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Frontal dysfunction in schizophrenia – a new electrophysiological classifier for research and clinical applications

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Abstract We determined whether schizophrenic patients can be reliably classified with electrophysiological tools. We developed a fully computerized classifier based on 5 minutes of EEG recording during an acoustical choice reaction time task (AMDP-module IV). We included factorized variables from the frequency domain and evoked potentials (N100/P200-complex) from central and frontal electrodes, which were preprocessed in a sample of 150 normal subjects prior to classification. We applied discriminant analyses to the electrophysiological data from depressive, schizophrenic and schizotypal subjects, most of them being unmedicated or drug-naïve. The classifier was developed on a training set (33 schizophrenics, 49 normals) and tested on an independent sample (32 schizophrenics, 49 normals). A simple three-variable classifier was found to classify schizophrenics and normals in 77 % of those tested correctly. Diagnostic specificity of the classifier proved to be low as the inclusion of depressive patients (n= 60) significantly decreased classification power. It was demonstrated that atypical but not typical neuroleptic drugs may influence the classification results. Correctly classified schizophrenics showed significantly more negative symptoms and slower reaction times than those schizophrenics who were misclassified as normals. In contrast, these misclassified schizophrenics showed a non-significant trend for more positive symptoms and shorter reaction times. As the correctly classified schizophrenics showed increased frontally pronounced delta-activity and decreased signal power of the N100/P200 amplitude, it was concluded that these schizophrenics show dysfunction of the frontal lobe. It is proposed that this new classifier can be useful for clinical and research applications when subtyping of schizophrenics with detection of frontal dysfunction as the aim.

Key Words Schizophrenia · Classification · EEG · Event-related potentials · Hypofrontality

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Introduction

During the past, electrophysiological classification studies of schizophrenic patients were usually performed with resting EEGs with closed eyes (Shagass et al. 1984; Ford et al. 1986; John et al. 1994; Winterer et al. 1995; Magdolen et al. 1997). Only a few studies included event-related potentials (Roemer et al. 1990; John et al. 1994). To our knowledge, no study has used task-related EEG, thus far. Although these studies usually achieved around 80 % correct classifications when comparing schizophrenics with normals, none of the resulting classifiers has found general acceptance. This is despite the fact that it would be highly desirable to have an objective classification instrument at hand which may help to establish the diagnosis, subtypes or physiological dysfunctions for clinical as well as research purposes. Several reasons may account for this failure to find acceptance: 1) laborious and time-consuming data acquisition and analysis, 2) questionable or unknown retest-stability with insufficient data about state and trait-related dependencies, 3) missing or incomplete data about sensitivity and specificity, and 4) classifiers were frequently based on a large number of electrophysiological variables which not only gave rise to doubts from a statistical perspective but also made it nearly impossible to interpret the classification algorithm in pathophysiological terms (validity).

In our study, we tried to address all of these objections. In order to develop a useful classifier, we basically performed a reductionist approach. 1) We used an electro-

physiological paradigm, that is, EEG during an acoustical choice reaction task, which we considered to be easily performed even in highly psychotic patients. This paradigm was recently introduced by the AMDP-working group *psychophysiology* of the "Arbeitsgemeinschaft für Methodik und Dokumentation in der Psychiatrie" (Winterer et al. 1997). The task takes 5 minutes and allows the parallel measurement of ongoing EEG and evoked potentials together with reaction time. For comparison, we also included 2 minutes of resting EEG. 2) For preprocessing of EEG variables, we first applied a factor analytical approach based on a large sample of healthy subjects. The resulting EEG factors and event-related potential measures were only used for the subsequent patient classification study, if they were shown in the sample of healthy subjects to be reliable and interpretable in physiological terms. By means of this, we also wanted to achieve a considerable reduction of the number of variables. 3) The developed electrophysiological classifier of patients on the basis of these variables was then tested for sensitivity, specificity and retest-stability in patients and normals. 4) We carefully checked the impact of medication on classification. 5) Finally, it was our notion that the small number of variables of the classifier should allow us to interpret the classification results in pathophysiological terms which might be validated by correlations with the concomitantly assessed neuropsychological measure (reaction time) and psychopathological variables. However, since it was the purpose of this study to develop an electrophysiological classifier, testing of pathophysiological hypotheses was not the primary aim of this study. This was done elsewhere on largely the same dataset (Winterer et al. 2000).

Method

Subjects

We investigated 254 healthy male (n = 139) and female (n = 115) volunteers (36.41 ± 12.67 yrs.) who were recruited by newspaper advertisements (Winterer et al. 1999). In the same way, a separate group of subjects with schizotypal personality (10 males, 11 females; 32.27 ± 11.89 yrs.) was recruited in that all healthy subjects were screened for schizotypy, using the German version (Wolff 1996) of *the Schizotypal Personality Questionaire* (SPQ) of Raine (1991). The diagnosis of schizotypal personality was established as defined by Raine (1991). All healthy participants and schizotypal subjects were paid for their participation. Health status was checked by a board certified psychiatrist with special reference to neurological and psychiatric disorders, previous drug abuse and medication as well as any other medical condition which might influence the EEG. Those volunteers, obviously fulfilling any of these exclusion criteria, had been withdrawn from further analysis in advance and are not included in this sample.

