ORIGINAL ARTICLE

FUNCTIONAL MAGNETIC RESONANCE IMAGING IN SELECTED EYE DISEASES

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SUMMARY

FUNCTIONAL MAGNETIC RESONANCE IMAGING IN SELECTED EYE DISEASES

In the study, an actual overview of eye's examinations by means of functional magnetic resonance focused on selected eye's diseases is presented. Special attention is paid to hypertension glaucomas, normotension glaucoma, age-related macular degeneration, and peeling of the epimacular membrane and the internal limiting membrane. The authors point out the decreased activity of the visual cortex in diseases in which the damage of retinal ganglion cells occurs.

Key words: functional magnetic resonance imaging, glaucomas, age-related macular degeneration, peeling of the epimacular membrane, and peeling the internal limiting membrane

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INTRODUCTION

Functional examination of the brain, including the visual cortex, is a relatively new method of examination. In the literature there are only a few studies dealing with functional magnetic resonance (fMR) of the visual cortex in serious diseases of the eye afflicting the ganglion cells of the retina, in which it is not possible to exclude the possibility of secondary alteration of the ganglion cells of the visual centre by means of transsynaptic (transnueronal) degeneration.

The aim of our studies was to employ fMR in order to examine patients with glaucoma, exudative, age-related macular degeneration (ARMD) and patients who had undergone surgical peeling of the epimacular membrane (EMM) together with the membrana limitans interna (MLI).

ARMD and glaucoma are serious progressive diseases, which are the most frequent cause of loss of visual functions in older adults in the developed world.

Despite the fact that the diagnosis and treatment of both diseases has advanced considerably in recent years, due to their irreversible nature these pathologies continue to have serious social impacts. These ensue from the fact of increased human life expectancy, with an attendant increase in the number of such patients. This increase leads not only to a burden on the system of social insurance but also on the healthcare system with the supply of new and expensive therapeutic methods. With the development of vitreoretinal and special macular surgery, conditions following EMM and MLI peeling for lamellar holes and pseudoholes of the macula have become a frequent subject of discussion concerning the benefit and deficiencies of MLI peeling in macular surgery.

These are the main reasons why this study also is focused on the above-stated diagnostic groups.

2. Definition of glaucomas and age-related macular degeneration

2.1 Glaucomas are still defined as a chronic, progressive neuropathy with excavation and atrophy of the disc of the optic nerve and subsequent changes in the visual field. This formulation does not do justice to the current knowledge, and requires correction. In the modern conception, it is possible to define glaucoma as a disease in which the progressive loss of the ganglion cells of the retina and its axons is manifested in changes in the visual field, with atrophy and excavation of the disc of the optic nerve. However, even this definition, which emphasises damage to the ganglion cells of the retina over its axons is not complete, because it does not simultaneously point to damage to the ganglion cells of the subcortical and cortical centres in the brain. The current definitions do not differentiate between hyper- (HTG) and normotensive glaucoma (NTG).

In comparison with HTG, NTG is different in a number of aspects: in addition to the level of intraocular pressure there are also changes in the visual field which damage the central part more in the case of NTG and have deeper sensitivity defects (1, 27, 28), the fibres are more damaged in the central part of the retina in the case of NTG and the damages are of a focal character (38), excavation is generally wider and deeper (9, 31), patients with NTG also suffer vasospasms (10), nocturnal system hypotension, reduction of ocular pulse amplitude and fluctuation of ocular perfusion pressure (31, 33, 37), constricted retinal veins, as well as even deteriorated haemorheological properties of blood (11, 12, 39) and other factors

2.2 Age-related macular degeneration (ARMD) is a disease in which damage to the choroidal blood vessels and the Bruch's membrane is conditional upon age, genetic and external factors. Lipoid infiltration and degeneration of collagen and elastic tissues primarily damage the abundantly vascularised macula. In the case of exudative form of ARMD, choroidal capillary damage leads to an increase of intracapillary pressure and a subsequent proliferation of neovascularisations, which penetrate via defects in the Bruch's mem-

