Clinical Electroencephalography, 2002, 33(3), 119-124.

Cognitive ERPs in Depressive and Anxiety Disorders During Tonal and Phonetic Oddball Tasks

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Key Words

Anxiety Disorders
Comorbidity
Depression
Event-related Potentials
Hemispheric Asymmetry
Principal Components Analysis (PCA)
P3
Tonal/Phonetic Oddball Tasks

ABSTRACT

This report compares event-related brain potentials (ERPs) of patients having a depressive disorder alone (n = 58), an anxiety disorder alone (n = 22), comorbidity of these disorders (n = 18), and healthy controls (n = 49). ERPs were recorded from 30 electrode sites during auditory oddball tasks using consonant-vowel syllables (phonetic) or complex tones (tonal). Overlapping ERP components were identified and measured using covariance-based principal components analysis. An early P3 subcomponent (P315) was larger in patients having an anxiety disorder alone when compared to depressed patients with or without an anxiety disorder and healthy controls, whereas a late P3 subcomponent (P400) was larger in patients having comorbidity of anxiety and depressive disorders than in the other groups. Also, the N2-P3 complex showed task-dependent hemispheric asymmetries, including larger N2-P3 amplitude over left than right temporoparietal sites during the phonetic oddball task. This hemispheric asymmetry was greatest in patients having a depressive disorder alone and smallest in patients having an anxiety disorder alone. The opposite nature of the alterations of hemispheric asymmetry and early P3 amplitude in depressive and anxiety disorders underscores the importance of taking comorbidity with anxiety into account in studies of cognitive ERPs in depressive disorders.

INTRODUCTION

There have been conflicting reports as to whether or not depressed patients show reduced amplitude of the P3 event-related potential (ERP). About half of studies using an auditory target detection (oddball) task have found reduced P3 amplitude in depressed patients when compared to normal controls.[1] Among the factors that may have contributed to the different P3 findings in these studies, two are particularly relevant to this report.

First, depressed patients in the various studies may have differed in comorbidity with anxiety disorders. The extent to which comorbidity with anxiety disorders influences cognitive ERP findings for depression is unknown. Behavioral and electroencephalographic (EEG) studies have found evidence that patients having a "pure" major depressive disorder (MDD) without an anxiety disorder differ from patients having a comorbid anxious depression in their asymmetries of right-left brain function.[2,3] There is evidence that anxiety disorders, such as social phobia or panic disorder, are associated with reduced left and greater right hemisphere activation,[4-6] which is the opposite direction of lateralized cognitive dysfunction reported for depressive disorders.[7-9] Given that P3 amplitude to tones has an asymmetric topography, being greater over right than left hemisphere sites in healthy adults,[10-13] the presence of a comorbid anxiety disorder could have an impact on P3 findings for depressed patients. Little attempt has been made, however, to compare the ERPs of patients having a depressive disorder alone with those having an anxiety disorder alone or comorbidity of these disorders.

Second, a reduction in amplitude may occur in only a subcomponent of P3. The most commonly studied subcomponent in "oddball" tasks is the classical P3b, which has a parietal maximum scalp distribution and a peak latency of 300-400 ms. This is often preceded by a subcomponent with a more frontocentral topography, i.e., P3a, which is thought to reflect alerting or orienting processes in the frontal cortex.[14-16] These P3 subcomponents and a later slow wave component usually overlap in time, making it difficult to measure them separately. The relevance of differentiating P3 subcomponents in studies of depressed patients is underscored by recent evidence that noradrenergic agonists and antagonists have a greater effect on the frontal P3a than P3b.[17] Studies generally have not examined differences in P3 subcomponents between depressed patients and healthy controls, and a reduction in P3a amplitude may have been obscured by variation in the other subcomponents.

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Table 1
Characteristics of anxiety disorder patients, comorbid patients, depressed patients and healthy control subjects

	Anxiety Disorder Alone (*n* = 22)		Comorbid Patients (*n* = 18)		Depression Alone (*n* = 58)		Healthy Control Subjects (*n* = 49)	
Variable	*N*	%	*N*	%	*N*	%	*N*	%
Gender								
Women	9	41	12	67	28	48	29	59
Men	13	59	6	33	30	52	20	41
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age (Years)	32.7	10.0	29.7	8.1	37.1	10.6	30.2	7.7
Education (Years)	15.3[a]	2.5	14.0	2.9	15.1[b]	2.4	15.6	1.8
Handedness (LQ)	80.3	28.8	80.7	25.5	87.9	25.4	79.2	20.9

