ACTA NEUROBIOLOGIAE EXPERIMENTALIS

Acta Neurobiol. Exp. 2003, 63: 55-63

Event-Related Potentials - the P3 Wave

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Review

Abstract. Event-Related Potentials (ERPs) are a basic, non-invasive method of neurophysiological investigation. They can be used to assess aspects of human cognitive information processing. They also can be used in experiments on higher mammals. The most important and the most studied component of the ERP record is the P3 wave. It consists of two parts, P3a and P3b. There is no doubt that, besides the use in neurophysiological and psychophysiological research, the P3 wave also has clinical importance. Changes in its latency, amplitude and topography are correlated with clinical findings in a wide range of different ailments. The mini-review we present summarises the current state of the P3 wave research in experimental and clinical studies.

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Key words: event-related potentials, evoked potentials, cognitive deficits, oddball, P3 wave, neurophysiology

INTRODUCTION

The recording of event-related potentials is a non-invasive electrophysiological investigation method. The term event-related potential (ERP) is used to distinguish their cognitive aspect from evoked potentials (EP), which reflect mainly sensory processing. The putative goal of ERP research is to evaluate some of the high level characteristics of information processing in the central nervous system. We expect that during the performance of a given task there is a change in the content of thought and the attentional resources that have to be used. A prerequisite for any ERP investigation is that we adopt the hypothesis that psychological processes that lead to completion of given task are reflected in a measurable change of electric potentials generated by the appropriate neuronal system (Stejskal 1993).

In the prototypical ERP trace, the most prominent and most studied is the P3 (or P300, the third positive wave, or the wave with a 300 ms latency). It was described in the 1960s by Sutton et al. (1965). The P3 wave is evoked by a task known as the odd-ball paradigm. During this task a series of one type of frequent stimuli is presented to the experimental subject. A different type of non-frequent (target) stimulus is sometimes presented (Squires et al. 1976). The task of the experimental subject is to react to the presence of target stimulus by a given motor response, typically by pressing a button, or just by mental counting to the target stimuli.

There are also alternative tasks which can be used to elicit the P3 wave. One of them is the "Single stimulus paradigm". In this task, a target tone occurs randomly in time, but the tone is sometimes replaced by silence and the subject is required to respond to every stimulus. Another possibility is to use a passive odd-ball task, where the subject in the above-mentioned classical paradigm does not need to respond to target stimuli (McIsaac and Polich 1992). Both these alternative tasks elicit the P3 wave with properties very similar to the wave recorded with the original paradigm. These properties include age dependency (see below), (Zenker and Barajas 1999). The last paradigm we mention is called the "Stimulus sequence paradigm". In this procedure a sequence of ten tones is presented. The first six are always the standard tones and randomly one of the next four is the target (Bennington and Polich 1999). Of course, before any experimental session one trial run is implemented to make the subject familiar with the task and to assure that the subject can distinguish two different stimuli and knows which one is the target.

Virtually, any sensory modality can be used to elicit the response. In descending order of clinical use these are: auditory, visual, somato-sensory, olfactory or even taste stimulation (Polich 1999). The shape and latency of the P3 wave differs with each modality. For example, in auditory stimulation, the latency is shorter than in visual stimulation (Katayama and Polich 1999). This indicates that the sources generating the P3 wave differ and depend on the stimulus modality (Johnson 1989). This finding is also supported by the higher correlation between Raven's Coloured Progressive Matrices and latency in visual paradigm than in auditory paradigm (Tanaka et al. 1998).

Amplitude, latency and age dependency of the P3 wave (see below) also varies with electrode site. Analysis of the topographic distribution of P3 latencies demonstrated that P300 latency was dependent on electrode location. A significant increase of P3 latency from frontal to parietal electrode sites was reported. Maximum amplitude of the P3 wave is at the Pz electrode site and midline electrodes. It was also found that an amplitude/age correlation is only present at parietal and central locations. In spite of these findings, controversy in the field remains (Anderer et al. 1996).

