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Abstract

To clarify the cognitive significance of event-related potential (ERP) abnormalities in schizophrenia, we examined the relationships of amplitudes and latencies of ERP components with performance on neuropsyhological tests in schizophrenic patients. Twenty patients underwent the Trail Making B Test (TM-B), which is sensitive to frontal lobe dysfunction, and the logical memory, verbal paired-association, and visual reproduction subtests of the Wechsler Memory Scale (WMS), which are sensitive to temporal lobe dysfunctions, and ERP recordings during performance of an oddball auditory discrimination task. Pearson product-moment correlations indicated that an increased P200 amplitude was correlated with poor performance on the TM-B, whereas a decreased P300 amplitude was correlated with poor performance on the verbal paired-association subtest of the WMS. These findings suggest that a P200 abnormality represents the frontal lobe dysfunction, and a P300 abnormality represents the left temporal lobe dysfunction in schizophrenia.

Keywords: schizophrenia; event-related potential; Trail Making B Test; Wechsler Memory Scale; verbal paired-association

1. Introduction

The scalp-recorded event-related potential (ERP), especially the P300 component, has been extensively studied as an index for assessment of information processing in the human brain (Donchin et al.,1988; Pritchard, 1981), and much attention has focused on the clinical application of this electrophysiologic factor for evaluating cognitive dysfunctions in neurological and psychiatric disorders (Levit et al., 1973; Goodin et al., 1978; Knight, 1984). Since the initial report by Roth and Cannon (1972), there have been numerous reports that schizophrenic patients manifest various ERP abnormalities. These findings suggest that ERP is an effective tool for investigating putative neurobiological mechanisms underlying schizophrenic symptomatology (Pritchard, 1986; Friedman et al., 1991). Not enough is known, however, regarding the type of information processing associated with the generation of each of the ERP components. This paucity of basic knowledge makes it difficult to interpret the pathophysiologic and clinical significance of the ERP data obtained from schizophrenic patients.

Several neuropsychological tests, used for cognitive assessment of patients with brain injuries, are also useful for cognitive assessment of schizophrenic patients. Many studies have demonstrated that schizophrenic patients have deficits in performance on neuropsychological tasks that are sensitive to frontal and temporal lobe functions and have suggested possible regional brain dysfunction in schizophrenia (Kolb et al., 1983; Gruzelier et al., 1988; Liddle, 1987; Liddle and Morris, 1991; Saykin et al., 1991).

One strategy for understanding the cognitive significance of schizophrenic ERP abnormality is to examine neuropsychological correlates of this abnormality. Therefore, the present study examined the correlation of amplitude and latency of ERP components recorded during performance of an auditory oddball task with performace of some neuropsychological tests which are known to be sensitive to dysfunction of the frontal or temporal lobes.

2. Methods

2.1. Subjects

Twenty subjects (14 men; 6 women) were recruited from the inpatient and outpatient facilities of the Department of Neuropsychiatry, Kanazawa University Hospital. All of the subjects satisfied the DSM-III-R criteria (American Psychiatric Association, 1987) for schizophrenia. Developmental disability, alcohol or drug abuse, hearing impairment, a history of previous electroconvulsive therapy, seizures, and/or neurologic damage were causes for exclusion from this study. The mean age was 24.2 (SD=5.2) years, the mean duration of illness was 43.5 (SD=56.1) months, the mean age of onset was 20.5 (SD=4.3) years, and the mean educational level was 11.8 (SD=1.8) years. Handedness was measured using a handedness inventory (Kameyama, 1981). Each of ten items about hand use in common actions (e.g., throwing a ball) is rated on a scale of 1-3: 1=use of the right hand; 2=use of both hands; 3=use of the left hand. Thirteen were right-handed (total score=10), 2 were left-handed (total score=21-30), and 5 were ambidextrous (total score=11-20). All patients had received neuroleptic treatment at the time of testing. The mean chlorpromazine equivalent daily dose was 672.0 (SD=591.7) mg/day. None of the patients had persistent, pronounced Parkinsonian side effects, which would influence the neuropsychological performance. Informed consent was obtained from each subject after the procedures were fully explained.

