World Applied Sciences Journal 27 (4): 462-468, 2013
ISSN 1818-4952

DOI: 10.5829/idosi.wasj.2013.27.04.13657

Dynamic Fractal Flickering as a Tool in Research of Non-Linear Dynamics of the Evoked Activity of a Visual System and the Possible Basis for New Diagnostics and Treatment of Neurodegenerative Diseases of the Retina and Brain

Marina Vladimirovna Zueva

Federal State Budgetary Institution "Moscow Helmholtz Research Institute of Eye Diseases", Ministry of Healthcare of Russian Federation, 14/19 Sadovaya-Chernogryazskaya Street, Moscow, Russian Federation, 105092

Abstract: This paper presents the author's scientific hypothesis on the effect of fractal flickering, which exhibits scale invariance with time, on the evoked responses of the retina [electroretinogram (ERG)] and visual cortex [visual-evoked cortical potentials (VEP)] in norm and neurodegenerative disorders. A new approach for ERG and VEP studies is proposed. In the proposed approach, standard stimuli are presented to patients as these patients adapt to the flickering background with specific chaotic interval variabilities between flashes (dynamic light fractal). We hypothesized that this approach could be applied to facilitate adaptation to non-linear flickering with fractal dimensions in electrophysiological diagnostics. This approach could be considered as a new strategy by which neuronal plasticity is affected. In theory, this method can be used to improve the condition of patients with diabetic retinopathy, glaucoma and severe neurodegenerative diseases, such as Parkinson's and Alzheimer's diseases.

Key words: Fractal · Non-linear dynamics · Non-linear flickering background · Electroretinogram · Visual-evoked potential · Neurodegenerative disease · Neural plasticity · Fractal therapy

INTRODUCTION

Fractal Geometry and Non-linear Dynamics: Fractal geometry is one of the instruments of chaos theory used in mathematics and physics to study several phenomena, which are chaotic in terms of Euclidean geometry and linear mathematics. The term "fractal" proposed by Benoit Mandelbrot in 1975 allocates irregular geometric objects with fractional metric dimension that exhibits self-similarity or scale invariance. Self-similarity refers to a particular case, in which a zoomed structure remains unchanged regardless of scale; fractal forms consist of subunits and the structure of these subunits is similar to that of a macroscopic object [1, 2]. Certain examples of the simplest mathematical fractals are Koch snowflake, Sierpinski triangle, Peano curve and many others.

Mandelbrot was the first to show that fractals are real models of many phenomena observed in the real world as irregularities, such as mountain ranges, clouds, roots, branching tree crown, wrinkly coastline and snowflakes. To model a wide range of "natural" fractals, such as rough surfaces of mountains and forests, accumulations of galaxies, flashes of lightning, basins of rivers and other similar geometric configurations, scholars in mathematics use stochastic (random) fractals, such as fractal Brownian motion. Synthetically designed fractals are economically important because of several advantages, such as price levels on stock exchange [3]. Fractals in physics arise when modeling of nonlinear processes, such as turbulent fluid flow, complex diffusion-adsorption processes and flames, among others [2]. Fractals in biology are used to model populations to describe systems of internal organs (arterial and venous trees; alveoli in the lungs) [4].

Corresponding Author: Marina V. Zueva, Pathophysiology, Dr. Biol. Sci., Head of the Laboratory of Clinical Physiology of Vision, Moscow Helmholtz Research Institute of Eye Diseases, 14/19 Sadovaya-Chernogriazskaya Street, Moscow 105062, Russian Federation. Tel: +7 916 576 2359.

The physical body of a human is a rich source of non-linear fractals [5, 6]. The examples include also the dichotomic ramifying tracheobronchial tree, His-Purkinje networks and neuronal networks in the brain. Fractal-like structures greatly increase the surface area that is available for absorption, facilitate and provide many other fundamental functions in the organism, for example, distribution, collection, transport and the information processing [cite by 5, 7]. Fractal concept can be applied to describe not only irregular geometric forms but also complex processes with the properties of self-similarity in its course in time (time scale invariance). Fractal processes generate irregular fluctuations across multiple time scales by analogy scale-invariant anatomical structures that are self-similar across multiple length scales.

