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ARTICLE

Corrected: Correction

Differences in eye movement range based on age and gaze direction

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Abstract

Purpose To determine the range of eye movement in normal human subjects and to investigate the effect of age and gaze direction on eye movement.

Patients and methods A prospective observational study. We enrolled 261 healthy subjects, 5–91 years of age. Photographs were obtained in the cardinal gaze positions and processed using Photoshop. The processed images were analyzed using the Image J program to measure the angle of eye movement. The angle of eye movement was quantified using a modified limbus test. We measured the angle of eye movement in adduction, abduction, elevation, and depression.

Results The ranges of eye movement were 44.9 ± 7.2° in adduction, 44.2 ± 6.8° in adduction, 27.9 ± 7.6° in elevation, and 47.1 ± 8.0° in depression. The ranges of eye movement in the younger group were higher than that in the older group in adduction, abduction, and elevation ($P < 0.001$, $P = 0.013$, and $P < 0.001$, respectively), except in depression ($P = 0.790$). There were significant negative correlations between the angles of horizontal and upward gazes and age ($R = -0.294$ in adduction, $R = -0.355$ in abduction, and $R = -0.506$ in elevation, all $P < 0.001$). However, the angle of downward gaze was not significantly correlated with age ($R = 0.017$, $P = 0.722$).

Conclusions The angle of upward gaze most rapidly decreased with age than the angle of other gaze. Unlike the age-related decline of range in horizontal and upward gazes, only downward gaze was not impaired by increasing age. Differences in eye movement range based on gaze direction and their associated aging mechanisms should be considered when assessing eye movements.

Introduction

Eye movements are an integral and essential part of the human visual system, helping in acquiring, fixating, and tracking visual stimuli [1]. These movements are very important for visual perception because frontal-eyed animals have a small retinal area, the fovea centralis, which covers only about 2° of the visual angle in humans [2]. To get a clear view of the world, the brain must shift the eyes so that the image of the object of focus falls within the sightline of the fovea [3]. Any failure in eye movement can lead to serious visual disabilities.

Despite an abundance of eye movement studies, few studies have evaluated the range of eye movements based on age. Some studies have measured eye movement ranges using light reflex or perimeters [4–8]. These methods not only often result in inaccuracies, but are also difficult to standardize [9, 10]. The scleral search coil method and video-oculography have been used as the gold standard for accurate eye movement measurements in oculomotor research [11–13]. However, even these methods are difficult to apply to measuring eye-movement range because the movement range is too large to obtain reliable and accurate measurements [14, 15].

We previously described a method to quantify the angle of eye movement from photographs [10, 16]. This quantitative and objective method requires photographs of the cardinal gaze positions with computer-assisted analysis and allows measurement of range of eye movement.

The goal of this study was to determine values for the range of eye movements in normal human subjects and the influence of age and gaze direction on these ranges.

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Subjects and methods

Participants and study design

This prospective study included a total of 261 healthy subjects (132 females and 129 males) ranging in age from 5 to 91 years, divided into nine age groups. There were about 30 subjects in each age group, except for the 80–91 years old group, which contained 14 subjects. We conducted a pilot study of 85 subjects of various ages to evaluate the range of eye movement according to age and gaze direction. The sample size for this study was calculated based on the results of the pilot phase. Exclusion criteria included presence of neurologic disease, eye movement dysfunction, orbital disease, strabismus, previous ocular surgery, and long (>26.5 mm) or short axial length (<21.0 mm). Our study protocol was complied with the Declaration of Helsinki and approved by the Institutional Review Board of Hanyang University Guri Hospital. Informed consent was obtained from all participants after the details of the study were explained.

Photographs of the cardinal gaze positions

Detailed methods for obtaining photographs and angle of eye movement measurements were described previously [10, 16]. Photographs were obtained at a distance of 1 m from the subject using a 36.8-megapixel digital single-lens reflex camera (D800; Nikon Inc., Tokyo, Japan) with a ring flash attached to the lens. All selected images had a resolution of 5520 × 3680 pixels. The subjects' heads were firmly fixed on a chin rest with a band wound around the head to prevent head movement, and then the subject was instructed to immobilize his or her head with the eyes in the primary position. Head position was examined to confirm the absence of an observable tilt or the chin-up or chin-down positions; after confirmation, we captured a photograph of the subject in the primary position. Then, the subject visually tracked the fixation target by shifting into maximum upward, downward, left, and right gazes, and we obtained photographs of each of the secondary positions. Verbal encouragement was provided to ensure stability of the head and maximum effort toward the gaze extremes.

