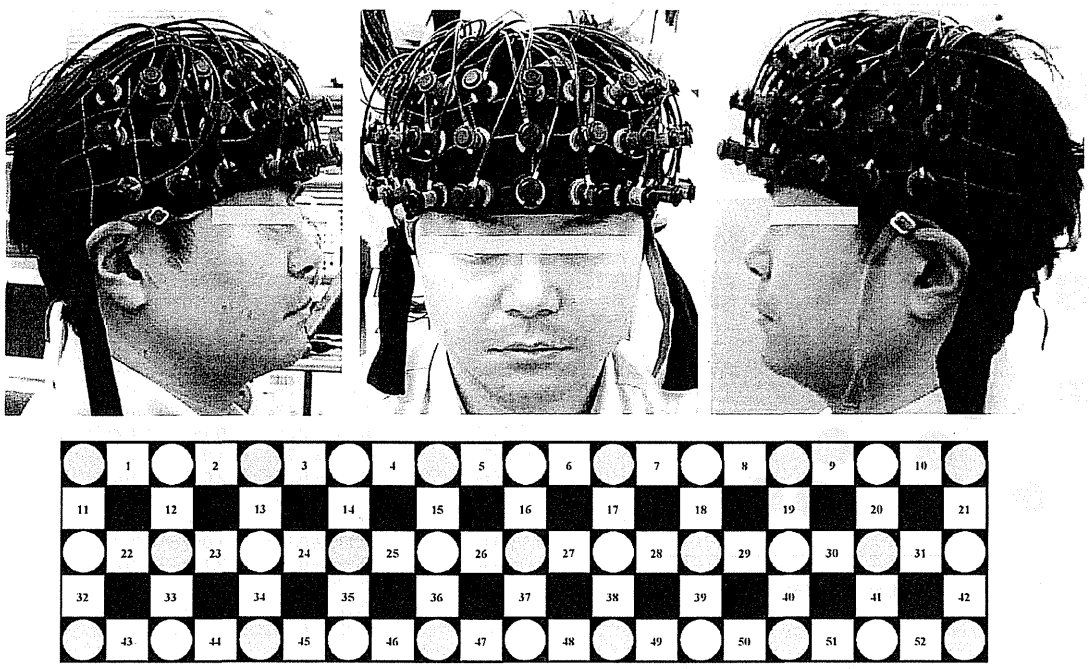

Fig. 1. Location of optical diodes and measurement points (channels). Channels 1 through 52 are depicted as white squares between laser diodes (emitters, gray circles) and photodiodes (detectors, white circles).

of sequential numbers during a visual search [2,11,33,46,49,51]. The TMT-A therefore targets speeded and unconscious VSWM operations representative of daily activity. The ATMT is highly similar to the TMT-A, but contains the following adjustments. The ATMT consists of two tasks, the Fixed Task (Task F) and Random Task (Task R). Task F and TMT-A procedures are very much alike, with the exception of Task F being administered by button pressing on a touch-sensitive panel, which allows the subjects to continue the task performance to induce enough cortical activation. A critical difference between the Task F and Task R is the latter's design to elicit activation related exclusively to motor factors to perform Task F [37,50].

Unlike other neuroimaging techniques such as MRI and PET, multichannel near-infrared spectroscopy (NIRS) is a non-invasive brain functional imaging method that does not restrict subject movement and is therefore a good choice for the ATMT. In addition, NIRS is not affected by electromagnetic noise from electric devices [34]. Near-infrared light is a powerful tool for biological analyses as it can not only penetrate deeply into tissues, but it is also differentially absorbed by hemoglobin (Hb) depending on the oxygenation state of the latter and the optical path length in the tissue (modified Beer–Lambert Law). The law is demonstrated as $A = \varepsilon CL + S$, in which A is the absorbance, ε is the molar absorption coefficient, C is the chromophore concentration, L is the optical path length between the emitter and the detector of the NIRS probe, and S is the optical attenuation related to scattering. This relationship is used in NIRS to measure relative changes in the concentration of oxygenated hemoglobin ([oxy-Hb]) and deoxygenated hemoglobin ([deoxy-Hb]) by emitting near-infrared light at several different wavelengths into brain tissue and detecting its remnant [18,24,28,47]. Areas of high neuronal activation show increased oxygen consumption and enhanced blood supply to ensure provision of oxygenated hemoglobin [19,23]. In other words, neural activation is measured by relative changes of regional cerebral blood volumes.

Several NIRS studies have reported frontal activation during TMT-A performance [33,46,52,53]. The cognitive factors measured by this task are similar to those assessed with Task F of the ATMT. The above-mentioned studies reported bilateral activation, primarily in the prefrontal cortex, although the measuring range in these experiments may have been too restricted. In the here-presented work, multichannel NIRS was used to provide wide coverage of the frontal area during the ATMT in an effort to detect VSWM-induced cortical subregions within the frontal cortex that show an activation pattern consistent with VSWM performance in daily-life activity. To confirm that Task F activation was indeed related to VSWM processing, we additionally measured activation during Task R, which is assumed to elicit exclusively motor factor-related activation. We hypothesized that the DLPFC and the VLPFC activation associated with speeded and unconscious VSWM processing in a paradigm mimicking VSWM performance in daily-life activity can be detected by using multichannel NIRS during ATMT performance.

2. Materials and methods

2.1. Subjects

Twenty-eight healthy volunteers were recruited for this study. Two were excluded due to left-handedness and excessive motion artifacts, leaving a total of 26 right-handed subjects (14 males and 12 females, age 27.2 ± 6.8 yrs; range, 19–40 years). None of the participants had a history of psychiatric or neurological disorders. This research was approved by the ethics committee of Osaka University Graduate School of Medicine and all procedures and methods were in keeping with the policies and principles contained in the Declaration of Helsinki. All subjects gave written informed consent prior to the experiments.

2.2. NIRS measurements

We measured relative changes in the concentration of oxygenated hemoglobin ([oxy-Hb]), deoxygenated hemoglobin ([deoxy-Hb]) and calculated total hemoglobin by combining the two former based on NIRS data (ETG-4000; Hitachi Medical Corporation, Tokyo, Japan) during ATMT performance. The ETG-4000 uses two kinds of near-infrared light, 695 nm and 830 nm. Seventeen laser diodes (emitter) and 16 photodiodes (detector) were mounted reciprocally at 3-cm intervals on a piece of elastic rubber headwear attached to the frontal area with adjustable straps. Approximate detection depth was 2–3 cm below the skin surface in 52 separate regions (approx. 6 cm high × 30 cm wide). The lowest center

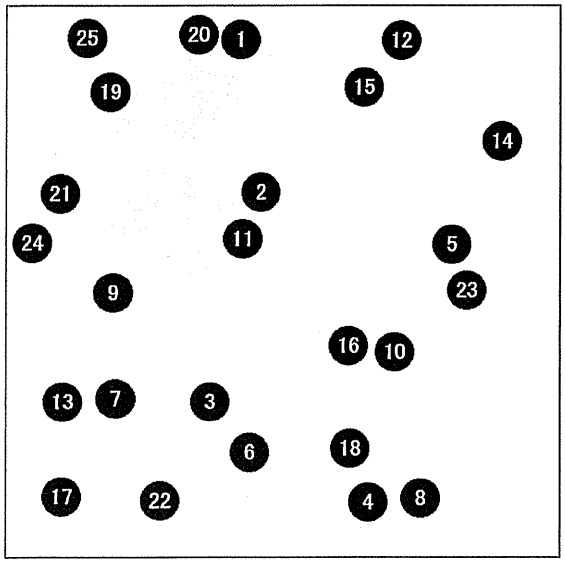

Fig. 2. An example of the Advanced Trail Making Test (ATMT) window on the touch-sensitive panel.

photodiode was located at Fpz according to the international 10/20 system for electroencephalography (EEG). The channels at the posterior edges corresponded to the T3-Cz-T4 line of the international 10/20 system or slightly anterior to this line (Fig. 1).

2.3. Tasks

Brain activation was measured with the Advanced Trail Making Test (ATMT). The ATMT was administered on a touch-sensitive panel (CV515PJ; Totoku Electric, Tokyo, Japan) connected to a personal computer. The subjects pressed 25 numbered black circles (buttons) displayed randomly on an 18 × 18 cm screen in numerical order with their dominant hand. Once a button is pressed, it disappears, and immediately a +25 numbered button appears on the screen (Fig. 2). The time lag between pressing a target button and the preceding button push was deemed reaction time. The participants were instructed to press the buttons as quickly as possible in numeric order from number 11 to the highest possible number within 90 s. Buttons corresponding to numbers 1 through 10 were pressed as part of a practice trial to ensure comprehension of the procedure prior to ATMT execution; data for buttons 1–11 were therefore excluded from data analysis. Before and after ATMT execution, the subjects gazed at the center of the screen and tapped their right index finger on this point at a uniform pace. This was considered as the baseline task.

In a variation of Task F where the location of the buttons remained unchanged when a correct number button was pressed, Task R rearranged the numbers randomly once the correct number was pushed. Task F allowed the subjects to memorize the locations of the buttons which have been found during the visual search, thereby enabling the subjects to shorten the reaction time compared to Task R by using VSWM operations [37,50].

2.4. Procedure

During data collection, the participant sat on a chair in front of a table in a silent room. The tasks including the first baseline task (30 s), the ATMT (90 s) and the second baseline task (60 s) were executed for each Task R and Task F, which were presented in counter-balanced order to each half of the subjects. Instructions for changing the tasks were given orally.

2.5. Data analysis

Changes in [oxy-Hb] and [deoxy-Hb] are expressed as the product of concentration of hemoglobin and optical path length, which produces a measurement of mM mm. In this study, we focused on changes in [oxy-Hb] (temporal resolution of 100 ms) because [oxy-Hb] is reported to be most sensitive to changes in regional cerebral blood volume, and strongly correlates with BOLD signal of fMRI, while the direction of changes in [deoxy-Hb] is determined by changes in venous blood oxygenation and volume [23,24,44,48].

