Nystagmus in patients with congenital stationary night blindness (CSNB) originates from synchronously firing retinal ganglion cells

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Abstract

Congenital nystagmus, involuntary oscillating small eye movements, is commonly thought to originate from aberrant interactions between brainstem nuclei and foveal cortical pathways. Here, we investigated whether nystagmus associated with congenital stationary night blindness (CSNB) results from primary deficits in the retina. We found that CSNB patients as well as an animal model (nob mice), both of which lacked functional nyctalopin protein (NYX, nyx) in ON bipolar cells (BCs) at their synapse with photoreceptors, showed oscillating eye movements at a frequency of 4–7 Hz. nob ON direction-selective ganglion cells (DSGCs), which detect global motion and project to the accessory optic system (AOS), oscillated with the same frequency as their eyes. In the dark, individual ganglion cells (GCs) oscillated asynchronously, but their oscillations became synchronized by light stimulation. Likewise, both patient and nob mice oscillating eye movements were only present in the light when contrast was present. Retinal pharmacological and genetic manipulations that blocked nob GC oscillations also eliminated their oscillating eye movements, and retinal pharmacological manipulations that reduced the oscillation frequency of nob GCs also reduced the oscillation frequency of their eye movements. We conclude that, in nob mice, synchronized oscillations of retinal GCs, most likely the ON-DCGCs, cause nystagmus with properties similar to those associated with CSNB in humans. These results show that the nob mouse is the first animal model for a form of congenital nystagmus, paving the way for development of therapeutic strategies.
Introduction

Congenital nystagmus (i.e., involuntary repetitive uncontrolled eye movements) [1,2] forms a heterogeneous group of eye-movement disorders with eye movements ranging from sinusoidal-like oscillations (pendular nystagmus) to highly asymmetrical repetitive eye movements (jerk nystagmus). Many patients suffering from congenital nystagmus also have a low visual acuity, which limits the quality of life. Congenital nystagmus is commonly thought to originate from aberrant interactions between brainstem nuclei and foveal cortical pathways. However, decades of research has yet to uncover the underlying pathophysiological mechanism(s) of congenital nystagmus or its associated reduced vision.

Our recent clinical research indicated that some types of congenital nystagmus may have a retinal origin [3]. We examined 11 infant boys aged 2 mo through 2 y who presented with a tonic downgaze of both eyes, a chin-up head posture, and a rapid horizontal congenital nystagmus. These infants also had congenital stationary night blindness (CSNB), reduced visual acuity, and mutations in either nyctalopin (NYX) or the L-type voltage-gated Ca-channel subunit 1F (CACNA1F) genes [3]. These proteins are highly specific to the photoreceptor to ON bipolar cells (BCs) synapse. NYX is located postsynaptically on the ON-BC dendrites [4,5], whereas CACNA1F is expressed presynaptically at the photoreceptor synaptic terminal [6–9]. Mutations in either of these genes abolish ON-BC light responses [8–11].

Here, we studied eye movements of nob mice, which lack nyx and are a well-established model for CSNB [7,8]. Strikingly, nob mice have a pendular nystagmus with a frequency similar to that found in young CSNB patients. Further analysis of retinal processing and eye movements shows that the oscillating eye movements are caused by a mechanism within the retina that induces synchronized oscillations in retinal ganglion cells (GCs), including the ON direction-selective retinal ganglion cells (DSGCs) that project to the accessory optic system (AOS). Our results show that this form of congenital nystagmus has a retinal origin.

Results

We reanalyzed video material of a group of young children (3 mo–2 y) with a disconjugate small-amplitude horizontal pendular nystagmus in combination with tonic downgaze [3]. These patients had mutations in genes coding for proteins expressed at the synapse between photoreceptors and ON-BCs [3]. The oscillation frequency of their horizontal pendular nystagmus was 6.25 ± 0.63 Hz (n = 3) (S1 Fig & S1 Movie). Because one of the patients carried a mutation in the NYX gene, we analyzed the eye movements of nob mice, which also lack functional NYX protein and are a well-established model of CSNB [7,8]. wt (wild-type) mice (Fig 1A, blue lines) followed a horizontally moving vertical sinusoidal grating (100% contrast, spatial frequency 0.1 cycles/deg, velocity: 10 deg/s) with smooth eye movements and kept their eyes fixated when the stimulus stopped (gray bars). In contrast, the nob littermates (red lines) initially followed the same horizontally moving vertical grating with smooth eye movements, but they could not maintain that movement, and they could not fixate their eyes when the grating stopped moving. Regardless of stimulus motion, they had spontaneous, small-amplitude oscillating horizontal eye movements (Fig 1A & 1B). Power spectral density (PSD) plots show that nob eye-movement oscillation frequency was approximately 5 Hz, both during the stationary (Fig 1C, solid red lines) and the moving phases (Fig 1C, dashed red lines) of optokinetic stimulation, whereas wt eye movements during both stationary and moving phases had no such peak (Fig 1C, solid and dashed blue lines, respectively). On average, the oscillation frequency of nob eye movements to stationary gratings was 5.17 ± 0.18 Hz (n = 17) (Fig 1C, solid red line, S2A Fig).
By varying the spatial frequency and orientation of the stationary gratings, we determined that a vertical grating with a spatial frequency of 0.1 cycles/deg generated eye-movement oscillations with the strongest power (Fig 1D & 1E, red). Darkness and horizontally oriented gratings failed to induce significant eye-movement oscillations (Fig 1D). Additionally, no vertical oscillating eye movements were detected (green).
Because the *nyx* mutation affects signaling by retinal ON-BCs [8–11], we asked whether *nob* mice show changes in their retinal output. We recorded activity from GC axons in the optic nerve (Fig 2A) and found that *nob* GCs showed oscillating burst-spiking behavior with a mean frequency of 4.79 ± 0.13 Hz (n = 46) (Fig 2B and S2A Fig), which did not differ significantly from the mean frequency of their eye-movement oscillations (Student *t* test, *t* = −1.53, df = 61, *p* = 0.13). These oscillations were absent in wt GCs (Fig 2A & 2B). Because of the widespread oscillations across *nob* GCs, we hypothesized that the signaling of retinal image motion might be affected.

