Biological Psychiatry, Vol. 18, No. 6, 1983

Event-Related Brain Potentials to High-Incentive Stimuli in Unmedicated Schizophrenic Patients

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Received October 13, 1982; revised December 24, 1982

Schizophrenic patients have been observed to have a significantly diminished P300 component of the event-related potential (ERP). We investigated whether this result would be obtained with high-incentive stimuli. We presented 14 unmedicated patients and 14 controls with two easily identified visual stimuli under three conditions: (i) a nonincentive condition, (ii) under the condition of $1 payment for each correct identification, and (iii) under the condition of $1 payment for each correct identification within a criterion time. The patients responded accurately but showed a significantly reduced P300 in the incentive conditions. We interpret our results as neurophysiological evidence for possible limbic system dysfunction in schizophrenia.

INTRODUCTION

The P300 component of the event-related potential (ERP) has stimulated an ever-increasing amount of research since its discovery by Sutton *et al.* in 1965. The P300 component is actually a complex of waves, most of which are of maximal amplitude over the parietal region of the scalp. It is a large amplitude positive wave peaking 275-450 msec after the presentation of a stimulus. The phenomenon is of interest because the amplitude of this component is in-

Supported by grants AA 02686 and in part by MH-07336 from NIMH, U.S. Public Health Service.

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0006-3223/83/0600-0661 $03.00/1

dependent of the physical characteristics of the eliciting stimulus except at extreme stimulus intensities (Roth *et al.*, 1980a), and is highly dependent on the "subjective significance" of the eliciting stimulus at all stimulus intensities (Courchesne *et al.*, 1975; N. K. Squires *et al.*, 1975).

A significant diminution of the P300 component of the event-related potential has been reported in schizophrenic patients. Roth and Cannon (1972) presented two tones of different frequency in a ratio of 85% common to 15% rare and reported decreased P300 amplitudes to the rare tone in schizophrenic patients compared to normal controls. Levit *et al.* (1973) presented a series of tones and flashes to normal subjects and schizophrenic patients under two conditions: (i) when subjects were told before the stimulus whether it would be a tone or a flash and (ii) when subjects were told to guess. Normal subjects showed a much greater increase in P300 amplitude to the uncertain condition than did the patients. This finding was confirmed by Verleger and Cohen (1978). Roth *et al.* (1980b) again observed a diminished P300 to the rare tone in a frequent/rare paradigm, as well as a diminished P300 to 100 dB bursts of white noise. In 1980 Pass *et al.* reported a diminished P300 in schizophrenic patients during the continuous performance task (CPT). In this paradigm subjects were instructed to watch a screen while six stimuli were presented in random sequence, and to press a button when one of the stimuli was presented. Schizophrenic patients had a significantly reduced P300 to target stimuli under both base-line and distraction conditions.

In normal individuals the amplitude of the P300 is a function of stimulus probability and task relevance (Squires, K. C. *et al.*, 1977). Begleiter *et al.* (1983) have recently reported on the ERPs of normal subjects to two equiprobable task-relevant stimuli under nonincentive and incentive conditions. The P300 component was significantly larger in the incentive conditions compared to the base-line condition. Since the incentive value of stimuli is a factor in determining the amplitude of the P300 component (Homberg *et al.*, 1980), it is possible that schizophrenics showed a much diminished P300 component in the above-mentioned experiments because for them the tone and flash stimuli were irrelevant and lacked the motivational properties that these same stimuli had for the controls. We presented schizophrenic patients and normal controls with equiprobable high-incentive task-relevant stimuli to ascertain if the well-documented reduction in amplitude of the P300 component of the ERP in schizophrenic patients obtains under high-incentive conditions.

In addition to incentive two other issues are addressed here. With the exception of the CPT study (Pass *et al.*, 1980), the work reviewed recorded event-related potentials to auditory or mixed auditory and visual stimuli. We wished to confirm these findings with purely visual stimuli.

