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Review

Low-Frequency Light Stimulation as a Potential Novel Countermeasure for Spaceflight-Associated Neuro-Ocular Syndrome

Peter Wostyn

Department of Psychiatry, PC Sint-Amandus, Reigerlostraat 10, 8730 Beernem, Belgium; wostyn.peter@skynet.be; Tel.: +32-472713719; Fax: +32-50-819720

Abstract

Spaceflight-associated neuro-ocular syndrome (SANS) is a high-priority health risk during long-duration spaceflight and a major challenge for future human exploration missions to the Moon and Mars. Its pathophysiology remains incompletely understood, and no current countermeasure provides complete protection. This narrative review proposes low-frequency light stimulation as a novel, non-invasive, ocularly targeted countermeasure strategy specifically for SANS-associated optic disc edema. Disturbed ocular glymphatic transport may contribute to SANS-associated optic disc edema by impairing fluid clearance from the optic nerve head during prolonged exposure to microgravity. In rodents, ocular glymphatic clearance is driven by the translaminar pressure difference and enhanced by low-frequency (1 Hz) light stimulation, with repeated pupillary constriction and possible ciliary muscle activity proposed as contributing mechanisms. The central hypothesis of this review is that, under microgravity-relevant conditions, low-frequency light stimulation increases ocular glymphatic outflow relative to unstimulated conditions and that this increase is sufficient to reduce fluid accumulation at the optic nerve head and attenuate SANS-associated optic disc edema. Although repeated pupillary constriction remains the primary candidate mechanism, this review also considers two biomechanical mechanisms through which concomitant ciliary muscle activity, if elicited during such stimulation, could additionally contribute to ocular glymphatic outflow. The light-stimulation approach is mechanistically distinct from existing SANS countermeasures, which primarily target upstream processes such as cephalad fluid redistribution, elevated intracranial pressure, or disruption of the translaminar pressure balance. Following successful initial physiological confirmation in humans and mechanistic validation in appropriate experimental models, the strategy could be evaluated both as a standalone intervention and, given its mechanistic complementarity, in combination with existing or emerging SANS countermeasures in controlled ground-based microgravity analog studies and subsequently during spaceflight. Successful completion of this staged research pathway, together with demonstration of an acceptable benefit–risk profile and operational suitability, could support the development of a wearable low-frequency light-stimulation system as a practical standalone or adjunctive countermeasure for preventing or mitigating SANS-associated optic disc edema during long-duration human space exploration.

Keywords: countermeasures; low-frequency light stimulation; microgravity; ocular glymphatic system; optic disc edema; spaceflight-associated neuro-ocular syndrome

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1. Introduction

A considerable proportion of astronauts who complete long-duration missions aboard the International Space Station (ISS) develop ophthalmic abnormalities, including optic disc edema, globe flattening, choroidal folds, and hyperopic refractive shifts [1]. These ocular findings were first described by Mader et al. [1] in 2011 and initially classified as "Visual Impairment and Intracranial Pressure (VIIP) syndrome". In recognition of uncertainties regarding its underlying pathophysiology and the unclear role of intracranial pressure (ICP), the term was later replaced by "Spaceflight-Associated Neuro-ocular Syndrome" (SANS) [2]. Optic disc edema, the hallmark manifestation of SANS, has been reported as clinically significant in approximately 12–19% of astronauts during or following long-duration spaceflight [3]. However, optical coherence tomography (OCT) studies suggest that early signs of optic disc edema may be present in up to 70% of crew members [3]. Given the potential implications of SANS for future human exploration missions, particularly in the context of a return to the Moon and a mission to Mars, the National Aeronautics and Space Administration (NASA) has identified the syndrome as one of the highest-priority risks to astronaut health and performance [4]. Accordingly, improving our understanding of the mechanisms underlying SANS and developing effective countermeasures are essential for safeguarding astronaut health and maintaining operational effectiveness during future space exploration missions [3].

In the present paper, I propose low-frequency light stimulation as a novel, ocularly targeted countermeasure strategy specifically for preventing or mitigating SANS-associated optic disc edema, rather than other manifestations of the syndrome, such as globe flattening, choroidal folds, or hyperopic refractive changes. The central hypothesis is that, under microgravity-relevant conditions, low-frequency light stimulation increases ocular glymphatic outflow relative to unstimulated conditions and that this increase is sufficient to reduce fluid accumulation at the optic nerve head and attenuate optic disc edema. This hypothesis rests on four intermediate assumptions: (1) the increase in ocular tracer transport observed during 1 Hz light stimulation in mice reflects a physiologically meaningful transport response relevant to ocular fluid clearance; (2) a comparable response occurs in humans and persists under microgravity-relevant pressure conditions; (3) increased ocular glymphatic outflow reduces net fluid accumulation at the optic nerve head; and (4) reducing this fluid accumulation attenuates SANS-associated optic disc edema. Repeated pupillary constriction represents the primary candidate mechanism, whereas the two biomechanical mechanisms proposed in this review describe a possible additional contribution from rhythmic ciliary muscle activity, if elicited during light stimulation.

To provide a framework for developing and evaluating the central hypothesis, the review examines the current understanding of SANS pathophysiology, with particular emphasis on mechanisms relevant to the hypothesis, and considers existing and emerging countermeasure strategies. It then discusses the rationale for using low-frequency light stimulation as a potential countermeasure for SANS-associated optic disc edema, with repeated pupillary constriction as the primary candidate mechanism, and considers two biomechanical mechanisms through which concomitant ciliary muscle activity, if elicited during stimulation, could provide an additional contribution to ocular glymphatic outflow. The review also examines how ICP could influence the light-stimulation response and considers the resulting implications for the potential application of low-frequency light stimulation in SANS. Finally, it outlines the experimental studies required to test the hypothesis and to evaluate the tolerability, safety, and potential effects on visual function of the proposed intervention, and considers how successful validation could support the future development of wearable light-stimulation devices for long-duration space exploration.

2. Materials and Methods

2.1. Review Design and Scope

This article was conceived as a narrative, hypothesis-generating review. Its objectives were to: (1) summarize current concepts regarding the pathophysiology of SANS, with particular emphasis on ICP, orbital cerebrospinal fluid (CSF) dynamics, and ocular glymphatic transport; (2) review current and emerging countermeasures for SANS; and (3) synthesize evidence from studies of ocular glymphatic clearance and ocular biomechanics, thereby generating the hypothesis that low-frequency light stimulation may represent a novel countermeasure option for SANS-associated optic disc edema.

2.2. Literature Search and Study Selection

Relevant literature was identified through iterative, targeted searches of PubMed/MEDLINE, Scopus, and Web of Science. Searches were conducted through September 2026 using relevant keywords, individually and in combination. The combinations of search terms were adapted iteratively to the topic being examined rather than applied as a single prespecified Boolean search strategy. Key search terms included "spaceflight-associated neuro-ocular syndrome", "SANS", "visual impairment and intracranial pressure syndrome", "microgravity", "head-down tilt", "optic disc edema", "intracranial pressure", "intraocular pressure", "translaminar pressure difference", "optic nerve sheath", "cerebrospinal fluid", "ocular glymphatic system", "glymphatic clearance", "light stimulation", "flicker", "pupillary constriction", "ciliary muscle", "accommodation", "choroid", "vitreous", and "countermeasure". Additional targeted searches addressed specific countermeasures, including lower body negative pressure (LBNP), venoconstrictive thigh cuffs (VTCs), impedance threshold devices (ITDs), artificial gravity, pressurized eye goggles, nutritional supplementation, and medications aimed at lowering ICP. Reference lists of relevant publications and articles citing key studies were also screened to identify additional sources.

English-language original research articles, reviews, consensus statements, case reports, and relevant conference abstracts were considered. Human studies conducted during spaceflight and in ground-based microgravity analogs were prioritized. Experimental animal and mechanistic studies were included when they provided evidence directly relevant to ocular glymphatic transport, translaminar pressure dynamics, ciliary muscle-choroid biomechanics, vitreous movement, or the physiological effects of light stimulation. Because research on the ocular glymphatic system and on the proposed mechanisms linking low-frequency light stimulation to enhanced ocular glymphatic outflow remains at an early stage, no restrictions were imposed on study design. Publications were selected on the basis of their relevance to the prespecified topics and their ability to inform the development or critical evaluation of the proposed hypothesis. Potentially relevant publications were assessed by the sole author on the basis of their titles, abstracts, and, when necessary, full texts. Because literature selection was iterative and relevance-based, no formal screening log, duplicate independent screening, or systematic study-selection protocol was used.

