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Review

Melanopsin-expressing retinal ganglion cells in aging and disease

Gema Esquiva[1] and Jens Hannibal[2]

[1]Department of Optics, Pharmacology and Anatomy, University of Alicante, Alicante, Spain and [2]Department of Clinical Biochemistry, Bispebjerg Frederiksberg Hospital, University of Copenhagen, Copenhagen, Denmark

Summary. Melanopsin-expressing retinal ganglion cells (mRGCs) constitute a system in the mammalian retina used for irradiance detection, regulating non-image forming functions, such as photoentrainment of circadian rhythms, control of the pupillary light reflex, masking response, light-regulated melatonin secretion, and modulation of the sleep/wake cycle. There are five subtypes of mRGCs differentiated by morphology and function. Recent years of research on mRGCs have identified a broad number of neurodegenerative diseases in the eye and the brain with altered physiologic light responses, leading to disturbances of non-image forming light response(s). In this review, we briefly summarise the melanopsin system in the normal retina and discuss its role in connection to human aging (sleep/wake problems) and retinal pathology in Alzheimer and Parkinson diseases, diabetic retinopathy, mitochondrial optic neuropathies, glaucoma, retinitis pigmentosa, and in photophobia during migraine and in seasonal affective disorder (SAD). Finally, we discuss the diagnostic tools that are being used to differentiate retinal diseases involving the melanopsin system in the rods and cones from the inner versus the outer retina.

Key words: Alzheimer's disease, Parkinson disease, Diabetic retinopathy, Retinitis pigmentosa, mRGCs

Offprint requests to: Gema Esquiva, Department of Optics, Pharmacology and Anatomy, University of Alicante, Alicante, Spain. e-mail: gema.esquiva@ua.es or Jens Hannibal, Department of Clinical Biochemistry, Bispebjerg Frederiksberg Hospital, University of Copenhagen, Copenhagen, Denmark. e-mail: j.hannibal@dadlnet.dk

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Introduction

The mammalian eye contains a subset of retinal ganglion cells which are intrinsically photosensitive due to the expression of the photopigment melanopsin (OPN4). The melanopsin-expressing retinal ganglion cells (mRGCs), which show maximum sensitivity to the short-wavelength blue light, have been recently identified as a class of photoreceptors that mainly support non-image forming (NIF) visual functions of the eye (Do and Yau, 2010). These include photo-entrainment of circadian rhythms, masking, sleep regulation, pupillary light reflex, and light-induced suppression of melatonin secretion. mRGCs also seem to be implicated in behavioural responses such as mood (Hattar et al., 2006; Ksendzovsky et al., 2017) and in vision forming pathways via input from the classical photoreceptors, the cones and rods. Recently, the role in colour vision and brightness perception has been described (Schmidt et al., 2014; Spitschan et al., 2017; Cao et al., 2018; Woelders et al., 2018; Zele et al., 2018).

Since the discovery in melanophores of frog skin (giving it its name) (Provencio et al., 1998), melanopsin was found in a subset of RGCs in mouse and monkey (Provencio et al., 2000), and was elegantly demonstrated in a later study to render these cells intrinsically photosensitive (Berson et al., 2002). Subsequently, melanopsin cells were detected in the human retina (Hannibal et al., 2004; Dacey et al., 2005). The discovery of the melanopsin system in the mammalian retina and its important role in NIF functions explains the fact that blind people with loss of vision due to diseases in the outer retina maintain the ability to stay

photoentrained and have an intact pupillary light reflex.

Diseases involving the neuroretina may affect mRGCs or input pathways and for this reason symptoms representing NIF behaviour and physiology should be routinely investigated during elucidation of eye diseases.

In the present review, we will evaluate the implication of melanopsin RGCs in human diseases after a short description of the melanopsin system in humans.

Melanopsin-expressing RGCs in the human retina

Melanopsin-expressing RGCs in the human and primate retina have many similarities with mRGCs in other mammalian species. Initially, two subtypes of cells were described in rodents, and were classified based on the localization of their soma either in the ganglion cell layer (GCL) or in the inner nuclear cell layer (INL), as well as by their content of melanopsin (Do and Yau, 2010). M1 cells were found in the GCL and in the INL and have a high content of melanopsin, while M2 cells were found in the GCL and have a significantly lower content of melanopsin (Hughes et al., 2012). In mouse, two different forms of OPN4 were identified, a long and a short isoform, while M1 and M3 cells express the short form, the long isoform is expressed in all the mRGCs (Pires et al., 2009). A similar classification was also used in the human and primate retina (Hannibal et al., 2004; Dacey et al., 2005). In later studies in rodents at least 5 subtypes of mRGCs was described and named M1-M5 (Schmidt et al., 2011), while in humans 4 subtypes was found named M1-M4 (Hannibal et al., 2017). Furthermore, M1 cells can be subclassified based on soma size, "gigantic M1 (GM1)", and the location of their cell bodies in the GCL or displaced in the INL (dM1) (Liao et al., 2016; Esquiva et al., 2017; Hannibal et al., 2017) (Fig.1).

The different subtypes of mRGCs are widely distributed in the entire retina and the total number of mRGCs varies from 0.2-0.8 % of the total number of RGCs. This is most likely due to the antibodies avidity and immunohistochemical amplification techniques used in the different studies. Although the amount of mRGCs subtypes and their distribution in the retina differs between studies, the highest content of mRGCs is found in the fovea and perifoveal retina and the lowest content in the peripheral retina (Figs. 2-3) (Hannibal et al., 2004, 2017; Dacey et al., 2005; Liao et al., 2016; Esquiva et al., 2017; Nasir-Ahmad et al., 2017). M1 cells constitute the majority of mRGCs, while M2 and M4 cells are found in higher density in the nasal retina (Fig. 2).

Human and primate melanopsin cell bodies have their dendritic stratification in the innermost stratum of the inner plexiform layer (IPL, S5) and in the outermost stratum (S1) (Hannibal et al., 2004, 2014; Dacey et al., 2005; Dkhissi-Benyahya et al., 2006; La Morgia et al., 2010; Neumann et al., 2011). One subtype classified as M3 presents their dendritic stratification in both S1 and S5 strata of the IPL (Fig. 1) (Liao et al., 2016; Esquiva et al., 2017; Hannibal et al., 2017).

The different subtypes and the uneven distribution of melanopsin cells in the human retina seem to be associated with different NIF functions, as the different expression levels of melanopsin immunoreactivity in the various subtypes result in differences in "intrinsic" photosensitivity of the M1-M5 cells (Hannibal, 2006; Pires et al., 2009; Berson et al., 2010; Ecker et al., 2010).

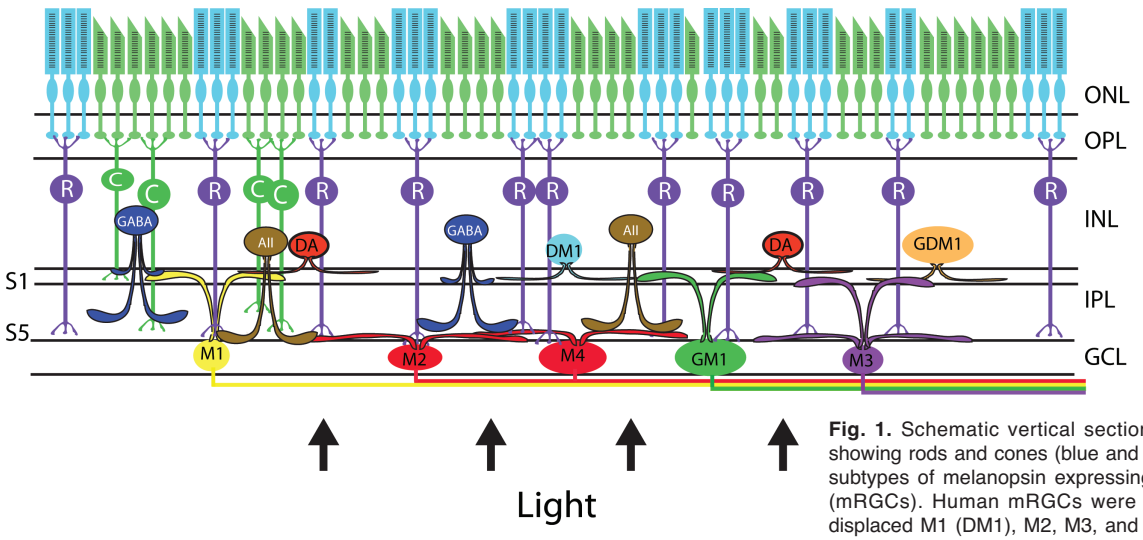

Fig. 1. Schematic vertical section of the human retina showing rods and cones (blue and green) and the diverse subtypes of melanopsin expressing retinal ganglion cells (mRGCs). Human mRGCs were sub-classified as M1, displaced M1 (DM1), M2, M3, and M4 cells. Furthermore, gigantic M1 cells located in the ganglion cell layer (GCL) (GM1) and displaced in the inner nuclear cell layer (INL) (GDM1) are shown. Dendritic processes from M1, GM1, GDM1and DM1 and M3 cells terminates in S1 of the inner plexiform layer (IPL) and dendritic processes from M2, M4 and M3 cells terminates in S5. Synaptic apposition between mRGCs and amacrine cells are found in S1, while synaptic appositions between mRGCs and rod bipolar cells are found in S5. ONL; outer nuclear cell layer, OPL; outer plexiform layer. (reproduction with permission from Wiley Global Permissions, reproduced from: J. Comp. Neurol. 525, 1934-1961, 2017.

mRGCs also express "extrinsic" photosensitivity due to different inputs to the various subtypes (Fig.1). In primates, including human retina, inputs to the mRGCs have been demonstrated in both inner and outer retina projecting dendrites showing synaptic appositions (Liao et al., 2016) with bipolar cells expressing the synaptic ribbon marker Ctbp2 (Jusuf et al., 2007; Grünert et al., 2011; Hannibal et al., 2017). The Ctpb2-containing synapses of bipolar cells have been suggested to mediate a yellow-ON response (Dacey et al., 2005). Specifically, rod bipolar axon terminals have been found in close apposition with M1, GM1, M2, and M4 cells in the GCL/innermost layer of the IPL (Hannibal et al., 2017). Furthermore, mRGCs also receive inputs from cone bipolar cells (Dacey et al., 2005; Grünert et al., 2011; Liao et al., 2016). In addition, mRGCs receive input from different kinds of amacrine cells (Bordt et al., 2017). Of these, AII amacrine cells make synaptic appositions with the innermost ON layer of the IPL, mostly with M1 and GM1 cells, and dopaminergic and GABAergic processes from amacrine cells to the outermost OFF layer of the IPL (Hannibal et al., 2017; Nasir-Ahmad et al., 2017; Vugler et al., 2007) (Fig. 1).

