
	=	(3)	(2)	(5)	(2)	(0)	(3)
		G = 0.38		G = 0.19		G = 0.16	
		$P < 0.05$		NS		NS	
$LQ_{anterior}$	↑	6	6	7	3	6	4
	↓	4	2	8	2	10	4
	=	(10)	(6)	(5)	(9)	(4)	(6)
		G = 0.11		G = 0.10		G = 0.17	
		NS		NS		NS	
$LQ_{posterior}$	↑	11	7	**14**	**5**	8	5
	↓	3	4	**3**	**4**	6	3
	=	(6)	(3)	(3)	(5)	(6)	(6)
		G = 0.20		G = 0.38		G = 0.03	
		NS		$P = 0.05$		NS	

Table 4. Numbers of patients (R, NR) with an increase (↑), decrease (↓) or no change (=) of the percentages PF3, PF4, PO1 and PO2 when comparing days 0, 1 and 2. To account for random fluctuations, as a criterion for change a value ≥2 was used – G index, *P* two tailed

		Days					
		0→1		0→2		1→2	
		R	NR	R	NR	R	NR
PF3	↑	12	6	6	6	**2**	**3**
	↓	1	2	5	0	**13**	**3**
	=	(7)	(6)	(9)	(8)	(5)	(8)
		G = 0.33		G = 0.29		G = 0.52	
		NS		NS		$P < 0.02$	
PF4	↑	7	6	7	6	5	2
	↓	3	4	3	4	9	4
	=	(10)	(4)	(10)	(4)	(6)	(8)
		G = 0.10		G = 0.10		G = 0.10	
		NS		NS		NS	
PO1	↑	7	3	12	2	11	4
	↓	7	5	5	4	3	5
	=	(6)	(6)	(3)	(8)	(6)	(5)
		G = 0.09		G = 0.39		G = 0.39	
		NS		NS		NS	
PO2	↑	**1**	**6**	**2**	**4**	5	2
	↓	**13**	**6**	**14**	**6**	9	4
	=	(6)	(2)	(4)	(4)	(6)	(8)
		G = 0.46		G = 0.38		G = 0.10	
		$P < 0.02$		$P = 0.05$		NS	

Table 5. Numbers of patients (R, NR) with an increase (↑), decrease (↓) or no change (=) of the individual coefficients of variation (CV) of the percentages PF3, PF4, PO1 and PO2 (mean values × 100) when comparing days 0, 1 and 2. To account for random fluctuations, as a criterion for change a value ≥2 was used – G index, *P* two-tailed

		Days					
		0→1		0→2		1→2	
		R	NR	R	NR	R	NR
CV-PF3	↑	11	7	8	6	**4**	**7**
	↓	5	6	8	5	**12**	**5**
	=	(4)	(1)	(4)	(3)	(4)	(2)
		G = 0.17		G = 0.04		G = 0.36	
		NS		NS		$P < 0.10$	
CV-PF4	↑	11	9	9	7	10	2
	↓	6	2	10	6	9	7
	=	(3)	(3)	(1)	(1)	(1)	(5)
		G = 0.07		G = 0.06		G = 0.21	
		NS		NS		NS	
CV-PO1	↑	9	4	7	2	7	6
	↓	7	7	11	4	9	4
	=	(4)	(3)	(2)	(8)	(4)	(4)
		G = 0.19		G = 0.08		G = 0.15	
		NS		NS		NS	
CV-PO2	↑	**14**	**6**	9	6	**2**	**7**
	↓	**1**	**4**	6	4	**12**	**5**
	=	(5)	(4)	(5)	(4)	(6)	(2)
		G = 0.44		G = 0.04		G = 0.46	
		$P < 0.05$		NS		$P < 0.02$	

effects. In particular, we determined for each individual variable the number of patients with an increase (↑), a decrease (↓), or no change (=) when comparing days 0, 1 and 2. As a criterion for change we used a difference of ≥0.05, which seemed to be appropriate on account of measurement accuracy. As a contingency measure between increase and decrease on the one hand and R and NR on the other, we used the G index (Holley and Guilford 1964) whose significance can be tested via normal distribution (Lienert 1973). Only those patients were considered who showed a change. A group difference was shown only for the variable AF3 (day 1→2; right side of Table 2).

