Is Mental Stress the Primary Cause of Glaucoma?

Ist Stress die primäre Ursache von Glaukom?

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ABSTRACT

The prognosis of going blind is very stressful for patients diagnosed with "glaucoma". Worries and fear of losing independence is a constant mental burden, with secondary risks of depression and social isolation. But stress is not only a result of glaucoma but also a possible cause (risk factor). This should not be surprising, given that chronic stress can trigger "psychosomatic" organ dysfunctions anywhere in the body. Why should the organ "eye" be an exception? Indeed, glaucoma patients often suspect that severe emotional stress caused their visual field loss or "foggy vision". The hypothesis that stress is a possible cause of glaucoma is supported by different observations: (i) acute and chronic stress increases intraocular pressure and (ii) long-term stress can lead to vascular dysregulation of the microcirculation in the eye and brain ("Flammer's syndrome"), leading to partial hypoxia and hypoglycaemia (hypo-metabolism). Even if nerve cells do not die, they may then become inactive ("silent" neurons). (iii) Degenerative changes have been reported in the brain of glaucoma patients, affecting not only anterograde or transsynaptic areas of the central visual pathway, but degeneration is also found (iv) in brain areas involved in emotional appraisal and the physiological regulation of stress hormones. There are also psychological hints indicating that stress is a cause of glaucoma: (v) Glaucoma patients with Flammer's syndrome show typical personality traits that are associated with low stress resilience: they often have cold hands or feet, are ambitious (professionally successful), perfectionistic, obsessive, brooding and worrying a lot. (vi) If stress hormone levels and inflammation parameters are reduced in glaucoma patients by relaxation with meditation, this correlates with normalisation of intraocular pressure, and yet another clue is that (vii) visual field improvements after non-invasive current stimulation therapy, that are known to improve circulation and neuronal synchronisation, are much most effective in patients with stress resilient personalities. An appreciation of stress as a "cause" of glaucoma suggests that in addition to standard therapy (i) stress reduction through relaxation techniques should be recommended (e.g. meditation), and (ii) self-medication compliance should not be induced by kindling anxiety and worries with negative communication ("You will go blind!"), but communication should be positive ("The prognosis is optimistic").

ZUSAMMENFASSUNG

Die Prognose durch „Glaukom" zu erblinden ist für Patienten psychisch extrem belastend, denn Sorgen und Ängste, die Selbstständigkeit zu verlieren, bedeutet Dauerstress mit dem Risiko von Depression und sozialer Isolation. Dass Stress nicht nur Folge, sondern auch Ursache (Risikofaktor) von Glaukom sein kann, sollte nicht überraschen, da chronischer Stress „psychosomatische" Organschädigungen im ganzen Körper auslösen kann. Warum sollte das Organ „Auge" da eine Ausnahme sein? In der Tat vermuten Glaukompatienten oft, starke emotionale Belastung sei Auslöser eines Gesichtsfeld-

verlusts oder „Nebelsehen“ gewesen. Diese Hypothese wird durch zahlreiche Beobachtungen unterstützt: (i) Stress erhöht akut und chronisch den Augeninnendruck und (ii) Dauerstress ist mit vaskulärer Dysregulation der Mikrozirkulation in Auge, Gehirn und anderen Organen assoziiert („Flammer-Syndrom“). Die Folgen sind partielle Hypoxie und Hypoglykämie (Hypometabolismus), die Neuronen nicht absterben lassen, sondern diese akut oder chronisch inaktivieren („stumme“ Neuronen). (iii) Bei Glaukompatienten wird von degenerativen Veränderungen im Gehirn berichtet, und zwar nicht nur in anterograden oder transsynaptischen Kerngebieten des zentralen Sehsystems, sondern auch (iv) in Kerngebieten, die an emotionaler Bewertung und physiologischer Stresshormonregulation beteiligt sind. Auch psychologische Beobachtungen unterstützen die Idee von Stress als Ursache: (v) Glaukompatienten mit Flammer-Syndrom zeigen typische Persönlichkeitsmerkmale, die mit geringer Stressresilienz assoziiert sind: Sie spüren oft kalte Hände oder kalte Füße, sind ambitioniert (beruflich erfolgreich), perfektionistisch, zwanghaft, grübeln viel und machen sich oft Sorgen. (vi) Wenn bei Glaukompatienten durch Meditation Stresshormonspiegel und Entzündungsparameter reduziert werden, korreliert dies mit einer Normalisierung des Augeninnendrucks und (vii) Gesichtsfeldverbesserungen nach einer Reizstromtherapie. Diese Art der Therapie, welche die Durchblutung und neuronale Synchronisation verbessert, ist bei Persönlichkeiten mit hoher Stressresilienz deutlich effektiver. Aus der Erkenntnis „Stress als Ursache von Glaukom“ folgt, dass ergänzend zur Standardtherapie (i) Stressreduktion durch Entspannungstechniken empfohlen werden sollte (z. B. Meditation) und (ii) zur Befolgung der Selbstmedikation keine Prognosen kommuniziert werden, die Angst und Sorgen erhöhen („Sie werden blind“), sondern solche, die Stress reduzieren („die Prognose ist optimistisch“).

The mental Suffering of Glaucoma Patients

The statement that “you will go blind” leads to enormous mental stress for patients and those around them as their thoughts are dominated by fear of a black future, often repeatedly throughout the day. They worry constantly that things regarded previously as “normal” (reading, watching television, recognising faces, driving or going for a walk) will no longer be possible. Patients brood, often obsessively, about how it will be when they can no longer take part in social life, lose their independence or rely in the future on the support of their family and social environment, thus becoming a “burden” to their friends and relatives.

This fear persists especially when visual impairment progresses slowly. These fears are usually overcome more readily with sudden loss of vision as patients can usually adjust well to the new situation after a period of “grieving” and can accept their visual impairment. The slow progression of glaucoma, however, means long-term sustained stress as vision deteriorates increasingly and there is no foreseeable “end” to the search for solutions. Patients should not be left alone with their stress as a result of vision loss.

In glaucoma, the rise in intraocular pressure at least can usually be treated successfully. Since raised intraocular pressure can in turn be a cause of or unfavourably affected by stress, however, we suggest that mental stress is not only the consequence of impaired visual performance but is also a primary cause – especially of glaucoma, but also of other eye disorders. This has far-reaching consequences for ophthalmology as both psychological and physiological brain mechanisms would have to be considered in the development and treatment of glaucoma.

