Journal of
Neurophysiology and Neurological Disorders

Research Article Open Access

P300 Evoked Potential and its Clinical Significance in the Diagnosis of Dementia and Mild Cognitive Impairment

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Received Date: February 06, 2024 **Accepted Date:** March 06, 2024 **Published Date:** March 09, 2024

Citation: Wojciech Derkowski (2024) P300 Evoked Potential and its Clinical Significance in the Diagnosis of Dementia and Mild Cognitive Impairment. J Neurophysiol Neurol Disord 12: 1-15

Abstract

This article presents the results of original cognitive event-related potential (ERP) research, with a specific focus on the P300 wave in the context of diagnosing dementia, Alzheimer's disease, and mild cognitive impairment (MCI). These potentials, employing specialized stimulation protocols, enable the investigation of higher brain functions, which can be crucial in the diagnosis of these disorders. Classical event-related potential studies have not provided effective diagnostic tools for Alzheimer's disease, prompting the exploration of more advanced methods. The P300 wave, as a cognitive event-related potential, allows for the analysis of decision-making processes in the brain cortex, which is significant in neurodegenerative diseases.

The research results conducted by the author confirm that studying the P300 wave can be useful in monitoring patients with Alzheimer's disease treated with donepezil, levetiracetam, or memantine. These medications, by influencing P300 wave parameters, may enhance cognitive functions in patients. Studies on the P300 wave in the context of diagnosing dementia, Alzheimer's disease, and mild cognitive impairment (MCI) have the potential to provide crucial diagnostic information.

Despite cognitive event-related potential analysis being over a quarter-century old, the procedures for conducting such studies are not yet fully standardized. Nevertheless, our research suggests that these procedures can be simplified, opening perspectives for further development and standardization of this method.

Conclusions from the research confirm that individuals with MCI or Alzheimer's disease exhibit increased P300 wave latency compared to healthy individuals. Treatment with pro-cognitive drugs affects the parameters of this wave, suggesting that the analysis of cognitive event-related potentials, especially visual ones, can be a valuable diagnostic tool in neurological disorders.

Keywords: Dementia; Alzheimer's disease; Pro-cognitive Drugs; Neurological Disorders, Mild Cognitive Impairment

Introduction

Today, with an aging population and an increasing number of individuals affected by neurodegenerative diseases such as dementia and mild cognitive impairment (MCI), the importance of effective diagnostic methods is growing. This article focuses on the analysis of the P300 event-related potential (ERP) and its role in the diagnosis of dementia and mild cognitive impairment.

Event-related potential studies constitute a recognized method for assessing brain function, allowing the analysis of neural pathways responsible for visual, auditory, and superficial sensory processes [1-4]. Cognitive event-related potential studies are still infrequently utilized in clinical settings. The P300 wave, as a cognitive event-related potential, reflects crucial aspects of cognitive functions, especially the decision-making process in the brain cortex. Its use becomes significant in the context of early diagnosis of disorders such as Alzheimer's disease or mild cognitive impairment (MCI), where characteristic changes in P300 wave latency and amplitude are observed [5,6].

This article focuses on the analysis of the P300 event-related potential and its clinical significance in the diagnosis of dementia and mild cognitive impairment. We provide an overview of current research, including studies conducted by the author, regarding the use of the P300 wave in assessing cognitive function, with a particular emphasis on its role in early detection and monitoring the progression of these diseases. Additionally, we analyze the effectiveness of various methods of recording and computer averaging of the P300 wave, aiming to develop an optimal diagnostic approach.

Understanding the role of the P300 wave in the diagnosis of dementia and MCI is crucial for improving assessment tools and supporting the effectiveness of therapeutic interventions. We aim to provide a comprehensive view of contemporary achievements in this field, directing further research towards refining the diagnosis and treatment of disorders related to cognitive function impairment.

Cognitive event-related potentials (ERPs) are potentials obtained through computer averaging of electroencephalographic (EEG) activity in response to stimuli engaging cognitive processes in the brain. In contrast to classical visual evoked potentials (VEPs), which inform about the efficiency of the visual pathway, cognitive event-related potentials (ERPs) are used to assess the effectiveness of further processing of visual stimuli in the brain cortex [7] (Figure 1, Figure 2).

Figure 1: EEG recording for averaging visual (and cognitive) evoked potentials. In the first channel, the pacemaker signal

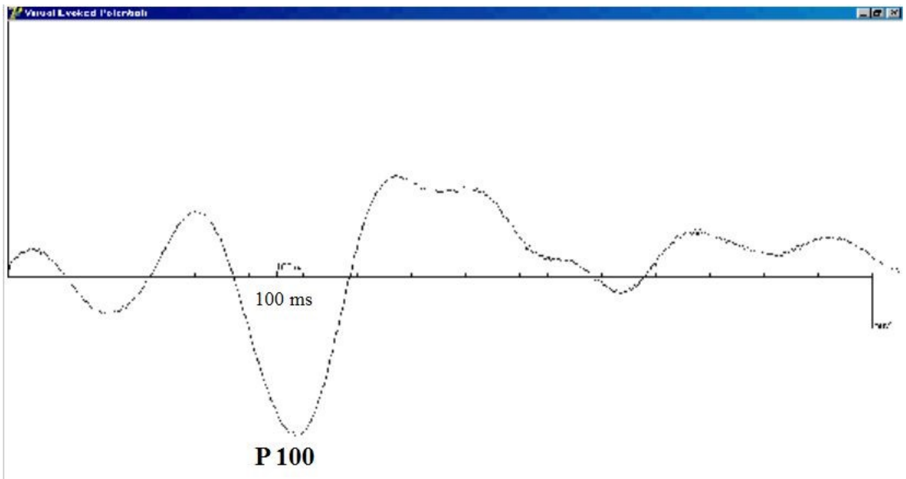

Figure 2: Classical visual evoked potential (VEP) obtained by averaging parts of the curves from Figure 1

Analyzing cognitive event-related potentials reveals the presence of specific deflections with defined latency and amplitude, like visual and auditory potentials. One of the most characteristic is the P300 wave, which arises from the stimulation of a series of repetitive stimuli, among which irregularly occurring others differ from the rest. It is essential for the subject to be prompted to register these distinctive stimuli, for example, by counting or pressing a button upon their appearance. The P300 wave is considered to reflect the decision-making process in the brain cortex. Reduced efficiency of cognitive processes, such as during Alzheimer's dementia, may make it more challenging for the subject to recognize stimuli that stand out from others and make decisions. These changes may be evident in the morphology, amplitude, or latency of the P300 wave (Figure 3).

