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Eur Arch Psychiatry Clin Neurosci (2009) 259:257–262
DOI 10.1007/s00406-008-0854-3

ORIGINAL PAPER

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EEG: a helpful tool in the prediction of psychosis

Received: 15 April 2008 / Accepted: 24 October 2008 / Published online: 11 April 2009

Abstract *Objective* EEG investigation in patients with an at risk mental state (ARMS) for psychosis and patients with a first episode of psychosis (FE) in comparison to healthy controls (HC) in a clinical follow up study of Early Detection of Psychosis. *Method* Seventy-three patients (42 ARMS, 31 FE) and 35 HC were investigated. ARMS patients were followed up in order to monitor transition to psychosis. Psychopathology was assessed with respect to positive and negative symptoms. At study baseline EEG was recorded using the 10/20 system. Two blinded neurologists analyzed the EEGs visually for presence of generalized or focal slowing and epileptiform discharges. EEG data were controlled for medication and substance abuse. For statistical analyses we used χ^2-tests, logistic regression, ANOVA, and receiver operating characteristics. *Results* Patients showed significantly more pathological EEG abnormalities than HC ($P < 0.05$), located more frequently in temporal or fronto-temporal regions ($P < 0.01$) of the brain, with twice as many pathologies in ARMS than in FE patients. The specificity of the prediction of psychosis could be increased from 59 to 73% by considering EEG pathology in addition to psychopathology alone. In contrast, sensitivity of prediction remained unchanged. *Conclusions* These results show that EEG investigation in patients at risk for psychosis can add to the identification of those patients who will not develop psychosis later on.

Key words psychosis · schizophrenia · EEG · marker · detection · prediction · neurophysiology

Introduction

The main role of EEG in the clinical diagnosis of patients with a schizophrenia-like syndrome is to detect organic brain diseases such as epilepsy or limbic encephalitis. While the schizophrenia-like psychosis of epilepsy [11, 15, 26] constitutes a special diagnostic difficulty, chronic and first episode schizophrenia itself may be associated with EEG pathologies in 23–44% [6, 24, 28], even if never treated with antipsychotic drugs [27]. However, no single pattern of EEG abnormality in chronic or first episode schizophrenia has been identified. Increased prevalence of EEG pathologies in patients with a first episode of psychosis (FE) [4, 24] remains controversial [18]. If present, these pathologies seem to be associated with a worse prognosis [12–14]. While relatives of schizophrenic patients showed an increase of slow activity [1, 4], no data is available on EEG recordings in individuals being clinically in a prodromal phase of the disease. Moreover, while some studies with FE patients were conducted, to our knowledge no longitudinal studies have been performed in individuals at risk for psychosis with or without later transition to psychosis.

The present investigation forms a part of a prospective, multilevel study to identify characteristics that allow the differentiation of patients with a true prodromal phase of schizophrenia from those with a similar clinical syndrome who will not develop psy-

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chosis later on [17]. The purpose of the present study was to evaluate the contribution of EEG to the assessment of the risk for transition to psychosis in at risk mental state (ARMS).

Methods

Patients

A specialized Early Recognition Clinic for Psychosis was established at the Psychiatric Outpatient Department of the University Hospital Basel, Switzerland. The referrals with suspected psychosis came mainly from general practitioners, psychiatrists in private practices, and from our Psychiatric Outpatient Department. The screening procedure using the Basel Screening Instrument for Psychosis [16] was based on the most important risk factors for and potential indicators of beginning schizophrenia (e.g. genetic risk, psychopathological and psychosocial changes). The inclusion criteria and the cut-off for transition to psychosis was defined using the Brief Psychiatric Rating Scale (BPRS) according to Yung et al. [30]. Subjects were included as at risk if they fulfilled the following criteria.

Criteria 1.1—"Attenuated psychotic symptoms" (scores of 2 or 3 on the hallucination item, 3 or 4 on the "unusual thought content" or "suspiciousness" items of the BPRS for at least several times a week and persisting for more than 1 week) or

Criteria 1.2—"Brief Limited Intermittent Psychotic Symptoms" (BLIPS—scores of 4 or above on the "hallucinations" item, or 5 or above on the "unusual thought content", "suspiciousness" or "conceptual disorganization" items of the BPRS, with each symptom lasting less than 1 week before resolving spontaneously) or

Criteria 2—genetic risk and at least two further risk factors according to the screening instrument, such as social decline or prodromal symptoms or

Criteria 3—a minimal amount and combination of unspecific risk factors according to the BSIP [16].