Additionally, we investigated 21 male and 20 female schizophrenic patients (32.83 ± 10.91 yrs.), who were medication-free for at least three days; 18 of them were drug-free for at least one year, 12 of them were drug-naive. Also, we included 34 female and 37 male, unmedicated depressive patients (medication-free for at least three days) in our study (40.69 ± 10.85 yrs.). All patients were in-patients and were diagnosed according to the ICD–10 classification system by their attending physician based on clinical interviews (Table 1). In all cases, it was the discharge diagnosis which was used for analyses. Applying a broad diagnostic concept, the diagnostic group of schizophrenic patients included all patients with a F2 diagnosis, the depressive group included all subjects with a F3 diagnosis. Patients with an additional diagnosis that might have influenced EEG recordings such as prior or current drug abuse or neurological disorder were not included in the study. Additionally, the schizophrenic patients were characterized by their attending physicians on the syndrome level by means of the German version of the AMDP scale (Gebhardt et al. 1983) at the day of EEG recording. This scale allows the description of clinical syndromes such as paranoid-hallucinatoric, depressive or apathic syndrome which were used in this study.

In addition to these medication-free groups, the subsequent medicated schizophrenic groups who received either typical or atypical neuroleptic drugs were included in our sample. All medicated patients received a single-drug therapy for at least one week (Table 2) with a mean treatment duration of 12.84 (4.12) days.

The study was approved by the Ethics Committee of the University Hospital Benjamin Franklin of the Free University of Berlin. All subjects gave written informed consent before investigation.

Table 2 Mean age (SD) and mean daily drug dose (SD) of medicated schizophrenic patients

Medication	n	age	Mean daily drug dose (mg)
Perazine	30	34.14 (12.24)	315.00 (171.35)
Haloperidol	10	35.50 (13.83)	9.29 (6.38)
Clozapine	14	33.35 (11.16)	367.85 (235.12)
Olanzepine	7	39.40 (14.13)	16.36 (10.75)

Recording

A more detailed description of recording conditions of the AMDP modules is given elsewhere (Winterer et al. 1997; 1999). The unmedicated patients were recorded within one week after admission, the medicated patients were recorded at different times during their hospitalization. After recording of two minutes of uninterrupted EEG with closed eyes in a relaxed position (AMDP-module I), an acoustical choice reaction time measurement was performed during a running EEG with closed eyes (AMDP-module IV). Sixty tones of different pitches (1,000 and 2,000 Hz, sine wave) were presented in random sequence and intervals (2.5–7.5 s) by loud speakers at 65 dB SPL. No determination of individual hearing level was performed. The interstimulus intervals were chosen in a way such that the total time of the trial was exactly 300 s. During this time, 60 (2 x 30) tones were always presented. Additionally, the sequence of tones was chosen in a fashion that guaranteed equal numbers of low and high tones. The sequence and interval of tones were pseudo-randomized. The patient had to switch off the tones as soon as possible by pressing one of two buttons. The two buttons were assigned in advance to the high and low tone, respectively. With the left hand the low tone has to be switched off, the right hand switches off the high tone. The computer registered the tones and the reactions. The number of mistakes, the mean reaction time and the standard deviation of the reaction time were calculated. Before the beginning of the measurement, one test run was carried out. Stability measurements of the mean reaction time latency with a retest interval of approximately six months revealed a Cronbach's Alpha coefficient of 0.896 for the 20 healthy subjects (reaction time std.: 0.63; number of mistakes: 0.68). Retest stability of the mean reaction time of patients (n =15) with variable retest interval (range: 1–10 weeks) was also found to be high with a Cronbach's Alpha: 0.986 (reaction time std: 0.906, n of mistakes: 0.596). All patients were unmedicated during their first recording session and treated with a variety of different drugs during their second recording.

Parallel to the reaction time assessment, EEG activity was measured. Each EEG was recorded with Ag/AgCl electrodes, electrode positions were defined according to the international 10/20 system (19 EEG-channels), and impedance was kept below 5 kΩ. Eye move-

