Journal of
Alzheimer's Disease & Parkinsonism

Ciuffini et al., J Alzheimers Dis Parkinsonism 2014, 4:5
DOI: 10.4172/2161-0460.1000158

Research Article Open Access

Visual Evoked Potentials in Alzheimer's Disease: Electrophysiological Study of the Visual Pathways and Neuropsychological Correlates

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Abstract

Visual Evoked Potentials [VEP] abnormalities are reported in Alzheimer's disease [AD] patients. It is necessary to understand the pathophysiology, clinical relevance and the relationship with the different visual pathways. We performed a study on AD patients compared to Multi-Infarct Dementia [MID] patients by means of different visual stimuli considered selective in stimulating Magnocellular [M], Parvocellular [P] and Koniocellular [K] system. All the patients underwent a neuropsychological assessment and evaluation of disability. Our results seem to confirm major involvement of both the M system and the K system in AD patients, in accordance with the pathophysiological hypotheses regarding visual disturbances in AD. Moreover, the neurophysiological data seem to be related both to the neuropsychological features of dysexecutive syndrome and apraxia and also to disability.

Keywords: Alzheimer's disease; Visual evoked potentials; Magnocellular; Parvocellular; Koniocellular; Dysexecutive syndrome

Introduction

Several data in literature suggest that Visual Evoked Potentials [VEP] could be useful as electrophysiological markers in Alzheimer's Disease [AD] [1-7]. The modifications of VEP seem to be related to the age of onset, the duration and the severity of the disease [8,9]. This connection has not been confirmed in other studies [10]. The delay of P2 component of Flash VEP [fVEP] with the relative normal latency of the P100 component of Pattern Reversal VEP [prVEP] has been proposed as being specific of AD [4,5]. However other authors refer the same kind of abnormalities in normal elderly people [11,12] and in patients suffering from different neuropsychiatric disorders such as Multi-Infarct-Dementia [MID] [13], Jacob Creutzfeldt's disease [14], Major Depression [15], Parkinson's Disease [16]. Moreover the results can be influenced by the mode of administration of the flashes [stroboscope, Ganzfeld, goggles] [6,17]. Both anatomic and physiologic knowledge of visual system and the features of the degenerative process in AD can provide some hypotheses to explain the changes of VEP. It is well acknowledged that visual information from the retina to the visual cortex is processed simultaneously via multiple parallel pathways with functional specialization [18]. The magnocellular [M] pathway works in a scotopic environment and gives information on depth and movement. It takes origin from the large retinal cells [rodes], projects, via the lateral geniculate nucleus [LGN], to the cortical medial temporal region and terminates in the posterior parietal area [19]. It has been defined as the "Where system" because its function is to determine the localization of the stimuli and whether or not they are moving [18]. The parvocellular [P] pathway works under photopic conditions and has to do with shapes and colors. It processes fine details and red-green information [20]. It starts from the small retinal cells [cones] and projects, via the LGN, to the inferior temporal area. It is defined as the "What system" because its competence lies within the identification of the stimuli. The third system or koniocellular [K] system originates from the small bistratified ganglion cells. Its function is less understood but it seems to contribute to processing blu-yellow information [21,22].

It has been proposed that flash response may be through the M system [23].

In AD the larger diameter neurons are primarily affected so the M pathway could be more involved [24]. While prVEP generate from the primary visual cortex fVEP are thought to be generated by both striate and extra striate cortex [25]. Anatomo-pathological data show that neurofibrillar tangles are more often found in association with cortex of the inferior temporal lobe [26]. This can explain delayed fVEP P2 response with normal prVEP P100 in AD.

Moreover neurotransmission in the M system is known to be cholinergic [27,28]. Several studies have demonstrated that anti cholinergic drugs provoke delayed fVEP P2 with normal prVEP P100 [29,30]. AD patients with cholinergic deficiency could reveal the same behavior.