2.3. Narrative Synthesis and Hypothesis Development

The identified evidence was synthesized narratively and organized into four principal domains: SANS pathophysiology, current and emerging countermeasures, regulation of ocular glymphatic transport, and biomechanical effects of ciliary muscle activity. Owing to substantial heterogeneity in study populations, experimental models, interventions, and outcome measures, no quantitative meta-analysis was performed. The proposed mechanisms linking low-frequency light stimulation to enhanced ocular glymphatic outflow were formulated by integrating findings from rodent studies of ocular glymphatic transport, non-human primate studies of accommodation-related displacements of the ciliary

muscle-choroidal elastic network and central vitreous structures, and human spaceflight and ground-based analog studies of SANS. Direct experimental evidence was distinguished from mechanistic inference, and areas of uncertainty were explicitly acknowledged. As this was a narrative rather than a systematic review, no formal protocol registration or standardized risk-of-bias assessment was undertaken.

3. Discussion

3.1. Current Understanding of SANS Pathophysiology

3.1.1. The Role of ICP in SANS

Despite intensive research, the pathophysiological mechanisms underlying SANS remain incompletely understood. Initially, SANS was thought to result from increased ICP caused by microgravity-induced cephalad fluid shifts [1]. These fluid shifts were proposed to cause venous stasis in the head and neck, thereby impairing CSF outflow and promoting cerebral venous congestion, ultimately leading to increased ICP [1]. However, in recent years, the role of elevated ICP as the primary driver of SANS has been increasingly questioned, and it remains uncertain whether optic disc edema observed in astronauts represents true papilledema, i.e., optic disc swelling secondary to increased ICP [2,5]. Lumbar puncture opening pressures measured in four astronauts with optic disc edema demonstrated only borderline to mildly elevated values of 21, 22, 28, and 28.5 cm H_2O, obtained at 19, 66, 12, and 57 days after return to Earth, respectively [1]. Because of their invasive nature, lumbar punctures have never been performed during spaceflight. Furthermore, in contrast to patients with idiopathic intracranial hypertension (IIH), a terrestrial condition characterized by increased ICP, astronauts generally do not exhibit the hallmark symptoms associated with this disorder, such as chronic headache, pulsatile tinnitus, and diplopia [2,5]. Additional evidence from a parabolic flight study involving short-duration exposure to microgravity further challenges the concept of pathologically elevated ICP during weightlessness [6]. During microgravity, ICP was lower than in the supine position on Earth but remained higher than in the 90° seated upright posture, suggesting that the absence of gravity prevents the normal reduction in ICP observed in the upright position [6]. Collectively, these findings suggest that elevated ICP is unlikely to represent the sole, or even predominant, mechanism underlying optic disc edema in astronauts, highlighting the need to explore alternative pathophysiological pathways involved in SANS [2,5].

3.1.2. Orbital CSF Compartmentalization

An alternative hypothesis proposes that optic disc edema in SANS results from localized CSF compartmentalization within the orbital subarachnoid space (SAS) [1,7]. The perioptic SAS may be particularly susceptible to disturbed CSF dynamics during prolonged exposure to microgravity because of its tightly confined, densely septated, and cul-de-sac-like anatomy [7]. Moreover, cephalad fluid shifts may impair CSF absorption through venous and lymphatic drainage pathways within the orbit, thereby allowing CSF to enter the optic nerve SAS while simultaneously limiting outflow [1,7]. Collectively, these factors may promote CSF sequestration within the orbital SAS, leading to localized elevation of optic nerve sheath (ONS) pressure, with or without a concomitant increase in ICP [1,7].

3.1.3. Ocular Glymphatic Dysfunction as a Potential Contributor to Optic Disc Edema in SANS

In 2016, Wostyn et al. [8] postulated the existence of a bidirectional glymphatic transport system between the eye and the optic nerve, involving passage across the lamina cribrosa. Building on this concept and the hypotheses outlined above, the authors sub-

sequently proposed in 2017 that disturbed ocular glymphatic transport may represent an additional pathophysiological mechanism contributing to the development of SANS-associated optic disc edema [9].

In 2020, Wang et al. [10] identified an "anterograde ocular glymphatic clearance system" in rodents, demonstrating transport from the intraocular compartment across the lamina barrier and along the optic nerve. This finding complemented previous evidence of retrograde CSF transport along perivascular spaces within the optic nerve [11]. Together, these studies support the concept of bidirectional ocular glymphatic transport along the optic nerve (Figure 1). To delineate the anterograde pathway, Wang et al. [10] injected fluorescently labeled human amyloid-β (hAβ) into the vitreous of mice. The tracer entered retinal ganglion cell (RGC) axons and perivenous spaces within the retina and optic nerve head before being cleared by the anterograde pathway [10,12–14]. Following its intra-axonal passage across the lamina barrier, hAβ was released from the axons, accumulated within the perivenous spaces of the optic nerve, and ultimately drained into the surrounding dural lymphatic vessels. This transport was shown to depend on the glial water channel aquaporin-4 (AQP4), as hAβ tracer transport was reduced in *Aqp4*-knockout mice. Specifically, *Aqp4* deletion significantly reduced both retinal hAβ penetration and hAβ transport along the optic nerve.

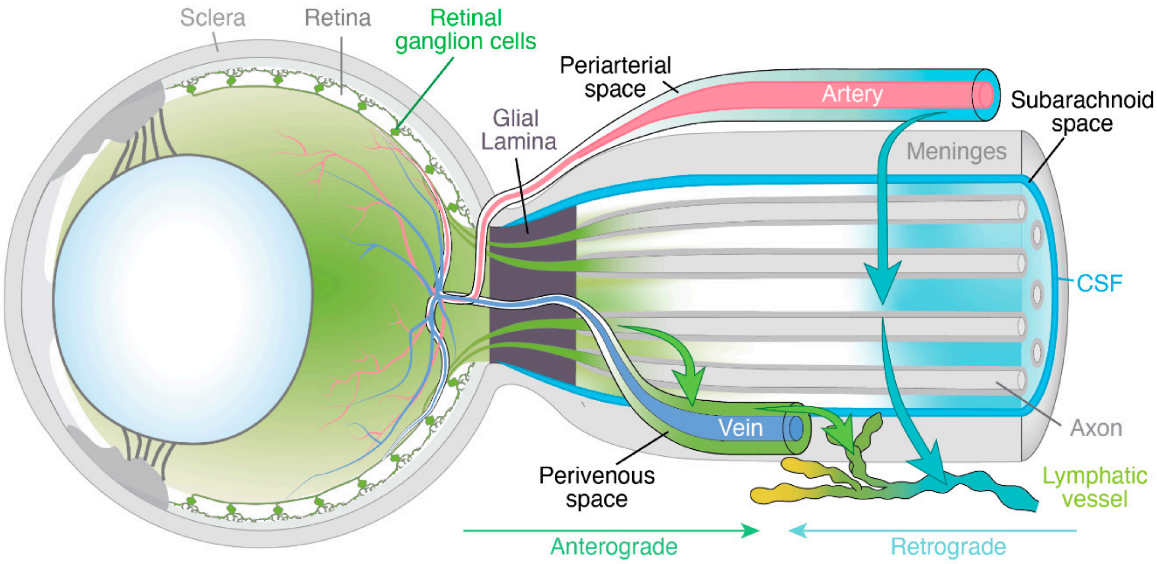


Figure 1. The ocular glymphatic system. Experimental studies in rodents indicate that the ocular glymphatic system comprises bidirectional fluid transport along the optic nerve, consisting of an anterograde pathway from the eye and a retrograde pathway originating from the brain. The anterograde pathway mediates the clearance of fluid and metabolic waste from the retina and optic nerve head toward the optic nerve. Following intravitreal tracer administration, molecules such as amyloid-β are transported through retinal ganglion cell axons and perivenous spaces within the retina and optic nerve head. After crossing the lamina barrier, these tracers are released from retinal ganglion cell axons and accumulate within the perivenous spaces of the optic nerve before ultimately draining into the surrounding dural lymphatic vessels. In contrast, the retrograde pathway describes the movement of cerebrospinal fluid (CSF) from the brain into the optic nerve along periarterial spaces, after which CSF tracers are cleared via the dural lymphatic vessels. Figure reproduced from Wostyn et al. [14], in which it was adapted from Wang et al. [13]. Reprinted from *Progress in Retinal and Eye Research*, Vol. 110, Xiaowei Wang, Christine Delle, Maiken Nedergaard, Peter Wostyn, "Glymphatic transport and ocular diseases", 101433, Copyright (2025), with permission from Elsevier.