The melanopsin-expressing RGCs constitute the neuronal monosynaptic pathway to retinal target areas in the brain involved primarily in non-image perception, a pathway known as the retino-hypothalamic tract (RHT) (Hannibal and Fahrenkrug, 2006). The major target areas of the RHT in primates are the brain clock located in the suprachiasmatic nucleus (SCN), the pretectum, the lateral geniculate complex (Hannibal et al., 2014), and the superior colliculus and the pretectum (Dacey et al., 2005; Hannibal et al., 2014). In primates, both the pretectum and the superior colliculus are involved in image forming perception (Dacey et al., 2005).

mRGCs in the aging human retina

During aging, many circadian regulated functions such as melatonin secretion, cortisol secretion and core body temperature are disrupted (Cajochen et al., 2006) with decreased amplitude, phase advancement and/or altered circadian period (Myers and Badia, 1995; Cajochen et al., 2006). Especially the sleep/wake cycle is often found affected in the elderly (Van Someren, 2000).

Several factors seem to be associated with circadian dysfunction in the aging process. While neurodegenerative changes in the SCN may alter the temporal organization of this structure, altered light

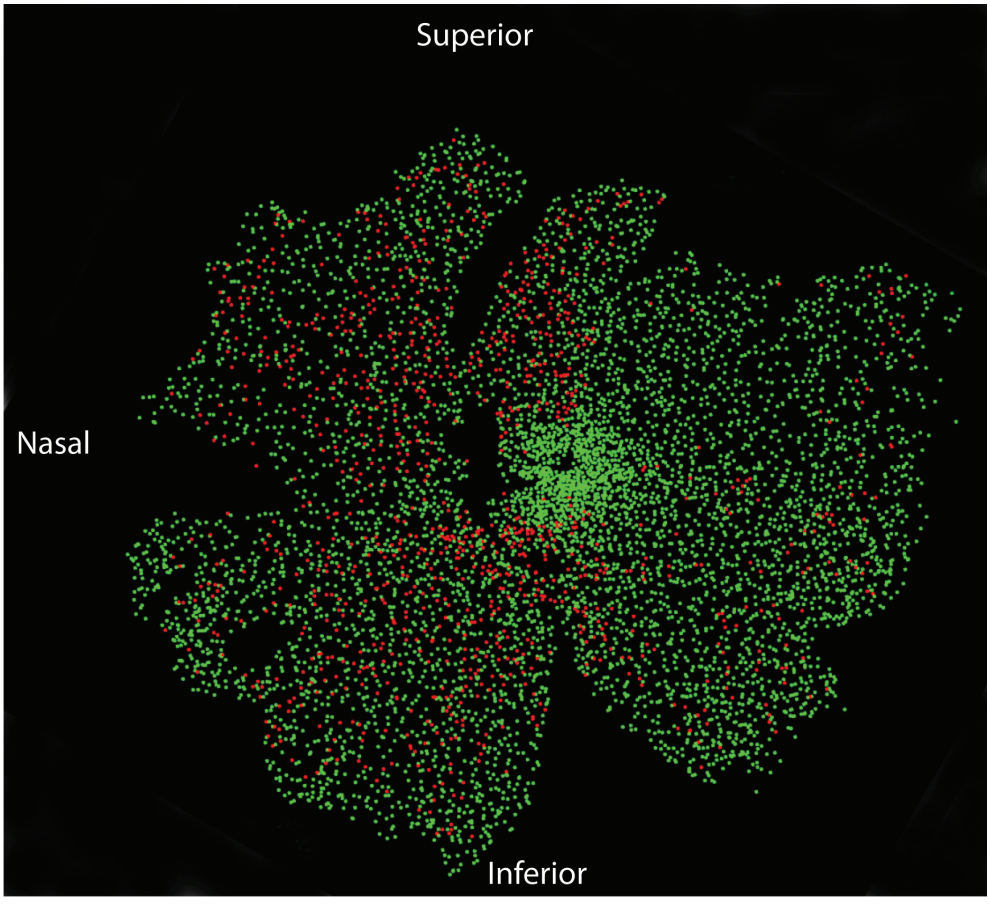

Fig. 2. Melanopsin immunoreactive retinal ganglion cells in a female human retina (age 67) with a total of 7046 mRGCs. M2 and M4 subtype of mRGCs are shown in red dots, other subtypes (see Fig. 1) are marked by green dots. Note the higher density of M2/M4 cells in the nasal part of the retina.

perception caused by a reduction in the capacity to transmit short wavelength light due to a semicataractous lens is observed in aged people (Hofman and Swaab, 2006). In addition, aging affects retinal functions and produces many degenerative changes in the retina and optic nerve (Johnson et al., 1987; Gao and Hollyfield, 1992; Curcio and Drucker, 1993; Harman et al., 2000; Eliasieh et al., 2007). These include the loss of RGCs (La Morgia et al., 2016), which has been associated with the disturbances in circadian timing (Van Someren, 2000; Karasek and Reiter, 2002). Alterations in retinal functions include disturbances in electroretinographic responses (Jackson et al., 2002), contrast and visual field sensitivity (Johnson et al., 1989; Elliott et al., 1990; Spry and Johnson, 2001), and adaptation to darkness (Jackson et al., 1999). Although mRGCs have demonstrated a high resistance to injury even in advanced stages of retinal degeneration (Esquiva et al., 2013; Cuenca et al., 2014; García-Ayuso et al., 2015; Lax et al., 2016), recent studies showed that in humans the mRGCs density and plexus decrease with age, correlating with the circadian rhythm dysfunction observed in people over 70 years of age (La Morgia et al., 2010; Esquiva et al., 2017). These observations in the human retina correspond to observations that have also been described in rodents (Semo et al., 2003b). Furthermore, the presence of

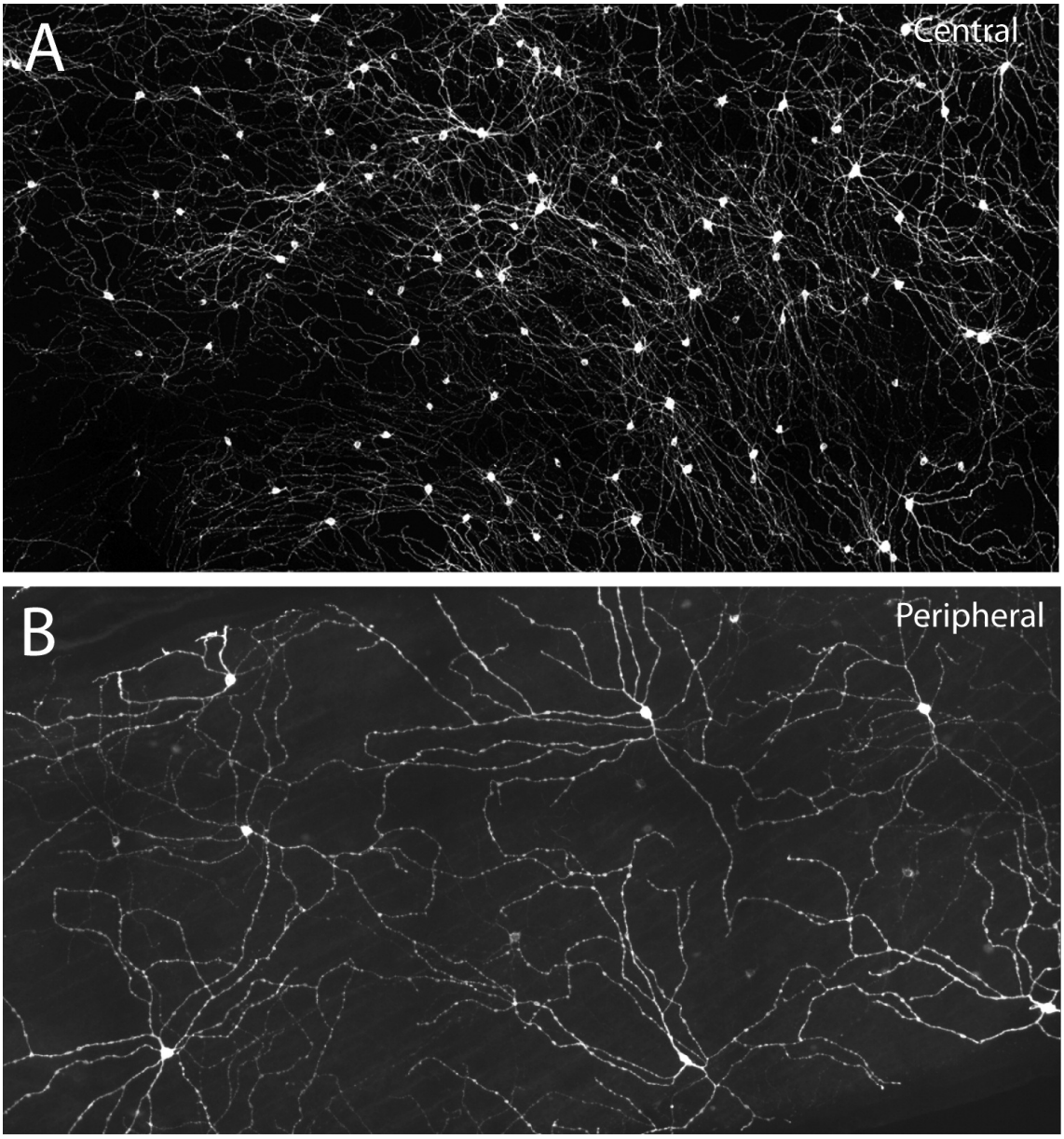

Fig. 3. Melanopsin immunoreactive RGCs in the human retina representing an area with high cell density **(A)** of the perifoveal/foveal retina and with low density of cells **(B)** from the peripheral retina.

lipofuscin found in melanopsin cells of increasing age could influence their functionality (Vugler et al., 2007). Lipofuscin is an autofluorescent photoinducible free radical generator which accumulates with age in active cells (Sparrow and Boulton, 2005). This accumulation of lipofuscin in mRGCs may lead to disrupted function and may play a significant role in the alterations of circadian rhythms with aging in humans (Hofman and Swaab, 2006).

mRGCs in human diseases

Alzheimer

Alzheimer's disease (AD) is a chronic neurodegenerative disease and the most common cause of dementia in older adults, characterized by the accumulation of amyloid-β protein in both cerebral and retinal blood vessels and neurofibrillary tangles (Arriagada et al., 1992). The disease is characterized by memory loss and can include confusion and behavioural disorders.

