THE EYE AS A WINDOW TO THE ALZHEIMER'S DISEASE BRAIN

by

Fred Guaraná de Oliveira Souza

Christianne E. Strang, PhD, CHAIR
Mark S. Bolding, PhD, ADVISOR
Lori L. McMahon, PhD
Alecia K. Gross Gutierrez, PhD
Thomas van Groen, PhD

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FRED GUARANA DE OLIVEIRA-SOUZA

VISION SCIENCE

ABSTRACT

Alzheimer's disease (AD) is a debilitating, and the most prevalent, type of dementia that is manifested by cognitive deficits, anomalous protein metabolism, cell loss, and pathological alterations in several neurotransmitter systems, particularly the cholinergic and glutamatergic systems. Moreover, AD is associated with visual deficits that have been reported to occur even in the early stages of the disease and may precede conspicuous cognitive impairment. To date, the underlying causes of the visual deficits and whether they stem from retinal or cortical abnormalities remain poorly understood. The following studies aimed at establishing whether the pathological changes observed in the cerebrum are also present in the retina and assessing AD's influence in retina's physiological responses. We used quantitative polymerase chain reaction and immunohistochemistry to assess changes in acetylcholine receptor (AChR) gene expression, gliosis, retinal cell number in the Tg-SwDI mouse model as compared to age-matched wild-type (WT). Young adults and middle-aged adults Tg-SwDI mice exhibited initial upregulation of AChR gene expression, but downregulation in old adults. Furthermore, young adult transgenic mice displayed significant cell loss in the inner retina and photoreceptor layer. Middle-aged adult and old adult mutants exhibited increased astrocytic gliosis and cholinergic cell loss. Electroretinography (ERG) was employed to measure the amplitude and

implicit time of retinal responses from TgF344-AD rat model and age-matched WT at 9 and 16 months of age. 9-month mutants exhibited higher responses from several retinal cells, but lower responses from off bipolar cells and Müller cells. 16-month TgF344-AD rats displayed lower scotopic critical flicker fusion threshold and photoreceptor responses, and slower implicit time for on bipolar cell responses, at several light intensities. These data collectively indicate that AD-related changes observed in the cerebrum are also present in the retina and may be, at least in part, responsible for the visual deficits associated with the disease. Furthermore, we demonstrated that AD pathology affects retinal cells' physiological responses and that ERG can be employed as a suitable means to detect AD-related visual changes to ultimately serve as an efficacious diagnostic tool to identify the disease in its earlier stages, thus improving treatment efficacy.

Keywords: Alzheimer's Disease, Vision, Retinal Cholinergic System, Electroretinography, Quantitative Real Time Polymerase Reaction, Immunohistochemistry.

DEDICATION

This dissertation is dedicated to my son Lucas, my parents Dr. Alsoires e Dra. Marlene, and my siblings Dra. Cristina and Alexandre.

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ELECTRORETINOGRAPHY (ERG) AS A POTENTIAL DIAGNOSTIC TOOL FOR ALZHEIMER'S DISEASE

LIST OF ABBREVIATIONS

Aβ	Amyloid beta
ACh	Acetylcholine
AChE	acetylcholinesterase
AChR	Acetylcholine receptor
AD	Alzheimer's Disease
APOE ε4	Apolipoprotein E ε4
APP	Amyloid precursor protein
ChAT	Choline acetyltransferase
CFF	Critical flicker fusion
CNS	Central nervous system
ERG	Electroretinography
FDA	Food and Drug Administration
GCL	Ganglion cell layer
GPCRs	G protein-coupled receptors
INL	Inner nuclear layer
IPL	Inner plexiform layer
LGICs	Ligand-gated ion channels
mAChR	Muscarinic acetylcholine receptor
MMSE	Mini-Mental Sate Examination

nAChR	Nicotinic acetylcholine receptor
NFL	Nerve fiber layer
NFTs	Neurofibrillary tangles
NMDAR	N-methyl-D-aspartate receptor
PS	presenilin
PS1ΔE9	Δ exon 9 mutant human presenilin-1
RPE	Retinal pigment epithelium
WT	Wild-type

GLOBAL INTRODUCTION

Alzheimer's Disease

Alzheimer's disease (AD) is a debilitating, and the most prevalent, type of dementia that is manifested by multiple cognitive deficits. AD is the 6th-leading cause of death (Doblhammer et al., 2015) and the 5th for people 65 and older (Kochanek et al., 2016). After AD diagnosis, the average life expectancy is between 4-8 years, but some patients may live up to twenty years with the disease (Brodaty et al., 2012; Todd et al., 2013; Tom et al., 2015). In 2017, the total AD-related healthcare costs are estimated to be U$ 818 billion for 36 million people worldwide (Prince et al., 2016; Wimo et al., 2017) and U$ 259 billion for 5.3 million cases in the United States (Association, 2013; Hebert et al., 2013). In 2010, there were 454,000 people newly diagnosed with AD (1 new case every 66 seconds) in the United States (Hebert et al., 2001a). As astonishing as these numbers are, they will not even compare to the projected costs in the future, as the number of new cases per year is estimated to be 959,000 (1 new case every 33 seconds) (Hebert et al., 2001a) and the total number of individuals with AD is projected to triple by 2050 (Alzheimers, 2016). These projections are tremendously staggering, as the current medications for AD only mollify the symptoms and do not eradicate the disease nor reverse cognitive decline. Furthermore, the diagnostic methods in existence lack the sensitivity to detect the disease before neuronal changes occur, which hinders the effectiveness of

treatment in prolonging the patient's memory and delaying cognitive deterioration.

According to the American Psychiatric Association's most recent Diagnostic and Statistical Manual of Mental Disorders (5th edition), AD is characterized by impairments in learning, memory, visuospatial, complex attention, executive function and language (American Psychiatric Association, 2013). AD has also been shown to affect non-cognitive behavioral domains, Behavioral and emotional disturbances include anxiety and (España et al., 2010; Filali et al., 2012), depressive symptoms (Lenoir et al., 2011; Diniz et al., 2013), aggressive behavior (Moechars et al., 1998; Alexander et al., 2011), increased locomotor activity (Cissé et al., 2011; Mori et al., 2013), as well as circadian rhythm and sleep disruptions (Wisor et al., 2005; Sterniczuk et al., 2010). AD's detrimental effects are not restricted to the behavioral and cognitive domains. As first reported by Lois Alzheimer in 1906 (Maurer et al., 1997; Kusne et al., 2016), AD also entails visual deficits that may arise in the preliminary phases of the disease (Cronin-Golomb et al., 1991; Uhlmann et al., 1991), before overt cognitive deterioration is observed (Sadun et al., 1987; Katz and Rimmer, 1989). Furthermore, there is evidence from studies in animal models and some in human AD patients, that amyloid beta (Aβ) plaque formation, one of the cardinal features of the disease, occurs in the retina prior to formation in the cerebrum (Katz and Rimmer, 1989; Trojanowski et al., 1993; Loffler et al., 1995; Blanks et al., 1996b; Parisi et al., 2001; Hardy and Selkoe, 2002; Parisi, 2003; Greeve,

2004; Ning et al., 2008; Dutescu et al., 2009; Perez et al., 2009; Liu et al., 2009b; Koronyo-Hamaoui et al., 2011; Koronyo et al., 2012).

The extensive neuropathological AD-associated alterations in the cerebrum are well characterized and have been shown to occur first in the medial temporal lobe (hippocampus and entorhinal complex) (Serrano-Pozo et al., 2011). These changes include dysregulation of calcium homeostasis (Bojarski et al., 2008; Small, 2009; Brawek and Garaschuk, 2014), gliosis (Beach et al., 1989; Bates et al., 2002), anomalous protein metabolism (Phillips et al., 1991; Tapia-Arancibia et al., 2008), cerebrovascular abnormalities (Fischer et al., 1990; Bergers and Song, 2005; Brown and Thore, 2011), cell loss (Fodero et al., 2004), substantial alterations in several neurotransmitter systems, particularly the glutamatergic and cholinergic systems (Doraiswamy, 2002; Francis et al., 2012), accumulation of intracellular neurofibrillary tangles (NFTs) and extracellular Aβ plaques (Figure 1) (Iqbal and Grundke-Iqbal, 2002; Palmer, 2002; Crews and Masliah, 2010; Ni et al., 2013). The time course and etiology of corresponding changes in the retina are not fully known.

Aβ plaques are insoluble, semi-crystalline deposits (Lesné et al., 2006) composed mainly by Aβ peptides (Aβ40 and Aβ42) that stem from the cleavage of amyloid precursor protein (APP), a type I transmembrane glycoprotein with a large amino-terminal extracellular domain (Kang et al., 1987; Hall and Roberson, 2013), by β-secretase and ϒ-secretase (which is composed of presenilin and other components) (De Strooper et al., 1998; Edbauer et al., 2003). Aβ42 is the more toxic form of this peptide, as it has a higher propensity than Aβ40 to aggregate

(Citron, 2010). NFTs are formed by the aggregation of hyperphosphorylated tau, a microtubule-associated protein (Brion, 1998).

Alzheimer's Disease Risk Factors

While AD is a very complicated and multifactorial neurodegenerative disorder with undefined etiology, some risk factors have been identified to play a role in the onset of the disease. These risk factors include genetic mutations, Apolipoprotein E ε4 (APOE ε4), gender, race, family history, educational level, lifestyle choices and aging (Figure 2).

Genetic mutations Autosomal dominant mutations to APP, presenilin 1 or presenilin 2, account for approximately 1-5 % of AD cases, and result in early onset of the disease (Campion et al., 1999; Bertram and Tanzi, 2005), as early as age 30 (Bekris et al., 2010). The know human APP mutations are named according to the region in which they were first reported, for example, Swedish, Dutch and Iowa mutations. Individuals inheriting a mutation in presenilin 2 have a 95% likelihood of developing AD, while those with certain mutations to the APP or presenilin 1 genes will unquestionably develop AD (Goldman et al., 2011).

Apolipoprotein E ε4 (APOE ε4) More than 90% of all AD cases are sporadic with a late onset (Bertram, 2004). The only gene that has been consistently linked to late onset AD is APOE ε4 (Schellenberg, 1995; Selkoe, 2001; Coon et al., 2007). Individuals possessing two copies of the APOE ε4 gene have 8-12-fold likelihood of developing AD, while individuals with one copy have a three-fold risk (Holtzman and Herz, 2012; Loy et al., 2014). A meta-analysis of 20 published studies, from 1985 until 2010, involving AD patients revealed that 56% had one copy of the

APOE ε4 gene, while 11% had two copies of the gene (Ward et al., 2012). Another publication found that 65% of 1770 patients from 26 AD centers had at least one copy of the APOE ε4 gene (Mayeux et al., 1998). APOE ε4 has been shown to play a very active role in AD pathology. APOE ε4 reduces glutamate receptor function and inhibits synaptic plasticity (Chen et al., 2010), increases tau phosphorylation and accumulation in soma and dendrites (Brecht et al., 2004; Harris et al., 2004; Andrews-Zwilling et al., 2010), increases Aβ accumulation and Aβ plaques formation (Deane et al., 2008; Verghese et al., 2013).

Gender and Race Women account for more than 62% of all the AD cases in the USA (Hebert et al., 2013). There are a number of different explanations for such a drastic disparity in incidence between males and females, including stronger interaction between APOE ε4 and estrogen (Yaffe et al., 2000; Kang and Grodstein, 2012), longer female lifespan (Seshadri et al., 1997; Hebert et al., 2001b) and lower educational level (Rocca et al., 2014). African Americans and Hispanics are (2 and 1.5 times, respectively) more likely to develop AD than Caucasians (Gurland et al., 1999; Potter et al., 2009). It is generally believed that the higher incidence in these minorities stem from non-genetic factors, such as health conditions, lifestyle and socioeconomic factors (Gurland et al., 1999; Yaffe et al., 2013).

Family History and Educational Level People with a first-degree relative (siblings or parents) with AD have a higher probability of developing the disease, than those with no familial history of AD (Green et al., 2002; Loy et al., 2014), which suggests that there may be other unknown genes involved or other non-genetic

factors. Individuals with both parents with AD are even more susceptible, 54% chance, to have the disease by the age of 80 (Lautenschlager et al., 1996). Individuals who had 10-18 years of formal education have a lower likelihood to develop AD and other dementias than those with 8-9 and 6-7 years, in that order (Sando et al., 2008). Lower financial means (McDowell et al., 2007), increased likelihood of working jobs that are not as mentally demanding (Fisher et al., 2014; Then et al., 2014; Grzywacz et al., 2016; Pool et al., 2016), smaller cognitive reserve (reduced ability to mitigate the cognitive symptoms resulting from cerebral changes) (Scarmeas and Stern, 2003; Roe et al., 2007; Stern, 2012) may all be factors responsible for the higher AD incidence in individuals with lower education.

Lifestyle Choices Obesity in midlife (Anstey et al., 2011; Loef and Walach, 2013), diabetes mellitus (Gudala et al., 2013; Malek-Ahmadi et al., 2013; Vagelatos and Eslick, 2013), hypertension (Launer et al., 2000; Ninomiya et al., 2011), high cholesterol (Kivipelto et al., 2001; Canevari and Clark, 2007) and smoking (Anstey et al., 2007; Ohara et al., 2015) have all been linked to a higher probability of AD. Unlike aging, genetic traits, race and gender, lifestyle choices can be modified to reduce one's risk for dementia. Physical activity (Erickson et al., 2012; Tan et al., 2017) and a healthy diet (Lourida et al., 2013; Hardman et al., 2016) have shown to be protective against AD and dementia.

Aging The most prominent risk factor for late-onset AD is aging, 10% of the population over the age of 65 has AD (Hebert et al., 2013). The risk for AD incidence increases significantly with age, from 3% in individuals 65-74 years old, to 17% age 75-84 and to 32% age 85 and older (Hebert et al., 2013).

Alzheimer's Disease Etiology Theories

There are three interrelated primary lines of inquiry into the etiology of the disease: the amyloid cascade hypothesis, the glutamatergic hypothesis, and the cholinergic hypothesis. There is evidence for the involvement of each of these systems in AD.

The amyloid cascade hypothesis, first proposed in 1992 (Hardy and Higgins, 1992), postulates that Aβ deposition is the first pathological event in AD that triggers the formation Aβ plaques, NFTs, neuronal cell loss, and finally dementia (Karran et al., 2011; Reitz, 2012). Although, there is extensive evidence for Aβ processing dysregulation in AD, there is little evidence that this dysregulation is causal (Wallace et al., 1991; Regland and Gottfries, 1992; Armstrong, 2006).

The glutamatergic hypothesis revolves around the notion that glutamatergic dysfunction is implicated in many of the neurochemical and behavioral deficits present in AD (Maragos et al., 1987). The glutamatergic hypothesis is progressively becoming more accepted (Danysz et al., 2000), perhaps due to the fact that, glutamate is the principal neurotransmitter at approximately two-thirds of synapses in the neocortex and is involved in all aspects of cognition and higher mental function (Francis et al., 2012). Fundamental to this premise is the crucial role of N-methyl-D-aspartate (NMDA) glutamate receptors in episodic and spatial memories (Tsien, 2000; Li and Tsien, 2013), while overactivation, under chronic conditions, leads to neuronal damage (Danysz et al., 2000; Francis PT, 2005).

The cholinergic hypothesis was the first theory to attempt elucidating the disease's etiology (Bartus et al., 1982; Bartus, 2000). This hypothesis proposes that decreases in choline transport, choline acetyltransferase (ChAT) levels and activity, along with alterations in acetylcholinesterase levels, acetylcholine (ACh) release, resulting in decreased ACh synthesis and concentration, along with selective impairment and/or loss of cholinergic neurons and the reduction of cholinergic fibers in the hippocampus, frontal and temporal areas of the brain, along with as changes in nicotinic and muscarinic ACh receptor expression all contribute to AD pathophysiology (Figure 3) (Geula and Mesulam, 1989, 1996, Slotkin et al., 1990, 2001; Dournaud et al., 1995; Francis et al., 1999, 2012; Terry and Buccafusco, 2003; Francis PT, 2005; Oddo and LaFerla, 2006; Xu et al., 2012). Furthermore, the improvement of cholinergic transmission alleviates the hippocampus-based episodic memory impairment manifested in the early stages of the disease (Hernandez et al., 2010). Once released from cholinergic neurons, ACh can bind and activate two types of receptors: nicotinic acetylcholine receptors (nAChRs) and muscarinic acetylcholine receptor (mAChRs), ligand-gated ion channels (LGICs) and G protein-coupled receptors (GPCRs), respectively (Figure 4) (Oddo and LaFerla, 2006). nAChRs are pentameric ligand-gated ion channels formed by a combination of α (2,3,4,5,6,7,9 & 10) and β (2,3&4) subunits. These subunits can form homomeric (e.g. α 7 nAChR) or heteromeric (e.g. α3β4) receptors. They are activated by ACh, carbachol, nicotine (except α 9), and they are blocked by curare (Smith et al., 2014). mAChRs are G-protein coupled receptors with five distinct subtypes: m 1-5. They

can be excitatory (m1, 3&5) or inhibitory (m2&4). These receptors are blocked by atropine and activated by ACh, carbachol, choline and muscarine (Smith et al., 2014) .

In 1936, Henry Dale and Otto Lewi were awarded a joint Nobel prize for the discovery of the first neurotransmitter, ACh (Contestabile, 2011). Since its discovery, our knowledge of ACh's functions and importance in neuroscience has advanced greatly. ACh has been shown to be involved in learning, attention, arousal, motivation, memory and other cognitive functions (Sarter and Bruno, 1997; Sarter et al., 2003; Gotti and Clementi, 2004; Matta et al., 2017), while cholinergic dysfunction has been linked to traumatic brain injury and several psychopathological conditions such as schizophrenia, delirium, depression, insomnia, amnesia, panic attacks and affective disorders (Bartus et al., 1982; Dilsaver and Coffman, 1989; Bymaster et al., 1999; Battaglia, 2002; Arciniegas, 2003; Mancama et al., 2003; Raedler et al., 2006; Luppi et al., 2006; Sellin et al., 2008; Hshieh et al., 2008; Dean, 2012; Carruthers et al., 2015). One of the most notable AChRs is α7 nAChR, which is a homomeric receptor formed by five α7 subunits (Couturier et al., 1990; Zhao et al., 2003). α7 nAChRs have been shown to be extremely involved in several psychiatric disorders (Freedman et al., 1995; Leonard et al., 1996; Ancín et al., 2010; Zhang et al., 2016), and neurological diseases such as Parkinson's disease (Quik et al., 2015) and AD (Medeiros et al., 2014).

ACh is one of the main neurotransmitters involved in visual processing in the retina (Keyser et al., 2017), an extension of the brain located in the back of the

eye that is responsible for relaying light information to the rest of the brain. The 5-layered retina structure consists of photoreceptors (rods and cones) which contain the machinery for phototransduction. They make synaptic contacts with horizontal and bipolar cells in the outer plexiform layer. The cell bodies of horizontal, bipolar, and amacrine cells are located in the inner nuclear layer. Ganglion cell somas are located in the innermost layer, the ganglion cell layer, their dendrites extend to the inner plexiform layer where they receive synaptic input from bipolar and amacrine cells. Ganglion cell axons leave the back of the eye and comprise the optic nerve (E Dowling, 1987). In the retina, the synthesis and release of ACh are performed by starburst amacrine cells (Masland, 1980; Masland et al., 1984b; Keyser et al., 2017), named as such due to their very distinctive physical attributes (Famiglietti, 1983; Famiglietti Jr., 1983; Vaney, 1984; Keyser et al., 2017). ACh is released in response to light changes (onset and offset) (Masland et al., 1984a; Tauchi and Masland, 1984; Masland and Cassidy, 1987; Schmidt et al., 1987) as well as tonic release (Famiglietti, 1983; Famiglietti Jr., 1983; Vaney, 1984; Keyser et al., 2017). AChRs have been shown to be expressed in numerous species and in several retinal cells, including amacrine, bipolar, displaced amacrine, ganglion, horizontal and photoreceptor cells (Keyser et al., 2000; Dmitrieva et al., 2007; Strang et al., 2007; Cimini et al., 2008; Smith et al., 2014). The retinal cholinergic system plays an essential role in ganglion cell responses (Schmidt et al., 1987; Kittila and Massey, 1997; Strang et al., 2005, 2007, 2010, 2015), retinal development (Stacy et al., 2005; Sun et al., 2008; Ford and Feller, 2012), cell differentiation and proliferation (Naruoka et al., 2003; Braga et al., 2013; Layer et al., 2013), and

electroretinogram responses (Jardon et al., 1989; Jurklies et al., 1996; Antal et al., 1999; Varghese et al., 2011; Moyano et al., 2013; Bedore et al., 2015).

It is evident that many systems are imperiled in AD and that there are many reciprocal interactions between the main players involved in AD pathology: Aβ, cholinergic system, NFTs and glutamatergic system. Acetylcholinesterase (AChE) concentration is diminished, over all, in the AD cerebrum, but it is augmented in regions where NFTs and Aβ plaques are present (Ulrich et al., 1990; Morán et al., 1993). Some postulate that this focal AChE increase arises as a result of Aβ's agonistic action on α7 nAChRs (Fodero et al., 2004). α7 nAChR activation improves cholinergic integrity (Hernandez et al., 2010), cognition and synaptic plasticity (Echeverria and Zeitlin, 2012), alleviates Aβ toxicity (Kihara et al., 2001; Hernandez et al., 2010) and reduces neuronal cell loss (Echeverria and Zeitlin, 2012). Conversely, tau phosphorylation significantly increases as a result of nAChRs activation, while the activation of mAChRs hinders it (Schliebs and Arendt, 2006). The m1 mAChR subtype plays a role in APP regulation (Cowburn et al., 1996), while the m2 subtype is involved in the modulation of several AD-relevant proteins, including tau (Hérnandez-Hérnandez et al., 1995). Glutamatergic excitatory neurotransmission is severely disrupted in AD, probably due to the oxidative stress associated with the Aβ42 increase (Tanović and Alfaro, 2006). This disruption is evident by increase N-methyl-D-aspartate receptor (NMDAR) activation and concomitant glutamate excitotoxicity (Tsien, 2000; Wenk et al., 2006; Li and Tsien, 2013). The anomalous glutamatergic hyperactivity associated with AD may be due to postsynaptic receptor and downstream defects

that produce inappropriately timed or sustained glutamate activation of NMDARs, leading to neuronal injury and death and cognitive deficits associated with dementia (Wenk et al., 2006). NMDAR activation has also been show to play an important role in Aβ production (Dinamarca et al., 2012; Revett et al., 2013); while Aβ, by binding with high affinity to α7 nAChRs (Wang et al., 2000; Dziewczapolski et al., 2009) producing an increase in intracellular calcium concentration in astrocytes (Sharma and Vijayaraghavan, 2001), which then release glutamate to activate NMDARs leading to disrupted neuronal signaling and glutamate excitotoxicity (Talantova et al., 2013). AD's pathology has a tremendously high degree of complexity and intricacy involving several proteinopathies, neurotransmitter systems disturbances and neuronal alterations, therefore mono-factorial theories cannot fully explain its etiology nor completely account for its multi-symptomatology (McDonald, 2002; McDonald et al., 2010). Therefore, it is my belief that the combination of these theories would provide a more accurate portrayal of the disease process and its etiology.

Alzheimer's Disease Treatment

The cure for AD has not as of yet been attained, despite of tireless research efforts and advancements in drug development: between 2002 and 2012, only one of 244 medications that underwent clinical trials was approved by the United States Food and Drug Administration (FDA) (Cummings et al., 2014). There are several factors that hinder the development of efficacious treatments for AD, including the disease's high degree of complexity, high monetary costs in the development of drugs and the FDA stringent approval requirements (Kinch, 2017). Because of the

neurotransmitter systems alterations in AD, current FDA approved AD medications, AChE inhibitors and (NMDAR) antagonists, target the cholinergic and glutamatergic systems, respectively (Cummings, 2004). AChE inhibitors increase ACh levels by hindering its hydrolysis into acetate and choline (Cummings, 2004). They are most efficient when used early in the disease process and used persistently without interruptions (Seltzer, 2006). The most commonly prescribed AChE inhibitor, Donepezil, is approved to treat all stages of the disease (Seltzer et al., 2004). However, in the later stages of the disease, the cholinergic system may be too deteriorated, so an alternative approach involves targeting the glutamatergic system. NMDAR hyperactivity leads to excitotoxicity, but its physiological activity is essential for normal function (Marambaud et al., 2009). This led to the more recent use of NMDAR antagonists as an alternative to cholinergic treatments (Reisberg et al., 2003). The most commonly prescribed NMDAR antagonist is Memantine. Memantine, unlike other NMDAR antagonists, preferentially blocks excessive NMDAR activity without disrupting normal activity (Lipton, 2004), by entering the receptor-associated ion channel preferentially when it is excessively open without accumulating in the channel due to its fairly fast off-rate (Lipton, 2004). Memantine treatment is associated with decreased Aβ40 (Alley et al., 2010; Ray et al., 2010), Aβ42 and secreted APP levels (Alley et al., 2010), decreased Aβ plaques deposition (Dong et al., 2008; Martinez-Coria et al., 2010), and improvements in fear conditioning (Martinez-Coria et al., 2010), hippocampus-based spatial learning (Alley et al., 2010) and memory (Martinez-Coria et al., 2010)

in animal models of AD. Memantine has been shown to improve cognitive function in patients with moderate to severe AD (Francis et al., 2012).

However, both Donepezil and Memantine, have been shown to influence other neurotransmitter systems. For example, Donepezil-associated ACh increase and the subsequent activation of α7 nAChRs can indirectly decrease glutamate excitotoxicity via downregulation of NMDARs (Kawamata et al., 2011). Memantine, in addition to its effects on NMDARs, has also been shown to increase ACh levels (Ihalainen et al., 2011) and protect cholinergic neurons from inflammatory processes (Willard et al., 2000). These synergistic effects have led to the treatment approach in which both medications are used together to preserve cholinergic integrity and prevent glutamate excitotoxicity for as long as possible (Ihalainen et al., 2011). The most recent available medication for AD is Namzaric, FDA approved in 2014, a combination of Donepezil and Memantine (FDA, 2014). However, available medications are most effective in early stages of the disease and, at best, only provide temporary and moderate effects. Current treatments are not capable of treating all of AD's manifestations or of changing the progression of the disease (Huang and Mucke, 2012; Anand et al., 2014). Therefore, early AD detection is crucial to prolonging cognitive function, and the advancement in knowledge of the disease mechanism is absolutely essential to assist in the development of early detection methods and more efficacious treatments.