More problematic is the question of medication. Ciganek (1959), Rappaport *et al.* (1975), Shagass *et al.* (1974), and Shagass (1976) have reported that

neuroleptics do not affect evoked potential amplitudes, but Saletu *et al.* (1971a; 1971b; 1972), Roemer *et al.* (1978; 1979), and Shagass *et al.* (1981) have reported amplitude changes associated with neuroleptic medication. All the studies which investigated P300 in schizophrenics involved samples where most or all of the patients were medicated, and no one has systematically investigated the effects of neuroleptics on P300 amplitude. We therefore tested unmedicated patients to determine whether a reduction in P300 amplitude is a feature of schizophrenia or a possible artifact of its treatment.

METHODS

Twelve of our 14 schizophrenic subjects were patients admitted to an open-door unit of a university teaching hospital. Two were referred outpatients. All patients were interviewed by two psychiatrists who concurred on a diagnosis of schizophrenia by DSM-III criteria. One of us (M.B.) performed one of the diagnostic interviews and administered a BPRS and a Philips Scale of premorbid adjustment in schizophrenia. For inclusion into the study patients had to be 18 to 55 years of age and free of any acute medical illness. Neurological illness, chronic drug or alcohol abuse at any time, and any other current Axis I diagnosis were exclusion criteria. The protocol required that patients not receive any neuroleptics, antidepressants, anxiolytics, or lithium for a least 2 weeks prior to testing. Prolixin decanoate was never administered within 6 weeks of testing. Patients were allowed either 30 mg of Dalmane or 65 mg of sodium amytal at bedtime, up to 3 days prior to testing. The need to keep unmedicated schizophrenics on a unit with an unlocked door resulted in a biased but relatively homogeneous sample of patients.

Informed consent was obtained from all subjects. Control subjects were solicited by advertisement. From a pool of controls a subgroup was selected to match the patients on the basis of age and sex. The patient group consisted of eight males and six females, mean age 32.64 years. The controls consisted of ten males and four females, mean age 27.35 years.

Electrodes

Gold cup electrodes were placed at midline frontal (Fz), central (Cz), parietal (Pz), and occipital (Oz) locations and at left parietal (P3) and right parietal (P4) according to the 10-20 International System. Electrode resistance was less than 5 kohm. The recordings were monopolar, using the combined ears as reference and the nasion as ground. Vertical eye leads were used to record and monitor the electrooculogram (EOG).

Procedure

Subjects were seated in a sound-attenuated chamber in front of a computer-controlled cathode ray screen. The head rested on an adjustable chin rest with the eyes positioned at the level of the center of the screen. Subjects were told to fixate on a green dot in the center of the screen. The computer generated two stimuli consisting of either the digits 0.00 or the digits 1.00. The stimuli were of 15 msec duration, equal in size and intensity and subtended 2.7° of arc. They were presented at randomly varying interstimulus intervals of between 2 and 5 sec. The subjects were told that they would see either 0.00 or 1.00 and to press button marked A when they saw 1.00 and to press button marked B when they saw 0.00. These buttons were microswitches actuated by a force of 30 g which recorded reaction time and activated a counter which enabled the experimenter to ascertain if the subject correctly identified the stimulus. Run 1 consisted of 30 stimuli of each type. In Run 2 the subjects were told that they would see the same stimuli and to press button A after 0.00 and button B after 1.00. They were told that they would get a dollar for each correct button press after the 1.00 stimulus. A dollar would be subtracted from their earnings for each stimulus that was responded to incorrectly or for which no response was made. Thirty stimuli of each type were again presented in random sequence. In Run 3 the buttons were unchanged but subjects were told that they had to press as quickly as possible. They were told they would get a dollar for every 1.00 stimulus to which they responded with the correct button press within a criterion time. A dollar would be subtracted from the total for every stimulus responded to inaccurately or not responded to within the criterion time. Criterion time was 350 msec. Thirty stimuli of each type were presented. Thus in all three runs the stimuli were equiprobable and task-relevant. In Runs 2 and 3 the stimuli had differential incentive value. In Run 2 accuracy was stressed and in Run 3 speed plus accuracy.