ments were checked separately: bipolar, each electrode 1 cm lateral to the corner of the eye. The recordings were carried out with a conventional 32-channel electroencephalograph (Walter Graphtek). Amplifiers were calibrated using a 0.5 Hz rectangle generator, notch filter: 50 Hz, time constant: 0.3 s. All channels (including separate ears A1 and A2) were recorded against a common reference (approximately at FpFz) with good properties. The resting EEG as well as pre- and post-tone EEG during the choice reaction task were digitized with a sampling frequency of 166.6 Hz. Anti-alias was performed in two steps. Analogue anti-alias at 1000 Hz sampling rate: Butterworth 4th order, 140 Hz and digital anti-alias: FIR 64 taps, 75 Hz. Data were stored on optical disks. Artifact detection (muscle, eye-movements, body movements) of the resting EEG was visually performed. Artifact detection of task-related EEG (during reaction time measurement) was automatically performed and visually checked, afterwards. Sweeps of EEG activity with obvious muscle, movement or eye artifacts were visually excluded from further study. Automatic artifact detection included the common rules: amplitude criterium (> 80 μV), muscle artifacts (increase of high frequency amplitudes) and amplitude below a minimum. Eye blinks and eye movement artifacts usually appeared together with pressing the button after the tones. Thus, they hardly affected the signal in the analyzed time window. However, we excluded all affected sweeps, especially when these artifacts were not restricted to Fp1 and Fp2 from visual inspection. In fact, all information from the electrodes Fp1 and Fp2 was not used for our subsequent analyses. Also, only subjects with at least 30 artifact-free pre- and post-tone EEG segments out of sixty were included for further investigation. Before and after the tone 1.536 seconds were also available for further analysis. For analysis of resting EEG, we selected an uninterrupted segment of 30 seconds of each subject and patient. Only resting EEG segments with a minimum of artifacts were chosen (visual exclusion). We have chosen this strategy of selecting a long uninterrupted segment instead of a series of short segments in order to account for dynamic aspects in the resting EEG. Due to these artifact-selection criteria, we exluded: 32 normals, 12 unmedicated schizophrenics, 10 depressive patients and 3 schizotypal subjects.

Parameterization

In accordance with the suggestions of Essl & Rappelsberger (1996) and Nunez et al. (1997) for coherence measurements, we used digitally computed traces with reference (A1+A2)/2 for all analyses. For quantitative EEG analysis, the recorded signals of obviously artifact-free EEG segments were submitted to spectral analysis using the fast Fourier transform with 128 spectral values in 0.651 Hz scans (= 1/1.536 s) up to the Nyquist frequency (0.5* 166.66 = 83.33 Hz). The square root of absolute power (magnitude), expressed in μV was computed. Frequency bands were defined in advance according to the factor solution of Herrmann et al. (1978) gained from resting EEG (occipital leads) with closed eyes: δF = 0.5–5.5 Hz, θF = 6–8 Hz, αF = 8.5–12 Hz, α_1F = 8.5–10 Hz, α_2F = 10.5–12 Hz, β_1F = 12.5–18 Hz, β_2F = 18.5–20.5 Hz, β_3 F = 21–30 Hz. In addition, we calculated the power for the complete alpha-frequency band and the total power. Power values were calculated for all electrode positions. For the same frequency bands, spectral coherences were computed from cross-spectra for selected electrode pairs (F7-F8, C3-C4, T5-T6, O1-O2, F7-C3, F8-C4, F7-T5, F8-T6, F7-O1, F8-O2, T5-O1, T6-O2). This selection was performed in order to keep the number of variables low.

EEG factor solution (resting EEG in healthy subjects)

EEG factor analysis (varimax rotation) was first performed on the basis of resting EEGs of 150 healthy subjects (Winterer et al. 1999). Factor analysis was performed separately for EEG power variables and coherence variables. The factor solution for the resting EEG is not depicted for reasons of brevity because a) the selected variables are practically identical with the selected variables from the factor analysis of the task-related EEG (see Table 3 and 4) and b) because resting the EEG does not play a major role for the discrimination of psychiatric patients (see Results section). The extracted factors were chosen according to the Eigenvalue criterium > 1 and also had to be stable with time, that is only factors with a stability coefficient > 0.75 (Cronbach's Alpha) as established by retest measurements (after six months) were taken under further consideration. For the resting EEG segment, we found a 4-factor solution as most appropriate for the frequency spectra (power). Essentially, the four factors reflect the frequency partition as previously established on data from occipital electrodes of resting EEG (Herrmann et al. 1978). However, the theta-frequency band is lost as a separate entity and split between the alpha1 and delta frequency band. Spatial information is only contained in the delta factor showing higher loading of frontal delta power variables.

For the spectral coherences, a 2-factor solution was chosen with one frontal and one posterior factor. In contrast to the 4 power factors, which hardly include spatial information, the two coherence factors neglect information from the frequency domain. They are both largely defined by spatial information.