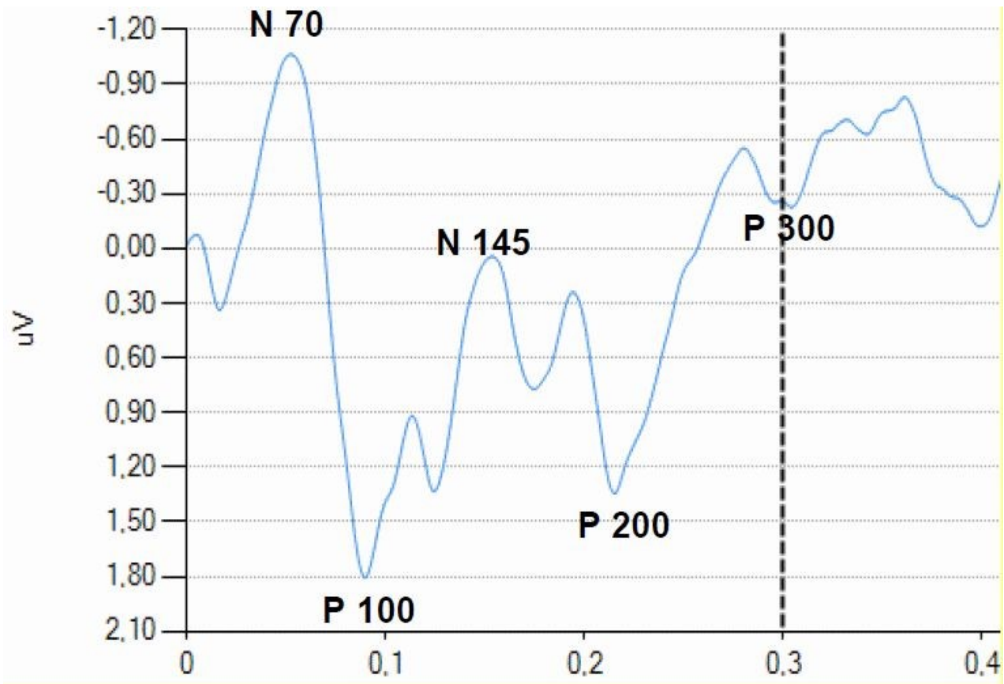

Figure 3: Normal visual evoked potentials

Materials and Methods

Research was a retrospective study of selected patients' medical records.

The documentation was kept in the Neurological Outpatient Clinic, of which the author is the owner and manager, and all research results were performed and described by the author.

The method for recording cognitive event-related potentials, including the P300 wave, is based on the application of electroencephalography (EEG) to record brain electrical activity. Below, I present details regarding our own methodology, equipment, and protocols used in studies on the P300 potential in the context of diagnosing dementia and mild cognitive impairment (MCI).

Initial studies were conducted using the Mindset MS-1000 apparatus, with EEG recording using specialized software from Nolan Computer Systems [8]. This apparatus provided basic electroencephalographic recording capabilities and was used to obtain preliminary data on cognitive event-related potentials.

Subsequently, studies on visual cognitive event-related potentials were expanded using two devices: Mindset MS-1000 and EBNeuro Neurotravel with a 32-channel cap. The Neurotravel cap had superior parameters, such as low noise levels, a high common-mode rejection ratio (CMRR), and the ability to adjust a broader range of sampling frequencies [9].

The EEG apparatus EBNeuro Neurotravel features specialized EEG Galileo .NET software, enabling advanced data analysis. The online multi-workstation collaboration module allows simultaneous examinations of multiple patients, enhancing the efficiency of the diagnostic process.

Stimulation utilized a protocol specifically developed by the author, involving the presentation of two hundred repeated visual stimuli. These stimuli included a pattern of a reversed chessboard with lines delineating light and dark fields. Additionally, irregularly appearing distinct patterns, such as a chessboard constrained by oblique lines, were included (Figure 4).

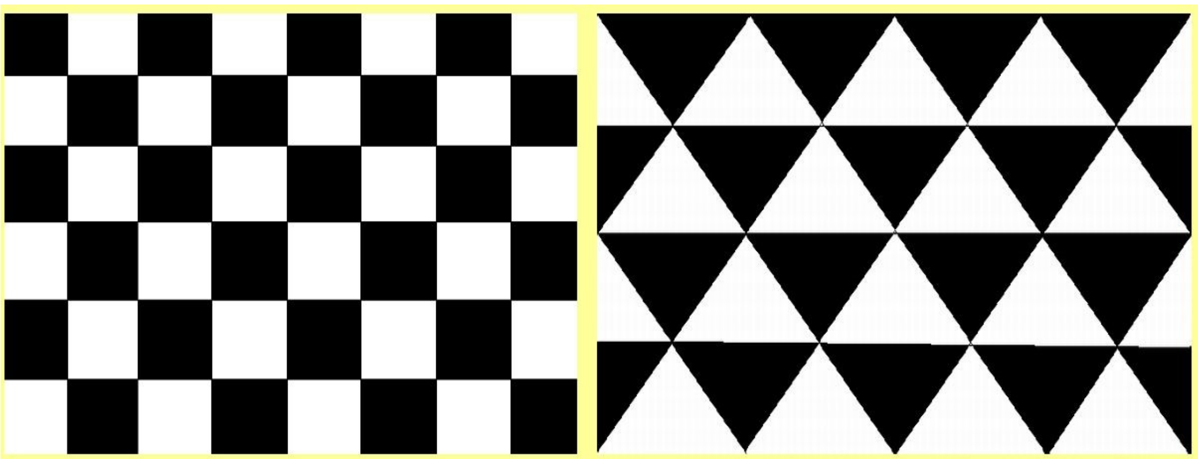

Figure 4: Two types of stimuli present in our ERP recording protocol

Prior to the study, participants were encouraged to actively engage by mentally counting distinct (oblique) chessboards. Motivation was reinforced by the promise of a reward for correct performance, further engaging the participants.

