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Cognitive Brain Potentials and their Application

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Computerised averaging methods have made it possible to extract and identify the electrical activity accompanying specific activities of the brain, including certain psychological processes, from the random background signals in electroencephalography (EEG). Event-related potentials (ERPs) and the way these change under various recording conditions are a powerful, non-invasive and relatively simple means of relating psychopathology to underlying physiology, and by comparing ERPs with imaging data it should be possible to compare electrical activity with changes in brain structure and blood flow in different disease states.

As the name suggests, event-related potentials are very small voltages generated in brain structures in response to specific events or stimuli. These tiny time-locked potentials are selected from the ongoing EEG activity by averaging epochs of EEG following repeated sensory stimuli such as a series of clicks or flashes of light.

It takes about 20 ms for information to reach the cortex from a peripheral sense organ, so early ERPs generated within this time mainly reflect neuronal activity in the sensory organ itself and in the afferent pathways of the brain-stem. For example, during the first 10 ms following a click, ERPs recorded from the scalp include five peaks representing neuronal activity in the acoustic nerve, cochlea nucleus, superior olive, lateral lemniscus and inferior colliculus (Jewett & Williston, 1971). Similar series of early event-related potentials are generated in the optic pathways following a flash of light and in the spinal cord and sensory afferent pathways of the brain-stem following a somatosensory stimulus. These early responses are termed 'exogenous' because they are generated regardless of what the subject is thinking, and they are quite independent of any response the subject may subsequently make to the stimulus. They are extremely useful clinically for detecting disorders of sensory end organs and the brain-stem, and are routinely used in audiology clinics and in the assessment of brain injury and coma (Halliday, 1982; Chiappa, 1983).

In contrast to these exogenous potentials, ERPs generated after about 70 ms often reflect the manner in which a stimulus is evaluated by the subject. These later components are termed 'cognitive' or 'endogenous' ERPs because their amplitude and latency may depend on the motivation of the subject and the cognitive, affective or motor response to that particular stimulus. One of the first observations of an endogenous potential was by Grey *et al* (1964), who described the contingent negative variation (CNV) or expectancy wave elicited during a test in which the subject heard a warning click followed three seconds later by a light flash and a button-press response to this. Immediately after the warning click a negative potential could be recorded from scalp electrodes and this CNV steadily increased in amplitude between the two signals, then resolved once the response (button press) had been performed. The CNV, which is now believed to incorporate more than one component, seems to reflect neuronal activity connected with the appreciation of the significance of the incoming signal and the preparation by the subject of a goal-directed act.

At about the same time Sutton *et al* (1965) described another late endogenous response, the P300, generated during the performance of a task which required the resolution of uncertainty. During this 'odd-ball' task, the subject is exposed to two different stimuli (e.g. a high-pitched and a low-pitched tone), one of which occurs relatively infrequently and is designated as a 'target'. When the subject's attention is directed to the target by counting or pressing a button, a positive potential is generated some 300 ms after this signal. This P300 response occurs with auditory, visual and somatosensory stimuli, and like the CNV it is relatively independent of the physical characteristics of the stimulus itself. A P300 response can be generated in the absence of a stimulus when there is a gap in an otherwise continuous series of sounds or flashes of light, which is evidence that this ERP is a reflection of mental activity and not merely a response to the stimulus itself.

The very large literature on P300 (Regan, 1989) has addressed but not yet resolved the question of which cognitive processes contribute to the generation of the P300 wave form. The latency of P300 increases with the difficulty of the task required of the subject (e.g. having to distinguish three tones rather than two tones will increase the latency). The amplitude of P300 increases with the unexpectedness of the target tone (Hillyard & Picton, 1987). The P300 is thought to be a complex mixture of at least three wave forms