Wang et al. [10] provided further evidence that ocular glymphatic efflux depends on the pressure difference between intraocular pressure (IOP) and ICP, with IOP normally

exceeding ICP under physiological conditions. To investigate this relationship, the authors manipulated ICP by withdrawing CSF or infusing artificial CSF without altering IOP. Increasing ICP from a baseline value of 3.6 ± 0.4 mmHg to 16.7 ± 0.6 mmHg was associated with a lower total hAβ tracer signal and a significantly lower peak intensity in the proximal optic nerve 30 min after intravitreal injection.

Importantly, the authors further found that low-frequency (1 Hz) light stimulation accelerated ocular glymphatic clearance by nearly twofold in mice compared with control mice maintained in darkness [10]. At 30 min after hAβ administration, this acceleration was reflected in marked increases across all three measured outcomes: total tracer signal, peak intensity, and transport distance along the optic nerve. A comparable light-stimulation-associated increase in hAβ tracer transport was observed in Brown Norway rats, while additional methodological validation experiments showed that varying the intravitreal hAβ infusion volume or rate did not significantly affect the overall optic nerve signal. In mice maintained in darkness, tracer accumulation increased slowly and reached a level comparable to that in light-stimulated mice by 2 h after intravitreal administration, suggesting that light stimulation accelerated the kinetics of tracer transport. No consistent effect of repeated light stimulation and associated pupillary constriction on IOP was detected. Based on these findings, the authors suggested that repeated pupillary constriction, possibly accompanied by ciliary muscle contraction, might promote intraocular fluid movement and thereby enhance hAβ tracer transport along the optic nerve. However, when 1 Hz light stimulation was combined with experimental ICP manipulation, it produced no additional change in the measured hAβ tracer transport outcomes compared with the corresponding unstimulated high- or low-ICP condition. The authors interpreted this finding as suggesting that sufficiently large ICP alterations may override the effect of light stimulation [10].

Although these findings provide an experimental rationale for investigating low-frequency light stimulation as a potential means of enhancing ocular glymphatic transport, an important methodological limitation of the study by Wang et al. [10] is its reliance on tracer-based measurements as indirect indicators of fluid transport. Accordingly, the light-stimulation-associated increases in total tracer signal, peak intensity, and transport distance do not by themselves establish an increase in net posterior fluid outflow or net fluid removal from the optic nerve head. At the same time, the observed pressure-dependent tracer transport led Wang et al. [10] to propose the existence of a posterior ocular fluid-efflux pathway. This proposal is physiologically plausible because hydrostatic pressure differences are major drivers of bulk fluid movement in other organs of the body [15], and a posteriorly directed pressure difference exists across the lamina barrier under physiological conditions. Although the volume of fluid exiting the eye through this pathway remains unknown and is likely substantially smaller than that cleared through anterior outflow routes [12], even a low-volume posterior outflow pathway could be functionally important for retinal and optic nerve homeostasis if fluid entry into and clearance from the optic nerve head are normally maintained in a finely balanced state. Under such conditions, even a modest reduction in posterior outflow could theoretically promote local fluid accumulation. Conversely, if the enhanced tracer transport observed during light stimulation reflects an increase in net posterior fluid outflow, even a modest increase could be physiologically relevant. Direct measurements of net posterior fluid flux and edema-related outcomes are required to determine whether these predicted effects occur.

Although the findings of Wang et al. [10] provide important mechanistic insight, translation of the specific transport mechanisms observed in rodents to humans requires careful consideration of relevant interspecies differences in ocular anatomy and physiology. One important anatomical distinction is that mice possess an astrocyte-rich glial lamina, whereas the human lamina cribrosa is characterized by a well-developed network of connective tissue

beams whose cores contain collagen and elastin [10]. Notably, however, Wang et al. [10] reproduced the light-stimulation-associated increase in optic nerve tracer transport in Brown Norway rats, which possess identifiable collagenous elements within the laminar region. This cross-species replication suggests that the observed transport response is not confined to the predominantly astrocytic glial lamina of the mouse eye. Nevertheless, the rat lamina remains anatomically distinct from the well-developed human lamina cribrosa, and the direct applicability of these findings to humans therefore remains uncertain, despite emerging evidence supporting the existence of an analogous glymphatic-like pathway in the human eye [13]. Studies in larger animal models with ocular anatomy and pressure dynamics more closely resembling those of humans could help clarify the translational relevance of the ocular glymphatic transport mechanisms observed in rodents and their response to low-frequency light stimulation before direct human studies are undertaken [13].

The principal experimental conditions and measured outcomes of the study by Wang et al. [10], together with the limitations relevant to interpreting its findings in the context of the present hypothesis, are summarized in Table 1.

Building on the concept that orbital CSF pressure may increase under microgravity conditions as a consequence of mildly elevated ICP, orbital CSF compartmentalization, or both, Wostyn et al. [9] had previously proposed that disturbed ocular glymphatic dynamics at the optic nerve head may contribute to the development of optic disc edema in astronauts. Specifically, prolonged microgravity-induced fluid shifts, together with individual variations in ONS anatomy and compliance, were hypothesized to promote the displacement of higher-pressure perioptic CSF into the optic nerve and optic disc through perivascular spaces surrounding the central retinal artery [9,16]. Supporting this concept, Cao et al. [17] recently demonstrated that CSF contents can enter the eye through a brain-to-eye glymphatic pathway in mice, even under conditions of normal ICP.

Table 1. Summary of the experimental evidence from Wang et al. [10] relevant to ocular glymphatic transport and low-frequency light stimulation.

Experimental Component	Species and Preparation	Experimental Conditions and Comparator	Measured Outcomes and Principal Findings	Major Limitations for Interpretation
Pathway Tracing and AQP4 Dependence	• Adult mice; C57BL/6J mice were used unless otherwise specified. • NG2-DsRed reporter mice were used for selected perivascular localization experiments. • *Aqp4*−/− and *Aqp4*+/+ mice were used for the AQP4-dependence experiments. • Fluorescently labeled human amyloid-β (hAβ) was injected intravitreally.	• hAβ distribution was examined in the retina, optic nerve head, across the lamina barrier, and along the optic nerve. • Tracer penetration and transport were compared between *Aqp4*-knockout and wild-type mice.	• hAβ entered RGC axons and perivenous spaces in the retina and optic nerve head. • After crossing the lamina barrier, it was released from axons, accumulated in optic nerve perivenous spaces, and drained into surrounding dural lymphatic vessels. • *Aqp4* deletion reduced retinal penetration and transport along the optic nerve.	• A limitation is the use of tracers to indirectly map fluid transport. • It does not quantify net posterior fluid flux or net fluid removal from the optic nerve head.

Table 1. *Cont.*

Experimental Component	Species and Preparation	Experimental Conditions and Comparator	Measured Outcomes and Principal Findings	Major Limitations for Interpretation
ICP Manipulation	• C57BL/6J mice (the default strain in the study). • Intravitreal hAβ with simultaneous ICP manipulation and IOP monitoring.	• ICP was altered by withdrawing CSF or infusing artificial CSF without changing IOP. • ICP was increased from 3.6 ± 0.4 to 16.7 ± 0.6 mmHg. • hAβ tracer outcomes in the proximal optic nerve were assessed 30 min after intravitreal injection.	• Higher ICP was associated with a lower total hAβ signal. • Peak intensity in the proximal optic nerve was significantly lower.	• The acute ICP manipulation and 30-min endpoint do not directly determine local perioptic pressure or net fluid removal. • The experiment does not define the pressure range relevant to SANS.
1 Hz Light Stimulation in Mice	• C57BL/6J mice (the default strain in the study). • Intravitreal hAβ administration.	• Low-frequency 1 Hz light stimulation was compared with maintenance in darkness. • Tracer outcomes were assessed at 30 min, with additional assessment at 2 h.	• At 30 min, light stimulation accelerated transport by nearly twofold and increased total signal, peak intensity, and transport distance along the optic nerve. • In darkness, tracer accumulation increased more slowly but reached a comparable level by 2 h. • No consistent effect on IOP was detected.	• The findings demonstrate faster tracer transport, which may be consistent with enhanced posterior clearance, but they do not by themselves establish increased net posterior fluid outflow or an edema-resolving effect. • Ciliary muscle activity was not measured.
Rat Replication and Injection Controls	• Two-month-old Brown Norway rats receiving intravitreal hAβ. • Separate controls of intravitreal hAβ infusion volume and rate performed in mice.	• The light-stimulation experiment was repeated in rats. • Separate controls varied the intravitreal hAβ infusion volume and rate.	• A comparable light-stimulation-associated increase in hAβ transport was observed in rats. • Varying the intravitreal hAβ infusion volume or rate did not significantly affect the overall optic nerve signal.	• The replication and injection controls support the robustness of the observed tracer-transport response but do not establish that it reflects increased net posterior fluid outflow. • Rodent-to-human translation remains uncertain.

