Université de Montréal

Towards a clinical test sensitive to the efficiency of photoreceptors to detect light

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Ce mémoire intitulé

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Résumé

La dégénérescence maculaire liée à l'âge (DMLA) est connue comme la principale cause de perte de vision chez les personnes âgées. Étant donné que la DMLA est une maladie progressive, un diagnostic plus précoce des signes et des symptômes peut permettre une intervention plus tôt et réduire la perte de vision à venir. Cependant, le premier stade de la DMLA est généralement asymptomatique alors qu'une déficience visuelle apparaît à des stades plus avancés de la maladie. Des découvertes récentes suggèrent qu'une diminution de la détection de la lumière par les photorécepteurs est un signe précoce de DMLA. Cependant, les tests fonctionnels cliniques actuels tels que l'acuité visuelle (AV) et la sensibilité au contraste (SAC) semblent être peu sensibles à une réduction de taux de détection des photorécepteurs puisque les patients au premier stade de la DMLA ont généralement une AV et une SAC dans les limites normales. Néanmoins, un test fonctionnel récemment développé, nommé le bruit photonique, devrait être sensible à une réduction de la détection de la lumière par les photorécepteurs. Dans ce mémoire, nous avons comparé différents tests potentiellement sensibles à une réduction du nombre de photons détectés par la rétine. Un test capable de détecter une réduction du nombre de photons détectés serait particulièrement utile s'il était spécifiquement sensible au taux de détection sans être sensible à d'autres facteurs tels que le flou optique. Des filtres de densité neutre ont été utilisés pour manipuler la quantité de lumière détectée par les photorécepteurs et différentes lentilles d'essai pour manipuler le flou de l'image de la rétine. Dans la première étude, les résultats ont montré que le bruit photonique et la sensibilité au mouvement à 15 Hz sont plus sensibles au taux de détection des photorécepteurs que les tests cliniques d'AV et de SAC. Les résultats de la deuxième étude ont montré que la SAC à faible luminance était plus sensible à une réduction de la détection de la lumière par les photorécepteurs que d'autres mesures cliniques de l'AV et de la SAC. Même si le bruit photonique et la sensibilité au mouvement à 15 Hz pourraient être des tests utiles pour détecter une diminution du taux de détection des photorécepteurs, ils nécessitent un écran avec des propriétés spécifiques ; ils sont donc actuellement difficilement applicables en clinique. La SAC à faible luminance a montré une excellente efficacité pour détecter une diminution du taux de détection des photorécepteurs et est facilement utilisable en clinique. Par conséquent, la SAC à faible luminance pourrait être un outil diagnostic utile pour le dépistage des premiers stades de la DMLA et favoriser une prise en charge plus tôt de la maladie.

Mots-clés : Dégénérescence maculaire liée à l'âge, taux de détection, acuité visuelle, sensibilité au contraste, bruit photonique, sensibilité au mouvement, photorécepteurs

Abstract

Age-related macular degeneration (AMD) is known as the leading cause of vision loss among elderly. Since AMD is a progressive disease, an earlier diagnosis of the signs and symptoms may allow an earlier intervention to postpone the upcoming vision loss. However, the early stage of AMD is usually asymptomatic while visual impairment appears in more advanced stages of the disease. Recent findings suggest that reduced detection of light by photoreceptors is an early sign of AMD. However, current clinical functional tests such as visual acuity (VA) and contrast sensitivity (CS) seem not to be very sensitive to a reduction in the detection of light since patients with early AMD generally had a normal VA and CS. A recently developed functional test, namely, photon noise should be sensitive to reduced light detection by photoreceptors. In this thesis, different tests that could be potentially sensitive to a reduction in the number of photons detected by the retina were compared. A test capable of detecting a reduction in detection of light would be particularly useful if it was specifically sensitive to the detection rate without being sensitive to other factors such as blur. Neutral density filters were used to manipulate the amount of light detected by the photoreceptors and different trial lenses to manipulate the blur of the retinal image. In the first study the results showed that photon noise and motion sensitivity at 15 Hz are more sensitive to the detection rate of photoreceptors than clinical VA and CS tests. The results of the second study showed that low-luminance contrast sensitivity (LLCS) is more sensitive to light detection by photoreceptors than other clinical measures of VA and CS. Although photon noise and motion sensitivity at 15 Hz could be useful tests to detect a decrease in the detection rate of photoreceptors, they require a screen with specific properties and, therefore, they are not easily accessible under clinical conditions. LLCS as an easily applicable clinical test showed to have an outstanding efficiency to detect a decrease in the detection rate. Therefore, LLCS could be a useful diagnostic tool for the early signs of AMD that could, in turn, lead to slow down the progress of the disease.

Keywords: Age related macular degeneration, detection rate, visual acuity, contrast sensitivity, photon noise, motion sensitivity, photoreceptors

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List of Acronyms and Abbreviations

AMD: Age-Related Macular Degeneration

AUC: Area Under the Curve

CC: Choriocapillaris

CNV: Choroidal Neovascularization

CS: Contrast Sensitivity

LLCS: Low-Luminance Contrast Sensitivity

LLVA: Low-Luminance Visual Acuity

ND: Neutral Density

OCT: Optical Coherence Tomography

PHCS: Pinhole Contrast Sensitivity

PHVA: Pinhole Visual Acuity

ROC: Receiver Operating Curve

RPE: Retinal pigment epithelium

VA: Visual Acuity

VEGF: Vascular Endothelial Growth Factor

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Introduction

Retinal diseases that damage photoreceptors can lead to vision loss. Photoreceptors are light-sensitive neurons in the neurosensory layer of the retina. Retina has two types of photoreceptors, rods and cones. Cones function under bright light (photopic vision) while rods function under low light levels (scotopic vision). Photoreceptors are responsible for phototransduction process, in which they detect light and convert it into an electrical signal. These signals are then conveyed to the brain through optic nerve. Since phototransduction is the basis of the sense of sight (Molday & Moritz, 2015), damage to photoreceptors due to retinal diseases may impair their ability to detect light. Consequently, severe damage to photoreceptors leads to severe visual impairments.

For some progressive retinal diseases, early detection of photoreceptor damage can be critical to enable early intervention (Boyer et al., 2007; Kaiser et al., 2007). Photoreceptor damage can be detected using different approaches including physiological (based on the structural changes in photoreceptors) and functional (based on the functional changes in photoreceptors). Previous studies have shown that for some retinal diseases, functional changes appear before structural changes (Owsley, Jackson, White, Feist, & Edwards, 2001). On the other hand, some visual functions such as visual acuity (VA, ability to see details) may remain intact at early stages of the disease when the photoreceptor damage is not severe. Therefore, a functional approach might help earlier detection of photoreceptor damage if it targets the right visual functions. Finding a test that can help to detect a modest decline in visual function may lead to earlier detection of photoreceptor damage that happens in some progressive retinal diseases. Therefore, such a test may help earlier diagnosis of progressive retinal diseases affecting photoreceptors.

Age-related macular degeneration

An example of the retinal diseases damaging photoreceptors is age-related macular degeneration (AMD), which is the most prevalent disease of the retina causing vision loss among older adults throughout the world and accounts for 8.7 percent of worldwide blindness (Klaver et al., 2001; Klein, Klein, & Cruickshanks, 1999; Wong et al., 2014). Besides that, AMD imposes financial burden on patients and impacts the economy. A recent study found a total annual cost of $18,943 for newly diagnosed AMD patients (Almony et al., 2021). AMD has an annual economic

burden of $2.6 billion on Canada's gross domestic product (M. Brown et al., 2005). Besides the economic impact, AMD severely affects the quality of life of patients (Coleman et al., 2010; Hassell, Lamoureux, & Keeffe, 2006; Mitchell & Bradley, 2006). The increased vision loss with the progress of the disease is also associated with an increased risk of depression, anxiety, and suicide (Casten & Rovner, 2008; T. Johnson, Rovner, & Haller, 2014). Studies revealed that 25 to 45 percent of older individuals with visual impairment experience depressive symptoms (Burmedi, Becker, Heyl, Wahl, & Himmelsbach, 2002; Dawson, Mallen, Gouldstone, Yarham, & Mansell, 2014; O'Donnell, 2005).

AMD is a vascular-metabolic-inflammatory disease in the retina that affects different structures of the eye such as photoreceptors, retinal pigment epithelium (RPE), choriocapillaris (CC, vascular layer of choroid that supplies nutrients and oxygen to RPE and retinal outer layer), etc. AMD gradually impairs vision and eventually causes a death of photoreceptor cells. The degeneration of the photoreceptors happens in the macula, which is the oval shaped central area of the retina with a high concentration of photoreceptor cells. The macula is responsible for central vision, therefore, deterioration of photoreceptors in the macula causes an irreversible loss of central vision. Consequently, patients have trouble with daily activities requiring central vision such as driving, reading, writing, navigating stairs, etc (Taylor, Hobby, Binns, & Crabb, 2016). Impaired social interaction due to difficulty recognizing faces and facial expression is another problem that patients with AMD may experience (Lane et al., 2018).

AMD can be classified into dry (atrophic or non-exudative) and wet (neovascular or exudative) forms. Dry AMD is more prevalent and accounts for 85 percent to 90 percent of the cases (Ambati & Fowler, 2012). In the dry form, the presence of drusen causes atrophic areas in the retina, but it does not involve exudation or leakage from blood vessels, therefore it is called dry, atrophic, or non-exudative. Dry AMD progresses slowly over years and may cause larger atrophic areas in the retina that are known as geographic atrophy. In some patients, AMD may progress into the wet form. Wet AMD is characterized by the presence of new vessels (i.e., neovascularization) that may leak blood and fluid; therefore, this form is known as neovascular, wet or exudative AMD. Wet AMD is less prevalent (10 to 15 % of the cases), but it counts for 90% of significant vision losses due to AMD (Age-Related Eye Disease Study Research, 2000; Ferris, Fine, & Hyman, 1984; Smith et al., 2001).

Pathophysiology and clinical features of AMD

The exact etiology of AMD is yet unknown. Aging is the most significant risk factor for progression of AMD (Hyman & Neborsky, 2002; VanNewkirk et al., 2000), therefore features of aging may contribute to the development of AMD. With age, accumulation of heterogeneous debris, proteins and lipids between RPE and Bruch's membrane form yellowish deposits known as drusen. The presence of drusen and macular pigmentary abnormalities which may be due to RPE dysfunction characterise the early stage of dry AMD (Bhutto & Lutty, 2012). At this stage, patients are usually asymptomatic, but some patients may experience mild visual distortion. A limited number of small-scale hard drusen (with a diameter of 63 μm or smaller) are part of normal aging and do not considerably impair vision (Klein, Klein, & Linton, 1992). However, even a minimal area of small drusen is associated with 50% increased chance of AMD progression (Klein et al., 2015). Increase in the number and size of drusen damages the RPE which has several important roles that are essential for renewal of photoreceptors such as transport of the nutrients, ions and water, phagocytosis of the shed membranes of the photoreceptors, etc. (Sparrow, Hicks, & Hamel, 2010). RPE damage and the subsequent inflammatory response lead to the degeneration of photoreceptors (Fritsche et al., 2014). With the progress of the disease to later stages, loss of RPE causes degeneration of the photoreceptors or atrophic areas in the macula known as geographic atrophy (McLeod et al., 2009; Sunness, 1999). Geographic atrophy progresses slowly (Joachim et al., 2013; Sunness, 1999), and patients may notice a scotoma in the center of their visual field, which enlarges slowly and affects activities requiring central vision such as reading, driving, recognizing faces, etc. (Taylor et al., 2016). The progress of a scotoma to more advanced stages can cause complete loss of central vision. However, at an early stage, fovea (a small pit in macula, responsible for high-acuity vision) is often spared from degeneration (Bird, Phillips, & Hageman, 2014).

Dysfunction of RPE cells may lead to CC loss (Korte, Reppucci, & Henkind, 1984) which is the main characteristic of wet AMD. The toxic environment of the CC due to accumulation of proinflammatory and complement components can cause loss or dysfunction of CC, which makes the adjunct RPE layer hypoxic (Kauppinen, Paterno, Blasiak, Salminen, & Kaarniranta, 2016). Hypoxic RPE cells will then secrete some angiogenic substances including vascular endothelial growth factor (VEGF), transforming growth factor beta and basic fibroblast growth factor (Adamis et al., 1993; Kitaoka, Bost, Ishigooka, Aotaki-Keen, & Hjelmeland, 1993; Sternfeld, Robertson,

Shipley, Tsai, & Rosenbaum, 1989). These factors can ruin the balance between angiogenic and anti-angiogenic growth factors, which leads to the new vessels development from CC known as choroidal neovascularization (CNV). Wet AMD is characterized by the presence of CNV. RPE and CC have a mutualistic relationship therefore pathology and dysfunction of each component will compromise either or both components (Bhutto & Lutty, 2012). The loss of the CC stimulates growth of drusen since ejection of the waste will be limited (Friedman, Smith, & Kuwabara, 1963). Accumulation of deposits in Bruch's membrane increases its thickness (Guymer, Luthert, & Bird, 1999) which at the non-exudative stage may forms cracks in it. In some patients, CNV may extend anteriorly through these cracks (Spraul, Lang, Grossniklaus, & Lang, 1999). Subretinal or intraretinal hemorrhage and exudation of fluid from these vessels can lead to sub-retinal fibrotic scars followed by destruction of photoreceptors, RPE and choroidal vessels. Hemorrhage can also raise RPE and macula from their normal position (Spaide et al., 2020). Therefore, at a neovascular stage, patient notices a rapid progressive loss of central vision with relative or absolute scotoma of the central vision and metamorphopsia (distortion in visual targets).

Risk factors for AMD

There are many risk factors for AMD. In fact, the progression of AMD is complicated and is not due to only one factor. The etiology of AMD is a confluence of genetic, environmental and lifestyle factors (Chakravarthy et al., 2010; Heesterbeek, Lorés-Motta, Hoyng, Lechanteur, & den Hollander, 2020). Risk factors of AMD can be divided into non-modifiable and modifiable risk factors.

Non-modifiable risk factors

Aging, genetic factors, ethnicity and sex are several of the non-modifiable risk factors associated with AMD, meaning that these factors cannot be altered or controlled by intervention, environment, or behaviour.

Aging: Aging is the most significant risk factor for AMD among individuals of 60 years old and older (Joachim et al., 2013; Shim, Kim, Bae, Yu, & Song, 2016). Early and late AMD have been reported to affect 24.1 and 2.2 percent of the people aged over 60 in Europe, respectively (Li et al., 2020). Previous reports showed the risk of AMD is 14.1 percent higher for people aged over 85 years compared to those aged 55 to 59 years (Colijn et al., 2017).

Genetic factors: Studies have shown a strong genetic component associated with AMD. Individuals with the highest genetic risk has shown to be 44 times more likely to have advanced AMD compared to those with the lowest genetic risk (Fritsche et al., 2013). Both common and rare variants at 34 different loci are currently found to associate in the risk of AMD development (Fritsche et al., 2016). Common variants on complement factor H and *ARMS2/HTRA1* loci, are associated with a significant risk of AMD progression (Joachim, Mitchell, Rochtchina, Tan, & Wang, 2014; Y. Yu, Reynolds, Rosner, Daly, & Seddon, 2012). Genetic variants in lipid related genes such as those involved in lipid metabolism and transfer are also found to associate with a higher risk of AMD (Chen et al., 2010; Conley et al., 2005).

Ethnicity: Studies found different prevalence for the two forms of AMD among individuals of different ethnic groups. The causes of the different prevalence among different ethnicities are not well known. Racial variations in melanin content (Weiter, Delori, Wing, & Fitch, 1985) and variation in prevalence and impact of genetic markers (Klein et al., 2013) are two non-modifiable causes likely contributing to this difference. Environmental/clinical factors are modifiable causes that may contribute to this difference (Klein, Knudtson, Cruickshanks, & Klein, 2008; Seddon, Cote, Davis, & Rosner, 2003). The prevalence of AMD for Africans, Hispanics, Chinese and Caucasians was 2.4%, 4.2%, 4.6% and 5.4%, respectively (Chang, Bressler, Munoz, & West, 2008; Clemons, Milton, Klein, Seddon, & Ferris, 2005).

Sex: Sex is another non-modifiable factor suggested to affect the risk of AMD progression. Some studies suggested a higher risk of AMD progression in female individuals (Joachim et al., 2014), but this finding is controversial (Shim et al., 2016).

Modifiable risk factors

Smoking, body mass index, sunlight exposure, diet and physical activity are some of the modifiable risk factors for AMD, meaning that these factors can be altered or controlled by intervention, changing behaviour and environment.

Smoking: Smoking is a significant risk factor associated with AMD (Chakravarthy et al., 2010; Velilla et al., 2013), possibly due to the toxic components in tobacco that may contribute to biochemical pathways damaging RPE and choroidal vessels (Heesterbeek et al., 2020).

Body mass index: Some studies revealed that individuals with a higher body mass index (> 30) are at more risk of developing late AMD than those with a normal body mass index (20-25) (Clemons et al., 2005; Lechanteur et al., 2012; Seddon, Silver, Kwong, & Rosner, 2015). Measurements of waist-hip ratio, waist circumference have also confirmed that obesity increases the risk to develop AMD (M. K. Adams et al., 2011; Jaisankar et al., 2018; Seddon et al., 2003).

Sunlight exposure: Increased sunlight exposure might increase the risk of AMD by increasing oxidative stress, however it has not been yet confirmed that there is an association between increased sunlight exposure and disease progression (Zhou, Zhang, Yu, & Xie, 2018).

Diet: A diet with a high consumption of carbohydrates is associated with increased risk of AMD progression (Chiu, Milton, Klein, Gensler, & Taylor, 2007; Kaushik et al., 2008), while a Mediterranean diet that is rich in antioxidants and limited consumption of red meat is linked to a lower risk of AMD progression (Merle et al., 2019).

Physical activity: Physical activity is associated with lower risks of both early and late AMD progression (Erke et al., 2014; Mares et al., 2011; Munch, Linneberg, & Larsen, 2013; Nidhi, Mamatha, Padmaprabhu, Pallavi, & Vallikannan, 2013). Small (i.e., even as little as three hours per week) to moderate amount of physical activity, may be sufficient to lower the risk of AMD progression (McGuinness et al., 2017). However, another study did not find a significant difference in 15-year incidence of AMD among two groups of participants with high physical activity and low physical activity after controlling for other confounding factors like smoking and body mass index (McGuinness et al., 2016). This suggests that the impact of physical activity on the progression of AMD could be explained by the fact that more physically active patients also tend to have a healthier diet and lifestyle hence a lower risk of AMD progression (Knudtson, Klein, & Klein, 2006). Nonetheless, these results suggest that some environmental factors influence the progression of AMD, but it is unclear whether it is physical activity, healthier diet or some other lifestyle factor.