Quotients as Calculated from Absolute Alpha Power. Group differences were shown for AQ_l (day 1→2), AQ_r (days 0→1) and $LQ_{posterior}$ (days 0→2).

Percentages of Absolute Alpha Power of One Lead Relative to the Sum of Absolute Alpha Power of all 4 Leads. Group differences resulted for PF3 (days 1→2), PO2 (days 0→1), and PO2 (days 0→2).

Coefficients of Variation. Clear group differentiating initial effects resulted for the CVs of alpha percentages only.

R and NR differed with regard to CV-PO2 (days 0→1) and CV-PO2 (days 1→2). Some differentiation ($P < 0.10$) was achieved by the variables CV-A02 (days 0→1) and CV-PF3 (days 1→2) which are not shown in the Table.

It must be stressed that when considering the baseline values only, no single variable was group differentiating (*t*-test).

Figure 3 depicts the time course of the two quotients of anteriorization which is representative for all the group differentiating initial effects mentioned.

Related to the baseline level (day 0) there was a comparatively more pronounced increase in AQ_l and AQ_r in R 2 h after oral intake of the test dose (days 0→1). Whereas in R the two quotients recovered the baseline level 24 h after drug intake, NR showed a further sluggish increase. The plasma level (ng/ml) was found to be higher with NR than R, both 2 h (day 1) and 24 h (day 2) following the test dose intake

(Mann-Whitney, $p < 0.10$, two-tailed – day 1: $\bar{x} = 58.8 \pm 71.5$ vs 23.4 ± 14.0; day 2: $\bar{x} = 16.5 \pm 10.3$ vs 9.7 ± 6.6). As can be seen from the 4-fold frequency distribution of patients (Tables 2, 3, 4, 5), the predictive power of the variables considered to be group differentiating was poor. Essentially, this should result from the fact that with each variable a considerable number of patients with no change will drop out. For instance, only 15 out of the 20 R could be classified according to PF3 (days 1→2) where 13 showed a decrease and 2 an increase, the remaining 5 showed no change. In an attempt to enhance the number of correctly classified patients, we investigated whether and how much this could be achieved by a combination of variables. We made use of a classification procedure based on the Bayes theorem which was proposed by Maxwell (1961) for qualitative data. The number of variables which can be considered simultaneously is limited by the number of subjects. With a sample of $n = 34$ these are two variables, at most. Allowing three qualities (↑), (↓), (=), a combination of two variables renders $3^2 = 9$ possible answer patterns. For each answer pattern the number of subjects (of R on the one hand and NR on the other) sharing this very answer pattern was determined. In a second step each answer pattern was allocated to either R or NR on account of their numerical proportion, also taking into account the a priori probability. The allocation enabled a reclassification of R and NR, and thus the assessment of the number of patients who were classified correctly or falsely. This procedure was applied to each 2-fold combination which resulted from our 11 group differentiating variables ($n = 38$).

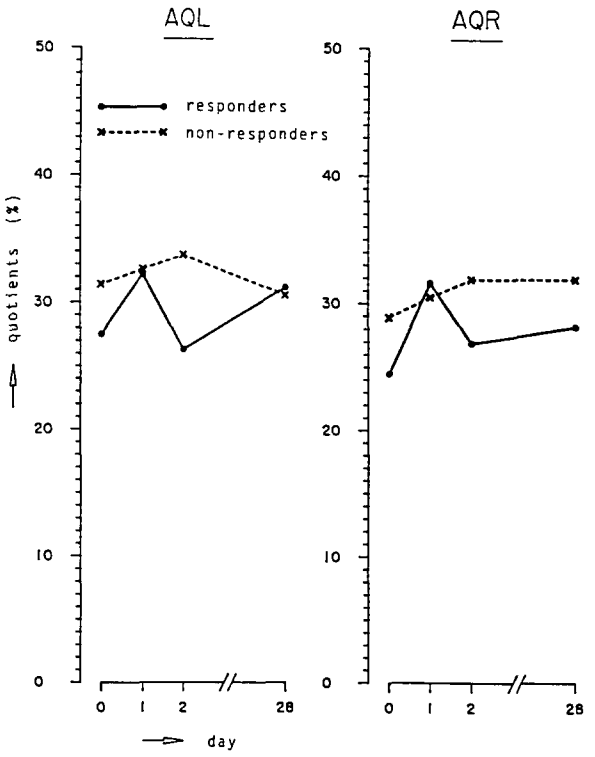

Fig. 3. Mean values of AQ_l and AQ_r on day 0 (baseline), day 1 (2 h after peroral intake of test dose of 150 mg perazine), day 2 (24 h after intake of test dose) and day 28 (after a neuroleptic treatment period with variable daily dosage)