Even if many authors report many changes in AD patients the relationship between the type of visual stimuli and the involvement of different visual pathway is not clear. Major critical review of the literature [18], on the basis of experimental data and through a speculative approach, suggest that P, M and K systems are mainly activated respectely by formal [pattern reversal], informal [flash] and colored [Blue/yellow] stimuli, emphasizing the phisical properties of the stimuli that are important for selective activation. M pathway is sensitive to low spatial and high temporal frequencies, P pathway is more sensitive to higher spatial and lower temporal frequencies and K

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Received August 01, 2014; **Accepted** October 01, 2014; **Published** October 06, 2014

Citation: Ciuffini R, Marrelli A, Necozione S, Marini C, Cavicchio A, et al. (2014) Visual Evoked Potentials in Alzheimer's Disease: Electrophysiological Study of the Visual Pathways and Neuropsychological Correlates. J Alzheimers Dis Parkinsonism 4: 158. doi: 10.4172/2161-0460.1000158

pathway contribute to blue/yellow information and motion processing. So multimodal visual stimuli more adequately assess the visual system.

The aim of this study is to analyze VEP responses due to different types of stimuli selective for the three major visual systems in AD patients compared to MID patients and correlate them with the course of the disease [age of onset, duration] the level/degree of cognitive impairment, the neuropsychological assessment and the disability.

Methods

Twenty six AD patients [10 M, 16 F, mean age 71,8 +/- 9,7] and twenty four MID patients [12 M, 12 F, mean age 76,2 +/-8,2] were referred for participation in the study. Diagnostic assessment was carried out before VEP testing was performed. AD patients met diagnostic criteria as outlined in the Diagnostic and Statistical Manual of Mental Disorders IV-R [31]. Moreover they submitted the McKhann criteria [32] and the diagnosis was supported by morphologic neuroimaging [brain MRI scan]. MID patients had an ischaemic score at Hachinsky score > 7 [33,34]. MRI or CT scan confirmed they have MID. Severity of dementia was assessed through the Mini Mental State Examination [MMSE] [35] and Global Deterioration Scale [GDS] [36]. The duration of the disease was 2,2 +/- 0,3 years for AD patients and 2 +/- 0,3 years for MID patients. The Hamilton depression score [37] was less than 16 for all patients. Both AD and MID patients were not taking any medications having significant effects on cognitive functions. The general educational level of AD and MID patients appeared comparable. Each subject also received a complete eye examination: patients with visual acuity inferior to 20/30 at Snellen chart [38] and/or cataract were excluded. Informed consent was obtained from all participants or their caregivers. The review board of The University of L'Aquila approved the study.

VEP stimuli were administered to preferentially activate the different, and functionally separate, pathways M, P and K. fVEP were administered using a Ganzfeld device. prVEP were performed by checkerboard pattern reversal displayed on a monitor subtending 15° x 12° at a viewing distance of 114 cm. The stimulus reversal rate was 1, 1 per second. Individual squares in the checkerboard patterns subtended a visual angle of 15°. The mean luminance of the stimuli was 112 cd/m^2 and the contrast was 98%. Colored stimuli were performed by horizontal blue/yellow and red/green bars at spatial frequency of 2 cycles/degree. Flash stimuli were presented by a Ganzfeld device on adapting background of 100 lux illuminate at the cornea. Standard EEG electrodes were placed at the Oz position of the 10-20 international system, the reference electrode was placed at Fz position and the ground electrode at Cz. Electrode impedance was less than 5000 ohm. The bandwidth of the recording system was digitized with a sampling rate of 256 samples per second and 11 bit resolution per sample. The time window was 300 msec. An automated baseline correction was applied for each entire trial Automated artifact rejection was provided. Two hundred fifty six individual trials were averaged. A repeated trial to verify reproducibility of the results was performed. The latency and the amplitude of the P100 of Pattern reversal VEP and of P2 of Flash VEP were measured. All the patients underwent neuropsychological assessment using MMSE, GDS, Instrumental Activities of Daily Living [IADL], Basic Activities of Daily Living [39], Weigl test [WT] [40], discrimination of segments and scrawls test [SST] [41].

A descriptive statistical analysis was conducted of the variables considered. The Wilcoxon rank sum test was used to evaluate the difference between VEP parameters, executive functions and disability scores in AD patients and in MID patients. The Spearman partial correlation was used to estimate the association between VEP parameters, executive functions and disability scores in AD patients taking into account the confounding effect of MMSE on the correlation among the variables [MMSE was taken as a covariance]. All statistical analyses were performed using SAS software [version 9.2, 2002-2008; SAS Institute, Inc., Cary, NC]

Results

The main purpose of this study was to confirm the usefulness of VEP testing in AD patients. We preferred to compare the results of electrophysiological studies between AD patients and MID patients to be confident about the specificity of the results as a marker of degenerative dementia according to the hypotheses mentioned above and with the majority of the studies published [41-45]. In Figure 1 the obtained waveforms for each component for an AD patient is depicted. A highly significant delay in latency of the fVEP

