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## Clinical utility of long latency 'cognitive' event-related potentials (P3): the pros

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The clinical utility of some electrophysiologic studies such as long latency 'cognitive' event-related potentials (ERPs) remains controversial. A number of authors have studied this question but no consensus of opinion had emerged. Most clinical studies on the ERP have been on the P3 or P300 component and my remarks will therefore be confined to a discussion of this component and its clinical role. P3 is an electropositive wave that occurs approximately 300 msec after an infrequently occurring stimulus to which the subject is attending. It has been linked experimentally to such variables as expectancy, task difficulty and memory. Because of this apparent relationship to 'cognitive' functions, it has been used to evaluate demented patients in order to distinguish 'true' dementia from the pseudodementia that can occur in depression or other psychiatric disorders.

Most authors agree that if the P3 response permitted this distinction to be made, the test would be of clinical value. Thus, the controversy that exists relates principally to the reliability of the test in making this distinction.

There are many reasons for the differences of opinion regarding the clinical utility of P3, including confusion about what constitutes clinical utility. An instructive example is to compare two

studies that were comparable in size, scope, and methodology. The studies of Squires et al. (1980) and Gordon et al. (1986) both found an abnormally prolonged P3 latency in a high percentage of demented patients (74% and 80%) but in only a small percentage of psychiatric patients (3% and 12%). Comparing these two studies statistically reveals no significant difference between the findings and these two studies would seem to be good replications of each other. Despite this, however, the conclusions reached were quite different. Squires et al. (1980) concluded that 'the P3 latency can provide a sensitive, perhaps specific, measure for differentiating organic dementia from functional disorders such as depression and schizophrenia.' Gordon et al. (1986) concluded that their results did not indicate that a 'delay in latency is specific for dementia' because a similar delay was encountered in 12% of non-demented psychiatric patients. However, even accepting the figures of this latter study (Gordon et al. 1986), the test remains useful in a clinical setting. Thus, in a patient with a 50% chance of being demented on clinical grounds, the finding of an abnormal P3 latency would increase the likelihood of true dementia to 90%.

Ideally a test that is applied in a clinical setting should be 100% sensitive and 100% specific. Rarely, however, do tests ever approach this ideal, even though they are useful in clinical practice. For example, an abnormal BAEP is a non-specific indicator of a functional disturbance in the auditory pathways and is produced by a variety of

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TABLE I

P3 latency in dementia and psychiatric disease.

Author	Percent abnormality <sup>a</sup>		
	Demented patients <sup>b</sup>	Psychiatric patients <sup>c,d</sup>	Non-demented patients <sup>d</sup>
Squires et al. (1980)	74% (58)	3% (33)	4% (51)
Brown et al. (1982)	61% (18)	0% (7)	
Syndulko et al. (1982)	83% (12)		
Pfefferbaum et al. (1984)	30% (37)	19% (54)	
Leppler and Greenberg (1984)	73% (15)		0% (5)
Slaets and Fortgens (1984)	38% (8)		17% (6)
St. Clair et al. (1985)	7% (14)		
Gordon et al. (1986)	80% (19)	12% (32)	
Polich et al. (1986)	28% (39)		
Goodin and Aminoff (1986)	61% (36)		
Patterson et al. (1988)	13% (15)	0% (8)	
Neshige et al. (1988)	41% (27)		
Total	51% (298)	11% (134)	5% (62)

<sup>a</sup> Numbers in parentheses indicate number of patient studies in each category.

<sup>b</sup> P3 latency significantly prolonged relative to normal, except in the study of Slaets and Fortgens (1984).

<sup>c</sup> Generally includes a mixture of depression and other psychiatric disorders.

