Exploring the efficacy of P300 as a potential biomarker in detecting Alzheimer's disease: A replication study

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Abstract

This paper details a theoretical research proposal to explore the efficacy of the event-related potential (ERP) component P300 as a potential biomarker in the early detection of Alzheimer's disease. To determine P300's efficacy as a biomarker, an electroencephalogram test, which monitors and generates data on the electrical activity of the brain via scalp electrodes, and an auditory oddball test, which aims to assess the cognitive functioning of participants, were performed. The auditory oddball test involved playing a series of tones of two different frequencies (one is the standard tone, and the other is the target tone) for participants and having participants press a button whenever they heard a target tone. Accuracy and reaction time were recorded. The aforementioned two tests depicted a strong association between P300 and the cognitive decline of patients with Alzheimer's Disease (AD), suggesting that this ERP component may be used for the early detection of AD, which may improve the efficacy of future treatment and the overall quality of life for diagnosed patients in the long run.

Introduction

Alzheimer's disease (AD) is an irreversible, progressive neurological disorder characterized by the degeneration of brain cells and atrophy of the brain. Due to these processes, AD remains the most common cause of dementia (a general term for the decline in cognitive skills such as memory and information processing), accounting for around 60-70% of the 50 million people who have been diagnosed with dementia around the world (World Health Organization, 2020). The progression of AD is typically divided into four stages: preclinical AD, Mild AD (early-stage), Moderate AD (middle-stage), and Severe AD (late-stage) (Alzheimer's Association, n.d.). Most AD patients enter the Mild AD stage in their mid-60s, displaying initial symptoms such as memory loss, poor judgement, and frequent wandering (National Institute on Aging [NIA], 2017). As the disease progresses onto later stages, the symptoms gradually worsen until the individual can no longer perform daily activities such as eating and walking without external assistance.

Treatments for AD, including cognitive-enhancing medications and self-care exercises, may temporarily alleviate symptoms, but without the existence of a definitive cure, the life expectancy of individuals with AD averages between three to 11 years after diagnosis (Mayo Clinic, 2019). Since quality of life significantly deteriorates as AD progresses within an individual, it is imperative to accurately diagnose AD as early as possible so that treatment efficacy is maximized in slowing the progression of the disease and preserving the patient's quality of life to the fullest possible extent. Current diagnoses for AD involve combinations of several tests, including mental status tests (to evaluate behavioral and cognitive functioning) and brain-imaging tests such as computed tomography (CT) and magnetic resonance imaging (MRI) (Martin, 1990; Mayo Clinic, 2019). These tests are utilized in tandem to assess current cognitive,

functional, and behavioral abilities and rule out other possible causes for symptoms, such as brain tumors or Parkinson's disease (NIA, 2017).

Due to the neurodevelopmental effects of AD, individuals with this disorder typically possess different proficiencies in cognitive abilities than neurotypicals, which, for the purpose of this study, refer to individuals who experience typical neurological and cognitive development (i.e. individuals without AD). Cognitive abilities are brain-based skills that pertain to functions such as attention span, memory, reasoning, and visual or auditory processing. The extent of this difference varies between individuals, so the goal of this theoretical research study is to quantify this extent across individuals who share similar demographics (i.e. age) through an auditory oddball test, which involves recording participant reactions to the presence of infrequent deviant stimuli within a sequence of repetitive stimuli. This reaction is quantified using the P300 component of event-related potentials (ERP), which are measured brain responses in terms of voltage to certain stimuli. The P300 ERP component will be captured using an electroencephalogram (EEG) machine, a device that records the electrical activity of the brain through scalp electrodes. Neurotypicals and individuals diagnosed with AD will be included in cohorts of equal size, and all participants will be asked to partake in the test under similar conditions (e.g. rooms with similar appearances and temperatures).

