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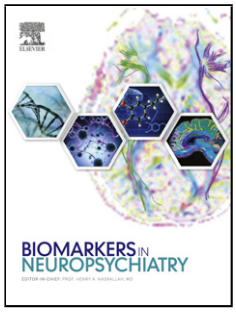

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Measures of Retinal Structure and Function as Biomarkers in Neurology and Psychiatry

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RUNNING HEAD: Retinal biomarkers

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Abstract

Investigators have increasingly turned to studying the retina as a window into brain structure and function. In neuropsychiatric diseases, retinal cell structure as assessed by optical coherence tomography (OCT) and retinal cell function as assessed by various forms of electroretinography (ERG) indicate the presence of notable changes. In addition, many studies indicate significant correlations between retinal changes and clinical features such as cognitive decline, overall illness severity, and progression of illness. Here, we review retinal findings in psychiatric (schizophrenia, autism, mood disorders, attention deficit hyperactivity disorder, anorexia nervosa), and neurologic (multiple sclerosis, Parkinson's disease, Alzheimer's disease and mild cognitive impairment, Huntington's disease, traumatic brain injury) conditions, in terms of their potential as biomarkers of disease onset, progression, severity, and outcomes. Consistency and variability in findings across studies are highlighted, and implications for future research are discussed. Potential confounds and methodological issues central to studies of retinal structure and function in neuropsychiatry are also considered. The review concludes with discussions of: a) recent advances in retinal imaging and their potential applications for studying brain disorders; and b) the potential for applications of artificial intelligence to increasing the predictive validity of retinal data.

Measures of Retinal Structure and Function as Biomarkers in Neurology and Psychiatry

Biomarkers of syndromes and diseases of the central nervous system (CNS[1]) typically involve aspects of brain structure or function. Increasingly, however, investigators have turned to studying the retina as a window into these issues (Blokhuis et al., 2016; Cabezon et al., 2012; Chu, Kolappan, Barnes, Joyce, & Ron, 2012; Dhillon & Dhillon, 2008; Frohman et al., 2008; Hassenstein, 2014; Jindal, 2015; London, Benhar, & Schwartz, 2013; Msall, 2006; Schonfeldt-Lecuona et al., 2016). The retina grows out of the same tissue as the brain in embryonic development, and the two structures share many features, including neurons, glial cells, similar neurotransmitters and receptor types, and a layered architecture (Dowling, 2012). There is a wide range of conditions that are considered brain disorders and where significant retinal changes have been reported, including multiple sclerosis, Parkinson's disease, Alzheimer's disease, mild cognitive impairment, Huntington's disease, traumatic brain injury, schizophrenia, autism, mood disorders, attention deficit hyperactivity disorder, and anorexia nervosa (Archibald, Clarke, Mosimann, & Burn, 2009; Brandies & Yehuda, 2008; Bubl, Dörr, et al., 2015; Bubl, Kern, et al., 2015; Dhalla, Pallikadavath, & Hutchinson, 2019; Djamgoz, Hankins, Hirano, & Archer, 1997; Doustar, Torbati, Black, Koronyo, & Koronyo-Hamaoui, 2017; Garcia-Portilla et al., 2019; Liu et al., 2015; London et al., 2013; Saidha et al., 2013; Silverstein, Fradkin, & Demmin, in press). In several of these conditions the extent of change in one structure is significantly correlated with the degree of change in the other (Costello & Burton, 2018; Deal et al., 2018; Devos et al., 2005; Djamgoz et al., 1997; Ferrari et al., 2017; Jindal, 2015; D. Liu et al., 2015; Ong et al., 2015; Roy, Roy, Williams, Weinberger, & Smelson, 1997; Roy, Smelson, & Roy, 1996; Satue et al., 2014a; Sedighi et al., 2014; T. Tian, Zhu, & Liu, 2011; Yu et al., 2014; Zimmerman, Oberwahrenbrock, Brandt, Paul, & Dörr, 2014). This suggests that retinal indices could potentially serve as biomarkers for these disorders. The purpose of this paper is to provide a brief overview of the nature of findings on altered retinal structure and function in neuropsychiatric

[1] A full list of all abbreviations used in this paper and their meanings can be found in Table 1.

conditions, and to highlight the potential applications of a number of retinal indices as biomarkers for disease risk, progression (including neurodegeneration), treatment response, and risk for relapse. In the discussion that follows, the neuropsychiatric conditions listed above will be considered in terms of evidence of changes in retinal structure using optical coherence tomography (OCT) and function using electroretinography (ERG). While these are not the only techniques that have generated data relevant to the issue of retinal biomarkers in neurology and psychiatry, data from these methods constitute the overwhelming majority of the available research findings so far[2]. The review of evidence is largely limited to studies involving humans receiving treatment. The sections on evidence from ERG and OCT studies follow two introductory sections on the nature of the retina, and a survey of techniques used to study its structure and function. The two final sections of the paper, prior to the Discussion, will cover forward looking applications including: 1) recently developed techniques for imaging retinal activity *in vivo* and their potential applications in neurology and psychiatry; and 2) potential confounds in studies of the retina in neuropsychiatric conditions.

Retina – basics

The retina is comprised of several types of neurons, cells that support neuronal activity (e.g., glial cells), vasculature, and key epithelia that facilitate early vision. A schematic drawing of retinal cell types and other structures is shown in Figure 1. The first neural layer, the photoreceptors, receives support for pigment production, waste removal, and other functions from the retinal pigment epithelium (RPE), and vascular nourishment from the choroid (which is situated between the neural retina and sclera). Bruch's membrane is a 5-layered structure that represents the innermost layer of the choroid and is also involved in a range of critical functions involving transfer of substances between the

[2] Visual evoked potentials (VEPs), which measure the strength and speed of the neural response from the retina to V1 will not be discussed here, due both to space considerations and to the significant contribution of post-retinal (e.g., optic nerve, LGN, optic radiation, V1) activity to this index. However, we wish to note that many important VEP findings have been demonstrated in the conditions we review [e.g. Bedwell et al., 2018; Buttner et al., 1996; Graham & Klistorner, 2017; Krasodomska, Lubinski, Potemkowski, & Honczarenko, 2010; Rub et al., 2015; Yap, Balendra, Almonte, & Cordeiro, 2019).

retina and vasculature. The photoreceptor layer consists of two neural cell types (rods, primarily involved low-light vision; and cones, primarily involved in color and high visual acuity vision in daytime conditions) and two layers, the inner and outer segments. The inner segment consists of cell structures such as the cell body, axon, and nucleus. The outer segment contains the disc membranes, which contain opsin, a protein that absorbs photons. Opsin is combined with pigment in the rods to create rhodopsin, and with pigments in the cones that respond maximally to different wavelengths of light to create photopsins that are maximally tuned to three spectrally diverse cone types in the trichromatic retina. In the dark, photoreceptors are continuously active (depolarized). This activity is often termed dark current. Absorption of light leads, as the result of a g-protein cascade that initiates phototransduction, to a complex series of chemical changes that drives photoreceptor hyperpolarization and a reduction in glutamate release into the synapse between photoreceptors and bipolar cells. This process leads to depolarization of ON (i.e., on-center, off-surround) bipolar cells and hyperpolarization of OFF (i.e., off-center, on-surround) bipolar cells.

The retinal layer containing the cell bodies of photoreceptors is referred to as the outer nuclear layer (ONL). Axon terminals of photoreceptors synapse onto dendrites of bipolar cells. This layer of neuropil is known as the outer plexiform layer (OPL). Further modulating the activity of the OPL are the lateral connections of the horizontal cells, which also provide laterally suppressive feedback to photoreceptors. Activity at this level is propagated to the inner nuclear layer (INL) which contains the cell bodies of bipolar and horizontal cells, in addition to Müller cells (a form of glial cell that supports and may facilitate neural function), and amacrine cells, which function as inhibitory interneurons affecting bipolar and ganglion cell activity. The axons of bipolar cells, the neuritic processes of amacrine cells, and the dendrites of retinal ganglion cells form the next layer, the inner plexiform layer (IPL). A cell type that receives input in the IPL and terminates in the OPL is known as an interplexiform cell. The function of this cell type is less well understood at this point than that of other retinal cell types. From

the IPL, signal is propagated to the retinal ganglion cell in what is termed the ganglion cell layer (GCL). Each ganglion cell sends a single output axon that travels along the vitreoretinal surface of the eye. The bundle of these axons is known as the retinal nerve fiber layer (RNFL). RNFL layer bundles are generally unmyelinated in the retina (Kodama, Hayasaka, & Setogawa, 1990; Straatsma, Foos, Heckenlively, & Taylor, 1981), but combine to form a single output at the optic nerve head where they gain a myelin sheath and form the beginning of the optic nerve that synapses at the lateral geniculate nucleus (LGN) of the thalamus. The RNFL is protected from the vitreous humor (gel of the inner eye globe) by the inner limiting membrane (ILM).

In addition to these layers, several geographic regions within the retina as imaged *en face* are of particular importance. Those most relevant to the present discussion include the macula, which is the functional center of the retina and the region responsible for the highest acuity vision. The macula also gives rise to the richest experience of color as it has a higher density of cones relative to more peripheral areas of the retina. In OCT, macula thickness is typically measured as the distance between the ILM and the RPE. Within the macula, the fovea provides further specialization that facilitates highest visual acuity. Cone density is highest here and there are virtually no rods. In most humans, the fovea is characterized by a depression in retinal thickness as the inner retinal neurons are radially displaced relative to their photoreceptor input, providing a clear path for photons to create the highest acuity image without scatter from inner retinal neurons. In most (but not all) humans, the fovea is also notably avascular of retinal circulation (termed the foveal avascular zone, FAZ) which puts special hemodynamic constraints on this area, but is believed to facilitate unimpeded (by blood vessels) high visual acuity. Another noteworthy geographic specialization is the region where the RNFL leaves the eye, which is called the optic nerve head (ONH) or optic disc. Because there are no rods or cones in this location, this is also the area of the native blind spot. The center of the optic disc is a pit known as the optic cup, which contains a depression of the collecting nerve fibers. The cup-to-disc ratio is an important variable

in neuro-ophthalmology. It has a normal ratio of 0.3, but with progression of eye disease (e.g., glaucoma), or in brain diseases [e.g., schizophrenia, Silverstein et al. (2015)] this ratio can increase.

Blood is supplied to the retina from two predominant circulation pools. One enters into the inner retinal layers from the central retinal artery which is located in the center of the optic nerve. This system is associated with a blood retinal barrier (BRB) via a non-fenestrated network of vessels that maintain tight junctions of the retinal endothelial cells. A second circulation source resides behind the photoreceptors and is called the choroid. This region is highly perfused and delivers the bulk of the metabolites and oxygen to the retina, especially to the adjacent photoreceptors which are highly metabolically active. Choroidal vessels are highly fenestrated making oxygen and nutrient exchange possible, though a (second) BRB is maintained by the tight junctional complexes between RPE cells and the barrier formed by Bruch's membrane (Cunha-Vaz, Bernardes, & Lobo, 2011; Fields, Del Priore, Adelman, & Rizzolo, 2019). Microcirculation in the retina is carried out via the retinal arterioles, capillaries and venules which share similarities and notable differences in the two circulation pools. Each circulation pool is sensitive to many systemic changes, including hypertension but also neuropsychiatric diseases (see below) (Cunha-Vaz et al., 2011).

The retina also receives neural input from the brain. These retinopetal (or centrifugal, or efferent) neurons enter the retina from the brain through the optic nerve bundle and modulate the responses of retinal cells. In humans, there are fewer retinopetal neurons than in many other species. However, there is extensive branching once inside the retina, and so they can affect multiple aspects of retinal function. To date, the only known retinopetal neurons in humans are histaminergic and serotinergic (Gastinger, Tian, Horvath, & Marshak, 2006; Labandeira-Garcia, Guerra-Seijas, Gonzalez, Perez, & Acuna, 1990; Ortiz, Odom, Passaglia, & Tzekov, 2017).

Retinal activity involves multiple neurotransmitters [see Kolb (2011) for a review]. The primary mode of feedforward transmission is via glutamate. Glycine and GABA carry out inhibitory functions,

especially with regard to amacrine cells. Glycine receptors are also contained by some bipolar cells (Wassle et al., 2009). The horizontal cells of many species contain GABA, although the extent of its involvement in the primate retina is unclear. GABA is, however, involved in interplexiform cell function in humans. Dopamine (DA) is released only by a subtype of amacrine cell. However, DA receptors (both D1 and D2 types) are found on most or possibly all retinal cell types. Retinal DA is released by amacrine cells into the extracellular fluid and moves through the retina by volume conduction rather than by synaptic transmission. One important function of DA in the retina is to weaken the gap junctions that couple horizontal and other cells (Piccolino, Neyton, & Gerschenfeld, 1984; Teranishi, Negishi, & Kato, 1983). This reduces the size of receptive fields (Xin & Bloomfield, 2000), and leads to reduced interaction between neurons signaling correlated features, and signaling light and dark portions of space, thereby enhancing center responses and reducing effects of surround responses (Hedden & Dowling, 1978). In general therefore, DA functions to optimize the signal-to-noise ratio in visual sensory processing, and vision in general, in daylight conditions (Witkovsky, 2004). Other neurotransmitters, such as serotonin and acetylcholine are also found in the retina and are contained in amacrine cells. Histamine containing cells have not been identified in the retina (Greferath et al., 2014), but as noted above, histamine and serotonin enter the retina via neurons originating in the hypothalamus and midbrain, respectively, and have modulatory functions.

Commonly used methods used to study retinal structure and function

Optical coherence tomography (OCT) OCT is an imaging technique that is widely used in ophthalmology, but also in other areas of medicine (e.g., cardiology) (Al-Mujaini, Wali, & Azeem, 2013; Chan & Chan, 2017; Chen & Lee, 2007). It is based on the method of using low-coherence interferometry with tissues that backscatter light and involves projecting near-infrared light into both tissue (e.g., the retina) and a reference mirror. The light reflected back from these sources is used to generate images, in a manner analogous to how sound is used to generate images with ultrasound. Several forms of OCT

have been developed, such as time-domain and frequency-domain OCT. Currently, the most widely used method in neuropsychiatry research is spectral domain OCT, a frequency domain method. In this case, it is the difference between the spectral frequency composition of light reflected back from the eye (i.e. the original spectral frequency profile minus what was absorbed by retinal structures), in comparison to the unaltered light spectra reflected back from the reference mirror, that is used to reconstruct images of retinal layers. OCT can typically visualize tissue to a depth of approximately 2 millimeters, with an axial resolution of 5 micrometers or less and a lateral resolution of 15-20 microns (uncorrected). In a typical scan, there may be close to 30,000 A-scans or axial scans per second that each image thickness through a single point in the retina. Data from the A-scans are then combined to create an image of the retina that contains all of the adjacent points (the B-scan; see Figures 2 and 3). In neuropsychiatry, OCT has been used to image the macula (both in terms of 2D thickness and 3D volume), the RNFL, the combined thickness of the GCL-IPL, and more recently, layers such as the INL and ONL, and the RPE and choroid. OCT also provides rich volumetric information enabling precise measurement of optic nerve cup-to-disc ratio. Recent innovations that have come to market include OCT angiography (OCT-A), which visualizes and determines the functional perfusion of the large and small vessels of the retinal and choroidal circulation. New devices can also measure the RNFL at both the periphery of the optic disc (peripapillary RNFL or pRNFL, which is the standard form of RNFL measurement) and at the periphery of the macula (macular RNFL or mRNFL). Nearly all studies reported in this review reflect pRNFL measurements, but studies reporting mRNFL measurements are beginning to appear. It will thus become important to determine the extent to which pRNFL and mRNFL values are similar, the degree to which they are correlated, and their relative sensitivity to disease states and predictive validity regarding disease-related outcomes. Another recent development is swept source OCT, which generates more A-scans per second than spectral domain OCT and appears to be superior

for imaging the RPE and choroid. This technique will be discussed further in the section on recent developments in retinal imaging, at the end of the paper.

