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Original Research Article

A study of P300 and Mini Mental State Examination in Mild Cognitive Impairment and Alzheimer's Dementia

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Abstract: Alzheimer's disease (AD) is the most common cause of dementia worldwide and its prevalence increases steadily with age. The present study was undertaken to appreciate neural dynamics in Alzheimer's Disease in terms of amplitude and latency of event related potentials (ERPs) giving an insight into working of neuronal pools sub-serving P300, an endogenous cognitive component of ERP. The results of present study define the role of P300 as an early predictor of conversion of Mild Cognitive Impairment to AD, wherein the component P300 could become a potential non-invasive, and economical, diagnostic and prognostic tool. The study was conducted in Departments of Physiology and Neurology at S.M.S. Medical College and Attached Hospitals, Jaipur. The age range of the study population was 55-70 years that was categorized into three groups namely, Alzheimer's disease (AD) group, Mild Cognitive Impairment (MCI) group and Healthy Control group using Mini-Mental State Examination (MMSE) score as per Diagnostic and Statistical Manual (DSM)-V criteria. The sample consisted of 5 patients with mild to moderate AD, 30 patients with MCI, and 30 were healthy controls. ERP was recorded at Fz, Pz and Oz electrode sites using visual oddball paradigm, in which the subject was presented with a series of 100 visual stimuli, each consisting of a string containing eleven "S" alphabets out of which 80 stimuli consisted of all blue coloured "S" alphabets and the remaining 20 stimuli consisted of all red coloured "S" alphabets presented in the background of white colour. The amplitude of P300 displayed a significant difference across the three groups at Fz electrode site while the latency of P300 was significantly increased at Fz in AD group as compared to that observed in healthy controls.The time-locked feature of Fronto-Occipital Neuronal Pool and (space) amplitude-locked feature of Fronto-Parietal Neuronal Pool elicit the limiting neural mechanisms underlying neurocognitive processes that are sub-served by the select neuronal pools through P300 wave-form, a finding that could contribute significantly to prevention and management of Alzheimer's disease.
Keywords: P300, Alzheimer's disease, Mild Cognitive Impairment, Event related potentials

INTRODUCTION

Dementia is defined as a heterogeneous group of disorders caused by gradual neuronal dysfunction and neuronal cell death. This disorder can be described clinically as a syndrome that causes a decline in cognitive domain (i.e., attention, memory, executive function, visual-spatial ability, and language [1].

In India, as per the dementia India report 2010, there were about 3.7 million Indians (2.1 million women and 1.5 million men) with dementia. The most common cause of dementia worldwide is Alzheimer Disease, accounting for over 70% of dementia cases in individuals of more than 70 years of age [2]. The

figures reflecting the global burden of Alzheimer's disease are an understatement because according to Alzheimer's Disease International [2], as many as 28 million of the world's 36 million people with dementia are yet to receive a diagnosis, and therefore do not have access to treatment, information and care.

The factor limiting the early and efficient diagnosis of dementia (and Alzheimer's disease of course) is the lack of reliable and cost effective assessment methods, more so in developing nations like India. The present study was undertaken to find whether the electrophysiological techniques like Event Related Potentials in association with Neuropsychological assessment like M.M.S.E. could provide a window and signature to effectively diagnose the Alzheimer's disease cases and the persons suffering from mild cognitive impairment so as to catch the potential candidates for the drug therapy and therapy by other disease modifying agents well in advance when the defect has not become irreversible. In this context, the present study compared the individuals with normal cognition, with mild cognitive impairment and with Alzheimer's disease {segregated using clinical assessment as per norms} using neuropsychological measures like Mini Mental State Examination (M.M.S.E.) and electrophysiological measures like event related potentials, particularly the late positive component P300.

Though EEG seems to be a powerful tool but limitation is imposed because EEG is a representation of a mixed up conglomeration of numerous different neural activity. The classical P300 deflection emerges in a time-locked record as a positivity typically appearing approximately 300 to 400 ms following stimulus presentation. Timing of this component may range widely, however, from 250 ms and extending to 900 ms, with amplitude varying from a minimum of 5 µV to a usual limit of 20 µV for auditory and visual evoked potentials [3].