EEG factor solution (task-related EEG in healthy subjects)

Factor analysis (varimax rotation) of EEG (spectral EEG variables x electrode positions) was again performed in 150 healthy subjects

Table 3 Factor solution (**task-related EEG**) based on frequency spectra (power) times all 17 electrodes (excluding of Fp1 and Fp2 from the original set of 19 electrodes) of 150 healthy subjects. Only EEG variables with highest factor loading (at least > 0.8) are displayed. Only positive loadings were observed. Bottom line: r = Cronbach's Alpha of factors (retest stability)

Factor 1 (Beta)	Factor 2 (Alpha1)	Factor 3 (Alpha2)	Factor 4 (Delta)
F3 Beta2	C3 Alpha1	F3 Alpha2	F3 Delta
F4 Beta2	C4 Alpha1	F4 Alpha2	F4 Delta
C3 Beta2	Cz Alpha1	F7 Alpha2	Fz Delta
F3 Beta3	P3 Alpha1	F8 Alpha2	C3 Delta
Fz Beta3	Pz Alpha1	Fz Alpha2	C4 Delta
C3 Beta3	T3 Alpha1	C3 Alpha2	P3 Delta
C4 Beta3	T4 Alpha1	C4 Alpha2	Pz Delta
Cz Beta3		Cz Alpha2	T3 Delta
P4 Beta3			
r =.8221	*r =.9075*	*r =.8433*	*r =.8533*

Table 4 Factor solution (**task-related EEG**) of spectral coherences based on all analyzed electrode pairs times frequency bands of 150 healthy subjects. Only EEG variables with highest factor loadings (at least > 0.6 (factor 1) and > 0.7 (factor 2)) are depicted. Only positive loadings were observed. Bottom line: r = Cronbach's Alpha of factors (retest stability)

Factor 1 (posterior coherence)	Factor 2 (frontal coherence)
C3-O1 Total	F7-F8 Alpha
C3-O1 Beta2	F7-F8 Alpha1
T5-T6 Delta	F7-C3 Alpha
C3-O1 Beta1	F7-C3 Alpha1
C3-O1 Beta3	F7-C3 Total Power
C4-O2 Total	F8-C4 Alpha
C4-O2 Beta2	F8-C4 Alpha1
C4-O3 Beta3	F8-C4 Total Power
r =.8101	*r =.8528*

(Tables 3 and 4). It was based on the 1.536 s prestimulus EEG during performance of the reaction time task and was again done separately for spectral coherence and spectral power variables (Winterer et al. 1999). The extracted factors were chosen according to the Eigenvalue criterium > 1 and also had to be stable with time, that is only factors with a stability coefficient > 0.75 (Cronbach's Alpha) as established by retest measurements (after six months) were taken under further consideration. The essential finding is that the factor solution for spectral power as well as coherence factors is practically identical to the factor solution gained from the resting EEG.

Signal-to-noise ratio

A detailed description of the calculation of the signal-to-noise ratio is given elsewhere (Winterer et al. 1999). For the post-tone EEG, we calculated the signal-to-noise ratio, signal power and noise power of the event-related EEG activity at the electrode positions Fz and Cz for a segment between 50–200 ms post-stimulus. (We restricted our measurements to these selected electrode positions as we could see from our visual inspection of the averaged evoked potentials in healthy subjects that the N100/P200 complex, which is to be found in the selected time window, is most strongly expressed at these electrode positions). Calculations were performed according to Möcks et al. (1988). That is, the data were decomposed into the two unobservable quantities, signal and noise power. The power measures the mean-squared amplitude of a series. The noise power estimate, roughly, is the mean power of all single sweeps minus the power of the averaged signal.

Upon performing these calculations, it is obvious that signal power, noise power and signal-to-noise ratio are dependent measures. The quotient is a derived quantity. However, it can be seen from the presented correlation analysis in Table 5 that signal and noise power exert independent influences on reaction time, although the main correlation is between signal power and reaction time. This correlation analysis is based on a linear model. A non-linear transformation would change the result and, therefore, only would make sense when principally other quantities were investigated (*for further details see* Winterer et al. 1999).

Reliabilities (Cronbach's Alpha) for signal power, noise power, and signal-to-noise ratio (measurement stability after six months) were at electrode position Cz: 0.92 (signal power), 0.94 (noise power), 0.91 (signal-to-noise ratio) and at electrode position Fz: 0.94 (signal power), 0.96 (noise power), 0.94 (signal-to-noise ratio).

Statistics

Group comparisons are based on the depicted factor solution (Tables 3 and 4) with the weighted sum of values (factor loading) for all variables within a factor. Group comparisons of reaction time latency and EEG factor values in patient groups were performed with Mann-Whitney U-tests (two-tailed). ANOVA was always performed when either age or sex correction or correction for the number of reaction time trials or artifact-free EEG sweeps became necessary due to significant group differences. Calculation of the correlation between AMDP syndrome scores and EEG factors or reaction time was also performed with Mann-Whitney U-tests (two-tailed). Based on the EEG factor variables, classification of EEGs was done with a stepwise linear discriminant analysis (Wilk's Lambda), calculated on a training group and then applied to an independent test group. Again, we corrected for age, sex and number of artifact-free trials. All statistics were calculated by using the statistical package SAS (Schuemer et al. 1990).

For visualization of classifications, we applied Sammon-Maps (Sammon 1969; Bezdek & Pal 1995). In these maps, each subject (data point), which is constituted by a n-dimensional pattern (n variables), is described in a 2-dimensional space (map). This is done in such a way that the distances between two n-dimensional data points are as similar as possible to the topological distances in the 2-dimensional space (map).