The ERP recording uses a standard EEG technique followed by averaging of traces aligned to the repeated stimulus. Target and non-target stimuli are recorded in separate channels. Recently, traces of EEG without averaging are also sometimes recorded. Among the EEG frequency bands, for the P3 with average instantaneous frequency, the band from 0.1 to 30 Hz is used. At the same time, the electrooculogram (EOG) has to be recorded. Artifacts caused by eye movements have to be suppressed by some automated procedure on-line or manually on-line or off-line. At least two runs of recordings are typically saved for the sake of reproducibility. Electrodes are placed using the standard EEG 10-20 layout.

The maximum amplitude of the P3 wave is seen at the parieto-occipital and fronto-central leads (Polich 1999). This is not dependent on the modality used in the task. The succession of waves elicited by the above-mentioned oddball paradigm is P1, N1, P2, N2 and P3 (N are negative and P are positive waves). With the exception of the last N2 and P3, the preceding waves correspond to the activation of primary sensory areas (Polich 1999). The latency of the P3 is from 300 to 500 ms, depending on the

modality. In 20 to 60 per cent of recordings, the P3 wave is composed of two separate peaks, the P3a and P3b. In these cases, the P3b is assumed to be the proper P3 wave.

The physical energy of the stimulus does not influence the shape, amplitude or latency of the P3 wave. Therefore, the P3 is also sometimes called the endogenous potential (Polich 1998, Polich 1999). The P3 is basically bilaterally symmetrical (Smith et al. 1990). In visual and auditory modalities it was found that amplitude was higher under all conditions in left-handed persons compared with right-handed. Smaller amplitudes were also described in females compared to males. In light of the previously reported gender and handed differences in *corpus callosum* size it could be suggested that P3 reflects callosal size differences (Hoffman and Polich 1999). There is a general consensus that the P3 reflects the timing of cognitive processes and is not correlated with reaction time (Kutas et al. 1977). We may think about this timing as relating to the succession and speed of mental processes (Antal et al. 2000b, Kutas et al. 1977, Polich 1998, Polich 1999, Sutton et al. 1965).

Experimental set-ups for eliciting the P3 wave have also been developed in animal (Arthur and Starr 1984, Wilder et al. 1981). Other conditions also directly or indirectly influence the latency and amplitude of the P3 wave. These include fluctuations of arousal, or periodic changes such as circadian, seasonal and menstrual changes as well as environmentally induced changes such as fatigue, medication, feeding state and so on. For a detailed description of these influences see Polich and Kok (1995).

PSYCHOLOGICAL AND PHYSIOLOGICAL INTERPRETATION

The interpretation of the P3 as a phenomenon accompanying mental processes has many caveats. There are several theories on the neural processes underlying the origin of the P3. The most cited and most criticised theory is the theory of Donchin and Coles (1988). Donchin's theory is referred as "updating of working memory". In this theory, the P3 is seen as an electro- physiological correlate of a steady revision of the representation of an environment in a working memory. According to this theory, the P3 pops out at the moment when an update of this representation of an environment is needed. More precisely, the P3 shows up when the inner model of an outer environment is about to be revised. The P3 reflects neural activities involved in the representation change (Donchin and Coles 1988). The latency of the P3 then corresponds to the speed of cognitive processing and the amplitude shows the allocation of brain energy resources (Kok 1997). The amplitude of the P3 also depends on expectation about stimulus, on whether the task is relevant (Wickens et al. 1983), on selective attention (Johnson et al. 1986), and on emotional attachment and motivation (Carillo-de-la Pena and Cadaviera 2000). The latency lengthens with the difficulty of the task and also during aging (Polich 1998). The first of the two components, the P3a, has its maximum located at a slightly more frontal region than the P3 proper. It is also about 50 ms earlier (Knight 1996). It is supposed to reflect the cognitive processes which identify the stimulus as the target (Squires et al. 1975). Lesion experiments by (Knight 1996) indicate that P3 depends on attention and attentional processing originating in the frontal lobe.

Another explanation of P3 origin is that it reflects the surprise associated with the occurrence of the less frequent stimulus (García-Larrea et al. 1992). This view is supported by findings of yet another novelty P3a - virtually identical to the P3a, elicited by yet another infrequent stimulus set into the odd-ball paradigm (Squires et al. 1975).