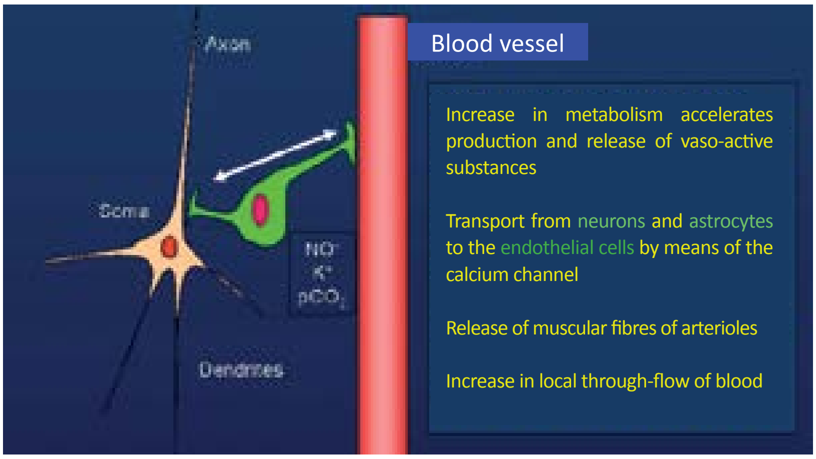

Fig. 1 Diagram of neurovascular structure: upon an increase in neuronal activity this mechanism leads to a local increase in blood through-flow

brane beneath the pigment epithelium, or further, between the pigment epithelium and the photoreceptors of the neuroretina, and generate exudation and haemorrhage, as well as detachment of the pigment epithelium of the neuroretina. All of these processes lead not only to primary destruction of the pigment epithelium and photorceptors, but also to secondary damage to the bipolar and ganglion cells (20).

3. Possibilities for examination of cortical visual centres using functional magnetic resonance (fMR)

Functional imaging of brain activity using magnetic resonance is a relatively new method. In comparison with positron emission tomography (PET), which was used a number of years previously in perfusion and functional studies on brain activity, fMR has several immediate advantages: better temporal resolution (the time of measurement of the image may be even considerably less than 1 s), better spatial resolution (size of basic voxel of matrix may be only a few mm3), and also the option of repeating a number of functional measurements on the same subject without any invasiveness. The method does not use ionic radiation or any externally administered contrast substance, and this fact makes this elegant method highly attractive, despite certain practical problems (e.g. relatively low signal/hiss ratio). By means of an inexhaustible number of testing tasks (“paradigms”) it is possible to study virtually any brain functions, conduct time-related or comparative studies on groups of selected subjects (e.g. patients versus healthy volunteers), under advantageous ethical and economic conditions.

The mechanism enabling the examination of the functional activity of brain centres by magnetic resonance is based on the difference in local blood supply, thus on changes in the flow and volume of cerebral blood vessels (Cerebral Blood Flow – CBF, Cerebral Blood Volume – CBV) and blood oxygenation. Upon activation of the brain cells a haemodynamic process is triggered, which must lead to a satisfaction of the increased energy consumption of the activated neurons. In other words, a change in the glucose metabolism must take place in the place of neuronal activity, and thus also an increase in the consumption of oxygen. The oxygen is distributed by means of blood haemoglobin. The increase in the supply of oxygen is ensured by a process known as neurovascular bonding (coupling). The activity of the neurons transmits information to the adjacent endothelial cells of the arterioles, and the subsequent generated vasodilation increases the through-flow of blood. Coupling leads to a local increase in blood through-flow (increase of CBF), a local increase in blood volume (increase of CBV) and a higher local concentration of oxyhaemoglobin (in comparison with a resting state).

The dynamic of the entire process can be described in the following manner: shortly after the beginning of activation (generally a few hundred ms) there is a local drop in oxyhaemoglobin (oxy-Hb) in the place of activation due to the immediate increased demand for oxygen caused by the acceleration of the glucose metabolism (7). Subsequently, however, within approximately 3-7 s a local increase of blood flow takes place (increase in CBF and CBV), and thus also a relative increase in oxyhaemoglobin in proportion to deoxyhaemoglobin (deoxy-Hb) within the proximity of the active neurons. The physiological increase in the supply of oxygen not only compensates for the increased consumption, but is sufficiently “redimensioned” that a change in the proportion of the concentration between oxy-Hb and deoxy-Hb takes place in the activated area, in favour of oxy-Hb. To date it is not entirely known why the disproportion between the increase of CBF (and thus also the increase in the concentration of oxy-Hb) and the consumption of oxygen by means of the glucose mechanism occurs. According to one theory, the “redimensioned” flow has a cooling effect, according to another its aim is to quickly flush out metabolic products. The entire cascade of events which accompany the activation of brain cells is illustrated schematically in fig. 1.