Despite the vast number of researches done in the context nothing conclusive has been obtained that clearly shows a direct relationship between the degree of cognitive impairment & derangement in ERP parameters. This study is a further attempt in order to gain a deeper insight into the functioning of human mind in relation to the cognitive decline in ERP parameters.

MATERIAL & METHODS

The present study was conducted in the Upgraded Department of Physiology in association with the Department of Neurology at S.M.S. Medical College and Attached Hospitals, Jaipur after obtaining the desired clearance from the Institutional Research Review Board (IRRB) and Ethics Committee of the Institution. The present study is an observational comparative research protocol.

Participants

As per the expected detectable differences in the mean of scores obtained on immediate word list of Mini Mental State Examination, the sample size was calculated. The sample population was segregated into three groups namely, Control Group, Mild Cognitive Impairment (MCI) Group and Alzheimer's Disease (AD) Group. The number of subjects for each group came out to be 58 subjects in each of the 3 groups, Hence, for study purpose 65 subjects were planned to be included in each of the three groups including 10 % attrition/drop out and loss to follow up. However, during the course of the study only 5 diagnosed cases of Alzheimer could be obtained. Also, with this consideration and assuming the Gaussian distribution of human population, 30 subjects were included in each group of control group and that of Mild Cognitive Impairment (MCI).

The subjects in each of the 2 groups namely, Alzheimer's disease and Mild Cognitive Impairment were selected from the Neurology OPD of S.M.S Medical College and Attached Hospitals, Jaipur. Age and sex matched healthy control subjects were then recruited from the general population.

Procedure

The participants of the study were subjected to the mini mental state examination, a questionnaire based tool that evaluates various domains of cognition related to orientation in space-time, registration, attention, calculation, recall/retrieval and language. The Mini Mental State Examination had a total 30 points and based on the scoring, the subjects were segregated accordingly into three groups namely, Control Group, group with Mild Cognitive Impairment /Mild Neurocognitive Disorder, and Alzheimer's Disease Group.

Participants were excluded from the study if they scored 14 or below 14 on the MMSE, and with a previous history of psychiatric or neurologic disorders, unable to consent, or history of addiction or visual problems. The final sample consist 5 patients with mild to moderate AD, 30 patients with MCI, and 30 healthy

controls. All participants gave informed consent to take part in the study.

EEG and ERP Recording, Analysis and Quantification

Subjects were seated on an ergonomic wooden chair in a sound attenuated, dimly lit, air conditioned room. EEG was recorded using Ag-AgCl EEG electrodes on a silicon bracket cap which was positioned on the subject's head according to known anatomical landmarks [4]. Electrodes were positioned on Fz, Pz and Oz electrode sites on the scalp according to the International 10-20 System [5,6].Ground electrode was placed at the forehead of the subject and the electrode on left mastoid served as reference.

Raw EEG was recorded using Brain Electro Scan System (BESS) Version 4.0 (Axxonet Systems Technologies Ltd., India). Impedance was kept below 5 Ω and electrical activities were amplified using an amplifier. A band pass filter of 0.5 to 70 Hz & notch filters of 50 Hz and 60 Hz with a delta of 6 were applied in order to remove the electrical line noise. The raw EEG recordings were digitized at sampling rate of 512 Hz. ERP was recorded using visual oddball paradigm as per set format in which each subject was presented with a series of 100 visual stimuli, each consisting of a string containing eleven "S" alphabets such that the string of all alphabets were displayed in a single line on centre of the display monitor. Out of the 100 stimuli presented, 80 stimuli consisted of all blue coloured "S" alphabets while the remaining 20 stimuli consisted of all red coloured "S" alphabets.

