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REVIEW

Mental stress as consequence and cause of vision loss: the dawn of psychosomatic ophthalmology for preventive and personalized medicine

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Abstract

The loss of vision after damage to the retina, optic nerve, or brain has often grave consequences in everyday life such as problems with recognizing faces, reading, or mobility. Because vision loss is considered to be irreversible and often progressive, patients experience continuous mental stress due to worries, anxiety, or fear with secondary consequences such as depression and social isolation. While prolonged mental stress is clearly a *consequence* of vision loss, it may also aggravate the situation. In fact, continuous stress and elevated cortisol levels negatively impact the eye and brain due to autonomous nervous system (sympathetic) imbalance and vascular dysregulation; hence stress may also be one of the major *causes* of visual system diseases such as glaucoma and optic neuropathy. Although stress is a known risk factor, its causal role in the development or progression of certain visual system disorders is not widely appreciated. This review of the literature discusses the relationship of stress and ophthalmological diseases. We conclude that stress is both *consequence* and *cause* of vision loss. This creates a vicious cycle of a downward spiral, in which initial vision loss creates stress which further accelerates vision loss, creating even more stress and so forth. This new psychosomatic perspective has several implications for clinical practice. Firstly, stress reduction and relaxation techniques (e.g., meditation, autogenic training, stress management training, and psychotherapy to learn to cope) should be recommended not only as complementary to traditional treatments of vision loss but possibly as preventive means to reduce progression of vision loss. Secondly, doctors should try their best to inculcate positivity and optimism in their patients while giving them the information the patients are entitled to, especially regarding the important value of stress reduction. In this way, the vicious cycle could be interrupted. More clinical studies are now needed to confirm the causal role of stress in different low vision diseases to evaluate the efficacy of different anti-stress therapies for preventing progression and improving vision recovery and restoration in randomized trials as a foundation of psychosomatic ophthalmology.

Keywords Low vision · Psychology · Psychosomatic medicine · Relaxation · Restoration · Stress · Predictive · Preventive · Personalized medicine

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Introduction

About 285 million people are estimated to be visually impaired worldwide, including 39 million which are blind [1]. Unlike refractive errors caused by diseases of the cornea or lens which can be corrected by optic means or surgery, diseases affecting the visual nervous system (retina, optic nerve, brain) are widely assumed to be irreversible. If patients are informed of such a grim diagnosis and poor prognosis, they typically experience anxiety and fear of becoming blind. This creates a psychological double-burden; not only do they experience fear-inducing difficulties in daily life with reading, orienting, or mobility, but a negative prognosis typically has a

severe emotional impact, leading to worries, anxiety, fear, depression, and social isolation [2]. Thus, vision loss and emotional responses go hand in hand. Unless these patients are properly consulted, a long-lasting psychosocial and socioeconomic burden ensues.

At the outset, it seems obvious that vision loss and blindness lead to mental stress, i.e., stress being the *result* or *consequence* of the disease. But as we will now discuss, stress may actually also be a *causal* factor, i.e., contributing to the onset and progression of vision loss. This causality of stress, however, has not been systematically considered despite its relevance for the pathophysiology of certain "eye" diseases with nervous system involvement. The aim of this review is therefore to summarize the literature with the goal to untangle the relationship between vision loss and psychological factors both in research and in the clinical context from a holistic point of view. The underlying assumption is that stress management can help activate residual vision and restoration [3], augmenting current approaches to prevent further vision loss and to enhance rehabilitative efforts such as vision training [4, 5] or brain current stimulation [6–9].

Stress and vision loss

The idea that mental distress is one of the main *causes* of vision loss dates back to ancient times. In a Sanskrit book entitled "SUSRUTA SAMHITA," believed to be written as early as 1.300 BC [10], i.e., over 3000 years ago, a famous Indian surgeon named Susruta, practicing the ancient Indian traditional Ayurveda medicine, lists 18 different causes of vision loss (see first chapter on "Basics of Eye Diseases" with an excerpt shown in Fig. 1). Among them, six "causes" or signs of bodily or emotional stress are listed: improper sleeping habits like day time sleeping, awakening at night, etc. (SWAPNA VIPARYAASCHA); continuous weeping (PRASAKTA SAMRODHANA); excessive anger (KOPA); grief (SHOKA); stress suffering—pain, physical, and mental exhaustion (KLESHA); and suppression of tears (BHASHPA GRAHATH).

In agreement with this ancient proposal—and based on our clinical experience amalgamated with a thorough literature review pertinent to the recently described Flammer syndrome (FS) [11, 12], we now wish to propose that psychological stress is not only a *consequence* or just a minor "risk factor." Rather, it is one of the main *causes* of certain (but not all) cases of vision loss, particularly certain forms of glaucoma and optic neuropathy. If this causality proposition could be substantiated with convincing and coherent arguments, then some disorders of the visual pathways might be considered to have psychosomatic components or may even represent a "psychosomatic" disorder. If confirmed, this new understanding could lead to better management and new treatment options.

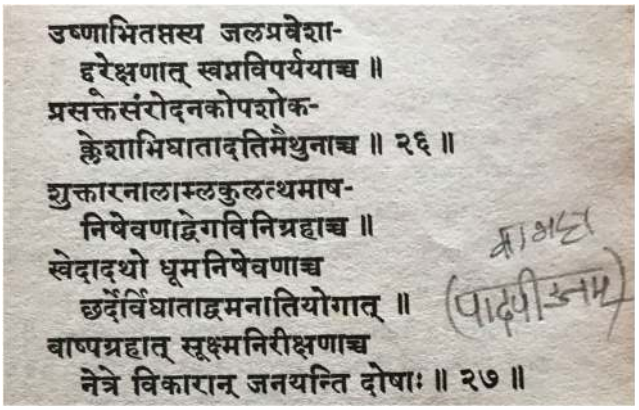

Fig. 1 Causes of vision loss taken from "SUSRUTA SAMHITA"[10], first chapter of "BASICS OF EYE DISEASES." The figure shows the original Sanskrit text passage with its transformation to Roman lettering and the respective English translation. Six causes of vision loss (printed here in **bold**) are related to emotional stress: 1. USNABHITAPTASYA JALAPRAVESHATH—Drinking or exposing to cool water after exposing to heat. 2. DOOREKSHANATH—Looking at the very distant objects regularly for a long time, may be without blinking. 3. **SWAPNA VIPARYAASCHA— Improper sleeping habits like daytime sleeping, awakening at night** etc. 4. **PRASAKTA SAMRODHANA—Continuous weeping**. 5. **KOPA— Excessive anger**. 6. **SHOKA—Grief**. 7. **KLESHA— Stress: suffering pain, physical, and mental exhaustion**. 8. ABIGHAATA—Minute irritative injuries or contusion injuries or perforating injuries. 9. ATI MAITHUNNA—Indulgence in excessive sexual intercourse. 10. SHUKTHA ARANALA AMLA—Vinegar and alcoholic beverages. 11. KULUTTA—Intake of horse gram excessively. 12. MASHA—Intake of black gram excessively. 13. ATISWEDA—Excessive sweating. 14. DHOOMA NISEVANATH—Exposing to smoke or tobacco smoking. 15. CHARDHIR VIGHATATH—Suppressing the vomit. 16. VAMANATHI YOGATH—Excessively indulging in inducing vomiting. 17. **BHASHPA GRAHATH—Suppressing tears**. 18. SUKSHMA NIREEKSHANATH—Observing the minute things or seeing too tiny objects

Before discussing our proposition in more detail, it is imperative to reveal a caveat: we do *not* suggest mental stress is the *exclusive* cause of vision loss, but our proposition is that stress should be considered as one of the cardinal causal factors and a major risk factor. This subject is not only important as an anecdote of suffering for individual patients but also a practical step forward to better manage an ever growing problem of general public interest. As an increasing number of people are affected by low vision every day and their number is growing in our aging societies, this issue becomes essentially pertinent.

Besides problems related to the optics of the eye, many diseases affecting the nervous system structures can cause vision loss and function which include glaucoma, optic neuropathy, diabetic retinopathy, retinitis pigmentosa (RP), and age-related macular degeneration (AMD). Primary open-angle glaucoma (POAG) is the main cause of irreversible blindness with a prevalence expected to grow from 64.3 million (2013) to 76.0 million (more than twice that of Alzheimer's disease) in 2020 (111.8 million in 2040). Of all causes of vision loss, glaucoma is the second leading cause of

blindness (first leading cause of "irreversible" blindness) [13, 14], with POAG and normal-tension glaucoma being the most common types [15]. Because vision loss is among the most perturbing diseases in the elderly precipitating anxiety and depression, understanding how stress affects the eye and vision-related brain circuits is an issue of immense cogent rationale.

Yet, the body of evidence for stress-based vision loss causality is rather limited and includes many old references (mostly before the 1960s). It is, therefore, important to understand that even if a comprehensive analysis is carried out, the best that can be done is to discuss the general role of stress in vision loss without making meticulous distinctions between different diseases. The premise of our proposal, therefore, is subject to certain inevitable limitations and constraints. For this reason, the discussion may appear to be rather obscure and devoid of objective precision about the etiological role of stress in specific diseases. For example, the term "glaucoma" is used for a variety of different pathologies such as closed- or open-angle glaucoma, pigment glaucoma, juvenile glaucoma, normal-tension glaucoma, secondary glaucoma, etc. Similarly, optic neuropathies can be with or without trauma, developmental anomalies, genetic mutations, etc. On the other hand, there are specific diseases, like normal-tension glaucoma and anterior ischemic optic neuropathy (AION), where stress can clearly be identified as a major cause. Whereas stress may play a greater role in younger patients with AION or glaucoma, in the elderly other factors are more likely to exist, such as arteriosclerosis.

Despite the uncertainty regarding whether or not, or to what extent, stress plays a role in a specific disease related to vision loss, we believe that stress (and certain personality dispositions) is a hitherto under-appreciated factor in the development of certain—but not all—diseases of the visual system.

Low vision, stress, and the brain

Challenging life events and any other stimuli that lead to stress are called "stressors". They are part of our daily lives. However, in what way the body and mind react to any specific stressor depends on the brain's interpretation and the bodily reaction to it. The brain's appraisal determines whether a physiological stress response is elicited and affects the body and, if so, how stress causes pathophysiology of vision loss.

Eye diseases are also brain and vascular diseases "in disguise"

Because the retina and eye are extensions of the brain [16], it may be conceivable that "ophthalmologic" diseases might actually also be "brain" diseases in disguise, both of which depend on the vascular system. For example, glaucoma is both an ocular and brain neurodegenerative disorder characterized by progressive damage of both the optic nerve head and different visual brain centers [16–19] as well as those that control emotions (amygdala) [20]. Since stress and emotional experiences affect the eye, brain, and vascular system by way of autonomic imbalance and/or stress hormone release thereby ensuing perfusion problems, and since neural circuits involved in vision and emotion have functional and physiological overlap, stress could have a direct impact on vision as well.