3.1 BOLD effect

Even if, from the perspective of the logic of physiological processes, the manifestation of the change in oxygenation is not of primary significance, its connection to the character of the MR signal has undoubtedly played the most important role in the history of fMR, and today also this effect is most commonly used in practice.

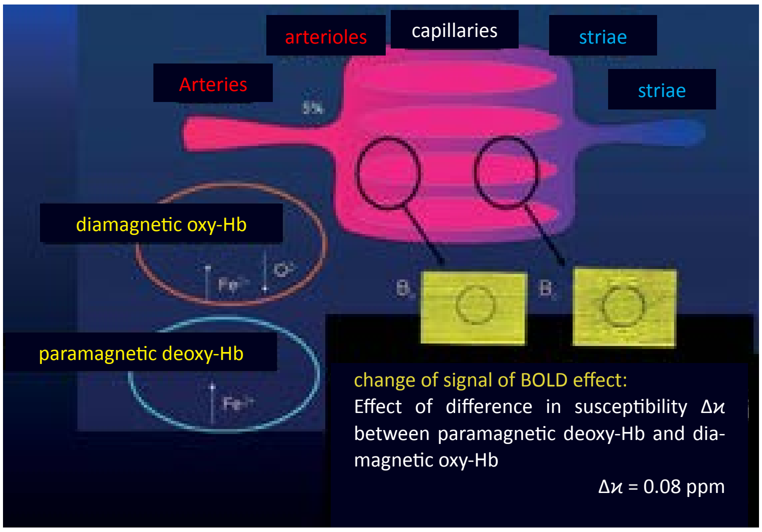

Fig. 2 Diagram of the difference in susceptibility of diamagnetic oxy-Hb and paramagnetic deoxy-Hb. This difference generates local heterogeneity of the magnetic field, which leads to a reduction of the MR signal. Changes in the balanced proportion of the concentrations of oxy-Hb and deoxy-Hb control the changes in the signal upon measurement of this BOLD effect.

Virtually all the oxygen in the blood is bound to haemoglobin. Up to four molecules of oxygen may be bound to one molecule of haemoglobin. Deoxygenated haemoglobin (deoxy-Hb) has compounds of iron with four unpaired electrons, which forms a substantial magnetic moment. The result is paramagnetic behaviour of deoxy-Hb, in contrast with oxygenated haemoglobin (oxy-Hb), which has no magnetic moment and is diamagnetic. The difference in the magnetic properties of the substances is expressed by their different susceptibility. Fully deoxygenated blood has a susceptibility of 0.2 ppm higher than fully oxygenated blood (5, 41, 42).

Mapping of the subtle changes in the magnetic field as a consequence of oxygenation of blood (42) shows a linear connection between susceptibility and blood oxygenation, measured at 1.5 Tesla. The relative difference in susceptibility of paramagnetic deoxy-Hb and the surrounding tissue is created by the local heterogeneity of the magnetic field, which may cause a decrease in the MR signal. The situation is schematically illustrated in fig. 2.

The possibility of studying changes in blood oxygenation using MR was first verified in a very high field (7 and 8.4 Tesla) and at a high resolution (65 mm) on rodents (29), and the effect was entitled the "Blood Oxygen Level Dependent" (BOLD) contrast. These studies demonstrated that the venous signal in the MR image corresponded well with the degree of oxygenation of the inhaled compound, and thus also to vascular oxygenation. The first successful imaging of human cerebral activity was demonstrated by Belliveau et al. using optic stimulation and intravenous application of a bolus of paramagnetic contrast substance (GD-DTPA) (2).