The background was kept white for all stimuli and the size of the alphabet was also kept the same. The sequence of presentation of these stimuli was pseudo randomized such that it was only after the presentation of enough blue colored string of "S" alphabets, a string of red colored "S" alphabets was displayed. Also it was ensured that no two consecutive strings of red colored "S" alphabets flashed on the screen. The stimuli consisting of string of red colored "S" alphabets served as target stimuli, while the string of blue colored "S" alphabets served as non-target item. The subjects were instructed to press a key on the keyboard on appearance of red colored alphabet strings. The digitized ERP data was displayed on a computer screen and was visually scored to identify portions of the data that needed deletion due to muscle movements and other sources of artefacts.

The raw EEG data so obtained for each subject was then subjected to further analysis by BESS software, where epochs were separated out for the target item using a pre-stimulus interval of 200 ms and an epoch length of 1020 milliseconds. Epochs in which the EEG signal exceeded ± 50 µV were rejected from further analysis. The obtained data was then selectively averaged separately for each electrode site.

Statistics

The data was analyzed using S.P.S.S.16 and Microsoft Excel 2010. One way ANOVA with post hoc analysis was used to analyze the data for the effect group (i.e. Healthy Controls, Mild Cognitive Impairment, and Alzheimer's disease) on the parameters of P300 (Amplitude and latency) at each electrode site.

RESULTS

The subjects of healthy control group had an M.M.S.E. score of 25-29, out of which majority of the subjects (eight) obtained a score of 25. The patients with Mild Cognitive Impairment (MCI) obtained a MMSE score of 19-24, out of which majority of the subjects (eight) obtained a score of 20, seven obtained a score of 21, while five obtained an M.M.S.E. score of 22 and 23, five patients with MCI obtained a score of 24 on the questionnaire based cognitive evaluation scale assessing the domains of language, memory, visuo-spatial orientation and registration.

The patients diagnosed as suffering from Alzheimer's form of dementia obtained a score of less than 19 on the M.M.S.E scale and out of total 5 patients of AD so recruited in the study, 3 patients obtained a score of 15, while the remaining 2 patients had a score of 16 points on the questionnaire based scale of cognition. On evaluation of the M.M.S.E. score, it was observed that patients of AD and MCI patients fell in the amnestic category of dysfunction of cognition. Minimal difference could be appreciated between Alzheimer's Disease group and MCI group regarding recall of objects and to follow a command along space-time.

Event Related Potentials:

The ERP wave-form data so evaluated and statistically processed exhibited the following trend: The local peak latency of P300 increased at all electrode sites i.e. Fz, Pz and Oz was observed at ANOVA (Analysis of Variance) F – test [a comparison of factors with total deviation] (with degree of freedom being 2 and 62) as 1.16, p-value 0.319 non – significant, NS; F (with degree of freedom being 2 and 62) 0.27, p-value 0.767 non – significant, NS; F (with degree of

freedom being 2 and 62) 1.94, p-value. 0.153, non – significant, NS, respectively .The values of F more than 1 at Fz EEG lead pair only refutes the null hypothesis that was framed at the start of the study, that observed no association between P300 and cognitive profile as categorized by M.M.S.E. scores on the scale of dementia, leading to the conclusion of an association, that is not significant, between P300 peal latency and M.M.S.E. score.

The local peak latency was more in Alzheimer's disease group than that observed in MCI and healthy control group at all the three EEG electrode sites of Fz, Pz, and Oz, respectively. No statistically significant effect could be appreciated when all groups compared together using ANOVA.

Table-1: Mean Amplitude (±SD) in µV of P300 wave for the target stimuli at Fz, Pz and Oz electrode sites

Electrode Site	Control Gp	MCI Gp	Alzheimer's Ds Gp
Fz	9.71(±6.29)	5.35(±2.80)	8.08(±0.80)
Pz	7.86(±6.38)	4.87(±4.16)	3.66(±2.89)
Oz	5.62(±3.91)	5.09(±4.37)	4.92(±1.63)

Table-2: Mean latency (±SD) in milliseconds of P300 wave for the target stimuli at Fz, Pz and Oz electrode sites

Electrode Site	Control Gp	MCI Gp	Alzheimer's Ds Gp
Fz	374.17(±80.07)	388.77(±94.37)	435.70(±23.53)
Pz	410.14(±81.05)	411.80(±103.99)	442.58(±86.38)
Oz	402.61(±86.68)	421.10(±114.17)	500.39(±114.01)