Studies have shown that healthy human physiological processes - the activity of neurons in the brain, the heartbeat rate, breathing, dynamics gait etc. characterize irregular fluctuations, repeating its structure at different scales of time [7]. Conversely, disease and aging are characterized by the disappearance of the irregularity in fluctuations of physiological functions and by the development of highly ordered rhythm [7, 8], that is, they may reduce the fractal dimension or the degree of chaos.

The Application in the Study of Neurodegenerative Disorders: In the study of the background electrical activity of healthy brain, the chaotic dynamics of alpha rhythm in the electroencephalogram (EEG) has been revealed [9]. The fractal dimension was proved also in the activity of individual neurons and neural networks [10], which showed many characteristics of chaotic behavior. The time-series studies of hormones levels in the blood serum [11], of menstrual cycle [12] and other studies have demonstrated the fractal fluctuations of neuroendocrine system parameters. The fractal variability in the step-to-step interval has also been observed in healthy persons, whereas the fractal dimension of step fluctuation has been decreased in patients with severe neurodegenerative diseases, such as Parkinson's and Huntington's diseases, which disrupt balance and gait [7, 13, 14].

Alzheimer's disease and Parkinson's disease are two of the most common incurable neurodegenerative diseases that cause the disability of the working-age adults. In an age group of >60 years approximately 1% suffers from Parkinson's disease [15]; in a population of individuals aged >85 years approximately 2.6% to 4% exhibits this disease [16, 17]. The possible etiological risk factors for Parkinson's disease are aging, genetic predisposition and environmental exposure. Parkinson's disease affects the structure of the extrapyramidal system - basal nucleus and *substantia nigra* [18]. Among the pathogenic mechanisms it has been noted the role of free radicals that formed during the oxidation of dopamine and may cause the lipid peroxidation in cell membranes and cell death [19].

Alzheimer's disease is observed in people aged >65 years [20] and the average life expectancy after diagnosis is approximately seven years [21]. To explain the possible causes of Alzheimer's disease different hypothesis were put forward. According to the 'cholinergic hypothesis', the disease is caused by the reduced synthesis of the neurotransmitter acetylcholine. According to the widespread 'amyloid hypothesis', the main cause of the disease are beta-amyloid protein deposits (Aβ) [22, 23], which disrupt calcium ions homeostasis in cells and cause apoptosis. In accordance with the 'Tau-hypothesis', the changes in the structure of the Tau protein (taupathy) trigger the cascade of disturbances [23].

Tau protein promotes assembly and stabilization of microtubules, which contributes to the normal neuronal function. Slow progressive neurodegeneration is associated with the intracellular accumulation of tau protein and the formation of neurofibrillary tangles inside the neurons [24] that cause their disintegration and destruction; biochemical signaling between cells is also disrupted [25, 26].

Magnetoencephalogram (MEG) and EEG analyses have been performed using different nonlinear methods [27]. EEG and MEG background activity in patients with Alzheimer's disease were more regular than those in healthy elderly persons and multiscale complexity in the electrical brain activity was reduced. The simplification of the background activity dynamics, reduction in fractal dimension has also been found in Parkinson's disease [28] and other brain disorders, such as schizophrenia [29] and epilepsy [30, 31].

Applications in the Study of Neuronal Plasticity and Retina Diseases: In neurodegenerative disorders of different etiologies, an important pattern observed includes the parallel changes found in the structure and electrical activity of the retina and the brain. This finding has been objectively confirmed in patients with multiple sclerosis [32-35]. In Alzheimer's disease, there were detected deposits of beta-amyloid protein in the eye tissues [36], taupathy in the retina and optic nerve [37],

reduced levels of acetylcholine, the destruction of retinal neurons (first of all, the ganglion cells) [38, 39, 40], the synaptic degeneration [41] and also visual disturbances, alterations in the background activity of visual cortex and in the electroretinogram [42]. In Parkinson's disease, psychophysical, electrophysiological and morphological signs of destruction in retinal structure and function have been also revealed [43, 44].

Various aspects of fractal geometry in ophthalmology attract the attention of researchers [45]. Fractal structure of blood vessel branching in the fundus has been well studied [46, 47]. In patients with diabetes mellitus the development of diabetic retinopathy is accompanied by a change in the density and complexity of the vascular tree and in its fractal dimension [46, 48]. Moreover, statistically significant reduction in the fractal dimension of the branching pattern of blood vessels has been detected in the macular region of patients with mild to moderate non-proliferative diabetic retinopathy [48].

