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Electroretinography as a Noninvasive Biomarker of Alzheimer's Disease and Related Dementias in Older Adults: A Systematic Scoping Review

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Abstract

Background

Despite the potential of electroretinography (ERG), defined as the summed mass electrical activity of the retina, as a non-invasive biomarker of cognitive dysfunction, the lack of comprehensive synthesis and standardized evaluation of ERG modalities has limited its clinical translation as a reliable biomarker in Alzheimer's Disease and related dementia (ADRD). This scoping review aimed to characterize the landscape of ERG and its clinical utility as a discriminant biomarker for ADRD in older adults and to identify gaps for future studies.

Methods and findings

Eight databases (Web of Science, Scopus, PubMed, Embase, Google Scholar, PsycINFO, CENTRAL, and ClinicalTrials.gov) were searched using controlled vocabulary and MESH terms without date or language restrictions. Retrieved articles were organized by databases and imported into covidence for screening by three independent team members with discrepancies resolved through discussion. Inclusion was limited to original research involving human participants aged ≥ 50 years and used ERG as a biomarker in ADRD and/or normal aging. Evidence was consolidated through adoption of the synthesis without meta-analysis (SWiM) framework. Of the 2,777 articles identified and screened, 25 were included. Most were comparative cross-sectional studies (n = 18) that utilized PERG (n = 14) non-portable ERG (n = 23). ffERG showed reduced a- and b-wave amplitudes, decreased PhNR/b-wave ratios, and prolonged implicit times, while PERG (P1, N1, P50, N95) and mfERG (N1, P1, N2) responses were consistently attenuated and delayed. Cognitive associations were modest and selective, with some studies reporting inverse relationships between ERG latencies, MMSE scores, and amyloid burden.

Conclusion

In conclusion, irrespective of ERG modality, ADRD was consistently associated with retinal dysfunction marked by impaired synaptic transmission and delayed neural processing across retinal circuits. These findings indicate both global and localized involvement of photoreceptor, bipolar, and retinal ganglion cell pathways, supporting the potential of ERG as a non-invasive, in vivo biomarker of retinal neurodegeneration. However, the modest and selective associations with cognitive outcomes suggest that ERG alterations, while reflective of underlying neurodegenerative processes, have limited direct correlation with cognitive severity. The current evidence base remains constrained by predominantly cross-sectional designs, small sample sizes, and the use of non-portable systems, limiting standardization and clinical translation. Nevertheless, emerging links with cognitive decline and amyloid pathology underscore the need for well-powered longitudinal and multimodal studies to clarify the clinical utility of ERG in ADRD.

Introduction

Alzheimer's disease (AD) and related dementias (ADRD) represent a growing public health crisis both in the United States and globally. In the U.S., one individual develops AD every 67 seconds, a rate projected to rise to every 33 seconds by 2050 [1]. Worldwide, an estimated fifty-one million people currently live with ADRD [2], a prevalence that has nearly doubled over the past three decades [3–5] and is expected to increase further with population aging and growth [5, 6]. Beyond the human toll, ADRD impose substantial economic [7–9] and societal burdens [10]. For instance, the economic costs of dementia rose from US$279.6 billion in 2000 to $948 billion in 2016, partly due to a surge in informal care costs from $95.1 billion to $401.9 billion and are projected to exceed $3 trillion by 2060 [7, 11]. At the individual level, annual costs range from US$468 for mild AD to $171,284 for severe disease [12], while societal costs include high lost productivity and leisure time for both caregivers and patients [10]. Taken together, addressing these challenges through effective prevention, early diagnosis, and innovative treatments could substantially reduce the human, economic, and societal burden of ADRD, improve quality of life for millions and alleviate long-term financial strain on families and healthcare systems.

Early detection of cognitive decline is essential for timely therapeutic intervention; however, current diagnostic approaches remain costly [13, 14], invasive [15], and resource intensive [16, 17]. Consistent with the ATN (amyloid-beta, tau, neurodegeneration)

framework, established neuroimaging modalities—such as magnetic resonance imaging (MRI) to assess medial temporal lobe atrophy, fluorodeoxyglucose positron emission tomography (FDG-PET) to identify posterior cingulate and temporoparietal hypometabolism, and amyloid PET to detect cortical amyloid deposition—provide critical mechanistic insights [18]; however, these modalities rely on specialized infrastructure and do not scale readily for population-level screening. Similar to amyloid-beta [19, 20], tau-PET provides a uniquely robust biomarker to differentiate AD from other tauopathies and strongly correlates with cognitive deficits [21, 22], yet wide-scale adoption in clinical practice requires methodological refinement and standardization [23, 24]. Fluid biomarkers, such as amyloid-beta, phosphorylated tau [25, 26], total tau [27, 28], and neurofilament light chain [29], and emerging biomarkers such as neurogranin, SNAP-25, and synaptotagmins, have improved diagnostic precision [30–32], except clinical deployment remains constrained by procedural invasiveness, laboratory complexity, and cost.

Behavioral instruments, such as the Montreal Cognitive Assessment (MoCA) [33, 34], Mini-Mental State Examination (MMSE) [34–36], and Clinical Dementia Rating (CDR) [36, 37] and CDR Sum of Boxes (CDR-SOB) [36], offer greater accessibility but lack are insufficient as standalone assessments. Collectively, these extrinsic and inherent methodological constraints delineate a critical gap and underscore the urgent need for affordable, non-invasive, and scalable approaches that is capable to detect and monitor early cognitive decline across both clinical and community settings.

ADRD and mild cognitive impairment (MCI), arise from a complex interplay of genetic, vascular, metabolic, and environmental factors [38, 39]. In AD pathology, mutations in amyloid precursor protein (APP), presenilin-1 (PSEN1), and presesenilin-2 (PSEN2) [40–42] or the presence of the APOE ε4 allele [43–45] promote abnormal amyloid-beta production and deposition [46], while tau hyperphosphorylation leads to neurofibrillary tangles that disrupt neuronal structure and function [47]. Mixed dementias combine these amyloid-tau pathologies with cerebrovascular lesions, including microinfarcts, hypoperfusion, and blood-brain barrier dysfunction [48, 49], whereas vascular dementia primarily reflects cerebrovascular compromise driving neuronal injury and cognitive decline [49, 50]. Across ADRD subtypes, mechanisms such as oxidative stress [51], mitochondrial dysfunction [52], impaired proteostasis [53], and chronic neuroinflammation [54] amplify synaptic loss and neuronal death [55]. Importantly, these neurodegenerative processes extend to the retina as a functional extension of the brain, where breakdown of retinal neural circuits, mirrors cortical pathology. Collectively, this retinal involvement results in structural thinning [56], vascular alterations [57–59], and electrophysiological dysfunction [33–35, 60–63], thereby positioned the retina as a sensitive, non-invasive window into CNS disease progression.

Electroretinography (ERG) represents a promising noninvasive approach for early detection of cognitive change ADRD, as it captures real-time functional responses of retinal neurons [64], including photoreceptors, bipolar cells, and retinal ganglion cells [33, 35, 60] that share developmental and physiological properties with central nervous system (CNS) pathways [65–67]. ERG is recorded by placing a small electrode on the surface of the eye, typically embedded in a contact lens or positioned near the cornea, while the individual views controlled visual stimuli such as flashes of light (ffERG), contrast-reversing (pERG) or hexagonal patterns (mfERG) [64, 68, 69]. These visual stimuli evoke electrical responses from retinal cells, which appear as waveforms [64, 68, 69]. A typical ERG session lasts about 15 to 45 minutes, depending on the protocol and level of detail required [64, 68, 69]. Because single responses can be noisy, the stimulus repeats multiple times, and the signals are averaged to produce a reliable trace [64, 68, 69]. The waveform is analyzed in terms of amplitude, which reflects the strength of the retinal response (measured in microvolts, μV), and latency (or implicit time), which indicates how quickly the response occurs after stimulus onset (measured in milliseconds, ms) [64, 68, 69]. Distinct waveform components correspond to activity in specific retinal cell populations, so ERG provides a functional readout of retinal integrity [64, 70]. Evidence shows ERG abnormalities, such as reduced amplitudes and delayed implicit times are associated with early neurodegenerative changes, even in preclinical [60] or mild cognitive impairment stages [63, 71, 72]. These functional alterations may precede detectable structural changes on optical coherence tomography [72] or overt cognitive decline, which suggests that retinal dysfunction reflects early synaptic and neuronal impairment linked to amyloid deposition, tau pathology, and neuroinflammation [35, 60, 73, 74]. ERG also provides advantages as an objective, relatively low-cost, and repeatable tool suitable for longitudinal monitoring and large-scale screening. Further, the emergence of portable ERG systems such as RETeval helps overcome the limitations of bulky traditional non-portable ERG systems [35, 36, 60] and may offer the added advantage of enabling home-based testing, particularly among individuals with limited mobility [33, 72, 75, 76]. As a result, ERG holds potential as an early biomarker for ADRD and as a method to track disease progression and evaluate therapeutic response, particularly when integrated with neuroimaging, cognitive assessments, and fluid biomarkers within a

multimodal diagnostic framework. However, systematic mapping of ERG findings across ADRD remains limited, and interpretation requires careful consideration of aging-related retinal changes that may overlap with disease effects.

Unlike ADRD, normal aging is associated with gradual structural and functional retinal changes that mirror broader neural aging, including reduced photoreceptor density [77], thinning of the retinal ganglion cell nerve fiber layers [78], modest reductions in ERG amplitudes, slight prolongation of implicit times [79, 80], and lower contrast sensitivity, particularly under low luminance [81]. Retinal synaptic efficiency falls with age [82], which impairs transmission from photoreceptors to bipolar and ganglion cells [79, 80] and reflects generalized neural vulnerability and slower processing that parallels cognitive decline. Mild cognitive impairment [63, 71] and AD produce earlier, larger, and spatially specific ERG deficits, particularly in the PhNR [35, 60] and pattern ERG components [76, 83, 84], alongside cerebral amyloid pathology [35]. Retinal ERG deficits correspond with synaptic loss [85, 86], impaired neurotransmission [87], and reduced network connectivity in the brain [74, 83], which link lower visual processing to deficits in attention, executive function, and memory [36, 72]. Given that the accumulation of amyloid beta and tau in retinal tissue precedes brain pathology [88, 89] supports ERG as a surrogate non-invasive in vivo biomarker of CNS neurodegeneration. Together, whiles aging establishes a baseline of retinal decline [79, 80], AD accelerates and amplifies these changes, highlighting the need to distinguish normative from pathological ERG alterations for early detection[33, 35, 60, 73, 90].

