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AVERAGED EVOKED POTENTIALS : EVENT RELATED POTENTIALS (ERPs) AND THEIR APPLICATIONS

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Abstract : Endogenous potentials are evoked responses that occur independent of the stimulus evoking them. They are related to different aspects of information processing. Two types of event related potentials (ERPs) are recorded, the P300 wave and contigent negative variation (CNV). The P300 wave is the most frequently studied factor in various clinical diseases and also for neurological research. Different tasks, paradigms can be used of which the oddball paradigm, consisting of target and non-target stimuli and their variations is most popular. The effect on P300 of physiological factors like age, IQ, pregnancy, exercise and others along with the clinical application in various neurophysiogical and psychiatric disorders are discussed. This review deals with various aspects of (ERPs), their methodology with a broad view of the scope and clinical horizon as regard their application in neurohysiological research.

Key words : Event related potentials (ERPs) physiological variations clinical applications

INTRODUCTION

Evoked potentials represent an obligate neuronal response to a given stimulus. The amplitude and latency depend on the physical characteristics of the eliciting stimulus. These are called exogenous or stimulus related potentials and are independent of the attention or interest shown by the subject being examined. The write up on short latency responses or stimulus related evoked response, incorporating auditory, somatosensory and visual evoked responses appeared earlier (1). The endogenous or event related potentials are another class of long latency potentials recorded in response to an external stimulus or an event, but is independent of the actual stimulus evoking it. It is similar in morphology and scalp distribution, irrespective of different signal modalities. However, they occur only when the subject is selectively attentive to the stimulus, and distinguishes one stimulus (the target) from a group of non-target stimuli. They depend on the setting in which the target stimulus occurs and are related to the storage of information processing i.e. sensory discrimination or response selection, before a person responds to a target stimuli (2).

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Since these represent aspects of cognitive function, they are called cognitive event related potentials.

The first description of cognitive event related potential was in the 1960's. Walter et al (3), described a slow negative shift in potential occurring between a warning and an imperative stimulus. This was termed contingent negative variation (CNV), whose maximum amplitude was just before the second stimulus. The response proved to be independent of the stimulus used. Sutton et al described another positive potential occurring after 300 msec (P3) and found that its amplitude correlated with the subject's certainty about the modality of the stimulus (4). Mismatch negativity (MMN) is a negative component of ERP peaking at 100–200 msec from stimulus onset, and occurs when any discriminable change occurs in a sequence of repetitive homogenous sounds. It occurs due to a change in frequency, intensity or duration of sound and does not depend on attention (5). The other event related responses include P165, P4, N400. Of all the responses the P300 wave is the most constant and frequently studied in both clinical and research fields. These varied cognitive events related potentials, have different categories of experiments used to evolve them. ERPs in selective attention experiment are thus different from those evoked by memory or language tasks (6).

Description of event related potential

The "oddball" paradigm : In this design of experiments the subject is presented with a sequence of two distinguishable stimuli, one of which occurs frequently (the frequent stimulus) and the other which occurs infrequently (the rare stimulus). The subject is required to count mentally or otherwise respond to one of the two stimuli. Cerebral responses to the rare and frequent stimuli are recorded and averaged separately.

Response to frequent stimulus : This consists of a series of waves, which relate to the sensory modality. For the auditory stimulus, the responses have been divided into an early latency (<10msec), mid latency (10–50 msec) and long latency (>50 msec) response. These reflect activity in the peripheral and brain stem region, the combination of muscle reflex activity and the neural activity in the thalamocortical radiations, the primary auditory cortex and association cortex. The neural generators of long latency responses are unknown. This consists of a large negative, positive complex, which can be elicited by auditory, visual and somato sensory stimuli and are independent of the subjects attention or level of arousal.

Response to infrequent stimulus

The averaged response to the target stimulus consists of an N1, N2 potential along with positive (P2, P3) complex (7). N1, P2 and N2 have maximum amplitude in the midline frontal and central regions of scalp, whereas P3 is largest in the centro parietal areas. P3 can be further divided into P3a, P270 that occurs earlier and has a frontal distribution and P3b, which is maximally in the parietal region. There is also a slow wave following P300, which is negative in the frontal region and reverses in polarity towards the parietal scalp. These appear as secondary peak, bumps, producing a delay

in the return to baseline. The positive waves are similar in position and topography in spite of diverging experimental conditions. It is related to several functional correlates like the amount of processing required in a decision (8), the decision itself (9), response difficulty (10), response selection (11), sustained attention to task performance (12), subject's preparation for next trial (13), the feedback response (14), assessment of the meaning of completed trial (13) or retrieval of information from working memory. More recently the positive slow wave is described as a non specific activity that signals completion of any synchronised operation following target detection (15).