2.2. Measurement of ERP

The auditory oddball paradigm was constructed as follows. The auditory stimuli were pure tones presented binaurally through a head phone at intervals of 1.25 s for 10 min. All tones were 100 ms in duration with a rise-fall time of 10 ms and were adjusted in intensity to a 70-dB sound pressure level. The pitches of standard and target tones were 1000 Hz and 2000 Hz, respectively. The presentation probability was 0.2 for the target tones. The subjects were instructed to press a button promptly and accurately with the right thumb in response to the target tones.

The electroencephalogram (EEG) was recorded with Ag/AgCl electrodes located at Fz, Cz, and Pz according to the international 10-20 system. All electrodes were referenced to linked earlobes, and the ground electrode was placed on the left side of the forehead. The electro-oculogram (EOG) was recorded from an electrode located at the supraorbital ridge of the right eye and referenced to linked earlobes. Electrode impedance was held below 5 kΩ.

EEG and EOG signals were amplified with a bandpass filter of 0.16 to 60 Hz. EEG epochs of 1000 ms, starting 200 ms before the presentation of target tones, were averaged off-line. Trials on which EEG or EOG signals exceeded ±100μV were automatically rejected. Amplitudes were calculated by subtracting the average voltage in the 200-ms prestimulus baseline from the peak voltage in the specified latency windows. The latency window for each component was as follows: N100, 70 - 125 ms; P200, 170 - 250 ms; P300, 250 - 500 ms. N200 was defined as the negative deflection immediately preceding P300. Latencies were measured from onset of the stimulus to the point of peak amplitude in the windows described.

ERP data of the patients were compared with those of age-matched healthy controls. The mean ages of healthy controls was 25.9 (SD=4.8) years (n=39).

2.3. Neuropsychological Measures

Several neuropsychological tests were performed within 1 week before or after the ERP measurements. The Trail Making B Test (TM-B; Reitan, 1958) was used to test for frontal lobe function and several subsets of the Wechsler Memory Scale (WMS; Wechsler, 1945) (adopted for Japanese speaking patients, Kiba et al., 1988) were used to test memory related to right and left temproal lobe functions (Milner,1975).

In the TM-B, the subjects are required to connect letters of the alphabet and numbers, alternately. The performance was quantitatively estimated as the time taken for subjects to complete the test. Thus, longer time indicates poorer performance on the test.

Verbal memory was assessed by the logical memory subtest of the WMS, which involves immediate recall of orally presented stories. Visual memory was assessed by the visual reproduction subtest of the WMS, which involves immediate recall of designs. Learning was assessed by the verbal paired-association subtest of the WMS. In this test, the subjects are presented with eight word pairs, half of which are highly associated and the other half of which have a low association. After presentation of these word pairs, subjects were presented with the first word of each pair and were required to respond with the appropriate associate. Three trials were presented to assess learning.

Neuropsychological data of the patients were compared with those of age-matched healthy controls. The mean ages of healthy controls was 25.4 (SD=3.9) years for TM-B (n=27) and 27.2 (SD=4.5) years for WMS (n=40).

3. Results

Means and standard deviations for neuropsychological performance of the schizophrenic patients are compared with those of age-matched healthy controls, as presented in Table 1. As found previously (Saykin et al.,1991), the performance of the schizophrenic patients on all tests was deviant.

The amplitude and latency of each ERP component is shown in Table 2. The amplitudes of N100 and P300 at Fz, Cz and Pz was smaller in the schizophrenic patients than those in the controls. On the other hand, the latencies of N200 at all sites and of P300 at Pz were prolonged in the patients, compared with those of the controls.

To examine the relationships of the amplitude and latency of each ERP component and performance of the neuropsychological tests, Pearson product-moment correlations were computed (Table 3). A significant positive relationship was found between P200 amplitudes at Cz and Pz and the time taken for performance of the TM-B. On the other hand, P300 amplitudes at Cz and Pz were correlated with the score for the verbal paired-association subtest of the WMS. There was no significant correlation with performance on the logical memory subtest or the visual reproduction subtest of the WMS. In addition, for the latencies of ERP components, none of the correlations with performance of the neuropsychological tests were significant.

Furthermore, to examine whether these correlations were artifacts of individual differences in demographic variables and medication, we also computed partial correlations in which we removed shared variance with these potential nuisance variables (age, age of onset, duration of illess, education level and medication). All of the aforementioned correlations that had been statistically significant remained significant when partialing out shared variance with the demographic and medication variables.