In addition to circadian alterations of melatonin, temperature rhythms and rest-activity, disruptions have been described in AD (Tranah et al., 2011) correlating with the severity of dementia (Dai et al., 1998), although not progressing at the same rate (Hatfield et al., 2004). Circadian rhythm dysfunctions are frequent in aging, but are even more pronounced in AD (Wu and Swaab, 2007) and the neuronal loss in the SCN has been considered one of the major risk factors for the circadian rhythms disturbances (Swaab et al., 1985; Stopa et al., 1999; Harper et al., 2008).

However, the loss of RGCs and/or degeneration of axons in the optic nerve has also been reported in AD patients (Hinton et al., 1986). The optic nerve shows a predominant loss of the magnocellular RGCs known to mediate specific visual funcions (Sadun and Bassi, 1990). AD neuropathy also affects the inner retina (Blanks et al., 1989). Interestingly, the decrease in RGCs is greatest in the central zone, more specifically in the foveal and parafoveal zone of the retina (Blanks et al., 2012), confirmed by OCT studies showing a significantly reduced number of RGCs in AD retinas vs. controls in the macular zone (Cheung et al., 2015), which is the area with the highest number of mRGCs. Despite the loss of mRGCs observed with aging that may contribute to circadian dysfunction in AD alone, a recent study described a greater loss of mRGCs in AD patients in comparison with controls of the same age. In this study a total loss of RGCs was reported, but mRGCs were specifically affected in AD, degenerating before visual bearing RGCs, even in younger patients with a normal RGCs count (La Morgia et al., 2016). Moreover, AD deposits were found inside and around the remaining mRGCs, which showed morphological abnormalities with a reduction of the dendritic diameter and axonal loss. Thus, it was proposed that mRGCs are primarily affected by AD pathology and their loss may contribute to the circadian dysfunction described in AD (La Morgia et al., 2016). Interestingly, this loss could be correlated with another NIF function of mRGCs, a reduction in amplitude of PLR (Tales et al., 2001; La Morgia et al., 2016).

Parkinson

Parkinson's disease (PD) is the second most common neurodegenerative disease, characterized by the loss of dopaminergic neurons in the substancia nigra, the formation of Lewy bodies, and the accumulation of α-synuclein phosphorylated at serine-129 (p-α-syn) (Fahn, 2006; Beach et al., 2009).

PD patients mainly suffer from motor clinical features such as rigidity, tremor, and bradykinesia (Fahn, 2006; Postuma et al., 2015; Ferreira and Massano, 2017). However, several non-motor symptoms including cognitive decline (Caballol et al., 2007), mood disturbance (Tan, 2012), visual disruption (Archibald et al., 2009; Weil et al., 2016), impairment of the pupillary reflex response (Wang et al., 2016), sleep dysregulation (Fahn, 2006; Postuma et al., 2015) and alteration of the circadian regulated secretion of melatonin also occur in PD (Bordet et al., 2003).

Visual problems include dry eyes, blinking, colour vision alterations, impaired motion perception, and lower contrast sensitivity (Archibald et al., 2011; Lin et al., 2015). The contrast sensitivity abnormalities are explained by the retinal dopaminergic depletion that occurs in PD (Bodis-Wollner, 1990; Harnois and Di Paolo, 1990). The connectivity between dopaminergic amacrine cells, RGCs and mRGCs (Zhang et al., 2008) could also explain the loss of RGCs occurring in PD (Lee et al., 2014; Yu et al., 2014a,b) affecting above all the temporal sector of the optic nerve (La Morgia et al., 2013; Yu et al., 2014a,b) containing the parvocellular component, in contrast to what has been described in AD above, which mainly affects magnocellular RGCs (La Morgia et al., 2017).

Dysfunction of circadian rhythms in PD has been explained recently among different mechanisms by the occurrence of Lewy pathology in the SCN from PD patients (De Pablo-Fernández et al., 2018). However, the occurrence of retinal pathology involving mRGCs may also contribute to circadian disturbance. Two studies have recently reported the presence of α-synuclein in the inner retina of PD patients in large cells resembling mRGCs (Beach et al., 2014; Bodis-Wollner et al., 2014), and it was recently shown that mRGCs are lost in PD patients compared to control subjects and furthermore, the remaining mRGCs demonstrated morphological alterations (Ortuño-Lizarán et al., 2018). As retinal mRGCs are responsible for light entrainment of circadian rhythms and nocturnal melatonin secretion and are involved in mood and sleep regulation, these morphological alterations in mRGCs could explain the circadian disruptions found in PD patients.

Diabetic retinopathy (DR)

Diabetic retinopathy (DR) is characterised by alterations in the retinal vasculature and is one of the major complications of diabetes (Keats and Khan, 2012) and the major cause of preventable blindness in developed countries (Congdon, 2003). DR symptoms can include floaters (dark spots), blurred vision, impaired colour vision, and vision loss (Cheung et al., 2010). Non-proliferative diabetic retinopathy is characterized by a breakdown of the blood-barrier, mycroaneurysm, pericyte, and vascular smooth muscle cell dropout and haemorrhages. Furthermore, in the advanced stages of the disease, in the proliferative phase, there is angiogenesis which can even lead to retinal detachment (Fletcher et al., 2007; Curtis et al., 2009). Despite its vascular nature, DR is also a neurodegenerative disease and clinical symptoms often occur after an alteration in the retina at the molecular, cellular and functional level (Bearse et al., 2004; Fletcher et al., 2007; Ng et al., 2008; Ola and Alhomida, 2014), affecting all types of retinal cells (Barber et al., 1998; El-Asrar et al., 2004; Kern and Barber, 2008). In a recent study, the expression of mRGCs in the ganglion cell layer and the inner nuclear layer of the human retina was found to be significantly reduced compared to age comparable control group (Obara et al., 2017). This loss could explain the alteration in circadian rhythms and sleep disturbances found in patients with severe DR and may also explain the pupillary defects and the abnormal regulation of melatonin and blood pressure during the day (Hikichi et al., 2011; Afsar, 2015; Kadono et al., 2016).

Altered post-illumination pupil response (PIPR) seems to develop prior to neurodegeneration of conventional RGCs (Su et al., 2008; Feigl et al., 2012) and could be used to identify early neurodegeneration at the initial stages of DR (see also below).

Mitochondrial optic neuropathies

Optic neuropathies due to mitochondrial dysfunctions found in Leber hereditary optic neuropathy (LHON) and dominant optic atrophy (DOA) are characterized by the loss of RGCs leading to the loss of vision (Carelli et al., 2004). Despite blindness, patients with these diseases preserve the pupillary light reflex (Wakakura and Yokoe, 1995; Bremner et al., 2001; Kawasaki et al., 2010; Ba-ali and Lund-andersen, 2017), light-induced melatonin suppression (Czeisler et al., 1995; Hatonen and Santavuori, 1998; Pérez-Rico et al., 2009), and intact circadian rhythm regulation (Moura et al., 2013).

La Morgia et al. corroborate the preservation of NIF functions carried out by mRGCs in these mitochondrial optic neuropathy patients and while mRGCs are lost and impaired in the elderly, they resist neurodegeneration due to mitochondrial dysfunction, while other RGCs are not resistant (La Morgia et al., 2010). These findings are in concordance with the preservation of the retinofugal pathway to the olivary nuclei of the pretectum described in LHON, the main target areas of mRGCs (Bose et al., 2005).

Several authors provide supporting evidence for the resistance of mRGCs to different injuries (Vugler et al., 2008; Cui et al., 2015). It has been suggested that factors contributing to the resistance of mRGCs, such as the abundant mitochondrial population found in these cells, result in specific metabolic properties and higher mitochondrial activity compared to the rest of RGCs (La Morgia et al., 2011). This could be coupled to their intrinsic photosensitivity provided by the melanopsin photopigment, which may protect from light damage and ROS overproduction (Osborne et al., 2014; González-Menéndez et al., 2015). Another possibility suggested is the expression of the neuroprotective pituitary adenylate cyclase-activating polypeptide (PACAP) in mRGCs (Hannibal et al., 2004) which could be involved in the increased resistance to injuries, although this is still being debated (Hannibal et al., 2002, 2004; Georg et al., 2017).

Glaucoma optic neuropathy

Glaucoma is an ocular neuropathy characterized by ganglion cell death and optic nerve fibre loss, resulting in a loss of peripheral vision (Weinreb et al., 2014). This loss of RGCs is more selective on magnocellular RGCs losing larger optic nerve fibres more rapidly and resembling the axonal loss described in AD (Quigley et al., 1988). The loss of RGCs is probably due to two common events in the pathophysiology of glaucoma, the increased intraocular pressure and the vascular dysregulation (Gupta et al., 2009).