[a] n = 20; [b] n = 56

The present study compared cognitive ERPs of patients having a depressive disorder alone, an anxiety disorder alone or comorbidity of these disorders, and healthy controls. ERPs were recorded during phonetic and tonal oddball tasks, which were previously shown to yield robust task-related hemispheric asymmetries of ERP components, i.e., N2 and P3.[12,18] Considering that anxiety and depression may be associated with opposite abnormalities of hemispheric asymmetry,[4-9] it would be important to directly probe lateralized functions in these disorders. Based on findings for perceptual asymmetry tests,[3,19] it was predicted that patients having a depressive disorder would differ from those having an anxiety disorder in task-related hemispheric asymmetries of the N2-P3 complex. Principal Component Analysis (PCA) methodology was used to identify and measure overlapping ERP subcomponents,[12,20] which enabled us to examine whether depressive and anxiety disorders are associated with an abnormality of a specific P3 subcomponent.

METHODS

Participants

The study was designed to allow comparison of the ERPs for four groups with all possible combinations of having or not having a depressive or anxiety disorder: (1) 58 patients having a depressive disorder but no anxiety disorder; (2) 22 patients having anxiety disorder but no depressive disorder; (3) 18 patients having comorbidity of these disorders; and (4) 49 healthy controls with neither disorder. Patients were recruited from the Depression Evaluation Service or the Anxiety Disorders Clinic at New York State Psychiatric Institute. Diagnostic evaluation of the patients were carried out by research psychiatrists at these units. Patients in group 1 met DSM-IV criteria for major depressive disorder (MDD) (n = 37), dysthymia (n = 12) or both disorders (n = 9). The patients in group 2 met DSM-IV criteria for one or more of the following anxiety disorders: social phobia (n = 16), panic disorder (n = 4), obsessive-compulsive disorder (n = 3) or generalized anxiety (n = 1). Patients in group 3 met DSM-IV criteria for MDD (n = 11), dysthymia (n = 1) or both disorders (n = 6) and also met criteria for one or more anxiety disorder: social phobia (n = 9), panic disorder (n = 7), obsessive-compulsive disorder (n = 2) or generalized anxiety disorder (n = 3). Healthy controls were recruited from hospital staff, colleges, and advertisements in local newspapers. They were screened using a semi-structured interview to exclude those with current or past psychopathology. Subjects were exluded from the study if they had a hearing loss greater than 30 dB in either ear at 500, 1,000 or 2,000 Hz or if they had an ear difference greater than 10 dB, and were also excluded if they had current substance abuse or a history of head trauma or other neurological disorder.

Table 1 shows the characteristics of the subjects in the four groups. A somewhat greater percentage of patients in the comorbid group were women when compared to the other groups and therefore gender was entered as a control variable in the statistical analyses. The four groups were comparable in age and education. All subjects were right handed and there was no difference among groups in handedness laterality quotient (LQ) on the Edinburgh Handedness Inventory.[21]

ERP Recording and Analyses

Patients were tested after a minimum drug-free period of 7 days. Details of ERP recording and analyses are given elsewhere.[18] Briefly, ERPs were measured in two auditory oddball tasks using either complex tones (fundamental frequency between 264 Hz and 528 Hz) or consonant-vowel syllables (/da/, /ta/, /ka/). Participants listened to a series of tones or syllables, in which only two different tones or syllables (infrequent targets and frequent standards with probabilities .2 and .8 respectively) were presented in a block. They were instructed to press a button as quickly as possible after infrequent target stimuli. For each task (tonal or phonetic), subjects were tested in either of two presentation formats: (1) 69 subjects received 8 blocks of 50 trials (80 targets, 320 nontargets); (2) 78 subjects received

4 blocks of 80 trials (64 targets, 256 nontargets), as well as an additional 2 blocks of a silent count condition that is not dealt with in this report. Both presentation formats were used for all four groups and it is unlikely that differences in presentation format would have contributed to the group differences in ERPs reported below. In half of these blocks, subjects responded with their right hand and half with their left hand. The order of the tonal and phonetic tasks and the associated response hand assignment were counterbalanced across subjects.