With the premise of above introductory remarks, we suggest that vascular dysregulation is a key mechanism of normal-tension glaucoma (NTG) pathogenesis [21–23]. It may arguably be caused by stress hormones circulating in the vascular system, which—in turn—are controlled by brain cognition and emotional response to stressors. Stress hormones influence vascular tone, particularly in and around the optic nerve and thereby impair vascular autoregulation. It is therefore conceivably that the patient's individual emotional response to stressors determines whether or not the brain induces the release of stress hormones. In this case, psychological factors would contribute to the development of NTG. While such a physiological hormonal state might be a necessary condition, it is not a sufficient cause because not everyone with emotional stress ends up with glaucoma. Therefore, other factors must underlie the ethiopathogenic picture to make the difference whether or not a stressed person develops NTG. Such factors could range anywhere from genetic susceptibility, stress sensitization, to a disturbed stress resilience system. As we will discuss below, such factors may contribute to the pathology of the ocular blood vessel endothelial cells. In other words, we could look upon the brain and patient's individual experiences as starting points for the pathogenesis of glaucoma, and presumably other vision problems as well (genetic/pathological conditions being the second rung in the ladder). Neither of the two factors alone should be considered sufficient to cause NTG, but it is rather the combined effect of both. This can be described by the following causal chain of events which is slightly different from high-tension glaucoma: (see also Fig. 2).

Normal-tension glaucoma:

Stressors (chronic or acute) → brain's cognitive interpretation → emotional response → stress-related biological responses (hormonal, vascular dysregulation) → retinal and optic nerve pathology → visual field loss.

High-tension glaucoma:

Stressors (chronic or acute) → brain's cognitive interpretation → emotional response → autonomic imbalance → rising intraocular pressure (IOP) → retinal and optic nerve pathology → visual field loss.

If mental stress causes vision loss and vision loss leads to stress, this results in a downward spiral: mental stress impairs vascular function in the ocular structures leading to vision loss; this causes emotional worry and stress, which, in turn,

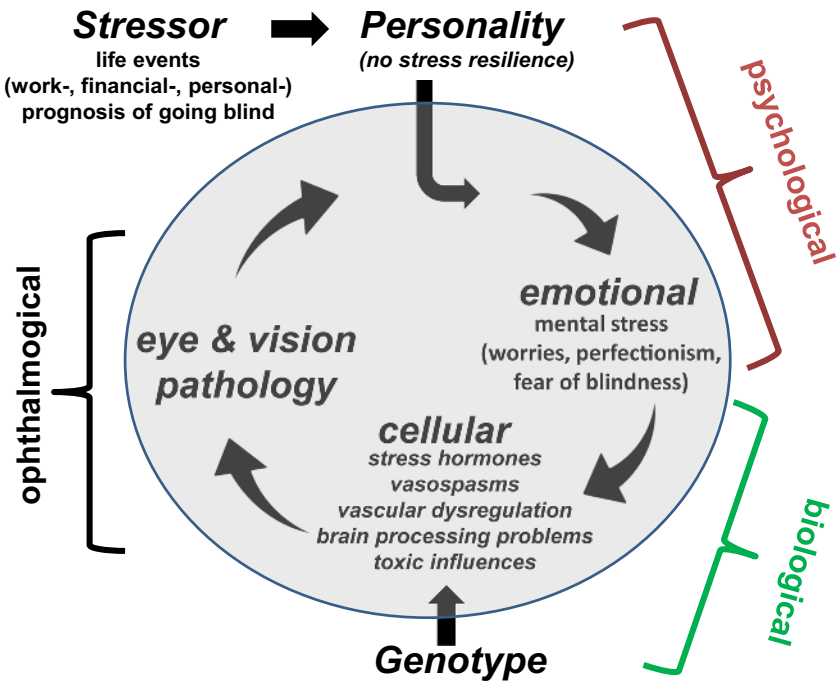

Fig. 2 Diagram of stressors (chronic or acute) and their effects showing the vicious cycle of mental stress and vision loss and the cause-effect relationship of stress and vision loss. According to this concept, low vision is both *cause* and *consequence* of vision loss. Note: the disease is involving different levels of analysis, psychological, biological, and pathological (ophthalmological)

aggravates vision loss and so on. Breaking this downward spiral might provide an opportunity for prevention and/or intervention.

The following case report exemplifies how vision and stress are related.

A case report

W.G., a 78-year-old woman, is happily married for 55 years. As a former business manager who worked 50+ h/week all her life as supervisor in a bank's IT department, she presented herself at SAVIR-Center in Magdeburg to receive treatment for her severe vision loss on both eyes.

Case history W.G. had cataract surgery on both eyes in 2001 with excellent outcome and clear vision thereafter. In January 2013, she lost vision on her left eye immediately after having undergone gynecological surgery under general anesthesia. In the morning of surgery, she received a tranquilizer to prepare her for general anesthesia. But because the surgery was delayed, she received additional injections of the tranquilizer throughout the day. The surgery finally started in the late afternoon and lasted more than 2 h. When she woke up, it was already dark outside. She slept well through the night, but next morning she noted that her left eye was completely blind and she had to vomit, which she never did before. She suspected that the blindness occurred as a result of the surgery, but she had not noticed it due to the darkness in the evening. Her vision recovered a bit spontaneously but remained severely impaired. The vision loss worried her a lot as she wondered how to manage her life with only one eye and how she could continue to take care of her frail husband who suffered from heart problems. It was a 24/7 burden. Three years later, in 2016, her husband's health suddenly deteriorated requiring immediate by-pass surgery. She worried not only about her vision problem but also that her husband might die and what her future would be like after 55 years of a happy marriage. On the day after her husband's surgery, her vision suddenly deteriorated also on the right eye and she suspected that the 3 years of continuous stress plus her acute worries were suddenly "discharged" in her vision loss. Though other factors might have contributed to her condition, stress was the main trigger for her vision loss. When asking her ophthalmologist if the vision loss might be related to stress, she was informed that stress had absolutely nothing to do with vision loss, though a cause was not found. Asking what her prognosis would be, she was told that once it is damaged, it will stay damaged forever. Shocked by this prospect, an assistant doctor made a remark without any sense of empathy: "whatever you try, you will go blind."

Medical The ophthalmological report indicates a history of Sicca syndrome in both eyes; left eye optic nerve atrophy due to NAION in 2013, and right eye NAION in Aug 2016, normal IOP, no fundus pathology except for a nasal vasoconstriction OD. Brain CT and lab values were normal, except for indication of hyperlipoproteinemia. No treatment recommendation for vision loss was given.

Vision testing Vision testing in October 2017 revealed an OD Humphrey visual field index of 12% (mean deviation − 25.97 dB). OS could not be measured due to fixation

problems. Supra-threshold stimulus detection (high-resolution perimetry, HRP) to measure residual vision showed detection rates of 43% OD (fixation of 100%) and 59% OS (fixation 99%) with reaction times of 600/500 ms, respectively. The discrepancy between near-threshold and super-threshold testing was surprisingly large. OD/OS visual acuity was 0.25/0 and contrast sensitivity 1.0 monocular on both eyes and 1.24 binocularly (see Fig. 3).

Subjective vision W.G. reported her vision to be reduced in both eyes; OD was worse as she could see only course shapes but no details. OS could recognize course shapes in temporal visual field sectors and shadows in the nasal half of the visual field which she perceived as gray ("foggy") vision. She could no longer read newspapers of her bank account statements, had problems recognizing faces, frequently bumped into people or objects, had painful glare with bright lights, adaptation problems from dark to light, dry eyes, and problems with black-white contrast; color perception was subjectively intact. Her eyes could move in all directions, but she had occasional extra-saccades while fixating.

Psychological assessment She was cognitively normal, understood and responded to questions adequately, and was intellectually quite alert. However, mental stress and worries in the past and at present were dominant. She showed signs reminiscent of the Flammer syndrome (FS) (see below): cold hands and fluctuations toward low blood pressure, slim body shape, tendency to worry a lot, ambitious and perfectionist attitude both at work and at home, problems falling asleep, lack of the feeling of thirst, and very pale skin in her face and extremities. In addition, she reported her thinking to be dominated by the wish to fulfill the expectations of others but ignoring her own desires, wishes, and needs. She was quite aware that stress has been—and still was—a problem, but she did not know what to do about it and was quite anxious to be ending up blind.

Case summary and conclusions It is likely that the vision loss on the left eye after her 2013 surgery may have been caused by the lengthy tranquilizer/anesthesia and might be explainable by closed angle glaucoma or perfusion problems (apparently not directly related to stress) as described by Flammer [24]. The subsequent loss on the right eye 3 years later, in all probability, is stress-related because of anxiety and worries about her own vision loss plus her husband's health problems, in conjunction with her tendency to neglect her own emotional needs. This might have induced a vasospasm as a consequence of her chronic (3-year) stress plus the acute stress due to her husband's heart surgery. It is conceivable that the earlier negative and stress-inducing prediction by the assistant doctor ("you will be blind") did not help the situation but rather potentiated the stress, increasing the probability of vision loss.

Treatment The patient was treated with the aim to improve blood circulation and brain synchronization to activate residual vision [3] by daily administration of alternating current stimulation [6–9], relaxation, and eye yoga exercises. In addition, she received psychological with the aim to develop greater stress resilience and improve coping. Though we do not know which therapeutic module was most effective, the combination of all treatments councelling that she received during a 2-week period improved her vision both objectively and subjectively (for further descriptions of these methods, [25]).

Treatment outcome After the 2-week treatment in the SAVIR-Center in Magdeburg, W.G. subjectively noted that her vision had improved: half way through the treatment, she could see at far distance again and her "gray" vision became brighter ("white") in the upper visual field sector. She was also able to see more details again. For example, she could see parts of her face again when looking into a mirror; she could see her eyes and hair again for the first time. She reported being able to read street signs again, but her central visual field still felt problematic. These subjective reports were confirmed by Humphrey visual fields which improved from 12 to 21% with no fixation losses or false positives at both time points (Fig. 3).

Another case, also shown in Fig. 3, is a 52-year-old woman, suffered from normal-tension glaucoma. When she came for treatment to the office of the first author (B.S.) for 10 days with alternating current, she did not improve much. She was a rather agitated and energetic woman with strong tendency to worry and perfectionism. When she returned for a second course of treatment about 12 months later, the psychological consulting from the first visit, together with a second course of 10-day treatment and psychological consulting, had a remarkable benefit for her vision which improved from 19 to 63% visual field index.