The direction of image motion is transmitted from the retina to the brain via two general pathways. ON-DSGCs, which are most sensitive to low temporal frequencies, low image velocities, and signal global motion project to the AOS [12–15] and are the primary neurons driving the optokinetic reflex [16]. In contrast, ON/OFF-DSGCs, which have a broad temporal frequency–response range, are mostly implicated in relative-motion detection and project mainly to the lateral geniculate nucleus (LGN) and superior colliculus (SC) [12–15]. To determine which of these two pathways is affected most in *nob* mice, we recorded the frequency-response curves of their eye movements induced by sinusoidally oscillating dot patterns with a constant peak velocity (Fig 1F). The frequency-response relation of *nob* (red symbols) and wt eye movements (blue symbols) differed, but only in the low frequency range, consistent with a malfunction in ON-DSGCs, suggesting that these GCs are predominantly involved in generating the nystagmus phenotype.

To test this idea, we recorded excitatory and inhibitory currents in *nob* ON-DSGCs, using *nob* mice crossed and backcrossed with SPARC-related protein-containing immunoglobulin domains 1 (SPIG1)*+* reporter mice in which ON-DSGCs coding for upward image motion are green fluorescent protein (GFP) labeled [17,18]. In contrast to wt ON-DSGCs, *nob* GFP*+* ON-DSGCs were visually nonresponsive, and both their excitatory and inhibitory currents oscillated with a mean frequency of 5.10 ± 0.22 Hz (n = 36) and 4.50 ± 0.38 Hz (n = 8), respectively (Fig 2C & 2D). The oscillation frequencies of *nob* eye movements, GC burst-spiking, and ON-DSGC excitatory and inhibitory currents did not differ significantly from each other (ANOVA: *F* = 1.320, df = 103, *p* = 0.272), indicating that a retinal oscillator, presynaptic to *nob* GCs, drives these oscillations (S2A Fig).

Using a multielectrode array (MEA), we recorded the activity of *nob* GCs extracellularly and assessed their light-evoked responses and oscillatory activity. *nob* ON-DGCs do not respond to light stimuli, and this makes it impossible to identify these neurons in MEA recordings. In the dark, about 55% (602 GCs; 10 retinas) of the *nob* GCs showed periodic variations in their autocorrelations (Fig 3A), indicating that they oscillated. We never observed such oscillations in wt GCs in either the dark or after a light flash (Fig 3Biv). To examine whether *nob* GCs oscillated synchronously, we selected nine oscillating *nob* GCs and, in the dark, aligned the activity of GC-2 through GC-9 such that their first spike in each of one hundred 2-s periods, spaced 3 s apart, corresponded with the first spike fired by GC-1 during the same period. The aligned traces were averaged (Fig 3Bi), and the averaged traces show that the spike patterns of GC-2 through GC-9 are unrelated to GC-1, indicating that their rhythmic firing differed in frequency and phase from the oscillations of GC-1. We also observed that the oscillations in the mean response of GC-1 reduced over time, suggesting that the frequency and phase of the spontaneous GC oscillations varied slowly over time. In contrast, a brief light flash synchronized oscillatory activity across all nine GCs (Fig 3Bii). In the light, their averaged traces of 100 repetitions showed clear oscillation patterns, indicating that light stimulation acted to phase-reset their activity and produced synchronized oscillations.

We found two clusters of *nob* GCs that oscillated in antiphase (Fig 3Biii). In one cluster, *nob* GCs responded initially to the light flash with a reduction in firing rate, identifying them
as OFF-GCs. In the other cluster, GCs’ mean firing rates remained unchanged during and after a light stimulation, suggesting they were ON-GCs, since all NOB-GCs are visually unresponsive. During the light flash, the oscillatory activity of NOB-GCs synchronized within each cluster, as revealed by their short-time cross-correlations (Fig 3C). Both ON-GC/ON-GC and OFF-GC/OFF-GC pairs showed multipeak correlograms with a positive correlation coefficient around zero lag time after light onset, indicating synchronized oscillatory firing. An ON-GC paired with an OFF-GC showed a similar multipeak correlogram but now had a negative correlation coefficient around zero lag time. This indicates that ON-GCs and OFF-GCs oscillate in antiphase. Fig 3D shows the mean cross-correlations for all ON-GC/ON-GC and OFF-GC/OFF-GC pairs and all the ON-GCs paired with all the OFF-GCs, before (blue) and during (red) the light flash. This behavior was found in all four retinas tested.