Recently Polich and his colleagues suggested that P3a may be generated by target *versus* standard discrimination rather than by stimulus novelty (Comerchero and Polich 1998). The P3b reflects the memorisation processes. This is supported by findings of Fabiani et al. (1986) in an experiment in which the P3 is elicited by word stimuli and the subject is asked to recall the word used in the previous trial. In one experiment they found that the P3 amplitude was not higher in all subjects after successful recall. It was higher only in those subjects who used one of two possible memorising strategies, the "rehearsal strategy" as opposed to the "elaborative strategy". Rehearsal or rote memorisation strategy depends only on the activation of the original representation whereas "elaborative strategy" depends on networks of associations formed as the words are presented. Another experimental procedure in which subject were not asked to memorise the words, and use of the "rehearsal strategy" (which is similar to the normal memorisation process without any task) led to the correlation with the heightened amplitude. As the "Rehearsal strategies" make use of short-term memory (Fabiani et al. 1986) this also support the Donchin theory (Polich 1998). Verleger's (1988) theory says that the paradigm eliciting the P3 is itself composed of many more elementary

successive stimuli. The chain of these stimuli is then interrupted by one infrequent stimulus. The P3 wave reflects the rebound of rather excessive activation caused by frequent elementary stimuli. In other words, during the series of frequent stimuli the infrequent stimulus template is kept in working memory and matching of this template leads to the termination of previous neural activation due to the expectations. The theory of Desmedt (1980) also states that the substrate of P3 is a transitory inhibition of non-specific modulator input from the mesencephalic reticular formation of the cortex. This inhibition is triggered from a hypothetical central processor in the prefrontal cortex. Recent work of Michalski (2001) supports the role of inhibition in the P3 generation. At the level of psychological terminology, the P3 reflects neither cognitive processing nor target stimulus identification, but rather a mechanism which ends the activation of the decisive machinery (Desmedt 1980). Rockstroh et al. (1996) argue that P3 mirrors the inhibition of regular processing in the sensory cortex, caused by the occurrence of the target stimulus.

CORTICAL AND INTRACRANIAL TOPOGRAPHY OF THE P3 WAVE GENERATORS

The question of the location of the P3 generator remains open, despite current progress in investigation methods. There are two possible approaches in the search for the origin of scalp recordings. The first approach is to get the highest possible spatio-temporal resolution of the surface recordings and then to use numerical techniques. The second approach is to combine electrical recordings with some other experimental technique, such as imaging based on computer tomography, provided its temporal resolution is high enough to enable the correlation of the electrophysiological and imaging techniques.

When using numerical techniques in comparison with the later approach, the solution may be not unique and there is a trade off between the noise level and the temporal resolution on one hand and the spatial resolution on the other. The methods of finding dipole sources, principal components and independent components of the generating structures are the most commonly used numerical techniques.

Among the methods used in combination with electrophysiology are: animal studies, imaging studies, pharmacological and lesional studies. We give here just some examples of these combined techniques: visual stimulation in human subject together with psychophysics and neural modelling was used by Thorpe et al. (1996) for the investigation of latency of the evoked potentials. The latency of unit response to visual stimuli was studied in macaque by extra-cellular recordings (Maunsell and Gibson 1992). The hippocampal *versus* neocortical origin of the auditory P3 in rat was studied by extra-cellular recordings (Brankačk et al. 1996). The P3 is possibly generated at many different places (Frodl-Bauch et al. 1999). Recordings from implanted electrodes show the contribution of the deep structures, especially in the medial temporal lobe. There is, however, new evidence against the involvement of the deep structures. First, the gross potential in hippocampus has a voltage too low to contribute to potentials recorded at the surface. Next, the investigation of patients after the temporal lobectomy shows that the P3 is not substantially distorted (Lutzenberger et al. 1987). Other investigation shows that limbic structures do not contribute to the P3 generation. In monkeys when the temporal lobes are removed bilaterally, P3 is not affected (Paller et al. 1992). Furthermore, investigation in epileptic patients after temporal lobectomy, who were chronically implanted with stimulating and recording electrodes in the hippocampus, do not show P3 deviations (Polich and Squires 1993).

