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Psychophysical Testing in Rodent Models of Glaucomatous optic neuropathy

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Abstract

Processing of visual information begins in the retina, with photoreceptors converting light stimuli into neural signals. Ultimately, signals are transmitted to the brain through signaling networks formed by interneurons, namely bipolar, horizontal and amacrine cells providing input to retinal ganglion cells (RGCs), which form the optic nerve with their axons. As part of the chronic nature of glaucomatous optic neuropathy, the increasing and irreversible damage and ultimately loss of neurons, RGCs in particular, occurs following progressive damage to the optic nerve head (ONH), eventually resulting in visual impairment and visual field loss. There are two behavioral assays that are typically used to assess visual deficits in glaucoma rodent models, the visual water task and the optokinetic drum. The visual water task can assess an animal's ability to distinguish grating patterns that are associated with an escape from water. The optokinetic drum relies on the optomotor response, a reflex turning of the head and neck in the direction of the visual stimuli, which usually consists of rotating black and white gratings. This reflex is a physiological response critical for keeping the image stable on the retina. Driven initially by the neuronal input from direction-selective RGCs, this reflex is comprised of a number of critical sensory and motor elements. In the presence of repeatable and defined stimuli, this reflex is extremely well suited to analyze subtle changes in the circuitry and performance of retinal neurons. Increasing the cycles of these alternating gratings per degree, or gradually reducing the contrast of the visual stimuli, threshold levels can be determined at which the animal is no longer tracking the stimuli, and thereby visual function of the animal can be determined non-invasively. Integrating these assays into an array of outcome measures that determine multiple aspects of visual function is a central goal in vision research and can be realized, for example, by the combination of measuring optomotor reflex function with electroretinograms (ERGs) and optical coherence tomography (OCT) of the retina. These structure-function correlations *in vivo* are urgently needed to identify disease mechanisms as potential new targets for drug development. Such a combination of the experimental assessment of the optokinetic reflex (OKN) or optomotor reflex (OMR) with other

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measures of retinal structure and function is especially valuable for research on GON. The chronic progression of the disease is characterized by a gradual decrease in function accompanied by a concomitant increase in structural damage to the retina, therefore the assessment of subtle changes is key to determining the success of novel intervention strategies.

Keywords

accessory optic system; glaucoma; lateral geniculate nucleus; optical coherence tomography; optokinetic; nystagmus; optomotor reflex; optic nerve head; retinal ganglion cell; superior colliculus; vestibular-ocular reflex

2. Introduction

The rod and cone photoreceptors of the retina respond to changes in light of the visual field, resulting in a cascade of electrical and biochemical signals to the interneurons of the retina (horizontal, bipolar and amacrine cells) and to the output neurons, the retinal ganglion cells (RGCs) (Baylor, 1996; Heidelberger et al., 2005). The RGCs' axons that form the optic nerve project to subcortical pathways, mainly the superior colliculus, and lateral geniculate nucleus (LGN) in the murine visual system, which in turn project to the visual cortex (Tenelle et al., 2013). Receptive field size and connectivity of these primary sensory neurons and interneurons determine both visual acuity and contrast sensitivity at the level of the retina. RGCs determine contrast of a visual stimulus through their receptive fields' center-surround organization, which is maintained in the visual pathway including the visual cortex, where neurons with the capacity to discriminate the orientation preference of a visual stimulus identify distinct patterns of the visual field and of a visual stimulus (Bopp et al., 2014). During the initial stages of disease development, RGCs are the first cells affected by neurodegeneration and cell death in the glaucomatous retina, resulting in a deficit of visual function before other cell types are affected (Burroughs et al., 2011; Kaja et al., 2011; Kaja et al., 2014). Direction-selective retinal ganglion cells (DS-RGCs) detect the motion of the stimuli in a preferred direction (Ackert et al., 2009; Giolli et al., 2006; Spoida et al., 2012; Stahl, 2004; van Alphen et al., 2010; Yonehara et al., 2009). The optomotor response (OMR) is used in behavioral tests to measure the ability of an animal to distinguish spatial frequency, the number of pattern repetitions over a given distance, and contrast sensitivity, the ability to distinguish individual parts of a visual image (Burroughs et al., 2011; Douglas et al., 2005; Kaja et al., 2014; Kandel et al., 2000; McGill et al., 2012b; Prusky et al., 2004). Behavioral tests measuring an animal's ability to resolve the spatial frequency and contrast of visual stimuli are employed to identify changes in visual acuity and contrast sensitivity thresholds, respectively, as critical first changes in glaucoma disease development (Burroughs et al., 2011; Kaja et al., 2011; Kaja et al., 2014).

This article covers the behavioral tests available for testing visual performance in rodents, with the potential for expansion to investigating rodent models of glaucomatous optic neuropathy.

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3. Basic overview of visual processing

Visual processing begins when light from the visual field enters through the cornea and is projected onto the retina (Poche and Reese, 2009). Retinal signals are transmitted passively through cyclic guanosine monophosphate (cGMP)-gated ion channels to produce graded changes of photoreceptor membrane potential causing a cascade of signaling events. In dark conditions, the cGMP concentration is high, allowing cGMP-gated channels to open and to generate an inward current. This influx of Na^+ and some Ca^{2+} ions is known as the dark current (Baylor, 1996; Heidelberger et al., 2005; Kandel et al., 2000; Korenbrot, 2012; Wen et al., 2014). This activity is accompanied by the continued outflow of K^+-ions and the cell stays in a depolarized state (-40mV) (Suryanarayanan and Slaughter, 2006; Thoreson et al., 2003), while Na^+/K^+ pumps maintain the intracellular ion homeostasis through active transport (Baylor, 1996; Kandel et al., 2000; Lohse et al., 2014; Luo et al., 2008; McCall and Gregg, 2008; Wen et al., 2014). Light stimuli elicit a reduction in cGMP levels, thereby close cGMP-gated channels resulting in hyperpolarization of photoreceptor cells corresponding to the stimulus intensity (Huettner, 2003; Kandel et al., 2000; Korenbrot, 2012; McCall and Gregg, 2008).