In the next series of experiments, we sought to establish a causal relationship between eye movements and GC oscillations in NOB mice. First, we pharmacologically blocked or modified the excitatory inputs to the GCs and measured both GC oscillations and eye-movement oscillations. Blocking excitatory α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and N-methyl-D-aspartate (NMDA) inputs in vitro with a cocktail of 50 μM 6-Cyano-7-nitroquinoxaline-2,3-dione (CNQX) (50 μM 6,7-dinitroquinoxaline-2,3-dione [DNQX]) and 10 μM D(-)-2-Amino-5-phosphonopentanoic acid (D-AP5) eliminated all NOB-GC oscillations (Fig 4Ai-iii). Similarly, intraocular injections of a similar cocktail in vivo eliminated eye-movement oscillations in awake and behaving mice (Fig 4Aiv). This shows that the eye-movement oscillations depend on retinal activity.

As functionally diverse GCs display oscillatory firing in NOB mice (Fig 3B) [10], these oscillations presumably arise from a common presynaptic source. As we find two groups of NOB GCs oscillating in antiphase (Fig 3B–3D), the AII amacrine cells (ACs) are a likely candidate for this presynaptic source, as they drive both ON- and OFF-GCs with opposite sign [19]. In mice with photoreceptor degeneration (retinal degeneration 1 [rd1] mouse), AII ACs generate intrinsic oscillations [20] that drive oscillatory firing of ON- and OFF-GCs in antiphase [21].
Fig 3. In the dark, *nob* mice GCs oscillate asynchronously, but light stimulation synchronizes their oscillations. Results based on GC spiking responses recorded on an MEA. (A) Autocorrelations of 9 representative *nob* GCs from one retina in the dark. Periodic variations in their autocorrelations indicate spontaneous oscillatory activity. (Bi) Each trace shows the mean normalized GC activity of 100 episodes of activity in the dark during the first 2 s of a 5-s window. All episodes were aligned to the first spike in the corresponding episode of GC-1 and then averaged. A clear oscillatory pattern is initially apparent for GC-1. In contrast, none of the other cells showed a similar pattern, suggesting that each *nob* GC oscillated with a frequency and/or phase, independent of GC-1. (Bii) Mean normalized activity of the same *nob* GCs in response to a 500-ms light flash (yellow shading). Note the presence of oscillation in all GCs, indicating that their phase was reset by the light flash. (Biii) Mean (± SEM) light-evoked oscillations of GCs could be separated into two clusters that oscillated in antiphase with each other. One cluster showed a decrease in spike rate just after light onset identifying them as OFF-GCs (bottom; *n* = 10), whereas the other cluster responded with a delay and in antiphase, suggesting they were ON-GCs (top; *n* = 13). (Biv) Mean responses of 21 wt GCs to the same stimulus used in (Bii-iii) show no oscillatory activity evoked by the light flash. (C) Short-time cross-correlations between mean responses of representative *nob* ON-GC/ON-GC, OFF-GC/OFF-GC, and ON-GC/OFF-GC pairs during the
In these rd1 mice, the oscillation frequency of AII ACs can be decreased by blocking glycine receptors with the antagonist strychnine (STR) [20]. Similarly, in nob retina, application of 10 μM STR reduced both ON-DSGC oscillation frequency (control: 4.25 ± 0.12 Hz; STR: 2.67 ± 0.07; n = 6; paired Student t test, t = 5.27, df = 5, p = 0.003) (Fig 4Bi—iii) and the eye-movement oscillation frequency (control: 5.55 ± 0.05 Hz; STR: 2.83 ± 0.63; n = 3; paired Student t test, t = 7.30, df = 2, p = 0.018) (Fig 4Biv). Although 1 μM of STR already induced a reduction of the GC oscillation frequency of 0.92 ± 0.23 Hz (n = 3; p = 0.022), we used a higher concentration to induce a large and robust shift in oscillation frequency. This dose may have induced an additional block of GABA receptors as well. We used linopiridine hydrochloride (LP) to block the M-type potassium current [20] essential for the AII AC oscillations [22–24]. LP (30 μM) decreased the oscillation frequency of the ON-DSGCs from 5.71 ± 0.53 to 2.83 ± 0.40 Hz (n = 6; paired Student t test, t = 7.45, df = 5, p = 0.0007) and decreased the eye-movement oscillation frequency from 5.00 ± 0.00 to 1.75 ± 0.50 Hz (n = 3; paired Student t test, t = 6.48, df = 2, p = 0.023) (Fig 4C).

Finally, we disrupted the gap-junction coupling between the ON-BCs and the AII AC network [25–27]. In rd1 mice, the gap-junction blocker meclofenamic acid (MFA) blocks the oscillations of the AII ACs [21,28]. MFA (100 μM) blocked the oscillation in GCs (Fig 4Di-iii) in nob mice, corroborating the evidence for AII ACs being the source of the oscillations. As the gap junctions themselves are composed of connexin 36 (Cx36), we crossed Cx36 knockout mice and nob mice. In these nob mice lacking Cx36, both the GC oscillations and the eye-movement oscillations were absent (Fig 4D).

For extended statistics of these pharmacological experiments, see S2B Fig. Together, the results of Fig 4 indicate that (1) the oscillator driving the oscillating eye movements is located in the retina, (2) the AII ACs are critically involved in generating the oscillations in nob GCs, and (3) there is a causal relation between the nob GC oscillations and their eye-movement oscillations.

