<table>
<thead>
<tr>
<th>項目</th>
<th>内容</th>
</tr>
</thead>
<tbody>
<tr>
<td>タイトル</td>
<td>原著：褐黄色変化の面議と心理検査の比較検討</td>
</tr>
<tr>
<td>著者</td>
<td>津野 仁；島村 善一；下橋 健雄；田嶋 義子</td>
</tr>
<tr>
<td>引用</td>
<td>琉球医学会誌 = Ryukyu Medical Journal, 21(3-4): 125-132</td>
</tr>
<tr>
<td>発行年</td>
<td>2002</td>
</tr>
<tr>
<td>URL</td>
<td><a href="http://hdl.handle.net/20.500.12001/3427">http://hdl.handle.net/20.500.12001/3427</a></td>
</tr>
<tr>
<td>権利</td>
<td>琉球医学会</td>
</tr>
</tbody>
</table>
Age related changes in event-related potentials and psychological testing in healthy elderly subjects

Jin Yu1, Kenichi Hiramatsu2, Yoriyuki Shimazaki3 and Yuko Takeda3

1Department of Neuropsychiatry, 2Department of Radiology, 3Center for General Medicine, University of the Ryukyus, 207 Uehara, Nishihara, Okinawa 903-0215, Japan

(Received on December 27, 2002, accepted on January 21, 2003)

ABSTRACT

P300 latency of event-related potentials (ERPs) have been assumed to increase with age, and to be roughly correlated with loss of cognitive functions. However, is P300 latency prolonged in all elderly subjects? To address this question, we selected 63 subjects from 60 to 91 years of age. Subjects were active, living at home, free from psychiatric or significant physical disorders, having high Mini-Mental State (MMS) score and low Geriatric Depression Scale (GDS) score, and showed no major signs of cerebral infarction on MRI (1.5T). ERPs were recorded with subjects engaged in auditory oddball tasks. We found no significant correlation between age and P300 component. Sex difference concerning P300 component with aging was also not detected. P300 latency prolongation and decreased visual retention (Benton test) were associated with lower MMS score, and visual retention was correlated with age. We conclude that P300 latency does not increase linearly with age in elderly subjects and that prolongation of latency is affected by subclinical organic changes in the brain than by aging itself. Ryukyu Med. J., 21(3,4) 125-132, 2002

Key words: Event-related potentials, P300, Aging, MMS, Elderly

INTRODUCTION

Event-related potentials (ERPs) are physiological indicators, which reflect information-processing functions such as attentiveness, recognition, and judgment. The amplitude of the P300 component of ERPs reflects information-processing capacity, while the information-processing speed is reflected by the latency.

Research into changes in the P300 latency associated with aging has resulted in nearly uniform agreement, that the latency becomes more prolonged with advancing age. Some researchers have reported a linear correlation between aging and latency1,2, while others report that the slope of this line becomes steeper after 40 years of age, and particularly after 60 years of age3,4. However, regarding the amplitude, some papers indicate age-related decreases5,6, while others were unable to show the age-related change7. No consensus has yet been obtained on the amplitude. There appears to be a general correlation between prolongation of P300 latency and deterioration of cognitive function among the elderly, as indicated by assessment instruments including Mini-Mental State Examination (MMS)8, Global Deterioration Scale (GDS)9, and Wechsler Adult Intelligence Scale-Revised (WAIS-R)10.

Is P300 latency prolonged with aging in all cases? Looking at data on plots of latency, as a function of age8,10, the latency is remarkably different, especially among elderly subjects, which may indicate individual differences in prolongation with aging. Which parameter is related with the difference? Studies have shown correlation between aging and increasing incidence of silent cerebrovascular disease11,12. The latency was prolonged in cases with silent cerebral infarctions compared with cases without them13,14. It appears that asymptomatic cerebrovascular
changes may have some effects on P300 latency, even in the absence of overt organic brain disease. However, among the studies performed on age-related changes in the P300 component in the elderly, only a few have mentioned cerebral MRI findings\textsuperscript{23,25}. Also, studies performed to date have been limited by small sample size in elderly subjects, and also by skewing of the age range within the elderly group.

Recent MRI evidence suggests that neuroanatomic structure may change more rapidly with age in men compared with women\textsuperscript{22,23}. In a previous study from our research facility, the sex difference on rate of change in P300 latency with age was examined in healthy normal subjects. The study revealed that compared with women in middle to old age, men may experience more rapid change of P300 latency, but not amplitude\textsuperscript{24}. However, in the study, although the total number of the subjects was 84 (42 men and 42 women, age range 15-85 years), the number of elderly subjects was only 12 (6 men and 6 women). Moreover, strict criteria of participation including psychological tests and cerebral MRI examination were not applied.

