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Review Article

The Use of Auditory Event-Related Potentials in Alzheimer's Disease Diagnosis

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Event-related potentials (ERPs) are important clinical and research instruments in neuropsychiatry, particularly due to their strategic role for the investigation of brain function. These techniques are often underutilized in the evaluation of neurological and psychiatric disorders, but ERPs are noninvasive instruments that directly reflect cortical neuronal activity. Previous studies using the P300, P3a, and MMN components of the ERP to study dementing illness are reviewed. The results suggest that particularly the P300 brain potential is sensitive to Alzheimer's disease processes during its early stages, and that easily performed stimulus discrimination tasks are the clinically most useful. Finally, these data suggest that the P300 ERP can aid in the diagnosis of dementia and may help in the assessment of early Alzheimer's disease.

1. Introduction

Alarmingly increasing prevalence of Alzheimer's disease (AD) due to the aging population in developing countries, combined with lack of standardized and conclusive diagnostic procedures, make accurate diagnosis of Alzheimer's disease, especially for its early stage also known as amnestic mild cognitive impairment (MCI), a major public health concern. While no current medical treatment exists to stop or reverse this disease, recent dementia-specific pharmacological advances can slow its progression, making early diagnosis all the more important. Behaviourally, both AD and MCI are traditionally diagnosed in relation to abnormalities in brain functions such as memory, cognition, perception, and language. Furthermore, the differentiation of probable AD from other dementing illnesses is generally obtained by excluding alternative causes for cognitive dysfunction. It is important therefore to determine whether AD and MCI can be characterized by functional deficits other than high-level abnormalities already described and whether, with further development, they are specific and sensitive enough to contribute to the search of early markers of the disease process.

In an attempt to facilitate the diagnosis of AD, several noninvasive biomarkers have been proposed, including event-related potentials (ERPs). ERPs are voltage changes time-locked to some physical or mental occurrence in the ongoing electrical brain activity (recorded as EEG). Depending on the type of sensory stimulus, the ERPs can be divided into somatosensory, visual, or auditory ERPs. This review concerns the auditory modality.

In auditory ERP studies, perhaps the most commonly used experimental approach is the active oddball paradigm. In this paradigm, typically two classes of stimuli are presented, one occurring frequently (standard) and the other occurring infrequently (target), and the subject is required to distinguish between the two stimuli and to respond to the stimuli that are predesignated as targets. Variations of this paradigm include the passive oddball paradigm, in which the subject is instructed to ignore the stimuli, and so-called novelty oddball paradigm, in which a third class of stimuli (novelty) are also presented intermixed with the standard and target stimuli.

ERPs offer a psychophysiological method for studying attentional processes, language, and memory functions, yielding information not available from behavioral studies.

A number of studies have suggested that ERPs are useful indices for assessing changes in cognitive brain functions. In particular, the P300 component of the ERP has been widely applied in the scientific study of age-related cognitive dysfunction, because it reflects attentional and memory processes. This ERP is most commonly elicited in a active oddball paradigm when a subject detects an occasional target stimulus in a regular train of standard stimuli. In the novelty oddball paradigm, in turn, deviant or unexpected tones elicit a frontal subcomponent of P300, namely, the P3a, which is considered as an electrophysiological marker of the orienting response [1]. Furthermore, in the passive oddball paradigm, at around 200 ms the deviant tones elicit a component called mismatch negativity (MMN). The MMN is thought to reflect the mismatch between a trace in a sensory memory (of the standard stimulus) and the representation of the current stimulus to which the trace is compared, and is considered to be an index of the preattentive stage of auditory information processing [2].

The present paper briefly reviews from the literature (especially from [3]) the background of clinical MMN and P300 applications.

2. P300 Responses

Auditory P300, a positive deflection occurring at about 300 ms from stimulus onset, is one of the most widely studied components of the ERP. It is generated by the activation of multiple neocortical and limbic regions, and has two functionally different components: the earlier P3a that is maximal over frontocentral regions, and the later P3b (hereafter called P300 in this review) that is maximal at posterior scalp locations [4].