Table 5 Correlation analysis (student t-test) between reaction time (RT), signal power (S), noise power (N) and signal-to-noise ratio (S/N) at electrode position Cz, n = 232, p < 0.05 (*), p < 0.01 (**), p< 0.001 (***), 1-tailed, uncorrected for age and gender

Correlation r	S	N	S/N	RT
Signal power S	1.0000	0.1029	0.8551***	–0.2929***
Noise Power N		1.0000	–0.2843***	–0.1453*
S/N ratio			1.0000	–0.1852**
Reaction time RT				1.0000

Results

For the different subject samples, reaction time latencies were calculated and are depicted in Table 6. Schizophrenics and depressive patients showed significantly longer mean reaction time latencies.

Based on a stepwise linear discriminant analysis (Wilk's Lambda), we performed classifications of schizophrenic and depressive patients and healthy controls (3-class problem). In a first approach, we included all EEG factor variables from resting and task-related EEG (2 x 6 variables) as well as signal power and noise power at Cz and Fz (evoked activity) (Table 7). The resulting classification is based on a 7-variable model (Table 8). Only unmedicated patients *and* schizophrenics who were treated with haloperidol or perazine were used for classification. This is because those schizophrenics, who were treated

Table 6 mean reaction time (s): in different groups of unmedicated psychiatric patients and schizotypal subjects compared with a normal control group. P< 0.001, 2-tailed (*)

Group	n	Mean (SD)
Normal Control	238	0.42 (0.08)
Schizophrenic	55	0.59 (0.20)*
Schizotypal	21	0.45 (0.10)
Depressive	67	0.60 (0.27)*

Table 7 Linear discrimination of schizophrenic and depressive patients and normals on the basis of EEG factor variables from resting EEG, task-related EEG, signal and noise power at Fz and Cz (corrected for age, sex and number of artifact-free trials). The classification is based on a 7-variable model. Numbers without parentheses refer to the training group; numbers with parentheses refer to the independent test-group

Actual Group	n	Predicted group membership		
		Normal	Schizophrenic	Depressive
Normal	47	53.2 %	17.0 %	29.8 %
	(47)	(48.9 %)	(19.1 %)	(31.9 %)
Schizophrenic	41	22.0 %	58.5 %	19.5 %
	(41)	(12.2 %)	(53.7 %)	(34.1 %)
Depressive	30	30.0 %	16.7 %	53.3 %
	(30)	(36.7 %)	(33.3 %)	(30.0 %)

Percent of "grouped" cases correctly classified: 55.08 % (45.76 %)

Table 8 Stepwise linear discriminant analysis of normals, schizophrenic and depressive patients based on a 7-variable model

Variables	Wilks' Lambda	p value
Delta Power (RT-EEG)	.8744	.0004
Signal Power Cz	.82883	.0003
Frontal Coherence (RT-EEG)	.7983	.0003
Delta Power (Resting EEG)	.7983	.0002
Alpha2 Power (RT-EEG)	.7399	.0002
Alpha1 Power (RT-EEG)	.7133	.0002
Noise Power Cz	.6835	.0001

with atypical neuroleptics (clozapine, olanzepine) – but not those patients who were treated with typical neuroleptics – showed significant differences with respect to a variety of EEG variables (Table 11). We included a correction for age and gender as well as number of artifact-free trials into the classification algorithm as these variables exert a significant influence on the classification results of all subsequently presented discriminant analyses (not depicted). Group comparisons are shown in Tables 9 and 10 for interpretation of the classification results. It becomes obvious from the classification result that resting EEG contributes to the classification only to a minor degree. In contrast, task-related (frontally pronounced) delta power and frontal coherence as well as signal power (evoked activity) discriminate well. It also becomes clear from the classification result that depressive patients are randomly distributed across all three classes and, therefore, strongly reduce the overall classification power.

In a second step, we performed the classification of patients with exclusion of resting EEG-factor variables and

Table 9 Group comparisons of task-related EEG factor scores with mean value (SD) between healthy controls and unmedicated patient groups (patients were unmedicated for > 3 days; a subgroup of the schizophrenic patients were unmedicated for > 1 year; schizotypal subjects were never medicated): $p \leq 0.1$ ($), $p < 0.05$ (#), $p < 0.01$ (+), corrected for age, sex and number of trials (ANOVA)

Patient Group	n	Delta Power	Alpha1 Power	Alpha2 Power	Beta Power	Posterior Coherence	Frontal Coherence
Control	238	7.16 (1.89)	3.63 (2.32)	0.54 (0.96)	3.02 (1.50)	0.49 (0.14)	0.52 (0.15)
Schizophrenic (> 3 days)	37	8.57 (2.02)+	3.26 (2.78)	0.86 (1.26)	3.93 (1.81)#	0.54 (0.18)	0.57 (0.14)$
Schizophrenic (> 1 year)	18	8.57 (1.90)$	3.58 (2.75)	0.99 (1.26)	3.64 (2.07)	0.51 (0.20)	0.55 (0.16)
Schizotypal (drug-free)	21	6.64 (1.72)	2.46 (2.31)#	0.91 (0.98)#	2.97 (1.53)	0.54 (0.20)	0.48 (0.14)
Depressive (> 3 days)	67	7.44 (2.13)	3.89 (2.78)	0.68 (0.91)	2.96 (1.59)	0.49 (0.10)	0.54 (0.15)#