By recording the differences in P300 between participants with AD patients and neurotypicals, the efficacy of P300 as a biomarker for AD may be observed. Biomarkers, short for biological markers, are objective, measurable indicators of normal or pathogenic biological states, such as the presence or severity of a disease (Strimbu & Tavel, 2010). Current biomarkers for AD include cerebrospinal fluid (CSF) proteins, which are present in abnormal amounts in patients with early-stage AD (NIA, 2020). The results of this study may support the use of P300

as an effective biomarker for early-stage AD. However, it is important to note that this study does not aim to discover a therapeutic cure for AD, but rather shed light on a potentially effective biomarker that could be used in the early detection of AD. Without a cure, AD will still progress in afflicted individuals, but the earlier an accurate diagnosis is conducted, the more benefits an individual will receive. For example, early diagnosis may increase the efficacy of medical and nonmedical interventions that lessen the burden of AD symptoms, allowing patients to preserve their cognitive, functional, and behavioral abilities for much longer. Additionally, earlier diagnosis allows patients to participate in a wider variety of clinical trials and gain access to the necessary legal, financial, and medical support before their conditions deteriorate even further (Alzheimer's Association, n.d.). Thus, if the cognitive functions between AD patients and neurotypicals differ greatly, the researchers of this study hypothesize that the difference between the P300 waveforms in AD individuals and neurotypicals will be statistically significant, thereby providing evidence that the P300 could be used as a biomarker for detecting early-stage Alzheimer's disease.

Literature Review

Event-Related Potentials

Event-related potential (ERP) is a cognitive metric that measures brain response to a stimulus. The significance of ERPs is astounding, as it provides a superb medium to understand neurotransmission and its implications on neurological dysregulation. ERPs appear as time epochs in electroencephalograms (EEG), ensuring high time-resolution and efficient administration (Kaiser et. al, 2020). Since ERPs are defined after the stimulus is displayed, they can be fragmented into ERP components that correlate to specific cognitive processing skills. The earlier ERP components mainly correlate with spatial attention, visual attention and processing, deviant stimuli processing, and sensory processes, whereas the later ERP components correlate more with error detection and processing, stimulus processing, evaluation of task relevance, and pre/motor preprocessing after a stimulus cue (Kaiser et. al, 2020).

The waveform of ERPs are described in accordance with two measurements: amplitude and latency. Amplitude is manifested in the EEG as the height differential between the peak of one wave and the trough of another wave, which is indicative of the magnitude of the response signal to a certain stimuli. Latency is the time delay between the stimulus and the response, which is displayed as the time interval between the positive or negative peak voltage deflection after the preceding peak. A certain EEG data point shown on the EEG may have different amplitude and latency values depending on the ERP component being studied.