Among all the risk factors associated with AMD, aging appears to be the most significant one (Joachim et al., 2013; Shim et al., 2016). Aging showed the highest odds ratio (i.e., the probability of an event occurring as a proportion of the probability of an event not occurring) with an odd ratio increase from 1 at the age of 55-69 to 4.42-8.70 at the age of 70-79 and 18.8-32.3 at the age of 80-86. Smoking showed to be the second most consistent risk factor associated with

AMD with an odd ratio ranging from 2.39 to 4.22 (Velilla et al., 2013). It is yet to be discovered if altering the modifiable risk factors affects the impact of non-modifiable risk factors. Nonetheless, studies have shown that a combination of avoiding smoking with a diet rich in antioxidants and more physical activity might decrease the number of people who develop AMD (Carneiro & Andrade, 2017). Therefore, earlier diagnosis provides more time for clinicians to give their patients nutritional advice and dietary modifications may help delay the progression of the disease (Gerson, 2017).

Treatment of AMD

Dry AMD

Currently, there is no effective treatment for dry AMD, but studies are exploring new treatment methods targeting dry AMD such as complement system inhibitors, neuroprotective medications, visual cycle modulators, anti-inflammatory agents and cell-based therapy (Ammar, Hsu, Chiang, Ho, & Regillo, 2020). Some antioxidants are suggested to delay the progression of dry AMD. Age-related eye disease study showed that daily use of an antioxidant and mineral supplement consisting of vitamin C (500 mg), vitamin E (273 mg), beta carotene (15 mg), zinc (80 mg) and copper (2 mg) can reduce the possibility of intermediate AMD development to advanced stage by 25% ("AREDS report no. 8," 2001). However, these supplements might not be appropriate for all patients, since they may increase the risk of other diseases, for example high doses of vitamin E can increase the heart failure risk and death in diabetic patients and patients suffering from cardiac illnesses (Lonn et al., 2005). Moreover, beta carotene may increase the risk of lung cancer in smokers. Therefore, the AREDS 2 study removed beta carotene from this formulation and replaced it with two other Carotenoids (i.e., zeaxanthin and lutein). AREDS 2 added 2mg of zeaxanthin and 10mg of lutein to the previous formulation and found an 18% lower risk of advanced AMD with this formulation comparing to the previous formulation. It also found no significant impact of omega 3 on reducing the risk of AMD development to advanced stages ("AREDS report no.2," 2012).

Wet AMD

Current treatment for wet AMD includes anti-VEGF agents that can effectively block the pathophysiologic process of AMD, increase and maintain the function of the neurosensory retina,

and recover retinal morphology (Kaiser et al., 2007; Rosenfeld et al., 2006). Laser photocoagulation (cauterizing CNV with laser surgery) and photodynamic therapy (injection of a light-sensitive medicine into bloodstream to block formation of CNV) are two other methods that, although rarely used now, were once the mainstay of medical intervention for wet AMD.

The use of anti-VEGF agents, which is usually given via intravitreal injection, is an effective treatment method for wet AMD. These agents are based on the inhibition of VEGF proteins which trigger the formation of new vessels in AMD. Pegaptanib or Macugen (Gragoudas, Adamis, Cunningham, Feinsod, & Guyer, 2004) was the first agent licenced by US Food and Drug Administration (FDA). Ranibizumab (Lucentis) was the second approved agent which showed considerable visual gain (Jacob et al., 2017). Bevacizumab (Avastin), a similar drug approved to treat some forms of cancer, is another agent that showed to have similar efficacy as ranibizumab, but at a smaller cost. Therefore, bevacizumab is widely used off-label by clinicians to treat AMD for patients not able to pay therapy with the approved drug (Michels, Rosenfeld, Puliafito, Marcus, & Venkatraman, 2005). Aflibercept (Eylea) is another agent that received FDA approval and is now widely used. Studies showed that a 2-monthly given aflibercept after a loading phase of 4 weeks results in similar acuity gain as monthly ranibizumab (Waldstein et al., 2016). Brolucizumab (Beovu, Novartis, Basel, Switzerland) is the most recent FDA approved anti-VEGF agent. It has showed to have a high effectiveness for treatment of wet AMD plus a rapid clearance from systemic circulation (Dugel et al., 2017; Dugel et al., 2020). Some AMD studies are currently investigating several new anti-VEGF agents including conbercept, faricimab, KSI-310. Gene therapy treatments including subretinal delivery of RGX-314 RegenexBio and intravitreal delivery of ADVM-022 gene are also being investigated (Ammar et al., 2020). Currently, there is no effective treatment option for patients with macular damage.

MARINA and ANCHOR studies showed that treatment with anti-VEGF agents had a greater VA gain while the CNV lesion was smaller (Boyer et al., 2007; Kaiser et al., 2007). These studies also revealed that increasing age was associated with a lower VA gain with anti-VEGF treatment. Another study by Blinder and his colleagues revealed a better level of VA of photodynamic treatment when CNV lesion was smaller (Blinder, 2003). Therefore, early diagnosis is crucial to screen the progress of the disease and start treatment methods before the damage to macula occur. The Beaver Dam Eye Study showed that late AMD in one eye is linked to the

development of AMD in the other eye, therefore earlier diagnosis and consequently earlier intervention may also help delay the progression of the disease in the fellow eye (Gangnon et al., 2015).

Detection of AMD

Imaging techniques such as fluorescein and indocyanine green angiography, optical coherence tomography (OCT) and fundus autofluorescence are common methods of diagnosing AMD. Fluorescein and indocyanine green angiography are techniques of examining the blood flow in the retina and choroid. These techniques add a dye (fluorescein or indocyanine green) to blood circulation which can re-emit the blue light used to illuminate retina. Then, the emitted light is captured by a camera and processed into an image. These techniques can help determine the presence of choroidal neovascularization. Fundus autofluorescence uses a similar technique of imaging but does not require a dye to detect geographic atrophy as well as alterations in RPE (e.g., increased density of lipofuscin). Among all techniques, OCT is the main technique currently used to specify the different stages of AMD. OCT allows to detect neovascularization, subretinal fluid, drusen, retinal tear and other physiological AMD modifications. This technique uses rays of light to capture high resolution cross-sectional images of the retina. This technique is highly sensitive to active AMD, non-invasive, easily accessible, fast and easy to perform.

Measuring macular pigment (MP) density is another suggested technique for diagnosing AMD. Studies suggest that low-level of dietary pigments (e.g., lutein, zeaxanthin) is correlated with a higher possibility of AMD progression (Bernstein, Delori, Richer, van Kuijk, & Wenzel, 2010; Koushan, Rusovici, Li, Ferguson, & Chalam, 2013), since these pigments protect retina against short-wave light that can cause photochemical reactions (Beatty, Boulton, Henson, Koh, & Murray, 1999; Hammond Jr, Wooten, & Curran-Celentano, 2001). However, other studies found no significant change in the density of macular pigment among AMD patients comparing to young control group (Ciulla & Hammond, 2004). Since genetic factors are one of the risk factors to progression of AMD, genetic testing might have a diagnostic value. According to research, both frequent and unusual variants contribute to the advancement of AMD and individuals with either common or rare variants might be at higher risk of AMD progression (Warwick & Lotery, 2018). Genetic testing helps evaluate the risk of developing AMD, but it cannot be used as a diagnostic tool of AMD (Gerson, 2017).

Functional consequences

Some studies revealed that AMD remains undiagnosed in 25 percent of the cases due to the absence of structural findings (Neely et al., 2017). All imaging techniques, including widespread techniques to diagnose AMD, are based on finding structural changes in the retina. Therefore, patients with early AMD who do not show noticeable structural changes might be undiagnosed. In fact, relying on structural deficits can be a reason that functional deficits are overlooked (Gerson, 2017). Interestingly, studies revealed that functional consequences of AMD can appear before the clinical evidence of drusen (Dimitrov et al., 2012; Neelam, Nolan, Chakravarthy, & Beatty, 2009; Owsley et al., 2001). Therefore, earlier diagnosis or risk of developing AMD may be made by evaluating the visual function in the patients.

Retinal structural changes in AMD can lead to a variety of functional consequences such as reduced visual acuity, color vision deficiencies, visual field deficiencies, etc. (Hogg & Chakravarthy, 2006).

Visual acuity

One of the functional consequences of AMD is reduced ability of the eye to see fine spatial detail (reduced spatial resolution or visual acuity). However, several previous reports have shown that early AMD has only a modest impact on standard distance VA that remains relatively well preserved until later stages (Chandramohan et al., 2016; Pondorfer et al., 2020; Wu, Ayton, Guymer, & Luu, 2014). Furthermore, VA is highly sensitive to optical imperfection, so a reduced VA is likely to be due to optical factors rather than AMD in the earlier stages of the disease (C. A. Johnson & Casson, 1995; Poulere, Moschandreas, Kontadakis, Pallikaris, & Plainis, 2013). Interestingly, AMD has a larger impact on VA under low luminance condition (i.e., Low-luminance visual acuity, LLVA) compared to standard VA test that is measured under high luminance conditions (Puell et al., 2012). LLVA is suggested as a marker of subsequent vision loss in AMD (Sunness et al., 2008). However, other studies found that early AMD did not significantly affect LLVA (Owsley, Huisingh, Clark, Jackson, & McGwin, 2016; Wu et al., 2014; Wu, Ayton, Luu, & Guymer, 2015).

Standard VA is measured under high contrast conditions while, under low contrast conditions, VA is more affected by AMD since it demands a higher visual system capability. Low-contrast visual acuity is measured using a chart consisting of low contrast letters. However, studies

found no significant difference between the impact of AMD on low contrast acuity while comparing with high contrast acuity (Abadi & Pantazidou, 1996; A. J. Adams, Wong, Wong, & Gould, 1988; Lovie-Kitchin, 1989). The SKILL card is a test that allows the evaluation of low contrast visual acuity under reduced luminance condition. It consists of two back-to-back printed near acuity charts with one side at high contrast and high luminance (black letters on white background) and the other at low contrast and low luminance (black letters on grey background). The test score is calculated as the difference of the performance on low contrast-low luminance side versus high contrast-high luminance side. The combination of reduced contrast and reduced luminance increases the strain on the visual system (Luckiesh, 1944). A study showed that early AMD significantly affects the score of the SKILL card (Feigl, Brown, Lovie-Kitchin, & Swann, 2004). Therefore, the impact of AMD on low contrast visual acuity may be more pronounced at a low luminance intensity. Consequently, the SKILL card may be an interesting test to detect early signs of AMD.

Studies also suggest that the progress of AMD at non exudative stages affects near VA. However, near VA is affected when a central scotoma is forming (Lovie-Kitchin & Feigl, 2005). Therefore, near VA remains unaffected or little affected at early AMD in which a scotoma does not exist and cannot be a good indicator of early AMD.

Contrast sensitivity

Standard contrast sensitivity (CS) is the eye's ability to segregate an object from its background, therefore, a CS test is based on a measure of contrast threshold required to see an object. CS declines across all spatial frequencies with the progress of AMD (Kleiner, Enger, Alexander, & Fine, 1988; Owsley, 2011). However, further investigations found no impact of early AMD on CS compared to the performance of healthy patients (Owsley, Huisingh, et al., 2016). In addition to that, CS is sensitive to blur especially at high spatial frequencies (Marmor & Gawande, 1988; Venkataraman, Winter, Unsbo, & Lundström, 2015). Pelli-Robson as a common CS test is at lower spatial frequency but it still could be affected by blur and might not be a good marker of early AMD. Early AMD has shown to affect CS at low luminance conditions (i.e., Low-luminance contrast sensitivity, LLCS) more than standard CS that is measured under high luminance condition (Maynard, Zele, & Feigl, 2016).

AMD seem to have a bigger impact on temporal processing than spatial processing (Phipps, Dang, Vingrys, & Guymer, 2004). Temporal CS can be measured by using a moving stimulus (i.e., motion CS). Motion CS declines with aging across all temporal frequencies (Allard, Lagacé-Nadon, & Faubert, 2013; Owsley, 2011). This is consistent with previous research that showed a greater sensitivity loss with flicker stimuli (Mayer et al., 1994; Phipps et al., 2004). Indeed, the flicker sensitivity loss is more pronounced for high temporal frequencies (Bi, Gillespie-Gallery, Binns, & Barbur, 2016). On the other hand, motion CS also depends on luminance intensity. At low luminance levels, CS is limited by spontaneous neural activity at retinal level or early noise (i.e., linear law), at medium luminance levels CS is limited by stochastic photon detection (i.e., de Vries-Rose law) and at high luminance levels CS is limited by spontaneous neural activity at the cortical level or late noise (i.e., Weber's law; Silvestre et al., 2018, Allard & Arleo, 2017a). Indeed, motion CS at high temporal frequencies is proportional to luminance intensity, especially at lower luminance intensities (i.e., linear law, Watson 1986; Allard & Arleo, 2017b). Furthermore, motion CS at low spatial frequencies is less affected by optical factors (Owsley, 2011). Therefore, motion CS at high temporal and low spatial frequencies might be more affected by early AMD, especially when measured at low luminance levels.

Visual field

Early AMD has been reported to be associated with central field defect, commonly in the parafoveal area. The Amsler chart, preferential hyperacuity perimetry, shape-discrimination hyperacuity, macular mapping and noise field perimetry are some of the techniques used to find visual field deficits such as scotomas and metamorphopsia (Aulhorn & Köst, 1988; Loewenstein et al., 2003; Trevino, 2008; Wilkinson, Wilson, & Habak, 1998). However, studies suggest that AMD affects these visual field measurements only at more advanced stages (Bartlett, Davies, & Eperjesi, 2005; Faes, Bodmer, Bachmann, Thiel, & Schmid, 2014; Kaiser et al., 2013; Koike, Hohenberger, Wannamaker, Trivedi, & Kylstra, 2015). Microperimetry is a type of visual field measurement that evaluates sensitivity of the retina to light stimuli. Using microperimetry, several studies have found that early AMD reduces the retinal sensitivity to light stimuli (Parisi et al., 2007; Vujosevic et al., 2011). Therefore, microperimetry might be a useful test to detect AMD at earlier stages. However, microperimetry is not easily accessible in clinics because of its cost and time-consuming process.

Electrophysiology

AMD may affect the electrical activity of retinal cells in response to visual stimuli. Different electroretinogram (ERG) techniques currently are accessible to evaluate the electrical response of different retinal cells including photoreceptors. Early AMD was not found to affect full-field ERG significantly (Kader, 2017; Walter, Widder, Lüke, Königsfeld, & Brunner, 1999). Some studies found that early AMD causes an abnormal cone-mediated focal and multifocal ERG (Binns & Margrain, 2007; Moschos & Nitoda, 2018), while another study did not find a significant impact of AMD on multifocal ERG (Feigl et al., 2004; Kader, 2017). Moreover, multifocal ERG is sensitive to optical factors (Fortune & Johnson, 2002). Therefore, an abnormal multifocal ERG might not be due to AMD. Further investigations are required to evaluate the impact of early AMD on different ERG techniques.

Colour vision

Different aspects of colour vision including colour discrimination, colour matching and colour contrast are affected by AMD. Early AMD affects yellow-blue colour vision more than red-green which could be due to the more significant impact of AMD on short wave-length sensitive cone cells (Vemala, Sivaprasad, & Barbur, 2017). Farnsworth Munsell 100 Hue and Farnsworth D-15 Panels are two techniques to evaluate color vision; however, these tests may not be sensitive enough to detect subtle color defects associated with early AMD (Downie, Cheng, & Vingrys, 2014).

Cone contrast techniques such as the Rabin cone contrast test (Rabin, Gooch, & Ivan, 2011) and Color Dx (Walsh et al., 2016) allow an evaluation of color contrast sensitivity of each type of cone cell. Multiple studies have evaluated the impact of AMD on the cone contrast test. One study found a colour deficiency for all three types of cones (red, green and blue; Arden & Wolf, 2004), while another study only found an S-cone (blue) deficit (Holz et al., 1995) and one study found an L-cone (red) deficit (Chandramohan et al., 2016). These discrepancies among studies could be due to the impact of lens opacity on colour discrimination since lens opacity blocks visible light. especially the short wavelengths. Therefore, it can affect colour discrimination corresponding to short wavelength rays of light. Furthermore, recent investigations did not find a significant impact of early AMD on the cone contrast test outcome (White et al., 2020).

Light and dark adaptation

Dark adaptation is one of the visual functions that seems to be considerably affected by early AMD (Owsley et al., 2001). Dark adaptation is the ability of the eye to recover visual sensitivity in darkness after being exposed to an intense light and is measured by using a dark adaptometer device. A recent study found an age-related loss of light sensitivity and delayed rod-mediated dark adaptation even when eye health was good based on standard clinical eye exams (Owsley, McGwin, et al., 2016). This finding corresponds well with other findings suggesting that rods are lost earlier than cones in AMD (Medeiros & Curcio, 2001).

On the other hand, degeneration of rods will cause a misalignment in cones and thereby will reduce their sensitivity to light (Curcio, Millican, Allen, & Kalina, 1993; Panda-Jonas, Jonas, & Jakobczyk-Zmija, 1995). This reduced detection of light by photoreceptors could be a preliminary sign of the upcoming progression of AMD, since patients with a delayed dark adaptation showed to be twice as likely to develop clinically evident AMD (Owsley, McGwin, et al., 2016). Therefore, finding a functional test capable of detecting a reduction in the detection of light by photoreceptors might aid earlier diagnosis of AMD.

AMD has different functional consequences on visual acuity, contrast sensitivity, colour vision, etc. that remain overlooked in the current diagnostic techniques. Evaluating visual function with different functional tests could help to detect various functional deficits in the eye that might be signs of early AMD. Some of the visual functions that are considerably affected in early AMD are: dark adaptation, CS under low luminance conditions, low-luminance, low- contrast VA (SKILL card) and motion CS. Longer dark adaptation with aging can be due to a reduced sensitivity of photoreceptors to light (Owsley, McGwin, et al., 2016). Thus, many functional impacts of early AMD could be due to a reduced sensitivity of photoreceptors to light. Consequently, a test sensitive to the amount of light detected by photoreceptors could be useful to detect early signs of AMD and other retinal diseases affecting photoreceptors.