Worldwide research activities on stress and ophthalmology

The above case report demonstrates that stress can lead to a dramatic, psychosomatic reaction in the visual system while reduction in stress and enhanced blood flow can notably improve the condition. There are, however, many similar stories of vision recovery and most clinicians are aware of visual field fluctuations. Rozanski et al. [26] proposed that visual field (VF) performance is not only a function of the actual vision loss itself but is highly variable due to anxiety and functional losses of vision. They presented a conceptual framework for the development of coping strategies and mindfulness-based interventions to reduce stress associated with negative thoughts and worries [26]. Though there are unexplained cases of vision loss and cases of unexpected recovery [27], yet the literature is surprisingly silent as to how the mosaic of stress, vision loss, vision recovery, and restoration are

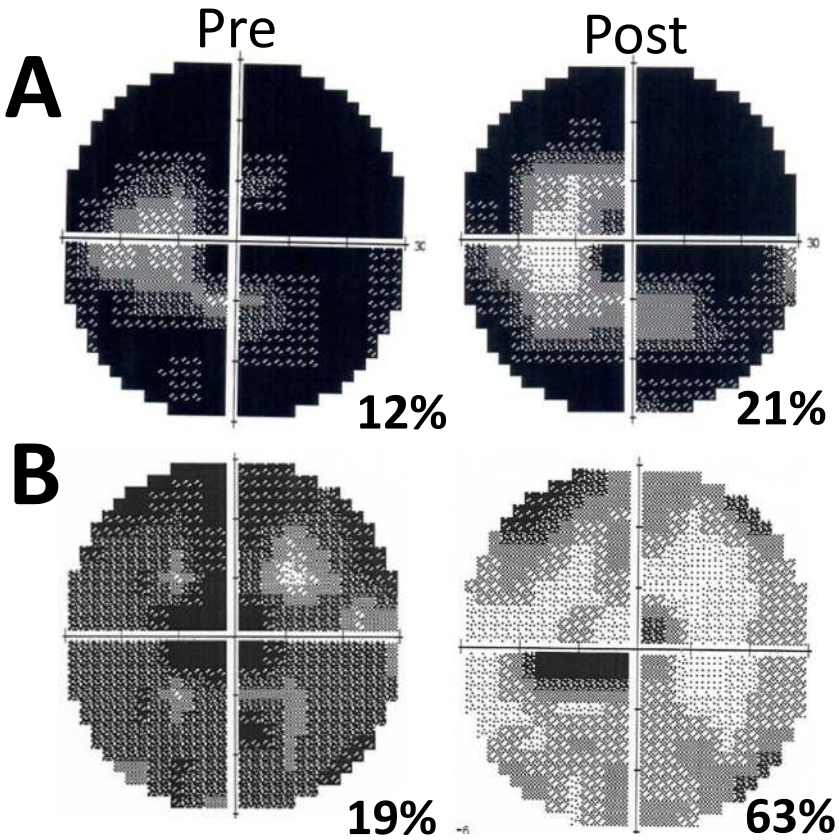

Fig. 3 Humphrey visual fields of a 78-year-old woman with stress-induced vision loss OD before vs. after a 10-day treatment. Treatment included alternating current stimulation plus relaxation exercises and psychological consulting. In both tests, she had neither any fixation loss nor any false positive responses. Visual field index improved from 12 to 21% (pre/post mean deviation: −25.97/−22.44 dB). Subjectively, the patients reported improvement from "gray" to "white" vision with noticeably better acuity. She did not notice any changes in the central visual field but could better recognize faces and street signs, and she was able to see her hair in the mirror again, with her upper visual field. The second case is also a woman who was treated for her glaucoma with current stimulation and various anti-stress methods such as psychological consulting and relaxation (see text for further details)

connected. It should not escape our notice that the term "unexplained" could have two meanings: no pathology found or pathological changes existed, but they could not explain the visual field.

Unfortunately, our scientific understanding is disconcertingly poor when it comes to the role of stress and the brain in ophthalmological diseases. The question nevertheless arises as to how much science exists about the role of stress in vision loss. We therefore counted on PubMed the number of scientific reports in the field of psychology/psychosomatics of vision loss (www.pubmed.org; Oct 2017). We reasoned this might reveal some clues of how comprehensively this field is being studied worldwide (Table 1).

We first searched for general terms in the fields of *Vision* and *Psychology* and recorded the total number of hits separately for "eye" (565,167), "vision loss"(58,052), and low vision" (16,338) as well as "stress" (756,926), "psychosomatic" (19,145), or "psychological stress" (137,084). But when combining the two fields, much fewer hits were recorded: "psychology vision loss" (4020), "stress low vision" (228), "mental stress vision loss" (146), "psychosomatic eye" (154), "psychosomatic ophthalmology" (95), or "mental stress low vision" (52); this means that of all studies of eye/vision loss (640,000), only 4700 (= 0.7%) addressed the topic of mental stress. Such a low value of < 1% was a surprise vis-à-vis the impact vision loss has on psychological well-being.

One might argue sensory functions are purely "physiological," i.e., not influenced by the patients' state of mind. To check if this "somato-centric" interpretation of vision is unique to ophthalmology, we carried out the same analysis for the sense of hearing for "ear" (172,353) or "hearing loss" (78,780). While the scientific output was only about one third of that related to "eye" and "vision," the number of publications of the combined term "mental stress hearing loss," was 1.2% (306), i.e., almost double that of vision. In other words, somato-centric thinking not only dominates vision research, but it creates also a negative bias against a role of mental-stress in vision loss.

This low number of scientific records addressing the interface of stress and vision loss dovetails what patients are also complaining about: that there is minimal interest (if any), or even a negative bias against, psychological concerns in the ophthalmology clinical and research community. Yet, there is a rich repertoire of literature on psychological treatments such as stress reduction, relaxation techniques (such as yoga and meditation), cognitive therapies, and psychotherapy. They might be valuable adjuvant methods for a more holistic approach in ophthalmology for treating the person behind the eye.

One could argue that ophthalmology shows less interest in psychobiological mechanisms of visual diseases because the patients and the public at large find psychological issue to be irrelevant for the understanding (or treatment) of vision

Table 1 Scientific and public interest in vision and stress research. This table shows the number of hits when searching Medline, Google, and Google scholar with the respective search terms. It shows the disconnection between public interest (Google hits) and scientific activity (number of Medline-listed publications) in the field of stress and low vision

Search term	Medline (M)	Google (G)	Ratio G:M	Google scholar (Gs)	Ratio Gs:M
General vision					
Eye	565,167	2,080,000,000	3680	4,340,000	7.68
Vision loss	58,052	3,110,000	53	147,000	2.53
Low vision	16,338	4,400,000	269	66,100	4.05
Sum	639,557	2,087,510,000	4003	4,553,100	14.26
General Stress					
Stress	756,926	719,000,000	949	6,050,000	7.99
Psychosomatic	19,145	4,580,000	239	591,000	30.87
Psychological stress	137,084	1,550,000	11	673,000	4.91
Sum	913,155	725,130,000	1,200	7,314,000	43.77
Combined vision/stress					
Psychology vision loss	4020	908	0.23	2	0.00
Stress low vision	228	2780	12	1	0.00
Mental stress vision loss	146	7,160,000	49,041	1	0.01
Psychosomatic eye	154	542	3.52	37	0.24
Psychosomatic ophthal.	95	256	2.69	4	0.04
Mental stress low vision	52	2,620,000	50,384	0	0.00
Sum	4695	9,784,486	99,444	45	0.29

loss. Because our clinical experience suggests otherwise, we next estimated general public interest in these topics by conducting a Google search. Table 1 shows the number of hits in *Google* as a metric of public interest and in *Google scholar* as a metric of academic interest. This could teach us how well (concordance vs discordance) scientific activity (PubMed hits) and public interest (Google hits) match. The results are astonishing: for every scientific publication identified by the two PubMed search terms "eye/vision" and "psychosomatics" separately, there are 4000/1200 Google items, respectively. That means the ratio of scientific activity and general public interest is in the order 1:1.000–4.000. However, when combining vision and psychological terms, this number is 1:100.000. In other words, for every science publication, there are 100,000 Google hits; a tremendous mismatch between general public interest and scientific activity! This confirms that many people are actively searching information about the role of mental stress in low vision. If one would ask how much scientific activity would have to increase to match public interest, the answer would be: by a factor of 25!

The rather disappointing conclusion of our Google analysis is as follows: though mental stress is of major subjective concern for low vision patients and the public at large, the topic is essentially ignored by the scientific community. This is surprising if one considers that stress is factor which is well-known to influence mental and bodily health; it is widely recognized particularly in psychosomatic medicine. Yet, there is a rather small body of evidence for the role of stress in vision loss which will now be reviewed.

Literature analysis

Our search revealed 139 papers (163-250), some published before the 1960s, but the majority after the year 2000 (n = 97) (Table 2). The publications discuss different eye diseases and different psychosomatic conditions. The most frequently studied disease is glaucoma (open angle or angle closure) (n = 46), followed by age-related low vision such as macular degeneration or cataract (n = 10), non-organic vision loss or functional vision loss (NOVL) (n = 9), retinitis pigmentosa (RP, n = 4), myopia (n = 3), and one paper each for dry eye syndrome (DES), diabetic retinopathy, and amblyopia. Methodologies used in such studies included measurement of visual fields (VFs), visual acuity (VA), contrast sensitivity (CS), the Adaptation to Age-Related Vision Loss Scale (AVL), and intraocular pressure (IOP). The study of psychosomatic consequences (or causes) varied as well, ranging from depression, anxiety, life stress, coping strategies, personality, self-concepts, and the study of the effects of various relaxing methods. The psycho-diagnostic tools to assess the mental state included the following: the NEI-VFQ-25 (National Eye Institute 25-Point Visual Functioning Questionnaire) and other tests such as the Patient Health Questionnaire-9 (PHQ-9), 36-Item Short Form Survey (SF-36), Generalized Anxiety

Table 2 Search results and their analysis of SCI publications related to the topic of stress and vision loss

Ref	First author	Year	Study topic				Methods used		Analysis	Cause or consequence	Result
			Paper type	Factor 1 (Vision)	Factor 2 (Psychology)	Sample	Vision	Psychology			
[163]	Zhang	2013	MC	1.VAL 2.VL	Depression	10,480	VF	Depression	SA	0	+
[164]	Burmedi	2003	RM	ALV	1. Emotion 2. Behavior 3. SF 4. Cognitive	267 studies	0	0	MA	0	+
[165]	Brennan	2002	MC	VL	Life stress	195	0	SF	SA	0	0
[166]	Rovner	2002	MC	ARMD	Depression	51	1. VA 2. VF	Depression	SA	0	+
[167]	Wulsin	1991	Ob	DR	Psycho	31	VL	SF	CO	0	+
[168]	Wahl	2006	Exp	ARMD	0	67	0	1. Depression 2. Adaptation	SA	0	0
[169]	Packwood	1999	MC	Amblyopia	Psycho	25	0	Symptom	SA	0	+
[170]	Rees	2010	MC	VA	Depression	143	0	Depression	SA	0	0
[171]	Huurre	1998	MC	VL	1. Depression 2. Distress	54	0	Depression	SA	0	0
[152]	Bittner	2010	Exp	RP	Stress	8	0	0	CO	0	0
[109]	Brennan	2000	RM	Age-related VL	Cognitive	498	VF	1. AVL 2. Depression	MA	0	0
[172]	Yochim	2012	MC	Glaucoma	1. Cognitive 2. Depression 3. Anxiety	41	0	1. Depression 2. Verbal function	SA	0	+
[82]	Kong	2015	MC	Glaucoma	1. Anxiety 2. Depression	150	0	1. Anxiety 2. Depression 3. Personality	SA	0	+
[173]	Erb	1999	MC	NTG	psychology	48	0	1. Personality 2. Depression	SA	0	+
[174]	Zhou	2013	MC	Glaucoma	1. Anxiety 2. Depression	506	1. VA 2. IOP 3. Vf	1. Anxiety 2. Depression	SA	0	+
[175]	Jampel	2007	MC	Glaucoma	Depression	607	VA	Depression	SA	0	+
[176]	Piers	1948	MC	ACAG	Emotion	30	0	0	0	0	+
[177]	Pappa	2006	MC	POAG	Depression	42	0	1. Distress 2. Depression	SA	0	+
[178]	Eramudugolla	2013	MC	ARED	1. Anxiety 2. Depression	662	1. VA 2. Vf	1. Depression 2. Bipolar disorder	SA	0	+

