Supplementary Table 4: Limitations, evidence gaps, future directions and clinical implications

Author, year	Limitation	Evidence Gaps (Unanswered Questions / Inconsistencies)	Clinical Implications
Alzheimer's Disease and Mild Cognitive Impairment			
Ariello *et al.*, 2025	All cognitively impaired subjects had MCI/mild dementia; fewer ERG participants; cross-sectional design	Extent to which optical coherence tomography (OCT) changes reflect amyloid pathology unclear; relationship between visual cortex amyloid load and IPL thickness uncertain	ERG may detect functional loss before OCT changes; standardization essential for multicenter utility
Asanad *et al*., 2021	Small sample size; exploratory approach; cross-sectional	Mechanisms of retinal pathology unclear; relationship with visual field testing	PhNR is robust, objective RGC function metric; potential non-invasive early biomarker
Sen *et al*., 2020	Did not evaluate MCI; small cohort of severe AD	Cause of mfERG dysfunction unclear (photoreceptor vs amyloid)	Ganglion cell layer thickness and mfERG are sensitive non-invasive early disease indicators
Zhao *et al*., 2021	Small sample (N=59); lack of Aβ/Tau biomarkers; cross-sectional	Specificity of ERG changes to AD vs other neurodegenerations; quadrant-specific RNFL changes	OCT and ERG alterations non-invasive; may indicate brain pathology
Vidal *et al.*, 2022	High variability in controls; small A+ dementia proportion	Inconsistency on color vision deficits in AD; outer retina sparing unclear	HF-ERG insensitive; CCT recommended for non-invasive progression monitoring
Trick *et al*., 1989	Small sample (n=13); FERG not recorded	Visual dysfunction vs pathophysiological abnormalities in SDAT unclear	Noninvasive, objective assessment of SDAT visual pathway damage
Sartucci *et al*., 2010	Small sample (n=15 AD); partial-field stimulation not done	Magnocellular vs Parvocellular pathway stream vulnerability unresolved	PERG/VEP detect subtle dysfunction; electrophysiological markers for AD
Rizzo *et al.*, 1992	PERG difficult due to blinking; only 3/6 patients reliable	Contrasts with subnormal acuity and optic nerve atrophy findings	ERG limited for primary AD diagnosis; useful to exclude other abnormalities
Parisi *et al.*, 2001	OCT morphometry small sample (n=17)	M-cell selective loss vs widespread loss; outer retina not entirely excluded	OCT combined with PERG quantify structural and functional retinal involvement objectively
Mavilio *et al*., 2020	Small sample (52); cognitive diagnosis via MMSE; single center	Phase standard deviation alterations: primary RGC vs transsynaptic degeneration; RE-PERG not studied in PD	RE-PERG quick, non-invasive; detects early RGC dysfunction, discriminates AD from VD
Krasodomska et al., 2010	Recording challenging due to defocus and behavioral issues	PERG results in AD inconclusive	PERG may detect bioelectrical dysfunction before OCT changes; reproducibility <10% variability
Prager *et al*., 1993	PERG sensitive to defocus/inattention; small sample	PERG abnormality detection in early AD unclear	PERG limited for early AD diagnosis; laser pointer recommended to reduce variability
Kergoat *et al.*, 2002	DAT subjects on cholinesterase inhibitors	Inner retina sparing controversy; retina ganglion cell loss	Functional loss involves magnocellular/parvocellular streams; upstream retinocortical pathways affected
Justino *et al.*, 2001	Visual field testing (DAT) unreliable due to compliance	Retinal nerve fiber layer vs Retinal ganglion layer alteration in Dementia of Alzheimer type (DAT)	fERG and oscillatory potential normal in early DAT; limited biomarker utility at this stage
Devos *et al.*, 2005	Small sample (16–17/group); L-DOPA may normalize function	α-synuclein retinal inclusions vs functional abnormalities unclear	ERG shows photopic/scotopic dysfunction in DLB; retinopathy contributes to symptoms

Li *et al*., 2021	Software constraints limited analysis of deeper retinal vessel parameters; EDI-OCT provides only static structural view; manual choroidal thickness measurement may introduce error; diurnal fluctuations may affect results; flash ERG data showed high variance due to small sample size	Unclear if foveal avascular zone area is more sensitive than general vessel parameters; need to determine if MoCA/MMSE sensitivity differences align with retinal imaging metrics; findings require verification via other methods (e.g., colour Doppler imaging)	OCTA is a promising non-invasive tool for early/mid-stage Alzheimer's type dementia diagnosis and monitoring; RETeval system provides a comfortable, feasible method for functional retinal assessment in patients intolerant to traditional electrodes; may facilitate early screening and intervention
Ngoo *et al.*, 2019	Cognitive dysfunction; limited recruitment of severe AD	PERG results inconclusive; effect of cholinesterase inhibitors unknown	RNFL + electrophysiology (PERG) sensitive neurodegeneration biomarkers
Katz *et al*., 1989	Small sample (6 patients + 6 controls); P2 identification difficult	Ganglion cell dysfunction secondary to neurotransmitter paucity unclear	PERG confirms retinal ganglion cell degeneration; correlates with associative cortical involvement
Moschos *et al*., 2012	Small sample (n=60); logistic regression unreliable	Cause of photoreceptor abnormality; RGC loss origin	Combined OCT + mfERG objective; detects early retinal damage
Nesher & Trick, 1991	Small SDAT group (n=13); retrospective	Relationship of steady-state PERG to transient waveform components unclear	Steady-state PERG may detect earlier dysfunction in retinal & optic nerve disease
Cronin-Golomb *et al*., 1991	PERG blinking artifacts; small test sample (n=4)	No direct evidence linking impaired performance to neuron subsets	Visual deficits detectable even without complaints; normal ERG suggests cortical origin
Normal Aging			
Justino *et al.*, 2001	Differences in stimulus/electrode conditions	Magnocellular vs parvocellular pathway degeneration inconsistent	Age-dependency of ERG critical for geriatric standardization
Freund *et al*. 2011	High stimulus strengths cause overlapping oscillatory potentials that slightly obscure implicit times, the study's healthy-only sample limits generalizability, and the 1.5-hour protocol may be too long for routine clinical use.	There is no consensus on age-related ERG changes, the exact retinal circuitry alterations driving these effects remain unclear, and the role of OFF bipolar cells in a-wave changes and the photopic hill effect needs further study.	Clinicians must consider normal age-related ERG changes to avoid false positives, enhancing protocols with photopic luminance-response and dark adaptation tests can improve sensitivity, these specialized ERGs may serve as endpoints in clinical trials, and age-related increases in a-wave implicit times offer a benchmark for normal aging.
DeBuc *et al.*, 2018	Small sample; poor image quality; reliance on MoCA	Association between ERG implicit time and vascular changes unclear	Low-cost multimodal portable ERG feasible for community monitoring
Fun *et al*., 2016	Small sample (n=36); unbalanced gender; pupil size not controlled	Effect of mild cognitive impairment on pERG; linear progression unknown	pERG detects early inner retina changes preceding OCT alterations

n: sample size; ISCEV: International Society for Clinical Electrophysiology of Vision; MMSE: Mini-Mental State Examination; MoCA: Montreal Cognitive Assessment; OCT: Optical coherence tomography; OCTA: Optical coherence tomography angiography; RNFL: Retinal nerve fiber layer, rps: Reversals per second, RGC: Retinal ganglion cell