Animal Models of Alzheimer's Disease

The majority of AD animal models have genetic mutations in presenilin proteins and/or in APP. These mutations are associated with increased levels of

Aβ, and are intended to mimic the disease's symptomology observed in early-onset AD patients (Hall and Roberson, 2013). The studies herein focused on two animal models with severe AD mutations: Tg-SwDI mouse and TgF344-AD rat. The inclusion of two different AD animal models may provide not only a between-species comparison but also the possibility for a better extrapolation into the disease process in humans.

Tg-SwDI mice express the human APP (isoform 770) with three mutations driven by the mouse Thy1 promoter: Swedish K670N/M671L, Dutch E693Q, and Iowa D694N mutations (Murrell et al., 1991) (Figure 5 Top Panel). TgF344-AD rats are generated on a Fischer 344 background with two mutated human genes driven by the mouse prion promoter: Swedish APP (isoform 695) and presenilin 1 deletion of exon 9 (PS1ΔE9) (Figure 5 Bottom Panel). (Cohen et al., 2013; Tsai et al., 2014).

The Swedish (K670N/M671L) mutation occurs at the β-secretase cleavage site (Hall and Roberson, 2013), with a double substitution: lysine and methionine by asparagine and leucine (Mullan et al., 1992). In the Dutch (APP E693Q) mutation, glutamic acid is substituted by glutamine (Levy et al., 1990). The Iowa (APP D694N) mutation is characterized by the substitution of aspartic acid by asparagine (Grabowski et al., 2001). Both, Dutch and Iowa mutations occur within the Aβ peptide sequence (Hall and Roberson, 2013), and result in increased Aβ40 levels (Shin et al., 2003; Levy et al., 2006) including cerebrovascular Aβ accumulation (Levy et al., 1990; Grabowski et al., 2001).

Tg-SwDI mice show extensive Aβ accumulation by 12 months of age (Van Vickle et al., 2008), but learning and memory impairment in the Barnes maze task occurs as early as 3 months of age (Xu et al., 2007), indicating that Aβ is not the initial trigger for cognitive decline. There is no report of any AD-related changes in retinal anatomy or visual function in these mice. TgF344-AD rats exhibit substantial neurovascular network dysfunction at 9 months of age (Joo et al., 2017), as well as tauopathy, amyloidosis, gliosis, frank neuronal cell loss, at 16 months of age, but start exhibiting cognitive disturbances, and impaired learning and memory at 15 months of age (Figure 6) (Cohen et al., 2013). Moreover, TgF344-AD animals also show retinal changes at 19 months of age, including Aβ plaques, choroidal thinning, hypertrophic retinal pigment epithelial (RPE) cells, and upregulation of complement factor C3 and inflammatory cells in the retina (Figure 6) (Tsai et al., 2014). Even though, 19 month old rats displayed lower visual acuity, there were no retinal vasculature alterations or retinal ganglion cell loss (Tsai et al., 2014).

Tg-SwDI mouse and TgF344-AD rat were included in the following experiments for being animal models with prominent phenotypical expression of AD. Furthermore, our studies were inspired by the widely accepted notion that AD-related retinal alterations may parallel cerebral changes, and that they may precede noticeable cognitive decline. The ultimate objectives of these studies are to advance the understanding of AD pathological alterations in vision and to assist in the development of timely diagnosis of the disease.

Hypotheses and Specific Aims

The influence of the cholinergic system in AD's pathophysiology, and its interweaving with Aβ and glutamatergic processes, are well-described in the cerebrum, that is why we chose to determine if the retinal cholinergic system of the Tg-SwDI mouse model exhibited similar pathological changes. We also chose to establish AD's impact on retinal cells physiological responses in the TgF344-AD rat model and if those changes were exacerbated by age. Lastly, we assessed the effectiveness of electroretinography (ERG) as a means to identify AD-related changes in retinal physiology.

Specific Aim I

We intended to establish whether the pathological changes observed in the cerebrum are also present in the retina. We used quantitative polymerase chain reaction and immunohistochemistry to assess changes in AChRs gene expression, gliosis, retinal cell number in the Tg-SwDI mouse model as compared to age-matched wild-type (WT). We predicted that there would be an initial upregulation followed by downregulation in AChRs expression and a reduced number of cells in the Tg-SwDI, as compared to age-matched WT animals.

Specific Aim II

We intended to assess AD's influence in retinal physiological responses and to evaluate the suitability of ERG as a diagnostics tool to detect the disease. ERG was employed to measure the amplitude and implicit time of retinal responses from

TgF344-AD rat model and age-matched WT at 9 and 16 months of age. Implicit time corresponds to the amount of time between the onset of the response and its peak amplitude. ERG measurements included a-waves (photoreceptors: rods and cones), b-waves (on bipolar cells), a-wave to b-wave ratio, initial corneal deflection of c-waves (RPE cells and/or Müller cells), d-waves (off bipolar cells), critical flicker fusion threshold (photoreceptors: rods and cones), oscillatory potentials (amacrine cells) and photopic negative response (ganglion cells), at various light intensities during dark-adapted and light-adapted conditions. We hypothesized that the TgF344-AD rats would exhibit retinal responses with decreased amplitude and increased implicit time, as compared to age-matched WT animals.

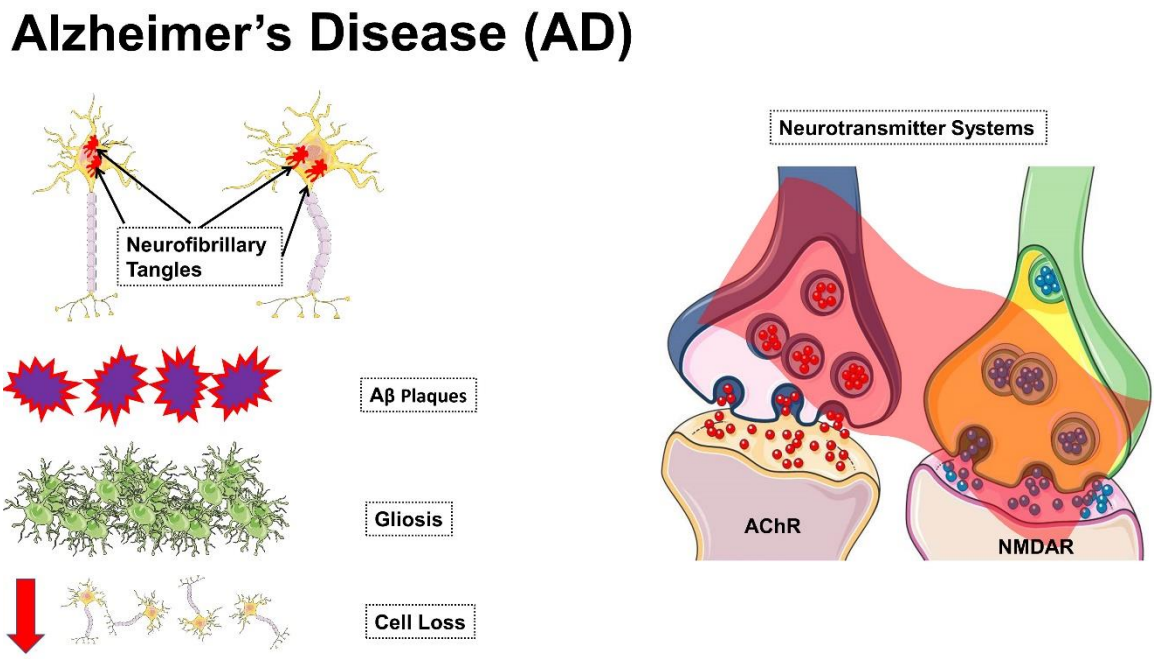

Figure 1. Alzheimer's disease (AD) pathology. AD is characterized by the accumulation intracellular neurofibrillary tangles, extracellular amyloid beta (Aβ) plaques, gliosis, cell loss, and alterations in several neurotransmitter systems (especially cholinergic and glutamatergic) (Beach et al., 1989; Bates et al., 2002; Doraiswamy, 2002; Iqbal and Grundke-Iqbal, 2002; Fodero et al., 2004).

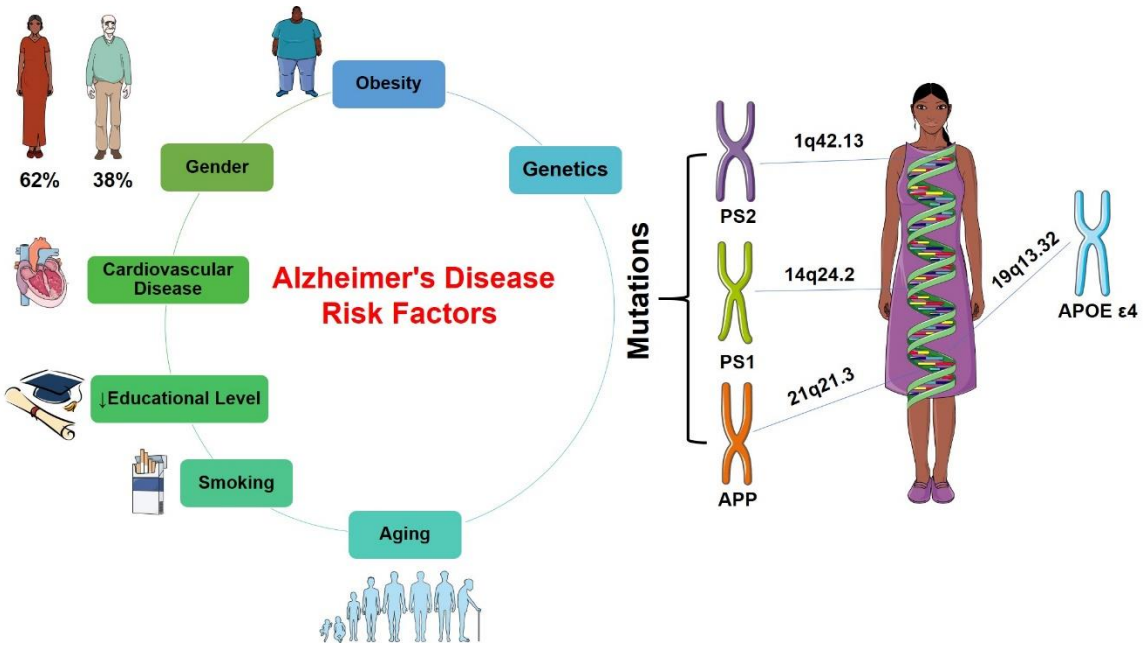

Figure 2. Alzheimer's disease (AD) risk factors. The risk factors for AD include gender, cardiovascular disease, aging, obesity, lower educational level, smoking, aging, 1-2 copies of the apolipoprotein E ε4 (APOE ε4) gene, and genetic mutations in amyloid precursor protein (APP), presenilin (PS) 1 and 2 (Schellenberg, 1995; Campion et al., 1999; Selkoe, 2001; Scarmeas and Stern, 2003; Bertram and Tanzi, 2005; Anstey et al., 2007, 2011; Coon et al., 2007; Hebert et al., 2013; Ohara et al., 2015).

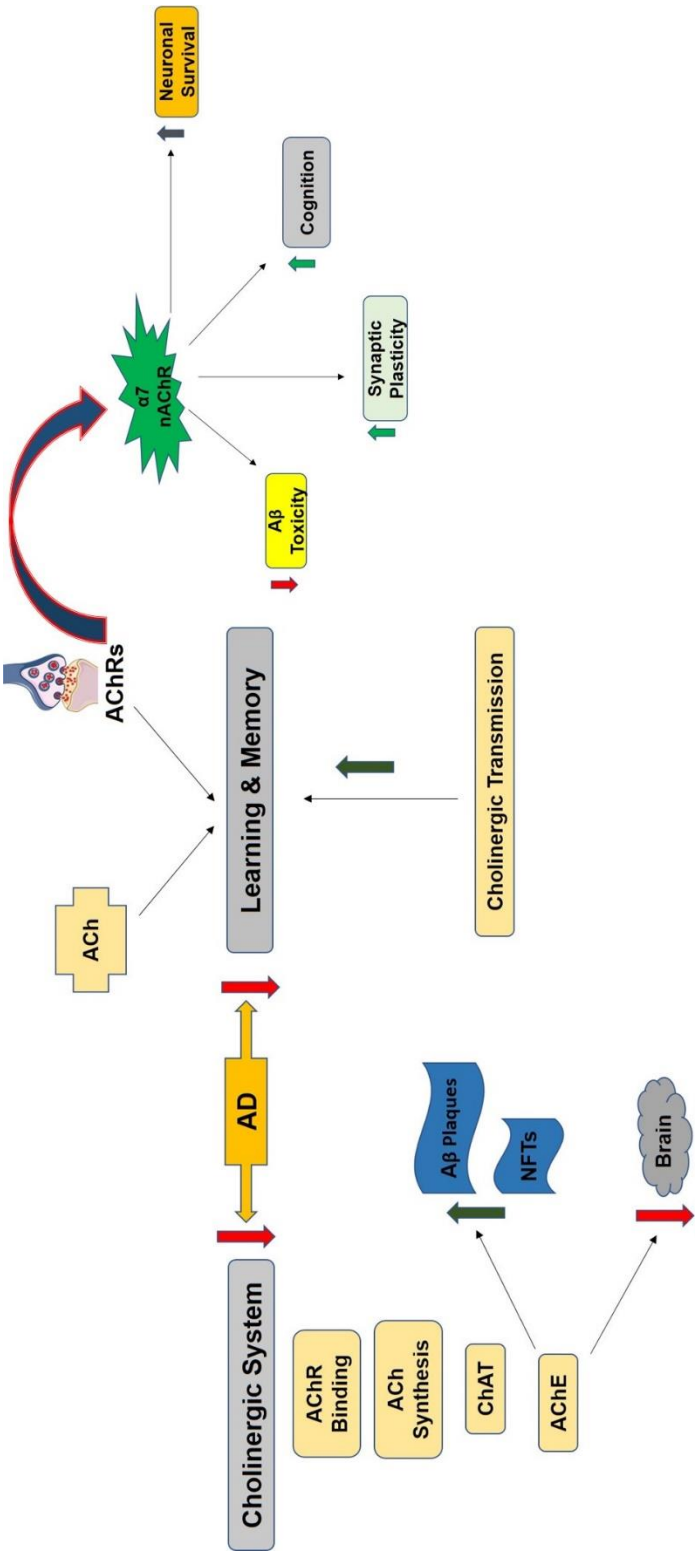

Figure 3. Alzheimer's disease (AD) and the cholinergic system. Alzheimer's disease (AD) is associated with cholinergic system alterations and cognitive

decline. Acetylcholine (ACh) and ACh receptors (AChRs) play crucial roles in cognitive functions (learning and memory) and in AD pathology, especially α7 nicotinic AChR (nAChR). The enhancement of cholinergic transmission can improve learning and memory (Ulrich et al., 1990; Morán et al., 1993; Kihara et al., 2001; Fodero et al., 2004; Hernandez et al., 2010; Echeverria and Zeitlin, 2012).

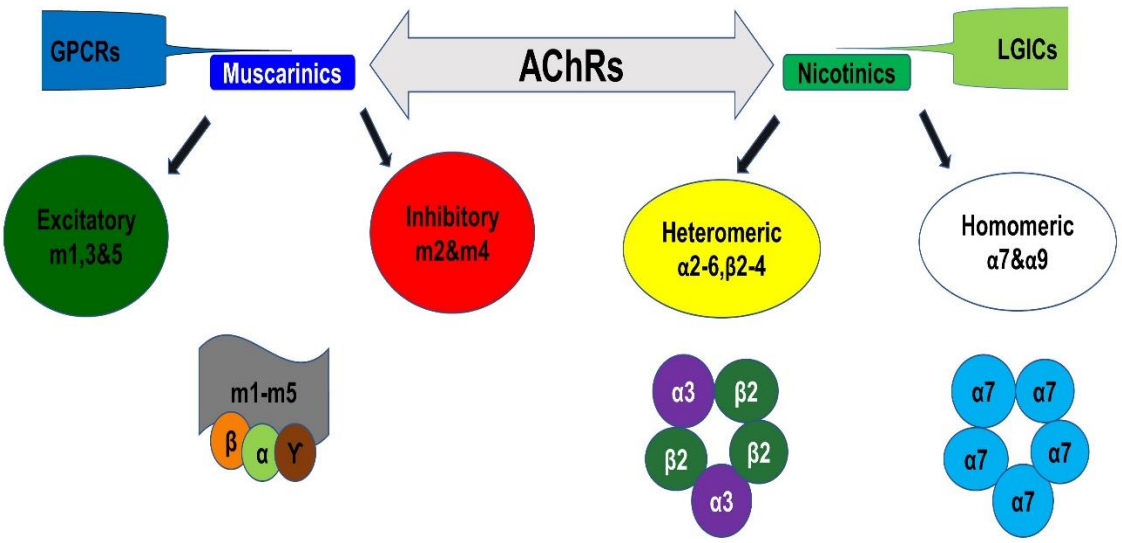

Figure 4. Acetylcholine receptors types. There are two types of acetylcholine receptors (AChRs), muscarinics and nicotinics. Muscarinics are G protein-coupled receptors (GPCRs) that can be excitatory or inhibitory. Nicotinics are pentameric ligand-gated ion channels (LGICs) formed by a combination of α and β subunits (heteromeric) or solely of α subunits (homomeric).

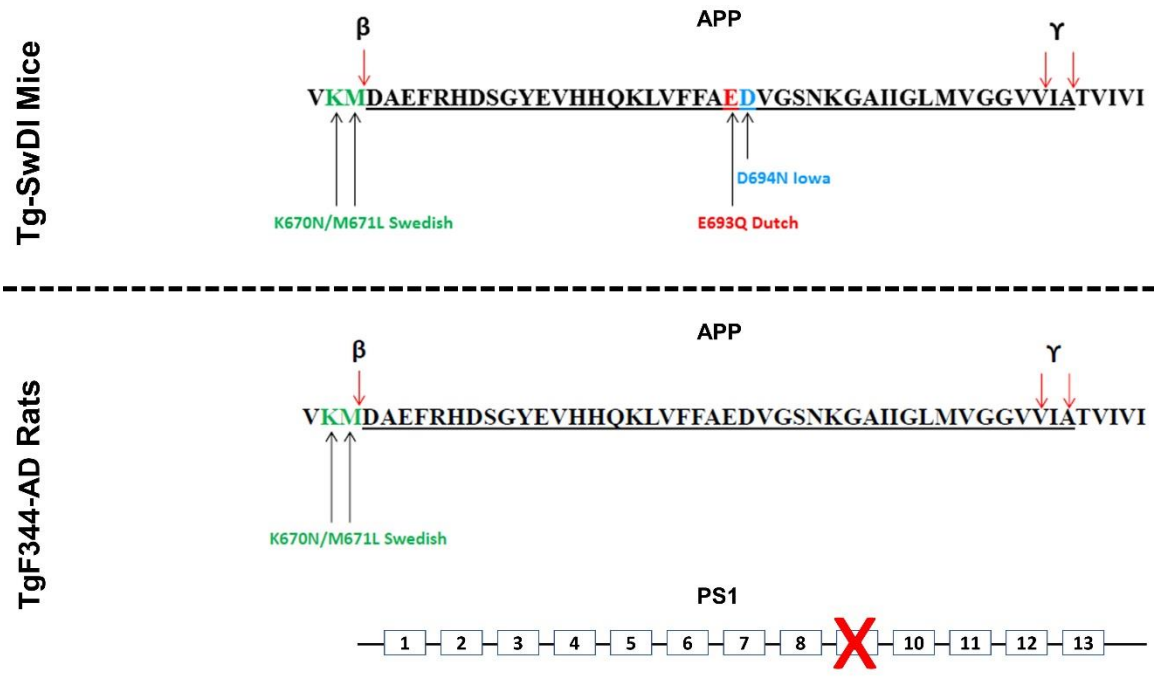

Figure 5. Tg-SwDI mouse and TgF344-AD rat mutations. Tg-SwDI mice have the Swedish, Dutch and Iowa mutations in the amyloid precursor protein gene (APP) (Murrell et al., 1991; Mullan et al., 1992). TgF344-AD rats have the APP Swedish mutation and presenilin 1 (PS1) exon nine deletion (Cohen et al., 2013; Tsai et al., 2014).

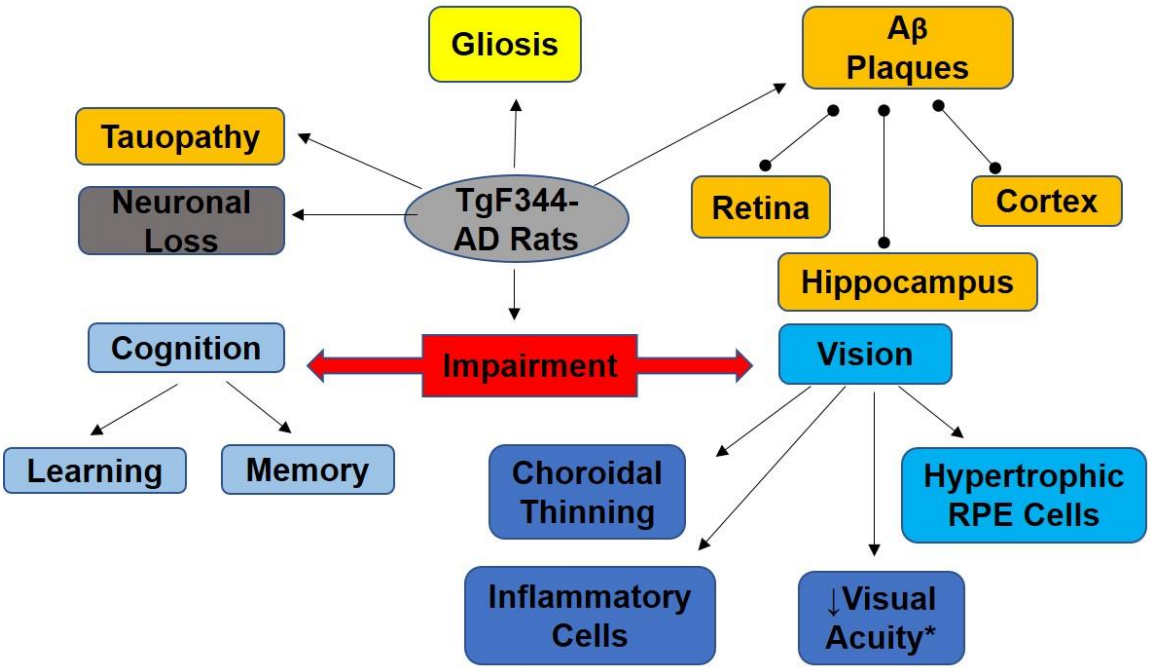

Figure 6. Alzheimer's disease pathology alterations in TgF344-AD rats. TgF344-AD rats display several of AD's cardinal features, such as tauopathy, neuronal loss, gliosis, amyloid beta (Aβ) plaques, and impairment in vision, learning and memory (Cohen et al., 2013; Tsai et al., 2014).

RETINAL CHANGES IN THE TG-SWDI MOUSE MODEL OF ALZHEIMER'S DISEASE

by

FRED G. OLIVEIRA-SOUZA, MARCI L. DERAMUS, THOMAS VANGROEN, ALEXIS E. LAMBERT, MARK S. BOLDING AND CHRISTIANNE E. STRANG

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Abstract

Alzheimer's disease (AD), a debilitating neurodegenerative illness, is characterized by neuronal cell loss, mental deficits, and abnormalities in several neurotransmitter and protein systems. AD is also associated with visual disturbances, but their causes remain unidentified. We hypothesize that the visual disturbances stem from retinal changes, particularly changes in the retinal cholinergic system, and that the etiology in the retina parallels the etiology in the rest of the brain. To test our hypothesis, quantitative polymerase chain reaction (qPCR) and immunohistochemistry (IHC) were employed to assess changes in acetylcholine receptor (AChR) gene expression, number of retinal cells, and astrocytic gliosis in the Tg-SwDI mouse model as compared to age-matched wild-type (WT). We observed that Tg-SwDI mice showed an initial upregulation of AChR gene expression early on (young adults and middle-aged adults), but a downregulation later on (old adults). Furthermore, transgenic animals displayed significant cell loss in the photoreceptor layer and inner retina of the young adult animals, as well as specific cholinergic cell loss, and increased astrocytic gliosis in the middle-aged adult and old adult groups. Our results suggest that the changes observed in AD cerebrum are also present in the retina and may be, at least in part, responsible for the visual deficits associated with the disease.

Keywords: Alzheimer's disease, qPCR, histology, retinal cholinergic system, vision, amyloid precursor protein mutation.

Abbreviations

- Aβ: Amyloid beta
- ACh: Acetylcholine
- AChR: Acetylcholine receptor
- AD: Alzheimer's Disease
- APP: Amyloid precursor protein
- ChAT: Choline acetyltransferase
- CNS: Central nervous system
- GCL: Ganglion cell layer
- GFAP: Glial fibrillary acidic protein
- IHC: Immunohistochemistry
- iINL: Inner inner nuclear layer
- INL: Inner nuclear layer
- IPL: Inner plexiform layer
- mAChR: Muscarinic acetylcholine receptor
- mo: Months old
- nAChR: Nicotinic acetylcholine receptor
- NFL: Nerve fiber layer
- oINL: Outer inner nuclear layer
- ONL: Outer nuclear layer
- qPCR: Quantitative polymerase chain reaction
- Tg-SwDI: Transgenic Swedish, Dutch and Iowa
- SEM: Standard error of mean

- WT: Wild-type

Alzheimer's disease (AD) is a debilitating neurodegenerative disorder that affects over 26 million people worldwide and the incidence is projected to quadruple by the year 2050 (Tsai et al., 2014). According to the Alzheimer's Association, in 2015 there were 5.3 million Americans suffering from AD. It is characterized by circadian rhythm dysfunction and the development of multiple cognitive deficits, including memory loss, confusion, apraxia, aphasia and agnosia (American Psychiatric Association, 2013; La Morgia et al., 2015).

AD is marked by the accumulation of neurofibrillary tangles (aggregates of hyper-phosphorylated tau protein), deposition of amyloid beta (Aβ) plaques, gliosis, and substantial neuronal and synaptic loss (Fodero et al., 2004). The pathophysiology of AD is extremely intricate and involves several biochemical pathways. These include defective Aβ protein metabolism and abnormalities of several neurotransmitter systems, particularly the cholinergic and glutamatergic systems (Doraiswamy, 2002; Francis et al., 2012).

In addition to cognitive decline and cortical changes, AD is also characterized by visual dysfunction ranging from simple (e.g. color discrimination) to complex (e.g. object recognition), including deficits in motion perception, contrast sensitivity, stereopsis, temporal resolution, acuity, color, and lower critical flicker fusion threshold (Cronin-Golomb et al., 1995; Rizzo et al., 2000). In 1906, Alois Alzheimer was the first to report the occurrence of visual disturbances in one of his patients Auguste D (Maurer et al., 1997; Kusne et al., 2016).