The stimulation protocol was constructed to include elements of both cognitive event-related potentials (ERPs) and classical visual evoked potentials (VEPs) in averaged visual responses (Fig 5). This combination allowed for the validation of the study's accuracy. Recordings were performed at all points of the classical 10-20 electroencephalographic system, which, according to the author, is crucial for comparing response morphology from different brain regions and often facilitates P300 wave identification. Unfortunately, this slightly extends the data analysis time but significantly enhances result reliability, for example, by eliminating artifacts.

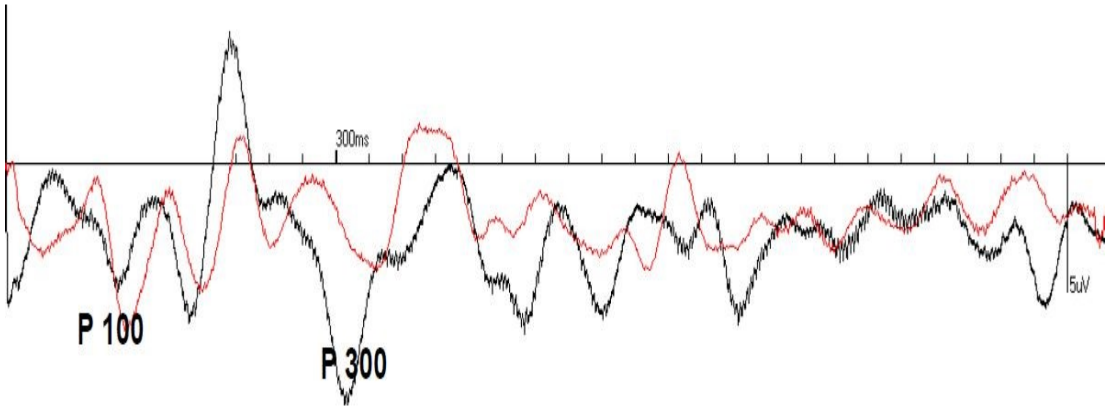

Figure 5: Evoked potentials averaged separately for the background stimulus (more frequent) and the second type stimulus

The black line (thicker) corresponds to the average response to the sparser stimulus (diagonal checkerboard), while the red line (thinner) corresponds to the classic response to the traditional checkerboard stimulus (left in Figure 4).

Custom applications written in C++ for the EB-Neuro Neurotravel apparatus and in Delphi for Mindset MS-1000 were used for data analysis. The response averaging process included both cognitive event-related potentials (ERPs) and classical visual evoked potentials (VEPs) (Figure 6).