Data Collection

At the beginning of each run the evoked potentials were monitored but not saved. When the subjects fixated their gaze on the fixation point, responded accurately, and did not blink upon stimulus presentation the evoked potentials were saved. The EPs were monitored throughout the experiment and if eye movements were observed the EPs were not saved and the subjects were instructed again. This procedure did not exclude eye movement from every trial but they were infrequent and randomly distributed throughout the recording epoch.

The subjects' reaction times were recorded by the computer and displayed along with the EPs on a cathode ray screen. The recording epoch for RT was 2500 msec.

Event-related potentials for each of the six electrodes and the vertical EOG were amplified 50,000 times by P511J Grass amplifiers. Band width was 0.1 Hz to 60 Hz. Analog signals were sampled every 7 msec for 700 msec and converted to digital data by a PDP 11-40 computer. The EEG recording during the 49-msec epoch preceding stimulus presentation was averaged and used as a base line. EPs were sorted and averaged by stimulus and run for each of the six channels and the EOG. A computer program computed the average event-related potentials on line. The individual responses constituting each average were also saved.

RESULTS

P300 Amplitude

The amplitudes and latencies for each peak were subjected to a four-way analysis of variance (Groups X Runs X Stimuli X Electrodes). The P300 amplitudes for each electrode are shown in Fig. 1, and the results of the statistical analysis are presented in Table I. For significant values of F the probabilities were also determined using the more conservative 1 and 27 degrees of freedom to take into account nonhomogeneity of variance and covariance introduced by the repeated measures design as described by Jennings and Wood (1976).

The schizophrenic patients had a significantly lower ($p < 0.01$) P300 amplitude than the controls across all runs and stimuli.

There are highly significant ($p < 0.005$) runs and runs by group effects (using conservative degrees of freedom for both effects). As shown in Fig. 1 schizophrenic patients demonstrated no change in P300 amplitude in Runs 2 and 3, while the controls showed an increase in P300 amplitude in Run 2 and a further increase in P300 amplitude in Run 3. The Runs X Group interaction was significant for all three between-run comparisons; Run 2 *vs.* Run 1 $p < 0.001$, Run 3 *vs.* Run 2 $p < 0.05$, Run 3 *vs.* Run 1 $p < 0.001$ (Scheffé method). The between-group difference in Run 1 was not significant ($p > 0.05$). Trend analysis revealed a significant linear trend in the responses across runs of the normal group ($_2F_{52} = 3.32$; $p < 0.05$). The quadratic trend in the normal group and both linear and quadratic trends in the schizophrenic groups were not significant.

There is a statistically significant stimuli ($p < 0.05$) and stimuli by group ($p < 0.025$) effect by both conventional and conservative criteria. The interaction effect demonstrates that the controls responded differently to the two stimuli across runs while the schizophrenics did not.

The runs by stimuli interaction was not significant. The three-way interaction Groups X Runs X Stimuli was not statistically significant. This result demonstrates that although the controls responded differentially to the two