Yet other studies argue for the contribution of hippocampus to the P3 origin (Halgren et al. 1995). Surface electrodes combined with fMRI corroborate that temporoparietal structures are especially responsible for P3 generation. In this combined recording the P3 amplitude decrease correlated with the neocortical tissue loss in schizophrenia, especially in the temporoparietal region (Ford et al. 1994). It also has been shown that the damage of the temporoparietal region leads to topographic distortion of the P3 wave (Yamaguchi and Knight 1991). In conclusion: current opinion takes for the P3 generation site the temporo-parietal junction and neighbouring parietal and temporal neo-cortical regions. The contribution of sub-cortical structures of the limbic system is indirect.

CLINICAL USE OF THE P3

Physiological changes of the P3

The changes of P3 latency during aging can be described as follows: the latency decreases during the development, reaching its minimum sometime between 20

and 25 years of age and then increases. Signal transmission among generators of ERP is delayed as a general effect of aging. Why the processing is slower remains largely unknown. There are several possible causes: a change of lipid composition of myelin, a decrease of a specific neurotransmitter, like acetylocholine, or a decline of energy utilisation. Since the P3 latency increases during physiological aging, for correct assessment of pathology we have to have norms for patients in all age groups. For calculation of these norms, healthy individuals without apparent neurological, psychiatric or internal diseases have to be selected and recorded under reproducible conditions (Kűgler et al. 1993). A rather simple task, manageable by individuals in higher age groups, should be chosen. Especially for patients with pre-existing cognitive deficits, some tasks can be too difficult and this can invalidate the results of the recordings (Kűgler et al. 1993, Polich 1998). Norms are constructed, using linear regression, for amplitudes and latencies. These norms can be then applied to check whether a latency rise is still within the physiological range (Squires et al. 1975). It must also be taken into account that in males the slope of latency as a function of age is steeper than in females, as recently described by Hirayasu et al. (2000).

Pathological changes of the P3 wave

The P3 wave is affected in several psychiatric and neurologic disorders, which are linked to changes in levels of various neurotransmitters (Frodl-Bauch et al. 1999). Changes in the amplitude and latency of the P3 wave have been described in a number of psychiatric and other disorders (Polich and Herbst 2001). We will only discuss some of the findings here. All the studies used the odd-ball paradigm and the auditory modality which is typically applied in the investigation of the disorders.

NEUROLOGICAL DISEASES

Alzheimer's disease and other dementias

The most prominent change in the auditory modality in Alzheimer's disease and other cortical dementias is a lengthening of latency, corresponding to the impairment of memory and attention in dementias (Polich et al. 1990). This impairment is associated with falling cholinergic transmission which dominates in Alzheimer's disease (Hollander et al. 1987). P3 can also be used as a diagnostic tool for distinguishing dementias of cortical and subcortical origin. Pseudo-dementia (the state occurring frequently in major depression) can also be distinguished. In pseudo-dementia the latency is not lengthened but the amplitude is lower (Polich et al. 1990). Latency lengthening is also found in Alzheimer's disease with visual modality stimulation. Lengthening is also found in the auditory modality in healthy individuals with higher risks of acquiring Alzheimer's disease. This may be used in early screening for this disease (Saito et al. 2001). In other dementias (Binswanger's disease, multiinfarction dementia, lacunar dementia) findings are analogous, i.e. latency lengthening correlated with the severity of the clinical stage (in the auditory modality, which is used most common in these studies). Minimal cognitive impairment is regarded as one of the risk factors in Alzheimer's disease. In this nosologic unit, latency lengthening and amplitude flattening in the auditory paradigm is one of the signs of cognitive impairment. This finding may be useful as a marker predicting future development of Alzeheimer's disease (Golob et al. 2001).

Parkinson's disease

The main P3 finding in Parkinson's disease is amplitude flattening (O´Donnel et al. 1987). Some studies show that amplitude changes in Parkinson's disease are correlated to the dementia due to the disease, rather than to the disease itself (Tanaka et al. 2000). Longer latency was also found in visual paradigms with longer inter-stimulus intervals. This finding goes hand in hand with the overall cognitive slowing in this disease (Wang et al. 1999). Recent finding by (Antal et al. 2000a) suggests the use of visual P3 can be useful in differentiating the (nosologic unit) essential tremor from Parkinson's disease (Philipova et al. 1997). Also, the latency change with age on is greater in Parkinson's disease than in control individuals (Tachibana et al. 1997).