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unit Unit1c;
{Autorem  aplikacji jest Wojciech Derkowski
wderkowski@hotmail.com}
interface
{Copyright Wojciech Derkowski}
uses
  Windows, Messages, SysUtils, Variants, Classes,
Graphics, Controls, Forms,
  Dialogs, FileCtrl, StdCtrls;
type
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    DirectoryListBox1: TDirectoryListBox;
    FileListBox1: TFileListBox;
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    Button1: TButton;
    RadioButton1: TRadioButton;
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    procedure RadioButton14Click(Sender: TObject);
    procedure RadioButton15Click(Sender: TObject);
    procedure RadioButton16Click(Sender: TObject);
    procedure RadioButton17Click(Sender: TObject);
    procedure Button1Click(Sender: TObject);
    procedure Button2Click(Sender: Tobject);
procedure Edit1Enter(Sender: TObject);
procedure TForm1.Edit1Enter(Sender: TObject);
begin
pocz:= StrToInt(Edit1.Text);
end;
procedure TForm1.FileListBox1Click(Sender: TObject);
var
InFile: file;
r: integer;
u: integer;
NumRead : integer;
 Buffer: array[1..128] of Byte;
 a: integer;
 ind: integer;
begin
for r:=1 to 9600000 do
   begin
   z[r]:=0;
   end;
AssignFile(InFile, FileListBox1.FileName);
Reset(InFile, 1);
r:=1;
repeat
  BlockRead(InFile, Buffer, SizeOf(Buffer), NumRead);
    for u:=1 to 128 do
      begin
      z[u+r*128-128]:= Buffer[u];
      end;
  r:=r+1;
until EOF(InFile) ;
CloseFile(InFile);
for ind:=1 to (9597952-32768*pocz) do
    begin
    z[ind]:=z[ind+2048+32768*pocz];
    end;
ind:=0;
 repeat ind:=ind+1; until
((z[32*ind-30]>116) or (z[32*ind-30]<98));
  indmin:=ind;
  ind:=ind+3; repeat
ind:=ind+1;
until ((97<=z[32*ind-30])and(z[32*ind-30]<=115));
indmax:=ind;
indsr:=(indmin+indmax)div 2;
for a:=1 to 6422528 do
   begin
    s[a]:=z[a+32*indmin];
   end;
end;
```

Figure 6: A fragment of the application written by the author for averaging cognitive evoked potentials

In the results analysis, attention was given to the characteristics of the P300 wave, including morphology, amplitude, and latency. Changes in these parameters can serve as indicators of decreased cognitive process efficiency, which is essential in the diagnosis of dementia and mild cognitive impairment.

In summary, the applied research methods, equipment, and stimulation and data analysis protocols constitute a comprehensive methodology, enabling the acquisition of significant information regarding cognitive event-related potentials, especially the P300 wave, in the context of diagnosing dementia and mild cognitive impairment.

