

# Clinical significance and pathogenesis of visual impairment in parkinson's disease

## Abstract

Among non-motor symptoms in patients with Parkinson's disease (PD) have a number of specific visual disturbances. This review describes the main visual problems associated with PD, referring to their basic anatomical aspects and pathophysiological mechanisms. A wide range of visual disorders includes changes in color vision and contrast sensitivity, change in the electrophysiological properties of the retina due to the insufficiency of the retinal dopaminergic system, features of visual field defects, visuospatial and visuoperceptual impairments. The use of modern electrophysiological, neurophysiological, psychophysiological and other research methods makes it possible to comprehensively assess the state of all parts of the visual analyzer from the retina to the higher cortical centers in patients with PD. The article discusses controversial questions about the relationship between changes in color vision, a decrease in the level of contrast sensitivity and severity of motor disorders in Parkinson's disease. Finally, we discuss the advantages of using threshold and blue-yellow perimetry as more sensitive methods in detecting visual field defects in patients with PD.

**Keywords:** parkinson's disease, visual impairment, electroretinography, contrast sensitivity, retinohypothalamic functional system, visual hallucinosis

Volume 7 Issue 7 - 2017

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**Received:** October 30, 2017 | **Published:** November 29, 2017

## Introduction

Visual impairments are not the core symptoms in PD, but gain in significance when accompanied by exacerbation of the primary symptoms, since visual impairments reduce compensation and adaptation the patient to motor disturbances. Most frequent complaints include fuzzy vision, photophobia, asthenopia (with eye fatigue, often accompanied by headache and blurred vision). Patients with PD often find it difficult to read and to orientate themselves in the dusk or a scarcely lit room.<sup>1,2</sup> However, when patients seek for ophthalmological help, routine examinations often do not reveal any eye disorder, while neurologists do not pay needful attention to such complaints, because they are not familiar enough with Parkinsonian visual disturbances.

Visual impairments in PD patients were first studied in late 1980s,<sup>3</sup> and the role of dopamine in the functional activity of amacrine cells in the retina and its reduction in PD patients was demonstrated in 1990.<sup>4</sup> Later studies showed that defects in the visual system contribute greatly to motor disorders in PD, such as freezing, walking disturbance, postural disorder and falls, and can also, among other factors, induce visual hallucination.<sup>5,6</sup>

It is currently known that human vision is carried out by complex system including the eye and a numerous structures of the CNS. Over the evolutionary process, the many cortical, subcortical and brain stem structures have formed and embraced the function of binding together the sensory and motor components of the vision. The sensory component includes direct perception of visual information in all aspects. The motor component is associated with various eye movements and pupillary reaction, which optimize visual perception in any circumstances of daily human activity. Moreover, there are non-visual eye functions conducted through the retinohypothalamic tract. PD pathology involves all levels of the visual system. The retina is the primary link in visual perception and is a peripheral component of the nervous system. Many mediators and neurotransmission systems are involved in the normal function of the retina.<sup>7</sup> In order to ensure that perception of the surrounding world is reliable and as

complete as possible, visual information is supplied to cortical centers through parallel-running channels which specialize in transmitting certain properties of surrounding objects. The information perceived by retinal cones and rods is further transmitted to the retinal ganglion cells (RGC), which gives rise to the magnocellular (M), parvocellular (P) and koniocellular (K) pathways. The M pathways is associated with perception of brightness, contrast, spatial depth, localization and spatial relationship between objects, as well as observing objects in motion. The P pathway transmits information about contours, shape, texture, also color perception especially in the red-green range. The function of the K pathway is currently less clear, although its role in perception of the blue color, in seasonal mood changes, in controlling pupillary reactions to light is known.<sup>7,8</sup> The retinal projections are further transmitted to the four main subcortical areas through the optic nerve.