Some examples of the changes in the structural complexity of the retina include the truncation and elongation of the dendrites and axons of retinal neurons and the disturbance in the wiring of neural network and synaptic connections in the later stages of photoreceptor degenerative diseases, resulting in the remodeling of the architecture and function of the retina, such as retinitis pigmentosa and retinal detachment [49, 50].

Interesting and potentially important phenomenon to understand the pathogenesis of neurodegenerative diseases has been recently discovered, that is, the reduction in fractal complexity of dendritic branching and length in magnocellular and parvocellular layers of the lateral geniculate nucleus in a primate model of glaucoma [51]. These animals have been subjected to memantine treatment; as a result, a simplified dendritic branching caused by glaucoma is expressed in a lesser degree than that without treatment. Thus, dendritic plasticity may represent the basis for the development of new strategies in the treatment of glaucoma. The disruption of dendritic branching is one of the distinctive features and one of potential mechanisms of neurodegeneration not only in glaucoma but also in Alzheimer's disease, resulting in a disorder in the structure of neural network [52]. Moreover, memantine is used as a neuroprotective agent to treat of cognitive impairment in Alzheimer's disease [53].

The fractal anatomy of the visual system has been studied for more than 20 years, whereas the chaotic dynamics of physiological processes determining visual functions remains practically not studied. The scientific knowledge of the non-linear dynamics of visual functions and regularities of their changes can enhance our understanding of the pathogenesis of neurodegenerative disorders. This knowledge can also contribute to the pathogenetic substantiation of new therapeutic strategies, in particular, using the nervous tissue plasticity.

Plasticity refers to the changes occurring in the structure (number, size, density packaging), function and in the contacts of neurons and glial cells in pathological conditions and under the influence of various factors [54]. Plasticity also refers to the most important aspects of the studied modern neuroscience, such as strengthening, weakening, or adding neural connections that characterize neuroplasticity; the management of these features can be very effective in the treatment of brain injury. In some situations, particularly in patients with brain lesions, healthy neurons can perform the functions of the damaged or destroyed nerve cells, allowing keeping at least some level of functionality of the damaged areas of the brain. Reorganization in the architecture of the nervous tissue develops in neurodegenerative diseases [55].

Neural plasticity (synaptic and non-synaptic) is manifested by various mechanisms. Axonal sprouting is one of the most common mechanisms. Germinated healthy axons form new nerve endings, which may be used to strengthen the existing connections between neurons or to repair damaged parts, contributing to the recovery of damaged nerve pathways and their functionality. Another well-known mechanism of neuroplasticity is dendrite plasticity [51] which is manifested in pathological conditions in the form of enhanced branching, growth of dendrites and truncation.

We can suppose that the achievements in the field of research of mechanisms in the control of neuronal plasticity will contribute to the restoration of the cerebral and overall functionality in persons with nervous tissue lesions. This position can be fully valid for the retina and the entire visual system.

The natural, low-amplitude electric background noise of the retina, including quantum noise, the noise of a photoreceptor's synapses and the correlated noise of ganglion cells, largely predetermines the electrical noise at the output of the retina and limits the transmission of information via parallel visual channels to higher brain centers [56]. In contrast to the background activity of the brain, which is successfully investigated by EEG and MEG, the fractal dynamics of the natural electrical noise of the retina is technically difficult to estimate by non-invasive methods.

In a single study of the long-term time-series of retina responses at flickering stimuli (the standard flicker electroretinogram - flicker ERG) have been recorded and the fluctuations in the inter-peak interval have been analyzed then with different methods [57]. This study is different from the classical analysis of inter-peak intervals of electrocardiogram and of brain alpha rhythm because the author has described visual evoked retinal responses, but not spontaneous activity. The non-linear character of the retina response to light stimulation has been revealed in the norm; changes in the phase portrait of the flicker ERG has also been shown in retinitis pigmentosa and Stargardt's disease.