Table 2 (continued)

Ref	First author	Year	Study topic				Methods used		Analysis	Cause or consequence	Result
			Paper type	Factor 1 (Vision)	Factor 2 (Psychology)	Sample	Vision	Psychology			
[179]	Wang	2001	Ob	1. VL 2. Cataract	Mortality	3654	0	0	0	0	+
[180]	Scott	2003	RM	NOVL	0	133	0	0	0	0	0
[181]	Hallemani	2012	MC	VL	Stress	80	0	0	SA	0	+
[182]	Lee	2007	RM	Glaucoma	0	151	0	0	0	0	+
[183]	Rivera	2008	RM	POAG	0	0	0	0	0	0	0
[184]	Recupero	2003	MC	POAG	0	62	IOP	0	SA	0	0
[185]	Lee	2004	MC	Myopia	0	636	1. IOP 2. AL	0	0	0	0
[186]	Sauerborn	1992	Exp	Myopia	Stress	38	Vf	HR	SA	0	0
[55]	Flammer	2001	RM	Glaucoma	0	0	0	0	0	0	0
[187]	Grom	1981	MC	Glaucoma	Personality	99	0	Color test	0	0	0
[111]	Pace	2009	RM	0	Meditation	61	0	1. Stress 2. BS	SA	0	+
[188]	Amihai	2015	RM	Autonomic	Meditation	0	0	0	0	0	+
[128]	Rosenkranz	2016	MC	Imflammatory	Meditation	68	0	1. Stress 2. BS	SA	0	+
[189]	Erb	1998	RM	Glaucoma	Psycho	0	0	0	0	0	0
[15]	Shindler	2004	RM	NOVL	0	0	0	0	0	0	0
[190]	Kemeny	2003	RM	0	Stress	0	0	0	0	0	0
[191]	Kloet	1992	RM	0	Stress	0	0	0	0	0	0
[192]	Ritvanen	2006	MC	Autonomic	Stress	28	0	Pain	SA	0	0
[193]	Gherezghiher	1990	Exp	IOP	0	cat	IOP	0	0	0	0
[194]	Emmerich	2010	RM	OAG	Psycho	0	0	0	0	0	0
[195]	Warrian	2009	MC	Glaucoma	Personality	189	VF	1. Personality 2. Depression	SA	0	0
[74]	Bruce	2010	RM	NOVL	0	0	0	0	0	0	0
[196]	Beatty	1999	RM	NOVL	0	0	0	0	0	0	0
[197]	Werring	2004	Exp	NOVL	FMRI	0	0	0	0	0	0
[198]	Burggraaff	2012	Exp	VL	0	122	0	1. Quality of life 2. AVL 3. Depression	SA	0	0
[4]	Kasten	1998	Exp	VL	0	38	HRP	0	SA	0	+
[102]	Schinazi	2007	RM	VL	Psycho	0	0	0	0	0	0
[49]	Na	2010	Exp	NTG	Autonomic	107	0	BP, ECG, HR	SA	0	+

Table 2 (continued)

Ref	First author	Year	Study topic				Methods used		Analysis	Cause or consequence	Result
			Paper type	Factor 1 (Vision)	Factor 2 (Psychology)	Sample	Vision	Psychology			
[48]	Riccadonna	2003	Exp	NTG	Autonomic	47	0	BP, HR	SA	0	+
[110]	Tang	2015	RM	0	Meditation	0	0	0	0	0	0
[136]	Wu	2008	Exp	0	Meditation	20	0	HR, RR	SA	0	+
[137]	Grossman	2004	RM	0	Mindfulness	0	0	0	MA	0	+
[199]	Galvin	2006	Exp	0	Relaxation	15	0	1. Cognitive 2. Depression 3. Anxiety	SA	0	+
[200]	Vøllestad	2011	Exp	0	1. Anxiety 2. Depression 3. Mindfulness	76	0	1. Anxiety 2. Depression 3. Mindfulness	SA	0	+
[201]	Chrousos	2009	RM	0	Stress	0	0	0	0	0	0
[202]	Matousek	2010	RM	Cortisol	Stress	0	0	0	0	0	0
[101]	Mabuchi	2005	MC	POAG	Personality	419	0	Personality	SA	0	0
[203]	Sehgal	2011	RM	0	Yoga	0	0	0	0	0	0
[112]	Taneja	2014	RM	0	Yoga	0	0	0	0	0	+
[204]	Haymes	1996	MC	RP	Psycho	18	1. VA 2. Vf	1. Personality 2. Behavior	SA	0	0
[205]	McEwen	1999	RM	HP	Stress	0	0	0	0	0	0
[206]	Gupta	2012	MC	Glaucoma	Life quality	178	0	Life quality	SA	0	0
[99]	Çakmak	2015	MC	Glaucoma	Personality	234	0	TCI	SA	0	+
[62]	Bali	2011	Exp	Glaucoma	Depression	312	0	Depression	SA	0	+
[249]	Denollet	2005	MC	0	Personality	3813	0	Personality	SA	0	0
[115]	Flaten	2006	Exp	Pain	1. Stress 2. Emotion	84	0	1.BS 2.Stress 3.Pain	SA	0	0
[98]	Freeman	2016	MC	POAG	Cognitive	180	0	Cognitive	SA	0	0
[122]	Jin	2014	Exp	arcuate nucleus	0	54	IOP	0	SA	0	0
[123]	Sudsuang	1991	Exp	0	Meditation	82	0	BS,BP,PR	SA	0	+
[56]	Toda	2011	RM	0	Stress	0	0	0	0	0	0
[207]	Weitzman	1975	RM	Glaucoma	0	11	IOP	BS	SA	0	0
[208]	Dampney	2015	RM	0	Stress	0	0	0	0	0	0
[209]	Nordmann	2003	MC	1. POAG 2. OHT	Life quality	13,352	VF	Life quality	SA	0	+
[210]	Keyworth	2014	Exp	1. DM 2. CHD	Meditation	40	0	1. Worry 2. Chronic thought suppression	SA	0	+

Table 2 (continued)

Ref	First author	Year	Study topic				Methods used		Analysis	Cause or consequence	Result
			Paper type	Factor 1 (Vision)	Factor 2 (Psychology)	Sample	Vision	Psychology			
[211]	Manchanda	2014	RM	CVD	Meditation	0	0	0	0	0	+
[132]	Newberg	2010	Exp	Memory	Meditation	14	0	0	SA	0	+
[212]	Hayman	2007	MC	VAI	Depression	391	1. VF 2. VA	1. Depression 2. Anxiety 3. SF	SA	Both	+
[65]	Nyman	2012	RM	VL	Emotion	0	0	0	0	Both	+
[213]	Méndez-Ulrich	2017	RM	Glaucoma	Psycho	66 Studies	0	0	0	Both	+
[214]	Niklewski	1982	RM	VF	Psycho	0	0	Personality	0	Both	+
[105]	Tolman	2005	MC	ARMD	Depression	144	AVL	1. Cognitive 2. Depression	SA	Cause	+
[215]	Grant	2011	Exp	ARMD	Depression	18	1. VA 2. AVL	Depression	SA	Cause	+
[216]	Barris	1992	Exp	NOVL	0	79	1. VF 2. VA	0	CO	Cause	+
[91]	Hahm	2008	MC	RP	Depression	144	VF	Depression	SA	Cause	+
[90]	Bittner	2011	MC	RP	Psycho	27	1. VF 2. VA 3. CS	1. Depression 2. Affect	SA	Cause	+
[100]	Bubella	2014	MC	OAG	Personality	50	Staging	1. Anxiety 2. Personality	SA	Cause	+
[217]	Khan	2006	SC	NOVL	0	1	0	0	CO	Cause	+
[218]	Taich	2004	MC	NOVL	0	71	0	Attention	SA	Cause	+
[219]	Toldo	2010	Ob	NOVL	0	58	1. VA 2. Vf 3. CV	Psychology	CO	Cause	+
[61]	Shily	1987	RM	ACAG	Stress	0	0	0	0	Cause	+
[220]	Cohen	1972	SC	ACAG	0	1	0	0	0	Cause	+
[221]	Inman	1929	SC	AG	Emotion	1	0	0	0	Cause	+
[222]	Ripley	1950	MC	OAG	Emotion	18	IOP	0	0	Cause	+
[223]	Grignolo	1977	MC	IOP	Stress	0	IOP	0	0	Cause	+
[224]	Weinstein	1975	MC	Glaucoma	1. Anxiety 2. Stress	0	0	0	0	Cause	+
[151]	Kaluza	1996	MC	OAG	Mental Stressor	23	IOP	1. Psycho strain 2. HR	SA	Cause	+
[150]	Kaluza	1995	Exp	OAG	Relaxation	23	IOP	0	SA	Cause	+
[108]	Schultz-Zehden	1977	Ob	Glaucoma	Psycho	52	Vf	0	CO	Cause	+

Table 2 (continued)

Ref	First author	Year	Study topic				Methods used		Analysis	Cause or consequence	Result
			Paper type	Factor 1 (Vision)	Factor 2 (Psychology)	Sample	Vision	Psychology			
[225]	Dane	2006	MC	IOP	Fitness	49	IOP	0	SA	Cause	+
[160]	Reinhardt	1996	MC	CVL	SS	343	VF	1. SS 2. AVL	SA	Cause	+
[226]	Moschos	2014	RM	VL	Depression	0	0	0	0	Cause	+
[153]	Ben-Zur	2005	MC	VL	1. SF 2. Personality	90	0	0	SA	Cause	+
[227]	Beining	1951	RM	Glaucoma	Psycho	0	0	0	0	Cause	+
[228]	Berger	1960	RM	Glaucoma	Emotion	0	0	0	0	Cause	+
[229]	Böhringer	1953	RM	POAG	Psychiatry	0	0	0	0	Cause	+
[230]	Flammer	1999	RM	Eye Disease	Psycho	0	0	0	0	Cause	+
[231]	Schultz-Zehden	1975	RM	Glaucoma	Psycho	0	0	0	0	Cause	+
[224]	Weinstein	1975	RM	Eye Disease	Psycho	0	0	0	0	Cause	+
[223]	Grignolo	1977	MC	IOP	Stress	90	IOP	0	SA	Cause	+
[60]	Iwata	2016	Exp	BS	Stress	Animals	0	0	SA	Cause	+
[232]	Abateneh	2013	MC	VL	Distress	230	0	Distress	SA	Conseq.	+
[233]	Thurston	2010	MC	VL	1. Mood 2. Cognitive 3. SF	18	VF	SF and MH	SA	Conseq.	+
[234]	Stevelink	2016	Ob	VF	Psycho	9	0	1.Depression 2.Anxiety 3.PTSD	CO	Conseq.	+
[86]	Williams	1998	MC	ARMD	Life quality	86	VA	Life quality	SA	Conseq.	+
[95]	Li	2011	MC	DES	1. Anxiety 2. Depression	162	OSDI	1. Anxiety 2. Depression	SA	Conseq.	+
[92]	Angi	1993	Ob	Myopia	1. Personality 2. Stress	57	1. PD 2. VA	1. BS 2. Anxiety 3. Stress	CO	Conseq.	0
[64]	De Leo	1999	RM	VL	Suicide	19 cases	0	Mental illness	CO	Conseq.	+
[2]	Kempen	2012	RM	VL	1. Depression 2. Anxiety 3. ADL, SS	148	0	1. Activity 2. Depression 3. SS	MA	Conseq.	+
[250]	Lim	2007	MC	OAG	Personality	108	0	Personality	SA	Conseq.	+
[157]	Stelmack	2001	RM	VL	Depression	0	0	0	MA	Conseq.	+
[81]	Skalicky	2008	MC	Glaucoma	Depression	165	Vf	Depression	SA	Conseq.	+
[83]	Mabuchi	2012	MC	Glaucoma	1. Anxiety 2. Depression	408	0	1. Anxiety 2. Depression	SA	Conseq.	+

