The processing of global and local visual information in Alzheimer's disease

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We examined the quantitative and qualitative difference of the pattern with visuo-cognitive processing impairment in patients with early onset AD (EOAD) and late onset AD (LOAD). We use a visual attention task introduced by Navon (1977) to examine the function to integrate local visual stimuli into global image. Although the ability to identify solid digits ether of large and small size presented at the same exposure duration, EOAD performance was poor in the global perception especially at the short duration (20 msec). We provide evidence that this dysfunction is attribute to the AD pathology specific to early onset type.

Keywords: Visual attention, global and local perception, Alzheimer's disease, age at onset

1. Introduction

In addition to memory and general conceptual disability, various neuropsychological impairments may develop in Alzheimer's disease (AD). The patterns of cognitive impairment in AD are reportedly different according to age at disease onset. Visuoperceptual dysfunction is one of that cognitive dysfunction, and is usually more prominent in patients with early onset AD (EOAD) than in late onset AD (LOAD). In this study, subdividing AD into two subtypes according to age at onset, we studied the visual attention function in patients with EOAD and in patients with LOAD, which was compared with that in healthy subjects age-matched to each onset group.

Evidence has been accumulated that a deficit of visual attention underlies the visuo-perceptual dysfunction in AD. Coslett and coworkers [1] reported two patients with early-onset AD who had progressive visuo-spatial deficits with a greater difficulty in reading letters written in a large size than those written in a small size. When the patients, given a large letter composed of a small letter, were requested to read either the global (i.e., large) or local (i.e., small) letter, they identified the large composed letter more slowly and less accurately than the small internal letter. This differed from the normal trait that response time for global stimulus is shorter than that for local stimulus. Visual perception is a sequential process in which the global structure of the stimuli is perceived before the local parts, and interference may occur in the processing of local information by irrelevant global level (global-to-local) [2]. Reporting the similar phenomenon in patients with early-onset AD, several investigators proposed a hypothesis of impaired "spotlight" of attention to explain the phenomenon [3,4]. The "spotlight" of attention is a function that is necessary for providing object recognition process in the visual field integrating visual features [5].

The present study examined whether patients with AD in general have a disturbance in regulating the size of the "spotlight" thereby integrating local visual stimuli into global image. We made use of a task procedure developed by Navon [2] to examine the function of visual attention to integrate local visual stimuli into global image. The stimuli were large digits composed of small digits. To recognize the large digit, a process to integrate the local digits synthesizing the global image of the large digit is required. We gave the stimuli with varied exposure duration, as it has been demonstrated in previous studies that patients with simultanagnosia had an impairment of the speed of processing in integrating parts into a whole image [6,7]. Accordingly, the visual system may have a critical processing phase of visual stimuli for perception. If patients affected by duration of stimulus exposure, it might have associa-

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tion with a general slowing of visual processing and visuo-perceptual disability. So we varied with stimulus exposure duration to examine whether the exposure duration affected processing dominance.

2. Methods

2.1. Subjects

All procedures of this study strictly followed the Clinical Study Guidelines of the Ethics Committee of Hyogo Institute for Aging Brain and Cognitive Disorders (HI-ABCD), Himeji Japan, in 1993, and were approved by the Internal Review Board. After a complete description of all procedures of this study, written informed consent was obtained from patients or their relatives, or from control subjects.