<sup>d</sup> P3 latency was not prolonged relative to normal in any of these studies.

conditions, but it is nevertheless a very sensitive indicator for the presence of a cerebellopontine (CP) angle tumor, with a false negative rate of generally less than 3% (Legatt et al. 1988). As such it can provide an excellent screening test for patients in whom a CP angle tumor is a diagnostic consideration despite its lack of specificity. Similarly, a test that is of low sensitivity but relatively high specificity may be clinically helpful. Thus the detection of epileptiform activity on the EEG of suspected epileptics (52% sensitive and 96% specific) is helpful diagnostically in the proper clinical context (Goodin and Aminoff 1984). In other circumstances a good test may be clinically unhelpful. For example, the finding of an abnormal VEP in a patient with optic neuritis provides no clinically useful information. Thus, the utility of a test depends upon the exact clinical question being asked and how well the test answers it, rather than upon an arbitrary definition of what constitutes acceptable levels of sensitivity or specificity.

With regard to the P3 in the distinction of dementia from pseudodementia, there is remarkable agreement between laboratories that the

latency of P3 is delayed in demented patients compared both to normal controls and to patients with depression or other psychiatric conditions (Table I). No study has shown a significant shift in the latency of P3 in this latter group of patients. There has been some variability, however, in the false positive and false negative rates reported in different studies. The false positive rate for patients with psychiatric disease is often low, but in two studies it was over 10% and in one study it was 19% (Table I). The most conspicuous discrepancy, however, concerns the sensitivity of the test. A sensitivity of greater than 60% is reported in many studies whereas in others it is considerably less (Table I). It is possible that some of the observed differences relate to differences in the method of eliciting the P3 response. For example, Pfefferbaum et al. (1984) used a complex task and observed almost 3 times the variability of P3 latency in normal subjects as that observed by others (Goodin 1986). Such an increase in normal variability will markedly increase tolerance limits and may obscure any clinically useful P3 change. This cannot, however, be the only explanation because other authors have reported a low sensi-

tivity even with low P3 variability (e.g., Polich et al. 1986). It is also possible that discrepancies in the sensitivity of the P3 test relate to variability in the severity of dementia among the patients studied. Thus patients with milder disease would be expected to have a less conspicuous change in the P3 response.

Another problem which arises in assessing the clinical usefulness of P3 is the fact that some patients do not generate a recognizable or reproducible response. Unlike other clinical evoked potential tests where such a finding is considered abnormal, this finding for the P3 response must be interpreted cautiously. Inattention to some or all of the stimuli can, even in normal subjects, result in either a small or absent P3 response (Goodin 1986). A high rate of absent or non-reproducible P3 responses – i.e., a high failure rate – will detract from its clinical utility and this rate differs widely between investigators. Most authors report a failure rate of 5% or less (Goodin et al. 1978; Squires et al. 1980; Sydulko et al. 1982; Pfefferbaum et al. 1984; St. Clair et al. 1985; Gordon et al. 1986; Polich et al. 1986; Neshige et al. 1988; Patterson et al. 1988), whereas some report a rate of 80% or more (Slaets and Fortgens 1984). The reasons for such a discrepancy are unclear.

The potential clinical use of the P3 is not, however, confined to the distinction of dementia from pseudodementia. It may have a role in following the clinical course of a dementing disorder, monitoring response to treatment or identifying patients who are at particular risk of developing dementia (Goodin et al. 1983, 1990). In this latter circumstance we have just reported our findings in patients infected with human immunodeficiency virus (HIV), where non-demented asymptomatic patients had a significant prolongation of the P3 latency. If these findings are confirmed and if they predict which patients subsequently develop overt HIV encephalopathy, then the recording of these ERPs may have an important role in determining prognosis or identifying those patients in need of more aggressive management.

In summary, it is encouraging that a significant prolongation of P3 latency has been so consistently present in dementia and so consistently absent in depression and other psychiatric dis-

orders. The sensitivity and specificity of the test in the more favorable reports or even in the average experience (Table I) would make it a useful test in some clinical settings although, as with any test, there are many circumstances in which it would be unhelpful. It is thus important for clinicians who order this test to be sure that the clinical context is appropriate. Before the ultimate clinical utility is known, however, there will need to be a large systematic study to determine the reason for the wide intercenter variability in reported sensitivity for the test. Perhaps it is important to use the simplest possible paradigm to elicit the response or perhaps the test is only sensitive in moderately advanced disease. In either case, however, it is doubtful that further studies using small numbers of subjects will shed much light on the controversy.

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