A novel functional test: the Photon noise test

The photon noise test is a recently developed functional test to evaluate the rate of photons detected by photoreceptors (Allard, Silvestre, Braham chaouche, & Arleo, under revision; Braham chaouche, Rezaei, Silvestre, Arleo, & Allard, 2021; Silvestre, Arleo, & Allard, 2018); it obviously

depends on the amount of light detected by photoreceptors. Thus, it could be useful to detect early signs of retinal diseases that affect the detection rate of photons by photoreceptors.

The number of photons detected by photoreceptors can be estimated based on three concepts. First, the detection of a photon by photoreceptors is probabilistic. Therefore, the number of photons detected by photoreceptors varies with time even when the luminance intensity is constant. This variability is a noise source, known as photon noise (Pelli, 1990). Interestingly, the variability in the number of photons detected follows a Poisson distribution: the variance in the photon detection equals the expected (or mean) quantity of photons detected (Hecht, Shlaer, & Pirenne, 1942; Mueller, 1951). Therefore, the mean number of photons being detected can be derived from the variability in the number of photons being detected (i.e., the photon noise).

Second, under some specific conditions, photon noise is the main noise source limiting contrast sensitivity (Figure 1, Silvestre et al., 2018). Specifically, a weak noise source has a negligible impact in the presence of a greater noise source; so, although various noise sources in the visual system can affect contrast sensitivity, only the greatest one considerably affects sensitivity. The conditions under which photon noise is the limiting noise source can be identified due to the properties of the photon noise. Because the number of photons detected follows a Poisson distribution, the impact of the photon noise on contrast sensitivity is proportional to the square root of the luminance intensity (Pelli, 1981; Pelli & Farell, 1999; Raghavan, 1995; Silvestre et al., 2018). If the variability is proportional to luminance intensity, then the standard deviation is proportional to the square root of the luminance intensity. Thus, the conditions under which photon noise is the main limiting noise source can be identified by measuring contrast sensitivity as a function of luminance intensity (blue area in Figure 1).

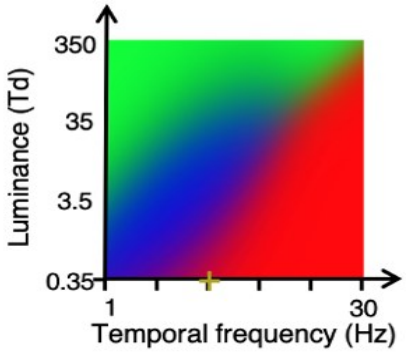

Figure 1. Limiting noise sources as a function of luminance intensity and temporal frequency. The blue area shows the viewing conditions (luminance intensity and temporal frequency) at which photon noise is the limiting internal noise source (Allard et al., under revision).

Third, the impact of an internal noise source (e.g., photon noise) can be evaluated by adding an external visual noise to the display (Figure 2, Pelli, 1981; Pelli & Farell, 1999; Raghavan, 1995). If the external noise added to the display has a weaker impact than the internal noise (flat asymptote, Figure 3), its impact would be negligible. Conversely, if the external noise has a greater impact than the internal noise (rising asymptote, Figure 3), then the impact of the internal noise would be negligible. The point at which the external noise starts to affect the contrast sensitivity (knee point, Figure 3) is the point at which the external noise has the same impact as the internal noise. This point is referred to as the equivalent input noise (Pelli, 1981, 1990) and provides a measure of the impact of the internal noise. Since the log-log slope for the rising asymptote is 1, and for the flat asymptote is 0, the knee point noise level can be evaluated by only two levels of added noise. Therefore, equivalent input noise can be derived by measuring contrast threshold with and without noise (Pelli & Farell, 1999).

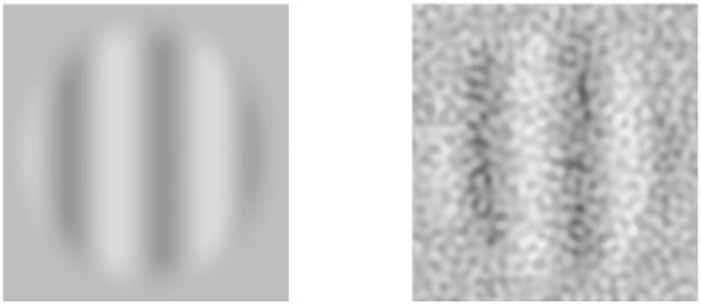

Figure 2. Examples of stimuli used to functionally evaluate the detection of light by photoreceptors.

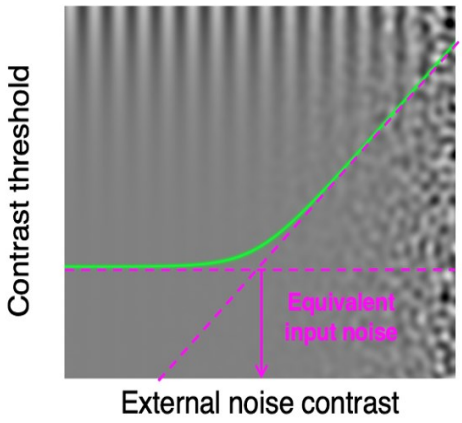

Figure 3. Contrast threshold as a function of external noise contrast, which can be used to evaluate the impact of the internal noise (equivalent input noise).

In summary, measuring the impact of the internal noise (i.e., equivalent input noise), under a condition in which photon noise is the limiting noise source, provides an estimate of the variability in the number of photons being detected and thereby provides an estimate of the mean number of photons actually being detected.

Motion Contrast Sensitivity

Another measure that is sensitive to the amount of light detected by photoreceptors is motion CS at high temporal frequencies. Indeed, motion CS at high temporal frequencies is proportional to luminance intensity even at high luminance intensities (i.e., linear law, Watson 1986; Allard & Arleo, 2017b). Thus, motion CS at high temporal frequencies would be sensitive to a reduced amount of light detected by photoreceptors. However, an abnormally low motion CS may not necessarily be due to a lower detection of light because motion CS does not depend solely on the detection rate of photoreceptors, it also depends on other processing factors such as neural noise, the temporal integration time of photoreceptors, and motion processing efficiency.

Contrary to motion CS that depends on various factors, the photon noise test should solely depend on the amount of light detected by photoreceptors. In fact, photon noise determines the amount of light detected by photoreceptors by measuring the difference between the contrast thresholds in the absence of external noise when performance is limited by photon noise and in high external noise. In the absence of external noise, performance is limited by photon noise and many other processing factors (i.e., calculation efficiency) and, in the presence of external noise,

the impact of the photon noise becomes negligible and performance is limited only by calculation efficiency (Silvestre et al., 2018). The subtraction of these two conditions provides an estimate of the photon noise, which directly depends on the amount of light detected by photoreceptors. On the other hand, motion CS at high temporal frequencies is proportional to luminance intensity (i.e., linear law, Watson 1986; Allard & Arleo, 2017b) in which case contrast thresholds are limited by early neural noise and calculation efficiency. Since the impact of early noise directly depends on the amount of light detected by photoreceptors (Silvestre et al., 2018) and early temporal integration (Allard & Arleo, 2017a), motion CS at high temporal frequencies depends on many factors. On the other hand, since motion CS limited by early noise is proportional to luminance intensity (i.e., linear law) and motion CS limited by photon noise is proportional to the square root of the luminance intensity (i.e., de Vries-Rose law; Pelli 1990; Braham chaouche et al., 2020), motion CS at high temporal frequencies is two times more sensitive to the amount of light detected by photoreceptors than photon noise. Furthermore, motion CS consists of only one measurement comparing to photon noise that needs two measurements. Therefore, motion CS is a faster test and could be helpful as a tool for screening retinal pathologies affecting the ability of photoreceptors to detect light. Normal results of motion CS would suggest that many processing factors (i.e., amount of light detected by photoreceptors, early temporal integration, early noise and calculation efficiency) are normal, but an abnormal motion CS at high temporal frequency might not necessarily be due to a reduced amount of light detected by photoreceptors as other processing steps of vision could be the cause. In sum, motion CS at high temporal frequency should be more sensitive to the amount of light detected by photoreceptors than photon noise, but it should also be less specific.

A clinically applicable test

As mentioned before, photon noise is a direct measure of the number of photons detected by photoreceptors. However, this test requires a screen with specific properties that is not easily accessible in clinic. Therefore, evaluating the capability of easily applicable clinical tests to detect the amount of light detected by photoreceptor might be useful. A test sensitive to the amount of light detected by photoreceptors could potentially help earlier diagnosis of AMD.

The number of photons detected by photoreceptors depends on two factors: the number of photons reaching the retina and the detection rate of photoreceptors (i.e., proportion of photons

detected). Therefore, a test sensitive to the number of photons detected by the photoreceptors would be equally sensitive to a reduction in luminance intensity and the detection rate of photoreceptors since both have the same functional consequence: less photons detected by photoreceptors. Thus, it is possible to estimate if a test would be sensitive to an impaired detection rate of photoreceptors by evaluating if it is sensitive to a reduction in luminance intensity.

The sensitivity of some clinical tests (e.g., VA, CS) to luminance intensity is already known. Reducing luminance intensity has a modest impact on VA. Previous studies showed a small change of 0.03 logMAR per one log unit of reduction in luminance intensity (Glover, Kelly, Wozniak, & Moss, 1999; Lee, Feis, & Clark, 2009). It should also be considered that VA is sensitive to optical factors such as a blur and pupil size. Thus, an abnormally low VA is more likely due to optical factors than a lower amount of light detected by photoreceptors (C. A. Johnson & Casson, 1995; Poulere et al., 2013).

Further reductions in luminance of the SKILL card by reducing the ambient luminance showed a linear reduction of the SKILL score with reducing luminance intensity. However, the high contrast side of the card showed small changes with the variations in the luminance intensity and the dependence of the test on luminance intensity was mainly caused by the low contrast side (Haegerstrom-Portnoy, Brabyn, Schneck, & Jampolsky, 1997).

CS at typical high luminance intensities depends on luminance intensity only at higher spatial frequencies (Haughom & Strand, 2013; Silvestre, Arleo, & Allard, 2019). Consequently, reduced luminance intensity has little impact on standard clinical measures of CS since they use medium spatial frequencies (i.e., Weber's law). On the other hand, CS is sensitive to blur across all spatial frequencies specially at higher spatial frequencies (Hairol, Arusulem, & Ying, 2017; Marmor & Gawande, 1988). Consequently, an abnormally low CS might not specifically be due to a reduced detection of light by photoreceptors. Therefore, standard VA and CS are easily accessible functional tests in clinics, but do not appear to be considerably affected by a reduction in the amount of light detected by photoreceptors.

The impact of reduced light detection is typically more pronounced at lower light levels. For instance, CS improves with luminance intensity at low luminance intensities and saturates at high luminance intensities (i.e., Weber's law; Pelli 1990, Silvestre er al., 2018). Thus, LLVA and

LLCS are expected to depend more on luminance intensity (Maynard et al., 2016; Wu et al., 2014) than standard VA and CS.

Another clinically accessible functional test is microperimetry. A previous study showed that reducing luminance intensity has a significant impact on microperimetry test results (Maynard et al., 2016; Nebbioso, Barbato, & Pescosolido, 2014). Therefore, microperimetry is sensitive to the amount of light detected by photoreceptors. Therefore, microperimetry might be a good indicator of reduced detection of light. However, microperimetry is a time-consuming test and may not be easily accessible in all clinics.

A study on the impact of reducing luminance intensity on multifocal ERG in three healthy subjects showed that reducing luminance intensity decreases the average amplitude and increases the latency of multifocal ERG (Yoshii et al., 2000). It should also be considered that ERG is sensitive to optical factors (Fortune & Johnson, 2002), therefore ERG may not be a good indicator of the reduced light detection.

Study Rationale

As mentioned before, widespread techniques to diagnose AMD, are based on identifying structural changes in the retina. Therefore, patients with early AMD who do not show noticeable structural changes might remain undiagnosed. On the other hand, functional consequences of AMD can appear before the structural changes. Therefore, earlier diagnosis or risk of developing AMD may be made by evaluating the visual function. Functional impacts of early AMD could be due to a reduced sensitivity of photoreceptors to light. Consequently, a test sensitive to the amount of light detected by photoreceptors could be useful to detect early signs of AMD and other retinal diseases affecting photoreceptors. Photon noise and motion CS at 15 Hz are two potential tests that are sensitive to the amount of light detected by photoreceptors. Therefore, the first study of this thesis evaluated the capability of photon noise and motion CS at 15Hz along with VA and CS as the most common functional tests. However, photon noise and motion CS at 15Hz are not currently easily implementable under clinical conditions because they require a dynamic display with specific properties. Adapting these tests for clinical use is not easy and would require a long process to develop a new apparatus. Therefore, before developing a new apparatus, it is important to seek more accessible tools that could be used instead. The second study of this thesis compared photon

noise and motion CS with various clinically accessible tests in their sensitivity to a reduction in light detection in order to find a test that is not only capable of detecting photoreceptor deficiencies affecting their detection rate, but also easily accessible in clinics. Finding a clinically accessible test that is also capable of identifying a reduced detection of light by photoreceptors might be helpful in earlier diagnosis of AMD.

It should also be considered that a decline in the visual function may not necessarily be due to reduced light detection by photoreceptors. An important factor that can affect the ability of a test to identify a reduction in the number of photons detected by photoreceptors is optical imperfection (i.e., blur). Indeed, a test sensitive to the amount of light detected by photoreceptors would be particularly useful if it is insensitive to optical imperfections. Otherwise, an abnormal result could be due to a deterioration of photoreceptors or to optical imperfections, which are common in elderly. Therefore, the studies in the current thesis tested the specific sensitivity of each test to the amount of light detected by photoreceptors by evaluating the ability of each test to discriminate between a reduced amount of light detected by photoreceptors and blurry vision (artificially induced using trial lenses).

Objectives

General objective

Finding an easily accessible functional test capable of detecting an abnormally low detection of light by photoreceptors

Specific objective 1

Compare the capability of psychophysical functional tests (i.e., photon noise and motion CS at 15 Hz) with current clinical functional tests (i.e., VA and CS) in detecting a reduced amount of light detected by photoreceptors.

The goal of this thesis was to find a test to evaluate the detection rate of light by photoreceptors. Therefore, the first study of this thesis compared novel psychophysical tests with current clinical tests in their capability to detect a reduced detection of light. This study, therefore, measured photon noise, motion CS at 15 Hz, VA and CS tests under different viewing conditions including normal (baseline) and reduced light detection. This study used neutral density filters to reduce the amount of light detected by photoreceptors. Then, the capability of the tests to dissociate between the normal (i.e., no filter added) and reduced detection of light (i.e., with filter added) conditions was evaluated. Moreover, a test capable of effectively identifying a reduced detection of light should ideally be insensitive to other factors. A factor that considerably affects vision is optical imperfection as a blurred retinal image can impact VA and CS. Therefore, the current study also evaluated the capability of the tests to dissociate between a reduced detection of light and increased blur (i.e., artificially induced using trial lenses). A test capable of effectively dissociating a reduced luminance condition from normal condition or a blurry condition might be helpful to detect earlier diagnosis of retinal diseases affecting photoreceptors.

Specific objective 2

Compare the capability of psychophysical tests (i.e., photon noise and motion CS at 15 Hz) with some clinically accessible functional tests (i.e., VA, low-luminance VA (LLVA), pinhole VA

(PHVA), CS, low-luminance CS (LLCS), pinhole CS (PHCS)) in detecting a reduced amount of light detected by photoreceptors.

To be clinically useful, a test capable of detecting reduced detection of light should also be easily accessible under clinical conditions. Although psychophysical tests might be sensitive to a reduction amount of light detected by photoreceptors, they are not easily accessible under clinical condition because they require displays with specific properties. Therefore, the second study was an endeavour to compare photon noise with several other clinical tests to find a test not only capable of discriminating a reduced detection of light from normal condition, but also easily accessible under clinical conditions. Therefore, the capability of the tests to dissociate between normal (i.e., no filter added) and a reduced amount of light detected by photoreceptors (i.e., with filter added) condition was compared. A test capable of effectively identifying a reduced detection of light should also be insensitive to blur. Therefore, the second study also evaluated the capability of the tests to dissociate between a reduced detection of light and increased blur. A test capable of effectively detecting a reduced amount of light detected by photoreceptors from normal condition or a blurry condition and easily accessible under clinical conditions might be useful to help earlier diagnosis of retinal diseases affecting the ability of photoreceptors to detect light.

Article 1: A new functional test sensitive to the amount of light detected by photoreceptors

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Status of the article: Submitted to Optometry and Vision Science journal

Contribution of the student: The candidate wrote and implemented the research protocol under supervision of her two directors and contributed to data collection. In addition, she participated in data processing and statistical analysis. She also contributed to writing of the article, which was edited by her two directors. The candidate is the sole first author of this article.

Abstract

Significance:

This study investigates a novel test sensitive to the amount of light detected by photoreceptors that might help earlier diagnosis of age-related macular degeneration (AMD) as a worldwide health concern with the aging of population.

Purpose:

Some retinal diseases, such as AMD, reduce the ability of photoreceptors to detect light at early stages even though standard clinical measures like visual acuity (VA) and contrast sensitivity (CS) remain relatively unaffected. Photon noise and motion CS at high temporal frequencies are two non-invasive functional tests, presumably sensitive to the amount of light detected by photoreceptors. This experimental study compared the capability of these functional tests to detect a reduction in the amount of light detected by photoreceptors.

Methods:

Twenty-one young healthy adults were recruited. The capability of six psychophysical tests (i.e., photon noise, motion CS at 15 Hz, Gabor VA, spatial CS at 0.75, 3 and 12 cpd) and three standard clinical tests (ETDRS VA, Pelli-Robson CS, Mars CS) to detect a reduction in detection of light by photoreceptors was compared when light level was reduced using neutral density filters of 0.5, 1.0 and 1.5.

Results:

The capability to detect a small reduction in detection of light by photoreceptors (filter=0.5) for photon noise test and motion CS test were near perfect (AUC=.95, AUC=.99, respectively) and significantly higher (p<.01) than the three standard clinical tests.

Conclusion:

Photon noise and motion CS at 15 Hz are more sensitive to a reduction in the amount of light detected by photoreceptors than some VA and CS standard clinical tests. Adapting these functional tests to clinical conditions could be useful to screen retinal diseases affecting the detection of light by photoreceptors.