3.2 Method of fMR examination

All measurements of functional MR imaging were conducted on the system Philips Achieva TX SERIES with a magnetic field of 3 Tesla. A 6-channel head SENSE RF coil was used for scanning, and subsequently a 32-channel head SENSE RF coil. Optical stimulation upon measurement by fMR was implemented using the commercial stimulation system Eloquence (In Vivo, Germany).

For measurement of BOLD using the fMR method a sequen-

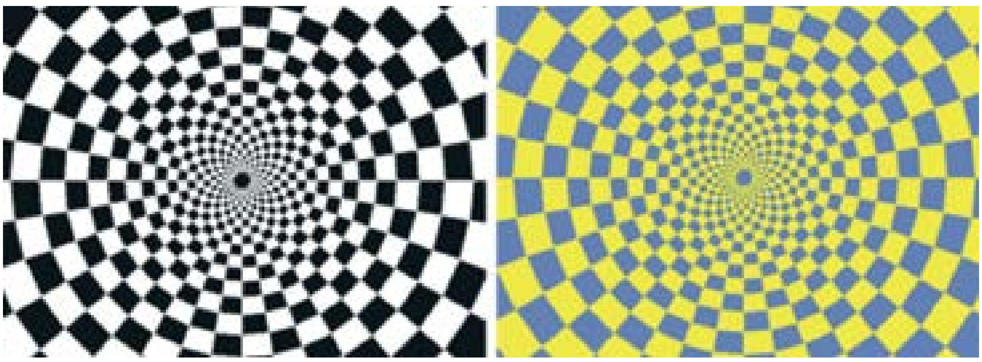

Fig. 3 Chequered field of black-white stimulation (a) and yellow-blue stimulation (b). During stimulation alternation of the chequered field occurs with its inversion by a frequency of 2 Hz

ce of gradient echo EPI with the following parameters was used: TE = 30 ms, TR = 3 s, angle of tilt 90°. The measured volume contained 39 connecting layers with a thickness of 2 mm and a size of the measured voxel (spatial resolution) was 2 x 2 x 2 mm3 (FOV = 208 x 208 mm2, matrix 104 x 104, reconstruction matrix 128 x 128, SENSE factor 1.8). During fMR scanning, an alternation of a black and white or yellow and blue chessboard was projected to the subjects (fig. 3). The size of the stimulation field was 25.8 x 16.2 degrees. Alternation of the image was with a frequency of 2 Hz. During the resting phase a static focusing cross was projected to the subjects, situated in the centre of the visual field. Each measurement formed a block schema with 5 intervals of the active phase of a length of 30 s (10 dynamic scans) and 5 resting intervals of the same length of duration. In total each measurement therefore contained 100 dynamics and lasted for 5 minutes.

The obtained data was processed using SPM8 software and a general linear model (GLM).

During the pre-process, the data was corrected by movement (realignment) and corrected to the temporal shift of the individual chains (slice timing), and subsequently flattened by a Gaussian filter with FWHM 6 x 6 x 6 mm and finally normalised to a standard space of MNI_152. For the statistical evaluation on the level of the individual subjects a GLM with a modelling function via convolution of the canonic function of the haemodynamic response function (HRF) was used, with a course of the used block schema of stimulation. The resulting statistical maps were thresholded on the level of statistical significance p = 0.05 with correction to multiple observations of FWE (Family Wise Error).

RESULTS

4.1 Normal values of fMR and ocular dominance

Upon separate stimulation of each eye, we recorded varying activity of the visual centres in the brain in healthy persons during the fMR examination. This led to a postulation of the hypothesis as to whether interocular variability is linked to ocular dominance.

For this reason we examined 20 eyes of ten healthy individuals (eight women with an average age of 50.2 years and two men with an average age of 59 years). We mentioned directional (hole-in-the-hand and pointing-a-finger test) and sensory dominance (Worth dot test and fogging test) in all the individuals. We conducted the fMR examination according to the above-stated method using a black and white chessboard with a size of 25.8 x 16.2 degrees.

In all persons we determined varying interocular fMR activity. The difference was not statistically significant (p = 0.85) and constituted 2.2%. Neither directional nor sensory ocular dominance corresponded with this finding (25).