Electroretinography (ERG) ERG is a technique for recording the electrical activity of retinal cells in response to a visual stimulus. Three types of ERG are in common use. One is the flash, ganzfeld flash, or full-field ERG. This involves presentations of unpatterned white or colored light stimuli against a lit or unlit background. The primary variables reported on from studies using flash ERG are a-wave and b-wave amplitudes and implicit times (latencies). The a-wave reflects primarily the hyperpolarization of photoreceptors, while the b-wave appears to reflect the depolarization of bipolar and/or Müller cells, with studies differing on the relative contributions of these two cell types (e.g., Newman & Odette, 1984; Perlman, 1995; Rager, 1979; Tian & Slaughter, 1995). Under higher background lighting conditions with colored stimuli, the b-wave is followed by a negative deflection known as the photopic negative response (PhNR), which reflects activity within a subset of retinal ganglion cells (see Figure 4). Implicit times for a-waves are typically between 10 and 30 milliseconds after the stimulus, and for b-waves are between 25 and 60 milliseconds post-stimulus, with the precise timing determined by a number of factors including whether testing is occurring in scotopic or photopic conditions, the nature (e.g., intensity) of the stimulus, subject age, and presence and extent of retinal disease (Corici et al., 2015). Other flash ERG variables, which are rarely reported in literature on CNS conditions, include the C-wave, which primarily reflects activity within the RPE, the d-wave, which reflects activity of OFF bipolar cells in response to a stepwise or ramp intensity stimulus with long duration luminance and sudden offset, and oscillatory potentials (OPs), which are small positive deflections on the ascending portion of the b-wave and which are thought to reflect feedback between bipolar, ganglion and especially amacrine cells (Perlman, 1995).

A second ERG technique is known as pattern ERG (pERG). This technique uses patterned stimuli (e.g., black and white reversing checkerboards or concentric rings with mean average luminance) to

maximally stimulate retinal ganglion cells with ON and OFF center-surround antagonism. The pERG has two main components corresponding to their voltage polarity and generalized implicit times. The P50 wave primarily reflects macula function, and the N95 component primarily reflects ganglion cell and optic nerve functioning (Holder, 2001) (see Figure 5). Because the pERG involves maintaining fixation on stimuli with longer durations than those of the single flashes involved in flash ERG, issues of patient motivation, cooperation, and ability to fixate become increasingly important with this method.

A third ERG technique is multifocal ERG (mfERG). This technique allows for assessment of functioning at many different locations on the retina. Typically, data from 61 or 103 loci are recorded (although at present recording from 250 sites is possible), at varying diameters up to about 30° from around the fovea. The typical stimulus used in mfERG involves multiple hexagonal patterns, with the pattern size increasing from the fovea to the periphery. The resulting waveforms are somewhat similar to those of flash ERG, but occur at each location: namely the N1 (a-wave), P1 (b-wave), and N2 (c-wave; but not the same c-wave as in flash ERG) (Hood, Odel, Chen, & Winn, 2003) (see Figure 6). While the mfERG provides information regarding regional functional deficits in the retina, it requires exceptional patient fixational stability or eye tracking for accurate spatial readout.

There are a number of electrode types used for ERG. In general, these can be grouped into three categories: 1) corneal contact lens electrodes, that typically require the eye to be anesthetized and the pupil to be dilated); 2) tape or filament-type (e.g., silver coated nylon fibers) electrodes (e.g., Dawson-Trick-Litzkow, or DTL electrodes) that are placed in the conjunctival sac, and which can be used with pupil dilation (but often are not); and 3) skin electrodes that are placed near but not on the eye (Creel, 2012) and that also can be used with or without pupil dilation. Signal-to-noise ratio (SNR) is highest with corneal contact lens electrodes and so only a small number of trials are needed per condition using this method. The SNR decreases with filament-type electrodes and decreases further with skin electrodes, requiring more trials in each condition to achieve robust results. At the same time, people generally find

corneal contact lens electrodes to be more unpleasant than filament-type electrodes, which are experienced as more unpleasant than skin electrodes (for which nothing actually touches the eye). Researchers always have to consider the balance between SNR, number of trials, and likelihood of subjects tolerating the procedure, when considering which ERG recording method to use.

Schizophrenia and high-risk populations

Schizophrenia is a severe psychiatric disorder that is characterized by hallucinations, delusions, disturbances in affect and reward processing, and impairments in social and every-day functioning. Impairments in cognition and brain activation, and loss of gray and white matter have been well documented (Cropley et al., 2017; Green, Horan, & Lee, 2019), supporting the view that schizophrenia is fundamentally a brain disorder characterized by neurodevelopmental and possibly neurodegenerative features (Kahn & Keefe, 2013). There are also well-documented visual perceptual disturbances in the condition (Silverstein, 2016). All of this evidence has led to a focus on the retina, both as a proxy for brain changes, and as a possible contributor to visual perceptual anomalies, which are common in the disorder (Silverstein, 2016). Research on the retina in schizophrenia has accelerated greatly in the past fifteen years. Papers have appeared using ERG or OCT, and multiple reviews of one or both of these literatures have been published in the past five years (e.g., Adams & Nasrallah, 2018; Gagne, Hebert, & Maziade, 2015; Garcia-Portilla et al., 2019; Gracitelli et al., 2015; Hosak, Sery, Sadykov, & Studnicka, 2018; Jerotić & Marić, 2018; Kazakos & Karageorgiou, 2020; Lavoie, Maziade, & Hebert, 2014; Lizano et al., in press; Pan, Zhou, Xiang, & Yu, 2018; Schonfeldt-Lecuona et al., 2016; Schwitzer et al., 2016; Silverstein et al., in press; Silverstein & Rosen, 2015). The evidence generated using each technique suggests that schizophrenia is associated with both retinal thinning and retinal functional impairment. However, the findings vary by study and this variability may be related to aspects of heterogeneity within schizophrenia, as well as issues such as clinical state and duration of illness, as is noted below.

OCT in schizophrenia - Studies on retinal structure in schizophrenia using OCT have been published since 2010. This literature was reviewed most recently in Silverstein et al. (2020). All published studies except for two (Chu et al., 2012; Silverstein, Paterno, Cherneski, & Green, 2018) have found RNFL and/or macula thinning, and the latter study found a trend for macula thinning and a significantly enlarged cup-to-disc ratio (Silverstein et al., 2018). Recent evidence converges on the conclusion that macula indices may be the most sensitive for discriminating people with schizophrenia from healthy controls. In addition to RNFL and macula findings, recent studies have investigated other structures. For example, Celik et al. (2016) reported GCL-IPL layer thinning in schizophrenia, as well as reduced choroidal thickness in treatment non-responsive patients. GCL-IPL changes were also reported by Jerotic et al. (Jerotic et al., in press). However, choroid changes were not demonstrated in another study that did find evidence of thinning in other layers (Topcu-Yilmaz, Aydin, & Ilhan, 2018). Samani et al (2018) demonstrated ONL and ISL thinning in multiple regions, and this was correlated with symptom severity. Thinning of the ONL was also reported by Bannai et al. (2020), but within the context of normal RNFL and GCL-IPL values and thickening of the OPL (and thickness values in some quadrants of the ONL and OPL were inversely correlated in this study). ONL thinning was associated with poorer cognitive functioning, and smaller total brain and white matter volume values. Of note, the sample in Bannai et al. was comprised of people with psychotic disorders or features and so included people with schizoaffective and bipolar disorders. Schönfelt-Lecuona et al. (2019) reported thinning of the INL, and also found that extent of RNFL thinning was inversely correlated with illness duration. Further evidence that retinal thinning is related to illness progression comes from an integration of findings that older patients demonstrate more severe thinning than younger patients (Lee, Tajunisah, Sharmilla, Peyman, & Subrayan, 2013), and the relationship between retinal measurements and illness duration becomes non-significant after controlling for age (Ascaso et al., 2015), yet more chronically ill patients demonstrate macula thinning (which does not vary significantly as a result of age), while first episode

schizophrenia patients are not characterized by retinal thinning (Lai, Crosta, & Silverstein, in press). A potential confound with this approach is that acute psychotic episodes may be associated with neuroinflammation and, consequently, retinal edema, which may mask evidence of tissue loss (Ascaso et al., 2015; Kaufhold et al., 2013; Topcu-Yilmaz et al., 2018). To address this, studies comparing chronically vs. acutely ill patients, matched for time since last psychotic episode, are needed. A finding suggesting that at least some aspects of retinal thinning may be trait- (endophenotype) related was recently reported (Kurtulmus et al., 2020). In this study, IPL (but not RNFL, macular, or GCL) thickness was reduced in schizophrenia patients and first- degree relatives. Interestingly, the magnitude of the between-group differences became stronger after controlling for a number of potential confounds (see section on this below), such as age, gender, smoking status, the presence of comorbid medical disease, and body mass index (BMI).

An additional unanswered question in this field is the extent to which retinal structural anomalies in schizophrenia are related to the many visual processing impairments associated with this condition, including in low-level vision (reviewed in Silverstein, 2016). Only one study has addressed this, and did find evidence for a relationship with decreased contrast sensitivity for low spatial frequencies (Samani et al., 2018). In short, findings generally indicate that retinal thinning (especially of the macula) occurs in schizophrenia and that it may be an aspect of illness progression and more pronounced in more severely ill patients (operationally defined as those experiencing persistence of symptoms over long periods of time). At the same time, there is intriguing preliminary evidence that retinal structure may be affected in people at genetic risk for the disorder. A major unresolved issue is the reason for the variation across studies in which retinal layers or sections of structures (e.g., quadrants of the RNFL) are characterized by thinning. Further improvements in imaging resolution and contrast advances will allow for more effective disambiguation of retinal structural loss vs. edema.

ERG in schizophrenia - All published studies of ERG in schizophrenia indicate one or more ERG anomalies [reviewed in Silverstein et al., in press). Nearly all studies have used flash ERG, and the most consistent findings involve reduced b-wave latency, and to a lesser extent, increased b-wave implicit time, although reduced a-wave amplitude has also been reported (Balogh, Benedek, & Keri, 2008; Demmin, Davis, Roche, & Silverstein, 2018; Warner, Laugharne, Peet, Brown, & Rogers, 1999). Findings are quite consistent across studies, and have been demonstrated in very large studies [e.g. with 150 schizophrenia patients, 151 bipolar disorder patients, and 200 healthy controls; (Hebert et al., 2020)]. Importantly, b-wave anomalies have been observed in young adults at genetic high risk for schizophrenia but who are not displaying symptomatology, suggesting that this index is tapping into the genetic basis for the disorder (Gagné, Moreau, St-Amour, Marquet, & Maziade, in press; Hébert et al., 2015). Reduced amplitude of the a-wave, in contrast, appears to be state-related as it is not found in young people at risk (Hébert et al., 2015), and it normalizes with treatment for an acute psychotic episode (Balogh et al., 2008). On the other hand, two studies found that b-wave amplitude covaries with levels of negative symptoms in clinically stable patients (Demmin, Mote, Beaudette, Thompson, & Silverstein, 2019; Demmin et al., 2018). The first study to examine the PhNR in schizophrenia (reflecting ganglion cell activity) indicated attenuated activity (Demmin et al., 2018). This was recently replicated in the context of a study that also demonstrated that multiple aspects of pERG data were attenuated compared to controls, at a trend level of significance (Moghimi et al., in press). Another recent study (Bernardin et al., 2019) found significant between-group differences on implicit times on both the pERG and flash ERG, and reduced amplitudes on the flash ERG. Of note, pERG implicit times were especially prolonged in patients who reported lifetime visual hallucinations. There have been no other published pERG studies in schizophrenia, and no mfERG reports to date. Overall, ERG data in schizophrenia indicate both trait and state effects, and involvement of multiple retinal cell types (e.g., photoreceptors, bipolar cells, Müller cells, ganglion cells). Although not a focus of this review, one issue is the extent to

which altered retinal function in schizophrenia is related to microvascular changes. There is little evidence on the latter issue but it has been observed that widened retinal venules were associated with schizophrenia, psychotic symptoms in childhood, and genetic risk for the development of psychotic symptoms (Meier et al., 2013, 2015).

Autism

Autism is a neurodevelopmental condition characterized by social and communication disturbances (e.g., poor eye contact, unresponsiveness to other people, difficulty understanding others' points of view or intentions), restricted interests and repetitive behaviors (including echolalia, and distress at disruption of rigid routines), and frequent intellectual impairment. Symptoms generally appear within the first two years of life and it is a lifelong condition. In the current edition of the Diagnostic and Statistical Manual for Mental Disorders (DSM-5) (American Psychiatric Association, 2013) it is recognized that autism is a spectrum condition, meaning that there is a wide range in severity of symptoms and level of impairment in people with the diagnosis. The new diagnostic label of *autism spectrum disorder* (ASD) includes the condition formerly known as Asperger syndrome (AS), which was viewed as a relatively mild form of autism, with relatively preserved language and intellectual abilities. The causes of autism are not known and are thought to involve a combination of genetic and other biological factors. The condition is associated with a number of CNS alterations such as neuroanatomical abnormalities (Ecker, 2017) and neuro-immune dysfunction (i.e., neuroinflammation). Visual processing changes have been well-documented in autism (Dakin & Frith, 2005), including reports of superior detail processing abilities [also found in olfaction: (Walker, Williams, & Moore, 2020)].

OCT in autism - In the first study of this issue, subjects with high-functioning autism (HFA) exhibited reduced global RNFL thickness compared to AS and control subjects (Gialloreti et al., 2014). Additionally, the AS subjects demonstrated thinning in the nasal quadrant of the RNFL compared to controls. The study also found that greater discrepancy between verbal and performance IQ – a

common index of brain dysfunction - was associated with decreased RNFL thickness. In contrast to these findings, (García-Medina et al., 2017) reported that autism spectrum disorder (ASD) individuals demonstrated significantly *greater* thickness in the inferior, nasal inferior, and temporal inferior quadrants of the RNFL compared to neurotypical individuals. ASD subjects also exhibited greater mean foveal and macular thickness for the total retina and total inner retina, as well as thicker macular IPL and INL measurements than the neurotypical group. The authors suggested that the greater retinal thickness in ASD may reflect neurodevelopmental abnormalities related to parenchyma growth or neuroinflammation. Additional findings demonstrated positive associations between the thickness of the temporal inferior portion of the RNFL and non-verbal, verbal, and composite IQ scores, as well as a positive correlation between inferior RNFL and composite IQ. These findings suggest that thicker retinal layers are associated with higher cognitive functioning in individuals with ASD. Taken together, although these two initial studies produced mixed results, which García-Medina et al. (2017) proposed may be due to differences in the fovea-to-disc adjustment procedures in the different OCT scanners used in the studies, the data suggest that abnormalities in retinal structure may exist in ASD. Therefore, further studies are needed to better localize these changes, and the factors affecting whether thinning or thickening is present. Of note, recent evidence in healthy elderly people suggests that there is a nonlinear relationship between GLC-IPL thickness and cognitive impairment (Liu et al., 2019). In this case, retinal thinning reflects neuronal loss whereas thickening reflects neuroinflammation and (in older adults) accumulation of deposits of amyloid β, amyloid precursor, and tau proteins. Therefore, future studies in ASD and other relevant conditions, especially in elderly samples (see section on Alzheimer's disease below), will need to characterize samples in terms of various factors that can affect retinal structure and create heterogeneity within samples.

ERG in autism - Given that previous literature has demonstrated high-level visual processing deficits in ASD (Simmons et al., 2009), studies have also focused on the investigation of retinal

functioning anomalies. Earlier findings indicated that individuals with ASD demonstrated reduced flash ERG b-wave amplitudes in scotopic conditions (Creel, Crandall, Pingree, & Ritvo, 1989; Ritvo et al., 1988, Realmuto, Purple, Knobloch, & Ritvo, 1989) found attenuated b-wave amplitudes in two of four ASD probands and six of their first-degree relatives (two of four siblings and two fathers). More recent evidence indicated that individuals with ASD demonstrate reduced photopic b-wave amplitude compared to controls, as well as decreased ON b-wave amplitude in response to a prolonged light flash (Constable, Gaigg, Bowler, Jägle, & Thompson, 2016). Overall, current findings suggest that ASD may be characterized by abnormalities in retinal functioning and structure. However, this research is in the beginning stages and additional studies are warranted to explore the potential use of retinal measures as biomarkers for ASD diagnosis and familial risk. It will also be important to investigate the extent to which OCT and ERG findings are related to other forms of neuro-ophthalmologic changes in ASD, as have been observed in case reports and small-sample studies (Brodsky, Barber, Lam, Merin, & Edelson, 1996; Denis, Burillon, Livet, & Burguiere, 1997).

