EVENT-RELATED POTENTIALS IN MONKEY AND MAN

PhD Thesis

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Publications related to the thesis

Full length papers and book chapters:

I. **Antal A,** Bodis-Wollner I, Ghilardi MF, Glover A, Mylin L, Onofrj M, Toldi J. (1993) The effect of levo-acetyl carnitine on visual "cognitive" evoked potentials in the behaving monkey. Electroenceph. clin. Neurophys. 86:268-274.

II. **Antal A**, Kovanecz I, Bodis-Wollner I. (1993) Visual discrimination and P300 are affected in parallel by cholinergic agents in the behaving monkey. Physiol. Behav., 56:161-166.

III. **Antal A,** Bodis-Wollner I. (1993) Animal models of Alzheimer's, Parkinson's and Huntington's disease. A minireview. Neurobiol., 1:101-122.

IV. Bodis-Wollner I, Tagliati M, Peppe A, **Antal A**. (1993) Visual and Visual-perceptual disorders in neurodegenerative diseases. In C. Kendall (Ed.) Bailliere's Clinical Neurology, Vol 2., pp. 461-491., Bailliere's Tindall, London.

V. Bodis-Wollner I, **Antal A.** (1995) On the functional significance of primate retinal dopamine receptors. In: Bonucelli U, Rabey JM. (Eds) Old and new dopamine agonists in Parkinson's disease. J. Neural Transm. Suppl. 45:67-74.

VI. Bodis-Wollner I, **Antal A**. (1995) Clinical aspects II. - Parkinson's Disease. In: Archer SN, Djamgoz MBA and Vallerga S (Eds): Neurobiology and clinical aspects of the outer retina pp:473-492, Chapman & Hall, London.

VII. **Antal A,** Bodis-Wollner I, Pfeiffer R. (1996) Simultaneously evoked primary and cognitive evoked potentials distinguish younger and older patients with Parkinson's disease. J. Neural Transm. 103:1053-1067.

Abstracts:

VIII. Bodis-Wollner I, **Antal A,** Kovanecz I. (1993) Low doses of scopolamine and acetyl-levo-carnitine dissociate "primary" from cognitive visual processing in the trained monkey. Inv. Ophthalmol. Vis. Sci., Suppl., 34:1174.

IX. Bodis-Wollner I, **Antal A,** Pfeiffer R. (1995) Visuo-cognitive processing in nondemented Parkinsonian patients - an event-related potential study. Neurol., 45(4):A340.

X. **Antal A,** Bodis-Wollner I. (1995) A clinically applicable method to evaluate visuo-cognitive processing. Neurobiol., 3:56.

CONTENT

Abbreviations:

AD	Alzheimer's disease
ALC	Acetyl-levo-carnitine
CNS	Central nervous system
CNV	Contingent Negative Variation
CPT	Central processing time
DM	Difference related to memory
EOG	Electrooculogram
ERP	Event-related potential
fMRI	functional Magnetic resonance imaging
MEG	Magnetoencephalography
MMN	Mismatch negativity
PD	Parkinson's disease
PET	Positron emission tomography
PP	Priming positivity
PRP	Priming positivity
SPECT	Single photon emission computed tomography
VEP	Visual evoked potential

1. INTRODUCTION

Almost everything we know about the brain stems from discoveries of the last few decades. In the IVth century, B.C., Aristoteles searched the origin of thoughts and feelings in the intestines and he thought that the function of the brain is simply to cool the body. More than a thousand years later Descartes believed that the brain is only a biological machine, and it is only the executive organ of the soul. Even at the beginning of this century the existence of neurones was doubtful. Currently neural science believes that all behaviour is a reflection of brain functions. Given that not only relatively simple behaviour such us walking and lying, but also affective and cognitive functions are the result of the activity of the brain, it seems to make sense that recording the brain activity can provide insights into the nature of human information processing. Event-related brain potentials (ERP) are physiological measures of the activity in the central nervous system that can be used in cognitive studies. Related measures include parameters of the spontaneous EEG and the magnetic homologues of the ERP, the magnetoencephalography (MEG). These electrical and magnetic measures have in common that they can provide records of brain activity at any scale of temporal resolution. This is especially important for studies involving fast-acting processes like rapid identification and categorization of stimuli. Nevertheless, measurements of ERP or MEG do not give enough information about the localization of intracranial sources. New neuroimaging methods like positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) have revealed the spatial location of many putative generators of cognitive processes by detecting changes in the metabolic activity of the brain. Recently PET and fMRI techniques have assumed a central role in identifying brain regions that may contribute to the performance of different cognitive operations. Although they have very high degree of spatial resolution, their lack of temporal accuracy currently offers limited value in the study of the dynamics of cognitive processing. Measures which rely on changes in the vascular system, cellular metabolism and neurotransmitter turnover do not reflect the temporal accuracy needed for chronometric studies. The importance of temporal factors make the ERP technique essential in these days. Since the first ERP studies appeared [149,150], many studies of human information processing were published but the vast ERP research has not solved major issues. This study tries to summarize recent knowledge derived from human and animal experimental ERP data of own experiments.

1.1. BACKGROUND

1.2. General aspects.

ERPs are averaged field potentials which are specifically related to the activity of neuronal circuits involved in the generation of brain's response to the stimulus. Most ERP studies focus on the time-locked activity up to 1000 ms following a stimulus. The components during this interval are divided into two broad categories based on their timing: (i) early or exogenous components are found between 0 and 200 ms, (ii) late or endogenous components occur between 200 and 1000 ms. Exogenous components are strongly dominated by physical parameters of the stimuli and their scalp distribution is determined by the modality of the eliciting stimuli. Endogenous components are much less sensitive to the physical properties of the stimuli and their components depend mainly on the presence and the nature of the cognitive task associated with the stimuli. It is thought that the amplitude of the endogenous components reflects the amount of information that is processed while their latency is determined by the speed with which the processing is accomplished [45,75,76,86].

1.3. Endogenous ERP components.

In different modalities and in different tasks many components of ERPs can be identified by their scalp distributions, timing and sensitivity for changing experimental conditions (for a review see[38]). ERP components which precede stimuli are the readiness potential (RP) or Bereitschaftspotential and the Contingent Negative Variation (CNV). RP is a precentral negativity that precedes the voluntary hand movement by as much as 1000 ms. CNV is a fronto-central negativity that occurs in a time interval when stimuli are presented in pairs. ERP components which can follow the stimuli are the processing negativity (Nd), Mismatch negativity (MMN), N200, P300, N400 and P4. The Nd wave is being isolated by taking the difference between two ERPs for the same stimulus when it is attended versus when it is unattended. MMN (sometimes called N2a) is a negativity around 200 ms following an auditory stimulus from the improbable stimulus group that can be task relevant or irrelevant. N200 component (sometimes called N2b) is a negativity for the task relevant stimulus that covaries with the P300. The P300 component is a most extensively studied component that can be evoked by an unexpected stimulus or by the absence of an expected stimulus. While previously mentioned negative components are elicited in response that are physically deviant from the context, N400 component is sensitive to a deviance in relation to the cognitive meaning of a stimulus (stings, words, sentences). P4 is a more posterior positivity than P300 elicited by feedback stimuli. These

waves are only representations of main components and it is possible that many of them represent overlapping components.

1.4. The P300 component.

The most completely studied endogenous component, the P300 or P3, is a positive component with a latency of at least 300 ms following the stimulus onset. It was first described by Sutton and colleagues[149,150], who showed that this potential can be elicited by an unexpected stimulus or the unexpected absence of a stimulus. Sutton's and his coworkers contribution was very substantial because they showed that P300 occurred in response to a stimuli which needed to be cognitively discriminated. P300 is most commonly recorded in a randomly ordered sequence of stimuli from minimum two classes, in which one stimulus occurs rarely - this stimulus is called a target stimulus -, while the other frequently - this stimulus is called a non-target stimulus - ("oddball paradigm", Ritter and Vaughan[123]). Sometimes two different types of stimulus occur rarely, one of them is the target stimulus and the other is a novel but non-target stimulus. The subject's task is to respond by pressing a button only for the target events and/or to keep a mental count of the number of presentation of the target stimuli and not to respond for the non-target stimuli. In this condition the P300 can be recorded with maximal amplitude at the parietocentral scalp distribution referred to the left and right mastoid processes[134,155]. P300 amplitude is characterized as being inversely related to the probability of the eliciting event, its latency is thought to vary with the time required for stimulus evaluation and to be independent of motor processing[86].

Using special tasks, more than one P300 component can be identified between 300 and 600 ms, the P3a, P3b (the measured P300 component is this wave) and slow wave. They can be differentiated by their distinct relationship to experimental manipulations because they are differentially sensitive for an improbable stimulus and they have different scalp distributions. The P3a is more frontal and it is not affected by whether the subject attending to the stimuli while the P3b and slow wave are more parietal in their scalp distribution and it is larger with attention[117].

The scalp distribution of P300 is controversial. Some studies suggested a modality specific distribution of P300[11,98] . Others found similar P300 distribution for different tasks and different modalities[145]. New neuroimaging methods such as PET, fMRI and MEG studies have revealed the spatial location of several putative generators of cognitive processes[121,124]. Recordings with intracerebral electrodes in patients who were candidates for neurosurgery have also provided important information about the intracerebral origins of P300. Many studies suggested the limbic system of the origin (or

one of the origins) of this potential[69,92,137,142] . Studies using MEG also support this theory[68,101]. Several investigators recorded similar activity in various regions of thalamus and basal ganglia with the same latency as recorded at the scalp P300[85,159] but others suggested that these regions may be active during the scalp P300 wave but they do not contribute significantly to the scalp recorded P300[137]. Studies have indicated the contribution of the medial temporal lobe (mainly the hippocampus) and the parietal lobe to the generation of scalp recorded P300[80]. A contemporary single photon emission computed tomography (SPECT) study also supports this hypothesis suggesting the importance of the medial frontal cortex in P3a and the occipito-temporal cortex in the P3b generation[54]. In spite of these, in a study it was pointed out that the integrity of the hippocampus is not necessary for the generation of P300 even though there is large hippocampal activity concurrent with or shortly after the P300 wave[137]. However, a recent study suggest the contribution of hippocampal region to novelty detection and P3a generation[83]. Other studies found that the integrity of the temporo-parietal junction is the most important in P300 generation[156]. Considering these data, it can be concluded that the scalp distribution of P300 varies significantly from experiment to experiment. It is possible that there is a basic P300 wave which can be superimposed by other potentials in different experimental conditions or, more possibly, there are multiple generators of P300 which are excited in different combinations in different experimental conditions. This theory is supported by a study where hemispheric ERP differences were found using different visual tasks[2]. If some generators are sensitive to - for example - the subjective probability and yet other generators are more sensitive to the cognitive meaning of a stimulus, then it is conceivable that several independent generators can be co-activated in different combinations. If so, the total number of generators involved in P300 generations depend on the nature of the task[81].

1.5. Variability of the normal P300.

Until recently relatively little consideration has been given to individual differences that can contribute to the wide statistical distribution of P300 measures in normal subjects. A primary difficulty in the application of ERPs to delineate abnormal responses in the patient populations is the large variability of the P300 in normals. Individual differences can be found in the P300 latency as well its amplitude.

Variability of latency.

Almost all studies agree that P300 latency increases with age and the age-related changes are similar in every modality. Most of the studies suggest that adults show a significant linear regression with age with a slope between 0.8 and 2 ms/year, other

suggest a curvilinear relationship between P300 latency and age. However, the interaction between P300 latency and task difficulty seems to be variable in different age groups in different studies (for a review see[118]). P300 latency is related to intelligence independently of age. A recent study[93] therefore suggests that P300 indexes some cognitive process that is connected to the general mental ability measured on IQ tests. No significant differences for P300 latency have been obtained between male and female subjects. Many studies found a marked genetic influence mainly on P300 latency in monozygotic and dizygotic twin pairs[118] and in alcoholic subjects and in their relatives[120]. Body temperature also has an effect on P300 latency[118].

Variability of amplitude.

Personality types have an effect on P300 as well. Extroverts have smaller P300 amplitudes than introverts suggesting that extroverts may have difficulties maintaining attention for a long period of time (for a review see[118]). Females have larger P300 potentials[118]. Several investigations found that recency of food and season of the year also have an effect for P300 amplitude[118].

Variability of scalp distribution.

Several authors suggested age-related changes in scalp distribution being the P300 larger in the frontal regions with increased age[111,113].