Table 6 shows those combinations which rendered the correct classification of at least 26 (76.5%) patients. Most powerful was the combination AF3 (days 1→2), + PF3 (days 1→2), giving a correct classification of 28 of the 34 patients (82.4%) or of 18 of the 20 R (90%) and 10 of the 14 NR (71%). These values related to groups, thus being irrelevant with respect to the desired individual prediction. When considering two variables simultaneously, each indi-

Table 6. Rank order of combined variables which allowed correct classification of at least 76.5% (R, NR) – G index

Combined variables					Correctly classified % (numbers in bracketts)			Contingency (G Index)[a]
					R + NR	R	NR	
AF3	(1→2)	+	PF3	(1→2)	82.35 (28)	90 (18)	71 (10)	0.647***
AQ_r	(0→1)	+	CV-PO2	(1→2)	79.41 (27)	85 (17)	71 (10)	0.588***
PO2	(0→1)	+	CV-PO2	(1→2)	79.41 (27)	85 (17)	71 (10)	0.588***
AF3	(1→2)	+	AQ_l	(1→2)	79.41 (27)	90 (18)	64 (9)	0.588***
LQ_p	(0→2)	+	CV-PO2	(1→2)	76.47 (26)	70 (14)	86 (12)	0.529**
AF3	(1→2)	+	PO2	(0→1)	76.47 (26)	95 (19)	50 (7)	0.529**
CV-PO2	(0→1)	+	CV-PO2	(1→2)	76.47 (26)	80 (16)	71 (10)	0.529**
PF3	(1→2)	+	CV-PO2	(1→2)	76.47 (26)	80 (16)	71 (10)	0.529**
CV-PO2	(1→2)	+	CV-AO2	(0→1)	76.47 (26)	90 (18)	57 (8)	0.529**
CV-AO2	(0→1)	+	CV-PF3	(1→2)	76.47 (26)	90 (18)	57 (8)	0.529**
AQ_l	(1→2)	+	PO2	(0→1)	76.47 (26)	90 (18)	57 (8)	0.529**
AF3	(1→2)	+	CV-PO2	(1→2)	76.47 (26)	90 (18)	57 (8)	0.529**

[a] ***: $P < 0.001$; **: $P < 0.01$; two-tailed

Table 7. Answer patterns (two-fold combinations) which occurred most frequently. Only those answer patterns ($n = 14$) were considered which indicated a clear response prediction (R, NR). 0: increase, 1: decrease, 2: unchanged

Combined variables				Answer pattern	R	NR
LQ_p	(0→2) +	CV-PO2	(1→2)	0 1	10	0
PF3	(1→2) +	CV-PO2	(1→2)	1 1	10	1
PO2	(0→2) +	CV-PO2	(1→2)	1 1	10	1
AF3	(1→2) +	CV-PO2	(0→1)	1 0	10	2
PF3	(1→2) +	CV-PO2	(0→1)	1 0	9	2
AQ_l	(1→2) +	PO2	(0→2)	1 1	9	2
PO2	(0→2) +	AF3	(1→2)	1 1	8	1
AF3	(1→2) +	LQ_p	(0→2)	1 0	8	1
LQ_p	(0→2) +	PF3	(1→2)	0 1	8	1
PF3	(1→2) +	PO2	(0→2)	1 1	8	1
AF3	(1→2) +	CV-PO2	(1→2)	1 1	7	1
AQ_l	(1→2) +	LQ_p	(0→2)	1 0	8	2
LQ_p	(0→2) +	CV-PO2	(0→1)	0 0	8	2
CV-AO2	(0→1) +	CV-PF3	(1→2)	0 2	5	0

Table 8. Distribution of R and NR according to frequency classes of response predicting answer patterns (AP)