Bipolar disorder

Bipolar disorder (BD) is a severe psychiatric disorder characterized by mood disturbances. A person with BD will have episodes that meet criteria for major depressive disorder, and at other times will experience mania or hypomania for at least a week at a time. Some people also experience episodes of mixed depressive and manic symptoms. The disorder is associated with significant impairments in occupational and social functioning and in subjectively experienced quality of life (Gitlin & Miklowitz, 2017; Sanchez-Moreno et al., 2009). Given that rates of misdiagnosis and psychiatric comorbidity are particularly high in BD (Hirschfeld, Lewis, & Vornik, 2003; Hirschfeld & Vornik, 2005), the identification of biomarkers of the disorder remains a key goal of current research efforts. While neuroimaging studies have consistently demonstrated anomalies in functional activity and structure in a variety of neural regions, including gray and white matter reductions (Phillips & Swartz, 2014), diagnostic markers and

markers of disease progression have not been identified. Therefore, recent studies have focused on structural and functional changes of the retina in BD to investigate markers of these issues.

OCT in bipolar disorder - Although in its early stages, research on retinal structure in BD suggests the presence of thinning in a variety of retinal layers. Several studies have found RNFL thinning in BD (Garcia-Martin et al., 2019; Kalenderoglu, Sevgi-Karadag, et al., 2016; Khalil, Saleh, Gohar, Khalil, & Said, 2017; Mehraban et al., 2016; Polo et al., 2019). However, as in schizophrenia, the particular RNFL regions where reductions have been found are mixed. For example, Mehraban et al. (2016) observed thinning in inferior, superior, and nasal areas, while other studies found no reductions in nasal areas (Garcia-Martin et al., 2019; Khalil et al., 2017), and one study only observed a significant reduction in global RNFL (Kalenderoglu, Sevgi-Karadag, et al., 2016). Evidence also indicates that people with BD demonstrate reductions in macular GCC (Khalil et al., 2017) and IPL thickness (Garcia-Martin et al., 2019), and GCL volume (Kalenderoglu, Sevgi-Karadag, et al., 2016; Polo et al., 2019) and thickness (Garcia-Martin et al., 2019; Polo et al., 2019) when compared to healthy controls. Using swept source OCT, Polo et al., (2019) observed reductions in macular and peripapillary GCL+ (RNFL to INL layers) and GCL++ (ILM to INL layers), as well as full macular (consistent with Garcia-Martin et al., 2019) and peripapillary retinal thickness in individuals with BD when compared to controls. Two studies reported no differences in choroidal thickness between subjects with BD and healthy controls (Kalenderoglu, Sevgi-Karadag, et al., 2016; Polo et al., 2019), suggesting that retinal changes may be related to neural layers. Interestingly, one study observed greater INL thickness in subjects with BD (Garcia-Martin et al., 2019).

Findings also suggest that retinal thinning may reflect BD progression, as Polo et al. (2019) found that full macular and RNFL thinning were associated with greater duration of illness. Additionally, reduced GCL volume was been associated with increased disease duration and illness severity, leading the authors to suggest an underlying neurodegenerative or inflammatory process (Kalenderoglu, Sevgi-

Karadag, et al., 2016). However, other studies found no relationship between illness severity and disease duration of BD and reduction of GCC (Khalil et al., 2017) or found that greater disease duration was associated with greater GCL thickness (Garcia-Martin et al., 2019). Some studies have focused on psychosis transdiagnostically and have included samples of subjects with BD or schizophrenia. Joe et al. (2018) observed reductions in macular thickness and no differences in choroidal thickness in a small sample of subjects with psychosis with either diagnosis (*n*=6). A recent meta-analysis focused on differences in OCT data from studies with subjects with BD or schizophrenia found RNFL and GCL-IPL thinning when compared to controls (Lizano et al., in press). As noted above, in a combined sample of people with schizophrenia, schizoaffective disorder and bipolar disorder, Bannai et al. (2020) reported ONL thinning (which was associated with poorer cognitive functioning, and smaller total brain and white matter volume values), but normal RNFL and GCL-IPL values, and thickening of the IPL. This study also found that level of RPE thinning in the sample was associated with more severe manic symptoms. Future studies are needed to differentiate which OCT abnormalities are associated with psychosis and which are diagnosis specific. Overall, findings suggest that individuals with BD demonstrate thinning in multiple retinal layers, although additional studies are needed to replicate these findings and distinguish which retinal sub-regions and layers consistently show thinning and are associated with disease progression.

ERG in bipolar disorder – There are even fewer ERG studies in bipolar disorder than there are OCT studies. The first published study to focus on retinal function as measured by ERG found no differences in cone functioning between subjects with BD and healthy controls (Balogh, Benedek, & Kéri, 2008). However, a recent study found decreased cone a-wave and mixed rod-cone a- and b-wave amplitude, in addition to greater b-wave latency, in a sample of subjects with BD and schizophrenia when compared to healthy control subjects. Importantly, subjects with BD and schizophrenia could be distinguished using ERG data with 0.86 accuracy, suggesting that ERG indices could be used as diagnostic

markers or aids (Hébert et al., 2020). Additionally, abnormalities in rod functioning were observed in ERG data of offspring of parents with a schizophrenia or BD diagnosis, leading the authors to suggest a common neurodevelopmental pathway between the two disorders (Hébert et al., 2010). Although these studies indicate that fERG anomalies may reflect markers of diagnosis and risk for BD or schizophrenia, additional studies are warranted to clarify the mixed findings related to cone functioning in BD and to investigate if initial ERG findings reflecting disease specificity and shared neurodevelopmental markers of risk can be replicated.

Major depressive disorder

Major depressive disorder (MDD) is a serious public health issue, with an estimated global point prevalence of 5% (Ferrari et al., 2013). Moreover, data suggests that one in every six adults will experience a major depressive episode within their lifetime (Bromet et al., 2011). MDD is also associated with a high rate of suicidal behavior and significant functional disability (e.g., unemployment). In addition to changes in mood, pleasure, cognitive functioning, appetite, and/or sleep (Otte et al., 2016), people with MDD may experience alterations in visual functioning. For example, a decrease in light and color perception (Friberg & Borrero, 2000), an increase in pattern glare (Qi et al., 2019), and a reduction in visual contrast discrimination (Fam, Rush, Haaland, Barbier, & Luu, 2013) have been reported in MDD. The pathophysiological mechanisms of depressive disorders are not completely understood, but are thought to involve both a number of changes such as reductions in gray and white matter volumes in limbic structures, the striatum, and frontal and temporal lobes (Bora, Fornito, Pantelis, & Yücel, 2012; Korgaonkar et al., 2011), alterations in brain-derived neurotrophic factor (BDNF) levels (Zou et al., 2010), increased inflammatory cytokines (Felger & Lotrich, 2013), monoamine (DA, serotonin, norepinephrine) neurotransmitter dysfunction (Haenisch & Bönisch, 2011), and altered hormone (cortisol, melatonin) levels (Bumb et al., 2016)] changes. It is only recently, however, that studies of retinal structure and function have been conducted in MDD.

OCT in MDD - Kalenderoglu et al. (2016) examined OCT parameters in patients with recurrent MDD, those reporting one episode of major depression (and not receiving antidepressant medication; i.e., first-episode), and healthy controls with no history of MDD. In both MDD groups the mean choroidal thickness was higher relative to controls. However, choroid thickness was significantly higher in the first-episode group as compared to recurrent MDD patients (Kalenderoglu, Çelik, Sevgi-Karadag, & Egilmez, 2016), suggesting a potential neuroinflammatory effect. Conversely, the researchers found that GCL and IPL volumes were reduced in both MDD groups in comparison to healthy controls, with the recurrent MDD group demonstrating the greatest volume reduction (Kalenderoglu, Çelik, et al., 2016), suggesting progressive thinning of neural layers with recurrent depressive episodes. However, in most studies, abnormalities in retinal cell structure have not been observed. Several studies have reported no significant reductions in RNFL thickness (Schönfeldt-Lecuona et al., 2018; Sönmez, Köşger, & Aykan, 2017; Yildiz et al., 2016) or volume (Schönfeldt-Lecuona et al., 2018) in MDD patients relative to healthy controls. Some studies have also failed to observe differences beween MDD patients and controls with regard to GCL-IPL (Schönfeldt-Lecuona et al., 2018; Yildiz et al., 2016), INL (Schönfeldt-Lecuona et al., 2018), OPL (Schönfeldt-Lecuona et al., 2018), and ONL (Schönfeldt-Lecuona et al., 2018) thickness or volume. Interestingly, despite limited evidence that retinal cell structure integrity is affected in MDD, in some studies a relationship between OCT anomalies and indicators of disease severity has been observed. In a study cited above, both GCL and IPL volume were negatively correlated with disease duration, depressive symptom severity, and overall clinical severity in MDD, and decreased choroidal thickness was associated with longer illness duration and more severe symptoms in MDD (Kalenderoglu, Çelik, et al., 2016). Moreover, a significant but moderate (-.31) negative correlation between RNFL nasal quadrant and GCL-IPL thickness and duration of the latest episode was reported (Yildiz et al., 2016). Surprisingly, greater total RNFL thickness was associated with more severe depressive symptomatology, although again not strongly (.28) (Yildiz et al., 2016). Importantly, most MDD patient samples in the

studies reviewed were receiving antidepressant medication (Schönfeldt-Lecuona et al., 2018; Sönmez et al., 2017; Yildiz et al., 2016). One potential mechanism underlying antidepressant efficacy is enhanced neural plasticity (Chittaranjan Andrade & Rao, 2010). Thus, it is possible that antidepressants may reduce retinal degeneration in MDD. Indeed, Kalenderoglu and colleagues (2016) observed several OCT anomalies in patients experiencing a first episode of depression who were not receiving antidepressant treatment. Additional studies are needed in medication-free samples, and in patients with varying illness courses, to better estimate the extent to which retinal cell structure is affected in MDD. At present, however, it appears that structural brain changes are more reliably associated with MDD than are retinal changes.

ERG in MDD – Several studies have reported anomalies retinal cell functioning using both pERG and fERG. Bubl et al. (2010) compared contrast gain functions of medicated MDD patients experiencing a current episode of depression to patients not receiving medication, and psychiatrically healthy controls. Both patient groups demonstrated a significant reduction in contrast gain relative to the healthy control group, and no significant differences between medicated and unmedicated patients were observed (Bubl, Kern, Ebert, Bach, & Van Elst, 2010). There were also no differences between patients with first-episode and recurrent depression in terms of contrast processing as assessed with pERG (Bubl et al., 2010). However, the authors did find that reductions in retinal contrast processing were linked with depressive symptom severity in MDD (Bubl et al., 2010). Consistent with this, a later study demonstrated a normalization of pERG-measured contrast gain after symptom remission (Bubl, Ebert, Kern, van Elst, & Bach, 2012), suggesting that pERG anomalies may be markers of disease severity. However, in contrast to these findings, Fam et al. (2013) observed no significant difference between patients with MDD (most of whom were receiving antidepressant treatment) and healthy controls on pERG contrast gain functions (Fam et al., 2013).

Several studies have also examined retinal function in MDD using fERG. Hébert et al. (2017) investigated abnormalities in retinal cell functioning in a large sample of 100 patients with MDD, 17 of whom were medication free (Hébert, Mérette, Paccalet, Gagné, & Maziade, 2017). In comparison to healthy controls, patients in the medicated MDD sample demonstrated a reduction in scotopic a-wave amplitude and an overall increase in photopic b-wave implicit time (Hébert et al., 2017). The medication-free MDD group also differed qualitatively from the healthy control group, demonstrating a medium-to-large increase in photopic b-wave implicit time and a decrease in scotopic b-wave amplitude (Hébert et al., 2017). These findings differ somewhat from an earlier study by Fornaro and colleagues (2011) in which the effects of antidepressant therapy on retinal functioning were examined in both patients with MDD and healthy controls (Fornaro et al., 2011). In that study, depressed patients did not differ from healthy controls on any fERG parameters at baseline, or after 12 weeks of treatment (Fornaro et al., 2011). However, baseline scotopic b-wave amplitude was higher in a subgroup of patients who ultimately achieved symptom remission, while there were no significant differences between responders, non-responders, and healthy controls at treatment end, suggesting that antidepressant medication may normalize ERG values (Fornaro et al., 2011). Nevertheless, several studies have reported no significant differences between patients with MDD (the majority of whom were taking medication) and healthy controls on a variety of fERG indices (Demmin, Netser, Roché, Thompson, & Silverstein, 2019; Fam et al., 2013; Fountoulakis, Fotiou, Iacovides, & Kaprinis, 2005). Together, these data indicate that retinal cell functioning alterations in MDD are likely to be state-linked and to improve with pharmacological treatment or clinical recovery.

ERG in Seasonal affective disorder - In seasonal affective disorder (SAD), major depressive episodes follow a pattern of recurrence, typically over the fall and winter months (Melrose, 2015). It has been hypothesized that this seasonal pattern of depression may be related to abnormalities in retinal light sensitivity (Beersma, 1990; Remé, Terman, & Wirz-Justice, 1990). Several researchers have

observed a season change in retinal sensitivity in patients with SAD, whereby unmedicated SAD patients demonstrate significantly reduced rod sensitivity (Hébert, Beattie, Tam, Yatham, & Lam, 2004; Hébert, Dumont, & Lachapelle, 2002; Lavoie et al., 2009) and maximal cone amplitude (Lavoie et al., 2009) during fall/winter months when compared to healthy controls, providing support for a retinal hyposensitivity hypothesis of SAD etiology. The magnitude of change in retinal sensitivity has also been related to degree of seasonality (Hébert et al., 2002) and symptom severity in patients with SAD and with subsyndromal seasonal depression. Additionally, in one study, a normalization of rod and cone response was observed in SAD patients during summer months and after four weeks of treatment with light therapy (Lavoie et al., 2009), providing further evidence of impaired state-related retinal sensitivity in SAD. Lam et al. (1992) observed abnormalities in retinal cell function in SAD when compared to healthy controls, however, the direction of change differed by gender; whereas scotopic b-wave amplitude was lower among female SAD patients compared to female controls, b-wave amplitudes were higher among male SAD patients relative to matched controls (Lam, Beattie, Buchanan, & Mador, 1992). However, given the relatively small sample size in this study, these results were considered preliminary. In another study, abnormalities in modulation of rod and cone responses were observed in patients with SAD relative to healthy controls during periods of symptom exacerbation in winter months, and also when symptoms remitted in summer months (Gagné & Hébert, 2011). These data suggested that some fERG anomalies may constitute trait markers. However, overall, studies in SAD suggest that changes in retinal cell functioning are closely linked with disease state.

Attention deficit-hyperactivity disorder (ADHD)

Attention-deficit/hyperactivity disorder (ADHD) is one of the most commonly diagnosed neurodevelopmental disorders with an estimated prevalence of 5.5% among children and adolescents worldwide (Erskine et al., 2017). The core symptoms of ADHD include impulsivity, hyperactivity and inattention (Ougrin, Chatterton, & Banarsee, 2010). A high degree of comorbidity between ADHD and

other psychiatric and neurological conditions has been reported, including ASD, Tourette's syndrome, mood disorders, anxiety disorders, conduct disorder, and oppositional defiant disorder (Gnanavel, Sharma, Kaushal, & Hussain, 2019). Furthermore, many individuals continue to experience symptoms of ADHD and neuropsychological impairment into adulthood (Polanczyk & Rohde, 2007; Polanczyk, Willcutt, Salum, Kieling, & Rohde, 2014). Greater insight into the neurobiological basis of ADHD may help to identify more effective psychopharmacological treatments, and there have been a small number of studies of retinal function (but none of retinal structure) in ADHD.