An analysis of the above results raised the question as to whether a role may be played in ocular dominance also by the size of the image projected onto the retina. We examined the same group of people as in the previous experiment, but this time we used two different sized visual fields for stimulation (25.8 x 16.2 and 2 x 2 degrees).

In all persons we determined varying interocular variability, but we recorded a larger difference in the smaller field. Neither directional nor sensory dominance correlated with the extent of activation of fMR, and we also did not record directional laterality following separate stimulation of each eye (24).

4.2 Functional MR in hypertensive and normotensive glaucomas

We have had doubts concerning damage which influences only axons of the ganglion cells of the retina in HTG since 1987, when we simultaneously measured pattern electroretinogram (PERG) and pattern visual evoked potential – PVEP. The measurement was conducted on a healthy, twenty year old man, initially at an intraocular pressure of 15 mmHg. We subsequently increased intraocular pressure to 40 mmHg using a suction cup and repeated the examination. To our surprise, a blockage of transmission of electrical changes of voltage occurred on the level of the ganglion cells of the retina, whilst we obtained a virtually unchanged PVEP response from the visual centre. On the basis of this finding, we came to the conclusion that the initial changes will not be on the level of the axons of the ganglion cells, but of the cells themselves (22).

Due to the virtually unchanged generated visual responses in the second attempt, we expressed a suspicion that the pathogenetic process in HTG involves not only the ganglion cells of the retina, but also the visual pathway and the cortical visual centres. In the period around 1987, only CT and SPECT instruments were available for imaging the brain. Neither of the examinations was capable of demonstrating damage on the level of the cells themselves. As a result, in 2002 we examined a patient with hypertensive glaucoma in both eyes using positron emission tomography. We demonstrated a deficit of the content of fluorodeoxyglucose (FDG) in the patient within the area of the visual cortex, and thus also damage to the cortical cells of the visual centre (23).

Because this concerned a financially demanding examination, which also burdened patients with radioactivity, we did not continue further with this diagnostic method. In 2010 we transferred to examination using fMR. The stimulus for this was the results of PERG and PVEP, which demonstrated that in the case of developed HTGs with defects of the visual fields, the electrical responses of the visual pathway differed from the responses in the case of NTG. With the help of PERG and PVEP we examined 80 eyes of 40 patients. Thirty of these had HTG of three different types: ten patients had primary open angle glaucoma (POAG), ten patients had pigment glaucoma (PG), ten had pseudoexfoliative glaucoma (PEXG) and ten had normotensive glaucoma (NTG). We compared the results of the structural and psychophysiological examinations with a group of 40 of 20 healthy individuals of approximately the same age and refraction.

With the help of PERG and PVEP we determined that in the case of hypertensive glaucomas of various etiology (POAG, PG, PEXG), damage to the entire visual pathway occurs (from the retinal ganglion cells up to the visual cortical centres in the brain). From this group, patients with PG suffered the largest damage to the visual pathway. In the case of NTG the responses of the retinal ganglion cells were normal, but significant changes were demonstrated in the visual pathway (17). On the basis of these results we stated that the cortical cells of the visual centre may be damaged in the case of HTG, in contrast with NTG.

Noteworthy results were produced by the structural examination of the peripheral part of the visual pathway. For an assessment of the size of the corpus geniculatum laterale (CGL) in the case of HTG and NTG we examined a group of 9 patients with HTG and 9 patients with NTG (Philips Achieva TX series release 3.2.1.1). The diagnosis was determined on the basis of a complex ophthalmological examination, which was supplemented by an examination of the visual field using a fast threshold program. The sum of sensitivities in the homolateral halves of the visual field (on a scale from 0 to 22 degrees) was compared with the size of the contralateral CGL. We compared the results of the measurement with a group of 9 healthy individuals and subjected the results to a statistical analysis using a Wilcoxon test and a Spearman's rank correlation coefficient. We determined a reduction of CGL in both HTG and NTG ($p = 0.0000$). The reduction of CGL was not statistically dependent upon the degree of progression of the changes in the visual fields in HTG for the right halves of the visual fields (RHVF) and left CGL $r = 0.3255$, $p = 0.3926$, and for the left halves of the visual fields (LHVF) and right CGL $r = 0.0033$, $p = 0.9934$).