EEG was recorded from 30 standard scalp placements (four midline and 26 paired homologous lateral sites) using a nose reference with an Fpz ground and impedances at 5 kΩ or less. Averaged ERP waveforms were submitted to a temporal PCA derived from the covariance matrix, followed by unscaled Varimax rotation. This results in the generation of distinctive PCA components (i.e., factor loadings) and corresponding weighting coefficients (i.e., factor scores) that describe the variance contributions of temporally and spatially overlapping ERP components.[20,22] The PCA factor loadings for the five components used in this study (N100, N215, P315, P400 and S850) are shown in Figure 1A, ordered by their peak latencies. Factor N100 peaked at 100 ms and overlapped the N1 peak in the ERP waveforms. Similarly, factor N215 peaked at about 200 ms and closely corresponded to the N2 peak. The factor scores associated with the N100 and N215 factors revealed topographies typically observed for N1 (vertex maximum) and N2 (lateral-temporal maximum for targets) amplitudes during tonal and phonetic oddball tasks.[12] Three factors with amplitude peaks at 315 ms, 400 ms and 850 ms after stimulus onset accounted for most of the variance in the late positive complex, revealing factor score topographies with mid-parietal or central-parietal maxima typically seen for P3 and late positive slow wave. Thus, the five principal components, which accounted for 88.6% of the overall variance after Varimax rotation, corresponded closely to known ERP components evident in the ERP waveforms (i.e., N1, N2, early P3, late P3 and slow wave). This report focuses on the factors corresponding to the early and late P3 components, as well as the N2-P3 complex that was previously shown to yield task-dependent hemispheric asymmetries.[12,18]

Statistical Analyses

PCA factor scores for target stimuli were submitted to repeated measures ANOVA with Group (depressive disorder alone, anxiety disorder alone, comorbidity, or healthy controls) and Gender as between-subjects factors, and Task (tonal/phonetic), Electrode Site (13 symmetric electrode pairs), Hemisphere (right, left) and Response Hand (right, left) as within-subjects factors. Response accuracy and latency for target stimuli were also analyzed using an ANOVA with the same grouping factors, and with Task and Response Hand as within-subjects factors. Greenhouse-Geisser epsilon (ϵ) correction was used to compensate for violations of sphericity when appropriate. The sources of significant interactions were systematically examined through simple effects and contrasts between groups.[23]

RESULTS

The mean percentage of correct responses to target stimuli was very high for all four groups and did not differ significantly across groups (means [%] ranged from 96.3 ±2.5 to 99.6 ±0.9 for the tonal and phonetic tasks). Similarly, the mean response times for correct responses did not differ significantly across groups and fell in a narrow latency range (means [ms] ranged from 451 ±112 to 506 ±127 for the tonal and phonetic tasks).

The grand average ERP waveforms at the Cz electrode site are shown in Figure 1B for patients having a depressive disorder alone, an anxiety disorder alone, or comorbidity of these disorders, and healthy controls with neither disorder (averaged over task, response hand and gender). The PCA factor loadings indicate that the factor P315 captures the early portion of the P3 potential, whereas factor P400 primarily reflects activity after the P3 peak. Note in Figure 1B that the early P3 amplitude was smaller in patients having a depressive disorder alone than in patients having an anxiety disorder alone. A main effect of Group in the ANOVA for factor P315 indicated that the early P3 subcomponent differentiated the groups, independently of task ($F_{[3,139]} = 3.70$, $p = .01$). As can be seen in Figure 2, patients having an anxiety disorder alone had larger P315 when compared to the comorbid ($F_{[1,139]} = 9.43$, $p < .01$), depression alone ($F_{[1,139]} = 7.08$, $p < .01$), and control ($F_{[1,139]} = 3.25$, p = .07) groups. Patients having comorbidity of depression and anxiety tended to have smaller P315 than controls ($F_{[1,139]} = 3.56$, $p = .06$). This was not evident for late P3 amplitude and, in fact, patients having comorbidity of depression and anxiety had a larger P400 subcomponent than the other groups (see Figure 2), which was reflected in a main effect of Group in the ANOVA for factor P400 (F[3, 139] = 3.37, $p < .05$). The comorbid group had a larger P400 when compared to anxiety alone ($F_{[1,139]} = 7.51$, $p < .01$), depression alone ($F_{[1,139]} = 8.85$, $p < .01$), and control ($F_{[1,139]} = 4.69$, $p < .05$) groups, while the other group contrasts were not significant. The topography of the P400 subcomponent had the parietal maximum typically seen for the P3b component, whereas the P315 subcomponent had a more frontocentral orientation.