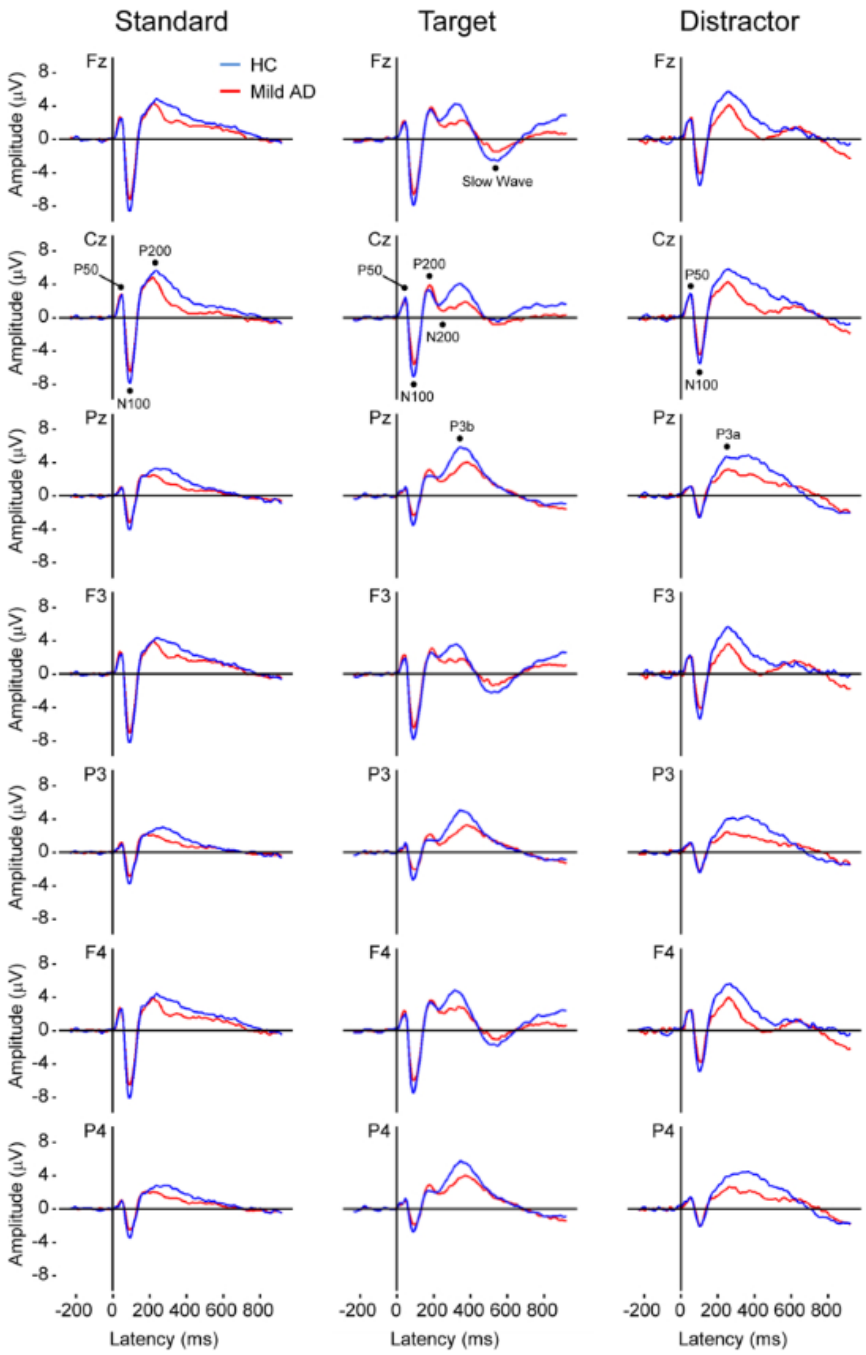
Clinical Trial on ERP Markers of Alzheimer's Disease (Oddball Test)

This study attempts to explore if event-related potentials (ERP) can provide a well-founded and valid standard to measure cognitive impairment that is linked with early signs

of Alzheimer's disease (AD). The cohort was divided into two main groups: 103 individuals with mild AD and 101 neurotypicals. To measure if ERP is a good indication of early-stage AD, all participants of the study were tested with a three-stimulus oddball paradigm. The three stimuli included: standard tones (1000 Hz), target tones (2000 Hz), and unexpected distractor tones (white noise). These tones were introduced in pseudorandom order, and participants were directed to respond to the target tones by pressing a button. From the ERP, the main features studied are the peak amplitude and peak latency that were recorded from electrode sites Fz, Cz, Pz, F3, P3, F4, and P4.

Figure 1

P300 Waveforms at different electrode sites



Note. The red line depicts the amplitudes and latencies of participants diagnosed with AD, while the blue line depicts the waveforms of neurotypical participants. The red (AD) amplitudes are visibly lower than the blue (neurotypical) amplitudes (Cecchi et al., 2015).