Type of ERP's 1) P300 2) CNV

1) The P300 wave: The P300 wave is a positive wave and occurs after 300 msec. It is related to many aspects of human information processing. It is initiated about the time the stimulus information becomes discriminative (16). It also represents updating of memory once sensory information has been analysed (17), or the updating of expectancies, i.e. the P3 evoking stimuli are initially unexpected and later become expected (18). Various neural generators of P300 have been discussed (19) and several methods namely intracranial recording, functional magnetic resonance imaging, positron emission tomography and recently magnetic encephalography (MEG) have been employed to delineate the source of P300 (20). The P3 is influenced by changes in the ease with which the target can be distinguished from non-target by alteration in the ratio of target to non target stimuli or shift in the attention of the subject. The response can also provide additional information about the reaction time.

Many factors can influence the amplitude and latency of the wave. The triarchic model of P300 amplitude suggests that variables in the subjective probability and stimulus meaning dimensions have independent and additive contribution to the overall P300 amplitude (21). The amplitude is also related to task relevance of eliciting events (22). It thus increases when stimulus becomes more improbable and more informative (16). Increasing the difficulty of detecting the target, decreases the amplitude and increases the latency of P3 wave. The stimulus intensity contributes to both latency and amplitude in important ways (23). The latency depends on the duration of stimulus evaluation suggesting that it is the manifestation of activity occurring when one model of environment must be revisited (22). However, other studies have suggested that it may/may not reflect the time of memory scanning during a sternberg paradigm (24). It is believed that a single stimulus can be quite reliable in both active and passive response conditions (25), and there is no major difference in the P300 from one, two and three stimulus auditory paradigms (26).

Methodology

Stimulus characteristics: Any sensory modality can be used although in clinical practice an auditory stimulus is most commonly employed. The auditory stimuli have different pitch and are delivered binaurally with a relative long variable interstimulus interval > 1 sec. In our lab we use an alternating tone burst with a starting condensation phase of 10 msec rise fall time, 100 msec duration (plateau time), intensity 70 db and a rate of one every 2 sec as target stimuli. 80% of total 160 tones are frequent, 1KHz and 20% are rare, 2 KHz

stimuli. A random sequence of stimuli, with signals in phase in the two ears are generally chosen.

The "oddball" paradigm and other common tasks.

In the "oddball" paradigm the more frequent (non-target) and target stimuli are used. The subject is asked to respond by pressing a button whenever a target infrequent stimulus is presented. In ERP associated with selective attention, the subject has to pay attention to and make decision about stimuli presented in one ear only. The tasks used for memory involve presentation of a memory set (digits or letters) followed by a probe stimulus. The subject has to make one response if they think that the probe was a part of the memory set and another if not. These are called positive and negative probes. The size of the memory set can be varied to estimate the increase in time taken to scan the memory set per additional item. The set may include vowels, or consonants, syllables as a visual representation or verbal stimuli such as digits, letters, using speech synthesizers connected to computers. The memory scanning tasks generally test for immediate memory. The recall process is difficult to evaluate with these techniques. In language tasks, simple words or complex tasks, may be used. Other tasks involving visual (27) and olfactory stimuli can also be used. (28)

The procedure

Preparation of patient

A medical check up initially ensures a normal hearing and vision of the subject. The subject is then briefed about the procedure and asked to lie down/sit in a standard audiometric sound proof and air conditioned room to ensure that he is relaxed at the time of recording. Sound stimuli are presented binaurally, and visual stimuli appear on a computer screen. The subject is asked to respond by pressing a button in response to the target stimuli. Different number of responses can be chosen.

The recording montage for P300

The setting is done with the electrodes placed according to the 10–20 international system. Ag/AgCl electrodes with collodion are used. Four recording channels are used. Responses from Fz, Cz and Pz electrodes are referenced to an indifferent scalp location. (e.g. mastoid, tip of nose or ear lobule (A1 + A2). Eye movements are known to contaminate the response, hence the last channel is used to monitor them and methods are employed to correct them (29). If possible by rejecting trials containing eye movements as it produces less noisy recordings. Alternatively the subject is asked to fix his eyes on a particular spot to improve the concentration and avoid artifacts due to eye movements. Since the frequency range of <10 Hz is expected in the recording, the low frequency cut off should not exceed 1Hz. For the P300 a time constant of 3 sec (3dB down at 0.05 Hz) is preferred. However, the choice of amplifier time constant depends upon the duration of analysis. A short shift can use an AC amplifier, while larger shifts require DC amplifiers.