ERG in ADHD - Elevated levels of "background noise" or "non-stimulus driven neural activity," potentially as a result of dysregulated DA activity, may be an underlying pathophysiological mechanism of ADHD (Brennan & Arnsten, 2008; Bubl, Dörr, et al., 2015; Sikström & Söderlund, 2007; Werner et al., 2019). Using pERG, Bubl et al. (2015) observed an increase in noise amplitude in a sample of unmedicated adults with ADHD, compared to healthy controls (Bubl, Dörr, et al., 2015). Additionally, the magnitude of noise in pERG amplitudes was correlated with severity of ADHD symptoms, and particularly inattention (Bubl, Dörr, et al., 2015). In another study, Werner et al. (2019) examined the effects of methylphenidate on pERG background noise in adults with ADHD (Werner et al., 2019). Methylphenidate is thought to improve inattention and distractibility through blockade of the DA transporter, resulting in an increase in extracellular DA (Engert & Pruessner, 2008). While retinal background noise was elevated among ADHD patients at baseline relative to controls, after treatment with methylphenidate levels of background noise were normalized (Werner et al., 2019). Additional pERG studies in child and adolescent populations will help determine whether increases in retinal neuronal noise may serve as a trait marker of widespread CNS disruptions in ADHD. To our knowledge, no prior studies have examined abnormalities in photoreceptor or bipolar cell functioning, via fERG, in ADHD.

Anorexia Nervosa

Anorexia nervosa (AN) is a psychiatric disorder characterized by fear of weight gain and persistent behavior to inhibit weight gain, as well as restrictive caloric intake resulting in low body weight (American Psychiatric Association, 2013). As is often stated, people with AN do not just want to be thin, they want to be thinn*er*. The diagnosis includes restrictive and binge-eating/purging subtypes. AN outcomes and prognosis remain poor due to high rates of mortality and psychiatric comorbidity (Steinhausen, 2009). A key characteristic of AN involves perceptual disturbances of oneself and studies have shown that individuals with AN demonstrate anomalies in visual perception and perceptual organization (Madsen, Bohon, & Feusner, 2013). Therefore, the investigation of retinal structure and function in AN may provide evidence that helps to elucidate factors that contribute to visual processing impairments in the disorder.

OCT in AN - There is currently limited data on retinal structure in individuals with anorexia nervosa (AN). Findings suggest that individuals with AN demonstrate RNFL thinning (Caire-Estevez, Pons-Vazquez, Gallego-Pinazo, Sanz-Solana, & Pinazo-Duran, 2012; Moschos et al., 2011) and reduced mean foveal thickness (Moschos et al., 2011; Moschos, Moustafa, Gonidakis, & Papageorgiou, 2016) also found reductions among females with AN in the central macula, GCC, choroid, and ORL (i.e., the distance between the external limiting membrane (ELM) and the RPE, or the length of the inner and outer segments of photoreceptors combined). However, subjects with AN demonstrated greater ORL thickness within the superior area than healthy controls. One study found evidence for more pronounced thinning in AN patients with the binge-purge subtype of AN (Moschos et al., 2011).

ERG in AN - AN may also be characterized by abnormalities in macular function, as indicated by mfERG findings showing reduced P1 amplitude within ring 1 in females with AN (Moschos et al., 2011; Moschos et al., 2016). Given that visual acuity losses may be more pronounced in the restrictive subtype of AN (Caire-Estevez et al., 2012), while (as noted above) retinal thinning on OCT was more pronounced among patients with the binge-purge subtype (Moschos et al., 2011), future research should continue to

study differences in retinal activity between AN subtypes. Additionally, it will be important to determine if retinal abnormalities reflect state or trait measures of AN and if retinal anomalies are associated with nutritional consequences of the disorder and can be reversed with proper nutrition.

Other eating disorders - To the best of our knowledge, no studies have investigated OCT and ERG abnormalities in individuals with other eating disorders. However, initial evidence suggests that retinal function may be related to binge eating. After administering a brownie to healthy participants, Nasser et al. (2013) found that greater cone b-wave amplitude increases relative to a baseline condition were associated with stronger food cravings and more binge eating behaviors. The increase in b-wave amplitude in the food consumption condition was also significantly correlated (.87) with the increase in response to 20mg (but not 10mg) of methylphenidate (assessed on a different day), suggesting that the food-related increase reflected DA-mediated reward mechanisms. Therefore, it would be reasonable to investigate if individuals with a binge eating disorder diagnosis demonstrate anomalies in ERG activity in future studies.

Multiple Sclerosis

Multiple sclerosis (MS) is a heterogeneous syndrome, with relapsing-remitting and progressive subtypes. It has traditionally been viewed as a disease of neuroinflammation and demyelination of neurons in the brain and spinal cord that leads to multiple disabling neurological symptoms including visual changes (e.g., blurry or double vision; blindness in one eye), problems with coordination and balance, muscle weakness, speech difficulties, numbness or tingling in the arms and legs, pain, fatigue, and cognitive difficulties (Karussis, 2017). Psychiatric changes are also common, especially mood changes such as depression (Persson et al., 2020). The cause of MS is not known, but is thought to involve genetic and environmental (including viral) changes that initiate excessive auto-immune activity (Milo & Kahana, 2010; Morandi et al., 2017). Due to the common visual findings in MS (Balcer, Miller,

Reingold, & Cohen, 2015), there has been extensive research on retinal structure and function in the condition.

OCT in MS - Since the late 1990s and especially in the past decade, OCT has been used extensively in studies of MS. A recent comprehensive review noted that there are now over 1500 studies listed on PubMed where OCT was used to investigate MS or optic neuritis (i.e., inflammation of the optic nerve; a frequent initial and later symptom of MS) (Graves, 2019). Multiple important OCT findings in MS have been replicated numerous times, and findings of relationships between retinal thinning and brain volume loss, visual function changes, cognitive decline, functional disability, and disease progression come from multiple cross-sectional and longitudinal studies (Britze & Frederiksen, 2018; Costello & Burton, 2018; Doustar et al., 2017; Graves, 2019; Sedighi et al., 2014; Yap et al., 2019). Findings are also mostly consistent across children and adults. One consistent finding involves thinning of the RNFL in patients with a history of optic neuritis, but also in patients without a history of that symptom. The mechanism of ganglion cell axon loss in the former is thought to involve retrograde trans-synaptic degeneration (RTSD) (Dinkin, 2017), wherein loss of neurons in the optic radiations (geniculocalcarine tract) leads to loss of ganglion cell axons that projected to them. RNFL thinning after the acute episode is related to the degree of inflammation during that episode (Burton et al., 2017), and reaches maximal extent 3-6 months after the acute episode before stabilizing (Pro et al., 2006). The cause of retinal thinning in MS without optic neuritis is not clear and several different mechanisms have been proposed (Britze, Pihl-Jensen, & Frederiksen, 2017). Regardless of the mechanism, RNFL and other retinal layer thinning in MS occurs after/between acute inflammatory episodes and is found even in younger patients and those with mild levels of disability (reviewed in Graves, 2019). The degree of RNFL thinning in MS is also associated with reduced visual function (e.g., poorer contrast sensitivity) (Graves, 2019) and with brain volume loss, suggesting a common basis for neural atrophy in the retina and brain (Gordon-Lipkin et al., 2007). Similar results have been observed for macula thickness and volume:

reductions in patients with or without a history of optic neuritis (Saidha, Syc, Ibrahim, et al., 2011; Trip et al., 2006), and correlations with visual function and brain loss, and also disability (Bock et al., 2012). Multiple studies also indicate GCL-IPL thinning in MS. Importantly, GCL-IPL thinning can be observed prior to RNFL thinning (Britze et al., 2017; Huang-Link, Al-Hawasi, & Lindehammar, 2015), similar to what is observed in glaucoma (Marshall et al., 2019), and is a stronger predictor of visual impairment and functional disability than RNFL changes (Nguyen et al., 2019; Saidha, Syc, Durbin, et al., 2011). GCL-IPL changes are also associated with grey matter loss (Saidha et al., 2013), and are useful as an index of treatment response in MS (Button et al., 2017; Lambe, Murphy, & Saidha, 2018). Some recent studies have also reported INL thinning (Gracitelli et al., 2015; Saidha, Syc, Durbin, et al., 2011), but relationships with other aspects of MS are not well established at this point. Taken together, OCT findings in MS strongly indicate that retinal atrophy is a characteristic of the illness, and that it can serve as a proxy for a number of important illness characteristics. These data also are helping to revise the view of MS as primarily a demyelinating disorder, since retinal neurons are generally unmyelinated. It should also be noted that retinal microvasculature changes are observed in MS (Jiang et al., 2016; Lanzillo et al., 2019) and so OCT findings will ultimately need to be understood in terms of these changes. Finally, while not a focus of this review, it is worth mentioning that retinal imaging provides highly accurate retinal tracking that is superior to Purkinje eye tracking. As a result, investigators have begun to quantify eye motion based on retinal image tracking to diagnose ocular motor deficits in MS (Sheehy, Beaudry-Richard, Bensinger, Theis, & Green, 2018).

ERG in MS - ERG studies in MS began many years prior to the development of OCT (Feinsod, Abramsky, & Auerbach, 1973; Gills, 1966), and the evidence generally indicates retinal functional impairment. However, while flash ERG, pERG, and mfERG have all been used in studied in MS, there are far fewer ERG than OCT studies of MS overall, and there are many conflicting findings within each method's literatures. Using flash ERG, two early studies (Coupland & Kirkham, 1982; Papakostopoulos,

Fotiou, Hart, & Banerji, 1989) demonstrated increased b-wave implicit times in MS patients with a history of optic neuritis. Hamurcu et al. (2017) reported that MS patients, regardless of history of optic neuritis, demonstrated attenuated cone (but not rod) waveforms, and increased implicit times on tests of cone (but not rod) function (Hamurcu, Orhan, Saricaoglu, Mungan, & Duru, 2017). Stronger findings for cone than rod implicit times were also observed by (Hanson et al., 2018). However, Gundogan et al. (2007) found a- and b-wave implicit time increases in MS patients and some of the a-wave findings were from tests of rod function. Both rod and cone impairment were also observed by (Forooghian et al., 2006), who reported rod and rod-cone b-wave implicit time increases, along with cone a-wave implicit time increases. Hanson et al., (2018) found reduced amplitude of the rod-cone a-wave, but *increased* amplitude of the rod and rod-cone b-waves in MS patients. Increased b-wave amplitude was also reported in an early study of MS patients with optic neuritis (Pierelli et al., 1985). Still another study did not find evidence of a- or b-wave changes, but did observe PhNR attenuation in patients with or without optic neuritis histories (Wang, Cheng, Hu, Tang, & Frishman, 2012). A number of studies have investigated the pERG in patients with MS. These studies consistently indicate retinal ganglion cell dysfunction, and some indicate that this is independent of optic neuritis (e.g., Gundogan, Demirkaya, & Sobaci, 2007; Janaky, Janossy, Horvath, Benedek, & Braunitzer, 2017; Rodriguez-Mena et al., 2013; Trip et al., 2005). However, other studies have found that pERG anomalies were limited to MS patients with a history of optic neuritis (Hokazono, Raza, Oyamada, Hood, & Monteiro, 2013; Serra, Carreras, Tugnoli, Manca, & Cristofori, 1984). Using mfERG, Gundogan et al. (2007) found no differences between MS patients (without a history of optic neuritis) and controls. Saidha (2011) also observed no implicit time changes in MS, but did observe reduced P1 amplitudes in most MS patients who also showed macula thinning on OCT. On the other hand, two studies indicate that P1 latency is increased in MS (Hanson et al., 2018) and is associated with illness progression (Neroev et al., 2016), while one study reported that N1 amplitude change was the best discriminator of MS patients from controls (Boquete et al., 2019). In

short, ERG findings in MS generally indicate impairment, but specific findings are often different across studies. This is likely due, at least in part, to study differences in factors such as equipment used, MS subtypes, length of illness and length of time since last acute episode, the proportion of subjects with a positive vs. negative history of optic neuritis, ERG data filtering methods, and other aspects of data analysis. Some recent work indicates that, at least for mfERG, novel data filtering and analysis methods can generate more reliable differences between MS patients and controls (Boquete et al., 2019; de Santiago et al., 2019). Other data analysis techniques, such as examining the discrete wavelet transform (DWT) may also provide a more fine-grained analysis that could better characterize between-group differences. As with Fourier analysis of a waveform into its component frequencies and their relative contributions to the overall waveform, but adding quantification of the timing of changes in activity at different frequencies, DWT analysis allows for characterization of multiple aspects of neural activity that follow a light stimulus, and that combine to generate the grosser measures of traditional waveform amplitude and latency (Gauvin, Lina, & Lachapelle, 2014; Gauvin, Little, Lina, & Lachapelle, 2015). Application of this technique to clinical studies is just beginning, but we expect to see papers using this method in MS and other disorders in the next few years. Finally, it should be noted that there are mixed findings regarding whether ERG changes in MS are related to retinal structural changes as observed with OCT. Most studies have found significant relationships (Almarcegui et al., 2010; Hanson et al., 2018; Neroev et al., 2016; Rodriguez-Mena et al., 2013; Sriram et al., 2014; Wang et al., 2012)] but some have not (Gundogan et al., 2007; Hanson et al., 2018)[3]. This variability in findings may be related to study sample differences in disease duration and extent of illness progression, as significant dysregulation and dysfunction in retinal cells can occur for several years prior to loss of neuritic processes and cell bodies (Banitt et al., 2013). Consistent with this, ERG anomalies have been detected in the absence of structural changes in other diseases such as (early) glaucoma and Parkinson's disease (Banitt et al.,

[3] In Hanson et al. (2018) significant correlations with OCT variables were observed with flash ERG, but not mfERG variables.

2013; Nowacka, Lubinski, Honczarenko, Potemkowski, & Safranow, 2015). Overall, data on the retina in MS clearly indicate retinal structural and functional impairment. The task for the near future is to determine if better characterization of illness heterogeneity and technical advances in data recording and analysis can help generate a coherent understanding of the inconsistencies in the literature.

Huntington's disease

Huntington's disease (HD) is a progressive neurodegenerative disorder that is characterized by involuntary movements (e.g., chorea and athetosis), cognitive decline, and emotional and behavioral disturbances. It is caused by a mutation in the CAG trinucleotide repeat of the huntingtin (*HTT*) gene. Age of onset is typically in adulthood (ages 30-50 years), but can be in childhood or adolescence, and has been inversely correlated with CAG repeat length (Gusella & MacDonald, 2000). Determination of whether a person has or will develop HD can be achieved via a blood test for the genetic mutation. However, what many researchers, clinicians and carriers want to know is when neuropathology emerges, when symptoms will begin, how rapidly the condition will progress, and how effective are treatments to slow progression. Biomarkers to address these issues are needed, and retinal markers are among those variables that are being investigated.

OCT in HD - Though retinal imaging studies in HD are limited, findings have been fairly consistent. While several studies have found no significant differences in overall mean RNFL thickness between HD patients and controls (Carlos Andrade et al., 2016; Gatto et al., 2018; Gulmez Sevim, Unlu, Gultekin, & Karaca, 2019; Kersten, Danesh-Meyer, Kilfoyle, & Roxburgh, 2015), region-specific reductions in temporal (Gatto et al., 2018; Gulmez Sevim et al., 2019; Kersten et al., 2015) and superior (Gatto et al., 2018) quadrants have been commonly reported. A decrease in average, central, and inferior macular choroidal thickness has also been observed in HD patients relative to controls (Andrade et al., 2016). Most recently, Glumez Sevim and colleagues (2019) reported a number of OCT anomalies in people with HD, including a reduction in GCL, IPL, OPL, and INL thickness and in IPL, RPE, and outer

macular volume (Gulmez Sevim et al., 2019). Interestingly, an increase in ONL and outer retinal later thickness was also reported in this study and attributed to possible swelling of cone cells, which has been observed in glaucoma (Gulmez Sevim et al., 2019; Nork, 2000). Despite a small number of studies in this area, some data suggest a relationship between retinal structural changes and disease severity in HD. Macular RNFL (Gulmez Sevim et al., 2019), temporal pRNFL (Kersten et al., 2015), GCL (Gulmez Sevim et al., 2019), and IPL (Gulmez Sevim et al., 2019) thickness and macular volume (Kersten et al., 2015) were inversely correlated with disease duration and severity of motor symptoms in HD patients. In addition, GCL, IPL, INL, and OPL thinning were associated with CAG repeat length (an indicator of HD acceleration rate) and disease burden score (comprising CAG repeat length and age; Gulmez Sevim et al., 2019). Therefore, retinal degeneration may reflect overall CNS atrophy and serve as an indicator of HD progression. Interestingly, in a case study of a presymptomatic patient with HD (i.e., tested positive for the *HTT* gene) no OCT abnormalities were observed (Knapp, VanNasdale, Ramsey, & Racine, 2018). Together, these findings suggest that anomalies in retinal structure in HD may be markers of disease severity but may not signify disease risk. However, given that retinal structural changes in HD have been assessed in only a small number of studies and cases to date, additional research is needed to determine whether retinal structural changes may be useful indicators of disease acceleration.