The Hypothesis: We propose a fundamentally different approach in the field of nonlinear dynamics of a visual system to examine the changes in the ERG responses and in visual-evoked cortical potential (VEP) responses at standard stimuli but were imposed on flickering background with a strictly defined non-linear dynamics of fluctuations of the intervals between the stimuli (dynamic light fractal). We aimed to determine the influence of the dynamic chaotic background, which exhibits scale-invariance in time, on the evoked responses of the retina and visual cortex. For this purpose, we assume it necessary to compare the responses when light stimuli are presented on a standard homogeneous background, on a fractal flickering background, on a regular flickering background of constant frequency and on the broadband flickering background (white noise).

We assumed that the confirmation of our hypothesis on the dependence of the evoked responses of the retina and the brain from the dynamic fractal light adaptation and from the flickering background of another temporal dynamics in the norm and pathologies can help obtaining new data on the pathophysiological mechanisms of neurodegenerative diseases. Scientific data regarding the effect of scale-invariant in time light environment on the functional activity of the retina and the brain in neurodegenerative diseases can be used as a basis to elaborate new technologies of diagnostics. These data can also be used to develop new pathogenically adequate therapy.

Few examples have been presented regarding the application of heterogeneous noise in medicine; for example, vibrating soles have been developed to ensure balance and gait in elderly individuals and patients with diabetic neuropathy as well as in the rehabilitation period after the stroke [58-60]. A decrease in the fractal dimension of fluctuations in the intervals between steps is usually observed in normal physiological aging; vibrating soles cause a significant increase of multiscale complexity in the intervals between the steps in elderly persons. This method can be used to improve the control of postural stability and dynamics of gait and is based on stochastic resonance [58] to facilitate the transmission of a signal by introducing noise to the system. However, these vibrations do not exhibit the properties of fractal dynamics.

Feedback-controllable phototherapy (chronotherapy) is also a known method to correct vision disorders; this method is based on the presentation of a colored geometric fractal [61] to a patient. The structure of a specific pattern on a monitor screen remains unchanged, but the rate of switching on and switching off of a fractal image is governed by the patient's pulse frequency and respiration according to the biological feedback method. However, the dynamics in the frequency of image presentation is not programmed on the principle of deterministic chaos.

We proposed for the first time the potential application of non-linear dynamic light noise (adapting background) with a fractal dimension to influence the mechanisms of nervous system plasticity. This approach can be theoretically applied to improve the condition of patients with diabetic retinopathy, glaucoma and severe neurodegenerative diseases, such as Parkinson's and Alzheimer's diseases.

REFERENCES

1. Mandelbrot, B.B., 1982. The fractal geometry of nature. New York: Freeman, pp: 468.
2. Crownover, R.M., 1995. Introduction to Fractals and Chaos, Jones and Bartlett Publishers, Boston – London, pp: 306.
3. Mandelbrot B.B. and R.L. Hudson, 2004. The (mis)behavior of markets. N.-Y.: BasicBooks, pp: 308.
4. Iannaccone, P.M. and M.K. Khokha, (Eds.) 1996. Fractal geometry in biological systems: an analytical approach. Boca Raton, FL: CRC Press.
5. Goldberger, A.L., D.R. Rigney and B.J. West, 1990. Chaos and fractals in human physiology. Sci. Amer, 262: 42-49.
6. Ayers, S., 1997. The Application of Chaos Theory to Psychology. 1997. Theory & Psychol, 7(3): 373-398.
7. Goldberger, A.L., L.A.N. Amaral, J.M. Hausdorff, P.Ivanov Ch., C.K. Peng and H.E. Stanley, 2002. Fractal dynamics in physiology: Alterations with disease and aging. Proc. Natl. Acad. Sci. USA (PNAS), 99(Suppl 1): 2466-2472.