In order to resolve some of the questions raised by previous studies, the present study enrolled a substantial number of subjects, applied strict in clusion criteria using the tests which evaluates cognitive functions and quality of life, adopted screening test for depression, and practiced cerebral MRI examination. In this study, not only age-related change in ERPs and psychological testing, but also the correlation between age, P300 component, cognitive function and, other parameters were examined. Sex difference was also examined.

**SUBJECTS AND METHODS**

**Subjects**

Subjects were 63 volunteers (men: 24, women: 39), whose mean age, SD and range were 72.0±8.0, 60-88 years of age for men, and 73.7±8.5, 60 to 91 years of age for women (Table 1). They were living at home and highly active as demonstrated by sustained participation in senior citizens clubs and/or group activities at senior citizen welfare centers. All subjects were dextral as determined by the handedness questionnaire of Raczkowski and Kalat\textsuperscript{20}. They were free from psychiatric and neurological diseases, mental retardation, and physical illnesses, which might affect cognitive function or produce hearing loss. No drug which might have affected the ERPs and the result of psychological tests had been taken by any subjects for at least 2 weeks before ERP recording. A total of 74 candidates had an MMS score of 24 or above, GDS score of 9 or below, and TMIG (Tokyo Metropolitan Institute of Gerontology) score of 11 or above. These 74 candidates underwent the examination of ERPs, and MRI of the brain. However, 4 subjects showed unclear ERP waves due to artifacts and 7 subjects showed multiple cerebral infarction and other abnormal findings on cerebral MRI. Those 11 candidates were excluded from the participation of this study, leaving a total of 63 for analysis. This study received prior approval by the participating medical institution. Informed consent was obtained from the individual subjects.

**Procedures**

Event-related potentials (ERPs): Audiometrical tests were performed before recording ERPs. The minimum audiometrical threshold for auditory stimulus (sound tone) was set at +65 dB. ERPs were recorded with the subject sitting on a chair in a semi-

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Men</th>
<th>N</th>
<th>Mean age (± SD)</th>
<th>Women</th>
<th>N</th>
<th>Mean age (± SD)</th>
<th>Total</th>
<th>N</th>
<th>Mean age (± SD) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>60 - 69</td>
<td>11</td>
<td>15</td>
<td>65.1 (± 2.6)</td>
<td>64.7 (± 1.9)</td>
<td>26</td>
<td>64.9 (± 2.1)</td>
<td>(41.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>70 - 79</td>
<td>8</td>
<td>11</td>
<td>73.8 (± 3.1)</td>
<td>74.1 (± 3.0)</td>
<td>19</td>
<td>74.0 (± 2.9)</td>
<td>(30.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>80 +</td>
<td>5</td>
<td>13</td>
<td>84.4 (± 2.9)</td>
<td>83.7 (± 3.2)</td>
<td>18</td>
<td>83.9 (± 3.1)</td>
<td>(28.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>24</td>
<td>39</td>
<td>72.0 (± 8.0)</td>
<td>73.7 (± 8.5)</td>
<td>63</td>
<td>73.0 (± 8.3)</td>
<td>(100)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

No significant sex differences on the number, mean age and SD was detected in each age group.
soundproofed shield room, focusing straight ahead with eyes open and listening to a series of sound tones from a speaker positioned 1.5 m in front of the subject. The subject was instructed to silently count the number of target stimuli. ERPs was obtained during an oddball task. Stimuli consisted of 1 kHz (frequent- nontarget stimulus) and 2 kHz (rare-target stimulus) tone- bursts. The respective probabilities of the rare and frequent stimuli were 0.2 and 0.8. Stimuli were presented in random order, the duration of each being 90 ms with a rise and fall time of 10 ms. The intensity was approximately 65 dB HL for each. The interstimulus interval was 1.7±0.1 sec. Although we adopted a criterion of 80% correct counting of the rare tones in any run, none had to be excluded. The subjects were instructed to count the number of rare tones and report it after each run. A run consisted of 80 stimuli, 3 to 4 runs being made for each subject. To familiarize the subjects with the task, short practice runs were made at first.