ERG in HD - Even fewer studies have investigated ERG anomalies in HD. Thus, it is currently unclear to what extent retinal functioning changes occur within the disorder. However, evidence from ERG studies on mouse models of HD suggest the presence of retinal cell dysfunction (Batcha et al., 2012; Helmlinger et al., 2002; Li et al., 2013; Ragauskas et al., 2014). To the best of our knowledge, only two ERG studies have studied retinal function in patients with HD and the findings of these studies are mixed. (Pearl et al., 2017) observed that patients with HD exhibited abnormalities in cone functioning, as indicated by significantly greater cone and mixed rod/cone b-wave amplitude, as well as increased (at a trend level of significance) cone activity in response to a flicker paradigm. Results further demonstrated

that the increase in amplitude was greatest in female patients with HD, which was particularly interesting since sex differences were not found among controls. Additionally, increased cone activity in response to a low light intensity stimulus was associated with a greater number of CAG repeats (Macdonald, 1993). This further suggests a link between HD and changes in retinal functioning, although the authors noted the small effect size of this result. In the second report of ERG in HD, (Knapp et al., 2018) observed weaker a- and b-wave amplitudes in a presymptomatic patient with HD under a variety of light- and dark-adapted conditions, including a 30 Hz flicker condition, when compared to a healthy control group. Additionally, the HD patient exhibited reduced dark-adapted OPs and mfERG P1 amplitude. The HD patient did not demonstrate abnormalities in implicit time measurements when compared to the control group. Although these two studies appear to show conflicting results, it is important to note that the studies involved tasks of different light intensities, included small sample sizes, and assessed patients at different points in HD progression. Taken together, the findings suggest the presence of retinal abnormalities in patients with HD, but additional studies with larger sample sizes are necessary to clarify the extent to which these anomalies are present, which are most sensitive to HD, and what the temporal progression of the changes is.

Parkinson's disease

Parkinson's disease (PD) is a neurodegenerative disease involving a progressive loss of dopaminergic neurons in the substantia nigra pars compacta, resulting in reduced DA levels in the striatum, and an abnormal aggregation of α-synuclein proteins (the primary component of Lewy bodies; see Poewe et al., 2017 for review). In addition to motor symptoms (e.g., bradykinesia, resting tremor, muscle rigidity), patients with PD commonly experience a number of nonmotor symptoms, including vision impairment. Importantly, clinical parkinsonism emerges long after neuropathological changes with up to 80% of dopaminergic cell loss having already occurred (Gaig & Tolosa, 2009). Therefore, accessible biomarkers are needed to better indicate PD onset, as this could allow for early delivery of

treatment. Significant overlap exists between PD and other neurodegenerative illnesses, such as progressive supranuclear palsy (PSP), multiple system atrophy (MSA), dementia with Lewy bodies (DLB), and corticobasal degeneration (CBD), contributing to a high rate of misdiagnosis in early disease stages. It is therefore essential to develop accurate diagnostic indicators that can reliably distinguish PD from other conditions. Given the important role of DA in retinal functioning, dopaminergic disruptions in PD may also be evident at the level of the retina. Indeed, postmortem studies indicate that retinal DA concentration is reduced in PD (Harnois & Di Paolo, 1990) and deficits in visual acuity, contrast sensitivity, and color perception have been linked with retinal DA deficiency (Brandies & Yehuda, 2008; Tian et al., 2011). Thus, it is important to clarify the extent to which retinal changes in PD reflect and predict aspects of disease progression.

OCT in PD - Evidence suggests that reduced dopaminergic input to retinal ganglion cells in PD may result in degeneration (Inzelberg et al., 2004; Tian et al., 2011); thus, a growing number of studies have investigated retinal structural changes in PD using OCT. Early works observed reduced RNFL thickness in PD patients compared to controls, though reports varied in terms of which subregions were most affected (Altintaş, Işeri, Özkan, & Çağlar, 2008; Hajee, 2009; Inzelberg, Ramirez, Nisipeanu, & Ophir, 2004; Marilita M. Moschos et al., 2011). RNFL thinning remains a robust finding in PD research today (Bayhan, Aslan Bayhan, Tanık, & Gürdal, 2014; Garcia-Martin et al., 2014; Garcia-Martin et al., 2012; Huang et al., 2018; Kaur et al., 2015; Kirbas, Turkyilmaz, Tufekci, & Durmus, 2013; L-J Ma et al., 2018; Moschos & Chatziralli, 2018; Rohani et al., 2013; Sari, Koc, Yazici, Sahin, & Ermis, 2014; Satue et al., 2013; Satue et al., 2014b; Ucak et al., 2016) with metanalyses suggesting significant overall (mean) RNFL deterioration and substantial reduction in nearly all sectors (see Chrysou, Jansonius, & van Laar, 2019; Yu et al., 2014). However, a small, but notable number of studies have reported no difference in RNFL thickness between PD patients and controls (Archibald, Clarke, Mosimann, & Burn, 2011; Eraslan et al., 2016; J.-Y. Lee et al., 2014; Pillai et al., 2016; Quagliato, Domingues, Quagliato, Abreu, & Kara-

Junior, 2014; Roth et al., 2014). This is contrasted by data indicating that RNFL thinning is significantly correlated with PD severity (e.g., scores on the Unified PD Rating Scale [UPDRS] or Hoehn and Yahr Scale: Altintaş et al., 2008; Bayhan et al., 2014; Sari et al., 2014; Satue et al., 2014) and also age (L-J Ma et al., 2018), suggesting that RNFL atrophy may correspond with overall CNS degeneration in PD. Moreover, in one study that did not find a significant reduction in RNFL thickness in PD patients when compared to controls, RNFL thickness was lowest among patients with visual hallucinations and cognitive decline, further supporting a relationship with disease progression and widespread CNS dysfunction (Lee et al., 2014). In several studies, RNFL thinning was negatively correlated with cognitive functioning in PD (Ucak et al., 2016), again providing evidence for an association with degeneration. One study observed greater thinning in the inferior and nasal quadrants of the RNFL in akinetic rigid PD patients as compared to tremor dominant patients, suggesting that some anomalies may be useful for distinguishing subtypes. Other structural changes have also been reported in PD and linked with disease progression. For example, reductions in ganglion cell complex (GCC; combined RNFL + GCL-IPL) (Bayhan et al., 2014; Moschos & Chatziralli, 2018), GCL (Garcia-Martin et al., 2014; Kaur et al., 2015; Unlu, Gulmez Sevim, Gultekin, & Karaca, 2018), IPL (Garcia-Martin et al., 2014; Unlu et al., 2018), combined GCL-IPL (Kaur et al., 2015; Sari et al., 2014; Ucak et al., 2016), OPL (Garcia-Martin et al., 2014), and choroidal (Moschos & Chatziralli, 2018) thickness have been observed in PD samples relative to controls. Further, GCC, GCL, and combined GCL-IPL thinning have been associated with disease severity (Bayhan et al., 2014; Sari et al., 2014) and duration (Garcia-Martin et al., 2014; Sari et al., 2014) in PD. In addition, a reduction in total macular thickness (L-J Ma et al., 2018; Satue et al., 2013; Satue et al., 2014b) and volume (L-J Ma et al., 2018) has been reported in some studies and linked with PD severity (Satue et al., 2014b) and age (L-J Ma et al., 2018), once more suggesting a correspondence between retinal structural loss and disease progression. However, changes in retinal structure in PD are not necessarily uniform, as increases in INL thickness (Garcia-Martin et al., 2014) and volume (Unlu et al., 2018) have also been

observed. Thus, specific patterns of OCT changes may be useful biomarkers for gauging the progression of PD. Finally, reduced microvascular density has been observed in most areas of the retina in PD using OCT angiography (OCT-A), and these impairments have been correlated with GCL-IPL thinning, suggesting that vascular abnormalities may contribute to retinal degeneration in PD (Kwapong et al., 2018). However, despite considerable evidence of OCT anomalies in PD, there are some limitations to this work. One potential limitation is the effect of medication on retinal structural integrity. For example, few studies have investigated OCT changes in drug naïve PD patients (Ahn et al., 2018; Sen, Tugcu, Coskun, Ekinci, & Nacaroglu, 2014), and studies have found both thickening and thinning of retinal layers in response to medication (see also below, section on Confounds). It is also possible that retinal layer thickening in PD could result from neuroinflammation (Liu et al., 2019), which has been observed in the illness (Wang, Liu, & Zhou, 2015). Nevertheless, collectively, these data suggest that retinal changes measured with OCT may be useful biomarkers for early diagnosis and disease progression.

ERG in PD - As reviewed above, DA is a critical neuromodulator of retinal activity. Thus, a substantial body of research has examined the effects of retinal DA depletion in PD on retinal functioning. Data from flash ERG studies in PD indicate that activity of both photoreceptor (i.e., a-wave; (Burguera, Vilela, Traba, Ameave, & Vallet, 1990; Gottlob, Schneider, Heider, & Skrandies, 1987; Nowacka, Lubiński, Honczarenko, Potemkowski, & Safranow, 2015) and bipolar-Müller (i.e., b-wave; (Burguera et al., 1990; Gottlob et al., 1987; Ikeda, Head, & K. Ellis, 1994; Nowacka et al., 2015) cells are reduced in PD relative to controls, under photopic and scotopic conditions. Some early PD studies also report an increase in b-wave implicit time (Jaffe et al., 1987). In one of these studies, a reduction in scotopic OP (OP1, 2, 3, 4) amplitude and an increase in OP (OP2, 3) latency was also observed in PD patients relative to controls (Nowacka et al., 2015). Moreover, prolonged OP latency in the PD sample was associated with greater frequency of reported DA-related visual disturbances, in, for example, light

adaptation, smooth pursuit, contrast sensitivity, and color vision (Nowacka et al., 2015). Importantly, several retinal functioning anomalies have been observed in early PD samples, who have never received dopaminergic treatment (e.g., Ikeda et al., 1994; Jaffe et al., 1987), suggesting that these functional changes may signal underlying disease processes. However, Devos et al. (2005) reported abnormalities in a- and b-wave amplitudes and implicit time in patients with dementia with Lewy bodies and visual hallucinations that were not observed in control or PD groups, indicating a lack of diagnostic specificity. Interestingly, levodopa administration has been shown to improve ERG amplitudes and implicit time in PD patients (Jaffe et al., 1987), again suggesting that these changes are indicative of global DA dysfunction. Impairments in retinal functioning have also been observed in PD using mfERG. In a study by Huang and colleagues (2018), PD patients demonstrated reduced P1 amplitude density and increased P1 implicit time in comparison to healthy controls. Moreover, P1 amplitude was positively correlated with macular volume, suggesting a relationship between retinal structure and function in PD (Huang et al., 2018). Studies in PD using pERG are somewhat mixed. Several studies have observed a decrease in pERG amplitude (Gottlob et al., 1987; Nightingale, Mitchell, & Howe, 1986) and an increase in P50 implicit time (Peppe et al., 1995) in PD with checkerboard and pattern reversal stimuli, particularly at 50% contrast. Similarly, a reduction in pERG amplitude in response to sinusoidal gratings at medium spatial frequencies has been reported in PD relative to controls (Peppe et al., 1998; Tagliati, Bodis-Wollner, & Yahr, 1996). Moreover, this same pERG impairment was not observed in patients who exhibited Parkinsonian symptoms due to traumatic basal ganglia lesions and who did not have dopaminergic dysfunction, providing additional evidence of a relationship between brain and retinal DA degeneration (Peppe et al., 1998). Administration of dopaminergic antagonists to healthy controls has also been shown to produce mid-spatial frequency impairments in pERG amplitude similar to those observed in PD, again supporting the role of DA in retinal functioning impairment in PD (Stanzione et al., 1995). Importantly, pERG anomalies have been reported in both medicated and unmedicated PD

samples (Gottlob et al., 1987; Peppe et al., 1995) and reversal of these impairments has been demonstrated with levodopa (Peppe et al., 1998; Peppe et al., 1995; Tagliati et al., 1996). Thus, pERG alterations may be an early indicator of disease onset in PD. However, some abnormalities, such as pERG tuning ratio (defined as the amplitude ratio of medium to low spatial frequencies), have been correlated with clinical stage of PD and thus may be markers of progression (Tagliati et al., 1996). Moreover, one study reported impairments in both pERG amplitude and latency in response to chromatic (i.e., red-green, blue-yellow, and yellow-black) horizontal gratings in recent onset PD relative to controls, but these same changes were not observed in multiple system atrophy (MSA), suggesting the potential for some pERG anomalies to differentiate PD from related disorders (Sartucci et al., 2006). Overall, these studies provide sufficient evidence of altered retinal functioning in PD as assessed by ERG. However, abnormalities have not been observed in all studies (e.g., Devos et al., 2005; Kupersmith, Shakin, Siegel, & Lieberman, 1982; Nightingale et al., 1986) and there is some inconsistency regarding which specific aspects of retinal functioning are impaired. These discrepancies may be partially attributed to generally small patient sample sizes. Nevertheless, changes in retinal functioning in PD may reflect the onset of disease processes and the state of dopaminergic degeneration in PD, and thus may aid in early diagnosis and monitoring of treatment effectiveness.

Alzheimer's disease and mild cognitive impairment

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by an accumulation of extracellular amyloid β plaques and neurofibrillary tangles (composed of tau proteins) resulting in a loss of synapses and neurons in the brain, which manifests clinically as progressive memory decline (i.e., dementia; see Lashley et al., 2018 for review). Typically, a probable AD diagnosis is given based on illness history and neuropsychological test performance (Lashley et al., 2018). However, some pathophysiological changes (e.g., amyloid β) may precede clinical symptoms by more than a decade (Herholz & Ebmeier, 2011), and therefore may aid in early diagnosis. Nevertheless, detection of these

neuropathological hallmarks (e.g., amyloid β, tau) in blood, cerebrospinal fluid or with brain imaging (e.g., positron emission tomography [PET]) can be costly, time-consuming, and invasive. Thus, there is an ongoing search for accurate and reliable biomarkers to better predict AD onset and progression.

While AD is associated with significant brain pathology, degenerative changes have also been observed at the level of the retina. Significant neuronal loss, specifically retinal ganglion cell loss, has been reported in a several post-mortem studies of AD patients (Blanks, Hinton, Sadun, & Miller, 1989; Blanks et al., 1996; Sadun & Bassi, 1990). Moreover, histological analyses have revealed amyloid β related neuropathology in the retina of deceased AD patients that paralleled changes in the brain (Koronyo-Hamaoui et al., 2011). Thus, the retina is a relevant site for investigating potential diagnostic and prognostic markers of AD.