Table-3: **ANOVA Table of the Data**

ANOVA						
		Sum of Squares	df	Mean Square	**F**	**Sig.**
Amplitude (Fz)	Between Groups	286.82	2	143.41	**6.46**	**0.003***
	Within Groups	1377.27	62	22.21		
	Total	1664.08	64			
Amplitude (Pz)	Between Groups	167.62	2	83.81	**3.01**	**0.056 NS**
	Within Groups	1725.56	62	27.83		
	Total	1893.18	64			
Amplitude (Oz)	Between Groups	5.11	2	2.56	**0.16**	**0.855 NS**
	Within Groups	1009.73	62	16.29		
	Total	1014.85	64			
Latency (Fz)	Between Groups	16773.19	2	8386.60	**1.16**	**0.319 NS**
	Within Groups	446962.17	62	7209.07		
	Total	463735.37	64			
Latency (Pz)	Between Groups	4652.53	2	2326.26	**0.27**	**0.767 NS**
	Within Groups	541395.42	62	8732.18		
	Total	546047.95	64			
Latency (Oz)	Between Groups	41306.74	2	20653.37	**1.94**	**0.153 NS**
	Within Groups	660895.16	62	10659.60		
	Total	702201.89	64			
Age	Between Groups	624.07	2	312.04	**21.74**	**0.000***
	Within Groups	889.87	62	14.35		
	Total	1513.94	64			
MMSE	Between Groups	800.51	2	400.26	**186.68**	**0.000***
	Within Groups	132.93	62	2.14		
	Total	933.45	64			

Table-4:Post Hoc Tests

Dunnett T3					
Dependent Variable	(I) Gr Cat	(J) Gr Cat	Mean Difference (I-J)	Std. Error	Sig.
Amplitude (Fz)	Control	MCI	4.3620*	1.2567	.004*
		Alzhemier's Disease	1.6271	1.2158	.461 NS
	MCI	Control	-4.3620*	1.2567	.004*
		Alzhemier's Disease	-2.7349*	.6504	.001*
	Alzhemier's Disease	Control	-1.6271	1.2158	.461 NS
		MCI	2.7349*	.6504	.001*
Amplitude (Pz)	Control	MCI	2.9856	1.3912	.105 NS
		Alzhemier's Disease	4.2035	1.8558	.125 NS
	MCI	Control	-2.9856	1.3912	.105 NS
		Alzhemier's Disease	1.2179	1.6316	.838 NS
	Alzhemier's Disease	Control	-4.2035	1.8558	.125 NS
		MCI	-1.2179	1.6316	.838 NS
Amplitude (Oz)	Control	MCI	.5295	1.0702	.945 NS
		Alzhemier's Disease	.7086	1.0813	.882 NS
	MCI	Control	-.5295	1.0702	.945NS
		Alzhemier's Disease	.1791	1.1391	.998 NS
	Alzhemier's Disease	Control	-.7086	1.0813	.882 NS
		MCI	-.1791	1.1391	.998 NS
Latency (Fz)	Control	MCI	-14.5997	22.5958	.888 NS
		Alzhemier's Disease	-61.5350*	18.7634	.011 NS
	MCI	Control	14.5997	22.5958	.888 NS
		Alzhemier's Disease	-46.9353	20.8621	.096 NS
	Alzhemier's Disease	Control	61.5350*	18.7634	.011*
		MCI	46.9353	20.8621	.096 NS
Latency (Pz)	Control	MCI	-1.6527	24.0710	1.000 NS
		Alzhemier's Disease	-32.4360	45.6535	.855 NS
	MCI	Control	1.6527	24.0710	1.000 NS
		Alzhemier's Disease	-30.7833	47.1775	.882 NS
	Alzhemier's Disease	Control	32.4360	45.6535	.855 NS
		MCI	30.7833	47.1775	.882 NS
Latency (Oz)	Control	MCI	-18.4900	26.1715	.859 NS
		Alzhemier's Disease	-97.7813	59.1603	.370 NS
	MCI	Control	18.4900	26.1715	.859 NS
		Alzhemier's Disease	-79.2913	60.6960	.527 NS
	Alzhemier's Disease	Control	97.7813	59.1603	.370 NS
		MCI	79.2913	60.6960	.527 NS
Age	Control	MCI	-1.667	.995	.268 NS
		Alzhemier's Disease	-12.067*	1.312	.000*
	MCI	Control	1.667	.995	.268 NS
		Alzhemier's Disease	-10.400*	1.466	.000*
	Alzhemier's Disease	Control	12.067*	1.312	.000*
		MCI	10.400*	1.466	.000*
MMSE	Control	MCI	5.333*	.389	.000*
		Alzhemier's Disease	11.667*	.375	.000*
	MCI	Control	-5.333*	.389	.000*
		Alzhemier's Disease	6.333*	.362	.000*
	Alzhemier's Disease	Control	-11.667*	.375	.000*
		MCI	-6.333*	.362	.000*
*. The mean difference is significant at the 0.05 level.					

