

Do Alzheimer's Disease Patients Appear Younger than Their Real Age?

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Abstract

Introduction: The most prominent risk factor of Alzheimer's disease (AD) is aging. Aging also influences the physical appearance. Our clinical experience suggests that patients with AD may appear younger than their actual age. Based on this empirical observation, we set forth to test the hypothesis with human and computer-based estimation systems. **Method:** We compared 50 early-stage AD patients with 50 age and sex-matched controls. Facial images of all subjects were recorded using a video camera with high resolution, frontal view, and clear lighting. Subjects were recorded during natural conversations while performing Mini-Mental State Examination, including spontaneous smiles in addition to static images. The images were used for age estimation by 2 methods: (1) computer-based age estimation; (2) human-based age estimation. Computer-based system used a state-of-the-art deep convolutional neural network classifier to process the facial images contained in a single-video session and performed frame-based age estimation. Individuals who estimated the age by visual inspection of video sequences were chosen following a pilot selection phase. The mean error (ME) of estimations was the main end point of this study. **Results:** There was no statistically significant difference between the ME scores for AD patients and healthy controls ($p = 0.33$); however, the difference was in favor of younger estimation of the AD group. The average ME score for AD patients was lower than that for healthy controls in computer-based estimation system, indicating that AD patients were on average estimated to be younger than their actual age as compared to controls. This difference was statistically significant ($p = 0.007$). **Conclusion:** There was a tendency for humans to estimate AD patients younger, and computer-based estimations showed that AD patients were estimated to be younger than their real age as compared to controls. The underlying mechanisms for this observation are unclear.¹

Introduction

Alzheimer's Disease (AD) is the most common neurodegenerative disorder in the elderly. The most prominent risk factor for AD is aging. Aging also influences the physical appearance of an individual, including facial features, which in turn determines the perceived age of a person. Our clinical experience over the years suggests that patients with AD may appear younger than their actual age. Based on this empirical observation, we set forth to test the hypothesis that AD patients look younger than their chronological age as compared to their peers. In order to test this hypothesis, we compared the estimated age of AD patients and age and sex-matched healthy subjects using both computerized methods as well as age estimation by humans.

Methods

Participants

Fifty early-stage AD patients were consecutively recruited at Istanbul University, Istanbul Faculty of Medicine, Neurology Department, Behavioural Neurology Outpatient Clinic. The

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eligibility criteria for inclusion in the study were: 1) age ≥ 64 years; 2) diagnosis of AD according to NINCDS-ADRDA criteria for probable AD (McKhann G, 1984); 3) Clinical Dementia Rating Scale score 0.5 or 1 (Hughes CP, 1982). As controls, 50 age- and sex-matched healthy individuals were recruited, among the family members of patients as well as volunteers among relatives of patients attending the general outpatient clinic. Inclusion criteria for healthy controls were: 1) Mini-Mental State Examination (MMSE) score ≥ 26 (Folstein MF, 1975), 2) no subjective or corroborated cognitive impairment, 3) no history of systemic, psychiatric or neurological disorder. Exclusion criteria for both patients and healthy controls were: 1) severe visual impairment or hearing loss; 2) history of facial botulinum toxin injection; 3) having any major facial scar; 4) history of facial palsy; 5) using antipsychotic medication; 6) having parkinsonism or significant apathy in the neurological examination; 6) Geriatric Depression Scale score >13 (Brink TL, 1982).

The study was approved by the Ethical Committee of İstanbul Faculty of Medicine. All subjects and/or their next-of kin (in case of patients) provided written informed consent for the anonymous use of their data and images for age estimation.

Facial image recordings

Facial images of all individuals were recorded using a video camera with high resolution, frontal view, and clear lighting. As automatic facial age estimation approaches also leverage facial dynamics during facial expressions, subjects were also recorded during natural conversations while performing MMSE, including spontaneous smiles. Video recordings consisted of RGB videos, recorded in 1920×1080 pixels at a rate of 25 frames per second. During recordings, none of the subjects used eyeglasses to avoid interference with computer processing and influence on age perception.

Age estimation

The images were used for age estimation by two methods: 1) automatic computer-based age estimation; 2) human-based age estimation.