The ETG-4000 analysis software was used in the integral mode. In this configuration, mean changes in [oxy-Hb] during baseline states 10 s just before the beginning of the activation task period or after 50 s from the end of the activation task period were corrected to 0 mM mm by linear fitting. The activation task period itself was set at 90 s, and the recovery period from the end of activation task until baseline stabilization was 50 s. To smooth out short-term motion artifacts we employed the moving average method with a 5 s window.

For behavioral data, we compared the mean reaction time for Task R and Task F using a paired, two-tailed Student's *t*-test, with $p = 0.05$ set as the significance threshold. Mean changes in [oxy-Hb] during the ATMT for each channel were calculated for each subject, followed by a two-tailed single-sample *t*-test which is equal to a paired *t*-test against zero (mean changes in [oxy-Hb] during baseline periods), for Task R and Task F respectively. Since the single-sample *t*-test was used for all 52

Table 1
The individual channel values in Task R of the ATMT.

Right channel	Activation	*t*	*p*	α	*r*
CH1	0.061 ± 0.092	2.052	0.051	0.002	0.175
CH2	0.031 ± 0.110	0.019	0.985	0.002	0.201
CH3	0.009 ± 0.110	<0.001	>0.999	0.002	0.159
CH4	0.028 ± 0.125	0.001	0.999	0.002	0.198
CH5	0.037 ± 0.110	0.003	0.997	<0.001	−0.012
CH11	0.066 ± 0.156	0.632	0.533	0.003	0.272
CH12	0.096 ± 0.184	1.320	0.199	0.004	0.381
CH13	0.051 ± 0.119	0.711	0.484	0.003	0.302
CH14	0.037 ± 0.101	0.263	0.795	0.003	0.238
CH15	0.045 ± 0.071	2.150	0.041	0.004	0.331
CH22	0.116 ± 0.201	1.858	0.075	0.005	0.391
CH23	0.153 ± 0.263	1.893	0.070	0.005	0.409
CH24	0.100 ± 0.146	2.183	0.039	0.003	0.246
CH25	0.067 ± 0.092	2.624	0.015	0.003	0.320
CH26	0.054 ± 0.134	0.823	0.418	0.005	0.398
CH32	0.105 ± 0.256	0.758	0.455	0.004	0.364
CH33	0.168 ± 0.284	1.973	0.060	0.005	0.412
CH34	0.160 ± 0.254	2.078	0.048	0.004	0.364
CH35	0.097 ± 0.143	2.322	0.029	0.004	0.323
CH36	0.062 ± 0.140	0.929	0.362	0.004	0.351
CH43	0.139 ± 0.302	1.081	0.290	0.004	0.361
CH44	0.170 ± 0.267	2.168	0.040	0.004	0.340
CH45	0.179 ± 0.210	3.253	0.003	0.003	0.299
CH46	0.127 ± 0.180	2.466	0.021	0.002	0.228
CH47	0.068 ± 0.142	1.124	0.272	0.004	0.328
Left channel	**Activation**	***t***	***p***	**α**	***r***
CH6	0.015 ± 0.08	<0.001	>0.999	0.002	0.106
CH7	0.002 ± 0.162	<0.001	>0.999	<0.001	−0.012
CH8	0.001 ± 0.200	<0.001	>0.999	0.001	0.081
CH9	−0.030 ± 0.189	<0.001	>0.999	0.001	0.100
CH10	0.018 ± 0.171	<0.001	>0.999	0.003	0.279
CH17	0.028 ± 0.148	<0.001	>0.999	0.002	0.210
CH18	0.020 ± 0.215	<0.001	>0.999	0.001	0.022
CH19	0.077 ± 0.167	0.382	0.890	0.003	0.274
CH20	0.023 ± 0.244	<0.001	>0.999	0.004	0.342
CH21	0.098 ± 0.197	1.300	0.206	0.004	0.357
CH27	0.045 ± 0.179	0.026	0.980	0.003	0.290
CH28	0.065 ± 0.146	0.703	0.489	0.002	0.226
CH29	0.113 ± 0.165	2.358	0.027	0.004	0.343
CH30	0.162 ± 0.295	1.557	0.132	0.004	0.331
CH31	0.119 ± 0.296	0.608	0.549	0.003	0.316
CH38	0.070 ± 0.127	1.627	0.116	0.004	0.338
CH39	0.121 ± 0.190	2.250	0.033	0.005	0.386
CH40	0.197 ± 0.246	3.124	0.004*	0.005	0.390
CH41	0.211 ± 0.334	2.287	0.031	0.005	0.406
CH42	0.149 ± 0.267	1.679	0.106	0.004	0.364
CH48	0.111 ± 0.155	2.707	0.012	0.004	0.369
CH49	0.134 ± 0.151	3.576	0.001*	0.004	0.377
CH50	0.226 ± 0.253	3.724	0.001*	0.006	0.457
CH51	0.189 ± 0.331	1.817	0.081	0.004	0.370
CH52	0.184 ± 0.344	1.536	0.137	0.004	0.367
Middle channel	**Activation**	***t***	***p***	**α**	***r***
CH16	0.031 ± 0.143	0.002	0.998	0.003	0.244
CH37	0.051 ± 0.209	0.027	0.979	0.003	0.317

Activation: the average across 26 participant's mean changes in [oxy-Hb] ± standard deviation (mM mm) during Task R of the ATMT in each channel, *t* and *p*: the values derived by comparing the 26 participant's mean changes in [oxy-Hb] during Task R with those during the baseline periods using the two-tailed single-sample *t*-test, which were corrected for multiple comparisons by the Dubey/Armitage-Parmar procedure, α: the adjusted critical α-level by the above procedure, *r*: the mean value of Pearson's correlation coefficients between the channel and the other 51 channels.

* Significant *p* values.

Table 2
The individual channel values in Task F of the ATMT.

Right channel	Activation	t	p	α	r
CH1	0.006 ± 0.181	<0.001	>0.999	0.003	0.294
CH2	−0.019 ± 0.164	<0.001	>0.999	0.002	0.201
CH3	−0.051 ± 0.269	<0.001	>0.999	0.001	0.069
CH4	0.023 ± 0.184	<0.001	>0.999	0.003	0.244
CH5	0.022 ± 0.168	<0.001	>0.999	0.003	0.245
CH11	0.031 ± 0.151	0.003	0.997	0.003	0.295
CH12	0.120 ± 0.177	2.434	0.022	0.005	0.386
CH13	0.025 ± 0.194	<0.001	>0.999	0.002	0.178
CH14	0.025 ± 0.159	<0.001	>0.999	0.004	0.324
CH15	0.044 ± 0.121	0.429	0.672	0.004	0.327
CH22	0.144 ± 0.169	3.321	0.003*	0.004	0.349
CH23	0.236 ± 0.194	5.131	<0.001*	0.003	0.301
CH24	0.146 ± 0.163	3.465	0.002*	0.003	0.276
CH25	0.069 ± 0.142	1.288	0.209	0.004	0.366
CH26	0.086 ± 0.156	1.503	0.145	0.003	0.277
CH32	0.159 ± 0.193	3.024	0.006	0.003	0.260
CH33	0.217 ± 0.211	4.252	<0.001*	0.004	0.361
CH34	0.268 ± 0.245	4.380	<0.001*	0.002	0.213
CH35	0.156 ± 0.188	3.161	0.004	0.003	0.309
CH36	0.083 ± 0.190	0.784	0.440	0.003	0.294
CH43	0.213 ± 0.261	3.097	0.005	0.003	0.315
CH44	0.292 ± 0.259	4.678	<0.001*	0.003	0.308
CH45	0.321 ± 0.283	4.640	<0.001*	0.003	0.257
CH46	0.176 ± 0.200	3.620	0.001*	0.005	0.435
CH47	0.091 ± 0.209	1.003	0.325	0.005	0.392
Left channel	**Activation**	t	p	α	r
CH6	0.008 ± 0.107	<0.001	>0.999	0.004	0.380
CH7	0.002 ± 0.215	<0.001	>0.999	0.002	0.216
CH8	0.035 ± 0.243	<0.001	>0.999	0.002	0.227
CH9	0.057 ± 0.155	0.340	0.736	0.003	0.267
CH10	0.033 ± 0.261	<0.001	>0.999	0.002	0.151
CH17	0.045 ± 0.202	0.004	0.997	0.003	0.259
CH18	0.062 ± 0.309	0.001	0.999	0.003	0.249
CH19	0.144 ± 0.212	2.273	0.032	0.003	0.296
CH20	0.068 ± 0.244	0.021	0.983	0.002	0.216
CH21	0.110 ± 0.211	0.964	0.344	0.002	0.121
CH27	0.083 ± 0.180	0.963	0.345	0.003	0.307
CH28	0.113 ± 0.191	1.762	0.090	0.003	0.303
CH29	0.207 ± 0.246	3.325	0.003*	0.004	0.374
CH30	0.280 ± 0.226	5.211	<0.001*	0.003	0.277
CH31	0.220 ± 0.245	3.250	0.003	0.002	0.142
CH38	0.131 ± 0.143	3.758	<0.001*	0.005	0.395
CH39	0.195 ± 0.215	3.570	0.001*	0.003	0.313
CH40	0.267 ± 0.284	3.712	0.001*	0.003	0.291
CH41	0.294 ± 0.264	4.662	<0.001*	0.004	0.335
CH42	0.260 ± 0.223	4.665	<0.001*	0.002	0.163
CH48	0.159 ± 0.209	2.758	0.011	0.005	0.399
CH49	0.211 ± 0.191	4.604	<0.001*	0.004	0.335
CH50	0.341 ± 0.211	7.194	<0.001*	0.005	0.397
CH51	0.334 ± 0.328	4.154	<0.001*	0.003	0.317
CH52	0.314 ± 0.303	4.226	<0.001*	0.003	0.309
Middle channel	**Activation**	t	p	α	r
CH16	0.038 ± 0.154	0.012	0.991	0.003	0.260
CH37	0.112 ± 0.207	1.484	1.150	0.003	0.295

Activation: the average across 26 participant's mean changes in [oxy-Hb] ± standard deviation (mM mm) during Task F of the ATMT in each channel, t and p: the values derived by comparing the 26 participant's mean changes in [oxy-Hb] during Task F with those during the baseline periods using the two-tailed single-sample t-test, which were corrected for multiple comparisons by the Dubey/Armitage-Parmar procedure, α: the adjusted critical α-level by the above procedure, r: the mean value of Pearson's correlation coefficients between the channel and the other 51 channels.

