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Age-Related Changes in Saccadic Eye Movements in Healthy Subjects and Patients with Parkinson's Disease

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Abstract—The age-related changes in saccadic eye movements (the latency, the duration of single saccades and the percentage of multistep saccades) were compared in healthy subjects and patients with Parkinson's disease. Healthy volunteers without neurological symptoms were divided into six age groups: (17–20, 21–30, 31–40, 41–50, 51–60, and 61–75 years of age); and parkinsonian patients, into three groups (41–50, 51–60, and 61–75 years of age). According to the data obtained, the saccade characteristics depend on the age in both the subjects without neurological symptoms and parkinsonian patients. In healthy volunteers, the percentage of multistep saccades and the mean saccade latency increase significantly after the age of 60 years. These parameters in patients with Parkinson's disease significantly exceed the values in healthy subjects from the age-matched groups. The "disease" factor has a greater influence on the saccade latency and the percentage of multistep saccades than the "age" factor. The duration of single saccades depends on age to a lesser degree and does not change in patients with Parkinson's disease. The peculiarities of the development of neurodegenerative processes in cases of normal aging and in idiopathic parkinsonism are discussed.

Keywords: saccadic eye movements, aging, Parkinson's disease.

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Aging is characterized by changes in the physiological processes, tissue biochemical composition, by a decrease in the ability of the body to adapt to the constantly changing environmental conditions, and increased susceptibility to diseases [1]. Aging involves all the systems of organs, including the nervous system. With age, the number of neurons decreases, especially in the basal ganglia, the cerebellum, the locus coeruleus, the nucleus basalis of Meynert, and the spinal cord [2], as does the number of dendrites and dendritic projections. In certain regions of the brain, the synapse density decreases, which is accompanied by an increase in the size of the remaining synapses; the neurotransmitter concentration and metabolism changes significantly [2–5].

Over the past 160 years, the life expectancy in the economically developed countries has been steadily increasing at an average rate of three months per year [2]. Along with the increase in the percentage of elderly individuals in the human population, the morbidity of neurodegenerative disorders is on the rise as well. Neuronal degeneration, with its relatively moderate manifestation in physiological aging, considerably increases in the cases of Alzheimer's disease, Parkinson's disease, and progressive supranuclear palsy. In this connection, an important problem is to differentiate between the processes of physiological aging and the changes linked to the development of various diseases.

One of the possible markers reflecting age-related pathological changes in the nervous system is the saccadic eye movements characteristics [6–10]. Saccades are rapid eye movements changing the point of the gaze fixation. A saccade preparation and performance are determined by coordinated operation of many brain structures, including the brainstem structures, subcortical nuclei, and different areas of the cerebral cortex.

The saccadic eye movements characteristics are known to depend on a number of factors, such as age and the state of health, and to change in certain diseases, e.g., Parkinson's disease, Alzheimer's disease, progressive supranuclear palsy, schizophrenia, etc. [6, 11–13]. Thus, analysis of the saccade parameters could be effective for comparing the rates of neurodegenerative processes and the process of physiological aging.

The aim of this work was to compare the age-related changes in the saccadic eye movements characteristics in subjects without neurological symptoms and in patients with Parkinson's disease.