3. Psychophysiology of P300

The P300 is parietocentral positivity that occurs when a subject detects an informative task relevant stimulus (first described by Desmedt et al. [5]; Sutton et al. [6]). It is most commonly elicited in an active oddball paradigm when a subject detects an occasional target stimulus in a regular train of standard stimuli. The P300 probably represent concurrent activity in multiple regions of the brain, including temporoparietal neocortical areas and higher limbic structures [7–16].

The major theoretical interpretation of the P300 component is that it indexes updating of activity in corticolimbic circuits in processes requiring attention and working memory [17, 18]. This context updating theory has its roots in Sokolov's model of the orienting response, which has been postulated to result from a change in the organism's neural representation of the stimulus [19]. P300 amplitude is also proportional to the amount of attentional resources devoted to a given task [20–22] and has been associated with superior memory performance [23, 24]. P300 amplitude can therefore be viewed as a measure of CNS activity that reflects the processing of incoming information when it is incorporated into memory representations of the stimulus and the context in which the stimulus occurs. Variation in P300 amplitude is, therefore, assumed to reflect the degree or quality with which that information is processed.

The P300 has a latency to peak of anywhere from 300 to 1000 ms, depending on task complexity and the clinical sample tested. A frequently observed phenomenon is that the P300 latency increases when categorization of the stimulus becomes more difficult. A general consensus seems to be that P300 is evoked after the stimulus has been evaluated [25]. Thus, the latency of P300 has been regarded as a measure of stimulus evaluation time [26, 27]) and is generally unrelated to response selection processes [28, 29]. It is therefore independent of behavioral reaction time [30, 31]. Indeed, it is just these properties that make the P300 a valuable tool for assessing cognitive function: because P300 latency is an index of the processing time required before response generation, it is a sensitive temporal measure of the neural activity underlying the processes of attention allocation and immediate memory. In addition, P300 latency is negatively correlated with mental functions in normal subjects, with shorter latencies associated with superior cognitive performance (e.g., [32–35]). The neuropsychological tests that are best correlated with P300 latency are those that assess how rapidly subjects can allocate and maintain attentional resources. This association is also supported by results indicating that P300 latency increases as cognitive capability decreases from dementing illness [27, 35–40]. Thus, P300 latency is directly associated with cognitive capability in both normal and patient populations.

4. Clinical Applications of P300

Changes in the latency, amplitude, and topography of the P300 correlate with clinical findings in a wide range of disorders and brain injuries. Since the P300 has been related to the fundamental cognitive events of stimulus evaluation and immediate memory in normals, and because its peak latency is correlated with neuropsychological tests of cognitive function, this ERP component may provide an objective index of the degree of dementing illness which can be distinguished from the electrophysiological changes found in normal aging. Indeed, the initial suggestion that the P300 component might be a useful tool for investigating cognitive functions came from studies of normal aging and dementia, since peak latency was found to be prolonged in individuals with dementing illness compared to similarly aged normal subjects [41, 42]. The extent of deviation varied with the aetiology of the disorder, being greatest with metabolic causes and brain tumours and least with degenerative disorders, such as AD [41]. The P300 latency changes were reversed by treatment in patients with metabolic encephalopathy, with latency returning to normal values when the disorder was corrected and cognitive functions were again normal [43, 44].

Several studies have now verified that P300 is an objective and sensitive tool for demonstrating cognitive impairment in AD, as these patients have increased P300 latency and decreased P300 amplitude compared to elderly controls

subjects [35, 45, 46]. P300 is sensitive to AD processes already during its early stages [47], and similar P300 alterations have also been demonstrated in MCI [48–50]. P300 amplitude or latency alterations may also identify preclinical changes in participants who are at relatively high risk for AD because of genetic predisposition [48, 51]. P300 may thus reveal neurophysiological changes prior to the emergence of clinical deficits, which could advance the early detection and diagnosis of AD.