1.6. P300 and its abnormalities.

P300 is used to study a wide variety of clinical disorders that have cognitive consequences, such us alcoholism, autism, attention deficit hyperactivity disorder, multiple sclerosis, schizophrenia, psychiatric disorders, AIDS and different types of dementias (for a review see[118,112]). In patients with chronic alcoholism P300 latency delay and amplitude decrease were also found. Recently it was suggested that in normal subjects P300 may even have predictive value as an index of vulnerability for alcoholism when well-designed paradigms are used to elicit ERPs[119]. In autism and in attention deficit hyperactivity disorder P300 amplitude decrease was found. In multiple sclerosis (MS) P300 latency delay was often observed but not in every patient. In MS deficient cognition is rarely reported and it has been often attributed non-direct consequences of the disease. Abnormal ERPs may suggest that cognitive decline in MS needs to be considered in the disease process. In schizophrenic patients asymmetrical P300 amplitude decrease was found being lower at the left side. In other psychiatric disorders such as in depression, the P300 wave is reduced and its latency can be increased slightly. Psychopathic patients have larger and later P300 while obsessive-compulsive patients have faster P300 component[112]. In patients with AIDS P300 latency delay was detected

even without dementia.

Since altered ERPs have been reported in demented patients[66], scientists have been searching for an easily administered, simple, reliable ERP method for diagnosing patients with dementia. In the last two decades many ERP studies of demented patients appeared in the literature. Even though these studies found alterations in ERP activity in patients, these alterations have lacked the diagnostic specificity necessary to distinguish clearly between patients and controls and among patients with different neurological diseases. On the other hand, the fact that the ERPs can be used to index changes in the timing of information processing has led to its use in characterizing the information processing abnormalities in patients with neurological and neurobehavioral disorders. ERP activity with any kind of movement disorders can be particularly informative because the timing and appearance of ERP components are independent of response selection and execution[86]. Using ERP component latencies in combination with response times makes ERP a unique tool for studying the nature of cognitive deficits. Modern imaging techniques such us PET and fMRI have low temporal accuracy and with these techniques difficult to track impaired timing, i.e. slowing down of cognitive processing in the course of the disease. ERPs and mainly the P300 component can be a diganostic tool in early stages of different types of dementias. It was also suggested that cognitive potentials can be used to differentiate between subcortical (Huntington's and Parkinson's disease, Progressive supranuclear palsy) and cortical (Alzheimer's disease, Multi infarct dementia) dementias on the basis of their early and late component latencies. Several investigators demonstrated the utility of P300 at differentiating between dementias and pseudodementia found in depression (for a review see[112]). However, the delays found in most type of early dementias have not been sufficiently large to reach the statistical criteria. The situation may change when more parameters of early and late ERP components, scalp topographies and additionally specific paradigms and tests are used.

2. VISUAL ERP STUDIES IN HUMANS.

In human studies auditory stimuli are more commonly used than visual or somatosensory stimuli to elicit ERPs. Nevertheless, visual cognitive evoked potentials geared great interest in clinical practice and in cognitive neurophysiological research during the last fifteen years. The usefulness and importance of using different modalities of stimulation have been extensively argued in the literature. The auditory paradigm is easier to be utilized but it gives less information and it appears that the auditory P300 habituates quickly while P300 from an active visual task is relatively constant over a long

series of trials[62] , so it can be used in clinical situations with confidence. In a recent study the interlaboratory consistence of visual ERPs was also proven[37].

Many types of visual stimuli are used. Earlier studies which investigated visual ERPs mainly utilized letters, numbers or symbols[16,35,52,59,60,80,90,131,135], words or sentences[1,15,87,147] and geometric shapes[110,125,141,151]. But more the complexity of the stimuli widens the variability of normal data and it suppresses the clinical usefulness of the tests. Recently there is an interest using less complex visual stimuli mainly for clinical purposes[81,95,104,119,143]. Most of these studies presented visual stimuli in a typical oddball paradigm.

The scalp distribution of visual components is a very important characteristic. The exogenous components (N70, P100, N140) are best recorded over the occipital cortex while the endogenous components (P200, N200, P300, N400, Slow wave) over the central-frontal and central parietal areas.

In visual tasks, the primary positive component (P100) of the visual evoked potential (VEP) is strongly dominated by physical parameters of the stimulus, such as spatial frequency, luminance or contrast of the pattern[31] while the P300 component, like in every modality, depends on the cognitive characteristics of the stimuli[46,86,149,150]. Some studies reported delayed P300 elicited in visual tasks in dementing disorders that also cause impaired primary visual processing and delayed P100[24]. This is particularly evident in Parkinson's disease (PD) where it is well known that a primary VEP deficit is dependent on specific stimulus attributes such as spatial frequency[19,70,107,144]. These findings raise the question, whether there is any relationship between P100 and P300 components of the visual ERP. If P300 reflects modality independent information processing related to discrimination only, it may be independent from the primary sensory potential. On the other hand, if there is some interdependence of P300 and P100, the normative data could help us to understand responses that are seen in pathology by statistically determining how much delay of the P300 component can be expected given a delayed P100. Previous studies using *simple* visual stimuli such as checkerboard or bar patterns, have not attempted to quantify the relationship of primary and cognitive ERPs in man[21,95,104,119,130,143,154]. By *simple* we mean stimuli, without obvious cognitive loading. In the present study we used two simple sinusoidal grating patterns presented in an oddball paradigm to consider the possible connection of the primary and cognitive components. From the point of view of task difficulty, this spatial frequency discrimination task of the two patterns one octave apart presents an "easy" task and hence is expected to be potentially useful for patients with presumed cognitive difficulties as well. Furthermore we have selected relatively low spatial frequency patterns to minimize

the effect of blur on the retinal image[32,33] and on primary electrophysiological responses[17]. A sinewave pattern is imaged as a sinewave pattern on the retina and blur and scatter cause only a loss of contrast not a change in waveform. It is also known that the effect of age on primary VEPs[18] is minimal to low spatial frequency sinusoidal grating. Therefore for studying the effect of aging on cognitive and not on optical aspects of vision, a spatial frequency discrimination paradigm of sinusoidal gratings appears advantageous for two reasons. Square wave and checkerboard patterns are spatially complex i.e. composites of several patterns, hence different components of such patterns may be differentially degraded by optical or neural factors. In particular, using complex stimuli optical imperfections associated with aging would be near impossible to control and to disentangle from neural aging effects. Secondly, the anatomy and physiology of processing sinusoidal grating responses in the visual system have been extensively explored in cats and in Old World monkeys[43,44,55,72] and also studied in humans[148].

A few previous studies both in PD[102,152] and other diseases[112] measures of P100 and P300 were not taken in response to the identical stimulus. Most visual ERP studies reported that a P300 latency delay is only found in demented PD patients[66,144,151,153]. However, the relationship between P300 latency and diverse dementia scales is controversial[110,116].

Two human studies were undertaken in order to clarify the following issues:

(1) To evaluate all the prominent deflections of the visual ERPs from P100 to P300 and establish normative parameters: absolute latency and amplitude values and interocular correlations. In contrast to the extensively explored visual P100 and P300, the intervening deflections, in particular the positive wave following N140 of the VEP (P200) and the negative wave preceding P300 (N200) received relatively little attention in previous studies.

(2) To determine if a relationship exists between primary and cognitive ERP components in healthy subjects (first study) and in PD patients (second study).

(3) Comparing group means of patients to normative standards may be misleading since given the relatively large interindividual spread, a "normal" latency may be abnormal for an individual subject. Based on these considerations we wished to develop a method to evaluate individual normal subjects and patients by normalizing cognitive ERPs to primary ERPs. We did this by measuring the amplitude ratio (P300/P100) and timing difference (called "cortical processing time" - CPT) of primary (P100) and P300 responses.

2.1. METHODS

Subjects of the first study.

Subjects were 41 normal individuals with no prior history of neurological or ophthalmological disorders, with a visual acuity score of at least 20/25 with or without correction. Their age range was 22 - 77 years (mean = 45.78±17.3 years; 23 females and 18 males).

Subjects of the second study.

Normal subjects were 20 volunteers with no history of neurological or ophthalmological disorders with a visual acuity of 20/25 or better with or without correction. The age range of the normal volunteers was 46 - 75 years (mean = 61.2±9.1 years) [8].

27 PD patients in the age range of 48-81 years (mean = 63.15±8.75 years) were tested with a visual acuity of 20/40 or better with or without correction. In 7 of the patients the behavioral and electrophysiological responses did not show good repeatability even in the same trial, they were excluded from the present analysis. The average duration of PD was 6.7±4.57 years, the averaged Hoehn & Yahr stage of the patients was 1.92±0.67 and the averaged Unified Parkinson's Disease Rating Scale motor score was 14.47±7.76. Disease duration was evenly distributed across the age range of the patients. At the time of the testing the patients were on different medication[8].

Stimuli.

Stimuli were horizontal gratings with a sinusoidal luminance profile, produced on a TV monitor under computer control. Two different spatial frequencies were used: the 0.5 cycles/degree (c/d) grating was presented rarely (20% and 30%), the 1 c/d grating frequently (80% and 70%). The stimulus duration was 500 msec. The repetition frequency was 1.22 Hz. The mean luminance and the contrast of the stimuli were 60 cd/m2 and 50%, respectively. When the pattern was off, the screen had the same luminance as the mean luminance of the pattern. Field size diameter was 13.5 x 13.5 degrees. The viewing distance was 1 m.

Recordings.

The subjects were asked to discriminate between the stimuli by pushing a button when a target stimulus occurred. After every trial they were asked to give verbal reports of the number of presentations of the "rare" (target) pattern. Each eye was tested separately and together. The non-tested eye was covered by a gauze patch to keep it light adapted. Subjects were asked to focus on a small cross in the middle of the screen and not to move their eyes. Previous ERP studies from this laboratory show that in this kind of

visual stimulus paradigm (i.e. two identical visual patterns occupying in sequence in the same central visual field and the task is discrimination), no systemic eye movements occur[21]. Each trial was initiated by the experimenter. A practice run was given to ensure that each subject understood and was able to perform the task. Their compliance and fixation were monitored by one of the experimenters. One trial consisted of the presentation of 30 patterns. A total of 12 trials was presented for each eye.

ERPs were recorded using gold cup electrodes (diameter of 6 mm, Nicolet products). Standard 10/20 placements were used. Primary visual evoked potentials were recorded at Oz referred to Fz and cognitive evoked potentials were recorded at Cz referred to linked mastoids (Rlm). The ground electrode was placed between Fz and Cz.

The signals were amplified 10,000 times. The data were collected and analyzed by an IBM compatible PC using Venus software (NeuroScientific Corporation). Filters were set at 0.3 and 70 Hz (-3 dB). The sampling rate was 256 Hz. Automatic artefact rejection was used if the amplitude of the response was higher than 50 μV.

P100 component was defined as the major positive component in the waveform following the onset of the stimulus in the time window 80-120 ms. N140 component was defined as a first major negative wave following P100 in the Oz - Fz montage in the time window 140-200 ms. P200 was defined as a first major positive wave in the Cz - linked mastoid processes montage in the time window 200-250 ms. N200 was defined as a major negative wave occurring before the P300 component in the time window 280-380 ms. P300 latency was measured for the major positive deflection occurring between 350 and 550 msec following the onset of the target stimulus. Amplitudes were measured from baseline. Baseline was established as zero volt at stimulus onset based on the first five points (19.5 msec). Amplitudes and latencies of the ERP components were expressed as the mean and $\pm$ 1 SD.

Statistical test of normality was performed using Kolgomirov-Smirnov analysis, showing the normal distribution of the data. Pearson's correlation coefficients were calculated to compare P100, N140, P200, N200 and P300 latencies and amplitudes and P300/P100 amplitude differences and age. The criterion of significance was $p < 0.05$.

2.2. RESULTS OF THE FIRST STUDY: NORMAL SUBJECTS.

Reproducible primary and cognitive evoked potentials were recorded in all (n=41) observers. The consistency and the reliability of the P300/P100 amplitude ratio were high across trials and in subjects. Fig. 1. shows averaged ERP potentials recorded to the target and the non-target stimuli in one subject. A typical trace for the non-target stimulus

consisted of N70, P100 and N140 components. The first of these, a negative component of the primary VEP, with a peak latency around 70 ms (N70), could not be identified in all recordings. N70 is not optimally obtained with low spatial frequency of stimulation[20,22] which was used in these experiments and we did not evaluate N70. A typical trace for the target stimuli consisted of P100 and N140 components in the Oz - Fz montage, followed by a positive component (P200), a negative wave (N200) and by a positive wave (P300) in the Cz - linked mastoids montage. Table I. shows the mean latency and amplitude values recorded to the target stimulus.

