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Auditory event-related potentials in panic disorder

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Abstract To investigate the psychophysiological features of panic disorder (PD), we recorded auditory event-related potentials (ERPs) in 12 patients with PD meeting the DSM-IV criteria and in 12 age-matched normal controls. The ERPs were recorded during a standard two-tone discrimination task (oddball task). The probabilities of the rare target (1200 Hz) and frequent non-target tones (1000 Hz) were 15 and 85%, respectively. The subjects were required to press a button in response to the rare target tones. Scalp electroencephalograms were recorded from Fz, Cz, Pz, C3, and C4. The State-Trait Anxiety Inventory and Manifest Anxiety Scale scores were assessed for clinical evaluation. Analysis of variance revealed that the N1 and N2 amplitudes for target tones and the N1 amplitude for non-target tones were significantly larger in the PD patients than those in the controls. The two groups did not differ significantly in P3 latency and amplitude. The larger N1 and N2 amplitudes in the PD patients are suggestive of alteration of early information processing in PD.

Key words Panic disorder · Event-related potentials · N1, N2, P3

Introduction

Panic disorder (PD) is a common, chronic illness associated with considerable morbidity, the features of which are recurrent panic attacks and associated avoidance. An epidemiological study using DSM-III-R PD criteria disclosed a lifetime prevalence of 3.5% (Kessler et al. 1994). Although panic symptoms have been well described for over a century, only in the past decade has PD become widely recognized as a distinct psychiatric illness (Abbey et al. 1995). Following the first definition of PD in the DSM-III, many biological studies of PD were conducted. Although no consistent findings on the pathophysiology of PD have been proposed, several etiological hypotheses have been presented. Some researchers have proposed that noradrenergic dysregulation is associated with PD (Charney et al. 1990; Gorman et al. 1989; Heninger et al. 1988; Nutt et al. 1990). Concerning psychophysiological functions, the electrodermal and cardiovascular activities in PD have been studied by many researchers (Stein et al. 1994), but electroencephalographic studies have not been intensively performed.

Event-related potentials (ERPs) are widely used to examine dysfunction of information processing in psychiatric illness (Picton and Hillyard 1988). The results of previous ERP studies in patients with PD and normal controls do not point to any consistent pattern with regard to anxiety, but a few studies have revealed that the early negative potentials of ERPs are altered in patients with PD or subjects in anxiety state (Knott et al. 1991; Weinstein 1995). Knott et al. (1991) reported that patients with PD exhibited increased N1 amplitude during a passive auditory task. Weinstein (1995) showed that, compared with the "Low-Anxious group," the "High-Anxious group" defined by the State-Trait Anxiety Inventory (STAI) scores showed higher amplitude of N1, using a visual semantic matching task in normal controls. The early negative potentials of ERPs reflect selective or automatic attention (Näätänen 1992). These studies may point to an alteration of early information processing in PD.

The auditory oddball task is a standard and well-established task used to examine the early negative components of ERPs (Fabiani et al. 1987). In this study, to examine the hypothesis that the early negative components of ERPs are altered in patients with PD, we recorded auditory ERPs of patients with PD and of healthy controls during this task.

Subjects and methods

Twelve outpatients with PD (6 males and 6 females), all of whom provided informed consent, were included in this study. All patients met the DSM-IV criteria for PD, and their mean age was

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Table 1 Mean scores (SD) of psychological tests

State-Trait Anxiety Inventory (STAI)		
	PD	Control
State Anxiety	40.3 (8.9)	34.3 (7.3)
Trait anxiety**	52.8 (8.9)	36.5 (8.1)
Manifest Anxiety Scale (MAS)		
	PD	Control
MAS*	24.3 (8.8)	11.8 (7.1)

*$p < 0.01$
**$p < 0.001$

34.4 years (SD 9.0 years). Five patients were diagnosed as "Panic disorder with agoraphobia," and 7 as "Panic disorder without agoraphobia." Exclusion criteria included meeting the DSM-IV criteria for other anxiety disorders, somatoform, disorders, dissociative disorders, schizophrenia, major mood disorders, substance abuse disorders, or having neurological disorders. The mean number of panic attacks during the week before the testing was 1.7. Eight of the patients were receiving benzodiazepines: 6 were receiving alprazolam (0.4-2.4 mg/day), 1 lorazepam (1.5 mg/day), and 1 bromazepam (15 mg/day) and etizolam (1.5 mg/day). Twelve healthy volunteers (7 males and 5 females) who had no history of psychiatric or neurological illness served as the control group (mean age 35.6 years; SD 9.9 years).