Table 2 (continued)

Ref	First author	Year	Study topic				Methods used		Analysis	Cause or consequence	Result
			Paper type	Factor 1 (Vision)	Factor 2 (Psychology)	Sample	Vision	Psychology			
[50]	Marc	2013	MC	POAG	Stress	151	1. IOP 2. Vf	Stress	SA	Conseq.	+
[235]	Casten	2004	RM	ARMD	Depression	0	0	0	0	Conseq.	+
[236]	Nyman	2010	RM	VL	Psycho	0	0	1. Depression 2. Anxiety 3. SS	MA	Conseq.	+
[237]	Carrieri	1991	MC	CSG	Mood	45	Vf	1. Depression 2. Anxiety	SA	Conseq.	+
[238]	Bambara	2009	MC	VL	Caregiver SP	96	0	1. SP solving 2. Depression 3. Satisfaction 4. Burden	SA	Conseq.	+
[239]	Altangerel	2003	RM	Glaucoma	Psycho	0	0	0	0	Conseq.	+
[240]	Teoli	2016	Exp	VF	Behavior	182	1. VA 2. Vf	1. Cognitive 2. Personality	SA	Conseq.	+
[241]	Vu	2005	MC	VL	Life quality	2530	0	Daily function	SA	Conseq.	+
[242]	Keeffe	2005	RM	VL	Psycho	0	0	0	0	Conseq.	+
[154]	Dreer	2005	MC	Low vision	SP	54	VF	1. SF 2. Depression	SA	Conseq.	+
[243]	Teitelman	2005	MC	Low vision	Psycho	15	0	0	SA	Conseq.	+
[244]	Heine	2002	RM	Sensory loss	Psycho	0	0	0	0	Conseq.	+
[245]	Datta	2014	RM	VL	Self concept	46 studies	0	0	0	Conseq.	+
[246]	Seybold	2005	RM	VL	Psycho	0	0	0	0	Conseq.	+
[247]	Scott	1999	MC	Low vision	Life quality	156	VF	Health	SA	Conseq.	+
[248]	Langelaan	2007	MC	VL	Life quality	128	0	Health	SA	Conseq.	+

Abbreviations are as follows: + = $P < 0.05$, 0 = $P \geq 0.05$ or no mention, *ACAG* acute closed-angle glaucoma, *ADL* activities of daily living, *AG* acute glaucoma, *AL* axial length, *ALV* age-related low vision, *ARED* age-related eye diseases, *AVL* adaptation to vision loss, *BP* blood pressure, *BS* body substance, *CHD* coronary heart disease, *CO* clinic observation, *CS* contrast sensitivity, *CSG* chronic simple glaucoma, *CV* color vision, *CVD* cardiovascular disease, *CVL* chronic vision loss, *DES* dry eye syndrome, *DM* diabetes mellitus, *DR* diabetes retinopathy, *Exp* experiment, *HP* hippocampal plasticity, *HR* heart rate, *IOP* intraocular pressure, *MA* meta-analysis, *MC* multiple case analysis, *MH* mental health, *NOVL* non-organic vision loss, *NTG* normal-tension glaucoma, *NV* normal vision, *OAG* open-angle glaucoma, *Ob* observation, *OHT* ocular hypertension, *OSDI* ocular surface disease index, *POAG* primary open-angle glaucoma, *RM* review or meta-analysis, *RP* retinitis pigmentosa, *RR* respiration rate, *SA* statistical analysis, *SC* single case report, *SF* social function, *SP* social problem, *SS* social support, *TCI* Turkish temperament and character inventory, *VA* vision acuity, *VAI* vision acuity impairment, *VF* vision function, *Vf* vision field, *VFI* vision function impairment, *VL* vision loss

Disorder 7-item (GAD-7), the Symptom Checklist-90-Revised (SCL-90), Beck-Depressions-Inventory (BDI), the Zung Self Rating Anxiety (SAS), and Depression Scales (SDS), to name but a few.

Whereas 32 papers indicate that psychosomatic factors are the *consequence* of eye diseases, another 32 seem to favor the opinion that psychosomatic influences are the *cause* of eye diseases. Yet others are ambiguous about it. Thus, the literature is evenly divided on this issue and the jury is still out if eye diseases are *cause* or *consequence*. The cause-effect issue, as we perceive it, may not be an "either/or" affair because stress is probably both, cause *and* effect of vision loss. Before discussing the role of stress in vision loss in more detail, we will briefly summarize the biological stress response systems.

The stress response

Acute as well as chronic stressors can elicit the onset, or worsen the course, of vision loss. Understanding the physiological mechanisms of the stress response is, therefore, a pursuit of pertinent and pragmatic interest.

Stress response systems

The brain has two outflow systems to control the adaptation of the body to stress: firstly, the neuronal sympathetic adrenomedullary system (SAM) which is part of the autonomic nervous system, and secondly a neuroendocrine stress response system, i.e., hypothalamic-pituitary-adrenal axis (HPA). Both are activated during stress, and both are controlled by neural brain networks which are involved in the control of stress and emotion. Critical brain regions are the brain stem, hypothalamus, prefrontal cortex, amygdala, and hippocampus.

The sympathetic adrenomedullary system

Walter Cannon suggested already in 1932 [28] that acute responses to threat involve activation of the sympathetic nervous system via autonomic centers in the brain stem, resulting in peripheral catecholamine release from the adrenal medulla. This sympathetic activation prepares the organism for increased activity by constricting blood vessels to redistribute blood flow to muscles and by increasing heart rate and pulmonary function, in order to maintain homeostasis under conditions of increased activation demand [29]. Sympathetic activation simultaneously also shuts down other bodily functions that are not needed at that moment such as feeding, reproduction, or sleep. Stomach and upper intestinal functions are inhibited so that digestion is slowed down. Thus, the stress response is adaptive for a "fight and flight" response, which is of great relevance for the survival of the individual and survival of the species in evolution. It increases metabolism for this action via glycogenolysis in the liver to raise glucose levels, and modulates brain function to increase vigilance, attention, and arousal. Here, central norepinephrine helps activating the HPA axis [16].

As the Flammer syndrome implies, repeated or chronic activation of this system can elicit vascular system dysfunction in patients, which have genetically susceptible endothelial cells that can promote development of vision loss. In addition, a sensitized system due to early-life adversity could represent a risk factor for developing vision loss in response to acute stressors [30]. This might be particularly true for genetically susceptible individuals [31].

Hypothalamic-pituitary-adrenal axis

While the SAM is rather a fast-reaction system, the HPA axis has a slower reaction to internal and/or external stress. The HPA axis is controlled by the CA3 region of the hippocampus, and corticotropin releasing hormone (CRH) and arginine vasopressin (AVP) neurons originating in the paraventricular nucleus of the hypothalamus. Activation of these neurons is elicited by combined input from cortical limbic and brain stem circuits. The prefrontal cortex and hippocampus inhibit the HPA axis and input from amygdala and noradrenergic brain stem nuclei activate it (see next section). Axons of CRH neurons (and co-secreted AVP) terminate in the median eminence onto small blood vessels (neuroendocrine transmission). Here, the neuronal signal is "translated" into a hormone "blood-borne" signal by releasing neuropeptides into the portal circulation of the pituitary gland from where they reach the anterior pituitary corticotrophic cells to stimulate the secretion of adrenocorticotropic hormone (ACTH). ACTH, in turn, stimulates the synthesis and release of glucocorticoids (e.g., cortisol in humans) from the adrenal gland into the blood circulation. Glucocorticoids then lead to increasing blood sugar through gluconeogenesis and provide the energy resources for the organism to flee or to fight. Because glucocorticoids modulate transcription of certain genes in the cell nuclei, the hormonal response to stress is slower and longer lasting than the faster SAM actions [32].

While the release of glucocorticoids during stress is good news for its adaptation necessary for survival, it is bad news under conditions of severe or chronic stress, such as early childhood trauma or patients receiving a negative medical prognosis (e.g., "you are going blind"). The overexposure of the brain to glucocorticoids can then become toxic to neurons, e.g. in the hippocampus and prefrontal cortex, and glucocorticoids can even be toxic to retinal tissues [33, 34]. Because of various feedback loops, glucocorticoid increase progressively damage the hippocampus, leading to further glucocorticoid release, then to even more damage of the brain; a vicious cycle.

Lower than normal levels of glucocorticoid release are also detrimental as this can have adverse effects on the proper regulation of hormones to control central stress responses and activation of the immune system [35, 36]. Hence, an optimal balance of glucocorticoid release during stress is critical for a healthy adaptation response to stress.

Brain circuits implicated in the stress response

Besides the systemic stressors and homeostatic imbalances, the response to psychological or emotional stressors is key, but this requires appraisal and processing activities by higher brain regions.

While brain stem nuclei regulate the activation of SAM and the HPA with ascending ("bottom-up") projections, several "top-down" processes are involved in eliciting the stress response. These brain structures include limbic forebrain structures, including the amygdala, the hippocampus, as well as the prefrontal cortex (PFC). While hippocampus and PFC atrophy in conditions of chronic stress, the amygdala volume increases. It is involved in autonomic regulation and fear learning [37–40], and its volume enlargement is found in glaucoma patients [20]. But how the brain's visual and emotional system interacts in cases of low vision is a yet unexplored issue of ardent importance.

Stress and inflammation

In addition to the HPA axis and the SAM, the immune system is another regulatory framework that is activated in response to stress. There are complex interactions between these three regulatory systems. For example, psychosocial stress can activate inflammatory responses, by neural activation of signaling pathways in immune cells, resulting in increased NFκB production, which induces the secretion of inflammatory mediators. [36, 41]. Inflammatory mediators in turn can activate central stress responses. Concerning vision loss, the role of inflammation is a topic long known to be critical for a variety of ocular maladies. A detailed overview of this field is, nonetheless, beyond the scope of this paper and we prompt the reader to read important reviews by others [41–47].