Inclusion criteria 1 and 2 correspond to the ARMS subjects (high risk) of Yung et al. [31], and criterion 3 additionally permits the inclusion of patients at presumably lower risk, who display only certain prodromal symptoms and social decline. All analyses were carried out on data concerning the total sample of ARMS high risk and ARMS low risk individuals.

Individuals in an at-risk mental state for psychosis (ARMS) were compared to patients with a FE and to healthy controls (HC). HC were recruited from trade schools, hospital staff and through advertisements. They had no history of psychiatric or neurological disease, no past or present substance abuse or head trauma. A formal neurological examination of all patients and HC showed normal findings. Patients with previously diagnosed schizophrenia, substance-induced psychosis, age below 18 years, inadequate knowledge of the German language, and intelligence below an IQ of 70 were excluded.

During the first year of follow-up, ARMS individuals were assessed monthly, during the second and third year every third month, and afterwards once a year. Transition to psychosis was monitored using the transition criteria [30].

During the first 3 years of inclusion we screened 206 individuals for beginning psychosis, 98 of whom were classified as being at risk for psychosis and 76 of them as psychotic, 32 had other psychiatric diseases (e.g. anxiety disorder). Of the remaining 174 patients, 58 ARMS individuals and 36 patients with a FE consented to participate in the study. Forty-two ARMS individuals, 31 first episode patients and 35 HC could be investigated with EEG. During a follow-up period of 72 months 12 of the 42 ARMS individuals made the transition to psychosis and eight were lost to follow-up. If during follow-up an ARMS individual was known to receive neuroleptic medication that person was considered as dropping out from the study. Data from the ARMS-patients were analyzed with regard to transition and no transition to psychosis. For sample description see Table 1.

At baseline, statistical differences were found between the groups' age, educational level, neuroleptics and cannabis intake. However, these differences were statistically balanced across subgroups with the consequence that post hoc-tests did not show any statistically significant differences. Differences in EEG were tested by χ^2 test and ANOVA with SPSS for Windows, Version 14.

Level of significance was set at $P < 0.05$. The study was approved by the local ethics committee. After complete description of the study to the subjects, written informed consent was obtained from all participants.

Study design

EEG recording and analyses

Routine EEG recordings were performed in a quiet room with the patients either sitting or in supine position with closed eyes; the recordings lasted for about 20 min and included several episodes of open and closed eyes, as well as hyperventilation and photic stimulation.

The EEGs were digitally recorded using the international 10/20 system. Impedances were kept below 5 kΩ. Amplifiers were calibrated using a 50 μV square pulse. Sampling frequency was 250 Hz with 0.5–70 Hz filters. All channels were recorded against the mastoids. Each EEG recording was independently analyzed by two neurologists who were blinded to the patients' clinical data and diagnostic group category. Generalized or focal slowing, spikes and sharp waves, as well as pathological rhythmic patterns were assessed, and special care was taken to identify normal variants. Pathological rhythmic patterns were defined as repetitive discharges not corresponding to one of the known benign EEG variants (e.g. signs of drowsiness such as rhythmic mid-temporal discharges (RMTD), subclinical rhythmic electrographic discharges in adults (SREDA) and wicket spikes, or midline theta rhythms, etc.). Multiple responses were possible. Because of an inter-rater reliability close to 1.0 there was no need to calculate the Kappa-value.

