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The Application of Computerized WCST and Long-term Evoked Potentials for Schizophrenia Analysis

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Abstract—**The purpose of this study is to characterize the cognitive functions of schizophrenic patients using different auditory and visual event-related potentials (ERPs) based on Wisconsin Card Sorting Test (WCST). From the experimental results, it is indicated that there is a slowness of automatic cognitive processing and controlled cognitive processing during WCST in comparison with ERPs for schizophrenic patients.**

I. Introduction

The question of whether cognitive slowing occurs in schizophrenic patients has long been debated (1). Evoked potentials from different stimulations are thought to reflect the anatomical and functional differences between auditory and visual pathways. The P300 event-related potentials (ERPs) are conducted in clinical application to detect cognitive functions. ERPs provide a means of measuring cognitive processing that is independent of motor speed and disability and reflects processes that occur between the stimulus and the response; therefore, ERPs provide information about their courses (2). P300 is a positive ERP recorded widely across the scalp approximately 300 ms after an auditory, visual, or somatosensory "oddball" stimulus, which must be random, must stand out, and must be followed by a response from the patient, such as the pressing of a button. P300 recorded from the scalp has several components that seem to be independently generated in different brain structures.These components include brain activities involved in selective attention, updating of work, and short-term memory in response to unexpected change in the environment (3,4). P300 latency, which is presumed to indicate the time required for task evaluation independent of motor processing, may be useful in studying the cognitive processing in the disease. There are some reports that provide evidence of cognitive slowing during auditory or visual oddball tasks by showing delayed P300 in schizophrenic patients. Roth and Cannon recorded reduced amplitude and delayed latency of the P300 waveform in patients with the disorder (5,6). There is now evidence that increased P300 latency and reduced amplitude are stable trait markers of risk of schizophrenia (4). However, there are only a few studies associated with schizophrenia, combinated auditory ERP and visual ERP togehter. The auditory hallucination is know as one of postive symptoms in schizophrenia, where as auditory ERP is possible mistaken with auditory hallucination.

The purpose of this study is to discrimination the cognitive function among normal control and schizophrenic patients by sound and image stimulation included auditable and visual Long-term Evoked Potentials. However, the correlation of Long-term Evoked Potentials (LEP) and Wisconsin Card Sorting Test (WCST) is prospected to be setup.

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II. Methods and Materials

A. Subjects

The study included 43 schizophrenic patients and 40 control subjects. The 43 schizophrenic patients (22 men and 21 women; mean ± SD age, 37.0 ± 7.9 years; range, 18-45 years) had a definite clinical diagnosis of schizophrenia according to *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IV*) criteria (American Psychiatric Association 1994). Any patients diagnosed as having dementia according to *DSM-IV* criteria were excluded from the study. The 40 control subjects (15 men and 25 women; mean ± SD age, 35.6 ± 9.2 years; range, 18-45 years) were without a history of psychiatric disease, neurological disease, or drug abuse. There were no differences in age, sex, marital status, and religion among subjects, but there was significant difference in education level. All the subjects gave signed informed consent after the purpose of the study and the protocol had been explained to them and before any procedures were performed.

B. Measurement of ERPs

The Brain Atlas III Computer of the Biologic System Company recorded the ERPs using the linked-ear reference in an auditory oddball paradigm. The system's versatility allows the user to record up to 4 sets of stimulus-evoked activity (including auditory ERP, visual ERP etc) and display and analyze the data in a variety of ways. The ERPs were