The subjects of this study were 40 Japanese patients with sporadic AD who were given a short-term admission to the infirmary of the HI-ABCD, a research-oriented hospital for dementia, for examination between September 1998 and March 1999. All patients were examined by both neurologists and psychiatrists and were given routine laboratory tests and standard neuropsychological examinations. In addition, electroencephalography, magnetic resonance (MR) imaging of the brain, MR angiography of the neck and head, and cerebral perfusion/metabolism studies by positron emission tomography or single photon emission computed tomography were done. All results were incorporated in the diagnosis. The inclusion criteria were; (i) fulfilling the Alzheimer's type and the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA) criteria for probable AD [8], (ii) minimal to mild functional severity (grades 0.5 and 1 on the Clinical Dementia Rating Scale (CDR) [9], the exclusion criteria were; (i) complication of other neurological diseases or ill physical conditions such as diabetes mellitus, thyroid diseases, vitamin deficiencies, malignant diseases and so on, (ii) history of previous mental illness or substance abuse before onset of dementia, (iii) evidence of focal brain lesions on MRI, (iv) presence of severe language, attention, or behavioral disorders that would make examinations difficult, and (v) inability to obtain informed consent from patients and their relatives for all procedures of this study. The ophthalmologic evaluation included assessment of refracted near and distant (Snellen) visual acuity, visual field testing by confrontation, opthalmoscopy, pursuit eye movements, and saccades to command and visual stimuli. The patients had impairment of visual acuity and visual field loss that might affect visual functioning testing also excluded.

The included patients consisted of 31 women and 9 men; the mean (standard deviation) age at examination was 68.8 (8.9) years and the mean educational attainment was 10.0 (2.6) years. The functional severity was 0.5 for very mild in 5 patients, 1 for mild in 35 patients as determined by the CDR. The mean value of the Mini-Mental State Examination (MMSE) [10] was 22.0 (3.1). The mean score of Alzheimer's Disease Assessment Scale (ADAS) [11] was 14.8 (5.3). The age at onset was ascertained through an interview with the primary caregiver. Age at onset was defined as the age of the first appearance of symptoms of sufficient severity to interfere with social or occupational functioning and the duration was defined as the time in months between the onset and the admission 10. Patients were divided into two groups according to age at onset before or after 65. Fifteen patients were classified into EOAD (4 male, 11 female), and the mean age at examination of the EOAD group was 58.8 (4.5) years. Twenty-five patients were classified into LOAD (5 male, 20 female), and the mean age at examination of the LOAD group was 74.3 (3.4) years. No statistically significant difference in males/females ratio, duration of illness, years of educational attainment, or MMSE score were found between the EOAD and LOAD (Table 1).

Twenty-seven healthy unpaid volunteers of similar age and sex distribution were recruited as the controls from spouses, friends, and caregivers of the patients. The controls were subdivided into two groups according to age to match to each disease onset group, i.e. 12 younger ($<$ 65 years old) control subjects (YCS: 4 male, 8 female; mean age was 57.8 (6.9)) and 15 older ($=$ 65 years old) control subjects (OCS : 6 male, 9 female; mean age was 71.4 (5.1)). All subjects had no history of psychiatric or neurological disorders and had 27 or more MMSE scores.

2.1.1. Neuropsychological examination

An extensive neuropsychological test battery was performed in all the patients including the Wechsler Adult Intelligence Scale-Revised (WAIS-R) [12] and Wechsler Memory Scale-Revised (WMS-R) [13], Raven Colored Progressive Matrices (RPCM) [14], and Rey-Osterreith Complex Figure Test. The tests were given according to their standardized method of administration as published in the test manual. Low score of each test was shown in the Table 2. Group difference with EOAD and LOAD were analyzed by using the two-tailed Student's t test.

Table 1
Demographic variables of patients and control subjects

	EOAD	YCS	LOAD	OCS
Sex (female:male)	11:4	8:4	20:5	9:6
Age (years)	58.8 ± 4.5 (48–64)	57.8 ± 6.9 (48–60)	74.3 ± 3.4 (68–80)	71.4 ± 5.1 (68–80)
Duration (months)	29.3 ± 14.6 (6–60)	–	26.4 ± 2.9 (6–60)	–
Education (years)	11.7 ± 1.7 (9–16)	11.1 ± 1.8 (9–14)	9.0 ± 2.7 (6–18)	10.0 ± 2.5 (6–16)
MMSE score	21.9 ± 3.4 (15–29)	28.9 ± 1.5 (27–30)	22.0 ± 3.2 (17–28)	29.1 ± 1.2 (27–30)

Mean ± SD (range)
EOAD: Early onset Alzheimer's disease patients, LOAD: Late onset Alzheimer's disease patients, YCS: Younger control subjects, OCS: Older control subjects, MMSE: Mini-Mental State Examination.