**Discussion**

This study reveals—for the first time, to our knowledge—a pathophysiological mechanism for a specific form of congenital nystagmus and shows that its origin is retinal. We propose the following mechanism (Fig 5A & S3 Fig). In wt mice, ON-DSGCs, which are sensitive to low-velocity global image motion, respond coherently when an image moves across the retina. Their coherent output reflects the direction and speed of global image movement: i.e., the retinal slip signal. This signal forms the input to the AOS, where it induces compensatory eye movements that stabilize the image on the retina. In nob mice, the network behaves quite differently. nob ON-DSGCs are nonresponsive to light stimuli and thus cannot detect image motion, which may underlie the lack of a well-developed optokinetic response (OKR). In addition, nob GCs oscillate spontaneously, which, as shown in this paper, induces a pendular nystagmus.

We propose that the origin of these oscillations is the AII ACs for the following reasons. Firstly, the source of the oscillations is presynaptic to GCs. Secondly, AII ACs contain an
intrinsic, membrane-potential dependent oscillator, consisting of a fast sodium channel, and both a fast and a slow (M-type) potassium channel [20]. When the AII AC membrane potential is outside its normal working range because of altered input from the ON-BCs, the AII ACs start to oscillate [20]. Finally, the oscillations of ON- and OFF-GCs are driven in antiphase, which AII ACs will do, since they drive ON- and OFF-GCs with opposite sign.

How could light stimulation synchronize the oscillations in the GCs? Since the oscillator in AII ACs is an intrinsic feature of the AII ACs, they could oscillate rather independently of each other, leading to asynchronous GC oscillations, as we find in the dark. We hypothesize that global light stimulation depolarizes the membrane potential of the AII ACs by crossover inhibition driven by GABAergic OFF ACs [29]. This will phase-reset and synchronize the AII ACs and subsequently synchronize in antiphase both the ON- and OFF-GCs they project to.

The consequence is that despite the absence of a classical visually evoked response in nob ON-DSGCs, their oscillations synchronize when the retina is stimulated with a global light stimulus. The combined activity of the synchronized oscillating nob ON-DSGCs is interpreted in the AOS as an oscillating retinal slip signal, and, in response, oscillating compensatory eye movements are generated: pendular nystagmus. On the other hand, when the oscillations of nob ON-DSGCs are asynchronous, such as in the dark, the integrated output to the AOS will not oscillate and will not evoke a pendular nystagmus.

Once initiated, oscillating eye movements over an image induce retinal activity that phase resets the retinal oscillator (AII ACs) and maintains the synchronous oscillations of ON-DSGCs and pendular nystagmus (Fig 5A). This represents a self-maintaining loop. Consistent with this idea, a horizontally oriented grating fails to induce oscillating eye movements, because horizontal eye movements over a horizontal grating appears as a stationary stimulus to GCs (Fig 5B). This will not modulate retinal activity and will not synchronize GC oscillations, and pendular nystagmus is absent (Fig 1D).

Although we suggested that the ON-DSGCs drive the oscillating eye movements, we cannot exclude contribution of other GCs. However, ON-DSGCs are the most important GCs to detect the direction of global retinal image motion that is used as a retinal slip signal by the AOS to induce compensatory eye movements [16]. Oscillations in these cells will therefore be especially effective in inducing oscillating eye movements.

The suggestion that AII ACs are the source of the oscillations implies that all ON-DSGCs oscillate. If this is the case, why is nystagmus in the CSNB patients and nob mice only horizontal when ON-DSGCs are tuned for image movement in three directions: naso-temporal,
Synchronous oscillations of retinal ganglion cells induce nystagmus

A

No synchronization ganglion cells

Synchronization ganglion cells

B

vertical gratings

horizontal gratings

Effective stimulation

Ineffective stimulation
upward, and downward [14]? One of the simplest explanations is that the retinal slip signals generated by synchronously oscillating ON-DSCGs tuned for upward and downward motion cancel each other. This can occur, for instance, at the neuronal level of the vestibular oculomotor nuclei or possibly even at the level of the eye muscles. In contrast, the naso-temporal signal is not canceled, as there is no, or only a few, opposing ON-DSCGs [14].

In the present paper, we discuss the origin of a specific form congenital nystagmus, i.e., spontaneous small-amplitude involuntary oscillating eye movements. This pathological condition is distinct from the OKR, in which the eyes follow the global movement of the stimulus followed by a fast reset saccade. The OKR, sometimes referred to as optokinetic nystagmus, is often reduced or absent in nystagmus patients. However, the conclusion that congenital nystagmus arises as a consequence of a mere absence of the OKR is unwarranted, since, for example, mice with mutations in FERM domain-containing protein 7 (FRMD7) [30] have no horizontal OKR but do not develop a pathological nystagmus.

It has been suggested that congenital nystagmus originates from a disruption in the interaction of the subcortical optokinetic pathways (AOS) and cortical foveal pursuit system [1]. However, our findings show that the cause of congenital nystagmus associated with CSNB lies within the retina in the afoveate mouse. Since the optokinetic systems of afoveate and foveate animals differ, generalizing our findings in nob mice to humans with CSNB requires caution.

That said, given the balance of our results, we proposed that the nob mouse model is relevant to human CSNB patients for the following reasons. Firstly, the nystagmus in young CSNB patients (S1 Fig) and nob mice is identical (Fig 1). Secondly, the photoreceptor to ON-BC synapse is highly conserved across mammals and even across vertebrates [31]. Thirdly, mutations in proteins specific for this synapse lead to the same CSNB phenotype in mice and humans [32], suggesting similar underlying retinal mechanisms. Fourthly, starburst amacrine cells (SACs), which are fundamental for generating direction-selective responses of GCs [30] and DSCGs [33], are found both in mouse and primate retina [34]. Finally, retrograde tracing experiments reveal retinal projections to the AOS in both mice and primates [35].