Stress and vision loss in glaucoma

Glaucoma is an appropriate example of how an eye disease can be influenced or caused by mental stress. The biological response to mental stress and the pathogenesis of glaucoma share numerous common features sufficient to justify the mental stress based etiology (see also Fig. 2). The principle mechanisms are intraocular pressure elevation, vascular dysregulation, and an imbalance of autonomic nervous system regulation and immunological aspects [48, 49].

Stress and intraocular pressure

The main cause and the only currently known modifiable risk factor for glaucoma is elevated intraocular pressure (IOP). This reduces blood flow in the eye due to physical pressure on the choroidal vascular system. The standard of care is lowering IOP by topical drugs or performing surgery with the aim to relieve the physical pressure and thus normalize blood flow. Several publications indicate that mental stress is associated with IOP elevation which is confirmed by molecular studies (see below) [50]. In patients who already have glaucoma, both acute and chronic stress raise IOP; when lasting for longer duration, stress may raise IOP even in those not having glaucoma [50, 51]. But 33–57% of all glaucoma cases [52] have normal-tension glaucoma (NTG). This shows that besides the physical influence of IOP, there are other causes of glaucoma as well: vascular dysregulation [53–55] and an imbalance of the brain and eye pressure [20] are two possible mechanisms which are either directly or indirectly controlled by the brain.

Blood flow, vascular dysregulation, and stress hormones

Besides IOP, primary vascular dysregulation is particularly relevant for both, POAG pathogenesis and NTG [56]. The connection between the ocular perfusion pressure and primary vascular dysregulation has been explicated in NTG by Flammer [53, 54].

Both POAG and NTG are caused, or accelerated, by stress hormones in the vascular system such as glucocorticoids, pro-inflammatory cytokines, and endothelin-1. They influence vascular tone, particularly in and round the optic nerve and thereby impair vascular autoregulation. Stress hormones all contribute to endothelial dysfunction (loss of autoregulation) possibly via downregulation of endothelial nitric oxide synthase (eNOS) expression, eNOS inactivation, decreased nitric oxide (NO) actions, and increased NO degradation, together with vasoconstriction counteracting against NO-induced vasodilatation. NO is a known regulator of ocular blood flow and the reduction of NO metabolites is known to be associated with glaucoma [57]. NO is involved in the control of basal blood flow in the choroid, optic nerve, and the retina via the maintenance of the autoregulation of ocular blood flow [58].

Autonomic nervous system imbalance

Stress being one of the main causes of sympathetic nervous system activation is an axiomatic fundamental of medical science. The evolutionary function of stress is to prepare the body and mind for the "fight flight" response. Sympathetic activity prepares the body for it, whereas parasympathetic influences are predominant during relaxation states. The autonomic nervous system is also a factor keeping the blood flow

in synch with metabolic demand of nerve cells. It controls autoregulation of the vasculature which is the intrinsic capacity to maintain constant flow despite changes in perfusion pressure. But if autoregulation fails in the ocular blood vessels, this can have a dramatic impact on ocular blood flow homeostasis thereby precipitating impairment. Hence, blood flow regulation may not match the metabolic demands of the retinal nerve cells which then fail to fire action potentials at the needed activity level or at the right point in time. It is to be noted that, similar to blood flow in the retina, blood flow in the brain is also autoregulated.

Na and Riccadonna [48, 49] showed that dysfunction of autonomic control is associated with NTG which they discovered by analyzing heart rate variability; autonomic dysfunction may, in fact, induce chronic ischemia of the optic nerve. The study of heart rate variability (HRV) under conditions of the cold provocation test confirmed the predominance of the sympathetic nervous system activity in NTG [59].

Inflammation

Psychological stress is also a major provocative factor in chronic inflammatory conditions which increases TNF-α (an anti-inflammatory myokine) and IL6 (a pro-inflammatory cytokine) [60]. As an example, elevated levels of IL6 are found in the aqueous humor of glaucoma patients, suggesting their contribution to glaucoma pathogenesis.

TNF-α is a cell signaling protein (cytokine) involved in systemic inflammation. Its levels are elevated in glaucoma patients and major depressive disorders revealing a trifaceted link between TNF-α, psychological stress, and glaucoma. Levels of pro-inflammatory mediators TNF-α as well as IL6 and IL8 are elevated in glaucoma and downregulated by meditation, which is associated with a normalization of IOP (Dada et al. 2017, personal communication). For further details about the relationship of psychological stress and the immune system, please refer to Segerstrom and Miller [42].

Mental stress: *consequence* or *cause* of vision loss

Our hypothesis that visual impairment has, at least in part, a psychosomatic component is based on two considerations: Firstly, patients suffering from low vision (for example due to glaucoma or optic neuritis) often report that their vision loss happened at a time of massive or prolonged mental stress (or shortly thereafter). The source of massive mental stress could be significant life events such as financial, marital, employment (retirement), or serious health problems. When asked about it, patients often mention their impression that their vision loss might have been triggered by stress.

The second consideration is the biological response chain following continuously (or acutely) elevated stress hormone levels in blood vessels (such as cortisol, adrenalin, endothelin). They cause vascular dysregulation which leads to insufficient amounts or the timing of oxygen supply in the eye (and possibly brain) tissue, with widespread consequences on the biochemical, physiological, and psychological level of analysis. The "Flammer syndrome" (FS) is one example of this, where endothelial cell dysfunction, possibly due to genetic abnormalities in combination with stress hormone exposure, leads to vascular autoregulation problems [12] (see below). However, direct proof of this hypothesis is still lacking.

The fundamental association of stress and glaucoma has already been proposed many times before [61, 62]. The general consensus is that mental stress is only the *consequence* of vision loss reducing quality of life (QOL) [63]. Constant anxiety and worries plague many patients as they anticipate a grim future of a progressing blindness. This fear severely impacts QOL and lifestyle [2] for the risks of losing employment, greater dependence on others, and declining self-esteem [64]. This is particularly relevant to acquired visual impairment, less so for blindness from birth [65].

Despite a compelling body of rationale, stress is of little concern to clinical ophthalmology because ophthalmologists are neither trained nor paid for helping with psychological problems which are for psychologists or psychiatrist to fix. If we accept the notion that stress is causal for vision loss, then there is considerable risk associated with situations when patients are informed by ophthalmologists with a negative prognosis like "get used to it," "blind stays blind," or "you are going to be blind." Clinicians are therefore advised to refrain from making such negative predictions for anxiety and fear may actually accelerate the vision loss. Such a conceptual layout makes a case for psychological counseling of patients where an ophthalmologist foresees poor prognosis.

Flammer syndrome and stress

FS and the science behind it is a starting point for our discussion of the concept that some diseases of low vision may be considered psychosomatic in nature. FS is found mostly in cases with NTG which was first described by Dr. Josef Flammer at the University Eye Clinic in Basel, Switzerland, who provided insight into how closely the mind and the body interact [11, 21, 53]. NTG often leads to visual field impairments but almost never to blindness. According to Flammer's proposal, stress hormone release in persons with endothelial dysfunction leads to vascular dysregulation. This, in turn, is a key mechanism of vision loss in NTG but not one in high pressure glaucoma. The discovery of the FS is a key advance in our understanding of the role of stress in certain forms of vision loss. It establishes a link between human psychology

(state of mind), pathophysiological susceptibility (endothelial integrity), and the biological stress response (stress hormone release signature), the combination of which leads (or at least predisposes) to vision loss. FS is most obvious in younger patients that have NTG, but the principles we learn from FS may also apply to other diseases of the visual system.

According to Flammer, the FS is inherited and its objective signs (such as endothelial dysfunction, capillary reaction to cold stress, altered gene expression, etc.) are stable across the life span, with or without stress. But FS persons (F+) react differently to stress than those without Flammer signs (F−). Their response to emotional stress includes vasoconstriction, whereas FS− subjects react with an imbalance of the ANS, which lead to tachycardia, high blood pressure, IOP rise, stomach pain, gastrointestinal upset, etc.

Stress, especially in younger patients with FS+, can provoke acute diseases such as AION or retinal venous vasoconstrictions because of vascular endotheliopathy. This vasoconstriction does not seem to be the result of stress hormone exposure alone. Rather, persons with vascular endotheliopathy are more susceptible to stress, i.e., with an altered responsiveness to stress hormones (mainly adrenalin and endothelin), to cold provocation, low atmospheric pressure at high altitudes, and mechanical insults. FS is thus the result of an interaction of genotype (biology) and psychology (= stress perception); though there may also be epigenetic mechanisms involved. Endothelial mitochondrial dysfunction seems to be the subcellular source of the problem [66] and this dysfunction is the only influence on the smooth muscles in the retina vessels, which are not controlled by the ANS.

These observations suggest that glaucomatous optic neuropathy (GON) is not only the result of some sort of "mechanical insult" due to elevated IOP on the optic nerve head (ONH) with subsequent degeneration of the inner layer of retina and optic nerve. As the FS demonstrates, this "mechanical" view of glaucoma is too simplistic because GON pathology is more complex. GON (i) involves not only the eye but the entire optic pathway including other parts of the brain, (ii) GON can develop at either elevated or normal IOP levels, and (iii) ocular blood flow (OBF) is reduced which affects not only the eye but also other body parts such as nail fold capillaries [67] and possibly the brain.

But not everyone with FS develops glaucoma because multiple co-factors have to be present: certain triggering factors, oxidative stress, reduced "repair" capacities, and a personality-based insufficient stress resilience (e.g. coping problems). FS is more prevalent in women (70%), and FS patients tend to be slender, have typically indoor rather than outdoor jobs, and they are more likely academics than blue collar workers [54]. And there are other symptoms such as prolonged sleep onset time, prolonged blood flow cessation in the finger capillaries after cooling, autoregulation problems of ocular blood flow, increased retinal venous pressure, stiffness of retinal vessels, and increased oxidative stress. FS+ individuals have also generally increased sensitivities to certain drugs, high altitudes (lower atmospheric pressure) changes, vibration, and pain sensation [54].

FS is influenced by environmental factors and genetic predispositions. And also FS patients have a characteristic psychology: FS+ patients are often worrisome and remarkably assiduous, sportive, and ambitious, with a tendency toward perfectionism. Such patients seem to have an urge to be good to everyone (like "Angles") and fulfill first and foremost needs of others like their spouses, family, friends, and coworkers. However, by being so good to others, they neglect their own emotional needs and desires. It is as if their brain is solely focused toward the social fabric in the outside world, neglecting the own self. Such persons tend to be ruled by self-denial and—to use psychoanalytic terms—their "super-ego" (strictly observing duties, rules, and satisfying expectations) dominates their "It" (pleasure, joy, emotional satisfaction). This super-ego domination, however, leads to long-lasting self-deprivation, increasing the level of anxiety, and fear with risk of depression. In fact, the FS bears similarities with the Takotsubo syndrome, a stress-induced cardiomyopathy, which also affects mostly women that have a similar psychology [68].