Under dark conditions, voltage-gated calcium channels in the terminals of depolarized photoreceptors are active and open (Heidelberger et al., 2005; Kandel et al., 2000). The resulting influx of calcium results in a tonic release of glutamate onto bipolar cells (Heidelberger et al., 2005; Kandel et al., 2000). Light-induced hyperpolarization of photoreceptors reduces the influx of calcium and consequently reduces the release of glutamate onto the bipolar cells (Kawai et al., 2001). One of the main contributors to the retina's organization into the parallel light stimulus ON- and OFF- systems, both molecularly and cellularly, are the ON- and OFF- bipolar cells, which differentially express distinct types of glutamate receptors facilitating the appropriate response to photoreceptor activity under light on or off conditions. Light stimuli in the center of the receptive field of ON-bipolar cells produce neuronal excitation while light in the surround portion of an ON-bipolar cell's receptive field generates inhibition (Chalupa and Günhan, 2004; Dumitrescu et al., 2009; Kandel et al., 2000). The opposite response is the case for OFF-center cells (Chalupa and Günhan, 2004; Kandel et al., 2000). Continual glutamate release by photoreceptor terminals under conditions of dark adaptation hyperpolarizes ON-bipolar cells and depolarizes OFF-bipolar cells (Chalupa and Günhan, 2004; Kandel et al., 2000). Horizontal cells, second-order interneurons of the outer retina (Heidelberger et al., 2005; Poche and Reese, 2009), laterally collect signals from several distant photoreceptors and provide input to bipolar cells (D. Lukasiewicz, 2005; Gollisch, 2013; Kandel et al., 2000), and feedback onto rods or cones (Kandel et al., 2000; Lamb, 2009; Peichl and Gonzalez-Soriano, 1994). These interneurons contribute to signal integration and adaptation to light stimulus intensity (D. Lukasiewicz, 2005; Gollisch, 2013; Lamb, 2009). Amacrine cells, second-order interneurons of the inner retina (Heidelberger et al., 2005), are responsible for laterally transmitting information from distant bipolar cells to RGCs (Kandel et al., 2000). Synaptic connections of morphologically distinct types of bipolar cells, amacrine cells and RGCs (Wassle et al., 1998; Yu et al., 2013) stratify in distinct levels of the inner plexiform

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layer with the outer half and the inner half serving as relay stations for the OFF- and for the ON-pathway, respectively (Yu et al., 2013).

RGCs are specialized projection neurons that represent the output signal of the retina to the brain (Yu et al., 2013). They are responsible for detecting movement, fine spatial details and color (Kandel et al., 2000). RGCs depend on the interneurons (bipolar, horizontal and amacrine cells) to combine signals from a wide-range of photoreceptors. The RGCs collect this information to relay precise spatial and temporal visual information to the brain through patterns of action potentials along the optic nerve which is formed by RGC axons (Gollisch, 2013; Kandel et al., 2000; Koulen et al., 1996; Wassle, 1988; Wassle and Boycott, 1991; Wassle et al., 1998). The spiking patterns from two types of RGCs, ON or OFF RGCs respectively, respond to and relay information about light stimuli in either the center or surround of a stimulus pattern, to higher centers in the brain (Gollisch, 2013; Kandel et al., 2000). Contrast perception and responses to rapid changes of light stimuli and illumination is critically determined by the center-surround organization of these primary and secondary interneurons, bipolar cells and RGCs (Gollisch, 2013; Kandel et al., 2000).

The axons of RGCs form the optic nerve, which project to three major subcortical regions of the primate brain: the pretectum, superior colliculus, and LGN (Kandel et al., 2000). In the murine brain, they project to two major regions: the superior colliculus (SC), and dorsal LGN (Tenelle et al., 2013) with a majority of axons projecting to the SC and a much smaller number to the LGN in rodents (Zhang et al., 2009). The SC receives retinal, auditory and somatosensory projections which are aligned with one another, and transmits information to the cerebral cortex. The information relayed from axons that terminate in the LGN is transmitted by projections to the visual cortex (Kandel et al., 2000). Recent studies have indicated that the mouse LGN has similar properties to those of cats and primates (Huberman and Niell, 2011). The primary visual cortex (visual area 1; V1; striate cortex) contains neurons that project to local areas as well as to other brain regions to integrate activity to the V1 layers (Kandel et al., 2000). The V1 of mice and other species is structured into six layers and has retinotopic organization (Huberman and Niell, 2011). Neurons in V1 respond preferentially to a specific orientation of a line or edge, termed “orientation preference” (Bopp et al., 2014; Huberman and Niell, 2011). This process of breaking down the visual field into short line segments of different orientation contributes towards a “primal sketch” or discrimination the outline of the visual stimulus and is critical for our understanding of the analyses relevant for the measurement of visual performance (Kandel et al., 2000).

Primary degeneration of RGC loss and a secondary degeneration of non-RGC cells i.e. retinal cells and neurons of the visual pathway, are affected during glaucoma (Hayashi et al., 2013; Krizaj et al., 2014; Sriram et al., 2012; Yucel and Gupta, 2008), therefore it’s important to elucidate the disease mechanisms that occur throughout the visual pathway during disease progression.