Keywords

Photoreceptor, Detection rate, Retinal pathologies, Photon noise, Visual acuity, Contrast sensitivity, Motion contrast sensitivity

Introduction

Some studies suggest that age-related macular degeneration (AMD) affects the ability of photoreceptors to detect light many years before atrophic changes happen (Elsner, Burns, & Weiter, 2002; Owsley, 2016). Thus, a functional test sensitive to a lower detection of light by photoreceptors might be clinically useful for screening AMD at earlier stages. AMD affects both spatial and temporal aspects of visual processing, but standard measures of visual acuity (VA) and contrast sensitivity (CS) remain relatively preserved in early AMD (Owsley, Huisingh, et al., 2016). This is consistent with the fact that AMD affects temporal processing more than spatial processing (Mayer et al., 1994; Phipps et al., 2004; Seiple, Greenstein, & Carr, 1989).

The greater impact of AMD on temporal processing can be explained by the fact that temporal processing is particularly sensitive to the amount of light detected by photoreceptors, especially at high temporal frequencies. Indeed, temporal contrast sensitivity at high temporal frequencies is known to be proportional to luminance intensity (i.e., linear law) even at relatively high luminance intensities (Watson, 1986), whereas spatial contrast sensitivity is proportional to luminance intensity only at very low luminance intensities (Haughom & Strand, 2013; Pelli, 1990; Silvestre et al., 2018). Consequently, contrast sensitivity to high temporal frequencies should be particularly sensitive to the amount of light detected by photoreceptors.

On the other hand, the amount of light detected by photoreceptors can be functionally evaluated by measuring contrast sensitivity in the presence and absence of visual noise added to the display (i.e., luminance variability added to each pixel of the stimulus) under some specific conditions of luminance intensity, spatial frequency and temporal frequency (Braham chaouche, Silvestre, Trognon, Arleo, & Allard, 2020; Silvestre et al., 2018, 2019). Indeed, the external noise paradigm (Pelli, 1981; Pelli & Farell, 1999) can be used to evaluate the total variability within the visual system limiting CS (i.e., the equivalent input noise). Under some specific conditions, the main source of this variability comes from the variability in the amount of light detected by photoreceptors (namely, photon noise), which directly depends on the average amount of light detected by photoreceptors (Braham chaouche et al., 2020; Pelli, 1990; Silvestre et al., 2018, 2019). Note that when photon noise is the main source of noise limiting CS, CS is proportional to the square root of the luminance intensity (Pelli, 1990), which corresponds to the de Vries-Rose law (de Vries, 1943; Rose, 1948) and has been observed at low temporal frequencies and intermediate luminance intensities (Silvestre et al., 2018). Consequently, the evaluation of photon noise derived

from two measures of CS under specific visual conditions can be used to evaluate the amount of light detected by photoreceptors (Braham chaouche et al., 2020; Silvestre et al., 2018, 2019).

It could be clinically interesting to have a test that can quantify the efficiency of photoreceptors to detect light to determine whether the amount of light detected by photoreceptors is abnormally low or not. The main aim of this study was to compare the capability of different clinical and psychophysical tests to discriminate between normal and abnormal amount of light detected by photoreceptors (i.e., determine if the amount of light detected by photoreceptors was normal or reduced). The current study used neutral density (ND) filters to artificially reduce the amount of light detected by photoreceptors. A test capable of effectively discriminating the reduced detection of light by photoreceptors (i.e., added ND filter) from baseline condition (i.e., no ND filter) would be sensitive to a reduced light detection. Since photon noise and motion CS at high temporal frequencies depends considerably on the amount of light detected by photoreceptors (Silvestre et al., 2018; Watson, 1986) while VA and CS are little affected by luminance intensity (Owsley, Huisingh, et al., 2016), it can be hypothesised that photon noise and motion CS at high temporal frequencies can better discriminate between a reduced light detection (i.e., with ND filters) from baseline condition (i.e., no ND filter) than VA and CS.

Furthermore, a test sensitive to the amount of light detected by photoreceptors would be particularly useful if it is insensitive to other common visual deficiencies such as optical imperfections. To test the specificity of each test to the amount of light detected by photoreceptors, the current study also evaluated if each test can discriminate between a reduced amount of light detected by photoreceptors (i.e., with ND filters) with blurry vision (artificially induced using trial lenses). Since photon noise and motion contrast sensitivity will be measured at low spatial frequencies (0.5 cpd), it should be hardly affected by moderate amounts of blur. Therefore, it can be hypothesized that photon noise and motion CS will be also more capable to discriminate a reduced amount of light detected by photoreceptors from increased spatial blur.

Method

Observers

Twenty-one healthy adults between 18 and 30 years old were recruited through the community of the School of Optometry of the Université de Montréal. After giving informed

written consent, each observer was screened and included only if his/her best corrected visual acuity (VA) was better than 20/25, he/she had no known history of ophthalmic or systemic diseases and was not taking medications that may affect vision. This research was reviewed by an independent ethical review board (Comité d'éthique de la recherche clinique of the Université de Montréal) and conforms with the principles and applicable guidelines for the protection of human subjects in biomedical research (See Appendix C).

Tests

The study included potential tests to detect reduced light detection including psychophysical tests that are performed in the laboratory and the tests performable under clinical conditions. Each test is defined as a functional measurement (e.g., CS or VA) that can be potentially used to detect an abnormal detection of light by photoreceptors. Hence, measuring VA or CS under different conditions (e.g., contrast sensitivity under different spatial frequencies) are defined as separate tests. Therefore, the current study evaluated the ability of three clinical (VA with the ETDRS chart, CS with the Pelli-Robson and Mars charts) and six psychophysical (photon noise, motion CS at high temporal frequencies, Gabor VA, spatial CS at 0.75, 3 and 12 cycles per degree) tests to detect a lower amount of light detected by photoreceptors under different viewing conditions**.** The spatial CS and VA tests were psychophysically assessed in the lab using a computer screen to compare with the similar clinical tests.

Clinical tests

Three clinical tests were performed in a standard eye-exam clinical room.

VA with ETDRS chart. VA was measured at 4 meters. The observer read as many lines of letters as possible, and VA was recorded in logMAR units. If the observer missed one or two letters from the last readable line, 0.02 logMAR units were added per letter missed. If the observer was able to read one or two letters of the following line, 0.02 logMAR units were subtracted per correct answer (Shamir, Friedman, Joskowicz, Mimouni, & Blumenthal, 2016).

CS with Pelli-Robson chart. CS with the Pelli-Robson chart was measured at 1 meter. To achieve a given CS, the observer needed to read successfully all three letters with the same CS value (Mäntyjärvi & Laitinen, 2001).

CS with Mars chart. CS with Mars chart was measured at 40 centimeters. The measurement was interrupted after two consecutive mistakes were made. The CS value was determined by the last letter correctly reported minus 0.04 log units for any mistakes made previously (Dougherty, Flom, & Bullimore, 2005).

Psychophysical tests

The psychophysical tests were performed in a lab with stimuli presented on a 22.5-inch LCD monitor designed for psychophysics (VIEWPixx), which has a 120-Hz refresh rate and a spatial resolution of 1920x1080 pixels. At the viewing distance of 4 meters, the spatial resolution of the screen was 256 pixels/degree of visual angle. The monitor was the only source of light in the room. The output intensity of each color gun was carefully linearized using a Minolta photometer. The Noisy-bit method (Allard & Faubert, 2008) implemented independently to each gun made the 8-bit display perceptually equivalent to an analog display having a continuous luminance resolution.

For all the six psychophysical tests, the stimuli were sinewave gratings (Figure 4). These psychophysical tests relied on measuring contrast thresholds except for VA, which measured high spatial frequency thresholds. All thresholds were measured using a 3down1up staircase procedure (Levitt, 1971) interrupted after 14 inversions. The thresholds were estimated as the geometric mean of the last 10 inversions. For the photon noise and motion CS at 15 Hz tests, observers were asked to discriminate the drifting direction of the Gabor patch (left or right). For VA and spatial CS, the task consisted in identifying the orientation (horizontal or vertical) of a static Gabor patch. Stimuli were presented for 500 ms including half-cosine onset and offset ramps of 125 ms. The spatial window was circular, and its size depended on the spatial frequency of the grating: diameter set to two cycles of the sinewave gratings plus a half-cosine ramp equal to 1/8 of a cycle. The observer answered by pressing one of two keyboard keys.

Photon noise. Photon noise, which is inversely proportional to the amount of light detected by photoreceptors, can be derived from contrast thresholds in presence (c_N) and absence (c_0) of visual noise under specific conditions (Braham chaouche et al., 2020). The spatial frequency of the grating was set to 0.5 cpd and the temporal frequency was set to 2 Hz. In the absence of noise, the luminance intensity was set to 2.5 cd/m^2. Under these settings, the main internal noise source is known to be photon noise (Braham chaouche et al., 2020). In the presence of noise, the luminance

intensity was set to 50 cd/m^2. The external noise added to the stimulus was truncated filtered noise (Jules Étienne, Arleo, & Allard, 2017) with a low-pass filter with a cut-off frequency of 1 cpd, temporally white (refreshed at 120 Hz), truncated at 1 standard deviation and set at 25% contrast, which resulted into a noise energy (N) of 323 µs deg^2. Measuring contrast thresholds under these two conditions enables to evaluate the photon noise using the following equation(Pelli & Farell, 1999):

$$photon\ noise = \frac{N}{\frac{c_N^2}{c_0^2} - 1},$$

where N is the energy of the external noise.

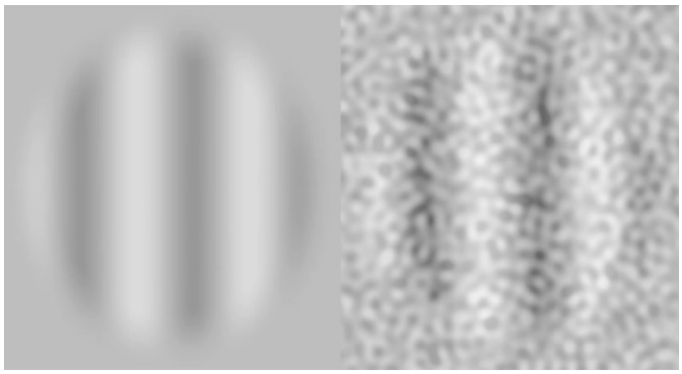

Figure 4. Examples of Gabor stimuli that were used to measure contrast sensitivity and visual acuity in the psychophysical lab conditions. Stimuli were sinusoidal gratings without (left) and with (right) visual noise.

Motion CS at 15 Hz. The spatial frequency, temporal frequency and luminance intensity were chosen to maximize the impact of the detection of light by photoreceptors on motion CS: 0.5 cpd, 15 Hz and 25 cd/m^2. Under these conditions, motion CS is known to be proportional to luminance intensity (Braham chaouche et al., 2020; Watson, 1986).

Spatial CS at low, medium and high spatial frequencies. For spatial CS tests, the stimuli were static, and the spatial frequency were either low, medium or high (0.75, 3 or 12 cpd). The display luminance intensity was relatively high to be analogous to clinical conditions: 50 cd/m^2.

VA with sinewave gratings. Contrast was fixed to 100% and the stimuli was static. The display luminance intensity was also 50 cd/m^2.

Viewing conditions

All tests were performed monocularly with the non-dominant eye covered. The dominant eye was determined using the Mile's test. Observers were wearing trial frames with their optimal correction for each testing distance, which varied across conditions. To maximize control of retinal illumination, observers wore an artificial pupil of 3mm positioned at the slot of their trial frame closest to the dominant eye.

Each of the nine tests was performed under seven viewing conditions. The baseline condition (no deficiency simulated) was performed without any ND filter and no optical blur was induced. The amount of light detected by photoreceptors was reduced under three viewing conditions using ND filters of 0.5, 1 and 1.5 density, which reduces luminance intensity by a factor of 3.1, 10 and 31, respectively. Furthermore, three conditions simulated optical degradations using convex lenses to create retinal blur: +0,50, +1,00 and +2,00D. Since the observers were corrected for the testing distance, adding a positive lens caused retinal blur.

Testing order

A total of 9 tests were conducted (3 clinical + 6 psychophysical) for each of the 7 viewing conditions (baseline, ND filter 0.5, 1.0 and 1.5, and blur +0,50, +1,00 and +2,00D), resulting into 63 measurements. Each measurement lasted about 2 minutes on average, resulting in a total of about two hours of testing. The clinical and psychophysical tests were performed in two separate sessions and the order of the two sessions were randomized. Within each session, the 7 viewing conditions were performed in a random order. For each viewing conditions, the tests (either three clinical tests or six psychophysical tests) were performed in a random order.

Statistical Analysis

The capability of each test to detect a reduced amount of light detected by photoreceptors was quantified by evaluating the area under the curve (AUC) of a receiver operating characteristic (ROC) curve. The AUC quantified the capability of a test to discriminate the lower luminance intensity condition relative to another condition. The AUC for the nine tests was calculated over a range of 12 combinations of viewing conditions: 3 conditions in which the amount of light detected by photoreceptors were reduced (0.5, 1.0 and 1.5 ND filters) relative to the 4 viewing conditions in which the amount of light detected was unaffected (baseline + 3 blur levels). The AUC of two

tests (e.g., photon noise and VA with ETDRS chart) were statistically compared using the StAR tool (Vergara, Norambuena, Ferrada, Slater, & Melo, 2008).

Results

Figure 5 represents the 9 types of measurement (i.e., 9 graphs) for the 7 viewing conditions (x-axis). Figure 6 represents the ROC curves derived from these data for the 9 tests illustrating the capability of each test to discriminate a condition with a reduced light detection (ND filters of 0.5, 1.0 or 1.5, left, middle and right columns, respectively) from a condition without a reduced light detection (baseline and +0.50, +1.00 and +2.00D blur conditions, first to forth rows, respectively). Thus, each ROC curve of a specific graph represents the capability to discriminate whether the amount of light detected by photoreceptors was reduced with a ND filter or not (baseline and blur conditions). The first row represents the ROC curves for discriminating a reduced light detection (ND filter of 0.5, 1.0 and 1.5, for left, middle and right graphs) relative to the baseline condition (i.e., no ND filter, no blur). As can be seen (especially for ND filter=0.5), the photon noise and motion CS at 15 Hz tests (green curves) were better to discriminate a reduced light detection relative and the baseline condition than the seven other tests (three clinical tests in red, psychophysical assessment of the VA in yellow and spatial CS at different spatial frequencies in blue). Indeed, the AUC for the photon noise and motion CS at 15 Hz tests were close to 1 even for detecting a light detection reduction of 0.5 log units (~3.2x; i.e., top-left graph in Figure 6, and ND filter 0.5 in Figure 7), whereas the seven other tests approached a AUC of 1 for detecting a light detection reduction of 1.5 log units (~31x; i.e., ND filter=1.5 vs baseline, top-right graph in Figure 6, and ND filter 1.5 in Figure 7). The greater AUC for each of the photon noise and motion CS at 15 Hz tests compared with each of the standard clinical tests (ETDRS visual acuity, Pelli-Robson CS and Mars CS) was found to be significant ($p<.01$ in all cases).

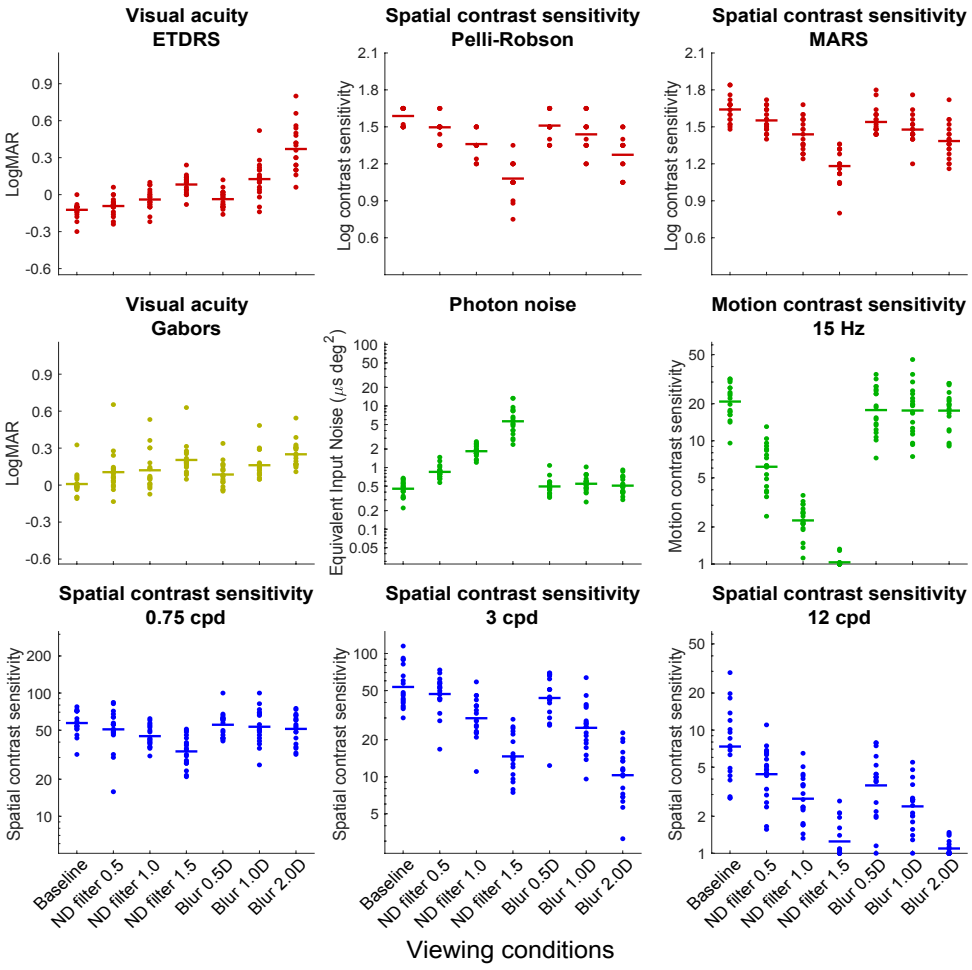

Figure 5. Results for each test (1 graph per test) as a function of the 7 viewing conditions (x-axis). The baseline (first conditions to the left of each graph) represents the viewing condition with no filter and no blur lens. The second, third and fourth conditions represents a reduction in luminance intensity (ND filter of 0.5, 1.0 and 1.5, respectively). The fifth, sixth and seventh conditions represents the blurry conditions (blur of 0.5, 1.0 and 2.0D, respectively). Each dot represents a measure of an observer. The horizontal lines represent the means in log units. The colors are set to match the tests with the subsequent Figures.