Visual deficits have been reported in the early stages of the disease, even before AD diagnosis is clearly established (Cronin-Golomb et al., 1991; Uhlmann et al., 1991). The effects of AD on visual attention and other higher visual functions can negatively impact one's quotidian activities such as reading, route finding, object localization and recognition (Rizzo et al., 2000). To date, the underlying causes of these visual dysfunctions and whether they stem from retinal or cortical abnormalities remain poorly understood (Tsai et al., 2014).

The excitatory neurotransmitter acetylcholine (ACh) plays a crucial role in myriad cognitive functions, including learning and memory; both of which are negatively impacted by AD. In the brain, ACh is released by cholinergic neurons and can bind to two different acetylcholine receptor (AChR) subtypes: nicotinics (nAChRs) and muscarinics (mAChRs), which are ionotropic and metabotropic receptors, respectively (Oddo and LaFerla, 2006). In early AD, there is impairment in hippocampus-based episodic memory that is improved through enhancement of cholinergic transmission (Hernandez et al., 2010).

In the retina, ACh is synthesized and released by starburst amacrine cells (Masland, 1980). Release of ACh is both tonic and light-evoked (Masland, 1980). AChRs are expressed by photoreceptor, bipolar, amacrine, displaced amacrine, horizontal and ganglion cells in several different species (Dmitrieva et al., 2007; Strang et al., 2007, 2010; Cimini et al., 2008; Smith et al., 2014). AChR activation has been shown to play a role in retinal development (Stacy et al., 2005; Sun et al., 2008; Ford and Feller, 2012) and affect ganglion cell responses (Schmidt et al., 1987; Kittila and Massey, 1997; Strang et al., 2005, 2007, 2010, 2015).

The main animal models of AD were designed to mimic the autosomal dominant mutations observed in hereditary early onset Alzheimer's. These models express mutations in amyloid precursor protein (APP) and/or in the presenilin proteins (PSEN1 and PSEN2). All of the identified mutations that cause autosomal dominant AD directly alter the production of Aβ through APP processing. APP is a type I transmembrane protein with a large amino-terminal extracellular domain (Hall and Roberson, 2013). Aβ is a peptide that stems from the cleavage of APP by the enzymes β-secretase and ϒ-secretase, which is composed of presenilin and other components (De Strooper et al., 1998; Edbauer et al., 2003).

Male and female transgenic Swedish, Dutch and Iowa (Tg-SwDI) mice were used for this study. These mice express the human APP, isoform 770, with the Swedish APP K670N/M671L, Dutch E693Q, and Iowa D694N mutations driven by the mouse Thy1 promoter (Murrell et al., 1991) . The Dutch and Iowa are missense mutations that occur on exon 17. In the Dutch APP E693Q mutation, glutamic acid (GAA) is replaced by glutamine (CAA) (Levy et al., 1990).

The Dutch mutation leads to cell death and loss of vessel wall integrity (Wisniewski et al., 1991), and is associated with severe Aβ deposition in cerebral vessels, hemorrhages, and diffuse plaques in brain parenchyma (Timmers et al., 1990). The Iowa APP D694N mutation is characterized by the substitution of aspartic acid (GAT) by asparagine (AAT) (Grabowski et al., 2001). The Dutch and Iowa mutations occur within Aβ and result in increased resistance to proteolysis (Hall and Roberson, 2013). The Swedish APP K670N/M671L is a

double mutation at the β-secretase cleavage site (Hall and Roberson, 2013), on exon 16, in which lysine (AAG) and methionine (AAT) are replaced by asparagine (AAT) and leucine (CTG) (Mullan et al., 1992). This mutation results in increased Aβ40 and Aβ42 (the more toxic form) production (Hall and Roberson, 2013).

In the Tg-SwDI mice, Aβ accumulation in the cerebrum is extensive by 12 months (Van Vickle et al., 2008). These mice show impaired learning and memory in the Barnes maze task as early as 3 months of age (Xu et al., 2007). At 6 months of age, these mice start developing gliosis with a prominent increase in the number of glial fibrillary acidic protein (GFAP) positive astrocytes in several brain regions (Miao et al., 2005).

Little is known about the retinal cholinergic system in many of the AD animal models and whether they display retinal abnormalities. Because these retinal changes may parallel AD etiology in the brain and precede severe cognitive impairment, they may be instrumental in the early diagnosis of AD. Thus, in the current study we assessed whether the AD-related changes in the retina are analogous to the alterations reported in the rest of the brain and identified possible causes for visual dysfunction by quantifying AChR gene expression, cholinergic cell count, total retinal cell count and astrocytic gliosis in Tg-SwDI mice as compared to wild-type (WT). The Tg-SwDI mice showed a decrease in the number of retinal cells, gliosis and alterations in AChRs expression.

Experimental Procedures

All animals were maintained in accordance with the National Institute of Health Guide for the Care and Use of Laboratory Animals (NIH Publications No. 80-23, revised 1996), the Global Statement on the Use of Animals in Research (Federation of European Neuroscience Societies, Japan Neuroscience Society, International Brain Research Organization and Society for Neuroscience) and protocols approved by the University of Alabama at Birmingham Institutional Animal Care and Use Committee. The eyes of male and female transgenic animals, and age-matched male and female WT animals were harvested immediately following euthanasia. All graphs were generated with GraphPad Prism 6 (Graph Pad Prism, La Jolla CA) and histological representations (figures 3 and 8) were created with Adobe Photoshop CS2 (Adobe Systems, Mountain View, CA). Cartoon figures 1 and 9 were made with Microsoft PowerPoint (Microsoft Corporation, Redmont, WA) and Servier Medical Art PowerPoint Image Bank with modifications (Creative Common Attributions 3.0 Unported license; www.creativecommons.org/licenses/by/3.0/legalcode).

We characterized the retinal changes of male and female Tg-SwDI mice as compared to age-matched C57Bl6J WT in three age groups: young adult, 6.5 to 8 months old (mo) (WT mean age: 7.2 mo; Tg-SwDI mean age: 7.1 mo), middle-aged adult, 9 to 10 mo (WT mean age: 9.3 mo; Tg-SwDI mean age: 9 mo), and old adult, 14-15 mo (WT mean age: 14.6 mo; Tg-SwDI mean age: 14.2 mo). These ages are roughly comparable to human age groups and were chosen in order to ascertain age-related differences in AD pathology.

The following experiments were intended to answer this question: does the retina display the same AD-related changes observed in the rest of the brain: cholinergic system disturbances, cell loss and gliosis?

Quantitative polymerase chain reaction (*qPCR)*

qPCR was employed to identify alterations in the retinal cholinergic system by quantifying AChR expression. AChR RNA transcripts were measured using qPCR of RNA extracted from whole retina. Retinas for qPCR were dissected from the eyecup of mice immediately following euthanasia, flash frozen, and stored at -80°C. The RNAqueous -4PCR Kit (Ambion; Austin, TX) was used for RNA extraction and DNAse treatment per manufacturer's protocol. RNA underwent reverse transcription using the iScript cDNA synthesis kit (BioRad; Hercules, CA). The resulting cDNA and previously designed and optimized primers (Smith et al., 2014) were then added to a SYBR® green supermix (100 mM KCl, 40 mM Tris-HCl, pH 8.4, 0.4 mM each dNTP, 50 U/ml iTaq™ DNA polymerase, 6 mM $MgCl_2$, SYBR® Green I, 20 nM fluorescein) (BioRad; Hercules, CA) and amplified using a BioRad iQ5 real-time PCR detection system (BioRad; Hercules, CA). Matched cDNA concentrations and optimal primer conditions (concentration and annealing temperature) were used for all experiments. Gene expression was normalized to the ryanodine receptor as the housekeeping gene and quantified using the ΔΔCT method. Two-tailed independent t-tests were used to test the statistical significance ($p<0.05$) of fold changes. Non-template reactions were used as negative controls.

Immunohistochemistry (*IHC)*

IHC and fluorescence microscopy were used to determine whether AD-related changes, gliosis and cell loss, reported in the cerebrum are also evident in the retina. Retinas were obtained from WT and Tg-SwDI mice after euthanasia and fixed in 4% paraformaldehyde and processed as whole mounts as previously described (Smith et al., 2014). Images were collected with a Zeiss AxioPlan 2 fluorescent microscope equipped with an AxioCam HRm camera and filters: DAPI, FITC/GFP, TRITC/Cy3 and Cy5 (Carl Zeiss Microscopy LLC, Thornwood, NY). Each channel was scanned separately and saved as digital graphics files. Antibodies against choline acetyltransferase (ChAT) (EMD Millipore Cat# AB144P, RRID: AB_11214092) (cholinergic amacrine cells) and Hoechst nuclear dye (Thermo Fischer Scientific Cat# 33342) (total cell number) were used to identify cell populations in different retinal layers within eight demarcated regions of interest for statistical analysis. The layers in each of the regions of interest included the ganglion cell layer (GCL; ganglion cells and displaced amacrine cells), the inner and outer portions of the inner nuclear layer (iINL; amacrine cells and oINL; bipolar cells and horizontal cells) and in the outer nuclear layer (ONL; photoreceptors) (Fig. 1). Gliosis was assessed in the nerve fiber layer (NFL) with an antibody against GFAP (Dako Cat# Z0334, RRID: AB_10013382). In mammalian retinas, astrocytes are present solely in the vascular regions (Schnitzer, 1988) and mostly in the retinal NFL (Ramírez et al., 1996). Image J software was used for semi-automated cell counts and gliosis assessment

(Kimbrough et al., 2015). Statistical significance ($p<0.05$) was assessed using two-tailed independent t-tests.

Results

qPCR: *Tg-SwDI retinas had significant alterations in AChR gene expression in all age groups.* There were statistically significant differences in the expression of AChR transcripts in the Tg-SwDI mice retinas, as compared to WT, in all age groups. Table 1 shows the mean fold regulation ± standard error of mean (SEM) and exact p values for all AChR subunits/subtypes. Downregulation is shown in parentheses. The bars in figure 2 enable the graphic comparison of AChR regulation changes across all three age groups.

In the young adult Tg-SwDI (Fig.2; Table 1), there was upregulation of several nAChR subunit transcripts: α2, α3, α4, α5, α6, α7, β3 and β4. There was also downregulation in nAChR subunit transcripts α9 and α10, as well as m4 and m5 mAChR transcripts. In the middle-aged adult Tg-SwDI (Fig.2; Table 1) there was greater upregulation in many of the same nAChR subunit transcripts including α2, α3, α4, α5, α6, β3 and β4. However, α7 was no longer significantly upregulated while α9 nAChR and m1 mAChR transcripts were strongly upregulated. Transcripts for α10 nAChR subunits and m5 mAChRs remained downregulated. In the old adult Tg-SwDI (Fig.2; Table 1), no significant upregulation of any cholinergic receptor was evident. Instead, there was downregulation of α4, α7, α9, and α10 nAChR subunit transcripts, as well as in m4 and m5 mAChR transcripts.

IHC: Tg-SwDI retinas had fewer cells in several layers and significantly increased gliosis in the NFL. ImageJ was used in defined regions of interest for cell counts in each retinal layer and to measure GFAP area (percentage). The drawings were mapped back onto the original digital images to confirm accuracy (Fig. 3). The transgenic retinas displayed significant cell loss that differed across age groups. All of the IHC data are shown in parentheses as the mean number of cells per mm^2 for cell count, or as the mean GFAP percentage area, ± SEM and exact p-value for Tg-SwDI vs WT.

Tg-SwDI mice displayed reduced number of total cells in the GCL in young adults (6.75 ± 0.45 vs 8.16 ± 0.39, p= 0.0318) and middle-aged adults (6.88 ± 0.31 vs 9.46 ± 0.6, p= 0.0169), that was no longer evident in the old adults (Fig. 4). There were no differences in the number of cells in the oINL in any age group. Additionally, Tg-SwDI mice displayed reduced cell count in the iINL (10.15± 1.02 vs 14.55 ± 1.03, p= 0.0118) (Fig. 4) and ONL (31.21 ± 1.71 vs 38.44 ± 1.59, p= 0.0079) (Fig. 5) that was evident only in the young adult group.

In the Tg-SwDI mice, the specific loss of retinal cholinergic cells occurred after loss of non-cholinergic cells. Significant cholinergic cell loss occurred in the GCL in the middle-aged adult group (1.33 ± 0.07 vs 1.80 ± 0.07, p= 0.0133) but was not apparent in the INL until after 14 months of age (1.20 ± 0.04 vs 1.47 ± 0.01, p= 0.0244) (Fig. 6).

Except for young adults, Tg-SwDI mice displayed astrocytic gliosis in the NFL, demonstrated by a larger GFAP area than WT animals (Fig.7): middle-aged adults (15.20 ± 1.50 vs 13.90 ± 1.30, p< 0.0001) and old adults (15.70 ± 2.20 vs

12.60 ± 1.30, p< 0.0001). Conversely, WT mice exhibited age-dependent reduction in the retina's percentage area exhibiting GFAP- immunoreactivity between the young adult and old adult groups (13.70 ± 1.20 vs 12.60 ± 1.30, p= 0.0197) and between the middle-aged adult and old adult groups (13.90 ± 1.30 vs 12.60 ± 1.30, p= 0.0020). Figure 8 shows representative regions of GFAP immunoreactivity from WT (left column) and Tg-SwDI (right column) mice for each group: young adults (A and D), middle-aged adults (B and E) and old adults (C and F).

Discussion

The present study revealed for the first time that the retinal alterations in this mouse model of AD are similar to the AD-associated changes previously reported in the rest of the brain (Fig.9): cell loss, gliosis, and disturbances in the cholinergic system (Doraiswamy, 2002; Fodero et al., 2004; Francis et al., 2012). There was an initial upregulation in the expression of several AChRs genes in young adult Tg-SwDI that considerably increased in the middle-aged adults. These genes were downregulated in the old adult animals. These data are consistent with reports of compensatory regulation of AChRs in mouse retina (Smith et al., 2014) and with initial cholinergic neuroprotection in AD (Teaktong et al., 2003, 2004; Chu et al., 2005; D'Andrea and Nagele, 2006).

The activation of α7 nAChR attenuates Aβ toxicity, promotes cholinergic integrity, and can improve synaptic plasticity, cognition and neuronal survival by activating phosphoinositide-3 kinase (Hernandez et al., 2010; Echeverria and Zeitlin, 2012). Thus, in early AD, α7 activation may provide neuroprotection.

However, the activation of nAChRs results in a significant increase in tau phosphorylation, while mAChR activation may prevent it (Schliebs and Arendt, 2006). m1 activation is involved in the regulation of APP (Cowburn et al., 1996), while m2 mAChR activation may influence the modulation of tau and other proteins involved in AD (Hérnandez-Hérnandez et al., 1995). Thus, the upregulation of AChR subunits/subtypes in the retinas of younger animals, as a result of AD, may be part of a compensatory mechanism that attempts to mitigate the detrimental effects from the loss of non-cholinergic cells in the GCL and INL of the young adult animals. The upregulation of AChRs prior to loss of cholinergic cells suggests disruption of cholinergic function, although there is no loss of cholinergic cells in the young adult animals. Nonetheless, with increasing age and disease severity, this compensation can no longer attenuate the detrimental effects, especially the loss of cholinergic cells, produced by AD.

Cholinergic cell loss occurred in the GCL in the middle-aged adult group, but was no longer evident in old adults; however, these old adults displayed decreased numbers of cholinergic cells in the INL. The loss of cholinergic cells in the middle-aged adults and old adults is consistent with the course of AD in the cerebrum which also includes reduction in synaptic markers, such as ChAT and [^{3}H] hemicholinium-3 binding, levels of ChAT activity, ACh synthesis, AChR binding, and high-affinity choline uptake (Slotkin et al., 2001; Schliebs and Arendt, 2006; Francis et al., 2012).

GFAP-immunoreactivity in the NFL of transgenic mice increased not only relative to WT retinas, but was also higher in the old adults relative to the young

adults and middle-aged adults, which suggests that the AD-dependent gliosis is an age-related phenomenon. WT animals also exhibited age-related differences between the young adult and old adult groups, but for WT animals there was a reduction in astrocytic gliosis with increasing age. Taken together, AD plays a pivotal role in exacerbating gliosis in an age-dependent manner.

Our results indicate that the retinal cholinergic system alterations, gliosis and the reduction in retinal cell number may be, in part, responsible for the visual deficits that occur in AD. These data highlight the crucial role of the cholinergic system in AD pathology. Because of ACh's essential involvement in visual processing in healthy retinas (Schmidt et al., 1987; Kittila and Massey, 1997; Strang et al., 2005, 2007, 2010, 2015; Varghese et al., 2011), characterizing the AD-related changes in the retinal cholinergic system may provide a better understanding of the causes for visual dysfunction. Early diagnosis and support of the cholinergic system may help AD patients retain a higher level of functioning for an extended period of time.

The eye is the only part of the CNS that can be visualized noninvasively (Hill et al., 2014; MacGillivray et al., 2014) and it shares many features with the rest of the brain (MacCormick et al., 2015), making it an ideal candidate for the development of biomarkers to diagnose CNS disorders. Visual assessments, such as optical coherence tomography and electroretinography, have been widely used, for over a decade, to detect several diseases, such as cerebral malaria (MacCormick et al., 2015), stroke (Baker et al., 2008), diabetes mellitus (Cheung et al., 2010), hypertension (Wong and Mitchell, 2007), cardiovascular

disease (Liew et al., 2011), schizophrenia (Chu et al., 2012; Silverstein et al., 2015) and Parkinson's disease (Tian et al., 2011; Lee et al., 2014).

Due to the tremendous necessity to quickly diagnose AD and the high cost of other diagnostic techniques, such as positron emission tomography (Franzco et al., 2017) and magnetic resonance imaging (Kusne et al., 2016), researchers have begun employing numerous visual tests to detect differences in the eyes of individuals suffering from AD, as compared to healthy controls (Berisha et al., 2007; Moschos et al., 2012; Frost et al., 2013; Coppola et al., 2015; Snyder et al., 2016). All these data combined have yielded very important findings. AD is linked to thicker retinal inner plexiform layer (IPL) (Snyder et al., 2016), thinner retinal NFL (Danesh-Meyer et al., 2006; Iseri et al., 2006; Paquet et al., 2007; Kesler et al., 2011; Gao et al., 2015; Thomson et al., 2015), a reduced number in ganglion cell axons (Blanks et al., 1996b; Danesh-Meyer et al., 2006), narrowing of retinal veins with decreased blood flow (Berisha et al., 2007), higher number of astrocytes in the NFL (Blanks et al., 1996a, 1996b), Aβ accumulation in GCL, NFL, IPL, outer retina (Alexandrov et al., 2011; Koronyo-Hamaoui et al., 2011) and lens (Goldstein et al., 2003), reduced amplitude and increased implicit times in ganglion cell responses (Katz et al., 1989; Trick et al., 1989; Krasodomska et al., 2010; Moschos et al., 2012), increased levels of inflammatory marker complement factor H in the retina (Alexandrov et al., 2011), and abnormalities in eye fixation, saccadic and pursuit movements (Chang et al., 2014; Shakespeare et al., 2015).

Proponents in AD research suggest that the integration of non-invasive retinal examination techniques, at different time points, may be a valuable diagnostic tool for detecting the disease and tracking its progression, as the retinal alterations may reflect the anatomical and pathological changes that are occurring in the deeper brain regions (Kesler et al., 2011; Chang et al., 2014; Hill et al., 2014). If AD is detected in its early stages, treatment can commence promptly and therefore be more effective in prolonging the patient's quality of life by delaying cognitive impairment. The current studies support the idea that characterization of the retinal cholinergic system provides a tremendous opportunity to develop non-invasive biomarkers for dementia and AD (Ikram et al., 2012; Chang et al., 2014; Hill et al., 2014; Kusne et al., 2016; Lim et al., 2016).

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editing this manuscript. Alexis E. Lambert participated in data analysis. The senior authors Mark S. Bolding and Christianne E. Strang assisted in the writing and editing of this manuscript. Christianne E. Strang was also involved in experimental design, data collection and data analysis.

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Table 1. qPCR: Tg-SwDI as compared to WT

	Young adult		Middle-aged adult		Old adult	
	Mean ± SEM	*p* Value	Mean ± SEM	*p* Value	Mean ± SEM	*p* Value
α2	3.74 ± 0.38	0.0018	14.54 ± 0.60	0.0002	(1.53) ± 0.22	0.5111
α3	1.70 ± 0.24	0.0327	19.26 ± 0.74	0.0008	(1.95) ± 0.51	0.2903
α4	2.66 ± 0.37	0.0130	8.65 ± 0.59	0.0027	(5.07) ± 0.32	0.0283
α5	2.42 ± 0.28	0.0043	6.53 ± 0.55	0.0028	2.17 ± 0.63	0.3395
α6	1.87 ± 0.23	0.0122	19.35 ± 0.71	0.0003	(1.79) ± 0.55	0.3960
α7	2.52 ± 0.43	0.0447	1.02 ± 0.27	0.9341	(3.81) ± 0.33	0.0082
α9	(3.16) ± 0.45	0.0215	4.67 ± 0.38	0.0005	(6.30) ± 0.36	0.0266
α10	(7.12) ± 0.44	< 0.0001	(4.90) ± 0.54	0.0073	(7.90) ± 0.79	0.0278
β2	(1.02) ± 0.30	0.9516	(1.04) ± 0.26	0.8908	(1.09) ± 0.49	0.9037
β3	2.38 ± 0.21	0.0003	3.77 ± 0.37	0.0012	1.19 ± 0.48	0.6641
β4	2.96 ± 0.33	0.0024	5.17 ± 0.47	0.0045	(1.31) ± 0.35	0.7307
m1	1.24 ± 0.26	0.4139	13.32 ± 0.69	0.0023	2.14 ± 0.83	0.2053
m2	1.87 ± 0.42	0.1451	1.05 ± 0.58	0.9305	1.88 ± 0.38	0.4115
m3	1.05 ± 0.33	0.8854	1.26 ± 0.35	0.5177	1.51 ± 0.36	0.5142
m4	(2.58) ± 0.18	< 0.0001	(1.09) ± 0.35	0.7957	(3.26) ± 0.40	0.0416
m5	(6.11) ± 0.54	0.0029	(8.48) ± 0.60	0.0024	(5.75) ± 0.91	0.0007

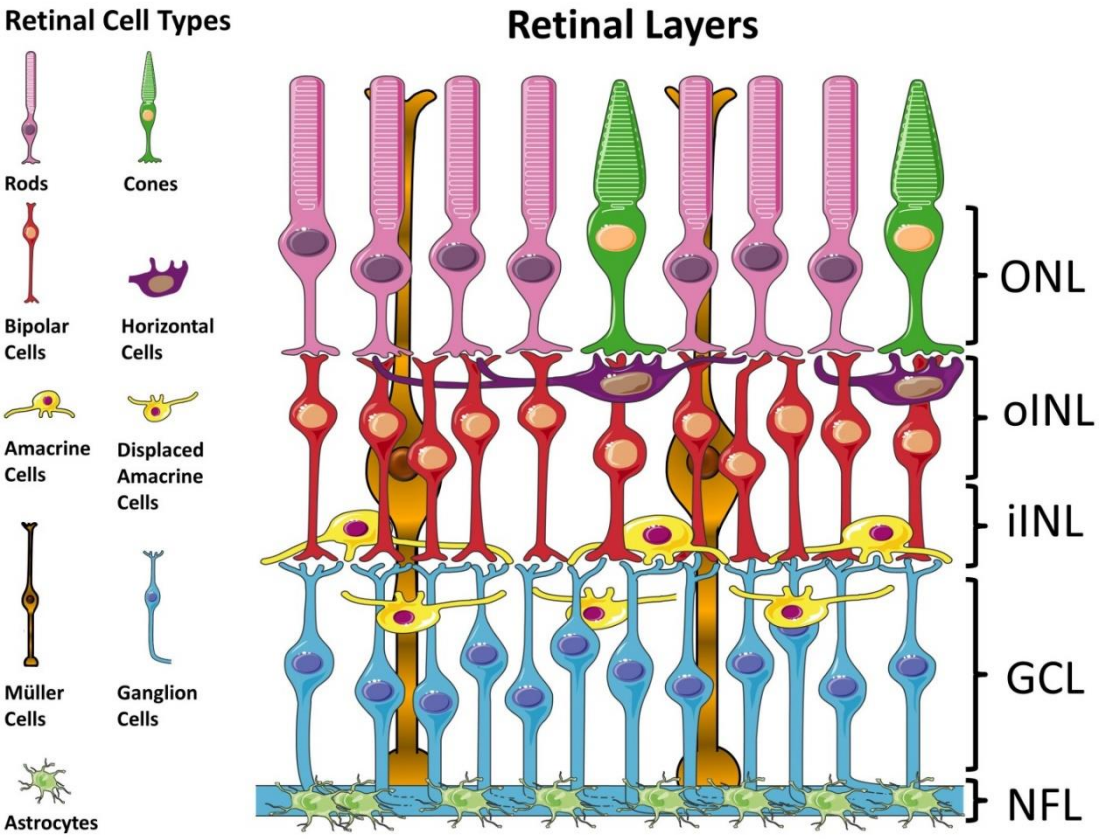

Figure 1. Retinal layers and cell types. This cartoon shows the cells types contained in each retinal nuclear layer. The labels on the right correspond to the layers imaged for cell count and astrocytic gliosis. ONL= photoreceptor cell bodies. oINL= horizontal and bipolar cell bodies. iINL=amacrine cells, including the population of cholinergic amacrine cells. GCL= ganglion cells and displaced amacrine cells, including the population of displaced cholinergic amacrine cells. NFL= astrocytes

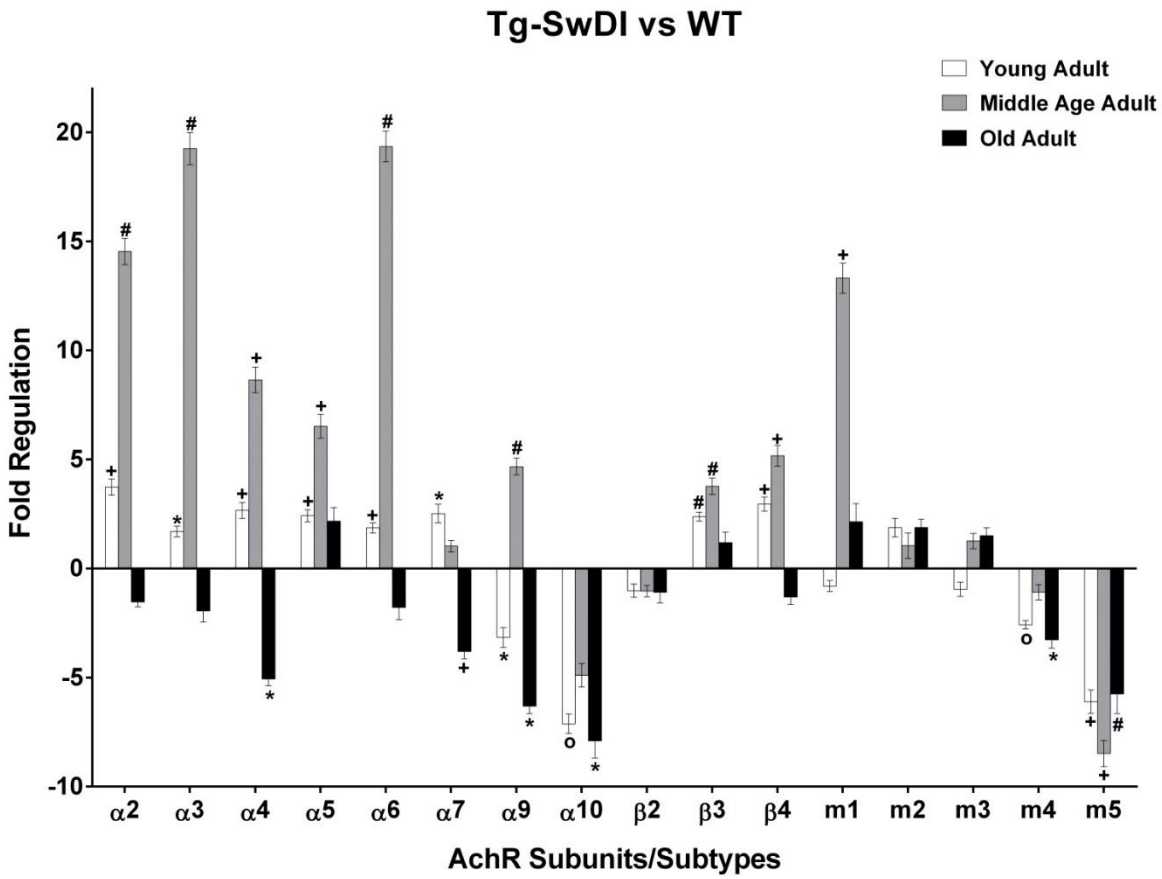

Figure 2. AChR gene expression. Young adults: Tg-SwDI (n=17) when compared to age-matched WT (n=18), displayed upregulation in several AChR genes and downregulation in α9 and α 10 nAchR and m4 and m5 mAChR. Middle age adults: Tg-SwDI (n=11) exhibited substantial upregulation in several AChR genes and downregulation in α10 nAchR and m5 mAChR, as compared to age-matched WT (n=9). Old adults: Tg-SwDI (n=15) revealed downregulation in several AChR genes, as compared to age-matched WT (n=12). (*) $p<0.05$; (+) $p<0.01$; (#) $p<0.001$; (o) $p<0.0001$. Error bars represent SEM.