The STAI (Spielberger 1983) and the Manifest Anxiety Scale (MAS; Taylor 1953) were administered to both groups at the time of testing. The scores for trait anxiety on the STAI and MAS in the patients with PD were significantly higher than those in the controls (Table 1).

ERP recording

Subjects performed a two-tone auditory discrimination task in a sound-proof room. They were presented with a series of 360 auditory stimuli with a fixed interstimulus interval of 360 auditory stimuli with a fixed interstimulus interval of 1500 ms. Eighty-five percent of the stimuli were tones of 1000 Hz, and the other 15% were tones of 1200 Hz. Stimuli were presented in a Bernoulli sequence. Subjects were instructed to press a button as quickly as possible upon hearing the infrequent high-pitch tones. The stimulus intensity was 75 dBSPL, and the tone duration 50 ms, with a rise/fall time of 10 ms.

The scalp electroencephalogram (EEG) was recorded with Ag/AG-Cl disc electrodes at Fz, Cz, Pz, C3, and C4 monopolarly according to the international 10–20 electrode system, referred to linked earlobes. The bandpass was set at 0.15–120 Hz. Vertical and horizontal electrooculograms (EOGs) were recorded from electrodes placed below and at the outer canthus of the right eye. The EEG samples were acquired every 2.5 ms from 40 ms before to 600 ms after the stimulus onset. Trials contaminated by peak to peak potentials of over 100 μV or accompanied by EOGs of over 75 μV were eliminated from the averaging. The responses to frequent and rare tones with correct reactions were averaged separately.

N1 was defined as the most negative peak between 75 and 150 ms post stimulus, P3 as the most positive peak between 250 and 500 ms poststimulus, and N2 as the most negative peak between N1 and P3. Amplitudes were measured with respect to an average voltage during the 40-ms prestimulus. Statistical analyses were performed using Student's *t*-test and analysis of variance (ANOVA). Behavioral data were compared using Student's *t*-test. The ERP indices were analyzed using three-way or two-way ANOVAs.

Results

Behavioral data

Table 2 shows the mean reaction time and correct response rate of the patients and the controls. The two groups did not differ significantly in reaction time or correct response rate (Student's *t*-test).

ERP components

Figures 1 and 2 show the grand average ERP waveforms for the target and for the non-target stimuli in the two

Table 2 Means (SD) of reaction time and correct response rate

	PD	Control
Reaction time (ms)	447.7 (157.4)	423.8 (121.6)
Correct response rate (%)	98.9 (1.7)	97.5 (3.5)

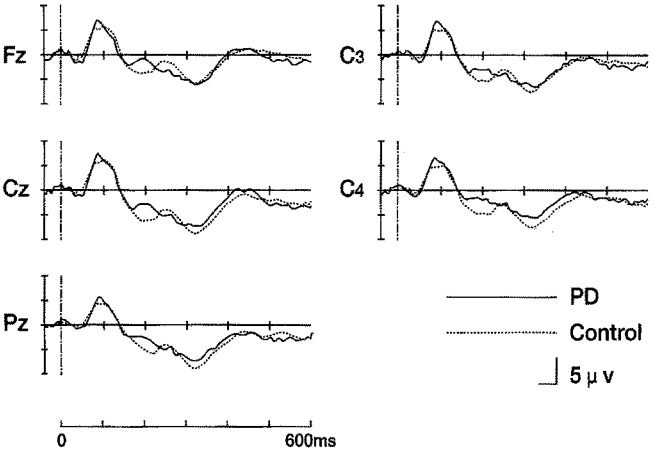

Fig. 1 Grand average ERP waveforms for target stimuli in the two groups. Negativity is upward