Prevalence and Aetiology

Of the 560,787 persons in Germany with severe disability in 2013, roughly 357,000 suffered from blindness and visual impairment [1]. Unlike refractive errors, diseases of the nervous system (retina, optic nerve, brain) are regarded as irreversible [2], as loss of vision is untreatable according to traditional medical orthodoxy. One of the largest disease groups is represented by glaucomatous damage of the optic nerve and retina (e.g., open-angle and angle-closure glaucoma), which can lead to visual field defects. Stress is not suspected as a cause since the main risk factor is thought to be raised intraocular pressure (IOP) only [3]. It is now known, however, that the situation is more complex as other mechanisms can also explain the ocular pathology. These include ischaemia/hypoxia and vascular spasm, endothelial dysfunction due to disorders of vascular autoregulation [4], mitochondrial dysfunction with oxidative stress [5], glutamate excitotoxicity [6], reduction in neurotrophins [7], inflammation and glial activation [8], nitrogen dysregulation [9] as well as central insulin resistance [10, 11]. The large number of these pathogenic mechanisms explains how glaucoma can occur despite normal IOP (“normal-tension glaucoma”) and how vision loss progresses despite lowering of the IOP (by surgery or eyedrops) [12]. These other potential causes are denoted in the recent literature as “non-IOP” mechanisms.

Since central nervous system control of the body in particular is greatly influenced by psychological factors and all organs can be affected by elevated stress hormone levels, this raises the question of the role of mental stress in the development of glaucoma. Could stress thus be not only the result but even the primary cause of glaucoma? Clinical experience shows that glaucoma patients often report that their vision loss occurred at a time of enormous or chronic stress due to occupational, financial, private or health problems. Many a person even suspects that this stress might be connected with the onset of the vision loss, though this has so far been largely disregarded.

Historical Consideration of Stress and Glaucoma

The important part played by the mind in visual impairment in general and glaucoma in particular has been a subject of discussion in Germany, especially since the 1950s, for instance in Böhringer’s “Psychiatry of primary glaucoma” (1953) [13], Schultz-

Zehden's presentation of "Psychosomatic medicine in ophthalmology" [14], or the beneficial effect of autogenic training on IOP in glaucoma published by Strempel et al. [15, 16].

The suggestion that stress can be one of the main causes – and not only the result – of loss of vision even goes back to antiquity. Similar indications are found in ancient scriptures from Europe and from the Middle and Far East:

The Old Testament of the Bible (psalm 6 verse 7; Job 17) [17], for instance, contains the following verse: "Surely there are mockers about me, and my eye dwells on their provocation. … My eye wastes away because of grief …".

The Koran (12 : 84) also states: "And he turned away from them and said: 'O my sorrow for Yusuf!'; his eyes became white (blind) from grief and so he held back his distress (sorrow)".

The old texts of traditional Indian ayurvedic medicine also hint at stress as a cause of visual impairment. The "Susruta Samhita" [18], a book written in Sanskrit about 3,000 years ago (1.300 BC) by the surgeon Susruta, is the major basis of traditional ayurvedic medicine, which is still popular in India today. The chapter on eye diseases gives 18 causes of the development of vision loss, one-third of which are associated with excessive stress. These include abnormal sleep habits, such as sleeping during the day or frequent waking at night (Swapna Viparyaascha), continuous weeping (Prasakta Samrodhana), excessive anger (Kopa), stress and pain, physical and mental exhaustion (Klesha), the suppression of tears (Bhashpa Grahath), as well as sorrow/distress (Shoka), which were also mentioned in the Bible and Koran.

It will repeatedly have struck the compassionate doctor that patients are often mentally very stressed when they first attend the ophthalmologist because of a visual field defect or learn about raised intraocular pressure and the risk of possible blindness from a routine test. Even though stress has repeatedly been described in the literature as the cause of vision loss [2], an association between "stress" and glaucoma is not recognised in clinical practice and is often vehemently denied, even when patients suspect such an association from their personal experience.

What is the scientific evidence that mental stress is not only a risk factor, but can also be a primary cause? Before addressing this question more closely, we shall first review the known psychological and biological mechanisms of the stress reaction and recall how extensively different organ systems apart from the eyes are affected by stress: the central and peripheral nervous system, the endocrine and cardiovascular system, and the immune system. All these systems are in turn dependent on the mental state or are influenced by it.

Stress, peripheral nervous System and Endocrinology

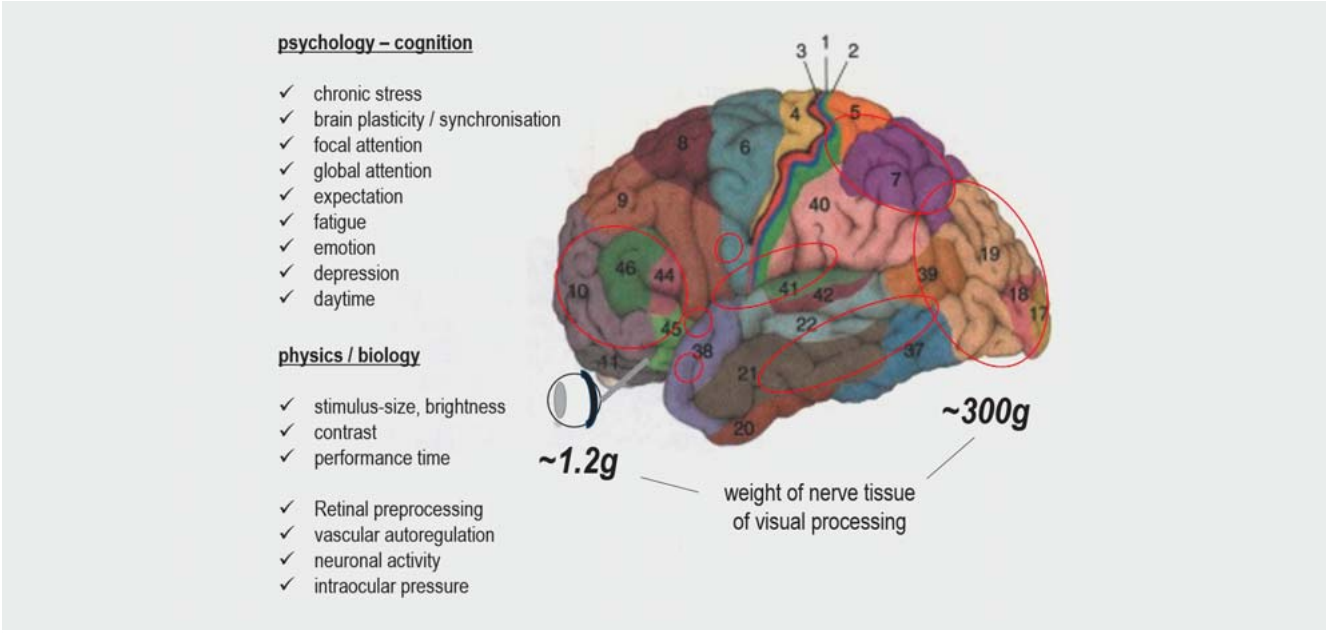
Both acute and chronic stress can have a negative influence on the onset or course of visual impairment [2]. Stress is caused by environmental stimuli ("stressors"), but the effect of these depends critically on how a person perceives this stressor subjectively. A hiker in the African savanna will experience a lion running straight towards him differently than a big game hunter who had to acquire an expensive hunting permit and is standing prepared with a loaded gun. Stressors are rarely life-threatening, but they are numerous in a world of boundless occupational, financial, personal and health challenges. Resistance (resilience) to stressors depends on personality structure, among other things, which can be described by a person's degree of openness, emotional stability (low neuroticism), reliability, agreeableness and extraversion.