The severity of EEG pathology was scored similar to Centorrino et al. [3] as follows: 0 = no abnormality, 1 = mild abnormality (theta and delta slowing), 2 = moderate abnormality (sharp waves, pathological rhythmic pattern), 3 = severe abnormality (combina-

Table 1 Demographic characteristics, neuroleptics, and cannabis abuse of healthy controls, ARMS individuals and patients with a first episode of psychosis

	HC ($N = 35$)	ARMS ($N = 42$)	FE ($N = 31$)	
Age (years ± SD)	23.9 ± 6.2	27.9 ± 8.7	31.7 ± 7.3	$F_{df=2,105} = 10.0$; $P < 0.001$
Gender (f/m)	13/22	17/25	9/22	$\chi^2_{df=2} = 1.04$; $P = 0.596$
Neuroleptics	0	0	6	$\chi^2_{df=2} = 20.6$; $P \leq 0.001$
THC use	0	13	10	$\chi^2_{df=2} = 17.7$; $P < 0.001$
Education (years ± SD)	11.2 ± 1.7	10.3 ± 2.4	10.0 ± 2.7	$F_{df=2,105} = 2.9$; $P = 0.059$

HC healthy controls, *ARMS* individuals in an 'at risk mental state' for psychosis, *FE* first episode patients

Table 2 Pathological EEGs (slow waves, pathological rhythmic patterns) of all patients versus healthy controls ($\chi^2_{df=2} = 6.2$; $P < 0.05$)

	HC ($N = 35$)	ARMS ($N = 42$)	FE ($N = 31$)
No pathology	31	27	24
Pathology	4	15	7

tion of 1 and 2). In order to clarify the existence of substantial associations between EEG pathology and psychopathology Scale of the Assessment of Negative Symptoms (SANS) mean summary score [2] and BPRS global score [29] were computed as function of the degree of EEG pathology.

Data analysis

First, any potential statistical interaction was tested for significance with χ^2 and ANOVA. Then, a binary logistic regression model was conducted and probabilities for developing psychosis were calculated in order to specify the contribution of EEG to the prediction of psychosis. Finally, based on these probabilities, receiver operating characteristics (ROC) were determined and cut-off values were derived in order to classify the ARMS individuals corresponding to those who actually transited to psychosis and those who did not.

Results

Nature and localization of EEG pathology

Patients showed significantly more EEG abnormalities (slow waves, pathological rhythmic patterns) compared to HC ($P < 0.05$). The highest proportion of pathological findings was observed in ARMS individuals (Table 2).

Epileptiform activity and pathological slowing

Four parameters were analyzed: (a) sharp waves, (b) spikes, (c) pathologic rhythmic patterns, (d) δ- and θ-activity. Twenty-four patients of the first episode group, 27 of the ARMS individuals, and 31 of HC showed no pathology at all. Moreover, no spikes were found in the whole sample. If more than one pathological sign was detected, patterns of combined EEG abnormalities were analyzed (see Fig. 1). In the ARMS group, the most prominent pathological finding was focal slowing, but no single pathological sign showed a significantly different prevalence between patients and HC ($P = 0.80$).

Pathological EEG findings were localized predominantly in the temporal or fronto-temporal region. Thirteen out of 42 ARMS individuals showed temporal or fronto-temporal localization, only one patient had an occipital pathology. No pathology could be detected in the parietal region of the brain. Three patients (two-first episode patients, one ARMS individual) showed generalized epileptiform activity which was ignored in the analysis of localized brain dysfunction. In total, 17 pathologies were unilateral, seven pathologies were bilateral, two patients showed both bi- and unilateral pathologies at different locations. There was no statistically significant difference between the groups. The localization of pathological findings in the fronto-temporal or temporal region