The responses are analysed by averaging them using principal component analysis and discriminate function analysis. N2 and

P3 in the oddball task are often assessed in the different waveforms obtained by subtraction of ERP to frequent stimuli from rare stimuli. In memory scanning tasks the ERP changes with each memory set and might be interpreted better from different wave forms e.g. ERP to positive and negative probes. In selective averaging techniques the simplest example is separation of trials according to whether or not a subject correctly identifies the target stimuli in the oddball task. This provides an average ERP to missed targets and prevents dilution of ERP to targets which pass unnoticed.

The predetermined stimuli rather than a randomly generated stimuli is generally preferred. An averaging computer with sufficient memory capacity enables categorization of trials related to different stimulus features and a correct/incorrect behavioural performance on a task. The adaptive filter technique involves identification of a component peak e.g. P3 in the ERP for each individual trial by cross correlating the trial with a template such as the average of the trials to be analysed and taking the peak response where this correlation is at its maximum.

CNV

The CNV is a index of central processing of subjective appraisal, expectancy, orientation and reaction time (30). The first component of CNV is the 0 wave (orientation wave) which seems to be associated with the process of orientation of S1, (the first stimulus) whereas the second component labelled as the E wave (Expectancy wave) seems to be related to motor preparation for a motor response prior to S2 (the second stimulus) (31). The CNV activity is generated in the frontal or parietal cortical areas, encompassing the premotor cortex, the supplementary motor area (SMA) for motor CNV's and the parietal association cortex for sensory CNVs. In motor CNV paradigms the E wave reflects activity in neuronal circuits involving not only premotor cortex but also the basal ganglia (32).

Methodology of CNV

The CNV paradigm used in our lab consists of 32 trials of an S1-S2 motor response sequence. A warning sound click stimulus (S1) is followed by an imperative stimulus (S2) delivered after 1 sec through SMP-4100, auditory/visual stimulator. Subject presses button to terminate the imperative stimulus S2. ERPs recorded are analysed by an inbuilt computer. CNV corresponds to high amplitude negative potential prior to S2 in S1-S2 inter stimulus interval. The P3 response and reaction time can also be noted using the CNV paradigm. The maximal CNV amplitude is scored as the largest negative ongoing potential immediately prior to S2 onset. Reaction time is generally the time between S2 and pressing the button for response. Our CNV normative data for adults have been mentioned earlier (30).

Physiological factors affecting P300

Age : Changes in the ERP occur in different age groups. In the children they are part of developmental change while in the elderly, they represent cognitive decline. It is seen that the α response/activity after

external stimulation changes with age. The developmental process is not complete by 11 yrs (33). In another study it was shown that in the age group of 11 to 21 years the peak latency and amplitude decreases (34). With increasing age a decrease in reaction time, errors of emission, N2 amplitude and N1 latency, increase in P2 amplitude for standard tones and decrease in N1, N2 amplitude, N1, N2, P3 latency and increase in P3 amplitude for target tones is reported in early childhood and adolescence (35).

The P3 wave has been studied extensively to evaluate the neurophysiological basis of cognitive decline associated with aging. Goodin and his colleagues initially reported that the P3 latency was longer in older subjects than in the young (36, 37) and a decrease in P3 amplitude occurred with age, but others have found it to be stable (38). In addition a change in scalp distribution with a larger P3 at mid frontal region compared to vertex in older subjects is reported (39). This could be due to a putative frontal lobe contribution to target P3b topography although similar mechanisms may modulate scalp distribution in both younger and older groups (40). Other indices of attention can be obtained by subtracting ERP elicited by standard stimuli in a response task, when subject responds in the same way and differently between a standard and deviant stimulus. These are delayed in the elderly, this could be one factor accounting for the age related slowing of later ERP components (41). Our results of amplitude and latency of P3 wave in young adults is comparable with age and sex matched results of the other workers mentioned earlier (42).

