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## CHAPTER FORTY-NINE

# The P300 Component of the Event-Related Brain Potential in Psychiatric Patients

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### INTRODUCTION

In the last two decades we have witnessed a significant increase in information dealing with the neuroanatomy, neurochemistry, and neurophysiology of the human brain. Much of our current knowledge concerning the electrical transactions of the human brain is derived from evoked brain potential studies.

Since the fundamental evoked potential observations by Dawson (1), scientific energies have been devoted in large measure toward a better understanding of the sensory evoked potentials (2-4). Study of the P300 of the event-related potential (ERP) did not begin until the seminal observation by Sutton et al. (5). Since that time, however, this endogenous late positive component has been the subject of intensive investigations which have resulted in an extensive literature. Interest in the P300 component is best illustrated by the number of recent books that have devoted a great deal of attention to this endogenous electrical phenomenon (6-12). The P300 or P3 component of the event-related potential occurs approximately between 300 to 500 msec after stimulus presentation and is positive in polarity. This particular component is often associated with a slower, long-lasting, positive slow wave (SW) originally observed by Squires et al. (13). The amplitude of the P300 is usually maximal at the midline parietal electrode (Pz) (14).

In recent years much research has been devoted to gaining a better understanding of the functional significance of the P300 component of the ERP. This research has been summarized in several reviews (15-18). The aforementioned reviews indicate that P300 amplitude may be related to stimulus probability, task relevance, subjective expectancy, equivocation, and context updating. Recently, some investigators have proposed that P300 may index the salience or subjective value or importance of the stimulus to the subject (19-21). A satisfactory monolithic or unified explanation of the functional significance of P300 is presently not available, despite numerous attempts to elucidate the variables that affect the P300 characteristics. However, it should be noted that such attempts may be extremely difficult in light of the recent evidence that suggests that the scalp-recorded P300 may be an amalgam of various processes (13, 22-24). These data suggest that the P300 component may not be a unitary process, but may in fact represent various components generated by multiple sources with different functional roles.

The latency of P300 provides a good measure of processing time which appears to be independent of the time required for response selection and execution. A number of investigators have suggested that P300 latency may index stimulus encoding uncontaminated by response processes (25-27).

The extensive evidence concerning the cognitive antecedents of the P300 component has resulted in much interest in the possible clinical

cal utility of this endogenous ERP component. It is assumed that since the P300 component has been of such utility in the study of normal cognitive processes, it should prove quite useful in the assessment of cognitive dysfunctions that characterize affective disorders, alcoholism, and schizophrenia.

Since the initial report of P300 deficits in schizophrenia by Roth and Cannon (28), numerous publications have appeared reporting P300 abnormalities in depression, alcoholism, (29) and schizophrenia (30, 31). Roth and Cannon (28) were the first to report a significantly reduced P300 component in schizophrenic patients. A number of investigators have replicated the original observations by Roth and Cannon (28) or obtained similar results (32–35).

In general, the experimental P300 paradigms used to examine schizophrenics have included passive procedures or have utilized target-selection paradigms in which infrequent target stimuli had to be identified by either counting or pressing a button. More recently Brecher and Begleiter (35) investigated the possibility that the decreased P300 amplitude observed in schizophrenic patients was due to the low motivational value of stimuli and tasks in many paradigms. They varied the incentive value (money) of equiprobable, task-relevant stimuli and once again observed a significantly lower P300 amplitude to high incentive stimuli in schizophrenic patients as compared to normal control subjects.

While the reduction in P300 amplitude observed in schizophrenics can be considered a valid and reliable phenomenon, the findings concerning P300 latency in schizophrenics are rather unclear. The initial P300 studies in schizophrenic patients found no significant difference in P300 latency between schizophrenics and controls (28, 32, 33, 36, 37). It should be noted that two recent studies of P300 in schizophrenia have observed a significantly increased P300 latency in schizophrenic patients compared to normal controls (31, 38). At present, while the data on P300 latency in schizophrenia appear inconsistent, the findings on P300 amplitude are quite consistent. Indeed, the reduction in P300 amplitude in schizophrenic patients is not only a consistent finding, but may very well be the most robust

and replicable finding in the literature on biological deficits in schizophrenia.