The studies resulted in significant differences between the two cohorts of participants. The most common distinction in individuals with mild AD and neurotypical controls is the changes in P3b (or P300) latency and amplitude. The P3b latency identifies the participant's stimulus evaluation and speed. The P3b amplitude establishes the number of attentional resources devoted when the working memory is updated. It was found that participants diagnosed with AD had longer P3b latencies and smaller P3b amplitudes than the neurotypical participants (Cecchi et al., 2015). It was also found that individuals with AD had a slow wave that follows the P3b, suggesting that they needed more time to process the stimulus and respond accurately. Since ERP is still not utilized to help diagnose AD, further research should be done to see if ERP is an effective biological marker in discovering the presence of mild AD.

Neuropsychological Correlates of the P300 in Patients with Alzheimer's Disease

In their study, well-renowned Korean researchers Lee et al. (2013) attempt to address how the P300 wave, an event-related potential (ERP) component, can indicate an individual's cognitive functions and how it can be a useful way to recognize signs of cognitive degradation in patients diagnosed with Alzheimer's Disease (AD). The P300 wave was evaluated in 31 patients with mild AD and 31 elderly neurotypical subjects. The two main measures of the P300 wave that were studied are the P300 amplitude and P300 latency. Larger P300 amplitudes are associated with better short-term and long-term memory. P300 latency reflects an individual's information processing speed before making a response. The study assessed the participants on their neurocognitive function, verbal fluency, K-BNT (Korean version of the Boston naming test), word list memory, word list recall, word list recognition test, and constructional recall.

The data was analyzed from 5 electrode sites (Fz, Cz, Pz, C5, and C6). Statistically, the mean scores of verbal fluency, word list memory, word list recall, word list recognition, constructional recall, and the K-BNT were all lower in the AD group than the control group. The graphs from an encephalogram (EEG) displayed that the AD group had lower P300 amplitudes compared to the control group, and out of all the five electrode sites, the Pz electrode site had the highest reading. Other results indicate a statistical difference in amplitude between the two groups at the right hemispheric C6 electrode site. There was no significant difference at the left hemispheric C5 electrode site. This proposes that patients with AD have a more impaired right hemisphere than the left hemisphere. As a result, the AD patients had a statistically significant decrease in P300 amplitudes as opposed to their control counterparts. However, there was no statistical significance reported between the two groups as far as P300 latency is concerned. Therefore, these results suggest that "P300 is responsive to the deterioration in language, memory, and executive functions observed in AD patients" (Lee et. al., 2013). This experiment further highlights the significance of P300 indices, as these indices have great potential to be used as a biomarker that can detect neuropsychological impairments in AD patients.

Relationship between P300 and Neurodegeneration

Through a high density EEF-3D vector field tomography, the relationship between various ERP potentials and cognitive decline is examined in a study done by Greek researchers (Papadaniil et al., 2016). This study assesses the differences between neurotypical controls and individuals with Alzheimer's Disease (AD) with an auditory oddball task. The oddball paradigm is an experiment that presents a sequence of stimuli that are interrupted by distracting stimuli. In this study, the mismatch negativity (MMN) and P300 ERP components are evaluated to detect

neurodegeneration. The data shows a significant decline in amplitudes in both the MMN and P300 ERP components in the AD cohort, suggesting that the magnitude of neurodegeneration in AD patients is significantly greater than that of their neurotypical counterparts (Papadaniil et al., 2016). Generally, there is higher brain activation in the inferior frontal and superior temporal gyri in the MMN component of ERP; however, the study found that AD participants experienced more intense activity in their parietal lobe. As for P300 values, the neurotypical controls experienced stronger activity in their frontal lobes, while the AD participants had P300 generators concentrated in the temporal lobe. Having weaker intensity in the inferior frontal space and maximal activation in the temporal and parietal areas of the brain signify greater possibility of lower cognitive function. Thus, the results suggest that increased MMN and P300 ERP latency and decreased amplitudes may be indicative of neurodegeneration, justifying the use of these ERP components in tracking the progression of AD and catching early symptoms of AD. Furthermore, the MMN and P300 waves studied can contribute to ERP research as it is an inexpensive, efficient, and non-invasive method of analyzing cognitive impairment.