* Significant p values.

channels, we corrected for multiple comparisons using the Dubey/Armitage-Parmar procedure which takes into account spatial correlations among the cortical regions and has been used in a comparable fashion in previous work using multichannel NIRS [16,43,45] (see Tables 1 and 2). Additionally, the number of activated channels in Task R and Task F were compared using a two-tailed Chi-square test with a significance level of $p < 0.05$. Statistical analyses were performed with SPSS software (version 12.0J).

3. Results

The mean reaction time ± standard deviation for button pressing during ATMT performance was 2919 ± 631 ms in Task R and 2043 ± 416 ms in Task F; the difference was statistically significant (d.f. = 25, $t = -10.33$, $p < 0.001$). We next generated the grand-average waveform corresponding to [oxy-Hb] changes across subjects for each channel (Figs. 3 and 4 for Task R and F, respectively). To detect activation, the mean changes in [oxy-Hb] during the ATMT were compared to those during the baseline task in all 52 channels, which indicated three channels (5.8%) for Task R (Table 1, Fig. 3) and 19 channels (36.5%) for Task F (Table 2, Fig. 4). The channels activated by Task R were also activated during performance of Task F. Chi-square test analysis demonstrated that Task F activated significantly more channels than Task R ($\chi^2 = 14.758$, d.f. = 1, $p < 0.001$).

4. Discussion

In the present study, frontal activation during Task F and Task R of the ATMT was measured by multichannel NIRS with 52 channels covering the entire frontal cortex. A larger number of channels were activated during Task F compared to Task R, primarily over the bilateral DLPFC and VLPFC. This suggests that these prefrontal areas are engaged during VSWM even when the limitation of subject's motor restrictions during speeded processing tasks is taken into account. Thus, this activation pattern is consistent with VSWM performance in daily activity. Because this study's Task F was very similar to the TMT-A, direct comparison to other work using that same test is possible, despite the difference in the number of channels used. Our findings are consistent with previous NIRS work that indicated VSWM-induced activation throughout the frontal area [33,46,52,53]. The TMT-A is sensitive to both cognitive and motor factors required for task execution, albeit motor factors to a lesser degree [51]. Task R, on the other hand, elicited activation only in cortical regions involved in the processing of motor factors. One may speculate that the cognitive factors engaged specifically during Task F but not Task R performance are closely related to VSWM [37,50].

Based on an anatomical craniocerebral correlation using the international 10/20 electrode placement system for EEG reported by Okamoto et al. [38], we can infer that regions activated by cognitive factors critical to Task F performance in this study correspond to the bilateral DLPFC and VLPFC (Fig. 4). Recent studies have provided substantial evidence that the lateral prefrontal cortex is part of the neural substrate of VSWM [1,12,20,22,39,40], which is considered a core cognitive factor assessed by Task F of the ATMT. Our findings are supported by those data, specifically prefrontal activation associated with VSWM processing. However, despite reports that the FEF and the SMA are also involved in VSWM [14,15,29,30,31,39,41], no significant activation was found in the superior channels overlying these cortical areas in our analysis.

The channels activated by Task R were also activated during Task F performance, which were restricted to part of the left VLPFC. This activation induced by Task R and Task F performance in our study might reflect motor factors involved in ATMT performance. This assumption is supported by recent reports indicating that the VLPFC is associated with motor functions such as complex hand movements and associative sensorimotor learning [8,9].

Based on the conceptual model of working memory suggested by Baddeley [6,7] and Hitch [5] proposing that the central executive administers three slave components (i.e., visuospatial sketchpad, phonological loop, and episodic buffer) to act together for executive function, it appears likely that the activation of DLPFC and VLPFC

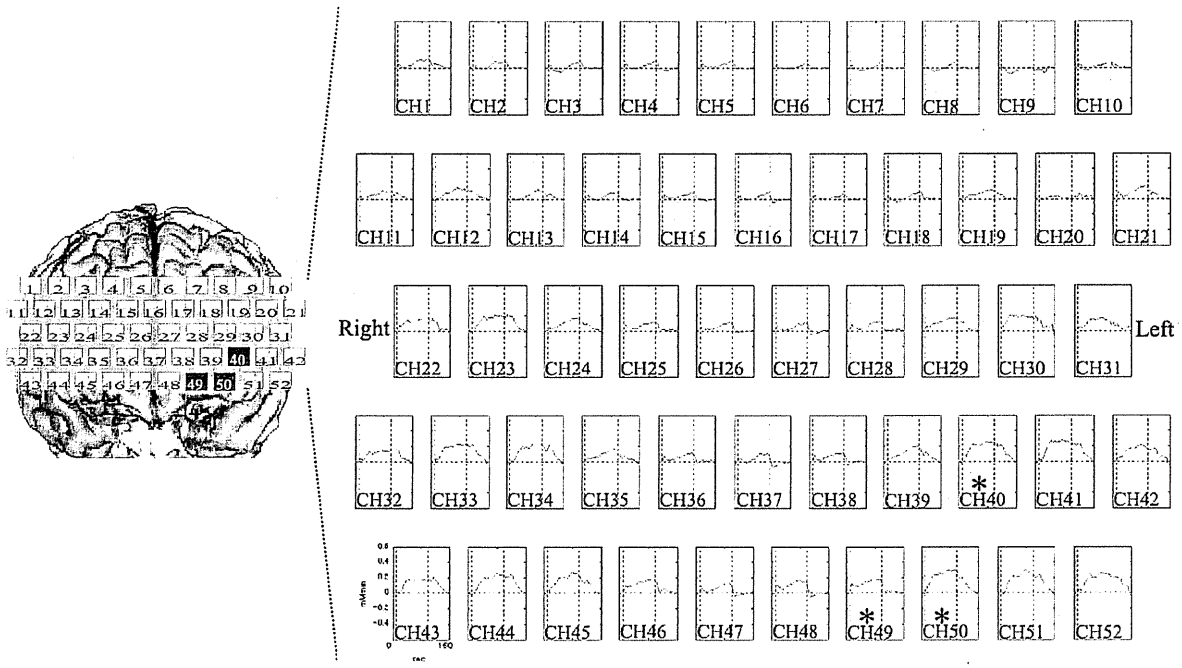

Fig. 3. Grand-average waveforms of changes in oxy-Hb concentration during Task R for all channels plotted as changes in [oxy-Hb] (mM mm) versus time (s). For each channel, the horizontal scale covers time from 0 to 160 s with the vertical scale indicating activation in between −0.6 and 0.6 mM mm. The task period is marked by two dashed lines at 10 and 100 s. The numbers superimposed on the standard brain surface indicate the channel numbers. The positions of the activated channels are indicated by black squares. CH: channel, *: channel with significant activation.

during Task F in our study was mainly associated with the central executive component. This argument is supported by the fact that the central executive is related to (1) retrieval of the location of the next number, (2) divided attention in the dual-task performance during the visual search, (3) active maintenance of rules and strategies related to simultaneous searching and memorizing, (4) continuous updating of memory representations [1,13,25,32,40]. The visuospatial sketchpad is thought to be associated with encoding and maintenance of memory representations of subsequent numbers and locations. Thus, its role may have been considerably small in our study as memory representations in the ATMT are only double-digit numbers with unified standard and those locations in a two-dimensional surface, which is approximately twice larger than the visual attention field [37,50].

The present study has several limitations. First, changes in [oxy-Hb] are relative values compared to the baseline state, and it is

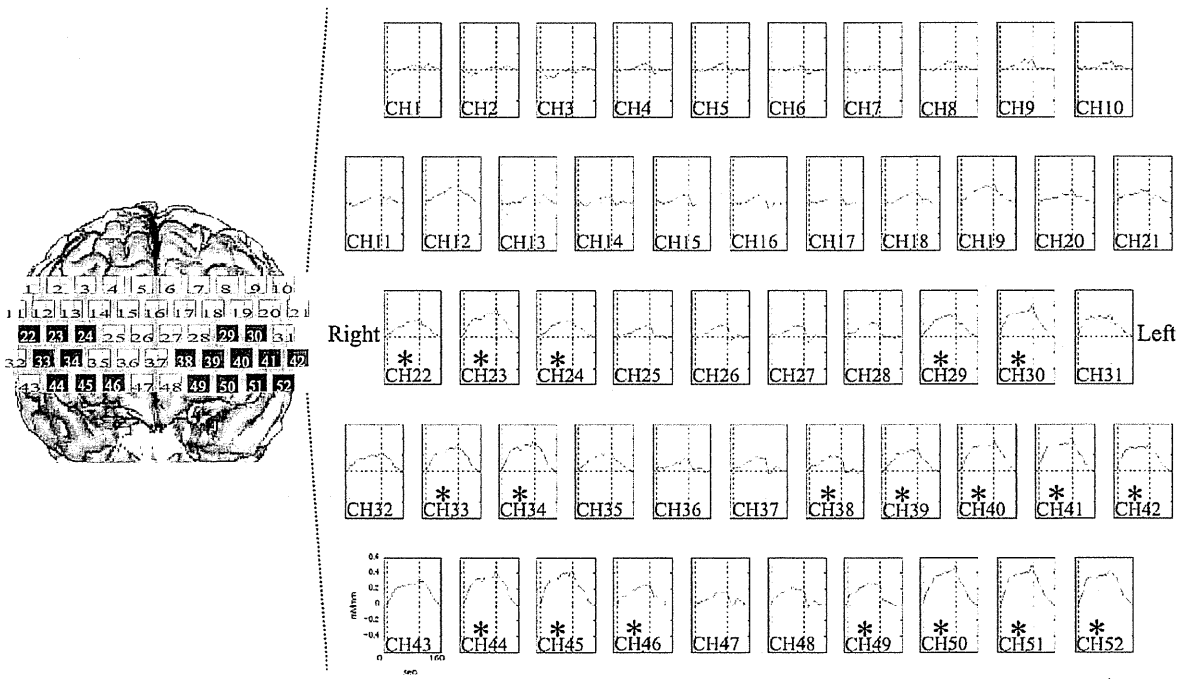

Fig. 4. Grand-average waveforms of changes in oxy-Hb concentration during Task F for all channels plotted as changes in [oxy-Hb] versus time. For details, see Fig. 3 legend.