registered by surface electrodes placed in the electrodes positions according to the 10-20 International System, with reference to both linked mastoid processes. The electrode sites were as follows: Fp1, Fp2, AF3, AF4, F7, F3, Fz, F4, F8, FC5, FC1, FC2, FC6, T7, C3, Cz, C4, T8, CP5, CP1, CP2, CP6, P7, P3, Pz, P4, P8, PO3, PO4, O1, and O2. However statistical method with factor analysis supported that electrode positions including Fz, Cz and Pz were indicators for schizophrenia. The EOG was monitored using a forehand-temple montage with a rejection level of $\pm$ 100μV. Electrode impedance was maintained below 5k [ohm]. The ERPs were elicited by tone pips of 50-ms duration (10-ms rise and fall times) using the stimulation rate of 1.3/s. The infrequent (16.7%) high-pitched tones (2,000 Hz, 80 dB) were presented randomly interspersed with frequent low-pitched tones (1,000 Hz, 80 dB) binaurally. The amplifier was used as follows: high filter, 30; low filter; 1.0; and gain, 20,000. The analysis time of 512 ms and sensitivity of 122.5 mV was used in auditory EP testing. Subjects were asked to count the presence of infrequent high-pitched tones and ignore the frequent low-pitched tones by mental process. The error index was used to display the accuracy of the count. The artefact of vertical eyeball movement was detected from electrodes placed above and below the right eye and horizontally from electrodes placed at the left outer canthus. The data were discarded if there were more than 5 artefacts and the subjects were retested after 5 minutes.

The subjects were seated comfortably in a dimly lit chamber with a portable eye-trek device (Olympus, FMD-20P) that was approximately 2 cm in front of their eyes. The visual oddball paradigm with full-field, 1 × 1, square, black and white flashes, stimuli rate of 1.3/s, bandpass of 30 and 1 Hz, analysis time of 512 ms, and sensitivity of 122.5 mV was used in visual EP testing. The latencies and amplitudes of the N100, N200, P100, P200, P300, and P400 waves were determined (7,8). All subjects were tested for four tasks, and each task lasted approximately 5 minutes. The four tasks were labelled auditory ERPs with counting, auditory ERPs without counting, visual ERPs with counting, and visual ERPs without counting.

C. Statistical Analysis

A two-tailed Student *t* test was used to compare the ERPs (N100 and N200 latency and amplitude and P200, P300, and P400 latency and amplitude) and WCST between the schizophrenic patients and the healthy subjects. The differences in mental process with counting in auditory and visual tasks were checked with the paired Student *t* test. The correlation of ERPs and WCST were submitted to cross-table analysis. The differences in latencies and amplitudes were submitted to a one-way analysis of variance (ANOVA) with patient and control groups. In order to avoid type I error, all *P* values were reported as two-tailed. $P<0.05$ was accepted as statistically significant. All the data were analyzed with SPSS statistical software version 10.0. One-way repeated-measures ANOVA was computed to study the effect of ERPs in the schizophrenic patient group and the healthy control group separately.

III. Results

The average waveforms of these two groups were displayed for midline electrode sites (Fz, Cz, and Pz) in amplitude and latency. In the amplitude component of auditory ERPs, there were significant differences between N100 (Fz, Cz, Pz), N200 (Fz, Cz), P200 (Fz), and P300 (Fz, Cz, Pz) in auditory ERPs with counting group and N100 (Cz, Pz), N200 (Cz), P200 (Fz), and P300 (Fz, Cz, Pz) in auditory ERPs without counting group. In the amplitude component of visual ERPs, there were significant differences between N100 (Fz, Cz, Pz) and N200 (Fz, Cz) in visual ERPs with counting group and N100 (Fz, Cz, Pz) in visual ERPs without counting group. In the control group, there were significant differences in the amplitude components of N200 (Cz) and P200 (Cz, Pz) and the latency components of N100 (Fz, Cz, Pz) and P200 (Pz) among different auditory stimuli with or without counting process. There were significant differences in the amplitude components of N200 (Fz, Cz), P200 (Fz, Cz), P300 (Cz, Pz), and P400 (Pz) among different visual stimuli with or without counting process in the control group. There were no differences in the latency components between visual ERPs with or without counting process in the control group. In the patient group, there were significant differences in the amplitude components of P200 (Fz, Cz, Pz) and P300 (Fz, Cz, Pz) and the latency component of N200 (Fz, Cz, Pz) among different auditory stimuli with or without counting process. There were significant differences in the amplitude component of P200 (Fz) and the latency component of P400 (Fz, Cz, Pz) among different visual stimuli with or without counting process in the patient group.(shown in Table1)