In order to examine whether the significant correlations reported in Table 3 were inflated due to outliers, we also computed Spearman rank-order correlations. The pattern of Spearman rank-order correlations was similar to that obtained using Pearson product-moment correlations. For example, the Spearman rank-order correlations of P200 amplitudes at Cz and Pz with the time taken for performance of the TM-B were .527 and .648, respectively. Also, the Spearman rank-order correlations of P300 amplitudes at Cz and Pz with the paired association of WMS were .647 and .627, respectively.

4. Discussion

The results demonstrated that an increased P200 amplitude is associated with poor performance on the TM-B, while a decreased P300 amplitude is associated with poor performance on the verbal paired-association of the WMS.

The TM-B is a visuomotor test of the ability to focus attention and alternate mental sets selectively (Walsh, 1985). The poor performance of schizophrenics on the TM-B is of particular interest because deficits in this test reflect disruptions of higher cortical functions, including those sensitive to frontal lobe damage (Lezak, 1983). In addition, it has been reported that P200 amplitude is greater in schizophrenic patients than in controls (Ogura et al., 1991). Therefore, increased P200 amplitude in schizophrenia might reflect the frontal lobe dysfunction characteristic of this disease.

However, this increased P200 amplitude may be related to decreased negativity rather than increased positivity because negative deflections, such as mismach negativity (MMN), N2b and negative difference (Nd) related to several cognitive processings, overlap temporally and spatially P200 component (N__t_nen, 1982, N__t_nen and Gaillard, 1983). Therefore, it would be necessary to separate out the exogenous P200 and endogenous negative deflections with the subtraction waveform. MMN and N2b obtained by subtracting the ERPs to frequent stimuli from those to rare stimuli are associated with the automatic and controlled mismatch detection processes, respectively (N__t_nen and Gaillard, 1983; N__t_nen and Picton, 1986). On the other hand, Nd obtained by subtracting ERPs to irrelevant from those to relevant stimuli is related to a selective attention process (N__t_nen, 1982). A reduction in Nd may be associated with poor performance on the TM-B presented in our study because it has been reported that Nd is affected by frontal lobe damage (Knight et al., 1981; Woods et al., 1986). These negative defelctions (MMN, N2b and Nd) has been reported to be reduced in schizophrenia (Javitt et al.,1995; Salisbury et al., 1994; Michie et al., 1990; Ogura et al., 1991). Further studies using the subtraction method are needed to clarify whether a reduction in these negative deflections is correlated with performance on the TM-B.

Our unpublished data indicate that poor performance of the Wisconsin Card Sorting Test (WCST; Heaton, 1981), which is another test for the frontal lobe function (Anderson et al., 1991), is associated with a decreased N100 amplitude in schizophrenic patients. Therefore, these two tests of frontal lobe function might detect impairment in different types of information processing: impairment in the earlier processing reflected by N100 is related to performance of the WCST and impairment in the later processing reflected by P200 is related to that of the TM-B.

A decreased P300 amplitude was associated with poor performance on the verbal paird-association subtest of the WMS, but not with that of the other subtests. Therefore, the information processing related to P300 generation might be associated with verbal learning. Our findings are consistent with the study of Heidrich et al. (1997), who reported an association between the reduction in left-sided P300 amplitudes and poor performance on the verbal paired-associates test, although our study did not examine the laterality of P300 amplitudes. Nestor et al. (1993) have reported that, in schizophrenia, poor performance on the verbal paired-association test is correlated with a volume reduction of the left posterior superior temporal gyrus. The reduced P300 amplitude observed in schizophrenia is also correlated with volume reduction of the same gyrus (McCarley et al., 1993). Furthermore, it has been reported that schizophrenic thought disorder is highly correlated with reduced volumes in the left posterior superior temporal gyrus (Shenton et al., 1992) and with decreased P300 amplitude (Higashima et al., 1998). From these findings, it is possible that, in schizophrenia, P300 abnormality, impaired verbal learning, and clinically observed thought disorder originate from a common pathology of the left posterior superior temporal gyrus.

The medial temporal lobe, including the hippocampus, is another candidate for schizophrenic pathology (Bogerts, 1997). Our recent study reported that a reduced P300 amplitude is associated with volume reduction of the left medial temporal lobe in schizophrenia (Kawasaki 1997), and many reports suggest that part of P300 recorded on the scalp generates from the medial temporal lobe (Okada, 1983). The present study could not determine which region of the temporal lobe, however, becomes a pathologic focus for P300 and neuropsychological abnormalities in schizophrenia.