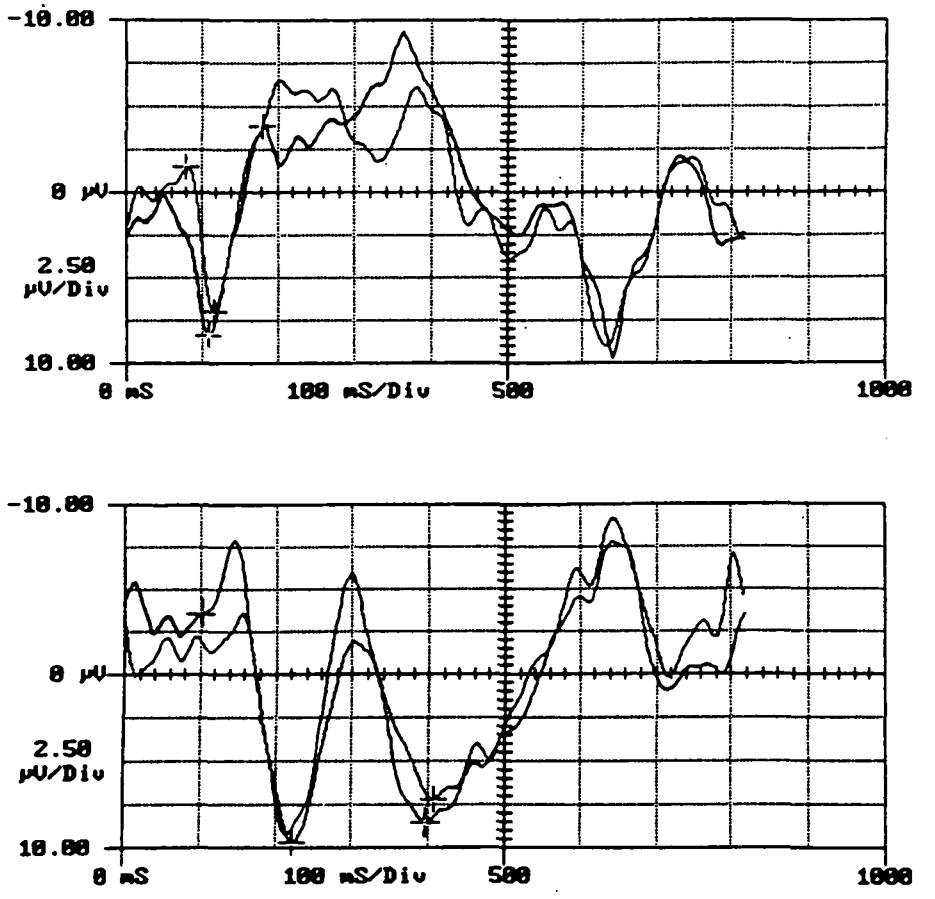

Fig. 1. Averaged (n=36) primary visual (active electrode Oz - reference electrode Pz) and cognitive (active electrode Cz - reference electrode linked mastoids) evoked potentials recorded in one subject for right eye stimulation. Positivity is downward.

TABLE I.

Right eye

	20% target		30% target	
	L	A	L	A
P100	117±17	6.11±3.9	115±14	5.61±3.5
N140	181±16	-4.23±4.6	181±16	-4.11±4.3
P200	244±21	5.68±3.0	239±26	5.13±3.4
N200	339±32	-1.54±3.1	340±34	-0.56±2.8
P300	452±42	7.84±3.6	447±41	7.43±3.2

Left eye

	20% target		30% target	
	L	A	L	A
P100	116±23	6.01±3.5	117±16	5.94±3.1
N140	178±23	-5.10±4.0	182±20	-5.02±4.4
P200	243±29	5.8±3.3	243±24	5.18±3.7
N200	330±37	-1.90±3.6	335.5±35	-1.53±2.8
P300	453±43	7.64±3.1	445±42	6.97±3.1

Both eyes

	20% target		30% target	
	L	A	L	A
P100	113±14	7.24±4.5	111.5±12	6.90±4.5
N140	177±20	-4.00±4.2	173±14	-4.22±4.7
P200	231±20	6.23±3.8	235±23	5.95±2.7
N200	329±38	-1.70±4.4	330±38	-1.38±3.3
P300	443.5±41	8.28±3.3	446±45	6.97±3.0

The table shows the mean latency (L:ms) and amplitude (A:μV) values of ERPs of 41 subjects for the target stimuli. The probability of the target stimuli had no significant effect on the latency and the amplitude of ERP components.

Correlations between monocular and binocular recordings. ERPs were recorded both monocularly and binocularly. There was a significant correlation in P300 latencies between monocular and binocular recordings (between right eye and left eye: $r=0.84$ (20%), $p<0.005$; $r=0.79$ (30%), $p<0.005$; between right eye and both eyes: $r=0.81$

(20%), $p<0.005$; $r=0.85$ (30%) $p<0.005$; between left eye and both eyes: $r=0.77$ (20%), $p<0.005$; $r=0.81$ (30%), $p<0.005$;). For P100 latency, there was a significant correlation between left and the right eye recordings ($r=0.76$ (20%); $p<0.005$); between the right and both eyes recording ($r=0.57$ (20%); $p<0.05$); and between the left and both eyes recording ($r=0.49$ (20%); $p<0.05$). Since we did not find any significant difference in the latency of the two monocular recordings, we present the results below for monocular ($n=82$) and for binocular ($n=41$) data.

The effect of age on the ERP. There was no effect of age on either the latency or the amplitude of P100, N140 and P200. A positive correlation was found between age and N200 latency (monocular: $r=0.49$ (20%), $p<0.05$; $r=0.59$ (30%); $p<0.05$; binocular: $r=0.49$ (30%) $p<0.05$). The slopes of the linear regression lines relating N200 latency were 0.88 ms/year (20%) and 0.94 ms/year monocularly and 0.85 ms/year (20%) and 0.90 ms/year (30%) binocularly. There was a positive correlation between age and P300 latency (monocular: $r=0.59$ (20%) $p<0.05$; $r=0.54$ (30%) $p<0.05$; binocular: $r=0.62$ (20%) $p<0.05$; $r=0.54$ (30%) $p<0.05$) (Figure 2.). The slopes of the linear regression lines relating P300 latency and age were 1.09 ms/year (20%) and 1.05 ms/year (30%) monocularly and 1.13 ms/year (20%) and 1.06 ms/year (30%) binocularly (Table II.). N200 and P300 amplitude did not correlate with age (Fig. 2.).

TABLE II.

	monocular		binocular	
	20%	30%	20%	30%
CPT	339±44	329±45	335±40	334±45
P300/P100 amp ratio	2.15±1.9	1.80±1.7	1.83±1.7	1.44±1.4

The table shows the mean latency (ms) and "normalized" (see text) amplitude (μV) ratios of different ERP components for the target stimulus. The probability of the target stimulus had no significant effect on these components or calculations.

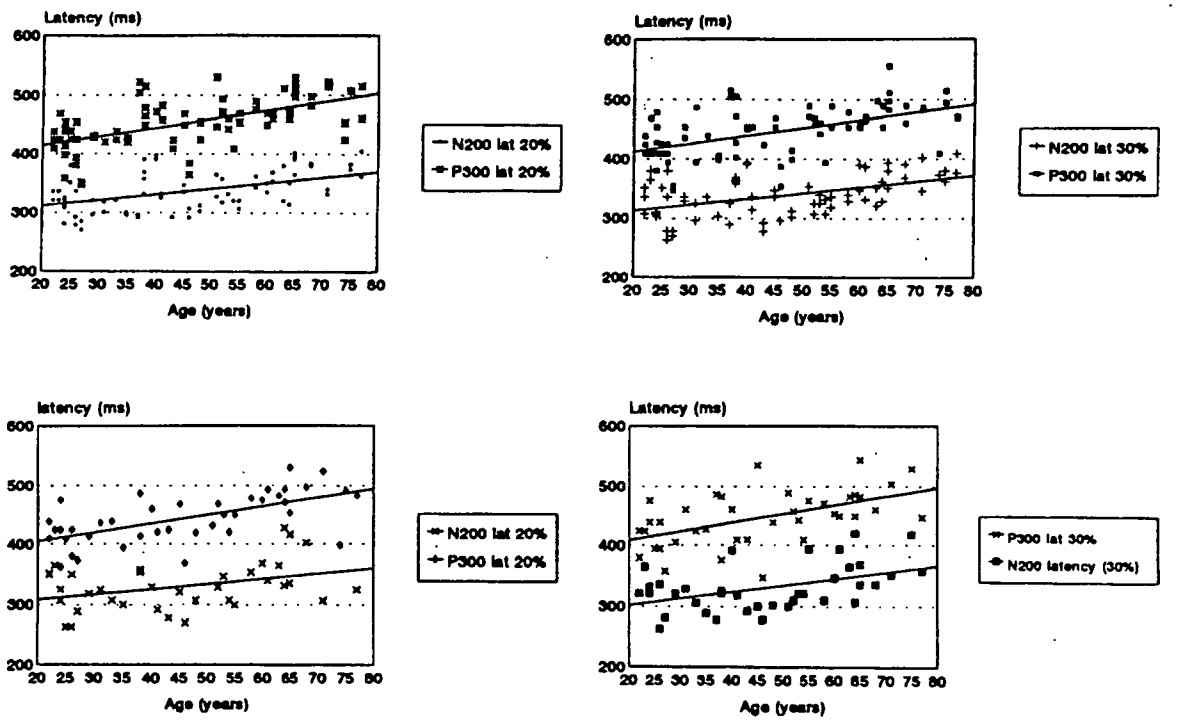

Fig.2. N200 and P300 latencies significantly increased with age (upper graphs - monocular recordings: N=82; lower graphs - binocular recordings:N=41). For slopes and correlation coefficients see Table II.

Age and P300/P100 amplitude ratio. The P300/P100 amplitude ratios were 2.15±1.9 (20%) and 1.80±1.7 (30%) for monocular recordings and 1.83±1.7 (20%) and 1.44±1.4 (30%) for binocular recordings. The P300/P100 ratio did not change significantly with age. The correlation coefficients were r=0.047 (20%) and r=0.02 (30%) in the monocular recordings and r=0.2 (20%) and r=0.03 (30%) in the binocular recordings (Fig. 3.).

Correlations between P300 and other components. There was only a positive correlation found between N200 latencies and P300 latencies (monocular: r=0.65 (20%), $p<0.05$; r=0.59; (30%), $p<0.05$; binocular: r=0.54 (20%), $p<0.05$; r=0.55 (30%), $p<0.05$).