In glaucoma patients, a number of symptoms related to loss of mRGCs functions has been described, such as the loss of circadian rhythms (Jean-Louis et al., 2008; de Zavalía et al., 2011), impairment of the pupillary light reflex (Feigl et al., 2011; Kankipati et al., 2011; Nissen et al., 2014), and an alteration of the PIPR (Feigl et al., 2011). Similar alterations have been found in an animal model of chronic ocular hypertension and glaucoma which demonstrates a reduced density of mRGCs (de Zavalía et al., 2011). However, studies of mRGCs in another animal model of glaucoma of high intraocular pressure obtained opposite results regarding mRGCs survival, indicating that several pathological mechanisms of glaucoma co-exist (Li et al., 2006).

However, the functional alterations of glaucoma have been corroborated more recently by Obara et al, who found a decrease in the density of mRGCs in human retinas with advanced stages of glaucoma, and with a significant loss primarily in the GCL and sparing of mRGCs in the INL (Obara et al., 2016). Moreover, a decreased PIPR in advanced glaucoma (Rukmini et al., 2015) seems to correlate with visual field defect (Kankipati et al., 2011), suggesting that advanced glaucoma affects both non-image forming (mRGCs) and

image-forming function.

Retinitis pigmentosa

Retinitis pigmentosa (RP) is an inherited neurodegenerative retinal disease characterized by a progressive peripheral and night vision loss because of different mutations in the rhodopsin encoding gene leading to rod degeneration at early stages. This rod disturbance leads to cone impairments with a consequent central vision loss in advanced stages of the disease and the loss of photoreceptors is accompanied by degenerative changes in the inner retina (Marc et al., 2003; Kolomiets et al., 2010) and a degeneration of RGCs (García-Ayuso et al., 2010).

P23H mutation in the rhodopsin gene is the most prevalent in RP patients (Dryja et al., 1990). Recently, NIF function such as circadian dysfunctions (Lax et al., 2011, 2016) and a significantly reduced PLR were demonstrated in patients with RP (Kardon et al., 2011). In accordance, RP patients have been shown to exhibit sleep/wake disorders (Gordo et al., 2001; Ionescu et al., 2001) and circadian rhythm alterations of blood pressure and heart rate (Cugini et al., 2001). In a casuistic report, patients with RP demonstrated a severe degeneration in all layers of the retina and only few mRGCs were identified (Hannibal et al., 2004). In a rat model of RP, the degeneration of mRGCs was relatively belated compared to non-melanopsin RGCs (Esquiva et al., 2013), corroborating previous studies in other animal models of RP (Semo et al., 2003a; Vugler et al., 2008). The decrease of mRGCs only in advanced stages of retinal degeneration supports the previous described resistance to cell injury (Robinson and Madison, 2004; Li et al., 2006, 2008).

Migraine (photophobia)

Migraine is a common episodic neurological dysfunction characterized by increased sensory perception (Noseda et al., 2010a). Migraine pain was thought to originate in different cortical areas, including the visual cortex, but recently it was suggested that the migraine process may occur at a retino-cortical pathway (Evans and Digre, 2003; Noseda and Burstein, 2011). This painful photophobia depends on both the optic and trigeminal nerve integrity (Lebensohn, 1951).

Migraineurs suffer from photophobia, experiencing headaches that intensify with light, increased perception of brightness, and visual discomfort. These alterations in the visual system give rise to visual hallucinations and visual aura (Noseda et al., 2019).

Much progress has been made in the knowledge of the visual pathways that contribute to photophobia in migraine, and recently activation of abnormal cone-driven retinal pathway has been proposed (Noseda et al., 2016) causing negative emotions during the migraine (Noseda et al., 2017).

Studies on photophobia in blind persons with intact inner retina/optic nerve and blind persons without optic nerve/eyes observed that blind subjects who still maintained light perception also presented photophobia in migraines, while blind subjects who no longer had any type of light perception did not present photophobia (Noseda et al., 2010b). These observations indicate a role of mRGCs in photophobia and migraine. Furthermore, mRGCs may control light aversion and negative phototaxis (Johnson et al., 2010; Matynia et al., 2012). However, future studies are needed to clarify neuronal pathways and mechanism coupling input from mRGCs and activation of the trigeminal nociceptors involved in painful photophobia (Dolgonos et al., 2011).

Seasonal affective disorder (SAD)

Seasonal affective disorder (SAD) is a subtype of mood disorder characterized by recurrent episodes of major depression occurring with a seasonal pattern starting during fall and winter and with full remission during spring and summer (Rosenthal et al., 1986). One major reason for the development of this condition seems to be the lack of bright light, supported by the efficacy of bright light therapy (Terman and Terman, 2005). With the discovery of mRGCs it has been hypothesized that light transmitted via the RHT regulating non-image forming functions, including melatonin secretion, could be involved in SAD (McClung, 2007). Melatonin is a night signal released from the pineal gland and targets the brain clock located in the SCN. Melatonin is strongly regulated by the SCN and by light, and the circadian secretion of melatonin is delayed in SAD patients compared to normal controls (Lewy et al., 1998; Pandi-Perumal et al., 2007). Bright light in the morning seems most effective due to its phase shifting properties causing early morning phase advance of the clock (Lewy et al., 1987), leading to synchronization of the circadian rhythm of melatonin and the sleep/wake cycle (Pandi-Perumal et al., 2007).

Demonstration of a missense variant (P10L and 1394T) of the melanopsin gene (OPN4) which may affect NIF light transmission has been associated with the occurrence of SAD (Roecklein et al., 2009, 2013). Furthermore, the PIPR often used for the evaluation of mRGCs function (see below) demonstrated that the 1394T, but not the P10L genotype, was affected in SAD patients (Roecklein et al., 2013). Interestingly, a study in non-seasonal major depression found normal PIPR in depressed patients similar to controls, suggesting that melanopsin function plays a minor role in the development of major depression (Feigl et al., 2018) .

Functional evaluation of the non-image forming system

Since the discovery of the melanopsin system in the mammalian eye, functional methods for evaluation of the NIF system is needed. Melanopsin-expressing RGCs located in the inner retina demonstrate a high sensitivity

for blue light with a higher threshold of activation compared to the rods and cones located in the outer retina. Both rods and cones contribute in the input to the mRGCs during non-image forming light perceptions (Do and Yau, 2010; Liao et al., 2016; Hannibal et al., 2017; Nasir-Ahmad et al., 2017). A simple, non-invasive method that seems to be able to discriminate diseases affecting the inner and outer retina is to measure the pupillary light responses (PLR) (Nissen et al., 2015; La Morgia et al., 2018; Rukmini et al., 2019). PLR are dependent on the integrity of mRGCs projections and the interaction between the outer and inner retinal photoreception, thereby indicating both outer retinal function of rod and cone photoreceptors, and inner retinal functions from mRGCs (Spitschan and Woelders, 2018; Kelbsch et al., 2019) .

In fact, PIPR and chromatic pupillometry may become clinical indicators of progressive changes in the retina (Ostrin et al., 2018) and a tool to evaluate the integrity of visual functions and localize retinal dysfunctions in various ocular diseases, like glaucoma and diabetes.

Conclusions

While it is well established that the loss of mRGCs is involved in circadian rhythms, sleep, cognitive, and mood pathologies, the role of these cells in different disorders is beginning to be understood. Recent research is stating the functions of mRGCs in human visual and non-visual diseases with advances in the description of the activity of these cells with aging, and in different diseases.

The discovery of the melanopsin system in the mammalian eye highlights the importance of the regulation of non-image forming function, which can be present even in cases of severe blindness. The measurement of PLR, which is already being used in some diseases such as age-related macular degeneration or diabetic retinopathy, may provide information on the state of the mRGCs and seems to be a promising technique for clinical evaluation in the control and progression of diseases involving the inner (mRGCs) and outer retina.

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References

Afsar B. (2015). Disruption of circadian blood pressure, heart rate and the impact on glycemic control in type 1 diabetes. Diabetes Metab. Syndr. Clin. Res. Rev. 9, 359-363.

Archibald N.K., Clarke M.P., Mosimann U.P. and Burn D.J. (2011). Visual symptoms in Parkinson's disease and Parkinson's disease dementia. Mov. Disord. 26, 2387-2395.

Archibald N.K., Clarke M.P., Mosimann U.P. and Burn D.J. (2009). The retina in Parkinson's disease. Brain 132, 1128-1145.

Arriagada P.V, Growdon J.H., Hedley-Whyte E.T. and Hyman B.T. (1992). Neurofibrillary tangles but not senile plaques parallel duration and severity of Alzheimer's disease. Neurology 42, 631-639.

Ba-Ali S. and Lund-Andersen H. (2017). Pupillometric evaluation of the melanopsin containing retinal ganglion cells in mitochondrial and non-mitochondrial optic neuropathies. Mitochondrion 36, 124-129.

Barber A.J., Lieth E., Khin S.A., Antonetti D.A., Buchanan A.G. and Gardner T.W. (1998). Neural apoptosis in the retina during experimental and human diabetes: Early onset and effect of insulin. J. Clin. Invest. 102, 783-791.

Beach T.G., Adler C.H., Lue L., Sue L.I., Bachalakuri J., Henry-Watson J., Sasse J., Boyer S., Shirohi S., Brooks R., Eschbacher J., White C.L. 3rd, Akiyama H., Caviness J., Shill H.A., Connor D.J., Sabbagh M.N. and Walker D.G. (2009). Unified staging system for Lewy body disorders: correlation with nigrostriatal degeneration, cognitive impairment and motor dysfunction. Acta Neuropathol. 117, 613-634.