assumed that optical path lengths are constant across subjects and at different measurement points. Hence, evaluations using NIRS machines which cannot measure absolute values must be considered estimates. Nevertheless, Ferrari et al. [17,18] argued that this type of NIRS instrument can accurately measure changes in [oxy-Hb] and [deoxy-Hb] because the path length does not change more than 10% across channels. Second, the cortical region/channel association in our study differed depending on subject head shape, as the channels departed from Fpz (according to the international 10/20 electrode placement system for EEG) on which we set the lowest center photodiode. Thus, a perfect cortical region/channel association is not guaranteed, and even the possibility that some channels were overlying superior temporal regions in some individuals cannot be excluded. Other NIRS instruments, for instance those equipped with two channels can obtain identical cross subject anatomical positioning based on personalized arrays of probes according to the subject's head shape [4,26]. Further development of NIRS machines addressing this issue will be necessary. Finally, third, since NIRS data are thought to be affected by anxiety and personality traits [27,36] as well as by systemic response [21,10], interpersonal comparison of NIRS data is not always reliable. The potential influence of particular individual factors on NIRS data needs further investigation.

In summary, we have demonstrated that multichannel NIRS during ATMT performance is a useful tool to detect bilateral DLPFC and VLPFC activation associated with speeded and unconscious VSWM processing in a paradigm mimicking VSWM performance in daily-life activity. This activation might be associated with the central executive component of VSWM. To our knowledge this is the first study using multichannel NIRS during ATMT performance. Since working memory is considered to be one of the most impaired cognitive functions associated with brain injury and neurologic diseases [2,22], future NIRS/ATMT applications may include assessments of patients suffering from neuropsychiatric conditions to help elucidate the neural network implicated in VSWM and to better understand the pathophysiological mechanisms of various brain disorders.

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Laughter and humor as complementary and alternative medicines for dementia patients

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Abstract

Background: The number of dementia patients has increased worldwide, with an estimated 13.7 million dementia patients in the Asia Pacific region alone. This number is expected to increase to 64.6 million by the year 2050.

Discussion: As a result of advances in research, there several pharmacological therapies available for the treatment of dementia patients. However, current treatments do not suppress the disease process and cannot prevent dementia, and it will be some time before these goals are realized. In the meantime, complementary and alternative medicine (CAM) is an important aspect in the treatment of dementia patients to improve their quality of life throughout the long course of the disease. Considering the individuality of dementia patients, applicability of laughter and humor therapy is discussed. Even though there are many things that need to be elucidated regarding the mechanisms underlying the beneficial effects of laughter and humor, both may be good CAM for dementia patients if they are applied carefully and properly.

Summary: In this debate article, the physiological basis and actual application of laughter and humor in the treatment of dementia patients are presented for discussion on the applicability to dementia patients.

Background

Because of the rapidly increasing elderly population, the need for psychogeriatric services will increase in coming years. In particular, a faster aging of the population has been observed in Asian countries compared with that in Western countries. The World Health Organization has proposed that for a society to be called 'aging', the proportion of elderly citizens (aged 65 years and older) must be 7%. Once this proportion reaches 14%, a society becomes an 'aged society' [1]. It took 24 years for Japan to move from an aging society (in 1970) to an aged society (in 1994); in comparison, in most Western countries this process takes 60-120 years [1]. Korea is expected to become an aged society by 2019, only 19 years after becoming an aging society (2000).

Considerable progress has been made in psychogeriatric services as a result of increased knowledge of brain science, neuroscience, molecular genetics, brain imaging, and many other new technologies [2]. The mechanisms underlying the cognitive impairment in dementia patients are now understood because of findings from brain science and neuropsychological investigations [3,4]. Electrophysiology (e.g. electroencephalography topography, event-related potentials (ERP), and magnetoencephalography (MEG), brain imaging (e.g. magnetic resonance imaging (MRI), single photon emission computed tomography (SPECT), positron emission tomography (PET) and even newer technologies, such as near-infrared spectroscopy (NIRS) and magnetic resonance spectroscopy (MRS), are versatile tools available to confirm psychogeriatric diagnoses [5]. Furthermore, genetic information is routinely used to evaluate the risk, as well as the prognosis, of a disease and a patient's response to drug treatment [6].

Treatment of behavioral and psychological symptoms of dementia (BPSD) remains one of the most unmet needs in psychogeriatrics [7,8], with more effective pharmacological [9,10] and non-pharmacological interventions [11-13] needed. Psychogeriatrics is, however, a clinical subspecialty in which treatment should be directed towards the person as a whole. Consideration of the person and holistic care are essential, including a bio-

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psycho-socio-ethical evaluation of each patient, because the life of the elderly is so different [1]. Furthermore, psychogeriatric services can be applied to patients in the prestages of dementia, including those with mild cognitive impairment (MCI) [14,15] and subjective cognitive impairment (SCI) [16]. Dementia patients, including those with MCI and SCI, can benefit from psychogeriatric services, and the specific application of laughter and humor therapy in the treatment of these patients is discussed in the present article.

Dementia patients require individualized and life-long intervention

In 2005, it was reported that there were 13.7 million dementia patients in the Asia Pacific region alone and that this number is expected to increase to 64.6 million by the year 2050, a 4.7-fold increase in just 45 years [1]. In addition to its high prevalence, the considerable disruption to patients' daily lives, the burden to caregivers, and the long duration of the disease make dementia, especially Alzheimer's disease (AD), the most malignant disease of our time.

The symptoms of AD differ between individual patients. At the onset of dementia in some patients, certain personality traits that had been well controlled in the past become accentuated, whereas in others there is a 'loss of personality', where the uniqueness of the patient's personality is lost. Some patients show a more rapid deterioration of cognitive function, whereas others show a slower rate of cognitive decline. Some patients exhibit various types of BPSD, whereas others exhibit few abnormal behaviors [7]. Furthermore, the physical, personal, familial, economic, and social environments differ between patients. Thus, each patient should be evaluated as an individual in terms of his/her needs for intervention, taking into account previous social functioning, family structure, and the patient's living environment in order to deliver the most appropriate care. Interventions for dementia patients need to be individualized further taking into consideration the different genetic and environmental factors that are specific to each patient.

The premorbid mental capacity differs between subjects and the symptoms exhibited by dementia patients vary quite widely. Considering the difference in symptoms of dementia patients, a more individualized treatment and management program should be considered taking into account of the emotional and affective responses of each patient individually. In this respect, the possibility of using laughter and humor therapy as a complementary and alternative medicine (CAM) for the treatment of dementia patients is discussed below.

Discussion

Laughter as a CAM

Although modern medical science has enabled correct diagnoses to be made and proper treatments to be initiated for acute diseases caused by exogenous pathogenic factors, there are still numerous chronic, incurable diseases caused by endogenous factors, such as cancer, dementia, hypertension, diabetes, chronic pain etc., for which there is no effective treatment, leaving patients with these conditions to suffer. To facilitate the better management of these chronic diseases, recent attention has focused on the use of CAM, together with Oriental and traditional medicines [17]. CAM is defined by the American Cancer Society as '...supportive methods used to complement evidence-based treatment. Complementary therapies do not replace mainstream treatment and are not promoted to cure disease. Rather, they control symptoms and improve well-being and quality of life'[18]. In contrast, alternative therapies, or alternative medicine, involve non-mainstream treatments that are sometimes used by patients instead of orthodox treatments. Examples of CAM include music therapy, drama therapy, aromatherapy, animal-assisted therapy, gardening, horse riding, exercise, bathing, herbal medications, acupuncture, moxibustion, shiatsu, and yoga among others [19]. However, these therapies have not been well defined. Some are simply based on legend or belief, whereas others are traditionally applied but without any scientific basis.

It is widely accepted that a patient's emotional state will affect the course of the disease. Human emotional behavior can be either negative or positive. Negative emotional behavior is accompanied by disgust, fear, or alarm, which induces a prompt, narrowed response to the stimulus responsible for the life crisis. The 'fight-or-flight' response is the general outcome of negative emotions, in which the sympathetic autonomic nervous system is dominant. Conversely, in safe and relaxing situations, positive emotional behavior is associated with joy, play, and humor, with predominant functioning of the parasympathetic system, which induces responses of extended open behaviors that are helpful in learning new behavioral patterns. Laughter associated with a pleasant feeling is often observed under positive emotional conditions.

Laughter has a unique position in CAM. The benefits of laughter have been recognized historically. As stated by Bertrand Russell, 'Laughter is the most inexpensive and most effective wonder drug. Laughter is a universal medicine'. Laughter has been regarded as beneficial for human health for a long time, with some of the benefits

attributed to laughter including improved immunological [20] and endocrinological [21] responses and increased pain tolerance [22]. Laughter therapy, humor therapy, laughter meditation, and laughter clubs all have unique implications as group programs and as self-management techniques. For practitioners to implement credible programs and effectively teach self-management techniques, further empirical research on the physical, psychosocial, and placebo effects of laughter and humor needs to be conducted.