- i. The lateral geniculate body (LGB) is the main subcortical center for transmitting information to the primary visual cortex. The M and P projections from the corresponding RGC form the two magnocellular and four parvocellular layers in the LGB, while the K projections diffusely located between them.
- ii. The superior colliculus involved in the orientive eye reflexes to light stimuli.
- iii. Pretectal area, which controls pupillary reactions to illumination
- iv. Hypothalamus, which regulates the circadian rhythms and other processes relying on illumination intensity and duration of daylight hours.

Information from the LGB is further supplied to the primary visual cortex where the magno- and parvo-systems remain separated. The M pathway is then projected to the medial temporal area and then to the parietal cortex. This so called «WHERE» system searches for a visual object in the surroundings and is very sensitive to motion (it ensures perception of motion). The P pathway is projected to the V4 area, then further to temporal cortex forming the so called «WHAT» system sensitive to color and various details of the perceived object.<sup>9</sup>

Starting from the middle of the 20th century, evidence has been accumulated suggesting that electromagnetic waves of a wide spectral range, when the eye is exposed to them, can contribute to regulating and influence different function of the human body and mind. These processes occur through the retinohypothalamic tract, i.e. the sensory pathway supplying respective impulses directly into the hypothalamus, and do not depend on visual perception per se. Moreover, secondary neural connections from the LGB have been described, which finish in the same hypothalamic nuclei (supraoptical and suprachiasmatic). The retinohypothalamic system transmits critical information about circadian rhythms, thanks to which biological rhythms, the wake-sleep cycle are regulated, locomotive activity and food consumption change during a day, etc. Most fibers comprised in this system are axons of RGC.<sup>10,11</sup> There also is the centrifugal hypothalamoretinal pathway starting from the hypothalamic neurosecreting fibers and finishing in the RGC, etc. Nowadays it is well known that this pathway is used in regulating retinal vascular pressure, changing retinal electric potential, regulates light sensitivity and adaptation of the eyes to darkness.<sup>10,11</sup> This aspect is crucial in understanding some disorders in the visual system in PD, e.g., association of visual hallucinations with evening and/or night time, etc. Moreover, changes in the retinohypothalamic system can play a substantial role in other PD symptoms dependent on circadian rhythms, e.g., disturbance of the wake-sleep cycle, onset or exacerbation of the restless legs syndrome in the evening or at night, and other phenomena.

Insufficiency of the retinal dopaminergic system (RDS) plays the key role in visual dysfunction in PD. Metabolic control and adjusting retinal sensory neurons activity based on the level of incoming information are considered one of the functions of RDS. Therefore RDS modulates neuronal activity of the retina in light perception, color and contrast discrimination, plays a great role in circadian rhythms, and is also responsible for the trophic function of its cellular elements.<sup>7</sup> Insufficiency of dopaminergic neurons of LGB and visual cortex is also important in visual defects in PD. Besides involvement of dopaminergic neurons, changes in the other neurotransmission systems obviously contribute to visual impairment.<sup>12</sup>

There are currently several methods of study: electrophysiological, psychophysiological, neurophysiological and imaging methods, which supply an assessment of all aspects of the visual system at all levels, from retina to cortical centers. Literary source often report disturbances of color discrimination in patients with PD. The defect in color perception is most pronounced in the blue-yellow part of the spectrum (tritan axis).<sup>3,4</sup> The higher vulnerability of the blue cone system in PD is attributed to the relatively small amount of retinal cones and their wide distribution away from each other, so they interact at a large distance, while the organization of their large receptive fields requires an adequate functioning of the dopaminergic interplexiform and amacrine cells in the retina, i.e. retinal elements which function with severe impairment in patients with PD. Moreover, specific disturbances in color discrimination can be revealed at the earliest stages of the disease.<sup>3,4</sup> Psychophysiological methods provide information of color vision (CV). There are nowadays about a dozen methods designed to reveal both congenital and acquired disorders of color vision. Various pseudoisochromatic charts (by Fellhage, Rabkin, Fletcher, and others) are used in clinical practice. However, panel tests which were created on the basis of Munsell color system are the most widely used and acknowledged methods for establishing acquired CV disorders. Farnsworth's multicolor tests with 15, 85 and 100 tones are widely used abroad. Studies based on these tests have revealed color discrimination disorders, mostly in the blue-green spectrum, in moderate and severe stages of PD, also a relationship has been found