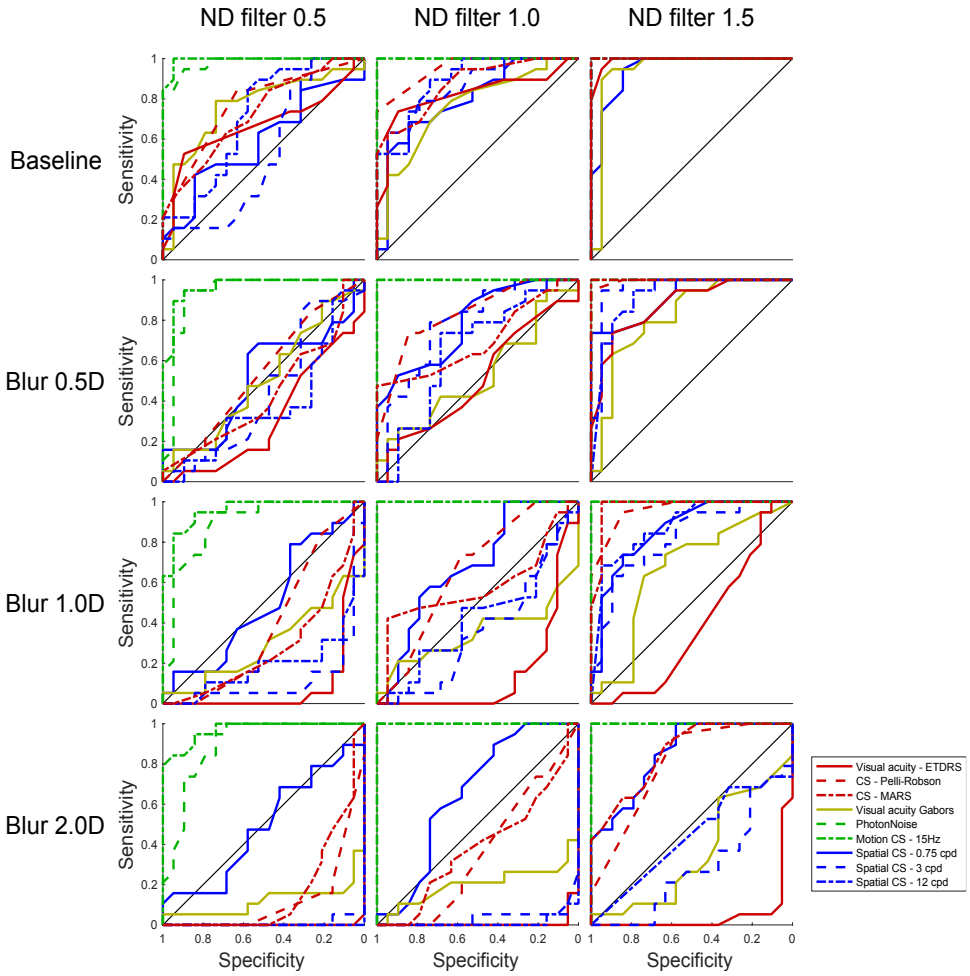

Figure 6. ROC curves representing the capability of each test to discriminate a reduction in luminance intensity (i.e., ND filter of 0.5, 1.0 and 1.5 represented in the first, second and third columns, respectively) from the baseline condition (i.e., no luminance reduction and no blur, first row) or blurry conditions (i.e., blur of 0.5, 1.0 and 2.0D represented in the second, third and fourth row, respectively).

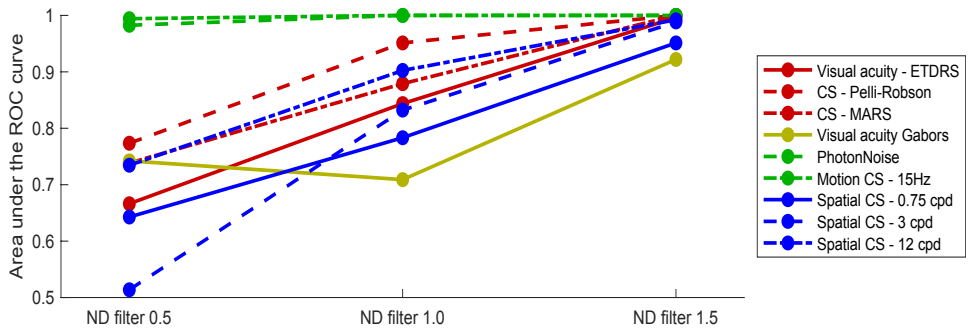

Figure 7. Area under the ROC curve for each measurement when comparing a reduction in luminance intensity (ND filters of 0.5, 1.0 and 1.5, x-axis) relative to the baseline condition (first row of Figure 6).

Furthermore, the photon noise and motion CS at 15 Hz tests were found to be relatively unaffected by blur (similar performances of the baseline Figure 5). as the capability to detect a reduced detection of light even when the control group is affected by a considerable blur (+2.00D; Figure 6 bottom row). This relative immunity to blur was expected as the stimuli in these two tests are at low spatial frequencies (0.5 cpd). Spatial CS at 0.75 cpd (blue solid line) was also found to be little affected by blur although it was not found to be very sensitive to a reduction in light detection even in absence of blur (top-left graph in Figure 5). The capability to detect a reduction in detected light for the other six tests were considerably affected even in the presence of a small amount of blur (+0.50D; second row in Figure 6), which was expected as they relied on higher spatial frequencies.

Unlike the eight other tests, the photon noise test relied on two measurements: motion CS at 2 Hz with and without noise added to the display. The outcomes of these two measurements are plotted in the two left graphs of Figure 8 and their ROC curves are plotted in the right graph. As can be seen, the capability to detect a reduction in detection of light was mainly driven by the noise free condition. With noise, performance was below chance, which is consistent with previous findings showing that motion CS at 2 Hz in noise can improve when reducing luminance intensity (Allard & Arleo, 2017b).

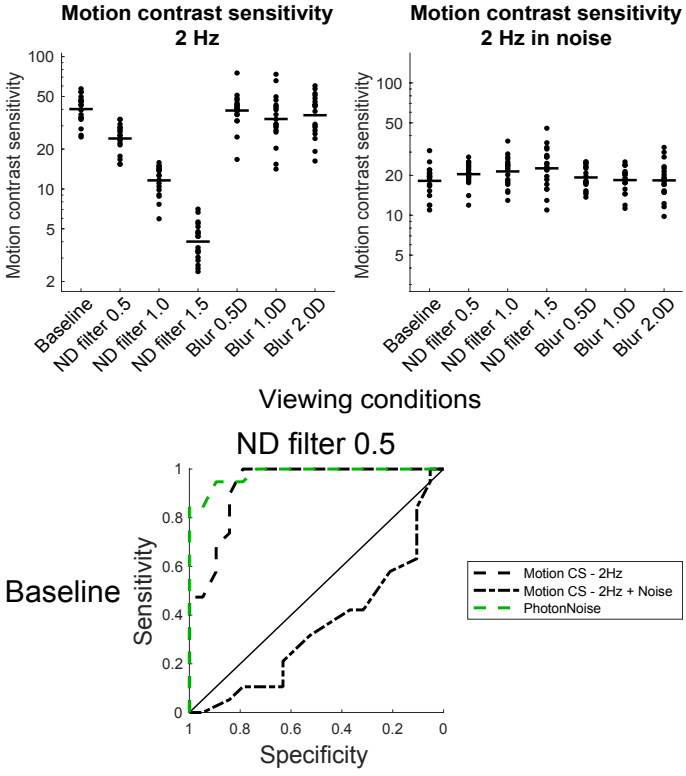

Figure 8. Results for the two measurements underlying the photon noise test (motion CS at 2 Hz without and with noise; left and center graphs, respectively) as a function of the 7 viewing conditions (x-axis). The legend is as defined in Figure 5. ROC curves (right graph) representing the capability of each test to discriminate a reduction in luminance intensity of 3.2x (i.e., ND filter=0.5) from the baseline condition (i.e., no luminance reduction and no blur). The ROC curve for the photon noise test is also plotted in green for comparison.

Discussion

The photon noise and motion CS tests were better at detecting a reduction in the amount of light detected by photoreceptors (i.e., discriminating between a condition with and without ND filter) than the three standard clinical tests (ETDRS VA, Pelli-Robson CS and Mars CS). Interestingly, because the two psychophysical tests relied on low spatial frequencies (0.5 cpd), the outcomes of these tests were hardly affected by moderate spatial blur. As a result, the capability to discriminate between a reduced detection of light by a factor of 3.1 and moderate spatial blur remains outstanding for these two psychophysical tests. In sum, these two tests are sensitive to a reduce detection of light by photoreceptors and are relatively robust to spatial blur. Conversely, the three clinical tests were found to be less capable to detect a reduced detection of light and were sensitive to optical blur. In other words, an impaired VA or CS may not indicate a reduced detection of light by photoreceptors as it could also be due to optical blur, so these tests would not be a good indicator of a decline in the efficiency of photoreceptors to detect light.

The fact that the two psychophysical tests (photon noise and motion CS at 15 Hz) were more capable of detecting a reduced amount of light detected by photoreceptors than the three clinical tests (ETDRS VA, Pelli-Robson CS and Mars CS) was not due to the fact that the psychophysical tests were performed under laboratory conditions with more precise measurements (e.g., better control of the environment light, more precise adaptive methods, more trials, using sinewaves gratings instead of letters). In fact, similar results were observed when measuring VA and spatial CS under laboratory conditions instead of clinical conditions. Photon noise and motion CS at 15 Hz tests were better at detecting a reduction in detection rate than VA and spatial CS tests under similar lab conditions, because of the nature of the test per se (i.e., drifting stimuli under specific conditions), not because they were conducted under laboratory conditions.

Photon noise and motion CS at 15 Hz tests showed similar capability to detect a reduction in the amount of light detected by photoreceptors. However, it is unclear which test would be more clinically useful. The motion CS test has the advantage of relying on a single CS measurement, whereas the photon noise test relies on two: motion CS at 2 Hz with and without external noise. Nevertheless, the sensitivity of the photon noise test to a reduction in light detection is mainly driven by motion CS without noise, as motion CS in the presence of noise varies little with the amount of light detected by photoreceptors. Thus, the clinical application of the photon noise test might not necessarily require two motion CS measurements. The motion CS in the presence of noise could be measured only when motion CS in absence of noise is abnormally low. Under the specific visual conditions used in the current study, motion CS at 2 Hz in absence of noise depends on two factors, photon noise and calculation efficiency (i.e., the ability of the system to extract the signal from noise), whereas motion CS at 2 Hz in presence of noise depends only on calculation efficiency (Braham chaouche et al., 2020; Pelli & Farell, 1999). Thus, if motion CS at 2 Hz in absence of noise was normal, this would suggest that both photon noise and calculation efficiency are normal, so there would be no reason to suspect a reduction in the detection of light. If motion CS at 2 Hz in absence of noise was not normal, motion CS at 2Hz in presence of noise could be measured to determine if the culprit is photon noise or calculation efficiency.

As expected, motion CS at 15 Hz was about two times more affected (in log units) by a change in the detection level than motion CS at 2 Hz used to derive the photon noise. This was expected from previous findings as motion CS at 15 Hz was found to be proportional to luminance intensity (i.e., amount of light detected by photoreceptors) and CS at 2 Hz is proportional to the square root of the luminance intensity (Braham chaouche et al., 2020). On the other hand, the inter-subject variance was also greater at 15 Hz resulting in similar capabilities for the photon noise and motion CS at 15 Hz to detect a reduced detection of light (Figure 7), albeit slightly greater at 15 Hz. However, motion CS at 15 Hz is presumed to depend on many internal factors (Braham chaouche et al., 2020): the amount of light detected by photoreceptors, early temporal integration, early neural noise occurring in the retina and calculation efficiency. Consequently, a deficiency at any of these processing levels would affect motion CS at 15 Hz, which could occur in some populations (e.g., elderly). Thus, an abnormal motion CS at 15 Hz might not specifically reflect a reduced detection of light by the photoreceptors, it could also be due to other factors also affecting motion CS at 15 Hz. On the other hand, photon noise is expected to depend only on the amount of

light detected by photoreceptors (Braham chaouche et al., 2020; Silvestre et al., 2019). Thus, although photon noise was not found to be more efficient than motion CS at 15 Hz in the current study, there are reasons to expect it to be more specific to the amount of light detected by photoreceptors for other populations. Further studies are required to determine which test, motion CS at 15 Hz or photon noise, would be more clinically useful to detect a decline in the amount of light detected by photoreceptors.

The photon noise and motion CS at 15 Hz tests were more sensitive to a reduction in the amount of light detected by photoreceptors than standard VA and CS tests. Consequently, the photon noise and motion CS at 15 Hz tests might be clinically useful to detect early signs of retinal pathologies affecting the amount of light detected by photoreceptors. For instance, AMD may affect the efficiency of photoreceptors to detect light even at early stages (Owsley, 2016) despite the fact that current standard clinical test fail to detect considerable functional decline (Owsley, Huisingh, et al., 2016), so the photon noise and motion CS at 15 Hz tests could be useful to detect early signs of AMD. Detecting photoreceptors deficiencies at an earlier stage could allow earlier treatment to stop or slow down the progression of the disease.

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Article 2: Low-luminance contrast sensitivity, a clinical test sensitive to the amount of light detected by photoreceptors

Authors: Maryam Rezaei, Asma Braham chaouche, Judith Renaud, Rémy Allard

Status of the article: In preparation to be submitted to Translational Vision Science & Technology journal

Contribution of the student: The candidate wrote and implemented the research protocol under supervision of Prof. Rémy Allard and collected the data. In addition, she participated in data processing and statistical analysis. She contributed to writing of the article, which was edited by her two directors. The candidate is the sole first author of this article.

Abstract

Purpose:

Phototransduction is a fundamental process of vision, but standard clinical measures like ETDRS visual acuity (VA) and Pelli-Robson contrast sensitivity (CS) are little affected by a reduction in the amount of light detected by photoreceptors. On the other hand, two novel psychophysical tests (photon noise and motion CS at high temporal frequencies) were recently found to be highly sensitive to the detection of light by photoreceptors, but they require a dynamic display. The purpose of the current study was to find a test sensitive to the amount of light detected by photoreceptors that is easily applicable under clinical conditions.

Method:

Two psychophysical measures (i.e., motion CS at 15 Hz and photon noise) and 6 clinical measures (i.e., ETDRS VA and Pelli-Robson CS, each under standard, low-luminance, and pinhole conditions) were measured in 33 young adults under normal detection of light, reduced detection of light (i.e., through neutral density filters) and increased blur (i.e., no neutral density filter, added convex lens) conditions. The capability of each test to detect a reduced light detection from normal detection of light and blur condition was then quantified using a binary classifier system known as ROC curve.

Results:

The capability of motion CS, low-luminance Pelli-Robson CS and photon noise tests to detect a reduced detection of light by photoreceptors relative to a normal or blurry condition was significantly higher ($p<.01$) than the ETDRS VA under standard, low-luminance and pinhole conditions, and Pelli-Robson CS under standard and pinhole conditions.

Conclusion:

Low-luminance CS is a test that is sensitive to the detection of light by photoreceptors and easily implementable under clinical conditions. It could be useful to screen for retinal pathologies that affect the ability of photoreceptors to detect light.

Keywords

Photoreceptors, Detection rate, Clinical functional tests, Photon noise, Motion contrast sensitivity

Introduction

Some retinal diseases are associated with progressive loss of vision, which highlights the importance of early diagnosis. Earlier detection of the signs and symptoms of a disease enables earlier intervention, assuming that an appropriate treatment is available. The ability of the retinal photoreceptor cells to detect light can be affected years before atrophic changes appear in some retinal diseases such as age-related macular degeneration (AMD; Elsner, Burns, & Weiter, 2002; Owsley, 2016)

Given that the transduction process in which light is detected by photoreceptors and converted into a neural response is an essential step of visual processing, a test that could detect an abnormally low detection of light by photoreceptors could be clinically useful for earlier screening of retinal diseases. This is especially the case given that some clinical tests, such as visual acuity (VA) and contrast sensitivity (CS), are not very sensitive to photoreceptor deficiencies (Owsley, Huisingh, et al., 2016) and the detection of light by photoreceptors (Rezaei, Chamaa, Rodrigue, Renaud, & Allard, under review).

Nonetheless, two recently developed psychophysical tests, namely the photon noise test and motion contrast sensitivity at 15 Hz test, are more sensitive to reduced detection of light by photoreceptors than standard clinical VA and CS tests (Rezaei et al., under review). Therefore, these new tests could potentially be useful to detect early signs of retinal pathologies affecting the detection rate of photoreceptors. Furthermore, these tests are simple and only require a few minutes to complete. However, in the previous study, these tests were performed under laboratory conditions and cannot be easily transferred to clinical environments because they require a specialized display with dynamic stimuli. The goal of the current study was to find a new test that is easily implementable under clinical conditions that would be specifically sensitive to the detection of light by photoreceptors.

Interestingly, measuring VA under low luminance conditions (LLVA for low-luminance VA) is a good marker of subsequent VA loss in AMD (Sunness et al., 2008). This test can easily be conducted under clinical conditions as it simply requires measuring the patient's best corrected VA after reducing luminance intensity using a neutral density filter of 2 log units (which reduces luminance by a factor of 100). However, VA heavily depends on optical factors and since the impact of optical factors increases with pupil size (Watson, 2013) and the pupil is large under low-

luminance conditions, LLVA is expected to be highly sensitive to optical factors. Also, the pupil size directly affects the retinal illumination and thereby the amount of light detected by photoreceptors, so if LLVA is sensitive to AMD because it is sensitive to the amount of light detected by photoreceptors, it would likely also depend on the pupil size. On the other hand, CS clinically assessed using the Pelli-Robson chart depends on lower spatial frequencies than VA, so it is undoubtedly less dependent on optical factors. Although CS as typically assessed during eye exams is little dependent on the amount of light detected by photoreceptors (i.e., luminance intensity, Rezaei et al., under review), low-luminance CS (LLCS) should depend more on the amount of light detected (Silvestre et al., 2018). In sum, LLVA and LLCS are two functional tests easily implementable under clinical conditions that could be more sensitive to the amount of light detected by photoreceptors than VA and CS, but these tests might also depend on the pupil size and/or optical factors.