Methodology

Participants

The participants of this observational study were recruited from two avenues: (1) personal acquaintances (e.g. friends, family members, coworkers) and, with prior approval, (2) public locations (e.g. Alzheimer's disease (AD) centers, hospitals, schools). All participants were required to fill out a survey to assess their diagnosis and eliminate those who experience comorbidity. Additionally, participants were asked to sign a consent form prior to partaking in this study, as participant data would be collected via an electroencephalogram. The sample

included 62 people (% male/ % female) and were separated into two cohorts of people: those who meet the criteria for a diagnosis of Alzheimer's disease (AD) and neurotypical individuals. The inclusion criteria for this study were individuals aged 65 and up with a MMSE score within the range of 20-24 (individuals who have a MMSE score in the range between 20 and 24 display early/mild dementia). Excluded were individuals who possessed any other pre-existing, clinically diagnosed psychiatric/neurological disorders other than AD and/or a medical history of a speech/learning disorder that could impede their proficiency to speak and read. The researchers also made sure to exclude any participants with secondary causes of cognitive impairment such as head trauma, alcohol and substance abuse, etc. Through this, comorbidities associated with AD were screened for. From the recruitment, the final sample consisted of 31 neurotypical (control group) participants and 31 participants who were clinically diagnosed with AD and met the inclusion criteria.

MMSE

Mini-Mental State Exam (MMSE) is an assessment that screens for cognitive function. The test evaluates a person's executive function, attention, language, awareness, and judgement. Although this test is not suitable for making a diagnosis, it can assist clinicians in discovering the presence of dementia as well as gauging the progressiveness and severity of the cognitive impairment. For diagnosis, clinicians take into consideration their MMSE score, history, symptoms, and results of other cognitive and physical tests. By answering a series of questions, one can get a maximum MMSE score of 30 points. Individuals with scores between 25 and 30 are considered neurotypical with no problem with their cognition. Individuals who score between 20 and 24 indicate mild dementia. Individuals who score between 13 and 19 suggest moderate

dementia and those who score less than 12 show severe cognitive impairment/progression of dementia. If given a diagnosis of Alzheimer's, one's MMSE score will gradually decline 2-4 points annually. To control the demographic characteristics in the participants of this study, the researchers limited the inclusive criterion to individuals who classify under mild dementia and have an MMSE score between 20 and 24.

Experimental Design

First, the researchers created and administered an online survey to recruit participants. The survey consists of filling in the bubble questions inquiring the participants about the following: name, whether they are within the age range of 65 and up, gender, race, and if they have been clinically diagnosed with AD. Based on the survey responses, the researchers then administered the Mini-Mental State Exam (MMSE) as an additional screening test. The researchers factored in MMSE scores to create two cohorts of participants: one with individuals clinically diagnosed with early-stage AD (MMSE score: 20-24), and the other with neurotypical individuals (MMSE score: 25-30).

The researchers then met with the participants and administered an auditory oddball paradigm. The subjects were seated in a comfortable but controlled environment. The auditory stimuli were presented via headphones. The infrequent target tones of 1500 Hz were randomly played along with frequent standard tones of 1000 Hz. The participants were instructed to respond with a button press for the target tones and ignore the button press for standard tones. The experiment took place over a 15 minute interval. Two types of errors were produced: the first being the participant pressing the button when the standard tone is played, and the second being the participant not pressing the button for the target tone.

These sessions were expected to take place over the course of several months, as these tests were administered individually. To collect electroencephalogram (EEG) data, the researchers used a standard EEG machine that consists of scalp electrodes (Fz-frontal, Pz-parietal, Cz-central), amplifiers, a computer control module, and a display device. The EEG detects electrical activity and patterns in the brain. The three common scalp electrodes (Fz, Cz, Pz) were used since P300 shows maximal amplitude at the central-parietal electrode. The EEGs took approximately 45 minutes to two hours and were conducted by an EEG technician. Two members of the research team recorded the EEG data, one member recorded observations about the participant, and another member administered the audio recording.

