Event Related Potentials (ERPS) in Schizophrenics and Their First Degree Relatives

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Abstract:

The auditory P_{300} event-related potential (ERP) was evaluated in 40 schizophrenic patients, 28 first-degree relatives and 22 controls. 50% of schizophrenics had small P_{300} amplitude and 40% had prolonged latency. 42.8% of unaffected first-degree relatives of schizophrenics showed small P_{300} amplitude and 20.8% showed prolonged latency. No statistical difference between left and right temporal leads neither in amplitude nor in latency in schizophrenics. The results confirm the previous research finding, namely P_{300} amplitude reduction in schizophrenics compared to controls and suggest that neurophysiological testing of relatives may help to clarify the mode of inheritance of schizophrenia in some families and to detect the relatives that are at high risk to develop schizophrenia.

Introduction:

Averaging segments of electro-encephalographic signals occurring after repeated presentations of exogenous stimuli has consistently demonstrated reduced amplitudes in specific components of event related potentials (ERPs) in schizophrenic patients.

These amplitude attenuations, occurring at latencies of approximately 300 msec (P_{300}) were first demonstrated by Roth & Cannon (1972), and have been observed by numerous other research teams using a variety of experimental paradigms and sensory modalities (Brecher and Begleiter, 1983; Faux et al., 1988 and Kutcher et al., 1989). They are apparently unaffected by neuroleptic medications, at least in the auditory modality (Duncan et al 1987).

Some investigators have also described prolonged P_{300} latency in schizophrenics or their relatives (Kutcher et al 1989 and Blackwood et al., 1991), although this finding is less consistently reported than amplitude attenuation and may be confounded by the effects of neuroleptic medication (Pfefferbaum et al., 1989) or filtering (Ebmeier et al., 1990).

Reduction in P_{300} amplitude has been related to cognitive deficits, brain structure abnormalities, chemical abnormalities, and/or clinical status (Ford et al 1992 and Dean et al., 1998). The association between P_{300} amplitude and clinical symptoms at a single time point has generally supported a relationship between small P_{300} and negative symptoms (Ford et al., 1994). Also, of interest has been the observation of lateral asymmetries in P_{300} amplitude in patients with schizophrenia. McCarley et al., (1989) recorded P_{300} from electrodes placed over the right (T_4) and left (T_3) temporal scalp sites and found greater P_{300} reduction at left than right temporal electrode sites in schizophrenics. This P_{300} asymmetry is linked to tissue volume asymmetry in the posterior superior temporal gyrus (Dean et al., 1998). Furthermore, in their study on first episode schizophrenic psychosis versus first episode affective psychosis Dean et al., (1998),

concluded that P_{300} asymmetry is specific to schizophrenic psychosis and present at initial hospitalization. This P_{300} asymmetry suggests left temporal lobe dysfunction at the onset of schizophrenia.

Methods and Subjects:

Patients: Forty schizophrenic patients who met the ICD-10 research criteria were studied. Mean age was 33.3 ± 11.0 years, mean duration of illness was 9.1 ± 8.8 years. Thirty-eight patients were right-handed, one patient was ambidextrous and one patient was left-handed. Non of the patients had concomitant neurological or medical diseases, alcoholism or drug abuse. Patients were excluded for a history of head injury resulting in loss of consciousness greater than 30 minutes hearing deficits greater than 30 dB at 500; 1000, and 2000 HZ in the better ear. All patients gave informed consent prior to their participation in the study. The patients were divided into acute and chronic groups and on- and off-medication groups.

Relatives: The relatives group consisted of 28 first-degree relatives of schizophrenic patients. Mean age was 35.6 ± 11.8 years. No history of neurological or psychiatric disorders or drug abuse was found.

Controls: The control group was comprised of 22 right-handed normal controls from the hospital staff and their relatives. Mean age was 29.2 ± 11.3 years. Exclusion criteria included neurological or psychiatric disorders, drug abuse, head traumas and hearing deficits.