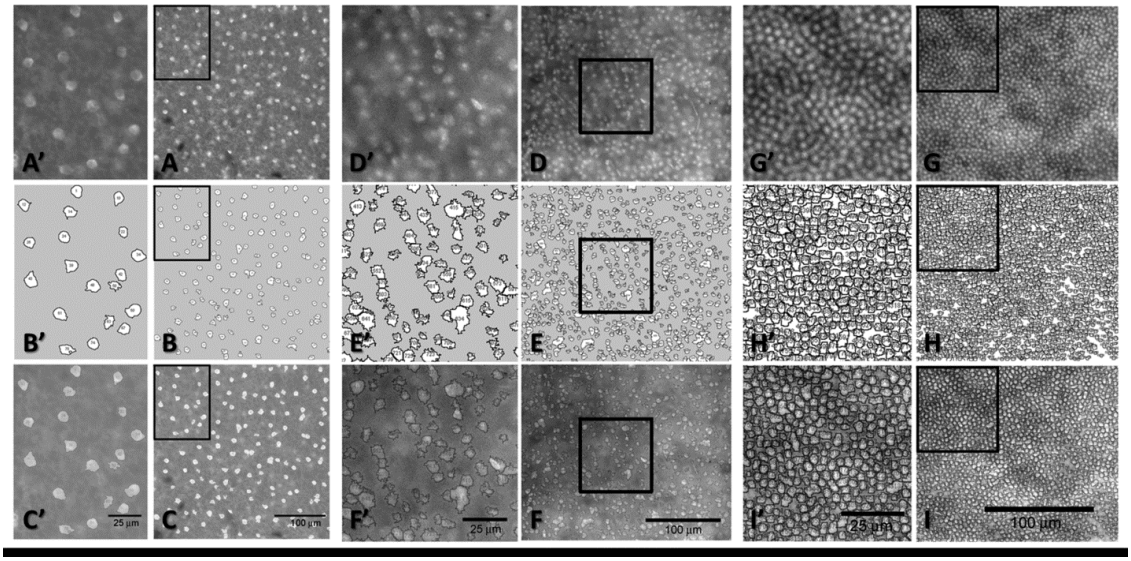

Figure 3. Histological representation of semi-automated cell counts performed in Image J in a Tg-SwDI mouse in the INL (ChAT) (A-C), GCL (Hoescht) (D-F) & ONL (Hoescht) (G-I). Panels A'-I' are the increased magnification of the black rectangles in panels A-I.

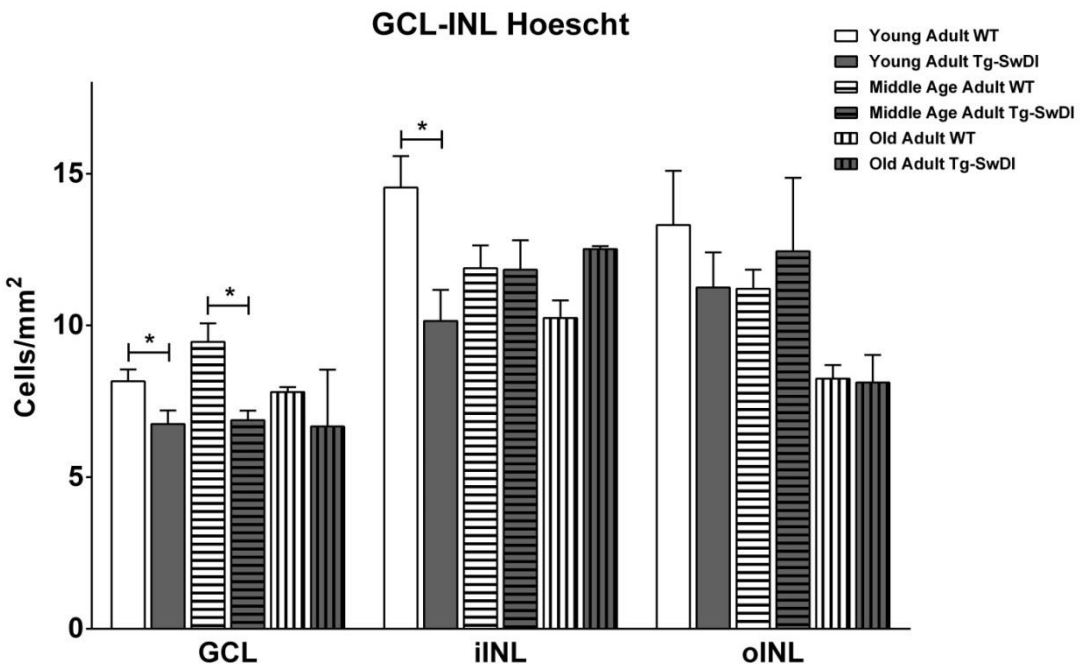

Figure 4. Tg-SwDI showed a reduced total number of cells per mm² in the GCL in the young adult [Tg-SwDI (n=72); WT (n=56)] and middle age adult [Tg-SwDI (n=56); WT (n=48)] groups and iINL in the young adult group [Tg-SwDI (n=72); WT (n=56)]. (*) $p<0.05$. Error bars represent SEM.

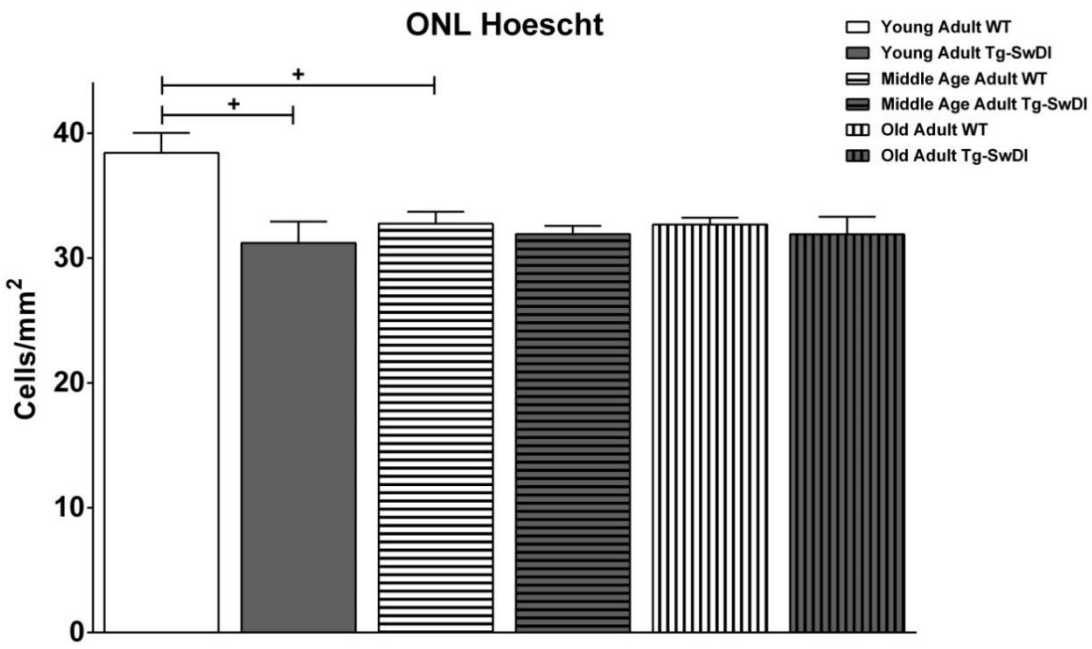

Figure 5. Tg-SwDI showed a reduced total number of cells per mm^2 in the ONL in the young adult group [Tg-SwDI (n=72); WT (n=56)]; (+) $p<0.01$. Error bars represent SEM.

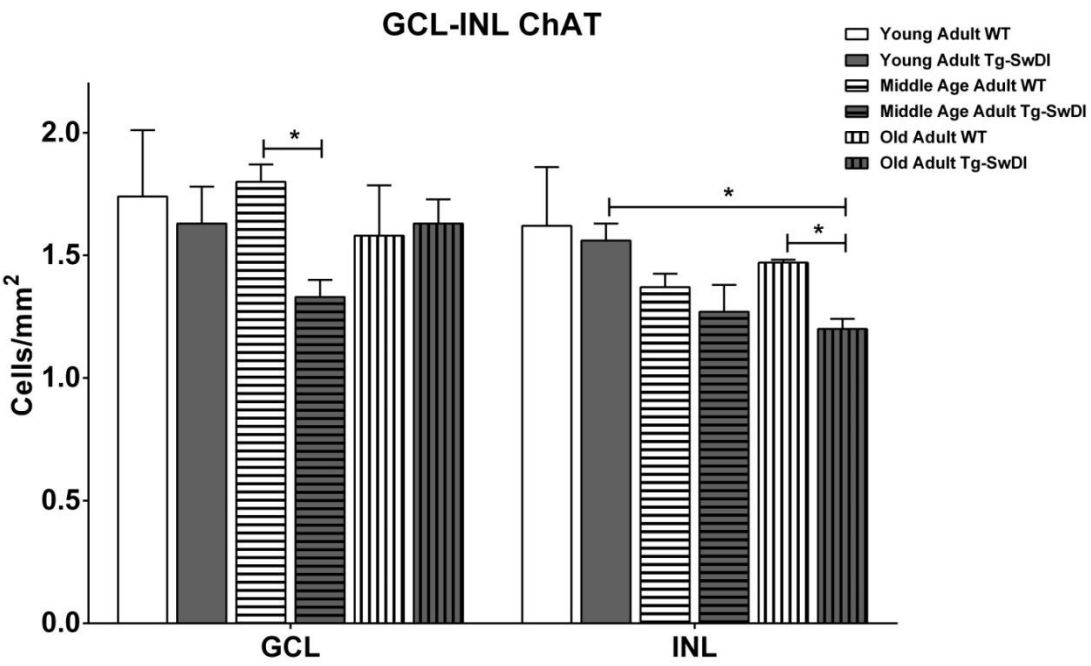

Figure 6. Tg-SwDI, as compared to age-matched WT, had fewer cholinergic cells per mm² in the GCL in the middle age adult group [Tg-SwDI (n=42); WT (n=42)] and INL in the old adult group [Tg-SwDI (n=24); WT (n=24)]. (*) $p<0.05$. Error bars represent SEM.

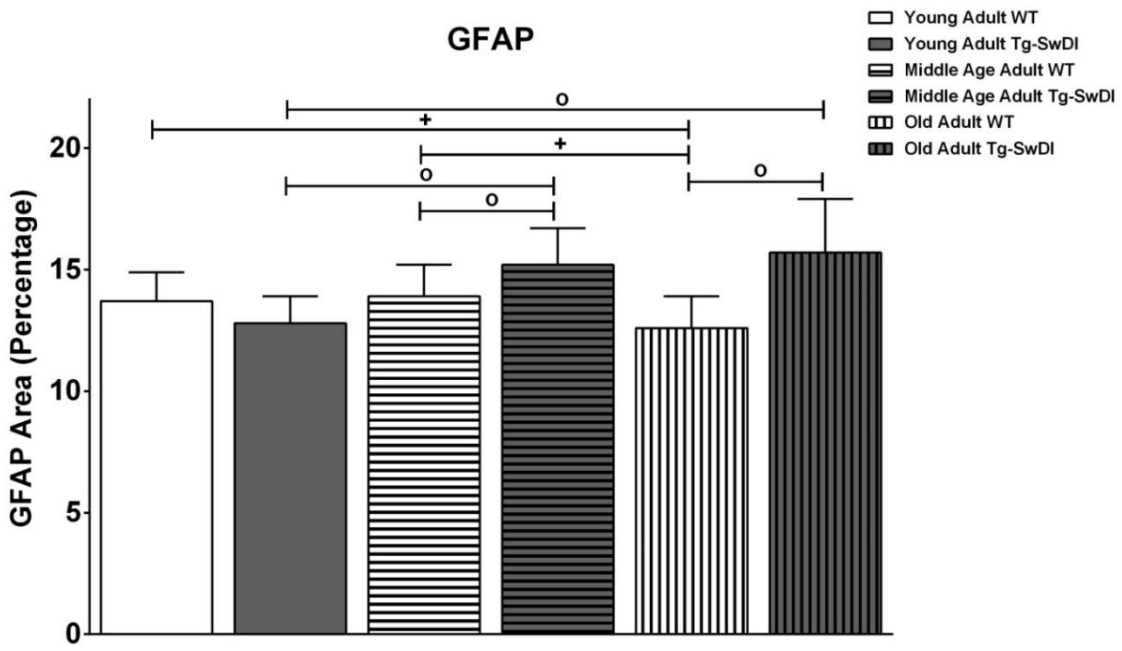

Figure 7. Tg-SwDI had more gliosis, larger GFAP area (percentage), than WT in the middle age adult [Tg-SwDI (n=58); WT (n=60)] and old adult [Tg-SwDI (n=16); WT (n=24)] groups. (*) $p<0.05$; (+) $p<0.01$; (o) $p<0.0001$. Error bars represent SEM.

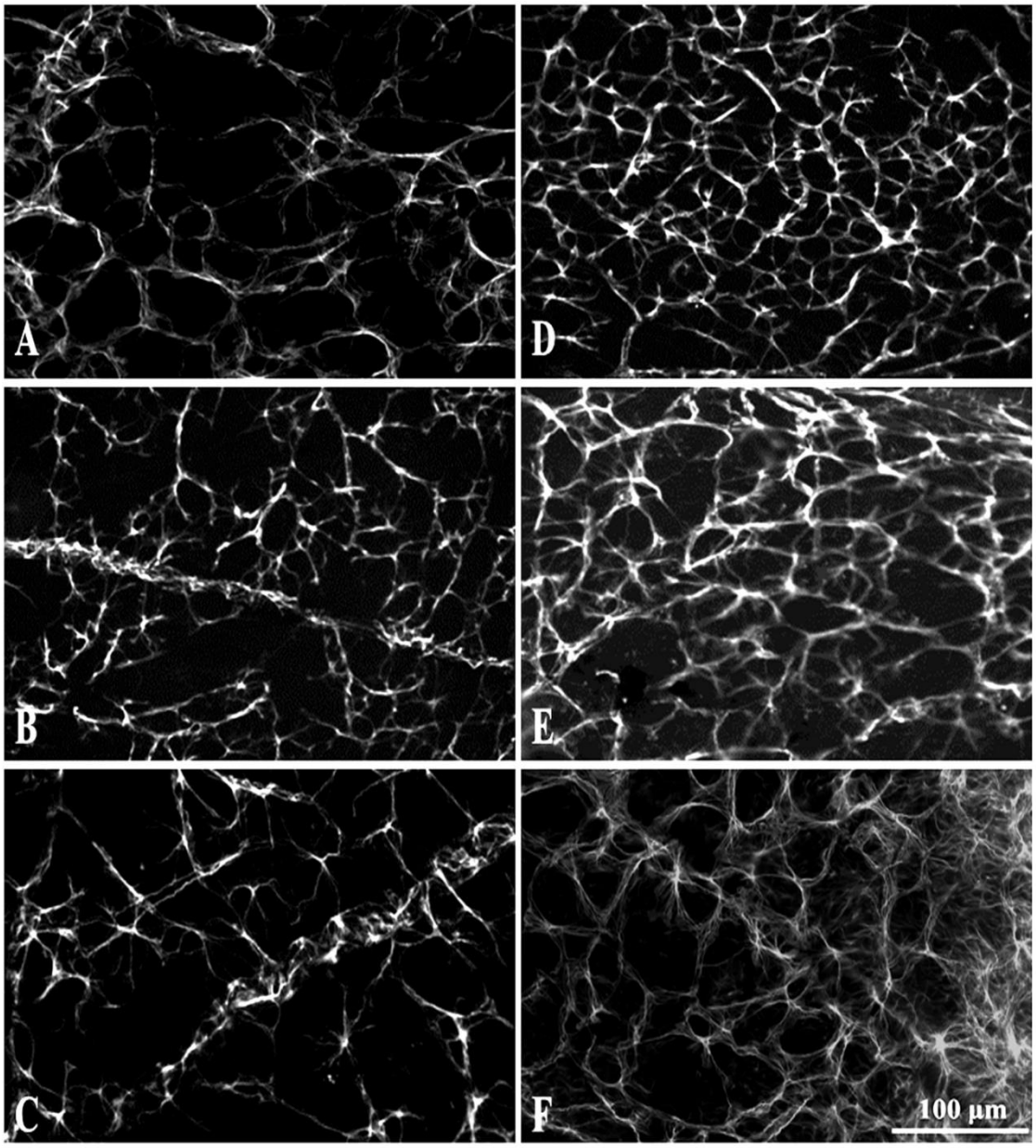

Figure 8. Tg-SwDI (D-F) showed significantly more gliosis than WT (A-C) in the middle age adult and the old adult groups. Panels A and D (young adults), B and E (middle age adults), C and F (old adults). Scale bar 100 µm.

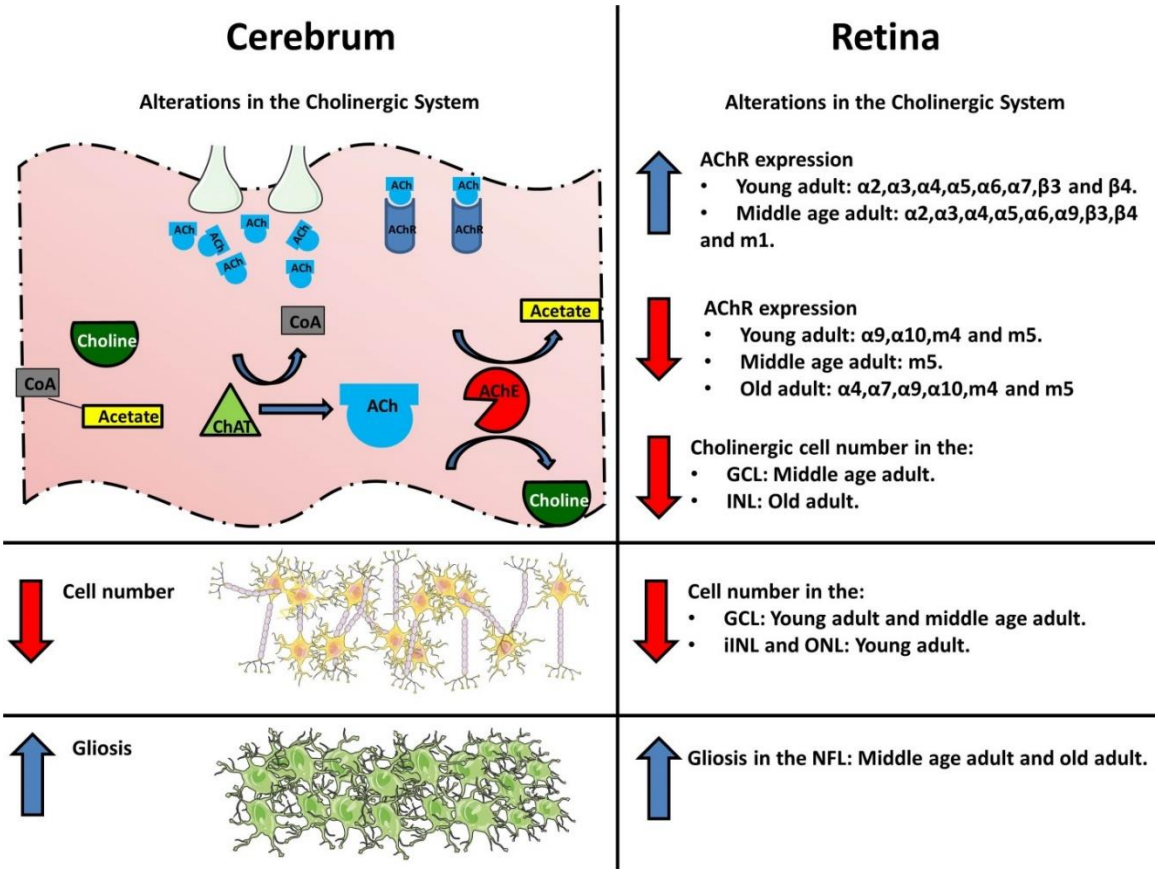

Figure 9. The current study demonstrated that known, previously published (Doraiswamy, 2002; Francis et al., 2012, Fodero et al., 2004), AD-associated changes in the cerebrum (left) were also present in the retina (right). Transgenic animals showed dysregulation in the cholinergic system, cell loss and gliosis.

ELECTRORETINOGRAPHY (ERG) AS A POTENTIAL DIAGNOSTIC TOOL FOR ALZHEIMER'S DISEASE

by

FRED G. OLIVEIRA-SOUZA, MARCI L. DERAMUS, ANTHONI M. GOODMAN, CHRISTIANNE E. STRANG, MARK S. BOLDING, LORI L. MCMAHON, TIMOTHY W. KRAFT.

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Electroretinography (ERG) as a Potential Diagnostic Tool for Alzheimer's Disease

Fred G. Oliveira-Souza[1], Marci L. DeRamus[1], Anthoni M. Goodman[3], Christianne E. Strang[3], Mark S. Bolding[4], Lori L. McMahon[2], Timothy W. Kraft[1].

[1]Optometry and Vision Science, University of Alabama at Birmingham, Birmingham, AL, [2]Cell, Developmental and Integrative Biology, University of Alabama at Birmingham, Birmingham, AL, [3]Psychology, University of Alabama at Birmingham, Birmingham, AL,[4]Radiology, University of Alabama at Birmingham, Birmingham, AL.

Corresponding author: Timothy W. Kraft (email address: twkraft@uab.edu; Phone number: 205-9752885; Fax number: 205-9345725; Physical address: 1720 2nd Ave S, VH 346B, Birmingham, AL 35294-0019.

Abstract

Alzheimer's disease (AD) is a devastating form of dementia that is symptomized by disruptions in several neurotransmitter systems, memory deficits, cell loss, and pathological protein processes. In addition to cortical disturbances, visual deficits have also been reported in AD, and may occur before the appearance of any noticeable cognitive impairment. Thus, we postulate that the use of visual assessment techniques, such as electroretinography (ERG), will demonstrate to be a valuable tool for the diagnosis of AD. To validate our hypothesis, we measured the amplitude and implicit time of responses from retinal cells through ERG in male

TgF344-AD rats and wild-type (WT) rats at 9 and 16 months of age. As compared to age-matched WT, 9-month old transgenic animals exhibited higher responses from several retinal cells, but lower responses from off bipolar cells and Müller cells, at neutral density (ND) 0.0; lower photoreceptor responses, at ND 2.4, and lower scotopic critical flicker fusion threshold at 16 months. 16-month old TgF344-AD rats also showed a higher implicit time for on bipolar cell responses, at several light intensities. These data collectively indicate that AD pathology affects the retinal cell responses and that ERG can be utilized as a reliable means to detect AD-related visual changes to ultimately serve as an efficient method for the timely diagnosis of the disease.

Keywords: Alzheimer's disease diagnosis, electrophysiology, in vivo, vision, Alzheimer's disease biomarkers, TgF344-AD, presenilin mutation, amyloid precursor protein mutation, Alzheimer's disease.