P300 latency increases systematically as cognitive function becomes worse in dementing illness, even though component size is not directly associated with the degree of mental impairment [27, 40, 52]. Recently, in a followup study, it was shown that the abnormalities in P300 in AD and MCI latency correlated with the severity of cognitive impairment. Furthermore, upon followup, one year later after the baseline study, the P300 latencies demonstrated significantly more prolongation than their baseline measures in AD and MCI patients, although their neurophysiological evaluation showed no statistical decline, suggesting that the P300 latency may reflect cognitive decline more sensitively than neuropsychological tests in the longitudinal followup of AD patients [53]. It has also been suggested that P300 latency is a valuable tool for the evaluation of cholinesterase inhibitors treatment in demented patients [54]. However, P300 latency does not seem to be capable of predicting which MCI patients will convert to AD [48], and therefore seems to have no predictive value for AD diagnosis.

Some reports have suggested that ERP measures may distinguish between subcortical (e.g., Huntington's and Parkinson's disease) and cortical (Alzheimer's, cerebral vascular accident) dementias [55, 56]. Other studies have indicated that P300 latency can separate individuals with dementia from those with depression-associated pseudodementia [37, 57].

Associations between P300 latency and the level of cognitive function also have been reported in neurological disorders, in confusional states, and for posttraumatic syndromes (cf. [34, 36, 38, 43, 44, 58–61]). Furthermore, the P300 component has been used to study psychiatric disorders such as alcoholism, depression, and schizophrenia (e.g., [62–67]). Taken together, these findings suggest that P300 may be clinically useful as an index of cognitive function, although its diagnostic utility is questionable (cf. [27, 37, 40, 68]). The P300 continues to be an important signature of cognitive processes such as attention and working memory and of its dysfunction in neurologic and mental disorders [69].

5. Psychophysiology of P3a

The P3a is a frontocentrally maximal positive ERP wave elicited by deviant or unexpected events [4, 70], and it is considered as an electrophysiological marker of the attentional switching, that is, the orienting response [1]. P3a is generated by a complex cerebral network, including the prefrontal, cingulate, temporo-parietal, and hippocampal regions [7, 71–74] and it is recorded over widespread anterior and posterior scalp sites [73]. It has been distinguished from P300 by a shorter peak latency, a more frontally oriented scalp topography and different elicitation conditions [4].

6. Clinical Applications of P3a

The P3a is affected in several psychiatric and neurological disorders. An enhanced P3a amplitude over the left frontal region has been found in chronic alcoholism [75]. An enhanced P3a are found in children with depression [76] and ADHD [77]. In addition, patients with closed head injuries show larger P3a amplitudes than control subjects [78, 79].

There are only a few studies published about P3a in AD and the findings have been to some extent inconsistent. Some authors found that AD patients are characterized by longer P3a latency than control subjects suggesting delayed orientation to deviant stimuli in AD [49, 80]. Furthermore, these authors suggested that separation of P3 subcomponents (P3a and P300) by dipole source analysis may increase sensitivity and specificity in correctly detecting AD patients from healthy subjects [49, 80]. On the other hand, some authors found no difference in the P3a between AD patients and controls but instead showed that the P3a was different in AD patients compared with patients with vascular dementia whereas the P300 was similar in these patients [81].

7. Psychophysiology of MMN

The mismatch negativity (MMN) is a frontal negativity at around 100–200 ms. It is generated automatically whenever the stimulus deviates physically from the immediately preceding context [82, 83]. MMN can be elicited by changes in simple tones, such as frequency or duration, and also by complex sounds such as phonemes [2]. The MMN is commonly derived by subtracting the ERP to the standard stimulus from that to the deviant stimulus. The MMN is thought to reflect the mismatch between a trace in a sensory memory (of the standard stimulus) and the representation of the current stimulus to which the trace is compared and is considered to be an index of the preattentive stage of auditory information processing [2]. In addition, by measuring the decay of the MMN amplitude as a function of the interstimulus interval, it is possible to estimate the duration of sensory memory. The MMN is generated mainly in the auditory cortex in the temporal lobes [84, 85]. Furthermore, a frontal MMN generator [86], has also been implicated.