To date, investigations dealing with P300 amplitude in the study of depression have yielded rather inconsistent results. Some studies have found a significantly decreased P300 amplitude in depressed patients compared to normal control subjects (31, 34, 37) while others have reported negative results (32, 39). The data pertaining to P300 amplitude in depression are currently inconsistent and therefore inconclusive. Investigations of P300 latency in depression have consistently demonstrated the lack of P300 latency differences between depressed patients and normal controls (37).

In recent years a number of investigations have been undertaken to study the P300 component of the ERP in abstinent alcoholics (40). Several studies have reported a significantly reduced P300 component in abstinent alcoholics compared to normal control subjects (41–45). While the aforementioned studies report a consistent decrease in the P300 component in abstinent alcoholics, it should be noted that Pfefferbaum et al. (46) did not find a significantly reduced P300 component, but instead observed a significantly increased P300 latency in alcoholic patients. At present, these seemingly inconsistent P300 findings in abstinent alcoholics can perhaps be accounted for by clinical differences in patient populations. The majority (75%) of patients tested by Porjesz and Begleiter (45) manifested neuropsychological and structural (CT scan) deficits. It should be noted that only 10% of the patients tested by Pfefferbaum et al. (46) manifested neuropsychological deficits. In addition to the decreased P300 amplitude reported by Porjesz and Begleiter (45), these alcoholic patients show brainstem deficits manifested by auditory brainstem potential interpeak latency delays (47). The brainstem deficits reported by Begleiter et al. (47) are in keeping with findings from other laboratories (48, 49). The differences in P300 findings between the Porjesz and Begleiter (45) studies and the investigations by Pfefferbaum et al. (46) may be due to the severity in organicity and cognitive deficits found in the various patient populations.

This rather cursory review of the literature on abnormalities of P300 amplitude and latency in alcoholism, depression, and schizo-

phrenia not only indicates the presence of inconsistencies in results but, most importantly, points to the fact that P300 has as yet not achieved diagnostic utility. The lack of clinical utility for the late positive complex in specified psychiatric disorders such as alcoholism, depression, and schizophrenia is in apparent contrast with the clinical use of early sensory evoked potentials in neurology.

The present volume can attest to the fact that the early components of the auditory, visual, and somatosensory evoked potentials have been of clinical utility in the assessment of the neurological patient. It may be worthwhile to compare the clinical utility of the early evoked potentials (i.e., auditory brainstem potentials) with those of the late positive complex of the ERP. This comparison may shed light on the difficulties in using the P300 component in the diagnostic assessment of psychiatric patients.

## COMPARISON

### Methods and Procedures

#### BRAINSTEM POTENTIALS

The experimental methods and procedures for recording the auditory brainstem evoked potentials are relatively homogeneous across laboratories. The homogeneity in recording procedures not only allows comparisons of data across laboratories but, most importantly, permits fundamental clinical comparisons of data collected in various disease entities.

#### P300

The experimental paradigms and methods for obtaining the P300 component typically differ from laboratory to laboratory and a standardized paradigm has not been adopted by ERP investigators. Moreover, different P300 paradigms are characteristically used to assess different psychiatric disorders. This experimental heterogeneity in P300 procedures has contributed to the lack of clinical utility.

### Task and Subject Variables

#### BRAINSTEM POTENTIALS

The auditory brainstem potentials do not appear to be related to task variables and are not sensitive to psychological states manifested by the subject (50). This lack of sensitivity to psychological variables may be of benefit in assessing the integrity of the auditory pathway in

subjects manifesting various psychological states.

#### P300

The P300 component of the ERP is quite sensitive to task variables and to motivational factors. This sensitivity provides the investigator with the ability to study complex cognitive processes. P300 abnormalities in psychiatric patients cannot be assumed to reflect deficits in simple cognitive processes but may reflect lack of task involvement, different cognitive strategies, and, most importantly, aberrant motivational factors. It should be noted that in general, psychiatric patients do not perform the simple behavioral tasks that accompany ERP studies as well as normal control subjects. This difference indicates that while patients and controls may be subjected to the same experimental conditions, the subjective level of task difficulty and the cognitive strategies may be significantly different between the two groups of subjects. The nonspecificity of ERP findings in psychiatric patients may reflect the motivational deficits that typically characterize psychiatric patients.