Table 2
Neuropsychological test scores in patients with Alzheimer's disease

	EOAD	LOAD	p-Value
ADAS total score	13.6 ± 5.3	16.0 ± 5.3	0.161
WAIS-R			
FIQ	81.2 ± 13.3	83.9 ± 12.6	0.515
knowledge	9.4 ± 4.4	7.3 ± 4.0	0.132
words	19.1 ± 8.3	18.7 ± 8.1	0.882
arithmetic	5.3 ± 2.3	6.4 ± 2.0	0.132
comprehension	10.9 ± 3.6	10.7 ± 4.8	0.861
similarities	8.6 ± 3.6	5.5 ± 4.6	0.327
picture completion	5.2 ± 3.9	6.3 ± 3.0	0.361
picture arrangement	4.2 ± 3.4	4.9 ± 2.3	0.428
block design	16.2 ± 12.5	17.4 ± 8.8	0.724
object assembly	16.9 ± 9.2	17.6 ± 6.4	0.768
digit symbol	21.3 ± 16.7	22.2 ± 9.6	0.816
WMS-R			
information	11.5 ± 1.9	10.9 ± 2.0	0.394
mental control	2.4 ± 1.9	3.2 ± 1.7	0.168
figural memory	5.0 ± 1.5	4.2 ± 1.7	0.173
logical memory	7.2 ± 4.0	7.2 ± 4.2	0.982
visual paired associate	4.6 ± 2.6	5.2 ± 3.3	0.551
verbal paired associate	8.1 ± 4.9	6.8 ± 4.0	0.407
visual memory span (forward)	4.1 ± 1.7	4.6 ± 0.8	0.165
visual memory span (backward)	3.8 ± 1.9	3.8 ± 0.9	0.989
visual reproduction	15.4 ± 8.0	23.5 ± 9.0	0.007
digit span (forward)	5.6 ± 1.0	5.2 ± 0.9	0.653
digit span (backward)	3.9 ± 1.0	3.8 ± 0.9	0.238
Rey-Osterreith Complex Figure Test	26.0 ± 9.9	27.5 ± 10.3	0.683
Raven's Coloured Progressive Matrices	20.7 ± 6.4	22.6 ± 5.9	0.355

Mean ± SD (range)
EOAD: Early onset Alzheimer's disease patients, LOAD: Late onset Alzheimer's disease patients, ADAS: Alzheimer's Disease Assessment Scale, WAIS-R: Wechsler Adult Intelligence Scale-Revised, WMS-R: Wechsler Memory Scale-Revised.

2.2. Experimental investigations

The stimuli were presented on a 15 inch Apple Color RGB monitor with resolution of 1280 × 1024 pixels and a refresh rate of 75 Hz (monitor laced). The stimulus presentations were controlled by Super lab software Ver.2.0 running on a Performa 650 (Macintosh Computer). Participant's chins rested on a chin rest located 40 cm from the display. The experiment was conducted with ordinary overhead room lighting. All stimulus events were black on a white surround. Display luminance was 95 cd/m^2. Each trial begins with a 5000 msec. blank followed immediately by a 500 msec. presentation of the central fixation point signaled the beginning of each trial. Subjects were instructed to look directly at the fixation point and not to move their eyes. After the fixation point was erased, followed by a 100 msec. pause and then a stimulus presentation in the center of the display.

2.2.1. Solid digit identification as a function of size

The stimuli were solid black digits (2, 3, 4, 5, 6, 8, and 9) of two different sizes presented for 20msec. on a

white background, i.e., 1.8 × 1.5 degree of visual angle (1.2 cm × 1.0 cm; small letter) and 10.8 × 9.0 degree of visual angle (7.2 cm × 6.0 cm; large letter). The small and large digits were just the same as the local and global digits the global versus local processing in digit identification task mentioned below. In the small-size and large-size sessions, each stimulus randomly appeared three times for a total of 21 trials. Subjects were instructed to identify the digit and speak it aloud. We recorded subject's answer and the percentages of correct response were calculated. The correct response rates were subjected to a repeated measures analysis of variance (ANOVA) with one between-subject factor, groups (EOAD, LOAD, YCS, OCS) and one within-subject factor (stimulus size: large and small).