Image-processing procedures

After collecting photographs of the cardinal positions, we processed the images using Photoshop 6.0 (Adobe, San Jose, CA, USA). After first opening the digital image of the primary position in Photoshop, we selected the secondary position image and copied it to the clipboard. The contents of the clipboard were then pasted onto the primary position image to create a separate layer. Next, the pasted layer was converted to a semitransparent image to help achieve better overlap with the primary position image. Using the blending tool, we converted a specific layer's light or dark portions to a transparent portion in order to identify the limbus margin. The resulting image was then saved as a TIFF file with no layers. Finally we overlapped and processed the photographs of the secondary gaze positions with the photograph of the primary position.

Measurement of the angle of eye movement

Based on the assumptions that (1) the shape of the eyeball is a perfect sphere, (2) the visual axis is the line that connects the center of the eyeball and the center of the cornea, (3) the rotating center of the eyeball is fixed, and (4) ocular diameter is the same as axial length, we calculated the degree of eyeball rotation. To quantify limbus-to-limbus distance, we loaded the processed image into the Image J program (software version 1.46; National Institutes of Health, Bethesda, MD, USA). We used the menu option Analyze/Measure to measure pixel dimensions, recorded those values, and then we repeated the process for subsequent images. The "Set Scale" function in Image J was used to convert pixel numbers to standard units.

Statistical analyses

We performed all statistical analyses using SPSS for Windows version 17.0 (SPSS, Inc., Chicago, IL, USA). We used the independent *t*-test to compare the mean angle of eye movements between horizontal gaze and vertical gaze, respectively. Two-way analysis of variance (ANOVA) was used to analyze the effect of age and gaze direction on the range of eye movement, and Turkey's post-hoc analysis was used to analyze differences in range of eye movement according to each direction. The subjects were divided into the younger and older age groups by median age, and the difference in the range of eye movement between the two groups in each direction was analyzed using independent *t*-test. Linear regression analyses assessed the relationship between angle of eye movements and age. All angles of eye movement were expressed as mean ± standard deviation (SD). $P < 0.05$ was considered significant.

Results

In total, 261 subjects were included in this study: 129 males and 132 females (age range, 5–91 years; mean, 41.2 years; median, 46 years). We grouped the subjects by age into decades and subject demographics and characteristics are shown in supplemental table with the subjects organized by age group. The mean spherical equivalent for the entire

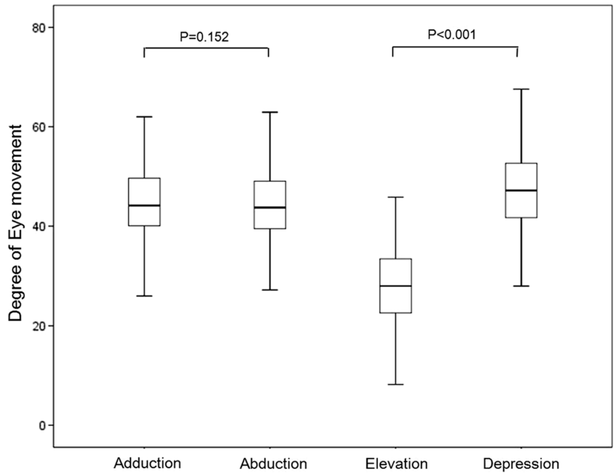

Fig. 1 Box plots showing the distributions of mean angles of eye movement. The mean angles of horizontal gaze were not significantly different (adduction 44.9 ± 7.2° vs. abduction 44.2 ± 6.8°; $P = 0.152$). On the other hand, the mean angle of elevation was significantly smaller than that of depression (elevation 27.9 ± 7.6° vs. depression 47.1 ± 8.0°; $P < 0.001$)

study population was −0.74 ± 1.32 diopters (D) (range, −4.25–3.0 D), and the mean axial length was 23.71 ± 0.82 mm (range, 21.30–25.81 mm).

The mean values for angles of eye movement for each gaze position were 44.9 ± 7.2° in adduction, 44.2 ± 6.8° in abduction, 27.9 ± 7.6° in elevation, and 47.1 ± 8.0° in depression. The mean angles of horizontal gaze were not significantly different ($P = 0.152$, independent *t*-test), whereas the mean angle of elevation was significantly smaller than that of depression ($P < 0.001$, independent *t*-test) (Fig. 1).