Results

Efficacy of Donepezil in Alzheimer's Patients (2012)

In 2012, we conducted a study evaluating the utility of cognitive event-related potentials in monitoring Alzheimer's patients treated with donepezil [10]. In a group of ten patients and a control group of ten healthy individuals, prolonged latencies of P300 waves were observed in Alzheimer's patients compared to the control group. Patients treated with donepezil showed improvement in cognitive function, confirmed by the Mini-Mental State Examination. During donepezil treatment, a shortening of P300 wave latencies was observed in some cases (Figure 7, Figure 8).

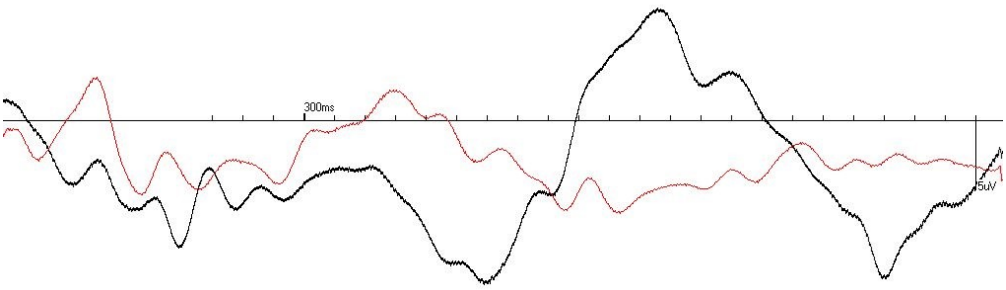

Figure 7: Cognitive evoked potential in a patient with Alzheimer's disease before the initiation of donepezil treatment, recorded from the left parietal area (79 years old). In the MMSE test, the result was fifteen points. (out of 30). P300 latency approximately 480 msec

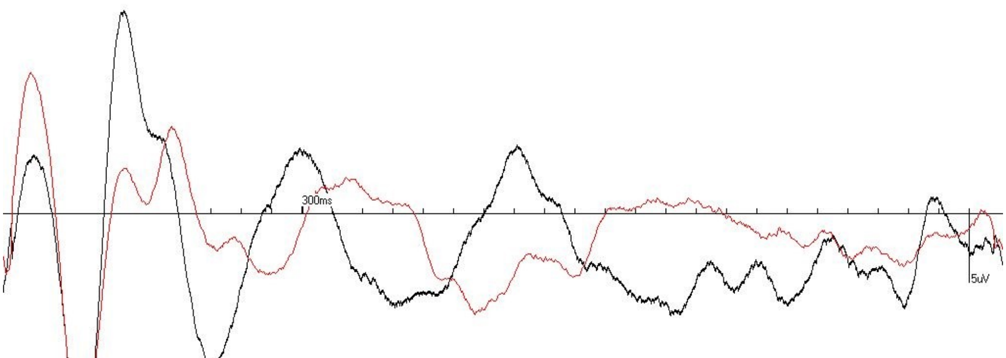

Figure 8: Cognitive evoked potential in the same patient as in Figure 7 after one month of treatment with donepezil. In the MMSE test, the result improved by four points. up to nineteen points (out of 30). P300 latency approximately 390 msec

Levetiracetam Treatment in Epileptic Patients and Cognitive Functioning (2012)

In 2012, we completed cognitive event-related potential studies in a group of twenty epileptic patients treated with levetiracetam [11,12]. We found that the P300 wave could be useful for assessing the cognitive functioning of patients in this group (Figure 9).

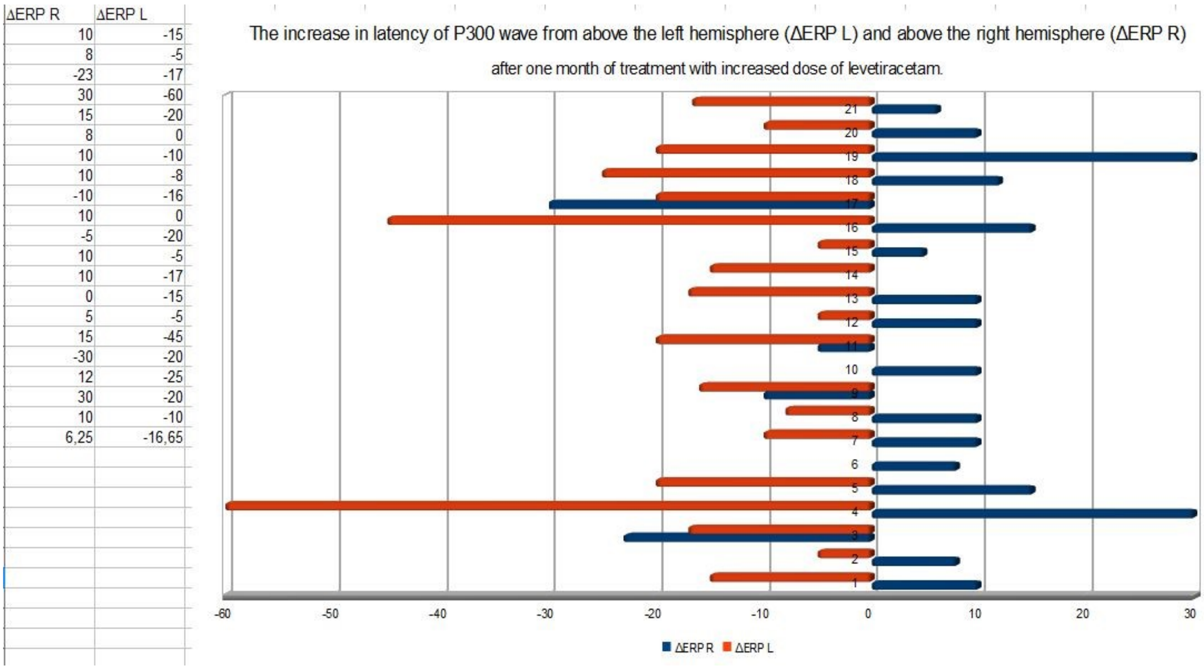

Figure 9: The increase in latency of P300 wave from above the left hemisphere (ΔERP L) and above the right hemisphere (ΔERP R) after one month of treatment with increased dose of levetiracetam

Impact of Donepezil and Memantine on Cognitive Event-Related Potentials (2015)

In 2015, I summarized studies on cognitive event-related potentials, specifically the P300 wave, in thirty patients treated with donepezil and memantine. The usefulness of the P300 wave in monitoring the impact of these pro-cognitive drugs on the cognitive processes of patients was observed [13] (Figure 10, 11, 12).

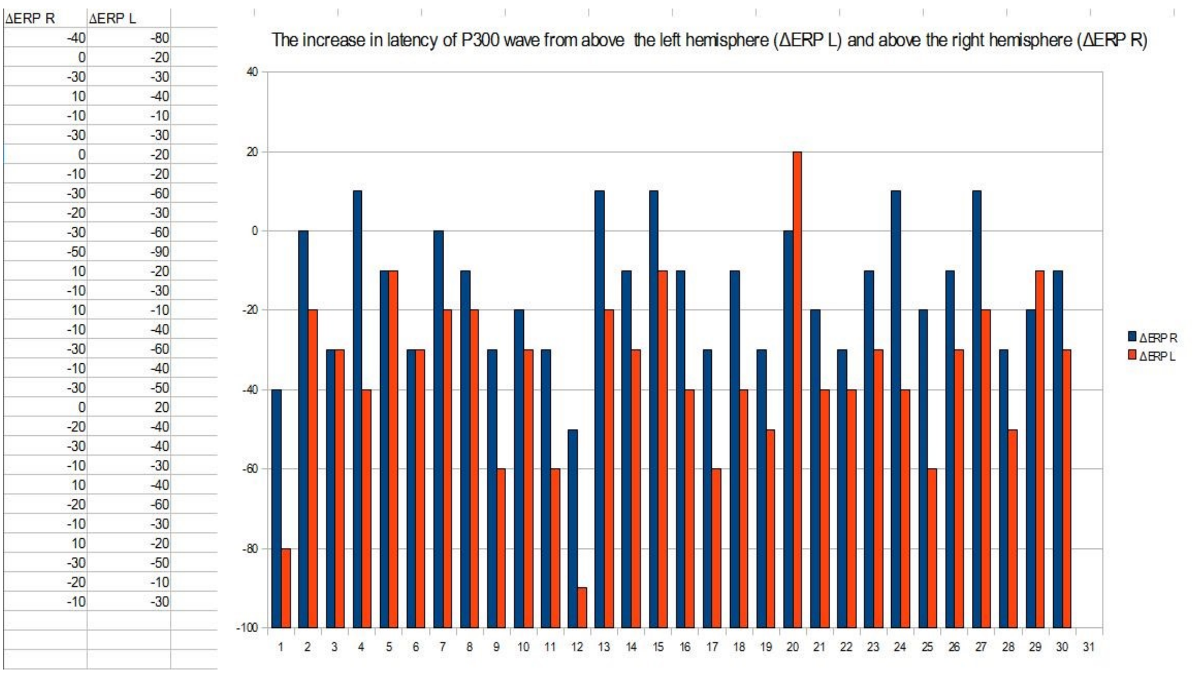

Figure 10: The increase in latency of P300 wave from above the left hemisphere (ΔERP L) and above the right hemisphere (ΔERP R) after one month of treatment with donepezil and memantine