### Neural Generators

#### BRAINSTEM POTENTIALS

The neural generators of the auditory brainstem potentials (BSPs) are not well understood. However, the BSPs are known to reflect the specific transformation of auditory stimuli along a specified neuroanatomical pathway. The use of auditory brainstem evoked potentials allows the diagnostician to assess the integrity of the peripheral end organ and to study conduction velocity along the brainstem pontine formation. This rudimentary knowledge of generator sources for the auditory brainstem evoked potential lends some support to the inferences concerning brainstem pathophysiology in individuals with abnormal BSPs.

#### P300

At present, the neural generators of the P300 component of the ERP are poorly understood. This late positive complex is quite likely to have multiple generators with overlapping components. Recent data indicate that the P300 may be generated in subcortical areas (51) while other investigators have suggested that the P300

component may in part be generated in the hippocampus (52, 53).

The lack of neuroanatomical specificity and paucity of knowledge about source generators are presently not conducive to the elucidation of pathophysiology in subjects with P300 abnormalities.

### Patient Population

#### BRAINSTEM POTENTIALS

At present, auditory brainstem potentials can be quite useful in determining the pattern and severity of abnormalities in an individual case. The clinical utility of this neurophysiological technique is the result of various factors. The fundamental normative data base established with this technique has enabled the clinician to ascertain in individual cases the departure from established norms.

In large measure, the clinical utility of auditory brainstem potentials is the result of numerous clinical studies dealing with relatively homogeneous groups of neurological patients with a well-defined and reliable diagnosis. The fundamental relationship between auditory brainstem potential abnormalities and clinical assessment in homogeneous patient populations with valid and reliable diagnoses has made this technique clinically useful.

While the auditory brainstem potentials are of some utility in disease entities with reliable diagnoses, it should be noted that they provide us with limited information concerning etiological factors. Moreover, the functional consequences of various auditory brainstem abnormalities are poorly understood.

#### P300

Various aforementioned reasons have been offered to explain the present lack of clinical utility for the P300 component of the ERP. Probably one of the most compelling reasons for the lack of clinical utility of P300 in psychiatric patients is the fact that, at present, clinical homogeneity cannot be obtained within a specific psychiatric diagnosis. In recent years the reliability of psychiatric diagnoses has begun to reach satisfactory levels (54, 55). However, the lack of patient homogeneity within a specific diagnostic entity (i.e., schizophrenia) makes it difficult to determine whether one or

more diseases are included in this particular diagnosis.

If the diagnosis of schizophrenia could be used to identify a homogeneous group of patients with a specific, well-delineated syndrome, it would be appropriate to use P300 to identify specific neurophysiological correlates of schizophrenia. The presence of excessive heterogeneity within a psychiatric diagnosis renders the assessment of P300 correlates among such patients a most difficult endeavor. Indeed, there may be as many types and degrees of P300 deficits as there are different diseases within the diagnosis of schizophrenia. The search for a potential P300 correlate of a psychiatric disorder may be vitiated by the severe clinical heterogeneity among patients within a specific psychiatric diagnosis and the possible extensive overlap across different psychiatric disorders.

The problem of heterogeneity in psychiatric patients is severely compounded by the fact that most psychiatric patients (i.e., schizophrenics, depressives) are taking medication and in many instances have been chronically medicated for several years. The problems of different medications, dose regimens, and medication history is further complicated by patients who respond differentially to medications.

Indeed some psychiatric patients are known to respond paradoxically to the same drug used to treat other patients. While investigators make genuine efforts to test schizophrenic patients off drugs for periods of 2 to 8 weeks, the effects of chronic intake of neuroleptics on the CNS is likely to be substantial. The interaction between patient heterogeneity and drug effects do not permit the clinical neuroscientist to differentiate clearly P300 effects owing to medication versus those directly related to the illness.