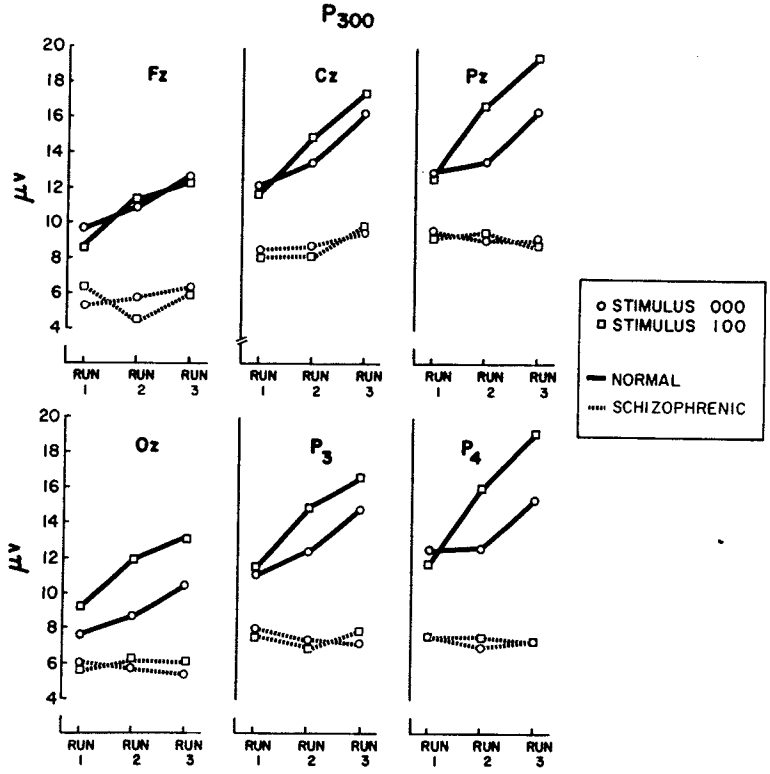

Fig. 1. P300 amplitude at each electrode plotted for each stimulus for both groups across the three conditions.

stimuli and the patients did not, this differential effect was not significantly affected by changes in motivational and task load.

P300 amplitude is significantly different at various recording sites on the scalp as reflected in the main electrode effect ($p < 0.001$). Analysis of the significant electrode effect showed Cz, Pz, and P4 to be significantly larger ($p < 0.01$) than Fz and Oz, and P3 to be significntly larger ($p < 0.05$) than Oz (Scheffé method). The Electrodes X Groups, Electrodes X Runs, Electrodes X Runs X Groups, and Electrodes X Stimuli X Runs interactions were not statistically significant. The stimuli by electrode effect was significant at the 0.001 level by conventional criteria and at the 0.025 level by conservative criteria. The Stimulus X Electrode effect reflects differences in response to the 1.00 stimulus compared to the 0.00 stimulus across electrodes. In this respect Oz and P4 showed significantly larger ($p < 0.01$) values for the 1.00 *vs.* the 0.00

Table I. Summary of Statistical Analysis Using Coventional and Conservative Degrees of Freedom

Source	F	Conventional df		Conservative df	
		df	p	df	p
Groups	8.17	1, 26	< 0.01	1, 27	< 0.01
Runs	10.56	2, 52	< 0.001	1, 27	< 0.005
Runs X Groups	9.53	2, 52	< 0.001	1, 27	< 0.005
Stimuli	5.20	1, 26	< 0.05	1, 27	< 0.05
Stimuli X Groups	5.74	1, 26	< 0.025	1, 27	< 0.025
Runs X Stimuli	1.79	2, 52	> 0.05		
Runs X Stimuli X Group	1.94	2, 52	> 0.05		
Electrodes	14.41	5, 130	< 0.001	1, 27	< 0.001
Electrodes X Groups	0.58	5, 130	> 0.05		
Runs X Electrodes	1.18	10, 260	> 0.05		
Runs X Electrodes X Group	1.26	10, 260	> 0.05		
Stimuli X Electrodes	4.98	5, 130	< 0.001	1, 27	< 0.025
Stimuli X Electrodes X Group	3.10	5, 130	< 0.025	1, 27	> 0.05
Runs X Stimuli X Electrodes	1.39	10, 260	> 0.05		
Runs X Stimuli X Electrodes X Group	0.92	10, 260	> 0.05		

compared to Fz and Cz; and Pz and P3 showed significantly larger ($p < 0.01$) differentials compared to Fz (Scheffé method).

The Stimuli X Electrode X Group interaction which was significant at the 0.025 level using 5 and 130 degrees of freedom was not significant at the 0.05 level using 1 and 27 degrees of freedom. This interaction reflects between-group differences in the differential response to the two stimuli across electrodes. Although the effect is of questionable statistical significance it was analyzed further to determine which electrodes showed between-group differences in the differential response to the two stimuli. At Pz, Oz, and P4 the controls showed a larger P300 to the 1.00 stimulus than to the 0.00 stimulus, which was significantly greater than the between-stimuli difference seen in schizophrenics (Scheffé method). At the P3 electrode this between-group difference was significant at the 0.05 level (Scheffé). The four-way interaction Groups X Runs X Stimuli X Electrodes was not significant.