Similarly, in the case of NTG we did not determine any statistically significant difference between RHVF and left CGL ($r = 0.0496$, $p = 0.1745$) or between LHVF and right CGL ($r = 0.5399$, $p = 0.1335$ (22)).

In order to confirm the hypothesis, based on the previous PERG and PVEP examinations, that the cortical cells of the visual centre may be damaged in the case of HTG, in contrast with NTG, we conducted an examination of the visual cortical centres of the brain using fMR.

The first study was focused on the range of activations of fMR in hypertensive glaucomas, with the aim of determining whether there was a correlation between the degree of progression of the disease and the range of activation in the case of HTG.

We examined nine patients with variously advanced changes using the BOLD method and stimulation using a black and white chessboard (fig. 3).

The complex ophthalmological examination was supplemented by an examination of the visual field using a glaucoma fast threshold program. The sum of sensitivities in the homolateral halves of the visual field (in a range of 0 to 22 degrees) was compared with the fMR activity of the contralateral hemisphere.

We compared the results with a group of eight healthy individuals. With the help of a non-parametric Spearman's rank correlation, the determined data demonstrated a medium -strong dependency between changes in the visual field and activations of fMR. For the right half of the visual fields and the left hemisphere $r = 0.0667$ ($p < 0.05$), for the left half of the visual fields and the right hemisphere $r = 0.767$ ($p < 0.016$).

In this study the results confirmed that fMR activity decreases with the progression of changes in the visual fields (16, 21, 23).

In a further study we used the same method to examine eight patients with NTG (incipient to medium stage), and we compared the results with a group of eight healthy individuals.

Similarly as in the previous study, we proceeded also in an evaluation of the results (non-parametric Spearman's rank correlation). The correlation coefficient indicated a weak, indirect correlation between changes in the visual field and fMR activity. The relationship between the sum of sensitivities of the right halves of the visual fields and activity of the contralateral occipital lobe was $r = -0.270$ ($p = 0.558$) and of the left haves and the contralateral occipital lobe was $r = -0.071$ ($p = 0.879$).

No relationship was demonstrated between changes in the visual field and fMR. The results demonstrated that pathogenic behaviour in NTG is different from HTG (18, 21, 23).

Because damage to all types of ganglion cells occurs in the case of HTG, it is evident that there must be a colour sensitivity disorder in HTG patients. This fact has been known since 1883, when it was demonstrated by Bullem (6) and subsequently confirmed also by other authors, who specified the defect within the yellow-blue region (8, 35, 36) and demonstrated progression with the advancement of HTG (13).

As a result, in a further study we attempted to determine whether fMR activity changes upon the use of various stimulation, and as a paradigm we used both black-white and yellow-blue stimulation, which had not previously been used in any cited study.

We examined eight HTG patients (various stages) and compared their results with the results of eight healthy individuals.

The results were surprising. We determined that the difference in the number of activated voxels in the HTG patients upon the use of black-white versus yellow-blue stimulation was 59%. In the control group this was only 2%.

Whereas in the case of HTG the difference between black-white and yellow-blue stimulation was statistically significant at 1606 voxels ($p = 0.039$), in the control group no difference was determined ($p = 0.18$).

We therefore demonstrated that there is a greater decrease of fMR activity in HTG upon the use of colour paradigms than black and white (21, 23, 24).

If HTG was pathogenically the same group as NTG, the fMR finding following colour stimulation would be similar.

For confirmation of this hypothesis, we examined eight patients with NTG and compared the results with the results of eight healthy individuals. The average number of activated voxels following black-white stimulation in the NTG patients was 7 626. In the control group the average number was 7 462. The average number of activated voxels following yellow -blue stimulation was 5 650 in the NTG patients, in the control group 6 353. This difference was not statistically significant.

The average value of the difference in the number of activated voxels between black-white and yellow-blue stimulation was 6% in NTG patients. In healthy individuals this difference was equal to 2% (19, 21, 23, 34).

By this experiment also, we demonstrated that the pathogenic behaviour of HTG is different from that of NTG.