Computer-based age estimation

Automatic computer-based system used a state-of-the-art deep convolutional neural network classifier to process the facial images contained in a single video session and performs frame-based age estimation. For a single video, this produces around 2000 frames with estimated ages. We fit a curve to all estimations of the session to predict a single age for the subject, which produces a better result compared to taking an average for non-Gaussian distributed predictions (Zeylan AE, 2019). An established automatic facial estimation database and protocols called FG-NET were used to verify the accuracy of the system. Due to low quality, 6 videos of healthy controls were excluded, in total 94 videos were analyzed.

Human-based age estimation

Individuals who estimated the age by visual inspection of video sequences were chosen following a pilot selection process as follows: among the employees of the Neurology Department, 15 volunteers were asked to estimate the age of randomly selected unfamiliar faces. The group included five individuals from the age group of 30-39, five from the age group of 40-49, and five from the age group of 50-59. They were shown video recordings of

31 individuals (including 11 healthy controls and 20 Alzheimer's patients) of various ages and were asked to estimate their ages. In each of the three age groups, the individual with the lowest MAE score (see below) was identified, these three individuals were defined as "estimators". They were then shown the video recordings of AD patients and healthy controls and asked to estimate their age. All three estimators used the same computer and standard screen adjustments for viewing the recordings (13.3-inch LED-backlit display with IPS technology). They were not aware of the diagnosis, and the videos of AD patients and healthy controls were shown in a mixed, random order.

MAE score was used to evaluate the accuracy of age estimation and to select the best estimators. Absolute error was defined as the difference in years between the estimated age and the real age of a subject. As shown below, MAE was calculated by adding absolute errors for all subjects without taking into account if a given estimation was higher or lower than the actual age. The total number in years was then divided by the number of subjects. Lower scores of MAE indicate more accurate estimations.

Mean error (ME) was the main end point of this study and calculated as follows: the errors in estimation for all subjects in a group were added together taking in account if the estimation was higher or lower than the actual age (whereby negative and positive values counteract each other) and then dividing the total number by the number of subjects in that group. Negative values of ME indicate that on average, subjects in that group were estimated to be younger than their actual age whereas positive values indicate that they were estimated to be older than their actual age. ME can be computed as follows:

$$ME = \frac{(\text{estimated age} - \text{actual age})_{n=1} + \dots + (\text{estimated age} - \text{actual age})_{n = \text{total number of subjects}}}{\text{total number of subjects}}$$

Statistics

Statistical analyses were performed using SPSS software version 22. Descriptive statistics were used to evaluate the sample population, and mean age and sex distribution were tested for statistically significant differences. Kolmogorov-Smirnov/Shapiro-Wilk's test was applied to analyze if the variables were normally distributed. There were 50 patients and 50 healthy subjects included in the human-based age estimation analysis. Age, MMSE, CDR scores, and ME values did not show normal distribution, so nonparametric Mann-Whitney U test and χ^2 test were used to compare the groups. In the computer-based estimation analysis, the number of the subjects was different (50 AD patients and 44 healthy subjects) data showing normal distribution, and parametric t test was conducted for comparison of the ME values of the groups.

Results

Demographic and clinical variables are summarized in Table 1. Age range, mean age, and gender distribution were comparable between the patient and control subjects ($p = 0.17$ and $p = 1.0$, respectively). The mean Mini- Mental State Examination score was 23.54 ± 4.26 in the AD and 28.84 in the control group.

Human-based age estimations

Figure 1 shows the actual and estimated ages of all subjects by the “estimators” and Table 2 shows the ME values for human-based and computer-based estimations. There was no statistically significant difference between the ME scores for AD patients and healthy controls (Table 2). Even though statistically not significant, there was a difference between the ME values of AD patients and control subjects in favor of younger estimation of the AD group. Difference between the ME values of AD versus control subjects for the 3 estimators was 1.68, 0.50, and 2.64 years, all in favor of the AD group.

Table 1. Demographic and clinical variables of patients and control subjects.

	AD (n = 50)	Healthy Control (n = 50)	p value
Age: mean, range (SD)	74.30, 64-87 (5.92)	72.84, 65-85 (5.81)	0.17 ^a
Gender: male, n (%)	27 (54%)	27 (54%)	1.0 ^b
MMSE score: mean, range (SD)	23.54 (4.26)	28.84, 24-30(1.31)	<0.05 ^c
CDR: mean, range (SD)	0.71 (0.25)	0 (0)	<0.05 ^b

Abbreviations: CDR: Clinical Dementia Rating Score; MMSE: Mini-Mental State Examination; SD: standard deviation. AD: Alzheimer's disease

^a The Mann-Whitney U test was used to compare variables between groups.