The P300 component has generally been reported to be of maximal amplitude at the Pz electrode. This result was also observed here. The greater amplitude at Pz reflects in part a larger signal-to-noise ratio. For these reasons the individual responses recorded at Pz were analyzed in greater detail.

For every subject the P300 amplitudes recorded at the Pz electrode in response to both stimuli were summed. Changes in this sum across runs reflect the effect of the change in incentive condition. Criteria were established to

grade the responses across runs. The response of each subject across the three conditions was scored on a scale of 1-6. The criteria were:

Score 1 if Run 2 larger than Run 1 by at least 2 μV and Run 3 larger than Run 2 by at least 2 μV.
Score 2 if Runs 2 and 3 larger than Run 1 by at least 2 μV.
Score 3 if Run 3 larger than Run 1 by at least 3 μV.
Score 4 if Run 3 greater than Run 1 by less than 3 μV.
Score 5 if Run 1 greater than Run 3.
Score 6 if Run 1 greater than Runs 2 and 3.

Scores of 1, 2, and 3 reflect increased P300 amplitude as the incentive was increased. Scores of 5 and 6 reflect a lack of response to the incentive conditions. Setting a criterion of 3 μV difference between Runs 3 and 1 served ad hoc to best subdivide the subjects into responders and nonresponders. Subjects with scores of 3 or less were classified as responders; subjects with scores of 4 or greater were classified as nonresponders. All of the controls and five of the patients were thus classified as responders, nine of the patients were nonresponders. Chi square for this distribution with Yates correction was 10.48, $p < 0.01$.

For each subject the P300 amplitude recorded at Pz to the 1.00 stimulus was divided by the P300 amplitude at Pz to the 0.00 stimulus. This quotient in Runs 2 and 3 reflects the differential electrophysiological response to the stimuli which had differential incentive value. Values greater than 1 reflect greater response to the 1.00 than to the 0.00 (this is the expected result); quotients less than 1 reflect greater response to the 0.00 than to the 1.00. The subjects were subdivided into differential responders and nondifferential responders on the basis of whether they had a greater response to the 1.00 in both Run 2 and Run 3. Of 14 controls, 11 were differential responders, while only 4 of the 14 schizophrenics showed a larger P300 to the 1.00 than to the 0.00 in both Runs 2 and 3. Chi square for this distribution with Yates correction was 5.169, $p < 0.05$.

Correlation of Behavioral Variables with P300 Amplitude

It is of interest whether behavioral variables are correlated with P300 amplitude across different runs or with the differential incentive value of the stimuli in each run. One-way analysis of variance of the patients' BPRS scores yielded an ${}_4F_{65}$ value of 3.72 ($p < 0.01$). This significant result was a consequence of the patients scoring significantly higher ($p < 0.05$) on the anergia factor than on the hostile/suspicious factor (Scheffé method). The sums and ratios of the P300 amplitude at Pz in each run were correlated with the total BPRS scores, the BPRS anergia score, the BPRS thought disorder score, and the

Philips premorbid adjustment score. None of the correlation coefficients approached the 0.05 level of significance. Ten of the 14 patients had a poor premorbid history as measured by the Philips scale.

A two-way analysis of variance was performed on the BPRS factor scores of the responder and nonresponder subgroups of schizophrenic patients. The between-group difference across all factors was not significant, nor was the Group X Factor interaction. Between-group T tests of total BPRS scores and Philips premorbid adjustment scores were also not significantly different.

Other Findings

The average number of correct responses in each run (maximum 60) for the control subjects was 59.16 (Run 1, 59.21; Run 2, 59.42; Run 3, 58.85). For the patients the average number of correct responses was 55.92 (Run 1, 57.35; Run 2, 55.64; Run 3, 54.78). There was a significant group difference ${}_1F_{26} = 7.77$, $p < 0.01$, but no significant Runs or Runs X Group interaction.