To understand the causal significance of stress in glaucoma (and other eye diseases), the physiological mechanisms of the stress reaction in particular are of fundamental importance as well as psychological features: when stressors at the emotional level produce mental stress, this causes a physical activation. The body has two physiological activation systems: the sympatho-adrenomedullary system (SAM), on the one hand, which is part of the autonomic nervous system, and on the other hand the neuroendocrine hypothalamic-pituitary-adrenal axis (HPA). Both systems are controlled through neural brain networks that are involved in processing emotions. These include nuclei in the brainstem, hypothalamus and pituitary, the prefrontal cortex (PFC), the cingulate gyrus, the amygdala and the hippocampus. These regions evaluate the emotional "valency" (importance) of a stimulus and initiate a corresponding mental and physical reaction [2]. Activation of the SAM leads to vasoconstriction of peripheral blood vessels, an increase in heart rate and blood pressure and an increase in lung function (respiration). The physical reaction serves to maintain homeostasis under conditions of increased (activation) need [19]. Corresponding changes can take place within an extremely short time and are associated with a reduction in parasympathetic activity. The body is prepared optimally for a "fight or flight" reaction by the release of stress hormones (e.g., cortisol), which is important for the individual's survival.

By contrast, the reaction of the HPA axis to a stressor is slower. Signal inputs into this system lead to activation of neurons in the paraventricular nuclear region of the hypothalamus. These secrete hormones (corticotropin-releasing hormone, vasopressin) into the portal vein system of the median eminence, which leads to release of adrenocorticotropin (ACTH) by the anterior pituitary (adenohypophysis). In the adrenal, this causes synthesis and secretion of glucocorticoids (cortisol), and energy is supplied accordingly to the organism by gluconeogenesis, which is urgently required in the event of flight or fight.

Immunological Aspects of Glaucoma

Besides the SAM and HPA axis, the immune system is another element that is activated in reaction to a stressor and its interaction with the SAM and HPA is complex. It has long been known that inflammation is of great importance in vision loss. A detailed overview would be beyond this review and can be found elsewhere [20 – 22]. As the following discussion shows, repeated chronic stress, which produces a sustained elevation of stress hormone levels, can lead to weakening of the immune system and blood supply (autoregulation disorder of the microcirculation, see below). Moreover, stress can also cause functional and morphological changes in brain structures that are responsible for controlling adaptation systems [23].



▶ **Fig. 1** Factors influencing the processing of visual stimuli.

Degenerative Changes in the Brain

The brain is the crucial control centre for processing visual stimuli as "vision" is not only a sensory stimulus but depends critically on numerous neural influences and brain functions (▶ **Fig. 1**). There have been increasing reports in recent times of the most varied degenerative changes in the brain of glaucoma patients, which can involve both visual and non-visual (emotional, cognitive) brain areas. This suggests that chronic stress leads to flooding of the brain with glucocorticoids in glaucoma patients, which can be toxic not only for the eye, the retina and the optic nerve. Apart from the primary optic tract, other brain areas also degenerate, such as the hippocampus, prefrontal cortex [24, 25], amygdala [26] and other structures (see ▶ **Table 1**). It is often assumed in glaucoma that the progressive loss of vision arises only due to the degeneration of ganglion cells, the sole "cause" of which is raised intraocular pressure. This point of view is too narrow, however, both as regards the extent of the damage and the cause of it. And further mechanisms ("non-IOD") are increasingly proposed (see above) as visual loss often progresses despite a reduction of the intraocular pressure [27]. Interestingly, pathological changes such as cell damage and cell death in the eye are also found in other neurodegenerative disorders of the brain such as Alzheimer's disease and Parkinson's disease [28], which cannot be explained only by anterograde or even transsynaptic degeneration. Accordingly, it is obvious that glaucoma and other neurodegenerative diseases have a common cause. For example, oxidative stress and glutamate toxicity play an important role in both neurodegenerative diseases and in damage to the visual system due to glaucoma [28]. In the latter disease, such damage is found not only in the retina and optic nerve but also along the primary optic tract such as the optic radiation [29], the lateral geniculate body nucleus of the thalamus (LGN) and the visual cortex [30]. In glaucoma patients a 41 % and 47 % reduction in dendrite complexity was found in magnocellular layer 1 and in parvocellular layer 6 of the LGN respectively compared with healthy subjects [31], and MRI measurements showed diminished LGB volume in glaucoma patients [32]. This is of functional significance as changes in these visual brain structures correlate with the severity of glaucoma, i.e., structural anomalies correlate with clinical parameters [26] and neurological findings [30]. Since disease severity in patients with primary open-angle glaucoma depends on the retinotopic pattern of cortical atrophy and the anomalies of cerebral blood flow (CBF) in the visual cortex [33], it has been suggested that CBF [33] and analysis of cortical thickness [34] should be used in the future as biomarkers.

Functional Networks in the Brain of Glaucoma Patients

Besides structural changes in volume, abnormalities of functional networks have also been observed in the brain of glaucoma patients, which are detectable from brain physiology rather than morphology (▶ **Table 1**). These include loss of the functional connection between the primary visual cortex (area 17) and the right inferior temporal gyrus, the left fusiform gyrus, the left middle occipital gyrus and between the primary visual cortex and the right superior occipital gyrus, the left postcentral gyrus, the right precentral gyrus and anterior regions of the cerebellum [35]. Increased functional connectivity between the primary visual cortex and the left cerebellum and right middle frontal gyrus among other areas has been described. From this it can be concluded that glaucoma is not only an "eye disease" but is also a degenerative brain disease, which is associated with changes in connectivity be-

▶ **Table 1** Structural and functional changes in glaucoma patients. Reports in the literature on structural brain changes in patients with glaucoma and other visual disorders.