PSYCHIATRIC DISEASES

Schizophrenia

The presence of P3 changes in schizophrenia is the most controversial issue in the diagnostic use of the P3 (Strik 1996). We will discuss this controversy at some length. The most remarkable finding is amplitude flattening (O´Donnel et al. 1999). This seems to be correlated with so-called negative symptoms (Pritchard

1986). Less is known about positive symptoms in relation to P3 (Ford et al. 1999). Longitudinal studies show that the P3 amplitudes fluctuate together with the actual severity of clinical symptoms. Only the auditory P3 can be regarded as a marker of schizophrenia (Mathalon et al. 2000). One clinical scale that is related to negative symptoms is the "Total Brief Psychiatric Rating Scale" and this scale was found to be related to the P3 (Bruder et al. 2001). This scale is correlated with verbal memory performance and with negative symptoms.

Another interesting finding is higher amplitude and shorter latency of early components in some modalities in schizophrenia. This is supposed to reflect an erroneous sensory input processing, a well-known hypothesis of the origin of hallucinations in schizophrenia. A more controversial finding is age-related latency lengthening, supposed to be higher in schizophrenics than in normal individuals. Some specific neural degeneration (O´Donnel et al. 1995) is the suspected cause.

Another research combined the P3 and fMRI method to study the correlation between grey and white matter volumes and P3 amplitudes. These findings support the hypothesis that some morphological (neuro-degenerative) process can contribute to schizophrenia. The role of the P3 as a marker for neuro-degenerative processes was investigated by Martín-Loeches et al. (2001) in this context. The results show a significant negative correlation between P300 amplitude and prefrontal CSF volume in the patient group. These results support the hypothesis that P300 amplitude may be interpreted as a marker of neurodegeneration in schizophrenia. Other studies show gradual flattening of amplitude during debilitating phase of the disease (Mathalon et al. 2000).

Frodl et al. (2001) found correlations between P3 amplitude and *corpus callosum* size in schizophrenia. This supports the theory that erroneous inter-hemispheric communication plays a role in pathogenesis of schizophrenia. Lateral asymmetry of the P3 was described in schizophrenia but it is not consistent in different studies even those which found flattened amplitude (Gruezlier et al. 1999). Another interesting idea suggests the use of P3 for genetic screening of schizophrenia. No clear results in this direction have yet been achieved (Turetsky et al. 2000, Winterer et al. 2001).

Depression

The main finding in major depression is amplitude flattening. This is clinically very useful because it can help with the differential diagnosis of true dementia and depressive pseudo-dementia (Gordon et al. 1986). A surprising finding is that the spectral analysis of amplitude flattening in schizophrenia and depression shows different spectral bands. This shows two different possible pathophysiological bases of the two disease groups. This is quite an encouraging finding in the electrophysiology of psychiatric diseases (Rőschke and Fall 1997). Another result shows that the latency lengthening may distinguish the group of pharmacotherapy non-responders among depressed patients (Vandoolaeghe et al. 1998). Bathien and Bange (1998) showed that changes in the P3 wave are still present even during remission of the disease. This may be the electrophysiological correlate of a psycho-motor retardation which is almost always present in depression.

CONCLUSION

ERPs are accessible for clinical use. Various mild neurological and cognitive deficits can be detected by ERPs. For example Alzheimer's disease is characterised by a longer latency of P3. In Parkinson's disease the P3 amplitude is flattened. ERP changes in schizophrenia are multiple and irregular and other methods should be employed to complement the ERP analysis. In depression amplitude flattening is most prominent change of P3 and in schizophrenia the amplitude flattening is accompanied by lateral asymmetry of ERP.

ACKNOWLEDGMENT

Supported by the GACR grant No. 305/00/P101 (CUni No. 201352) to T.H. and P.M. Thanks to A. Burman, E. Růžička and Z. Wűnsch.

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Received 3 July 2002, accepted 18 December 2002