It should be noted that the difference between groups was small, 3.24 correct responses per run, and that the patients performed the task with a high degree of accuracy. This high degree of accuracy confirms that they were attending to the stimuli. The significant difference between groups resulted from the very low degree of variability in the number of correct responses.

In Run 3 the mean number of correct responses within the criterion time was 17.49 for controls and 4.50 for the patients ($T < 0.02$).

The schizophrenic patients' N1 component was significantly less negative than the controls (${}_1F_{26} = 8.50$, $p < 0.01$). Significant interaction effects were not noted for this component.

No significant effects of any variable or combination of variables were observed for the latencies of N1, P2, N2, or P3. No differences were noted in P300 amplitude between those patients who received 65 mg of sodium amytal at bedtime between 4 and 14 days prior to testing and those patients who did not receive it.

In Run 2 significant between-group differences in reaction time were not observed to either stimulus. In Run 3 the mean reaction time to the 0.00 stimulus was 466 msec for the controls and 674 for the patients ($p < 0.05$). The mean reaction time for the controls to the 1.00 in Run 3 was 419 msec and 614 msec for the patients ($p < 0.005$).

Both groups responded more quickly to each stimulus in Run 3 compared to Run 2 ($p < 0.01$ for patients, $p < 0.001$ for controls). In both conditions the controls responded significantly faster to the 1.00 than to the 0.00 ($p < 0.05$, Run 2; $p < 0.01$, Run 3). The patients did not show a significant difference in reaction time between stimuli in either Run 2 or Run 3.

DISCUSSION

The finding of a reduced N1 component in the patient group is difficult to interpret. Selective attention is the variable whose influence on the amplitude of the N1 component is best understood, but selective attention was not manipulated in our experimental design. Schizophrenics have been reported (Baribeau-Braun *et al.*, 1980) to show a reduced N1 component compared to normals under conditions of selective attention at higher rates (2 per sec) of stimulus presentation.

Our results demonstrate a reduced P300 component of the evoked potential in unmedicated schizophrenics to high-incentive stimuli under various incentive conditions. Previous reports of a diminished P300 in schizophrenics can be questioned on the grounds that the stimuli were not ecologically relevant to the patients. The reliability of this diminution under high-incentive conditions suggests that a reduced P300 component is a valid neurophysiological manifestation of some cases of schizophrenia.

It is unlikely that the between-group differences in P300 amplitude reported here were a consequence of a difference in accuracy between groups. The groups differed by an average of only 3.23 correct responses per run out of a total of 60 responses. It has also been shown that when performance is equated between controls and schizophrenics by averaging only trials with correct responses, the P300 component is still observed to be reduced in schizophrenic patients (Steinhauer and Zubin, 1982).

It is also unlikely that increased reaction times account for the diminished P300 amplitudes in schizophrenic patients. First, there were no significant between-group differences in reaction time in Run 2. Roth *et al.* (1980c) have also shown that P300s computed separately from short and long reaction time trials are both significantly lower in schizophrenics compared to controls.

These results confirm those of Pass *et al.* (1980) who found a diminished P300 to purely visual stimuli in schizophrenic patients. The reduced P300 to purely visual stimuli along with similar findings to purely auditory stimuli (Roth and Cannon, 1972; Roth *et al.*, 1980b) and to mixed auditory/visual stimuli (Levit *et al.*, 1973; Verleger and Cohen, 1978) demonstrate that the P300 abnormality in schizophrenics is not a modality-specific deficit.

These results provide clear evidence that the reduced P300 observed in schizophrenics is not a medication effect. Roth and Cannon (1972), Levit *et al.* (1973), and Roth *et al.* (1980b) did not observe any correlation between medication dosage and P300 amplitude. This does not exclude a nonlinear relationship or nonspecific medication effects on attention or motivation. Pass *et al.* (1980) did not observe a difference in P300 amplitudes between the 11 subjects on medication and the 6 who were drug free. However, the sample sizes were small and the unmedicated patients may have differed from the medicated subgroup in other significant ways.