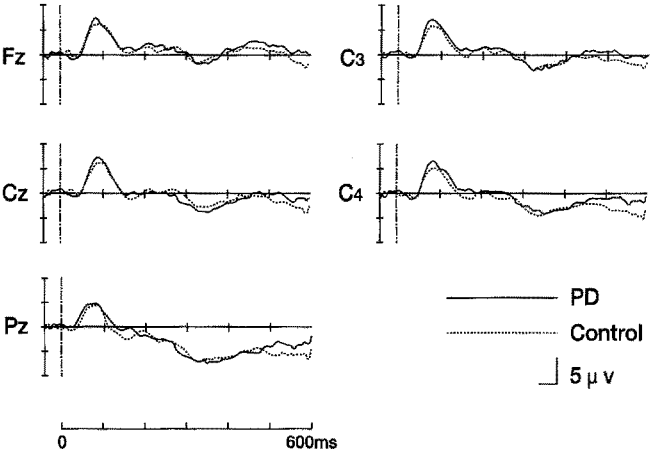

Fig. 2 Grand average ERP waveforms for non-target stimuli in the two groups. Negativity is upward

Table 3 Means (SD) of latencies and amplitudes of event-related potential components

		Target			Non-target
Latency (ms)		N1	N2	P3	N1
Fz	Control	89.2 (7.4)	220.2 (32.7)	333.8 (27.1)	86.5 (6.0)
	PD	88.3 (12.9)	220.8 (44.9)	341.0 (33.3)	85.3 (8.9)
Cz	Control	87.9 (6.2)	229.5 (30.0)	337.5 (25.4)	86.3 (6.0)
	PD	87.4 (12.7)	206.2 (52.0)	344.4 (30.5)	85.7 (8.0)
Pz	Control	86.6 (7.6)	225.3 (33.5)	329.2 (20.3)	84.9 (6.3)
	PD	85.9 (13.5)	196.3 (46.6)	341.0 (48.9)	86.8 (7.3)
Amplitude (μv)		N1[a]	N2[b]	P3[c]	N1[d]
Fz	Control	7.0 (3.0)	2.8 (3.4)	5.1 (3.7)	6.5 (2.5)
	PD	9.4 (3.1)	6.1 (4.0)	3.9 (4.5)	8.4 (1.9)
Cz	Control	6.6 (2.7)	1.6 (3.1)	7.8 (3.4)	6.4 (2.6)
	PD	9.1 (4.6)	3.7 (4.2)	6.6 (5.2)	7.9 (2.0)
Pz	Control	4.7 (2.4)	−0.7 (2.9)	10.8 (2.9)	4.8 (2.2)
	PD	6.9 (3.7)	1.8 (3.5)	10.1 (5.1)	5.4 (1.9)

Two-way ANOVAs:
[a] Group: $p < 0.01$; electrode site: $p < 0.05$
[b] Group: $p < 0.01$; electrode site: $p < 0.01$
[c] Electrode site: $p < 0.0001$
[d] Group: $p < 0.05$; electrode site: $p < 0.01$

groups, respectively. Table 3 shows the means and standard deviations of amplitudes and latencies of ERP components.

For the N1 amplitude and latency, three-way ANOVA by group (patients/controls) and electrode site (fz/Cz/Pz) and stimulus (target/non-target) was performed. For the N1 amplitude, there were effects of group ($F = 15.480$, $p < 0.001$) and of electrode site ($F = 10.183$, $p < 0.001$), but no significant interaction effect. For the N1 latency, there was no significant effect. Separate two-way ANOVAs for the N1 amplitude and latency by group and electrode site were performed in each stimulus category. For the N1 amplitude in response to target stimuli, there were effects of group ($F = 9.06$, $p < 0.01$) and of electrode site ($F = 3.16$, $p < 0.05$), but not an interaction effect. For the N1 latency, there was no significant effect. For the N1 amplitude in response to non-target stimuli, there were effects of group ($F = 6.629$, $p < 0.05$) and of electrode site ($F = 8.183$, $p < 0.001$), but not an interaction effect. These results indicated that the N1 amplitudes for both target and non-target stimuli were significantly larger in the patients as compared with those in the controls. For the N2 and P3 indices, two-way ANOVAs by group and electrode site were performed. The N2 amplitude showed effects of group ($F = 9.60$, $p < 0.01$) and electrode site ($F = 6.78$, $p < 0.01$), but not an interaction effect. The N2 latency showed no significant effect. These results indicated that the N2 amplitude was larger in the patients as compared with that in the controls. For the P3 amplitude, there was an electrode site effect ($F = 11.17$, $p < 0.0001$), but not a group effect or an interaction effect. For the P3 latency, there was no significant effect.