Despite the potential of ERG in the diagnosis and monitoring of ADRD, no study has systematically assessed the full range of ERG protocols, modalities, and their practical clinical or research applicability. ERG includes multiple techniques targeting specific retinal layers and neuronal populations. For instance, ffERG evaluates global rod and cone function along with downstream bipolar and ganglion cell responses [34, 35, 79] whiles pERG evaluates ganglion cell function via patterned stimuli such as checkerboards or gratings [76, 83, 84]. Further, mfERG maps localized retinal responses to detect regional deficits potentially linked to early ADRD pathology [36, 91, 92]. Because ffERG captures a summed, whole-retina response, it may overlook subtle, region-specific dysfunction, whereas mfERG provides spatially resolved data that is more sensitive to localized changes that can occur early in ADRD [70, 93]. Moreover, based on ERG modality, key metrics such as amplitude, implicit time, and waveform ratios which reflect the functional integrity of specific retinal circuits [64] are evaluated across studies[35, 36, 60, 72]. For instance, alpha and beta amplitude represents the strength of the retinal electrical response, implicit time denotes the latency from stimulus onset to peak response, and the PhNR-to–b-wave ratio indexes ganglion cell function relative to bipolar cell activity [35, 60, 64]. In addition, P1 and N1 in multifocal ERG represent outer and inner retinal responses, with N1 linked to photoreceptors and P1 to bipolar cells, while P50 and N95 in pattern ERG reflect macular and ganglion cell function, where P50 arises from combined photoreceptor and bipolar activity and N95 reflects retinal ganglion cell output [36, 91].

Before incorporating ERG methods into routine cognitive assessments, it is critical to consider possible complicating factors, including strength of diagnostic evidence, the heterogeneity of ERG protocols, variability in outcome measures, small and clinically diverse study populations, and the lack of standardized thresholds for interpretation. Practical constraints, including long test times, equipment variability, and limited portability, also need to be assessed, as they may hinder clinical adoption, particularly in older populations. This scoping review aims to fill this gap by evaluating the utility of ERG in assessing change across the ADRD continuum by synthesizing evidence across full-field, pattern, and multifocal ERG approaches, compare their sensitivity to early neurodegenerative change, and examine their practicality for use in both clinical and research settings. In addition, the review aims to fill this gap by evaluating the utility of ERG in assessing change across the ADRD continuum by synthesizing evidence across full-field, pattern, and multifocal ERG approaches, compare their sensitivity to early neurodegenerative change, and examine their practicality for use in both clinical and research settings. In addition, the review aims to identify methodological inconsistencies, gaps in longitudinal and large-scale validation studies, and opportunities to advance portable and scalable ERG technologies to enhance early detection and disease monitoring.

Methods

Study design

This scoping review, registered on the Open Science Framework (OSF; ID: 10.17605/OSF.IO/PM8XC), was conducted according to a pre-registered protocol and guided by the Population, Concept, and Context (PCC) framework. Reporting follows the PRISMA-ScR

checklist (see **Supplementary Table 1**), and data synthesis employs Synthesis Without Meta-analysis (SWiM) to ensure methodological rigor and transparency. Findings are organized across thematic domains to facilitate interpretation.

Search strategy

Comprehensive searches were conducted in Web of Science, Scopus, PubMed, Embase, Google Scholar, PsycINFO, and CENTRAL to identify published studies, and in ClinicalTrials.gov to capture ongoing research. The search strategy combined two keyword groups using Boolean operators. The first group included terms related to retinal electrophysiology: "electroretinography," "electroretinogram," "ERG," "retinal electrical response," and "retinal function test." The second group targeted cognitive outcomes: "cognitive decline," "cognitive impairment," "cognitive dysfunction," "cognitive deficit," "neurocognitive impairment," "mild cognitive impairment," "MCI," "dementia," "Alzheimer disease," "neurodegenerative disease," and "neuropsychiatric disorder." No language or publication date restrictions were applied. All searches were performed by the first author (I.O.D.J.). The citations from the searches were imported and sorted by databases and subsequently imported into Covidence© for screening and data extraction.

Screening and selection

Two sequential screening stages were conducted following PRISMA-ScR guidelines. Titles and abstracts were first assessed for relevance, followed by full-text evaluation against prespecified eligibility criteria (see Fig. 1). Each record was independently reviewed by two reviewers, and discrepancies were resolved through discussion. The selection process is documented in a PRISMA flow diagram (see Fig. 1). Studies were included if they were original research involving human participants aged ≥ 50 years and used ERG as a biomarker in ADRD and/or normal aging. Studies were excluded if they involved pediatric or adolescent populations, animal or in vitro models, primary ophthalmic conditions without cognitive outcomes, non-original research (e.g., reviews, editorials, case reports, conference abstracts), lacked validated cognitive assessments or clear diagnostic criteria, provided insufficient methodological detail, or had inaccessible full texts.

Data extraction and synthesis

Data extraction encompassed over 20 variables, organized into three sections. Section 1 captured descriptive characteristics, including author (year), study objective, country, study design, sample size and composition, and participants' education status. Section 2 recorded ERG-specific measures, such as portability, modality, biomarker outcomes, stimulus protocols, and other neuroimaging assessments. Section 3 documented study limitations, evidence gaps, and other relevant variables to support subsequent analysis. Extracted data were synthesized in accordance with SWiM guidelines using a combination of tables, text, and figures.

Results

A total of 2,777 records were identified through database searches. After removal of 954 duplicates (34 manually and 920 automatically), 1,823 unique records remained for screening. Of these, 1,759 records were excluded based on title and abstract screening. Sixty-four (n = 64) full-text articles were assessed for eligibility, of which 39 were excluded for the following reasons: wrong disease focus (n = 30), wrong population (n = 1), wrong study design (n = 1), conference papers (n = 5), no full-text (n = 1), review articles (n = 2), and review articles (n = 2). Twenty-five (n = 25) studies met the inclusion criteria and were included in the final analysis (see Fig. 1).

Descriptive characteristics of included studies

A total of 25 studies were included, with eight conducted in the United States [60, 62, 63, 84, 94–97], four in Canada [37, 61, 79, 80], three in Italy [72, 76, 83], two each in Brazil [35, 98], China [33, 34], and Malaysia [71, 74], and one each in India [36], France [99], Poland [73], and Greece [91]. Eighteen (18) studies used a comparative cross-sectional design [33–37, 60–62, 72, 74, 76, 79, 80, 83, 84, 95, 97, 99], and seven were case-control studies [63, 71, 72, 91, 94, 96, 98]. Across all studies, 578 patients (540 with Alzheimer's disease or related dementias, 38 with mild cognitive impairment or other cognitive impairment) and 682 controls were

enrolled, for a total of 1,260 participants. Sample sizes ranged from 12 to 106. Sex distribution was generally balanced, although several cohorts were predominantly female [60]. Education was reported inconsistently, ranging from 6 to 18 years where available [34, 63, 94, 98] (see Table 1).

Table 1
Summary and Characteristics of Included Studies

Serial (No)	Author, year	Objective	Country	Study design	Sample size	Sample composition (Patients / Controls)	Sex (Patients / Controls)	Education Status (Mean ± SD) in years
Alzheimer's Disease and Mild cognitive impairment								
#1	Ariello *et al.*, 2025 [35]	Evaluate retinal structural (OCT) and functional (ERG) responses in a cohort classified by clinical and biological (amyloid PET) criteria.	Brazil (South America)	Cross-sectional	58	22 Aβ+ / 36 Aβ− / 29CI/ 30CU	Aβ+: 7M/15F; Aβ−: 10M/F16 CI: 12M/17F CU: 8M/22F	Not reported
#2	Asanad *et al.*, 2021 [60]	Assess ERG in cognitively healthy individuals with preclinical AD to discriminate normal vs pathological CSF biomarkers with normal retinal morphology.	United States (North America)	Cross-sectional	29	15 CH-PAT / 14 CH-NAT	CH-NAT: 10F/4M; CH-PAT: 12F/3M	Not reported
#3	Sen *et al.*, 2020 [36]	Evaluate structural and functional macular and optic nerve changes in AD patients versus healthy subjects.	India (Asia)	Cross-sectional	60	20 AD / 40 HC	Not reported	Not reported
#4	Zhao *et al.*, 2021 [34]	Explore ocular (functional and structural) abnormalities in AD and MCI in relation to hippocampal atrophy as potential biomarkers.	China (Asia)	Cross-sectional	59	17 AD / 23 MCI / 19 HC	HC: 8M/11F; MCI: 12M/11F; AD: 9M/8F	HC: 10.74 ± 3.00 MCI: 12.78 ± 3.48 AD: 10.47 ± 3.47
#5	Vidal *et al.*, 2022 [98]	Assess color vision and retinal processing in AD and MCI versus controls and correlate with brain glucose metabolism and β-amyloid.	Brazil (South America)	Case-control	53	13 AD / 23 MCI / 18 HC	F: Control 8, MCI 5, AD 5; M: Control 10, MCI 18, AD 8	HC: 15.5 ± 4.4; MCI: 10.2 ± 4.7; AD: 6.9 ± 4.5
#6	Trick *et al.*, 1989 [84]	Determine retinal ganglion cell dysfunction contribution to visual loss in SDAT.	United States (North America)	Cross-sectional	43	13 SDAT / 30 HC	Not reported	Not reported
#7	Sartucci *et al.*, 2010 [83]	Evaluate M, P, and K visual pathway involvement in AD via chromatic/luminance PERG and VEP.	Italy (Europe)	Cross-sectional	25	15 AD / 10 HC	AD: 9F/6M; Controls: 5F/5M	Education levels of controls analogous to patients