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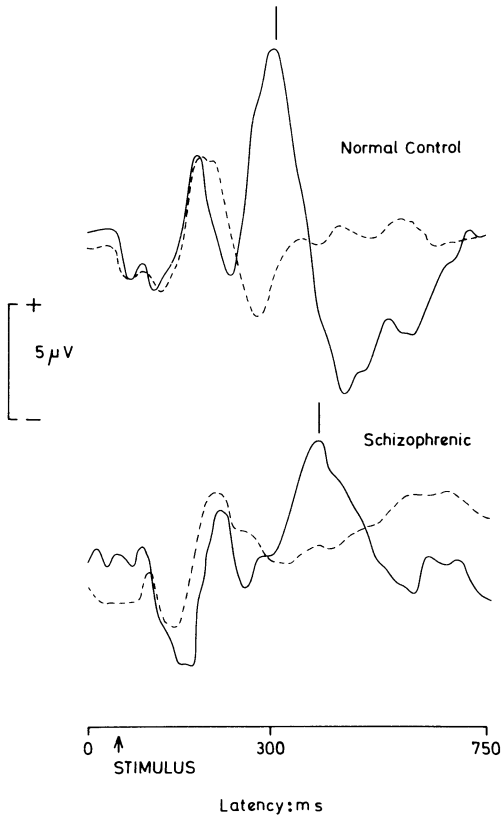


FIG. 1 The upper trace illustrates a P300 response recorded from a normal control subject during the performance of an 'odd-ball' test. The subject was asked to count infrequent high-pitched tones (1500 Hz) randomly embedded in a series of low-pitched tones (1000 Hz). The averaged EEG response recorded from the vertex over 750 ms is shown by the dotted line and includes a negative deflection at around 100 ms (N1) and a positive wave at about 200 ms (P2). The continuous line is the averaged response to the high-pitched 'target' tones and includes a large positive potential at 300 ms (P300) preceded by a negative deflection (N2). The lower trace recorded from a drug-free schizophrenic subject illustrates reduced amplitude and delayed latency of P300, such as is frequently found in schizophrenia and in several forms of dementia.

and these, together with the N1, P2 and N2 waves which precede it (see Fig. 1), probably reflect various aspects of information processing required for the recognition, retrieval from memory and judgements about the significance of a signal. Overall the P300 seems to reflect mental processes that allow us to anticipate significant events in our environment and to react to unexpected changes. Recognising a familiar face in a crowd or being alerted by a slight change in frequency or loudness of a previously regular sound (e.g. a ticking clock) are probably everyday examples of an 'odd-ball' response. It was therefore an obvious step to record these late endogenous ERPs, including the P300, in psychiatric patients with conditions such as dementia, depression and schizophrenia, which are associated with disordered attention, since ERPs might contribute to diagnosis and provide a method for monitoring cognitive change in response to specific treatments. Figure 1 illustrates the P300 response in a control subject and a schizophrenic.

ERPs in dementia

Goodin *et al* (1978) were the first to investigate P300 as a measure of cognitive function in dementia. Twenty-seven demented patients (9 with pre-senile dementia and 18 with a wide variety of diagnoses including metabolic encephalopathies) were compared with non-demented neurological and psychiatric patients and a third group of normal controls. Dementia, even in this mixed group of diagnoses, was associated with reduced amplitude and increased latency of P300 using an auditory odd-ball paradigm. Many studies have confirmed these initial findings (Pfefferbaum *et al*, 1984; St Clair *et al*, 1985; Gordon *et al*, 1986; Neshige *et al*, 1988). Polich *et al* (1986), also studying a diagnostically mixed group of dementia patients (including Alzheimer's disease, alcohol dementia, vascular disease and other diagnoses), reported a direct association between P300 latency and the degree of cognitive impairment. However, there are weaknesses in studies of mixed groups of dementia patients since correlations between P300 latency and specific memory deficits may depend on diagnosis and are, for example, different in Alzheimer's compared with Korsakoff patients (Blackwood *et al*, 1987*a*).

Subtypes of dementia distinguished by P300

By recording P300 in carefully defined groups of demented patients some interesting results have emerged suggesting that P300 may show different patterns of change in different diseases. St Clair *et al* (1985) recorded auditory P300 from a group of patients meeting strict diagnostic criteria for Alzheimer's dementia, a group with alcoholic Korsakoff 's syndrome, and normal controls. The Alzheimer's patients had delayed latency and reduced amplitude of P300, but surprisingly the Korsakoff 's group as a whole did not differ significantly from controls, despite showing very severe memory disturbance.