Scalp EEGs were recorded from 16 Ag-AgCl disk electrodes placed at Fp1, Fp2, F7, F3, Fz, F4, F8, C3, C4, T5, P3, Pz, P4, T6, O1, and O2, according to the International 10/20 system. All the electrodes were referred to linked earlobes. Electrode impedance was maintained at less than 5 KΩ. The electro-oculogram (EOG) was recorded from electrodes placed above and below the right eye. Amplifiers had a bandpass of 0.16 (time constant (Tc) = 1.0 sec) -30Hz. The EEGs and EOG were sampled at the rate of 2.4 msec per point with a laboratory computer (NEC-SANEI, DP1200, Japan). ERPs were averaged separately for the rare and frequent stimuli. Trials were automatically rejected if at any point during the averaging epoch the voltage exceeded±100 μV in the EOG lead. The averaged potentials were baseline to the mean potential of the 120-msec period preceding them. Runs in which the EOG amplitude exceeded 100 μV were excluded from averaging. Averaged waveforms were smoothed using a 25-point (40 Hz) digital filter. The most positive deflection appearing 280 to 480 ms after stimulus was designated as the P300 peak, and Pz values for P300 peak amplitude and latency were measured.

Cerebral MRI: Brain MRI was performed by using a Magnetom Vision unit (Siemens, 1.5T) with T1-weighted imaging using a FLASH (Fast Low Angle Shot) sequence. Imaging parameters: TR=35 ms, TE=5 ms, Flip angle=45 deg, matrix=256 × 256, pixel=0.94 × 0.94, slice thickness=1.5 mm (voxel size 0.94 × 0.94 × 1.5 mm), field of view (FoV) =240 mm, scan time=12 minutes 48 seconds. MRIs were evaluated by experienced radiologists under blinded conditions.

Psychological test: MMS is a simple screening test which was developed by M.F. Folstein and colleagues to provide a bedside assessment of a broad array of cognitive function including orientation, attention memory, construction and language. The maximum total score is 30 points. High scores indicate high cognitive function.

The Benton Visual Retention Test was developed by A.L. Benton. This was to provide an assessment of visual-motor deficits and visual-figure retention. At first, ten graphical figures are presented to the subjects for 10 seconds. Subjects are asked to recall the graphical figures immediately. Then the number of correct responses are determined by a technician.

The Japanese version of the Geriatric Depression Scale (GDS) was applied. GDS has been validated as a screening instrument to identify residents with depressive symptoms among the elderly.

Evaluation of quality of life: The TMIG Index of Competence (TMIG) was developed by Tokyo Metropolitan Institute of Gerontology to measure the functional capacity of the elderly.

Data analysis: Differences in these indicators between men and women were analyzed by one-way ANOVA, and correlation to age was determined by Pearson’s correlation coefficient. Two-way ANOVA was performed regarding age range and sex as the categorical explanatory variables. Moreover, since individual indicators are not independent of one another, we studied the association of the P300 component on other indicators, as well as the effects of other indicators on the P300 component. In order to practice this, we applied multiple regression analysis with the component as an independent variable as well as a dependent variable.

RESULTS

The number of subjects, their mean age and SD are shown in Table 1. No significant sex difference on these numbers was detected in each age group.

Fig. 1 illustrates the latencies (upper panels) and
the amplitudes (lower panels) of P300 plotted as a function of age in the subjects. Lines are the predicted regression function. No significant age-related change was found in men and women in either the latency or the amplitude.

The latency and amplitude of P300, the scores of MMS, Benton, GDS and TMIG in elderly subjects are shown in Table 2 for the 3 age groups (60 to 69, 70 to 79, and 80 or older). Results of 2-way ANOVA, using age and sex as the categorical explanatory variables, showed no main effects of age on the latency or the amplitude, and no reciprocal interaction between age and sex. Results also indicated no main effects of age on MMS score, and no reciprocal interaction between age and sex for MMS score. However, on the score of Benton, age had a significant effect (P < 0.01) with the mean scores of 6.1 (±1.6) at 60 to 69 years of age, 5.2 (±2.0) at 70 to 79 years of age, and 4.1 (±1.9) at 80 years of age or older. Among women, on the score of Benton, age had a significant effect (P < 0.05).

Table 3 shows Pearson’s correlation coefficients between age and the scores of MMS, Benton, GDS and TMIG. Significant inverse correlation was noted between age and the score of MMS in total subjects (r = -0.34, P < 0.01). When data for men and women were separately analyzed, the correlation coefficient for men was almost identical to that for women, but the correlation was significant in only women (r = -0.33, P < 0.05). Significant correlation between age and the score of Benton was found (r = -0.45, P < 0.001), however, when data for men and women were analyzed separately, the correlation was statistically significant in only women (r = -0.47, P < 0.01). The score of TMIG correlated with age (r = -0.27, P < 0.05) in total subjects.