Serial (No)	Author, year	Objective	Country	Study design	Sample size	Sample composition (Patients / Controls)	Sex (Patients / Controls)	Education Status (Mean ± SD) in years
Alzheimer's Disease and Mild cognitive impairment								
#8	Rizzo *et al.*, 1992 [94]	Assess retinocalcarine pathway abnormalities in AD-related visual dysfunction.	United States (North America)	Case-control	73	38 AD / 35 elderly controls	13F/12M AD; controls matched	AD: 13.7 ± 3.5 HC: 14.7 ± 2.4
#9	Parisi *et al.*, 2001 [76]	Evaluate RNFL thickness and pERG function in AD and correlation with disease.	Italy (Europe)	Cross-sectional	34	17 AD / 17 HC	AD: 8M/9F; controls sex-matched	Not reported
#10	Mavilio *et al.*, 2020 [72]	Evaluate re-test PERG (RE-PERG) for inner retinal anomalies in early-onset AD.	Italy (Europe)	Case-control	52	17 AD-MCI, 16 VD-MCI / 19 HC	AD: 5M/12F; VD: 9M/7F; NC: 12M/7F	Education level equivalent to 8th grade (USA)
#11	Krasodomska *et al.*, 2010 [73]	Assess retinal and optic nerve function (PERG, PVEP) in early AD with normal ophthalmology.	Poland (Europe)	Cross-sectional	60	30 early AD / 30 HC	AD: 20F/10M; controls sex-matched	Not reported
#12	Prager *et al.*, 1993 [95]	Quantify effects of optical defocus or attention on PERG in AD versus controls.	United States (North America)	Cross-sectional	52	16 AD / 16 controls / 20 young healthy normals	AD: 9M/7F; Controls: 8M/8F; Young: 7M/13F	Not reported
#13	Kergoat *et al.*, 2002 [37]	Evaluate primary visual pathway function in DAT using pattern-reversal ERG and VEPs.	Canada (North America)	Cross-sectional	54	27 mild-moderate DAT / 27 controls	13M/14F both groups	Not reported
#14	Justino *et al.*, 2001 [61]	Examine distal retinal cell (photoreceptors, bipolar/Mueller, amacrine) function in early-to-moderate DAT.	Canada (North America)	Cross-sectional	46	23 DAT / 23 controls	Not reported	Not reported
#15	Devos *et al.*, 2005 [99]	Investigate flash ERG in DLB patients with visual hallucinations and post-mortem structural changes.	France (Europe)	Cross-sectional	49	16 DLB, 17 PD / 16 controls	DLB: 11M/5F; PD: 9M/8F; Controls: 5M/11F	Not reported
#16	Li *et al.*, 2021 [33]	Evaluate retinal vessel parameters and choroidal thickness in ATD via OCTA, and retinal function via flash ERG	China (Asia)	Cross-sectional	55	29 ATD, 26 age-matched controls	ATD: 15 M / 14 F; Control: 10 M / 16 F	Not specified

Serial (No)	Author, year	Objective	Country	Study design	Sample size	Sample composition (Patients / Controls)	Sex (Patients / Controls)	Education Status (Mean ± SD) in years
Alzheimer's Disease and Mild cognitive impairment								
#17	Ngoo *et al.*, 2019 [74]	Study RNFL thickness and visual electrophysiology (PERG, PVEP) in AD.	Malaysia (Asia)	Cross-sectional	50	25 AD / 25 controls	AD: 13M/12F; HC: 21M/4F	Not reported
#18	Katz *et al*., 1989 [62]	Assess whether optic nerve anatomical changes in AD reflect in PERG, FERG, PVEP, FVEP tests.	United States (North America)	Cross-sectional	12	6 AD / 6 controls	AD: 2F/4M; Controls: 2F/4M	Not reported
#19	Moschos *et al*., 2012 [91]	Assess macular/RNFL thickness and mf-ERG activity in AD.	Greece (Europe)	Case-control	60	30 AD / 30 HC	AD: 15M/15F; controls sex-matched	Not reported
#20	Nesher & Trick, 1991 [96]	Compare transient vs steady-state PERG in patients with retinal versus optic nerve disease.	United States (North America)	Case-control	31	13 SDAT/ 18 HC	Not reported	Not reported
#21	Cronin-Golomb *et al*., 1991 [97]	Describe visual functions in AD vs elderly controls, document normal aging, and evaluate retino-calcarine pathway contribution.	United States (North America)	Cross-sectional	106	59 AD, 35 ECS, 12 YCS	Not reported	Not reported
#24	Cabrera DeBuc *et al*., 2018 [63]	Correlate retinal vascular complexity with neurodegenerative changes in cognitive impairment using multimodal approach.	United States (North America)	Case-control	39	20 CI / 19 HC (initially 32 CI)	CI: 4M/16F; HC: 3M/16F	The three groups matched for education level (6–18 years)
#25	Fun *et al*., 2016 [71]	Examine PERG changes in urban elderly with MCI.	Malaysia (Asia)	Case-control	36	18 MCI / 18 controls	MCI: 5M/13F; HC: 16M/2F	Not reported
Normal aging								
#22	Justino *et al.*, 2001 [80]	Examine effects of advanced aging on inner retina and visual pathways in individuals ≥ 75 years.	Canada (North America)	Cross-sectional	58	30 young healthy / 28 elderly healthy	Young: 22F/8M; Elderly: 19F/9M	Not reported
#23	Freund *et al*. 2011 [79]	To evaluate the ffERG to assess age-related changes in retina function in humans	Canada (North America)	Cross-sectional	65	20–39 years (n = 27)/ 40–59 years (n = 20)/ 60–82 years (n = 18)	Not reported	Not reported

AD: Alzheimer’s Disease, ATD: Alzheimer’s Type Dementia, SDAT: Senile Dementia of the Alzheimer Type, MCI: Mild Cognitive Impairment, HC: Healthy Control, M: Male, F: Female, DLB: Dementia with Lewy Bodies, CH-NAT: cognitively healthy with normal amyloid/tau ratio, CH-PAT: cognitively healthy with pathologic amyloid/tau ratio.

ERG modality and stimulus conditions

Table 2 shows the ERG modality, portability, ERG-biomarker discriminant and cognitive correlates in ADRD.

Table 2
ERG Biomarker and Cognitive Correlates in ADRD

Study	Portability of ERG	ERG Modality	ERG biomarker discriminant†	Cognitive Associations
Alzheimer's Disease and Mild cognitive impairment				
Ariello *et al.*, 2025 [35]	Non-portable	ffERG	Aβ + individuals exhibited reduced PhNR_BT amplitude (8.02 ± 4.0 vs 11.62 ± 4.6 μV; p = 0.013), reduced PhNR_BT/b-wave ratio (0.23 ± 0.1 vs 0.31 ± 0.1; p = 0.009), prolonged a-wave latency (17.05 ± 0.9 vs 16.01 ± 0.9 ms; p = 0.033), reduced a-wave amplitude (28.49 ± 10.9 vs 39.64 ± 8.1 μV; p = 0.002) and reduced b-wave amplitude (117.40 ± 61.0 vs 162.92 ± 48.0 μV; p = 0.022).	There is a significant inverse correlation between MMSE scores and cerebral amyloid deposition (r = -0.62, p < 0.001). a-wave implicit time correlated positively with SUVr (r = 0.59, p < 0.001), b-wave implicit time correlated negatively with SUVr (r = -0.42, p = 0.001), b-wave amplitude correlated negatively with SUVr (r = -0.34, p = 0.006). PhNR did not show significant correlations with SUVr (p>0.05)
Asanad *et al*., 2021 [60]	Non-portable	ffERG, pERG	• *pERG*: No significant differences (N95: 6.1 ± 1.7 vs 5.7 ± 2.3 μV; P50: ~2.8 vs ~ 3.2 μV; ratio: ~2.5 vs ~ 2.0; all p > 0.05). • *ffERG*: Delayed implicit times in CH-PAT (a-wave: 14.1 ± 1.8 vs 15.5 ± 1.7 ms, p = 0.006; b-wave: 31.9 ± 1.2 vs 33.5 ± 2.7 ms, p = 0.01) with similar amplitudes (a-wave: 29.0 ± 21.2 vs 33.0 ± 17.1 μV; b-wave: 91.3 ± 30.5 vs 106.1 ± 37.2 μV; flicker: 74.8 ± 39.4 vs 90.1 ± 36.0 μV; all p > 0.05). • *PhNR*: Reduced amplitude in CH-PAT (~ 56 vs ~ 28 μV, p = 0.003) with similar implicit time (~ 86 vs ~ 89 ms; p > 0.05).	Not applicable.
Sen *et al*., 2020 [36]	Non-portable	mfERG	• *mfERG*: Responses were reduced and delayed in AD, with lower P1 (853.62 ± 228.93 vs. 1180.54 ± 237.65 nV), N1 (451.18 ± 122.12 vs. 613.77 ± 104.32 nV), and N2 (686.87 ± 189.43 vs. 988.48 ± 199.42 nV) amplitudes, and prolonged P1 implicit time (49.18 ± 4.47 vs. 44.65 ± 3.30 ms) (all p < 0.001).	• *PVEP*: Showed decreased P100 amplitude (7.62 ± 2.97 vs. 11.04 ± 2.89 μV) and increased latency (120.01 ± 6.99 vs. 108.36 ± 4.84 ms) in AD (p < 0.05). • *mfERG and Cognition*: Lower P1 and P1/N1 amplitudes correlated with greater cognitive impairment (P1 vs. CDRSOB: r = -0.41, p = 0.009; P1/N1 vs. MMSE: r = -0.572, p < 0.001). • *Disease Progression*: P1 amplitude decreased with longer disease duration (r = -0.447, p = 0.006).