Physiology of laughter and smiling

Speech and laughter are unique to humans. Although there is considerable information regarding the neuronal representation of speech, little is known about the neural mechanisms of laughter. As described by Charles Darwin, laughter, which is a ubiquitous and unique maneuver of humans that results in a totally defenseless posture involving movement of such a wide area of musculature, should have some beneficial meaning in terms of the evolution of this species [23]. Laughter should mean a lot to our lives.

Newborn babies smile within the first 5 weeks after birth and laugh within the first 4 months. Some smiles are voluntary and smiling can be differentiated into 16 different expressions [24], but there is only one expression of laughter. When we smile, the mouth angles are lifted and the orbits of the eye become thin and surrounded by wrinkles as a result of the simultaneous contraction of the muscularis zygomaticus major and orbicularis oculi. In addition to these muscles, when a person is laughing a wider area of the musculature, including facial, pharyngeal, and respiratory muscles, is simultaneously contracted [24].

Laughter and smiling are usually produced as a message of good will to others. In primates, facial expressions showing bared teeth mean friendliness and primates use these expressions to transmit their sociability and the fact that they have no hostile feelings. Because some forms of smiling are voluntary and easily faked, laughter, which requires a more synergetic contraction of the wider musculature, is believed to have evolved in humans to express a secure, safe message to others.

Neural circuits of laughter and smiling

Laughter is the physiological opposite of crying and is usually an expression of happiness involving typical facial movements and contractions of the respiratory muscles [25]. Neural correlates for laughter may include the anterior cingulate gyrus, which provides emotional consciousness to an individual's experience and is partially under the control of the frontal cortex [26]. The caudal hypothalamus is also involved, acting as the center coordinating emotional changes, including laughter, whereas the temporal amygdala may provide emotional coloring to perceptions and aid in understanding humor [26,27]. Finally, the ventral pontomedullary center for laughter coordinates facial expressions, expirations, and emotional vocalization.

The expression of laughter depends on two partially independent neuronal pathways. One is the 'involuntary' system involving the amygdala, thalamic, hypothalamic and subthalamic areas, and the dorsal brain stem [27]; the other is 'voluntary' and originates in the premotor opercular areas, leading through the motor cortex and the pyramidal tract to the ventral brain stem.

The neural circuit underlying laughter may have three main brain components: (i) cognitive areas, such as sections of the frontal lobe that help a person understand the situation; (ii) a movement area (probably the supplemental motor area) that triggers muscle movements to induce a smile or laughter; and (iii) an emotional component that actuates the perception of happiness after an amusing experience, possibly facilitated by the nucleus accumbens [28].

Neural circuits of humor

Humor can be broadly defined as 'something that is, or is designed to be, comical or amusing'. More specific definitions vary, but humorous communication certainly causes increased feelings of happiness and laughter in those who respond to it, whether due to witty comments or amusing behavior.

Freud's psychodynamic viewpoint described humor as the strongest form of the defense mechanism that allows an individual to face problems and avoid negative emotion [29]. Humor is believed to be effective in distancing oneself, framing problems with perspective, and proactively managing distress [30-32].

Although physiological research on the effects of humor on the body is only just developing, there may be quantifiable health care benefits of humor. Research involving additional measurements of a sense of humor, including self-reported instruments, peer ratings, and comedy monologues, suggests that humor moderates the impact of stressful life events on mood disturbances, such as depression and anxiety, salivary immunoglobulin, and positive affect [33-35]. Similar moderating effects of humor have been identified for depression, insomnia, loneliness, and self-esteem, although not for anxiety [36-39].

Good humor makes people laugh just like pain makes people cry, but humor requires complex neural circuits. Humor is perceived at the beginning as surprise or disharmony, then the paradox is solved, and, finally, the punch line is understood in association with a pleasant feeling. The appreciation of humor requires a wide area of neural circuits covering attention, working memory,

flexible thinking, extraction of word meaning, and positive mood. Patients with lesions in the right frontal lobe have difficulty appreciating humor because of impaired integration of cognition and emotion. Different brain areas are activated by jokes/puns and comics [40]. Humor is present in any social situation, and the nature of what is perceived as amusing varies widely among individuals, societies, and cultures. Everyone enjoys laughing, but a misjudged humorous comment can cause offense, so although laughter is almost always positive, humor itself can provoke mixed emotional responses.

Classification of laughter and smiling

Laughter and smiling can be classified into one of three categories based on evolutional staging as follows: (A) that evoked by a release of tension; (B) that associated with pleasant feelings; and (C) that used for social communication (Table 1).

Laughter or smiling caused by a release of tension is the most basic biological form, and occurs spontaneously in an individual who experiences release from a strenuous tension. The purpose of laughter in this context has been hypothesized to be the release of inner energy accumulated in response to the stress [23]. Laughter to relax is important for the maintenance of mental health. Long-lasting mental tension is accompanied by a hyperaroused state of the sympathetic nervous system, which can be released by laughing [24]. From the viewpoint of mental health, laughter evoked in response to the release of tension is the most important.

The second category, laughter that is provoked or accompanied by pleasant feelings, can be further subdivided into laughter caused by: (B1) fulfillment of instinctive needs; (B2) fulfillment of expectations; (B3) a feeling of superiority; and (B4) recognition of mix-ups. As early as 5 weeks after birth, babies smile after feeding. This is the first laughter observed in human life, elicited by a fulfillment of instinctive needs. Similar laughter is observed in adults after a good meal or a good sleep. When our expectations are realized, especially after hard work and/or endeavor, we usually laugh in association with pleasant feelings, which can be amplified by colleagues sharing in our achievement, with the most explosive form of laughter then being observed. Laughter caused by a feeling of superiority is a type of scornful laughter or a cold smile that has been proposed by some researchers to be the prototype of laughter [23]. Laughter associated with disharmony and/or mismatch is caused by simple mistakes or funny happenings that cause no harm. This sort of laughter can be elicited only when the disharmony is sudden, unexpected, and the results of the misunderstanding are harmless.

Table 1: Relationship between laughter/smiling and the progression of dementia

Type of laughter/smile	Preservation in dementia	
	Early stages	Advanced stages
A1. Release from strong tension	+	+
A2. Release from weak tension	+	+
B1. Fulfillment of instinctive needs	+	+
B2. Fulfillment of expectations	+	-
B3. Feelings of superiority	+	-
B4. Feelings of disharmony	+/-	-
C1. Cooperative	-	-
C2. Defensive	-	-
C3. Aggressive	-	-
C4. Devaluating	-	-

The type of laughter and/or smiling can be classified into one of three categories: (A1,2) that evoked by a release of tension; (B1-4) that associated with pleasant feelings; and (C1-4) that used for social communication. Laughter and smiling induced by a release of tension is regarded as the most basic type and is preserved as the phylogenetically primitive type. Laughter and smiling associated with pleasant feelings has developed with the evolution of humans. Laughter and smiling as communication tools are the most sophisticated and have developed with the sociability of humans. Dementia patients lose the ability to laugh and smile as the disease progresses. Laughter and smiling as communication tools may be lost in the early stages of dementia, when the clinical symptoms of dementia appear. Of the different forms of laughter and smiling associated with pleasant feelings, those induced by disharmony may be lost in early stages of dementia because of the cognitive impairment that may limit a patient's understanding. However, laughter and smiling induced by feelings of superiority, fulfillment of expectations, and fulfillment of instinctive needs are preserved until the advanced stages of dementia. Laughter and smiling in response to a release of tension are preserved in most dementia patients.

The third category of laughter is that used as a communication tool. Facial expressions are important components of laughter and we use these expressions to transmit our intention to be friends with others. Laughing and smiling used to communicate with others can be further subdivided into laughter and smiling for cooperation, defense, aggression, and devaluation. A typical example of cooperative smiling is that used as a greeting. We usually say hello and shake hands while smiling. A defensive smile can be observed when someone is trying to conceal their inner feelings, whereas aggressive laughter can also be called scornful laughter. Everyone dislikes being laughed at and, consequently, aggressive laughter is

extremely powerful. Smiling to devalue something is often used in daily life; for example, when the train door shuts in our face, we often give a wry smile to cancel out the impact of the event.

Laughter in dementia patients

Laughter is usually provoked or accompanied by positive emotions. In clinical settings, it is always desirable for patients, their families, and staff to share relaxed and happy feelings, because patients are often under continuous strain and enormous pressure as a result of their illness. The more serious the illness, the more overwhelming the strain to the patients and their families. Dementia patients are usually under considerable strain, at least at the beginning of their illness. Patients' families are placed under even more stress because of the burden of care [41]. A positive emotion, together with laughter, may enable dementia patients to cope with their illness better, improve immune function, increase pain tolerance, and decrease the stress response. When a positive attitude is shared by patients and staff, it can have a positive effect on the emotional-affective and cognitive functioning of the patients [42,43].

Because the social life of dementia patients is impaired by their illness, they can easily feel isolated. Thus, a feeling that unites them, or provides some sort of bond, with their family and the community can be very beneficial. Dementia patients are often encouraged to participate in daily activities with other people and the positive emotions that are shared by the patients and the care staff help the patients maintain social contact.

Several psychosocial interventions are applied to dementia patients in clinical settings [44]. Examples include cognitive rehabilitation, reminiscence therapy, art therapy, drama therapy, and aerobic exercise [45]. In these activities, a positive attitude of patients is essential and it is always true that a greater effect can be expected when patients participate willingly with a positive outlook. In the case of cognitive rehabilitation, active participation is the condition under which good outcomes can be expected. If the patients are reluctant to participate in the activities, it is unlikely that the program will have any beneficial effects.

Dementia patients become anxious and irritated because they are unable to glean sufficient information from their surroundings due to their impaired cognitive functioning [46]. They are easily trapped in a state in which they feel unsafe, alarmed, and insecure, which, in turn, reduces their ability to process information from their surroundings. With even less secure information, they become more alarmed, leading to negative emotional behavior.