A test effectively identifying photoreceptor deficiencies needs to be specifically sensitive to the amount of light detected by photoreceptors and not sensitive to other deficiencies such as optical imperfections. The use of a pinhole as an artificial pupil can be used to bypass optical imperfections (Abdul et al., 2009). Pinhole narrows aberrant peripheral rays of light and, therefore, minimizes the effect of optical imperfections. Another advantage of pinholes is that they significantly reduce retinal illumination. For LLCS and LLVA, using a neutral density filter of 2 log units reduces luminance intensity by a factor of 100. Under these conditions, the size of the pupil for young adults should be around 6 mm (Maqsood, 2017). Using a 1-mm pinhole instead of a neutral density filter would result in an effective pupil that is 6 times smaller, which would reduce retinal illumination considerably (~36x). Therefore, pinhole visual acuity (PHVA) and pinhole contrast sensitivity (PHCS) are two easily implementable functional tests that, even under clinical conditions, could be sensitive to the amount of light detected by photoreceptors, while being relatively immune to pupil size and optical imperfections.

The objective of the current study was to compare the capability of various functional tests currently applicable under clinical (i.e., VA, CS, LLVA, LLCS, PHVA and PHCS) and laboratory (photon noise and motion CS at 15 Hz) conditions in detecting a reduction in the number of photons detected by photoreceptors despite various levels of optical imperfections. Reducing retinal illuminance is an efficient way to artificially reduce the number of photons detected by

photoreceptors. Therefore, the current study used neutral density filters to reduce retinal illuminance and thereby reduce the amount of light detected by photoreceptors. Thus, reducing retinal illumination has the same functional consequence as a retinal pathology affecting the detection rate of photoreceptors: they both affect the number of photons detected by photoreceptors. The current study evaluated each of the eight measurements under four viewing conditions: baseline and three reduced-light conditions. Then, the difference of each test outcome under the reduced detection of light condition (i.e., added ND filter) from the normal detection of light condition (i.e., baseline, no ND filter) provided the test sensitivity. A test capable of effectively dissociating the reduced detection of light by photoreceptors from normal detection of light condition would be more sensitive to a reduced light detection. Such a test should also be specifically sensitive to the amount of light detected and not sensitive to other visual deficiencies such as optical imperfection. Therefore, the current study artificially induced optical imperfection by causing retinal blur using optical lenses. Then, the deduction of the test outcome under the reduced light detection from increased blur (i.e., added convex lens) was measured to determine the test specificity. A test capable of effectively dissociating a reduced light detection from increased optical blur would be more specific to reduced light detection (i.e., not sensitive to optical factors). A test sensitive and specific to the amount of light detected by photoreceptors should allow an efficient discrimination of these two groups and could be helpful in earlier diagnosis of retinal diseases, such as AMD, that affect photoreceptors.

Method

Observers

Thirty-five healthy young adults between the ages of 18 and 30 years participated in the current study after giving their informed consent. All participants were screened and included only if they had a good VA (≥20/25) in their dominant eye. Participants with any known ophthalmic, neurologic (e.g., epilepsy), systemic pathologies affecting vision (e.g., diabetes) or symptoms of COVID-19 were excluded from the study. None of the participants were taking medications altering vision such as Benzodiazepine. Ethical approval was obtained from the Comité d'éthique de la recherché clinique (CERC) of Université de Montréal (See Appendix D).

Apparatus

For the psychophysical tests, a 22.5-inch VIEWPixx LCD screen with a refresh rate of 120 Hz with a spatial resolution of 1920x1080 pixels and a mean luminance of 50 cd/m^2 was used. At the viewing distance of 4 meters, the spatial resolution of the screen was 256 pixels/degree of visual angle. The Noisy-bit method (Allard & Faubert, 2008) implemented independently to each color gun made the 8-bit display perceptually equivalent to an analogue display having a continuous luminance resolution. The output intensity of each color gun was carefully linearized using a Minolta photometer.

The clinical tests were performed using two clinical charts. VA, LLVA and PHVA were measured using an ETDRS acuity chart: Bailey-Lovie Chart #5, National Vision Research institute of Australia, Carlton, Australia (Bailey & Lovie, 1976; Ferris III, Kassoff, Bresnick, & Bailey, 1982). CS, LLCS and PHCS were measured using the Pelli-Robson chart: Clemente Clarke International, Edinburg way, United Kingdom (Pelli, Robson, & Wilkins, 1988).

Tests

The current study evaluated potential tests to detect a reduced detection of light by photoreceptors. Tests included psychophysical tests typically performed in the laboratory and clinical tests typically performed under clinical conditions. Each test is defined as a functional measurement (e.g., CS or VA) that can be potentially used to detect an abnormal detection of light by photoreceptors. Hence, measuring VA or CS under different conditions (e.g., VA, LLVA and PHVA, or CS, LLCS and PHCS) are defined as separate tests.

After an optometric evaluation including subjective and objective refraction**,** six clinical tests (VA, LLVA, PHVA, CS, LLCS and PHCS) and two psychophysical tests (15 Hz motion CS and photon noise) were performed.

Clinical tests

Visual acuity (VA): VA was measured with the (ETDRS) chart at the recommended testing distance of 4 meters. Each participant read letters from top to bottom and from left to right (Bailey & Lovie, 1976) until three or more mistakes were made on a line (Carkeet, 2001). Then, the score was recorded in logMAR units based on the total number of correct answers using the formula: (1.1-

$0.02T_c$) where T_c is the total number of letters read correctly on the chart (Oduntan, Mashige, & Raliavhegwa-Makhado, 2009).

Low-luminance visual acuity (LLVA): LLVA was measured with the same chart and procedure used for VA testing, the only difference being that illumination was reduced by adding a neutral density filter of 2.0 log units in front of the viewing eye.

Pinhole visual acuity (PHVA): PHVA was measured with the same chart and procedure used for VA testing, the only difference being that an artificial pupil of 1 mm was added in front of the viewing eye.

Contrast sensitivity (CS): CS was measured with a Pelli-Robson chart at a testing distance of 1 meter. The subject was asked to read the chart from left to right and from top to bottom until two or three of the letters in one group are incorrectly named. The score is the log contrast sensitivity of the final correct letter (Pelli et al., 1988).

Low-luminance contrast sensitivity (LLCS): LLCS was measured with the same chart and procedure used for the CS test. The only difference was that illumination was reduced by simply placing a neutral density filter of 2.0 log units in front of the eye.

Pinhole contrast sensitivity (PHCS): PHCS was measured with the same chart and procedure used for the CS test with the only difference being an artificial pupil of 1 mm in front of the viewing eye.

Psychophysical tests

For the two psychophysical tests, the stimuli were sinusoidal gratings (Figure 9) presented for 500 ms at a viewing distance of 4 m. The orientation of the grating was vertical, the grating was randomly drifting to the left or right. A direction discrimination task (grating drifting to the left or right) was performed using a two-alternative forced-choice procedure. After each response auditory feedback was given to help the participant to stay focused. All thresholds were measured using a 3down-1up staircase procedure (Levitt, 1971) that interrupts after 14 inversions. The threshold was estimated as the geometric mean of the last 10 inversions. In the baseline condition, an artificial pupil of 3 mm was added for the two psychophysical tests to control retinal illumination as defined for these tests (Rezaei et al., under review).

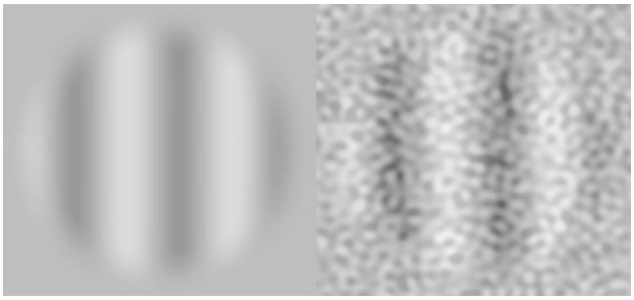

Figure 9. Example of stimuli used to measure photon noise and 15Hz motion CS (gratings drifting left or right). Stimuli was sinusoidal gratings without (left) and with (right) visual noise.

Photon noise (PN): Photon noise was derived from two contrast thresholds (Rezaei et al., under review): motion contrast sensitivity in the presence (c_N) and absence (c_0) of visual noise under very specific conditions. The grating had a spatial frequency of 0.5 cpd (which is standard for motion sensitivity), temporal frequency of 2 Hz and luminance intensity of 11 cd/m^2. Under these conditions, photon noise is the main internal noise source (Braham chaouche et al., 2021; Braham chaouche et al., 2020) which can be evaluated using the following equation:

$$photon\ noise = \frac{N}{\frac{c_N^2}{c_0^2} - 1},$$

where N is the energy of the external noise. The external noise added to the stimulus was truncated dynamic filtered noise (Jules Étienne et al., 2017) with a low-pass filter with a cut-off frequency of 2 cpd, noise refreshed at 120 Hz, truncated at 1 standard deviation and set at 50% contrast, which results in a noise energy (N) of 323 μs.deg^2.

15 Hz motion contrast sensitivity: The spatial frequency was set to 0.5 cpd, which is standard for motion contrast sensitivity. The temporal frequency and luminance intensity were chosen to maximize the impact of the light detection by photoreceptors on motion contrast sensitivity: 15 Hz and 35 cd/m^2 (under these conditions, motion contrast sensitivity is proportional to luminance intensity, Watson 1986).

Viewing conditions

All clinical and psychophysical tests were performed monocularly with the non-dominant eye covered. The dominant eye was determined using the Mile's test. Observers wore trial frames with their optimal correction for the dominant eye according to each testing distance. This viewing condition without any simulated deficiency served as the baseline. The non-dominant eye was covered with a black occluder.

The amount of light detected by photoreceptors was manipulated by reducing the amount of light reaching the retina using neutral density filters under three levels: 0.3, 0.6 and 0.9 density (i.e., reducing luminance intensity by a factor of 2, 4 and 8 respectively). The level of optical blur was manipulated by adding trial lenses to the trial frame: +0.25, +0.50. Consequently, each of the 8 tests described above (VA, CS, LLVA, LLCS, PHVA, PHCS, photon noise and 15 Hz motion CS) was performed under six different viewing conditions: baseline, three levels of reduced luminance intensities, and two levels of induced optical blur resulting in 48 measurements. Table 1 represents a summary of all tests and viewing conditions.

Table 1. Summary table of the tests and viewing conditions

		Clinical tests						Psychophysical tests	
	Tests (across) Viewing conditions (down)	VA	CS	LLVA	LLCS	PHVA	PHCS	Photon noise	Motion CS 15Hz
Baseline	No filter/lens								
Reduced detection rate	ND=0.0.3								
	ND=0.6								
	ND=0.9								
Increased blur	+0.25D lens								
	+0.50D lens								

Statistical Analysis

The capability of each test to detect a reduced amount of light detected by photoreceptors was quantified by evaluating the area under the curve (AUC) of a receiver operating characteristic

(ROC) curve. The AUC quantified the capability of a test to discriminate between the lower amount of light detected conditions (ND filter 0.3, 0.6 and 0.9) and normal detection of light conditions (baseline, +0.25D blur and +0.50D blur). One AUC was calculated for each of the eight tests. Note that the three lower light detection conditions (ND filter 0.3, 0.6 and 0.9) were combined and the three normal detection of light conditions (baseline, +0.25D blur and +0.50D blur) for the analysis. See supplementary material for the AUC for discriminating two specific conditions (

Figure ***S2***). The AUCs of each pair of tests (e.g., photon noise and VA) were statistically compared using the StAR tool (A. Brown, Dobson, & Maier, 1987).

Results

Measurements for each of the 8 tests (i.e., 8 graphs) for the 6 viewing conditions (x-axis) are presented in Figure 10. For each test, a ROC curve was derived from these data (Figure 11, left graph). An ROC curve represents the capability of each test to discriminate the reduced light detection conditions (ND filter of 0.3, 0.6 or 0.9) from the normal detection of light conditions (baseline, +0.25D blur, or +0.50D blur). The capability to discriminate these conditions can be quantified by calculating the area under the ROC curve (AUC; Figure 11, right graph). The closer the AUC is to 1, the better the test is at discriminating the two conditions. As can be seen, the capability to discriminate reduced light detection conditions from the normal detection of light conditions was outstanding (i.e., >.9; Hosmer Jr, Lemeshow, & Sturdivant, 2013, Manderkar, 2010) for the motion CS at 15 Hz and LLCS tests (AUC of 0.96 and 0.92, respectively), excellent (i.e., >.8) for the photon noise tests (AUC of 0.86), acceptable (i.e., >.7) for LLVA, PHVA and PHCS (AUC of 0.77, 0.77 and 0.76, respectively), and near chance (i.e., ~.5) for CS and VA with an AUC of 0.63 and 0.57, respectively.

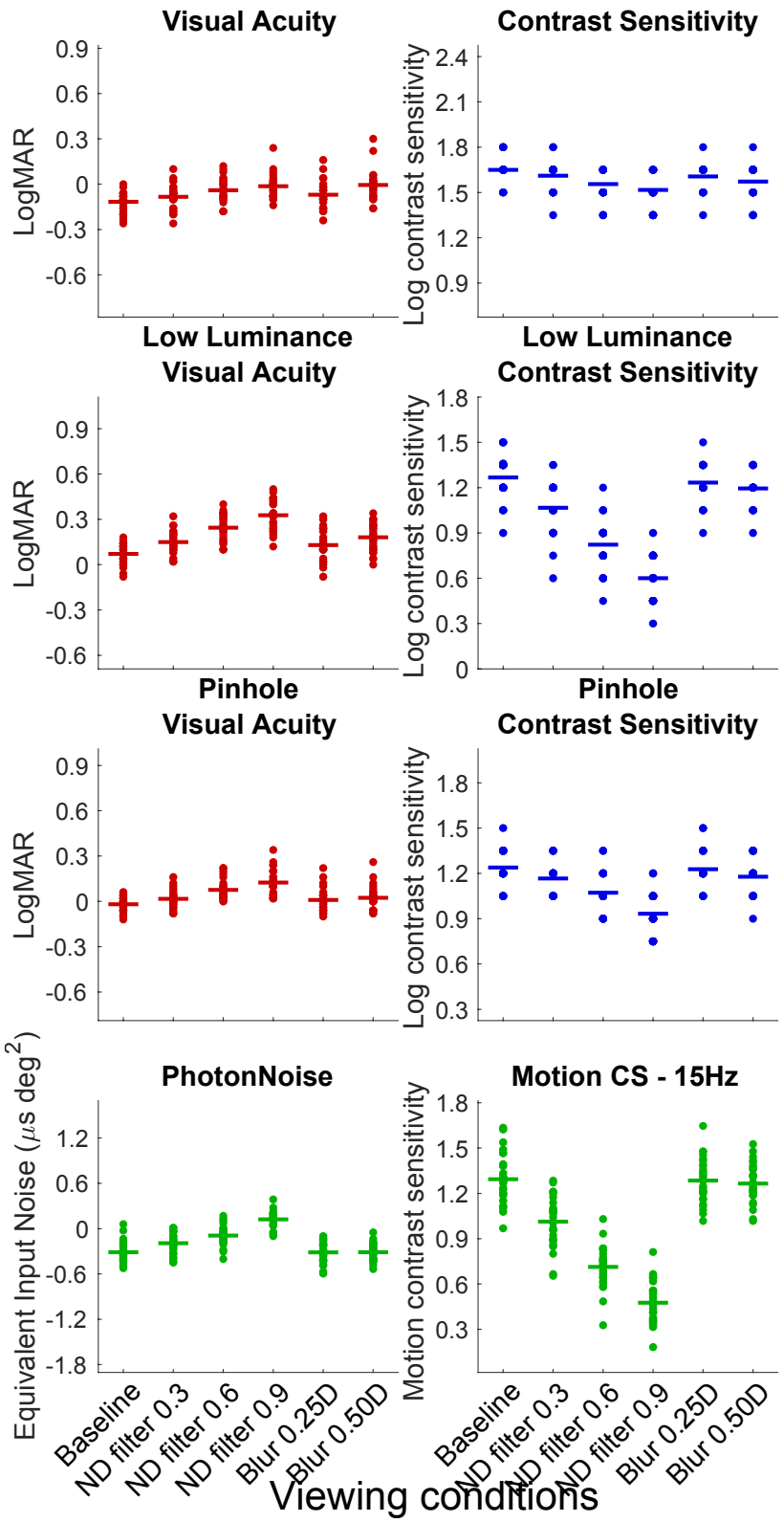

Figure 10. Results for each test (1 graph per test) as a function of the 6 viewing conditions (x-axis). The baseline viewing conditions (first conditions to the left of each graph) is represented with ND filter of

0.0 (i.e., no filter) and Blur of 0.0D (no blur). The second, third and fourth conditions represents a reduction in luminance intensity (ND filter of 0.3, 0.6 and 0.9, respectively). The fifth and sixth conditions represent the blurry conditions (blur = 0.25 and 0.5, respectively). Each dot represents a measure for a participant. The horizontal line represents the mean in log units.

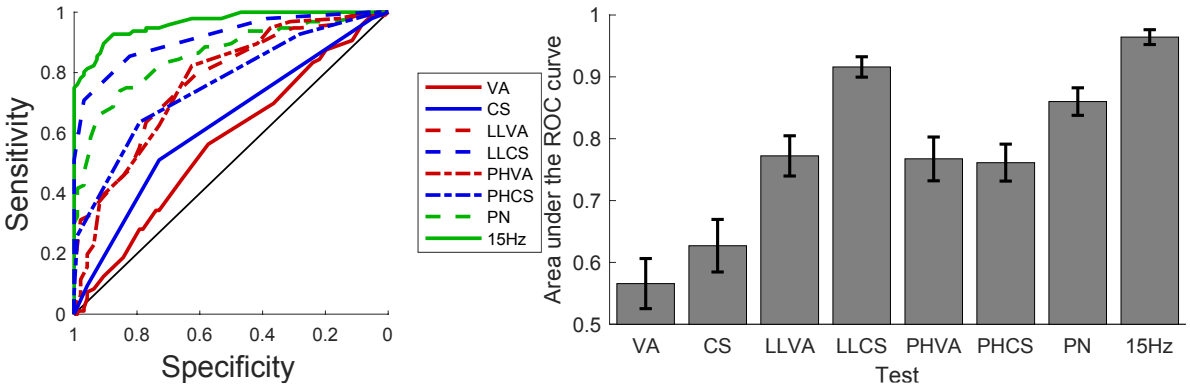

Figure 11. Left. ROC curves representing the capability of each test to discriminate a pathologic condition (i.e., ND filter of 0.3, 0.6 and 0.9) from the normal condition (i.e., baseline, blur 0.25D and blur 0.5D). Right. Area under the ROC curve (AUC) for each condition. Error bars represent standard error of the mean estimated using Bootstrap method (Stine, 1989).