Study	Portability of ERG	ERG Modality	ERG biomarker discriminant†	Cognitive Associations
Alzheimer's Disease and Mild cognitive impairment				
Zhao *et al*., 2021 [34]	Non-portable	ffERG	• *Rod and rod-cone fERG*: AD showed prolonged scotopic rod latency (59.47 ± 9.76 ms vs NC 49.93 ± 6.63 ms) and rod-cone latency (50.82 ± 10.65 ms vs NC 41.36 ± 7.21 ms; p < 0.017). MCI showed intermediate rod-cone latency increases (50.50 ± 10.52 ms vs NC 41.36 ± 7.21 ms; p < 0.017) whereas amplitudes were largely unchanged. • *Photopic fERG and 3 Hz flicker*: AD exhibited delayed 3.0 Hz flicker latency (30.63 ± 5.72 ms vs MCI 26.31 ± 5.90 ms and NC 25.85 ± 4.11 ms; p < 0.017). Cone latencies (ms) and amplitudes (μV) remained comparable across groups.	•*pVEP alterations*: P100 amplitude was reduced in AD (4.61 ± 2.17 μV vs MCI 6.92 ± 3.48 μV; p <0.017) while latencies were slightly prolonged in MCI (104.33 ± 10.69 ms) and AD (104.65 ± 14.54 ms) versus NC (99.89 ± 8.31 ms). N75 measures (latency ms, amplitude μV) were unchanged. •*VEP*: Only P100 amplitude correlated significantly with hippocampal volume (r = 0.389 μV; p = 0.003) •*ffERG*: amplitudes and latencies (μV, ms) did not correlate with hippocampus or cognition (ADAS-cog β; MMSE and MoCA; p>0.05).
Vidal *et al*., 2022 [98]	Non-portable	HF-ERG	• 36 *Hz HF-ERG amplitude*: MCI participants showed higher amplitudes (7.65 ± 1.45 μV) than AD patients (4.91 ± 2.84 μV), with a significant difference (p = 0.03); no significant differences between NC vs. MCI (p = 0.31) or NC vs. AD (p = 0.41). •*12 Hz harmonics*: No significant amplitude or phase differences were observed across NC, MCI, and AD groups (p>0.05).	• *HF-ERG with cognition*: HF-ERG parameters showed no significant associations (p > 0.05) with MMSE or RAVLT scores.
Trick *et al*., 1989 [84]	Non-portable	pERG	•*PERG Reductions in SDAT*: At 16.0 rps, mean amplitudes were 1.28 ± 0.76 μV (1st response) and 1.33 ± 0.82 μV (2nd response), showing significant reductions compared to controls (p<0.01)	•*VEP Sensitivity in SDAT*: Mean amplitude at 4.0 rps was 2.31 ± 1.51 μV (within normal limits; p >0.05), whereas at 16.0 rps it was 1.62 ± 0.74 μV, falling below reported normal values (p<0.01).
Sartucci *et al*., 2010 [83]	Non-portable	pERG	• *Luminance pERG*: P1 latency prolonged (61.0 ± 5.2 vs 38.1 ± 2.4 ms; p ≤ 0.01), N1 latency prolonged (96.1 ± 5.8 vs 73.4 ± 8.6 ms; p ≤ 0.05), P1 amplitude reduced (0.2 ± 0.3 vs 0.3 ± 0.2 μV; p ≤ 0.05), N1 amplitude reduced (0.36 ± 0.59 vs 1.5 ± 0.90 μV; p ≤ 0.05). • *Chromatic pERG*: RG P1 amplitude reduced (0.2 ± 0.14 vs 0.50 ± 0.3 μV; p ≤ 0.05); BY N1 amplitude reduced (1.30 ± 0.45 vs 3.31 ± 1.55 μV; p ≤ 0.05).	Not applicable.
Rizzo *et al*., 1992 [94]	Non-portable	ffERG foveal ERG, pERG	•*ffERG amplitudes and implicit times*: normal across blue, white, and red flashes; foveal ERG normal (0.29–0.43 μV; 35–38 ms). •pERG showed mixed patterns (normal and abnormal values)	• Pattern VEP were normal in all patients who could be tested reliably.
Parisi *et al*., 2001 [76]	Portable	pERG	•*PERG implicit times*: prolonged (P50 54.1 ± 2.24 vs 43.4 ± 4.32 ms; N95 80.51 ± 5.94 vs 70.18 ± 2.92 ms; P150 103.24 ± 2.9 vs 88.13 ± 4.12 ms; all p < 0.01). •*PERG amplitudes*: reduced (P50–N95 0.68 ± 0.10 vs 1.41 ± 0.32 μV; N95–P150	• No significant correlations (p>0.05) were found between any PERG measures and the scores for MMSE, ADAS, or IVSM.

Study	Portability of ERG	ERG Modality	ERG biomarker discriminant†	Cognitive Associations
Alzheimer's Disease and Mild cognitive impairment				
			0.79 ± 0.23 vs 1.85 ± 0.13 μV; p < 0.01).	
Mavilio *et al*., 2020 [72]	Portable	RE-pERG	•*PERG amplitude reductions in AD-related MCI*: AD-MCI patients showed significantly lower PERG amplitudes compared with healthy controls (1.33 ± 0.28 μV vs. 1.67 ± 0.16 μV; p = 0.01), whereas differences between AD-MCI and VD-MCI or VD-MCI and controls were not significant. •*Increased intrinsic phase variability in AD*: The RE-PERG SDph, reflecting intrinsic phase variability, was markedly higher in AD-MCI (0.32 ± 0.19) than in both VD-MCI (0.12 ± 0.04) and controls (0.12 ± 0.03), with highly significant differences (p < 0.001). •*VD-MCI resembles healthy controls*: VD-MCI patients showed no significant differences from healthy controls in either amplitude (p = 0.260) or SDph (p = 0.950), suggesting that RE-PERG phase variability specifically discriminates AD-related retinal dysfunction.	•MMSE showed a very weak negative correlation with PERG amplitude (Pearson Correlation Coefficient = -0.05, p = 0.710) and virtually no correlation with PERG SDph (CC = -0.006, p = 0.970); neither was statistically significant.
Krasodomska *et al*., 2010 [73]	Non-portable	pERG	• *pERG differences in amplitude and implicit times (AD vs control)*: P50 amplitude 3.1 ± 1.4 μV vs. 4.9 ± 1.4 μV (p < 0.0001), N95 amplitude 4.4 ± 1.8 μV vs. 7.1 ± 2.2 μV (p < 0.0001), P50 implicit time 51.8 ± 4.1 ms vs. 49.9 ± 2.4 ms (p < 0.03); N95/P50 ratio unchanged (1.5 ± 0.4 vs. 1.5 ± 0.2, NS).	• *PVEP differences amplitude and latency (AD vs control)*: 1°4' P100 amplitude 1.9 ± 0.7 μV vs. 2.2 ± 1.4 μV (NS), latency 113.9 ± 7.6 ms vs. 105.0 ± 5.6 ms (p < 0.0001); 16' P100 amplitude 2.5 ± 1.4 μV vs. 2.5 ± 1.6 μV (NS), latency 123.0 ± 7.6 ms vs. 114.1 ± 7.1 ms (p < 0.0001). • *Retinocortical time (RCT) delays*: RCT 1 (16' checks) 72.2 ± 6.4 ms vs. 64.2 ± 7.0 ms (p < 0.0001), RCT 2 (1°4' checks) 62.1 ± 6.5 ms vs. 55.1 ± 5.9 ms (p < 0.0001).
Prager *et al*., 1993 [95]	Non-portable	pERG	• *pERG amplitudes* were slightly lower in AD compared with controls (focused: 2.62 vs. 2.87 μV; inattentive: 2.20 vs. 2.65 μV), with higher relative increase during focused conditions (19% vs. 8%).	•pERG showed no significant correlation (p>0.05) with MMSE.
Kergoat *et al*., 2002 [37]	Non-portable	pERG	• *ERG amplitude*: P50, N95, and steady-state responses show no significant change relative to controls (p > 0.05). • *ERG latency*: P50 latency shows no significant change, comparable to controls (p > 0.05).	• *VEP (Cortical)*: Amplitude shows no significant change (p > 0.05); P100 latency is significantly delayed across all test conditions (p = 0.0164). • Retinocortical *transmission*: Time difference between VEP and ERG latencies is significantly prolonged in DAT subjects (p = 0.0101).
Justino *et al*., 2001 [61]	Non-portable	ffERG	• *Flash ERG of the a- and b-waves preserved*: ERG a-wave (Control 75 ± 6 μV vs DAT 69 ± 5 μV) and b-wave (Control 195 ± 10 μV vs DAT 188 ± 9 μV) amplitudes and latencies (~ 23–46 ms) showed no significant differences (p > 0.05). • *Oscillatory potentials (OP2) intact*: OP2 amplitude (Control 39 ± 3 μV vs DAT 34 ±	Not applicable

Study	Portability of ERG	ERG Modality	ERG biomarker discriminant†	Cognitive Associations
Alzheimer's Disease and Mild cognitive impairment				
			3 μV) and latency (~ 26 ms) were comparable between groups (p > 0.05).	
Devos *et al.*, 2005 [99]	Non-portable	ffERG	•*Maximum ERG*: a-wave implicit time is increased in DLB (32 [31/34] ms vs 31 [30/31] ms, p = 0.02) and a-wave amplitude is reduced (-134 [-177/-88] mV vs -175 [-208/-142] mV, p = 0.04). •*Cone ERG*: a-wave implicit time is slightly delayed in DLB (28 [27/30] ms vs 27 [26/28] ms, p = 0.01); b-wave implicit time is significantly delayed (52 [51/53] ms vs 49 [48/50] ms, p = 0.001); amplitudes show no significant change. •*Rod ERG*: b-wave implicit time is delayed in DLB (106 [102/115] ms vs 99 [98/104] ms, p = 0.005) with reduced amplitude (173 [85/209] mV vs 220 [191/250] mV, p = 0.004). •*Blue ERG*: b-wave implicit time is delayed in DLB (94 [89/102] ms vs 87 [85/93] ms, p = 0.01) with amplitude reduced (205 [124/250] mV vs 248 [213/295] mV, p = 0.01).	Not applicable
Li *et al*., 2021 [33]	Portable	ffERG	•*ERG findings*: ATD patients showed significantly reduced average b-wave amplitude compared to controls (130.97 ± 21.73 vs. 149.54 ± 30.90 μV; p = 0.034)	Not applicable
Ngoo *et al.*, 2019 [74]	Non-portable	pERG	• *PERG amplitude reduced and latency prolonged*: AD patients show significantly delayed P50 latency (63.88 ± 7.94 ms vs 54.76 ± 8.24 ms, p < 0.001) and markedly reduced P50 (1.79 ± 0.64 μV vs 4.49 ± 1.44 μV, p < 0.001) and N95 amplitudes (2.43 ± 0.90 μV vs 6.21 ± 2.65 μV, p < 0.001); N35 and N95 latencies are not significantly different.	•*PVEP amplitude and latency impaired*: AD patients have significantly delayed P100 (119.00 ± 9.07 ms vs 106.68 ± 10.53 ms, p < 0.001) and N135 latencies (145.20 ± 8.53 ms vs 130.20 ± 7.94 ms, p < 0.001) with reduced P100 (3.71 ± 1.60 μV vs 9.78 ± 2.82 μV, p < 0.001) and N135 amplitudes (3.67 ± 2.02 μV vs 10.52 ± 3.49 μV, p < 0.001); N75 latency shows no significant difference.
Katz *et al*., 1989 [62]	Non-portable	pERG, ffERG	• *PERG*: b-Wave amplitude reduced in Alzheimer's (1.34 ± 0.59 μV) vs controls (2.57 ± 0.53 μV), p = 0.004; a-wave (38.08 ± 4.73 vs 35.83 ± 2.81 ms, p = NS) and b-wave latency (60.83 ± 4.55 vs 62.92 ± 2.60 ms, p = NS) •*FERG*: a-wave (23.6 ± 3.77 vs 24.2 ± 1.48 ms, p = NS), b-wave latency (45.67 ± 3.72 vs 46.7 ± 4.08 ms, p = NS) and b-wave amplitude (195.8 ± 78.52 vs 286.13 ± 41.04 μV, p = NS)	•*PVEP*: N1 (87.1 ± 5.91 vs 78.13 ± 8.16 ms, p = NS), P2 (115.75 ± 8.29 vs 112.42 ± 4.49 ms, p = NS), N2 (160.58 ± 10.27 vs 148.83 ± 9.22 ms, p = NS) — all not significant. •*Retinocortical time*: AD 50.7 ± 8.51 ms vs controls 49.5 ± 4.86 ms, p = NS.
Moschos *et al*., 2012 [91]	Non-portable	mfERG	•mfERG P1 amplitude reduced in fovea (136.69 ± 64.6 vs 294 ± 7.83 nV/deg²; p < 0.0001). No amplitude differences in rings 2–3 (p > 0.05). P1 latency shorter in ring 2 (37.32 ± 2.83 vs 40.6 ± 4.35 ms; p = 0.0401).	Not applicable.
Nesher & Trick, 1991 [96]	Non-portable	pERG	• *Steady-State PERG (SSPERG)*: 37% reduction in AD/SDAT versus controls (p < 0.05), indicating significant impairment.	Not applicable.