Multiple regression analysis was performed in order to examine the association of the score of MMS on age, the latency and the amplitude of P300, the scores of Benton, GDS and TMIG. Results showed no significant effect of any of these indicators on either the latency or the amplitude. To examine the effects of the latency and the amplitude on age and the scores, multiple regression analysis was performed. The score of MMS was significantly affected by the latency and the score of Benton (Table 4).

**DISCUSSION**

The elderly subjects were active, living at home, free from diseases which might affect cognitive function such as psychiatric and neurological diseases as well as physical illness. They had good cognitive function, and showed few symptoms of depression. Candidates in whom cerebral MRI showed multiple cerebral infarctions or a cerebral infarction at least 5 mm in size were excluded from the
Table 2  Latency and amplitude of P300, and the scores of MMS, Benton, GDS and TMIG with age group in elderly subjects

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Latency (msec) Mean (±SD)</th>
<th>Amplitude (uV) Mean (±SD)</th>
<th>MMS score Mean (±SD)</th>
<th>Benton score Mean (±SD)</th>
<th>GDS score Mean (±SD)</th>
<th>TMIG score Mean (±SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men 60 - 69 (N=11)</td>
<td>377.6 (±40.8)</td>
<td>10.4 (±4.8)</td>
<td>29.2 (±1.1)</td>
<td>6.0 (±1.6)</td>
<td>2.4 (±2.3)</td>
<td>12.7 (±0.6)</td>
</tr>
<tr>
<td>Women 70 - 79 (N=11)</td>
<td>401.6 (±21.1)</td>
<td>9.0 (±5.3)</td>
<td>29.1 (±1.0)</td>
<td>5.9 (±1.9)</td>
<td>2.5 (±2.4)</td>
<td>13.0 (±0.0)</td>
</tr>
<tr>
<td>Total 70 - 79 (N=19)</td>
<td>393.5 (±40.1)</td>
<td>8.5 (±5.3)</td>
<td>27.1 (±2.0)</td>
<td>4.6 (±2.0)</td>
<td>2.6 (±2.2)</td>
<td>12.2 (±1.5)</td>
</tr>
<tr>
<td>Men 80 - (N=5)</td>
<td>393.4 (±29.8)</td>
<td>13.0 (±4.7)</td>
<td>27.6 (±1.6)</td>
<td>4.0 (±1.9)</td>
<td>3.6 (±2.4)</td>
<td>11.8 (±1.6)</td>
</tr>
<tr>
<td>Women 80 - (N=13)</td>
<td>393.4 (±29.8)</td>
<td>12.2 (±5.2)</td>
<td>27.7 (±1.6)</td>
<td>4.4 (±1.9)</td>
<td>4.2 (±2.4)</td>
<td>11.9 (±1.5)</td>
</tr>
<tr>
<td>Total 80 - (N=18)</td>
<td>393.4 (±29.8)</td>
<td>11.2 (±5.2)</td>
<td>27.7 (±1.6)</td>
<td>4.0 (±1.9)</td>
<td>3.6 (±2.4)</td>
<td>11.9 (±1.5)</td>
</tr>
</tbody>
</table>

Peak latency and peak amplitude of P300 were from an electrode at Pz. (**P<0.01, *P<0.05)
MMS: Mini-Mental State Examination, Benton: Benton Visual Retention Test, GDS: Geriatric Depression Scale, TMIG: The TMIG Index of Competence

Table 3 Pearson’s correlation coefficients between age and the scores

<table>
<thead>
<tr>
<th></th>
<th>Men (N=24)</th>
<th>Women (N=39)</th>
<th>Total (N=63)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMS score</td>
<td>-0.34</td>
<td>-0.33*</td>
<td>-0.34**</td>
</tr>
<tr>
<td>Benton score</td>
<td>-0.39+</td>
<td>-0.47***</td>
<td>-0.45***</td>
</tr>
<tr>
<td>GDS score</td>
<td>-0.07</td>
<td>-0.15</td>
<td>-0.08</td>
</tr>
<tr>
<td>TMIG score</td>
<td>-0.17</td>
<td>-0.29+</td>
<td>-0.27*</td>
</tr>
</tbody>
</table>

**P<0.001, *P<0.01, +P<0.05, +P<0.1

As a result, the elderly subjects participating in this study were naturally quite healthy and active.

Significant correlation between age and the values of P300 component was found in our previous study. Age-related changes in P300 latency have been reported by many researchers, such as Goodin and colleagues. There is almost a complete agreement that latency increases as subjects grow older. The correlation between the age and latency has been reported to increase in a linear function, fitting a primary regression equation. It has also been reported to show a steepening slope in the elderly, fitting a secondary regression. Regression of P300 latency on age was reported, with a slope ranging between 1.0 to 2.0 msec/year. P300 amplitude has been reported to decrease with age. However, a previous report has suggested the possibility that this is not due to changes in amplitude per se, but rather to change in superimposed slow wave.