In the WCST study (Table1), the nine items of “Total number of errors”, ”Perseverative responses”, “Perseverative errors”, “Non-perseverative errors”, “Number of categories completed”, ”Number of trials to complete first category”, “Percent conceptual level responses”, “Failure to maintain set” and “Learning to learn” were compared within control and schizophrenic groups. The students’ t test showed only six items significant between two groups. They were “Total number of errors”, ”Perseverative responses”, “Perseverative errors”, “Non-perseverative errors”, ”Number of trials to complete first category” and “Learning to learn” . The cross-table analysis were performed to correlate the six items of WCST with auditory ERPs and visual ERPs. In the comparison of WCST and auditory ERPs in control group, there was no any correlation between WCST items and auditory ERPs. In the comparison of WCST and visual ERPs in control group, there were visual P300 (Fz, Cz, Pz) latency correlated with “Perseverative errors” item of WCST. In the comparison of WCST and auditory ERPs in schizophrenic group, there were auditory P200(Fz, Cz, Pz) latency correlated with “Total number of errors” item of WCST;

auditory P200(Fz, Pz) amplitude correlated with "Perseverative errors" item of WCST; auditory P200(Fz) amplitude correlated with "Non-perseverative errors" item of WCST; auditory N200(Pz) latency correlated with "Perseverative errors" item of WCST; auditory N200(Fz, Cz, Pz) latency correlated with "Non-perseverative errors" item of WCST and auditory P300(Cz) latency correlated with "Non-perseverative errors" item of WCST. In the comparison of WCST and visual ERPs in schizophrenic group , there were visual N100(Fz, Cz) latency correlated with "Total number of errors" item of WCST; visual P300(Cz) amplitude correlated with "Non-perseverative errors" item of WCST; visual P400(Fz, Cz, Pz) latency correlated with "Non-perseverative errors" item of WCST and visual P400(Cz) amplitude correlated with "Non-perseverative errors" item of WCST.

TABLE I
THE SIGNIFICANT FINDINGS BETWEEN CONTROL AND SCHIZOPHRENIC GROUPS

	Amplitude	Latency
Auditory ERP without counting	N100(Cz,Pz),N200(Cz) P200(Fz), P300(Fz, Cz, Pz)	N200(Fz, Cz, Pz), P300(Fz, Cz, Pz)
Auditory ERP with counting	N100(Fz,Cz,Pz), N200(Fz,Cz),P200(Fz), P300(Fz, Cz, Pz)	N200(Fz, Cz, Pz), P300(Fz, Cz)
Visual ERP without counting	N100(Fz, Cz, Pz)	P300(Fz, Cz, Pz)
Visual ERP with counting	N100(Fz,Cz,Pz), N200(Fz, Cz)	-
WCST	Total number of errors (NERR) Perseverative responses (PR) Perseverative errors (PE) Non-perseverative errors (NPE) Number of trials to complete first category (FIRST) Learning to learn (LTL)	

IV. DISCUSSION

Clinically, the delay of P300 latency is a nonspecific change in psychiatric disorder. It can be found in dementia, schizophrenia, depression, and other organic mental disorders (9). The aim of this study was to assess whether the visual ERPs can be a clinically effective tool for differential diagnosis in schizophrenic patients. However, the ERPs induced by the mental process regardless of the modality of auditory and visual input in the same brain structures were also examined. The paired Student *t* test was performed to compare signal processing models, assuming a unique and common mechanism as the locus of action of this effect, which includes visual or auditory ERPs with or without counting process. For this purpose, ERPs were recorded with serially presented tones or flashes, which could be in either the auditory or visual modality.

In the paired Student *t* test analysis of case and control groups, the latency components of P300 (Fz, Cz, Pz) in visual ERPs without counting or N200 (Fz, Cz, Pz) and P300 (Fz, Cz) in auditory ERPs with or without counting were significantly different between the case and control groups. This finding means delayed latency of N200 and P300 in auditory ERPs and P300 in visual ERPs could be indicated for clinical correlation of schizophrenic patients. However, the amplitude components of N100 (Fz, Cz, Pz) and N200 (Fz, Cz) in visual ERPs with counting; N100 (Fz, Cz, Pz) in visual ERPs without counting; N100 (Fz, Cz, Pz), N200 (Fz, Cz, Pz), P200 (Fz), and P300 (Fz, Cz, Pz) in auditory ERPs with counting; or N100 (Cz, Pz), N200 (Cz), P200 (Fz), and P300 (Fz, Cz, Pz) in auditory ERPs without counting were significantly different between case and control groups. This finding means decreased amplitude of N100, N200, and P300 in auditory ERPs and N100 in visual ERPs could be indicated for clinical correlation of schizophrenic patients.

