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Originals

Longitudinal Changes in Quantitative EEG and Event-related Potentials in Healthy Elderly Volunteers : A 4-year Follow-up Study

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SUMMARY

Age-related changes of cognitive brain function are reflected by neurophysiological measurements such as quantitative electroencephalograms (EEG) and event-related potentials (ERP). However, longitudinal changes in these neurophysiological parameters in healthy elderly individuals have remained largely unreported. In the present study, quantitative EEG and ERP were measured prospectively twice, at an interval of 4 years, in 21 physically and cognitively healthy geriatric volunteers (age at first session, 66.3 ± 2.6 years). EEG data collected from 18 electrode sites on the cranial surface according to the 10-20 International System were used for quantitative analysis of waveform recognition for 1 min under resting, awake, eyes-closed conditions. ERPs were elicited using an auditory oddball paradigm. With each subject, we compared EEG and ERP data obtained at the 2 sessions. The 4-year follow-up of quantitative EEG revealed a significant increase in the incidence of $Q\theta 1$ band waves and a significant decrease in the incidence of $\alpha 2$ band waves at nearly all sites. Although no changes in P300 amplitudes were observed, P300 latencies were significantly increased at the 2nd session at all sites, with mean prolongation of 4.7 ± 0.7 ms/year. These results are consistent with those of previous cross-sectional studies, and provide the first prospective demonstration of subtle slowing of cognitive processes in normal elderly subjects.

Key Words : normal aging, ERP, P300, quantitative EEG, cognitive decline

INTRODUCTION

Cognitive brain function in aging is an important research topic in geriatric psychiatry. Electrophysiological analysis can detect subtle age-related changes of human cognitive function. The P300 event-related potential (ERP), which is recorded at about 300 ms after the occurrence of a rare unexpected stimulus, has been extensively studied as an indicator of age-related cognitive changes. Cumulative evidence has consistently shown that, in normal elderly people, P300 latencies are prolonged and P300 amplitudes are either stable or moderately reduced, compared to young controls[1~4]. In addition to P300 analysis, quantitative electroencephalograms (qEEG) have been studied for indications of slowing of resting EEG in late senescence[5~8].

In previous studies[1~4], which involved a large number of healthy controls over a wide range of ages, the extent of age-related P300 latency prolongation varied with methodological details of recording. Longitudinal changes in the neurophysiological parameters of healthy elderly individuals have remained largely unreported. Prospective study of changes in neurophysiological function during normal aging is needed to obtain normative data, so that such findings can be differentiated from

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those corresponding to early signs of dementia among the elderly population.

To this end, we examined parallel determination of qEEG and ERP in healthy geriatric individuals in the present prospective and longitudinal study, in which measurements were performed twice at an interval of 4 years.

SUBJECTS

The subjects were 21 physically and cognitively healthy geriatric volunteers (11 men, 10 women) who were attending college courses for seniors. Verbal and written explanations of this study's examinations were provided, and written informed consent was obtained prior to participation in the study. Examinations were conducted twice, in 1997 and 2001 (1^{st} and 2^{nd} sessions, respectively). Each session's examinations consisted of psychiatric interview, blood biochemistry, clinical hematology, urinalysis, brain computed tomography (CT), neurophysiological examinations (qEEG and ERP), and Mini-Mental State Examination (MMSE). We excluded individuals suspected of having one of the following disorders, or who had a history of one of them : psychiatric or neurological disease, serious somatic disease, suspected dementia. We also excluded those currently using psychotropic medication. No subjects exhibited emergence of novel or age-related disability affecting neurophysiological function between the 2 sessions. Mean age was 66.3 ± 2.6 years at the 1^{st} session and 70.3 ± 2.6 years at the 2^{nd} ; thus, mean interval between sessions was 4.0 ± 0.1 years (Table 1).

METHODS

MMSE, qEEG and ERP were evaluated at the 1^{st} and 2^{nd} sessions, with an interval of 4 years. For qEEG, we performed a quantitative analysis procedure using waveform recognition for 1 min under resting, awake, eyes-closed conditions (i.e., artifact-free) from running EEG data recorded from 18 electrode sites according to the 10-20 International System (Fp1, Fp2, F3, Fz, F4, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1, Oz, and O2). Quantitative analysis involved calculation of wave incidence (wave % time) for each of 8 frequency bands : δ, $\_\theta 2$, $\_\theta 1$, $\alpha 1$, $\alpha 2$, $\alpha 3$, $\beta 1$ and $\beta 2$ ($0.5 \leqq \delta < 4.0$; $4.0 \leqq \theta 2 < 6.0$; $6.0 \leqq \theta 1 < 8.0$; $8.0 \leqq \alpha 1 < 9.0$; $9.0 \leqq \alpha 2 < 11.5$; $11.5 \leqq \alpha 3 < 13.0$; $13.0 \leqq \beta 1 < 18.0$; $18.0 \leqq \beta 2 < 30.0$).