Affected structure	Change (structural, functional)	Reference
Visual brain structures		
Retina	▪ Degeneration of retinal ganglion cells	[28, 31, 76 – 78]
	▪ Atrophic peripapillary retinal nerve fibre layer	[41]
Optic nerve	▪ Degeneration	[30, 79]
Optic tract	▪ Degeneration	[28]
Lateral geniculate nucleus	▪ Degeneration	[27, 28, 30 – 32, 80, 81]
	▪ Reduction in volume	[26]
Optic radiation	▪ Degeneration	[28, 79]
Primary visual cortex	▪ Degeneration	[27, 28, 30, 33, 82]
	▪ Changes in functional connectivity	[35, 39]
	▪ Reduction in volume	[26]
	▪ Bilateral cortical thinning	[34]
	▪ Reduction in activity	[77]
Non-visual brain structures		
Anterior cingulate cortex	▪ Altered spontaneous brain activity	[39]
Insula	▪ Altered functional connectivity	[35, 40]
	▪ Altered spontaneous brain activity	[41]
Angular gyrus	▪ Increase in volume of grey matter	[36]
	▪ Reduction in amplitude of low-frequency fluctuations	[38]
Fusiform gyrus	▪ Cortical thinning	[34]
	▪ Altered spontaneous brain activity	[41, 42]
	▪ Altered functional connectivity	[35]
Precentral/postcentral gyrus	▪ Altered functional connectivity	[36, 39 – 42]
	▪ Decrease in volume of grey matter	
	▪ Altered spontaneous brain activity	
Cerebellum	▪ Altered functional connectivity to V1	[35]
	▪ Altered spontaneous brain activity	[39, 42]
Precuneus/cuneus	▪ Changes in volume of grey matter	[36]
	▪ Altered spontaneous brain activity	
	▪ Altered functional connectivity	[38 – 40, 42]
Frontal gyri	▪ Altered spontaneous brain activity (superior and middle frontal gyrus)	[38, 39, 41, 42]
	▪ Altered functional connectivity (middle and inferior frontal gyrus)	[40]
	▪ Reduction in volume of the grey matter (superior and inferior frontal gyrus)	[36]
	▪ Reduction in cortical thickness (frontal pole)	[26]
Temporal gyri	▪ Cortical thinning (middle temporal gyrus)	[34]
	▪ Altered functional connectivity	[35]
	▪ Increase in volume of grey matter (middle temporal gyrus)	[36]
Occipital gyri	▪ Altered spontaneous brain activity	[41, 42]
	▪ Altered functional connectivity	[35, 40]
	▪ Changes in volume of grey matter	[36]
Amygdala	▪ Reduction in volume	[26]

tween the visual cortex and associated visual areas [35 – 37] and frontal lobe [38].

In addition to these changes in visual brain structures, glaucoma patients show significant reductions in the grey matter of non-visual areas such as the lingual gyrus, calcarine gyrus, right cuneus and right supramarginal gyrus compared with control subjects. Increases in volume, on the other hand, are found in the middle temporal gyrus, superior parietal gyrus and precuneus [36]. An

abnormally altered pattern of spontaneous brain activity was also detected in these areas (anterior cingulate cortex, middle frontal gyrus, precentral gyrus and postcentral gyrus) [39] as well as altered (greater or lower) neural activity in the visual and sensorimotor cortices, in the frontal lobe and in the fronto-parietal network [40–41], that is, extensive abnormalities in areas that control cognitive functions and emotions [42]. These changes in non-visual areas of the brain support our hypothesis that mental stress is a possible cause of glaucoma.

Nevertheless, the cause-and-effect relationship between altered brain areas and stress is unclear: does stress damage brain areas and the retina or does the brain damage lead to an altered emotional assessment or processing of stressors and thus to increased experience of stress? This is a question that requires further research.

Stress, Vision Loss and vascular Dysregulation

Sustained elevations of stress hormone levels in the blood can ultimately lead to organ damage in the eye and brain through complex biological reaction chains. Not only is insufficient oxygen supplied to neural tissue at the time of increased need (for example when reacting to a visual stimulus), it can also have wide-ranging consequences at biochemical, physiological and psychological level [2]. This also suggests that stress – through its effect on blood vessels – is causally involved in the development of glaucoma. If this assumption of causality can be confirmed with further supplementary arguments, disorders of the visual system would also have to be regarded as psychosomatic diseases. This interaction (stress leads to vision loss and vision loss leads to stress) would then produce an insidious downward spiral: stress interferes with vascular function in visual structures and leads to vision loss. This vision loss then triggers emotional worry and stress, which in turn increases the loss of vision and so on [2]. The microcirculation possibly plays a crucial part in this vicious cycle (see ▶ **Fig. 1**–**4** below).

Since chronic activation of the stress system leads to glaucomatous changes in only a fraction of people, it must be assumed that the effect of stress on the microcirculation depends on a genetic predisposition, that is, whether endothelial cells in the eyes and brain (or their mitochondria) demonstrate a dysfunction, such as that found with "vascular dysregulation" [43]. In this condition, blood flow becomes unstable, resulting in mild but repeated reperfusion injury and oxidative stress, which particularly impairs the function of the mitochondria in the optic nerve [44]. Apart from vision loss due to glaucoma (especially in normal-tension glaucoma), this can also affect other brain functions, leading to the tinnitus, hearing loss, vertigo or stroke [45]. The description of Flammer syndrome (FS) was an important advance in our understanding of stress in certain forms of vision loss [46–48]. It represents a link between the biological stress reaction, the pathophysiological susceptibility of the microcirculation (endothelial cell integrity) and psychological influences, which are associated with a loss of vision when they occur together [46, 49–51]. FS has a hereditary component and is expressed by cold hands/feet, diffuse hypotension, slender stature and problems with falling and staying asleep [4]. These signs (probably) persist throughout life.

Persons with FS (FS^+) react differently to stress than persons without FS. These differences include imbalance in the autonomic nervous system, gastro-intestinal disturbances, tachycardia and increase in IOP [52]. In general, signs of FS are found at a physiological (increased sensitivity to pain and medications), hormonal (raised cortisol and endothelin-1) and psychological level [51]. From the psychological point of view, FS^+ persons exhibit a characteristic personality predisposition, which is characterized by perfectionism, ambition, excessive rumination and worrying. FS^+ patients have a tendency always to satisfy the demands of others while neglecting their own wishes and needs [2]. This is a source of permanent stress, which triggers a cascade of elevated stress hormone levels in association with endothelial dysfunction, resulting in vascular dysregulation [48]. This in turn results in neural inactivation due to insufficient supply of oxygen and glucose [51].