Table 10 Signal power (S) and noise power (N) (μV) with group comparisons of the mean value (SD) at electrode positions Fz and Cz between healthy controls and unmedicated patient groups, corrected for age, gender and number of artifact-free trials (ANOVA),): $p \leq 0.1$ ($), $p < 0.05$ (#), $p < 0.01$ (+) not corrected for number of statistical tests. Schizophrenic patients were unmedicated for > 3 days; a subgroup of these 29 patients were unmedicated for > 1 year. Schizotypal subjects were never medicated; depressive patients were unmedicated for at least three days

Patient Group	n	S Fz	S Cz	N Fz	N Cz
Control	222	1181.10 (1070.56)	1586.14 (1350.75)	2209.00 (1035.51)	2288.38 (1050.52)
Schizophrenic (> 3 days)	29	794.93 (592.47)$	901.28 (954.80)#	2627.84 (967.56)	2729.55 (1217.61)
Schizophrenic (> 1 year)	14	828.42 (688.07)	1043.26 (1340.09)	2756.76 (923.79)	3061.53 (1029.67)$
Schizotypal	18	930.56 (875.69)	1076.90 (825.98)	2527.29 (2462.29)	2789.89 (2566.62)$
Depressive (> 3 days)	62	1091.33 (858.81)	1204.25 (953.36)$	2276.04 (867.48)	2260.83 (1034.81)

Table 11 Group comparisons of task-related EEG factor scores with mean value (SD) between drug-free schizophrenics (unmedicated > one year) and different groups of medicated patients: $p < 0.05$ (#), $p < 0.01$ (+), $p < 0.001$ (*), 2-tailed, Mann-Whitney U-test. (Not depicted is that almost the same group differences were found for resting EEG factors; patients treated with clozapine and olanzepine also showed significantly reduced signal-to-noise ratio at Fz and Cz ($p < 0.001$)).

Schizophrenic Group	n	Delta Power	Alpha1 Power	Alpha2 Power	Beta Power	Posterior Coherence	Frontal Coherence
Drug-fee	18	8.57 (1.90)	3.58 (2.75)	0.99 (1.26)	3.64 (2.07)	0.51 (0.20)	0.55 (0.16)
Perazine	30	8.75 (1.58)	3.34 (2.64)	0.57 (0.90)	3.44 (1.60)	0.54 (0.10)	0.55 (0.14)
Haloperidol	10	8.61 (2.23)	4.16 (3.23)	0.44 (1.06)	3.57 (2.69)	0.44 (0.14)	0.60 (0.12)
Clozapine	14	12.0 (2.64)*	3.34 (2.90)	0.76 (1.03)	3.11 (2.25)	0.59 (0.17)#	0.48 (0.10)#
Olanzepine	7	10.1 (4.96)	3.53 (1.05)	0.72 (0.49)	3.07 (1.33)	0.53 (0.16)	0.47 (0.06)+

without the depressive patients. Thus, linear discriminant analysis was performed with six EEG-factor variables from task-related EEG as well as signal and noise power at Cz and Fz. Schizophrenic patients were either unmedicated or treated with haloperidol or perazine. The resulting classification algorithm from the training set was again applied to an independent test set of schizophrenics and normals. For explorative reasons, we also tested the resulting classification rule from the training set (schizophrenics versus normals) on a set of schizotypal subjects as these individuals are believed to be genetically prone to schizophrenia (Siever et al. 1995; Battaglia et al. 1999). It becomes obvious from Table 12 that schizophrenics and normals can be well classified with a three-variable model, whereas schizotypal subjects are almost randomly distributed across both classes (schizophrenics versus normals). Each of the three variables is highly discriminant: 1) delta power (RT-EEG): 0.78 Wilks' Lambda, 0.0026 (p-value), 2) signal power (Cz): 0.68 (Wilks Lambda, 0.0007 (p-value), 3) alpha2 power (RT-EEG): 0.65 (Wilks' Lambda), 0.0013 (p-value). Re-test stability (Kappa) of this classifier was established based on 20 normals and 11 schizophrenic patients, who were unmedicated during their first recording and medicated with a variety of different drugs (including atypical neuroleptics) during the second recording (re-test interval: 1–10 weeks). Sammon mapping (Fig. 1) clearly shows that there is a broad overlap between schizophrenics and normals.