between the CV disturbances and deteriorating visuospatial orientation and cognitive functions.<sup>13</sup> However, the relationship between color vision disturbances and motor disturbances is controversial and not confirmed. Some studies have reported that CV deteriorated along with the progress of the disease.<sup>13,14</sup> Other studies have demonstrated that there was no correlation between the degree of CV in PD and the dopaminergic nigral degeneration examined by single-photon emission tomography, which proves that the origin of visual disorders in PD is extranigral.<sup>15</sup> Some authors have argued that RDS insufficiency exists throughout the disease at the same level and does not depend on nigral dopamine insufficiency. So now there are several questions remaining to be investigated: which is the first to originate, motor defect or CV disturbance; if there is not relationship between PD severity and CV disturbance severity, why do levodopa drugs improve both the motor function and color vision simultaneously?

One of the most typical features of PD is reduced contrast sensitivity (CS), which is also assessed by psychophysiological methods.<sup>4,5</sup> In this respect, Hamilton test, Pelli-Robson's charts and software options such as Zebra 3 showing different chromatic and achromatic sinusoidal grids of different spatial frequency. The term "sinusoidal" refers to gradually reducing contrast between two colors, perceived by the human eye. The spatial frequency is determined by the width and number of stripes of a certain color on the screen and is measured in Herz units (Hz). It is acknowledged that PD is normally associated with a CS reduction in the low and medium spatial frequencies (1-8 Hz),<sup>16</sup> however, studies conducted at our clinic have revealed a reduction in CS at all spatial frequencies, moreover, the reduction of CS for the blue color was most pronounced, blue was followed by green and then red with respect to CS reduction. CS to achromatic grids was lower and was usually observed in patients with moderate and severe PD. A correlation analysis showed that reduced achromatic and chromatic CS occurred independently. Authors from other countries have pointed out the independence of magno and parvocellular pathways deterioration.<sup>8</sup> It is acknowledged that age-related changes in the retina can influence the electrophysiological parameters of interest, but more recent studies have demonstrated that age-related disturbances are different from PD-associated changes. Indeed, rod-mediated scotopic sensitivity deteriorates faster with aging due to the slowdown in rhodopsin regeneration, than cone-mediated photopic vision.<sup>17</sup> Some authors have argued that a significant reduction in CS confirming the progress of the PD and playing a key role in exacerbation of visual functions can predispose freezing phenomena during a walk. A relationship between walking velocity and deteriorating CS has also been reported.<sup>18</sup> An interesting fact is that CS variability in different parts the day, with higher CS in the morning and lower CS in the evening, and also the influence of circadian rhythms on the levels of retinal dopamine has been established.<sup>19</sup> The most prominent interaction between CS disturbance and retinal dopamine has been revealed in patients with motor fluctuations during the «on» and «off» periods. Our evidence of improved CS during the «on» period and reduced CS during the «off» period is agreement with data published by authors from other countries and demonstrates that CS can vary due to the effect of levodopa drugs.<sup>20-22</sup> However, what defines the variability of CS fluctuation in different patients is still unknown. Maybe it depends of PD degree or clinical type of PD or the effectiveness of drug therapy.

The data obtained by electroretinography (ERG) support the RDS's contribution to visual dysfunction. Retinal bioelectric activity recorded in varying conditions of light stimulation is helpful in revealing local lesions, and supply a basis for differentiating the vascular, toxic degenerative disorder. Indeed, pattern ERG (one of