8. Fadel, P.J., S.M. Barman, S.W. Phillips and G.L. Gebber, 2004. Fractal fluctuations in human respiration. J Appl Physiol, 97: 2056-2064.
9. Lehnertz, K., C.E. Elger, J. Arnhold and P. Grassberger (Edit.), 1999. Chaos in brain? Proceedings of the Workshop, Bonn University, Germany, pp: 131-132.
10. Izhikevich, E.M., 2007. Dynamical Systems in Neuroscience. 2007. The Geomentry of Excitability and Bursting. The MIT Press: Cambride, Massachusetts, pp: 441.
11. Noguchi, T., N. Yamada, M. Sadamatsu and N. Kato, 1998. Evaluation of self-similar features in time series of serum growth hormone and prolactin levels by fractal analysis: effects of delayed sleep and complexity of diurnal variation. Journal of Biomedical Science, 5: 221-225.
12. Derry, G.N. and P.S. Derry, 2010. Characterization of chaotic dynamics in the human menstrual cycle. Nonlinear Biomedical Physics, 4:5. http:// www.nonlinearbiomedphys.com/ content/4/1/5
13. Dingwell, J.B. and J.P. Cusumano, 2000. Nonlinear time series analysis of normal and pathological human walking. Chaos, 10: 848-863.
14. Terrier, P. and O. Dériaz, 2011. Kinematic variability, fractal dynamics and local dynamic stability of treadmill walking. Journal of NeuroEngineering and Rehabilitation, 8(12): 1-13.
15. Samii, A., J.G. Nutt and B.R. Ransom, 2004. Parkinson's disease. Lancet, 363(9423): 1783-1793.
16. Jahno, N.N. and D.R. Shtul'man (Ed..), 2001. Bolezni nervnoj sistemy [Nervous system diseases]. Moscow.: Medicina, 2: 744. (in Russ)
17. de Lau, L.M. and M.M. Breteler, 2006. Epidemiology of Parkinson's disease. Lancet Neurol, 5: 525-535.
18. Obeso, J.A., M.C. Rodríguez-Oroz, B. Benitez-Temino, F.J. Blesa, J. Guridi, C. Marin and M. Rodriguez, 2008. Functional organization of the basal ganglia: therapeutic implications for Parkinson's disease. Mov Disord, 23(Suppl 3): S548-S559.
19. Carvey, P.M., A. Punati and M.B. Newman, 2006. Progressive dopamine neuron loss in Parkinson's disease: the multiple hit hypothesis. Cell Transplant, 15: 239-250.
20. Brookmeyer, R., E. Johnson, K. Ziegler-Graham and H.V. Arrighi, 2007. Forecasting the global burden of Alzheimer's disease. Altzheimer Dement, 3(3): 186-191.
21. Mölsä, P.K., R.J. Marttila and U.K. Rinne, 1995. Long-term survival and predictors of mortality in Alzheimer's disease and multi-infarct dementia. Acta Neurol Scand, 91(3): 159-164.
22. Hardy, J. and D.J. Selkoe, 2002. The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. Science, 297: 353-356.
23. Mudher, A. and S. Lovestone, 2002. Alzheimer's disease - do tauists and baptists finally shake hands? Trends Neurosci, 25(1): 22-26.
24. Goedert, M., M.G. Spillantini and R.A. Crowther, 1991. Tau proteins and neurofibrillary degeneration. Brain Pathol., 1(4): 279-286.
25. Iqbal, K., C. Alonso Adel, S. Chen, M.O. Chohan, El-E. Akkad, C.X. Gong, S. Khatoon, B. Li, F. Liu, A. Rahman, H. Tanimukai and I. Grundke-Igbal, 2005. Tau pathology in Alzheimer disease and other tauopathies. Biochim. Biophys. Acta, 1739(2-3): 198-210.
26. Chun, W. and G.V. Johnson, 2007. The role of tau phosphorylation and cleavage in neuronal cell death. Front Biosci, 12: 733-756.
27. Hornero, R., D. Abásolo, J. Escudero and C. Gómes, 2009. Nonlinear analysis of electroencephalogram and magnetoencephalogram recordings in patients with Alzheimer's disease. Phil Trans R Soc A, 367(1887): 317-336.
28. Anninos, P.A., A.V. Adamopoulos, A. Kotini and N. Tsagas, 2000. Nonlinear analysis of brain activity in magnetic influenced Parkinson patients. Brain Topogr, 13(2): 135-44.
29. Kotini, A. and P. Anninos, 2002. Detection of non-linearity in schizophrenic patients using magnetoencephalography. Brain Topogr, 15(2): 107-113.
30. Saermark, K., J. Lebech, C.K. Bak and A. Sabers, 1989. Magnetoencephalography and Attractor Dimension: Normal Subjects and Epileptic Patients. Brain Dynamics, 2: 149-157.
31. Lehnertz, K., 1999. Non-linear time series analysis of intracranial EEG recordings in patient with epilepsy - an overview. Int J Psychophysiol, 34: 45-52.
32. Parisi, V., G. Manni, M. Spadaro, G. Colacino, R. Restuccia, S. Marchi, M.G. Bucci and F. Pierelli, 1999. Correlation between morphological and functional retinal impairment in multiple sclerosis patients. Invest Ophthalmol Vis Sci., 40: 2520-2527.