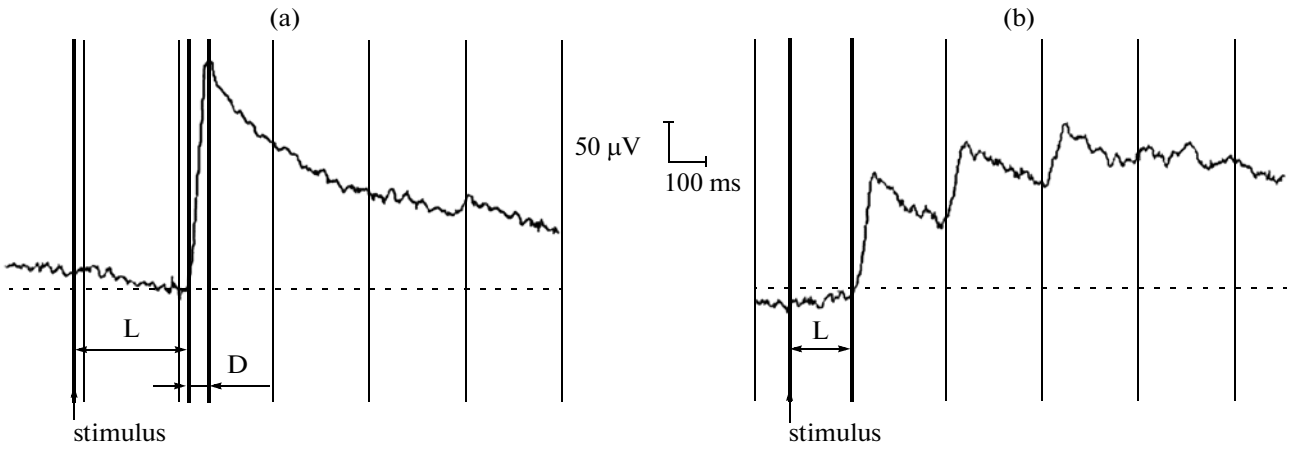

Fig. 1. Electrooculographic record of saccadic eye movements: (a) single saccade; (b) multistep saccade. L, saccade latency; D, saccade duration.

MATERIALS AND METHODS

Seventy subjects took part in the study: 46 subjects without neurological symptoms (the control group) and 24 patients with idiopathic parkinsonism (the PD group). The control group included 23 men and 23 women in age from 17 to 73 years. PD group included 10 men and 14 women in age from 43 to 75. The patients were diagnosed at the Department of Neurology, Moscow Regional Scientific Research Clinical Institute n.a. M.F. Vladimirsky. All the patients were divided to stage I–II according to the Hoehn–Yahr scale [14]. Previously, none of them received specific therapy. The cognitive state of all the patients were within the normal limits of MMSE test (28–30 points).

The study was conducted in compliance with the principles of the Helsinki Declaration of Human Rights; the protocol of the experiment was approved by the Ethics Committee of the Vladimirskii Regional Research Clinical Institute, Moscow.

During the study, the subjects were seated in a dark, sound-proof screened chamber in an armchair with a headrest preventing head movements. At a distance of 57 cm from the eyes of the subject, a panel with five red light-emitting diodes used for visual stimulation was installed. One of the light-emitting diodes arranged at the center of the panel was used as the central fixation point. The remaining four light-emitting diodes arranged on the right, on the left, below and above at a distance of 6.7° from the central one were used as peripheral stimuli. The duration of exposure of the central fixation stimulus varied between 700 and 1000 ms; and of the peripheral stimuli, between 1000 and 1300 ms. Two visual stimulation paradigms were used. The conditions in each of them enable to involve different brain structures connected with the preparation and performance of saccadic eye movements. In paradigm I (No gap), the peripheral stimulus was presented immediately after switching off the central fixation stimulus; in paradigm II (Gap), the peripheral stimulus was presented 200 ms after switching off the central stimulus. The subjects were instructed to fix the gaze on the central stimulus and, when one of the peripheral stimuli appeared, to shift the gaze quickly in its direction.

A complex experimental unit controlled by a CONAN-m integrated system was used for automated stimulus presentation and recording the electrophysiological values. The electrooculogram was recorded using a Nihon Kohden 17-channel polygraph (Japan).

Saccadic eye movements were recorded using the monocular electrooculographic method. The bandpass during the electrooculogram recording was 0.1–60 Hz. The analog-to-digital transform was carried out at 512 Hz.

The saccade latencies, the duration of single saccades, and the percentage of multistep saccades were analyzed. The saccade's latency was determined as the time interval between switching on the peripheral stimulus and the onset of the saccade; duration, as the time interval between the onset of the saccade and its completion (Fig. 1a). Multistep saccades were determined as a fragmented gaze shift to the peripheral stimulus during which the subjects performed several, instead of one, saccades of a lower amplitude (Fig. 1b).

In order to assess the age-related changes in the saccadic eye movements characteristics, the control group was divided into six age groups: 17–20 years, 21–30 years, 31–40 years, 41–50 years, 51–60 years, and 61–75 years; the PD group into three age groups: 41–50 years, 51–60 years, and 61–75 years. In each age group, the average latency and saccade duration values, as well as the percentage of multistep saccades, were calculated. The saccade's characteristics were compared in different age groups, as well as in groups of healthy volunteers and those with Parkinson's disease.