^b χ^2 test was used to compare variables between groups.

^c t test was used to compare variables between groups.

Table 2: ME values of the human age estimators and computer-based estimation.

	AD (n = 50)	Healthy Control (n = 50)	p value
Estimator 1, ME (SD)	1.68 (6.76)	3.36 (6.95)	0.32 ^a
Estimator 2, ME (SD)	-1.76 (6.21)	-1.26 (4.96)	0.79 ^a
Estimator 3, ME (SD)	-0.56 (7.90)	2.08 (5.93)	0.08 ^a
Mean value of the 3 estimators*, ME (SD)	-0.21 (5.89)	-1.39 (5.10)	0.33 ^a
	AD (n = 50)	Healthy Control (n = 44)	p value
Mean value of the computer-based age estimation, ME	-9.7	-4.48	0.007b

Abbreviations: AD, Alzheimer’s disease; ME, mean error; SD, standard deviation.

^a The Mann-Whitney U test was used to compare variables between groups.

^b t test was used to compare variables between groups.

* Mean ME was calculated by pooling together error in estimations of all 3 estimators.

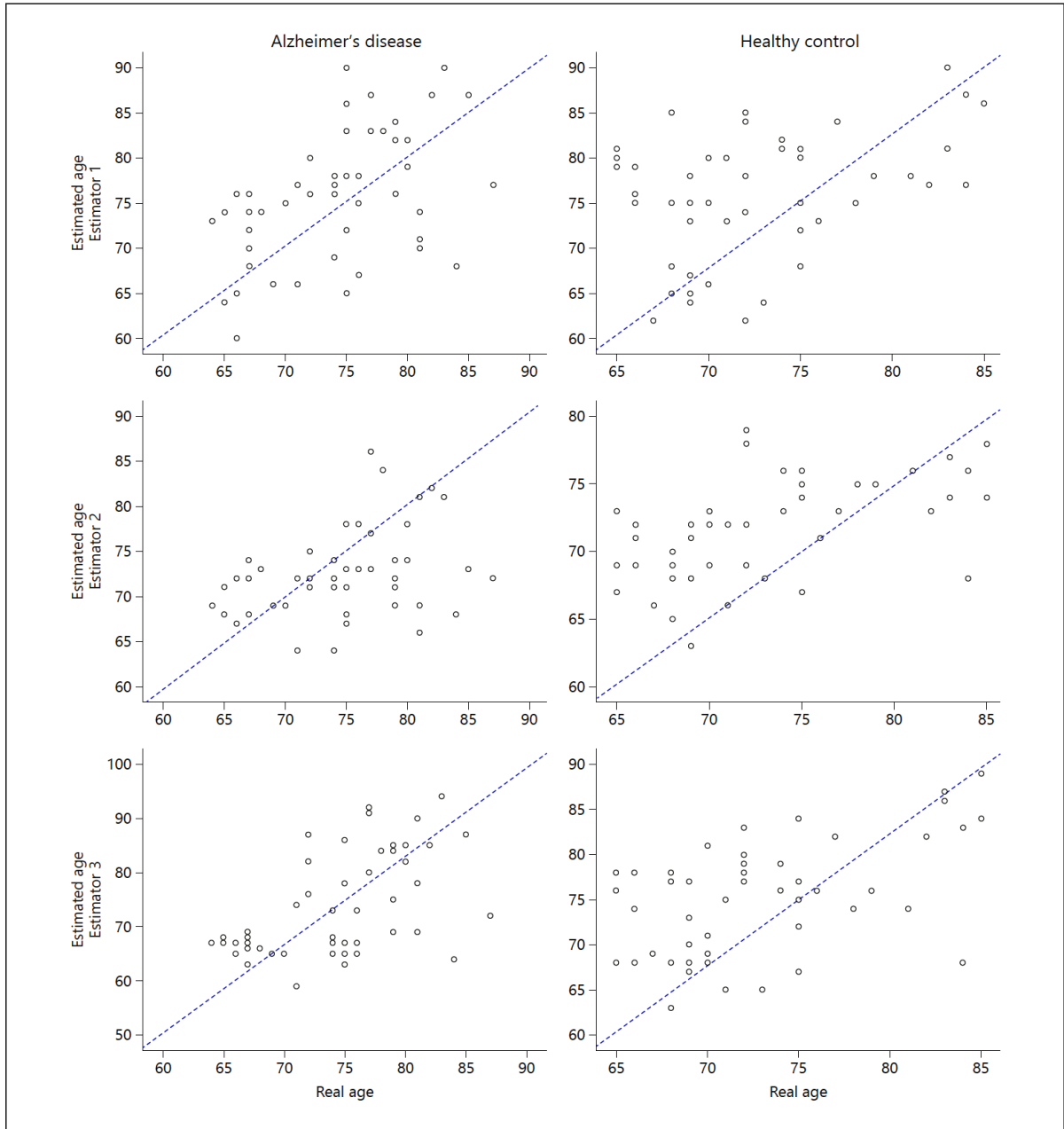


Figure 1: The actual and estimated ages of all subjects with human-based estimation. Each dot represents 1 subject. Dots below the blue line represent cases in which the estimated age was lower than the actual, and dots above the blue line represent cases in which the estimated age was higher than the actual age. .

Computer-based age estimation

Table 3 shows the MAE and ME values of the computer-based estimations. The average MAE scores of the AD patients were higher than healthy subjects with a p-value of 0.057. Average ME scores of the AD patients were significantly different between the AD patients and healthy control subjects where the estimated age of AD patients was 5.22 years younger than the estimated age of healthy subjects ($p= 0.007$).

Discussion

In this study, there was a tendency for the ages of both healthy and AD subjects estimated to be younger than their actual age in computer-based estimations. Although statistically not significant, there was a tendency for humans to estimate AD patients younger than their actual age as compared to controls. Computer-based estimations showed that ages of AD patients were estimated to be significantly younger than the control subjects.

Factors underlying for a younger estimation of AD patients are unclear. Appearance of age is closely related to the physical changes which emerge with aging. Health status and environmental factors such as, sun exposure, smoking, BMI, social class, and marital status may all influence the perceived age (Mayes AE, 2010; Rexbye H, 2006). Wrinkles and white hair are obvious influences on the estimated age, but additional factors such as facial expressions may also influence our estimations. AD pathology initially affects the limbic areas of the brain, which are highly associated with memory functions and emotions. They have connections with the nucleus of facial nerve, which innervates