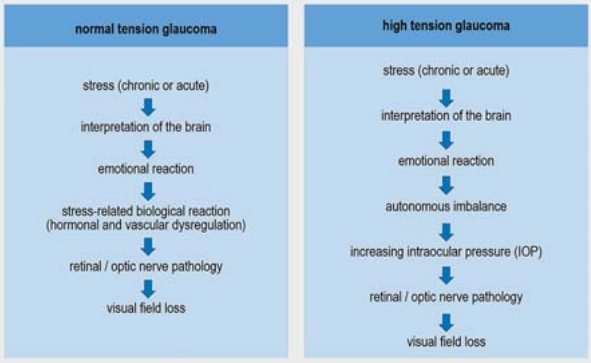
Vision Loss, Stress and the Brain

We propose that elevated stress hormone levels can be an important starting point for the development of glaucoma and possibly other forms of eye disease. The release of stress hormones is controlled by the interpretation of the stress-triggering stimulus by the brain (that is, one's own thoughts). Only stimuli that are experienced emotionally as stress generate a stress reaction. In other words, the brain and the individual experiences of the patient are a crucial starting point for the pathogenesis of glaucoma (and possibly other visual disorders) [2]. FS^+ patients in particular exhibit a markedly increased stress risk. The causal chains of events for the development of high-tension and normal-tension glaucoma are shown in ▶ **Fig. 2**.

Since the retina is brain tissue ontogenetically [10], glaucoma could also be regarded as a "brain disease in disguise", which relies on a functioning vascular system [2]. Visual perception is thus not only a "product" of the eyes but is above all the result of complex information processing in the brain. However, if the function of the eyes and brain is impaired because of vascular dysregulation, this increases the probability that neurons of the visual system are suffering from a hypo-metabolic state, which impairs central nervous system signal processing due to oxygen and glucose deficiency. This could also have direct consequences for other brain functions that have an influence on good vision such as: focal and global attention, fatigue, acute and chronic stress, emotions and microsaccades, which are used for high-resolution vision. There are other factors that can act indirectly on the eyes and brain and can influence vision. These include atmospheric pressure ("weather sensitivity"), intracranial pressure and circadian rhythms [53]. The brain is thus important for the (impaired) visual perception in two ways. On the one hand, it plays an important part in visual consciousness through its analysis and processing of visual stimuli. On the other hand, the emotional evaluation of a stimulus by the brain is the starting point for induction of a stress reaction, which itself can in turn cause vision loss. This shows that many factors "beyond" the eye must be considered, namely, the interaction of the eye, brain and vascular system.

The brain-eye-vascular Triad

The brain-eye-vascular triad (BEV) controls the psyche's "general terms and conditions" and ensures that all processes required for optimal visual performance work together in synchrony. ▶ **Fig. 3** shows the numerous interactions between these three organ systems. On the one hand, such complex interactions are a disadvantage as the most varied mechanisms can interfere with vision. On the other hand, however, this complexity also offers varied possibilities for improving visual performance. Because of the complexity of visual perception, it would make sense to understand and treat eye diseases in a "system approach" in the context of different organs and systems (including stress) [53]. Even if only a few regulatory mechanisms change (due to stress, intoxication or unhealthy lifestyle), this has an influence on the BEV triad and a sensitive balancing act determines if, how and when visual impairment will occur.



▶ **Fig. 2** Flowchart showing the development of normal-tension vs. high-tension glaucoma from a psychological perspective.

Stress and Personality

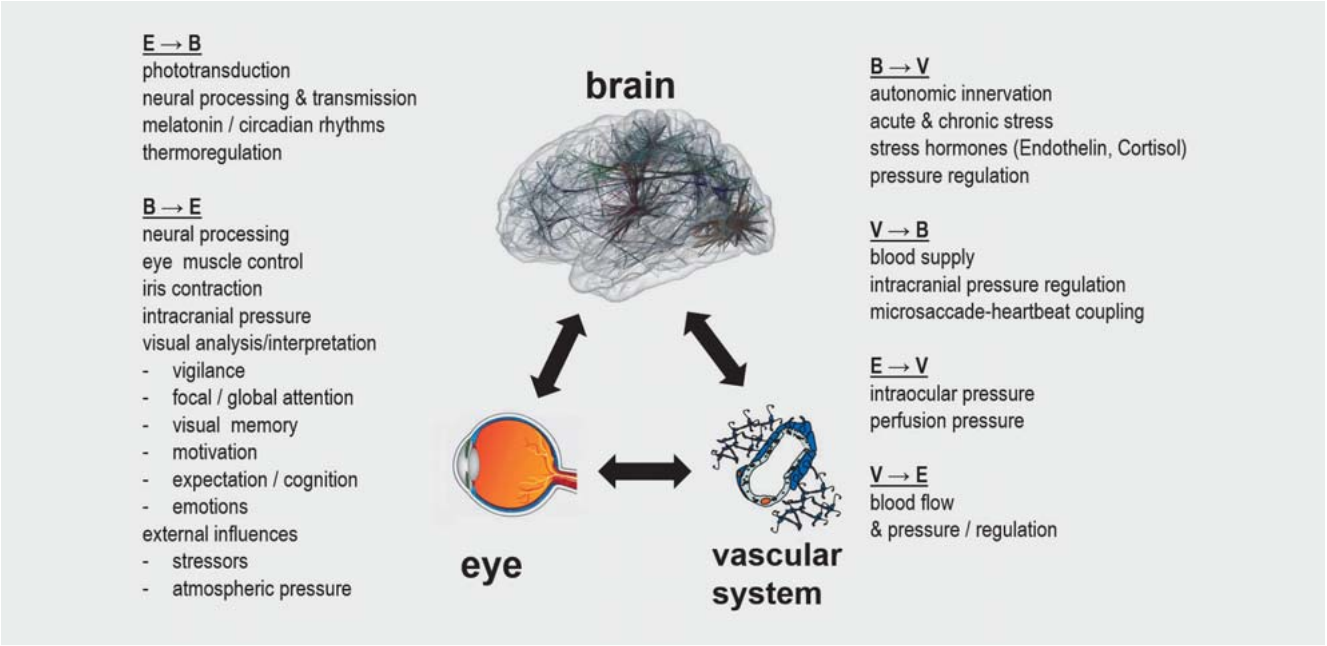
If a person suffers from sustained stress, this reduces their quality of life and is a burden for them and those around them [54]. To prevent this, people have different ways of reacting to stress and coping appropriately (adaptively) with stress. Whether a person is resilient or vulnerable to stressors is determined by their personality. Meta-analyses [55] have linked optimism, extraversion, conscientiousness and agreeableness with greater commitment in coping with stress, whereas greater neuroticism was associated with poor coping [56–58]. Maladaptive coping strategies and specific personality patterns (significantly higher neuroticism scores) were also found in glaucoma patients [59–61]. Hence, patients with specific personality features (negative coping styles) are exposed to a greater risk of glaucomatous visual impairment [2]. ▶ **Fig. 4** summarises the different aspects and shows how different disciplines (ophthalmology, biology, psychology) interact in a vicious cycle in the development of glaucoma.