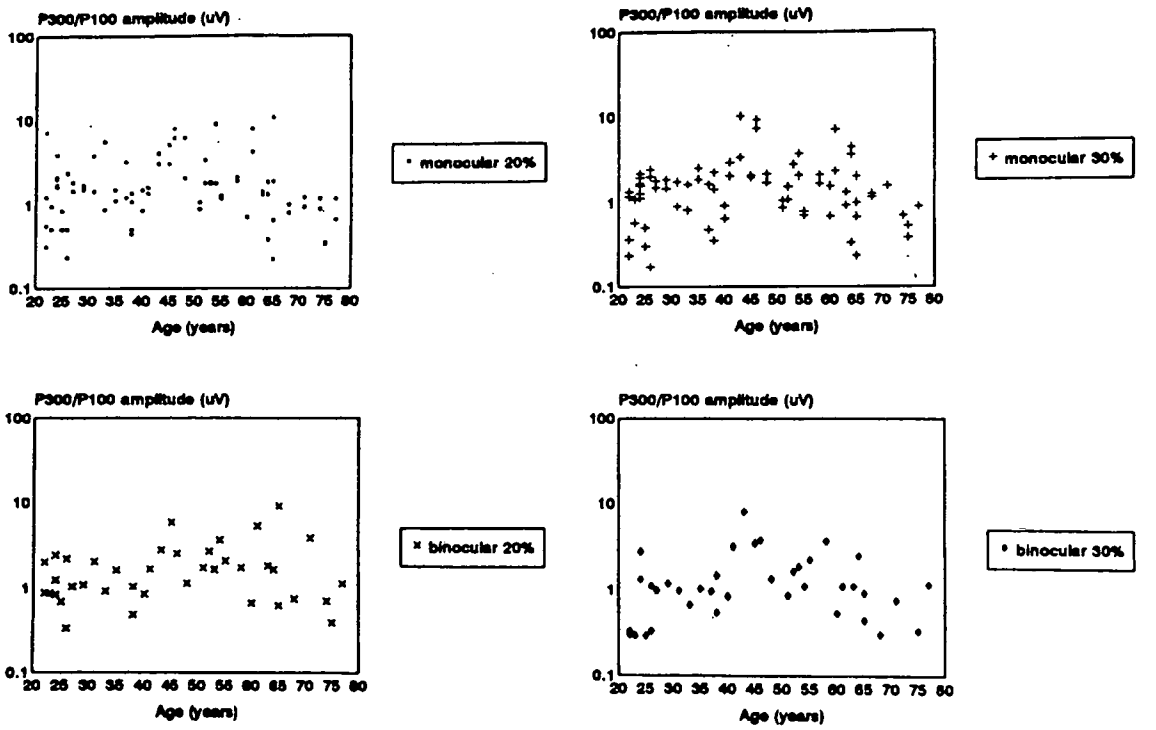

Fig. 3. The P300/P100 amplitude ratio did not change remarkably with age although the values tend to be slightly lower for younger and for older subjects (monocular recordings: N=82; binocular recordings: N=41).

2.3. RESULTS OF THE SECOND STUDY: NON-DEMENTED PARKINSONIAN PATIENTS.

Correlation between P300 and other ERP components within each group.

ERP latencies. In controls a significant correlation was found between N200 and P300 latencies in the right eye at 20% ($r=0.86$; $p<0.001$), at 30% ($r=0.66$; $p<0.05$) stimulus probability, in the left eye ($r=0.58$; $p<0.05$) and both eyes at 20% ($r=0.68$; $p<0.05$) and at 30% ($r=0.59$; $p<0.05$) probability. In the PD group significant correlation was found between N200 and P300 latencies in the right eye at 20% probability ($r=0.62$; $p<0.05$), in the left eye at 20% ($r=0.62$; $p<0.05$) and 30% ($r=0.72$; $p<0.05$) probability and in both eyes ($r=0.73$; $p<0.001$) at 30% probability. Fig. 4. shows an averaged ERP in a younger and in an older patient.

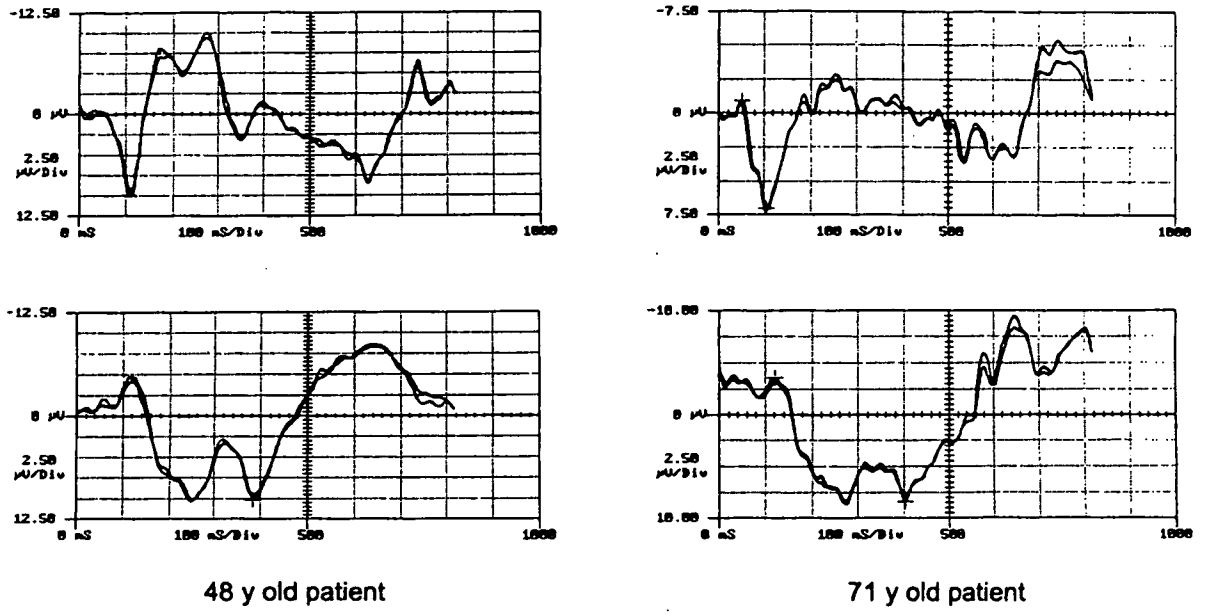

Fig. 4. Primary (active electrode Oz - upper graph) and cognitive (active electrode Cz - lower graph) evoked potentials recorded in one younger (48 year old) and one older (71 year old) PD patients for right eye. (Positivity is downward).

ERP amplitudes. In controls and in patients there was no significant correlation between P300 amplitude and other ERP amplitudes. Table III.a.b. shows averaged ERP data for controls and PD patients (Table III.).

ERP differences between patients and controls. There was no latency difference between groups while P300 amplitude was significantly reduced in PD patients for the right eye at 20% ($F(1,39)=7.121$; $p<0.05$), in the left eye at 30% probability ($F(1,37)=5.996$; $p<0.05$) and in both eyes in 20% probability ($F(1,38)=4.639$; $p<0.05$).

TABLE III.a.

Right eye

	20% target		30% target	
	L	A	L	A
P100	116±21	4.4 ±2.8	110±15	4.46±3.7
N140	186±15	-3.64±3.7	180±15	-3.32±3.0
P200	248±22	4.67±2.9	244±25	4.56±2.4
N200	348±29	-1.6±2.2	351±31	-0.61±2.4
P300	467±39	7.23±2.8	460±41	6.8±2.8

Left eye

	20% target		30% target	
	L	A	L	A
P100	119±18	5.17±3.2	117±19	5.1±2.3
N140	180±24	-3.77±3.3	180±23	-4.44±3.6
P200	254±25	5.1±3.3	243±19	4.56±3.1
N200	347±32	-1.85±2.4	349±30	-1.62±2.3
P300	475±40	6.5±2.6	464±41	6.4±2.9

Both eyes

	20% target		30% target	
	L	A	L	A
P100	113±17	5.9±4.4	111±15	5.41±4.6
N140	180±26	-3.62±4.3	177±14	-3.76±4.2
P200	264±40	5.28±3.6	237±24	5.58±2.8
N200	343±41	-2.46±2.7	344±40	-1.2±2.05
P300	464±41	7.31±3.2	464±43	6.32±2.9

The table shows the mean latency (ms) and amplitude (μV) values of the main ERP components of 20 control subjects for the target stimuli.

Table III.b.

Right eye

	20% target		30% target	
	L	A	L	A
P100	114±17	5.3±3.5	113±19	5.65±3.6
N140	181±17	-5.3±4.4	182±21	-4.53±5.2
P200	234±30	3.9±2.6	244±40	4.05±4.3
N200	372±28**	-0.66±3.3	363±29	-0.15±2.8
P300	472±39	5.31±3.5*	453±44	4.7±3.2

Left eye

	20% target		30% target	
	L	A	L	A
P100	123±17	4.74±2.4	123±16	4.46±3.0
N140	192±26	-5.5±3.2	193±26	-5.1±3.0
P200	256±39	4.6±2.9	251±42	4.26±3.1
N200	361±32	-0.7±2.4	366±37	-0.78±2.6
P300	468±44	5.0±3.0	454±49	4.85±2.8*

Both eyes

	20% target		30% target	
	L	A	L	A
P100	114±15	5.98±3.2	111±14	6.03±3.5
N140	183±16	-5.78±5.8	182±19	-6.4±4.7
P200	279±51	5.2±3.1	249±34	5.51±3.4
N200	346±37	-0.69±3.0*	352±35	-0.49±2.6
P300	444±46	5.73±2.9*	454±48	5.1±3.5

The table shows the mean latency (ms) and amplitude (μV) values of the main ERP components of 20 PD patients for the target stimuli. The stars show significant differences from the control group (MANOVA; *:$p < 0.05$).

The effect of age on processing time (CPT) in patients and in controls. Some individual patients tended to have longer CPT than controls but the group differences were not significant (Table IV.). CPT increased with age both in controls and PD patients. After

visual inspection of the data, it became apparent that the correlation is not linear (a break occurring in the "beginning" of the sixth decade). Therefore we separated the data for younger (48-60 years) and older (60-81 years) patients as well as younger (46-60 years) and older (60-77 years) control subjects. Both in the control and patient groups the mean CPT was longer in the older group than in the younger group. In the younger control group and in the younger patient group CPT increased with age while in the older control group and in the older patient group it did not. The slopes of CPT increase were between 2.75 and 6.75 ms/year in the younger control group and between 3.75 ms/year and 7.25 ms/year in the younger patient group. Thus the aging effect on CPT is steeper in younger PD patients than in controls. In the older patient group the values were close to those in the control group (Fig. 5.).

The normalized P300 amplitude and age. The P300/P100 amplitude ratio was smaller in PD patients than in controls. (right eye at 30% ($F(1.38)=6.368$; $p<0.05$) and in both eyes at 30% ($F(1,38)=4,639$; $p<0.05$) stimulus probability of the patients (Table IV.). In controls P300/P100 amplitude ratio decreased with age while in the PD group it did not. We separated the data of younger and older subjects. Both in the younger and older control groups the P300/P100 ratio decreased with age although not each correlation (eye, probability, age) reached significance. On the other hand there was a significant difference of the normalized P300/P100 amplitude ratio only between younger PD patients and controls (right eye $F(1,39)=9.376$; (20%); $F(1,39)=26,143$; (30%); left eye $F(1,39)=6.753$; (30%); both eyes $F(1,38)=13.654$ (20%); $F(1,38)=8.327$ (30%); $p<0.05$) (Fig. 6.).

TABLE IV.

	Control subjects		PD patients	
	CPT	P300/P100 A	CPT	P300/P100 A
Right 20%	355±42	2.60±2.8	359±44	1.18±1.1
Right 30%	349±35	2.30±2.3	340±52	1.26±1.9*
Left 20%	366±54	2.10±2.3	345±51	1.45±1.6
Left 30%	346±51	1.85±1.6	331±52	1.49±1.0
Both 20%	356±38	2.14±2.1	333±49	1.30±1.2*
Both 30%	352±47	2.38±1.0	346±46	1.87±0.5

The table shows the mean CPT (ms) and the mean P300/P100 amplitude ratio (μV) values in the control and PD groups. A significant difference was found only in the P300/P100 amplitude ratio (*: $p<0.05$; MANOVA).

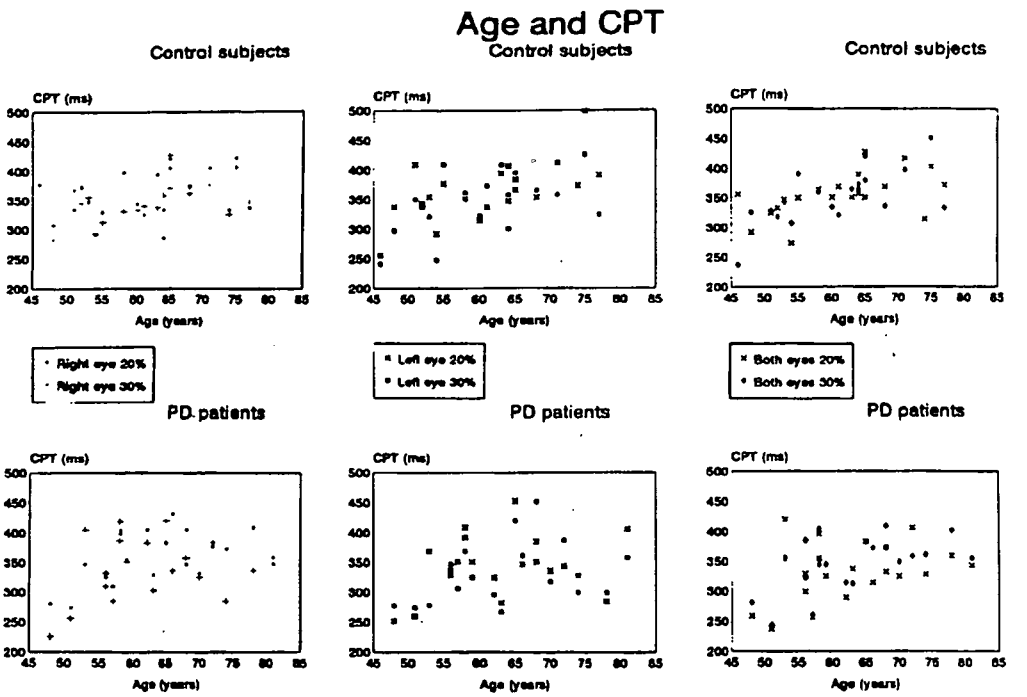

Fig. 5. The aging effect on CPT was significantly steeper in younger PD patients than in younger controls. In the older patient group the values were close to those in the control older group. For slopes and correlation coefficients see Results.