Abbreviations

- **Aβ: Amyloid beta**
- **AD: Alzheimer's Disease**
- **APP: Amyloid precursor protein**
- **CFF: Critical flicker fusion**
- **ChAT: Choline acetyltransferase**
- **CNS: Central nervous system**
- **DA: Dark-adapted**
- **ERG: Electroretinography**
- **GCL: Ganglion cell layer**
- **IPL: Inner plexiform layer**
- **ISI: Inter-stimulus interval**
- **LA: Light-adapted**
- **mAChR: Muscarinic acetylcholine receptor**
- **MMSE: Mini-Mental Sate Examination**
- **mo: Months old**
- **ND: Neutral density**
- **NFL: Nerve fiber layer**
- **ONL: Outer nuclear layer**
- **OP: Oscillatory potential**
- **RPE: Retinal pigment epithelium**
- **PS1: Presenilin 1**
- **PS1ΔE9: Δ exon 9 mutant human presenilin-1**

- **RPE: Retinal pigment epithelium**
- **TgF344-AD: Transgenic Fischer 344 Alzheimer's Disease**
- **SEM: Standard error of mean**
- **WT: Wild-type**

Originally described by Lois Alzheimer in 1906, Alzheimer's disease (AD) is a devastating, and the most common form, of dementia. It is symptomized by circadian rhythm dysfunction and the emergence of numerous cognitive abnormalities, including unusual thinking and behavior, memory impairment, apraxia, aphasia, agnosia and confusion (American Psychiatric Association, 2013; La Morgia et al., 2015). In the cerebrum, AD is manifested by gliosis, accumulation of amyloid beta (Aβ) plaques and neurofibrillary tangles (aggregates of hyper-phosphorylated tau protein), detrimental effects to synaptic integrity, reduction in the number of neuronal cells (Fodero et al., 2004), as well as substantial alterations in several neurotransmitter systems, especially the cholinergic and glutamatergic systems (Doraiswamy, 2002; Francis et al., 2012).

In addition to cognitive disturbances, alterations in visual perception have also been reported in AD, even in its early stages (Cronin-Golomb et al., 1991; Uhlmann et al., 1991), and may occur before the appearance of any noticeable cognitive impairment (Sadun et al., 1987; Katz and Rimmer, 1989). AD-related visual complications include decreased acuity, lower critical flicker fusion (CFF) threshold (Cronin-Golomb et al., 1991; Rizzo et al., 2000), and deficits in depth perception (Katz and Rimmer, 1989; Cronin-Golomb et al., 1991; Mendez et al., 1996; Lee and Martin, 2004), color discrimination (Katz and Rimmer, 1989; Cronin-Golomb, 1995), motion perception (Katz and Rimmer, 1989; Jackson and Owsley, 2003; Lee and Martin, 2004), temporal resolution, stereopsis (Cronin-Golomb et al., 1995; Rizzo et al., 2000) and contrast sensitivity (Cronin-Golomb et al., 1991; Hutton et al., 1993; Gilmore and Whitehouse, 1995). In 1906, Alois

Alzheimer was the first to report the occurrence of visual disturbances in one of his patients Auguste Deter (Maurer et al., 1997; Kusne et al., 2016). The effects of AD on higher visual functions, such as visual attention, can have a deleterious impact on people's routine activities such as route navigation, reading, face recognition, object localization and identification (Rizzo et al., 2000).

Currently, there are approximately 5.3 million reported cases of AD in the United States alone, and more than 26 million worldwide. Due to increasing life expectancy, AD's prevalence is estimated to quadruple by 2050 (Tsai et al., 2014). In the United States, the monetary cost of dementia treatment in 2010 was over 157 billion dollars (Hurd et al., 2013). By 2040, based on Aging, Demographics, and Memory Study prevalence rates, the monetary costs for dementia are projected to be between 379 to 511 billion dollars (Hurd et al., 2015). These estimations are extremely alarming, because AD is currently incurable, definitive diagnosis can only be achieved through autopsy, treatment is only palliative (placate cognitive deficits rather than extinguishing them) and existing detection methods lack the ability to identify the disease in its early phases, where treatment would be more effective at extending patients' intellectual faculties.

Presently, AD research relies vastly on animal models that express mutations in the presenilin (1 and 2) proteins and/or in the amyloid precursor protein (APP) gene. All of the known hereditary, autosomal dominant, AD mutations result in abnormal APP processes that increase the production of toxic Aβ (40 and 42) (Hall and Roberson, 2013). Aβ is a peptide formed from the

cleavage of APP by the enzymes β-secretase and ϒ-secretase (which is composed of presenilin and other components) (De Strooper et al., 1998; Edbauer et al., 2003). The most common AD animal models are generated in mice, but they generally fail to recapitulate several key aspects of AD pathology, such as robust tauopathy and extensive neuronal loss (Wyss-Coray et al., 1997; Oddo et al., 2003; Padmanabhan et al., 2006; Colton et al., 2008). Rats are 4-5 million years closer to humans than mice (Yang et al., 2004) and may serve as a better model for human diseases. Thus, transgenic Fischer 344 Alzheimer's Disease (TgF344-AD) rats were used in the current study. This AD animal model is generated on a Fischer 344 background by co-injecting rat pronuclei with two human genes driven by the mouse prion promoter: Swedish mutant human APP 695 and Δ exon 9 mutant human presenilin-1 (PS1ΔE9)(Cohen et al., 2013). The Swedish K670N/M671L is a double mutation at the β-secretase cleavage site (Hall and Roberson, 2013), on exon 16, in which lysine (AAG) and methionine (AAT) are replaced by asparagine (AAT) and leucine (CTG), respectively (Mullan et al., 1992). This mutation results in increased Aβ40 and Aβ42 (the more toxic form) production (Hall and Roberson, 2013). TgF344-AD rats display age-dependent cerebral amyloidosis, tauopathy, gliosis, apoptotic neuronal loss, cognitive disturbance, and impaired learning and memory(Cohen et al., 2013), Aβ plaques (in the hippocampus, cortex, and retina), hypertrophic retinal pigment epithelium (RPE) cells, inflammatory cells, choroidal thinning and upregulation of complement factor C3 (Tsai et al., 2014). They also have lower visual acuity,

even though there are no reported significant differences in retinal ganglion cell number and retinal vasculature at 14 or 19 months of age (Tsai et al., 2014).

The generation of animal models has prominently advanced our understanding of AD's pathological manifestations and has led to the development of medications designed to extend patients' level of independence and well-being by alleviating cognitive deficits. The general consensus among researchers and clinicians is that commonly prescribed AD medications, acetylcholinesterase inhibitors and N-methyl-D-aspartate receptor antagonists, are exponentially more effective when administered earlier in the course of the disease, before the onset of mild cognitive impairment. Early intervention necessitates early detection, but in spite of strenuous ongoing research efforts, spanning over a century, the pressing need to establish an effective tool to promptly identify the disease still remains (Brookmeyer et al., 1998; Sloane et al., 2002; Levey et al., 2006; Miller and Drachman, 2006; Welsh-Bohmer, 2008; Petersen, 2009; Wilson et al., 2010; Frost et al., 2013). Based on the notion that AD-related visual disturbance precede cerebral changes (Uhlmann et al., 1991; Cronin-Golomb et al., 1995), the current study intended to determine possible alterations in retinal responses due to AD pathology and age, as well as to evaluate electroretinography (ERG) as a viable method to detect those changes in TgF344-AD rats, as compared to age-matched wild-type (WT). ERG is a noninvasive procedure, recorded from the corneal surface of the eye, used to measure the electrical activity of retinal neurons in response to light stimuli in various luminance levels (Clark and Kraft, 2012) to simulate the different

classifications of vision: scotopic, mesopic and photopic. Scotopic vision, primarily driven by rod photoreceptors, is achromatic and occurs in the presence of very dim light (e.g. nighttime). Photopic vision, responsible for color perception, occurs primarily due to cones and occurs under well-lit (e.g. daytime) conditions. Mesopic vision, a mixture between scotopic and photopic vision, originates from the combination of rods and cones responses and occurs in moderate luminance levels (e.g. twilight). Vision occurs when photoreceptors are activated by light and relay the perceptual information, with the aid of other retinal cells (bipolar, amacrine and horizontal), to ganglion cells, which in turn, transmits the visual information to the rest of the brain (Figure 1). ERG is the main technique to measure the electrophysiological responses from retinal cells. Our results showed that transgenic rats displayed abnormal responses in several retinal cell populations and higher implicit times at several light intensities.

Experimental Procedures

All animals were handled and maintained in accordance with the principles of the Association for Research in Vision and Ophthalmology Statement for the Use of Animals in Ophthalmic and Vision Research, the National Institute of Health Guide for the Care and Use of Laboratory Animals (NIH Publications No. 80-23, revised 1996), the Global Statement on the Use of Animals in Research (Federation of European Neuroscience Societies, Japan Neuroscience Society, International Brain Research Organization and Society for Neuroscience) and protocols approved by the University of Alabama at Birmingham Institutional Animal Care and Use Committee. Animal colony was housed and bred in an

animal facility at the University of Alabama at Birmingham, illuminated by fluorescent lights (mean luminance = 140 lux) under cyclic (12-hour light and 12-hour dark) conditions.

Figure 1 was generated with Microsoft PowerPoint (Microsoft Corporation, Redmont, WA) and Servier Medical Art PowerPoint Image Bank with modifications (licensed under a Creative Common Attributions 3.0 Unported license; https://creativecommons.org/licenses/by/3.0/legalcode). Figure 2 was generated with IGOR PRO (Wavemetrics Inc., Lake Oswego, OR), Microsoft PowerPoint (Microsoft Corporation, Redmont, WA) and Servier Medical Art PowerPoint Image Bank with modifications (licensed under a Creative Common Attributions 3.0 Unported license; https://creativecommons.org/licenses/by/3.0/legalcode). All bar graphs were generated with GraphPad Prism 6 (Graph Pad Prism, La Jolla CA). IGOR PRO (Wavemetrics Inc., Lake Oswego, OR) was used for data analysis and the generation of graphs with representative responses.

ERG

ERG was employed to identify AD-related alterations in retinal cells' physiological responses under different light intensities in male TgF344-AD rats and age-matched male WT in two age groups: 9 months old (mo) [WT (n=6) mean age: 9.1 mo; TgF344-AD (n=5) mean age: 9.1 mo] and 16 mo [WT (n=11) mean age: 16.1 mo; TgF344-AD (n=13) mean age: 16.2 mo]. These age groups were chosen to establish age's involvement in ERG responses.

We quantified, under different recording conditions, the amplitude and implicit time of responses from several retinal cell populations. Implicit time refers to the time interval between response onset and its maximum amplitude. The following measurements were obtained: a-waves (photoreceptors: rods and cones), b-waves (on-bipolar cells), c-waves (RPE cells and Müller cells), d-waves (off-bipolar cells), photopic negative responses (ganglion cells), oscillatory potentials (OPs) and CFF threshold (Figure 2). OPs, believed to be generated predominantly by amacrine cells, are small high-frequency wavelets present in the ascending phase of the b-wave (Ogden, 1973; Wachtmeister and Dowling, 1978; Wachtmeister, 1998; Tzekov and Arden, 1999; Hancock and Kraft, 2004). CFF threshold can be defined as the lowest frequency at which a flickering light elicits the same retinal response as a steady light of the same luminous intensity. Albino animals (such as the Fischer 344 rats) display attenuated (or absent) c-waves (Pautler and Noell, 1976; Weidner, 1976; Graves et al., 1985), therefore our assessment focused primarily on measuring the initial corneal negative deflection component of c-waves. Rats were sedated with 3% isoflurane in a chamber and then anesthetized via intraperitoneal injection of xylazine (9.09 mg/kg) (AnaSed LA; VetOne, Boise, ID) and ketamine (90.9 mg/kg) (Zetamine; VetOne, Boise, ID). Corneas were anesthetized with 0.5% proparacaine hydrochloride (Apexa; Akorn, Inc., Lake Forest, IL). The pupils were dilated with topical 2.5% phenylephrine hydrochloride (Akorn, Inc., Lake Forest, IL) and 1% tropicamide (Akorn, Inc., Lake Forest, IL). The rat was placed in a Faraday cage with head fixed by a bite-bar and body temperature was maintained around 37^0 C

by a heating pad (Braintree Scientific, Braintree, MA), during experiments. The recording electrode (4 mm in diameter), composed of a platinum wire loop embedded in the tapered end of a hollowed out Plexiglas rod containing the fiber optic (Rubin and Kraft, 2007), was placed in the left eye. The reference electrode, a platinum wire loop, was placed in the non-stimulated contralateral eye. In order to ensure that the eyes remained moist while the animals were sedated, 2.5% hypromellose ophthalmic demulcent solution (Gonak; Akorn, Inc., Lake Forest, IL) was applied to both electrodes, and to both corneas, before and after recordings.

For CFF recordings, a green light emitting diode was used to generate flicker with stimulus frequencies 0.1 to 30 Hz for scotopic and 0.1 to 55 Hz for photopic intensities. For all other measurements, the light source was a 100-W tungsten-halogen lamp focused on to one end of a fiber optic. Stimulus duration was controlled with a shutter with a 6-mm aperture (Uniblitz; Vincent Associates, Rochester,NY). The energy output of the flashes was calibrated daily as the photon flux at the retinal surface in the Ussing chamber. Stimulus strength was controlled by a set of calibrated inconel neutral density (ND) filters that allowed attenuation in steps of approximately 0.3 log units up to a maximum of 6.9 log units attenuation. The unattenuated stimulus was calibrated daily with an optical power meter (Graseby Optronics, Orlando, FL). We used a 505 nm (35 nm bandwidth) stimulus that was determined by a three-cavity interference filter (Andover Co., Salem, NH). The amplifier (Astro-med CP122W; GrassTelefactor, W. Warwick, RI) was set to DC during CFF, c and d-waves measurements; and

to AC 1.0 for all the other measurements. Responses were amplified 2000 X and low-pass filtered at 300 Hz. The ERG voltage and stimulus monitor signals were digitized with hardware (MIO16) and software (LabView) from National Instruments, Austin, TX (Hancock et al., 2005; Rubin and Kraft, 2007). Rats were dark-adapted for at least 6 hours prior to recording. The protocol (Table 1) consisted of dark-adapted (DA), scotopic, and light-adapted (LA), photopic recordings with a wide array of light intensities, stimuli and inter-stimulus intervals (ISI). In order to isolate cone driven responses, photopic conditions, the eyes were exposed to an adapting (rod- saturating) background light for 3 minutes prior to the delivery of bright flashes.

Results

a-waves (photoreceptors). Transgenic animals displayed higher DA a-waves than WT (303.0 vs 226.7 μv) in response to bright stimulus (camera flash), at 9 months (Figures 3 and 4); but lower DA a-waves (ND 2.4) (20.3 vs 29.5 μv) at 16 months (Figure 4).

b-waves (on bipolar cells). There were no statistically significant differences in b-waves amplitude and implicit time between transgenic and WT groups at 9 months, but at 16 months, transgenic animals had higher b-waves at ND 3.6 (198.7 vs 156.1 μv) (Figure 5), and ND 2.4 (522.1 vs 425.8 μv) (Figures 5 and 6), but slower implicit time at NDs 2.4, 1.2, 0.6 and 0.0 (Figure 7).

a-wave to b-wave ratio. TgF344-AD rats displayed higher a-wave to b-wave ratio in response to a bright camera flash during LA conditions at 9 months;

but lower in the 16 mo group at NDs 3.6, 2.4, 1.2 and 0.6 during DA conditions (Figure 8).

Initial corneal negative deflection component of c-waves (Müller and RPE cells): As compared to WT, 9 mo TgF344-AD rats had higher response amplitude (Figures 9 and 10) and faster implicit time at ND 0.0 (Figure 11), but at 16 months, there were no statistically significant differences in amplitude or implicit time. Interestingly, it was entirely absent in 16 mo in both transgenic and WT rats at ND 0.0. This is likely due to hypertrophic RPE cells (Tsai et al., 2014) and pigment deficiency in the RPE.

d-waves (off bipolar cells): Transgenic rats, at 9 months, had higher d-waves at NDs 2.7 and 1.5 (Figure 12), but lower at ND 0.0 with slower implicit time (Figure 13). 16 mo TgF344-AD also displayed significantly higher amplitude d-waves than WT, but only at ND 3.3 (Figures 12 and 14).

CFF (photoreceptors): There were no statistically significant differences at 9 months, but at 16 months, TgF344-AD had lower scotopic CFF than WT (Figures 15 and 16).

OPs (amacrine cells). TgF344-AD had higher DA OPs than WT in both age groups (Figure 17).

Photopic negative responses (ganglion cells): There were no statistically significant differences between TgF344-AD as compared to WT in either age group (Figure 18), which is consistent with a previous study that showed no significant differences in retinal ganglion cell number in TgF344-AD rats at 14 or 19 months of age (Tsai et al., 2014).

Discussion

Definitive diagnosis of the disease can only be attained postmortem through histopathological analysis of the brain to detect the presence of Aβ plaques and neurofibrillary tangles (Serrano-Pozo et al., 2011; Beach et al., 2012). Probable diagnosis of AD can be achieved somewhat anecdotally, through clinical assessment that relies greatly on mental status scales, self-reports and accounts from family members or caregivers. The most common and widely used mental status scale is the Mini-Mental Sate Examination (MMSE) (Folstein et al., 1975, 1983). This scale takes around 10 minutes to administer and evaluates cognitive function in the areas of visual construction, memory, orientation, calculation, attention, and language (Dick et al., 1984; Kurlowicz and Wallace, 1999; Wallace and Kurlowicz, 1999; B. and M., 2005; Galea and Woodward, 2005; Stein et al., 2012). The MMSE should not be perceived as a diagnostic test, it is merely a screening test with relatively modest sensitivity (Sheehan, 2012). Other ways for detecting AD involves expensive and/or invasive methods such as magnetic resonance imaging (Jagust et al., 2006; Davatzikos et al., 2008), positive electron tomography (Jagust et al., 1991; Engler et al., 2006; Barrio et al., 2008; Kusne et al., 2016; Franzco et al., 2017), and cerebral spinal fluid levels of Aβ 42 and tau (Diniz et al., 2008; Bouwman et al., 2009; Bateman et al., 2012; Fagan et al., 2014; Scheltens et al., 2016). These methods fail to detect AD before considerable cognitive decline has taken

place (Petersen, 2004). Because these assessment techniques may only detect amnestic (memory deficits) indicators of the disease, they lack the sensitivity to identify prodromal non-amnestic manifestations, such as deficits in visuospatial ability, which has been shown to occur three years prior to probable diagnosis (Johnson et al., 2009). Many postulate that treatment would be most effective if the disease is diagnosed sooner, thus clinical investigators are striving to move the diagnostic threshold for AD to earlier stages of progression (Brookmeyer et al., 1998; Sloane et al., 2002; Levey et al., 2006; Miller and Drachman, 2006; Petersen, 2009; Wilson et al., 2010; Frost et al., 2013).

For millennia, philosophy and poetry have described the eye as being the window to the soul. More recently, the scientific concept that the eye may serve as a window to the central nervous system (CNS) has been rapidly gaining popularity among researchers. The eye is an ideal candidate for the discovery of biomarkers for CNS diseases, as it is the only part of the CNS that can be visualized easily and noninvasively (Hill et al., 2014; MacGillivray et al., 2014), and the retina has many similarities with the rest of the brain (MacCormick et al., 2015). Optical coherence tomography, ERG and other visual tests have been extensively employed to detect numerous diseases, such as Parkinson's (Price et al., 1992; Harris et al., 1992; Inzelberg et al., 2004; Archibald et al., 2009, 2011, Bodis-Wollner, 2009, 2013; Tian et al., 2011; Albrecht et al., 2012a; Toner et al., 2012; Tsironi et al., 2012; Vitório et al., 2012; Kirbas et al., 2013b; Satue et al., 2013, 2014; Sauerbier and Ray Chaudhuri, 2013; Lee et al., 2014; Roth et al., 2014; Schneider et al., 2014; Yu et al., 2014; Garcia-Martin et al., 2014b;

Hipp et al., 2014; Mailankody et al., 2015; Slotnick et al., 2015; Chorostecki et al., 2015; Normando et al., 2016; Pillai et al., 2016; Weil et al., 2016; Hill et al., 2016), hypertension (Stanton et al., 1995; Wong and Mitchell, 2007; DellaCroce and Vitale, 2008), cerebral malaria (Lewallen et al., 1993; Beare et al., 2004; Maude et al., 2009; White et al., 2009; MacCormick et al., 2015), schizophrenia (Kim et al., 2005, 2006; Krishnan et al., 2005; O'Donnell et al., 2006; Balogh et al., 2008; Butler et al., 2008; Silverstein and Keane, 2011; Chu et al., 2012; Yoon et al., 2013; Lee et al., 2013; Bolding et al., 2014; Silverstein et al., 2015a, 2015b; Tschacher et al., 2015; Gagné et al., 2015), diabetes mellitus (Klein and Klein, 1995; Ewing et al., 1998; Nwosu, 2000; van Reyk et al., 2003; Cheung et al., 2010a; Ratchford et al., 2013), cardiovascular disease (Wong et al., 2006; Liew et al., 2011), multiple sclerosis (Kerrison et al., 1994; Patel and Lundy, 2002; Chen and Gordon, 2005; De Seze et al., 2006; Fisher et al., 2006; Kallenbach and Frederiksen, 2007; Henderson et al., 2008, 2010; Pueyo et al., 2008; Toledo et al., 2008; Frohman et al., 2008; Burkholder et al., 2009; Pula and Reder, 2009; Green et al., 2010; Khanifar et al., 2010; Petzold et al., 2010; Talman et al., 2010; Garcia-Martin et al., 2011, 2014a; Saidha et al., 2011; Sakai et al., 2011; Watson et al., 2011; Davies et al., 2011; Albrecht et al., 2012b; Gundogan et al., 2012; Chatziralli et al., 2012; Walter et al., 2012; Galetta et al., 2012; Klistorner et al., 2013; Ratchford et al., 2013; Balcer et al., 2015; Graham et al., 2016), CNS lymphoma (Buggage et al., 2001; Matsuyama et al., 2014), and stroke (Wong et al., 2001a, 2001b, 2002; Wong, 2004; Patton et al., 2005;

Baker et al., 2008; Kalesnykas et al., 2008; Cheung et al., 2010b, 2017; De Silva et al., 2010).

To address the immense urgency to detect AD in its early stages and the necessity to find better alternatives to replace costly and invasive diagnostic tools, visual assessment procedures have been employed to identify ocular differences in AD, as compared to healthy individuals (Katz and Rimmer, 1989; Granholm et al., 2003; Berisha et al., 2007; Moschos et al., 2012; Frost et al., 2013; Chang et al., 2014; Coppola et al., 2015; Snyder et al., 2016). These studies have determined that AD is associated with narrowing of retinal veins with decreased blood flow (Berisha et al., 2007; Williams et al., 2015), reduced number in ganglion cell axons (Blanks et al., 1996b; Danesh-Meyer et al., 2006), but higher number of astrocytes in the nerve fiber layer (NFL) (Blanks et al., 1996a, 1996b; Oliveira-Souza et al., 2017), thicker retinal inner plexiform layer (IPL) (Snyder et al., 2016), but thinner retinal NFL (Danesh-Meyer et al., 2006; Iseri et al., 2006; Paquet et al., 2007; Kesler et al., 2011; Kirbas et al., 2013a; Marziani et al., 2013; Ascaso et al., 2014; Shi et al., 2014; Thomson et al., 2015; Gao et al., 2015; Liu et al., 2015; Oktem et al., 2015), ganglion cell layer (GCL)(Garcia-Martin et al., 2016), choroid (Bayhan et al., 2015) and macula (Iseri et al., 2006), cell loss in increased levels of inflammatory marker complement factor H in the retina (Alexandrov et al., 2011), elevated oxygen saturation in retinal arterioles and venules (Einarsdottir et al., 2015), phosphorylated tau deposition in the NFL and GCL (Du et al., 2015), reduced amplitude and increased implicit times in ganglion cell responses (Katz et al.,

1989; Trick et al., 1989; Krasodomska et al., 2010; Moschos et al., 2012), abnormalities in pupillary responses to light (Fotiou et al., 2000, 2007; Granholm et al., 2003; Scinto, 2007), eye fixation, saccadic and pursuit movements (Chang et al., 2014; Shakespeare et al., 2015), Aβ accumulation in outer retina, NFL, IPL,GCL, (Alexandrov et al., 2011; Koronyo-Hamaoui et al., 2011), photoreceptors (Du et al., 2015) and lens (Goldstein et al., 2003), reduced cell number, including cholinergic cells, in several retinal layers and alterations in the retinal cholinergic system (Oliveira-Souza et al., 2017).

The current study revealed that TgF344-AD animals, as compared to age-matched WT, exhibited higher responses from several retinal cells, but lower responses, at neutral density (ND) of 0.0, from off bipolar cells, and RPE and Müller cells, at 9 months; at 16 months, lower photoreceptor responses, at ND of 2.4, and lower scotopic CFF threshold. 16-month TgF344-AD rats also showed a higher implicit time for on bipolar cell responses, at several light intensities. These data collectively indicate that AD pathology affects retinal responses and that ERG can be utilized as a reliable means to detect AD-related visual changes to ultimately serve as an efficient method for the diagnosis of the disease. Our results have shown that ERG is able to identify AD-related changes in TgF344-AD rats as early as 9 months of age, substantially earlier than the emergence of observable cognitive deficits. These rats only start showing learning and memory impairment at 15 months (Cohen et al., 2013). As the ocular changes may be analogous to the pathological alterations occurring in the cerebrum (Kesler et al., 2011; Chang et al., 2014; Hill et al., 2014), we believe that ERG in conjunction

with other ocular exams, such as optical coherence topography, may facilitate AD's early detection, tracking the disease progression and treatment efficacy. The results of the current study are congruent with the notion that characterizing AD-related visual changes may support the development of non-invasive biomarkers capable of detecting AD sooner (Ikram et al., 2012; Chang et al., 2014; Hill et al., 2014; Kusne et al., 2016; Lim et al., 2016). Detecting AD in its beginning phases would foster earlier therapeutical intervention, which could potentially increase treatment effectiveness in delaying the onset of cognitive deficits, thus extending the patient's quality of life.

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Authors' contributions: Fred G. Oliveira-Souza performed the vast majority of data collection, analysis, experimental design and manuscript preparation. Marci L. DeRamus and Anthoni M. Goodman assisted in editing this manuscript and performed data collection. Lori L. McMahon provided all the animals used in these experiments and assisted in editing this manuscript. Timothy W. Kraft, Mark S. Bolding and Christianne E. Strang assisted in the writing and editing of this manuscript. Timothy W. Kraft was also involved in experimental design and data analysis.