Beach T.G., Carew J., Serrano G., Adler C.H., Shill H.A., Sue L.I., Sabbagh M.N., Akiyama H., Cuenca N., Caviness J., Driver-Dunckley E., Jacobson S., Belden C. and Davis K. (2014). Phosphorylated α-synuclein-immunoreactive retinal neuronal elements in Parkinson's disease subjects. Neurosci. Lett. 571, 34-38.

Bearse M.A., Han Y., Schneck M.E. and Adams A.J. (2004). Retinal function in normal and diabetic eyes mapped with the slow flash multifocal electroretinogram. Invest. Ophthalmol. Vis. Sci. 45, 296-304.

Berson D.M., Castrucci A.M. and Provencio I. (2010). Morphology and mosaics of melanopsin-expressing retinal ganglion cell types in mice. J. Comp. Neurol. 2422, 2405-2422.

Berson D.M., Dunn F.A. and Takao M. (2002). Phototransduction by retinal ganglion cells that set the circadian clock. Science 295, 1070-1073.

Blanks J.C., Hinton D.R., Sadun A.A. and Miller C.A. (1989). Retinal ganglion cell degeneration in Alzheimer's disease. Brain Res. 501, 364-372.

Blanks J.C., Torigoe Y., Hinton D.R. and Blanks R.H. (2012). Retinal pathology in Alzheimer's disease. I. Ganglion cell loss in foveal/parafoveal retina. Neurobiol. Aging 17, 377-384.

Bodis-Wollner I. (1990). Visual deficits related to dopamine deficiency in experimental animals and Parkinson's disease patients. Trends Neurosci. 13, 296-302.

Bodis-Wollner I., Kozlowski P.B., Glazman S. and Miri, S. (2014). α-synuclein in the inner retina in Parkinson disease. Ann. Neurol. 75, 964-966.

Bordet R., Devos D., Brique S., Touitou Y., Guieu J.D., Libersa C. and Destée A. (2003). Study of circadian melatonin secretion pattern at different stages of Parkinson's disease. Clin. Neuropharmacol. 26, 65-72.

Bordt A.S., Long Y., Kouyama N., Yamada E.S., Hannibal J. and Marshak D.W. (2017). Wavy multistratified amacrine cells in the monkey retina contain immunoreactive secretoneurin. Peptides 94, 33-42.

Bose S., Dhillon N., Ross-Cisneros F.N. and Carelli V. (2005). Relative post-mortem sparing of afferent pupil fibers in a patient with 3460 Leber's hereditary optic neuropathy. Graefes Arch. Clin. Exp. Ophtalmol. 243, 1175-1179.

Bremner F.D., Tomlin E.A., Hoffmann J.S., Votruba M. and Smith S.E. (2001). The pupil in dominant optic atrophy. Invest. Ophtalmol. Vis.

Sci. 42, 675-678.

Caballol N., Martí M.J. and Tolosa E. (2007). Cognitive dysfunction and dementia in Parkinson disease. Mov. Disord. 22, 358-366.

Cajochen C., Münch M., Knoblauch V., Blatter K. and Wirz-Justice A. (2006). Age-related Changes in the Circadian and Homeostatic Regulation of Human Sleep. Chronobiol. Int. 23, 461-474.

Cao D., Chang A. and Gai S. (2018). Evidence for an impact of melanopsin activation on unique white perception. J. Opt. Soc. Am. A. Opt. Image Sci. Vis. 35, B287-B291.

Carelli V., Ross-Cisneros F.N. and Sadun, A.A. (2004). Mitochondrial dysfunction as a cause of optic neuropathies. Prog. Retin. Eye Res. 23, 53-89.

Cheung C.Y.L., Ong Y.T., Hilal S., Ikram M.K., Low S., Ong Y.L., Venketasubramanian N., Yap P., Seow D., Chen C.L.H. and Wong T.Y. (2015). Retinal ganglion cell analysis using high-definition optical coherence tomography in patients with mild cognitive impairment and alzheimer's disease. J. Alzheimer's Dis. 45, 45-56.

Cheung N., Mitchell P. and Wong T.Y. (2010). Diabetic retinopathy. Lancet 376, 124-136.

Congdon N.G. (2003). Important causes of visual impairment in the world today. JAMA 290, 2057-2060.

Cuenca N., Fernández-Sánchez L., Campello L., Maneu V., De la Villa P., Lax P. and Pinilla I. (2014). Cellular responses following retinal injuries and therapeutic approaches for neurodegenerative diseases. Prog. Retin. Eye Res. 43, 17-75.

Cugini P., Cruciani F., De Rosa R., Pellegrino A.M., Fontana S., Coda S., De Francesco G.P., Mastromatteo A., Antonelli B., Vingolo E.M. and Regine F. (2001). Alterations of blood pressure and heart rate circadian rhythmic structure in non-blind patients affected by retinitis pigmentosa. J. Hum. Hypertens. 15, 577-581.

Cui Q., Ren C., Sollars P.J., Pickard G.E. and So K.-F. (2015). The injury resistant ability of melanopsin-expressing intrinsically photosensitive retinal ganglion cells. Neuroscience 284, 845-853.

Curcio C.A. and Drucker D.N. (1993). Retinal ganglion cells in Alzheimer's disease and aging. Ann. Neurol. 33, 248-257.

Curtis T., Gardiner T. and Stitt A. (2009). Microvascular lesions of diabetic retinopathy: clues towards understanding pathogenesis? Eye 23, 1496-1508.

Czeisler C., Shanahan T., Klerman E., Martens H., Brotman D., Emens J., Klein T. and Rizzo J. (1995). Suppression of melatonin secretion in some blind patients by exposure to bright light. N. Engl. J. Med. 332, 6-11.

Dacey D.M., Liao H.-W., Peterson B.B., Robinson F.R., Smith V.C., Pokorny J., Yau K. and Gamlin P.D.R. (2005). Melanopsin-expressing ganglion cells in primate retina signal colour and irradiance and project to the LGN. Nature 433, 749-754.

Dai J., Swaab D.F., Van Der Vliet J. and Buijs R.M. (1998). Postmortem tracing reveals the organization of hypothalamic projections of the suprachiasmatic nucleus in the human brain. J. Comp. Neurol. 400, 87-102.

De Pablo-Fernández E., Courtney R., Warner T.T. and Holton J.L. (2018). A histologic study of the circadian system in parkinson disease, multiple system atrophy, and progressive supranuclear palsy. JAMA Neurol. 75, 1008.

de Zavalía N., Plano S.A., Fernandez D.C., Lanzani M.F., Salido E., Belforte N., Sarmiento M.I.K., Golombek D.A. and Rosenstein R.E. (2011). Effect of experimental glaucoma on the non-image forming visual system. J. Neurochem. 117, 904-914.

Dkhissi-Benyahya O., Rieux C., Hut R.A. and Cooper H.M. (2006). Immunohistochemical evidence of a melanopsin cone in human retina. Invest. Ophthalmol. Vis. Sci. 47, 1636-1641.

Do M. and Yau K. (2010). Intrinsically photosensitive retinal ganglion cells. Physiol. Rev. 1547-1581.

Dolgonos S., Ayyala H. and Evinger C. (2011). Light-induced trigeminal sensitization without central visual pathways: Another mechanism for photophobia. Investig. Ophthalmol. Vis. Sci. 52, 7852-7858.

Dryja T.P., McGee T.L., Reichel E., Hahn L.B., Cowley G.S., Yandell D.W., Sandberg M.A. and Berson E.L. (1990). A point mutation of the rhodopsin gene in one form of retinitis pigmentosa. Nature 343, 364-366.

Ecker J.L., Dumitrescu O.N., Wong K.Y., Alam N.M., Legates T., Renna J.M., Prusky G.T. and Berson D.M. (2010). Melanopsin-expressing retinal ganglion-cell photoreceptors: cellular diversity and role in pattern vision. Neuron 67, 49-60.

El-Asrar A.M.A., Dralands L., Missotten L., Al-Jadaan I.A. and Geboes K. (2004). Expression of apoptosis markers in the retinas of human subjects with diabetes. Investig. Opthalmology Vis. Sci. 45, 2760-2766.

Eliasieh K., Liets L.C. and Chalupa L.M. (2007). Cellular reorganization in the human retina during normal aging. Invest. Ophthalmol. Vis. Sci. 48, 2824-2830.

Elliott D., Whitaker D. and MacVeigh D. (1990). Neural contribution to spatiotemporal contrast sensitivity decline in healthy ageing eyes. Vision Res. 30, 541-547.

Esquiva G., Lax P. and Cuenca N. (2013). Impairment of intrinsically photosensitive retinal ganglion cells associated with late stages of retinal degeneration. Invest. Ophthalmol. Vis. Sci. 54, 4605-4618.

Esquiva G., Lax P., Pérez-Santonja J.J., García-Fernández J.M. and Cuenca, N. (2017). Loss of melanopsin-expressing ganglion cell subtypes and dendritic degeneration in the aging human retina. Front. Aging Neurosci. 9, 1-17.

Evans R.W. and Digre K.B. (2003). Light sensitivity in migraineurs. Headache 43, 917-920.

Fahn S. (2006). Description of Parkinson's disease as a clinical syndrome. Ann. NY Acad. Sci. 991, 1-14.

Feigl B., Mattes D., Thomas R. and Zele A.J. (2011). Intrinsically photosensitive (melanopsin) retinal ganglion cell function in glaucoma. Invest. Ophthalmol. Vis. Sci. 52, 4362-4367.

Feigl B., Ojha G., Hides L., Zele and A.J. (2018). Melanopsin-driven pupil response and light exposure in non-seasonal major depressive disorder. Front. Neurol. 9, 1-5.

Feigl B., Zele A.J., Fader S.M., Howes A.N., Hughes C.E., Jones K.A. and Jones R. (2012). The post-illumination pupil response of melanopsin-expressing intrinsically photosensitive retinal ganglion cells in diabetes. Acta Ophthalmol. 90, 230-234.

Ferreira M. and Massano J. (2017). An updated review of Parkinson's disease genetics and clinicopathological correlations. Acta Neurol. Scand. 135, 273-284.