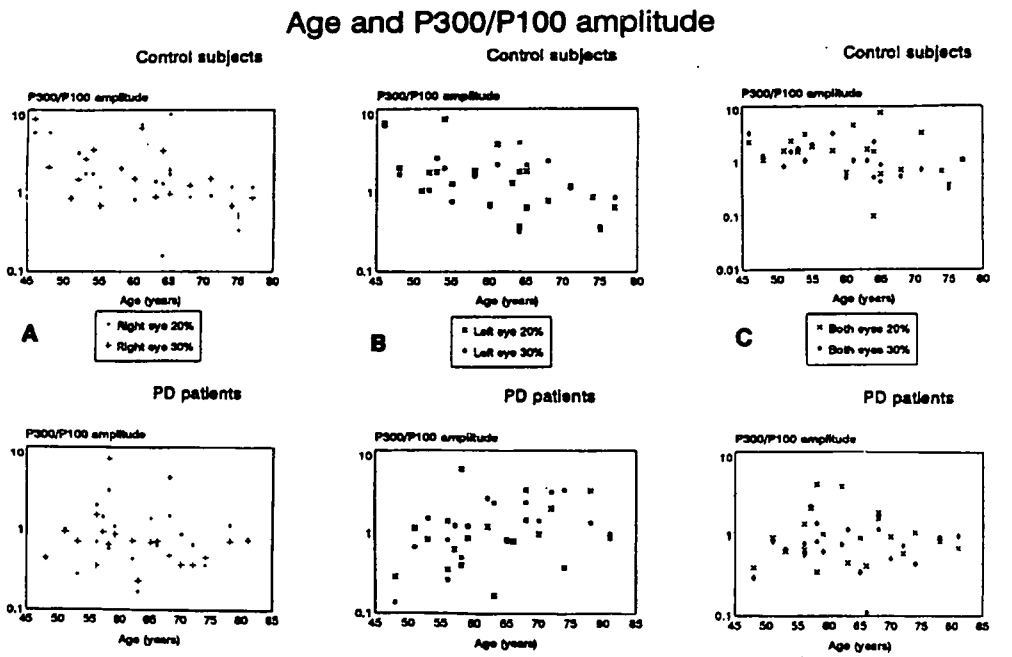

Fig. 6. The P300/P100 amplitude ratio decreased with age in normal subjects, while it slightly increased or remained constant in the patients. A: right; B: left; C: both eyes.

The effect of disease duration and dopaminergic medication. There was no correlation between CPT and the duration of the disease either in the younger or in the older patient group. We did not find any correlation either between the duration of the dopaminergic therapy and CPT and P300/P100 amplitude ratio.

2.4. CONCLUSIONS

In the first study we recorded ERPs for monocular and binocular stimulations and established the normative parameters of ERP. Most ERP studies test both eyes together or only one eye. Although we found, as expected, high interocular correlation, the binocular recordings would be misleading in neurological disorders affecting predominantly or exclusively one eye and its visual pathway, as in PD[25,26,99].

Our study also establishes normative parameters for some of the well known but also some less explored major deflections of the visual ERP obtained in an oddball paradigm. We found that in addition to P100 and P300, a positive deflection, we termed P200, and the succeeding negative deflection, N200, are constant features of the visual ERP. The P200 component did not correlate with age and with P300. The significance of P200 is not yet known. Our recent findings show that visual P200 can be recorded in patients with different neurological disorders even when N200 and P300 components cannot be seen. The fact that we found a reliable N200 deflection and that it correlated with P300, is worthy of note. A few studies suggest that visual N200 appears not only for target but also for non-target stimuli[3,104,109,140,158]. It is well known that one can record N200 for non-target stimuli if the probability of non-target stimuli is reduced and the target stimuli become frequent (from 90% non-target - 10% target to 10% non-target - 90% target)[140] or if there are two or more target stimuli[39,97], all rare stimuli (which can be non-target or target) elicit N200. In our study we recorded N200 in all observers and eyes only for target stimuli. This component, we labelled N200, has a longer latency than reported in a previous study using a similar paradigm[104]. In agreement with other studies, the latency of N200 had a significant positive correlation with P300 latency and its slope and correlation coefficient of age fall within the range of those reported by previous studies[14,88,109]. In PD there are effectively no data available on N200 using visual stimuli. Using auditory paradigms, the latency of the negative wave preceding the auditory P300 was prolonged in demented and non-demented PD patients[53,67,100]. As opposed to the definitely normal P300 latency in our non-demented PD patients and consistent with previous studies, N200 was often delayed even when neither P100 nor P300 was delayed, suggesting parallel information processing.

We found no age effect on P100. This result is consistent with an earlier VEP study that demonstrated the lack of aging effect on primary VEPs[18] using low spatial frequency sinusoidal grating stimuli, which as we mentioned earlier, are hardly affected by blur[17,32] . Therefore using these stimuli and the observed lack of age on P100 allowed us to unequivocally affirm an age effect (as distinct from optical factors) on N200 and P300 latency. However there is a noteworthy difference between N200 and P300: age has an effect on both but it is more evident for P300 than for N200. Since individual N200 latency positively correlates with P300 latency it would seem that N200 reflects an intermediate and somewhat parallel stage of stimulus processing between primary and cognitive stages since it is less dependent on aging than the P300. As a support for this suggestion of partial independence of N200 from other ERP components, we quote a recent ERP study that reported a significant correlation between P100 and N200 latencies only in demented parkinsonian patients but not in normals[152]. It is also possible that stimulus evaluation and decision time, which is related to the P300 component, can be assumed to occur earlier, at the N200 component. Our results therefore suggest that in studies of cognitive decline it would be useful to consider N200 separately from P300.

We also observed that the "normalized" P300/P100 amplitude ratio does not vary with age suggesting that raw P300 amplitude as a function of age can be misleading as a sign of cognitive aging, since nonspecific generally low voltage recordings may be a cause for low amplitude ERP-s.

Charting the course and rate of progression in neurodegenerative diseases is of interest both from the view of pathophysiology and for evaluating neuroprotective therapies that may alter the progression of the disease. In patients who are not demented the most commonly studied abnormalities occur in visuo-spatial perception and declarative memory. Our current study was geared to evaluate visuo-cognitive electrophysiological responses in non-demented PD patients. Most previous cognitive electrophysiological studies in dementing illnesses concentrated on the latency of the P300 deflection and prevailing evidence suggests that group mean P300 latency is delayed only in demented PD patients. Our present data that show no delays in a group of non-demented PD patients in agreement with this interpretation. However, in disagreement with the conclusions of previous studies[70], we found a significantly smaller P300 amplitude in non-demented PD patients than in age-matched normal subjects. In order to avoid confounding factors of absolute amplitude we also evaluated ERP responses normalized to primary visual responses. Using this individually normalized P300 amplitude, we could affirm not only differences between PD patients and controls but in addition to it, a significant abnormality became apparent for younger PD patients. CPT

also distinguished younger from older PD patients. The slope of CPT increase was significantly higher in the younger patient group than in age matched subjects. These results suggest that normalized visual ERP amplitude and CPT may be useful for charting the course of cognitive decline in PD. Several studies suggest that dementia is more prevalent in older than in younger PD patients. Our patients were not demented and the results show that younger PD patients are easier to distinguish from normals suggest that visuo-cognitive dysfunction is possibly affected separately and earlier than global intellectual functions in PD. It is doubtful but possible that this difference of younger compared to older PD patients is related to therapy. The effect of antiparkinsonian medication on cognition and ERPs is controversial: some authors have found a positive effect of medication on cognitive processing[4,122,144,146] others have not[67,74]. It has even been suggested that dopamine precursor therapy is responsible for cognitive decline in PD. Younger patients of our study were more likely to be on therapy with MAO-B inhibitor and while we doubt a deleterious effect of MAO-B inhibitor therapy on P300/P100 amplitude ratio and CPT, these differences should be further scrutinized in long term studies of the effects of diverse antiparkinsonian medications.

In summary:

(1) In order to enhance the clinical use of P300 potential, it is important to know if any correlation exists between the primary and the late cognitive components in normal observers. Our results support the independence of these components in normal subjects.

(2) We have evaluated the prominent deflections of visual ERP. Our findings emphasize the importance of visual N200 in addition to P300 and the technical usefulness of normalized amplitude values in normal subjects and recommend the spatial frequency paradigm of the present study for dissecting primary visual changes from visuo-cognitive changes in aging.

(3) We found that the method of normalizing late ERP components to the major positive deflection of the concurrent VEP provides a useful measure of visuo-cognitive ERPs elicited in a *simple* visual paradigm. P300 latency in themselves did not discriminate non-demented PD patients from controls. The P300/P100 amplitude ratio of the visual ERP was significantly decreased and central processing time acceleratedly increased in the younger group of patients compared to controls. These measures may be useful to chart the course of PD specific cognitive decline (rather than global dementia) in this disease. Apparently normalized measures of simultaneously obtained cognitive and primary visual ERPs delineate a younger group of PD patients from controls. These results suggest that ERPs may be useful for a "bottom-up" approach in studies of visual and cognitive processing in PD.

3. VISUAL ERP STUDIES IN MONKEYS

Although ERP components were first characterised in humans, critical evidence for clarifying the neurophysiological substrates of different ERP components are mainly derived from animal studies (for a review see[106,114,63]). The primary usefulness of animal models arises from the application of neuropharmacological techniques for determining the neural basis of ERP. The clinical value of animal models from this point of view is linked to the interest in using selective neurotoxins for developing animal models of neurodegenerative diseases[7]. Their purpose is to provide better understanding of the neurophysiopathology, behavioral and cognitive aspects of these disorders and to develop new therapeutic avenues.

The variety of animal species in which P300 like responses have been recorded suggest that underlying processes may be a universal feature of mammalian brains. Nevertheless, rigorously validating a P300 like response in a nonhuman species would require demonstrating the important characteristics of the human P300. Even though many characteristics are listed, there is little consensus about which ones are sufficient for identifying the P300 component. There are three main criteria of P300 that are important for identification: (1) Functional characteristics, such as the parametric effects of task manipulations on the presumed P300; (2) Waveform characteristics, such as latency, amplitude, polarity, wave shape; (3) Neuronal characteristics refer directly to the neuronal elements that can be responsible for P300 generation[106]. In recent studies, given the goals of using ERPs to study cognition, the waveform criterion seems to be less important than the functional and neuronal criteria.

Visual animal studies in non-human primates are scarce[65]. It is well established that the P300 component is associated with cognitive processing in the monkey, too, but not much is known which neurotransmitter or neuromodulator systems are involved in the production or modulation of P300. Given that P300 may have many sources, it is likely that many neurotransmitter systems are involved. The cholinergic and the chatecholaminergic systems both play a role in cognitive functions[128,144]. Manipulations of the cholinergic system using antagonists had a dissociative effect on explicit memory in normal young human subjects[84,128] , and in monkeys it produced deficits in sustained attention[28] and impaired the performance in different visual tasks[12,77,105]. The possible role of dopamine was suggested by studies testing monkeys suffering from PD[64]. Studies in which the noradrenergic system has been manipulated pharmacologically also indicated substantial effect on human and monkey P300 latency and amplitude[115]. In human dementing illnesses, such as PD and Alzheimer's disease (AD) a deficiency of cholinergic

system has been implicated in cognitive decline[34,50]. In order to explore the possible role of cholinergic mechanisms of P300, we have performed an extended study in a well-trained adult monkey, using two different drugs, acetyl-levo-carnitine (ALC) and scopolamine.