The current study in elderly subjects did not reveal any correlation between age and P300 component in both men and women. The aging process is accompanied by progressive morphologic changes in the brain, particularly cerebrovascular changes. Kobayashi studied MRI findings from 242 healthy elderly subjects and reported a significant age-related increase in the incidence of asymptomatic cerebral infarction. According to the report by Ozawa over 73 healthy elderly volunteers, MRI detected lacunae was 47%, and visual spatial perception score was significantly lower in the lacuna group than in the normal group.

In a study of age-related changes in P300 latency, Yamashita and colleagues found that patients with cerebral infarctions showed a greater rate of age-
related prolongation of P300 latency than that of healthy subjects. Numerous researchers have reported a correlation between prolongation of P300 latency, cerebral infarction, and multiple lacunar infarcts. It thus appears that cerebrovascular changes may affect P300 latency. Based on reports available to date concerning the correlation between aging and P300, the possibility cannot be ruled out that lacunae or some other forms of cerebrovascular abnormality may be present in some healthy elderly subjects. As a natural part of the aging process, such subclinical organic degeneration in the brain occurs more frequently in the elderly. However, this abnormality may not proceed in a simple linear relationship to age. In order to confirm these findings, more research will be required among elderly populations regarding the correlation between aging and P300 component. Moreover, detailed and precise measurements of cerebral degeneration will be needed.

Sex difference on age-related change of P300 component was not detected in the elderly subjects. The reason is probably that the age-related increase of P300 latency itself was not seen in this study.

Studies have been performed regarding the correlation between prolongation of P300 latency and cognitive functions, by using a variety of cognitive function assessment scales. Lai and colleagues reported an inverse correlation between P300 latency and MMS score in elderly subjects, while Goodin and colleagues found that changes in dementia severity were reflected by the latency by practicing in a vertical study on dementia patients. Studies on patients with dementia have shown an inverse correlation between prolongation of latency and Wechsler Adult Intelligence Scale (WAIS) score. These findings suggest that correlation exists between prolongation of latency and cognitive impairment.

Multiple regression analysis was performed to determine the effects of various indicators on P300 component. The results showed no significant effect on either the latency or the amplitude. However, when multiple regression analysis was applied to determine the effects of the latency and the amplitude, on the scores of MMS, Benton, GDS and TMIG, significant effects of both the latency and the score of Benton on the score of MMS were found. These findings suggest that a correlation exists among age, P300 latency, the scores of MMS and Benton. As represented by the score of MMS, overall cognitive function in the elderly decreases with lower visual retention. This is shown by the Benton test and by longer auditory information processing speed which is reflected by P300 latency. Among them, visual retention is more intensely and directly affected by age than by P300 latency.

In conclusion, although P300 latency have been assumed to increase with age, among elderly subjects who have little cerebral organic deterioration, high MMS score, and good quality of life, there was no obvious age-related prolongation of P300 latency. P300 latency does not increase linearly with age among the elderly subjects. It can be assumed that the prolongation of the latency is affected by subclinical organic changes in the brain than by aging itself.

### Table 4 Major findings of multiple regression analysis using MMS score as the dependent variable

<table>
<thead>
<tr>
<th></th>
<th>SE</th>
<th>B</th>
<th>Beta</th>
<th>t</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.028</td>
<td>-0.252</td>
<td>0.082</td>
<td></td>
</tr>
<tr>
<td>P300 latency</td>
<td>0.005</td>
<td>0.254</td>
<td>0.032*</td>
<td></td>
</tr>
<tr>
<td>P300 amplitude</td>
<td>0.038</td>
<td>0.139</td>
<td>0.242</td>
<td></td>
</tr>
<tr>
<td>Benton score</td>
<td>0.109</td>
<td>0.269</td>
<td>0.045*</td>
<td></td>
</tr>
<tr>
<td>GDS score</td>
<td>0.083</td>
<td>-0.179</td>
<td>0.136</td>
<td></td>
</tr>
<tr>
<td>TMIG score</td>
<td>0.183</td>
<td>0.197</td>
<td>0.133</td>
<td></td>
</tr>
</tbody>
</table>

Multiple R=0.58, R Square=0.34, P<0.01
(*P<0.05)
ACKNOWLEDGEMENT

The authors greatly thank Prof. Chikara Ogura, Department of Neuropsychiatry, University of the Ryukyus for critical reading of the manuscript. We also thank the staff of the Department of Radiology, University of the Ryukyus and Health Center for the Elderly for their cooperation.

REFERENCES