In conclusion, in schizophrenia, increased P200 amplitude might represent frontal lobe dysfunction whereas a decreased P300 amplitude might represent temporal lobe dysfunction. For the present study, the sample size was small and limited types of neuropsychological tests were chosen. Therefore, our data are best considered as preliminary. Furthermore, anatomical regions related to schizophrenic ERP abnormality remain unclear. To link this abnormality to a specific regional pathology of the brain, future studies using more sophisticated ERP paradigms or brain imaging techniques will be necessary.

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Table 1. Mean and Standard deviation of Neuropsychological Assessments

Test		Schizophrenia		Normal	
		Mean	SD	Mean	SD
Trail Making Test	Part B	109.2 **	30.7	54.15	12.13
Wechsler Memory Scale	Logical memory	6.0 **	4.8	11.5	3.0
	Verbal paired association	14.6 **	3.2	18.0	2.3
	Visual reproduction	10.9 *	2.6	12.4	1.3

The difference between schizophrenic and normal subjects was determined by means of unpaired two-tailed t-test: *$p<0.005$; **$p<0.0005$.

Table2. Amplitudes and Latencies of the ERP Components

		Amplitude (μV)				Latency (ms)			
		Schizophrenia		Normal		Schizophrenia		Normal	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD
N100	Fz	-5.02 *	1.60	-6.69	2.23	95.1	20.0	95.3	19.1
	Cz	-4.03 *	1.67	-6.40	2.73	96.7	18.9	95.5	20.0
	Pz	-2.46 *	2.01	-4.20	2.15	98.1	19.4	87.9	24.3
P200	Fz	1.63	3.46	1.49	3.87	173.9	24.1	165.0	23.3
	Cz	3.56	3.25	1.46	4.08	175.0	24.7	163.9	30.1
	Pz	4.84	2.91	3.01	3.84	179.7	29.9	164.1	31.1
N200	Fz	-6.20	3.79	-3.21	4.27	246.5**	29.5	210.2	34.1
	Cz	-3.53	3.72	-2.38	4.80	241.0**	26.9	209.4	27.1
	Pz	0.44	3.83	0.71	4.22	235.6**	23.9	198.4	29.8
P300	Fz	4.41 **	5.02	11.58	8.14	363.1	36.1	330.3	55.4
	Cz	7.01 **	5.39	14.11	6.16	352.2	34.8	329.0	55.1
	Pz	9.60 **	5.09	15.80	5.34	352.7**	27.8	319.1	25.5

The difference between schizophrenic and normal subjects was determined by means of unpaired two-tailed t-test: $*p<0.005$; $**p<0.0005$.

Table 3. Relationship between ERP Components and Neuropsychological Assessments

			TM-B	WMS Logical memory	WMS Paired association	WMS Visual reproduction
Amplitude	N100	Fz	-.273	.068	-.127	.191
		Cz	-.163	.162	.040	.306
		Pz	-.053	.237	.248	.305
	P200	Fz	.416	-.112	.254	-.313
		Cz	.498 *	-.110	.295	-.327
		Pz	.536 *	-.100	.412	-.338
	N200	Fz	.124	-.100	-.403	.131
		Cz	.010	-.110	.004	-.074
		Pz	-.269	-.031	-.348	-.094
	P300	Fz	-.020	.245	.403	.132
		Cz	.257	.206	.651 **	.062
		Pz	.331	.197	.617 **	-.021
Latency	N100	Fz	-.300	.153	.285	.330
		Cz	-.105	.089	.265	.129
		Pz	-.180	.128	.310	.116
	P200	Fz	.112	.069	.266	-.141
		Cz	.034	.047	.279	-.045
		Pz	.069	.146	.394	.160
	N200	Fz	.300	-.123	.184	.190
		Cz	.288	-.159	.130	.240
		Pz	.141	-.199	.057	.312
	P300	Fz	-.325	.313	.196	.414
		Cz	-.099	-.030	-.005	.265
		Pz	-.041	-.106	.093	.238

Values show Pearson correlation coefficients. * $p < .05$ ** $p < .01$.

Abbreviations: Wechsler Memory Scale (WMS)

Trail Making Test (TM-B)