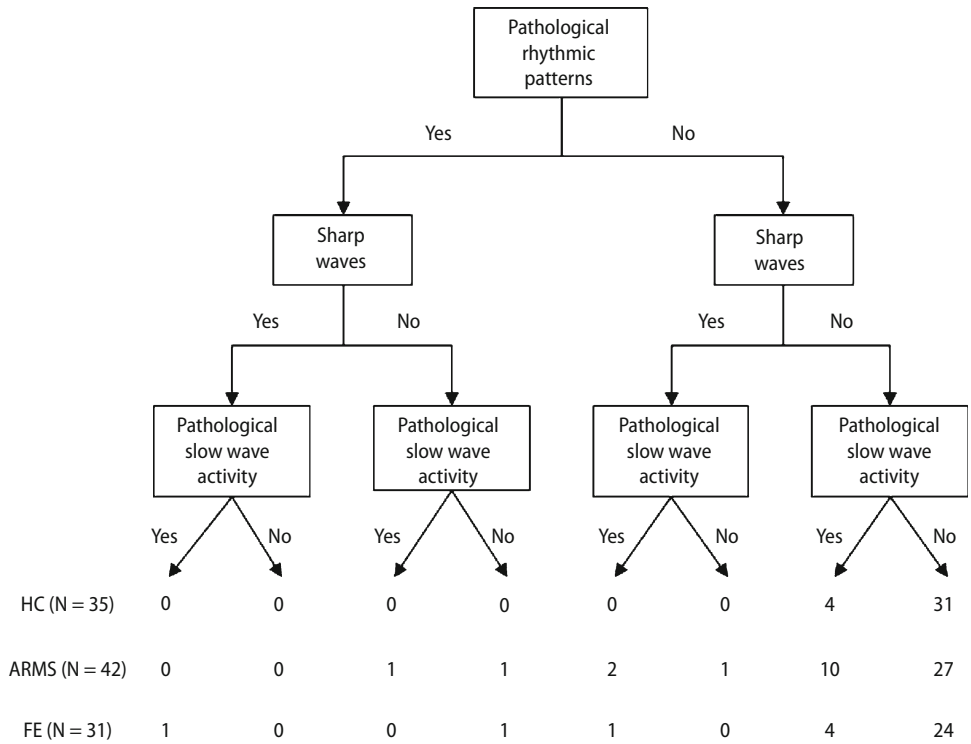

Fig. 1 Pathological slowing and epileptiform activity

compared to other localizations was one of the most stable findings of our study ($P < 0.01$).

EEG pathology and psychopathology in ARMS patients and FE

Psychopathology as assessed by BPRS (global score) and SANS (summary score) was neither in ARMS nor in FE associated with severity of EEG pathology.

EEG pathology and psychopathology in ARMS individuals with and without transition to psychosis during a 7-year follow-up period

During the maximum follow up of 7 years 12 ARMS individuals with an initial EEG recording transited to frank psychosis (ARMS-T), further eight individuals refused participation during follow-up and were therefore lost for prospective analysis. Twenty-two individuals did not make the transition to psychosis during follow-up (ARMS-nT).

Seven (58%) out of 12 ARMS-T showed EEG pathologies ($N = 5$ slow waves, and $N = 2$ slow waves and sharp waves), whereas only six (27%) out of 22 ARMS-nT did ($N = 4$ slow waves, $N = 1$ sharp waves, and $N = 1$ slow waves and sharp waves). Differences between groups were not statistically significant, probably due to the relatively small sample size. There was no relationship between SANS summary score, EEG pathology and group assignment to ARMS-T and ARMS-nT.

However, psychopathology measured by the BPRS global score at inclusion showed a significant interaction ($F_{3,29} = 3.27$; $P = 0.035$) of group assignment with presence or absence of pathological EEG (Fig. 2).

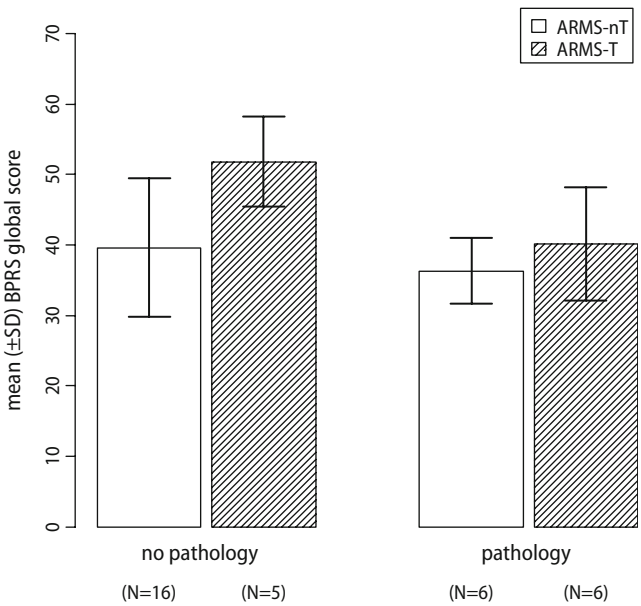

Fig. 2 Mean BPRS Global Score as function of the transition to psychosis and EEG pathology. Significant interaction of group assignment (ARMS-T vs. ARMS-nT) with pathological EEG ($F_{3,29} = 3.27$; $P = 0.035$)

ARMS-T individuals with EEG pathology had lower BPRS global scores compared to those without.