OCT in AD - Retinal structural changes have been reported in a number of OCT studies in AD, suggesting that these anomalies may be indices of disease susceptibility. One of the most consistently reported findings is a reduction in RNFL thickness among AD patients compared to healthy controls (Ascaso et al., 2014; Berisha, Feke, Trempe, McMeel, & Schepens, 2007; Cheung et al., 2015; Cunha et al., 2017; Cunha et al., 2016; Eraslan et al., 2015; Ferrari et al., 2017; Gao, Liu, Li, Bai, & Liu, 2015; Güneş, Demirci, Tök, Tök, & Demirci, 2015; Kesler, Vakhapova, Korczyn, Naftaliev, & Neudorfer, 2011; Kromer et al., 2014; Kwon, Yang, Han, & Kim, 2017; Marziani et al., 2013; Oktem et al., 2015; Polo et al., 2016; Salobrar-Garcia et al., 2015; Trebbastoni et al., 2016). Moreover, meta-analyses suggest that thinning occurs in all RNFL quadrants (V.T.T. Chan et al., 2019; Coppola et al., 2015). Notably, RNFL thinning has been correlated with impaired cognitive functioning (Cunha et al., 2016; Moreno-Ramos, Benito-León, Villarejo, & Bermejo-Pareja, 2013; Oktem et al., 2015; Trebbastoni et al., 2016), disease duration (Eraslan et al., 2015), and age (Oktem et al., 2015) in AD, and thus may be an indicator of illness progression. In addition to RNFL thickness changes, several other OCT anomalies have been reported in AD. For example, studies demonstrate that the combined thickness of the GCL-IPL is significantly thinner

among patients with AD in comparison to healthy controls (Cheung et al., 2015; Cunha et al., 2016; Laura Ferrari et al., 2017; Marziani et al., 2013; Yoon et al., 2019), and GCL-IPL thinning has been associated with poorer cognitive functioning in AD (Choi, Park, & Kim, 2016; Ferrari et al., 2017). Macular thinning has been reported across all sectors of the macula in AD, but the greatest reduction may be within the inner inferior sector according to a recent meta-analytic review (Chan et al., 2019). Additionally, macular volume has been shown to be significantly reduced in AD compared to healthy controls (Gao et al., 2015; Iseri, Altina, Tokay, & Yüksel, 2006; Salobrar-Garcia et al., 2015) and is inversely related to cognitive performance (Iseri et al., 2006). The GCC is also significantly reduced in AD patients relative to healthy controls (Eraslan et al., 2015). Choroidal thickness has been shown to differ between AD patients and controls (Bulut et al., 2016; Gharbiya et al., 2014), and negatively correlates with degree of cognitive impairment (Bulut et al., 2016). Finally, in OCT-A studies a significant reduction in superficial capillary plexus vessel density and perfusion density has been reported in AD when compared to controls (Yoon et al., 2019). Thus, a wide range of retinal anomalies have been observed in patients with AD using OCT, suggesting structural changes in the retina may be markers of neurodegeneration.

OCT in MCI - Interestingly, many of the same OCT anomalies reported in AD have been observed in people with mild cognitive impairment (MCI), an intermediate stage between health and AD. For example, several studies report RNFL thinning in people with MCI (Ferrari et al., 2017; Gao et al., 2015; Kesler et al., 2011; Oktem et al., 2015). In some studies these changes are attenuated in comparison to AD samples (Ascaso et al., 2014; Kesler et al., 2011), and thus may indicate disease risk and progression. Moreover, RNFL thinning has been associated with poorer cognitive test performance in MCI (Oktem et al., 2015; Shen et al., 2014), again underscoring its potential utility as a marker of cognitive deterioration. GCL-IPL (Ferrari et al., 2017) and choroidal (Bulut et al., 2016) thinning have also been reported in MCI and demonstrated relationships with poorer cognitive functioning (Bulut et al., 2016;

Ferrari et al., 2017). Lastly, a significant reduction in macular volume has been observed in people with MCI when compared to healthy controls (Gao et al., 2015). These findings suggest that some retinal structural anomalies may signal the onset of neurodegenerative processes. However, only a small proportion of those with MCI (~30%) are later diagnosed with AD, and therefore these retinal structural changes may lack diagnostic specificity. Additionally, in a small number of studies of AD these same impairments in retinal structure (e.g., RNFL thinning - Gharbiya et al., 2014; Helene Kergoat et al., 2001; Lad et al., 2018, and GCL-IPL thinning - Lad et al., 2018) have not been confirmed and, in some cases, a link between retinal neurodegeneration and cognitive test performance has not been observed (Gao et al., 2015; Gharbiya et al., 2014; Güneş et al., 2015). Moreover, one study demonstrated that patients with AD, dementia with Lewy bodies, and dementia associated with PD showed similar reductions in RNFL thickness (Moreno-Ramos et al., 2013), while another study reported no significant differences in RNFL thickness, GCL thickness, or macular volume among patients with MCI, AD, non-AD dementia, PD, and healthy controls (Pillai et al., 2016). Therefore, at present, there is not sufficient evidence to suggest that anomalies in retinal structure may be specific indicators of AD risk. Instead, these changes may be markers of overall CNS neurodegeneration and an increased (but not 100%) likelihood of later expression of a neuropsychiatric disease. Longitudinal studies will help clarify the diagnostic and prognostic specificity of these OCT anomalies.

ERG in AD and MCI - While there is a large body of literature on retinal structural anomalies in AD, far fewer studies have investigated changes in retinal functioning. Nevertheless, these data suggest that abnormalities in retinal ganglion cell function may be detected in AD with pERG. In one of the first pERG studies in AD, Katz et al. (1989) observed a significant reduction in amplitude in a small number of AD patients, in comparison to controls. This finding was replicated in a larger sample of AD patients, who again showed reduced pERG amplitudes compared to healthy controls, particularly during the high frequency checkerboard reversal condition (Trick, Barris, & Bickler-Bluth, 1989). Specific reductions in

P50 and N95 waveform components have also been reported in AD (Krasodomska, Lubiński, Potemkowski, & Honczarenko, 2010; Parisi et al., 2001), in addition to an increase in N35 (Parisi et al., 2001), P50 (Krasodomska et al., 2010; Parisi et al., 2001), and N95 (Parisi et al., 2001) implicit times. In another study using steady-state pERG, N1-P1 amplitude was attenuated in patients with AD compared to healthy controls, and was of similar magnitude to that observed in a retinal disease (i.e., glaucoma) group (Nesher & Trick, 1991). More recently, Sartucci et al. (2010) observed a reduction in P1 and N1 amplitude, and an increase in P1 and N1 implicit time in AD patients using a luminance (yellow-black) sinusoidal grating stimulus intended to preferentially activate the magnocellular (M) pathway. Importantly, groups did not significantly differ when chromatic stimuli targeting parvocellular (P) and koniocellular (K) pathways were used, suggesting M-pathway specific retinal dysfunction (Sartucci et al., 2010). One study, however, found no changes on pERG in AD (Kergoat et al., 2002). While some ERG anomalies have been observed in early AD samples (e.g.,(Kamila Krasodomska et al., 2010), changes in retinal cell signaling have not been observed in MCI (Ling et al., 2017), although there is a shortage of research in this area. Interestingly, studies of flash ERG indices in AD have reported normal functioning (Justino et al., 2001; Rizzo, 1992), indicating that photoreceptor and bipolar cell function may be preserved in MCI. Nonetheless, overall, the weight of the evidence suggests retinal ganglion cell dysfunction in AD and thus these impairments, and their potential correlates, warrant further investigation.

Traumatic brain injury

Traumatic brain injury (TBI) refers to the situation where an open or closed head injury leads to evidence of brain dysfunction. TBI can range from mild to severe, and the manifestations can vary widely depending on the site(s) of the injury. TBI can occur with or without a loss of consciousness. Frequent symptoms of TBI include headache, confusion, dizziness, ringing in the ears, fatigue, sleep changes, mood and behavior, and reductions in one or more aspects of cognitive functioning. With more

severe cases, seizures, poor coordination, speech difficulties, weakness or numbness in arms and legs, and restlessness or agitation can occur (Capizzi, Woo, & Verduzco-Gutierrez, 2020). The search for non-invasive biomarkers of TBI is an active and ongoing one (Huie et al., 2020). Visual changes are also common in TBI (Merezhinskaya et al., 2019; Reynolds, Barker, Merezhinskaya, Oh, & Stahlman, 2019), and this has led to increased attention to the potential for retinal indices to serve as biomarkers of brain structure and function changes in the condition.

OCT in TBI – Research focused on the investigation of retinal structure following traumatic brain injury (TBI) is in the beginning stages. However, evidence suggests that the development of retinal biomarkers for use in people following a traumatic brain injury or repeated blows to the head may help elucidate the extent of subsequent neural damage and augment current literature on visual abnormalities following TBI (Mufti et al., 2019). One reason for this is that progressive brain volume loss (~5% per year) has been observed in moderate-severe TBI, with the situation being less clear for mild TBI (Harris, de Rooij, & Kuhl, 2019). Therefore, retinal screening tools for CNS tissue loss could be relevant in many cases. One case-study of a patient with a severe TBI following a motorcycle accident demonstrated progressive RNFL thinning when compared to measurements conducted 10 months prior to the accident, which the authors suggest was likely due to RTSD (Vien, DalPorto, & Yang, 2017). In the first OCT study of a group of people with TBI (combat veterans), GCL and RNFL thinning were observed (Chan, Hills, Bakall, & Fernandez, 2019). These data are consistent with evidence from SD-OCT studies on rodent models of TBI, which found RNFL thinning in the superior-temporal quadrant three months following a blast-mediated injury (Mohan, Kecova, Hernandez-Merino, Kardon, & Harper, 2013), as well as reduced inner retinal thickness following repetitive mild TBI (mTBI) (Tzekov et al., 2014). Researchers have also recognized the need to assess the neuropathological impact of repeated head blows, as there is no definitive diagnostic measure to assess and monitor brain damage as a result of recurrent head injury, aside from post-mortem evaluation (Childs, Barker, Gage, & Loosemore, 2018). In a study of

Olympic boxers, Childs et al., (2018) demonstrated reduced macular and RNFL indices in athletes when compared to sedentary healthy controls. Similarly, evidence from another study showed RNFL thinning in collision sport athletes, which included boxers, football players, and hockey players, compared to controls, with boxers demonstrating the lowest RNFL measurements. Results also indicated that boxers exhibited thinning of the GCC compared to controls (Leong et al., 2018). Because white matter changes have been observed even after a single season of soccer in female high-school athletes (Myer et al., 2019), it will be important to determine the maximal sensitivity of OCT indices to short-term changes in cases of mild TBI.

ERG and microvasculature in TBI – The rodent studies discussed earlier found reduced pERG responses following a blast-mediated injury (Mohan et al., 2013), as well as weaker PhNR following repetitive mTBI (Tzekov et al., 2014). Although these studies suggest that retinal dysfunction may result from TBI, one study focused on human subjects with mTBI did not find ERG waveform abnormalities (Freed & Hellerstein, 1997). As this is an understudied area of investigation, additional ERG studies are required to clarify the potential effects of TBI and repetitive head injury on retinal cell functioning.

Confounds and considerations

A critical methodological issue in studies of disease populations is that the group being studied may differ from a healthy control group on factors that are related to the dependent variable. Therefore, it is usually not enough to match groups on variables such as age, sex, or socio-economic status. In this section we briefly review some of these factors.

Comorbid medical disease and associated medications Several of the conditions discussed above are associated with comorbid features that are associated with retinal changes. For example, MS and Parkinson's disease have increased rates of depression (Persson et al., 2020; Schrag & Taddei, 2017), and schizophrenia is associated with elevated rates of diabetes and hypertension (Hoffman, 2017), which have negative effects on retinal health (Modi & Arsiwalla, 2018; Alibhai et al., 2018),

including retinal thinning (Chhablani et al., 2015; Chhablani, Ambiya, Nair, Bondalapati, & Chhablani, 2018; Dumitrescu et al., 2017; Z. Wang et al., 2015), and impaired function (Gundogan et al., 2008; Lecleire-Collet et al., 2011; Tyrberg et al., 2011), even in the absence of diagnosable retinopathy (Zeng et al., 2019). Antipsychotic medications, used to treat schizophrenia but also commonly used for Huntington's disease and other dementias (e.g., Alzheimer's disease), can also affect retinal function (Bartel et al., 1990a, 1990b, 1990c) and cause retinal disease (Tong, Pai, Heydon, & Young, 2017) (Faure, Audo, Zeitz, Letessier, & Robert, 2015). Conversely, L-DOPA, used to treat Parkinson's disease, can normalize retinal function (Brandies & Yehuda, 2008). At the very least, these data suggest that comorbid medical diseases, and current and lifetime exposure to certain medication types should be reported in papers, along with associations with retinal findings.

Smoking Nicotine can cross the BRB (Tega, Kubo, Yuzurihara, Akanuma, & Hosoya, 2015) and can affect ERG amplitudes (Varghese, Reid, Hartmann, & Keyser, 2011) and cause retinal thinning (El-Shazly, Farweez, Elewa, Elzankalony, & Farweez, 2017; Kucuk & Akkaya, 2018; Teberik, 2019) but see Rosso et al., 2019). It can also cause cortical thinning (Karama et al., 2015), which could affect the retina via RTSD. Populations such as people with schizophrenia (de Leon & Diaz, 2005; Dervaux & Laqueille, 2008; Williams & Gandhi, 2008), and Huntington's disease (Ehret, Day, Wiegand, Wojcieszek, & Chambers, 2007), typically have elevated rates of smoking (along with other forms of substance abuse), and so study groups should be matched as closely as possible on this variable, in addition to quantifying smoking frequency and examining relationships between this and dependent variables.

Substance abuse Populations with psychiatric or physical disabilities, including TBI, often have increased rates of substance abuse (Glazier & Kling, 2013; Graham & Cardon, 2008), and this can affect retinal function. For example, cannabis increases noise in the fERG (Lucas et al., 2019), and increases implicit times in both the flash ERG (Schwitzer et al., 2018) and pERG (Schwitzer et al., 2017). Cocaine use and withdrawal (associated with DA depletion) has been associated with reduced

amplitudes in the blue cone b-wave in humans (Roy et al., 1997; Roy et al., 1996), and with both a- and b-wave amplitude reduction in an animal model (Sanchez-Villarejo et al., 2014). Animal research also indicates a negative effect of chronic alcohol use on retinal function (Sancho-Tello et al., 2008), as well as effects of a variety of other substances (Su, Robson, Xu, Lightman, & Sarraf, 2017; Toyonaga, Adachi-Usami, & Yamazaki, 1989). Essentially, any substance that crosses the BRB (Cunha-Vaz et al., 2011; Hosoya, Tomi, & Tachikawa, 2011) can affect retinal function. There has been little research using OCT to quantify effects of substance use on retinal structure, but abuse of alkyl nitrites ("poppers") has been associated with altered structure at the junction of the inner and outer segments as revealed by OCT, and many other substances are known to affect the retina [reviewed in (Peragallo, Biousse, & Newman, 2013)]. To the extent possible then, researchers should take substance use into account when estimating the extent of that portion of between-group differences that are related to the primary disease.

Obesity Groups may also differ in weight, body mass-index (BMI) and levels of obesity, and this can be related to retinal findings, as demonstrated in a recent OCT study (Laiginhas et al., 2019). Schizophrenia is associated with increased BMI and obesity, even at the first episode, and this is not all due to medication effects (McDaid & Smyth, 2015). Therefore, studies of schizophrenia in particular need to quantify the contributions of these factors to study data if groups are not matched on them. While obesity may be a risk factor for MS and its progression (Alfredsson & Olsson, 2019), a recent meta-analysis indicated that BMI in MS patients is actually lower than in the general population (Dardiotis et al., 2019), and so significant weight differences between groups could lead to an underestimate of MS-related retinal pathology. Effects of obesity on retinal function are less clear, but one mouse study indicated that high-fat diets can lead to reduced amplitudes in OPs in the flash ERG, which was correlated with development of glucose intolerance and occurred before microvasculature changes (Rajagopal et al., 2016).