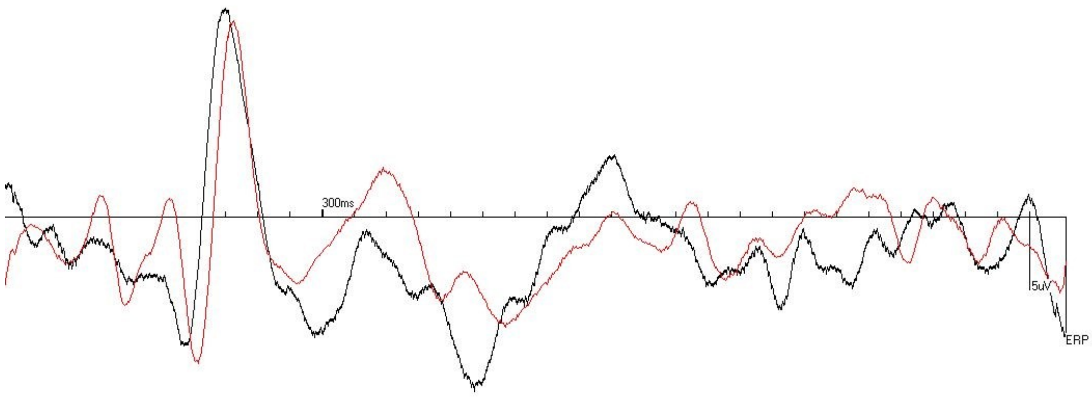

Figure 11: Man, age 66. Event-related potentials from above the left hemisphere (ERP L) before treatment

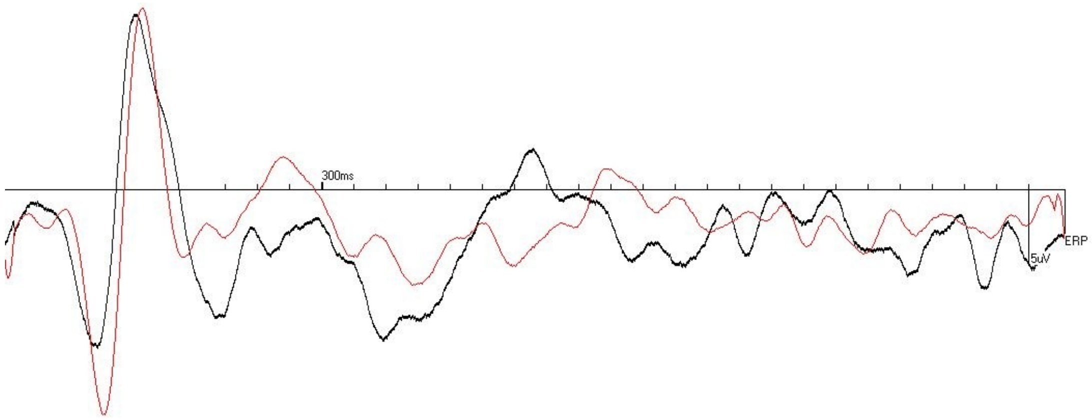

Figure 12: Man from Figure 11, age 66. Event-related potentials from above the left hemisphere (ERP L) during treatment

New Averaging Protocol for Visual Evoked Potentials (2016)

In 2016, I introduced a new protocol for averaging visual cognitive event-related potentials [14]. It was compared to the previous protocol, revealing that the new method facilitated and expedited the studies. Patients with MCI and Alzheimer's disease showed prolonged latencies of the P300 wave, and pro-cognitive drugs could influence its parameters.

Diagnosis of Mild Cognitive Impairment and Alzheimer's Disease (2018)

In 2018, we conducted research on the utility of the P300 wave in diagnosing cognitive function in patients with mild cognitive impairment (MCI) and Alzheimer's disease, comparing them with a control group [15]. It was demonstrated that P300 wave latency increases in the initial stages of Alzheimer's disease, and its value is elevated in MCI.

Parkinson's Disease and the P300 Wave (2019)

In 2019, we completed studies on the utility of the P300 wave in diagnosing cognitive function in patients with Parkinson's disease [16,17]. A slight increase in P300 wave latency was observed in these patients, but significantly less significant than in Alzheimer's patients. Pharmacological treatment of Parkinson's disease had no significant impact on P300 wave parameters (Figure 13, 14).

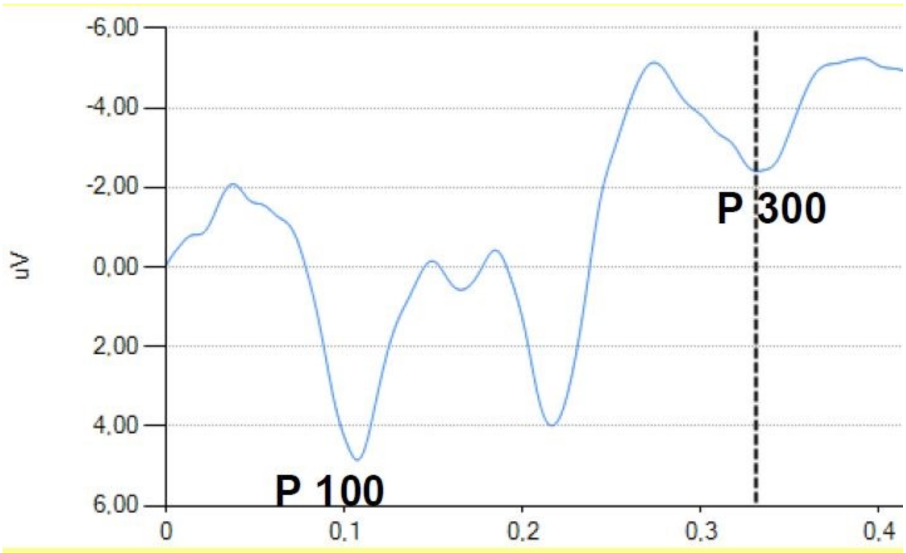

Figure 13: Cognitive visual evoked potential in a man with Parkinson's disease (man, 85 years old; P300 wave latency approximately 331 msec

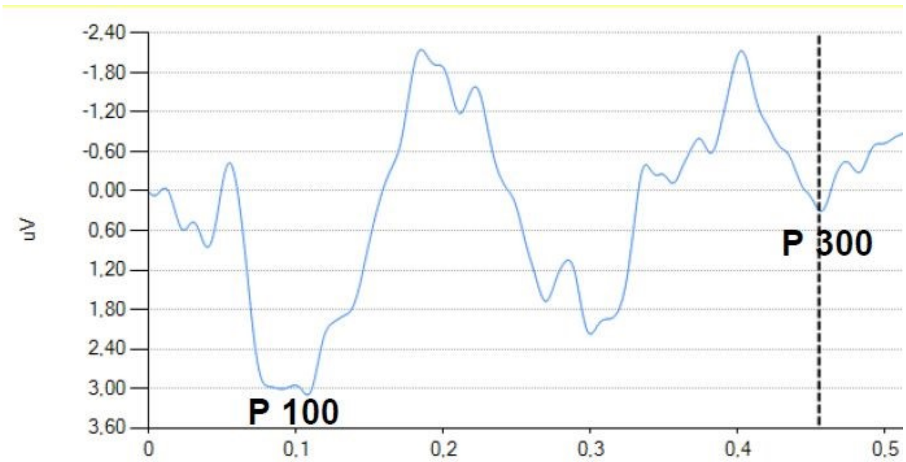

Figure 14: Cognitive visual evoked potential in a woman with Alzheimer's disease (woman., 80 years old; P300 wave latency approximately 454 msec

EEG and Basic Functioning in Alzheimer's Disease (2023)

In 2023, we conducted a study on a group of one hundred Alzheimer's patients, combining a full EEG examination with cognitive event-related potentials [18]. EEG recordings in individuals with Alzheimer's disease revealed a slowdown in basic functioning, correlating with the degree of dementia. Changes in the frequency of basic functioning were observed depending on the disease's advancement.