In the experiment to evaluate time locked event-related potentials, the mean amplitude (± SD) increased at EEG electrode pair at Fz site while the mean amplitude was reduced at Pz and Oz sites as denoted by F (with degree of freedom being 2 and 62) 6.46, p-value 0.003, significant, S; F (with degree of freedom being 2 and 62) 3.01, p-value 0.056, non – significant, NS; F (with degree of freedom being 2 and 62) 0.16, p-value 0.855, non – significant, NS . Discussed further in the discussion.

Post-hoc comparisons showed that the P300 amplitude in Fz was more in both healthy controls and AD patients than in MCI. No significant differences could be appreciated between groups at EEG lead pairs at Pz and Oz sites. However, as expected because of the disease process and its profile, age and M.M.S.E. exhibited significant difference in healthy controls, MCI and AD group.

DISCUSSION

The age group of the study population was designed in the range of 55 – 70 years in an effort to minimize the potentially confounding effects of age [7] and sex [8] on the parameters of Event Related Potentials (ERP) [9,10].

The normal control group and dysfunctional dementias group of MCI and AD all had a predominance of males and the age distribution was also in the range of 60-70 years, though patients with Alzheimer's and MCI have been documented to have a predilection for the female sex, however several longitudinal studies have shown inconsistent sex and gender differences. It has also been reported that females fare better on verbal memory task and males are more adept at manoeuvring the Visuo-spatial tasks [11-14].

The age range of patients with MCI and that of normal healthy controls of the study population was between 55-60 years (the < 60 years' group) and patients with AD as expected had an increasing age range of more than 65 years, i.e., in the range of 65-70 years that supports the premise of the dependence of AD on time and age

The ERP paradigm proposed and used in the present study was visual ERP, a premise so adopted to minimize the effects of culture and education on neurocognitive profiling using P300 component of ERP. The electrophysiological component P300 recorded with visual odd-ball paradigm appears to be insensitive to trans-cultural variations. Lai *et al*.[15] used auditory stimulation which is known to lead to faster P300 latencies in adults than visual stimulation [16, 17]. These two studies show similar P300 latencies suggesting that the P300 component might not vary significantly as functions of the background education.

The results of the present study have demonstrated no statistically significant difference in the peak amplitude and peak latency of P300 amongst the groups of Alzheimer's Disease, Mild Cognitive Impairment and Healthy Controls, leaving aside the readings so obtained from EEG lead pair at Fz site in terms of amplitude and latency. Statistically significant difference between groups could be appreciated in the P300 amplitude only at Fz site when the data was subjected to ANOVA evaluation that was also validated when pattern recognition was not done *a priori* and data dredging was subjected through *post hoc* analysis of the data. Statistically significant difference in values of latency of P300 wave generation could not be appreciated on ANOVA, though when the data was subjected to post hoc evaluation difference in values that were statistically significant was observed again at the EEG lead pair at Fz site in patients with Alzheimer's Disease.