We can conclude that whatever the auditory stimuli (with or without mental counting), the amplitude components of N100, N200, P200, and P300 and the latency components of N200 and P300 were significantly different between control and schizophrenic patients. However, the amplitude of N200 (Fz, Cz) induced by the visual stimuli with mental counting was significantly different between control and schizophrenic groups. The latency of P300 was not different between the two groups, which means that some mental processing occurs at the N200 level during visual stimuli but that schizophrenic patients lack this ability. However, when the schizophrenic patients tried to use mental counting in visual stimuli, the P300 latency was not different between the two groups, which means that the time of mental processing would not be delayed among schizophrenic patients.

There were no detailed studies concerning the interrelationships between ERPs and many clinical mental test batteries. In this study, we analyzed the correlation between the parameters of ERPs and scores of WCST tests in order to clarify the significance of ERPs on clinical medicine. Syed et al (2000) reported that the WCST generates three sets of scores: the number of categories attained (CA), the number of perseverative errors (PE), and the total number of errors (TE). The perseverative error score has often been taken as the more specific measure of frontal lobe dysfunction. In our

study, the students' t test showed only six items significant between control and schizophrenic groups. They were "Total number of errors", "Perseverative responses", "Perseverative errors", "Non-perseverative errors", "Number of trials to complete first category" and "Learning to learn" The result of three items was the same with Syeds'. Of course, we found the other three items "Perseverative responses", "Non-perseverative errors" and "Learning to learn" were significant difference among two group. The two items"Perseverative responses", "Non-perseverative errors" also belong to perseverative error score. The item of "Learning to learn" was noted significantly between two groups. It was obvious that the schizophrenic patients perform worse in "Learning to learn" than the normal control. Syed et al found that subjects with schizophrenia performed poorly on the WCST (which is thought to depend, at least in part, upon the integrity of frontal lobe function), and failed to exhibit a significant increase in dorsolateral prefrontal cortical rCBF such as could be detected in normal subjects while performing the test. The possibility that frontal lobe mechanisms may be dysfunctional in schizophrenia has been investigated using neuropsychological (Wisconsin Card Sorting Test, WCST) and functional neuroimaging (regional cerebral blood flow, rCBF) techniques [10].

There are some clear limitations to the information that can be provided by the endogenous potentials. The scalp-recorded potentials measure only that part of cerebral activity that is sufficiently synchronized and sufficiently organized to create electrical fields at a distance. Much cerebral activity therefore goes undetected in the event-related potential. Nevertheless, any theory of the cerebral basis for cognitive activity must explain what is recorded in the ERP during cognitive processing. Any change in the ERP related to changes in cognition indicates a difference in the underlying processing at that latency. A major goal of research with the endogenous evoked potentials is to refine our experimental paradigms so as to delineate more clearly the temporal structure of cognition.

A second limitation for the endogenous evoked potentials is the problem of inferring the cerebral origins of a scalp-recorded potential. No unique configuration of sources generates a given surface potential. However, other information - the neuroanatomy of the possible sources, the cerebral location of metabolically active regions during the recording, and the concurrent magnetic fields - can constrain the possible source configurations for a surface potential so that only one configuration is reasonable.

V. Conclusion

In summary, our study on visual ERPs indicates that there may be a slowness of automatic cognitive processing and controlled cognitive processing in schizophrenia. The P300 latency implies that controlled cognitive processing in schizophrenia is influenced by slower information input at mismatched negativity, which reflects activation of neural structures within primary auditory cortex (Heschl's gyrus) or adjacent supratemporal auditory regions. However, N200 reflects activity primarily within the auditory association cortex and P3 reflects activity in prefrontal, temporoparietal, and, potentially, other polysensory association regions of the cortex.

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