Consistent with previous evidence showing that the N2-P3 complex accurately reflects the phonemic categorization of speech stimuli,[12,24] there were task-dependent hemispheric asymmetries for N2 and P3. As in our prior studies,[12,18] an overall N2-P3 index was computed by subtracting factor scores for N215 from the sum of the factor scores for the P3 subcomponents (P315 + P400). Figure 3 shows the N2-P3 topographic maps for tonal and phonetic target stimuli, and for the corresponding tonal-minus-phonetic differences. A Task by Hemisphere interaction in an ANOVA of N2-P3 scores confirmed the existence of

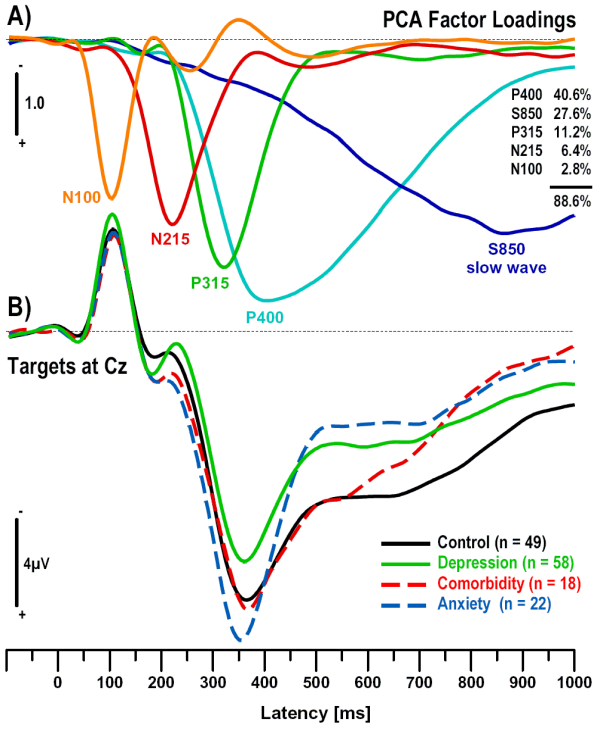

Figure 1. (A) Factor loading waveforms of the first five PCA factors extracted and percentage of variance explained after Varimax rotation. Factor labels reflect both the time course of factor loadings and polarity of the associated ERP component. (B) Grand average ERP waveforms to target stimuli at vertex (Cz) for patients having a depressive disorder alone, an anxiety disorder alone, or comorbidity of both disorders, and control subjects (averaged over task, response hand and gender).

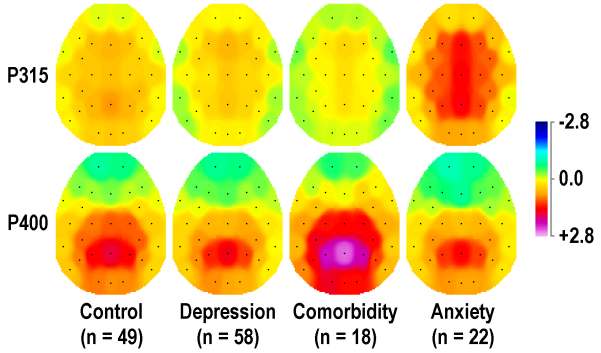

Figure 2. Topographies of PCA factor scores at 30 electrode sites (top view, nose upwards) corresponding to early P3 (Factor P315) and late P3 (Factor P400) for the patient and control groups (target stimuli only, averaged over task, response hand, and gender).

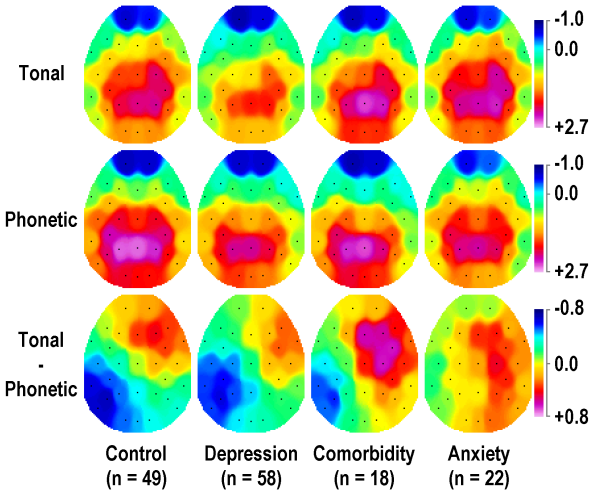

Figure 3. Topographies of N2-P3 amplitude (differences in PCA factor scores, i.e., P315 + P400 - N215) for the patient and control groups (averaged over gender and response hand). Maps were computed for tonal and phonetic target stimuli and for tonal-minus-phonetic differences.