The values of F-Test at *post hoc* analysis were above 1 for values of amplitude at Fz and Pz EEG lead pairs site and exhibited a similar trend for values of latency at Fz and Oz scalp sites, implying a cognizable association between the designate domains of P300 wave. The study so designed and its results act as a window into appreciation of neural processing and dynamics representing appreciation of alphabets (bits and bytes) of language .

However, no difference could be appreciated in the values of latency and amplitude in patients of MCI at the EEG lead pairs under evaluation namely, at Fz, Cz and Pz sites. In the context of a male preponderance and advancing age of the experimental cohort under study, a plausible rationale for the above findings could be the dysfunctional neurophysiological processing and synchronization (sub-serving neural dynamics of cognition) taking place in the area of the neocortex lying under the Fz site that essentially represents the frontal and pre-frontal cortical areas. Various studies have focused on amnestic MCI patients whose age was closer to that known to be associated with late-onset sporadic AD and whose education reflects the level reached by individuals of this age [18-20]. Lai *et al* [15] have also investigated the value of

combining the study of the P300 with neuropsychological variables in patients with AD and MCI that validate the concept that the use of the P300 in the assessment of AD could overcome and buttress one of the most challenging issues in neuropsychological testing namely, the cultural background of the assessed population [20] .

Lastra *et al*. [21] and Lai *et al*. [15] have observed that the latency of P300 is a useful marker in the early diagnosis of AD. This suggestion was proved by the observations with prolonged P300 latencies, where in patients, despite scoring 30 points on the MMSE, went on to develop AD in their lifespan. Recent studies of abnormal P300 parameters (i.e., long latencies and small amplitudes) in asymptomatic carriers of a gene mutation which later develop familial AD [22] almost 10 years before the disease onset support the validity of this test as a valid, specific and sensitive psychophysiological marker for AD. Neuropsychological tests and P300 variables have been used in the evaluation of the therapeutic response to anticholinesterase drugs in AD patients [23-27].

Tests such as recall of objects pose greater demands on cognitive processing and on the background education [20]. As AD impacts on early top-down attentional processes from its preclinical stages [28-30], such an assessment would identify early cognitive decline that is not accounted for by limited cognitive reserves, compared to, neuroimaging techniques (fMRI, PET or SPECT).

The present study was undertaken to evaluate the P300 profile on three EEG lead pair recording sites of Pz, Fz and Oz, where the P300 component exhibits its optimal parameters in terms of latency and amplitude [31]. The limitation of the present study was the small sample size. Subsequently, post-*hoc* analyses were undertaken to examine if the small size could limit the validity of the results so presented in the present study. Despite the relatively small sample size used in present study, the results were statistically significant in the domains of the ERP correlate of P300 at EEG lead pair at Fz site giving a plausible conclusion that patients with dysfunctional and compromised neurocognitive profile clinically manifested as Mild Cognitive Impairment and Alzheimer's Disease could be categorized, classified and monitored if neuropsychological and P300 variables are considered together. Future studies should further investigate this preliminary observation. The data of the present study fits recent suggestions of using multiple biomarkers to increase the sensitivity and specificity of detection methods for neurodegenerative dementias in general and AD in particular [32]. The combined use of measures from different levels (neuropsychology and neurophysiology) implies a more adequate integrated approach to AD and MCI research [33].

SUMMARY AND CONCLUSION

AD group fared badly on the neurocognitive scales of orientation and recall of objects. The patients of AD could answer leading questions and could follow the commands, though the attention span was severely compromised. A definite difference existed in the parameters of the local peak measurements of ERPs in three group's i.e. Normal Healthy Controls, Mild Cognitive Impairment and Alzheimer's disease.The latency is more in Alzheimer's disease and MCI group than healthy controls that clearly shows memory impairment and by P300 recording it can be recognized in early stages so preventive measures can be undertaken.

The time-locked feature of Fronto-Occipital Neuronal Pool and (space) amplitude-locked feature of Fronto-Parietal Neuronal Pool elicit the limiting neural mechanisms underlying neurocognitive processes that are sub-served by the select neuronal pools.

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