Table 1

	N	M/F	Age	Interval	MMSE
1997	21	11/10	66.3 ± 2.6	4.0 ± 0.1	29.29 ± 0.9
2001			70.3 ± 2.6		29.43 ± 0.8

ERPs were recorded from the same 18 electrode sites used for recording qEEG data, utilizing an auditory oddball task. The oddball paradigm involved 2 types of tone-burst auditory stimuli : duration, 100 ms ; rise/fall time (both), 10 ms ; target stimulus, 2000 Hz (presentation frequency, 20%) ; stimulus intensity, 85 dB ; standard stimulus, 1000 Hz (presentation frequency, 80%). Stimuli were randomly presented at 1.5-s intervals, and subjects were required to press a button to react to the target stimulus. Amplitudes $\geqq 100\ \mu V$ were excluded, and the number of target stimuli to be included was set at 45. Peak latencies and amplitudes were measured for N100, P200, N200 and P300 components. We used the Wilcoxon single-ranks test for comparison of the following parameters between the 1^{st} and 2^{nd} sessions : MMSE scores, wave incidence for each frequency band of EEG, and peak latencies and amplitudes of each ERP component. Differences with a p value of < 0.05 were considered statistically significant.

RESULTS

Mean MMSE score did not differ significantly between 1^{st} and 2^{nd} sessions (29.29 ± 0.9 and 29.43 ± 0.8, respectively). For qEEG, at nearly all sites, there was a significant increase in the incidence of $\theta 1$ band waves ($p < 0.05$), and a significant decrease in the incidence of $\alpha 2$ band waves ($p < 0.05$, Figure 1). There were no significant changes for any other frequency band at any electrode.

Examination of ERP revealed significant prolongation of P300 latency at all sites ($p < 0.05$), with mean prolongation of 4.66 ± 0.7 ms/year (Figure 2). There were no significant changes in P300 amplitude at any electrode sites. There were no significant changes in N100, P200 or N200 components.

There was no correlation between qEEG and P300, according to Spearman's rank correlation.

DISCUSSION

To our knowledge, the present study is the first

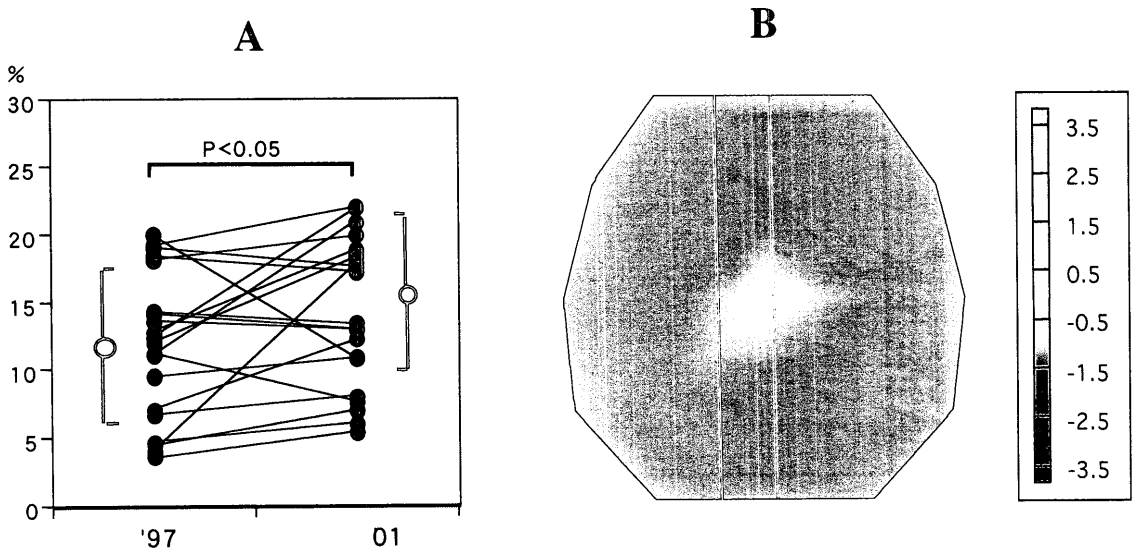

Fig. 1 Changes in % time for $\theta 1$ band wave

A : At C4, wave % time of $\theta 1$ band wave increased significantly over the 4-year follow-up period. We used the Wilcoxon single-ranks test for comparison of wave incidence for each frequency band of EEG between 1st and 2nd sessions (N = 21).