Table 1. *Cont.*

Experimental Component	Species and Preparation	Experimental Conditions and Comparator	Measured Outcomes and Principal Findings	Major Limitations for Interpretation
Light Stimulation During ICP Manipulation	• C57BL/6J mice (the default strain in the study). • Intravitreal hAβ under experimentally manipulated low- or high-ICP conditions.	• Hz light stimulation was combined with experimental ICP manipulation. • Comparators were the corresponding unstimulated high- or low-ICP conditions.	• Light stimulation produced no additional change in measured hAβ outcomes relative to low or high ICP alone. • The authors suggested that sufficiently large pressure changes can override the light-associated tracer response.	• The pressure threshold at which the light response is lost was not defined. • Effectiveness under microgravity-related conditions was not established.

Abbreviations: AQP4, aquaporin-4; CSF, cerebrospinal fluid; hAβ, fluorescently labeled human amyloid-β; ICP, intracranial pressure; IOP, intraocular pressure; RGC, retinal ganglion cell; SANS, spaceflight-associated neuro-ocular syndrome.

In addition, Wostyn et al. [9,18] proposed that impaired ocular glymphatic outflow from the eye toward the optic nerve may represent another mechanism contributing to SANS-associated optic disc edema. Under normal physiological conditions on Earth, the translaminar pressure difference (TLPD), defined as the difference across the lamina cribrosa between IOP and ONS pressure, is directed posteriorly because IOP exceeds ONS pressure. Prolonged microgravity exposure was hypothesized to increase ONS pressure, thereby reducing or even reversing this posteriorly directed TLPD and partially or completely impairing ocular glymphatic efflux toward the optic nerve [9,18]. This proposed mechanism is indirectly supported by the findings of Wang et al. [10], demonstrating the importance of the TLPD in regulating ocular glymphatic transport.

A further hypothetical interaction may involve venous congestion. If microgravity-induced cephalad fluid redistribution promotes intracranial or orbital venous congestion, elevated downstream venous pressure could impede venous drainage from the eye and promote venous distension, which could in turn narrow adjacent perivenous spaces and increase resistance to perivenous outflow across and beyond the lamina cribrosa [14]. This increase in downstream resistance could further compromise ocular glymphatic efflux that may already be impaired by a reduced TLPD, thereby promoting fluid stasis at the optic nerve head and contributing to optic disc edema.

Beyond impaired posterior fluid outflow from the eye, increased entry of CSF-derived substrates into the eye [9,17], increased capillary filtration at the optic nerve head [19], and transudation of fluid from the choroidal vasculature to the optic nerve head via the border tissue of Elschnig [20] could add to the fluid and solute burden within the prelaminar region. Acting alone or in combination with impaired clearance, these and other possible mechanisms could promote prelaminar fluid accumulation and thereby contribute to SANS-associated optic disc edema.

Although the ocular manifestations of SANS are well documented, the relative contributions of the underlying pathophysiological mechanisms remain uncertain. ICP alterations, orbital CSF compartmentalization, and ocular glymphatic dysfunction are particularly relevant to the present hypothesis but remain proposed explanations rather than established causal mechanisms. Whether, and to what extent, impaired ocular glymphatic outflow contributes to SANS-associated optic disc edema remains to be determined. These mechanisms therefore represent only part of the likely multifactorial pathophysiology of SANS. Other

pathogenic processes may also contribute to its complex clinical phenotype, with different mechanisms potentially producing overlapping clinical findings.

3.2. Current and Emerging Countermeasures for SANS

As NASA advances its Moon-to-Mars exploration strategy, future long-duration exploration missions, particularly crewed missions to Mars, may expose astronauts to substantially longer periods of microgravity, potentially increasing the risk and severity of SANS [21]. Recognized as one of NASA's highest-priority risks to astronaut health and mission performance, SANS therefore represents a critical challenge for future human space exploration, highlighting the urgent need for effective countermeasures to prevent or mitigate its clinical manifestations [21]. To date, the only proven and reliable countermeasure for SANS is the use of space anticipation glasses (or contact lenses) to correct the hyperopic refractive shifts associated with the condition [3]. However, because this approach does not address the underlying pathophysiological mechanisms of SANS, several additional countermeasures targeting proposed disease mechanisms have been investigated. These approaches are discussed below.

3.2.1. Mechanical Countermeasures Targeting Cephalad Fluid Redistribution

Lower Body Negative Pressure

LBNP has been extensively investigated as a mechanical countermeasure for SANS [22]. By applying subatmospheric pressure, typically between 20 and 30 mmHg, to the lower extremities, LBNP promotes a fluid shift toward the lower body, thereby simulating the effects of gravity [3].

Petersen et al. [23] evaluated the effects of LBNP on ICP during simulated intracranial hypertension by 15° head-down tilt (HDT), a ground-based analog model of microgravity. Increasing LBNP from 0 to 50 mmHg in 10 mmHg increments reduced invasively measured ICP in a non-linear, dose-dependent manner, with 20 mmHg identified as the optimal pressure for lowering ICP while preserving cerebral perfusion pressure [23]. Furthermore, Marshall-Goebel et al. [24] reported that 5 h of exposure to 20 mmHg of LBNP reduced the HDT-induced increase in ONS diameter.

More recently, Laurie et al. [25] showed that daily exposure to 25 mmHg of LBNP for up to 6 h throughout 30 days of strict 6° HDT bed rest reduced the internal jugular vein cross-sectional area and IOP and was well tolerated. Likewise, Hearon et al. [26] found that eight hours of nightly exposure to 20 mmHg of LBNP attenuated increases in choroidal area and volume induced by three days of supine bed rest compared with the control condition. Because choroidal engorgement is considered an early marker of ocular remodeling associated with SANS [26], these findings suggest that LBNP may attenuate some of the early ocular changes associated with simulated microgravity. In contrast, nightly LBNP did not consistently mitigate the increase in global Bruch membrane opening (BMO)-minimum rim width, which has been proposed as a potential marker of early optic disc edema [26]. Similarly, He et al. [27] found that participants receiving LBNP during 30 days of strict HDT bed rest still exceeded the NASA-defined threshold for OCT-determined optic disc edema, defined as an increase in total retinal thickness of more than 20 μm measured 250 μm from BMO (ΔTRT250).

The effects of LBNP have also been investigated during spaceflight. Pardon et al. [28] reported that brief in-flight exposure to 25 mmHg of LBNP for 10 to 20 min did not alter optic nerve head or retinal morphology in crew members during 6- to 12-month ISS missions, suggesting that longer treatment durations may be required and/or that mechanisms beyond cephalad fluid shifts contribute to SANS. Arbeille et al. [29] found that 30 min of in-flight exposure to 25 mmHg of LBNP during long-duration ISS missions reduced jugular

vein volume and portal vein cross-sectional area while counteracting the microgravity-induced increase in middle cerebral vein blood flow velocity. Greenwald et al. [30] further demonstrated that brief application (10 to 20 min) of 25 mmHg of LBNP during long-duration ISS missions reduced IOP to values comparable to those measured in the seated posture on Earth, although choroidal thickness remained unchanged.

Despite these encouraging findings, accumulating evidence suggests that the various ocular manifestations of SANS do not respond equally to LBNP [3]. For example, as discussed above, Hearon et al. [26] demonstrated that although eight hours of nightly LBNP over three days reduced choroidal engorgement, it did not consistently attenuate an OCT-derived marker of early optic disc edema. Moreover, the effectiveness of LBNP depends on its differential effects on ICP and IOP [3]. Macias et al. [31] showed that exposure to 25 mmHg of LBNP for 10 min attenuated HDT-induced elevations in both IOP and ICP. To optimize the TLPD, LBNP should ideally induce a greater reduction in ICP than in IOP [3]. Finally, despite its promising effects, the operational implementation of LBNP remains challenging. A recent expert consensus concluded that current LBNP systems are impractical for routine use during spaceflight, particularly if prolonged exposure (e.g., 8 h daily) is required, as this could interfere with astronauts' ability to perform important mission tasks [21].

Venoconstrictive Thigh Cuffs

Besides LBNP, other mechanical countermeasures aimed at mitigating microgravity-induced cephalad fluid shifts include VTCs, resistive inspiratory breathing using an ITD, and artificial gravity via centrifugation [22,32]. VTCs promote fluid sequestration in the lower extremities by applying external pressure to the thighs [3]. Early studies demonstrated that VTCs can impede headward fluid shifts and reduce jugular vein size during HDT [33,34].