There is only one significant correlation in the literature between P300 amplitude and psychopathology. Roth *et al.* (1980b) reported a correlation of −0.63 between formal thought disorder and P300 amplitude to rare tones. We did not observe any significant correlations between indices of psychopathology as measured by the BPRS and P300 amplitude, but the instrument used to measure thought disorder and the experimental paradigms was different in the two studies.

The increase in P300 amplitude seen across runs in normal individuals (Begleiter *et al.*, 1982) is attributable to the difference in the incentive value of the stimuli across runs. That incentive value alone was sufficient to elicit large P300s in normal individuals suggests that the limbic system may be involved in generating this wave.

There is good evidence that the P300 derives, at least in part, from subcortical sources. Wood *et al.* (1980) studied the evoked responses of a group of patients undergoing exploratory surgery for excision of an epileptic focus. Using a depth frontal-central electrode he recorded P300s to rare clicks and median nerve shocks which were similar to the P300s recorded at the scalp. Halgren *et al.* (1980) studied another group of epileptic patients using common and rare visual and auditory stimuli. They recorded a large P300 to the rare tones and visual patterns on the cortical surface and a generator for the P300 was found in the hippocampal gyrus, hippocampus, and amygdala.

The direct demonstration of a limbic system contribution to the scalp-recorded P300 is in accord with this system's role in integrating drive-related behavior. Simons (1982) has reported that college students who score high on the Chapman *et al.* (1976) anhedonia scale show significantly lower P300s to tones signaling an upcoming erotic stimulus than nonanhedonic college students. This finding with sexual stimuli, like our finding with financial incentive, documents a neurophysiological difference in individuals who differ from normals in their behavior response to high-incentive stimuli.

Thus, stimuli of high-incentive value generate P300s in normals which arise in part from regions in the limbic system. Schizophrenics and anhedonics do not show P300s in a variety of test paradigms which suggest limbic system dysfunction in these individuals. There is additionally one anatomical report documenting a limbic system abnormality in schizophrenia. Based on autopsy data Scheibel and Kovelman (1981) have reported a disordered arrangement of pyramidal cell orientation in the hippocampi of some schizophrenics, a finding not observed in individuals who were not schizophrenic premorbidly.

Both our schizophrenic patients who showed a decreased P300 to stimuli associated with monetary reward and Simons' (1982) anhedonics who did not respond electrophysiologically to stimuli associated with nude figures share what Meehl called schizotypy. In his seminal paper Meehl (1962) postulated that anhedonia, cognitive slippage, interpersonal aversiveness, and ambivalence were the behavioral expressions of the genetic factors predisposing to schizo-

phrenia and that these traits were the core features of the personality which became clinically schizophrenic when subjected to environmental and social stress. The generation of large P300 waves by high-incentive stimuli and the failure of the same stimuli to elicit P300s in schizophrenics and anhedonics suggest that the P300 may be a marker for anhedonia and as such may be a marker for vulnerability to schizophrenia.

Until recently, clinical research in schizophrenia has assumed thought disorder to be the critical variable. However, thought disorder has been shown by Pope and Lipinski (1978) to have little diagnostic specificity and little prognostic utility. Affect has been largely ignored because of difficulty in measuring it reliably. In recent years Chapman *et al.* (1976), Abrams and Taylor (1978), and Andreasen (1979; 1982) have reliably measured affect and anhedonia. Furthermore, affect has been shown by Pope and Lipinski (1978) and Knight *et al.* (1979) to predict outcome in acute schizophrenia. This growing focus on affective factors and anhedonia in schizophrenia may give clinical relevance to the P300 component of the event-related potential.

These electrophysiological findings in experimental paradigms which parallel core symptoms of schizophrenia begin to link psychopathology and neurophysiology. This connection is a step toward understanding both overt schizophrenia and vulnerability to schizophrenia in physiological terms and may contribute to a more informed subclassification of the syndrome of schizophrenia.

ACKNOWLEDGMENT

We thank Charles Chou for computer programming and Marion Gillespie for valuable assistance.

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