ERP Testing:

All recordings were made in a sound-attenuated room, with each subject seated in a comfortable reclining armchair. Unipolar recordings referred to the left ear were made between silver / silver chloride electrodes at five sites-frontal (Fz), central (Cz), parietal (Pz), left temporal (T_3), and right temporal (T_4) positions-according to the 10-20 electrode system (Jasper 1983). Two electrodes measured the EOG-one at the left supraorbital position and another at the lateral canthus of the left eye. A ground electrode was positioned at the right ear lobe. Electrode impedances were less than 5 kilohms.

The subjects were informed that they would hear low-pitched (1000-HZ) tones interspersed occasionally with high-pitched (1500-HZ) tones, and that they were required to silently count the high pitched tones. They were told that at the end of the trial they would be asked how many high tones they had heard. Recordings were considered satisfactory if counting error was less than 10%. Subjects were instructed to relax and to keep as still as possible during the test.

The parietal lead (Pz) gave good diseriminatron between groups and gave the highest amplitude allowing comparison with other studies (e.g., Faux et al., 1988; Ebmeier et al., 1990).

Results:

From table (1) the P_{300} amplitude shows the differences between schizophrenic and control groups which were highly significant at mid-parietal region (Pz). And the schizophrenic group showed smaller amplitude than the control group. In schizophrenia, P_{300} latency was prolonged compared to controls but the difference was non-significant.

The schizophrenic relatives had smaller amplitude and longer latency compared to controls but the difference was non-significant as shown in table (2).

Table (3) presents the mean scores, standard deviations of the P_{300} amplitude and latency for the schizophrenics and their relatives. The differences were non-significant.

Table (4) shows comparison between acute and chronic schizophrenics regarding P_{300} amplitude and latency. The differences between the two groups were non-significant.

Comparison between schizophrenic patients on & off treatment revealed that there was no significant difference between the two groups neither in P_{300} amplitude nor in latency as shown in Table (5).

To address specific issues in the literature regarding P_{300} recorded at T_3, T_4 and P_{300} amplitudes and latencies at those sites were compared in schizophrenics and found not be significantly difference as shown in table (6).

Table (1): Comparison Between Schizophrenics & Controls As Regards P_{300} Amplitude & Latency

P_{300}	Schizophrenics (n=40) X ± SD	Controls (n=22) X ± SD	t	P-Value
Amplitude (uv)	7.3 ± 4.9	13.4 ± 8.73	3.0	<0.01
Latency (ms)	368.4 ± 51.7	338.6 ± 78.3	1.6	> 0.05 (NS)

Table (2): P_{300} Amplitude (Uv) & Latency (Ms) Recorded From Parietal Region In Schizophrenic Relatives & Controls.

P_{300}	Relatives (n=28) X ± SD	Controls (n=22) X ± SD	t	p-value
Amplitude (UV)	9.4 ± 6.04	13.4 ± 8.73	1.81	> 0.05 NS
Latency (ms)	357.8 ± 103.7	338.4 ± 78.3	0.75	> 0.05 NS

Table (3): Comparison Between Schizophrenics & Relatives As Regards P_{300} Amplitude & Latency.

	Schizophrenics (n=40) X ± SD	Relatives (n=28) X ± SD	t	p-value
Amplitude (UV)	7.3 ± 4.9	9.4 ± 6.04	1.52	NS
Latency (ms)	368.4 ± 51.7	357.8 ± 103.7	0.5	NS

Table (4): Comparison Between Acute & Chronic Schizophrenics As Regards P_{300} Amplitude & Latency

	Acute (n=12) X ± SD	Chronic (n=28) X ± SD	T	p-value
Amplitude (UV)	6.05 ± 5.24	6.4 ± 4.16	0.11	NS
Latency (ms)	353.6 ± 51.6	336.2 ± 52.7	0.04	NS

Table (5):Comparison Between Schizophrenic Patients On & Off Treatment As Regards P_{300} Amplitude & Latency.