Prediction of psychosis

In order to evaluate the predictive value of the EEG findings two logistic regression procedures were performed. In both cases the dependant variable was the binary coded group membership (ARMS-T vs. ARMS-nT). While the first model addressed only psychopathology measured by BPRS, a second model considered both the psychopathology and the EEG pathology. In both models psychopathology was positively related to the transition to psychosis. Severity of EEG pathology as additionally entered in the second model likewise showed a positive relationship to the transition to psychosis.

Prediction of psychosis with psychopathology alone

The logistic regression procedure showed a significant model predicting group assignment by psychopathology measured by BPRS ($\chi^2_{df=1} = 3.9$; $P = 0.049$). The odds-ratio for suffering from transition to psychosis was estimated to increase by an amount of 1.08 ($\text{Wald}_{df=1} = 3.56$, $P = 0.059$) with BPRS score at baseline increasing by one unit.

Moreover, based on the predicted probabilities as yielded by the logistic regression procedure, a cut-off value was derived by means of the ROC curve in selecting a particular probability-value ($P = 0.276$) according to a maximized sensitivity as well as specificity. The cut-off value was equivalent to a BPRS score of 39. This procedure resulted in a sensitivity of 82% of correctly classified ARMS-T experiencing a transition to psychosis and a specificity of 59% of correctly classified ARMS-nT without transition to psychosis (see Table 3).

Prediction of psychosis by combining psychopathology and pathological EEG severity

In comparing alternative models the best choice was one that specified psychopathology as well as pathological EEG severity modeled as the main effect. The

Table 3 Contingency table observed versus predicted ARMS (transited = T and non-transited = nT) based on a binary logistic regression using only BPRS global score as predictor

	Observed	
	ARMS-nT	ARMS-T
Predicted		
ARMS-nT	13	2
ARMS-T	9	9

Table 4 Contingency table observed versus predicted ARMS (transited = T and non-transited = nT) based on a binary logistic regression using BPRS global score as well as EEG pathology as predictor

	Observed	
	ARMS-nT	ARMS-T
Predicted		
ARMS-nT	16	2
ARMS-T	6	9

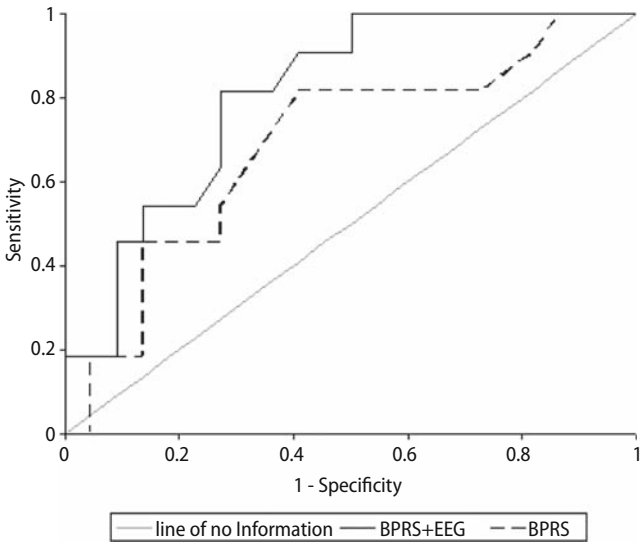

Fig. 3 Receiver operating characteristic derived from predicted probabilities for transition to psychosis. The *dashed line* indicates the ROC belonging to the BPRS-only model (AUC = 0.70), the *solid line* indicates the ROC derived from the BPRS-EEG-severity combined model (AUC = 0.81)

model was highly significant ($\chi^2_{df=2} = 10.5$; $P = 0.005$) and estimated the contribution of psychopathology to the prediction of psychosis by an odds-ratio of 1.15 ($\text{Wald}_{df=1} = 5.69$, $P = 0.017$) whenever BPRS increased by one unit. Most importantly, the odds-ratio of suffering from transition to psychosis increased by a value of 5.89 ($\text{Wald}_{df=1} = 5.07$, $P = 0.024$) if the severity of EEG pathology was considered.