Study	Portability of ERG	ERG Modality	ERG biomarker discriminant†	Cognitive Associations
Alzheimer's Disease and Mild cognitive impairment				
			•Transient PERG (TPERG) components (N1-P1, P1-N2, and P1-N2/N1-P1 ratio): Reductions of 17–28% in AD/SDAT versus controls ($p > 0.05$).	
Cronin-Golomb *et al*., 1991 [97]	Non-portable	ffERG, pERG, foveal ERG	• *ERG measures*: All testable AD patients showed normal amplitudes and latencies.	No statistically significant association ($p>0.05$) between ERG and backward masking and color discrimination.
Cabrera DeBuc *et al*., 2018 [63]	Non-portable	ffERG, 30 Hz flicker ERG	• *Amplitude reduction*: Cognitive impairment group showed a significantly lower ERG amplitude (12.6 μV [10.9–14.4]) compared with cognitively healthy participants (37.4 μV [36.6–38.2]); $p < 0.001$. • *Prolonged implicit time*: Implicit time was significantly longer in the cognitive impairment group (31.2 ms [29.6–32.8]) versus healthy controls (29.6 ms [29.4–29.8]); $p < 0.001$.	Not applicable.
Fun *et al*., 2016 [71]	Non-portable	pERG	• *pERG amplitudes (MCI vs controls)*: No significant differences for P50 (1.86 ± 0.65 vs 1.54 ± 0.74 μV; $p = 0.173$) and N95 (2.61 ± 1.16 vs 2.60 ± 1.25 μV; $p = 0.977$). • *pERG implicit times (MCI vs controls)*: P50 (56.27 ± 6.20 vs 56.15 ± 4.98 ms; $p = 0.947$) and N95 (94.66 ± 5.76 vs 97.18 ± 6.35 ms; $p = 0.221$).	Not applicable
Normal Aging				
Justino *et al*., 2001 [80]	Non-portable	pERG	*ERG amplitudes* significantly lower in older vs young across transient P50 (3.82 vs 2.46 μV), N95 (6.05 vs 4.09 μV), steady state (3.47 vs 2.20 μV) (all $p < 0.0001$). *ERG latencies* significantly delayed by 5–8 ms (e.g., 1 Hz: 52.82 vs 59.32 ms; $p < 0.0001$).	*Transient and steady state amplitude of VEP reduced in older adults (75–88 years) relative to younger (20–32 years) ones*: Transient (3.91 ± 0.32 vs 5.81 ± 0.47 μV; $p<0.01$) and steady state (*21 minarc; 98% contrast; 8 Hz*: 3.20 ± 0.27 vs 4.17 ± 0.40μV, $p<0.05$; *21 minarc; 50% contrast; 8 Hz*: 2.40 ± 0.20 vs 3.41 ± 0.27μV, $p<0.01$). *Transient and steady state latencies of VEP reduced in older adults relative to younger ones*: 21 minarc; 98% contrast; 1 Hz (120.93 ± 1.63 vs 106.97 ± 0.92ms, $p<0.0001$); 21 minarc; 50% contrast; 1 Hz (127.42 ± 1.80 vs 109.79 ± 1.00 ms, $p<0.0001$)
Freund *et al*. 2011 [79]	Non-portable	ffERG	*Photopic and dark-Adapted responses*: In subjects 60+, photopic recordings show reduced "hill effect" and increased a- and b-wave amplitudes at high stimulus strengths ($p <0.001$), while dark-adapted responses show reduced a-wave amplitudes, stable b-waves (higher B/A ratio), and prolonged implicit times correlated with age ($p = 0.033$). *Adaptation and recovery dynamics*: Older age associates with delayed dark adaptation for rod and L/M cone responses and transiently faster dark-	Not applicable

Study	Portability of ERG	ERG Modality	ERG biomarker discriminant†	Cognitive Associations
Alzheimer's Disease and Mild cognitive impairment				
			current recovery between 0.9 and 2 seconds ($p < 0.05$).	

†Mean ± Standard deviation; DPERG : Pattern Electroretinography; ffERG : Full-Field Electroretinography; PhNR : Photopic Negative Response; mfERG : Multifocal Electroretinography; FERG : Flash Electroretinography; PVEP : Pattern Visual Evoked Potential; HF-ERG : High-Frequency Electroretinography; Foveal ERG : Foveal Electroretinography; OPs : Oscillatory Potentials; 30 Hz Flicker ERG : 30 Hertz Flicker Electroretinography; ADAS : Alzheimer's Disease Assessment Scale; ADAS-cog : Alzheimer's Disease Assessment Scale–Cognitive Subscale; CDR-SOB : Clinical Dementia Rating Sum of Boxes; HAMD : Hamilton Depression Scale; ICARS : International Cooperative Ataxia Rating Scale; IVM : Immediate Visual Spatial Memory; MoCA : Montreal Cognitive Assessment; RAVLT : Rey Auditory Verbal Learning Test; SARA : Scale for the Assessment and Rating of Ataxia; UPDRS : Unified Parkinson's Disease Rating Scale.

Most studies utilized non-portable ERG systems (n = 22), while a few employed portable devices (n = 3), primarily the RETeval system (see **Supplementary Table 2**). The most frequently used ERG modalities were transient or steady-state PERG (n = 14), followed by ffERG (n = 10), mfERG (n = 2), HF-ERG (n = 1), and foveal ERG (n = 1). Four studies used both ffERG and PERG, as shown in Table 2. A variety of ERG systems and recording protocols were employed, generally adhering to ISCEV standards. Most studies used either Ganzfeld or pattern-based stimulation with corneal (DTL, ERG-jet, or gold foil) or skin electrodes, and light- or dark-adaptation periods ranged from 5 to 30 minutes depending on the protocol [34–36, 60, 83, 84, 98]. Full-field ERG studies commonly utilized white or red flashes on photopic or scotopic backgrounds, with flash durations between 1–4 ms and frequencies from 0.1 to 30 Hz [33, 61, 94]. Pattern ERG protocols predominantly employed black-and-white checkerboards or sinusoidal gratings, with contrasts of 90–98%, luminance around 17–120 cd/m², and spatial frequencies ranging from 0.3 cycles/degree to 1.7 cycles/degree [37, 72–74, 76]. Multifocal ERG studies typically used hexagonal arrays with high contrast and varying stimulus frequencies [36, 91, 92], while chromatic and harmonic stimuli were used in some studies to probe specific retinal pathways, including luminance and color opponency [83, 98] (see **Supplementary Table 2**). Of note, cognitive, neuroimaging and other ocular biomarkers used across studies are summarized (see **Supplementary Table 3)**.

ERG changes in normal aging

Normal aging is associated with measurable declines in retinal function. Older adults show reduced pERG amplitudes, reflecting diminished RGCs responsiveness and weaker retinal output, which translates to decreased VEP amplitudes and prolonged latencies in the visual cortex. These effects are strongest when both magnocellular and parvocellular pathways are engaged [80]. Full-field ERG in adults ≥ 60 years reveals reduced photopic "hill effect," increased a- and b-wave amplitudes at high stimulus strengths, and dark-adapted responses with lower a-wave amplitudes, stable b-waves, elevated B/A ratios, and prolonged implicit times [79]. Aging also slows adaptation, delaying dark adaptation for rods and L/M cones while briefly accelerating dark-current recovery (0.9–2 s) [79]. Overall, aging impairs photoreceptor, post-receptor, and RGC function, slowing retinal signal transmission and altering recovery dynamics.