Stress, Plasticity and Recovery of the visual System

Initial evidence for an association between stress, personality and visual impairment was demonstrated by a study on the role of personality factors in the recovery of visual performance. Neural damage in the retina and brain is partially reversible in glaucoma, as in other diseases of the optic pathway. Vision can (partially) recover when patients are treated with intensive vision training or with non-invasive microcurrent [62]. This recovery is possible because there are "silent" neurons in partially damaged areas of the retina and other parts of the brain. These neurons survive but cannot fire any action potentials to transmit visual stimuli because of a hypo-metabolic state (hypoxia, hypoglycaemia); however, they are activatable in principle. The brain has an enormous capacity for adaptation to damage-induced changes [63–65], which is denoted by the term "neuroplasticity". According to the residual vision activation theory [66] the damage of the visual system is typically not complete but there are sometimes pronounced regions with partial cell loss termed "areas of residual vision". "Silent" neurons, which can be activated and which represent the physiological foundation for ophthalmological and neurological rehabilitation, are probably located here. One reason for the hypo-metabolic state of the "silent" neurons could be an impaired blood supply, for instance caused by partial ischaemia or "vascular dysregulation", due to the so-called Flammer syndrome [52]. According to the neurovascular hypothesis of residual vision activation [67] reactivation of hypo-metabolic neurons is a key mechanism for the recovery or restoration of residual vision. Stress – and the associated vascular dysregulation – could be particularly important here. To find out whether stress is a cause and not only a consequence of glaucoma, the parameter "stress" (independent variable) is varied and the effect on vision (dependent variable) is investigated. We conducted two studies: (i) we studied the influence of the personality of patients with visual field defects (due to glaucoma or other diseases) on the extent of their functional recovery of vision after microcurrent therapy [51] and (ii) we had a group of glaucoma patients practise stress-reducing mindfulness meditation and studied the effect on IOP and associated changes in immunological and stress biomarkers [12].

Stress is an Obstacle to Recovery of Vision

In the first study, using the NEO-FFI personality profile questionnaire (NEO five-factor inventory to measure the degree of neuroticism, extraversion, openness to experience, agreeableness and conscientiousness), we recorded the stress level and signs of the Flammer syndrome in patients with glaucoma and other eye diseases after they had completed a rehabilitation programme to improve vision by microcurrent therapy [51]. This study explored the question of whether and how personality influences the treatment outcome. This idea arose from our clinical observation that people reacted very differently to the treatment. While about one third of the patients do not respond to the treatment, it is moderately to enormously successful in 2/3 of patients [62]. Non-responder patients often came across as nervous, tense and obsessive. This clinical experience was confirmed by our study as the non-responders showed high neuroticism scores in the personal-

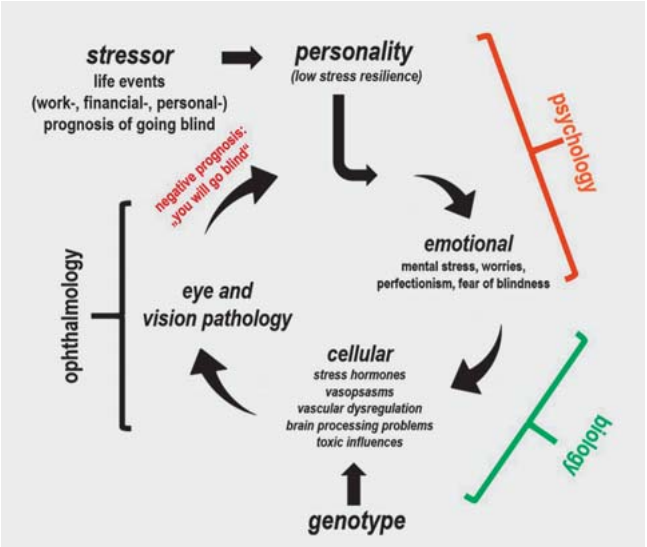


▶ **Fig. 3** Interactions between the eye (E), brain (B) and vascular system (V), showing the respective functions of the organs and their influence on, and interactions with, other organs and functions. Source: Reprinted from Restorative Neurology and Neuroscience 36, Sabel BA, Flammer J, Merabet LB, Residual vision activation and the brain-eye-vascular triad: Dysregulation, plasticity and restoration in low vision and blindness – a review. 767–791, Copyright (2018) with permission from IOS Press The publication is available at IOS Press through http://dx.doi.org/10.3233/RNN-180880 [rerif].

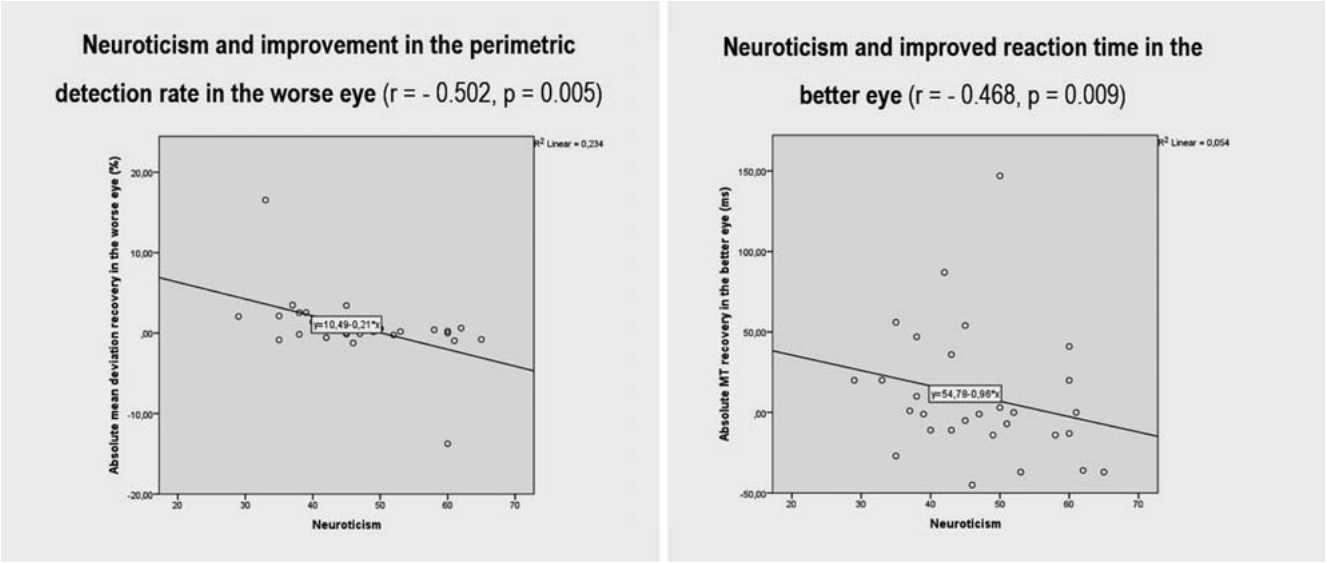
ity test and lower scores in conscientiousness, agreeableness, openness or extraversion (▶ **Fig. 5** and **6**), which corresponds to a "stress personality". Good recovery of vision, by contrast, was associated with lower neuroticism scores and higher conscientiousness scores. And individual questionnaire items that indicated a greater degree of extraversion, openness and agreeableness were also associated with a greater improvement in vision, as was the presence of FS. Interestingly, FS^+ patients not only react more sensitively to stimuli like emotional stress (or cold), but also show more obvious improvement with pharmacological therapy such as with calcium antagonists [68]. A possible explanation for the greater recovery of residual vision is that FS^+ patients have a greater proportion of inactive ("silent") nerve cells due to the vascular dysregulation, which can benefit from therapy (whether microcurrent or pharmacological).