3.1. Glaucomatous damage to the visual pathway

Glaucoma is characterized by progressive ONH damage, loss of RGCs and of optic nerve fibers, and subsequently visual field loss, as well as by increased intraocular pressure (IOP)

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in some forms of the disease (Bessero and Clarke, 2010; Chidlow et al., 2007; Chiu et al., 2010; Sena et al., 2010; Zhang et al., 2009). Visual deficits are usually not detected until there is significant loss of RGCs and their axons (Kaushik et al., 2014). Alterations in metabolic events, gene expression, and degeneration of RGC axonal anterograde and retrograde transport occur during the early stages of glaucoma (Della Santina et al., 2013). This causes dendritic pruning and RGC death, but there are pockets of RGCs in the retina that remain relatively unaffected (Della Santina et al., 2013). The protein composition of post-synaptic elements in the inner plexiform layer is altered in a rat glaucoma model (Park et al., 2014), while the inner nuclear layer remains relatively unaffected with the exception of trans-synaptic secondary degeneration (Sriram et al., 2012). This secondary degeneration involves the loss of neurons in the visual pathway downstream of retinal neurons (Hayashi et al., 2013). Several investigators have conducted experiments in monkey models of experimental glaucoma to demonstrate the effect of increased IOP on neuronal morphology and neuron counts (Weber et al., 2000), dendritic changes (Gupta et al., 2007; Ly et al., 2011), as well as loss or shrinking of neurons in the LGN (Ito et al., 2009; Yucel et al., 2000; Yucel et al., 2001). There is a topographic relationship between RGC loss and/or damage and effects on the posterior visual pathway during glaucoma disease progression (Hayashi et al., 2013; Kaushik et al., 2014), where trans-synaptic degeneration is the major cause of wide-spread disease progression following initial RGC loss (Kaushik et al., 2014; Yucel and Gupta, 2008; Zhang et al., 2009).

The primary and secondary degeneration to RGCs and other elements of the visual pathway due to glaucoma necessitates behavioral tests that are capable to assess the whole visual pathway, in order to adequately identify glaucoma disease mechanisms and potential therapeutic strategies.

4. Behavioral assays measuring deficits in rodent visual processing

The number of methods employing animal behavior to measure rodent vision is limited (Benkner et al., 2013). Historically, visual studies were performed in frontal-eyed carnivores and non-human primates due to their similarity to humans with respect to visual acuity and higher visual signaling pathways (Huberman and Niell, 2011; Prusky et al., 2004; Prusky et al., 2000b; Wong and Brown, 2006). Some non-human primates, such as macaques, model the human physiology with respect to the existence of a fovea and three cone photo-pigments allowing the study of trichromatic color vision (Huberman and Niell, 2011). While the mouse retina is distinct from the human retina due to distribution and properties of photoreceptors, mice photoreceptors have distinct similarities to the human’s, e.g. the sensitivity and response to light stimuli (Huberman and Niell, 2011). Major experimental advantages using mice and rats as a model system to study visual function are attributable to their well-described anatomy and physiology, low-cost, straightforward care and use, and short lifespan among others. Furthermore, there are a variety of transgenic models available that provide labelled, defined cell types and neural circuits, thus enabling the modulation of specific molecular targets with relevance to human disease (Huberman and Niell, 2011; Prusky et al., 2000b; van Alphen et al., 2010; Wong and Brown, 2006).

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Visual impairment resulting from glaucoma is caused by the primary degeneration of RGCs and secondary degeneration affecting cell types up- and downstream in the visual signaling pathway, such as other retinal or CNS neurons (Li et al., 2014; Melamed, 2002; Yoles et al., 1999). Therefore, the most common tests for the assessment the effects of glaucomatous optic neuropathy on visual performance are visual water task (two-way forced choice swimming test) and OMR tests, as they are highly reliant on the appropriate response of functioning RGCs and involve the whole or most components of the visual pathway. However, the visual water task requires the often time-consuming training of the animal, whereas the OMR test does not require such training, because it relies on an existing reflexive feedback function, making it a more rapid, reliable test of visual performance. Reinforcement discrimination tests are very time-consuming as they require training of the animal (Benkner et al., 2013; Prusky et al., 2004), and are usually limited to younger mice due to their ability to learn the task rapidly (Prusky et al., 2004) resulting in a distinct disadvantage when investigating age-related disorders or diseases with age as a contributing or predisposing factor.

The following examples are behavioral tests that are used, or have the potential to be used, for the determination of mechanisms behind disease progression in glaucomatous rodent models.

4.1. The Optokinetic test as a measurement of the entire visual pathway determining visual acuity and contrast sensitivity

When the environment is moving or drifting across the retina, there are reflexes that consist of involuntary image-tracking and resetting motions of the body and / or head (OMR) or of the eyes (OKR) stabilizing the image on the retina (Kretschmer et al., 2013). Experimentally, this reflexive behavior is used to assess a variety of CNS circuits, including visual performance (Cahill and Nathans, 2008). The most common approach to elicit this reflex, is to present the animal with a visual stimulus of moving vertical alternate black and white stripes (Cahill and Nathans, 2008). In lateral-eyed animals, such as rodents, the visual field encompasses a large ~270° in the horizontal plane (Cahill and Nathans, 2008). In order to cover the whole visual field, the animal is usually positioned in the center of a cylinder (or simulated computerized cylinder) displaying the rotating black and white gratings (Cahill and Nathans, 2008). By using this method, it is possible to measure either the OKR by fixing the rodents' head in position and tracking the eyes with a scleral search coil or infrared video camera, or the OMR by manually or automatically determining head-tracking behavior (Cahill and Nathans, 2008).