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Table 1. Experimental Protocol							
Dark Adapted Recordings							
		Stimulus					
	ND	Duration (ms)	Delay (ms)	Number of Sweeps	ISI (s)	Points/ Sweep	ms/ point
Scotopic Flashes	4.2	2	250	10	1.3	2000	0.50
	3.6			10	2.2		
	2.4			4	2.2		
	1.2			3	10.2		
	0.6			3	30.2		
	0.0			3	30.2		
Camera Flash	0.0			3	90.0		
CFF	3.6	5000	500	6	10	24000	0.25
DC Steps (c- and d-waves)	3.3	5000	500	5	12	18000	0.50
	2.7						
	1.5						
	0.0						
Photopic Negative	1.5	2	250	10	1.3	2000	0.50
	0.9						
	0.0						
Light Adaptation (3 minutes)							
Light Adapted Recordings							
Camera Flash	2.7	2	250	3	90	2000	0.50
CFF	0.0	5000	500	6	10	24000	0.25

Table 2. a-waves: Photoreceptors (Rods and Cones)					
9-Month-Old					
			Amplitude		
			WT	TgF344-AD	p-value
Scotopic Flashes		ND	Mean±SEM (μV)		
		4.2	4.1±0.5	4.6±0.7	0.52
		3.6	6.3±1.3	6.3±1.3	0.99
		2.4	11.9±2.6	7.6±1.6	0.22
		1.2	16.0±3.6	13.2±2.4	0.55
		0.6	25.7±4.2	27.5±3.7	0.76
		0.0	52.3±9.9	58.3±6.8	0.65
Camera Flashes	DA	0.0	226.7±21.4	303.0±24.0	0.04
	LA	2.7	156.8±13.4	195.6±16.6	0.10
16-Month-Old					
			Amplitude		
			WT	TgF344-AD	p-value
Scotopic Flashes		ND	Mean±SEM (μV)		
		4.2	11.0±0.6	10.4±0.7	0.54
		3.6	14.4±0.9	12.7±1.0	0.201
		2.4	29.5±2.4	20.3±1.8	0.0055
		1.2	51.0±2.4	45.3±2.5	0.12
		0.6	86.2±5.6	79.6±5.6	0.42
		0.0	134.1±7.1	133.8±8.9	0.98
Camera Flashes	DA	0.0	224.4±6.1	248.9±15.6	0.18
	LA	2.7	67.1±8.2	68.3±9.1	0.92

Table 3. b-waves: On Bipolar Cells								
9-Month-Old								
			Amplitude			Implicit Time		
			WT	TgF344-AD	p-value	WT	TgF344-AD	p-value
Scotopic Flashes		ND	Mean±SEM (μV)			Mean±SEM (ms)		
		4.2	22.8±3.1	25.38±5.42	0.67	117.4±14.7	77.5±11.1	0.07
		3.6	52.9±9.1	64.2±9.4	0.41	93.3±14.7	87.2±15.4	0.78
		2.4	240.8±44.1	329.6±46.6	0.20	103.4±6.8	103.62±9.3	0.99
		1.2	505.0±70.1	677.4±81.6	0.14	93.5±7.1	106.2±5.7	0.21
		0.6	553.2±71.0	768.2±76.6	0.07	75.0±2.1	82.9±3.2	0.07
		0.0	564.8±75.4	774.0±81.0	0.09	57.8±1.6	61.8±3.2	0.27
Camera Flashes	DA	0.0	718.5±67.4	894.2±84.0	0.13	67.0±2.2	59.7±7.8	0.36
	LA	2.7	406.7±33.0	429.6±36.7	0.65	45.3±2.1	45.1±4.9	0.96
16-Month-Old								
			Amplitude			Implicit Time		
			WT	TgF344-AD	p-value	WT	TgF344-AD	p-value
Scotopic Flashes		ND	Mean±SEM (μV)			Mean±SEM (ms)		
		4.2	70.2±6.9	83.8±5.1	0.12	82.8±7.1	96.4±6.2	0.16
		3.6	156.1±14.2	198.7±13.5	0.041	92.0±6.0	102.3±2.9	0.12
		2.4	425.8±25.7	522.1±34.5	0.041	87.1±2.7	101.3±4.3	0.014
		1.2	583.3±20.8	679.2±44.8	0.081	63.5±1.6	72.6±1.8	0.0015
		0.6	640.1±27.1	713.4±49.2	0.23	56.4±1.3	62.3±1.2	0.0035
		0.0	710.6±25.6	789.7±51.8	0.21	56.2±1.1	62.8±1.4	0.0023
Camera Flashes	DA	0.0	761.4±22.3	845.1±50.9	0.17	60.0±2.0	61.2±2.1	0.68
	LA	2.7	232.6±13.0	229.5±16.4	0.89	52.1±2.5	52.0±2.2	0.97

Table 4. a-wave/b-wave Ratio					
9-Month-Old					
			WT	TgF344-AD	p-value
Scotopic Flashes		ND	Mean±SEM (%)		
		4.2	21.1±5.2	19.9±3.8	0.99
		3.6	14.3±4.5	9.8±2.1	0.41
		2.4	5.8±1.6	2.4±0.5	0.089
		1.2	3.2±0.5	2.0±0.3	0.078
		0.6	4.6±0.3	3.6±0.4	0.097
		0.0	9.0±0.8	7.6±0.6	0.19
Camera Flashes	DA	0.0	31.7±1.4	34.4±1.9	0.27
	LA	2.7	37.5±2.1	45.6±1.0	0.0102
16-Month-Old					
			WT	TgF344-AD	p-value
Scotopic Flashes		ND	Mean±SEM (%)		
		4.2	17.5±2.1	13.2±1.4	0.086
		3.6	10.4±1.3	6.8±0.8	0.023
		2.4	7.2±0.6	4.2±0.6	0.003
		1.2	8.8±0.5	6.9±0.4	0.002
		0.6	13.4±0.6	11.3±0.5	0.011
		0.0	18.9±0.7	17.1±0.7	0.10
Camera Flashes	DA	0.0	29.6±0.8	29.6±0.8	0.99
	LA	2.7	28.0±2.5	28.6±2.4	0.86

Table 5. c-waves						
9-Month-Old						
	Amplitude			Implicit Time		
	WT	TgF344-AD	p-value	WT	TgF344-AD	p-value
ND	Mean±SEM (μV)			Mean±SEM (ms)		
3.3	56.1±7.8	51.6±8.2	0.73	293.2±32.9	307.5±27.0	0.78
2.7	137.5±15.3	117.1±14.3	0.41	265.8±17.1	253.5±7.6	0.6004
1.5	212.2±22.2	235.6±14.1	0.47	266.8±35.5	248.6±11.4	0.701
0.0	94.1±8.3	139.4±13.9	0.028	458.3±39.3	335.8±13.8	0.043
16-Month-Old						
	Amplitude			Implicit Time		
	WT	TgF344-AD	p-value	WT	TgF344-AD	p-value
ND	Mean±SEM (μV)			Mean±SEM (ms)		
3.3	147.3±8.9	136.1±12.6	0.49	171.3±24.9	210.2±18.3	0.21
2.7	171.2±12.2	178.6±17.1	0.74	160.4±30.1	209.1±22.9	0.21
1.5	105.5±9.3	129.7±13.8	0.18	249.5±27.3	290.7±32.6	0.36
0.0	Virtually Inexistent					

Table 6. d-waves: Off Bipolar Cells						
9-Month-Old						
	Amplitude			Implicit Time		
	WT	TgF344-AD	p-value	WT	TgF344-AD	p-value
ND	Mean±SEM (μV)			Mean±SEM (ms)		
3.3	118.2±9.1	144.8±13.4	0.16	169.0±12.3	184.0±5.0	0.38
2.7	91.4±8.4	127.5±11.8	0.048	151.4±15.8	137.0±12.8	0.55
1.5	63.3±4.3	83.1±6.4	0.042	147.2±8.4	133.5±8.3	0.33
0.0	111.8±3.7	94.8±2.2	0.0095	164.0±10.8	122.5±9.5	0.034
16-Month-Old						
	Amplitude			Implicit Time		
	WT	TgF344-AD	p-value	WT	TgF344-AD	p-value
ND	Mean±SEM (μV)			Mean±SEM (ms)		
3.3	92.2±4.7	111.3±5.6	0.019	115.1±6.5	121.8±8.0	0.54
2.7	76.3±3.5	85.1±4.6	0.16	103.0±5.5	113.3±6.5	0.25
1.5	64.9±3.8	65.5±3.0	0.89	104.0±7.2	112.0±6.0	0.401
0.0	98.2±4.5	104.5±5.6	0.41	83.2±5.7	88.3±5.7	0.54

Table 7. CFF (Photoreceptors: Rods and Cones) and Oscillatory Potentials (Amacrine Cells)						
9-Month-Old						
	CFF: Photoreceptors (Rods and Cones)			Oscillatory Potentials: Amacrine Cells		
	WT	TgF344-AD	p-value	WT	TgF344-AD	p-value
	Mean±SEM (Hz)			Mean±SEM (μV.s)		
DA	21.1±0.5	22.0±1.1	0.45	1.7±0.1	2.5±0.2	0.0085
LA	37.9±0.6	39.1±1.8	0.52	1.8±0.1	2.1±0.2	0.29
16-Month-Old						
	CFF: Photoreceptors (Rods and Cones)			Oscillatory Potentials: Amacrine Cells		
	WT	TgF344-AD	p-value	WT	TgF344-AD	p-value
	Mean±SEM (Hz)			Mean±SEM (μV.s)		
DA	30.1±1.0	26.5±1.3	0.048	1.5±0.1	1.9±0.1	0.016
LA	31.1±0.9	31.6±0.9	0.73	0.7±0.1	0.6±0.1	0.81

Table 8. Photopic Negative Responses: Ganglion Cells						
9-Month-Old						
	Amplitude			Implicit Time		
	WT	TgF344-AD	p-value	WT	TgF344-AD	p-value
ND	Mean±SEM (μV)			Mean±SEM (ms)		
1.5	20.9±2.7	21.5±4.1	0.92	114.5±2.1	107.4±4.7	0.201
0.9	70.9±7.5	82.4±9.8	0.39	126.7±4.1	124.8±1.6	0.704
0.0	112.1±11.4	142.4±12.7	0.12	153.5±6.2	154.2±7.9	0.95
16-Month-Old						
	Amplitude			Implicit Time		
	WT	TgF344-AD	p-value	WT	TgF344-AD	p-value
ND	Mean±SEM (μV)			Mean±SEM (ms)		
1.5	29.7±2.8	74.6±27.4	0.15	88.0±8.0	102.7±5.6	0.14
0.9	52.0±6.2	125.6±43.9	0.14	98.1±10.4	96.0±6.1	0.86
0.0	118.5±11.9	192.9±43.2	0.16	74.4±2.3	97.6±12.7	0.13

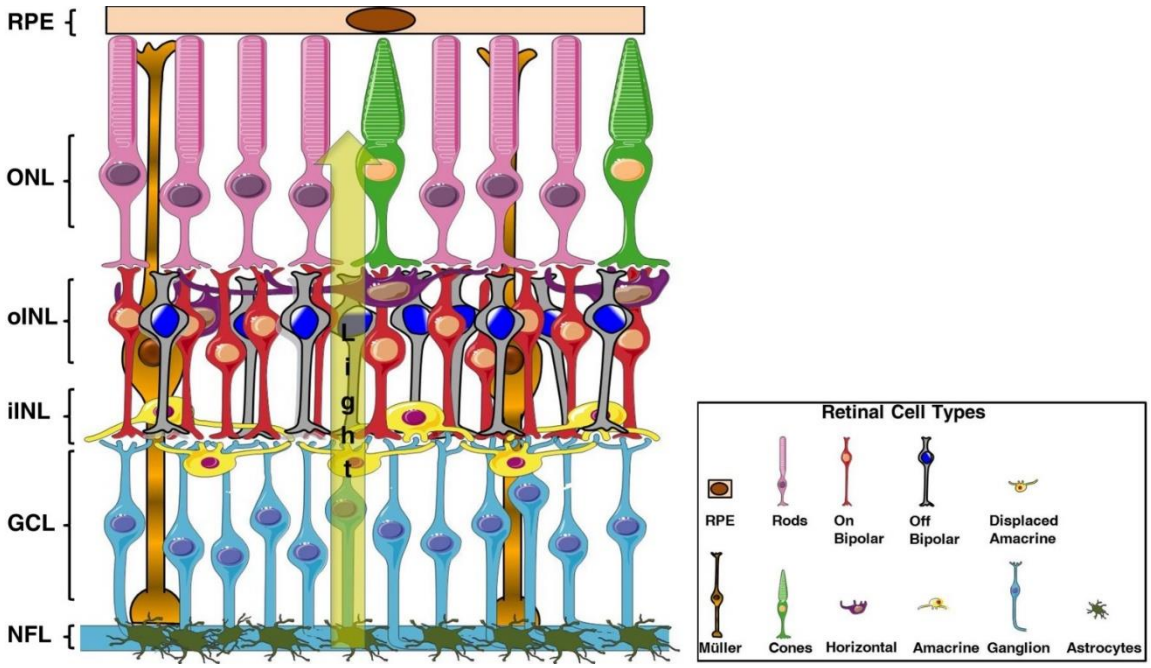

Figure 1. Retinal layers and cell types. This cartoon figure depicts the cell types contained in each retinal layer. Retinal pigment epithelium (RPE) = RPE cells. Outer nuclear layer (ONL) = photoreceptor cell bodies. Outer inner nuclear layer (oINL) = horizontal and bipolar cell bodies. Inner inner nuclear layer (iINL) = amacrine cells. Ganglion cell layer (GCL) = ganglion cells and displaced amacrine cells. Nerve fiber layer (NFL) = astrocytes.

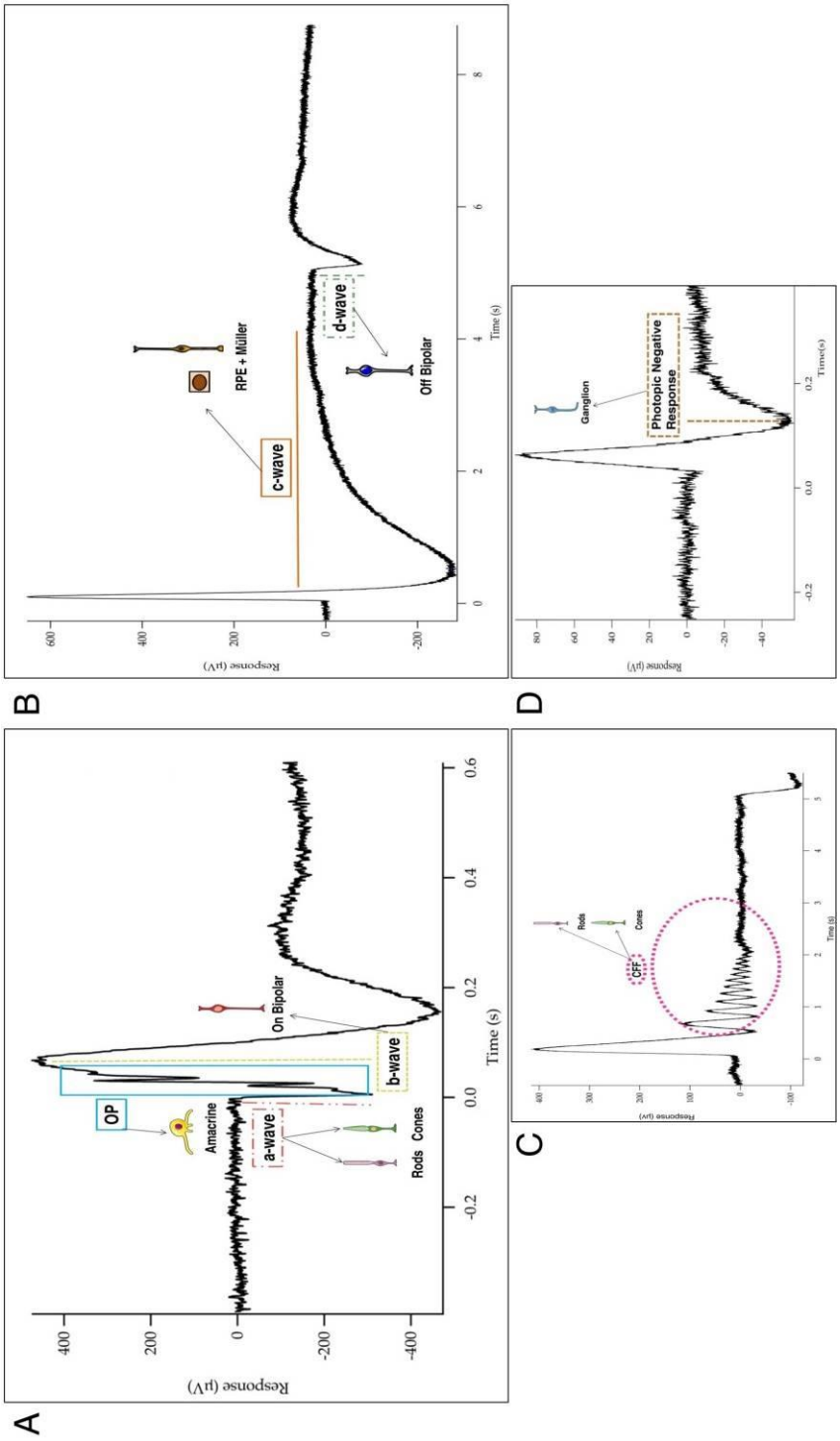

Figure 2. ERG responses and the cell types that elicit them. Panel A: a-wave represents photoreceptor (rods and cones) responses; b-wave originates from on

bipolar cell; oscillatory potential (OP) is from amacrine cells. Panel B: c-wave represents retinal pigment epithelium (RPE) cells and Müller cell responses; d-wave is from off bipolar cells. Panel C: critical flicker fusion (CFF) emanates from photoreceptors. Panel D: photopic negative response stems from ganglion cells.

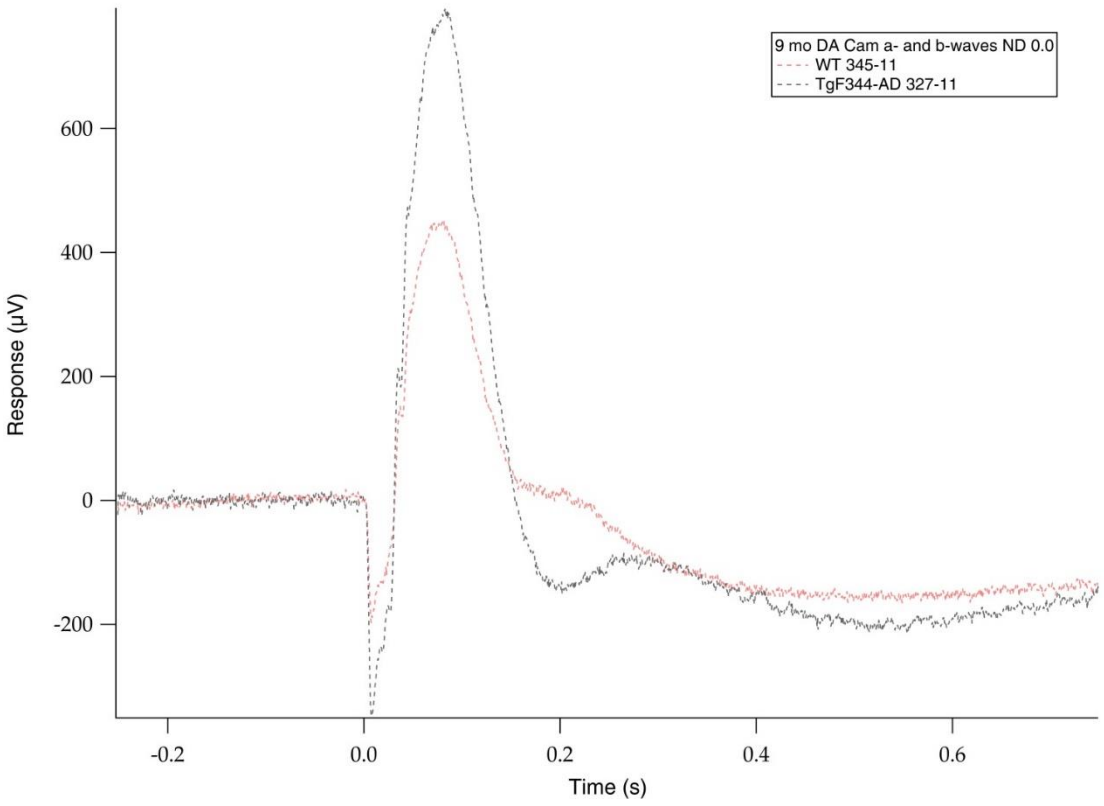

Figure 3. Representative a-wave traces in response to a bright stimulus, from 9-Month-Old (mo) animals. 9 mo WT (light red) had lower a-waves than 9 mo TgF344-AD (gray).

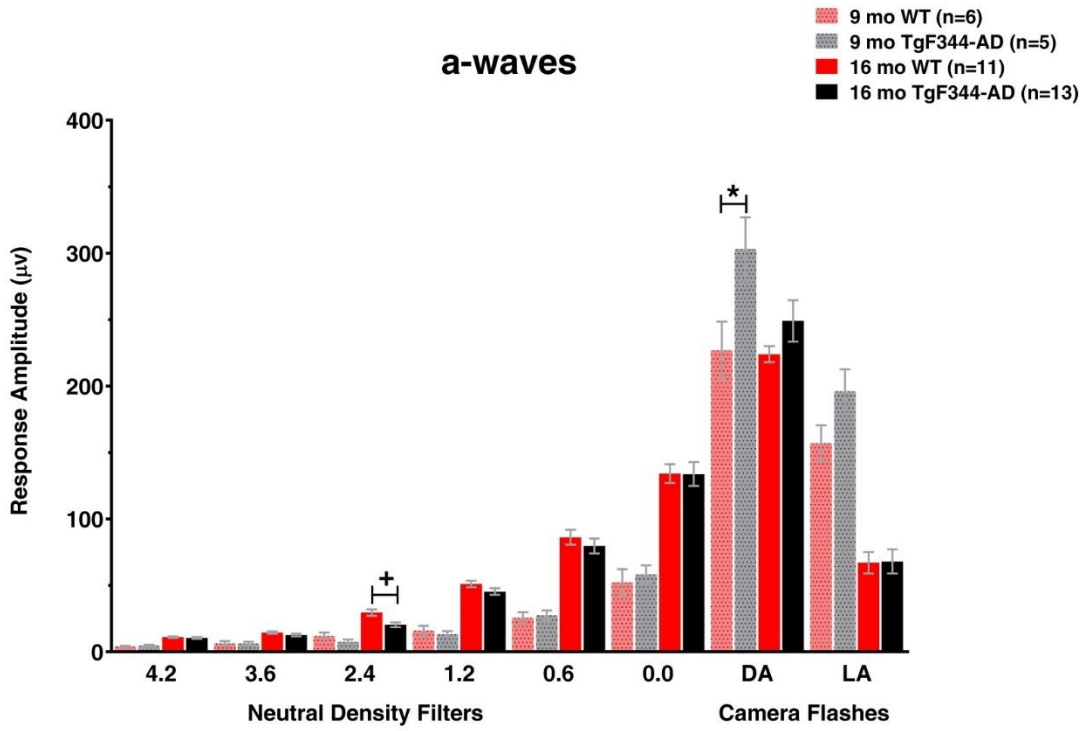

Figure 4. a-waves results. As compared to WT, TgF344-AD animals had higher a-wave responses to a bright stimulus at 9 mo, but smaller responses at 16 mo at ND 2.4. [9 mo WT (light red); 9 mo TgF344-AD (gray); 16 mo WT (dark red); 16 mo TgF344-AD (black). (*) $p<0.05$; (+) $p<0.01$. Bars represent standard error of mean (SEM).]

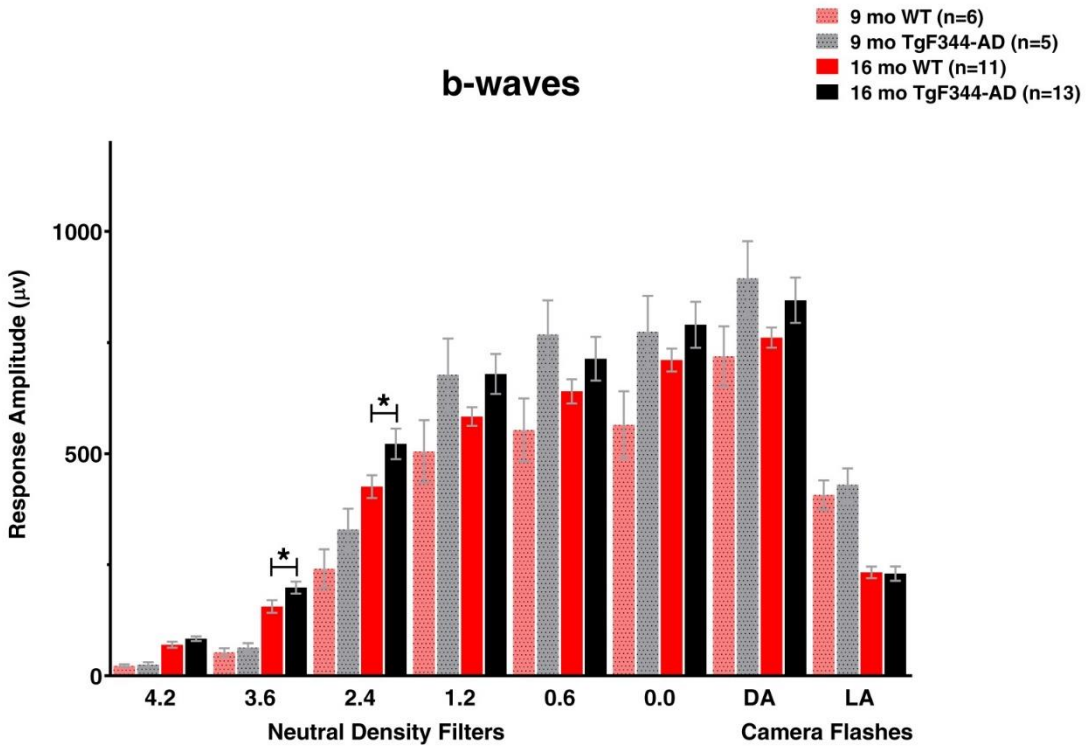

Figure 5. b-waves results. As compared to WT, 16 mo TgF344-AD rats displayed higher b-wave responses at ND 3.6 and 2.4. [9 mo WT (light red); 9 mo TgF344-AD (gray); 16 mo WT (dark red); 16 mo TgF344-AD (black). (*) $p<0.05$; Bars represent SEM.]