The ranges of eye movement in adduction, abduction, elevation, and depression are shown with age in Fig. 2. Two-way ANOVA was applied to the range of eye movement. The result revealed a significant influence of the age, the direction of gaze, and both the factors together on the range of eye movement (all $P < 0.001$). Turkey's post-hoc test indicated that the range of upward gaze was significantly smaller than that of horizontal and downward gaze ($P < 0.001$). There was no significant difference in range of eye movement between abduction, adduction, and depression (all $P > 0.05$).

In an analysis between two groups divided by median age, the ranges of eye movement in the younger group were higher than that in the older group in adduction, abduction, and elevation ($P < 0.001$ in adduction, $P = 0.013$ in abduction, and $P < 0.001$ in elevation). In depression only, the range of eye movement was not significantly different between the two groups ($P = 0.790$; Fig. 3)

There were significant negative correlations between the angles of horizontal gaze and age ($R = -0.294$ in adduction, $R = -0.355$ in abduction; all $P < 0.001$; Fig. 4a, b). The angle of upward gaze more rapidly decreased with age than the angle of horizontal gaze ($R = -0.506$, $P < 0.001$; Fig. 4c). In contrast to the horizontal and upward gazes, there was no correlation between angle of downward gaze and age ($R = 0.017$; $P = 0.722$; Fig. 4d).

Discussion

We investigated the range of eye movements in normal subjects, applying a photographic approach. We found that the ranges for angles of horizontal gazes were symmetric among all ages, whereas the vertical gaze ranges was asymmetric, with the upward gaze being significantly smaller than the downward gaze. Analyzing the age-dependent changes in eye movements for each direction separately, the ranges for the horizontal gazes decreased with advancing age, and the ranges for upward gaze decreased more rapidly than those for the horizontal gaze. On the other hand, there was no association between the range of downward gaze and age.

Evaluation of eye movement ranges is important for diagnosing neurologic disorders. This evaluation can provide information about the localization of neurologic dysfunction, allowing ophthalmologists to identify abnormalities in individual muscles or in particular cranial nerves [17]. Various methods have been used for quantitatively measuring the range of eye movement. A few studies have measured range of eye movement using lateral version light reflex [5, 18]. Although useful in a clinical setting, this method can cause significant parallax errors and is affected by standardization errors in measuring light reflex [10]. Other studies have shown that a perimeter can be used to measure range of eye movement. [4, 6–8] However, the perimeter method depends on the availability and subjective experience of a trained technician; hence, it is vulnerable to potential inaccuracies [9].

Scleral search coils and video-oculography (VOG) are generally accepted as reliable methods for measuring eye movement [11]. Although allowing precise measurement of eye movement, these methods may reduce the accuracy of a large range of eye movement measurements. Scleral search coils can lead to underestimates due to interference from its fine wires with the eyelids [5, 15], and in the VOG system, position measurements can be influenced by a distorted and unfocused image [19]. Thus, these eye-tracking methods can be subject to several types of errors in measuring the range of eye movement. Moreover, these methods are neither simple nor practical to apply to children.

Herein, we describe our efforts to apply a photographic method for measuring the angles of eye movements, which is quantitative, objective, and uses computer-assisted analysis. In a prior study of subjects ranging 20–40 years of