Statistical data processing was carried out with the STATISTICA software. The significance of the differ-

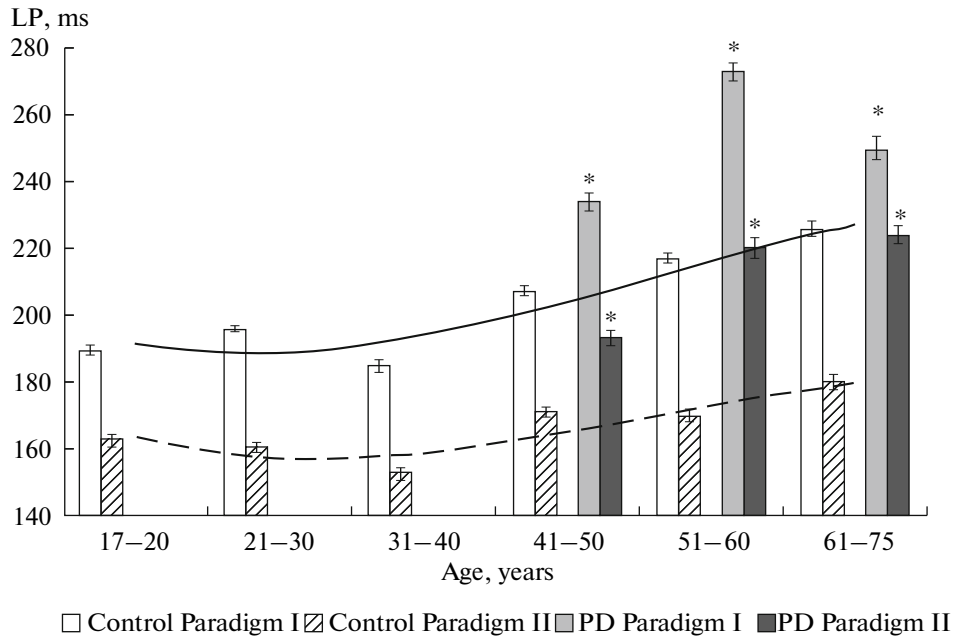

Fig. 2. Mean ±(SE) latency of saccadic eye movements in subjects without neurological symptoms (the control group) and in patients with Parkinson's disease (the PD group) in the visual stimulation paradigms I and II. The number of subjects in the control group is 46; in the PD group, 24. The solid line of the polynomial trend reflects the tendency for latency to change with age in the subjects without neurological symptoms in paradigm I; the dashed line, in paradigm II. * Significant difference from the age-matched control group (Mann–Whitney test, $p < 0.001$).

ences between the mean latencys and saccade durations in the groups was determined using the nonparametric Mann–Whitney test (U test). The significance of differences between the percentages of multistep saccades was determined using Z-test for the differences between two proportions. When the saccade parameters in different paradigms of visual stimulation were compared, nonparametric the Wilcoxon signed-rank test was used. Nonparametric ANOVA/MANOVA analyses were used to determine the degree of changes in the values analyzed, depending on the age, the visual stimulation conditions, and the "disease" factor.

RESULTS

The histogram in Fig. 2 demonstrates the age-dependent change in the saccade latency in subjects without neurological symptoms and in PD patients. In paradigm I, mean saccadic latency in healthy subjects in age from 17 to 30 are approximately at the same level and decline insignificantly in subjects aged 31–40 years (185 ± 2 (SE) ms). After 40 years, the average latency values gradually increase ($F = 88.9$, $p < 0.001$), attaining the maximal values in the group aged 61–75 years (226 ± 2 (SE) ms).

In paradigm II, the latency values in all the age groups are 27–47 ms significantly lower than in paradigm I ($Z = 2.2$, $p < 0.05$ according to the Wilcoxon signed-rank test; $F = 3234.0$, $p < 0.001$). The age dependence of latency is retained, but its degree is lesser ($F = 32.0$, $p < 0.001$). As in paradigm I, the minimal mean saccadic latency in paradigm II was obtained in the group of subjects in age from 31 to 40 years and was 153 ± 2 ms; the maximal value was observed in the 61- to 75-year-old group (180 ± 2 ms).