ERG types) is a response to a striped or checkered-field stimulus and is determined by the functional state of RGC.<sup>23</sup> Pattern ERG revealed the greatest changes when stimulation is effected with the same spatial frequencies as the ones associated with maximal CS reduction.<sup>17</sup> Examinations by chromatic pattern ERG with red-green and blue-yellow grids, as well as black-white grids used during achromatic pattern ERG provides a discriminating approach to revealing disorders in parvo, konio and magnocellular pathways. Previous studies have shown an inhibition of pattern ERG amplitude, both to chromatic and achromatic stimuli, in PD, moreover, when exposed to blue-yellow grid stimuli, an increased latency of the principal peaks was revealed beside an essential reduction of the amplitude.<sup>24</sup> The different degrees of parvo-, konio- and magnocellular subsystems involvement in PD is further confirmed by visual evoked potentials (VEP) with achromatic and chromatic reverse checkered patterns of blue-yellow and red-green checks. As with pattern ERG, the examination with VEP revealed a predominant change of parameters of the main peaks in response to blue-yellow checker stimulation, moreover, the K pathway disorder was revealed at the earliest stages of PD.<sup>25,26</sup> It is known that general ERG reflects the activity of most retinal-cell elements in response to light stimulation and the magnitude of its responses depends on the number of healthy functional cells and features of the stimulus. In reviewing a general ERG, special attention is paid to the amplitude of a, b and c waves, their magnitude can be more or less reduced, and attention is also paid to b/a wave amplitudes ratio, which should not be less than 2. Based on the inhibitory degree of the main waves in general ERG, the following types are distinguished: normal, subnormal (plus-negative (reduction to isoline), minus-negative (below isoline)), non-recordable (types according to G.Karpe, H.E.Henkes). Our studies have shown abnormal types of general ERG in all PD subjects (these studies involved patients without ophthalmological diseases), moreover, the minus-negative type was the most frequent in advanced stage of PD. A significant reduction of the b/a wave amplitudes ratio was also found in almost all the subjects.<sup>27</sup> According to literary sources, a reduction in this measure can suggest an ischemic or degenerative retinal disorder. A rhythmic ERG, in which the eye is stimulated by light flashing at varying frequency, is used to assess to the retinal cells' potential to reproduce the flashing rhythm: the normal frequencies for the rod system and the cone system are 20Hz and 100 Hz, respectively. We have revealed that rhythmic response fell more than by half as compared to the normal values and this did not depend on PD stage or clinical form, but actually depended on the activity period of the levodopa therapy. In subjects usually in initial stages of PD, the rhythmic response approached the normal value during the «on» period, while in the «off» period the rhythmic response was significantly lower. In patients in the advanced stages, even those with motor fluctuation, reproduction of rhythmical flashing remained low regardless of dosing time, which could be indicative of specific non-reversible changes in the retina.

Literary sources have reported examinations of visual field defects by testing with static automated perimetry in patients after posterior pallidotomy, which is associated with a risk of visual tract injury or optic radiation and a 5%-10% risk of upper quadrantscopy due to involvement of Meyer's loop in the temporal lobe.<sup>28</sup> However, standard perimetry can only assess general light sensitivity in all retinal regions, and is not specific for a certain type of ganglion cells of retina. Since the pathways transmitting certain aspects of visual information in subjects with PD are involved in different degrees, it makes sense to use special perimetric methods which can establish visual field defects on a selective basis with regard to changes in the function of the respective channel. Such methods include color perimetry, more specifically blue-yellow perimetry (BYP) supplying

a selective assessment the condition of K channel, as well as various types of threshold perimetry, etc.