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Goodin & Aminoff (1986) recorded auditory ERPs from 22 subjects meeting strict criteria for Alzheimer-type dementia, 13 patients with Huntington's disease, and 13 patients with dementia associated with Parkinson's disease. The results were compared with those from a normal control group, and the analysis included four potentials, the N1, P2, N2 and P300 wave forms recorded from the vertex. Not only did the three patient groups differ significantly from controls, but ERP latencies and amplitudes could distinguish between the three types of dementia. The ERP changes were judged to be secondary to the dementing process since asymptomatic but 'at-risk' members of Huntington's families and non-dementing Parkinson's patients had normal ERPs. In all demented groups the peaks of N2 and P300 occurred much later than in normal controls. The Huntington's and Parkinson's demented groups (classified by the authors as having 'subcortical' dementia) differed from the Alzheimer's group (classified as 'cortical' dementia) in showing a greater degree of N2 and P300 prolongation and by greater latency of the earlier N1 and P2 components. In Huntington's disease the changes in P2 were significantly greater than in Parkinson's disease. Hence all three diagnostic groups could be classified with reasonable accuracy on the basis of ERPs.

Changes in ERPs suggestive of both 'cortical' and 'subcortical' dementia have recently been reported in patients infected with HIV (Goodin *et al*, 1990). Changes were particularly marked in patients showing signs of dementia, but 28% of non-demented patients also had a longer latency period in at least one ERP component, leading the authors to propose that ERP may be useful in the early detection of AIDS dementia and for the selection of patients for specific drug treatments. Serial recording of ERP latencies could be used to follow the progress of the disease and to monitor the response to treatment.

The P300 response has also been shown to change with the onset of Alzheimer-type dementia when it occurs in subjects with Down's syndrome in middle age. In Down's syndrome the behavioural and cognitive changes of dementia are accompanied by increased P300 latency and reduced P300 amplitude, and these changes could be useful in the early detection of dementia and the measurement of its course (Blackwood *et al*, 1988; Muir *et al*, 1988).

The effect of pharmacological interventions on auditory P300 has been examined in both Parkinson's disease and Alzheimer's dementia. Parkinson's patients have a shorter P300 latency during their 'on-phase' as opposed to their 'off-phase' (Starkstein *et al*, 1989), supporting the notion that auditory P300 latency may reflect the activity of dopaminergic systems in the brain. In visual pathways also, Bodis-Wollner *et al* (1982) had demonstrated that delayed ERPs in Parkinson's disease could be modified by treatment with *l*-DOPA.

However, changes in other neurotransmitter systems may also affect the auditory P300. The destruction of ascending noradrenergic fibres by lesions of the locus ceruleus alters the scalp-recorded P300 in monkeys (Pineda *et al*, 1989), and P300 latency is increased following the administration of the muscarinic antagonist scopolamine to control subjects (Callaway, 1983). Surprisingly, in patients with Alzheimer's dementia an infusion of the cholinomimetic drug physostigmine had no effect in reducing the abnormally delayed P300 (Blackwood & Christie, 1986), suggesting that the pharmacology of P300 may vary in different disease states.

P300 in schizophrenia and depression

Pfefferbaum *et al* (1984) compared P300 in dementia, schizophrenia and depression. Patients with schizophrenia, like the dementia group, had an increased latency and a reduced amplitude of the auditory P300, while the depressed group did not differ from controls. Other studies have confirmed that P300 latency and amplitude could help to distinguish depression from dementia (Goodin *et al*, 1978; Gordon *et al*, 1986) and changes in P300 and other long-latency ERPs, especially those which reflect selective attention (Barrett *et al*, 1986), are now well established in schizophrenia. A reduction in P300 amplitude during auditory detection tasks has been reported in schizophrenia (Roth & Cannon, 1972; Shagass *et al*, 1977, 1978; Verleger & Cohen, 1978; Levit *et al*, 1973; Baribeau-Braun *et al*, 1983; Morstyn *et al*, 1983; Pfefferbaum *et al*, 1984; Blackwood *et al*, 1987*b*; Romani *et al*, 1987), in schizophrenic children (Erwin *et al*, 1986) and in relatives of schizophrenic subjects (Saitoh *et al*, 1984; Blackwood *et al*, 1990). A number of studies have also found that P300 latency is increased in schizophrenia (Pfefferbaum *et al*, 1984; Blackwood *et al*, 1987*b*; Romani *et al*, 1987; Ebmeier *et al*, 1989) although this has not always been found, possibly owing to variation in P300 recording techniques. In particular, the choice of low band-pass filter may affect P300 latency and an increase in P300 latency in schizophrenia has been reported only in studies where a band-pass frequency of 0.5 Hz or above has been employed (Ebmeier *et al*, 1989; Selzer & Asbury, 1990).