ERG changes in Alzheimer's disease (AD) and mild cognitive impairment (MCI)

Electroretinography studies in AD and MCI consistently revealed retinal dysfunction, predominantly affecting inner retinal and ganglion cell pathways across all ERG modalities.

ffERG findings

Full-field ERG demonstrated consistent functional retinal alterations in AD, including reduced PhNR and b-wave amplitudes, as well as prolonged a-wave, b-wave, rod, and flicker implicit times [33–35, 37, 60, 100]. Notably, some studies, reported significant correlations between specific ffERG parameters and cerebral amyloid deposition, supporting the notion that retinal dysfunction

may reflect underlying ADRD pathology [35]. One study show a relatively decreasing trends among patients relative to control but this was not statistically significant [62] whiles two studies show no noticeable differences between groups [61, 94, 97]. Furthermore, among studies that examine associations between ERG measures and cognitive test scores, none report statistically significant relationships [34, 97] Importantly, these results suggest that retinal dysfunction is detectable even when standard cognitive assessments remain within normal ranges. This indicates that ffERG may capture early neurophysiological changes that precede clinically measurable cognitive decline, which highlights its potential as a sensitive, non-invasive biomarker of AD-related neurodegeneration (**see** Table 2).

pERG findings

Pattern electroretinography studies revealed retinal ganglion cell dysfunction, with reduced P50, N95, P1, N1, and N2 amplitudes, as well as prolonged latencies across these components [62, 72–74, 76, 84, 96, 101]. Although some studies showed a lower trend in AD patients relative to controls this was not statistically significant [37, 95] whereas another found no differences in PERG N95 amplitude between groups [60]. One study focused on MCI patients observed a decreasing trends in P50 and N95 amplitudes and implicit times yet relative to controls this differences did not research statistical significance [71]. Contrary to controls, one study showed increased phase variability in MCI [72]. PERG measures showed weak or non-significant correlations with global cognitive assessments, including the MMSE [72, 76, 95], Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog)[76], and Immediate Verbal Memory Score (IVSM)[76]. The lack of strong correlations despite clear electrophysiological abnormalities suggests that pERG may detect early retinal changes that standard cognitive tests may miss, highlighting its potential as a sensitive biomarker in ADRD (see Table 2).

mfERG findings

mfERG findings demonstrate consistent central retinal dysfunction in AD, characterized by reduced amplitudes for P1, N1, and N2, along with prolonged P1 implicit time (all $p < 0.001$)[36]. A marked reduction in P1 amplitude is observed in the fovea ($p < 0.0001$), with no significant differences in peripheral regions, while shorter P1 latency in intermediate rings ($p = 0.0401$) indicates regional variability in temporal responses [102]. Reduced P1 amplitude correlates with greater disease severity and longer duration, with significant associations with CDR-SOB ($r = -0.41$; $p = 0.009$) and disease duration ($r = -0.447$; $p = 0.006$), supporting the role of mfERG alterations as indicators of progressive neurodegeneration [36] (see Table 2**)**.

HF-ERG findings

HF-ERG recordings showed no significant group differences for 12 Hz chromatic ($p = 0.31$) or 36 Hz luminance stimuli ($p = 0.41$). However, individuals with MCI exhibited higher 36 Hz amplitudes compared with those with Alzheimer's disease (7.65 ± 1.45 vs 4.91 ± 2.84 μV; $p = 0.03$). HF-ERG measures were not significantly correlated with global cognition or verbal memory performance, as assessed by MMSE and RAVLT ($p > 0.05$). The lack of correlation with cognitive scores suggests that HF-ERG may detect retinal dysfunction before measurable cognitive decline, indicating its potential sensitivity as an early biomarker of disease-related retinal changes [98].

Limitations of included studies

Most investigations involved small sample sizes [62, 72, 76, 83, 84, 91, 96, 97], often focusing on either severe AD or MCI/mild dementia [35, 36], which limits generalizability across the disease spectrum. Cross-sectional designs were common [33–37, 60–62, 72, 74, 76, 80, 83, 84, 95, 97, 99], constraining causal inference, and heterogeneity in cohorts, including high variability among controls and low A+ dementia (participants with dementia who tested positive for amyloid-beta (Aβ) pathology) proportions, further complicated interpretation [98]. Technical and methodological challenges were frequent: ERG recordings were sensitive to blinking, defocus, and behavioral compliance[33, 73, 94, 95], visual field testing was sometimes unreliable [61], and OCT or choroidal measures could be affected by manual analysis, diurnal fluctuations, or software constraints [33, 76]. Additionally, pharmacological or cognitive confounds, such as cholinesterase inhibitors or L-DOPA, may have influenced retinal function [37, 99]. In MCI studies, exploratory designs, small and unbalanced samples, and variable stimulus/electrode conditions further limited conclusions [63, 71, 80]. Collectively, these limitations highlight the need for larger, longitudinal, standardized studies to clarify retinal biomarkers in cognitive decline (see **Supplementary Table 4**).

Discussion

This scoping review aimed to characterize the landscape of ERG evidence supporting its potential as a discriminant biomarker for ADRD in older adults. Most studies predominantly employed PERG rather than ffERG or mfERG, although a few combined PERG and ffERG. Non-portable ERG systems were more commonly used than portable systems (see Table 2).

Across studies, ffERG consistently showed reduced a-wave and b-wave amplitudes, decreased PhNR/b-wave ratios, and prolonged a-wave and b-wave implicit times [33–35, 60, 99]. pERG components, P1, N1, P50, and N95, were mostly delayed or attenuated [34, 60, 62, 72, 74, 76, 83, 84], while mfERG showed reduced N1, P1, and N2 amplitudes with prolonged implicit times [36, 91], with only occasional correlation with disease severity [36]. This suggests that mfERG may be a weaker and less sensitive marker of cognitive decline. Overall, cognitive associations were modest with a subset of studies that reported inverse correlations between ERG latencies, MMSE scores, and amyloid burden (see Table 2).

Neuropsychological continuity [103] and neurodegenerative models [104] suggest that retinal abnormalities reflect broader CNS pathology and capture early functional disruption in neuropsychiatric and neurodegenerative conditions [103, 104]. The neurocognitive efficiency hypothesis emphasizes that slowed retinal signal transmission, indicated by reduced amplitudes and prolonged implicit times, compromises neural processing speed [105], while predictive coding accounts link retinal dysfunction to elevated prediction errors and impaired perceptual inference [106, 107]. Cognitive reserve theory moderates these pathways by proposing that individual resilience can buffer the cognitive impact of retinal deficits [108]. Taken together, the convergence of retinal physiology and neurodegeneration supports the growing interest in ERG as a potential biomarker for ADRD. To this end, and in line with the theoretical models, this study proposes that specific ERG abnormalities may reflect early retinal dysfunction and mirror initial CNS changes in ADRD, offering a sensitive, non-invasive *in vivo* biomarker to detect disease onset and track progression (see Fig. 2).

Consistent with this conjecture, individuals living with ADRD demonstrate reduced a-wave and b-wave amplitudes alongside prolonged implicit times across ffERG studies compared with healthy controls, supporting the presence of early retinal dysfunction [33–35, 37, 60, 100] (see Table 2). Reduced amplitudes likely reflect impaired synaptic transmission and diminished photoreceptor to bipolar cell signaling [86, 109, 110], whereas delayed implicit times suggest slowed neural conduction within retinal circuits [60, 63, 111]. Previous studies by Pereira *et al*. showed elevation of presynaptic markers (synaptosomal-associated protein 25, SNAP25; growth-associated protein 43, GAP43), postsynaptic markers (neurogranin, NRGN), and axonal markers (neurofilament light chain) in early AD pathology, that is, in amyloid-β-positive individuals without tau pathology, which suggests a compensatory synaptic response rather than simple neuronal loss in response to early amyloid-β, where neurons upregulate synaptic and axonal proteins to maintain communication despite emerging dysfunction [112]. Presumably, longitudinal ERG assessments may recapitulate this transition at the functional level by detecting early preserved or elevated responses, followed by progressive reductions in amplitude and delays in implicit time as compensatory mechanisms fail and functional decline emerges. However, given that all studies are cross-sectional snapshots we believe that - as disease progresses - this compensatory capacity likely declines, which results in measurable functional deficits on ERG recordings (see Table 2). These abnormalities align with experimental evidence from AD mouse models, where accumulation of tau and amyloid-β disrupts axonal transport and synaptic integrity in the retina, which leads to neuronal dysfunction that may precede overt brain pathology [88, 113]. Importantly, the pooled evidence supports retinal ERG as an in vivo proxy for CNS neurodegeneration, where alterations reflect cognitive changes.

Similar to ffERG findings, PERG studies in ADRD show reduced amplitudes and delayed latencies across multiple components, including P1, N1, P50, and N95 [62, 72–74, 76, 84, 96, 101]. While ffERG assesses global retinal function, reflecting the combined activity of photoreceptors, bipolar cells, and downstream retinal circuits, PERG provides localized measurements of RGCs activity [70, 93], whose axons form the optic nerve and transmit visual information to the primary and secondary visual cortices. RGCs display vulnerability in ADRD due to their high metabolic demand [114], long axonal projections, and direct connectivity to central neural pathways [65], a vulnerability amplified by amyloid-beta (Aβ) accumulation and tau pathology detected in human and animal retinas [115, 116]. Functionally, P1 and N1 reflect initial RGC depolarization and early post-synaptic processing [96, 101], P50 ascending phase reflects summed RGC depolarization influenced by bipolar cell input, and N95 descending phase reflects RGC spiking activity [73, 76]. Aβ deposits disrupt synaptic transmission between photoreceptors, bipolar cells, and RGCs, that impair P1 and N1 responses [83, 96], while tau aggregation within RGC axons compromises axonal transport and spiking activity [88, 117], producing delayed and reduced P50 and N95 components [73, 76]. Collectively, these electrophysiological alterations indicate inner retinal circuit dysfunction linked to hallmark AD pathology and mirror cortical and subcortical neurodegeneration (see

Table 2). Together, these findings suggest that PERG provides precise, cell-specific insights into inner retinal dysfunction to complement ffERG's global retinal health.

Furthermore, evidence from mfERG also revealed a reduced N1, P1, and N2 amplitudes with prolonged implicit times in ADRD relative to healthy controls (see Table 2) which suggest both weakened synaptic output and delayed retinal signal transmission [36, 91]. The N1 and P1 components primarily reflect the activity of photoreceptors and bipolar cells [118], whereas the N2 is associated with inner retinal processing, particularly ganglion cell and amacrine cell function [118]. The attenuation of these components suggests that ADRD-related neurodegenerative processes disrupt synaptic integrity and slow neurotransmission across multiple retinal layers [36, 91]. These retinal deficits likely parallel CNS pathology, including synaptic protein dysregulation and impaired neuronal connectivity [36, 91]. Collectively, mfERG alterations pinpoint localized retinal circuit dysfunction which may be of clinical utility for early detection and monitoring of ADRD.

Of the study that utilized HF-ERG found a distinct difference between MCI and AD at high but not lower stimulus thresholds (see Table 2). Specifically, individuals with MCI exhibited higher 36 Hz amplitudes than those with AD, while no differences appeared for 12 Hz chromatic or 36 Hz luminance, suggesting that specific high-frequency retinal pathways were affected differently as the disease progressed [98]. HF-ERG measures did not correlate with global cognition (MMSE) or verbal memory (RAVLT), indicating that these retinal changes occurred independently of overt cognitive decline [98]. This dissociation supported the concept that retinal ERG could detect subclinical dysfunction, potentially reflecting early synaptic loss, impaired retinal ganglion cell signaling, or disruptions in photoreceptor–bipolar circuitry before deficits appeared in cognitive tests [98]. The sensitivity of HF-ERG to subtle functional alterations highlighted its potential as an early biomarker capable of identifying individuals at risk for AD or monitoring disease progression prior to clinical onset [98]. Collectively, the findings also emphasized the importance of examining multiple stimulus parameters, such as frequency and chromaticity, to capture the nuanced patterns of retinal changes in neurodegeneration (see **Supplementary Table 2**).