In PD patients, the minimal latency values in both paradigms of visual stimulation were observed in the group aged 41–50 years: 234 ± 3 ms for paradigm I and 193 ± 3 ms for paradigm II. It should be noted that these values significantly ($p < 0.001$, the Mann–Whitney test) exceed the reference values not only in the age-matched group (from 41 to 50 years) but even in the oldest group of subjects without neurological symptoms (61–75 years; $p < 0.05$, the Mann–Whitney test). With age, mean latencies in patients increase; however, significant differences between the age-matched PD and control groups are still retained.

MANOVA revealed a significant "age" and "disease" factors effect on saccadic latency. The "disease" factor has a greater influence ($F = 434.7$, $p < 0.001$ in paradigm I and $F = 430.2$, $p < 0.001$ in paradigm II) compared to the "age" factor ($F = 55.3$, $p < 0.001$ in paradigm I and $F = 26.9$, $p < 0.001$ in paradigm II).

As in the subjects without neurological symptoms, latency in the group of PD patients was shown to depend on the paradigm of visual stimulation ($F = 386.7$, $p < 0.001$). Mean group latencies in patients from all the age groups in paradigm II were 26–53 ms lower than in paradigm I ($Z = 17.6$, $p < 0.001$, the Wilcoxon signed-rank test).

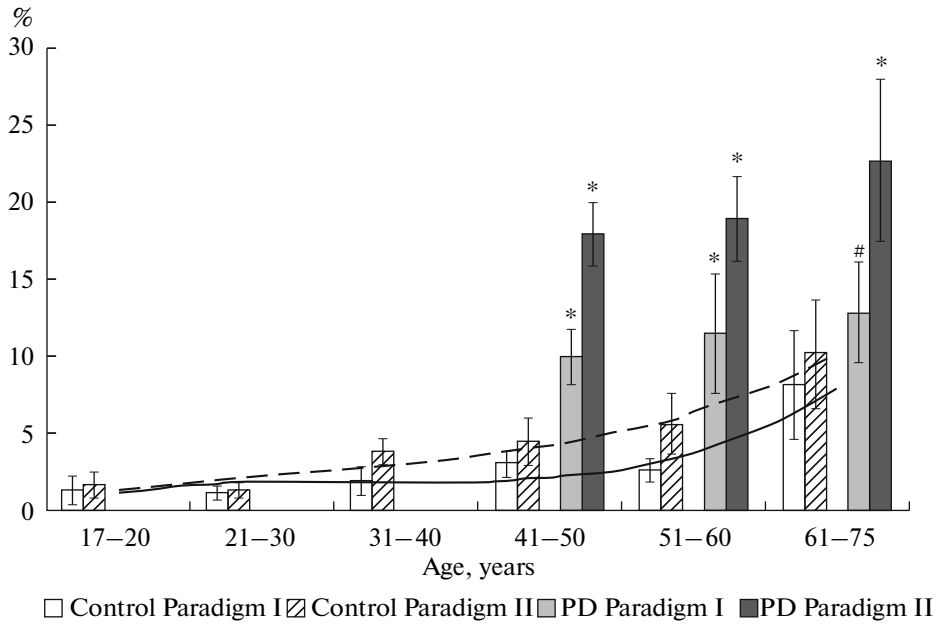

Fig. 3. Mean ± (SE) percentage of multistep saccades (%) in subjects without neurological symptoms (the control group) and in patients with Parkinson's disease (the PD group) in the visual stimulation paradigms I and II. The solid line of the polynomial trend reflects the tendency for the percentage of multistep saccades to change with age in subjects without neurological symptoms in paradigm I; the dashed line, in paradigm II. #, * Significant difference from the aged-matched control group (the z test of comparing proportions, $p < 0.05$ and $p < 0.001$, respectively). See Fig. 2 for the other designations.