ALC is a neuroactive agent with cholinomimetic properties (for a review see[23]) and reported to retard cognitive decline in chronically treated humans[139]. Onofrj et al.[103] reported that ALC increases the amplitude and reduces the latency of P300 obtained in a passive auditory oddball paradigm in monkeys. In this study we report the highly reproductible effects of ALC and scopolamine used either independently or in the same session on primary and cognitive components of the monkey ERP.

3.1. METHODS

Subject.

Charlie, a 4 year old male Cynomolgus monkey weighting 6 kg at the time of the study, served as a subject for this study. He had extensive training and consistently performed above 95 % accuracy in the visual discrimination task we used for this study of P300[5].

Testing procedure.

Charlie was placed in a chamber directly in front of the stimulus screen. To minimize extraneous movements, a light weight vest was placed on it and then tethered to the rear of the chair. Masking noise (55 dB nHL) was introduced through an overhead loudspeaker. Infrared illumination of the chamber was provided and the animal was constantly monitored by a camera. Juice was delivered via a reinforcement nipple by a remotely located liquid-solenoid valve.

Stimuli.

The stimuli were 2.5 c/d sinusoidal gratings presented at two different orientations (0 and 45 degrees) in the on-off mode. The vertical orientation was presented rarely (0.25 - 0.35 - target stimuli), the oblique frequently (0.65 - 0.75 - non-target stimuli). the mean luminance and the contrast were 85 cd/m2 and 50%, respectively. Stimulus duration was 742 ms and the repetition frequency was 0.27 Hz. The monkey had to discriminate correctly between the stimuli by keeping a lever depressed for the non-target stimuli (correct rejection) and releasing it for the target stimuli (hit) between 535 and 1798 ms (response window). For correct responses he was rewarded with 0.25 ml juice. Errors were followed by a time-out period of 5 seconds and were signalled by a 2 kHz tone (Fig. 7.) Six or seven blocks of 75 trials were obtained during each recording session.

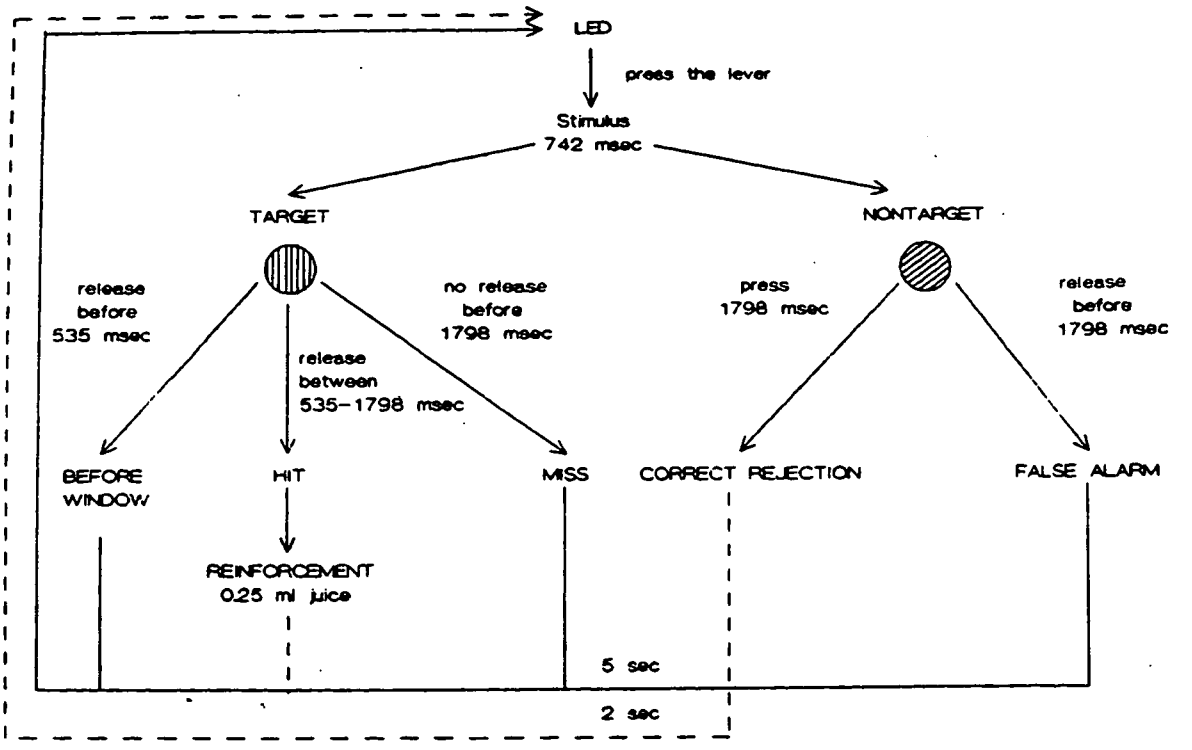

Fig. 7. The sketch of the visual oddball paradigm. For explanation see text.

Recordings.

After the training, when the monkey began to discriminate between the stimuli with 65% accuracy, 11 miniature solid silver-silver chloride electrodes were implanted under sterile surgical conditions to the surface of the dura. After the recovery of the surgery, electrophysiological testing was initiated. Five active recording sites were used. The primary positive component (P100) was recorded from Ro, while the late cognitive component from Cz referred to Fz. Filters were set 0.3 Hz and 100 Hz. Eye movements were monitored with electrodes above and below the right eye. ERPs were monitored on-line using a Nicolet 1170 averager while all data were collected and analyzed by a PDP 11-23 computer.

Normative responses were obtained for over a year prior to the pharmacological experiments. Both the primary potentials (N70, P100, N140) and the late positive

components (P200, N200, P300) were measured. The latency of the primary major positive component was identified as the timing of the most positive peak, occurring between 60-80 ms after the stimulus presentation. This deflection is analogous to the human P100[132]. The latency of the P300 component was identified as a positive component peaking between 350 and 500 ms. Baseline amplitudes were taken into account (Fig. 8.).

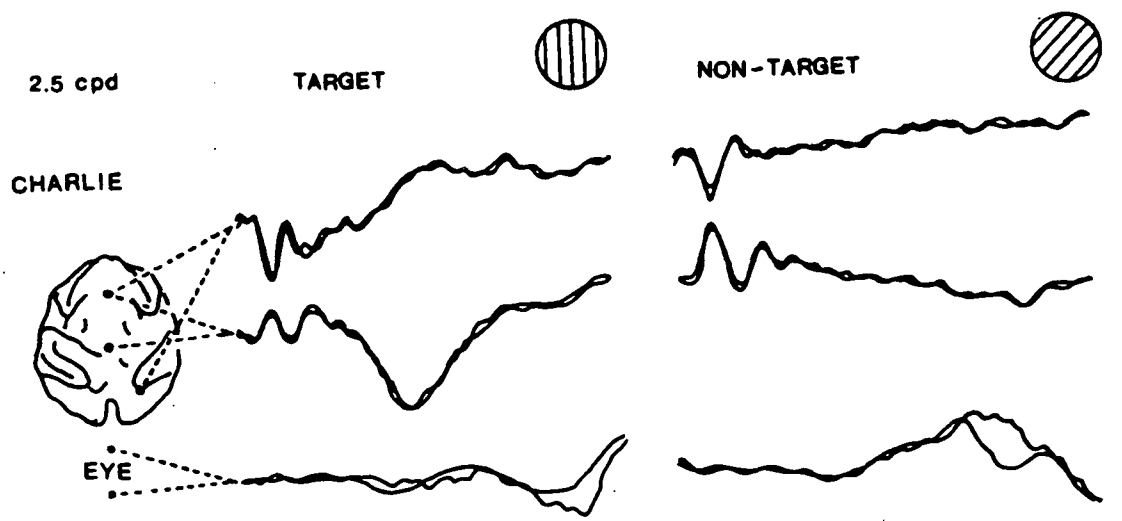

Fig. 8. Evoked potentials and electrooculogram (EOG) recorded to the target and non-target stimuli in the trained monkey. The primary visual evoked potential can be seen at the occipital derivation for both stimuli. At the centro-parietal derivation P300 can be seen for the target stimuli only. Positivity is downward.

ANOVA and Wilcoxon matched pairs signed ranks statistical analysises were used to determine if there was any effect of either drug or in combination.

Dosing procedure

Three different drug conditions were explored: ALC and scopolamine alone and in combination. For the acute experiments 50 mg/kg or 75 mg/kg ALC was dissolved in juice and it was given to the monkey orally. Scopolamine was explored in three different

concentrations. The following conditions were used:

1. 0.02, 0.01 or 0.005 mg/kg scopolamine i.m.
2. 0.005 mg/kg scopolamine i.m. and 50 mg/kg ALC p.o.

These doses of ALC and scopolamine were selected and based on available behavioral data of our preliminary experiments. The smallest dose of scopolamine represents the lowest effective dose under the monkey continued to discriminate in the visual task with a normal performance. After the drug administration ERPs were recorded for 50-70 minutes. The monkey had no more than a maximum of two drug experiments a week. On each day the session started without any drugs. The size of pupil was measured before and 30 minutes after scopolamine administration. As a control experiment we have studied the effect of cyclopentolate hydrochloride (Cyclogyl) eye drops (0.1 %) on visual ERPs. These eye drops cause temporary accommodation deficiency and large pupils. The purpose of these experiments was to evaluate if scopolamine has an effect on visual P300s could be attributed to an effect on the pupillomotor system of the monkey.

The intervals between the measurements were different depending on the speed of the monkey and the computer analysis. This made a minute-by-minute comparison of the treatments somewhat difficult. For this reason, we report the data for five minute time windows (Table V.).

3.2. RESULTS

The effect of ALC. ALC had no significant effect on the amplitude and latency of the primary evoked potentials. In contrast, the P300 latency significantly decreased after the ALC administration. (Table V.). The maximum peak latency decrease occurred between 30 and 40 minutes. The effect of ALC on P300 amplitude was less consistent (Fig. 9.)

TABLE V.

	Pre-ALC	Post-ALC
P100 lat	74.2±1.8	75.6±8.1
P100 amp	20.7±4.6	24.2±6.8
P300 lat	432.0±15.0	397.8±15.5*
P300 amp	32.4±2.1	34.3±4.2

* $p < 0.05$, ANOVA

The acute effect of 50 mg/kg ALC on P100 and P300. The table shows averaged predrug latencies (ms) and amplitudes (μV) and the same measures at the time of the maximum action of ALC.

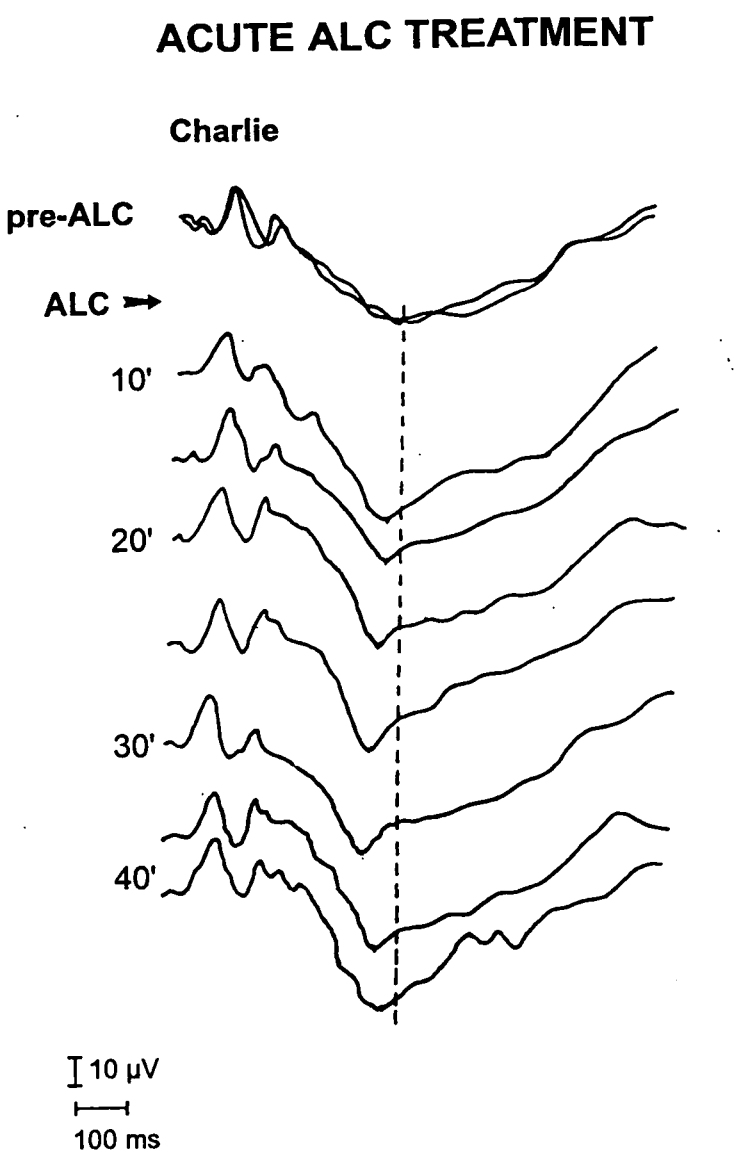

Fig. 9. P300 traces (obtained at the centro-parietal derivation) illustrating the acute effect of ALC.