Other People with neuropsychiatric disorders may also differ from control groups on factors such as arousal, attention, motivation, and working memory. While, in theory, this should not affect ERG data since this can be thought of as a passive task, in fact, the internal state of the subject can affect retinal activity via input of retinopetal neurons (Ortiz et al., 2017). At present, the only known neurons to enter the retina from the brain are histaminergic and serotonergic (Gastinger et al., 2006; Labandeira-Garcia et al., 1990; Ortiz et al., 2017), and these systems are involved in arousal and motivation (Li et al., 2016; Luo, Li, & Zhong, 2016; Ma, Hangya, Leonard, Wisden, & Gundlach, 2018). It has also been demonstrated that ERG activity can be affected by attention (Eason, 1984; Eason, Flowers, & Oakley, 1983) and motivation (Demmin et al., 2019; Nasser et al., 2013). Because several of the populations reviewed above (e.g., schizophrenia, Alzheimer's disease, MS) are characterized by motivational and attentional impairments (Foussias et al., 2015; Koutsouraki, Kalatha, Grosi, Koukoulidis, & Michmizos, 2019; Perry & Hodges, 1999), these factors should be quantified so that the proportion of variance they account for can be determined, while at the same time, not removing variance that they share with disease severity (e.g., Miller & Chapman, 2001). There is recent preliminary evidence that obstructive sleep apnea (OSA) is associated with thinning of the RNFL, and that treatment with a continuous positive airway pressure (CPAP) device can restore thickness values to normal levels (Lin et al., 2019). Because psychiatric and neurological conditions are often associated with sleep disturbance, risk factors for central and obstructive sleep apnea (e.g., disturbed regulation of breathing and obesity, respectively), and sleep apnea itself (Crosta, Desideri, & Marini, 2017; Lin, Krishnan, & Eckert, 2017), assessment of the proportion of variance in group data that is accounted for by sleep issues may be important. Psychiatric and neurologic conditions may also manifest in oculomotor abnormalities such as inconsistent fixational control and nystagmus. These symptoms have the potential to degrade signal quality, increase noise, and lead to rejection of trials, all of which can lead to between-group differences in the number of high-quality data points included in statistical analyses, thereby increasing the risk of

spurious findings. Even when eye tracking is used during retinal assessment, subtle differences in eye movements may be missed. This issue needs further attention in future studies. Finally, groups may differ in their ability or tendency to self-report changes in visual function, and this may affect data on the relationships between laboratory measurements and subjective visual complaints.

New developments relevant to future research in neuropsychiatry

Clinically, retinal imaging has been the gold standard for evaluating disease, progression and treatment response based on gross retinal anatomy. We are now at a transitional period where retinal function, in addition to structure, may be possible to image in the living retina. Like ERG, retinal functional imaging is objective and thus may have advantages over subjective measures (e.g., perimetry, contrast sensitivity or other behavior-based metrics). Objective measures of retinal function not only provide an opportunity for more sensitive and repeatable measurements, but are also essential for assessing non-verbal/non-responding patients such as very young children or those with severe psychiatric or neurological deficits.

In recent years, several technical advances have made the prospect of retinal functional imaging possible. Faster camera speeds have enabled mitigation of motion blur, which is problematic for functional analysis (Bedggood & Metha, 2012). This is especially important when imaging eyes that may have abnormal ocular motility [as is seen, for example, in schizophrenia (Egana et al., 2013; Karoumi, Ventre-Dominey, Vighetto, Dalery, & d'Amato, 1998) and MS (Sheehy et al., 2018)], or gaze control (as in schizophrenia and bipolar disorder; Thakkar, Schall, Logan, & Park, 2015). In combination with fast camera speeds, the digital imaging revolution now enables quantitative imaging and facilitates image registration, which is critical for revealing a functional signal which is time dependent.

Once the retina has been imaged at sufficiently fast camera speeds and eye motion has been corrected, tiny changes in retinal appearance over time (milliseconds to seconds) have the potential to reveal the functional state of the retina [reviewed in (Hunter, Merigan, & Schallek, 2019)]. Several

exciting innovations are enabling the ability to report on the ensemble activity of the retina and even on neural function at the single cell level. This of course has the potential to reveal the neural underpinnings or sequelae of psychiatric or neurological disease. For example, spectral domain OCT resolution and acquisition speeds are becoming sufficiently fast to reveal tiny changes in photoreceptor (Hillmann et al., 2016; Zhang et al., 2017) and ganglion cell function (Pfaffle et al., 2019). Changes in cell structure and reflectance in response to visual stimulation are believed to reflect an osmotic shift in cell structure that can be reported as a functional metric of neural cell physiology (Azimipour, Migacz, Zawadzki, Werner, & Jonnal, 2019; Lu et al., 2017; Zhang et al., 2017). Recently, swept-source OCT (Grulkowski et al., 2012) has also become commercially available. This technique achieves scanning speeds in excess of 100,000 A-scans per second by virtue of its swept illumination across narrowly tuned wavelengths. This is superior to the typical scanning speed of 25,000-30,000 A-scans per second achieved by spectral domain OCT, which uses broadband light sources. Benefits of swept source include potentially deeper imaging through the RPE and into the choroid by using longer wavelengths that reduce scatter (Gabriele et al., 2011; Grulkowski et al., 2012; Miller et al., 2017). A number of studies have begun deploying swept source OCT to examine blood flow-related changes in retinal vessels using swept source OCT angiography in schizophrenia (Lizano et al., 2020; Schonfeldt-Lecuona et al., 2016), as well as retinal thickness changes associated with bipolar disorder (Polo et al., 2019). It is expected that faster imaging speed will not only enable better images in cases of neurological and psychiatric disease, but also will enable better functional assessment without the confounds of motion blur which can erode image integrity and make image registration fraught with challenge.

Toward the goal of imaging single neurons and their function, adaptive optics technology achieves single retinal cell resolution by measuring and correcting for the eye's aberrations. Imaging with adaptive optics now achieves near ~1 micron resolution which enables the study of single neurons in the living eye (Liang, Williams, & Miller, 1997; Liu, Kurokawa, Zhang, Lee, & Miller, 2017; Rossi et al.,

2011; Williams, 2011; F. Zhang, Kurokawa, Lassoued, Crowell, & Miller, 2019). Beyond structure, the functional capacity of single cells has also been studied (Hofer, Singer, & Williams, 2005; Roorda, 2011; Roorda & Williams, 1999; Sabesan, Hofer, & Roorda, 2015; Zhang et al., 2019). Photopigment densitometry (Roorda & Williams, 1999) as well as near infrared intrinsic signal imaging has revealed the activity of single photoreceptors (Cooper, Tuten, Dubra, Brainard, & Morgan, 2017; Grieve & Roorda, 2008). Recent innovations in imaging with phase contrast adaptive optics has also revealed translucent horizontal cells (Guevara-Torres, Williams, & Schallek, 2015), ganglion cells (Guevara-Torres, Williams, & Schallek, 2020; Z. Liu et al., 2017; Rossi et al., 2017), nerve fiber bundles and glia (Liu et al., 2017). Now that imaging such cell populations has been realized, study of the function of these distinct cell types may also be studied with further advances.

In addition to imaging the neurons and glia of the CNS through the eye, the blood supply and associated dysfunction in neurovascular regulation have the potential to be captured by a number of new imaging modalities. Intrinsic signal optical imaging (Abramoff et al., 2006; Hanazono, Tsunoda, Kazato, Tsubota, & Tanifuji, 2008; Schallek et al., 2009; Schallek & Ts'o, 2011), magnetic resonance imaging (MRI) (Berkowitz, Bissig, & Roberts, 2016) and functional (fMRI) based on the blood oxygen level dependent (BOLD) signal (Duong, 2014; Duong, Ngan, Ugurbil, & Kim, 2002) have the potential to reveal vascular control dysfunctions that associate with CNS disease. In addition, revolutions in imaging capillary function using OCT-A (de Carlo, Romano, Waheed, & Duker, 2015; Jia et al., 2012) and blood cell velocimetry in all retinal vessels of all size are now possible (Bedggood & Metha, 2012; Duan, Bedggood, Bui, & Metha, 2016; Gu et al., 2018; Guevara-Torres, Joseph, & Schallek, 2016; Joseph, Guevara-Torres, & Schallek, 2019; Tam, Tiruveedhula, & Roorda, 2011; Zhong, Huang, Chui, Petrig, & Burns, 2012). Imaging the blood supply and its response and regulation subsequent to a neural stimulus or challenge has the potential to reveal abnormalities of the neurovascular unit which can be disrupted in the brain in the presence of neuropsychiatric disease (Zhu et al., 2017).

While the above retinal imaging innovations have largely focused on the study of retinal disease, there is a paucity of work on applying these approaches to the study of neuropsychiatric diseases which, as demonstrated throughout this review, typically have retinal manifestations. Continued improvements in camera speed, image registration and elucidation of the key biophysical reporters revealed in these imaging modalities will allow for more sensitive assessments of whether the biophysiology of the retina is altered in tandem with conditions normally associated with the brain proper. An additional potential benefit of these new technologies is that they may help resolve the discrepancies across studies, within groups of patients with the same primary diagnosis, regarding the layers where retinal thinning occurs, the location of that thinning (e.g., RNFL quadrant), and the nature of the retinal dysfunction. As is clear from the evidence reviewed above, studies have differed in their findings, and even if non-disease-specific factors (e.g., age, gender, smoking status, comorbid medical conditions, medication use) could be completely taken into account, it is still likely that there will be heterogeneity across people with the same condition in terms of retinal findings. One possibility is that differences across patients with the same condition reflect multiple interacting factors (e.g., genetics, vascular factors, protective factors, etc.). The situation may be analogous to what occurs in epilepsy, in that a common biological change (e.g., creation of a seizure focus; retinal ganglion cell body and axon loss) may emerge from a diverse set of factors that can affect different biological parameters (e.g., blood supply, neuronal connections, glial cell support, cell metabolism, neurotransmitter activity), leading to heterogeneity in the type and location of the outcome (e.g., seizure focus location, quadrant(s) of retinal thinning) (Mitchell et al., 2013). The situation may be different for which retinal layer(s) are affected in that disorders that are thought to involve RTSD (e.g., MS, Alzheimer's disease) should, at least initially, demonstrate the most severe thinning in the RNFL and/or GCL. Advances in imaging resolution and capacity (e.g., the improved ability to image the RPE and choroid provided by swept source OCT), in addition to better characterization of vascular influences on neuronal function, should allow for improved understanding

of individual differences in retinal findings, and the extent to which there is specificity of findings to specific diagnoses.

Discussion

Changes in retinal structure are characteristic of several neuropsychiatric disorders, and, in the case of dementias, they also predict the development of cognitive decline and later diagnosis of the disorder (Mutlu et al., 2018). Similarly, changes in retinal function are associated with multiple neuropsychiatric disorders and in some cases appear to reflect genetic risk for a condition [e.g., (A. Gagné et al., in press)]. Thus, retinal markers can be useful both for screening for potential CNS change, and for risk of further decline, including in otherwise healthy people (Deal et al., 2018; Ko et al., 2018). The diagnostic specificity of any single retinal sign is not known, and while some studies suggest the possibility of diagnostic specificity (reviewed in Schonfeldt-Lecuona et al., 2016), there is considerable overlap between diagnoses in the literature as a whole, as reviewed above. However, even if/where diagnostic specificity turns out to be low, the predictive validity of retinal findings in neuropsychiatry is still likely to be high, as they are likely to indicate the concurrent presence of cognitive decline and illness emergence or progression. They may also be useful for quantifying treatment effects (as has been shown in schizophrenia and MS), and therefore potentially for screening for likely treatment responders. Thus, retinal markers may have an important role to play in the development of personalized medicine approaches, especially for syndromes and disorders that are heterogeneous. Another advantage of incorporating retinal metrics into research studies and clinical practice is that they can be noninvasive (e.g., ERG using skin electrodes, OCT), and are fast and relatively inexpensive, especially compared to procedures such as PET and fMRI. They may, therefore, prove to be useful as a first-line screening tool, or as a complementary assessment procedure when brain imaging is used. Retinal measures may also alert clinicians to the potential for current or impending visual changes that may have clinical and functional relevance. We therefore recommend that OCT and ERG, in addition to procedures such as

OCT angiography and recently developed methods to image activity within the retina, be increasingly incorporated into studies of disease risk, heterogeneity, progression, and treatment response within neuropsychiatry.

To achieve even greater advances than has been the case to date, it may be useful to rely increasingly on methods such as machine learning and other forms of artificial intelligence (AI). As noted above in the discussion of the DWT, traditional retinal indices (e.g., a-wave amplitude in the flash ERG) are comprised of multiple underlying sources of data (e.g., different frequencies whose power within the overall signal varies at any given time, and that can change at different times). Beyond the DWT, however, there may be meaningful patterns within ERG and OCT data that have not yet been discovered, and that might never be discovered under typical clinical or research conditions, due to human limitations on the number of variables that can be simultaneously mentally represented, integrated and manipulated. Such patterns could nevertheless be used as novel indices of retinal structure or function in future studies and clinical applications. In addition, AI methods can integrate data on retinal structure, retinal function, neuropsychological functioning, symptoms, development, illness course, genetics, and other biomarkers (e.g., blood, CSF, PET, MRI findings) to identify novel risk factors and the most robust predictive (single or sets of) biomarkers in the retina that associate with specific neuropsychiatric diseases and their subtypes. This could provide useful examples of what the International Medical Device Regulators Forum (IMDRF) has called software as a medical device (SaMD). Neuropsychiatric disorders may be leading candidates for this type of analysis, given the heterogeneity in several of these conditions, the variability in prior findings that are likely to reflect this, and the many unknowns that remain about etiology, pathophysiology, development, and progression of these conditions. Finally, application of AI methods is allowing for new discovery in terms of the range of illness features that retinal variables can predict. A recent example of this indicated that deep learning models trained on a large dataset (N=284,335) and validated on two independent data sets predicted a

number of cardiovascular risk factors not previously known to be quantifiable in retinal images (Poplin et al., 2018). Another study demonstrated that convolutional neural networks could successfully characterize smoking status from retinal images (Vaghefi et al., 2019). Findings such as these suggest the possibilities that retinal indices, and the field of *oculomics* in general (Wagner et al., 2020), may lead to as-of-yet unimagined discoveries regarding neuropsychiatric disorders, and that they could help parse the proportions of variance in retinal data due to primary disease versus comorbid diseases and other associated features. In short, continued research on retinal changes in neuropsychiatry, and application of novel analysis methods to these data can combine to enhance the value of incorporating retinal variables into biomarker development and predictive analytic efforts, and to accelerate clinical and scientific discovery.

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Table 1. List of abbreviations, in alphabetical order.

AD – Alzheimer's disease, AI – Artificial intelligence, AS – Asperger syndrome, ASD – Autism spectrum disorders, BMI – Body mass index, BOLD – Blood oxygen-level dependent, BRB – Blood-retina barrier, CAG – Cytosine, adenine, guanine (three of the 5 nucleotides), CBD – Corticobasal degeneration, CNS – Central nervous system, CPAP – Continuous positive airway pressure, DA – Dopamine, DLB – Dementia with Lewy bodies, DTL – Dawson-Trick-Litzkow, a filament-type of ERG electrode, DWT – Discrete wave transform, ELM - External limiting membrane, ERG – Electroretinography, FAZ – Foveal avascular zone, fMRI – Functional magenetic resonance imaging, GABA – Gamma aminobutyric acid, GCC – Ganglion cell complex (RNFL+GCL+IPL), GCL – Ganglion cell layer, GCL-IPL – Combined ganglion cell layer and inner plexiform layer, HD – Huntington's disease, HFA – High functioning autism, ILM – Inner limiting membrane, INL – Inner nuclear layer, IPL – Inner plexiform layer, IQ – Intelligence quotient, ISL – Inner segment layer, MCI – Mild cognitive impairment, MSA – Multiple system atrophy, mfERG – multifocal electroretinogram, MRI – Magnetic resonance imaging, mRNFL – macular retinal nerve fiber layer (RNFL measured adjacent to the macula), mTBI – Mild traumatic brain injury, MS – Multiple sclerosis, OCT – Optical coherence tomography, OCT-A – Optical coherence tomography angiography, ONH – Optic nerve head, ONL – Outer nuclear layer, OP – Oscillatory potential, OPL – Outer plexiform layer, OSA – Obstructive sleep apnea, PD – Parkinson's disease, pERG – pattern electroretinogram, PET – Positron emission tomography, PhNR – Photopic negative response, pRNFL – Peripapillary retinal nerve fiber layer (RNFL measured adjacent to the optic nerve head), PSP – Progressive supranuclear palsy, RNFL – Retinal nerve fiber layer, RPE – Retinal pigment epithelium, RTSD – Retrograde trans-synaptic degeneration, SaMD – Software as a medical device, SNR – Signal to noise ratio, SS-OCT – Swept source OCT, TBI – Traumatic brain injury, UPDRS – Unified Parkinson's Disease Rating Scale, VEP – Visual evoked potential

Figures and Captions

Figure 1. Illustration of retinal cell types and layers. Cells: RPE, retinal pigment epithelium (support to photoreceptors); C, cone photoreceptor; R, rod photoreceptor; H, horizontal cell (interneuron); B, bipolar cell (interneuron); M, Müller cell (radial glial cell); Am, amacrine cell (interneuron); DA, displaced amacrine cell (interneuron); G, ganglion cell (output neuron). Müller cells (M) form the ELM, and their foot processes partially form the ILM. Layers: ChC, choriocapillaris (capillary bed for RPE and photo-receptors); BrM, Bruch's membrane (vessel wall and RPE substratum); ELM, external limiting membrane (junctional complexes); ONL, outer nuclear layer; OPL, outer plexiform layer (synapses); INL, inner nuclear layer; IPL, inner plexiform layer (includes ganglion cell dendrites, bipolar cell axons, and amacrine cells); GCL, ganglion cell (body) layer; NFL, nerve fiber layer (ganglion cell axons); ILM, inner limiting membrane. Image, and the majority of the figure caption reproduced from Fig. 2c in: Zheng W, Reem RE, Omarova S, Huang S, DiPatre PL, *et al.* (2012) Spatial Distribution of the Pathways of Cholesterol Homeostasis in Human Retina. PLOS ONE 7(5): e37926. https://doi.org/10.1371/journal.pone.0037926 via a Creative Commons Attribution (CC BY) license.