33. Costello, F., W. Hodge, Y.I. Pan, E. Eggenberger and M.S. Freedman, 2010. Using retinal architecture to help characterize multiple sclerosis patients. Can J. Ophthalmol., 45: 520-526.
34. Saidha, S., M.A. Ibrahim, C. Eckstein, C.V. Watner, S.K. Farrell, J.D. Oakley, M.K. Durbin, S.A. Meyer, L.J. Balcer, E.M. Frohman, J.M. Rosenzweig, S.D. Newsome, J.N. Ratchford, Q.D. Nguyen and P.A. Calabresi, 2011. Primary retinal pathology in multiple sclerosis as detected by optical coherence tomography. Brain, 134(Pt 2):518-533.
35. Neroev, V.V., M.V. Zueva, I.V. Tsapenko, L.V. Brylev, M.N. Zakharova, V.S. Lysenko, O.V. Zaytseva, E.D. Lin, M.A. Ampleeva, E.K. Eliseeva, M.I. Grinchenko, I.A. Zavalishin and C.V. Rezvykh, 2012. Nejrodegenerativnye izmenenija v setchatke u bol'nyh remitirujushhim rassejannym sklerozom i retrobul'barnym nevritom: morfofunkcional'nye paralleli. Rossijskij oftal'mologicheskij zhurnal [Neurodegenerative alterations in the retina in relapsing-remitting multiple sclerosis and retro-bulbar neuritis: structural-functional parallels], 5(4): 63-68. (In Russ)
36. Koronyo-Hamaoui, M., Y. Koronyo, A.V. Ljubimov, C.A. Miller, M.K. Ko, K.L. Black, M. Schwartz and D.L. Farkas, 2011. Identification of amyloid plaques in retinas from Alzheimer's patients and noninvasive in vivo optical imaging of retinal plaques in a mouse model. Neuroimage, 54: S204-S217.
37. Ho, W.L., Y. Leung, A.W.T. Tsang, K.F. So, K. Chiu and R.C.C. Chang, 2012. Review: Tauopathy in the retina and optic nerve: does it shadow pathological changes in the brain? Molecular Vision, 18: 2700-2710.
38. Blanks, J.C., S.Y. Schmidt, Y. Torigoe, K.V. Porrello, D.R. Hinton and R.H. Blanks, 1996. Retinal pathology in Alzheimer's disease. 2. Regional neuron loss and glial changes in GCL. Neurobiol Aging, 17: 385-395.
39. Parisi, V., R. Restuccia, F. Fattapposta, C. Mina, M.G. Bucci and F. Pierelli, 2001. Morphological and functional retinal impairment in Alzheimer's disease patients. Clin Neurophysiol, 112: 1860-1867.
40. Guo, L., J. Duggan and M.F. Cordeiro, 2010. Alzheimer's disease and retinal neurodegeneration. Curr Alzheimer Res., 7: 3-14.
41. Arendt, T., 2009. Synaptic degeneration in Altzheimer's disease. Acta Neuropathologica, 118(1): 167-179.
42. Krasodomska, K., W. Lubinski, A. Potemkowski and K. Honczarenko, 2010. Pattern electroretinogram (PERG) and pattern visual evoked potential (PVEP) in the early stages of Alzheimer's disease. Doc Ophthalmol, 121: 111-121.
43. Bodis-Wollner, I. and M.D. Yahr, 1978. Measurements of visual evoked potentials in Parkinson's disease. Brain, 101: 661-671.
44. Inzelberg, R., J.A. Ramirez, P. Nisipeanu and A. Ophir, 2004. Retinal nerve fiber layer thinning in Parkinson disease. Vision Res., 44: 2793-2797.
45. Mission, G.P., G. Landini and P.I. Murray, 1992. Fractals and ophthalmology. Lancet, 339: 872.
46. Daxer, A., 1993. The fractal geometry of proliferative diabetic retinopathy: Implications for the diagnosis and the process of retinal vasculogenesis. Curr Eye Res., 12: 1103-1109.
47. Jelinek, H., M. De Mendonça, F. Oréfice, C. Garcia, R. Nogueira, J. Soares and R. Junior, 2009. Fractal analysis of the normal human retinal vasculature. Int J Ophthalmol Vis Sci, 8(2). http:// ispub.com/ IJOVS/8/2/9788
48. Avakian, A., R.E. Kalina, E.H. Sage, A.H. Rambhia, K.E. Elliott, E.L. Chuang, J.I. Clark, J.N. Hwang and P. Parsons-Winerter, 2002. Fractal analysis of region-based vascular change in the normal and non-proliferative diabetic retina. Curr Eye Res., 24(4): 274-280.
49. Jones, B.W., M. Kondo, H. Terasaki, Y. Lin, M. McCall and R.E. Marc, 2012. Retinal remodeling. Jpn J Ophthalmol, 56: 289-306.
50. Fisher, S.K., G.P. L ewis, K.A. Linberg and M.R. Verardo, 2005. Cellular remodeling in mammalian retina: results from studies of experimental retinal detachment. Prog. Ret. Eye. Res., 24: 395-431.
51. Ly, T., N. Gupta, R.N. Weinreb, P.L. Kaufman and Y.H. Yücel, 2011. Dendrite plasticity in the lateral geniculate nucleus in primate glaucoma. Vision Res., 51(2): 243-250.
52. Moolman, D.L., O.V. Vitolo, J.P. Vonsattel and M.L. Shelanski, 2004. Dendrite and dendritic spine alterations in Alzheimer models. J. Neurocytol., 33: 377-387.
53. Reisberg, B., R. Doody, A. Stoffler, F. Schmitt, S. Ferris and H.J. Mobius (For the Memantine Study Group) 2003. Memantine in Moderate-to-Severe Alzheimer's Disease. The N Engl J. Med., 348: 1333-1341.