Discussion

Research on classical evoked potentials (visual, auditory, or somatosensory) has thus far failed to provide effective diagnostic tools for Alzheimer's disease [19]. Basic analyzers, focusing on fundamental levels of perception, do not consider processes involving more advanced information processing in the cerebral cortex, associated with the formation of perceptions [20-22].

Cognitive event-related potentials, especially the P300 wave, offer hope for a breakthrough in Alzheimer's disease diagnostics [23,24,14]. These specially designed stimulation protocols allow the examination of higher brain functions, providing more detailed information than classical evoked potentials [25-27].

The examination of the P300 wave is a particularly valuable diagnostic tool in the early diagnosis of mild cognitive impairments and initial stages of Alzheimer's disease [28]. In addition to the analysis of the P300 wave, studies utilize other elements of cognitive responses, such as "mismatch negativity" (MMN) or the P600 wave [5]. These additional components allow for a broader understanding of cognitive functions [29].

Although Alzheimer's disease remains incurable, the use of symptomatic drugs such as donepezil or memantine, by stimulating the cholinergic system of neurons in the brain, can improve cognitive functions [13]. Results from the studies suggest that changes in cognitive event-related potential parameters may be an indicator of the effectiveness of these drugs. Conventional diagnostic methods, such as brain imaging or psychological tests, have their limitations. The emergence of cognitive event-related potentials provides hope for the introduction of more objective and specific diagnostic methods [10].

In the context of dementia diagnostics, visual cognitive event-related potentials, especially the assessment of P300 wave latency and amplitude, may play a significant role [10]. The results of our studies suggest that this method can be effectively used in clinical practice.

Even though cognitive event-related potential studies have been around for over a quarter of a century, they are still less known and not as widely used as classical visual, auditory, and somatosensory evoked potentials. According to the author, this is unjust for cognitive event-related potentials. While the principles of conducting studies are not yet fully standardized, especially when compared to classical evoked potentials, our research suggests that these