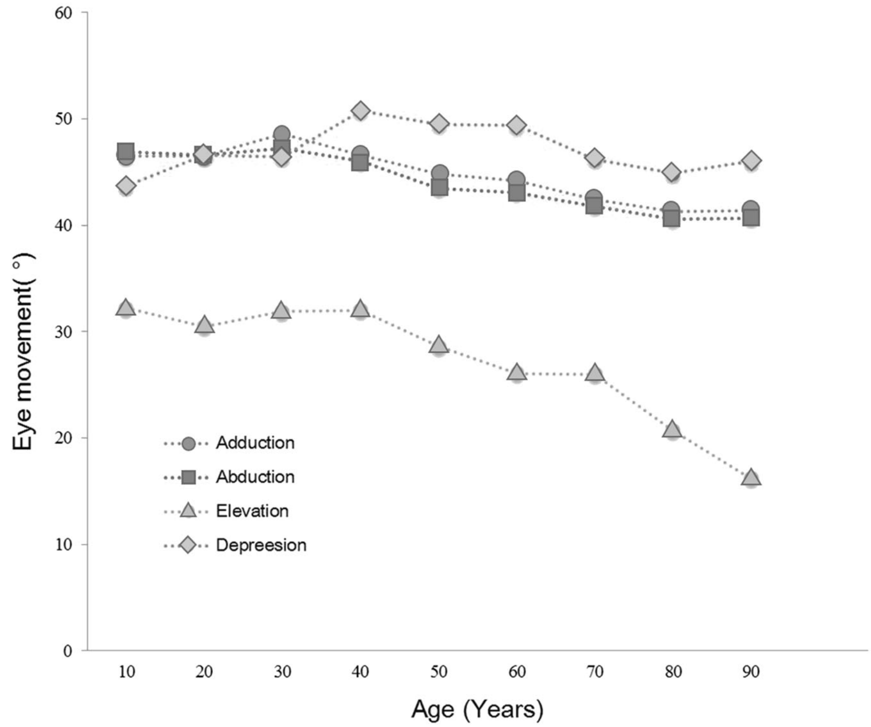

Fig. 2 Graph showing the age-dependent changes in eye movements for each direction. The ranges for the horizontal gazes (adduction and abduction) decreased with advancing age, and the ranges for upward gaze decreased more rapidly than those for the horizontal gaze. On the other hand, there was no association between the range of downward gaze and age

Fig. 3 Graph showing the range of eye movement in each direction in the younger and older groups. In the older group, significant reduction of the range of eye movement was observed in adduction, abduction, and elevation ($P < 0.001$ in adduction, $P = 0.013$ in abduction and $P < 0.001$ in elevation). However, there was no significant difference in the range of eye movement in depression between the two groups ($P = 0.790$)

age, we demonstrated that our photographic method can objectively measure the angles of eye movements and can be easily applied to clinical settings because it is reproducible, easy to use, affordable, and noninvasive [10]. This technique not only allows measurement of large angles of eye movements, but is also comfortable to apply to children. Thus, it can be used for measuring the range of eye movement across all age categories, including children and the elderly.

In this study, we found that the mean angles of the horizontal gazes were symmetric, and this symmetry was consistent across all age groups, when we divided subjects into