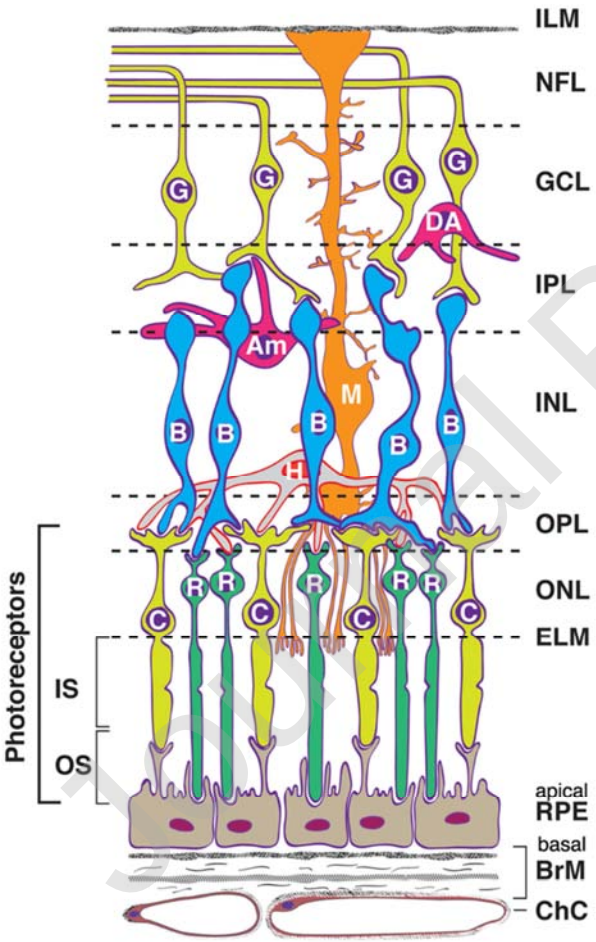


Figure 2. Peripapillary RNFL scan of a left eye generated by OCT. Inner limiting membrane (ILM; red line); RNFL (orange area just beneath ILM); GCL and IPL layers (beneath RNFL); optic disc (area indicated by width of tan lines and the area between the black circles); optic cup boundaries (white line). Cup-to-disc ratio is the width of the cup divided b the width of the disc. T, temporal; N, nasal.

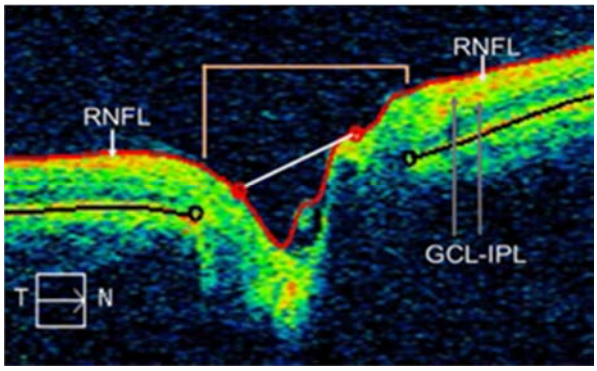


Figure 3. OCT images generated by macula scan. A) The vertical white line has been added to demonstrate the depth of the scan, from the inner limiting membrane (ILM) at the top to the retinal pigment epithelium (RPE; in red, beneath the photoreceptor layer). B) Topographic map showing the region of the macula scan. Scan depth indicated by concavity in blue line at the position of the scan axis (purple line).

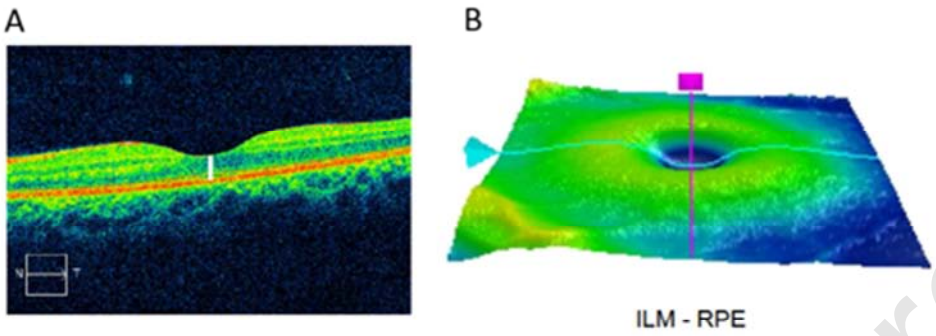


Figure 4. Typical flash ERG waveform response. The a-wave reflects primarily the hyperpolarization of photoreceptors, while the b-wave primarily reflects the depolarization of bipolar and/or Müller cells. Under some lighting conditions, the b-wave is followed by a negative deflection known as the photopic negative response (PhNR), which reflects activity within a subset of retinal ganglion cells. Amplitude is typically reported in microvolts (μV), and implicit time (latency) is reported in milliseconds (ms). Amplitude and timing are determined by a number of factors (e.g., light- or dark-adapted testing, stimulus intensity, background light intensity, retinal pathology, etc.). Less frequently observed waveforms are mentioned in the main text.

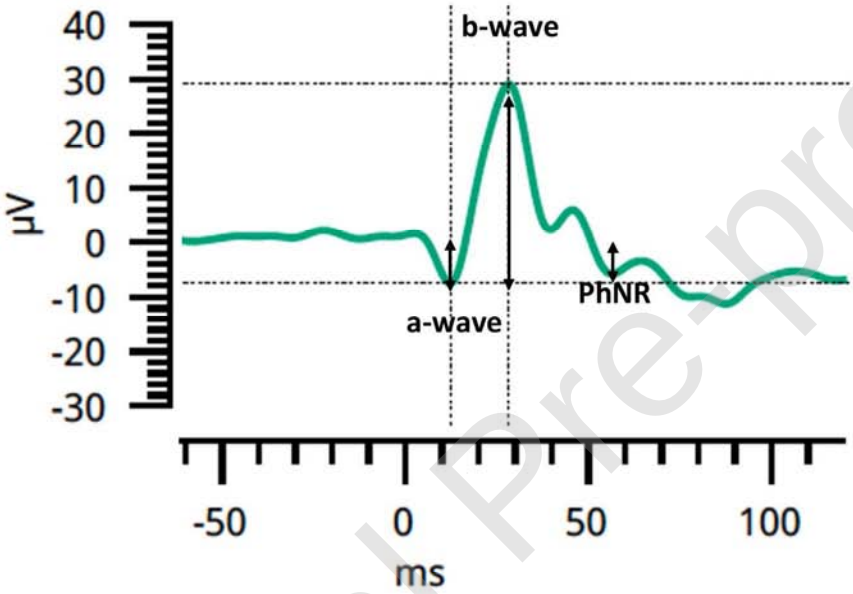


Figure 5. Typical pERG waveform response. The pERG has two main components corresponding to their voltage polarity and generalized implicit times. The P50 wave primarily reflects macula function, and the N95 component primarily reflects ganglion cell and optic nerve functioning.

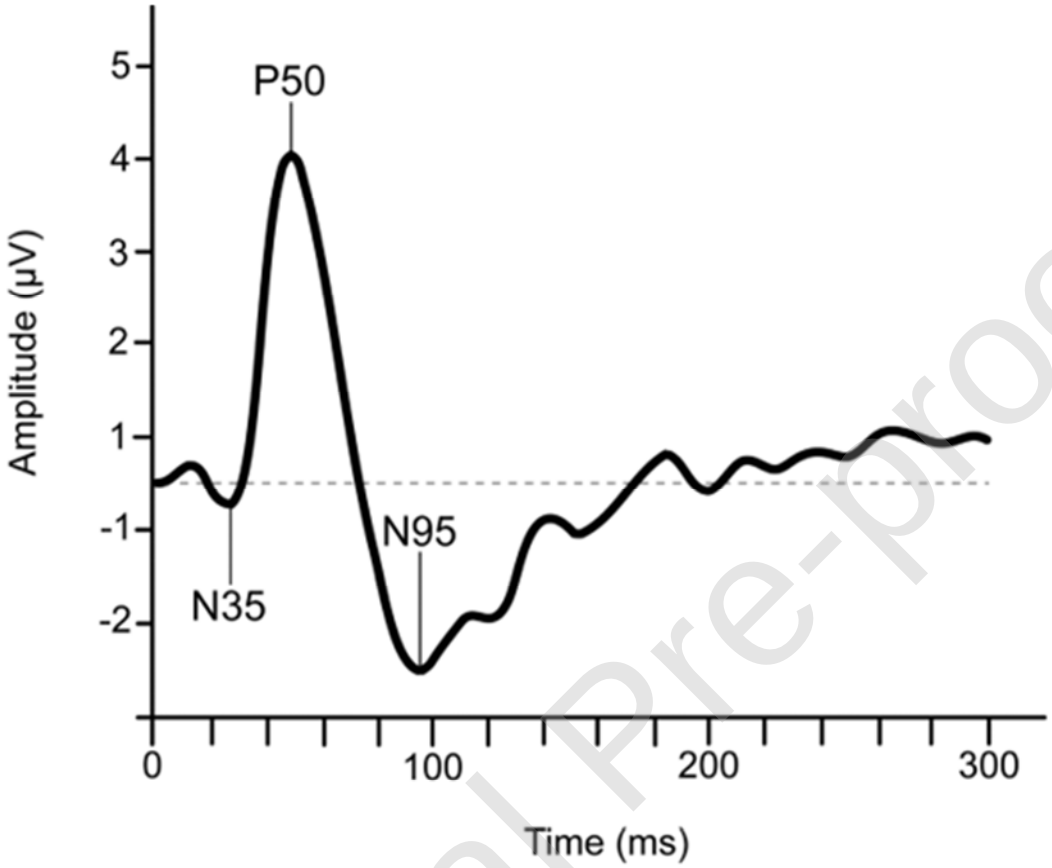
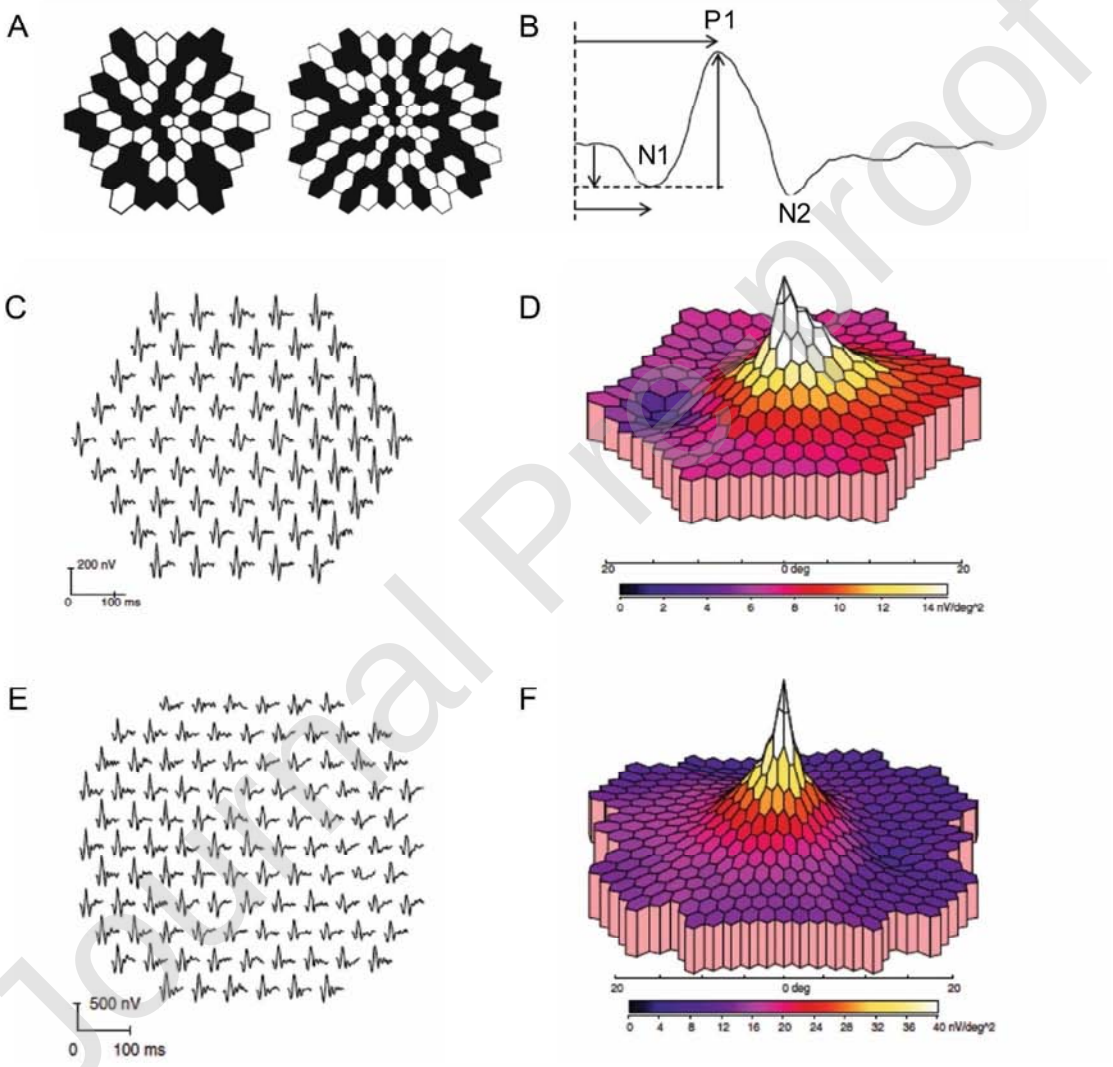


Figure 6. Multifocal ERG (mfERG) stimuli and data. A) Hexagonal mfERG stimulus array with 61 (left) and 103 (right) elements scaled with eccentricity. Roughly half of the elements are illuminated at any one time. B) Diagram of an mfERG response to show the designation of the major features of the waveform. C, E) Sample mfERG trace arrays (field view) with 61 elements (C) and 103 elements (E). D, F) The 3-D response density plots (field view) associated with panels C and E. Image and caption reproduced from Hood, D. C., Bach, M., Brigell, M., Keating, D., Kondo, M., Lyons, J. S., & Palmowski-Wolfe, A. M. (2008). ISCEV guidelines for clinical multifocal electroretinography (2007 edition). *Documenta Ophthalmologica*, *116*(1), 1-11.



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Measures of Retinal Structure and Function as Biomarkers in Neurology and Psychiatry

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Declarations of interest: none

Highlights

- Severe mental illnesses and many neurodegenerative disorders are characterized by thinning of retinal structures as indicated by optical coherence tomography (OCT) and by retinal dysfunction as indicated by electroretinography (ERG).
- In many cases, studies indicate significant correlations between retinal changes and clinical and neuropathological features such as cognitive decline, brain volume loss, overall illness severity, and progression of illness.
- Retinal indices have the potential to serve as biomarkers of disease onset and progression, relapse, course, and treatment response.
- Recent advances in imaging of retinal activity in vivo, and in data analysis techniques, have the potential to significantly improve the predictive validity of retinal measures.