Other physiological factors and their relationship with ERP have been studied. The latency of P3 wave correlates with intelligence quotient (IQ). Individuals with a higher IQ are endowed with slower, multisynaptic parallel neural circuits that enable them to do task better but not faster (43). Increase in exercise frequency is associated with an increase in amplitude of P300 probably because of increased cerebral blood flow (44). The amplitude and latency of P3 wave is also seen to increase in pregnancy although no causative reason has been found (45). Several long latency ERPs are markedly influenced by sleep. The auditory P1-N1-P2 vertex complex is most frequently studied. At sleep onset N1, gradually declines in amplitude due to decrease in the level of attention (46). P1 at 50 msec, P2 at 200 msec are altered and P2 amplitude may increase in NREM sleep (47), although the change may not be consistent (48). An increase in amplitude of N2 at 350 msec at sleep onset is also reported (49). K complexes evoked in NREM sleep are known to be accompanied by slow negative potential resembling P300 (50).

In addition to diminished arousal level in sleep, a similar state has been observed when general anaesthesia with propofol/ alfantanil is given. P1N1P2 complex is delayed and positive waves are comparable to the changes during stages II-IV of sleep (51). Other aspects like recognition of familiar faces (52), a greater amplitude of P300 with emotionally positive and negative stimuli compared to neutral ones (53), different aspects of language (54), are some aspects of human behaviour which can be studied using ERP. It can be expected that response to some of these related potentials

have shown that some effects like decrease in P2, P3 amplitude, P2 latency P3b, latency, and enhancement of N2, increase in P3a latency are seen that cannot be explained by the process of habituation (55).

ERP and clinical application

The ERP data has not proved very useful in the clinical diagnosis probably because the tests are too insensitive or perhaps they are not designed or applied correctly. The validity of the tests is another aspect that needs to be examined. The cognitive tests should have different difficulty index in order to quantify the loss and correlate it with a particular pathology.

Goodin et al first reported abnormal P300 in dementia (56). P300 latency has been used for knowing the possible etiology, of dementia and to differentiate it from Korsokoff syndrome (57). In addition increase in N400 latency in Alzheimer's disease (58) a slow reaction time, reduced amplitude of N170, delayed P250, delayed and attenuated N290, a broad late negative shift between 577 and 735 msec, is reported in temporal lobe epilepsy (59). In Parkinson's disease (PD), increase in N2 P3 latency, decrease in amplitude of N2 smaller MMN component is seen (60). Arteriosclerosis, the most probable cause of Leukoaralosis (a radiological entity) is associated with increase in P300 latency (61). This is also seen in hepatic encephalopathy (62). Another clinical application of P300 is to use it in cases of subjects malingering amnesia along with other lie detecting measures (63). Our studies have shown that persistent chronic pain also causes increase in P3 latency indicating that cognitive dysfunction occurs in these patients (64). Factory workers exposed to different ambient intoxicants also show abnormality in cognition as evidenced by delayed P3 wave (65).

ERP in psychiatric disorders

In addition to neurological diseases, the ERP techniques have been widely applied in a number of psychiatric disorders. In alcohol addicts the alteration in MMN component of auditory ERP has been reported (66). Cocaine abusers, have a longer P300 latency, (67) while chronic morphine usage increases the P300 amplitude (68). Other studies have shown increase of P3a latency and decreased amplitude in both alcohol and cocaine dependants (69). Attention deficit hyperactive children, were found to have normal CNV, P1, N1 suggesting that early processing and ability to mobilise resources for target identification and categorisation were not different. The P3 amplitude decreases, and latency increases with a late frontal negative component suggesting reduced involvement in post decisional processing in these children (70). In depression there is decrease in P2, P3, CNV with the P300 amplitude negativity related to suicidal risk (71), along with a slow P1 and prolonged processing of stimulus response compatability after P3b (72). Schizophrenia is associated with reduced P300 amplitude for target stimuli, may be associated with impairment of inhibition of activated neural pathways to perform tasks (73). A low MMN is a chronic marker and indicates predisposition to the development of schizophrenia (74). In obsessive compulsive neurosis there is a larger N2,

while other changes are less well defined (75).

In conclusion, event related potentials represent a diagnostive pandora box for the cognitive aspect of various clinical disorders. In the near future their use can be extended for early diagnosis of cognitive disorder, before appearance of clinical syndrome, as an Alzheimer's disease. They can also be used for therapeutic evaluation of drugs believed to enhance memory and for examining the scientific basis of various meditation practices that claim to improve attention and concentration. However their value still remains as accessory tool, to support the main diagnositc methods, that confirm the clinical diagnosis.

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