More recently, Laurie et al. [25] reported that daily use of VTCs for 6 h on 6 days per week, following 1 h of moderate aerobic exercise throughout 30 days of strict 6° HDT bed rest, reduced the internal jugular vein cross-sectional area and was well tolerated. Balasubramanian et al. [35] found that bilateral application of VTCs at 60 mmHg for 10 min attenuated the increase in IOP and choroidal changes during HDT.

The effects of VTCs have also been investigated in dry immersion, another ground-based analog of microgravity. Robin et al. [36] showed that daily use of VTCs for 10 h attenuated fluid redistribution and body fluid loss during a 5-day dry immersion. Recently, Kermorgant et al. [37] reported that 5 days of dry immersion increased retinal nerve fiber layer (RNFL) thickness in the temporal quadrant and ONS diameter, whereas IOP remained unchanged. Daily use of VTCs for 10 h only tended to attenuate the increase in ONS diameter and had no effect on the increase in RNFL thickness, suggesting that their ophthalmological benefits may be limited.

As with LBNP, the effectiveness of VTCs may depend on their relative effects on ICP and IOP [3]. Whether VTCs preferentially reduce ICP to a greater extent than IOP, thereby favorably influencing the TLPD, remains unclear [3].

Impedance Threshold Device

Resistive inspiratory breathing using an ITD reduces intrathoracic pressure, augmenting the pressure gradient between the peripheral circulation and the right atrium, thereby enhancing venous return to the heart and reducing ICP [3,32]. Marshall-Goebel et al. [32] compared the effects of three mechanical countermeasures—LBNP, VTCs, and resistive inspiratory breathing using an ITD—on the headward fluid shift induced by the transition from a seated to a supine posture. Compared with the supine control condition, the internal jugular vein cross-sectional area decreased by 48% with LBNP, 31% with VTCs, and 56%

with ITD. Among the individual countermeasures, only LBNP reduced the non-invasive index of ICP. The authors concluded that both VTCs and ITD produced favorable effects and may represent useful alternatives when LBNP is unavailable or contraindicated.

Artificial Gravity by Centrifugation

The potential of artificial gravity to mitigate ocular changes associated with simulated microgravity has also been investigated. Laurie et al. [38] reported that 60 days of strict 6° HDT bed rest resulted in increased peripapillary total retinal thickness, consistent with subtle signs of optic disc edema, as well as the development of chorioretinal folds. However, 30 min of daily exposure to either continuous or intermittent artificial gravity generated by short-arm centrifugation did not attenuate these structural ocular changes. Similarly, Sater et al. [39] reported an increasing degree of posterior globe flattening during 60 days of strict 6° HDT bed rest, which was likewise unaffected by 30 min of daily short-arm centrifugation, whether applied continuously or intermittently. Further studies are needed to determine whether longer or more intensive centrifugation protocols could mitigate SANS-related clinical manifestations [3].

3.2.2. Modulation of the Translaminar Pressure Difference

A potential complementary countermeasure for SANS is the modulation of the TLPD using pressurized eye goggles [3,22]. Because microgravity may increase ONS pressure, thereby reducing or even reversing the normally posteriorly directed TLPD, restoring this pressure gradient has emerged as a potential strategy for mitigating SANS [22].

Scott et al. [40] investigated interventions aimed at modulating the TLPD and found that exercise during 15° HDT reduced both IOP and the estimated TLPD, whereas wearing swimming goggles increased both parameters relative to the corresponding control conditions. The authors concluded that although swimming goggles represent a simple and promising approach for modulating the TLPD, further studies are needed to determine the optimal magnitude and duration of IOP elevation during spaceflight. They also highlighted the importance of carefully evaluating the safety of prolonged or repeated goggle use, as elevations in IOP, although small with goggles, may compress the lamina cribrosa and potentially increase the susceptibility of RGC axons to damage, a mechanism implicated in glaucomatous optic neuropathy. Accordingly, they recommended that future studies assess structural changes of the lamina cribrosa and systematically evaluate both serious and non-serious adverse events associated with long-term goggle use. Reassuringly, however, the available evidence suggests that wearing swimming goggles is not associated with either an increased prevalence of glaucoma [41] or alterations in optic nerve head blood flow [42].

More recently, Shen et al. [43] investigated whether experimentally increasing IOP unilaterally could mitigate the ocular consequences of elevated ICP in mice. Overall, they found no clear protective effect of IOP elevation on ICP-related visual dysfunction. Photopic contrast sensitivity was more reduced in IOP-elevated eyes than in control eyes, whereas scotopic contrast sensitivity declined similarly in both groups. However, preservation of a TLPD close to normal was associated with better maintenance of scotopic contrast sensitivity. Structural changes, including optic nerve axon loss, greater optic nerve disorganization, and RGC loss, were comparable between IOP-elevated and control eyes. The authors concluded that increasing IOP in the presence of elevated ICP may counterbalance some effects on visual function while exacerbating others, underscoring the complex interplay between IOP, ICP, and the TLPD.

Overall, the potential use of pressurized eye goggles as a SANS countermeasure remains an area of ongoing investigation [22]. Future studies are needed to define the optimal pressure profile for reducing SANS-related ocular changes while establishing the long-term

safety of this strategy [3]. In this regard, the development and evaluation of multi-pressure dial goggles with adjustable pressure settings may allow more precise modulation of the TLPD and represents a promising direction for future SANS countermeasures [3].

3.2.3. Nutritional and Pharmacological Approaches

Nutritional Supplementation

The association between B-vitamin status, genetic variants involved in one-carbon pathway metabolism, and susceptibility to SANS has identified a potential avenue for both preventive and therapeutic strategies [3,44–46]. Future countermeasures may include genetic screening to identify astronauts at increased risk of developing SANS, as well as targeted B-vitamin supplementation in individuals with genetic susceptibility or suboptimal B-vitamin status [3]. In addition to its potential preventive effects, in-flight improvement of SANS-related findings has been reported following B-vitamin supplementation in an astronaut with severe SANS and predisposing risk factors, although a causal relationship could not be established [46].

Although these findings are encouraging, larger studies are required and are currently underway to evaluate the effects of daily B-vitamin supplementation as a nutritional countermeasure against SANS [3]. Further research is also needed to establish the optimal dosage, duration, and combination of supplementation for astronauts with increased metabolic susceptibility [3]. Ongoing investigations of single nucleotide polymorphisms involved in one-carbon metabolism may further clarify the genetic and metabolic factors that influence individual susceptibility to SANS [3].

ICP-Lowering Medications

The use of ICP-lowering medications, such as acetazolamide and topiramate, has also been considered as a potential strategy to mitigate SANS [3,21]. However, acetazolamide is currently not considered a viable countermeasure for SANS due to its adverse effect profile, including cognitive dysfunction, acidosis, and an increased risk of nephrolithiasis, which would be unacceptable during extended missions [3,21]. Similarly, the cognitive adverse effects associated with therapeutic doses of topiramate represent a major limitation for its use in spaceflight [21].

Glucagon-like peptide 1 (GLP-1) receptor agonists have emerged as a potential alternative approach for modulating ICP. Preclinical studies in rat models have demonstrated that GLP-1 receptor agonists may influence CSF secretion and reduce ICP [21,47]. These findings are supported by a recent randomized clinical trial showing that exenatide, a GLP-1 receptor agonist, significantly reduced ICP in patients with active IIH [48]. The treatment was generally well tolerated, with nausea being the most frequently reported adverse event after treatment initiation and no serious adverse events occurring [48]. Furthermore, GLP-1 receptor agonists have an established safety profile in individuals with obesity [49]. Collectively, these findings suggest that GLP-1 receptor agonists may represent a future countermeasure for SANS, either as a preventive intervention or following diagnosis [21]. However, further studies are needed to better define the role of ICP in SANS and to determine whether ICP modulation with GLP-1 receptor agonists could provide clinical benefit in this context [3].

In conclusion, although several promising countermeasures have been identified, none has yet demonstrated complete protection against SANS [21,22]. Given the multifactorial nature of the syndrome, future mitigation strategies will likely require a multimodal approach combining mechanical, nutritional, pharmacological, and other complementary interventions [22]. Such integrated strategies will be particularly important for future long-

duration exploration missions, including a crewed mission to Mars, where SANS remains a major risk to astronaut health and mission performance.