Because of these personality traits, FS patients experience chronic mental stress. The source of this trait is rather different among different individuals, but childhood adversity and programmed stress sensitivity may be among possible causes. Two patients the author (BS) has seen in the clinic had reported sexual abuse in their childhood, and this trauma may have led, with a speculative pretext, to programmed (learned) stress sensitivity. FS symptoms and signs—resulting from the common denominator of endothelial dysfunction in conjunction with chronic stress—are examples that certain low vision problems are, at least in part, psychosomatic disorders.

From a clinical perspective, vascular dysregulation is not limited to the eye but it is found also in non-eye diseases. Concerning eye diseases, FS is found in normal-tension glaucoma, retinitis pigmentosa [69], increased retinal venous pressure due to a dysregulation of venous outflow from the eye [53, 70], retinal vein occlusion [71], optic nerve compartment syndrome [54], and preoperative ischemic optic neuropathy [72]. Other body parts affected by FS are inner ear with diseases such as tinnitus or sudden hearing loss [54], and it may play a role in other diseases such as multiple sclerosis [73] (Figure 2).

In summary, the syndrome that Flammer has uncovered is a more *holistic* perspective of mechanisms underlying some diseases of vision loss. It considers different levels of analysis including molecular, cellular, physiological, and behavioral (psychological) symptoms.

Vision loss: a psychosomatic disorder?

Others have also suggested psychosomatic components in vision loss, some looking upon it as a *consequence*, but others as a *cause*. The available literature is summarized in Table 2 and some psychosomatic considerations are now discussed. Though the general consensus seems to be that stress is only the *consequence* of vision loss, numerous studies indicate that stress can be a triggering (or risk) factor for visual impairment. Though it is unclear if stress alone is a sufficient condition to induce vision loss, it is a least a well-recognized and critical co-factors when other pathological conditions are present, such as arteriosclerosis, inflammation, or, as in the case of FS, an endothelial dysfunction.

Non-organic vision loss

One rather frequent observation is quite revealing: vision loss can happen without any indication of pathological abnormalities as examined with blood tests, electrophysiological evaluation, retina imaging, computed tomography (CT), or magnetic resonance imaging (MRI). These cases are referred to as n*on-organic* or *functional* vision loss [15]. Except for purposeful feigning or exaggeration of symptoms, many of these non-organic visual disorders are called somatoform or conversion disorders [74]. In addition, vision loss has been associated with psychosocial problems. For example, Lim [75] reported that 36% of 140 adults and children with vision impairment reported concomitant psychosocial problems such as psychological trauma in adulthood or problems with their social interactions in childhood.

Glaucoma

Odberg [76, 77] examined the psychological impact of glaucoma in 589 patients and found that 80% reported negative emotional reactions after knowing that they had glaucoma and one third were afraid of going blind. Higher levels of anxiety [78, 79] and depression [80, 81] have been reported in patients with primary angle closure glaucoma (PACG) than in those with open-angle glaucoma (POAG) [82]. Younger age was found to be a risk factor for anxiety, while an older age and increased glaucoma severity were risk factors for depression [83]. Diniz-Fiho [84] reported that faster progression of visual field loss in glaucoma was associated with the occurrence of depressive symptoms.

AMD

There is little literature on the psychological impact of AMD. Casten [85] studied 114 elderly AMD patients and found high rates of depression which exacerbates physical disability. Similarly, other group [86] tested 86 elderly adults with AMD and found them to suffer significant emotional distress with profoundly reduced QOL and impairments in their daily activities. Psychological control strategies were studied in 90 AMD patients by Wahl et al. [87]. Shortly after the initial diagnosis, the patients used compensatory primary control strategies which were related to functional loss in instrumental daily activities. But within 1 year, there was an increase in compensatory secondary control strategies which were associated with functional loss in instrumental daily activities. Thus, the strategies of control play a role in coping with anticipated or real functional loss.

Retinitis pigmentosa

Retinitis pigmentosa is a set of hereditary retinal diseases characterized by degeneration of rod and cone photoreceptors [88]. A group of retinitis pigmentosa (RP) patients ($n = 970$) also showed significant anxiety and intense phobic pathology [89]. Greater visual field (VF) variability was found to be associated with reduced visual fields, less physical activity, or increased negative psychosocial states [90]. Hahm [91] found that patients with depression have worse vision than those without depression.

Myopia

Myopia, a condition where light focuses in front of rather than on the retina, is mainly caused by anomalies in shape of eyeball and imprecise refraction by the optical system of the eye (cornea, lens). While myopia can be fixed by glasses or contact lenses, myopia is not merely a physical problem. Rather, contrary to generally held belief, it also depends on the psychological state. Until now, it is not clear if stress could have a causal role in myopia. While Angi [92] found that the personality profile and psychophysical stress did not play a role in the pathophysiology of myopia, Avetisov [93] concluded that acute psychogenic stress could lead to myopia. After the 1988 earthquake in Armenia, they examined 762 residents who had never complained of their vision before but 30% developed pseudo-myopia. Pseudo-myopia is caused by a spasm in ciliary muscles, which thickens the lens and shortens the focal length by a shift of the focal point away from the retina rather than on it. In fact, pseudo-myopia is thought to be caused (at least in part) by an imbalanced autonomic nervous system function, here parasympathetic activation [94].

It is conceivable that vision acuity loss is affected by mental stress (and/or fatigue) because stress might lead to tension of the tissues and muscles around the eyes, changing the shape of the eye ball. And vision acuity could be modulated by problems with eye muscle tone, eye movements (microsaccades), vascular changes in the eye or brain, or by brain mechanisms of visual signal resolution.

Other ocular diseases

There are reports of other eye conditions with psychosomatic involvement as well. This includes dry eye syndrome (DES) which is caused, among other reasons, by low tear production. Psychological stress is well known to result in a sympathetic predominance of the ANS which reduces the activity of bodily glands, such as saliva and tear production. When Li et al. [95] compared 89 DES patients with 73 control subjects, DES patients scored high on anxiety and depression on the Zung Self Rating Anxiety Scales (SAS) and Zung Self Rating Depression Scales (SDS) which correlated significantly with the DES scores of the Ocular Surface Disease Index (OSDI).

Scrutiny, analysis, and interpretation of all the available evidence of associations between psychosomatic indicators and vision loss is beyond the scope of this paper. Table 2 however, lists the available references. Many papers are silent with regard to the issue of whether stress is cause or consequence; to this effect, those that are explicit about it, half argue in favor of stress as a *consequence* of vision loss and the other half as a *cause*.

Mental stress and personality

Psychology is the science of mind and behavior, including all aspects of conscious and unconscious experiences as well as thought (cognition) [13]. When a person suffers from prolonged psychological (mental) stress, this reduces QOL and is a burden to him/her and also to their social environment [14]. People have different mechanisms for coping with stress, i.e., being able to react to stress in an adaptive manner. But if stress is too high or lasts too long, or if the person does not have sufficient resilience capacities or coping skills because of his/her personality disposition, mental fatigue, burnout, anxiety/fear, or depression may ensue. This can go hand-in-hand with organic/somatic problems like feeling non-organic pain or non-organic vision loss [15, 74, 75], especially if such persons have a predisposing genotype. There are many diseases in medicine that are characterized by both somatic and psychological aspects, and psychosomatic medicine is a well-established discipline. Its task is to help reducing the impact of psychological problems to improve patient's well-being and providing coping resources for their physical diseases or disabilities [48, 49, 67, 84, 85, 91, 96, 97]. But because diseases of the visual system have traditionally been viewed as an exclusive affair of biology and physics (optics), the interaction between ophthalmology and psychosomatic medicine is practically non-existent.

If an individual is resilient or susceptible to stressors depends largely on their personality. Maladaptive coping strategies and specific personality patterns are found in patients with glaucoma [98–100]. Mabuchi [101] observed that PAOG patients have significantly higher mean neuroticism scores (N), and agreeableness (A) as well as conscientiousness (C) were significantly lower in male POAG patients. The mean extraversion score (E) was significantly lower in female POAG patients. Freeman et al. [98] observed that those patients that use denial when confronted with their first POAG diagnosis had a faster progression of the visual field loss.

Individuals who are blind or have low vision face the constant challenge of psychologically and socially adjusting to their disability [102]. A person's personality determines if their coping strategy is sufficient to handle stressful events or not. Meta-analyses [103] link optimism, extraversion, conscientiousness, openness, and agreeableness to more engagement in coping; so does, in contrast, neuroticism which leads to less disengagement in coping [94]. Benn [104] studied two personality traits: neuroticism and optimism and five coping strategies: distancing, accepting responsibility, escape-avoidance, effective problem solving, and positive reappraisal. The result indicates that personality and coping (primarily distancing and escape-avoidance) appeared to exert their effects directly on adaptation. Neuroticism and escape-avoidance were associated with reduced adaptation, and optimism and distancing were related to greater adaptation. It is well known that adaptation through coping is a psychological defense mechanism. Tolman et al. [105] used the "Adaptation to Vision Loss Scale" and tested 144 patients with AMD. The study suggested that legally blind older adults with AMD who were more adapted to their vision reported fewer depressive symptoms.

This puts the studies by Flammer in context. He observed that the FS happens more frequently in females (70%) and FS women tend to be characterized by stereotypic feminine traditional gender socialization, which is an important determinant for anger suppression and all the FS+ signs [106].

To summarize, since personality traits determine how a person reacts to everyday stressors and because many patients with vision loss (especially glaucoma) are poorly adapted to stress, we propose that patients with specific personality traits related to negative coping styles are more prone to vision loss and its progression. If it is agreed that prolonged mental stress can be a major (though not only) cause of vision loss, then ophthalmologists, psychologists, psychiatrists, and other related professionals should be encouraged to offer stress management interventions to vision loss patients with the goal to reduce stress and thus prevent or halt the progression of vision loss. Furthermore, if such stress reduction methods are successful, then conclusive evidence is needed for the proposition that stress is *causal*, and not just the *consequence* of vision loss. The study that meditation can normalize IOP is one such study (Faiq et al. 2018, submitted), and many several other observation show how stress reduction can help in the management of vision loss.

Psychological treatments to reduce stress in vision loss

Considering the discussion above, relaxation, psychotherapy, or other stress reduction programs should be helpful in reducing the impact of low vision. There are several such reports in the literature. For example, relaxation and visual imagery techniques can reduce IOP [107], psychotherapy can be beneficial for glaucoma patients during surgical or drug therapy [108], and meditation, yoga, breathing exercises, and coping strategies can help people reduce stress [109–112].

In fact, relaxation techniques and psychotherapy are the most promising methodologies with a potential to reduce the progression of vision loss or even improve vision recovery. Relaxation to counteract stress has always been part of human societies, ranging from hallucinogenic drugs (such as legal use of marijuana) to music and sports, and it is practiced in different schools of thought, religions, wellness programs, and psychology institutions. Furthermore, relaxation is part of traditional (alternative) medicine and healing traditions and has recently become the focus of modern evidence-based medicine.