2.2.2. Global versus local processing in digit identification task

The experiment was analogues to that of Navon (1977) [2]. As illustrated in (Fig. 1), the compound stimuli consisted of digit letter (3, 5 and 8) at either the global or local level. The large global letters consisted from small letters arranged within 5 × 6 grid. The large letters were 10.8 × 9.0 degree of visual angle (7.2 cm × 6.0 cm) and the small letters were 1.8 × 1.5 degree (1.2 cm × 1.0 cm). The large letter of a stimulus item never matched the small letter (e.g., a large "5" made up made up of small "3"). The examination consisted of six blocks of 40 trials. Subjects were instructed to identify the large letter (global directed attention condition) in half of the blocks and to identify the small letters (local directed attention condition) in others half blocks. Subjects gave their answer by speaking the digit aloud. Each condition consisted of three blocks that corresponded to one of three exposure duration; short (20 msec), middle (100 msec) and long (200 msec). After the completion of each block of trials, subjects were given a few minute rest periods. A half of the subjects performed the global directed condition first and the local directed condition later. In the remaining half of the subjects, the order was reversed. The percentage of correct response in each attention condition and each exposure condition were calculated.

The correct response rates were tested by using analysis of variance (ANOVA). The performance of the solid digit identification was analyzed with one between-subject factor, groups (EOAD, LOAD, YCS and OCS) and one within-subject factor (stimulus size). The performance of the global versus local processing in digit identification task was analyzed with one between-subject factor, groups (EOAD, LOAD, YCS and OCS) and two within-subject factor (exposure duration and attend levels). Post-hoc comparisons were made using a Tukey HSD test at the 0.05 level for significance.

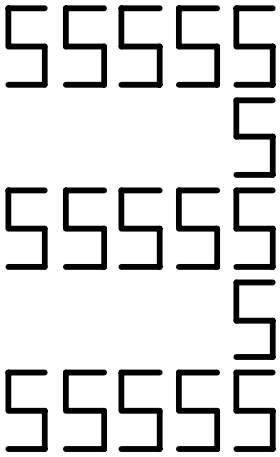

Fig. 1. Example of large-digit made up small-digits.

3. Result

3.1. Neuropsychological test

Performance on the ADAS, WAIS-R, WMS-R, RPCM, and Rey-Osterreith Complex Figure Test were comparable between EOAD and LOAD. The mean score and SD of each group showed in Table 2. For the subtest scores, only the mean WMS-R visual reproduction subtest score was significantly worse in the EOAD group than the LOAD group ($t = 2.37$, $p = 0.02$).

3.2. Solid digit identification as a function of size

On the small size session, the mean correct response rate was 92.2 (15.7) % in the EOAD group and 94.5 (10.3) % in the LOAD group, respectively, and was 99% in each control group. On the large size session, the mean correct response rate was 96.7 (11.6) % in the EOAD group and 94.4 (17.1) % in the LOAD group, respectively, and was 99% in each control group. An ANOVA showed no significant main effects of size ($F(1, 63) = 0.58$, $p = 0.44$) and group ($F(3, 63) = 1.41$, $p = 0.248$). The two-way interaction was not significant ($F(3, 63) = 0.743$, $p = 0.53$).