3.3. Low-Frequency Light Stimulation as a Potential SANS Countermeasure

3.3.1. Rationale for Targeting Ocular Glymphatic Dysfunction in SANS

As discussed above, impaired ocular glymphatic outflow has been hypothesized to contribute to fluid accumulation within the optic nerve head during long-duration spaceflight [9,18]. Therefore, interventions capable of enhancing ocular fluid clearance may represent an additional strategy for mitigating SANS-associated optic disc edema. In this context, I propose low-frequency light stimulation as a novel, mechanistically distinct, ocularly targeted countermeasure option that could enhance ocular glymphatic clearance and thereby prevent or mitigate optic disc edema in astronauts. Wang et al. [10] demonstrated that ocular glymphatic clearance is influenced not only by the TLPD but also by repeated pupillary constriction and potentially ciliary muscle contraction. Supporting a potential role for these light-induced biomechanical effects, mice exposed to 1 Hz light stimulation exhibited a nearly twofold increase in hAβ tracer transport along the optic nerve compared with control mice maintained in darkness [10].

3.3.2. Conditional Biomechanical Mechanisms Involving Ciliary Muscle Activity

Repeated pupillary constriction remains the primary candidate mechanism by which 1 Hz light stimulation may enhance ocular glymphatic transport. Wang et al. [10] also mentioned ciliary muscle contraction as a possible contributor to this effect but did not directly measure ciliary muscle activity. Although it remains unknown whether the specific 1 Hz light stimulation paradigm considered here elicits concomitant rhythmic ciliary muscle activity, Yu et al. [50] reported a significant interaction between lighting mode and the accommodative response. The authors investigated human accommodative responses and pupil diameters under different ambient illumination conditions while the stimulus of accommodation and convergence remained constant. The dynamic lighting condition comprised measurements at seven illuminance levels (5, 100, 200, 500, 1000, 2000, and 3000 lux), whereas the static lighting condition comprised seven repeated measurements at a constant illuminance of 1000 lux. They found that the ranges of change in accommodative response and pupil diameter were greater under dynamic than static lighting and that higher light intensities were associated with greater accommodative responses and smaller pupil diameters. Because ocular accommodation depends on the crystalline lens-ciliary muscle apparatus, these findings provide indirect evidence consistent with illumination-associated modulation of ciliary muscle activity in humans under fixed accommodative and convergence demands. However, the study did not directly quantify ciliary muscle activity or motion, involved a fixed near-viewing stimulus, and did not use a 1 Hz light stimulation paradigm. Future studies should determine whether changes in illumination alone, particularly low-frequency light stimulation, can elicit rhythmic ciliary muscle activity in the absence of a near-viewing stimulus. The following mechanisms are therefore presented strictly as conditional biomechanical possibilities rather than as established components of the light response. Specifically, I hypothesize that if low-frequency light stimulation elicits concomitant rhythmic ciliary muscle activity of sufficient magnitude, such activity could promote ocular glymphatic outflow through two complementary biomechanical mechanisms: (1) repetitive movement of an interconnected ciliary muscle-choroidal elastic network, which could transiently alter the geometry and hydraulic resistance of posterior ocular glymphatic pathways and (2) oscillatory movement of central vitreous structures and associated transient pressure gradients, which could promote convective fluid transport within these pathways.

First, the ciliary muscle and the choroid functionally constitute an elastic network extending from the trabecular meshwork to the posterior pole of the eye [51]. Posteriorly, this network attaches to the elastic fiber ring surrounding the optic nerve and to the lamina cribrosa, while also surrounding blood vessels that enter the prelaminar and laminar regions of the optic nerve head [51]. The ciliary muscle plays a central role in mediating the accommodative movement of this elastic network [51]. In rhesus monkeys, Croft et al. [51,52] demonstrated that during centrally stimulated accommodation, the posterior attachments of the ciliary muscle to the choroid pull the choroid and retina anteriorly. This displacement was reported to reach approximately 1 mm at the ora serrata and 0.1 mm at the optic nerve head, thereby exerting tensile forces on the elastic fiber ring surrounding the optic nerve and the lamina cribrosa [51,52]. If low-frequency light stimulation elicits rhythmic ciliary muscle activity and corresponding movement of this elastic network, the resulting cyclic changes in the geometry of posterior ocular fluid pathways could transiently reduce their hydraulic resistance and thereby facilitate fluid clearance through the ocular glymphatic system (Figure 2).

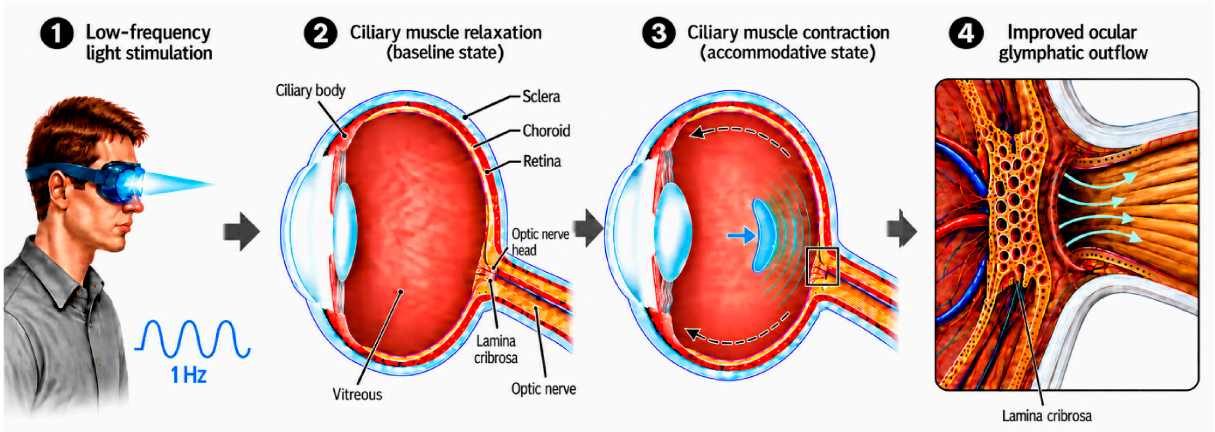


Figure 2. Conditional ciliary muscle-mediated mechanisms by which low-frequency light stimulation could enhance ocular glymphatic outflow. (**1**) Low-frequency (1 Hz) light stimulation induces rhythmic pupillary constriction, which remains the primary candidate mechanism for enhanced ocular glymphatic transport. Whether such stimulation also elicits concomitant rhythmic ciliary muscle contraction remains unknown. The waveform in panel (**1**) schematically represents periodic 1 Hz stimulation. (**2**,**3**) Panels (**2**,**3**) compare the relaxed baseline state (panel (**2**)) with the accommodative state (panel (**3**)). The structural displacements illustrated in panel (**3**) are based on experimental observations made during accommodation and have not been demonstrated during low-frequency light stimulation. They provide the biomechanical basis for the conditional mechanisms proposed here. During accommodation-related ciliary muscle contraction, the posterior attachments of the ciliary muscle to the choroid pull the choroid and retina anteriorly (black dashed arrows). Concurrently, central vitreous structures move posteriorly toward the optic nerve region, a movement that may be associated with a transient pressure gradient directed toward this region (blue graphical elements). (**4**) If present during low-frequency light stimulation, rhythmic ciliary muscle activity is hypothesized to produce repetitive movement of the ciliary muscle-choroidal elastic network and oscillatory displacement of central vitreous structures. These conditional movements could alter the geometry and hydraulic resistance of posterior ocular fluid pathways and generate transient pressure gradients, thereby potentially promoting posterior fluid outflow through a pump-like mechanism. Together, these complementary biomechanical effects could enhance ocular glymphatic outflow from the eye to the optic nerve (green arrows).

Second, Croft et al. [51,53] demonstrated that central vitreous structures move posteriorly toward the optic nerve region during centrally stimulated accommodation in rhesus monkeys and in the opposite direction during disaccommodation. Based on these findings,

the authors proposed that the accommodative response may generate a transient pressure gradient directed toward the optic nerve region [51]. If low-frequency light stimulation elicits rhythmic ciliary muscle activity, the resulting cycles of contraction and relaxation could produce oscillatory displacements of central vitreous structures and associated transient pressure gradients. When superimposed on a posteriorly directed TLPD, these oscillations could augment net posterior fluid outflow along ocular glymphatic pathways through a pump-like mechanism, provided that they generate greater outward than inward fluid displacement over each cycle (Figure 2). Notably, Wang et al. [10] also cited previous evidence of vitreous pressure transients during ciliary body contraction in primates.