Pearson product moment coefficients were calculated between the scores of psychological tests and ERP indices. In the patients with PD, the scores of state anxiety were correlated with the N1 amplitude at Cz ($r = 0.596$, $p < 0.05$). In the controls, the scores of trait anxiety were correlated with the P3 latency at Pz ($r = 0.636$, $p < 0.05$). In the patients with PD, Pearson product moment coefficients were calculated between the number of panic attacks during the week before the testing and ERP indices. The number of panic attacks was correlated with the N1 amplitude at Fz ($r = 0.671$, $p < 0.05$), Cz ($r = 0.761$, $p < 0.01$), and Pz ($r = 0.765$, $p < 0.01$), the N2 amplitude at Pz ($r = 0.654$, $p < 0.05$), and the P3 latency at Cz ($r = 0.716$, $p < 0.01$).

Discussion

In this study, the N1 and N2 amplitudes for target stimuli and the N1 amplitude for non-target stimuli in the patients with PD were increased significantly in comparison with those in normal controls. Although there was a significant group effect for N2 amplitude, the N2 peak was not distinct in the grand average ERP waveforms, which appeared to suggest some unreliability for the N2 difference. This indistinct N2 peak may be due to the comparable large variabilities of the N2 latencies for the two groups. N1 reflects selective attention and N2 automatic attention and/or stimulus deviation (Näätänen and Picton 1987). Accordingly, these results indicated the alteration of early information processing in patients with PD.

However, neither N1 nor N2 is a unitary component, but instead each is composed of some subcomponents. Näätänen and Picton (1987) reported that the auditory N1 wave comprised six main subcomponents, of which three are exogenous and are difined by stimulus parameters. The three other subcomponents are early processing negativity (PN), late PN, and mismatch negativity (MMN). The PN reflects selective attention and MMN automatic attention (Näätänen 1992). Some abnormalities of these three subcomponents may be associated with the change in N1 amplitude in PD. Näätänen (1990) further reported that N2 comprised three main subcomponents: PN, MMN, and N2b. N2b reflects effortive detection of stimulus deviation, and its onset is usually approximately at 200 ms poststimulus. The PN occurs at approximately 50 ms and

MMN around the N1 peak latency. Considering that PD showed enhanced N1 and N2 amplitudes, it is suggested that PN and/or MMN is altered in patients with PD, but it is not clear which subcomponents are most associated with the increased N1 and N2 amplitudes in PD based on the results of this study. Weinstein (1995) suggested that PN is associated with the increased N100 amplitude in high-anxious subjects, but he drew no clear conclusion. As both the target and non-target N1 amplitudes were increased in our patients, enhanced PN is suggested in PD. To clarify this problem, further research efforts are necessary, using a selective attention task and an ignore task (Squires et al. 1975) in order to examine PN and MMN individually.

Concerning the N1 amplitudes for both target and non-target stimuli and the N2 amplitude for target stimuli, there was not an interaction effect between group and electrode site. These results may indicate the absence of a deficit in a specific part of the brain in patients with PD. The N1 amplitude at three electrode sites in PD was correlated with the frequency of panic attacks and the scores of state anxiety, which suggests that the increased N1 amplitude in PD is associated with the severity of this disease and/or the degree of anxiety. The P3 component was elicited in response to target stimuli in both groups. The two groups did not differ significantly in P3 amplitude or latency. The P3 amplitude is associated with effortive cognitive process, and P3 latency with stimulus evaluation time (Donchin and Coles 1988; Magliero et al. 1984). The normal latency and amplitude of P3 in the patients with PD, together with the absence of significant differences in behavioral indices between the two groups, may correspond to the preservation of the controlled processes involved in information processing, with neither impairment nor facilitation, in this disease.