facial mimic muscles, and they have interconnections with cortical and subcortical areas, which were thought to be involved in the generation of emotional facial expressions (Tucker DM, 2000). AD patients were found to have altered facial mimic activity and expressions of emotions during emotional states (Burton KW, 2006). Since facial mimics and expressions are one of the important clues used in estimating ages, altered facial mimics in AD patients may be the reason for their relatively younger appearance.

There are several caveats to our findings. We recruited patients older than 65 years at earlier stages of the disease. We also excluded patients with depression. We have done so in order to obtain a homogenous population typical of AD and also to exclude changes in facial expression associated with apathy in the later stages of the disease or due to depression. These limitations may render our results not generalizable in all cases. An open question is if the static properties, facial dynamics, or both of these influenced the younger appearance of AD patients in the computer-based analysis. In recent years, many computer-based approaches have been developed for age estimation for different purposes, such as forensics (Albert AM, 2007). Most of the automatic facial age estimation approaches use static features. Recently, dynamic features were also introduced, arguing that aging changes the muscle tone in the face. Facial dynamics are also affected by morphological changes such as, muscle loss, fat tissue, and cartilage growth. Automatic facial age estimation studies established that facial dynamics can provide additional cues about the age of a person (Dibeklioglu H, 2012). Fusing facial dynamics with static appearance features may enhance age estimation.

In conclusion, in this study, AD patients were estimated to look younger than their actual age as well as compared to their age-matched healthy controls, in particular by computer-based estimations. The difference is, however small, that these results must be interpreted cautiously and need confirmation. If confirmed in other studies, a mismatch between chronological and facial age may be an indicator of Alzheimer's disease. In order to assess if this is a phenomenon inherent to dementia of any cause, future studies may evaluate patients with other forms of degenerative dementias.

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Statement of Ethics:

All the procedures performed in this study were in accordance with ethical standards laid down in 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. All patients gave their written informed consent before study enrollment.

Conflict of Interest Statement:

The authors declare that they have no conflict of interest to declare.

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