task-dependent hemispheric asymmetries ($F_{[1,139]}$ = 34.10, p < .001). This reflects the relatively greater N2-P3 amplitude over right than left frontotemporal sites for the tonal task, whereas N2-P3 amplitude was greater over left than right temporoparietal sites for the phonetic task. Although each group showed a significant Task by Hemisphere interaction, the effect was strongest in patients having depression alone ($F_{[1,139]}$ = 41.77, p < .001) and weakest in patients having an anxiety disorder alone ($F_{[1,139]}$ = 5.37, p < .05). The Task by Hemisphere interaction was intermediate for the comorbid ($F_{[1,139]}$ = 18.94, p < .001) and control ($F_{[1,139]}$ = 19.60, p < .001) groups. As can be seen from the blue regions in the bottom portion of Figure 3, the left-greater-than-right asymmetry of N2-P3 for phonetic as opposed to tonal stimuli was most prominent over temporoparietal sites. This task-related asymmetry was largest for the depression alone group and smallest for the anxiety alone group.

DISCUSSION

There were clear task-dependent hemispheric asymmetries of N2-P3 across groups, which replicates prior findings for healthy adults.[12] The left-greater-than-right asymmetry of N2-P3 over temporoparietal sites in a phonetic oddball task was greatest in patients having a depressive disorder alone and smallest in patients having an anxiety disorder alone. This is consistent with dichotic listening findings, where patients having a "pure" depressive disorder had a larger left hemisphere advantage for perceiving words or syllables when compared to patients having an anxiety disorder alone or comorbid anxiety and depressive disorders.[3,25] The small left-lateralized N2-P3 in a phonetic task for patients having an anxiety disorder alone also agrees with reports of left hemisphere hypofunction in patients having anxiety disorders,[5,26] and decreased metabolism or cerebral blood flow in left temporoparietal cortex in patients having panic disorders.[27,28] These results provide further evidence of the dramatic difference in hemispheric asymmetry of function between depressive and anxiety disorders.

There were also differences in P3 subcomponents between patients having depressive and anxiety disorders. The early P3 subcomponent (P315) was larger in patients having an anxiety disorder alone when compared to depressed patients with or without an anxiety disorder and

healthy controls. The timing and frontocentral orientation of the early P3 subcomponent resembles that typically seen for P3a or novelty P3.[13-16] Turetsky and Fein[17] found that the α_2- noradrenergic antagonist yohimbine resulted in higher tension ratings and increased P3a amplitude, whereas the agonist clonidine decreased P3a amplitude. This suggests a possible explanation of the greater early P3 in patients having an anxiety disorder alone. The somatic arousal in anxiety disorders may be associated with an increase in orienting or alerting responses to "oddball" stimuli, which is reflected in enhanced amplitude of the frontal P3a subcomponent. Depressed patients did not, however, differ significantly from healthy controls in early P3, although those with a comorbid anxiety disorder did tend to have smaller amplitude.

In contrast, patients having comorbidity of depressive and anxiety disorders had a *larger* amplitude of the late, parietal maximum P3 subcomponent when compared to patients having either disorder alone or healthy controls. One interpretation of the enhanced late P3 amplitude in the patients having comorbid depressive and anxiety disorders is that it represents an increase in cognitive effort to compensate for a deficit in earlier processing reflected by their smaller early P3 subcomponent. There was no significant difference in the late P3 between patients having a depressive disorder alone and healthy controls. In this study, therefore, there was no evidence that depressed patients have reduced P3b amplitude. The demands of the tonal and phonetic oddball tasks may not be challenging enough to reveal the subtle cognitive deficits in depressive disorders.[29]

In conclusion, depressive and anxiety disorders differed in the amplitude of P3 subcomponents and in task-related hemispheric asymmetries of the N2-P3 complex. Patients having an anxiety disorder alone had greater early P3 amplitude and those having comorbidity of depressive and anxiety disorders had greater late P3 amplitude. Moreover, the markedly greater N2-P3 complex over left temporoparietal regions in depressed patients during phonetic processing was less evident in patients having an anxiety disorder, which agrees with behavioral evidence of different lateralized cognitive function in these disorders. The findings underscore the importance of taking comorbidity into account in studies of cognitive ERPs in depressed patients.

ACKNOWLEDGEMENTS

This research was supported by a National Institutes of Health Grant MH36295. We thank Dr. Deborah Deliyannides and members of the Depression Evaluation Service and the Anxiety Disorders Clinic, where diagnostic evaluations of patients were conducted; and Barbara Stuart for assistance with data collection. Software developed by Charles L. Brown to display ERP waveforms is gratefully acknowledged.

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