B : This topographic map is a diagrammatic representation of the z-value obtained from the Wilcoxon signed-ranks test. In the central region, wave % time of $\theta 1$ band wave decreased significantly.

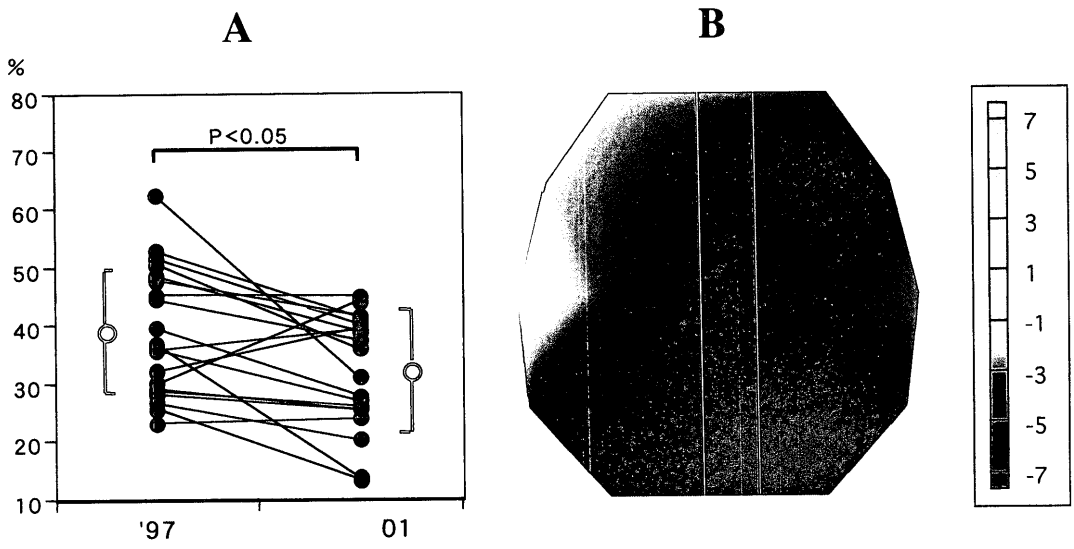

Fig. 2 Changes in % time for $\alpha 2$ band wave

A : At C4, wave % time of $\alpha 2$ band wave decreased significantly over the 4-year follow-up period. We used the Wilcoxon single-ranks test for comparison of wave incidence for each frequency band of EEG between 1st and 2nd sessions (N = 21).

B : This topographic map is a diagrammatic representation of the z-value obtained from the Wilcoxon signed-ranks test. In almost all areas, wave % time of $\alpha 2$ band wave decreased significantly.

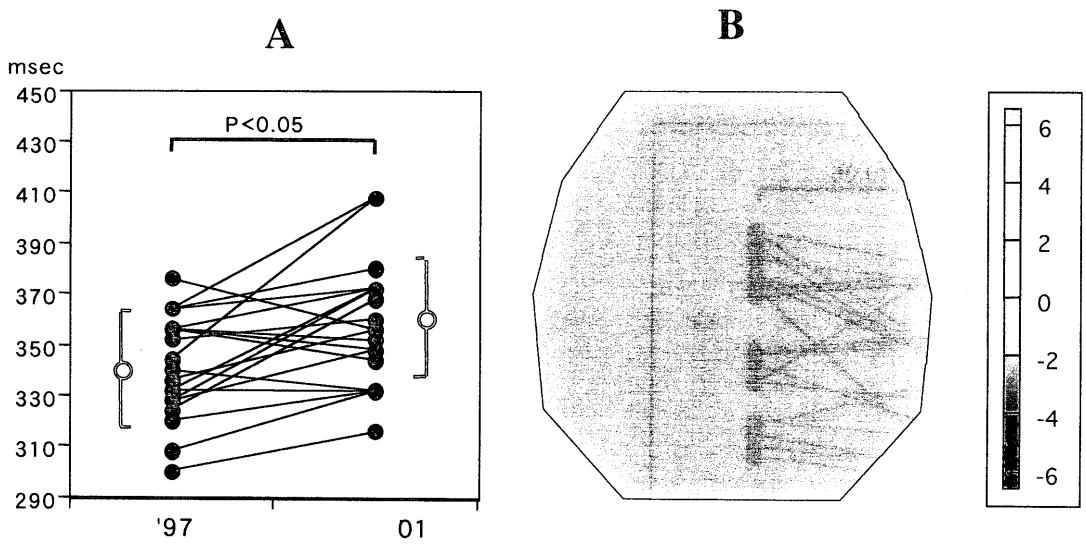

Fig. 3 Changes in P300 latency

A : At C4, P300 latency increased significantly over the 4-year follow-up period. We used the Wilcoxon single-ranks test for comparison of peak latencies and amplitudes for each ERP component between 1st and 2nd sessions (N = 21).