AP	R	NR
0– 3	4	12
4– 6	7	2
7– 9	5	0
10–12	4	0

vidual patient can exhibit one answer pattern out of the 9 which are theoretically possible. A prediction could only be based on a single answer pattern if it were highly specific for R or NR or if the remaining answer patterns occurred quite rarely. Yet this was far from being the case. When comparing the various combinations of variables, the answer pattern occurring most frequently (in 12 out of 34 patients) was 1/0, resulting from the combination AF3 (1→2) + CV-PO2 (0→1) (Table 7). Therefore, we tried to base an individual prediction on a multitude of selected combinations of variables. Toward this end the answer patterns occurring most frequently were selected, considering only those which were clearly predictive of R.

Thereupon, we determined the number of response-predicting answer patterns for each individual patient. We were governed by the idea that a patient who exhibits the total of the 14 response-predicting answer patterns can be regarded as R with much higher probability than a patient who exhibits only 7 or even 0 of them.

Table 8 shows that NR predominated within class 0 to 3 (75% NR), whereas R predominated within class 4 to 6 (78% R). All 9 patients with ≥ 7 answer patterns were R (100%).

Discussion

First of all it may be stated that clinically defined R and NR exhibit certain differences with respect to their EEG dynamics of vigilance. Because of considerable inter-individual variability such differences cannot be used for individual prediction of therapy response.

Compared with NR, R showed a tendency towards a higher proportion of non-A epochs. These non-A epochs overwhelmingly corresponded to low voltage desynchronized activity, more or less interspersed with fast beta activity. This result, although only of marginal statistical significance, appears to be the first quantitative confirmation of earlier claims based on eyeball evaluation (Igert and Lairy 1962; Bente 1963; Itil et al. 1966 etc.). Following Bente (1965) we hold that low voltage desynchronized activity occurring under resting conditions essentially corresponds with subvigilance (stage B_1) and not with arousal. This view is substantiated, among other things, by repeatedly replicated findings of a progredient increase of non-A epochs starting between minutes 4 to 6 of the recording period when recording under resting conditions (Ulrich et al. 1986, 1987). Thus, a higher degree of dynamic variability or a broader range of systems control of spontaneous vigilance fluctuations (dynamic lability) can be inferred from a comparatively higher frequency of non-A epochs (R). Correspondingly, a lower degree of dynamic variability or a narrower range of systems control (dynamic rigidity) can be inferred from a comparatively lower frequency of non-A epochs (NR).

Furthermore, we found that R and NR also differed with respect to their time-dependent changes of non-A epoch frequencies before medication. While R showed a monotonic increase which is typical for normals, NR did not. Remarkably this monotonic increase applied to the baseline EEG only. So it may be asked whether and in how much the neuroleptic drug modifies the dynamics of vigilance. Considering the baseline EEG it might be concluded that the transition between waking and sleeping takes place in a physiological manner with R, but not with NR. R would thus be assumed to be closer to normals than NR. In this connection the findings obtained from

comparison between endogenous-depressive groups of on-drug R and NR gain in interest. Unlike schizophrenics, only the NR showed a monotonic increase of non-A epochs, whereas the R did not (Ulrich et al. 1986).

Furthermore, we found that R and NR could be differentiated by their test dose-induced changes of certain topographical ratios of absolute alpha power. Remarkably, the drug-free baseline EEG did not permit such a differentiation. Differentiating initial effects were found on each of the three levels of description characterized by a different degree of topographical inter-dependency. Differentiation was also afforded by certain coefficients of variation, a measure of the temporal variability (within 300 2-s epochs) of the topographical variables.