Here we describe mechanisms and behavioral tests available for tracking the eye-movements generated by the OKR, and the less well-studied OMR.

4.1.1. The Optokinetic reflex (eye-tracking)—Saccadic eye movements are rapid eye shifts that align the fovea to a visual stimulus targeted in the periphery of vision. Eye movements characterized by a smooth pursuit of a moving target, on the other hand, provide the appropriate alignment of an image to the fovea (Kandel et al., 2000). As is typical for lateral-eyed animals, rodents lack a fovea (Sugita et al., 2013), and do not exhibit robust, if

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at all, smooth pursuit and saccadic eye movements, unlike animals with a fovea such as primates (Beraneck and Cullen, 2007; Iwashita et al., 2001; Stahl, 2004). However, animals without a fovea do exhibit rapid, saccade-like head movements which may be related either directly or indirectly and functionally to eye saccades of animals with a fovea (Stahl, 2004). Smooth pursuit is driven by a small visual stimulus, such as a bird in flight, enabling the observer to see the object in greater detail, whereas the OKR responds to larger stimulus across the whole retina, such as the observation of telephone poles whilst on a moving train (Schraa-Tam et al., 2009). The OKR comprises eye movements that reduce and stabilize the movement of an image across the retina (called the retinal slip) in a compensatory fashion (Ackert et al., 2009; Cahill and Nathans, 2008; Hung et al., 2013; Iwashita et al., 2001; Katoh et al., 2005; Krause et al., 2014; Stahl, 2004; Sugita et al., 2013; Thomas et al., 2010; van Alphen and De Zeeuw, 2002; Yonehara et al., 2009). Retinal slip identified as the difference between the velocities of the image movement and of the eye's corresponding tracking behavior, is detected by a distinct class of RGCs called direction-selective (DS) RGCs (Ackert et al., 2009). DS RGCs strongly respond to movement of a visual stimulus and typically display a preferred direction for such stimuli (Ackert et al., 2009). The computation of time differences in excitatory and inhibitory inputs to RGCs conveys their directional selectivity (Lee and Jung, 2009). Critical in controlling this process are starburst amacrine cells, GABAergic interneurons that also release acetylcholine as a co-neurotransmitter (Ackert et al., 2009; Lee and Jung, 2009). The mouse retina has a particularly high number of DS-RGCs, comprised of approximately half of the overall number of RGCs (Huberman and Niell, 2011). Two types of DS-RGCs are responsible for image motion: ON-OFF and ON types (Yonehara et al., 2008). The axons of DS-RGCs, particularly of the ON type, project to the accessory optic system (AOS) (Ackert et al., 2009; Giolli et al., 2006; Spoida et al., 2012; Stahl, 2004; van Alphen et al., 2010; Yonehara et al., 2009) whereas the ON-OFF DS-RGCs project to the dorsal LGN and superior colliculus (Yonehara et al., 2009). The AOS system, as the first relay point for RGCs to mediate the OKR, is therefore critical for visual acuity (Yonehara et al., 2009). The AOS converts the retinal signal to a rotation estimate of the moving stimuli (Spoida et al., 2012; Stahl, 2004; Yonehara et al., 2009). In animals without a fovea, the DS-RGCs are particularly important in providing directional information to the AOS system, and are ultimately responsible for generating the OKR (Krause et al., 2014; Sugita et al., 2013). This reflex is elicited when the environment is in motion and drifts across the retina, which results in the eyes beginning to follow the visual stimulus' direction (Sugita et al., 2013). Continuous repetition of the stimulus results in a slow tracking and fast saccadic-like resetting motion, called optokinetic nystagmus (OKN) (Cahill and Nathans, 2008; Stahl, 2004; Sugita et al., 2013). There are, in fact, two main oculomotor reflexes, the OKR and vestibule-ocular reflex (VOR), that work together to reduce retinal slip (Andreescu et al., 2005; Iwashita et al., 2001; Katoh et al., 2005; Stahl, 2004; Tanaka et al., 2013; Thomas et al., 2010; van Alphen et al., 2010; Yoshida et al., 2007) and are mainly controlled by subcortical circuits (Cahill and Nathans, 2008). The semicircular canals of the vestibular system provide an estimate of head rotation in response to head movement which elicits the VOR that generates eye movements to compensate for the head rotation (Stahl, 2004; Tanaka et al., 2013; van Alphen and De Zeeuw, 2002). In response to head rotation, the OKR also generates eye movements, however, this estimate is based on the motion of the

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image across the retina (Stahl, 2004). The VOR has a better response to rapid head rotation whereas the OKR responds best to slow changes in head position (Stahl, 2004; van Alphen et al., 2010). The combined responses elicit good image stability during any natural head rotation (van Alphen et al., 2010). The OKR is controlled by the accessory optic system (AOS), pons, and dorsal medulla (Stahl, 2004), with the VOR driven by neuronal activity stemming from the vestibular system, midbrain, pons, dorsal medulla, and cerebellum (Cahill and Nathans, 2008; Stahl, 2004; Tanaka et al., 2013). Therefore, measuring the OKR of a subject is considered a measure of the integrated activity of the retina, AOS, vestibular system and relevant brain regions providing additional control of these networks (Shirai et al., 2013).

This reflex can be used in behavioral tests to determine mechanistic information about the reflex and the underlying neural pathways, and whether dysfunction to these reflexes occurs during disease progression.