Dementia patients often show various types of BPSD during the course of their illness. Aggression, refusal to cooperate, negativity, and apathy are common, all of which contribute to the further isolation of these patients. In this sense, it is important to keep patients with BPSD within the community.

Because BPSD can often be the most formidable barrier to the care of dementia patients, it is highly recommended that the occurrence of BPSD is prevented. To reduce the occurrence of BPSD in dementia patients, patients should be kept in a stable and safe environment, efforts should be made to ensure good communication with the patients, and patients should be kept feeling relaxed and safe. By doing so, the patients are more likely to laugh and smile.

It is true that laughter and smiling decrease over time in most dementia patients, but it is important to note that not all forms of laughter and smiling are equally reduced. The ability to laugh for social communication is readily lost by dementia patients at the onset of their illness, concomitant with the loss of a social life and their ability to process information, but laughter in response to the release of tension is preserved until the advanced stages of the disease. When dementia patients are released from either physical or mental strain, they always smile. Laughter caused by feelings of disharmony is not usually preserved in dementia patients because of impaired cognitive functioning and because these patients are no longer able to understand the meaning of complicated situations, which means they often cannot understand the punch lines of jokes or appreciate humor.

As discussed above, laughter associated with pleasant feelings can be further subdivided into four types, fulfillment of instinctive needs, fulfillment of expectations, a feeling of superiority, and recognition of mix-ups. Most laughter associated with pleasant feelings is preserved in dementia patients, with observations indicating that these patients laugh and smile when they are exposed to pleasant stimuli. They smile when they are well fed and when they have had a good sleep. They also smile and laugh when they have attained self-set goals. Laughter associated with feelings of superiority is clearly preserved in most dementia patients; they become happy and pleasant when their superiority is recognized. Conversely, when these patients feel humiliated, they become angry and insulted.

Thus, the basic form of laughter is preserved in dementia patients, but the social form of laughter is sometimes lost in the advanced stages of the disease. It is important to ensure that dementia patients are kept in a safe and relaxed environment (and not in alarmed and tensioned),

which will make it more likely that these patients will be able to laugh and smile.

Humor in dementia patients

Humor has positive physiological and psychological effects in a variety of situations. The psychiatric literature purports humor as an effective tool in psychiatric illness and psychotherapy. Benefits of humor in business, management, education, and clinical settings are widely recognized because the right perspective facilitates problem solving both interpersonally and in a group setting. Furthermore, humor puts people at ease, promoting the expression and exchange of ideas. Not only can humor benefit patients, but the use of humor can facilitate the effective management of staff and others in the health care setting [22].

Humor is delicate and sensitive by nature. Humor can be properly appreciated when it is expressed in the right time, right place, and on the right occasion. Confidence, or trust, between the sender and receiver is an important aspect of humor. Establishing this trust is a prerequisite for the introduction of appropriately timed humor. No humor can be appreciated by patients when there is no trust between the patient and care staff. If one side is defensive or angry, he/she may find that the use of humor by the other party is offensive or insulting [47,48]. Patients may also become upset about jokes made at their expense, fearing humiliation and stigmatization [49]. The appropriateness of humor depends on the culture, education, and cognitive function of the receiver. Therefore, the use of humor must be timed wisely and it must be used carefully.

Dementia patients may be more sensitive to jokes or humor than healthy people because patients in the early stages of the disease know that they have difficulties understanding complicated things. Dementia patients with cognitive impairment have difficulty appreciating the disharmony in information sent as humor. Humor should be presented to dementia patients after close evaluation. There are no definitive rules, but humor should generally be introduced slowly; if there is no response or the response is negative, it may be a good idea to abandon all attempts to introduce humor, at least during that clinical encounter [50]. Humor can be used as a defense mechanism in an adverse setting and has obvious value for dementia patients if it is properly addressed and accepted. But the impaired cognitive function of dementia patients must be kept in mind so that humor is presented at the right time, in the right place, and on the right occasion. Everyone enjoys laughing, but a misjudged humorous comment can cause offense, so although laughter is almost always positive, humor itself can provoke mixed emotional responses.

> The other reactions--anger, depression, suppression, denial--took a little piece of me with them. Each made me feel just a little less human. Laughter made me more open to ideas, more inviting to others, and even a little stronger inside. It proved to me that, even as my body was devastated and my spirit challenged, I was still a vital human being. Scott Burton [51]

Summary

Dementia patients should be cared for taking into consideration their individual capacities, which differ from patient to patient. Most laughter and smiling is preserved in dementia patients until the end of the clinical course, even though laughter and smiling as a means of communication is lost during the early stages of the disease. Laughter and smiling associated with pleasant feelings, with the exception of laughing in response to feelings of disharmony, and laughter induced by the release of tension can be used in the treatment of dementia patients. The use of humor, covering issues of the fulfillment of instinctive needs and expectations, as well as feelings of superiority (Table 1), can be a good and effective complementary and alternative intervention in the treatment of dementia patients.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

MT, TK, and TT discussed the importance of laughter and humor to dementia patients and drafted the manuscript. MO, ST, and TM searched for the data on the topics in the literatures. MT, RH, and GS devised the table. All authors have read and approved the final manuscript.

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ORIGINAL ARTICLE

Long-term multiple risk factor interventions in Japanese elderly diabetic patients: The Japanese Elderly Diabetes Intervention Trial – study design, baseline characteristics and effects of intervention

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Aim: To evaluate long-term, multiple risk factor intervention on physical, psychological and mental prognosis, and development of complications and cardiovascular disease in elderly type 2 diabetes patients.

Methods: Our randomized, controlled, multicenter, prospective intervention trial included 1173 elderly type 2 diabetes patients who were enrolled from 39 Japanese institutions and randomized to an intensive or conservative treatment group. Glycemic control, dyslipidemia, hypertension, obesity, diabetic complications and atherosclerotic disease were measured annually. Instrumental activity of daily living, cognitive impairment, depressive symptoms and diabetes burden were assessed at baseline and 3 years.

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Results: There was no significant difference in clinical or cognitive parameters at baseline between the two groups. The prevalence of low activities of daily living, depressive symptoms and cognitive impairment was 13%, 28% and 4%, respectively, and was similar in the two groups. A small, but significant difference in HbA1c between the two groups was observed at 1 year after the start of intervention (7.9% *vs* 8.1%, $P < 0.05$), although this significant difference was not observed after the second year. With the exception of coronary revascularization, there was no significant difference in fatal or non-fatal events between the two groups. Composite events were also similar in the two groups.

Conclusions: This study showed no significant differences in fatal or non-fatal events between intensive and conventional treatment. The present study might clarify whether treatment of risk factors influences function and quality of life in elderly diabetic patients.
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Keywords: diabetes mellitus, elderly, geriatric assessment, intervention, vascular complications.

Introduction

The prevalence of diabetes increases with age, with approximately 15% of elderly people in Japan having the disorder.[1] These patients often suffer from diabetic microvascular and macrovascular complications.[2] Treatment goals in this elderly diabetic population are to maintain functional abilities and quality of life, and to prevent diabetic complications. Physical functional activities[3,4] and cognitive function[5,6] are more impaired in elderly diabetic patients, with depression and low well-being being major concerns.[7,8] It is therefore important to evaluate the effects of clinical interventions on physical, psychological and mental functions, as well as on disease-related variables, such as diabetic complications, atherosclerotic disease and mortality.

The impact of intensive blood glucose, blood pressure or multiple risk factor intervention on diabetic complications in type 2 diabetes has been evaluated in the United Kingdom Prospective Diabetes Study (UKPDS),[9,10] Kumamoto Study[11] and Steno-2 Study.[12] As only a few elderly people were included in these studies, little is known on the effects of multiple risk factor intervention on diabetic complications and functional prognosis.

We therefore carried out a randomized clinical trial to evaluate the efficacy of multiple risk factor intervention on functional prognosis, and development and/or progression of diabetic complications and cardiovascular disease in elderly people with type 2 diabetes. The present study presents baseline demographic and biomedical characteristics, and describes the major outcome variables measured at baseline.

Methods

Participants

The participants recruited for the Japan Elderly Diabetes Intervention Trial (J-EDIT) were diabetic outpatients at 39 representative hospitals in Japan between March 2001 and February 2002. Written informed consent was obtained from all participants before screening, consistent with the Helsinki Declaration and the guidelines of each center's institutional ethical committee.

Initial screening tests included glycated hemoglobin A1c (HbA1c), body mass index (BMI), blood pressure, serum total cholesterol, triglycerides and high-density lipoprotein cholesterol (HDL-C). Inclusion criteria included age 65–85 years, HbA1c ≥ 7.9% or HbA1c ≥ 7.4% with at least one of following criteria: BMI ≥ 25 kg/m^2, blood pressure ≥ 130/85 mmHg, serum total cholesterol ≥ 200 mg/dL (or low-density lipoprotein cholesterol [LDL-C] ≥ 120 mg/dL in participants without coronary heart disease [CHD]) or ≥180 mg/dL (or LDL-C ≥100 mg/dL in participants with CHD), triglycerides ≥ 150 mg/dL and HDL-C < 40 mg/dL. Exclusion criteria included a recent (<6 months) myocardial infarction (MI) or stroke, acute or serious illness, aphasia and severe dementia.

Randomization and intervention

A total of 1173 diabetic outpatients were enrolled and randomly allocated to either the intensive or conventional treatment group. The randomized factors were age, sex, diabetes treatment, HbA1c, total cholesterol, triglycerides, HDL-C, blood pressure, diabetic

Table 1 Treatment goals of multiple risk factor intervention studies in patients with type 2 diabetes

	J-EDIT	UKPDS	Steno-2 Study
Mean age (years)	72	52	55
Range	(65–84)	(25–65)	(40–65)
Treatment goals			
Glucose control			
FPG (mmol/L)		<6.0	
HbA1c (%)	<6.9		<6.5
Blood pressure control (mmHg)	<130/85	<150/85	<140/85 (1993–1999) <130/80 (2000–2001)
Cholesterol (mg/dL)	<200 (<180) if one has CHD	none	<190 (1993–1999) <175 (2000–2001)
Triglycerides (mg/dL)	<150	none	<150
HDL-C (mg/dL)	>40	none	>40
Other interventions	BMI <25		Smoking cession Aspirin use

CHD, coronary heart disease; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol, J-EDIT, Japan Elderly Diabetes Intervention Trial; UKPDS, United Kingdom Prospective Diabetes Study.

microangiopathy, atherosclerotic disease, hypertension, hyperlipidemia and institutions.