Attention should be paid to the different time courses of the group differentiating effects. Some variables like AQ_r and CV-PO2, showed this effect 2 h after the test dose intake (days $0 \rightarrow 1$). Others showed this effect only for days $0 \rightarrow 2$ ($LQ_{posterior}$) or for days $1 \rightarrow 2$ (AQ_1, PF3, CV-PO2). This indicates the high complexity of the relationship and the difficulty of interpretation in brain functional terms. Under the premise that the increase in alpha anteriorization (AQ_r), which appears as soon as 2 h after the test dose intake, corresponds to a neuroleptic-induced lowering of the EEG vigilance (Bente 1963, 1981) it seems warranted to assume that the group differences observed have been caused by different plasma levels of perazine. Accordingly, NR could differ from R by for instance a poor resorption or a slower rate of metabolism. Rather surprisingly the opposite was true. A (bilateral) change of this kind has been found to be a typical EEG effect of neuroleptic treatment (e.g. Bente 1963). Figure 3 shows that this increase was far steeper with R than with NR. At 24 h after the test dose intake (day 2) R had recovered the baseline while NR showed a further (non-significant) sluggish increase. Dynamic behaviour of the same kind also applied for other group differentiating variables: R showed a prompt and ample deflection and the same recovery of baseline. In contrast, NR (in spite of a higher mean plasma level of perazine) showed no significant deflection at all.

The central importance of EEG reactivity regarding therapeutic outcome was indicated more than two decades ago by a number of authors (Selbach and Selbach 1956; Bente 1963; Helmchen and Künkel, 1964; Dasberg and Robinson 1971).

A deeper understanding of the physiology underlying our findings may be gained from the conception of Selbach (1964, 1976) which was founded upon the biological cybernetics (biologische Regellehre) of Wagner (1954). According to Selbach (1964), intake of a psychopharmacological agent can be considered as a feed-forward disturbance and thus as an unbalancing of homeostasis (which is already unbalanced in patients compared to the physiological state). As a consequence a control action is brought into action, whose intensity should be dependent on the initial value. Referring to Hassenstein (1973), Selbach (1976) distinguished different dynamical types of control. The behaviour observed with our R (Fig. 3) corresponded to the ideal constant controller (idealer Halteregler), which in the wake of an initial deflection of the system recovers the set value quickly and without overshoot. A less dynamic controller effects a positively damped transient response with decelerated equalization to the set value (controller lag, nachhinkender Regler). The latter corresponds to the behaviour observed with the NR. As Selbach stated, the respective mode of control should be dependent on the initial value as well as the intensity of the disturbance factor. A hyperstable system (low system pressure) needs a stronger impulse than an unstable system (high system pressure). Aiming at the predictor question Selbach contended: "From the point of view of dynamic control the prognosis is the more favorable the less the systems' controllability had become rigid, i.e., the better it had preserved its flexibility under the condition of a feedforward disturbance; this can be measured by means of autonomous parameters or of EEG. A general theory of diseases has to distinguish between balanced, highly unstable, and rigid systems.". Referring to our own findings obtained from the investigation of the dynamics of vigilance, R and NR groups seem to be different in their baseline EEG, the former showing a tendency towards a higher frequency of subvigilant non-A stages, a finding which was interpreted as a reflection of increased spontaneous vigilance fluctuations or a comparatively higher degree of dynamic unstableness with R.

According to Selbach (1976) systems control becoming unstable should also be reflected in the domain of behavior, i.e., in increased restlessness, excitement, unstable affectivity, sensory supersensitivity, delayed sleep onset, loss of appetite, impotency, etc. This, essentially corresponds to Janzarik's (1959) notion of dynamische Unstetigkeit (unsteadiness of system's dynamics), behaviour which showed a much better response to neuroleptics than its counterpart dynamische Insuffizienz (dynamic insufficiency). Thus a working hypothesis could be formulated that prediction of therapeutic outcome can be based inter alia on behavioural measures or on their changeability under a neuroleptic test dose.

The extent to which we succeeded in our endeavour to reach the goal of our study, namely to in-

dividually predict the therapeutic outcome by means of initial changes of certain topographical relationships of absolute alpha power, can only be proven by a prospective validating study which is under way. In the future we hope to include group differentiating variables derived from other domains of observation (for instance clinical phenomenology, behavioural physiology and biochemistry) in addition to the EEG.

Such a widening of the number of variables could result in a further increase of predictive power. Besides, by simultaneously considering a greater number of qualitative parameters derived from each individual patient – an approach which seemed to be advisable in view of considerable inter-individual variability of the EEG data – it becomes possible to recover the quantitative level of statistical analysis (Abt 1977). It is our impression that data should be handled preferrably on the qualitative level of (↑), (↓) and (=) in a first exploratory step, i.e. when searching for those variables which are group differentiating.

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