Table 2 represents the p-values comparing the area under the ROC curve of each pair of tests. The AUC of motion CS at 15 Hz was significantly greater than all other tests. The AUC of photon noise and LLCS were significantly greater than LLVA, PHVA, PHCS, CS and VA. The AUCs of LLVA, PHVA and PHCS were significantly greater than standard VA and CS.

Table 2. P-values comparing the areas under the ROC curve of each test relative to other tests. Numbers in bold represent a significant difference (p<.05).

	15Hz	LLCS	PN	LLVA	PHVA	PHCS	CS	VA
VA	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	0.260	
CS	**<0.001**	**<0.001**	**<0.001**	**0.003**	**0.004**	**0.005**		
PHCS	**<0.001**	**<0.001**	**0.020**	0.812	0.895			
PHVA	**<0.001**	**<0.001**	**0.035**	0.919				
LLVA	**<0.001**	**<0.001**	**0.043**					
PN	**<0.001**	0.084						
LLCS	**0.030**							
15Hz								

Discussion

The clinical measures under standard luminance condition (VA and CS) performed significantly worse in detecting a lower amount of light detected by photoreceptors than all other tests including the corresponding pinhole conditions (PHVA and PHCS) and low-luminance conditions (LLVA and LLCS). Indeed, VA and CS were near chance (diagonal line in left graph of Figure 11) in discriminating conditions with a lower reduction in the amount of light detected by photoreceptors (ND filters of 0.3 to 0.9, which corresponds to 2x to 8x) from conditions without ND filters (baseline, +0.25D blur and +0.50D blur), so they should not be very useful to detect similar reduced amount of light detected by photoreceptors due photoreceptors deficiencies. This finding was expected since standard VA and CS tests are known to be little affected by luminance intensity (A. Brown et al., 1987; Rabin, 1994), and thereby the amount of light detected by photoreceptors.

Using a pinhole reduces retinal illuminance, controls retinal illumination, which becomes independent of pupil size, and reduces optical aberration. The use of a pinhole was expected to minimize the impact of pupil size and optical imperfections, which was expected to make VA or CS more specific to the amount of light detected by photoreceptors. However, such expected advantage was not observed in the current results as the pinhole tests did not outperform the low-luminance tests. Indeed, no significant difference was observed between PHVA and LLVA in their capability to discriminate a low detection condition (ND filter of 0.3, 0.6 and 0.9) from a normal detection of light condition (baseline, +0.25D blur and +0.50D blur). Although PHVA showed to be less sensitive to blur than LLVA (second and third row of supplementary Figure S1 and

Figure ***S2***, see appendix A&B), it was not more sensitive to the amount of light detected by photoreceptors (Table 2 and first row of supplementary Figure S1, see appendix A). On the other hand, LLCS showed to be more capable of detecting a reduced detection of light than PHCS (Table 2). So, although using a pinhole was expected to have the advantage of minimizing the impact of optical imperfections (and thereby, blur), it was not more effective than testing under low luminance intensity.

The poorer performance of LLVA test to discriminate the reduced detection of light conditions (i.e., ND filter of 0.3, 0.6 and 0.9) from the normal detection of light conditions (i.e., baseline, +0.25D blur and +0.50D blur) compared to the performance of LLCS test could be due

to the fact that VA depends more on optical factors. Indeed, since the impact of optical factors increases with pupil size (Watson, 2013) and the pupil size is larger under lower luminance intensities, the effect of optical factors is expected to be greater for LLVA than VA. Ideally, a test aiming to detect be sensitive to the amount of light detected by photoreceptors should not be sensitive to the other factors like optical blur; otherwise, it would not enable to determine whether a lower performance is due to more optical imperfections or a lower detection rate of photoreceptors. Thus, LLVA may not be a good indicator of a reduced detection rate as it is less capable of discriminating a reduced detection rate from blur than LLCS. The relative robustness of LLCS (i.e., Pelli-Robson under low luminance) to blur can be explained by the fact that it is based on lower spatial frequencies, so it is less affected by optical imperfections. LLVA was found to be more sensitive to early AMD than VA, but the result of the current study suggests that LLCS could be even more sensitive to AMD than LLVA, which is consistent with the fact that CS is more sensitive to early AMD under lower luminance conditions (Maynard et al., 2016).

The results of the current study are consistent with the previous finding that the capability of the photon noise and motion CS at 15 Hz tests to detect a reduction in the amount of light detected by photoreceptors is better than clinical tests like VA and CS. The stimuli of these novel psychophysical tests use low spatial frequencies (i.e., 0.5 cycles/degree), which makes them relatively immune to small optical imperfections. Interestingly, the motion CS at 15 Hz test was more sensitive to a reduction in the amount of light detected by photoreceptors than the photon noise test. This can be explained by previous findings suggesting that motion CS is more sensitive to luminance intensity at 15 Hz than at 2 Hz at which photon noise is measured. Indeed, motion CS is proportional to luminance intensity (i.e., amount of light detected by photoreceptors) at high temporal frequencies and proportional to the square root of the luminance intensity at low temporal frequencies (Watson, 1986). Nevertheless, this does not imply that the motion CS at 15 Hz test would be clinically more useful than the photon noise test. Indeed, photon noise should depend only on the amount of light detected by photoreceptors, whereas, although CS at 15 Hz depends more on the amount of light detected by photoreceptors, it also depends on various internal factors like early temporal integration, early neural noise and calculation efficiency (Braham chaouche et al., 2020). Thus, an abnormal photon noise level should be related to reduced detection of light by photoreceptors, whereas an abnormal motion CS at 15Hz might not.

Motion CS at 15Hz and photon noise are sensitive to the amount of light detected by photoreceptors, but they are difficult to implement under clinical conditions as they require a specialized display capable of presenting dynamic stimuli. On the other hand, LLCS is an easily accessible clinical test that showed an outstanding efficiency in detecting a reduction in light detection by photoreceptors, so it could be an easily applicable test under clinical conditions that could be sensitive to retinal diseases affecting the ability of photoreceptors to detect light. However, the LLCS test has a considerable drawback: its outcome undoubtedly depends on the pupil size because it directly affects the amount of light being detected by photoreceptors. Indeed, contrary to the motion CS at 15 Hz and photon noise tests in which a 3-mm artificial pupil was used, the pupil size was not controlled for LLCS. The impact of the pupil size was minimized in the PHCS test, but this test turned out to be less sensitive to the amount of light detected by photoreceptors. In the current study, all the participants were young adults, so they likely had similar pupil sizes, but the pupil size is known to considerably vary with aging (Bitsios, Prettyman, & Szabadi, 1996). A smaller pupil size reduces the number of photons reaching the retina and, therefore, directly affects the amount of light detected by photoreceptors. Consequently, a lower LLCS could be due to photoreceptors per se or to a smaller pupil. Another important factor that must be considered for the LLCS test is the chart illumination, which also directly affects the amount of light reaching the retina. Although the chart is theoretically supposed to be set under a specific luminance level (85 cd/m^2), in practice, the ambient light level likely varies between exam rooms. In the current study, the same clinical room under a fixed chart illumination (80 cd/m^2) was used for all participants who were young adults likely to have similar pupil sizes, so the impact of pupil sizes and chart illumination was minimized. Under clinical conditions, however, the impact of these factors could be considerable and these limitations would need to be taken into account.

Conclusion

The current study replicates previous findings (Rezaei et al., under review) that photon noise and motion CS at 15 Hz tests have are more sensitive to the amount of light detected by photoreceptors than clinical VA and CS tests. Even though these psychophysical tests could potentially be useful to screen for retinal diseases affecting their ability to detect light, they are not easily implementable under clinical condition. The current study shows that LLCS is a clinically accessible test that is very sensitive to a reduction in the detection of light by photoreceptors.

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General discussion

The goal of this thesis was to find a functional test easily applicable under clinical conditions and sensitive to a reduced detection of light by photoreceptors, which could reveal an early sign of retinal disease affecting the photoreceptors. The first study showed that photon noise and motion contrast sensitivity (CS) at 15 Hz were better indicators of reduced detection of light by photoreceptors than standard functional tests such as ETDRS visual acuity, Mars CS and Pelli-Robson CS. The second study revealed that the Pelli-Robson CS chart under low luminance conditions might be a good indicator of reduced light detection and has the advantage of being easily accessible in clinical conditions. This study also showed that motion CS at 15 Hz detects reduced light absorption more efficiently than photon noise.

The high capability of photon noise and motion CS at 15 Hz to discriminate a reduced detection of light is in accordance with previous studies suggesting photon noise as a reliable measure of light detection rate in photoreceptors (Allard et al., under revision; Silvestre et al., 2018). This finding can be explained by two facts. First, these two tests depend on luminance intensity: at high temporal frequencies (e.g., motion CS at 15Hz), CS is proportional to luminance intensity i.e., linear law (Watson, 1986) and, at low temporal frequency (i.e., photon noise), CS is proportional to the square root of the luminance intensity (i.e., de Vries-Rose law; Pelli, 1990). Second, these measurements are hardly affected by moderate amounts of blur since they rely on the processing of a low spatial frequency (0.5 cpd).

Motion CS at 15 Hz showed to be more efficient at demonstrating reduced light detection than photon noise, but this does not necessarily imply that motion CS at 15 Hz would be more clinically useful than photon noise because, although motion CS at 15 Hz is more sensitive to a reduced detection rate, photon noise is more specific to the detection rate. Indeed, photon noise should only depend on the number of photons detected by photoreceptors, whereas motion CS at 15 Hz also depends on other internal factors such as early temporal integration, early neural noise, and calculation efficiency (Braham chaouche et al., 2020). In fact, abnormal motion CS at 15 Hz might not always be due to a reduced detection of light by photoreceptors, but due to a deficiency at other processing steps of vision. Therefore, motion CS at 15 Hz can be used as a screening tool that is faster and more sensitive to reduced detection of light than photon noise. Normal results of motion CS would determine that these factors are all normal, while abnormal results of motion CS

at 15 Hz would show that there is a reduced detection of photons or a deficiency at any of other processing levels. Patients with abnormal motion CS could then undergo other diagnostic tests like photon noise to determine if there is a deficiency in detection rate. The independence of photon noise from internal factors makes it a more specific test and a direct measure of reduced detection rate. Photon noise determines the detection rate by measuring the difference between the contrast thresholds in the presence and absence of external noise. Without external noise, performance is limited by photon noise and all other internal noise sources and, with noise, performance is limited only by internal noise sources (Silvestre et al., 2018). The difference of these two conditions yields a pure measure of detection rate. Therefore, neurologic conditions such as cognitive impairment are not expected to affect photon noise. It should be considered that, in the present thesis, only young participants were tested while for some populations (e.g., elderly) in which other factors vary considerably, motion CS might be less sensitive than photon noise. Photon noise and motion CS at 15 Hz both have some other advantages; Both tests are fast and not invasive. They also do not require pupil dilation in patients with miosis a common condition in elderly.

Photon noise and motion CS at 15 Hz were found to be sensitive to the amount of light detected by photoreceptors and, thus, could be useful to detect photoreceptor decline, affecting their ability to detect photons. However, a reduction in the number of photons detected by photoreceptors may not necessarily be due to less efficient photoreceptors, it could also be due to other factors affecting retinal illumination. Indeed, if less light reaches the photoreceptors, they will detect less light. There are two common causes of a reduction in retinal illumination: pupil size and lens opacification. The size of the pupil affects the amount of light reaching the retina, therefore changes the amount of light detected by the photoreceptors (Pokorny & Smith, 1997). Importantly, elderly tend to have smaller pupil (miosis), which reduces the amount of light reaching the retina and consequently reduces the number of photons detected by photoreceptors. In the present thesis, the impact of the pupil size was neutralized by adding an artificial pupil of 3mm to control retinal illuminance. Regarding the opacification of the lens, which occurs with aging, this physiological change also reduces the amount of light reaching the retina by blocking the short wavelengths and thereby reduces the number of photons reaching the retina (Edwards & Gibson, 2010). An interesting feature of photon noise and motion CS at 15 Hz is that the impact of lens opacification on these tests can be minimized by simply changing the stimulus to a red grating (long wavelength). Because less light is expected to reach the photoreceptors with aging due to

pupil miosis and opacification of the lens, these factors would need to be considered when evaluating the amount of light detected by photoreceptors in elderly patients. The two studies in the current thesis were conducted on healthy young observers who probably had similar pupil sizes and no considerable yellowing of the lens, so these two factors were not an issue.

In the present thesis, only central vision was assessed, but measuring the detection rate of photoreceptors in peripheral retinal locations could also be useful since different retinal diseases affect cones and/or rods. For example, glaucoma mainly affects peripheral vision while AMD affects central vision. Photon noise could be adapted to evaluate different retinal locations by moving the stimuli to various locations of the visual field. Therefore, photon noise not only can help detect AMD, but also other retinal diseases. Additionally, central vision is mediated by cones while some studies suggest that the loss of rod photoreceptors precedes the loss of cones (Medeiros & Curcio, 2001). Therefore, it could be clinically relevant to evaluate the function of rods to detect earlier signs of retinal diseases. Since rods function under dim light conditions and are mostly located in parafoveal areas of the retina, the photon noise test could be adapted for evaluating rods simply by reducing luminance intensity to scotopic levels and moving the stimuli from the center of the screen to the periphery. Therefore, photon noise could also be helpful to detect different retinal diseases affecting rods, cones, or both.

It is important to have a test that is easy to use in clinical conditions. Photon noise and motion CS at 15 Hz are capable of identifying a reduced detection of light by the photoreceptors and could be good indicators of functional problems in the photoreceptors that may be caused by retinal diseases. However, these tests are not currently easily implementable under clinical conditions because they require a dynamic display with specific properties. Adapting these tests for clinical use is not easy and would require a long process to develop a new apparatus. Therefore, before developing a new apparatus, it is important to seek more accessible tools that could be used instead. One easily accessible tool is the Pelli-Robson contrast sensitivity test which, in previous studies, has been shown to be sensitive to early AMD under low luminance conditions (i.e., LLCS; Maynard et al., 2016). In the second study of the present thesis, the Pelli-Robson's LLCS was also shown to be a good indicator of reduced light detection. These results suggest that LLCS could be a useful clinical tool that simply requires the use of neutral density filters for clinicians to be able to screen for a decline in the detection of light by photoreceptors.

Before developing a new test, several studies are warranted. First, it is important to determine if it is clinically useful to evaluate the detection rate of photoreceptors. If an optometrist or ophthalmologist notes an abnormally low detection rate, what should be done? If a lower detection rate is an early sign of a retinal disease like AMD, then it would be clinically useful to measure the detection rate of photoreceptors during eye exams to help earlier diagnosis and provide earlier intervention to delay the progression of the disease. Currently, one study is investigating the impact of early AMD on the detection rate of photoreceptors. Since early AMD has been shown to be associated with a delayed dark adaptation (Owsley, McGwin, et al., 2016), the potential outcome of this study would be that detection rate of photoreceptors is reduced in early AMD.

Second, it is important to consider other factors that could affect the amount of light detected by photoreceptors including yellowing of the lens and pupil size. The two studies in the current thesis were conducted on healthy young observers for which yellowing of the lens was not an issue but would likely be an issue for older observers as the lens yellows with aging. Consequently, when testing older adults, the yellowing of the lens needs to be considered. For instance, only long wavelengths (Braham chaouche et al., 2020; Silvestre et al., 2019) could be used as they are little affected by the yellowing of the lens (Mellerio, 1987). Pupil size would also be an issue for older observers as the pupil narrows with aging (senile miosis). Therefore, when testing older adults, the size of pupil should also be considered. Therefore, it could be relevant to use an artificial pupil or a pinhole. In the current study, Pelli-Robson LLCS was used as it is typically used in the literature, which does not control for the pupil size. However, we also introduced a CS test with a pinhole (PHCS) that considerably reduces luminance intensity and also controls the pupil size. Despite the impact of the pupil size was minimized by using a pinhole in the PHCS test, this test turned out to be less sensitive to the amount of light detected.

Other than these two important factors, there are others that should also be considered. For instance, high myopia is often associated with morphological changes in photoreceptors, such as tilting and stretching, which could affect the amount of light detected. Consequently, if the photoreceptors of a patient detect less light, this might not be related to a retinal disease such as AMD, it could also be related to myopia. Further studies are required to quantify the impact of myopia on the detection of light by photoreceptors and to dissociate the impact of myopia vs retinal

diseases. In sum, further studies are required to determine a test that can take into account these various factors affecting light detection.

Third, external factors can also affect the amount of light detected by photoreceptors since the amount of light detected depends on the brightness of the chart. For the Pelli-Robson test, the room illumination is supposed to be set so that the chart has a specific luminance intensity (Cox, Norman, & Norman, 1999). However, the luminance of the chart likely varies depending on the conditions of the examination room such as brightness, the type of light used or other ambient light sources (e.g., windows, reflected light from objects, color of the walls and objects in the room, other displays, etc.). In the current study, the room lighting conditions were kept constant (one room, under identical conditions), but a widely applicable test would involve these external factors. Therefore, it could be interesting to investigate if other tests that are less sensitive to room illumination could be sensitive to the detection of light.

Photon noise and motion CS at 15 Hz are independent of room and chart illumination. Perimetry techniques (e.g., Humphrey, microperimetry) are also potential techniques to investigate because they are implemented under dim room illumination with the patient positioned in front of a uniformly illuminated bowl. Therefore, they should not be adversely affected by room illumination. Perimetry could also be useful to evaluate the visual function at different retinal locations, which could be relevant for other diseases affecting peripheral vision like glaucoma, retinitis pigmentosa, etc. Perimetry could be modified to lower luminance intensities to evaluate the rod function. Photon noise can also be adapted for evaluating rods, but adapting Pelli-Robson LLCS to measure the detection rate of rods is challenging because there are no rods in the fovea and letter recognition ability reduces in the periphery (D. Yu, Legge, Wagoner, & Chung, 2014).