The treatment goal in the intensive treatment group was HbA1c < 6.9%, BMI < 25 kg/m^2, systolic blood pressure (SBP) < 130 mmHg, diastolic blood pressure (DBP) < 85 mmHg, HDL-C > 40 mg/dL, serum triglycerides < 150 mg/dL and serum total cholesterol < 180 mg/dL (or LDL-C < 100 mg/dL if patients had CHD) or <200 mg/dL (or LDL-C < 120 mg/dL if patients did not have CHD; Table 1). If HbA1c levels did not reduce to <6.9%, oral hypoglycemic drugs (sulphonylurea, biguanides, α-glucosidase inhibitors and pioglitazone) or insulin therapy was introduced by the physician. If total cholesterol or LDL-C levels did not reach the treatment goal, the physicians were advised to use atorvastatin. Patients with a history of cerebral infarction also had antiplatelet therapy where possible.

The conventional treatment group continued their baseline treatment for diabetes, hypertension or dyslipidemia without a specific treatment goal.

Each participant had a standardized medical history and physical examination at baseline, and then annually. Baseline information included age, sex, medical history, family members with whom they lived, education, employment, height, bodyweight, waist-to-hip ratio, maximum body weight, diabetes duration, family history of diabetes and diabetes treatment. Standardized questionnaires were used to obtain self-reported data on smoking, alcohol, hypoglycemia frequency, nutritional status, dietary habits and adherence, self-efficacy, activities of daily living (ADL), physical activities, comprehensive cognitive function, and psychological status including diabetes burden and depressive symptoms.

Basic ADL was assessed by the Barthel index,[13] whereas functional disabilities were examined by the Tokyo Metropolitan Institute of Gerontology (TMIG) Index of Competence.[14] This index includes 13 items and three subscales: instrumental ADL, intellectual activity and social role. The index is well validated and is widely used to measure functional abilities in community-dwelling or institutionalized elderly subjects.[15]

Physical activities were assessed using the Baecke questionnaire.[16] The Folstein Mini-Mental State Examination (MMSE) was carried out to assess comprehensive cognitive function including orientation, memory recall and calculations.[17]

Depressive symptoms were evaluated using a short form of the Geriatric Depression Scale (15 items, GDS-15),[18] whereas diabetes-specific burden and concerns were examined using the elderly diabetes burden scale (EDBS).[19] EDBS is a short revised version of the elderly diabetes impact scale reported previously,[4] and consists of six subscales: symptom burden (4 items), social burden (5 items), diet restrictions (4 items), concern (4 items), treatment satisfaction (3 items) and burden by tablets or insulin (3 items). Each of the 23 EDBS items was rated on a four-point multiple-choice scale. The elderly diabetes burden score was calculated by reversing the scores of the treatment satisfaction subscale and summing the scores of the six subscales. EDBS has good test–retest reliability, construct validity, convergent validity and satisfactory internal consistency.

The frequency of mild or severe hypoglycemia was assessed using questionnaires (number of hypoglycemic episodes and number of comas or emergency hospital visits or admissions as a result of hypoglycemia in a year, month or week). Mild hypoglycemia episodes included the appearance of or recovery from hypoglycemic symptoms. Severe hypoglycemia episodes were defined as

coma, convulsion or incapacity of the patient sufficient to require the assistance of another person.

Nutritional intake was assessed for 1 week using the Yoshimura food frequency questionnaire[20] that estimated food and total energy intake, carbohydrate-, protein- and fat-to-energy ratios, and intake of cholesterol, salt, iron, calcium, vitamins and dietary fiber from portion sizes (relative to the standard amount) and frequency (intake number for 1 week) of 29 food groups.

Measurements

Venous blood was drawn for determination of blood glucose, HbA1c and serum concentrations of total cholesterol, HDL-C and triglycerides at baseline, and then at least twice a year. Plasma glucose was measured by the glucokinase method, and HbA1c by ion-exchange high-performance liquid chromatography. The Japan Diabetes Society (JDS) has standardized several HbA1c assays with the international standard value adjusted by the equation of HbA1c (JDS) (%) plus 0.4%. Serum insulin was measured by an enzyme immunoassay, and total cholesterol, triglycerides, HDL-C, white blood cells, red blood cells, hematocrit (Ht), blood urea nitrogen (BUN), serum creatinine, uric acid, total protein and albumin by established methods.

Blood pressure was measured with a mercury sphygmomanometer using a cuff of appropriate size. Diastolic blood pressure was determined as Korotkoff phase V. Body mass index was calculated as weight in kilograms / (height in meters)^2.

Microangiopathy (retinopathy, nephropathy and neuropathy), macroangiopathy (ischemic heart disease [IHD]), stroke and peripheral vascular disease [PVD]) were assessed at baseline, and then annually. Funduscopic examinations were carried out on dilated pupils by experienced ophthalmologists using direct ophthalmoscopy. Retinopathy status was assessed by the Japanese Diabetes Complication Study method and classified into five stages: stage 0: no retinopathy; stage 1: dot hemorrhages, hemorrhages or hard exudates; stage 2: soft exudates; stage 3: IRMA or venous deformities; stage 4: neovascularization, preretinal proliferative tissues, vitreous hemorrhages or retinal detachment. Diabetic maculopathy was assessed according to findings of hemorrhages, local edema, hard exudates and diffuse edema at macular areas. Uncorrected and corrected visual acuities, the occurrence of cataract, corneal opacity, glaucoma, age-related macular degeneration, laser photocoagulation, cataract operations and vitrectomy were assessed. Urinary albumin was measured by immunological assay. Mean urinary albumin-to-creatinine ratio (ACR; μg/mg creatinine) in two or three successive urinalyses was used to classify diabetic nephropathy as no nephropathy (ACR < 30), microalbuminuria (30 ≤ ACR < 300) or persistent proteinuria (ACR ≥ 300 or urinary protein ≥30 mg/dL). Diabetic neuropathy was defined as loss of Achilles tendon reflexes and diminished vibration sensation, and/or neuropathic symptoms including paresthesia.

Follow up

The annual examinations included bodyweight, BMI, waist-to-hip ratio, treatment of diabetes, fasting plasma glucose, serum insulin, total cholesterol, triglycerides, HDL-C, lipoprotein(a), white blood cells, red blood cells, Ht, platelet, BUN, serum creatinine, uric acid, total protein, albumin, blood pressure, visual acuity, microalbuminuria, deep tendon reflexes, neuropathic symptoms, resting electrocardiogram (ECG), chest X-ray, and the occurrence of retinopathy, nephropathy, neuropathy, IHD, stroke and PVD. HbA1c and ACR were measured biannually. Basic ADL, functional abilities, cognitive function, depressive symptoms and nutrition were assessed every other year. Use of medications, including insulin and hypoglycemic, antihypertensive, antihyperlipidemic, antiplatelet and anticoagulant drugs, was checked annually.

Data management and analyses

The main database was stored at the data management and statistical analysis center. A data sheet of each patient was mailed from the study institutions to the data management and statistical analysis center each year. The data was validated by range, combinatorial and historical checks of compatibility with previous data. A visual check of the list of abnormalities and information in the data sheets was carried out by trained staff. The study institutions were notified of unexplained abnormalities in the data that were completed or corrected before entry into the main database.

Data are presented as means ± SD or as proportions, unless otherwise specified. Data for analysis was extracted from the main database, and statistical analysis was carried out using the SAS computer programs. For univariate analysis, we used unpaired *t*-test and χ^2-test to compare baseline clinical characteristics in the two treatment groups. $P < 0.05$ was considered statistically significant.

Data security was maintained by exclusion of patient identities, password access and secure output within the data management and statistical analysis center.

End-points

Fatal and non-fatal events during follow up were certified by at least two members of the expert committee, masked to the participants' diagnosis and risk factor status. Death as a result of diabetes was defined as sudden death or death from atherosclerotic CHD (MI or heart failure as a result of ischemia) or stroke, death as

a result of renal failure, hyperglycemia or hypoglycemia. The history of macroangiopathy was obtained from medical records. Ischemic heart disease was classified as present when the patient had (i) a history of MI characterized by a typical clinical picture (chest pain, chest oppression and dyspnea), typical ECG alterations with occurrence of pathological Q waves and/or localized ST variations) and typical enzymatic changes (creatine phosphokinase); and (ii) a history of angina pectoris, positive treadmill ECG test or positive postload cardiac scintigram, confirmed by coronary angiography. Stroke was defined as clinical signs of a focal neurological deficit with rapid onset persisting ≥24 h, confirmed by either brain computed tomography or magnetic resonance imaging. No cases of asymptomatic lesions detected by brain imaging (i.e. silent infarction) were included. PVD was defined as the absence of dorsal pedal artery or posterior tibial artery pulsation and ankle–brachial index <0.8 or the presence of foot gangrene or ulcers.

All events related to diabetes were defined as any complications of cardiovascular events, fatal or non-fatal stroke, sudden death, renal death, diabetic foot complications and heart failure. All events included death unrelated to diabetes, as well as all events related to diabetes.

End-point validation

Possible clinical end-points were noted in the annual data sheets, with the diagnostic criteria for each end-point being predetermined. When an end-point was notified on a data sheet, the administrator requested full information from the data management and statistical analysis center, followed by a review by two clinical assessors of the event assignment committee. Two separate assessments for each end-point were entered on a special data sheet. If there was disagreement on the assessment, a final decision was made after discussions of the committee. The definition of the end-points is shown in the Appendix.