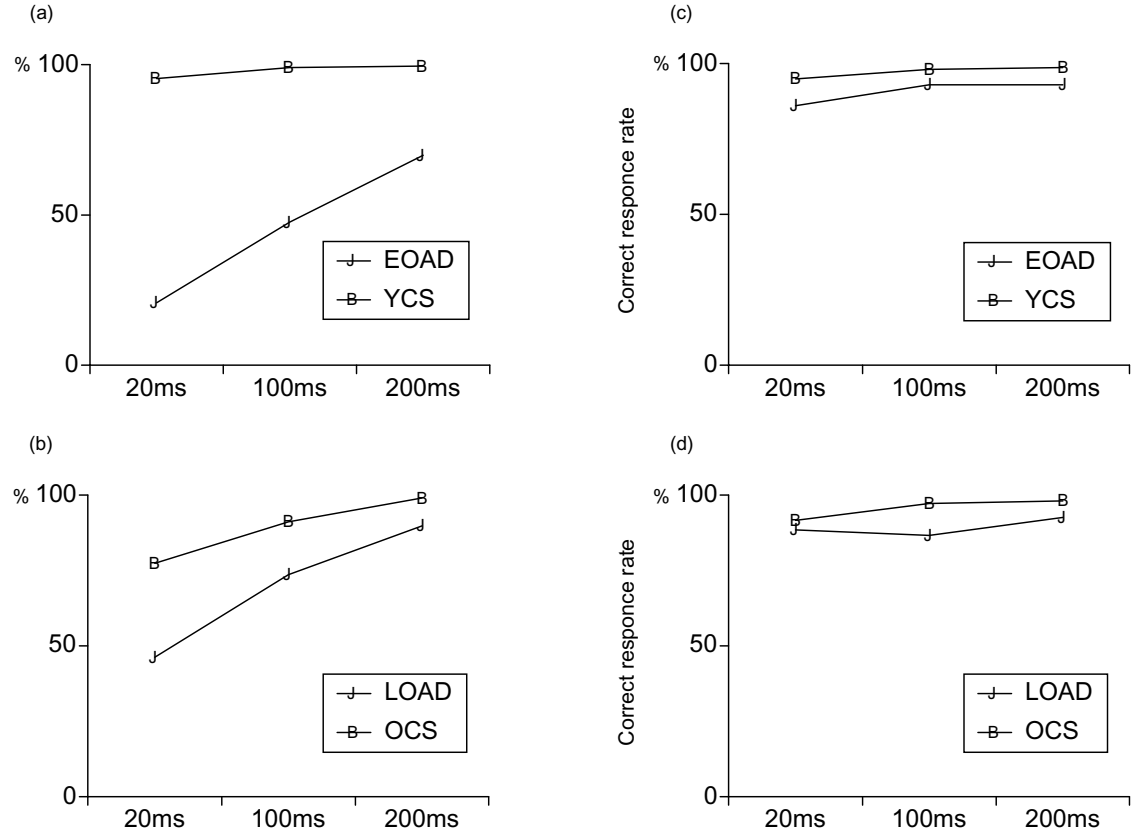

Fig. 2. Mean percentage of correct response to global and local targets as a function of the exposure duration for early onset Alzheimer's disease patients (EOAD), late onset Alzheimer's disease patients (LOAD), younger control subjects (YCS) and older control subjects (OCS). Fig. 2(a) showed response to global targets in EOAD and YC S. Fig. 2(b) showed response to global targets in LOAD and OCS. Fig. 2(c) showed response to local targets in EOAD and YCS. Fig. 2(d) showed response to local targets in LOAD and OCS.

3.3. Global versus local processing in digit identification

The mean correct response rates of each group and condition are presented in (Table 3). An ANOVA revealed significant main effects of group ($F(3, 63) = 15.68$, $p < 0.0001$), attend condition ($F(1, 63) = 30.70$, $p < 0.0001$), and exposure duration ($F(2, 126) = 75.50$, $p < 0.0001$). The three-way interaction was significant ($F(6, 126) = 3.05$, $p < 0.01$). The post hoc Tukey HSD test was revealed the results of EOAD group attend to global stimuli was significantly worse than YCS group at each exposure duration condition (short; $p < 0.0001$, middle; $p < 0.0001$, long; $p < 0.0001$). In LOAD group, they made much error than OCS group at short duration condition ($p < 0.0001$). However, there were no significant difference between LOAD and OCS at middle and long duration (middle; $p = 0.135$, long; $p = 1.000$). Compared among AD patients groups, in EOAD group was significantly worse than LOAD patients at all duration condition (short; $p = 0.00046$, middle; $p = 0.00026$, long; $p = 0.034$).