From a therapeutic point of view, our results suggest that the primary pathogenic condition in patients with this form of congenital nystagmus occurs in the retina in the form of synchronized oscillations of GCs. Therapeutic interventions aimed at desynchronization of the oscillating GCs in the retina may serve to reduce or eliminate the nystagmus.

**Material and methods**

**Animals**

All animal experiments were carried out under the responsibility of the ethical committee of the Royal Netherlands Academy of Arts and Sciences (KNAW), acting in accordance with the European Communities Council Directive of 22 July, 2003 (2003/65/CE), or the University of Louisville Animal Care and Use Committee. All experiments we conducted under license...
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wt mice, *Mus musculus*, were obtained from Janvier labs. Nob and Cx36 knockout mice were obtained from the McCall lab (University of Louisville, Louisville, KY, United States), and SPIG1+ mice were obtained from the Noda lab (National Institute for Basic Biology, Oka-zaki, Japan). Nob/Spig1+ and Cx36 knockout mice were crossbred to accomplish a double knockout with labeled ON-DSGCs. Since the nob mutation is X-linked, only male animals were used. For wt SPIG1+, both male and female animals were used. All mice were kept in a C75BL/JRj background. The age of the animals ranged from 4 wk to 1 y.

**Eye-movement recordings**

**Surgical preparation.** Prior to the start of experiments, adult animals were equipped with a head-fixation pedestal, an aluminum bit with an integrated magnet, attached to the parietal bones of the skull using dental cement (Super Bond, Sun Medical). Surgery was performed under general isoflurane/O2 anesthesia and topical anesthesia (bupivacaine). Analgesia was offered by subcutaneous injection of metacam (2 mg/kg). The recovery time was at least 2 d after pedestal surgery. During experiments, the animal was placed head-fixed in the experimental setup using a custom-made adapter, which allowed panoramic vision.

**Optokinetic stimulator.** For the optokinetic experiments, two experimental setups were used. In the first system, a modified Marquee 9500 CRT projector (100 fps) generated a large panoramic visual surround (545 nm) onto three large back-projection screens (1.47 × 1.18 m; Stewart Filmscreen) that were placed around the animal to create a combined field of view of 270˚ × 77.5˚. The average luminance of the visual stimulus was 10 cd/m2. Michelson contrast of the grating stimuli was about 90%. In the second setup, two Benq XL2420t high-performance monitors (120 fps, gamma-1.745) were placed in V-formation around the animal, and the closest distance between the screen surface and the mouse head was 16.5 cm. Screen dimensions were 56.9 × 33.8 cm (combined field of view: 240˚ × 50˚). Michelson contrast of the grayscale grating stimuli approached 100%. The average luminance of the sine grating stimuli was 71.6 cd/m2. For measurements in darkness, the displays were switched off. Visual stimuli consisted of sine wave gratings, homogeneous grayscale images, and dotted patterns (dot radius 1˚, center-to-center distance 5.35˚). All stimulus patterns were computer generated and corrected for perspective distortion by projection onto a virtual sphere centered on the animal’s head.

**Eye-movement recordings.** Eye movements were recorded using an infrared video tracking system (JAI RM-6740CL monochrome CCD camera, 200 fps). In a few instances (Fig 1A–1C), pilocarpine (2%) eye drops were used to reduce pupil dilatation. A 2D eye position was computed from the relative distance between pupil center and corneal reflections of the infrared LEDs [36] and pupil size [37,38]. Epochs containing saccades, eye blinks, and motion artifacts were excluded from analysis. Eye velocity was smoothed using a Gaussian smoothing kernel with a SD of 7.5 ms (25-Hz cutoff). For monocular visual stimulation (Figs 1D, 3Aiv, 3Biv and 3Ciii), a miniature blackout cap was placed over the contralateral eye.

**Intraocular injections.** Intravitreal injections were administered under brief isoflurane/O2 sedation and topical anesthesia applied to the injection spot (0.4% oxybuprocaine). The eye movements were measured after the mouse recovered completely from the anesthesia. We used injection volumes ranging between 1 and 3 μL. To block AMPA receptors, we used either DNQX (Tocris, 50 μM final concentration) or CNQX (Tocris, 50 μM final concentration). CNQX and DNQX were assumed to act equally. To block NMDA receptors, we used D-AP5.
(Tocris, 10 μM final concentration). To block glycnergic inhibition, we used STR (about 10 μM final concentration). The high dose of STR might have blocked GABA receptors as well. To block the M-type K current, we used LP (Tocris, 30 μM final concentration). Drugs were dissolved in Hank’s Balanced Salt Solution (Sigma-Aldrich).

**Analysis of eye-movement recordings.** PSDs were computed from angular eye velocity using Welch’s method with a 4-s window length, 75% overlap between windows, and a Hann window function. The fundamental frequency was computed by weighted averaging the frequencies with a magnitude > 90% of the maximum power in the PSD. For comparisons between different stimulus conditions in nob mice, PSDs were normalized to the average power ≤ 2 Hz.