Findings and Data Analysis

Participant Demographics

The study was separated into two different cohorts: participants clinically diagnosed with early stages of Alzheimer's disease (AD) and neurotypical participants (control). Table 1 reveals and compares the clinical characteristics of the two groups. To solely measure the difference in ERP values, age and years of education did not have any statistical significance to eliminate new variables. However, the MMSE score was significantly lower in the AD group than the control group. This difference is statistically significant with a p-value of <0.01.

Table 1

Participant Demographics of AD and Control Group

	Alzheimer's (N=31)	Control (N=31)
	Mean ± SD	Mean ± SD
Age (years)	72.8 ± 0.84	69.7 ± 0.98
Gender (% male)	41.93 (13/31)	54.83 (17/31)
Education (years)	15.2 ± 0.45	14.9 ± 0.36

MMSE Score	22.5 ± 0.15	29.4 ± 0.09

Behavioral Data

The AD participants and control participants were administered an auditory oddball test. According to Table 2, there is no significant difference between the groups in response time (ms) ($p=0.52$) and number of accepted epochs ($p=0.08$) as their p-value > 0.05. However, between both groups, the % of correct hits ($p=0.00$) significantly differed as the p-value << 0.05. AD participants have much lower accuracy rates hitting the button to the correct stimuli compared to the neurotypical control participants.

Table 2

Behavioral Data for AD and Control during the Auditory Oddball Test

	AD	Control		
N=31 for each group	Mean ± SD	Mean ± SD	t-value	p
Response time (ms)	556.76±129.06	535.63±105.22	0.64	0.52
% Correct hits	59.58±38.31	88.75±15.87	− 3.78	0.00
# Accepted epochs	49.65±8.50	53.13±6.82	− 1.78	0.08

ERP: P300 Amplitude and Latency

The magnitude of the P300 amplitude is proportional to short-term/long-term memory and how much attention is devoted to the task being done. P300 latency indicates an individual's processing and stimulus classification speed, unrelated to behavioral responses. Table 3 indicates that the P300 amplitudes of participants with AD were significantly lower than the P300 amplitudes of neurotypical participants. Statistical comparisons from Table 4 showed decreased amplitudes in the mild AD participants ($t= -2.33$, $p=0.023$), as the p-value < 0.05. As for P300 latency, the neurotypical participants had relatively shorter latency than the mild AD group, but

the difference was not statistically significant across all different midline electrode placements, as the p-value > 0.05.

Table 3

Amplitudes and Latency of P300 ERP Graph per Electrode Site

	Amplitude (μV)	Latency (ms)
N=31 for each group	Mean ± SD	Mean ± SD
Alzheimer's		
Fz	3.50 ± 3.41	362.52 ± 44.23
Pz	4.12 ± 2.57	385.16 ± 38.58
Cz	4.06 ± 2.82	362.23 ± 43.52
Control		
Fz	6.59 ± 6.57	359.61 ± 38.52
Pz	7.95 ± 3.87	371.13 ± 34.67
Cz	6.04 ± 4.99	364.42 ± 39.25