Figure 3 shows the age-related changes in the percentage of multistep saccades in the control and PD group subjects. In subjects without neurological symptoms, mean percentage of multistep saccades is correlated with age ($r = 0.84$, $p < 0.05$ in paradigm I and $r = 0.94$, $p < 0.05$ in paradigm II). In paradigm I, mean percentage of multistep saccades in subjects aged 17–60 years differ little; they are 1–3%. At the same time, the average percentage of multistep saccades is sharply increased and attains 8.1 ± 3.6% in the oldest group of subjects. When we compared the percentage of multistep saccades in this group with the percentage of multistep saccades in younger groups (17–20 and 21–30 years), significant differences ($Z = 2.3$, $p < 0.05$ and $Z = 2.4$, $p < 0.05$, respectively) were obtained.

In paradigm II, mean percentage of multistep saccades in the control group increase, beginning with 31 years ($F = 3.0$, $p < 0.05$), and attain the maximal values in the oldest group of subjects (10.2 ± 3.4%). As in paradigm I, the differences between the percentages of multistep saccades in the group aged 61–75 years and in younger groups (17–20 and 21–30 years) are significant ($Z = 2.6$, $p < 0.01$).

In PD patients, we also showed the age effect on the percentage of multistep saccades ($F = 30.8$, $p < 0.001$ in paradigm I and $F = 76.2$, $p < 0.001$ in paradigm II). The minimal percentage of multistep saccades was revealed in patients aged 41–50 years; the maximal percentage, in those aged 61–75 years. In contrast to the control group subjects, the percentage of multistep saccades significantly depends on the paradigm of visual stimulation: the percentage of multistep saccades in paradigm II is significantly greater than in paradigm I ($Z = 3.7$, $p < 0.01$, Wilcoxon signed-rank test).

In both paradigms of visual stimulation, the mean percentages of multistep saccades in PD patients are significantly higher than in patients without neurological symptoms ($p < 0.001$, z-test for the differences between two proportions). These differences are the most pronounced in paradigm II, in which the percentage of multistep saccades in PD exceeds the reference normal values by a factor of 2–4.

According to the results of MANOVA, the "disease" factor, in contrast to the "age" factor, exerts a marked influence ($F = 9.6$, $p < 0.01$ in paradigm I and $F = 26.7$, $p < 0.001$ in paradigm II) on the percentage of multistep saccades in both visual stimulation paradigms.

The histogram in Fig. 4 shows the change in the duration of single saccades with age in the control and PD groups. As distinct from the latency and percentage of multistep saccades, the duration of a single saccade does not change considerably with age. In subjects without neurological symptoms, the average duration values increase significantly with age ($F = 24.8$, $p < 0.001$ in paradigm I and $F = 66.0$, $p < 0.001$ in paradigm II), but these differences are no greater than 5 ms. The minimal duration values were obtained in the groups of subjects aged 17–20 years and 31–40 years (52 ± 1 ms); the maximal ones, in the group of