54. Pascual-Leone, A., A. Amedi, F. Fregni and L.B. Merabet, 2005. The plasic human brain cortex. Annu Rev Neurosci, 28: 377-401.
55. Wall, J.T., J. Xu and X. Wang, 2002. Human brain plasticity: an emerging view of the multiple substrates and mechanisms that cause cortical changes and related sensory dysfunctions after injuries of sensory inputs from the body. Brain Res. Brain Res. Rev., 39(2-3): 181-215.
56. Ala-Laurila, P., M. Greschner, E.J. Chichilnisky and F. Rieke, 2012. Cone photoreceptor contributions to noise and correlations in the retinal output. Nat Neurosci, 14(10): 1309-1316.
57. Rilk, A.J., 2003. The Flicker Electroretinogram in Phase Space: Embeddings and Techniques. Inaugural-Dissertation zur Erlangung des Doktorgrades der Medizin. Tübingen: Aus der Universit.ats-Augenklinik Tübingen, http://tobias-lib.uni-tuebingen.de/ volltexte/ 2003/ 1029/ pdf/FlicERG.pdf
58. Costa, M., A.A. Priplata, L.A. Lipsitz, Z. Wu, N.E. Huang, A.L. Goldberger and C.K. Peng, 2007. Noise and Poise: Enhancement of postural complexity in the olderly with a stochastic-resonance-based therapy. EurophysLett. Author manuscript; available in PMC 2007 August 15. http:// www.ncbi.nlm.nih.gov/ pmc/articles/PMC1949396/
59. Ross, S.E., 2007. Noise-enhanced postural stability in subjects with functional ankle instability. Br J. Sports Med., 41(10): 656-659.
60. Priplata, A.A., J.B. Niemi, J.D. Harry, L.A. Lipsitz and Collins J.J. Lancet, 2003. Vibrating insoles and balance control in elderly people Lancett, 362(9390): 1123-1124.
61. Zaguskin, S.L., 2000. Fraktalnaya korrektsiya, mnogochastotnyiy rezonans i spektralnaya pamyat ierarhii ritmov kaltsiya, strukturyi vodyi i zol-gel perehodov v kletke [Fractal correction, multifrequency resonance and spectral memory in hierarchy rhythms of calcium, water structure and sol-gel transitions in a cell]: In the Proceedings of the 2nd International Conference “Low and superlow fields and radiations in biology and medicine, Saint-Petersburg, pp: 3-4.