The two proposed mechanisms could operate independently but could also reinforce each other. Conceptually, the first mechanism could enhance eye-to-optic-nerve outflow if cyclic changes in pathway geometry reduce the effective hydraulic resistance under a posteriorly directed TLPD, which, when present, would provide the persistent background pressure gradient. Independently of these geometry changes, the second mechanism could augment cycle-averaged net outflow by superimposing transient pressure gradients on the background TLPD, but only if the oscillatory component produces greater outward than inward fluid displacement over each cycle. If the outward and inward fluid displacements attributable to the oscillatory component are equal, the oscillations may increase local mixing but would not, by themselves, augment the cycle-averaged net posterior fluid outflow driven by the background TLPD. A synergistic interaction could arise if outward-directed pressure transients coincide with phases of reduced pathway resistance, thereby favoring posterior fluid movement. Future studies should therefore quantify the effects of each mechanism separately and in combination and determine whether any observed increase in ocular tracer transport reflects enhanced local mixing or a measurable increase in net posterior fluid outflow.

Whether 1 Hz light stimulation elicits ciliary muscle activity and whether any such activity produces associated ocular structural displacements remain to be determined. Direct measurements should therefore quantify ciliary muscle activity and characterize the direction and magnitude of any accompanying structural movements relative to those observed during accommodation. Failure to demonstrate ciliary muscle activity or the associated structural displacements would argue against the two conditional ciliary muscle-mediated mechanisms proposed here but would not exclude an effect on ocular glymphatic transport mediated by repeated pupillary constriction or another mechanism.

3.3.3. Interaction with ICP and Implications for SANS

It should be noted that Wang et al. [10] found that, under experimentally induced high-ICP conditions, 1 Hz light stimulation produced no additional change in net hAβ tracer transport compared with high ICP alone, suggesting that a marked increase in ICP may override the effect of 1 Hz light stimulation. In a separate experiment characterizing the effect of ICP manipulation, ICP was increased from 3.6 to 16.7 mmHg, representing an absolute increase of approximately 13.1 mmHg and a rise to approximately 4.6 times the baseline value. The exact ICP reached in the combined high-ICP and light-stimulation experiment was not reported separately. Because IOP remained unchanged in the high-ICP experiment, the increase in ICP markedly reduced the IOP-ICP difference used in the study as an estimate of the TLPD. However, pressure within the perioptic SAS was not measured directly, and the local pressure difference across the lamina barrier was therefore inferred rather than directly determined.

The ICP increase of approximately 13.1 mmHg produced in the separately characterized high-ICP experiment appears substantially larger than the mild to borderline ICP elevations commonly hypothesized to occur in SANS. If SANS involves less pronounced

pressure alterations than those induced by Wang et al. [10], it remains biologically plausible that rhythmic light-induced modulation of pupillary dynamics and, potentially, ciliary muscle activity could enhance ocular glymphatic transport. Accordingly, the absence of an additional effect of 1 Hz light stimulation under the experimental conditions used by Wang et al. [10] should not necessarily be extrapolated to the conditions associated with SANS development during spaceflight. This reasoning does not, however, establish that the pressure conditions experienced by astronauts fall within a range in which light stimulation could enhance ocular glymphatic transport.

It should also be noted that the available lumbar puncture opening-pressure measurements in astronauts were obtained after return to Earth and were not paired with individual preflight lumbar CSF opening-pressure measurements. Consequently, they establish neither absolute in-flight ICP nor the change from each astronaut's baseline. Moreover, lumbar CSF opening pressure does not directly measure pressure within the perioptic SAS. Absolute ICP or lumbar CSF pressure alone therefore does not define the pressure difference relevant to ocular glymphatic outflow, which depends on both IOP and the pressure immediately posterior to the lamina cribrosa. It remains to be determined whether low-frequency light stimulation can enhance ocular glymphatic transport across a range of IOP-ICP differences generated by graded combinations of IOP and ICP designed to model plausible microgravity-related conditions.

Furthermore, future countermeasure strategies could combine 1 Hz light stimulation with mechanical interventions aimed at reducing microgravity-induced cephalad fluid shifts and any associated ICP elevation. By attenuating fluid redistribution toward the head, such interventions could modify ICP, perioptic SAS pressure, IOP, or the relationships among these pressure variables in a manner that might favor ocular outflow. Because attenuation of cephalad fluid redistribution and associated ICP elevation could theoretically preserve or enhance pressure conditions favorable to light-induced ocular glymphatic transport, combining these interventions has a plausible mechanistic rationale. However, targeting different proposed mechanisms does not, by itself, establish additive or synergistic benefit.

Initial combination studies could prioritize interventions that can be applied in a standardized and graded manner, particularly LBNP, because the applied negative pressure can be precisely adjusted and its interaction with light stimulation can be investigated in ground-based microgravity analogs. Controlled studies should compare light stimulation alone, the mechanical intervention alone, their combination, and an appropriate control condition. Concurrent measurements of IOP and, where feasible, ICP or perioptic SAS pressure, together with pupillary responses, ocular glymphatic transport, and SANS-associated optic disc edema, would help determine whether the mechanical intervention enhances, leaves unchanged, or attenuates the light-stimulation response. Whether the combined approach provides greater protection against SANS-associated optic disc edema than either intervention alone remains unknown and should be determined experimentally.

3.4. Experimental Validation and Future Development of Wearable Light-Stimulation Devices

If ocular glymphatic dysfunction contributes to the development of optic disc edema during long-duration spaceflight, low-frequency light stimulation could theoretically enhance ocular glymphatic transport and thereby facilitate fluid clearance from the optic nerve head. Such an approach would represent a fundamentally different countermeasure strategy, as it aims to restore impaired ocular fluid clearance rather than primarily targeting upstream mechanisms involved in SANS pathogenesis, such as cephalad fluid redistribution, ICP elevation, or disruption of the translaminar pressure balance. Although cephalad fluid shift-related mechanisms are likely to remain key drivers of SANS pathogenesis, enhancing

ocular glymphatic transport through light stimulation may represent a complementary approach to reduce the risk of optic disc edema.

The first stage of validation should consist of brief, controlled human studies under normal terrestrial conditions using conservative exposure parameters. The primary question at this stage is whether 1 Hz light stimulation produces reproducible rhythmic pupillary constriction and whether it is accompanied by accommodative changes or ciliary muscle activity, while remaining tolerable and safe. Responses should be compared with both a no-stimulation condition involving no experimental light exposure and a non-flickering illumination condition matched for mean luminance, spectral composition, visual field coverage, and exposure duration, thereby distinguishing a flicker-specific response from effects attributable to mean illumination. Initial human dose-ranging and repeated-exposure studies should evaluate overall tolerability and safety while documenting pupillary responses and monitoring for accompanying accommodative changes. Age and presbyopia should be considered as potential effect modifiers, because age-related reductions in pupillary responsiveness and mobility of the ciliary muscle-choroidal apparatus and vitreous structures could attenuate the proposed response. These studies should therefore include participants across the age range relevant to astronauts and quantify pupillary dynamics, accommodative function, ciliary muscle-choroidal displacement, vitreous mobility, and, where feasible, ocular glymphatic transport to determine whether the proposed response is preserved in middle-aged individuals. Alongside these physiological and biomechanical assessments, they should monitor self-reported adverse symptoms, including asthenopic or other visually induced symptoms such as eye strain, visual fatigue, blurred vision, headache, nausea, dizziness, photophobia, glare-related discomfort, migraine provocation, and visual disturbances such as afterimages. They should also evaluate potential changes in visual acuity, contrast sensitivity, oculomotor function, and performance on vision-dependent operational tasks during and after stimulation. Individual susceptibility, including a history of migraine, photophobia, or photosensitive epilepsy, should also be considered. Progression to mechanistic validation would require a reproducible flicker-specific ocular response, acceptable tolerability, and no clinically meaningful impairment of visual or oculomotor function or performance on vision-dependent operational tasks.

If the relevant human physiological response is confirmed, the second stage should focus on mechanistic validation in animal or other appropriate experimental models. The primary questions at this stage are whether the physiological response produces a reproducible increase in net directional ocular glymphatic transport and, if so, which mechanisms mediate this effect. These studies should define the light-stimulation parameters required to maximize ocular glymphatic transport, including stimulation frequency, light intensity, spectral composition, modulation depth, temporal waveform, pulse duration and duty cycle, visual field coverage, and session duration. Because Wang et al. [10] evaluated only a single stimulation frequency (1 Hz), it remains unknown whether this frequency represents the optimal stimulus for enhancing ocular glymphatic transport. Characterization of the frequency-response relationship will therefore be essential to determine whether lower or higher frequencies provide greater enhancement of ocular glymphatic clearance. Experimental groups should include a no-stimulation control condition and a non-flickering illumination condition matched to the flickering stimulus for mean luminance, spectral composition, visual field coverage, and exposure duration. These comparators would determine whether any observed transport response is specifically attributable to flicker rather than to mean illumination. Mechanistic animal experiments should combine quantitative measurements of ocular glymphatic transport with synchronized pupillometry, direct measurements of ciliary muscle activity where feasible or high-resolution imaging of ciliary muscle or ciliary body motion, and dynamic imaging of associated displacements of the

ciliary muscle-choroidal network and central vitreous structures. Experimental conditions that dissociate pupillary constriction from ciliary muscle activity could help determine whether repeated pupillary constriction alone is sufficient to enhance ocular glymphatic transport and whether concomitant ciliary muscle activity provides an additional contribution. Failure to demonstrate ciliary muscle activity during low-frequency light stimulation would argue against the two ciliary muscle-mediated mechanisms proposed here but would not necessarily exclude an effect mediated by repeated pupillary constriction or another mechanism. Preclinical studies should also evaluate whether continuous or intermittent stimulation and different schedules of repeated sessions can sustain enhanced ocular fluid transport. Progression to ground-based analog testing would require a reproducible increase in net posterior ocular fluid outflow relative to the matched control conditions, rather than merely increased tracer dispersion attributable to local mixing, together with evidence linking the transport response to a defined ocular physiological mechanism. The response should also be evaluated across experimentally defined IOP-ICP differences designed to model plausible microgravity-related pressure conditions.