During the longitudinal ALC therapy there was a statistically significant decrease in peak latency of P300. A few days of discontinuation of the ALC administration increased the P300 latency (Fig. 10.).

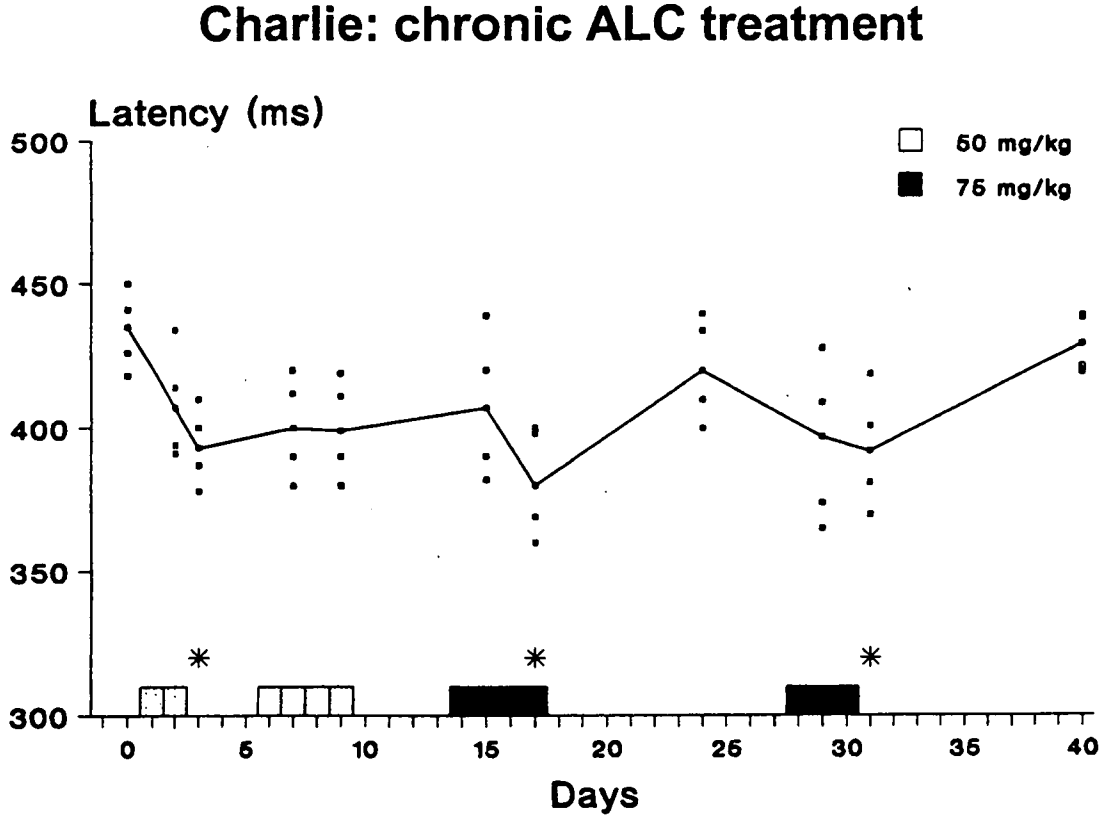

Fig. 10. Longitudinal effects of ALC. ALC (50 mg/kg) was administered orally for 2 days, suspended for 3 days, reinstated for 4 days, suspended for 4 days, then a higher dose (75 mg/kg) was given for 4 days, suspended for 10 days and reinstated for 3 days. Individual data points represent measurements of independent traces. There were significant changes on days 3, 18, and 31 compared to the normative data ($p<0.05$). By day 40, P300 latency returned to pre-treatment value.

The effect of scopolamine. The latency of primary positive component did not change significantly at any dose of scopolamine although its amplitude decreased by nearly 20 % in 35-40 minutes following its administration. Pupil diameter was 5±1 mm before and 8± 1 mm 25-30 minutes following scopolamine and ALC administration. Apparently scopolamine acted independently on the pupil. In fact it is known that ALC alone has no measurable effect on pupil size or accommodation.

The mean latency and the mean amplitude of P300 were 434.0±1.0 ms and 32.3 ± 2.8 μV in the predrug experiments at 25 % target probability. Eye movements showed no relationship to P300. The accuracy of the monkey was 98-100 % on each experimental day. When the pupil was dilated with Cyclogyl, the latency of P300 did not change: In six

blocks of trials the mean latency was 435±8 ms. However following pupillary dilation P300 amplitude was higher 47±2.5 μV than in the normative experiments.

We have performed three different series of scopolamine experiments. Two series with relatively high doses of scopolamine (0.02 and 0.01 mg/kg) were based on behavioral studies of Bartus et al[12]. Scopolamine was injected i.m. 10 minutes prior the behavioral testing. These doses had a major effect on the animal's behaviour. The monkey became erratic and excited although he continued to work slowly and intermittently. Thirty to forty minutes following the 0.02 mg/kg dose, performance accuracy decreased to chance level. Reducing this dose of scopolamine to 0.01 mg/kg, caused a performance decrement to 79%. The number of "false alarms" and "before windows" increased. The reaction time of "hits" did not change compared to the predrug experiments and remained in the range between 580 and 700 ms. With 0.01 mg/kg scopolamine P300 latency increased and its amplitude decreased so that by thirty to forty minutes following scopolamine administration P300 disappeared. P300 was not apparent in any trial when the monkey responded with a "false alarm". Further halfing the scopolamine dose to 0.005 mg/kg, did not affect the monkey's performance: his accuracy remained the same (97.5±2.5%) as in the predrug experiments (98.1±1.9%). Following this small dose of scopolamine, P300 latency increased in four of five experiments while there was no change in one session. This variability suggests that 0.005 mg/kg scopolamine may be near to the sensitivity threshold of this animal for this drug. Twenty to forty minutes following 0.005 mg/kg scopolamine administration, P300 latency increased by 30 ms on the average of only four of five experiments. This P300 delay was only marginally significant at 30-34 minutes (Wilcoxon, $T=1.5$, $Z=-1.61$, $p=0.0528$) compared to the predrug measurements. P300 amplitude increased in forty minutes following the drug administration ($T=0$, $Z=-1.82$, $p<0.05$). The behaviour of the monkey did not change during the experiment and his accuracy remained at a high 96.0± 4.0% level throughout.

The combined effect of scopolamine and ALC. In contrast to the effect of scopolamine given alone, when 0.005 mg/kg scopolamine administration was followed 10 minutes later by 50 mg/kg ALC, P300 latency increased in 25 minutes and then remained stable for another 20 minutes after it returned to the baseline. P300 amplitude reached its highest value in 25 minutes and then it remained stable for another twenty minute (Fig. 11.). Table VI. shows averaged ERP latency and amplitude data before and after the administration of the drugs.

TABLE VI.

Scopolamine					Scopolamine+ALC			
Time (min)	L (ms)	SD	A (μV)	SD	L (ms)	SD	A (μV)	SD
P300								
Pred	434	10.0	32.3	2.8	434	12.0	34.6	3.5
15-19	456	39.0	37.0	6.4				
20-24	440	9.0	31.4	2.1	432	12.0	40.0	10.0
25-29					466*	18.0	44.0	10.0
30-34	465*	20.5	31.2	7.6	474*	27.0	40.5	9.0
35-39	441	13.0	35.5	3.7	473	40.0	43.0*	4.1
40-44	454	21.0	37.0	2.2	477*	28.0	44.0*	3.8
45-49	439	19.0	38.0*	1.8	475*	27.0	45.0*	5.6
50-54	435	39.0	39.0*	1.3				
55-60					454	15.0	38.0	6.4
P100								
Pred	75.3	2.1	18.6	4.6	74.2	1.8	18.8	4.6
15-19	69.8	5.3	19.3	3.8				
20-24	72.6	2.9	18.8	1.8	77.0	0.5	20.0	0.2
25-29					78.0	1.4	20.3	5.4
30-34	72.6	5.9	14.4	4.5	72.8	5.1	20.3	5.4
35-39	71.8	3.0	15.8	2.2	73.0	7.9	20.0	5.7
40-44	75.5	3.2	17.8	1.9	71.8	5.8	16.0	3.7
45-49	71.8	3.0	16.0	1.0	75.3	3.0	15.9	2.8
50-54	72.3	3.3	13.3	5.0				
55-60					76.5	1.8	18.0	2.8

* $p < 0.05$, Wilcoxon

The acute effect of scopolamine and scopolamine + ALC administration on P100 and P300 potentials.

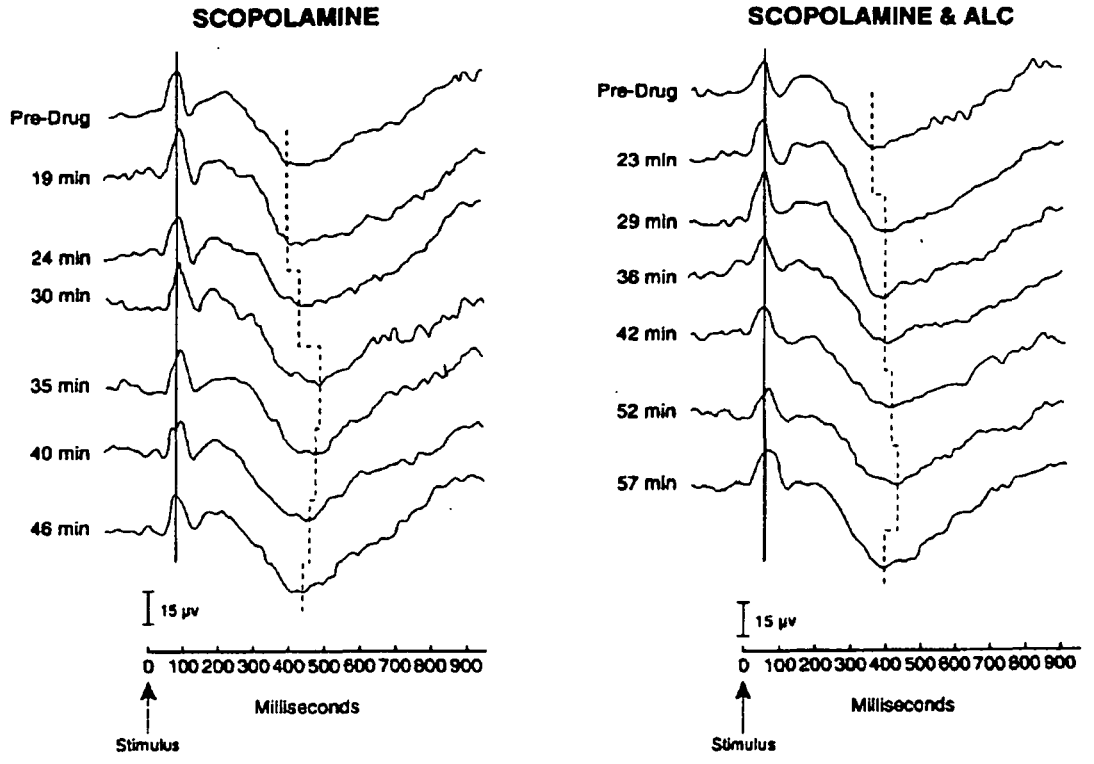

Fig. 11. P300 traces (obtained at the centro-parietal derivation) illustrating the acute effect of scopolamine and scopolamine & ALC administration. Positivity is downward. The effect of the drugs was significant after 25 minutes of scopolamine administration ($p < 0.05$). Note that previous studies have shown (Fig. 9.) that when ALC is administered alone, a significant P300 amplitude increment occurs in 15 minutes while a maximal P300 latency decrease occurs between 26 and 32 minutes following the administration of the drug. Apparently scopolamine pretreatment only partially attenuates ALC's effect on P300 amplitude while it completely reverses ALC's effect on P300 latency.