4.1.1.1. Behavioral tests assessing the OKR: Tests measuring the OKR are achieved by using an optokinetic drum to induce an OKN, i.e. tracking motion following the stimulus, and an accompanying eye movement of opposite direction resetting the image (Valmaggia et al., 2004) in the rodent. The head of the rodent is immobilized during testing by surgically embedding a headpost to the skull and subsequently clamping it to a restrainer that holds the animal. The restrainer consists of a plastic cylinder located on a stage in the center of the optokinetic drum, where visual stimuli, such as alternate black and white gratings, are rotated to elicit the reflex (Cahill and Nathans, 2008). Eye movement is measured by using scleral search coil or infrared video camera (Cahill and Nathans, 2008). Using a scleral search coil involves anaesthetizing the animal and implanting the coil subconjunctivally around the margin of the eye (Stahl et al., 2000). Scleral search coils have been reported to impact on free eye movements in smaller animals, such as mice (van Alphen et al., 2010). Video-oculography is an alternative method to tracking eye movements. The infrared camera can monitor the location of the pupil and corneal reflection without surgical intervention (Cahill and Nathans, 2008; Faulstich et al., 2004; Iwashita et al., 2001; van Alphen et al., 2009, 2010).

Commercial software is available to calculate the difference between the pupil and corneal reflection coordinates to create a time series of the OKR (Cahill and Nathans, 2008). Determining the ratio of the slow speed eye movement and the stimulus speed identifies the quality of the OKN, also called the optokinetic gain (Valmaggia et al., 2004). This technique has its disadvantages, since surgical intervention demands a high level of technical ability and an increased risk of animal loss. However, automated pupil tracking software makes this test objective and reproducible.

4.1.1.2. Applications of behavioral testing of the OKR in glaucoma: This technique has been used in rodents to determine mechanistic functional data about the OKR and VOR (Faulstich et al., 2004; Iwashita et al., 2001; Katoh et al., 2005; Stahl, 2004; Sugita et al., 2013; van Alphen et al., 2010; Yoshida et al., 2007); the influence of age and gender (van Alphen et al., 2009) and impact of genetic and drug-induced variation (Cahill and Nathans, 2008) on the OKT and VOR; and in transgenic models to determine the OKR and VOR

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dysfunction during disease (Alagramam et al., 2005), amongst others. For glaucomatous applications, the OKN has been used in clinical settings, however there is a lack of use with this technique in glaucomatous rodent models. Tong et al., recorded the OKN in 7 healthy and 9 primary open angle glaucoma (POAG) patients, and found that the reverse OKN was absent in the glaucomatous eyes (Tong et al., 2002). The authors suggested that these are due to the magnocellular retinal ganglion cell defects seen in POAG patients (Tong et al., 2002). Severt et al., found that they could discriminate between normal and POAG patients using certain variables of the OKN. Specifically, an altered signal to noise ratio may cause deficits in eye movements in glaucoma patients (Severt et al., 2000). Abe et al., showed that using a drifting pattern of horizontal stripes to induce OKN to determine contrast sensitivity was more effective at detecting optic nerve damage in patients suffering with glaucoma, optic neuritis and optic atrophy than using stationary stripes for subjective testing (Abe et al., 1993).

The OMR is a head-tracking reflex that follows a visual stimulus in a similar manner to the OKR, where it is thought to share common neural pathways, however the neural origins are much less studied and less well-known then the OKR.

4.1.2. The optomotor or head-tracking response—Shi and Stell, 2013, define the optokinetic response, or OMR, as “a simple, unlearned reflex turning of the head and neck (therefore also called the “optocollic” response) to follow the rotation of a global visual pattern in the horizontal plane.” (Shi and Stell, 2013), specifically in animals, such as mice and chickens, which have laterally placed eyes. Several studies suggest that the systems used in OKR are likely common to generating the OMR (Cahill and Nathans, 2008; Douglas et al., 2005; Prusky et al., 2006; Thomas et al., 2010) which manifests itself as involuntary head or eye movements in animals with laterally placed eyes (Benkner et al., 2013), with limited information available on the neural origins of the OMR, however. Cortical lesions in rodents appeared to have been shown to have no effect on the visual thresholds using the OMR, suggesting that the cortex has minimal input into the OMR in mice and rats for the optomotor testing (Douglas et al., 2005). Therefore using the OMR may represent the afferent projections of the retina to the AOS (Douglas et al., 2005).

There is a discrepancy in the terminology used in peer-reviewed literature, which allows several terms to be used to describe the same head movements seen using an optokinetic drum. Some examples of the terminology used in peer-reviewed literature from the last 10 years to describe the same head-turning movement using the same experimental set-up include optokinetic reflex (Barabas et al., 2011; Franco et al., 2009; Lu et al., 2010a; Zulliger et al., 2011), optokinetic response (Benkner et al., 2013; Della Santina et al., 2013; Ho et al., 2012; Joly et al., 2014; Lodha et al., 2010; Lu et al., 2010b; McGill et al., 2007; Prusky et al., 2006; Thompson et al., 2014; Tsai et al., 2014; Wang et al., 2010), optokinetic tracking (Della Santina et al., 2013; McGill et al., 2012a; McGill et al., 2012b; Volz et al., 2014; Wright et al., 2014; Wright et al., 2013), optokinetic nystagmus (Bricker-Anthony et al., 2014; Savigni et al., 2013; Selt et al., 2010), optomotor testing (Zhou et al., 2009), OMR (Abdeljalil et al., 2005; Kretschmer et al., 2013; Lund et al., 2006; Prusky et al., 2004; Puk et al., 2009; Rangarajan et al., 2011), optomotor reflex (Barabas et al., 2011; Barabas et al., 2013; Redfern et al., 2011), optomotor tracking (Burroughs et al., 2011; Douglas et al.,

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2005; Kaja et al., 2014), head-tracking reflex (Hoelter et al., 2008; Puk et al., 2008), reflexive head movements (Wang et al., 2010). Of the aforementioned terms, the optokinetic reflex/ optokinetic nystagmus should be used to describe eye-tracking, and the optokinetic response/ optokinetic tracking/ optomotor testing/ optomotor response/ optomotor reflex/ optomotor tracking/ head-tracking reflex/ reflexive head movements used to describe head-tracking.