Fletcher E., Phipps J., Ward M., Puthussery T. and Wilkinson-Berka J. (2007). Neuronal and glial cell abnormality as predictors of progression of diabetic retinopathy. Curr. Pharm. Des. 13, 2699-2712.

Gao H. and Hollyfield J.G. (1992). Aging of the human retina. Differential loss of neurons and retinal pigment epithelial cells. Invest. Ophthalmol. Vis. Sci. 33, 1-17.

García-Ayuso D., Salinas-Navarro M., Agudo M., Cuenca N., Pinilla I., Vidal-Sanz M. and Villegas-Pérez M.P. (2010). Retinal ganglion cell numbers and delayed retinal ganglion cell death in the P23H rat

retina. Exp. Eye Res. 91, 800-810.

García-Ayuso D., Di Pierdomenico J., Esquiva G., Nadal-Nicolás F.M., Pinilla I., Cuenca N., Vidal-Sanz M., Agudo-Barriuso M. and Villegas-Pérez M.P. (2015). Inherited photoreceptor degeneration causes the death of melanopsin-positive retinal ganglion cells and increases their coexpression of Brn3a. Invest. Opthalmol. Vis. Sci. 56, 4592-4604.

Georg B., Ghelli A., Giordano C., Ross-Cisneros F.N., Sadun A.A., Carelli V., Hannibal J. and La Morgia C. (2017). Melanopsin-expressing retinal ganglion cells are resistant to cell injury, but not always. Mitochondrion 36, 77-84.

González-Menéndez I., Reinhard K., Tolivia J., Wissinger B. and Münch T.A. (2015). Influence of Opa1 mutation on survival and function of retinal ganglion cells. Invest. Opthalmol. Vis. Sci. 56, 4835-4845.

Gordo M.A., Recio J. and Sánchez-Barceló E.J. (2001). Decreased sleep quality in patients suffering from retinitis pigmentosa. J. Sleep Res. 10, 159-164.

Grünert U., Jusuf P.R., Lee S.C.S. and Nguyen D.T. (2011). Bipolar input to melanopsin containing ganglion cells in primate retina. Vis. Neurosci. 28, 39-50.

Gupta S., Agarwal P., Saxena R., Agrawal S. and Agarwal R. (2009). Current concepts in the pathophysiology of glaucoma. Indian J. Ophthalmol. 57, 257-266.

Hannibal J. (2006). Regulation of melanopsin expression. Chronobiol. Int. 23, 159-166.

Hannibal J. and Fahrenkrug J. (2006). Neuronal input pathways to the brain's biological clock and their functional significance. Adv. Anat. Embryol. Cell Biol. 182, 1-71.

Hannibal J., Hindersson P., Knudsen S.M., Georg B. and Fahrenkrug J. (2002). The photopigment melanopsin is exclusively present in pituitary adenylate cyclase-activating polypeptide-containing retinal ganglion cells of the retinohypothalamic tract. J. Neurosci. 22, RC191.

Hannibal J., Hindersson P., Ostergaard J., Georg B., Heegaard S., Larsen P.J. and Fahrenkrug J. (2004). Melanopsin is expressed in PACAP-containing retinal ganglion cells of the human retinohypothalamic tract. Invest. Ophthalmol. Vis. Sci. 45, 4202-4209.

Hannibal J., Kankipati L., Strang C.E., Peterson B.B., Dacey D. and Gamlin P.D. (2014). Central projections of intrinsically photosensitive retinal ganglion cells in the macaque monkey. J. Comp. Neurol. 522, 2231-2248.

Hannibal J., Christiansen A.T., Heegaard S., Fahrenkrug J. and Kiilgaard J.F. (2017). Melanopsin expressing human retinal ganglion cells: Subtypes, distribution, and intraretinal connectivity. J. Comp. Neurol. 525, 1934-1961.

Harman A., Abrahams B., Moore S. and Hoskins R. (2000). Neuronal density in the human retinal ganglion cell layer from 16-77 years. Anat. Rec. 260, 124-131.

Harnois C. and Di Paolo T. (1990). Decreased dopamine in the retinas of patients with Parkinson's disease. Invest. Ophthalmol. Vis. Sci. 31, 2473-2475.

Harper D.G., Stopa E.G., Kuo-Leblanc V., McKee A.C., Asayama K., Volicer L., Kowall N. and Satlin A. (2008). Dorsomedial SCN neuronal subpopulations subserve different functions in human dementia. Brain 131, 1609-1617.

Hatfield C.F., Herbert J., Van Someren E.J.W., Hodges J.R. and Hastings M.H. (2004). Disrupted daily activity/rest cycles in relation to daily cortisol rhythms of home-dwelling patients with early Alzheimer's dementia. Brain 127, 1061-1074.

Hatonen T. and Santavuori P. (1998). Bright light suppresses melatonin in blind patients with neuronal ceroid lipofuscinoses. Neurology 50, 1116-1120.

Hattar S., Kumar M., Park A., Tong P., Tung J., Yau K. and Berson D.M. (2006). Central projections of melanopsin-expressing retinal ganglion cells in the mouse. Comp. Gen. Pharmacol. 349, 326-349.

Hikichi T., Tateda N. and Miura, T. (2011). Alteration of melatonin secretion in patients with type 2 diabetes and proliferative diabetic retinopathy. Clin. Ophthalmol. 5, 655-660.

Hinton D.R., Sadun A.A., Blanks J.C. and Miller C.A. (1986). Optic-nerve degeneration in Alzheimer's disease. N. Engl. J. Med. 315, 485-487.

Hofman M.A. and Swaab D.F. (2006). Living by the clock: The circadian pacemaker in older people. Ageing Res. Rev. 5, 33-51.

Hughes S., Welsh L., Katti C., González-Menéndez I., Turton M., Halford S., Sekaran S., Peirson S.N., Hankins M.W. and Foster R.G. (2012). Differential expression of melanopsin isoforms Opn4L and Opn4S during postnatal development of the mouse retina. PLoS One 7, e34531.

Ionescu D., Driver H.S., Heon E., Flanagan J. and Shapiro C.M. (2001). Sleep and daytime sleepiness in retinitis pigmentosa patients. J. Sleep Res. 10, 329-335.

Jackson G.R., Ortega J., Girkin C., Rosenstiel C.E. and Owsley C. (2002). Aging-related changes in the multifocal electroretinogram. J. Opt. Soc. Am. A. Opt. Image Sci. Vis. 19, 185-189.

Jackson G.R., Owsley C. and McGwin G. (1999). Aging and dark adaptation. Vision Res. 39, 3975-3982.

Jean-Louis G., Zizi F., Lazzaro D.R. and Wolintz A.H. (2008). Circadian rhythm dysfunction in glaucoma: A hypothesis. J. Circadian Rhythms 6, 1.

Johnson B.M., Miao M. and Sadun A.A. (1987). Age-related decline of human optic nerve axon populations. Arch. Ophthalmol. 10, 5-9.

Johnson C.A., Adams A.J. and Lewis R.A. (1989). Evidence for a neural basis of age-related visual field loss in normal observers. Invest. Ophthalmol. Vis. Sci. 30, 2056-2064.

Johnson J., Wu V., Donovan M., Majumdar S., Renteria R.C., Porco T., Van Gelder R.N. and Copenhagen D.R. (2010). Melanopsin-dependent light avoidance in neonatal mice. Proc. Natl. Acad. Sci. 107, 17374-17378.

Jusuf P.R., Lee S.C.S., Hannibal J. and Grünert U. (2007). Characterization and synaptic connectivity of melanopsin-containing ganglion cells in the primate retina. Eur. J. Neurosci. 26, 2906-2921.

Kadono M., Nakanishi N., Yamazaki M., Hasegawa G., Nakamura N. and Fukui M. (2016). Various patterns of disrupted daily rest–activity rhythmicity associated with diabetes. J. Sleep Res. 25, 426-437.

Kankipati L., Girkin C.A. and Gamlin P.D. (2011). The post-illumination pupil response is reduced in glaucoma patients. Invest. Ophthalmol. Vis. Sci. 52, 2287-2292.

Karasek M. and Reiter R.J. (2002). Melatonin and aging. Neuroendocrinol. Lett. 23 (Suppl 1), 14-16.

Kardon R., Anderson S.C., Damarjian T.G., Grace E.M., Stone E. and Kawasaki A. (2011). Chromatic pupillometry in patients with retinitis pigmentosa. Ophthalmology 118, 376-381.

Kawasaki A., Herbst K., Sander B. and Milea D. (2010). Selective wavelength pupillometry in Leber hereditary optic neuropathy. Clin. Exp. Ophthalmol. 38, 322-324.

Keats E.C. and Khan Z.A. (2012). Vascular stem cells in diabetic complications: evidence for a role in the pathogenesis and the

therapeutic promise. Cardiovasc. Diabetol. 11, 37.

Kelbsch C., Strasser T., Chen Y., Feigl B., Gamlin P.D., Kardon R., Peters T., Roecklein K.A., Steinhauer S.R., Szabadi E., Zele A.J., Wilhelm H. and Wilhelm B.J. (2019). Standards in pupillography. Front. Neurol. 10, 129.

Kern T.S. and Barber A.J. (2008). Retinal ganglion cells in diabetes. J. Physiol. 586, 4401-4408.

Kolomiets B., Dubus E., Simonutti M., Rosolen S., Sahel J.A. and Picaud, S. (2010). Late histological and functional changes in the P23H rat retina after photoreceptor loss. Neurobiol. Dis. 38, 47-58.

Ksendzovsky A., Pomeraniec I.J., Zaghloul K.A., Provencio J.J. and Provencio I. (2017). Clinical implications of the melanopsin-based non-image-forming visual system. Neurology 88, 1282-1290.