4. Discussion

In both EOAD and LOAD groups, the global perception at the short exposure duration (20 msec) was significantly defective, although the ability to identify solid digits ether of large and small size presented at the same exposure duration was intact. The EOAD group had a more difficulty in the global perception than the LOAD group did. The performance of the global identification at the short exposure duration was poorer in the old healthy controls than in the younger healthy controls. This is explained by an effect of aging on visual function and general perceptual speed. However, the poor performance to identify the global aspect of the forms in the EOAD group is not attributable to

aging, as the EOAD group was younger than LOAD group. At the longer exposure duration (100 msec and 200 msec), the performance of the global identification in the EOAD group significantly differed from the age-matched healthy controls, while the performance in the LOAD group was comparable to that in the age-matched healthy controls. Therefore, the disturbance of the global identification is independent from aging and general cognitive impairment, and specific for EOAD. Our results are consistent with the findings of previous studies that visuospatial function is more affected in EOAD than in LOAD [16,17], and suggests that patients with EOAD have a disturbance in integrating local visual stimuli into global image.

The difference of the performance between the EOAD and LOAD groups cannot be explained by the difference in general cognitive functions including attention and concentration, as the performance on the neuropsychological tests were comparable between the two groups. One possible account is that the impairment demonstrated by EOAD patients have been attributed to impairment in visual selective attention. Previous studies [1,3,4] described EOAD patients presenting with progressive visual disturbance, and they recognized of large objects more difficult than small objects. When the patients, given a large letter composed of a small letter, read either the global (i.e., large) or local (i.e., small) letter, the patients showed a difficulty in identifying the large composed letter. They postulated [1,3,4] that the patients' disturbance was attributable to functionally restricted attention "spotlight". Because of restriction of "spotlight", the patients perceived a local feature of the object but failed to perceive some features enough to integrate and recognize the object shape as a whole. They followed TreismanŠs selective attention model [5], that the visual selective attention serves as the 'glue' which binds together visual feature information displayed in visual future maps.

The performance of the global reading in patients with EOAD improved as the exposure time increased. However, as a latency of more than 100 msec. is required before initiating reflexive and voluntary ocular movement, the poor performance at short exposure duration of less than 100 msec. cannot be attributed to a disturbance of gaze if any, which may develop in some patients with AD as a part of Balint syndrome. Several studies of pattern recognition indicated that a global image of object was obtained when nearly half of the whole image was processed simultaneously [17, 18]. Ikeda [17] investigated how mach of the field of view is needed to recognize a picture by limited useful visual field size and exposure duration. The effective factor determining useful visual field size was not an absolute visual angle, but rather the proportion of the picture area. If the effective visual field was restricted to be small, a longer time duration was needed to arrive at a certain level of perception of the a whole image. It suggested that the delayed visual processing in the EOAD group make more difficult to integrate the whole image within the limited exposure duration. The slowing of the visual process may cause visuo-cognitive disturbance in the EOAD group. This supports the view that attribute to simultanagnosia [1,6]. Patients with simultanagnosia have a difficulty in seeing a picture as a whole although they may be able to describe a part of picture clearly. Simultanagnosia is attributable to two impairments, the first is a capacity limitation in the process by which integrate local structural descriptions and the second is a slowing of the shifting from one structure to another [1].

Recent neuroimaging studies provide evidence that several neural systems are involved in the global/local information processing [20–22], the right lingual gyrus is activated during paying attention to a global aspect of the figures, the left inferior occipital cortex is activated during paying attention to the local aspects, and the temporo-parietal area is activated when the number of target switches from local to global and vice versa [17]. It has been postulated that the temporo-parietal area exerts attention control over the neural transformation occurring in the primary visual cortex. The patients with early-onset AD have a more severe reduction of regional glucose metabolism in the fronto-temporo-parietal association cortices, while LOAD patients show a more prominent metabolic deficit in the paralimbic area [22,23]. Our results showed the difference of the global-local performance between early- and late-onset AD groups. Such individual group pattern may reflect not only aging but also AD's pathological specificity of age onset type.

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