P_{300}	On III (n=30)	Off III (n=10)	t	P-value
Amplitude (uv)				
Pz	5.0±2.3	7.56±5.1	1.49	
T_3	3.76±1.4	5.6±4.14	1.38	NS
T_4	4.82±1.1	5.0±3.38	0.18	
Latency (ms)				
Pz	354.2±49.6	337.2±53.34	0.12	
T_3	338.0±76.3	362.7±102.5	0.57	NS
T_4	353.0±51.9	378.7±95.6	0.76	

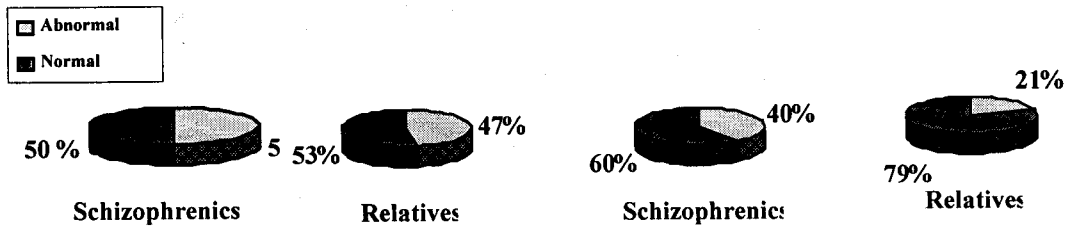
Table (6): Comparison between T_3, T_4 P_{300} in schizophrenics.

P_{300}	T_3	T_4	t	P-value
Amplitude (UV)	4.6 ± 4.0	4.4 ± 3.1	0.25	NS
Latency (ms)	378.6 ± 64.5	357.3 ± 66.9	1.45	NS

Table (7): The Demographic Characteristics Of Sehizophrenic Relative And Control Groups.

	Schizophrenics (n=40)	Relatives (n=28)	Controls (n=22)
Age (X ± SD)	33.3 ± 11.0	35.6 ± 11.8	29.2 ± 11.3
Sex (M:F)	24:16	16:12	15:7
Handedness (R:L)	38:1	28:0	22:0
(Ambidex)	1	-	-

Figure (1): The percentage of patients



Discussion:

Reduction in amplitude of the late positive component of the event-related brain potential (ERP), P_{300}, is one of the most replicable biologic observations of schizophrenia. In the first part of this report, our study confirmed the findings from a large literature on ERPs and schizophrenia. Auditory P_{300} amplitude is reduced in schizophrenics compared to controls (Pritchard 1986; Ford et al., 1992, 1994, Souza et al., 1995, & Dean et al., 1998). Like others we found that P_{300} latency is prolonged in schizophrenics (Kutcher et al., 1987; Michie et al., 1990 and Ford et al., 1994) but not significantly so. The interpretation of P_{300} amplitude reduction is based on an understanding of the antecedents of P_{300} in normal controls. Johnson (1986) suggested a model which stimulus expectancy and meaning and attention all contribute to P_{300} amplitude. Although it is tempting to assume that group differences in P_{300} amplitude are due to any or all of these processes, chemical (e.g, MHPG levels) and structural (e.g., brain tissue volume or skull thickness) factors. Independent of these psychological mechanisms, must also be considered. Souza et al., 1995) reported that schizophrenics performed significantly less well than bipolar and control groups on tests of verbal fluency. And within the schizophrenic, a significant correlation was found between the latency of P_{300}, as well as P_{300} amplitude and verbal fluency rest scores.

We also, addressed the sensitivity of the ERP to antipsychotic medication treatment. In spite of significant clinical improvement with antipsychotic treatment, the effects on P_{300} were minimal, showing no difference between the withdrawn period and the antipsychotic treatment period, consistent with Blackwood et al (1987) and Ford et al (1994). Thus, medication related delays and reductions in ERP latencies and amplitudes (Roemer and Shagass 1990 & Roth et al 1991) may be due to group membership differences (i.e., whether patients could or could not be withdrawn from medication) rather than to the medication, perse.