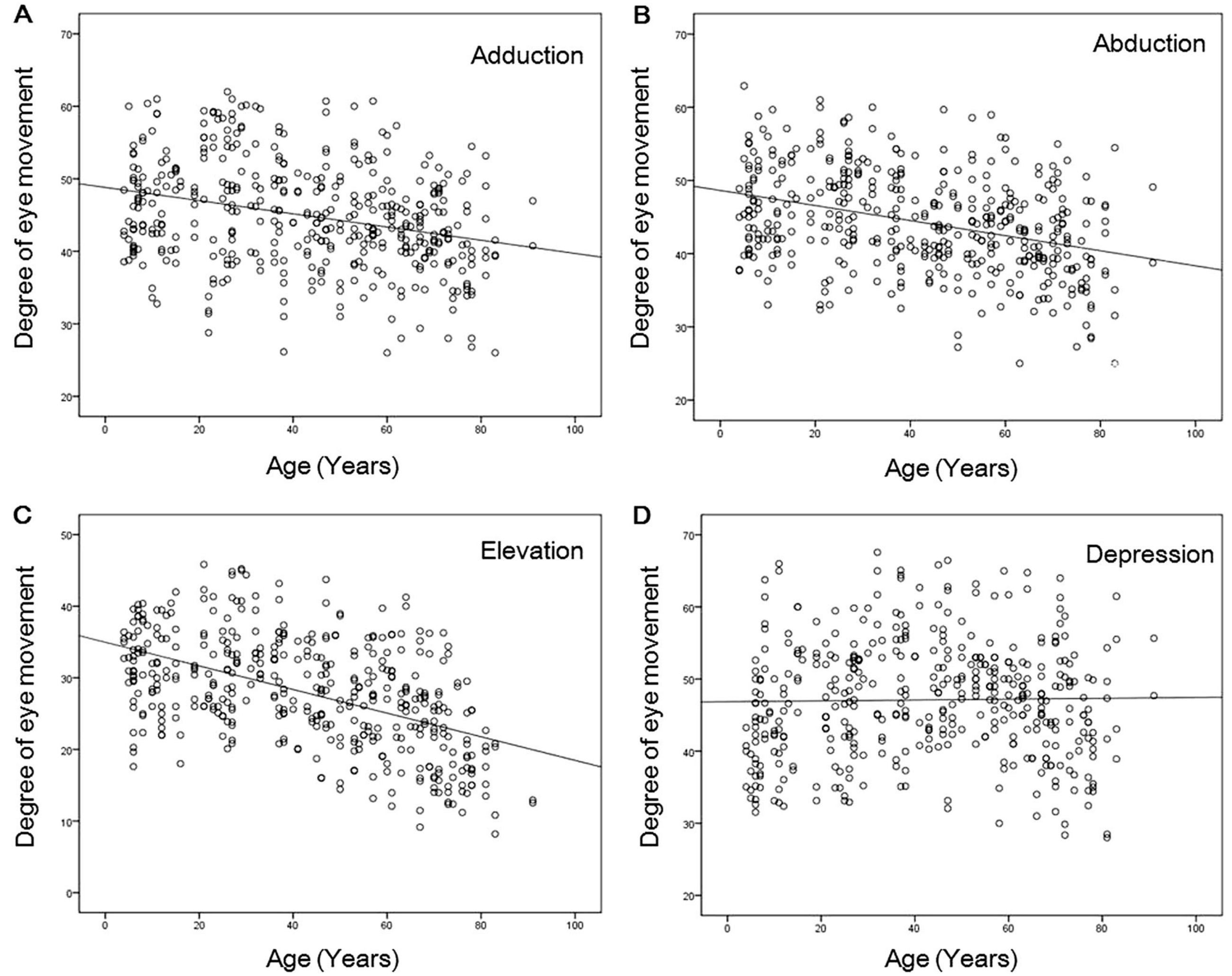

Fig. 4 Scatter plots showing distribution of the angle of eye movement with age. A,B,C shows significant negative correlations between the angles of eye movement and age ($R = -0.294$ in adduction, $R = -0.355$ in abduction, and $R = -0.506$ in elevation; all $P < 0.001$). In D, there was no correlation between angle of depression and age in contrast to the other eye movements ($R = 0.017$; $P = 0.722$)

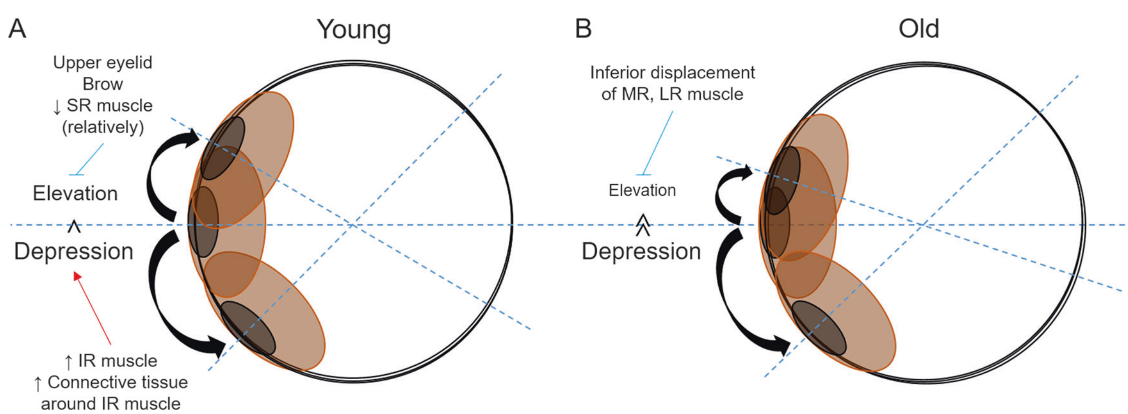

Fig. 5 Schematic illustration showing the discrepancy of vertical gaze. In young individuals, the downward gaze is enlarged by the developed inferior rectus muscle and surrounding tissue, but upward gaze is limited by eyelid and brow (**a**)In the elderly, the limitation of upward gaze is augmented by the inferior displacement of the horizontal extraocular muscles. However, downward gaze is not much different from young individual (**b**)

decadal age groups. Symmetric horizontal gazes across all age groups suggest that the brainstem mechanisms for horizontal conjugate eye movements are not affected by age-related neurodegeneration. The brainstem pathway that generates conjugate horizontal eye movements is composed of a number of nuclei and nerves in the brainstem [20, 21]. Therefore, maintaining symmetry of the horizontal gaze with aging may indicate selective preservation of this brainstem pathway despite neurodegeneration. The importance of this finding seems to lie in a proper recognition of the conjugacy of horizontal eye movement for all age groups.