It is important to note that most major psychiatric disorders are characterized by a cluster of symptoms that are known to wax and wane over time. Indeed, schizophrenic patients may experience acute psychotic episodes with florid symptomatology, periods when chronic symptoms are well known to emerge and manifest themselves, and periods of spontaneous remission. The ability of the neuroscientist to search

for P300 indices of schizophrenia is further impeded by qualitative and quantitative changes that are known to occur in the course of a schizophrenic illness. The difficult differentiation between P300 correlates of trait versus state imposes additional limitations on the clinical utility of the P300 component of the ERP.

## DISCUSSION

To date, the clinical utility of the late positive complex of the ERP has not equalled the widespread clinical utility of the brainstem potential. Nevertheless, the potential future utility of the late positive complex in psychiatric disorders must be viewed with optimism. Most investigators dealing with psychiatric disorders have utilized the P300 component of the ERP in the hope that this component could be used to classify psychiatric patients. At present, this approach is premature and therefore has obviously not yielded satisfactory results.

While the P300 deficits observed in schizophrenics or alcoholics do not currently appear to be disease specific, these late potentials may be used to improve our present understanding of psychiatric diseases. Our knowledge concerning the P300 manifestations of cognitive processes may be utilized to test specific hypotheses about cognitive dysfunction in psychiatric patients (56). The late positive complex appears ideally suited to assess various cognitive deficits. It should be noted that various cognitive deficits may not be endemic to a specific psychiatric condition, but may in fact be general and found across various psychiatric disorders.

If we consider our present state of knowledge about neurocognitive dysfunctions in psychiatric patients, it does not behoove us to focus solely on one particular component (i.e., P300) at the exclusion of all others. Indeed, the simultaneous assessment of various neurocognitive systems in psychiatric patients may allow the clinical neuroscientist to establish specific clusters of ERP deficits. Our present technical capabilities would allow the study of various ERP components (i.e., N1, Nd, NA, N2a, N2b, P3a, P3b, SW, N4, and so forth). While the underlying neurophysiological mechanisms of these ERP components remain to be elucidated,

these components are being extensively studied in healthy subjects and can be predictably manipulated with specific task variables. A large body of literature documenting the specific sensitivities of each of these components is expanding rapidly. These fundamental and systematic studies provide a critical background of normative data for each component with which psychiatric patients can be studied and eventually evaluated.

In light of the existence of many "cognitive" ERP components, the use of one such component to assess brain dysfunction in psychiatric patients may represent a formidable statistical sampling problem. The present lack of knowledge about pathophysiological mechanisms in psychiatric patients necessitates the creative development of productive challenges to numerous brain systems to obtain a better profile of dysfunction. This comprehensive approach would combine the use of sensory and cognitive evoked potentials to elucidate and characterize neurocognitive deficits in psychiatric patients. This comprehensive approach dictates the inclusion of both task-sensitive and task-insensitive evoked potentials. Moreover, this clinical neurocognitive approach would allow the investigator to examine the relationship between various aspects of different event-related potentials and the possibility of establishing clusters of deficits. This cluster or profile of electrophysiological deficits could be either related to individual symptoms (57, 55) or, as has been proposed, could be used as a novel neurophysiological diagnostic taxonomy (58).

## SUMMARY AND CONCLUSION

To date, the use of late event-related potentials to diagnose psychiatric patients has not been successful. A number of methodological, clinical, and experimental difficulties have severely restricted the clinical utility of the ERP. The late positive complex of the ERP may be used to test hypotheses about specific cognitive dysfunctions in well-diagnosed homogeneous sets of psychiatric patients (59). Our knowledge about brain dysfunction in psychiatric patients may be increased if we were to study the relationship between the late positive complex and other ERP components. This approach may include the use of sensory and cognitive event-related potentials and may lead to the devel-

opment of a new taxonomy based entirely on electrophysiological profiles. These newly derived profiles might be used as independent variables with the accompanying clinical descriptions as dependent variables. The clinical use of event-related potentials in the assessment of psychiatric disorders is most likely to succeed if a change in current experimental strategies comes about in the near future.

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