**In vivo optic nerve recordings**

**Surgical preparation.** All surgical procedures were performed at light-adapted levels and have been published previously [39,40]. Briefly, anesthesia was induced with an intraperitoneal injection of a Ringer’s solution containing ketamine and xylazine (127 and 12 mg/kg). Anesthesia was maintained with supplemental subcutaneous injections (about every 45 min) of anesthetic at 50% of initial concentration. The head was secured in a stereotaxic frame (David Kopf Instruments, Tujunga, CA, USA), a craniotomy was performed, and the overlying cortex was removed to expose the optic nerve. Throughout the experiment, body temperature was maintained at 37˚C with a feedback-controlled heating pad (TC-1000; CWE, Ardmore, PA, USA). Topical phenylephrine hydrochloride (2.5%) and tropicamide (1%) ophthalmic solutions were applied to dilate the pupils and paralyze accommodation. Clear zero-powered lenses [41] moistened with artificial tears kept the cornea from drying. At the end of the experiment, animals were euthanized with an overdose of anesthetic followed by cervical dislocation.

**Extracellular GC axon recordings.** Action potentials were recorded extracellularly from single optic nerve axons using sharpened tungsten microelectrodes (impedance = 30–100 MΩ). A reference electrode was inserted subcutaneously. Action potentials from single GC axons were isolated, amplified (X3+Cell; FHC, Bowdoinham, ME, USA), digitized at 15 kHz (Power1401, Cambridge Electronic Design, Cambridge, United Kingdom), and stored for offline analysis. Isolated spike trains were simultaneously displayed on an oscilloscope and computer monitor and played over an audio monitor to obtain direct feedback of the cell’s response to visual stimuli. Responses were analyzed offline using Spike2 software v4.24 (Cambridge Electronic Design, Cambridge, United Kingdom). Spikes were accumulated within a 50-ms bin width and displayed as poststimulus time histograms (PSTHs). Each average PSTH was smoothed by fitting it with a raised cosine function with a 50-ms smoothing interval to minimize alteration of the peak firing rate and maximize signal-to-noise ratio [39].

**Recording and analysis of GC spontaneous activity.** Spontaneous activity was determined for GCs in the dark over durations up to 200 s. The presence of a rhythmic component in the spontaneous activity was assessed using a fast Fourier transform (FFT) that produced a power spectrum (Spike2 4.24; Cambridge Electronic Design, Cambridge, UK). A peak fundamental frequency was considered significant if its power was three standard errors (SEs) above the mean power between 0.5 and 30 Hz [42]. To estimate the consistency of the rhythmic activity, the recorded spontaneous activity was divided into segments of 20 s, and FFTs were performed on each segment to identify the fundamental peak. The mean fundamental frequency and its SE were computed across all segments.

**MEA recordings of GCs**

Mice were dark-adapted for at least 1 h, euthanized with a mixture of CO₂/O₂, and cervically dislocated. Under dim red light, the eyes were removed and placed in oxygenated Ames
medium. The eyecup was prepared by removing the cornea, lens, and as much vitreous humor as possible. Using a fine forceps, the retina was carefully dissected away from the sclera. Small incisions were made to flat-mount the retina. Regardless of whether the isolated retinas were used in the MEA recordings or for whole-cell patch clamp recordings, they were continuously superfused with Ames’ medium or Ringer’s solution and gassed with a mixture of O₂ and CO₂ at pH of 7.4 and 29–36˚C.

Recording of MEA data. Isolated retinas were placed photoreceptor side up on a perfo-rated 60 electrode array (60pMEA200/30IR-Ti using a MEA2100 system: Multichannel systems, Reutlingen, Germany) in a recording chamber mounted on an Nikon Optiphot-2 upright microscope and viewed under IR with an Olympus 2x objective and video camera (Abus TVCC 20530). Extracellular multiunit GC activity was recorded at 25 kHz in MC rack (Multichannel systems, Reutlingen, Germany), zero-phase bandpass filtered (250–6,250 Hz) with a fourth-order Butterworth filter in Matlab (MathWorks, Natick, MA, USA), and sorted into single-unit activity with “offline spike sorter” (Plexon, Dallas, TX, USA). Spikes were detected using an amplitude threshold > 4σₙ, where σₙ is an estimation of the background noise

σₙ = median \left\{ \frac{|x|}{0.6745} \right\}

with x being the bandpass-filtered signal [43]. The detected spikes were manually sorted into single units based on principal component or amplitude variables versus time. The clustering versus time approach allowed us to track changes in extracted features of single units occurring over extended recording periods and with differing firing rates.

Optical stimulator. Light stimuli were generated with Psychophysics Toolbox Version 3 [38]. Stimuli were projected onto the retina from the photoreceptor side by a DLP projector (Light Crafter 4500, Wintech, Carlsbad, CA, USA) using a custom-built 2x water immersion objective. One pixel of the DLP projector had a size on the retinal surface of 2.1 μm. Only white light stimuli were used. The “dark” light intensity was 6 μW/m², and the maximal “light” intensity was 176.2 μW/m².

Analysis of MEA data. For MEA recordings, rhythmic components in the spontaneous activity were assessed using single-unit activity during 600 s of darkness. Spike trains were binned into 1-ms intervals and then divided into 5-s nonoverlapping periods. Each segment was baseline subtracted, and the PSD and autocorrelation were evaluated over 120 segments, which were then averaged. The autocorrelations were normalized such that they were equal to 1 at zero lag. PSD was estimated by Welch’s modified periodogram using 4-s windows, with 75% overlap, multiplied by a Hamming window function, and a 4-s discrete Fourier transform length.