3.3. CONCLUSIONS

It is known that the cholinergic system is involved in the modulation of electrocortical activity[91]. The main origin of the cortical and hippocampal cholinergic network is in the basal forebrain both in monkey and man[96] which has been suggested as a source (or one of the sources) of endogenous potentials recorded from the scalp[69,101].

ALC is considered to have (among other possible effects) centrally acting cholinomimetic properties[78]. Scopolamine has known effects on learning and memory in monkey[12,13] and man[49] and it has also been reported to affect human ERPs[94]. ALC shortened the latency of P300 while primary visual EPs were little or not at all affected. These results suggest that ALC improves the speed of cognitive processing in primate, independently of any possible primary sensory effects. The present monkey data may be relevant to humans. Deficient cholinergic mechanisms have been implied in both AD and PD[51] , and in both groups the P300 can be characteristically abnormal. AD patients treated with ALC orally for a year exhibited a slower rate of deterioration than the untreated group[139].

P300 amplitude changes were less consistent in both the acute and chronic experiment. There was a trend for P300 amplitude to change following ALC administration, initially it increased then decreased. This is clearly different from the results obtained in a P300 study using a passive auditory oddball paradigm[103]. In humans both amplitude and latency of P300 increase when the task is made more difficult. An augmented amplitude is thought to reflect the task novelty or uniqueness. Perhaps the initial P300 amplitude increase we observed in our study is due to some non-specific and short lived alerting effect. A later amplitude reduction could be interpreted as an enhancement of a more automatic mode of stimulus categorization.

In trying to relate our results using scopolamine in the monkey to human studies, the gross similarities are apparent. Using a visual oddball task, 0.0057 mg/kg scopolamine had no effect on the amplitude of the human P300 although it did delay peak latency[126]. Nevertheless, we found a rather noteworthy difference in respect to human studies[29,30] which reported that in humans P300 latency increased significantly following 1.2 mg scopolamine but did not note any change in the performance of the visual stimulus evaluation/response selection task, while we found a significant increase in P300 latency and decrease in performance after the administration of about the same dose of scopolamine.

The results of our experiments using both scopolamine and ALC are noteworthy. When scopolamine was administered prior to ALC, P300 was affected in a complex manner: its latency increased as after scopolamine administration alone while P300 amplitude was augmented although not as much as if ALC had acted alone[5] (Fig. 11.). While we cannot explain this dissociation between response amplitude and latency, a more detailed scrutiny of the dynamics of the interaction of the two drugs may give further insight into the significance of P300 changes in general and into the possible multifaceted effects of ALC. It may be relevant that recently it has been also reported that ALC has an effect not only on cholinergic, but also on central dopaminergic systems in

aging rats[133].

It is worth emphasizing that while scopolamine in our hands influenced P300, it had no significant effect on the latency of the major positive component of the pattern VEP of the monkey. Compared to human studies this result is not surprising. Equally negative results were reported in two human studies where 0.6 mg of scopolamine s.c. had no significant effect on the pattern VEP[9,136] . This was recently confirmed in a study that reported that 0.4 mg scopolamine i.m. had no effect on the pattern reversal VEP[40]. However in the same human study an increase of amplitude of the flash VEP was observed under the same dose of scopolamine. Indeed, while the effect of scopolamine on pattern VEP amplitude appears minimal or non-existent, several studies agree that 0.5-0.6 mg scopolamine delays late components of the flash evoked potential in humans[10,129]. This apparent dissociation between flash and pattern VEP effects under scopolamine is similar to what is seen in AD, where the flash VEP is and the pattern VEP is not affected[10]. Therefore our results in the monkey, dissociating pattern VEP and P300 effects of scopolamine, are noteworthy in reference to animal models of dementia. Nevertheless, our results in the monkey concerning the effect of scopolamine and ALC on ERPs do not completely support an exclusive muscarinic theory of P300 impairment in AD. For instance, we have noted that P300 latency responded to cholinergic treatment while P300 amplitude did not change. On the other hand, in AD several studies[79,118] reported P300 amplitude changes. The published data concerning similarities of memory deficits observed in AD and scopolamine-induced amnesia are contradictory. While some studies suggest that the cognitive profile of scopolamine injected young subjects is more similar to that of the nondemented elderly than to that of AD patients[57], others report that scopolamine produces anterograde memory deficits that are similar to those observed in mild or moderate senile AD[36,61,84,89]. It was also found that scopolamine had no significant effect on verbal short term memory in aged matched volunteers in contrast to AD but it induced impairment at visuospatial short-term memory tests similar to AD[84]. In normal subjects visual and auditory vigilance tests are sensitive to scopolamine blockade[27] while patients with AD and normal elderly subjects performed normally on these test[89]. Although the heterogeneity of cognitive deficits found within AD patients[9] makes group comparisons difficult, the above data suggest that the spectrum of memory impairments observed in AD differs from that found in scopolamine-induced amnesia. A recent study, using Biperiden, an anticholinergic drug, found that only the task-dependent visual P300 was affected by the drug, suggesting that the process of selective attention is dependent more on cholinergic pathways than P300 generators[73]. Interactions between the cholinergic and other neurotransmitter or neuromodulator systems including

norepinephrine, dopamine, serotonin, GABA, opioid - and other neuropeptides, such us somatostatin, galanin, substance P and angiotensin II, may be important in learning and memory and in the cognitive impairment associated with aging and AD (for a review see[42,157]). Enlargement of the lateral ventricular volume due to pathologic cell loss of different types of neurones[41] or nonselective changes in regional cerebral glucose metabolism and energy failure[58] also may be responsible for the memory deficits and the nature of the cognitive decline in AD. Recent PET and fMRI studies show significant changes in hippocampal and in frontal, temporo-parietal and occipital areas of AD patients associated with memory impairments[108].

In summary, visual P300 latency is a useful measure to index behavioral effects of CNS muscarinic blockade, and in low concentrations scopolamine may be a valuable tool to study visual cognitive processes independently from primary sensory changes. In reference to human neurodegenerative diseases, our studies suggest the possibility of using electrophysiology to dissect out selected aspects of visual cognitive impairment. Further ERP studies in both human and monkeys may be useful to evaluate the relative effectiveness of cholinergic and non-cholinergic agents on the speed and accuracy of visual discrimination and different stages in cognitive processing.

4. GENERAL DISCUSSION

During the last three decades diverse suggestions have been made but none has clearly explained what the P300 potential really means. Initial studies proposed that P300 is associated with the decision that something important happened (that time P300 generally was referred as the "Aha" wave). The main problem with this idea was that a subject can press a button accurately before the P300 occurs so the decision preceded the P300 wave. Later it was suggested by Picton et al[113] that P300 represents the transfer of information to controlled processing or consciousness. Evidence against this hypothesis might come from the fact that P300 can be recorded in patients who are not conscious. In these cases it is possible that some information reached consciousness but was not sufficiently recognised. In the context updating model Donchin[48] proposed that the memory might be updated after incoming information has been evaluated[46] and the P300 may represent the control of this updating process. The problem is with the updating model that P300 occurs in situations wherein one would not think that updating is necessary (e.g. a simple oddball task). However, the relationship between P300 and memory is controversial. Klimesch[82] argues that the P300 component corresponds to some sorts of episodic memory search. He suggests that if P300 stems from phase-locked

hippocampal theta activity, the functional meaning of the P300 should be related only to the encoding of contextual and the encoding of new information. On the other hand, Hardcastle[71] suggests that P300 does more than indicate increased episodic memory demands. She thinks that the function of P300 should not be tied so closely to mnemonic processes. Indeed, at least three different positivities within the P300 time window can be distinguished in the context of memory: priming positivity (PRP), recognition positivity (RP) and difference related to memory (DM). PRP is detected in visual tasks using a sequence of words within occasionally targets (non-words or special words) need to be detected. It is a broad positive-going shift (between 250 and 700 ms) evoked by repeated words relative to ERPs of the first presentation[127]. RP and DM can be recorded in a paradigm when two lists of stimuli are presented, one after the other. RP is recorded during the presentation of the second list when stimuli from the first list can be correctly recognized within the stimuli of the second list. The topography of this positivity is different from P300[138]. When ERPs are recorded during the presentation of the first list of the former paradigm, DM is recorded for stimuli which later will be correctly recognized[138]. Some authors interpret this wave as an enhancement of P300[56] but this positivity is more evenly distributed on the scalp than P300 and it is longer lasting (400-800 ms). These results suggest that may be more evident to study other ERP components than P300 when mnemonic tasks are used. However, it is possible that these positivities can be subcomponents of P300 and that way the P300 component really does more than simply index "memory codes".

The next problem is that the relationship between what is happening in the brain and what we observe at the scalp is not completely understood. First, there are undoubtedly numerous functionally important neuronal processes that cannot be detected using the ERP technique. Second, the activity recorded at any particular scalp site is not necessarily attributable to activity in brain regions close to the recording. However, the recorded P300 at any given electrode site is the sum of the activity of all of the simultaneously activated generators. Many studies provided clear evidence that multiple neuronal processors reflecting the simultaneous action of different aspects of stimulus information, underlie P300 activity recorded at the Pz electrode site[11,80,81], and this fact helps to understand the clinical suitability of this wave despite of the uncertainties mentioned before. If the minimal configuration required for component identification is used, ERPs may provide a general index of cognitive processing. When the P300 wave is abnormally small or delayed, there is probably some abnormality of cognitive processing. The use of P300 latency is important in such conditions as early dementia or cognitive problems occur with metabolic disorders. P300 measurements can be used to shift the

probability of a diagnosis in one direction or the other. Because of ERP technique can be easily investigated in the clinical practice, it is possible to use it for long term studies to follow up the status of a patient during therapy. If ERPs can definitely provide an early index of dementia it can be an important diagnostic tool in the near future: for example when a patient has suspected dementia (the results of other dementia scales are not obvious or negative), neuroprotective therapies can be started before the symptoms gain progressive.

In clinical studies it is always necessary to understand the limits of normal, and these are far easier to be determined for a simple test than for one that have many parameters. However, a simple test may miss the abnormality or so nonspecific that unhelpful. What we need is to adjust paradigms to specific disorders and patients. The testing situation needs to be structured so that normal variations of P300 are minimized by maintaining identical recording conditions even in interlaboratory studies. The relationship between P300 values and other measures of other cognitive neurophysiological and psychological functions needs to be established for specific disorders to enhance greatly the clinical utility of ERPs.

During the last decade there is a renewed interest in animal models of cognitive dysfunction. ERPs can be useful tools to compare animal and human information processing. Given the limited facilities for experimentation on humans, and considering the close phylogenetic relationship and the similarities of brain anatomy, physiology, electrophysiology, and behaviour between monkey and man, the monkey seems to be the most appropriate subject for these studies. Indeed, there is evidence that non-human primates are suitable to evaluate the repeatability and the pharmacological properties of P300 and hence may provide a reasonable model to study the cognitive decline observed in humans.

We are living in the Decade of the Brain. In the last few years we have witnessed an enormous development in neuroscience. Just about a hundreds years ago T.H. Huxley wrote (1885):

"It would be a revolution in the physiology if a biologist could study the structure of the living tissue with physical or chemical tools, like the astronomer observes the celestial bodies with spectroscopy."

Now we have more than a "tool", we can utilize MRI, PET and other techniques to get an approximate picture of the working brain. One may wonder that these new methods make

the old ones extinct. But the fact that the temporal accuracy of these techniques is more than a second (usually several tens of seconds) and the expenses, the technical complexity of them at present are such that they cannot be used as simple screening tests. There is a large and encouraging effort to provide secure links between functional anatomy developed from PET or fMRI studies and time-dependent measures using ERP. In this context it is quite possible that the greatest contributions of ERPs lie ahead. These studies would allow us to study the plasticity of the human brain during the execution of various levels of skills. We believe that recording the brain's electrical activity using ERP has already made a significant contribution in several areas of cognitive research and ERP remains a very important supplementary method to study normal and abnormal information processing in the brain.

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