The abnormal P300 response in schizophrenia may be useful as a physiological marker which could help

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to define the clinical boundaries of the schizophrenia spectrum. P300 latency appears to be independent of the effects of medication and clinical state since there was no apparent change in the P300 first recorded from patients when acutely psychotic and drug free and then retested several months later when on medication and relatively free from psychotic symptoms (Blackwood *et al*, 1987*b*). P300 changes similar to those in schizophrenia have been found in subjects with borderline/schizotypal personality disorder (Blackwood *et al*, 1986; Kutcher *et al*, 1987) and in a study of large multiply affected schizophrenic pedigrees, abnormalities of P300 latency and amplitude were found in relatives of schizophrenic probands, including many relatives who were entirely free of symptoms (Blackwood *et al*, 1990). These results suggest that along with other measures such as abnormal eye-tracking responses (Holzman *et al*, 1974; Matthysse *et al*, 1986) P300 changes may be a useful vulnerability trait marker in schizophrenic families.

Another candidate vulnerability trait that appears to show consistent impairment in unmedicated and medicated schizophrenics is the P50 component of the auditory event-related response following the presentation of paired clicks. In normal subjects this scalp-recorded response some 50 ms after the stimulus is much reduced in amplitude following the second compared with the first click. Among schizophrenics little or no reduction occurs and this has been interpreted as an impaired ability to selectively filter incoming information (Adler *et al*, 1982; Freedman *et al*, 1983). A disorder of P50 habituation is also present among relatives of schizophrenic subjects. Siegel *et al* (1984) studied 14 first-degree relatives in nine families of schizophrenic probands and reported loss of P50 habituation in approximately half of the siblings and usually one parent of each proband. They suggest it may be a trait marker for schizophrenia which is also associated with other alterations in event-related potentials, including a reduced N100 and P200 amplitude (Freedman *et al*, 1987; Waldo *et al*, 1988).

It is clear that several components of event-related potentials are abnormal in schizophrenia. Another example is the auditory P200 component, the positive potential some 200 ms after a single stimulus, which is of lower amplitude in schizophrenics compared with controls (Jones & Callaway, 1970; Saletu *et al*, 1971; Roth & Cannon, 1972; Roth *et al*, 1980; Pfefferbaum *et al*, 1984; Shenton *et al*, 1989).

These ERP findings suggest that several aspects of information processing are disordered in schizophrenia, but it is not clear how these physiological changes relate to underlying pathology. Romani *et al* (1987) performed computerised tomography scans and recorded auditory P300 on 20 schizophrenic subjects. Although the schizophrenic group had enlarged ventricles and P300 responses differing in latency and amplitude from controls, there was no consistent association between P300 changes and ventricular size. McCarley *et al* (1989) reported that P300 amplitude reduction in schizophrenia was significantly correlated with enlargement of the left Sylvian fissure and with ratings for positive symptoms in schizophrenia.

Conclusions

Event-related potentials are easy to record using procedures which are well tolerated by quite disturbed patients. They are non-invasive and evidence to date would suggest that changes in components of endogenous ERPs may be useful in studying dementias and as biological markers for schizophrenia, providing a means for defining schizophrenia-spectrum disorders. It is a further possibility that studies using magnetic resonance imaging or measurements of cerebral blood flow will reveal the anatomical and neuropathological changes which give rise to the ERP amplitude and latency shifts, thus linking brain pathology with disorders of specific aspects of information processing.

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