Statistical analysis and criteria for stopping the study

Differences in end-points (deaths or complications) between the two groups were analyzed using the log–rank test. Uni- and multivariate survival analyses were carried out using Cox proportional hazard regression models. All major analyses were according to assigned allocations (intention to treat), without exclusion of protocol deviants.

The Data and Safety Monitoring Committee examine the end-points annually and will stop the study when the difference in diabetes-related deaths or complications (disease) between the two groups becomes significant ($P < 0.001$, log–rank test).

Results

A total of 1173 outpatients with diabetes, aged over 65 years, were registered between March 2001 and February 2002. After randomization, 585 and 588 patients were allocated to intensive or conventional treatment, respectively. There were no significant differences between the two groups for age, sex, diabetes treatment, BMI, HbA1c, SBP and DBP, total cholesterol, triglycerides, HDL-C levels (Table 2), and number of risk factors (data not shown).

At baseline, the proportion of patients with a low ADL (TMIG Index of Competence ≤ 9), depressive symptoms (GDS-15 ≥ 5), or cognitive impairment (MMSE ≤ 23) were 13%, 28% and 4%, respectively. The prevalence of low ADL, depressive state and cognitive impairment was similar in the two groups (Table 2).

The dropout rate after 6 years was 8.9% (104 cases). HbA1c, total cholesterol, triglycerides, blood pressures and BMI at baseline and during follow up are shown in Table 3 and Figures 1–4. A small, but significant difference in HbA1c between the two groups was observed at 1 year after the start of intervention (7.9% *vs* 8.1%, $P < 0.05$), although this significant difference was not observed after the second year. Although SBP and DBP, total cholesterol and triglycerides levels tended to decrease by the sixth year compared with the baseline data in both groups, no significant differences in these variables were observed between the two groups during follow up (Figs 1–4). BMI and HDL-C levels did not change over the follow-up period in either group.

Table 4 shows the fatal and non-fatal events during follow up in the two groups. With the exception of coronary revascularization, there were no significant differences in fatal or non-fatal events between the groups ($P < 0.05$, log-rank test). Composite events (death as a result of diabetes, death unrelated to diabetes, coronary vascular events, stroke, total diabetes-related events and all events) were also similar in the two groups (Table 5).

Discussion

The J-EDIT study has the potential to determine whether multiple risk factor intervention prevents aggravation of complications and quality of life, and reduces mortality in elderly diabetic patients. The study has three characteristics. First, it is a large-scale study of multiple risk factor intervention in elderly diabetic patients. No or very few elderly patients were included in the UKPDS[9,10] or Steno-2 Study.[12] Second, the multiple interventions involved control of blood pressure, serum lipids, bodyweight and blood glucose. The treatment goals in the intensive treatment group were similar

Table 2 Clinical characteristics of the participants at baseline

	Conventional treatment (n = 588)	Intensive treatment (n = 585)
General characteristics		
Age (years)	71.7 ± 4.7	71.9 ± 4.6
Male (%)	46.3	46.3
Duration of diabetes (years)	18.0 ± 9.9	16.7 ± 8.5
Body mass index (kg/m^2)	24.3 ± 7.3	24.0 ± 3.9
Waist (cm)	83.6 ± 9.9	84.3 ± 10.4
Waist-to-hip ratio	0.89 ± 0.07	0.90 ± 0.07
Smoking (%) (non-/ex-smoker/current smoker)	16:31:53	15:29:56
Smoking (package × years)	848 ± 762	789 ± 601
Family history of diabetes (%)	45.8	39.7
Systolic BP (mmHg)	137 ± 17	137 ± 16
Diastolic BP (mmHg)	75 ± 10	76 ± 10
Clinical status		
Ischemic heart disease (%)	16.3	14.9
Cerebrovascular disease (%)	12.4	13.3
Retinopathy (%)		
Stage 0	53.6	51.7
Stage 1	30.5	31.4
Stage 2	7.8	9.1
Stage 3	3.3	3.4
Stage 4	4.7	4.7
Nephropathy (%) (no/microalbuminuria/persistent proteinuria)	51:30:19	53:30:17
Loss or weakness of ATR (%)	56.8	57.1
Paresthesia (%)	18.5	22.3
Laboratory data		
HbA1c (%)	8.5 ± 0.9	8.4 ± 0.8*
Fasting plasma glucose (mg/dL)	170 ± 53	168 ± 49
Fasting insulin (mIU/mL)	10.9 ± 12.0	10.3 ± 9.6
Total cholesterol (mg/dL)	202 ± 34	203 ± 34
Triglycerides (mg/dL)	131 ± 70	137 ± 110
HDL-C (mg/dL)	56 ± 18	57 ± 19
Uric acid (mg/dL)	5.1 ± 2.0	5.1 ± 1.4
Blood urea nitrogen (mg/dL)	16.9 ± 5.9	17.2 ± 6.1
Creatinine (mg/dL)	0.93 ± 1.2	0.83 ± 0.36
Treatment		
Treatment of diabetes (diet/OHA/insulin)	9.0:60.7:30.3	8.7:61.0:30.3
Sulfonylurea drugs	54.6	56.0
α-Glucosidase inhibitors (%)	30.5	28.0
Biguanides (%)	16.4	15.5
Pioglitazone (%)	4.5	5.2
Glinides (%)	2.3	2.1
Antihypertensive drugs (%)	56.4	57.4
ACE inhibitors (%)	22.9	23.3
ARB (%)	10.1	9.3
Calcium blockers (%)	42.9	41.0
β-Blockers (%)	6.2	5.7
α-Blockers (%)	6.1*	3.4
Diuretics (%)	5.1	7.5
Antihyperlipidemic drugs (%)	40.2	36.8
Statins (%)	30.3	26.5
Fibrates (%)	3.4	3.9
EPA (%)	0.7*	2.7
Nicotinates (%)	1.3	1.4
Probucol	2.2	1.6
Antiplatelet drugs (%)	25.9	27.4
Aspirin (%)	13	15
Geriatric Assessment		
Barthel index (full score: 20)	19.8 ± 0.9	19.8 ± 0.8
Prevalence of any disabilities (%)	11	14
Functional abilities (TMIG index of competence) (full score: 13)	11.6 ± 2.2	11.6 ± 2.2
Geriatric depression scale (full score: 15)	4.3 ± 3.3	4.0 ± 3.2
Depressive symptoms (%) (Geriatric depression scale ≥5)	41	36
MMSE (full score: 30)	28.0 ± 2.4	27.8 ± 3.0
Cognitive impairment (%) (MMSE ≤23)	7	6
Visual impairment (%) (≤0.1)	9	12

ARB, angiotensin II receptor blockers; ACE, angiotensin-converting enzyme; ATR, Achilles tendon reflex; BP, blood pressure; EPA, eicosapentenoic acid; HbA1c, glycated hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; MMSE, Mini-Mental State Examination; OHA, oral hypoglycaemic agents; TMIG, Tokyo Metropolitan Institute of Gerontology. *P < 0.05.

Table 3 Changes in bodyweights, glycated hemoglobin A1c, serum lipids, and blood pressure at baseline and during the follow-up period

	Conventional treatment							Intensive treatment						
Follow up (years)	0	1	2	3	4	5	6	0	1	2	3	4	5	6
BMI (kg/m^2)	23.6	23.6	23.6	23.4	23.5	23.5	23.4	23.9	23.8	23.8	23.8	23.8	23.7	23.5
HbA1c (%)	8.5	8.1	8.0	7.9	7.9	7.9	7.8	8.4	7.9	7.8	7.8	7.8	7.8	7.7
TC (mg/dL)	202	200	199	195	193	190	190	202	196	198	194	190	188	188
TG (mg/dL)	112	111	109	108	103	101	101	114	110	110	108	110	104	104
HDL-C (mg/dL)	56	56	55	56	55	55	54	57	54	54	55	55	55	55
SBP (mmHg)	137	137	135	135	135	135	134	138	136	136	133	134	136	134
DBP (mg/dL)	75	74	73	72	72	72	71	74	73	74	72	71	71	71

BMI, body mass index; DBP, diastolic blood pressure; HbA1c, glycated hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides.

Table 4 Comparison of fatal events and non-fatal events during the 6-year follow-up period in the conventional and intensive treatment groups

		Number	*P*-value
Fatal event	Myocardial infarction	12	0.083
	Sudden death	13	0.993
	Stroke	6	0.656
	Death due to renal failure	3	0.084
	Death due to hyper/hypoglycemia	1	0.322
	Malignancy	37	0.506
	Pneumonia	10	0.525
	Others	13	0.570
	Subtotal	95	0.291
Nonfatal event	Myocardial infarction	17	0.998
	Angina pectoris	21	0.517
	Coronary revascularization	18	0.0282
	Hospitalization due to heart failure	15	0.190
	Stroke	63	0.281
	Diabetic ulcer or gangrene	12	0.564
	Subtotal	146	
Total		241	

Table 5 Comparisons of composite events (death due to diabetes, death unrelated to diabetes, coronary vascular events, stroke, total diabetes-related events and all events) in the conventional and intensive treatment groups

	No. events	*P*-value (log–rank test) Conventional *vs* intensive
Death due to diabetes	35	0.8495
Death not related to diabetes	59	0.2991
Coronary vascular events	55	0.9868
Stroke	67	0.2915
All events related to diabetes	155	0.5573
All events	206	0.2239

Death due to diabetes was defined as sudden death or death from atherosclerotic coronary heart disease (myocardial infarction or heart failure due to ischemia) or stroke, death due to renal failure, hyperglycemia or hypoglycemia. All events related to diabetes were defined as any complications of cardiovascular events, fatal or non-fatal stroke, sudden death, renal death, diabetic foot complications and heart failure. All events included death unrelated to diabetes, as well as all events related to diabetes.