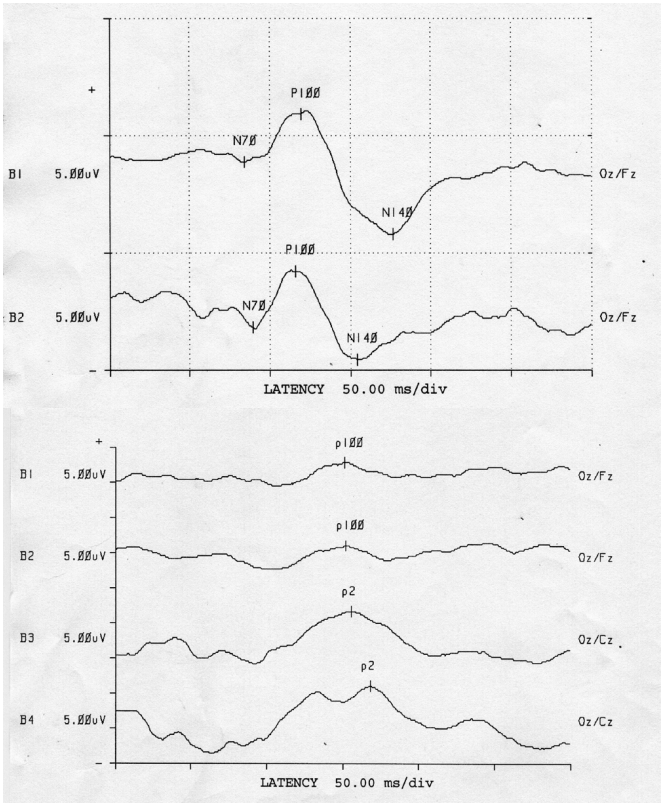

Figure 1: PR VEP (a), b/y PR VEP (b) and F VEP (c) in a AD patient.

	AD	MID	P
	Mean +/-D	Mean +/-D	
Flash VEP P2 latency	129.04 +/- 7.77	118.84 +/- 8.93	0.0003
Pattern Reversal Blue/ yellow VEP P100 amplitude	6.36 +/- 2.33	7.27 +/- 3.69	0.0036
Pattern Reversal Blue/ yellow VEP P100 latency	112.32 +/- 10.6	106.11 +/- 7.54	<0.0001
MMSE	18.78 +/- 3.79	21.29 +/- 6.26	0.027
IADL	4.38 +/- 3.03	6.25 +/- 2.13	0.030
BADL	4.69 +/- 1.56	6.33 +/- 1.12	0.0001
WT	6.84 +/- 4.39	10.5 +/- 6.61	0.036

Table 1: Differences between neurophysiological parameters, cognitive functions and disability in AD/MID patients (Wilcoxon rankum test).

P2 response was found in AD patients (Table 1). The second aim was to examine the role of the different visual pathways. A highly significant delay of latency and increase of amplitude of the pr-b/y VEP P100 component in the group of subjects affected from AD was found. Sartucci and Porciatti [16] report higher vulnerability of the b/y chromatic pathway in Parkinson Disease according with the hypothesis that the blue-cone pathway is early and predominantly affected in post-retinal degenerative disease.

These data seem to confirm the major involvement of the M pathway in AD but also of the K system. From a neuropsychological point of view the two group did not differ in terms of gender, age and duration of the disease. Nevertheless the two groups showed significant differences in term of MMSE, WT and the IADL and BADL scores (Table 1). In AD patients a significant correlation was found between the fVEP P2 latency and MMSE, GDS, BADL and SST and between pr-b/y VEP P100 latency and GDS, IADL, and WT. A significant correlation was found between pr-b/yVEP P100 amplitude and the duration of the disease (Table 2).

In Figure 2 scatter plots depicting correlations between fVEP-P2 latency, GDS and SST are depicted.