Results of the second study revealed that functional tests at lower luminance intensities are more sensitive to reduced light detection than at high luminance intensities. This finding is consistent with previous studies suggesting that AMD affects visual function at low luminance more than high luminance (Maynard et al., 2016; Wu et al., 2014). This could be explained by the fact that at high luminance intensity sensitivity does not depend on luminance intensity (i.e., Weber's law). Therefore, modifying functional tests that were shown in previous studies to be sensitive to early AMD, such as microperimetry (Wu et al., 2015)., to lower luminance intensities

might be useful to demonstrate a lower detection rate. Future studies are required to compare the capability of these tests with photon noise.

In the present research, only young healthy participants were tested while retinal diseases such as AMD typically affect elderly people. The visual decline in seniors could be due to reduced light detection by photoreceptors or to various other causes such as lens opacification, refractive error, miosis, etc., all of which can affect the ability of the test to evaluate photoreceptors' function. Therefore, future studies should evaluate the photon noise test and any other test capable of detecting reduced detection rate for their capability to discriminate between patients with early AMD and healthy patients. Obviously, if a new functional test cannot discriminate between healthy and early AMD patients (which are currently identified using retinal imaging techniques), then they would not be clinically useful. However, a new functional test considerably sensitive to early AMD might be capable to detect signs or risk of AMD earlier than the current "gold standard". This possibility could be tested in a longitudinal study to determine if it can predict the onset of the disease earlier than tests such as OCT. If the photon noise test can effectively discriminate AMD patients from healthy patients, a longitudinal study could determine if photon noise can indicate the upcoming progression of the AMD. If photon noise can predict the progression of AMD earlier than OCT, then photon noise could be useful to help earlier diagnosis of AMD. Earlier diagnosis of AMD enables clinicians to provide patients with dietary and lifestyle advice (e.g., more physical activity, avoiding smoking, etc.) to delay the progression of the disease. Earlier diagnosis will also help delay the progression of the disease in the fellow eye (Gangnon et al., 2015). Earlier treatment would also reduce the financial burden for the patients and the society and improve patients' quality of life (Mitchell & Bradley, 2006; Mulligan et al., 2020). Additionally, photon noise is not an invasive test and does not require pupil dilation for testing in patients with miosis. It should also be considered that the photon noise test could also help in the diagnosis of other retinal diseases affecting the detection rate of photoreceptors as well.

One limitation of this study was the lower inter-subject variability due to the recruitment of healthy young participants. AMD is prevalent among elderly people who demonstrate a greater inter-subject variability in almost any measure. In vision testing, at least some of this variability may be due to miosis, cataract, cognitive impairment, and fatigue. Cognitive impairments such as memory problems associated with aging can affect visual outcomes since functional tests are not

only dependent on sensory capacity , but also on cognitive ability of the patient to understand the instructions and to respond appropriately (Ciocler Froiman & Dantas, 2013).

Another limitation of this study to be considered is that, in this study, room and chart illumination was properly controlled by using the same room with the same conditions, while it might not be the case in clinical settings because different clinical rooms tend to differ in brightness, the type of light used and other ambient light sources (e.g., light reflecting from objects, windows, etc.). Therefore, further investigations utilizing tests that are less sensitive to room illumination, such as Humphrey perimetry and ERG, might be helpful.

Conclusion

The current thesis was an endeavour to find a test that is highly sensitive to the detection rate of photoreceptors. Since the amount of light detected by photoreceptors is affected in early stages of retinal diseases, functional tests sensitive to reduced detection rate might help earlier diagnosis of these retinal diseases. Phototransduction, as the fundamental process in vision, lacks good evaluation during eye exams. The results of this thesis show that standard clinical tests (e.g., VA and CS) are considerably less sensitive to a reduced detection of light by photoreceptors than the photon noise test and motion CS at 15 Hz. However, these tests are not easily applicable under clinical conditions. Nonetheless, LLCS is a test that showed a high sensitivity to the reduced light detection by photoreceptors, and it could be an easily applicable test under clinical conditions. Therefore, LLCS might eventually help in earlier screening of AMD, but it can be affected by internal and external factors. Future studies to find an easily accessible test that is sensitive to reduced detection rate but that also controls for these factors, such as Humphrey perimetry, could be helpful. Future studies could also target facilitating the clinical accessibility of photon noise as a test that is suggested as a pure measure of detection rate and can be easily adapted for common conditions associated with aging such as miosis and lens opacification.

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Appendix A

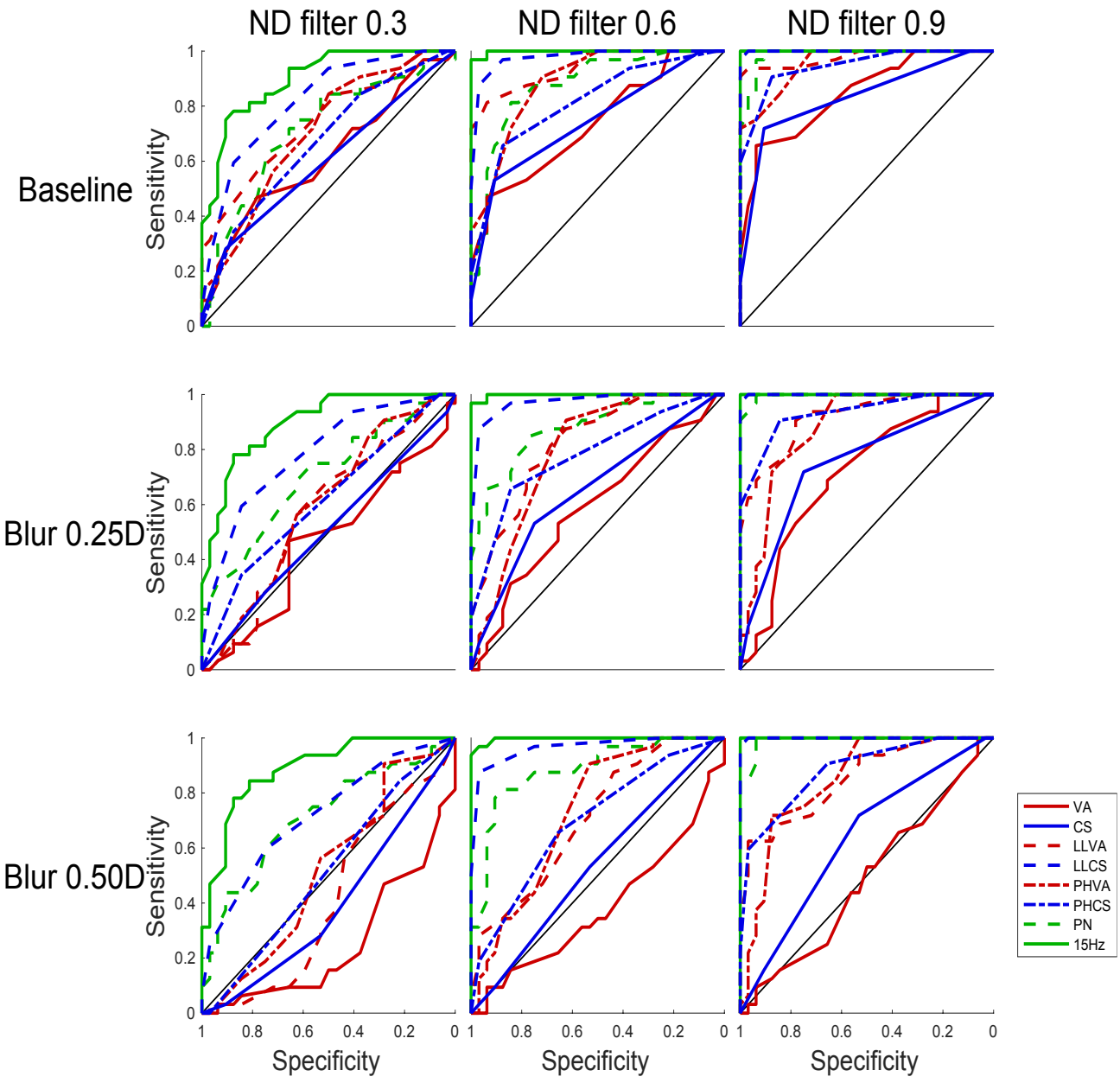

Figure S1. ROC curves representing the capability of each test to discriminate a reduction in luminance intensity (i.e., ND filter of 0.3, 0.6 and 0.9 represented in the first, second and third columns, respectively) from the baseline condition (i.e., no luminance reduction and no blur, first row) or blurry conditions (i.e., +0.25D blur and +0.50D blur represented in the second and third row, respectively).

Appendix B

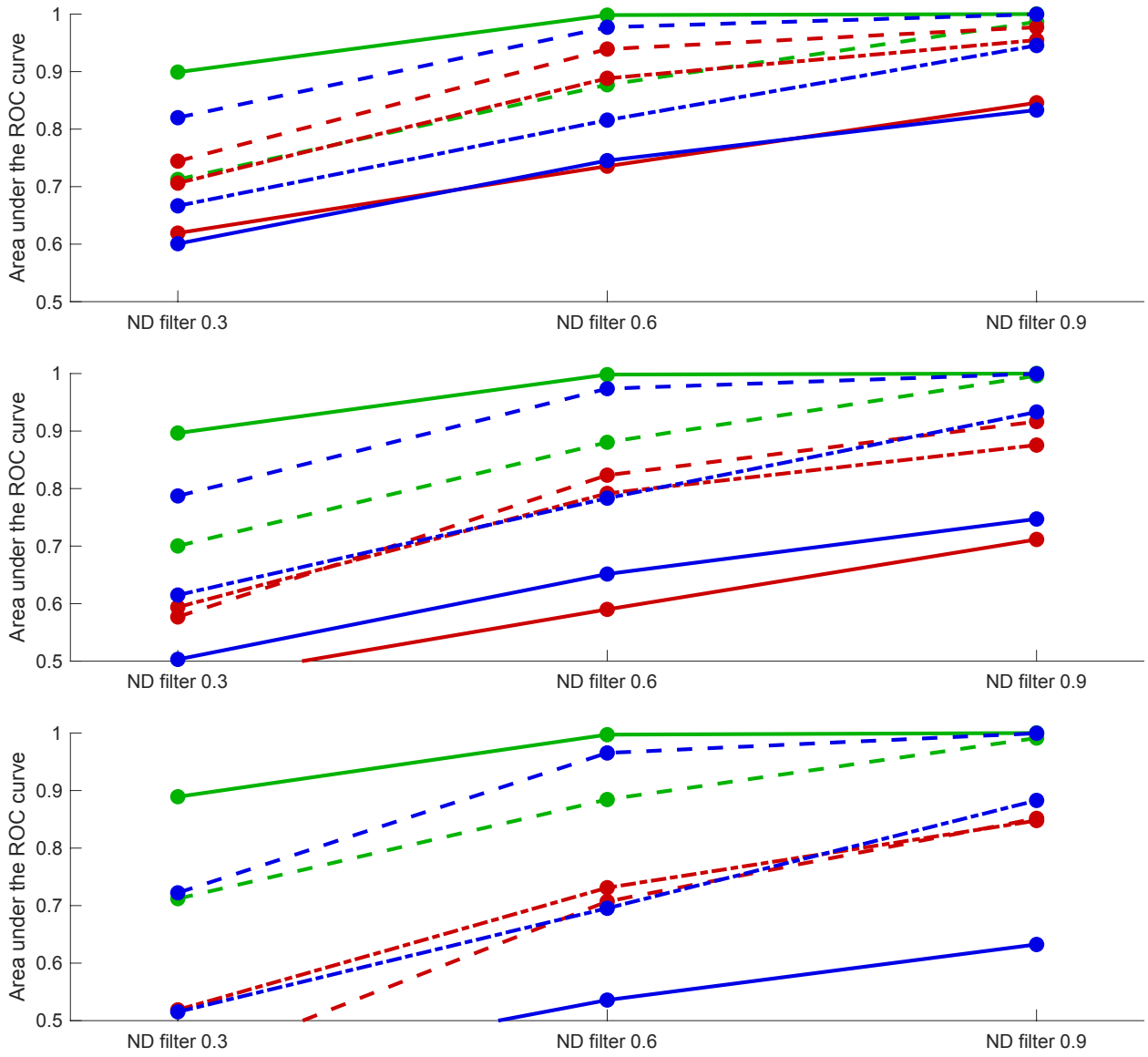

Figure S2. Area under the ROC curve for each measurement when comparing a reduction in luminance intensity (ND filters of 0.3, 0.6 and 0.9, x-axis) relative to the baseline (first row), +0.25D blur (second row) and +0.50D blur (third row) conditions. Data derived from the data presented in the first, second and third row of supplementary Figure S1, respectively. See supplementary Figure S1 for the legend.

Appendix C

Université de Montréal

Comité d'éthique de la recherche clinique (CERC)

CERTIFICAT D'APPROBATION ÉTHIQUE
- Réémission-

Le Comité d'éthique de la recherche clinique, selon les procédures en vigueur et en vertu des documents relatifs au suivi qui lui a été fournis conclu qu'il respecte les règles d'éthique énoncées dans la Politique sur la recherche avec des êtres humains *de l'Université de Montréal*

Projet	
Titre du projet	**Quantification de la capacité de certains tests cliniques et psychophysiques à détecter un déficit d'absorbtion des photorécepteurs de la rétine**
Étudiants requérants	**Gerry Nour Chamaa** , candidat au doctorat de 1er cycle, École d'optométrie **Clément Rodrigue** , candidat au doctorat de 1er cycle, École d'optométrie **Maryam Rezaei** , candidate à la maîtrise, École d'optométrie
Sous la direction de:	Rémy Allard, professeur adjoint, École d'optométrie, Université de Montréal & Judith Renaud, professeure agrégée, École d'optométrie, Université de Montréal.
Modifications depuis l'approbation initiale :	Ajout d'un financement (16 novembre 2020)

Financement	
Organisme	Université de Montréal//Fondation des maladies de l'œil
Programme	Fonds de démarrage du directeur de recherche
Titre de l'octroi si différent	//Using motion sensitivity to detect early signs of age- related macular degeneration
Numéro d'octroi	//Lettre datée du 20 avril 2020
Chercheur principal	Rémy Allard
No de compte	

MODALITÉS D'APPLICATION
Tout changement anticipé au protocole de recherche doit être communiqué au Comité qui en évaluera l'impact au chapitre de l'éthique. Toute interruption prématurée du projet ou tout incident grave doit être immédiatement signalé au Comité. Selon les règles universitaires en vigueur, un suivi annuel est minimalement exigé pour maintenir la validité de la présente approbation éthique, et ce, jusqu'à la fin du projet. Le questionnaire de suivi est disponible sur la page web du Comité.

[redacted]

Insaf Salem Fourati
Responsable de l'évaluation éthique continue
Comité d'éthique de la recherche clinique
Université de Montréal

16 novembre 2020
Date de délivrance du renouvellement ou de la réémission*

1er novembre 2021
Date du prochain suivi

7 octobre 2020
Date du certificat initial

1er novembre 2021
Date de fin de validité

*Le présent renouvellement est en continuité avec le précédent certificat

Appendix D

Comité d'éthique de la recherche clinique (CERC)

Bureau de la conduite responsable en recherche

Université de Montréal

31 mars 2021

Rémy Allard, professeur adjoint
École d'optométrie
Université de Montréal

OBJET :	Projet # 2021-217 - Approbation éthique finale Finding a clinically applicable test sensitive to retinal photoreceptor deficiencies Financement : Réseau de la recherche en santé de la vision et Fondation des maladie de l'oeil

M. Allard,

Nous accusons réception des précisions et corrections demandées via le formulaire de conditions F20 ainsi que des documents en vue de l'approbation finale du projet mentionné en rubrique. Suite à la révision de ces documents, le tout ayant été jugé satisfaisant, j'ai le plaisir de vous informer que votre projet de recherche a été approuvé à l'unanimité par le CERC.

Les documents que le CERC a approuvés et que vous pouvez utiliser pour la réalisation de votre projet sont disponibles dans la section **Documents approuvés par le CER**, située sous l'onglet "Fichier" de votre projet.

Cette approbation éthique est valide pour un an, à compter du 31 mars 2021 jusqu'au 31 mars 2022. Il est de votre responsabilité de compléter le formulaire de renouvellement (formulaire F9) que nous vous ferons parvenir annuellement via Nagano un mois avant l'échéance de votre approbation, à défaut de quoi l'approbation éthique délivrée par le CERC sera suspendue.

Dans le cadre du suivi éthique continu, le Comité vous demande de vous conformer aux exigences suivantes en utilisant les formulaires Nagano prévus à cet effet :

- Soumettre, pour **approbation préalable**, toute demande de **modification** au projet de recherche ou à tout autre document approuvé par le Comité pour la réalisation du projet (formulaire F1).
- Soumettre, dès que cela est porté à votre connaissance, tout nouveau renseignement, informations supplémentaires et/ou correspondances diverses (formulaire F2).
- Soumettre, seulement pour essais cliniques sous la juridiction de Santé Canada et dès que cela est porté à votre connaissance, tout événement indésirable grave et inattendu (EIGI) survenu dans votre site ou dans un site pour lequel le Comité a juridiction (formulaire F3).
- Soumettre, dès que cela est porté à votre connaissance, tout incident ou accident lié à la réalisation du projet de recherche (formulaire F5).
- Soumettre, dès que cela est porté à votre connaissance, l'interruption prématurée du projet de recherche, qu'elle soit temporaire ou permanente (formulaire F6).
- Soumettre, dès que cela est porté à votre connaissance, toute déviation au projet de recherche susceptible de remettre en cause le caractère éthique du projet (formulaire F8).
- Soumettre le rapport de la fin du projet de recherche (formulaire F10).

Nous vous rappelons que la présente décision vaut pour une année et peut être suspendue ou révoquée en cas de non-respect de ces exigences.

Le CERC de l'Université de Montréal est désigné par le ministre de la Santé et des Services Sociaux aux fins de l'application de l'article 21 du Code civil du Québec. Il exerce ses activités en conformité avec la *Politique sur la recherche avec des êtres humains* (60.1) de l'Université de Montréal ainsi que l'*Énoncé de politique des trois conseils* et les *Bonnes pratiques cliniques* de la CIH. Il suit également les normes et règlements applicables au Québec et au Canada.

Cordialement,

Pour la présidente du CERC, Nathalie Folch,

Camille Assemat
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