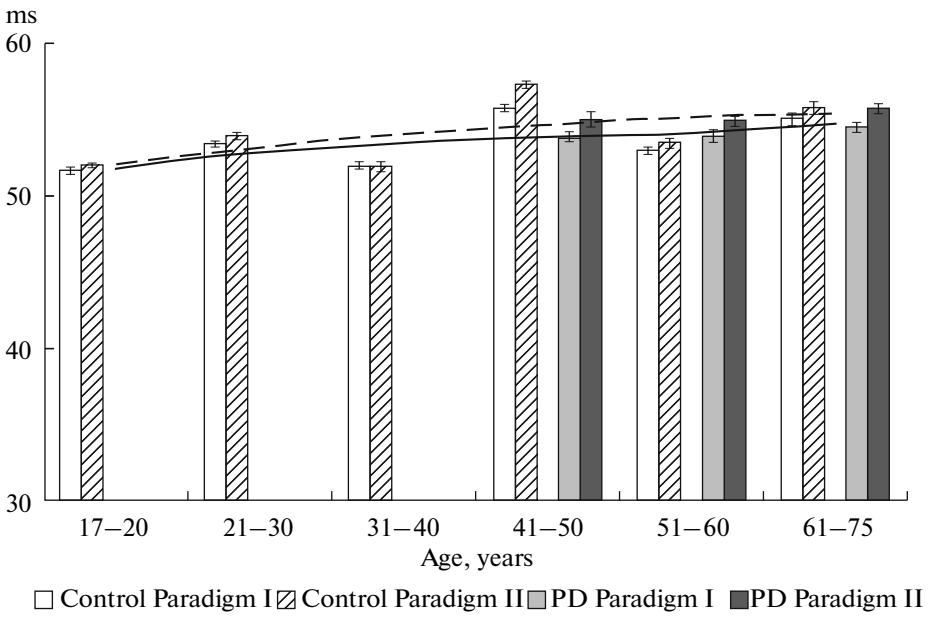

Fig. 4. Mean ± (SE) duration (ms) of single saccades in subjects without neurological symptoms (the control group) and in patients with Parkinson's disease (the PD group) in the visual stimulation paradigms I and II. The solid line of the polynomial trend reflects the tendency for the single saccade duration values to change with age in subjects without neurological symptoms in paradigm I; the dashed line, in paradigm II. See Fig. 2 for the other designations.

subjects in age from 41 to 50 years (56 ± 1 ms in paradigm I and 57 ± 1 ms in paradigm II).

In PD patients, mean durations of single saccades are within the normal range (54 ± 1 ms in paradigm I and 55 ± 1 ms in paradigm II). No age-related changes in duration were revealed in PD patients. Mean durations in the two paradigms of visual stimulation did not differ significantly in either the patients or healthy subjects.

DISCUSSION

All the saccadic eye movements characteristics studied in the subjects without neurological symptoms are age-dependent. The age-related changes are more pronounced in saccade latency and percentage of multistep saccades; to a lesser degree in duration of a single saccade. Supposedly, such changes in the saccadic eye movements characteristics are determined by gradual neuronal degeneration, which involves different levels of the saccadic system and lasts during the entire life span [6].

Neuroanatomical and neuroimaging studies [3, 5] showed the growth of the degenerative changes in the cerebral cortex with aging. Such changes involve, in particular, the frontal and parietal areas [4] known to be involved in saccadic eye movements programming. Evidently, with age, saccades preparation time on cortical level increases, which results in latency prolongation (Fig. 2). According to the data obtained, a progressive increase in the saccadic latency in healthy subjects begins after 40 years, which agrees with the data reported by a number of researchers [6, 15, 16].

The suggestion that neurodegenerative processes in the cortex and the age-related changes in saccade latency are interrelated is confirmed by the results of the comparative analysis of the age-related dynamics of latency in different paradigms of visual stimulation. In paradigm I, the age dependence is clearly seen, because the visual stimulation conditions in this paradigm require a greater involvement of the cortical structures in the process of saccade preparation than in paradigm II. In paradigm II there is no visual stimuli in the subject's visual field during an interval in 200 ms between central fixation point switching off and appearing of peripheral stimulus. A number of the authors [17, 18] suppose that, during the interstimulus interval, the saccadic system gets rid of central fixation, which aids in a quicker preparation of saccadic movements with the involvement of the subcortical structures and results in considerable shortening of saccade latency [6, 16, 19, 20]. The differences between the mean saccadic latencies in paradigm I and paradigm II are observed in all the age groups and increase with age from 27 ms in the youngest group of the subjects (17–20 years) to 46 ms in the oldest group (61–75 years). This fact also supports the suggestion that the saccade latency increases due to the gradual degeneration of the cortical neurons.

However, the increase of the saccadic latency with age might be determined not only by degenerative changes in the cortex but also by a decrease in the number of neurons in the basal ganglia, including the

substantia nigra. This is shown by a considerable increase of saccade latency in PD (Fig. 2). The disease is caused by a progressive degeneration of dopamine neurons in substantia nigra. The dopamine deficiency in the striatum leads to the dysfunction of the basal ganglia and affects to the cortical oculomotor fields through thalamocortical projections [12, 21]. As a result, the mechanisms of the preparation and initiation of saccades require more time, which leads to increasing of saccade latency.