8. Clinical Applications of MMN

MMN is an important ERP measure as it may reveal deficits of both sensory memory storage and of fundamental automatic mismatch detection mechanism [87, 88]. MMN is attention independent and therefore particularly suitable for studies with subjects who do not cooperate at all or cooperate very poorly. Clinical research lines using the MMN involve schizophrenia, dyslexia, autism spectrum disorders, coma, alcoholism, and dementia (for a review, see [89]).

Early studies on the aging effects on the MMN show that the MMN is smaller and prolonged in the ERPs of the normal old compared to those of the young (e.g., [90, 91]). In subsequent studies, Pekkonen et al. [92, 93] found that with frequency changes this effect was confined to conditions with long inter-stimulus intervals (ISIs), indicating that it is sensory memory rather than perception that is affected by aging. Similarly, several studies have found fairly unaffected MMN in AD at short ISIs [94]; (for review, see [95]), whereas MMN was reduced at long (3s) ISI in these patients [96]. These results suggest that AD appears to reduce the duration of auditory sensory memory when sound frequency is involved.

Interestingly, the pattern with duration MMN is quite different, with the age-related MMN-amplitude decrement being present even with short ISIs (for a review, see [95]). However, in patients with AD automatic stimulus discrimination to duration change in the auditory cortex is preserved as compared with normal aging [97]. These findings imply that although the preattentive discrimination to duration deviance is attenuated in aging, it is not further damaged in the early phase of AD. This may be due to the fact that the neurodegenerative changes underlying AD mainly affect mesial temporal structures like hippocampus, whereas the lateral aspects of the temporal lobes, where the MMN is generated, are less damaged [97].

In summary, studies on MMN in AD demonstrate that older controls and patients with AD produce MMNs that are reduced in amplitude relative to the younger subjects, but the differences between older controls and AD subjects are relatively small. Also, the fact that the AD subjects can produce significant MMN responses suggest that they do have a relatively intact MMN, albeit reduced in amplitude compared to controls [94]. In all the aforementioned studies, patients had minor to moderate cognitive impairment and taking into account the acknowledged cholinergic hypothesis in AD, probably their cholinergic defect was not sufficient to cause MMN generator impairment per se at short ISIs, but in some studies, impaired the duration of the memory trace [96].

As reviewed here, the value of the MMN in the early diagnosis of AD is somewhat limited. However, more pronounced MMN alterations have been found in demented Parkinson's disease (PD) patients relative to normal controls or patients with AD and dementia with Lewy-bodies, indicating that demented PD patients to a larger degree than the control groups have a deficit in automatic auditory change detection [98]. Furthermore, MMN may aid in the differentiation of normal pressure hydocephalus (NPH) from NPH with concomitant AD [99]. Thus, the MMN may aid in the differentiation of AD from other dementing illnesses. These findings also have implications for understanding cognitive and behavioural functioning in patients with dementia.

9. Conclusion

Alzheimer's disease is a neurodegenerative disorder, causing neuronal death that leads to cognitive function decline. Two misfolded proteins, β-amyloid that causes plagues and hyperphosphorylated-τ that causes neurofibrillary tangles are often blamed, yet, the genesis of these proteins, and in fact the true cause of the disease, are still unknown. While no current medical treatment exists to stop or reverse this disease, recent dementia-specific pharmacological advances can slow its progression, making early diagnosis all the more important.

Application of the auditory ERPS to the study of dementing illness and AD has produced positive findings. The P300 response, in particular, has become popular in studies of dementia. Because the P300 response is related to fundamental aspects of cognitive function in normals, it should be useful in the diagnosis of dementia, especially that of the Alzheimer's type. In general, this assertion is supported by a wide variety of previous findings that include the spectrum of dementias. Although the P300 does not appear to differentiate between types of cortical dementias, it does accurately reflect the level of cognitive dysfunction caused by these disorders. Furthermore, the auditory evoked potentials (including the MMN) might offer an additional tool to index cholinergic dysfunction in aging and in neurodegenerative diseases such as AD. Moreover, when variables which affect P3 measures such as task parameters and population differences are well controlled, the P3 ERP can differentiate between early AD patients and normal controls. Given these effects, it is reasonable to suppose that further refinement of the test procedures would facilitate the delineation of differences in the P3 response for the early diagnosis of AD.

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