There are several reports regarding ERPs in patients with PD and in normal subjects in which the effect of anxiety was taken into consideration. Knott et al. (1991) studied ERPs in 12 patients with PD and 10 normal controls during a passive auditory task. In their task, 1 KHz tone bursts were presented binaurally at 1.0 s interstimulus intervals. They reported that for N1 amplitude there was a significant group effect but not an interaction effect between group and electrode site, which is simular to the sets of results in this study. In the study by Weinstein (1995), subjects were required to decide whether visually presented words (probes: positive, neutral, or threat) matched semantically with previous priming sentences (threat or positive) displayed on a computer screen. In their results, a four-way ANOVA of N100 amplitude by group (high-anxious vs low-anxious), prime (threat vs positive), probe (threat vs positive vs neutral), and electrode site revealed a significant group effect and prime effect, but not a probe effect. Accordingly, Weinstein's results may suggest that the increased N100 amplitude in high-anxious group was not caused by their being alerted by stimuli that would be threatening, but rather by their higher level of arousal or attention induced by threatening primes. Weinstein suggested that highly anxious individuals deploy more processing resources in response to threatening information. These results do not seem to conflict with those of the present study. Drake et al. (1991) reported auditory ERPs in patients with generalized anxiety disorder according to DSM-III-R criteria. They reported no difference between the patients and normal controls for the amplitude or latency of any of the N1, N2, and P3 component. Chattopathyay et al. (1980) reported larger P300 amplitude in anxiety patients as compared with that in normal controls. These results may suggest that anxiety disorders other than PD have pattens of ERPs different from that of PD. The results of the present study seem to be consistent to those of electrodermal studies in patients with PD. Roth (1990) recorded skin conductance response in patients with PD and reported slowed habituation, more non-specific fluctuations, higher skin conductance levels, and a shorter response latency to the first stimuli in PD. These results indicate the high arousal level in patients with PD, which may be associated with the increased early negative potentials in this study.

Various researchers have reported that the amplitude of early negative components (N1, N2, PN, or MMN) is reduced in schizophrenia (Prichard 1986; Ward et al. 1991), infantile autism (Ciessielski et al. 1990), and drug abuse (Iwanami et al. 1993, 1995). Although the findings are not fully consistent, the reduced amplitude of early negative potentials appears to suggest the dysregulation of noradrenergic function (Pineda et al. 1989). The results of this study may support the concept that noradrenergic dysregulation exits in PD. Enhanced early negative potentials of ERPs have been reported only for obsessive-compulsive disorder (OCD). Tower et al. (1994) reported increased N2 and PN amplitudes in patients with OCD as compared with those in normal controls, and noted that these findings are correlates of the overfocused attention characteristic of this disorder. Considering that PD has characteristics in common with OCD, in that both disorders are regarded as anxiety disorders and selective serotonin reuptake inhibitors are effective for both, it is suggested that PD may involve information processing dysfunction similar to that in OCD. However, the relationships between the early negative potentials of ERPs and neurotransmitters in the central nervous system are not fully established. Further studies should be conducted to examine the relationships between ERP components and neurotransmitters.

At the time of testing, 8 of the patients were receiving benzodiazepines. Previous studies indicated that benzodiazepines reduce the amplitudes of N1, N2, and P3 of ERPs (Kulikowski et al. 1984; Milligan et al. 1989; Rockstroh et al. 1991). Accordingly, we speculated that benzodiazepines might not have contributed to the increased amplitudes of N1 and N2 in PD; however, the effects of medication in this study could not be ruled out and should be regarded as a confounding factor. Further studies of unmedicated subjects are needed using a larger sample size.

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