Functional disorders of the basal ganglia in PD also lead to an increase in the percentage of multistep saccades (Fig. 1, *B*), which exceeds the normative values several times (Fig. 3). Multistep saccades in patients occur much more frequently under the paradigm II conditions, when the influence of the cortex on the process of saccade preparation and performance is not so pronounced and the oculomotor reactions depend more on the activity of the basal ganglia [13].

In healthy subjects, multistep saccades occur in all the age groups (Fig. 3), but they are few (less than 5% in subjects up to 50 years old). Although the percentage of multistep saccades in the oldest group significantly increases, it does not attain values common for PD patients. The decrease in number of neurons in the basal ganglia in healthy subjects seems to occur much more slowly, as distinct from progressive neurodegeneration in PD; therefore, the increase in the percentage of multistep saccades is observed in older individuals only. Histological studies [22] revealed that, in the process of physiological aging, the number of the pigmented substantia nigra neurons decreased, but cell hypertrophy was observed. A similar phenomenon may be considered to be a compensatory mechanism of sustaining the motor functions during the aging process, which is disrupted in PD.

As distinct from latency and the percentage of multistep saccades, the mean duration of a single saccade changes little with age and is not differentiated in parkinsonian patients and subjects without neurological symptoms (Fig. 4). The duration of saccadic eye movements is known [23] to be encoded by a brainstem saccade generator, which combines the centers controlling horizontal and vertical eye movements, and is located in the paramedian reticular formation of the pons and in the reticular formation of the midbrain. A slight increase in the duration in the process of physiological aging shows that the degenerative changes in the brainstem oculomotor centers are less marked compared to the cortex and the basal ganglia, and its functional properties change little with age [6].

Turning back to PD, it should be noted that the increase in latency and the percentage of multistep saccades results from the combination of two processes: pathologic neurodegenerative and the process of physiological aging. It is debatable which of the processes is more significant in the development of PD. As shown by the results of the studies of the olfactory function [24], the neurodegenerative process in PD occurs more quickly than in normal aging. Other authors assign a more significant role to aging in the pathogenesis of PD [22, 25]. It was shown that the older the patients, the less sensitive to levodopa they are, and the stiffer their movements and greater their cognitive deviations [22]. According to the PD–aging relationship model proposed by Levy [25], the patient's age rather than the duration of the disease is more important in the development of the clinical presentation of PD.

Our results allows a suggestion that the pathological neurodegenerative process plays the primary role in the development of PD. This is shown by a more marked influence of the "disease" factor on latency and the percentage of multistep saccades, compared to the "age" factor. The oculomotor disorders in PD are so pronounced that, even in the youngest patients aged 41–50 years, mean latencies and the percentage of multistep saccades (in paradigm II) significantly exceed the reference normal values not only in the age-matched group, but also in the oldest group of healthy subjects (aged 61–75 years). With age, mean latencies and the number of multistep saccades in patients increase; however, the difference between the reference normal values and the values in parkinsonian patients remain approximately the same in each age group (Figs. 2, 3). This suggests that, irrespective of the age of the patients, the rate of development of a pathologic neurodegenerative process in PD remains similar. However, in older patients, pathological processes add to more pronounced natural degenerative processes determined by physiological aging, which eventually results in the development of more severe disorders.

Summing up the results obtained, we can conclude that, in the process of physiological aging, gradual neuronal degeneration, more pronounced in the cortex and basal ganglia and involving the brainstem oculomotor centers to a lesser degree, occurs in different parts of the oculomotor system. In PD, the neurodegenerative process in the midbrain substantia nigra proceeds more progressively and influences the functioning of the basal ganglia and the cortex.

CONCLUSIONS

(1) The mean saccade latencies and the percentage of multistep saccades increase with age both in subjects without neurological symptoms and in patients with Parkinson's disease.

(2) In patients with Parkinson's disease, the latency of saccadic eye movements and the percentage of multistep saccades are significantly greater than in age-matched control subjects without neurological symptoms.

(3) The mean saccade duration is less age-dependent than the latency and the percentage of multistep saccades. Mean saccade durations are not different in

parkinsonian patients and subjects without neurological symptoms.

(4) The influence of two factors on the saccadic eye movements has been revealed in patients with Parkinson's disease: the "age" factor and the "disease" factor. The "disease" factor exerts a greater influence compared to the "age" factor.

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