4.1.2.1. Behavioral tests measuring the OMR: Behavioral tests measuring OKR and the OMR present a rodent with moving gratings combined with the evaluation if the animal is tracking the stimulus or not (Douglas et al., 2005; Prusky et al., 2004). Implementations of this assay include either a motorized cylindrical drum which can be lined with various removable cards printed with alternating vertical black and white stripes arranged to produce a known frequency (Abdeljalil et al., 2005; Hoelter et al., 2008; Puk et al., 2008; Savigni et al., 2013; Thaung et al., 2002) or custom (Benkner et al., 2013; Kretschmer et al., 2013; Redfern et al., 2011; Thomas et al., 2010; Wang et al., 2010) and commercial computer-generated virtual cylinders, such as the popular OptoMotry system from Cerebral Mechanics (Barabas et al., 2013; Burroughs et al., 2011; Douglas et al., 2005; Franco et al., 2009; Ho et al., 2012; Joly et al., 2014; Lu et al., 2010a; Lu et al., 2010b; McGill et al., 2012a; McGill et al., 2007; McGill et al., 2012b; Prusky et al., 2004; Puk et al., 2009; Rangarajan et al., 2011; Thompson et al., 2014; Tsai et al., 2014; Volz et al., 2014; Wright et al., 2014; Wright et al., 2013; Zhou et al., 2009; Zulliger et al., 2011). The computer program displays rotating contrasting gratings at a constant speed in a virtual cylinder that also maintains a defined distance to the head of the animal (Burroughs et al., 2011; Douglas et al., 2005; Prusky et al., 2004). Visuospatial measurements can be obtained by changing two variables of the visual stimulus: varying the cycles per degree to measure visual acuity; or varying contrast between the gratings to measure contrast sensitivity (Burroughs et al., 2011; Douglas et al., 2005; Prusky et al., 2004). Testing requires gratings to be rotated at increasing cycles per degree at 100% contrast or to include changes in contrast at constant cycles per degree rates until a threshold is reached, when tracking is no longer detected (Burroughs et al., 2011; Douglas et al., 2005; Prusky et al., 2004). The speed of the rotation of the spatial frequency gratings can also be altered. Thomas et al, 2010, scored the quality of the head-tracking in mice and rats with varying stripe widths and grating speeds, and determined that these were vital factors in eliciting the maximum head tracking response (Thomas et al., 2010). They showed that mice prefer a narrower stripe and faster grating speed compared to rats, whom prefer a wider stripe and slower grating speed (Thomas et al., 2010). They explained these difference between species could be due to eye size, receptive field and visual processing centers, therefore care must be taken when choosing stimulus parameters between different species and strains (Thomas et al., 2010).

One of the main advantages of the optomotor test is that it is non-invasive and rapid (Benkner et al., 2013). However, this test still relies on a user to manually watch the responses of the animal and decide as to whether an OMR to a particular grating speed or contrast percentage was elicited, which can produce inaccurate results if the user is inexperienced (Benkner et al., 2013; Douglas et al., 2005). This also means it is more consistent to keep the same user throughout a project, making it difficult to plan a large-

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scale project as one user can only assess so many mice per day, therefore testing must be done in small batches. Additionally, it is recommended that a second observer verifies the results obtained by the original user, increasing testing time and users for one study (Douglas et al., 2005). However, there is an impressive amount of consistency amongst the threshold levels obtained from different laboratories, compared in table 1. Showing that the OMR is a reliable tool for measuring visuospatial thresholds (visual acuity and contrast sensitivity) (Douglas et al., 2005). The test relies on the OMR, therefore no reinforcement training of the animal is required (Shirai et al., 2013), and it can be used in both young and old mice, from the day they open their eyes (Benkner et al., 2013). It is a straightforward conceptual research approach with straightforward analysis and interpretation. For the computer-generated virtual drum, the design can be semi-automated, where the software produces the grating cycles per degree or contrast and generates the threshold data automatically at the end of the test. The test is non-invasive and, for the OptoMotry test from Cerebral Mechanics, the animal moves freely on the platform, therefore minimal stress is elicited. While this is an obvious advantage this also represents a disadvantage in that the animals can elect to stop co-operating leading to inaccurate measurements as a failure to respond can be misinterpreted as the animal having reached a detection threshold. The optokinetic drum has the capacity to quantify contributions of individual eyes allowing for a direct correlation with other structural and functional measurements in the same eye (Douglas et al., 2005). This is particularly important in rodent models of glaucoma, as often times one eye will be glaucomatous whereas the other eye may display normal vision, either by disease development (e.g. in DBA/2 mice) or experimental design (e.g. microbead occlusion model).