The fact that patients with a stress-prone personality benefit less from a treatment emphasises the significance of psychosocial factors and stress for the success of (neuro-) rehabilitation. This supports our aforementioned hypothesis that stress is not only the result of vision loss but is also a main risk factor or cause of neuronal inactivation [51].

To underpin this causality, in a second study we reduced the stress factor by meditation training and examined whether this has an effect on IOP.



▶ **Fig. 4** Vicious cycle of stress, psychophysiological changes and vision loss . Negative prognoses increase stress with the risk of accelerated progression of visual field loss. Source: Sabel BA, Wang J, Fähse S et al. Personality and stress influence vision restoration and recovery in glaucoma and optic neuropathy following alternating current stimulation: implications for personalized neuromodulation and rehabilitation. The EPMA journal 2020, 66: 901. doi:10.1007/s13167-020-00204-3



▶ **Fig. 5** Higher neuroticism scores in the personality test correlate significantly with the recovery of visual performance through microcurrent therapy. The percentage improvement compared to the initial value (baseline) in the perimetric detection rate in the poorer eye (left) and the reaction speed in the better eye (right) are shown.

Mindfulness Meditation reduces Stress and normalises intraocular Pressure

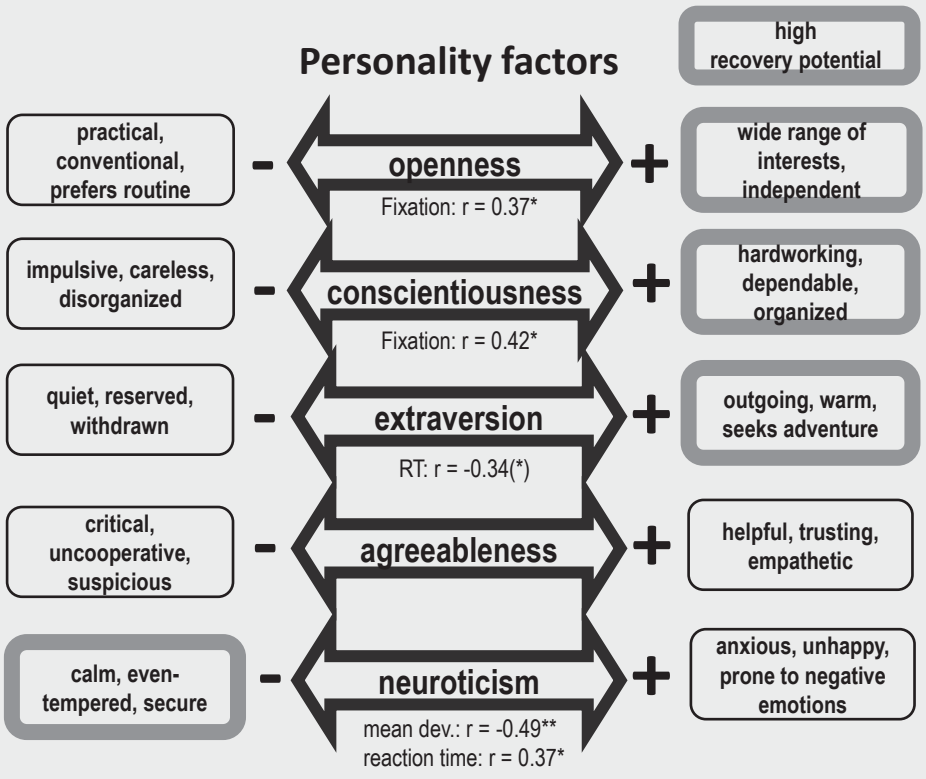
We investigated the effect of stress reduction by relaxation more closely in a clinical study with an Indian research group [12]. Patients with primary open-angle glaucoma practised mindfulness meditation for one hour daily for four weeks, an ancient and proven method of deep relaxation. Since elevation of IOP is regarded as the main cause of glaucoma and stress increases IOP [69], we measured the IOP before and after participation in the meditation programme [12]. Compared with a control group, those practising meditation showed normalisation of the IOP, increased quality of life and positive changes in stress biomarkers in the blood: increases in the β-endorphin level and brain-derived neurotrophic factor (BDNF), diminished stress hormone levels (cortisol, IL6, TNFα reduced) and various changes in gene expression. These results support the hypothesis of mental stress as one – or perhaps the decisive – cause of glaucoma.

The topic of "mental stress" has received too little attention to date in glaucoma research although the subject is of great public interest.

Scientific versus public Interest in Stress and Eye Disease

Despite the long-recognised risks of chronic stress for all organ systems of the body and its importance in medicine, the role of stress in the development of vision loss and restoration of vision is unknown. However, an analysis of the global literature database PubMed and Google confirms an astonishing disparity between scientific activity and public interest in the role of stress. We analysed a number of scientific reports in the area of psychology, psychosomatics and vision loss in various online platforms (as of 2020) (▶ **Table 2**). The total number of scientific studies on the subject of "Eyes and vision loss" (465,064) is relatively large but only a vanishingly small percentage of 1.12% had a reference of the topic of "mental stress" (5,210). This is surprising in view of the effects that stress can have on vision loss and this loss in turn on mental well-being. This extraordinarily low interest of (ophthalmological) research in the interface between stress and vision loss confirms what many patients complain of: the "lack of interest" of (research and practising) ophthalmology in addressing the psychological causes and consequences of "impending blindness".