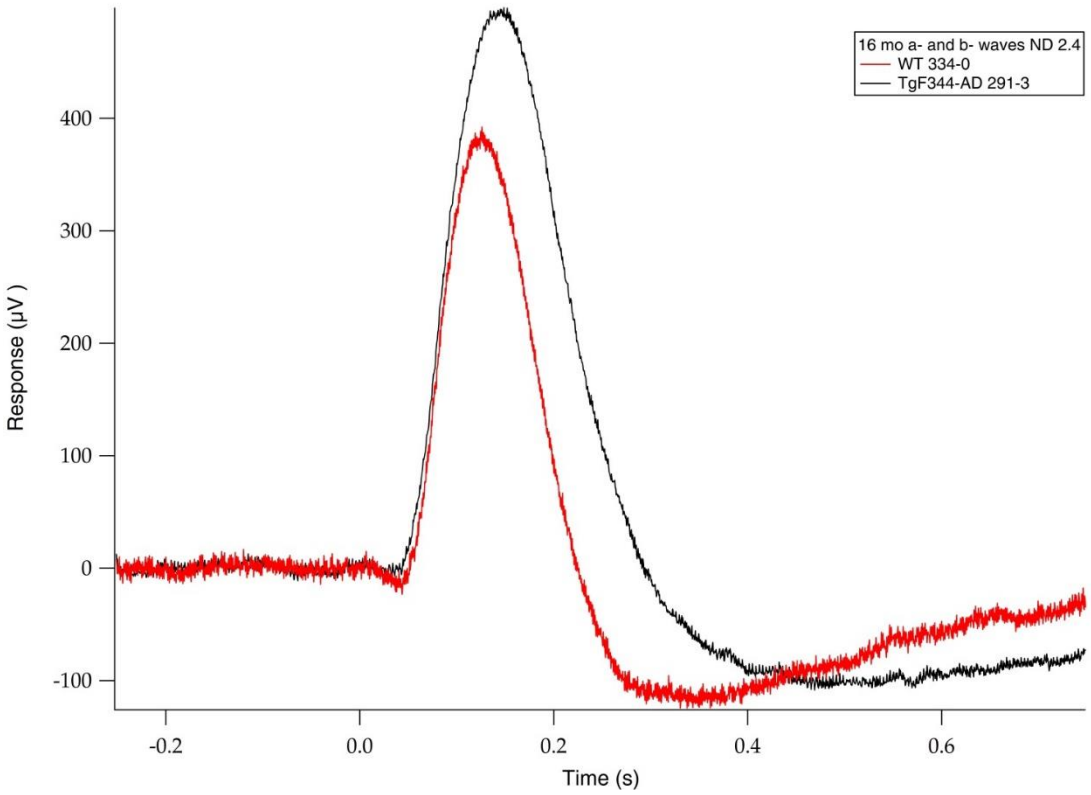

Figure 6. Representative b-wave traces showing that 16 mo TgF344-AD (black) rats displayed higher responses than WT (dark red) at ND 2.4.

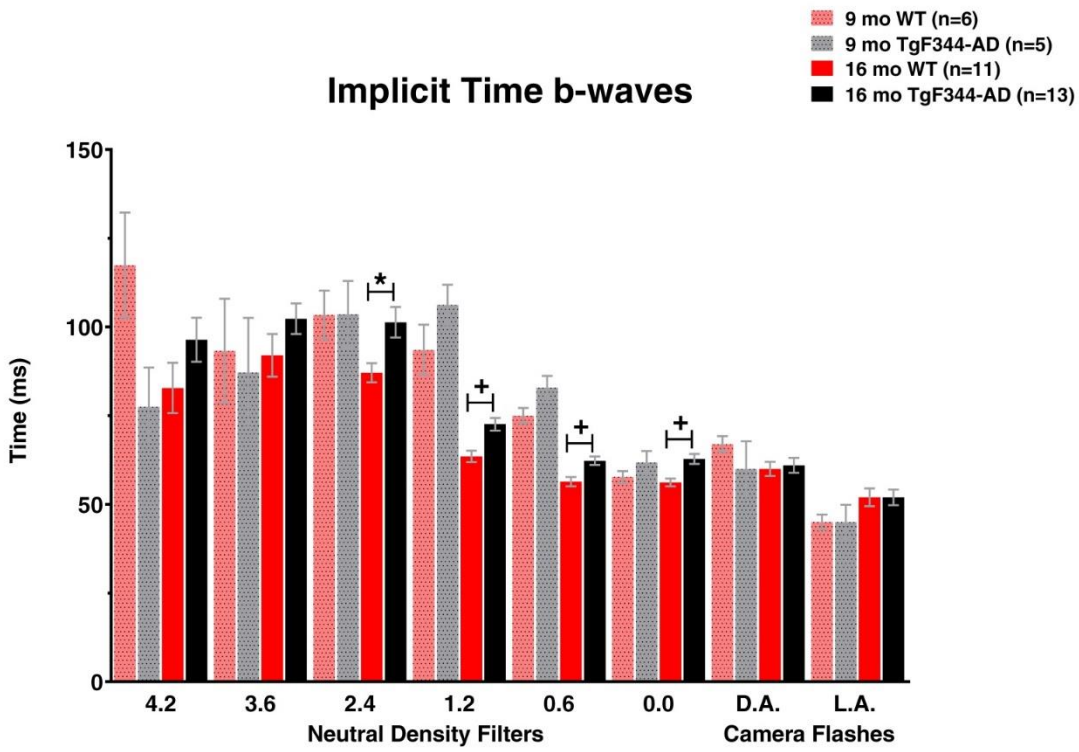

Figure 7. Implicit time b-waves results. As compared to WT, 16 mo TgF344-AD rats displayed slower implicit time at ND 2.4, 1.2, 0.6 and 0.0.]9 mo WT (light red); 9 mo TgF344-AD (gray); 16 mo WT (dark red); 16 mo TgF344-AD (black). (*) $p<0.05$; (+) $p<0.01$. Bars represent SEM.]

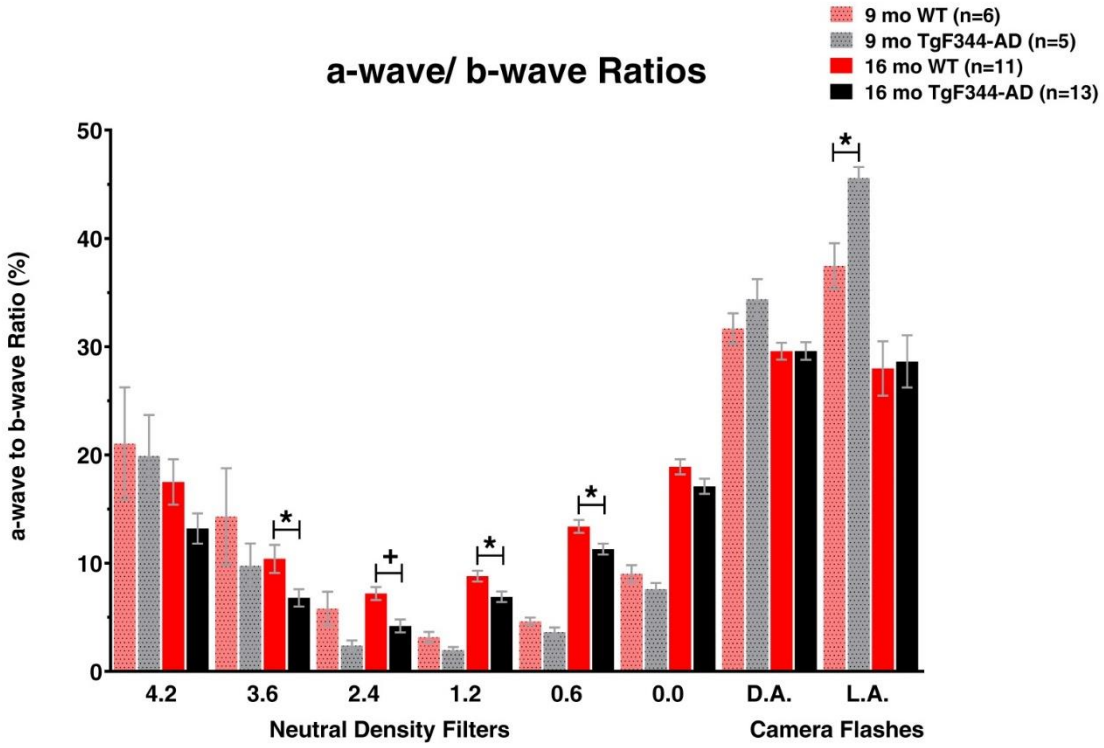

Figure 8. a-wave to b-wave ratios. As compared to WT, 9 mo TgF344-AD rats displayed higher a-wave to b-wave ratio to a bright stimulus; but lower for 16 mo at ND 3.6, 2.4, 1.2 and 0.6. [9 mo WT (light red); 9 mo TgF344-AD (gray); 16 mo WT (dark red); 16 mo TgF344-AD (black). (*) $p<0.05$; (+) $p<0.01$. Bars represent SEM.]

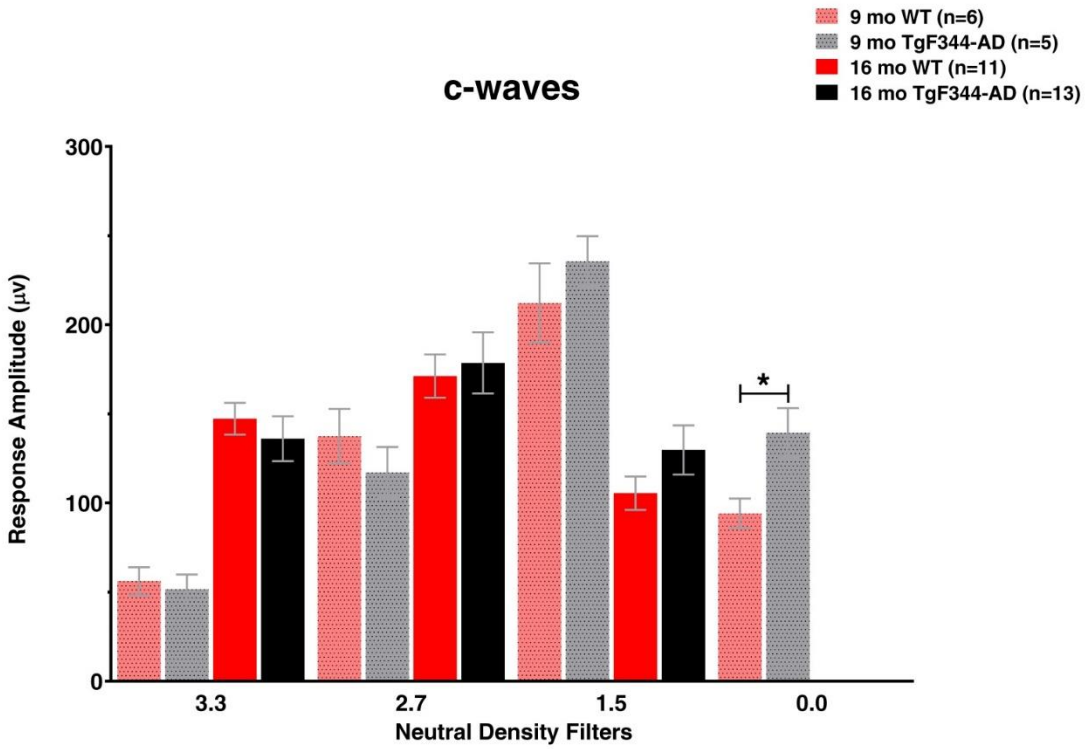

Figure 9. c-waves results. As compared to WT, 9 mo TgF344-AD rats displayed higher c-wave corneal negative deflection amplitude at ND 0.0, which was entirely abolished in 16 mo animals. [9 mo WT (light red); 9 mo TgF344-AD (gray); 16 mo WT (dark red); 16 mo TgF344-AD (black). (*) $p<0.05$. Bars represent SEM.]

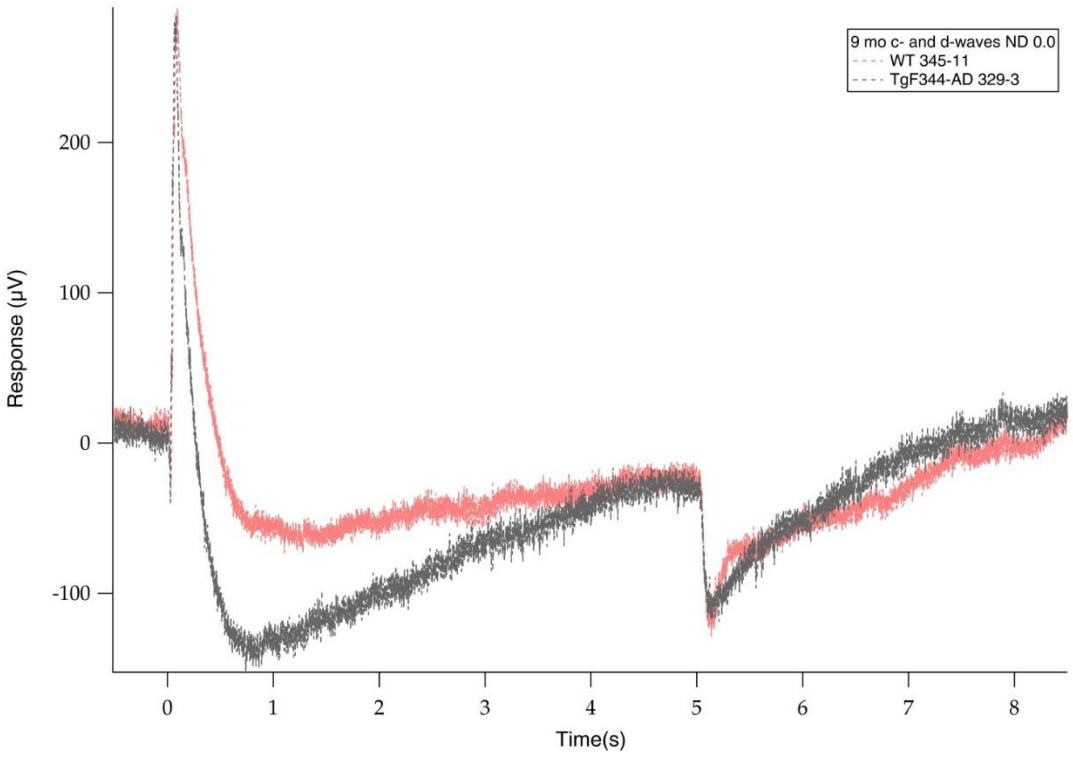

Figure 10. Representative c-wave traces from 9 mo animals. TgF344-AD (gray) displayed higher c-wave corneal negative deflection component, as compared to WT (light red).

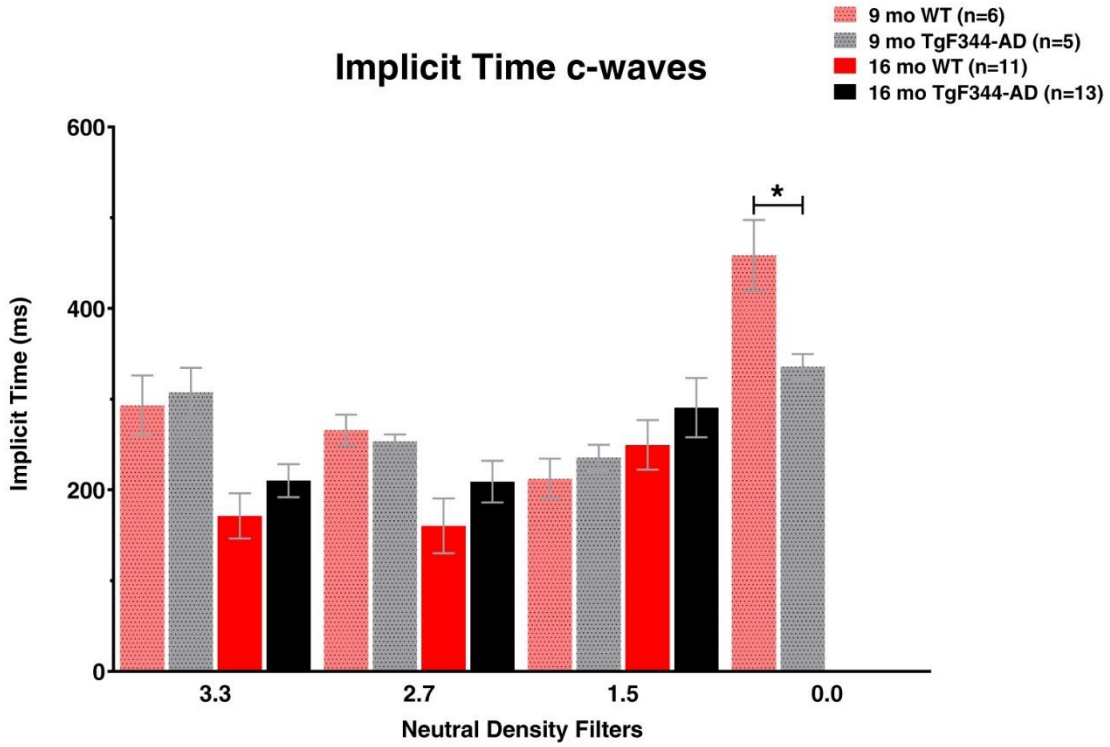

Figure 11. Implicit time c-waves corneal negative deflection results. 9 mo TgF344-AD rats, as compared to WT, displayed faster implicit time at ND 0.0. [9 mo WT (light red); 9 mo TgF344-AD (gray); 16 mo WT (dark red); 16 mo TgF344-AD (black). (*) $p<0.05$. Bars represent SEM.]

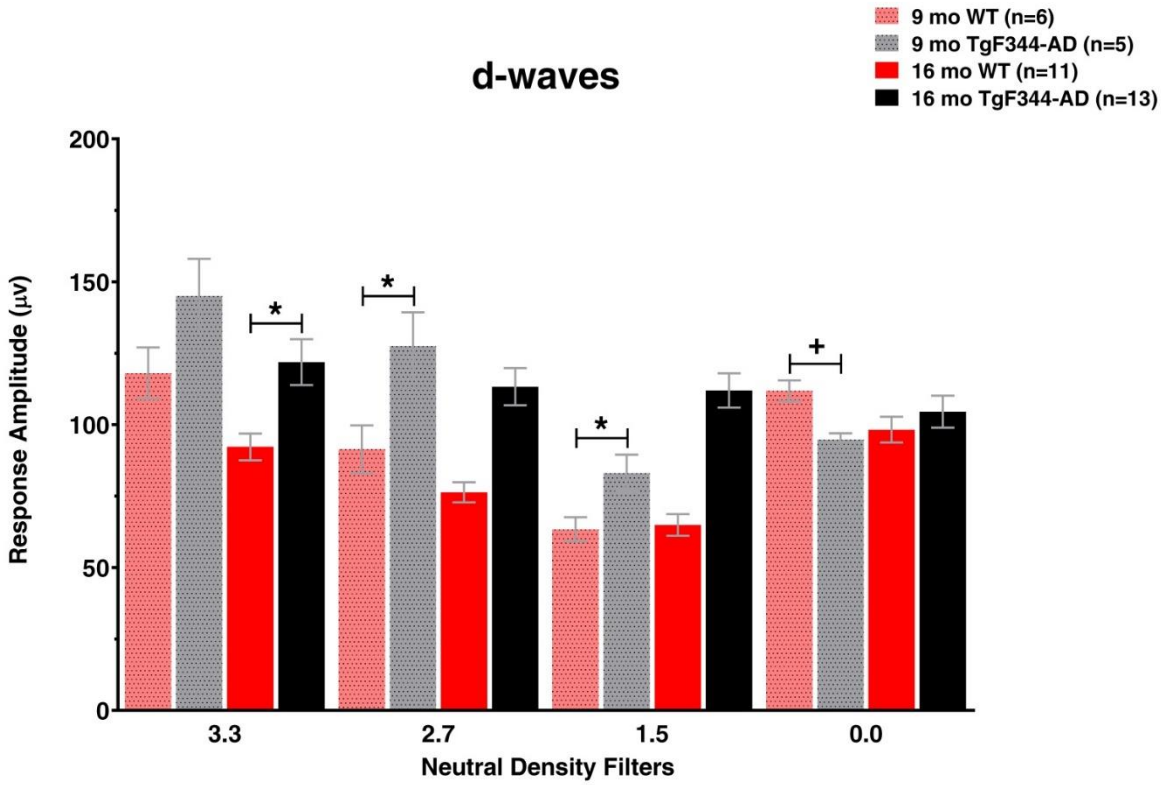

Figure 12. d-waves results. As compared to WT, TgF344-AD rats displayed higher d-waves at ND 2.7 and 1.5, but lower responses at ND 0.0, at 9 mo; and higher responses at ND 3.3 at 16 mo. [9 mo WT (light red); 9 mo TgF344-AD (gray); 16 mo WT (dark red); 16 mo TgF344-AD (black). (*) $p<0.05$; (+) $p<0.01$. Bars represent SEM.]

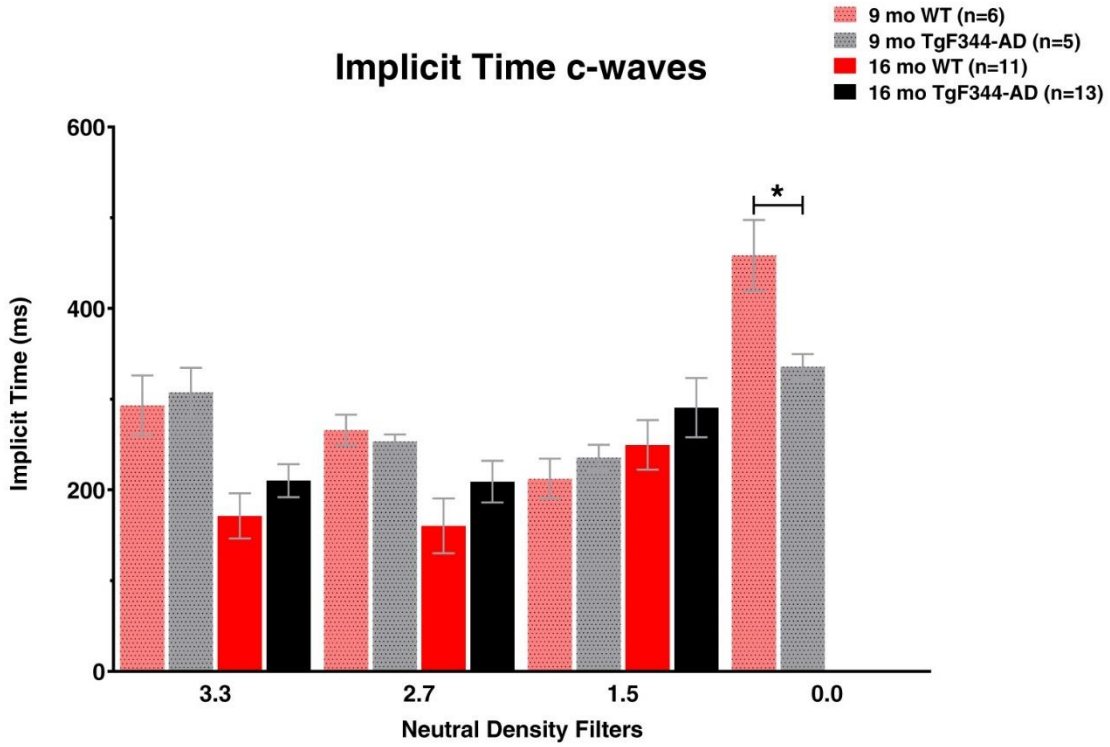

Figure 13. Implicit time d-waves results. 9 mo TgF344-AD rats displayed faster implicit time than WT at ND 0.0. [9 mo WT (light red); 9 mo TgF344-AD (gray); 16 mo WT (dark red); 16 mo TgF344-AD (black). (*) $p<0.05$. Bars represent SEM.]

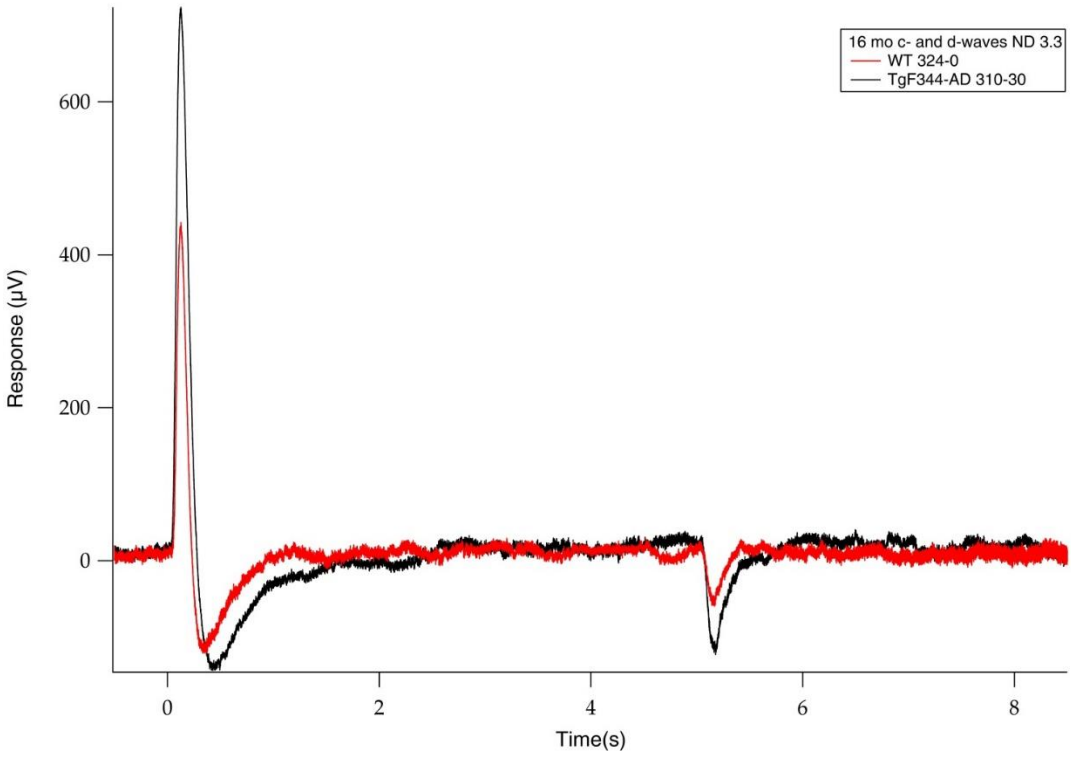

Figure 14. Representative d-wave traces showing that 16 mo TgF344-AD (black) rats displayed higher responses than WT (dark red) at ND 3.3.