In contrast to symmetric horizontal gazes, the mean range for upward gazes was significantly smaller than that of the downward gazes, and this difference was found among all age groups. Although this asymmetry in vertical gazes is similar to those previously reported using light reflex, video cameras, and various perimeter techniques [4–6, 8, 10, 22], our study is the first to determine the asymmetry of vertical gazes in children. The limitation of the upward gaze across all ages could be due to a restriction of an antagonist or decreased action of an agonist. In a cadaver study, the connective tissue system around the inferior rectus muscles was among the most developed, and the inferior rectus muscles had the largest number of septal connections to the adjacent periorbital area [23]. Moreover, the maximal cross-sectional area of the inferior rectus muscle was found to be greater than that of the superior rectus muscle [24]. Finally, the upper eyelid and brow can give more restrictions on upward gaze because they act in the direction of pushing the eyeball by gravity, unlike the lower eyelid which supports the eyeball relatively (Fig. 5a). We assumed that these inherent anatomical factors, rather than age-related changes, are responsible for limitations in the upward gaze across all ages.

In our study, the range of upward gaze was most impaired with age. Although we found weak associations with age, the horizontal gazes also decreased significantly with advancing age. These findings are consistent with results of previous studies, which also found an effect of age on the range of eye movements [4, 5, 12, 22]. However, in contrast to those previous studies, we did not find a significant effect of age on the downward gaze. Unlike age-related decreases in other gazes, only the downward gaze was maintained by a steady range of eye movement until the 10th decade of life. Although no exact value of downward gaze angle has been estimated, Chamberlain reported that downward rotations did not seem to change with age and continued to approach the limit permitted by an individual's eyelid and cheek [4]. These findings suggest that the mechanism for age-related changes in eye movement is different for different directions of eye movement.

Although the aging mechanisms of eye movements are unknown, degenerative neuronal loss of motor neurons is a possible mechanism of age-related changes. Commands for horizontal movements are produced by premotor neurons in the pons and medulla [25]. For vertical saccades, the pulse is generated in the paramedian pontine reticular formation [26], and the step of tonic innervation is probably generated in the vestibular nuclei and the interstitial nucleus of Cajal [27]. The amplitude of eye movement is determined by the discharge rate of the population of motor neurons; thus, the selective neuronal loss associated with aging might cause this difference in the decline ratio between the eye movement directions.

It can be argued that disuse of elevators might lead to diminution of the upward gaze in the elderly, whereas an enhanced use of globe depression might not lead to impairment in the range of the downward gaze [4, 10]. In a magnetic resonance imaging study, Clark and Demer proposed inferior displacement of the horizontal extraocular muscles in the elderly as an important mechanism [28]. They suggested that inferior displacement converts the force of the EOMs to the downward gaze and contributes to the impairment of the upward gaze in older people (Fig. 5b). Further studies are necessary to understand whether the aging mechanisms of eye movements are related to central or peripheral factors and whether these mechanisms can be classified as neurodegenerations or consequences of disuse.

Our study demonstrates that the range of the upward gaze is significantly smaller than that of the downward gaze, and that age-dependent changes in eye movements differ according to eye-movement direction. These results offer the clinically valuable insight that the vertical gaze is asymmetric, irrespective of senescence, and provide evidence that the aging mechanisms of eye movements are different depending on gaze direction. Furthermore, our study emphasizes the critical importance of considering the expected eye movement changes associated with age during any motility evaluation. Finally, our baseline data provide diagnostic norms for clinical assessment of eye movement disorders during neurologic examination.

Summary

What was known before

- Some studies have measured eye movement ranges, however, these methods were inaccurate and difficult to standardization.

What this study adds

- We apply a photographic method for measuring the angles of eye movements, which is quantitative, objective, and uses computer-assisted analysis.

- Our study demonstrates that age-dependent changes in eye movements differ according to eye-movement direction.
- The ranges for the horizontal gazes decreased with advancing age, and the ranges for upward gaze decreased more rapidly than those for the horizontal gaze.
- On the other hand, there was no association between the range of downward gaze and age.

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Compliance with ethical standards

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

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