Literary sources describe not uncommon visual-field defect in patients with PD, similar to those found in glaucoma, moreover, these examination covered only subjects with eliminated ophthalmological disorders, without glaucoma in their family histories; a post hoc analysis proved absence of glaucoma during subsequent time.<sup>29</sup> Threshold perimetry revealed most frequently changes in visual field in the lower and temporal areas, which were often topographically concordant with the thin areas in the retina found by optical coherent tomography. This could be an evidence of disturbed trophic processes due to insufficient RGC. Although post mortem examination also confirmed reduced dopamine level in the retina in PD, no degeneration of dopaminergic neurons and no changes of cellular elements density in the retina were found. Opposite opinions have been expressed as to relation between visual defect defects and thinning retinal layers, however, the latter is found in PD patients much more frequently than in the control group.<sup>30</sup> This controversy is probably due to the lack of a single methodological approach in studies, which are conducted without proper consideration of such factors as duration and degree of the disease, etc. For example, beside the threshold perimetry, in our studies we have used the BYP and found, in some not infrequent cases, visual field defects in subjects with moderate and severe PD, but these defects, undiscovered by standard statistical perimetry, were often localized in the upper segments. Retinal dopamine insufficiency is one of the key factors underlying specific visual disturbances in PD, but it cannot completely account for the local visual field defects. More and more evidence has been accumulated recently as to the existence of functional visual-field defects. Different diseases (endocrinological diseases, toxicity, etc.) can induce changes in the perceptual visual space and in color borders of the visual field. A transitory homonymous right-side hemianopsy during an endogenous depression episode has been described, as well as visual field disturbances with different topography and color features (relative scotomas) in subjects receiving tranquillizers, antidepressants, without toxic injuries to the retina and visual nerve.<sup>31,32</sup> The mechanisms of visual disorders are often attributed to indirect effects of psychotropic therapy in RGC through the structures of the limbic-reticular complex. In our view, it is more acceptable to explain functional defects of visual fields in PD patients by disorders in the centrifugal encephaloretinal projections which selectively affect RGC functional state, probably based on their somatotopic organization.

Such changes in the structures receiving and supplying visual information in distorted form to upper CNS parts contribute greatly to complicated syndromocomplexes associated with PD and often involving other functional systems. For instance, dynamic visual acuity requires a normal function of the oculomotor system, which is often specifically impaired in PD (not included into this review). Since cortical and subcortical levels are involved, complicated processes are also disturbed and this manifests itself in impaired ability to distinguish shapes or distance between objects, disturbance of visuospatial orientation.<sup>33</sup> These are seen both in perception and in examinations of spatial praxis.<sup>34</sup> Specific impairments of higher functions related to the visual system and associated with PD include disturbances in visuospatial orientation, including difficulties in passing a prescribed route, and assessing verticality. Visual attention and motion perception are significantly impaired and prevent the patient from completing tasks involving visual search, e.g. many patients can find it difficult to read, recognize faces in the crowd, drive a car or understand navigation. As regards motion, spatial disturbances reveal themselves when a subject is trying to copy complicated geometrical and three

dimensional shapes.<sup>34-36</sup> All this significantly exacerbates cognitive processes in general and the motion defect, too, leading to a higher risk of injuries from falls.<sup>33,37,38</sup>

Defects in visual processes both in the peripheral and in the central level give rise to visual hallucinosis, which is a quite frequent PD complication, its clinical manifestations and pathogeny are similar to Charles Bonnet hallucinosis. Visual hallucinosis in PD results from a complicated interaction of cognitive, affective, medicinal, sensory and other factors determining its features in each case.<sup>32,39,40</sup>

## Conclusion

In conclusion, number of visual disturbances associated with specific disorders at all levels of the visual system organization are characteristic of Parkinson's disease. Main problems of visual disorders in PD includes changes in color vision and contrast sensitivity, change in the electrophysiological properties of the retina due to the insufficiency of the retinal dopaminergic system, features of visual field defects, visuospatial and visuoperceptual impairments. These visual deficits cause problems in the performance of everyday visual tasks, including reading, mobility activities, walking, driving, orientation in space, which makes a significant contribution to Parkinson's inability and makes the patient's social adaptation difficult. Despite the growing interest of researchers and a large number of publications on this issue, the following questions still require further research:

- i. How are visual disorders related to other PD symptoms?
- ii. Can certain types of visual impairments be used as predictors as to progress rate of the disease and emergence of complications?
- iii. Can specific visual impairments found in a patient be used as a basis for early differential diagnostics of PD and atypical Parkinsonism?

With regard to the variety of impairments, the problem discussed here covers many fields of knowledge and dealing with it requires psychophysiological and cutting-edge instrumentative methods, as well as contribution of neuroophthalmologists, neuropsychologists and neurophysiologist.

## Conflicts of interest

None.

## Acknowledgements

None.

## Funding

None.

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