By applying the same strategy as above, a cut-off value was determined using the ROC curve. Again, this resulted in a sensitivity of 82%, but specificity increased to a value of 73% (Table 4). Specificity and sensitivity were associated with a cut-off value of $P = 0.340$ (predicted probability).

This means that the detection of false positives ARMS who will not make the transition to psychosis could be improved by considering their EEG recordings which are free of pathologies (Fig. 3).

Discussion

Pathological signs are significantly more prevalent in EEGs of FE and of ARMS than in those of HC, and were predominantly localized in temporal or fronto-temporal regions of the brain. However, there is no association between the severity of both the psychopathology and the EEG pathology. This is true with regard to FE compared to ARMS on the one hand an ARMS-T compared to ARMS-nT on the other hand. ARMS-T showed a higher proportion of EEG pathologies than ARMS-nT even though this could not be significantly testes against chance. When prediction of psychosis is considered, the additional contribution of EEG assessment increases the specificity of the prediction of psychosis but leaves sensitivity unchanged.

In general, patients (ARMS, FE) showed a higher proportion of pathological abnormalities in the EEG than HC. This indicates a higher vulnerability of brain abnormalities in FE and even in its prodromal state.

EEG pathologies were mostly located in the temporal or fronto-temporal region. This result is in accordance with earlier studies [5, 6, 15, 21, 22, 25]. While in some of them, left-sided pathology was the most frequent finding, others found bilateral alterations [9, 10, 20, 23]. Unilateral pathologies predominated in our patients, but left-sided locations did not outweigh right-sided ones. As the present study is based on visual analysis of EEG, the absence of findings like diminished alpha activity or increased beta activity as reported from quantitative EEG studies [4, 7, 8, 19] is limited to effects large enough to significantly influence the visual analysis of clinical EEG, which is aimed at the discovery of clear-cut pathology in the individual rather than group effects.

Out of 35 HC in our study, four individuals showed pathological slow wave activity, but none of them had sharp waves, spikes or pathological rhythmic patterns. The high percentage of slow wave pathologies in the control group could have occurred by chance due to a relatively small sample size.

While in the present study, ARMS individuals were defined by clinical signs and symptoms, others who examined patients with a purely genetic risk also found a correlation between the mental state and the severity of EEG pathologies [1].

The prediction of transition to psychosis based on psychopathology alone is corresponding to a BPRS global score of 39 and above. This means that any patient presenting with a value of 39 or more is classified as ARMS-T. Any patient who scores below this value is viewed as not being at risk for transition to psychosis.

Although more ARMS who later made the transition to psychosis had shown EEG pathologies than ARMS without later transition this difference was not significant. Also, the sensitivity of prediction does not change when EEG pathology additionally to psychopathology is considered. The value of 82% sensitivity remains unaffected, regardless of the psychopathology alone or in combination with EEG. In contrast,

the specificity of prediction increases from 59–73% when EEG is considered in addition to psychopathology.

In other words, ARMS individuals that would have been incorrectly classified as ARMS-T based on psychopathology alone were reclassified when EEG findings were considered additionally, thereby increasing specificity but not sensitivity. A detailed analysis revealed that subjects with a high BPRS score (>39) could be correctly reclassified as not making a transition to psychosis later on if the EEG at baseline investigation was normal.

As EEG is an easily available and economic test, this result is clinically important and may have implications for the care of individual patients.

The value of the study lies in the prospective investigation of a sample of patients in a prodromal state of psychosis. Limitations of the study are due to the relatively small sample size, the lack of a cross-validation procedure and possible selection bias of HC.

Acknowledgments This project was supported by the Swiss National Science Foundation no. 3200-057216.99, no. 3200-057216/3 and no. PAIBA-102388/1. Dr. Pflueger has received research support from Astra-Zeneca and the "Freiwillige Akademische Gesellschaft Basel".

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