Synchronized firing between units was assessed by cross-correlation after stimulation with a full field light stimulus presented for 500 ms. The flash was preceded and followed by a 500- and 1,000-ms period of darkness. Individual-unit spike trains were binned into 5-ms interval, and the response to 100 repetitions was averaged. The mean responses were divided into 250-ms windows, detrended, and then cross-correlated. For short-time cross-correlations, a 250-ms window was used that advanced in 25-ms steps.

Voltage-clamp recordings of GCs

Whole-cell voltage-clamp recordings were performed from GFP-labeled GCs in retinas mounted (GC side up) in a recording chamber (Warner Instruments, Hamden, CT, USA). The recording chamber was mounted on a Nikon Eclipse E2000FN microscope (Nikon,
Synchronous oscillations of retinal ganglion cells induce nystagmus

Tokyo, Japan) and viewed with a Nikon 60x water immersion objective with infrared differential interference contrast and a video camera (Philips, Eindhoven, the Netherlands). The GFP-labeled cells were identified using a short flash of 450–490 nm light.

**Solutions.** Ames’ medium supplemented with 1.9 g/L of NaHCO3 was used as the external bath solution, and whole-cell patch pipette solution contained [mM] 112 Cs-Methanesulphonate, 8 CsCl, 10 EGTA, 10 HEPES, 2 ATP-Mg, and 0.3 GTP-Na3, pH adjusted to 7.2 with CsOH, ECl = −69.92 mV, except for data shown in Fig 4Aiii. Here, we used a bicarbonate buffered Ringer’s bath solution containing [mM] 125 NaCl, 2.5 KCl, 1 MgCl2, 1.25 NaH2PO4, 20 glucose, 26 NaHCO3, and 2 CaCl2 and a whole-cell patch pipette solution containing [mM] 120 Cs-glucconate, 1 CaCl2, 1 MgCl2, 10 Na-HEPES, 4 ATP and 1 GTP, and 1% LY. In these experiments, freshly prepared CNQX (Tocris) or DNQX (Tocris), D-AP5 (Tocris), and STR were added to the bath solution to block AMPA, NMDA, and glycine receptors, respectively. CNQX and DNQX were assumed to act equally. A cocktail of 50 μM DNQX and 10 μM D-AP5 in the external bath solution was prepared freshly before the experiment. For the dose-response curve of STR, the following concentrations were used: 1, 10, 20, 50 and 100 μM STR. Chemicals were obtained from Sigma-Aldrich (St. Louis, MO, USA) unless otherwise indicated.

**Optical stimulator.** Light stimuli were generated with Psychophysics Toolbox Version 3 [38]. Light stimuli were projected onto the retina from the photoreceptor side by an Acer C20 picoprojector via the microscope condenser. One pixel of the projector had a width of 4.8 μm on the retinal surface. The “dark” light intensity was 0.3 cd/m², and the maximal “light” intensity was 450 cd/m².

**Recording equipment.** Whole-cell data were recorded with a HEKA EPC10 patch clamp amplifier using PatchMaster software. The data were sampled at 10 kHz and filtered at 5 kHz with a four-pole Bessel low-pass filter. In a second setup, data were collected with a Multiclamp 700B amplifier using Digidata 1322A digitizer (MDS Analytical Technologies, Union City, CA, USA) and Clampex 10.2 software (MDS Analytical Technologies, Union City, CA, USA) to generate command outputs, trigger the light stimulus, and acquire and analyze analog whole-cell voltages. These data were sampled at 10 kHz and filtered at 2.4 kHz with a four-pole Bessel low-pass filter. Matlab (MathWorks, Natick, MA, USA) and Igor.pro (WaveMetrics, Portland, OR, USA) were used to analyze the data.

**Statistics**

Statistical analyses were performed using Origin Pro 8 (Northampton, MA, USA) or Matlab (MathWorks, Natick, MA, USA). All mean values are presented ± SEM. Statistical significance was tested using a (paired) Student t test or a one-way ANOVA. Normality was tested using the Shapiro-Wilk test. The distribution of the frequencies of the eye movements (df = 17, p = 0.28), the GCs optic nerve recordings (df = 46, p = 0.71), and the GC excitatory currents (df = 38, p = 0.26) were normally distributed. Differences with p < 0.05 were considered statistically significant.

**Supporting information**

S1 Fig. Eyes of CSNB patients oscillate horizontally at 6 Hz. The patients studied by Simonsz and colleagues [3] had horizontal pendular nystagmus combined with tonic downgaze and a low-frequency, upgaze-evoked nystagmus. Although the tonic downgaze disappeared at 2–3 y of age, the horizontal nystagmus remained. We quantified the nystagmus of three patients (age: 3.5, 3.5, and 5 y) whose video material was of sufficient quality. The original UMATIC video movies were digitized, and the digital clips were stabilized and aligned using the
compositing program Nuke (The Foundry, London, UK). The nasal corner of the eye and the surrounding area were used as references for the stabilization. After stabilization of the movie, a circle with a fixed diameter the size of the iris was fitted through the iris (see S1 Movie). The coordinates of the center of the circle were used as measure for the eye position, and the resulting time series of eye positions were Fourier transformed using Matlab. No attempt was made to calibrate the amplitude of the oscillations, and hence, the amplitudes are given in pixels.