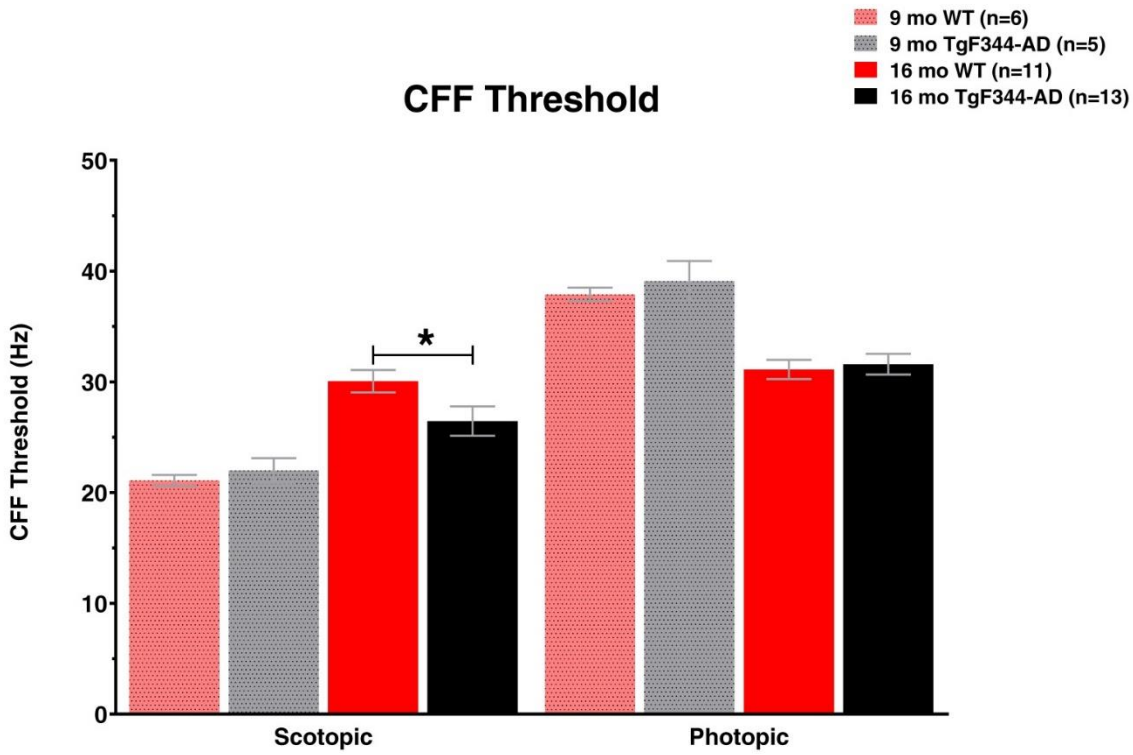

Figure 15. Critical flicker fusion (CFF) results. 16 mo TgF344-AD rats exhibited lower scotopic CFF than WT. [9 mo WT (light red); 9 mo TgF344-AD (gray); 16 mo WT (dark red); 16 mo TgF344-AD (black). (*) $p<0.05$. Bars represent SEM.]

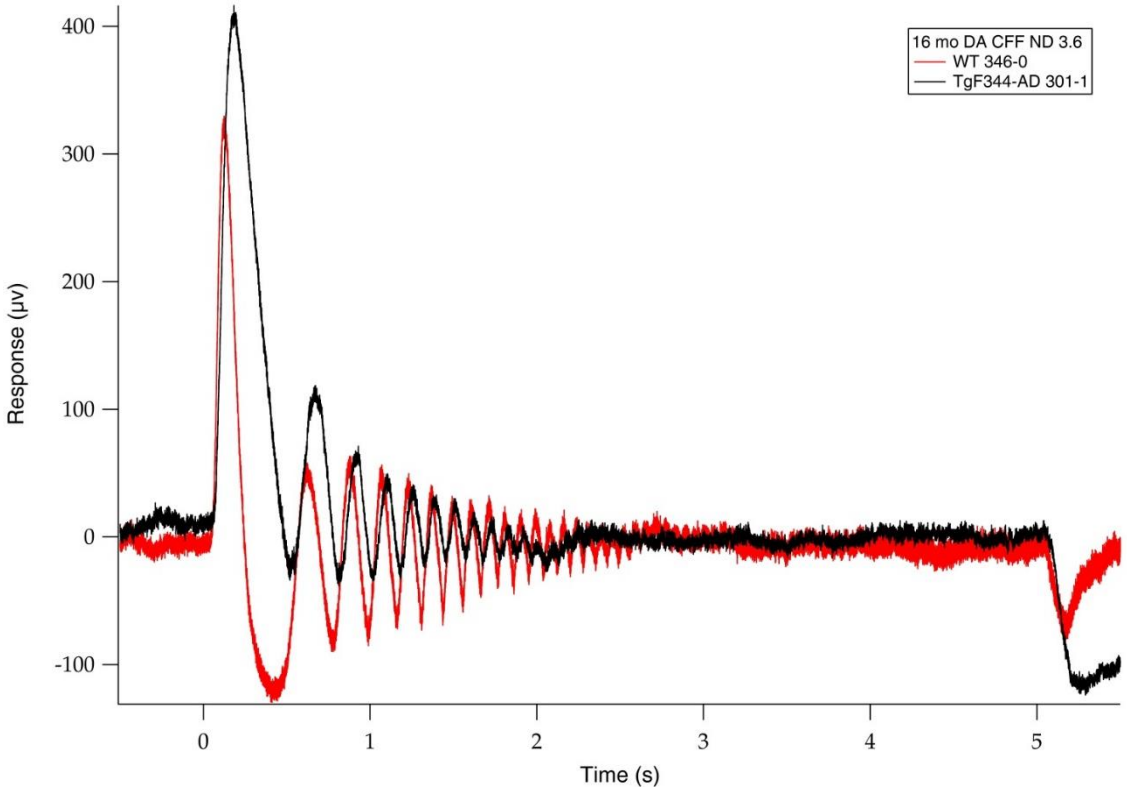

Figure 16. Representative scotopic critical flicker fusion (CFF) traces showing that 16 mo TgF344-AD (black) rats displayed lower scotopic CFF responses than WT (dark red).

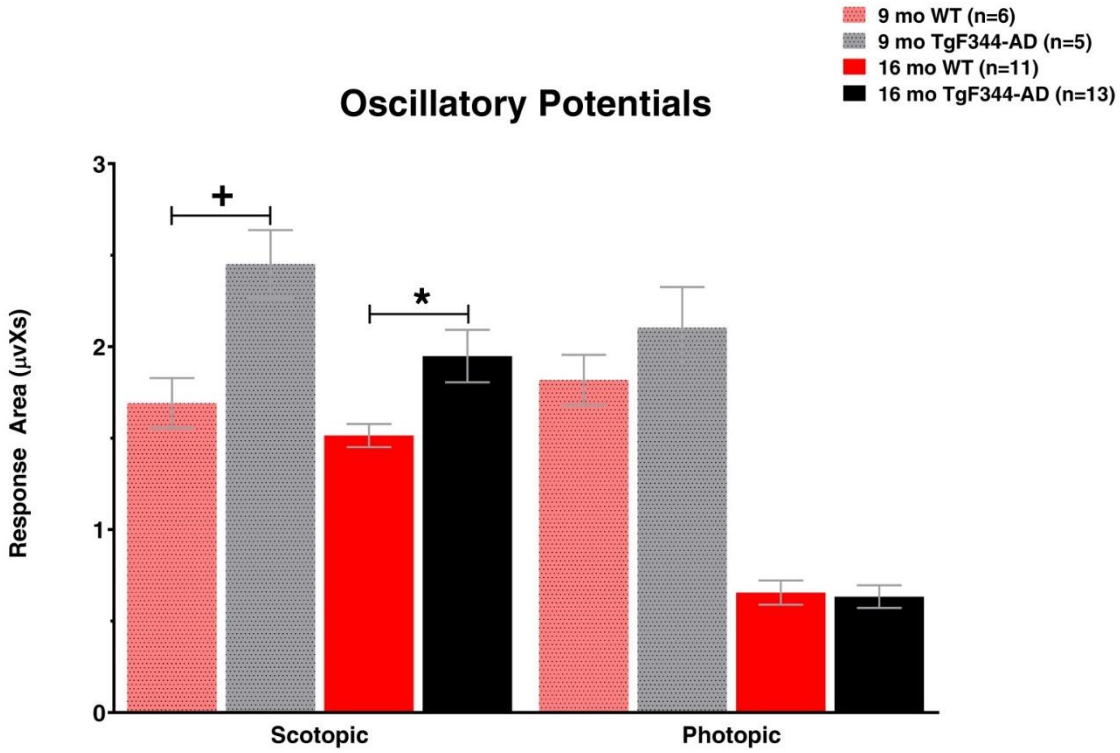

Figure 17. Oscillatory potentials (OPs) results. 9 and 16 mo TgF344-AD rats displayed higher scotopic OPs than WT. [9 mo WT (light red); 9 mo TgF344-AD (gray); 16 mo WT (dark red); 16 mo TgF344-AD (black). (*) $p<0.05$; (+) $p<0.01$. Bars represent SEM.]

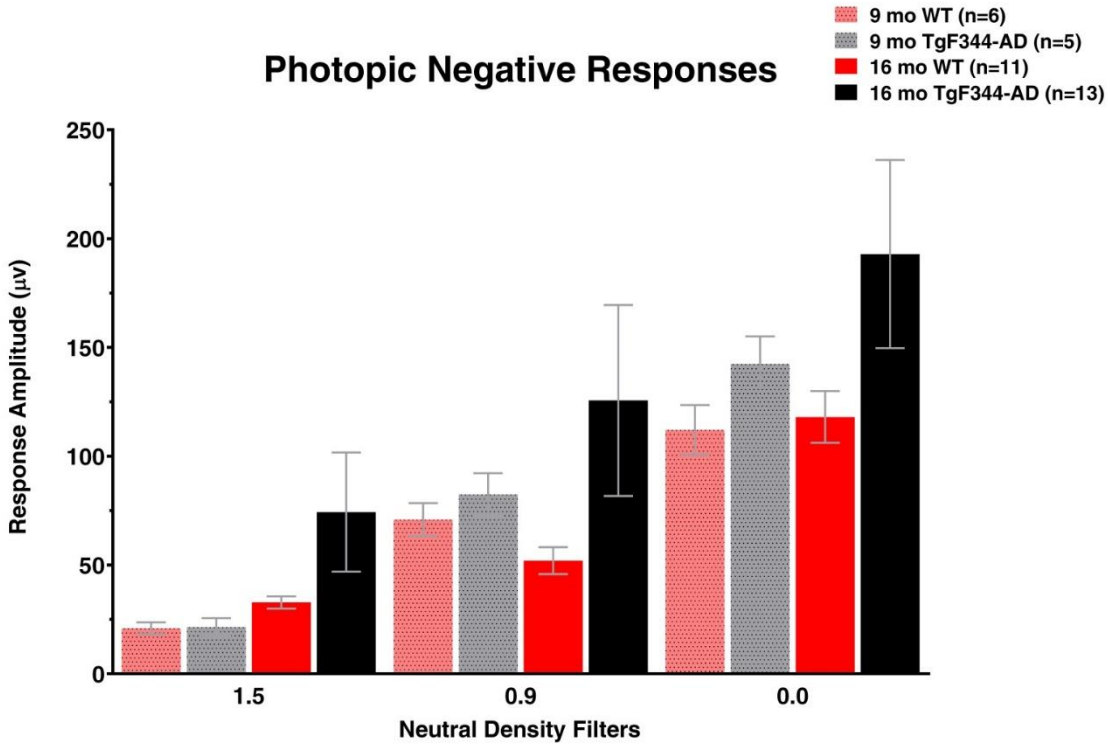

Figure 18. Photopic negative responses results. There were no statistically significant differences, in either age group, between TgF344-AD and WT in ganglion cell responses. [9 mo WT (light red); 9 mo TgF344-AD (gray); 16 mo WT (dark red); 16 mo TgF344-AD (black). Bars represent SEM.]

GLOBAL SUMMARY

Overview

The first set of studies, using the Tg-SwDI mouse model of Alzheimer's Disease (AD), revealed that the retina exhibits, molecularly and histologically, several AD-related manifestations (cell death, cholinergic system deterioration and gliosis) that occur in the rest of the brain. The second set of studies, using the TgF344-AD model, successfully demonstrated that AD can cause functional changes to retinal physiological responses and that electroretinography (ERG) can reliably and noninvasively detect AD-related visual changes in vivo.

Specific Aim I

These studies (Oliveira-Souza et al., 2017) aimed to establish whether AD-related pathological changes displayed in the cerebrum also happened in the retina. We employed immunohistochemistry to measure retinal cell number and detect gliosis, and quantitative polymerase chain reaction to quantify acetylcholine receptor (AChR) expression in Tg-SwDI mice as compared to age-matched wild-type (WT) mice. Young adult and middle-aged adult Tg-SwDI mice exhibited initial upregulation in several AChR subunits/subtypes, but only downregulation in old adults. Young adult transgenic mice displayed significant cell loss in the inner retina and photoreceptor layer. The middle-aged adult group displayed a reduced number of cholinergic cells in the ganglion cell layer (GCL); while the old adult group displayed cholinergic cell loss in the inner nuclear layer

(INL), with no evident reduction in cholinergic cell number in the GCL. The nerve fiber layer (NFL) of transgenic mice showed higher astrocytic gliosis in the middle-aged adults and old-adults, as compared to WT. Furthermore, the gliosis in the Tg-SwDI mice intensified with increasing age, old adults had higher gliosis than young adult and middle-aged adult mice. Conversely, gliosis in WT mice decreased with age: old adult WT displayed less gliosis than younger cohorts. Taken together, this suggests that the higher gliosis observed in the transgenic group is directly related to AD pathological manifestations, but it is also age-related, as it exacerbates with increasing age.

Although AD pathology is known to disturb numerous neurotransmitter systems, the cholinergic system appears to be the most affected (Francis et al., 1999). In the beginning stages of AD, α7 nicotinic acetylcholine receptor (nAChR) plays a neuroprotective role by supporting cholinergic integrity, attenuating Aβ toxicity, and by promoting cognition, neuronal survival and synaptic plasticity (Hernandez et al., 2010; Echeverria and Zeitlin, 2012). Nevertheless, nAChRs activation has been linked to significantly raise tau phosphorylation, while the activation of muscarinic acetylcholine receptors (mAChRs) has been shown to prevent it (Schliebs and Arendt, 2006). Therefore, the AD-related upregulation of retinal AChR subunits/subtypes observed in the young adult and middle-aged adult groups, may be involved in a compensatory mechanism that has the purpose to alleviate the damage caused by non-cholinergic cell loss in the INL and GCL. This suggests that cholinergic disruption precedes cholinergic cell loss. The loss of cholinergic cells occurred first in the middle-aged adult group, and yet, the

compensatory mechanism remained active, as evidenced by the sustained AChR upregulation. But, as the disease become more severe and as the animals get older, the compensatory mechanism becomes inept at lessening the AD-associated pathological damage; which is evidenced by the deterioration of cholinergic function, namely, AChR downregulation and reduction in the number of cholinergic cells observed in the old adult animals.

ACh and its receptors have been consistently shown to play an essential role in normal visual processing (Schmidt et al., 1987; Kittila and Massey, 1997; Strang et al., 2005, 2007, 2010, 2015; Varghese et al., 2011). Whereas, the data obtained from our studies accentuate the pivotal importance of the retinal cholinergic system in AD pathology. We effectively demonstrated that some of the significant AD-pathological alterations (gliosis, cell loss and cholinergic system alterations) observed in the cerebrum also occur in the retina, and may be partially responsible for the visual deficits reported in AD. The results from these studies support the notion that identifying specific alterations in the retinal cholinergic system may assist in the development of non-invasive biomarkers for the disease (Ikram et al., 2012; Chang et al., 2014; Hill et al., 2014; Kusne et al., 2016; Lim et al., 2016).

Specific Aim II

We intended to assess AD's influence in retinal physiological responses and to evaluate the suitability of ERG as a diagnostics tool to detect the disease. We employed ERG, under light-adapted and dark-adapted conditions, to measure retinal cells' responses, at different light intensities in 9 and 16-month-

old TgF344-AD rats and age-matched WT. 9-month-old mutants exhibited higher responses from several retinal cells, but lower responses from off bipolar cells and Müller cells. 16-month-old TgF344-AD rats displayed lower scotopic critical flicker fusion threshold and photoreceptor responses, and slower implicit time for on bipolar cell responses, at several light intensities. Cognitive deficits in TgF344-AD rats have only been reported at 15 months of age (Cohen et al., 2013), but our data showed measurable visual changes as early as 9 months of age. Collectively, these results show that AD can exert influences in retinal physiological responses and that ERG is an effective method to detect AD-related alterations in visual function before the onset of cognitive decline.

Several studies, including our results in specific aim I (Oliveira-Souza et al., 2017), have demonstrated that retinal changes may parallel the pathological AD-related changes observed in the rest of the brain (Kesler et al., 2011; Chang et al., 2014; Hill et al., 2014) and may be responsible for the differences in retinal responses observed in TgF344-AD rats, as compared to WT animals. Therefore, it is our belief that ERG, along with other ocular assessment tools, can be utilized to facilitate AD's early detection, follow the progression of the disease and assess the effectiveness of therapeutical interventions. The data in specific aim II are consistent with the concept that identifying AD-related ocular changes may assist in the emergence of biomarkers that are able to detect AD in its earlier stages (Ikram et al., 2012; Chang et al., 2014; Hill et al., 2014; Kusne et al., 2016; Lim et al., 2016). Detecting AD sooner can potentially extend patients' life

quality by delaying the appearance of cognitive deficits through early intervention, which could possibly boost treatment efficacy.

Conclusion

AD can only be definitively diagnosed through brain autopsy by detecting the presence of its cardinal features: amyloid beta (Aβ) plaques and neurofibrillary tangles (NFTs) (Serrano-Pozo et al., 2011; Beach et al., 2012). Probable diagnosis of AD can be performed clinically via neuropsychological assessments, such as the Mini-Mental Sate Examination (MMSE), the most widely employed by health professionals (Folstein et al., 1975, 1983). These medical assessments are intended to evaluate cognitive deficits in attention, episodic memory, language, semantic memory, praxis, executive function and working memory (Huff et al., 1987; Hodges et al., 1992; Salmon et al., 1999; Baddeley et al., 2001), and to track the disease progression (Welsh et al., 1992; Locascio et al., 1995; Albert, 1996; Schmitt et al., 2000). However, many believe that the MMSE and other similar clinical tools, that greatly depend on the patient's self-reports and personal accounts from caregivers and/or family, only possess modest sensitivity and should not be regarded as a diagnostic assessment, rather, they should be perceived as a screening test (Sheehan, 2012).

In the recent years, other diagnostic methods have emerged: cerebral spinal fluid exams to assess Aβ42 and tau levels (Diniz et al., 2008; Bouwman et al., 2009; Bateman et al., 2012; Fagan et al., 2014; Scheltens et al., 2016), magnetic resonance imaging (Jagust et al., 2006; Davatzikos et al., 2008), and

positive electron tomography (Jagust et al., 1991; Engler et al., 2006; Barrio et al., 2008; Kusne et al., 2016; Franzco et al., 2017). However, these methods are extremely costly and/or invasive, fail to detect the disease before cognitive deficits appear (Petersen, 2004) and lack the capability to detect non-amnestic deficits, such as visuospatial perception, which is known to occur several years before probable diagnosis is determined (Johnson et al., 2009). Furthermore, there are data suggesting that AD-related neuronal changes start occurring as early as twenty years before the patient become symptomatic (Jack et al., 2009; Bateman et al., 2012; Reiman et al., 2012; Villemagne et al., 2013). The vast majority of health professional and researchers believe that a quicker diagnosis of the disease would increase treatment efficacy, thus there is a tremendous motivation to diagnose AD in its beginning stages (Brookmeyer et al., 1998; Sloane et al., 2002; Levey et al., 2006; Miller and Drachman, 2006; Petersen, 2009; Wilson et al., 2010; Frost et al., 2013).

The eye is an outstanding potential candidate for the development of biomarkers for central nervous system (CNS) disorders, as the retina shares many traits with the cerebrum (MacCormick et al., 2015) and is the only part of the CNS that can be visualized noninvasively (Hill et al., 2014; MacGillivray et al., 2014). Based on this belief, scientists have employed ocular examination techniques such as ERG, fundoscopy, and optical coherence tomography to detect several diseases including schizophrenia (Kim et al., 2005; Tschacher et al., 2015), CNS lymphoma (Buggage et al., 2001; Matsuyama et al., 2014), stroke (Kalesnykas et al., 2008; Cheung et al., 2017), cerebral malaria (Beare et

al., 2004; Maude et al., 2009), multiple sclerosis (Watson et al., 2011; Garcia-Martin et al., 2014), diabetes mellitus (Klein and Klein, 1995; van Reyk et al., 2003; Ratchford et al., 2013), Parkinson's (Hipp et al., 2014; Hill et al., 2016), hypertension (Stanton et al., 1995; Wong and Mitchell, 2007; DellaCroce and Vitale, 2008) and other cardiovascular diseases (Wong et al., 2006; Liew et al., 2011).

Visual assessment techniques have also been prevalently utilized in AD research (Granholm et al., 2003; Chang et al., 2014; Coppola et al., 2015). Collectively, these studies have been able to identify a myriad of AD-related visual perception alterations. These alterations include deficits in depth perception (Katz and Rimmer, 1989; Cronin-Golomb et al., 1991; Mendez et al., 1996; Lee and Martin, 2004), motion perception (Katz and Rimmer, 1989; Jackson and Owsley, 2003; Lee and Martin, 2004), stereopsis (Cronin-Golomb et al., 1995; Rizzo et al., 2000), contrast sensitivity (Curcio and Drucker, 1993; Gilmore and Whitehouse, 1995), color discrimination (Pache et al., 2003; Salamone et al., 2009), temporal resolution (Cronin-Golomb et al., 1995; Rizzo et al., 2000), ganglion cell responses (increased implicit time, but lower amplitude) (Katz et al., 1989; Krasodomska et al., 2010; Moschos et al., 2012), pattern electroretinogram responses (Trick et al., 1989; Nesher and Trick, 1991; Sartucci et al., 2010), , visual field defects (Trick et al., 1995; Valenti, 2013), lower critical flicker fusion (CFF) threshold (Sahakian et al., 1989; Levine et al., 1993; Curran and Wattis, 2000; Curran et al., 2004), and decreased visual acuity (Sadun et al., 1987; Uhlmann et al., 1991; Lakshminarayanan et al., 1996), which was shown

to be sometimes accompanied by visual hallucinations (Chapman et al., 1999; Murgatroyd and Prettyman, 2001). AD-related ocular deficits also include abnormal pupillary light reflex (Fotiou et al., 2000, 2007; Granholm et al., 2003; Scinto, 2007) and eye movement abnormalities, including visual fixation instability (Fletcher and Sharpe, 1986; Bylsma et al., 1995; Schewe et al., 1999; Mosimann et al., 2004), abnormal saccadic eye movements (higher latency with reduced maximum speed and accuracy) (Jones et al., 1983; Abel et al., 2002; Shafiq-Antonacci et al., 2003; Crawford et al., 2005) and smooth pursuit abnormalities (horizontal and vertical: increased latency and decreased gain) (Hutton et al., 1984; Fletcher and Sharpe, 1988; Kuskowski et al., 1989; Zaccara et al., 1992; Shakespeare et al., 2015), All of these visual shortfalls can negatively affect one's quality of life and daily actions, such as, face and object recognition, route navigation, and reading (Rizzo et al., 2000).

In addition to overt physiological changes, molecular and histological ocular examinations, have yielded a tremendous amount of evidence showing AD's detrimental effects in the eye, that may account for the visual deficits observed in patients. Studies have revealed that the AD eye exhibits a larger population of astrocytes in the nerve fiber layer (NFL) (Blanks et al., 1996a, 1996b) and increased astrocytic gliosis (Oliveira-Souza et al., 2017); phosphorylated tau accumulation in the GCL and NFL (Du et al., 2015); Aβ deposition throughout the retina, which has been shown to precede cerebral deposition (Koronyo-Hamaoui et al., 2011), including photoreceptors (Du et al., 2015), retinal vasculature (Zhang-Nunes et al., 2006; Liu et al., 2009a), lens

(Goldstein et al., 2003), inner plexiform layer (IPL), GCL, NFL and outer retina (Alexandrov et al., 2011; Koronyo-Hamaoui et al., 2011); lower blood flow, likely due to narrowing of retinal veins (Berisha et al., 2007; Williams et al., 2015) and elevated oxygen saturation in retinal arterioles and venules (Einarsdottir et al., 2015); ganglion cell loss (Danesh-Meyer et al., 2006; Paquet et al., 2007); higher inflammatory marker complement factor H levels (Alexandrov et al., 2011); smaller ganglion cell axon count (Blanks et al., 1996b; Danesh-Meyer et al., 2006); narrower macula (Iseri et al., 2006), ganglion cell layer (GCL) (Garcia-Martin et al., 2016), choroid (Bayhan et al., 2015) and NFL (Iseri et al., 2006; Marziani et al., 2013; Shi et al., 2014; Gao et al., 2015; Oktem et al., 2015; Thomson et al., 2015), but thicker IPL (Snyder et al., 2016).

AD is known to produce many cerebral changes and affect visual perception, albeit the causes for visual dysfunction remain incompletely understood. In specific aim I, we successfully demonstrated that AD-related changes, including gliosis, cell loss and cholinergic system alterations, also exist in the retina. The aforementioned changes can potentially affect retinal physiological function especially, stemming from the mammalian cell populations (bipolar cells, amacrine cells, ganglion cells) that are known to express AChRs. Most notably, the initial upregulation in AChR expression in the younger Tg-SwDI cohorts is consistent with previous findings that the cholinergic system's increased activity, in early AD's process in humans, is part of a compensatory mechanism to placate the disease's detrimental effects (Vorobyov and Bobkova, 2015; Douchamps and Mathis, 2017). The results from specific aim I, especially

the initial cholinergic upregulation, can result in increased excitation and partially explain the augmented ERG responses displayed by TgF344-AD rats in specific aim II. If our assumptions are correct, this compensatory mechanism will no longer be able to mitigate AD-pathology in older transgenic animals. The lower CFF threshold observed in the oldest TgF344-AD is consistent with human results (Cronin-Golomb et al., 1991), and is the first measurable indication of the compensatory mechanism deterioration. Collectively, the data from our current studies indicate that AD-related changes observed in the cerebrum are also present in the retina and may be, at least in part, responsible for the visual deficits associated with the disease. Furthermore, we demonstrated that AD pathology affects retinal cells' physiological responses and that ERG can be employed as a suitable means to detect AD-related visual changes to ultimately serve as an efficacious diagnostic tool to identify the disease in its earlier stages, thus potentially improving treatment efficacy.

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