La Morgia C., Ross-Cisneros F.N., Sadun A.A., Hannibal J., Munarini A., Mantovani V., Barboni P., Cantalupo G., Tozer K.R., Sancisi E., Salomao S.R., Moraes M.N., Moraes-Filho M.N., Heegaard S., Milea D., Kjer P., Montagna P. and Carelli V. (2010). Melanopsin retinal ganglion cells are resistant to neurodegeneration in mitochondrial optic neuropathies. Brain 133, 2426-2438.

La Morgia C., Ross-Cisneros F.N., Hannibal J., Montagna P., Sadun A.A. and Carelli V. (2011). Melanopsin-expressing retinal ganglion cells: implications for human diseases. Vision Res. 51, 296-302.

La Morgia C., Barboni P., Rizzo G., Carbonelli M., Savini G., Scaglione C., Capellari S., Bonazza S., Giannoccaro M.P., Calandra-Buonaura G., Liguori R., Cortelli P., Martinelli P., Baruzzi A. and Carelli V. (2013). Loss of temporal retinal nerve fibers in Parkinson disease: a mitochondrial pattern? Eur. J. Neurol. 20, 198-201.

La Morgia C., Ross-Cisneros F.N., Koronyo Y., Hannibal J., Gallassi R., Cantalupo G., Sambati L., Pan B.X., Tozer K.R., Barboni P., Provini F., Avanzini P., Carbonelli M., Pelosi A., Chui H., Liguori R., Baruzzi A., Koronyo-Hamaoui M., Sadun A.A. and Carelli V. (2016). Melanopsin retinal ganglion cell loss in Alzheimer disease. Ann. Neurol. 79, 90-109.

La Morgia C., Ross-Cisneros F.N., Sadun A.A. and Carelli V. (2017). Retinal ganglion cells and circadian rhythms in Alzheimer's disease, Parkinson's disease, and beyond. Front. Neurol. 8, 162.

La Morgia C., Carelli V. and Carbonelli M. (2018). Melanopsin retinal ganglion cells and pupil: Clinical implications for neuro-ophthalmology. Front. Neurol. 9, 1-8.

Lax P., Otalora B.B., Esquiva G., Rol M.D.L.Á., Madrid J.A. and Cuenca N. (2011). Circadian dysfunction in P23H rhodopsin transgenic rats: Effects of exogenous melatonin. J. Pineal Res. 50, 183-191.

Lax P., Esquiva G., Fuentes-Broto L., Segura F., Sánchez-Cano A., Cuenca N. and Pinilla I. (2016). Age-related changes in photosensitive melanopsin-expressing retinal ganglion cells correlate with circadian rhythm impairments in sighted and blind rats. Chronobiol. Int. 33, 374-391.

Lebensohn J.E. (1951). Photophobia: mechanism and implications. Am. J. Ophthalmol. 34, 1294-1300.

Lee J.-Y., Ahn J., Kim T.W. and Jeon B.S. (2014). Optical Coherence Tomography in Parkinson's Disease: Is the Retina a Biomarker? J. Parkinsons. Dis. 4, 197-204.

Lewy A.J., Bauer V.K., Cutler N.L. and Sack R.L. (1998). Melatonin treatment of winter depression: a pilot study. Psychiatry Res. 77, 57-61.

Lewy A.J., Sack R.L., Miller L.S. and Hoban T.M. (1987). Antidepressant and circadian phase-shifting effects of light. Science 235, 352-354.

Li R.S., Chen B.-Y., Tay D.K., Chan H.H.L., Pu M.-L. and So K.-F. (2006). Melanopsin-expressing retinal ganglion cells are more injury-resistant in a chronic ocular hypertension model. Invest. Ophthalmol. Vis. Sci. 47, 2951-2958.

Li S.-Y., Yau S.-Y., Chen B.-Y., Tay D.K., Lee V.W.H., Pu M.-L., Chan H.H.L. and So K.-F. (2008). Enhanced survival of melanopsin-expressing retinal ganglion cells after injury is associated with the PI3 K/Akt pathway. Cell. Mol. Neurobiol. 28, 1095-107.

Liao H.-W., Ren X., Peterson B.B., Marshak D.W., Yau K.-W., Gamlin P.D. and Dacey D.M. (2016). Melanopsin-expressing ganglion cells on macaque and human retinas form two morphologically distinct populations. J. Comp. Neurol. 524, 2845-2872.

Lin T.P., Rigby H., Adler J.S., Hentz J.G., Balcer L.J., Galetta S.L., Devick S., Cronin R. and Adler C.H. (2015). Abnormal visual contrast acuity in Parkinson's disease. J. Parkinsons Dis. 5, 125-130.

Marc R.E., Jones B.W., Watt C.B. and Strettoi E. (2003). Neural remodeling in retinal degeneration. Prog. Retin. Eye Res. 22, 607-655.

Matynia A., Parikh S., Chen B., Kim P., McNeill D.S., Nusinowitz S., Evans C. and Gorin M.B. (2012). Intrinsically photosensitive retinal ganglion cells are the primary but not exclusive circuit for light aversion. Exp. Eye Res. 105, 60-69.

McClung C.A. (2007). Circadian genes, rhythms and the biology of mood disorders. Pharmacol. Ther. 114, 222-232.

Moura A.L.A., Nagy B.V., La Morgia C., Barboni P., Oliveira A.G.F., Salomão S.R., Berezovsky A., de Moraes-Filho, M.N., Chicani, C.F., Belfort R., Carelli V., Sadun A.A., Hood D.C. and Ventura D.F. (2013). The pupil light reflex in Leber's hereditary optic neuropathy: Evidence for preservation of melanopsin-expressing retinal ganglion cells. Investig. Opthalmology Vis. Sci. 54, 4471-4477.

Myers B.L. and Badia P. (1995). Changes in circadian rhythms and sleep quality with aging: Mechanisms and interventions. Neurosci. Biobehav. Rev. 19, 553-571.

Nasir-Ahmad S., Lee, S.C.S., Martin P.R. and Grünert U. (2017). Melanopsin-expressing ganglion cells in human retina: Morphology, distribution, and synaptic connections. J. Comp. Neurol. 520, 633-655.

Neumann S., Haverkamp S. and Auferkorte O.N. (2011). Intrinsically photosensitive ganglion cells of the primate retina express distinct combinations of inhibitory neurotransmitter receptors. Neuroscience 199, 24-31.

Ng J.S., Bearse M.A., Schneck M.E., Barez S. and Adams A.J. (2008). Local diabetic retinopathy prediction by multifocal ERG delays over 3 years. Invest. Opthalmol. Vis. Sci. 49, 1622.

Nissen C., Sander B., Milea D., Kolko M., Herbst K., Hamard P. and Lund-Andersen H. (2014). Monochromatic pupillometry in unilateral glaucoma discloses no adaptive changes subserved by the ipRGCs. Front. Neurol. 5, 15.

Nissen C., Rönnbäck C., Sander B., Herbst K., Milea D., Larsen M. and Lund-Andersen H. (2015). Dissociation of pupillary post-illumination responses from visual function in confirmed OPA1 c.983A > G and c.2708_2711delTTAG autosomal dominant optic atrophy. Front. Neurol. 6, 5.

Noseda R. and Burstein R. (2011). Advances in understanding the mechanisms of migraine-type photophobia. Curr. Opin. Neurol. 24, 197-202.

Noseda R., Kainz V., Jakubowski M., Gooley J.J., Saper C.B., Digre K. and Burstein R. (2010a). A neural mechanism for exacerbation of headache by light. Nat. Neurosci. 13, 239-245.

Noseda R., Kainz V., Jakubowski M., Gooley J.J., Saper C.B., Digre K. and Burstein R. (2010b). A neural mechanism for exacerbation of headache by light. Nat. Neurosci. 13, 239-245.

Noseda R., Bernstein C.A., Nir R.R., Lee A.J., Fulton A.B., Bertisch S.M., Hovaguimian A., Cestari D.M., Saavedra-Walker R., Borsook D., Doran B.L., Buettner C. and Burstein R. (2016). Migraine photophobia originating in cone-driven retinal pathways. Brain 139, 1971-1986.

Noseda R., Lee A.J., Nir R.-R., Bernstein C.A., Kainz V.M., Bertisch S.M., Buettner C., Borsook D. and Burstein R. (2017). Neural mechanism for hypothalamic-mediated autonomic responses to light during migraine. Proc. Natl. Acad. Sci. 114, E5683-E5692.

Noseda R., Copenhagen D. and Burstein R. (2019). Current understanding of photophobia, visual networks and headaches. Cephalalgia (in press).

Obara E.A., Hannibal J., Heegaard S. and Fahrenkrug J. (2016). Loss of melanopsin-expressing retinal ganglion cells in severely staged glaucoma patients. Invest. Opthalmol. Vis. Sci. 57, 4661-4667.

Obara E.A., Hannibal J., Heegaard S. and Fahrenkrug J. (2017). Loss of melanopsin-expressing retinal ganglion cells in patients with diabetic retinopathy. Invest. Opthalmol. Vis. Sci. 58, 2187-2192.

Ola M.S. and Alhomida A.S. (2014). Neurodegeneration in diabetic retina and its potential drug targets. Curr. Neuropharmacol. 12, 380-386.

Ortuño-Lizarán I., Esquiva G., Beach T.G., Serrano G.E., Adler C.H., Lax P. and Cuenca N. (2018). Degeneration of human photosensitive retinal ganglion cells may explain sleep and circadian rhythms disorders in Parkinson's disease. Acta Neuropathol. Commun. 6, 90.

Osborne N.N., Núñez-Álvarez C. and del Olmo-Aguado S. (2014). The effect of visual blue light on mitochondrial function associated with retinal ganglions cells. Exp. Eye Res. 128, 8-14.

Ostrin L.A., Strang C.E., Chang K., Jnawali A., Hung L.-F., Arumugam B., Frishman L.J., Smith E.L. and Gamlin P.D. (2018). Immunotoxin-induced ablation of the intrinsically photosensitive retinal ganglion cells in rhesus monkeys. Front. Neurol. 9, 1-13.