4.1.2.2. Applications of behavioral testing of the OMR in glaucoma: The OMR has been used in experimental and genetic mouse models of glaucoma. Della Santina et al., 2013, performed intraocular injections of microbeads in mice in order to increase intraocular pressure (IOP) with injection of saline in the contralateral eye as controls. The authors determined visual acuity in both eyes and showed that optokinetic tracking was reduced in the microbead-injected eyes and accompanied by cell death (Della Santina et al., 2013). The DBA/2 mouse model of pigmentary glaucoma is the result of spontaneously developed mutations and characterized by chronic age-related retinal neurodegeneration with multiple similarities to the human disease condition (Burroughs et al., 2011; McKinnon et al., 2009), as is the case for many other animal models of glaucomatous optic neuropathy. There have been several studies that have reported reproducible visuospatial measurements of disease severity in glaucoma using the DBA/2 glaucoma mouse model (Burroughs et al., 2011; Kaja et al., 2014; Rangarajan et al., 2011; Zhou et al., 2009). However, two articles have also reported that the OMR required to track moving visual stimuli was not observed in this mouse strain, independent of retinal function and glaucoma (Barabas et al., 2011; Puk et al., 2008) which may be due to a discrepancy in the testing of this mouse model. The DBA/2 strain may require some time in the presence of a homogenous gray stimulus in the system before testing in order to acclimatize the animal to the box, as recommended by Prusky et al, 2004 (Prusky et al., 2004). During testing, presentation of a black or white screen, tapping on the lid or high-pitch noises can facilitate the enhancement of an animal's focus on the test stimuli and a reduction of locomotion (Prusky et al., 2004). As discussed previously, mice

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prefer a narrower stripe and faster grating speed a therefore a higher or lower spatial frequency level may elicit the maximum OHT response in this strain, allowing for easier tracking detection (Thomas et al., 2010). DBA/2 mice have also been reported to have high activity levels and a short attention span (Rangarajan et al., 2011), therefore requiring longer testing times than the standard wild-type C57 strain, due to the time needed to refocus the mouse to the stimuli. More work needs to be performed on the whole visual system in order to elucidate deficiencies related to the OMR in different strains.

4.2. The visual water task as a tool to assess visual function behaviorally

The underlying principle of the Visual Water Task (VWT) is an animal's ability to distinguish grating patterns that are associated with an escape from water, in a swimming task, enabling the measurement of the animal's visual acuity as a correlate of successful completion of the task (Prusky et al., 2000b). Prusky and colleagues developed a computer-based two-way forced choice swimming task paradigm, which measures the visual acuity and contrast sensitivity of rodents (Prusky et al., 2000b). In this task, the animal is forced to swim in and has to navigate a Y-maze where an escape from the water is only possible via a hidden platform in front of the screen displaying the grating (Prusky et al., 2000b). This test can determine both visual acuity and contrast sensitivity, however it does not consider detection of motion nor does it allow the analysis of the visual performance of an individual eye. Investigators have used this technique to determine the difference of visual performance in various mouse and rat strains (Douglas et al., 2005; Prusky et al., 2000b; Wong and Brown, 2006), the effect of protein or structural changes on vision (McGill et al., 2007; Origlia et al., 2012; Thompson et al., 2014; Tschetter et al., 2011) and how the environment of which the mouse is kept affects visual performance (Prusky et al., 2000a).

Some disadvantages of this test include the training regimen required, which can be time-consuming and lead to inaccuracies that are independent of visual performance (Prusky et al., 2004). Long periods of training or testing can lead to tiring and changes in body temperature of the animals leading to inaccurate results (Prusky et al., 2000b). Rodents can also display spatial bias, therefore preferring one choice over the other; the resulting need to continually alternate choices can make it difficult to obtain accurate measurements of visual function (Prusky et al., 2000b). Varying the viewing distance will alter the spatial frequency of the stimulus, making it difficult to control the exact nature of the stimulus with this test (Prusky et al., 2000b). Finally, it takes many trials to obtain a threshold value for mice about 60 trials and for rats about 150 trials, which can result in up to 2-3 days of data acquisition (Prusky et al., 2000b).

4.2.1. Applications of the VWT in glaucoma—Wong and Brown have used this model to test for visual acuity in several strains of mice, including DBA/2J mice (Wong and Brown, 2006), visual acuity and test performance in aged DBA/2J mice compared to wild-type (Wong and Brown, 2007), and found IOP-lowering drugs improved visual performance in DBA/2J mice as they aged (Wong and Brown, 2012).

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4.3. Running tasks as measurement of photoreceptor thresholds

For the running task, a mouse is placed on a running wheel and runs toward a light source (Naarendorp et al., 2010). The mouse is trained to stop when there is a change in luminescence, where it will receive a treat i.e. food or water, as a reward for stopping (Naarendorp et al., 2010). The mouse ceasing to run due to this visual cue indicates that it can see and detect this change, therefore, visual threshold levels can be measured and calculated.

4.3.1. Applications of running tasks in glaucoma—Although glaucoma is primarily characterized by RGC loss and optic nerve damage, it has been shown that there are non-RGC cells that are affected in the retina using ERGs in glaucomatous humans (Korth et al., 1994) and mice (Harazny et al., 2009), as well as histologically (Fernandez-Sanchez et al., 2014). Running tasks may be useful as a behavioral counterpart to ERGs and histological studies when investigating global retinal damage due to glaucoma in the future.

4.4. Go/No-Go licking tasks combined with imaging of cortical neurons as an assessment of visual cortex function

This test requires the training of mice to lick a reward liquid only in the presence of an appropriate visual stimulus; random licking or licking in response to an inappropriate stimulus result in the reward not being given and a time period in which rewards are not being provided (Andermann et al., 2010). Visualization of the neuronal circuitry of the visual cortex *in vivo* has been made possible with the development of two-photon microscopy for high-resolution imaging in light-scattering tissue combined with optogenetic labeling (Andermann et al., 2010; Petersen and Crochet, 2013).