procedures can be simplified, opening perspectives for further development and standardization of this method. From my studies, the underestimation of the significance of cognitive event-related potentials was due to the lack of a truly effective methodology for their registration. This article, presenting the author's own experiences and the laboratory he created, attempts to reverse this trend, and encourage broader application, especially in the diagnosis of dementia and mild cognitive impairments (Figure 15, 16).

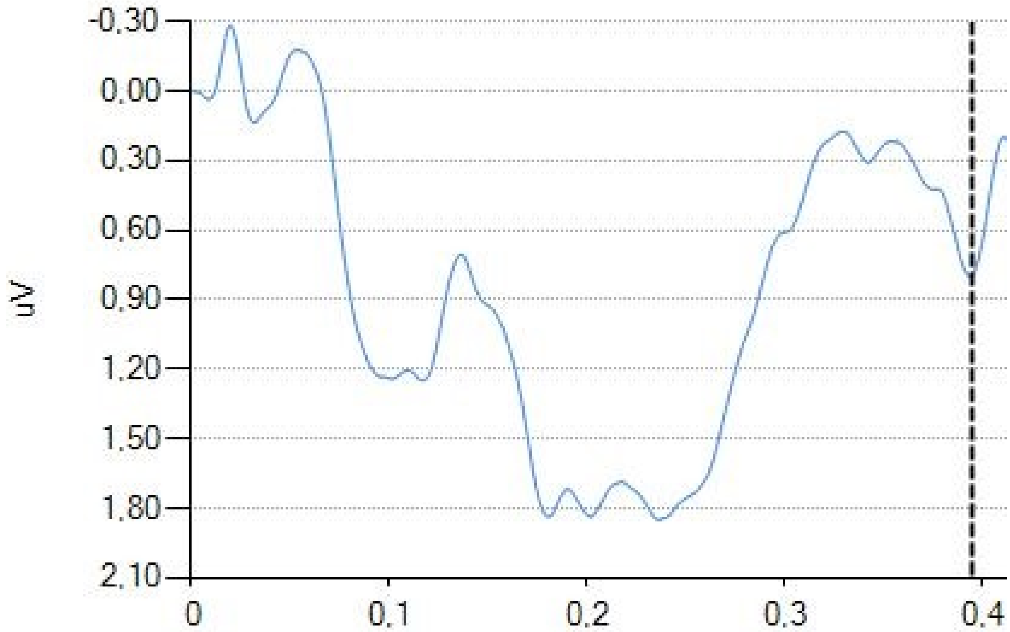

Figure 15: Man, 72 years old, Alzheimer's disease, treated with donepezil and memantine; examination of cognitive responses evoked to visual stimuli revealed the presence of a P300 wave with a latency of approximately 394 msec over the left hemisphere

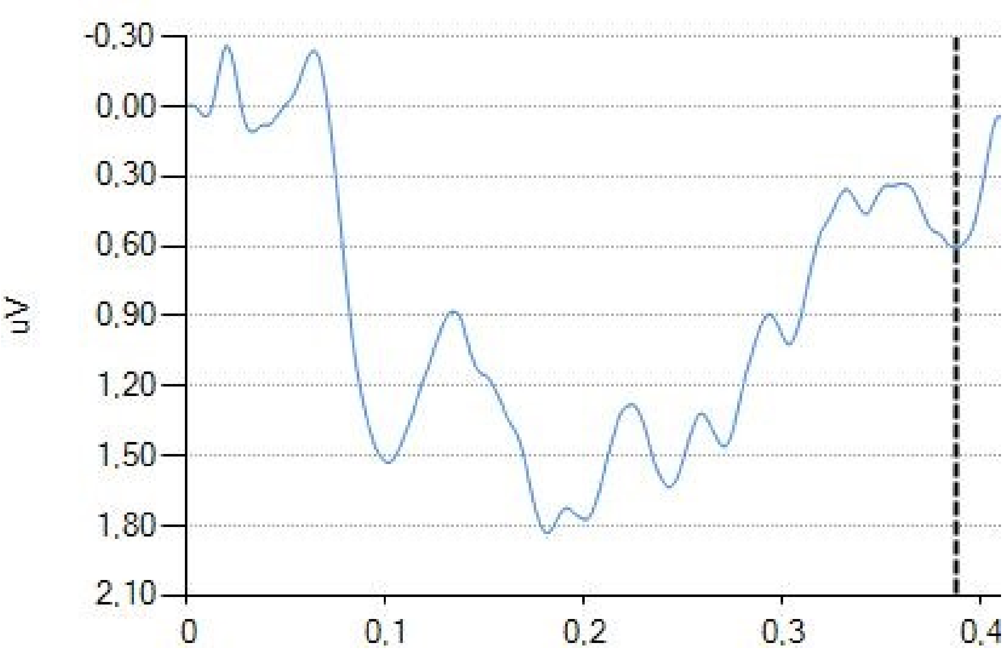

Figure 16: The same patient as in Fig. 15, examination of cognitive responses evoked to visual stimuli showed the presence of a P300 wave with a latency of approximately 386 msec over the right hemisphere

It is worth noting that studies on cognitive event-related potentials are not limited to Alzheimer's disease. Current findings indicate their potential application in the diagnosis of schizophrenia, addiction disorders, and psychiatric disorders following brain injury [5]. Attempts have also been made to use event-related potentials in constructing brain-computer interfaces [30-32].

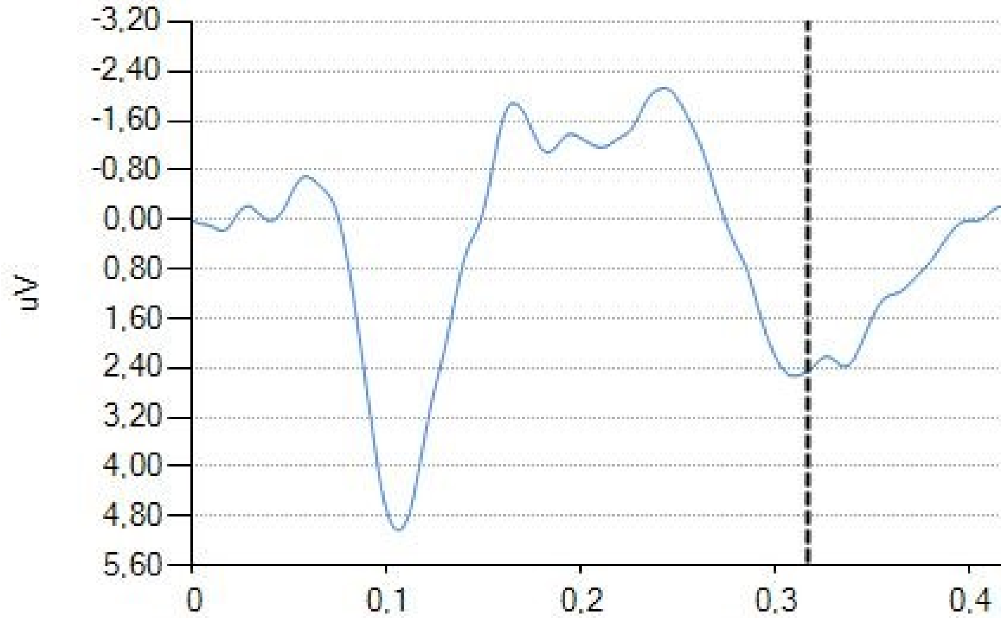

Figure 17: Woman., 75 years old, mild cognitive impairment (MCI); examination of cognitive responses evoked to visual stimuli revealed the presence of a P300 wave with a latency of approximately 317 msec over the left hemisphere

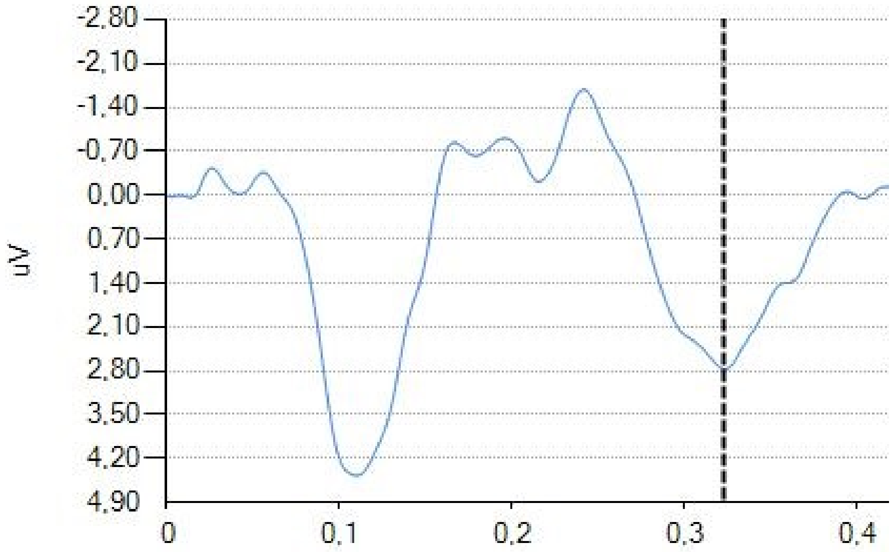

Figure 18: The same patient as in Fig. 17, examination of cognitive responses evoked to visual stimuli revealed the presence of a P300 wave with a latency of approximately 321 msec over the right hemisphere

Conclusions

The research confirmed increased latency of the P300 wave in individuals with Mild Cognitive Impairment (MCI) and Alzheimer's disease. Our P300 wave registration protocol proved to be valuable. Treatment with pro-cognitive drugs such as memantine or donepezil influenced the parameters of the P300 wave, and in some cases, dual-peak P300 waves were observed. Visual cognitive event-related potentials enable the assessment of cognitive processes.

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