For comparison with the electrophysiological classification, we also performed a classification of schizophrenics and normals with reaction time alone (mean latency with standard deviation, mean error rate), as schizophrenics showed significantly prolonged reaction times ($p< 0.0001$). This resulted in an overall correct classification of 72 % (training set) and 77.05 % (test set). Normals were more accurately classified (training set: 87.8 %, test set (89.6 %) than schizophrenic patients (training set: 56.3 %, test set: 64.5 %). A combination of the electrophysiological variables and reaction time variables (mean latency with standard deviation, mean error rate) improved the overall classification only marginally (training set: 83 %, test set: 78.19 %). Nevertheless, it became clear from this combination that slow reaction time clusters together with the three variables of the electrophysiological classifier.

Finally, we compared whether the correctly and falsely classified schizophrenics differ with respect to their correlation with the AMDP psychopathology syndromes. A significant correlation was found between the 3-variable classifier and the apathy syndrome (z=2.60; p=0.0094). The correctly classified schizophrenics showed a higher mean rank (20.9) than the falsely classified schizophrenics (mean rank: 10.93). In contrast, a weak, non-significant trend was found for the paranoid syndrome (z=1.6; p=0.12), with falsely classified schizophrenics showing a higher mean rank (23.56) than correctly classified schizophrenics (17.05).

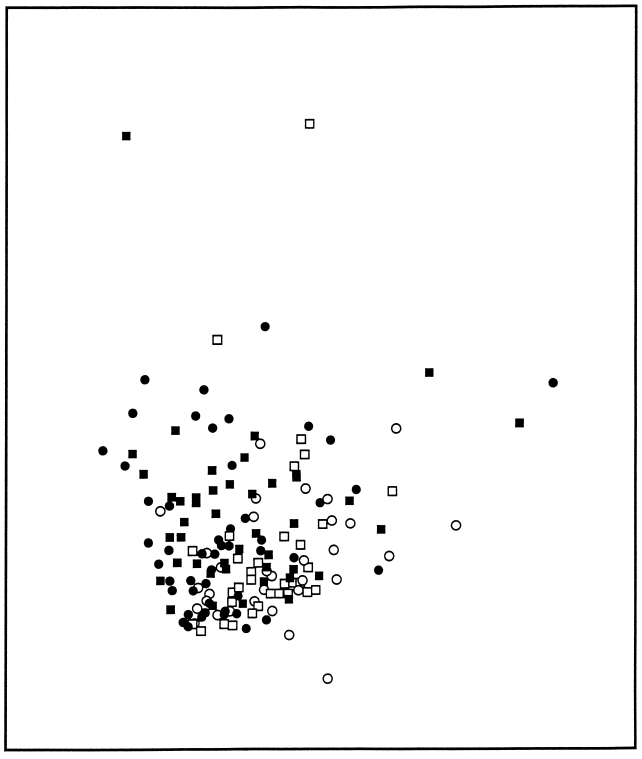

Fig. 1 Sammon map (2-class problem) of schizophrenic (traing set: n=33 (o); test set: n=32 (□)), normals (training set: n=49 (●); test set: n=49 (◆)) based on 3 electrophysiological variables: delta power factor (RT-EEG), signal power at Cz and alpha2 power factor (RT-EEG).

Table 12 Linear discriminant analysis of schizophrenic patients and normals on the basis of EEG factor variables from task-related EEG, signal and noise power at Fz and Cz (corrected for age, sex and number of artifact-free trials). The classification is based on a 3-variable model. Numbers without parentheses refer to the training group; numbers with parentheses refer to the independent test-group.

Actual Group	n	Predicted Group membership	
		Normal	Schizophrenic
Normal	49 (49)	77.6 % (77.6 %)	22.4 % (22.4 %)
Schizophrenic	33 (32)	24.2 % (25 %)	75.8 % (75 %)
Schizotypal	(18)	(66.7 %)	(33.3 %)

Percent of "grouped" cases correctly classified (2-class problem without schizotypal subjects): 78.9 % (77.3 %)

Discussion

This study primarily addressed the question in as much electrophysiology can contribute to the classification and subtyping of psychiatric disorders. For this purpose, we investigated schizophrenic patients and compared them with normals, schizotypal subjects and depressive patients. We have chosen a paradigm which includes resting EEG, task-related EEG and evoked potentials. Our approach differed from previous investigations in that we 1) included task-related EEG, 2) only applied variables with high re-test sta-

bility and 3) performed a variable reduction on data of healthy subjects by means of factor analysis prior to discriminant analysis of patient groups. By means of this, we hoped to be able to develop a classifier which is basically stable enough and valid in terms of a meaningful pathophysiological interpretation to meet the requirements of clinical and research applications.

The subsequent results were achieved. First, we found that our electrophysiological discriminant analyses reliably distinguish schizophrenic patients from normal subjects. However, depressive patients and schizotypal subjects cannot sufficiently be separated from normals and schizophrenic patients. The latter may be due to different reasons. Thus, it can be envisaged that our definition of depression was too broad and that a narrow definition of clinical depression might have resulted in better classification results. However, our depressive patients were practically randomly distributed across classes which is a point against this notion. Similar considerations may hold true for our schizotypal subjects. Another possibility is that our factor analytical approach – in order to reduce the number of variables and to achieve higher retest stability – resulted in a significant loss of information, for instance, from the spatial domain. Here it might be argued that the selection of factor variables for patient classification does not favor this notion. This is because those factors that include spatial information (the two coherence factors) did not play a major role in the discrimination of patients. However, as these factors were developed on normal EEGs, the theoretical possibility remains that these factor solutions do not fit the conditions in patients.