There are many every-day activities that can help people to relax and enhance their well-being such as sports, reading, sleeping, mind-wandering, prayer, or listening to music. But if the level of stress and tension is too high or consistently persistent for long periods, these everyday methods may be insufficient and more systematic and powerful relaxation techniques are needed to calm down the body and mind. Such techniques include meditation (transcendental and mindfulness meditation), yoga, autogenic training, progressive muscle relaxation, fantasy journeys, or slow/deep breathing exercises ("pranayama"). What they all have in common is that they counteract stress and tension by rebalancing the autonomic system by reducing sympathetic and activating parasympathetic nervous system activity. Such relaxation techniques have a positive impact on all levels of the psycho-neuro-endocrine axis.

For example, meditation counteracts symptoms of the stress response by slowing the breathing rate, relaxing muscles, and normalizing blood pressure [113, 114]. On the biochemical level of analysis, relaxation increases levels of plasma endorphins, endogenous opioid neuropeptides which, in turn, inhibits pain signaling and triggers the feeling of euphoria [115]. Meditation also influences a plethora of molecular processes including oxidative metabolism, epigenetics, gene repair, aging, blood pressure, organ system maintenance, and neuroendocrine health (Dada et al. 2017, unpublished; [116]) and it can improve cardiovascular functions [117] and counteract brain aging-associated changes [118]. In fact, even a single session of relaxation can acutely reduce IOP [119].

Despite this long tradition, relaxation techniques are somehow novel for the treatment of visual disorders.

Several biological mechanisms are influenced by relaxation exercises, which ameliorate POAG. Endorphins, by way of modulation of the brain's arcuate nucleus [120], can be beneficial through its ability to reduce IOP in rabbits [121, 122], appease depression symptoms and cortisol levels [123] with concomitant decrease in blood pressure [124]. Relaxation techniques where shown to be able to reduce IOP [125], improve neuroendocrine regulation [111] of ciliary body production of aqueous humor and normalize IOP [126]. Furthermore, relaxation brings down inflammation and decreases glial activation [127, 128]. It also elevates brain and aqueous nitric oxide [129], improves outflow pathways, and normalizes IOP [130]. Other observations related to relaxation are improved glutamate metabolism and decreased glutamate-mediated toxicity [131], modulation of extracellular matrix, and the integrity of the trabecular meshwork to maintain aqueous outflow, improved perfusion of cerebral tissue [132], and parallel gene expression changes through epigenetic modulation [133].

Though relaxation techniques may be viewed with some skepticism because of their traditional use in esoteric or religious contexts, different relaxation techniques are, nevertheless, systematic and powerful modulators of nervous system function with a widespread impact on both mental and bodily health. Moreover, in modern medicine, everything is subject to validation. Relaxation-based techniques and their efficacy can be—and have been—validated through well-designed clinical trials with methodological rigor and empirical reasoning.

Meditation

Meditation encompasses a family of complex practices that include mindfulness meditation, mantra meditation, yoga, tai chi, and chi gong [134, 135]. Meditation was shown to increase parasympathetic activity to reinstate sympathovagal balance [136] and help patients to cope with their clinical and non-clinical problems [137]. In a classical study of short-term yoga-based meditation, Netam et al. [138] found reduced IL6 levels in patients with chronic inflammatory conditions, and mind-body therapies reduced inflammation markers [139]. In a recent randomized trial (Dada et al. 2017, unpublished), a 3-week meditation-based stress reduction program significantly normalized IOP, reduced stress biomarkers, and changed gene expression in such a way so as to help induce a neurotrophic response.

Music therapy

Music has been used since ancient times to enhance well-being and reduce pain and suffering [140]. Steady rhythms entrain regular respiratory patterns, and listening to classical music increases heart rate variability (a measure of cardiac autonomic balance), whereas listening to noise or rock music

decreases heart rate variability [141, 142]. A meta-analysis [143] indicates that music alone and music-assisted relaxation techniques significantly decreases arousal due to stress. In the Knight study [144], 89 undergraduate students were exposed to a cognitive stressor task. This significantly increased their anxiety, heart rate, and systolic blood pressure. But when they were exposed to music therapy, there was a significant reduction of anxiety by 28%, in systolic blood pressure by 26% and in heart rate by 36%.

Biofeedback

Biofeedback is a method of gaining greater awareness of the body's physiological state using instruments that provide information on the activity of different bodily parameters such as brain wave activity, muscle tone, heart rate, or skin temperature. The goal is learn to manipulate these functions at will to achieve a state of relaxation [145]. Though biofeedback has been used to improve visual fields in patients [146], it has so far only been used as a means to induce relaxation in normally seeing subjects. Amore et al. [146] reported that biofeedback-relaxation can increase finger temperature and cardiac output and decrease systemic vascular resistance and respiratory rate. Likewise, Moser et al. [147] employed biofeedback-assisted relaxation which increased fingertip temperatures. Also, Bernat and coworkers [148] and Del Pozo et al. [149] used it to increase heart rate variability in patients with coronary artery disease. Besides des Amore study, the application of biofeedback to improve the condition of low vision patients (here: AMD) has not been studied at all.

Autogenic training

Autogenic training is a relaxation technique introduced by the German psychologist Schultz early last century (1932). It was used for the treatment of ophthalmological diseases by Strempel and her colleagues who reported it to be beneficial for IOP normalization in open-angle glaucoma patients. Each patient's IOP could be reduced by an average of 3 mmHg, and it benefited their psychological state. At the end of the experiment, 43% of her patients reduced or even stopped taking eye drops. The other 57% of the patients continued to take their medicine or changed their medicine with associated IOP reduction to levels well below their lowest values before [107, 150, 151].

Coping strategies

There are different strategies for better coping with medical problems. They include cognitive restructuring such as optimism (looking not only at the rear mirror but looking forward), looking at the situation in relative terms such as "there are so many worse things" to keep vision loss in perspective [152]. Other methods are focusing on what one can still do and not dwelling in the past, positive social comparisons [153], and a positive prognosis that there are different means to improve vision or ways to compensate for the loss. There are also more general methods to help with emotional anger including psychotherapy or even simply "kicking and screaming" [152]. Considering that a negative problem orientation significantly predicted depression and emotional distress, while rational problem-solving skills predicted life satisfaction [154], Garnefski concluded that both cognitive and goal-related coping could be an important intervention for patients with vision loss [155].

Another interesting intervention to improve coping in patients with vision loss was described by Bryan and Lu [156]. They studied patients with Stargardt's disease, a rare condition of macular degeneration who received an expressive writing intervention for 3 to 6 weeks. This had a positive impact on their psychological health outcomes at 3-week follow-up and self-reported physical health at 6-week follow-up. The authors suggest that expressive writing is an effective, practical, and low-cost psychological intervention to improve QOL.

Social support

Decreased visual acuity, visual field loss, or blurred ("foggy") vision are also associated with decreased QOL [157]. Family members can play an important role in the adaptation of patients, providing encouragement for the initiation and completion of rehabilitative services [158, 159]. In Reinhardt's [160] study, scores for support by family members were higher than those for friend. As compared to friends, family members are relied upon more often for both instrumental (practical) and emotional support [161].

Conclusions and expert recommendations

On the one hand, vision loss reduces subjective QOL due to anxiety, fear, and depression, i.e., stress being the consequence of low vision. On the other hand, we now propose that mental stress is also a *cause* of different visual diseases, perhaps even the main cause of some of them. Both cause and *consequence* interact in a downward spiral manner. Stress leads to vision loss which causes stress, which in turn worsens the vision loss, making the stress even worse and so on (Fig. 2). It is important for doctors, researchers, caregivers, and patients to know about this downward spiral and finding ways of breaking it. Owing to the extensive interactions between the eye, brain, and vascular system, ophthalmological diseases are not only a matter of physics and biology but also one of the psychology and the persons' state of mind (Sabel, Flammer, Merabet, unpublished). An increased understanding of the precise biological mechanisms that translates stress into visual

disease may open up completely new mechanism-driven/pathophysiology-informed intervention strategies that directly target these mechanisms.

This new psychosomatic perspective has several implications for clinical practice. (i) Stress reduction and relaxation techniques should be recommended not only as complementary to traditional treatments of vision loss but possibly as preventive means to reduce progression of vision loss. (ii) Doctors should try their best to inculcate positivity and optimism in their patients while giving them the information the patients are entitled to, especially regarding the important value of stress reduction and relaxation. Statements of a grim future such as "you will go blind" should be strictly avoided. This induces unnecessary anxiety and fear, possibly accelerating vision loss progression (Fig. 4). (iii) Medical treatments might aim at reducing the biochemical effects of stress hormones on the blood vasculature, and (iv) various psychological interventions, well established in clinical psychology such as coping strategies, relaxation techniques, or psychotherapy should become adjuvant methods of standard ophthalmologic care. In this spirit, the relationship of stress and vision loss can help reach the recently proposed need to turn more attention to predictive, preventive, and personalized medicine as outlined by Golubnitschaja et al. [162]. "Predictive" because the level of mental stress could help predict how vision loss progresses on the one hand and predicting the outcome of new therapies on the other hand. "Preventive" in that reducing or preventing stress could reduce the progression and/or prevent the development of vision loss. And "individualized" in that it helps tailor medical and psychological interventions to the individual patients psychomedical needs and personal circumstances.

The FS is thus a kind of "rediscovery" that psychosocial factors play a crucial role in ophthalmological diseases. By linking the concept of biological stress, vascular dysregulation, and vision loss, Josef Flammer has provided new insight into the tight interaction of biological and psychological factors in glaucoma. In that sense, the discovery of the Flammer syndrome offers ophthalmology a holistic perspective that vision loss may not just be a problem of physics and biology, but also one of the human mind. This will help to fill the void of the long felt need by many patients that their subjective experiences and feelings regarding vision loss matter and should not be ignored. Considering psychosomatic factors offers new leads for interventions to supplement existing concepts of treating vision loss by means that go beyond mere eye drops and surgery. In that sense, the Flammer syndrome is a starting point for the dawn of psychosomatic ophthalmology. Such a new path will help us address the most important subject matter: the person behind the eye.

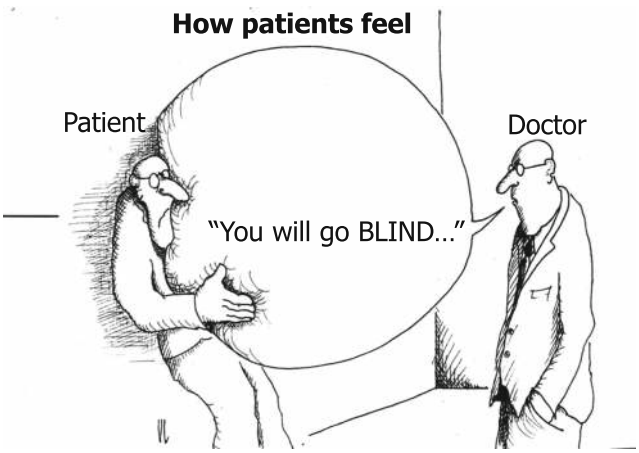

Fig. 4 Cartoon displaying how the patient feels when confronted with a negative prognosis

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Compliance with ethical standards

Conflict of interest B. Sabel is co-owner of a private medical practice (www.savir-center.com) where the two patients described in this paper were treated.

Ethical statement For this type of study, formal consent is not required. We thank our patients for their consent to publish their case histories.

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