It could be argued that the lack of involvement by ophthalmology research in psychobiological mechanisms of stress is due to the fact that both patients and the public regard psychological aspects as unimportant for the understanding and treatment of visual impairment. Since clinical experience suggests the opposite, however, we also performed a Google search and assessed the number of hits as a metric for "public interest" and compared it with the number of hits in PubMed (a metric of scientific activity). We found a surprising discrepancy between "interest of researchers" and "interest of the public": for each scientific publication yielded by the search terms "vision" and "eye" there are 1,486 and 16,074 Google hits respectively. This means that the ratio between scientific activity and general interest is 1 : 1.486–16.074. When visual and psychological terms are combined, the ratio is still 1 : 282. The rather sobering conclusion of the search is thus that although mental stress is of great importance for the public and especially for patients with visual impairment, the topic is largely ignored by the scientific community. In view of the fact that stress is a known risk factor that can also impair other mental and physical health, this result is all the more surprising.



▶ **Fig. 6** Influence of personality factors (NEO-FFI) on the functional recovery of visual performance after alternating current therapy. R values of the correlation of personality factors and perimetry results (mean deviation, fixation and reaction time [RT]; $^{(*)}p < 0.10$; $^{*}p < 0.05$, $^{**}p < 0.01$).

▶ **Table 2** Scientific versus public interest in the subject of visual impairment due to stress, quantified by the number of hits in an internet search in PubMed, Google and Google Scholar with the corresponding search terms.

Search terms	Medline (M) – PubMed	Google (G)	G : M ratio	Google Scholar (Gs)	Gs : M ratio
References to vision					
"eye"	451,776	6,340,000,000	14,033.50	4,840,000	10.71
"vision loss"	8,236	4,370,000	530.60	202,000	24.53
"low vision"	5,052	7,630,000	1,510.29	97,400	19.28
Total	**465,064**	**6,352,000,000**	**16,074.39**	**5,139,400**	**54.52**
References to stress					
"stress"	913,381	1,060,000,000	1,160.52	6,550,000	7.17
"psychosomatic"	21,902	6,680,000	304.99	626,000	28.58
"psychological stress"	122,252	2,540,000	20.78	954,000	7.80
Total	**1,057,535**	**1,069,220,000**	**1,486.30**	**8,130,000**	**43.56**
Combination of vision/stress					
"psychology vision loss"	4,443	994	0.22	3	0.00
"stress low vision"	309	6,820	22.07	2	0.01
"mental stress vision loss"	173	5	0.03	2	0.01
"psychosomatic eye"	205	1.110	5.41	40	0.20
"psychosomatic ophthalmology"	7	1.780	254.29	123	17.57
"mental stress low vision"	73	5	0.07	2	0.03
Total	**5,210**	**10,714**	**282.09**	**172**	**17.81**

Date of search: 27.04.2020

Conclusions for Practice and Outlook

Because of the variety of mechanisms that (can) lead to the development or progression of glaucoma, it is not sufficient to select only a single treatment approach (e.g., reduction of intraocular pressure). Traditional treatments such as eyedrops or surgery should be supplemented by a "holistic" approach that also considers psychological factors. The concept of "holistic" should not be confused with the term "alternative" as established methods are supplemented and not replaced in order to take as many relevant factors as possible into consideration in patient care [53]. Different treatment approaches can be combined to maximise residual vision and expand the patients' individual resources. For example, relaxation training can be recommended in parallel with the use of eyedrops to reduce IOP. This can include meditation, yoga, progressive muscle relaxation and autogenic training [15–16], which have been proven to reduce stress permanently [2, 69], normalise blood pressure [70–71] and IOP [72], and reduce stress hormones and strengthen immunity [12]. Psychological counselling should be suggested for particularly severe cases, so to improve coping strategies and develop a new outlook on life [53]. Transorbital alternating current stimulation (ACS) is another option. This procedure induces synchronous activation of neurons in the retina and brain on the one hand [77] and, on the other hand, produces better perfusion [53], which promotes the reorganisation of neuronal communication networks in the brain [73]. We are convinced that activation of "silent" neurons is possible by the use of holistic treatment approaches, which can contribute to partial restoration of vision [74].

Loss of vision, on the one hand, reduces subjective quality of life because of worry, anxiety and depression, where stress is a consequence of visual impairment. On the other hand, stress also induces numerous processes that, in the case of glaucoma, can ultimately result in its development or steady deterioration. Cause and consequence reinforce one another in a vicious cycle of progressive vision loss: stress leads to vision loss, which in turn leads to stress, which then worsens the vision loss and so on. Doctors, researchers, nursing and care staff and patients should be aware of the risk of this downward psycho-pathological spiral. We need to find ways to interrupt this vicious cycle. Because of the extensive interactions between the eye, brain and vascular system, ophthalmological diseases should be considered from physiological, biological and psychological points of view.

The proposal that stress is a cause of vision loss in glaucoma has a number of implications for clinical practice: (i) stress reduction techniques should be recommended not only as a supplement to established treatments of the vision loss but also as a means of preventing its progression. (ii) Doctors are urged to communicate positivity and optimism to their patients and absolutely avoid statements such as "You will go blind" so as not to increase the stress level unnecessarily, thereby hastening progression. Instead, adherence (e.g., to eyedrops) can be achieved by positive statements (e.g., "If you use the drops regularly, the prognosis is optimistic"). Positive encouragement is indicated, not generation of fear. (iii) Information about the importance of stress reduction and relaxation should also be provided and future medical treatments should aim to reduce the biochemical effects of stress hormones on the vascular system, and (iv) psychological interventions such as coping strategies, relaxation techniques or psychotherapy could become adjuvant methods of standard ophthalmological care. We need more openness and the knowledge that neurology, neuroscience and psychology can support and enhance ophthalmology in the treatment of glaucoma [67]. A holistic approach means providing new treatment elements based on a systemic (and not only eye-centred) perspective. In this context, recognition of the association between stress and vision loss can contribute to greater attention being paid to the proposal of predictive, preventive and personalised medicine [75]. We thus appreciate not only the eye as a single organ but also "the person behind the eye". Specifically, therefore, in addition to standard treatment, (i) stress reduction by relaxation techniques (e.g., meditation) should be recommended and (ii) for adherence to self-medication, no prognosis should be communicated that increases anxiety and worry ("you will go blind"), but rather communication that reduce stress ("the prognosis is optimistic").

Acknowledgements

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Conflict of Interest

B. Sabel is shareholder of an outpatient clinic (SAVIR-Center), where patients are treated with the procedures described here.

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