4.3Changes of fMR in age-related macular degeneration

Boucard et al. used MR to examine the grey matter of the cerebral cortex in patients with glaucoma and ARMD. The conclusion of their study was that long-term retinal pathology acquired in later life is connected to a reduction of the density of grey mater of the occipital cortex (3).

This conclusion is in accordance with our results on hypersensitive glaucoma. However, we could not find a correlation between damage to visual cortical cells and ARMD. In the case of ARMD, which is characterised by primary damage to the pigment epithelium and the photoreceptors of the retina, damage to the ganglion cells of the retina, primarily in the exudative form of ARMD, is secondary and transsynaptic degeneration, and it is possible to assume an association between the damage to the ganglion cells of the retina and alteration of the ganglion cells of the visual cortex.

Damage to the pigment epithelium and photoreceptors of the retina in ARMD, as well as to the ganglion cells of the retina themselves, was described by Kim et al. and by Medeiros and Curcio (14, 29).

In our study we attempted to find a relationship between the degree of progression of wet form ARMD and activity of the visual centre. We included ten patients with variously advanced bilateral exudative form ARMD (9 women and 1 man) with an average age of 74.7 years in our study cohort. We conducted functional MR with the help of stimulation using a black and white chessboard with a size of 25.8 x 16.2 degrees. With regard to the pronounced alteration of central visual acuity, we conducted the examination simultaneously in both eyes. We compared the findings with the results of nine healthy individuals with an average age of 54.1 years. In order to compare the results of both groups, we adjusted the results of the healthy group to the average age of the first group.

We processed the results using a Mann-Whitney U test. Through a comparison of both groups we determined a statistically significant difference between the groups ($p = 0.0247$). We concluded that patients with ARMD have lower fMR activity than the healthy population (20).

4.4 Changes of fMR following peeling in symptomatic lamellar macular hole and macular pseudohole

Upon peeling of the epiretinal membrane (ERM) with the membrane limitans interna (MRI) in the case of lamellar macular holes and macular pseudoholes of the retina, it is not possible to prevent direct damage not only to the axons of the ganglion cells of the retina (15), but also to the Muller cells (MC) themselves, since the MLI is a component of these cells. MC have immense metabolic activity, and amongst other factors convert also excitotoxic glutamate into non-toxic glutamine. The accumulation of glutamate in the damaged retina may lead to apoptosis of the ganglion cells of the retina (4).

The aim of our study was to determine whether ERM or MLI peeling in the case of macular hole and pseudohole can lead to a reduction of the fMR response to light stimulation. We included 20 eyes of 10 patients (7 women and 3 men) with an average age of 75.1 years, on whom pars plana vitrectomy with MLI peeling had been performed in one eye (between January and October 2009), in the study. The patients did not have any other ocular or neurological pathologies. Over the course of four years, fMR was performed on all the patients with stimulation using a black and white chessboard (fig. 3) with a size of 25.8 x 16.2 degrees in each eye separately and both eyes simultaneously. For the statistical processing we used a pair t-test. In all the patients we determined a decrease of fMR activity following stimulation of the operated eye. The analysis demonstrated a statistically significant difference between the operated and non-operated eye ($p = 0.0049$). The results demonstrated that following ERM and MLI peeling there is a decrease in fMR activity after a certain time (27).

Reduction of fMR activity of the visual centre following MLI peeling can be explained by means of damage to the retinal ganglion cells (either directly through perioperative damage to their axons or indirectly via damage to the Muller cells of the retina) and subsequent damage to the cortical ganglion cells via transneuronal (transsynaptic) degeneration.

CONCLUSION

In our studies we demonstrated the relationship between damage to the ganglion cells of the retina and fMR activity of the visual cortex of the brain in HTG, exudative ARMD and following EMM and MLI peeling for lamellar hole and pseudohole of the macula.

On the contrary, in the case of NTG, in which the ganglion cells of the retina do not manifest signs of damage, the values of fMR are without alteration.

Lower fMR activity following EMM and MLI peeling in the operated eye had not hitherto been described, and represents a certain warning against excessive radicalism in these operations.

Also of large significance is the finding of damage to the visual centre of the brain in patients with ARMD, for whom worldwide treatment has focused only on therapy of the outer layers of the retina.

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