Table 4

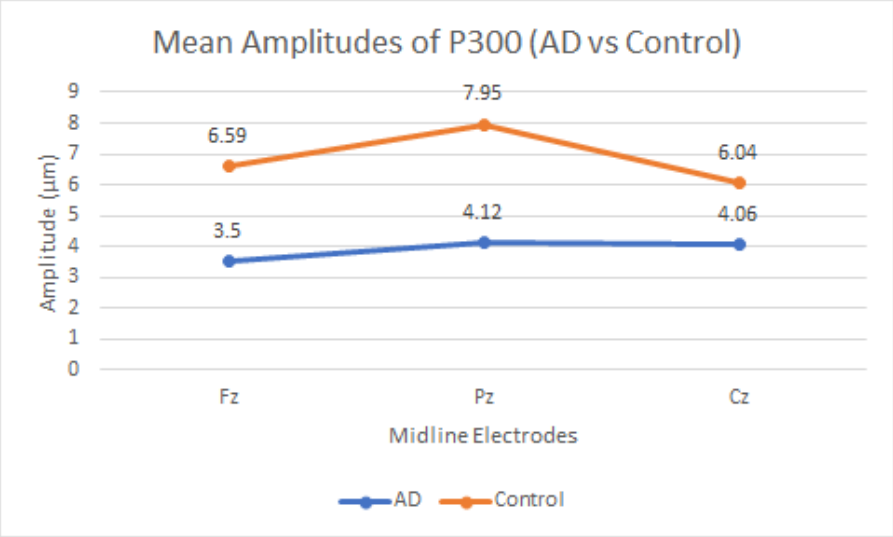
Statistical Significance of Comparison between AD and Control (Amplitude and Latency)

	t-value	p-value
Fz (Amplitude)	− 2.330	0.023
Pz (Amplitude)	− 4.593	0.000
Cz (Amplitude)	-1.929	0.058
Fz (Latency)	0.276	0.784
Pz (Latency)	1.506	0.137
Cz (Latency)	− 0.208	0.836

*$p < .05$, two-tailed

Figure 2

Mean Amplitudes of P300 (AD vs Control)

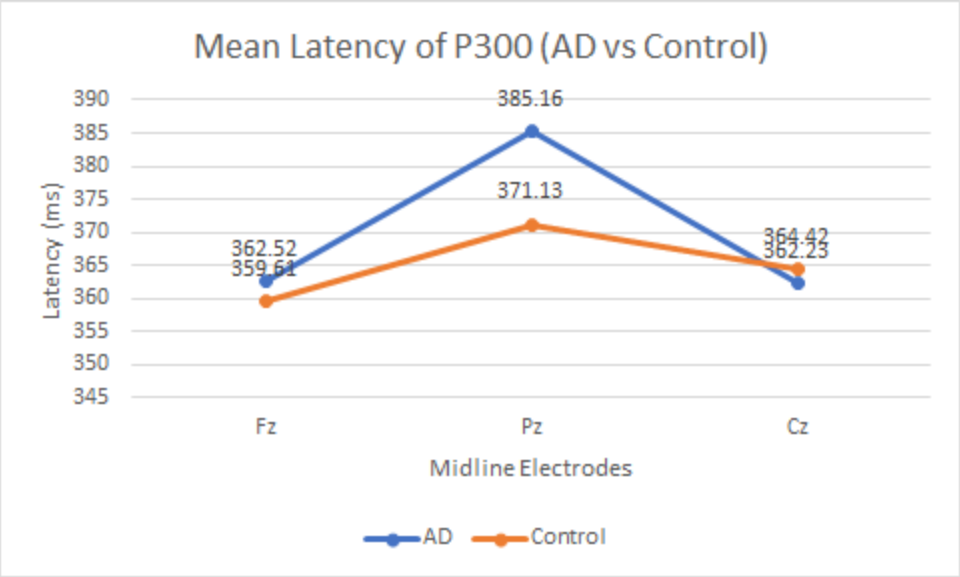


Note. The amplitudes of the Pz electrode site have the highest amplitudes for both groups.

With further analysis on the midline electrodes of the ERP values, the Pz electrode site had the highest amplitudes for both groups. By reviewing the results and the mean amplitudes in the mild AD group, the researchers found that the Fz electrode maintained the lowest amplitude. The Fz reference points for the EEG electrodes were concentrated in the anterior part of the head, which measures the brain activity in the frontal lobe. The frontal lobe is the part of the brain that manages cognitive and executive functions such as: planning, organizing, interpreting feedback from the environment, forming memories, and some motor skills. The decreased Fz amplitudes in mild AD participants in Figure 2 reveals that there is a significant decrease in cognitive function and more frontal region damage, suggesting that this metric may be used to quantify cognitive deficit in early stages of AD.