Upon closer examination, it also becomes obvious that our classifier may not be primarily useful to discriminate schizophrenic patients from normals or other groups of patients but rather to subtype schizophrenic patients. Accordingly, two subtypes of schizophrenics could be delineated. One subtype obviously encompasses a group of patients with predominant negative symptoms (apathy) and prolonged reaction times which was classified as abnormal, whereas the second subtype, which is classified as normal, may be characterized by a trend to show paranoid-hallucinatoric symptoms and shorter reaction times. Remarkably, the classifier is largely based on variables from task-related EEG and evoked activity, clearly outperforming resting EEG variables. In this context, it is also noteworthy that those variables with the highest classification power directly point to frontal lobe dysfunction. Thus, an increase of frontally pronounced delta activity in schizophrenic patients was repeatedly related to decreased prefrontal blood flow and glucose utilization (Ingvar & Franzen 1974; Guich et al. 1989). Similarly, a decreased amplitude of signal power, which in our paradigm largely reflects the N100/P200 amplitude, was also shown to reflect frontal lobe function or reduced attention way (Näätänen & Picton 1987). This is because our N100 complex is similarly elicited like the mismatch negativity, e. g., stimuli are presented in random order and interval. Moreover, we were recently able to show by means of source localization that this reduction of the N100/P200 wave in schizophrenics reflects reduced activation of the anterior cingulate lobe (Mulert et al. 1999). The interpretation of frontal lobe dysfunction is further validated by reports from the literature, which consistently related negative symptoms to frontal pronounced EEG slowing (Fenton et al. 1980; Dierks et al. 1989; Guich et al. 1989). Noteworthy, the fact that we found reduced signal power of the evoked activity together with EEG-slowing is also a strong point against the notion that (frontal) EEG-slowing in schizophrenics is merely an expression of increased eye movement activity (Karson et al. 1987; Dierks et al. 1989). However, the work of Karson et al. (1987) has found that slowing is observed in schizophrenics at anterior and posterior electrode sites independently of eye movements although eye movements may explain an excess of frontal slow activity compared with other areas of the brain in schizophrenics. Nevertheless, we cannot exclude completely that eye movements have contributed to the increased of delta activity as expressed by higher values of the delta EEG factor. However, since we did not include the usually contaminated frontopolar electrodes and carefully excluded those sweeps with evidence for eye movement contamination, this seems to be not very likely. From this perspective, our classifier does not seem to distinguish primarily schizophrenics or a psychopathological schizophrenic subtype from normals or other patients but detects those subjects with frontal lobe dysfunction. Accordingly, the classifier may also detect normals or depressive patients with frontal lobe dysfunction or subjects with reduced motivation to perform the task appropriately. Actually, this interpretation of data is also suggested by the Sammon map (Fig. 1) which demonstrates a substantial overlap between patients and normals. The fact that subjects with reduced motivation may also be classified as frontal lobe dysfunctional may be considered as a confounding influence. However, this is counter-balanced by the simplicity of the task which does not require a large amount of motivation or high frustration threshold, at least, when compared with more complex psychological tasks.

At this point, we want to mention that we have meanwhile performed more sophisticated and complex EEG analyses on the same data set. However, the examined parameters are currently not useful for classification purposes. These investigations indicate that schizophrenics as well as schizotypal subjects show an increased amount of electrical noise with a higher level of baseline delta activity and reduced stimulus-locking (phase-locking) of ongoing EEG activity. This is not observed in the depressive patients and normal subjects (Winterer et al. 2000). Reduced phase-locking is specifically observed in the 0.5–5 Hz range and goes along with reduced EEG coherence between the temporal lobes and increased coherence between the frontal lobe and virtually all other parts of the brain. In a previous study (Winterer et al. 1999), we could show that up to a certain point, cortical noise may be favorable for information processing (stochastic resonance phenomenon) and facilitate the switching between functional brain attractors. However, past a certain point – as in our schizophrenic patients with prefrontal hypoactivation – this may no longer be the case.

In summary, the simplicity of the task (AMDP-module IV) may be regarded as the main advantage of our paradigm, as it allows the investigation of almost every patient, even when highly psychotic. As the resulting classification algorithm is also reliable and pathophysiologically meaningful, it is suggested that the classifier – in its basic version – may serve as a useful tool to detect frontal lobe dysfunction, which may be applicable to clinical and research questions. This is further emphasized by the observation that our classifier is basically insensitive to confounding influences from typical neuroleptics since drug-induced changes frequently are a major drawback of electrophysiological parameters for diagnostic purposes.

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