Pandi-Perumal S.R., Smits M., Spence W., Srinivasan V., Cardinali D.P., Lowe A.D. and Kayumov L. (2007). Dim light melatonin onset (DLMO): A tool for the analysis of circadian phase in human sleep and chronobiological disorders. Prog. Neuro-Psychopharmacology Biol. Psychiatry 31, 1-11.

Pérez-Rico C., De la Villa P., Blanco R., Germain F., Paz-Moreno J. and Arribas-Gómez I. (2009). Alterations in nocturnal melatonin levels in patients with optic neuropathies. Arch. Soc. Esp. Ophtalmol. 84, 251-257.

Pires S.S., Hughes S., Turton M., Melyan Z., Peirson S.N., Zheng L., Kosmaoglou M., Bellingham J., Cheetham M.E., Lucas R.J., Foster R.G., Hankins M.W. and Halford S. (2009). Differential expression of two distinct functional isoforms of melanopsin (Opn4) in the mammalian retina. J. Neurosci. 29, 12332-12342.

Postuma R.B., Berg D., Stern M., Poewe W., Olanow C.W., Oertel W., Obeso J., Marek K., Litvan I., Lang A.E., Halliday G., Goetz C.G., Gasser T., Dubois B., Chan P., Bloem B.R., Adler C.H. and Deuschl G. (2015). MDS clinical diagnostic criteria for Parkinson's disease. Mov. Disord. 30, 1591-1601.

Provencio I., Jiang G., De Grip W.J., Hayes W.P. and Rollag M.D. (1998). Melanopsin: An opsin in melanophores, brain, and eye. Proc. Natl. Acad. Sci. USA 95, 340-345.

Provencio I., Rodriguez I.R., Jiang G., Hayes, W.P., Moreira E.F. and Rollag M.D. (2000). A novel human opsin in the inner retina. J. Neurosci. 20, 600-605.

Quigley H.A., Dunkelberger G.R. and Green W.R. (1988). Chronic human glaucoma causing selectively greater loss of large optic nerve fibers. Ophthalmology 95, 357-363.

Robinson G.A. and Madison R.D. (2004). Axotomized mouse retinal ganglion cells containing melanopsin show enhanced survival, but not enhanced axon regrowth into a peripheral nerve graft. Vision Res. 44, 2667-2674.

Roecklein K.A., Rohan K.J., Duncan W.C., Rollag M.D., Norman E., Lipsky R.H. and Provencio I., (2009). A missense variant (P10L) of the melanopsin (Opn4) gene is associated with Seasonal Affective Disorder. J. Affect. Disord. 114, 279-285.

Roecklein K.A., Wong P.M., Miller M.A., Donofry S.D., Kamarck M.L. and Brainard G.C. (2013). Melanopsin, photosensitive ganglion cells, and seasonal affective disorder. Neurosci. Biobehav. Rev. 37, 229-239.

Rosenthal N.E., Sack D.A., Jacobsen F.M., James S.P., Parry B.L., Arendt J., Tamarkin L. and Wehr T.A. (1986). Melatonin in seasonal affective disorder and phototherapy. J. Neural. Transm. Suppl. 21, 257-267.

Rukmini A.V., Milea D. and Gooley J.J. (2019). Chromatic pupillometry methods for assessing photoreceptor health in retinal and optic nerve diseases. Front. Neurol. 10, 1-20.

Rukmini A.V., Milea D., Baskaran M., How A.C., Perera S.A., Aung T. and Gooley J.J. (2015). Pupillary responses to high-irradiance blue light correlate with glaucoma severity. Ophthalmology 122, 1777-1785.

Sadun A.A. and Bassi C.J. (1990). Optic nerve damage in Alzheimer's disease. Ophthalmology 97, 9-17.

Schmidt T.M., Chen S.-K. and Hattar S. (2011). Intrinsically photosensitive retinal ganglion cells: many subtypes, diverse functions. Trends Neurosci. 34, 572-580.

Schmidt T.M., Alam N.M., Chen S., Kofuji P., Li W., Prusky G.T. and Hattar S. (2014). A role for melanopsin in alpha retinal ganglion cells and contrast detection. Neuron 82, 781-788.

Semo M., Lupi D., Peirson S.N., Butler J.N., Foster R.G., Lupi A.D., Peirson A.S.N., Butler J.N. and Foster R.G. (2003a). Light-induced c-fos in melanopsin retinal ganglion cells of young and aged rodless/coneless (rd/rd cl) mice. Eur. J. Neurosci. 18, 3007-3017.

Semo M., Peirson S., Lupi D., Lucas R.J., Jeffery G. and Foster R.G. (2003b). Melanopsin retinal ganglion cells and the maintenance of circadian and pupillary responses to light in aged rodless/coneless (rd/rd cl) mice. Eur. J. Neurosci. 17, 1793-1801.

Sparrow J.R. and Boulton M. (2005). RPE lipofuscin and its role in retinal pathobiology. Exp. Eye Res. 80, 595-606.

Spitschan M. and Woelders T. (2018). The method of silent substitution for examining melanopsin contributions to pupil control. Front. Neurol. 10, 76.

Spitschan M., Bock A.S., Ryan J., Frazzetta G., Brainard D.H. and Aguirre G.K. (2017). The human visual cortex response to melanopsin-directed stimulation is accompanied by a distinct perceptual experience. Proc. Natl. Acad. Sci. 114, 12291-12296.

Spry P.G. and Johnson C.A. (2001). Senescent changes of the normal visual field: an age-old problem. Optom. Vis. Sci. 78, 436-441.

Stopa E.G., Volicer L., Kuo-Leblanc V., Harper D., Lathi D., Tate B. and Satlin A. (1999). Pathologic evaluation of the human suprachiasmatic nucleus in severe dementia. J. Neuropathol. Exp.

Neurol. 58, 29-39.

Su W., Guo Z., Randall D.C., Cassis L., Brown D.R. and Gong M.C. (2008). Hypertension and disrupted blood pressure circadian rhythm in Type 2 diabetic db/db mice. AJP Hear. Circ. Physiol. 295, H1634-H1641.

Swaab D.F., Fliers E. and Partiman T.S. (1985). The suprachiasmatic nucleus of the human brain in relation to sex, age and senile dementia. Brain Res. 342, 37-44.

Tales A., Troscianko T., Lush D., Haworth J., Wilcock G.K. and Butler S.R. (2001). The pupillary light reflex in aging and Alzheimer's disease. Aging (Milano) 13, 473-478.

Tan L.C.S. (2012). Mood disorders in Parkinson's disease. Parkinsonism Relat. Disord. 18 (Suppl. 1), S74-6.

Terman M. and Terman J.S. (2005). Light therapy for seasonal and nonseasonal depression: efficacy, protocol, safety, and side effects. CNS Spectr. 10, 647-663; quiz 672.

Tranah G.J., Blackwell T., Stone K.L., Ancoli-Israel S., Paudel M.L., Ensrud K.E., Cauley J.A., Redline S., Hillier T.A., Cummings S.R. and Yaffe K. (2011). Circadian activity rhythms and risk of incident dementia and mild cognitive impairment in older women. Ann. Neurol. 70, 722-732.

Van Someren E.J.W. (2000). Circadian and sleep disturbances in the elderly. Exp. Gerontol. 35, 1229-1237.

Vugler A.A., Redgrave P., Semo M., Lawrence J., Greenwood J. and Coffey P.J. (2007). Dopamine neurones form a discrete plexus with melanopsin cells in normal and degenerating retina. Exp. Neurol. 205, 26-35.

Vugler A.A., Semo M., Joseph A. and Jeffery G. (2008). Survival and remodeling of melanopsin cells during retinal dystrophy. Vis. Neurosci. 25, 125-138.

Wakakura M. and Yokoe J. (1995). Evidence for preserved direct pupillary light response in Leber's hereditary optic neuropathy. Br. J. Ophtalmol. 442-446.

Wang C.-A., McInnis H., Brien D.C., Pari G. and Munoz D.P. (2016). Disruption of pupil size modulation correlates with voluntary motor preparation deficits in Parkinson's disease. Neuropsychologia 80, 176-184.

Weil R.S., Schrag A.E., Warren J.D., Crutch S.J., Lees A.J. and Morris H.R. (2016). Visual dysfunction in Parkinson's disease. Brain 139, 2827-2843.

Weinreb R.N., Aung T. and Medeiros F.A. (2014). The pathophysiology and treatment of glaucoma. JAMA 311, 1901-1911.

Woelders T., Leenheers T., Gordijn M.C.M., Hut R.A., Beersma D.G.M. and Wams E.J. (2018). Melanopsin- and L-cone–induced pupil constriction is inhibited by S- and M-cones in humans. Proc. Natl. Acad. Sci. 115, 792-797.

Wu Y.-H. and Swaab D.F. (2007). Disturbance and strategies for reactivation of the circadian rhythm system in aging and Alzheimer's disease. Sleep Med. 8, 623-636.

Yu J., Feng Y., Xiang Y., Huang J., Savini G., Parisi V., Yang W. and Fu X. (2014a). Retinal nerve fiber layer thickness changes in Parkinson disease: A meta-analysis. PLoS One 9, e85718.

Yu J.G., Feng Y.F., Xiang Y., Huang J.H., Savini G., Parisi V., Yang W.J. and Fu X.A. (2014b). Retinal nerve fiber layer thickness changes in Parkinson disease: A meta-analysis. PLoS One 9.

Zele A.J., Adhikari P., Feigl B. and Cao D. (2018). Cone and melanopsin contributions to human brightness estimation. J. Opt. Soc. Am. A. Opt. Image Sci. Vis. 35, B19-B25.

Zhang D.-Q., Wong K.Y., Sollars P.J., Berson D.M., Pickard G.E. and McMahon D.G. (2008). Intraretinal signaling by ganglion cell photoreceptors to dopaminergic amacrine neurons. Proc. Natl. Acad. Sci. 105, 14181-14186.

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