We addressed also the issue of lateral differences in P300 amplitude and found no significant difference between T_3 & T_4. McCarley et al., (1989) recorded P_{300} from electrodes placed over the right (T_4) and left (T_3) temporal scalp sites and found greater P_{300} reduction at left than right temporal electrode sites in schizophrenic. Koga et

al., (1987) found that schizophrenics had reduced P_{300}, over both the right and left hemispheres, but more significant differences were found in P_{300} recorded over the left. However, Kemali et al., (1988) found no evidence for lateral asymmetry in either the schizophrenics or controls, nor did Pfefferbaum et al., (1989). Differences across laboratories may be due to the use of different paradigms (counting vs button press) and reference electrode differences (Ford et al., 1994).

In the second part of this report we found that 47.2% of the first degree relatives had small p_{300} amplitude and 20.8% had prolonged latency. Compared to control the relatives had smaller amplitude and longer latency but the difference was not statistically significant. Also there was no statistical difference between schizophrenics and their relatives neither in amplitude nor in latency.

An increased incidence of P_{300} abnormalities (both latency increase and amplitude reduction) was found among asymptomatic and drug naive relatives. Schizophrenic relatives with an abnormal P_{300} had a similar range of neuroepsychological deficits as were found in the schizophrenics and relatives with a normal P_{300} response performed as well as the normal (Roxborough et al., 1993).

Black et al (1992) found that 40% of patients with schizophrenic spectrum disorders and 10% of their relatives had abnormal P_{300} responses. Also, Kidogami et al., (1991) found that both the first degree relatives and the schizophrenic patients showed lower P_{300} amplitude than controls and no significant difference between the first degree relatives and schizophrenic patients in P_{300} amplitude & latency.

These results would indicate that a low P_{300} amplitude is a trait marker of schizophrenia. Also these results suggest that neurophysiological testing of relatives may help to clarify the mode of inheritance of schizophrenia in some families.

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الجهد المستثار للفصاميين وأقارب الدرجة الأولي

لقد تم تقييم الجهد المستثار الناتج بعد عمل مثيرات سمعية متتالية وذلك لعدد ٤٠ من مرضى الفصام ، و ٢٨من أقارب الدرجة الأولى ، و ٢٢ شخصا كمجموعة ضابطة. ولقد بينت النتائج أن ٥٠% من الفصاميين كانت شدة الموجة (ب ٣٠٠) لديهم أقل مقارنة بالأسوياء و٤٠% منهم لديهم تأخير في ظهور الاستجابة. كما تبين أن ٤٢,٨ % من أقارب الدرجة الأولي غير المصابين بالفصام كانت شدة الموجة (ب ٣٠٠) لديهم أقل مقارنة بالأسوياء و٢٠,٨ % منهم لديهم تأخير في ظهور الاستجابة.

ولم توجد أية فروق إحصائية ذات دلالة بين التسجيلات الكهربائية للجهة اليسرى والجهة اليمني من الفص الصدغي لدى الفصاميين ، وذلك فيما يخص شدة الاستجابة أو تأخر الاستجابة.

وبهذا فإن نتائج هذه الدراسة تدعم ما وصلت إليه دراسات متعددة سابقة من قلة في شدة الموجة مقارنة بالأسوياء. بالإضافة فإن الدراسة الحالية تشير بأن استخدام الاختبارات العصبية الفسيولوجية لأقارب الدرجة الأولي من الفصاميين قد تسهم في توضيح طريقة التوريث في مرض الفصام لدى بعض الأسر ، و قد تسهم في الاكتشاف المبكر لأقارب الفصاميين الذين لديهم استعداد مرتفع للفصام.