Changes in ERG reflect cortical processing, whereas ffERG patterns fluctuate in normal aging; this distinction may be key for differentiating typical age-related retinal changes from those associated with cognitive decline (see Table 2). For instance, older adults showed reduced pERG amplitudes which suggest a diminished RGC responsiveness and weaker retinal signal output. Interestingly, these retinal deficits corresponded decreased VEP amplitudes and prolonged latencies, which indicate slower and less synchronized cortical processing [80]. Effects appear strongest under stimuli that engage both magnocellular and parvocellular pathways and weaker under stimuli that favor a single pathway [80]. Further, in normal aging, photopic responses retain dynamic range, with a modestly reduced "hill effect," which allows a- and b-wave amplitudes to rise at higher stimulus strengths, while scotopic responses show slight a-wave reductions and mildly elevated B/A ratios [79]. In AD, ERG amplitudes fall across photopic and scotopic conditions, the hill effect flattens, and retinal responsiveness declines globally (see Table 2). Of note, the measurable ERG signals persistence demonstrates that retinal pathways remain partially functional and provide a sensitive window to detect neurodegenerative changes beyond normal age-related decline [79, 80]. Taken together, these results suggest that retinal dysfunction in aging slows and desynchronizes cortical processing, whereas AD produces widespread retinal impairment that may serve as an early indicator of disease progression.

Most studies predominantly employed PERG rather than ffERG or mfERG (see Table 2), reflecting a focus on RGC function, which is particularly vulnerable in the early stages of ADRD [119]. PERG captures localized responses from the inner retina, providing sensitive measures of RGC integrity and optic nerve conduction, whereas ffERG assesses global retinal function, integrating photoreceptor, bipolar cell, and downstream circuit activity [70, 93]. In contrast, mfERG, which maps localized responses across the central retina, was used less frequently, likely due to its greater technical complexity, longer testing times, and limited availability in clinical research settings [36, 91]. The relatively few studies that combined PERG and ffERG suggest an emerging interest in capturing both localized and widespread retinal dysfunction, allowing for a more comprehensive assessment of retinal circuitry alterations [60, 62, 94, 97]. Mechanistically, reductions in PERG amplitude and delayed latencies may indicate synaptic dysfunction or axonal degeneration of RGCs, paralleling early cortical and subcortical changes observed in ADRD [34, 60, 62, 72, 74, 76, 83, 84]. Together, the high utility of PERG highlights its potential as a robust proxy for retinal dysfunction in ADRD. Nevertheless, mfERG offers unique positional information on localized retinal performance that PERG and ffERG cannot provide [120]. Its limited use in ADRD research represents a missed opportunity, as incorporating mfERG could reveal early, region-specific retinal changes and provide a more comprehensive assessment of retinal circuitry [36, 91, 120]. Expanding mfERG use alongside

PERG and ffERG may improve detection sensitivity and help clarify the relationship between retinal dysfunction and cognitive decline.

A preponderance of studies utilized non-portable ERG systems relative to portable ones (Table 2). Given the bulkiness of non-portable ERG, one might have expected their lower usage compared with portable systems. While the observed pattern reflects an overreliance on conventional laboratory-based equipment for standardized and high-fidelity recordings, it should also be viewed in the context of the recent emergence of portable ERG devices, such as the RETeval system. Given the their relative simplicity [121–123] and high reproducibility [124–126], portable ERG devices may provide important opportunities, particularly for older adults affected by ADRD, who face mobility limitations, fatigue, or difficulty traveling to clinical or research centers [127]. To capitalize on the advantages of portable ERG devices, we recommend that researchers and clinicians use these systems in longitudinal studies, particularly for older adults with ADRD who face mobility or health-related barriers. Researchers should implement standardized protocols to ensure consistent electrode placement, stimulus conditions, and environmental control, even in home or bedside settings Focus should be placed on sensitive metrics such as a- and b-wave amplitudes and implicit times, pERG P50/N95 responses, oscillatory potentials, and mfERG measures, which can respectively detect global and/or localized retinal dysfunction across multiple retinal regions. Combining ERG with cognitive tests, OCT imaging, and other biomarkers can strengthen links between retinal and cortical changes, while repeated measurements over time may allow early detection of dysfunction and track disease progression. Taken together, using portable systems in diverse and community-based populations can improve accessibility, compliance, and generalizability, ultimately providing robust evidence to support the use ERG in ADRD diagnosis.

This review has several notable strengths. Using the PRISMA-sCR framework, eight medical and public databases were systematically searched to provide a comprehensive mapping of existing evidence on ERG utility in ADRD. The use of a pre-registered protocol, along with systematic search and SWiM reporting guidelines, ensured methodological rigor, transparency, and reproducibility. Despite variation in ERG modalities and protocols across studies (see **Supplementary Table 3**), the evidence consistently supports retinal ERG as a reliable, non-invasive biomarker of cognitive dysfunction, often detecting functional retinal loss before structural changes appear on OCT. PERG, including steady-state and RE-PERG, provides robust measures of retinal ganglion cell (RGC) function and can discriminate AD from vascular dementia, while mfERG and ganglion cell layer thickness offer sensitive, localized assessment of retinal circuits. Combined OCT and electrophysiology approaches allow objective evaluation of structural and functional involvement, and PhNR, VEP, and PERG detect subtle visual pathway dysfunction. Portable multimodal ERG systems provide ecologically valid avenues for early screening, monitoring progression, and linking retinal changes to cortical pathology, while accounting for normal age-related variations (see **Supplementary Table 4**). Some limitations include the predominance of cross-sectional or case-control designs with small sample sizes, which restrict causal inference, generalizability, and longitudinal tracking, as well as limited studies correlating ERG outcomes with cognitive assessments (see **Supplementary Table 4**). Collectively, these gaps highlight the need for future research using portable ERG devices to expand longitudinal evidence, assess preclinical changes, monitor disease progression, and evaluate intervention effects.

Conclusion

This scoping review demonstrates that individuals living with ADRD exhibit consistent and marked reductions in ERG signatures, reflecting widespread retinal dysfunction across inner and outer retinal pathways (see Fig. 3).

Although associations with cognitive performance are generally modest and variable, the convergence of layer-specific ERG abnormalities suggests that retinal electrophysiology captures neurobiological changes that are only partially reflected in conventional clinical assessments. This dissociation highlights the potential of ERG as a sensitive functional biomarker of neurodegeneration across the cognitive spectrum. Despite promising findings, current evidence is limited by cross-sectional designs, small cohorts, and reliance on non-portable systems, constraining clinical translation. The emergence of portable ERG technologies offers new opportunities for scalable, real-world application. Future research should prioritize longitudinal validation, harmonization of ERG acquisition and analysis protocols, and integration with cognitive, structural, and vascular imaging measures. Together, these approaches may enable a more comprehensive and mechanistically grounded framework for early detection, disease monitoring, and therapeutic evaluation in ADRD.

Abbreviations

ADRD
Alzheimer’s disease and related dementia
CDR-SOB
Clinical Dementia Rating Sum of Boxes
ChPERG
Chromatic PERG
ERG
Electroretinography
ffERG
Full-field electroretinography
fERG
Flash electroretinography
GCIPL
Ganglion Cell–Inner Plexiform Layer
MCI
Mild Cognitive Impairment
mfERG
Multifocal electroretinography
MMSE
Mini–Mental State Examination
MoCA
Montreal Cognitive Assessment
MRI
Magnetic resonance imaging disease
OCT
Optical coherence tomography
OSF
Open Science Framework
PET
Positron emission tomography
PhNR
Photopic negative response
pERG
Pattern electroretinography
PRISMA-ScR
Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews
RNFL
Retinal Nerve Fiber Layer
ssPERG
Steady-state PERG
SWiM
Synthesis Without Meta-analysis
tPERG
Transient PERG.

Declarations

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Authors Contribution

Conceptualization and design: I.O.D.J and C.M.G.; **Project administration:** I.O.D.J, K.J.H, D.S.R., T.B. and C.M.G.; **Resources:** I.O.D.J, K.J.H, D.S.R., T.B. and C.M.G.; **Methodology:** I.O.D.J, K.J.H, D.S.R., T.B. and C.M.G.; **Investigation:** I.O.D.J, K.J.H, D.S.R., T.B. and C.M.G.; Data curation and formal analysis: I.O.D.J. and C.M.G.; **Software:** I.O.D.J. and C.M.G.; **Writing original draft:** I.O.D.J. and C.M.G.; **Writing reviews and critically editing for important intellectual content**: I.O.D.J, K.J.H, D.S.R., T.B. and C.M.G.; **Approved the final version of the manuscript:** I.O.D.J, K.J.H, D.S.R., T.B. and C.M.G.; **Agreement to be accountable for all aspects of the study:** I.O.D.J, K.J.H, D.S.R., T.B. and C.M.G.; **Correspondence:** I.O.D.J and C.M.G.; Supervision: C.M.G.

Conflict of interest statement

The authors declare that they have no competing interests.

Consent for publication

Not applicable

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Data Availability

The data supporting the conclusions of this work are included within the manuscript and its associated supplementary files.