(Ai) Total horizontal (blue) and vertical (red) eye movements of patient #1 in pixels. Large-amplitude horizontal and vertical eye movements occurred, as the children could shift their gaze freely. On top of these large-amplitude eye movements, small-amplitude oscillations are visible only for the horizontal eye movements, which is also evident in the power spectrum (Aii). There are two peaks visible in the power spectrum: one broad peak below 2 Hz and one narrow peak around 7 Hz. The low-frequency component results from gaze shift. The two components were separated by calculating the moving average over a window of 5 frames (Bi) and subtracting this average from the original traces (Ci). The power spectra of these two components are shown in Bii and Cii. For each patient, four separate episodes were analyzed, and the episodes selected do not contain eye blinks. (D) The power spectra of the horizontal eye movements of the individual episodes per patient. All traces show peaks in the range of 5–8 Hz. (E) The mean power spectra per patient. (F) Box plots of the oscillation frequency for the various video clips for each patient. The oscillation frequencies across the various patients did not differ significantly (ANOVA: $F = 3.75$, df = 11, $p = 0.06$), and the mean peak oscillation frequency over all patients was $6.25 \pm 0.63$ Hz ($n = 3$) (age range: 3 mo–3 y). This oscillation frequency is considerably lower than the 10–20 Hz reported by Pieh and colleagues in a patient population that included the same patients as described by Simonsz and colleagues [3,44] and analyzed in this paper. Since Pieh and colleagues [45] did not disclose the methods of how the eye movements were analyzed, it remains puzzling why their estimated eye-movement oscillation frequency differs so much from ours. We complied with relevant ethical regulations applicable to clinical eye-movement recording at the time. Patient data: The three video recordings of the children aged 0–3 y were made in 1990 and 1992 in the Kantonsspital St. Gallen, Switzerland, as a clinical recording of eye movements in the course of their diagnostic work-up and treatment by their treating ophthalmologist (HJS). All clinical investigations have been conducted according to the principles expressed in the Declaration of Helsinki. Informed consent for publication of the video recordings of the eye movements of the patients had previously been obtained from the parents. Renewed written permission to publish the video material was obtained from the patients themselves, who are now adults. The data underlying this figure can be found at https://figshare.com/account/home#/projects/65990.

(EPS)

S2 Fig. Statistical data of the GC and eye-movement oscillation frequencies. The black open square indicates the mean of all results, the box indicates the interquartile range (25%–75%), the vertical lines indicate the 5%–95% range, and the colored circles indicate the individual data points. (A) Box plots of all measurements in control conditions. (B) Box plots of all pharmacological experiments for both the GC oscillations and the eye-movement oscillations. The data underlying this figure can be found at https://figshare.com/account/home#/projects/65990. GC, ganglion cell.

(EPS)

S3 Fig. Schematic diagram of the wiring of BCs, AII ACs, SACs, and ON-DSGCs. wt retinal circuit (top panel) compared to the nob retinal circuit (bottom panel). wt rod ON-BCs provide an excitatory input to AII ACs. All ACs are electrically coupled with each other and to cone ON-BCs, and they provide a glycinergic inhibitory input to cone OFF-BCs. Cone ON- and
OFF-BCs provide a direct excitatory input to ON- and OFF-GCs. The pathway from rod > rod ON-BC > AII ACs > GCs is the primary rod pathway. AII ACs also receive a glycnergic inhibitory input. ON-DSGCs receive excitatory input from cone ON-BCs and are inhibited by ON-SACs. The interaction between ON-BC excitation and ON-SACs inhibition produces direction-selective responses in ON-DSGCs. OFF-BC excitatory input to AII ACs is relayed to cone ON-BCs via electrical coupling as well as via crossover inhibition between the ON and OFF pathways. In nob retina, signaling from the rod and cone photoreceptors to ON-BCs is lost because the synapse between photoreceptors and ON-BCs is nonfunctional. The consequence is that ON light responses are absent and that the GCs have oscillating burst spike activity. These oscillations most likely originate in AII ACs just as in rd1 mice [21]. Interaction between fast sodium and potassium channels in AII ACs, in combination with a slow potassium channel, can lead to a bursting spiking behavior with a burst frequency dependent on the AII AC membrane potential [21]. In rd1 mice, the input to AII ACs is lost with rod and cone degeneration, leading to a change in AII AC membrane potential, which induces oscillations of about 10 Hz. In nob mice, AII ACs lose only their ON input. We hypothesize that as a result, the AII AC membrane potential will not shift as far in nob mice as in rd1 mice, and the AII ACs oscillations will be slower (5 Hz). The nob AII ACs transmit this oscillating signal back to the BC-synaptic terminals and to the GCs, which induces 5-Hz oscillations in both the excitatory and inhibitory inputs of the GCs. Since the sign of the AII AC inputs is opposite in ON-BCs and OFF-BCs, the nob ON- and OFF-GCs oscillate in antiphase. In the dark, the AII ACs oscillate independently of each other. A global light stimulus resets all AII ACs and thereby synchronizes the oscillations, leading to synchronized oscillating output to the AOS, where the signal is translated into an oscillating eye movement. AC, amacrine cell; AOS, accessory optic system; BC, bipolar cell; GC, ganglion cell; ON-DSGC, ON direction-selective GC; rd1, retinal degeneration 1; SAC, starburst AC; wt, wild type.

EPS
S1 Movie. Movie of the eye movements of one of the patients.
(MOV)

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