Once these mechanistic criteria have been met, the third stage should consist of controlled studies in ground-based analogs of microgravity, such as HDT bed rest. The primary questions at this stage are whether low-frequency light stimulation retains its physiological and mechanistic effects under microgravity-analog conditions and whether it attenuates optic nerve head and peripapillary changes relevant to SANS-associated optic disc edema. Participants should be assigned to 1 Hz light stimulation or an appropriate control condition, preferably non-flickering illumination matched for mean luminance, spectral composition, visual field coverage, and exposure duration. A no-stimulation control could be included where feasible. Mechanistic endpoints should include pupillary dynamics, accommodative responses, and validated biomarkers of ocular glymphatic transport when available. Clinically relevant endpoints should include OCT-derived measures of optic nerve head and peripapillary changes, including peripapillary total retinal thickness, together with visual acuity, contrast sensitivity, refractive status, tolerability and safety. Performance on simulated vision-dependent mission tasks should also be assessed during and after stimulation to determine whether the intervention could interfere with critical operational procedures. Progression to spaceflight evaluation would require evidence of the intended ocular physiological response, an acceptable tolerability and safety profile, a favorable effect on prespecified optic nerve head and peripapillary outcomes relevant to SANS-associated optic disc edema compared with the control condition, and no clinically meaningful impairment of visual or operational performance.

Only after the preceding progression criteria have been met should the fourth stage, evaluation during spaceflight, be initiated. Initial studies could use a randomized or within-participant controlled design, with no-stimulation or matched non-flickering illumination as the comparator. The primary question would be whether the intervention reduces the development or progression of SANS-associated optic disc edema without impairing visual or operational performance. Endpoints should include serial OCT measures of the optic nerve head and peripapillary retina, the intended pupillary response, visual function, adverse symptoms, adherence to the stimulation protocol, and interference with mission tasks. Progression toward operational implementation would require an acceptable safety profile, reproducible induction of the intended ocular physiological and fluid-transport responses, and evidence of a clinically meaningful reduction in optic disc edema relative to the comparator.

If validated through this staged pathway of human physiological confirmation, mechanistic experimental studies, controlled ground-based analog studies, and subsequent spaceflight evaluation, this concept could provide the basis for the development of a wear-

able light-stimulation device as a practical countermeasure option for SANS-associated optic disc edema. Recent advances in wearable systems delivering gamma-range visual stimulation, including 40 Hz stimulation, provide a relevant but limited engineering precedent for the technical feasibility of delivering temporally modulated light at a controlled stimulation frequency using a wearable platform [54]. However, they do not establish the physiological effectiveness, tolerability, safety, or mission suitability of the proposed low-frequency intervention. Moreover, the proposed low-frequency (1 Hz) light-stimulation paradigm is mechanistically distinct from 40 Hz visual stimulation approaches, which aim to entrain gamma-band neural activity and have primarily been investigated for their effects on cognitive function and their potential therapeutic applications in neurological disorders, particularly Alzheimer's disease [55]. By contrast, the rationale for low-frequency light stimulation in SANS is based on the hypothesis that ocular fluid dynamics may be mechanically influenced by repeated pupillary constriction, by concomitant rhythmic ciliary muscle activity if elicited, or by both processes.

For any such wearable light-stimulation system, tolerability and safety should be central design requirements. Visual discomfort from flicker is not determined by stimulation frequency alone but may be influenced by multiple interacting stimulus characteristics and exposure conditions [56]. Potentially relevant parameters for the proposed paradigm include peak and mean stimulus luminance, temporal luminance contrast or modulation depth, temporal waveform, spectral composition, ambient illumination, stimulated visual field area, and exposure duration.

From an operational perspective, the feasibility of such a device would depend on key design considerations, including ease of use, mass and volume, power consumption, and maintenance needs. A wearable device could combine individually adjustable stimulation parameters with a closed-loop system that adapts stimulus delivery in real time using feedback from pupillary responses or, when available, from validated ocular biomarkers of enhanced ocular glymphatic transport. This approach could enable delivery of the lowest effective stimulus dose. Stimulation sessions would need to be scheduled outside critical operational procedures. Immediate user-controlled interruption, automatic session limits, intermittent stimulation, and scheduled rest periods may further improve acceptability during long-duration missions. Before any operational use during spaceflight, the intervention should undergo a formal benefitrisk and mission-suitability assessment evaluating the potential effects of cumulative exposure, tolerability and safety during repeated use, individual susceptibility, potential visual interference, and consequences for mission-critical performance. A system demonstrating an acceptable benefitrisk profile and mission suitability across these domains could be integrated into routine mission operations, either independently or in combination with existing SANS countermeasures.

4. Conclusions

SANS remains a major challenge for future long-duration human spaceflight, and current countermeasures have not demonstrated complete protection against its neuro-ocular manifestations. Given the multifactorial nature of the syndrome, additional strategies targeting pathophysiological mechanisms beyond cephalad fluid redistribution may offer opportunities to prevent or mitigate SANS-associated optic disc edema.

Emerging evidence from rodent studies suggests that ocular glymphatic transport may contribute to intraocular fluid and solute clearance and is influenced by translaminar pressure dynamics. Furthermore, 1 Hz light stimulation was associated with enhanced ocular tracer transport in these animals, with repeated pupillary constriction and possible ciliary muscle activity proposed as contributing mechanisms. On this basis, I propose low-frequency light stimulation as a novel, non-invasive, ocularly targeted countermeasure strat-

egy that could mitigate SANS-associated optic disc edema by enhancing ocular glymphatic transport. Repeated pupillary constriction remains the primary candidate mechanism, whereas the two ciliary muscle-mediated biomechanical mechanisms developed in this review represent conditional secondary hypotheses that would apply only if stimulation is shown to elicit rhythmic ciliary muscle activity and the associated structural displacements.

It remains unknown whether the light-stimulation-associated increase in tracer transport observed in rodents reflects a physiologically meaningful increase in net posterior fluid outflow, whether a comparable response occurs in humans and persists under microgravity-relevant pressure conditions, and whether enhanced outflow reduces fluid accumulation at the optic nerve head sufficiently to attenuate optic disc edema. Although efficacy for SANS-associated optic disc edema has not yet been demonstrated, these questions define a clear, staged research program.

Initial studies should confirm reproducible ocular physiological responses in humans under normal terrestrial conditions. Mechanistic studies in appropriate experimental models should then quantify net directional fluid transport, followed by controlled ground-based microgravity analog studies evaluating the relevant physiological, transport, and optic disc edema outcomes before subsequent spaceflight evaluation. During these later stages, the strategy could be assessed both independently and in combination with existing or emerging SANS countermeasures, including interventions targeting cephalad fluid shifts.

Existing wearable 40 Hz platforms, although developed to entrain gamma-band neural activity rather than modulate ocular fluid dynamics, provide an encouraging engineering precedent for compact systems capable of delivering temporally modulated light at a controlled stimulation frequency. They do not, however, establish the physiological effectiveness, tolerability, safety, or mission suitability of a low-frequency intervention. Successful completion of a staged research program, together with demonstration of an acceptable benefitrisk profile and operational suitability, could enable the development of a wearable low-frequency light-stimulation system as a practical standalone or adjunctive countermeasure for preventing or mitigating SANS-associated optic disc edema during long-duration human space exploration.

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Conflicts of Interest: Peter Wostyn is named as the inventor and applicant on a pending patent application concerning light-stimulation methods intended to enhance ocular glymphatic clearance, including their potential use in preventing or mitigating SANS-associated optic disc edema.

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