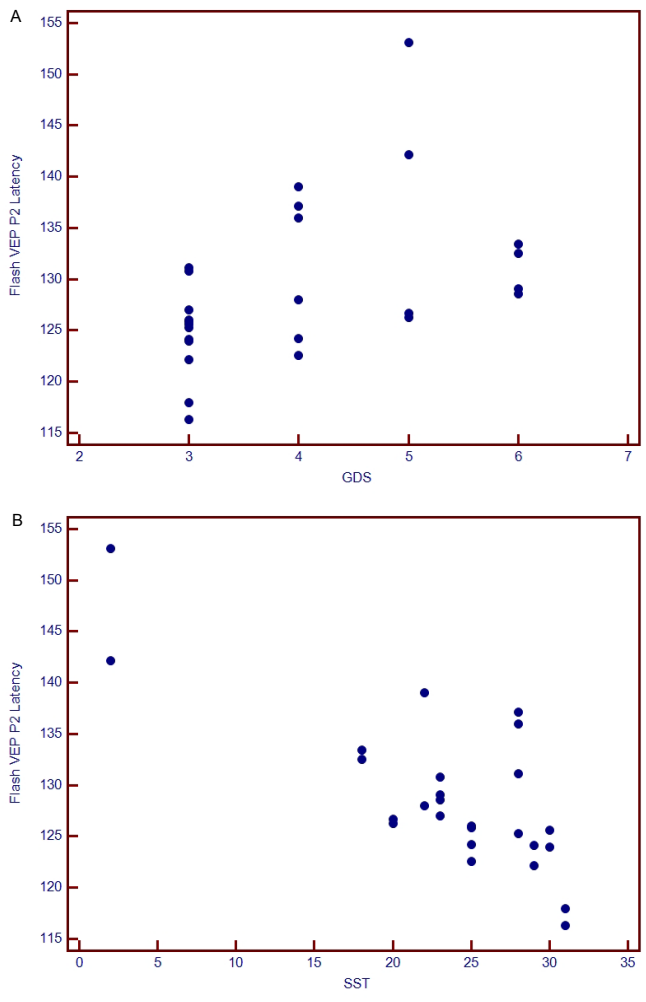

Figure 2: Correlations between flash VEP P2 Latency and GDS (a) and between flash VEP P2 Latency andST (b).

		r	p
Flash VEP P2 Latency	**GDS**	0.39	0.05
	SST	-0.559	0.0037
Pattern Reversal Blue/ yellow VEP P100 latency	**GDS**	-0.488	0.013
	WT	0.398	0.04
Pattern Reversal Blue/ yellow VEP P100 amplitude	**Disease duration**	0.605	0.0014

Table 2: Correlations of neurophysiological parameters, cognitive functions and disability in AD patients (Spearman partial correlation test).

Conclusion

It is well known that definitive diagnosis of AD is brain biopsy or autopsy when the patient is deceased. Differential diagnosis with other dementias, mainly MID, is crucial not only for prognosis but also for treatment. Neurophysiological approaches could provide some useful aids in the diagnosis and could be related to the pathogenesis of the disease. Delayed and decreased fVEP P2 component is considered to be a reliable electrophysiological marker of AD and could be proposed as an ancillary test both in the first step and in monitoring the course of the disease. Our results seem to underline the major involvement of delayed latency of fVEP-P2 in the larger diameters fibers of M system. Both latency delay and amplitude decrease of the pr-b/y VEP P100 seems to be evident in AD patients. Moreover enhanced knowledge of the visual pathophysiology underlines the role of the different visual pathways. The disturbances of neural transmission along the M system but also the K system seem to be more related to the pathogenesis of AD. The small sample size does not allow adequate statistical analysis. Moreover the complex interactions between the visual pathways in the retina, sub-cortical and cortical areas need to be explained by means of combined electrophysiological studies which include electroretinogram.

It is worthwhile to mention that both M and K pathways alterations seem to be related to the severity of the disease and to the disability scores. fVEP-P2 latency is related to poor SST results while pr-b/y VEP P100 latency seem to relate to poor WT results. pr-b/y VEP P100 amplitude is related to the duration of the disease. Weigl-Goldstein-Scheerer Color Form Sorting test [46] involves the sorting of different blocks and shapes and it has been used to study frontal lobe functions mainly involved in the dysexecutive syndrome. SST is considered a testing model for ideomotor and ideational apraxia. The correlations between VEP modifications and the dysfunction of executive functions and apraxia need to be explained as interaction between visual competence and higher motor functions. Moreover it is necessary to understand the relationship between the abnormalities of specific visual pathways and different cognitive impairment in AD patients so more complex neuropsychological assessment is needed to be done.

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