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Figures

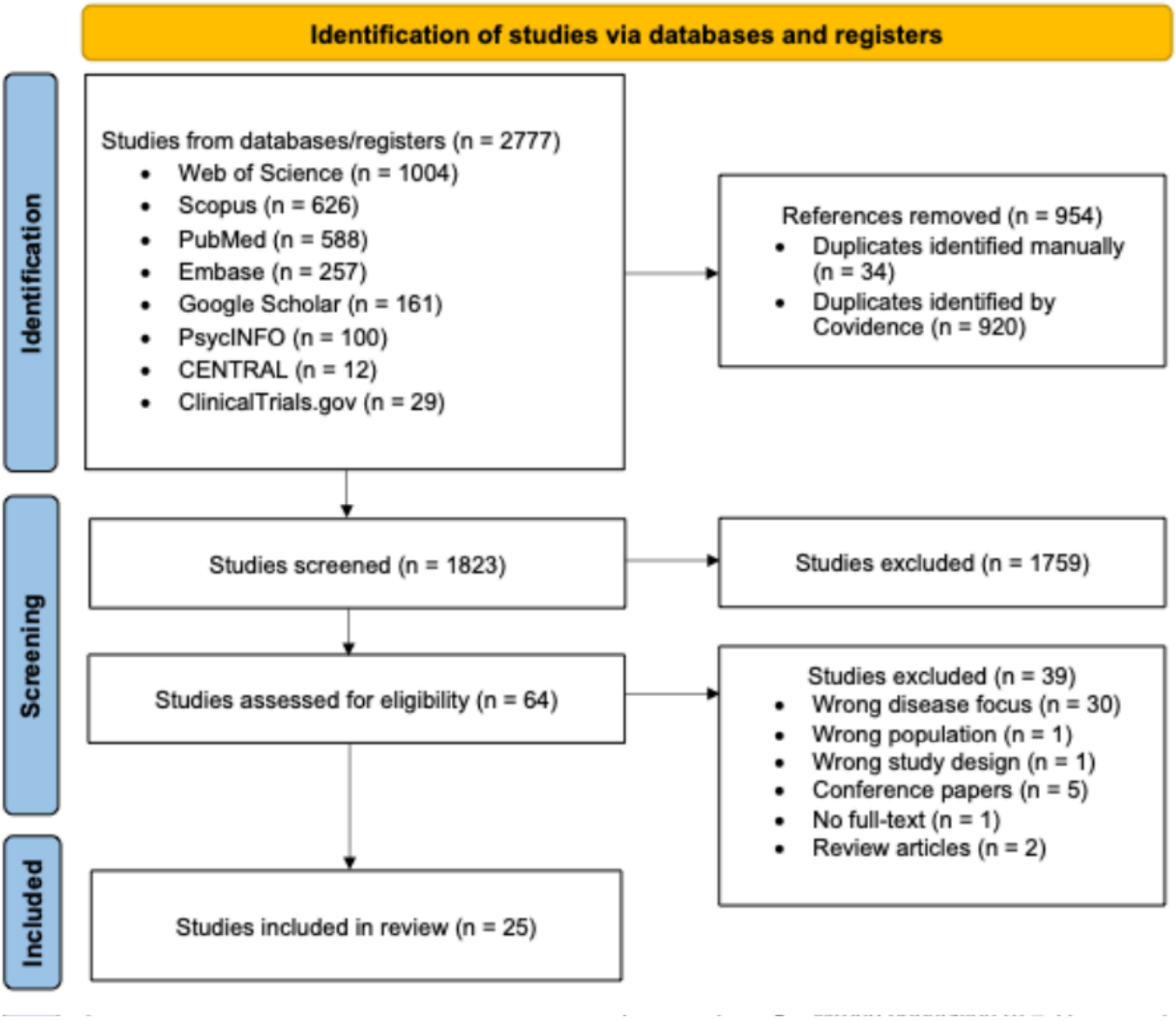


Figure 1

PRISMA flow diagram for study selection. A structured PRISMA-style flow diagram summarizing the study selection process: 2,776 records were identified across major databases and trial registries, with 954 duplicates removed. After screening 1,823 records, 64 full-text articles were assessed for eligibility. Thirty-nine (39) were excluded for predefined reasons, resulting in 25 studies included in the final review.

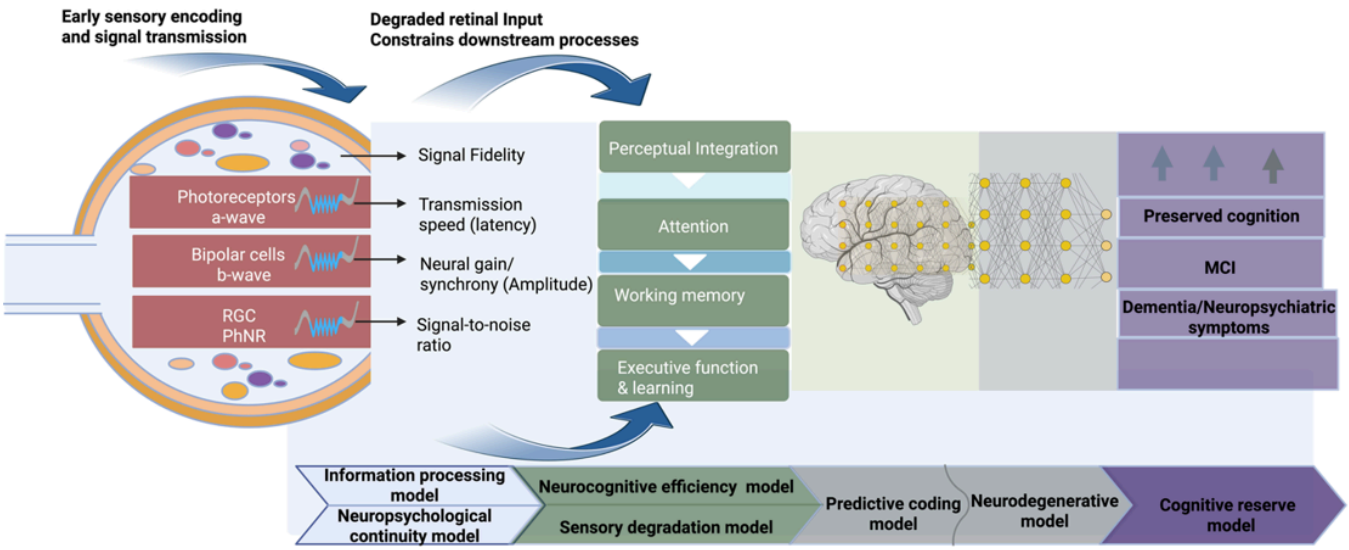


Figure 2

Theoretical framework that explains interrogation of ERG as an upstream index of neural integrity and cognitive function across lifespan. This framework positions core ERG parameters such as a-wave, b-wave, PhNR, implicit time, and oscillatory potentials as upstream indicators of retinal neural integrity that, through complementary models of brain function, converge on key cognitive domains including attention, memory, executive function, and processing speed. Created in BioRender. Osei Duah, I. J. (2026) https://BioRender.com/6g4zpcl

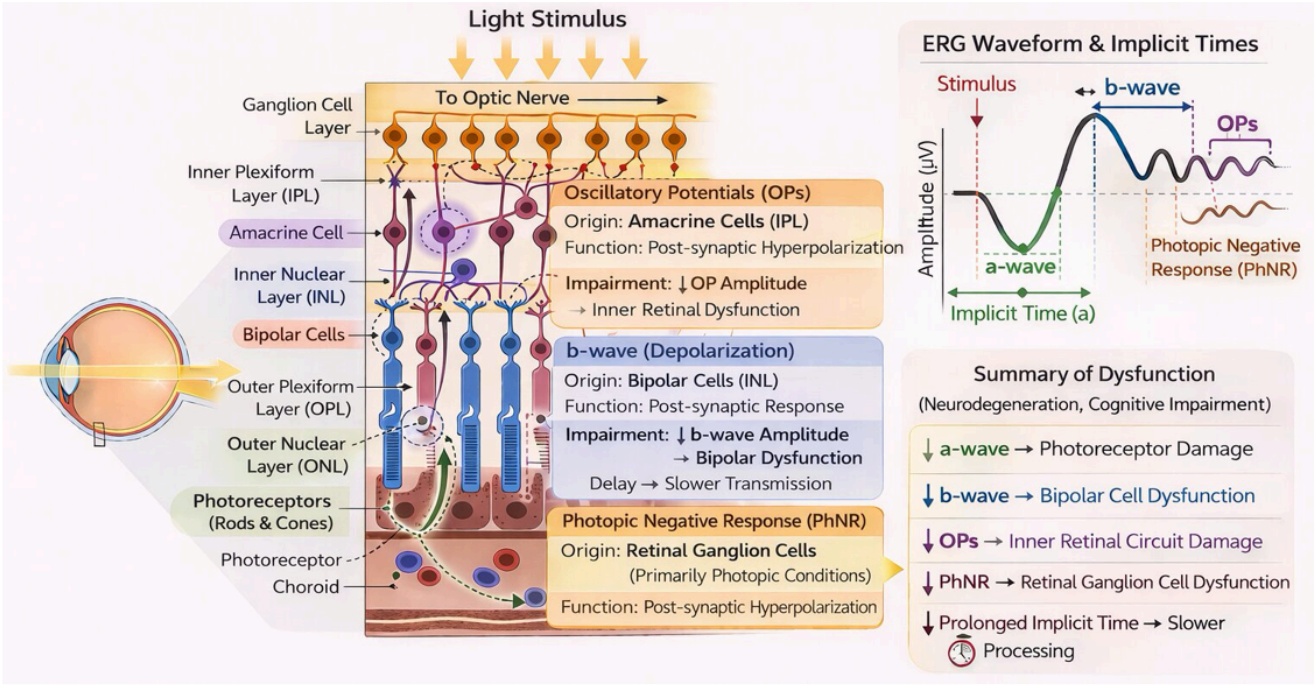


Figure 3

Conceptual mapping of ERG alterations in neurodegenerative and/or neuropsychiatric conditions.
Electroretinography (ERG) captures functional activity across the 10 retinal layers. Outer retinal dysfunction, including the retinal pigment epithelium, photoreceptor layer, external limiting membrane, outer nuclear layer, and outer plexiform layer, primarily affects the a-wave and its timing. Inner retinal involvement, spanning the inner nuclear and inner plexiform layers, alters the b-wave and oscillatory potentials through bipolar and amacrine cell disruption. Ganglion cell layer and nerve fiber layer pathology reduces the photopic negative response and pattern ERG amplitudes. Although the inner limiting membrane does not generate ERG signals, structural abnormalities may influence waveform morphology. Collectively, layer-specific ERG changes provide a functional map of retinal impairment that parallels central neurodegenerative processes. Created in BioRender. Osei Duah, I. J. (2026) https://BioRender.com/hx44ksk

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryTable1PRISMAScRFillableChecklist.pdf
- SupplementaryTable2ERGsystemandRecordingProtocol.pdf
- SupplementaryTable3CognitiveandRetinalMeasures.pdf
- SupplementaryTable4Limitationsandimplications.pdf