B : This topographic map is a diagrammatic representation of the *z*-value obtained from the Wilcoxon signed-ranks test. P300 latency was significantly prolonged in all areas examined.

prospective investigation of parallel measurements of P300 and qEEG in normal elderly individuals over an extended period. In qEEG, over the 4-year follow-up period, there was a significant increase in the incidence of θ-band waves and a significant decrease in the incidence of α-band waves. A previous study, which involved a large number of healthy controls over a wide range of ages, demonstrated that EEG patterns typical of old age are characterized by increasing incidence of θ-band waves and decreasing incidence of α-band waves[9]. There have been several prospective studies involving long-term follow-up of EEG in normal aging[5~7]. In 2 of those studies, there were no changes in incidence of θ- or α-waves[5] or α/θ ratio[7]. Conversely, in our previous 9-year follow-up study, there was an increase in θ-waves and a decrease in α-waves in late senescence[6]. In the present study, of the 3 types of α-waves examined (α1, α2 and α3), only α2 waves exhibited a significant decrease in incidence.

Whereas decreased mean frequency reportedly correlates with cognitive impairment in senile dementia of Alzheimer type[10], there is controversy over whether there is a subtle slowing of EEG in normal aging. Nonetheless, decreased EEG frequency *per se* may prove to be an important indicator of geriatric depressive patients who are prone to develop demantia[11]. Further refinement of quantitative EEG in conjunction with sensitive examination of cognitive performance may allow early detection of patients with mild cognitive impairment who are at increased risk of developing dementia.

Second, and more importantly, in the present study, cognitively intact elderly subjects exhibited significant prolongation of P300 latency (4.66 ± 0.7 ms/year) over a 4-year period. A number of previous cross-sectional studies, involving large healthy populations covering a wide age range, have revealed age-related changes in P300 latency, with a mean increase of 0.3 to 3 ms/year[2~4]. In these previous studies, the P300 latency/age relationships were nonlinear, with accelerated latency in elderly subjects-the increase in P300 latency/year was greater in elderly subjects (> 60 years old) than in younger subjects[2~4]. Furthermore, heterogeneous subject populations make it difficult to accurately determine relationships between age and P300, as suggested by the large variations in values in such studies[12].

Kugler[1] pointed out the necessity of longitudinal studies for differentiation of normal and pathological aging of cognitive functions. In the present study, there were no significant changes in MMSE scores over the 4-year follow-up period. This indicates that the present subject

population constituted a homogeneous population that was more suitable for determination of prolongation of P300 latency in healthy elderly people than deduction from the slopes of P300 latency/age curves, which has been used in previous cross-sectional studies[2~4]. In the present prospective study, P300 latency values of the 1st session (340 ± 18.3 ms) were within the normal range, and prolongation of P300 latency was 4.66 ± 0.7 ms/year over the 4-year follow-up period. Although the magnitude of yearly prolongation of P300 in the present study is greater than those of a number of previous cross-sectional studies[3, 4], it is similar to the magnitudes of previously obtained P300 latency slopes (ms/year) for normal people more than 60, 70 and 80 years old (2.72, 4.78 and 13.45 ms/year, respectively)[2]. In any case, prolongation of P300 latency in normal aging is likely to represent slowing of the processes of stimulus discrimination and evaluation[1]. In contrast, the lack of change in N100, P200 or N200 components in the present study suggests that they are not strongly affected by normal aging, a finding consistent with that of a previous report[13].

Recent studies show that patients with mild cognitive impairment exhibit marked prolongation of P300 latency (416 ms), compared to healthy elderly subjects (372 ms)[14]. Thus, prospective investigation of P300 latency in elderly subjects may open new avenues of research into differentiation between healthy and cognitively impaired individuals.

In conclusion, 21 healthy geriatric individuals underwent qEEG and ERP twice, at an interval of 4 years. On qEEG, at nearly all sites, there was increased incidence of $\theta 1$ band waves and decreased incidence of $\alpha 2$ band waves. Examination of ERP revealed increased P300 latency at all sites, with a mean increase of 4.66 ± 0.7 ms/year. These findings provide the first prospective evidence that P300 latency prolongation may be a sensitive indicator of slowing of stimulus discrimination and evaluation in normal elderly subjects.

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