Figure 3

Mean Latency of P300 (AD vs Control)



Note. The latencies of the Pz electrode site have the highest amplitudes for both groups. The participants with AD have a higher mean latency than the neurotypical participants at the Cz electrode site.

Based on Table 3 and Figure 3, individuals with mild AD possess delayed P300 latency in the Fz and Pz midline electrode site and comparable P300 latency in the Cz midline electrode site. This further signifies that participants diagnosed with AD will have more concentrated damage in the frontal and parietal regions of the brain than the central regions.

Discussion

Limitations

There were several limitations to this research that are worth mentioning. When conducting any study focusing on mental disorders, accessibility usually poses a barrier to obtaining participants and sufficient results. Additionally, the nature of AD itself renders the result-gathering process difficult, as AD patients experience limited mental functioning

capacities. Furthermore, research in this area often revolves around and prioritizes interaction with the participants in both the control group and patient group, so restrictions on movement during the COVID-19 pandemic impeded the progression of a research project involving any form of interaction with participants. Thus, a replication study that relies on findings from a previous research experiment was determined to be the most appropriate avenue to conduct the researchers' own study.

A limitation of this study and the replicated study is the low specificity of P300 as a biological marker for AD. Changes in P300 can be caused by several neuropsychiatric disorders such as schizophrenia, dementia, and melancholic depression; thus, the changes in P300 are not limited to solely AD. Participants can be comorbid with AD and other neuropsychological disorders that can influence the amplitude of the P300. However, the meaningful difference between the P300 results from AD individuals and neurotypicals suggests that this ERP component could still be invoked in the early diagnosis of AD, although not in isolation.

Finally, the study presents no discussion of the demographics of the control and AD participants. Without knowledge of the social backgrounds of each participant, the researchers can not conclude whether the study is representative of a holistic population. It is important that the data collected is applicable to groups of different socioeconomic, cultural, geographical, and ethnic backgrounds. AD patients that encounter disparities are subject to a lack of accessibility to progessive AD studies. The study does not have information about the cost of the study; thus, it is not known whether this study can be replicated in different situations and different regions. The regions that are economically insufficient will lack the resources to replicate the study efficiently. Replication in research is a primary factor in determining the validity, reliability, and

generalizability of research, so it is important to take the aforementioned concerns into consideration to facilitate future replication of this study.

Conclusion

Alzheimer's disease (AD) is a serious, progressive neurodegenerative disorder, with symptoms of disordered executive functioning and working memory attenuation. Unfortunately, current treatments for AD fail to revert the cognitive deterioration that has already progressed in a patient (Papadaniil et. al., 2016). Numerous studies explore the correlation between P300 amplitude and latency with AD detection and progression, many of which discovering statistically significant results that support the validity of P300 as a viable metric. In order to further examine this correlation, the researchers have conducted a replication study that involves two cohorts of participants selected through their comprehensive survey and the MMSE results. The results indicated that increased P300 amplitudes and latency of Fz and Pz have statistically significant correlation with increased short-term and long-term memory cognition. As far as accuracy rates are concerned, the AD cohort demonstrated a markedly lower accuracy in pushing the correct buttons as opposed to their neurotypical counterparts.

The limitations posed by this replication study serves as a thorough diagnosis of the variables, correlations, and experiment conditions that require further investigation. Thus, considering the results of this study, future research in this area should focus on increasing the diversity of participants as well as expanding socioeconomic accessibility to address the practical limitations that have impeded further analysis of P300 as a useful biological marker for AD. With more thorough and detailed research into this problem, the efficacy of P300 as a biomarker for early-stage AD may be established and eventually strengthened, which will hopefully

facilitate the early detection of AD, drastically improve treatment outcomes, and ultimately enhance the overall quality of life of diagnosed patients.

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