4.4.1. Applications of Go/No-Go licking tasks in glaucoma—To our knowledge, this test has not been employed for glaucomatous applications to date, however this would be useful to further assess the extent of glaucomatous disease damage on the neural circuitry of the visual cortex using rodent models of GON.

5. Clinical relevance of data derived from behavioral assays measuring rodent visual performance in pre-clinical settings

Rodents are small, inexpensive alternatives to other animals normally used in visual studies, such as non-human primates or rabbits (Burroughs et al., 2011). Therefore, using the aforementioned behavioral techniques in rodent models that display disease etiology that is similar to humans, such as the DBA/2 mouse, allows us to conduct studies that obtain valuable information on disease mechanisms and therapeutic strategies at considerably lower cost with more data points. We can use these techniques in mice to evaluate therapeutic intervention in rodent models of disease (Adamus et al., 2012; Cahill et al., 2011; Krempler et al., 2011; Savigni et al., 2013), and RGC axon regeneration (de Lima et al., 2012), test variables such as age and gender (van Alphen et al., 2009), neuronal and RGC disease mechanisms in glaucomatous mice (Burroughs et al., 2011; Feng et al., 2013; Kaja et al., 2011), similar to the assessment of visual deficits in other animal models of disease (Pinto et al., 2007; Pinto et al., 2005; Puk et al., 2009; Richards et al., 2008; Roeser

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and Baier, 2003; Schmucker and Schaeffel, 2006; Umino and Solessio, 2013). Such data contribute to the pre-clinical development of promising therapeutic interventions prior to human clinical trials and benefit from their non-invasive and comprehensive nature resembling many of the aspects of human clinical trials.

6. Future developments

The progressive nature of glaucoma ultimately results in neurodegeneration, not only of the retina, but also of downstream elements of the visual pathway producing visual field loss (Burroughs et al., 2011). This neurodegenerative process necessitates a comprehensive assessment of the ensuing loss of visual performance. Many studies combine the use of behavioral measures such as testing of the optomotor reflex to obtain visual acuity and contrast sensitivity data with physiological readouts such as electroretinography or structural assays such as OCT to obtain a more comprehensive overall assessment of retinal and neuronal health of a given subject. These methods have been employed in combination to assess visual differences amongst mouse strains (Puk et al., 2008), visual deficits in zebrafish models (Allwardt et al., 2001; Bahadori et al., 2006; Biehlmaier et al., 2007; Bilotta et al., 2002; Brockerhoff, 2006; Brockerhoff et al., 1995; Kainz et al., 2003; Le et al., 2012; Stujenske et al., 2011; Van Epps et al., 2001), therapeutic effects of compounds in goldfish (Mora-Ferrer et al., 2005), normal retinal function (Ho et al., 2012), therapies in visually impaired mice (Boye et al., 2010) and rats (McGill et al., 2007). The correlation of these parameters with morphological changes in the retina (McGill et al., 2012a; McGill et al., 2012b), was used to assess changes during retinal degeneration (Barabas et al., 2013; Cammas et al., 2010; Pang et al., 2011; Samardzija et al., 2014; Wright et al., 2013) and dysfunction (Hoelter et al., 2008; Lodha et al., 2010), eye blast trauma (Bricker-Anthony et al., 2014), visual deficits in diabetes mouse (Aung et al., 2013; Aung et al., 2014) and rat models, after transgenic modification of RGCs (Tomita et al., 2010) or bipolar cells (Lagali et al., 2008) or after transplanting photoreceptors in the retina to improve vision (Schmucker and Schaeffel, 2006; Thompson et al., 2014). The combination of these assessments has the enormous potential to increase our knowledge of the normal function of the retina and visual system and of disease mechanisms to both enable and hasten the development of much needed novel effective therapies.

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Abbreviations

AOS accessory optic system

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DS	direction-selective
ERG	electroretinogram
GON	Glaucomatous optic neuropathy
LGN	lateral geniculate nucleus
M	magnocellular
MT	medial temporal
OCT	optical coherence tomography
OKN	optokinetic nystagmus
OKR	optokinetic / optomotor reflex
ONH	optic nerve head
P	parvocellular
RGC	retinal ganglion cell
SC	superior colliculus
V	visual area
VOR	vestibular-ocular reflex

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- The manuscripts critically reviews psychophysical testing rodent models of glaucomatous optic neuropathy.
- A specific emphasis is placed on techniques measuring the optokinetic reflex.
- The review covers an emerging technology with increasing relevance for assessing visual impairment in pre-clinical studies.
- The review discusses the potential of integrating psychophysical testing into an array of outcome measures determining multiple aspects of visual function and performance.

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Table 1

Table comparing visual acuity and contrast sensitivity measurements among species, where the OMR was used to determine threshold levels.

Species	Age	Visual Acuity (cyc/deg)	Contrast Sensitivity	References
C57 mice	2-3m	0.4	-	(Joly et al., 2014)
	1-12m	0.45-0.5	-	(Ho et al., 2012)
	P70-P360	0.38	27.8	(Lu et al., 2010a)
	6w	0.379	-	(Franco et al., 2009)
	60-150d	0.399	~17-20	(Douglas et al., 2005)
	P24-adult	0.4	-	(Prusky et al., 2004)
Long-Evans rats	30d	0.54	56.15	(Cuenca et al., 2014)
	-	0.427	-	(McGill et al., 2012a)
	-	0.53	-	(McGill et al., 2007)
	60-150d	0.54	~35-40	(Douglas et al., 2005)
Zebrafish	adult	0.589	25.24	(Tappeiner et al., 2012)