EURETINA MEETING, AMSTERDAM
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ERGs in Clinical Practice: The Electronegative ERG

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Eye

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Negative electroretinograms: genetic and acquired causes, diagnostic approaches and physiological insights

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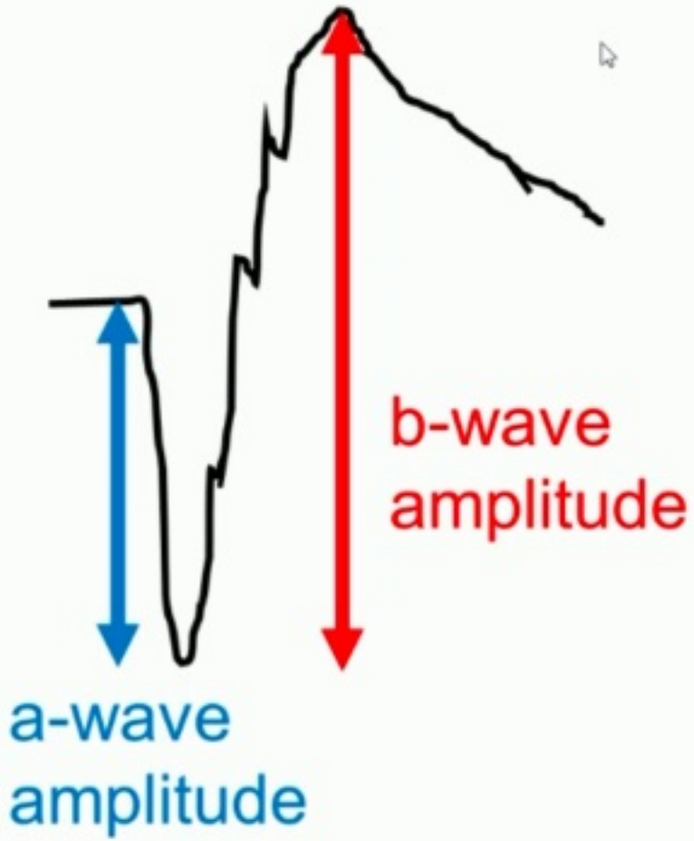
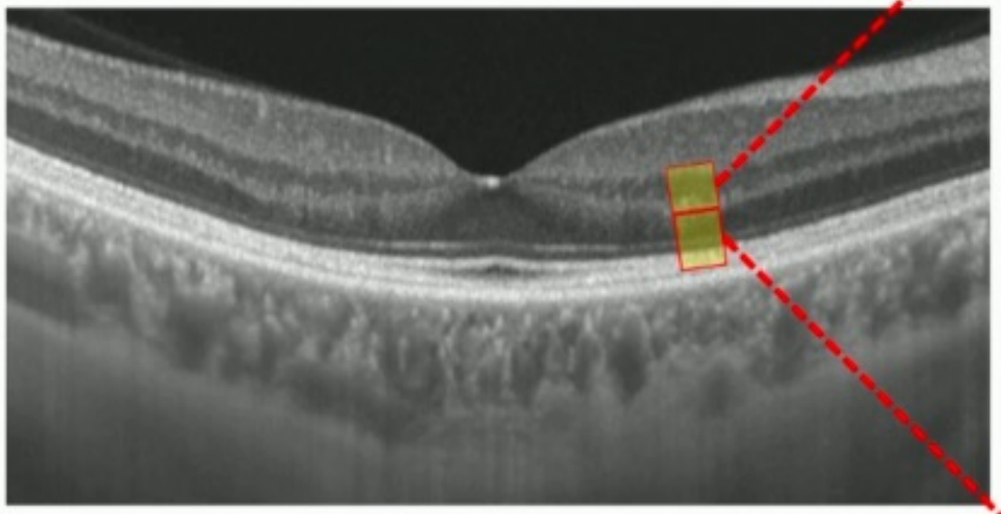
Healthy DA 10 response

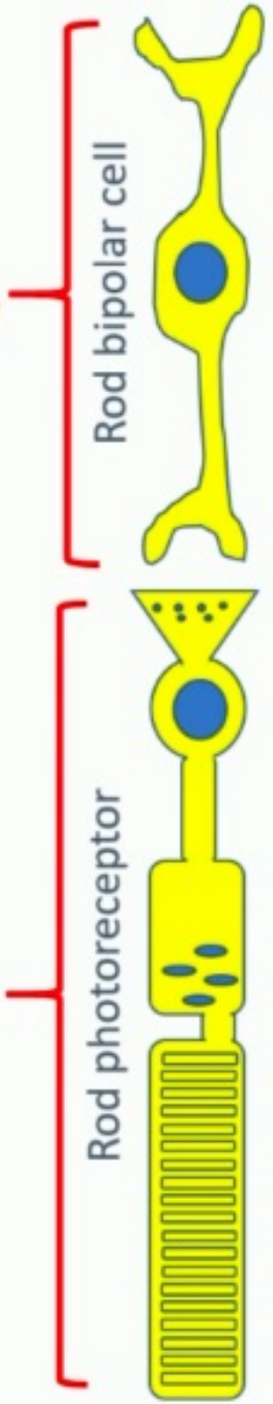


Negative ERG

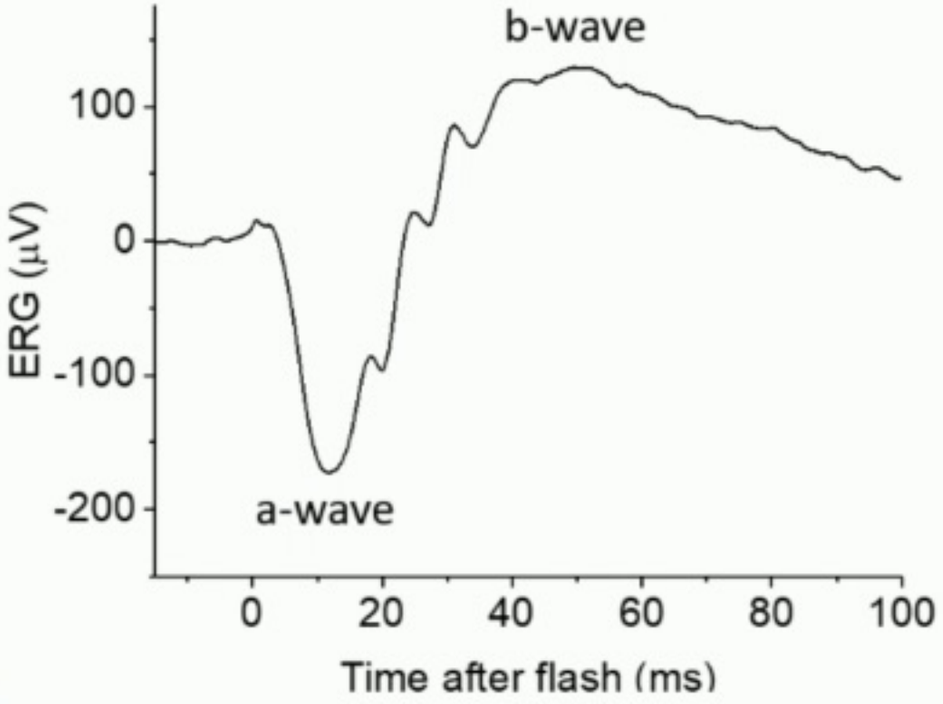
Outline

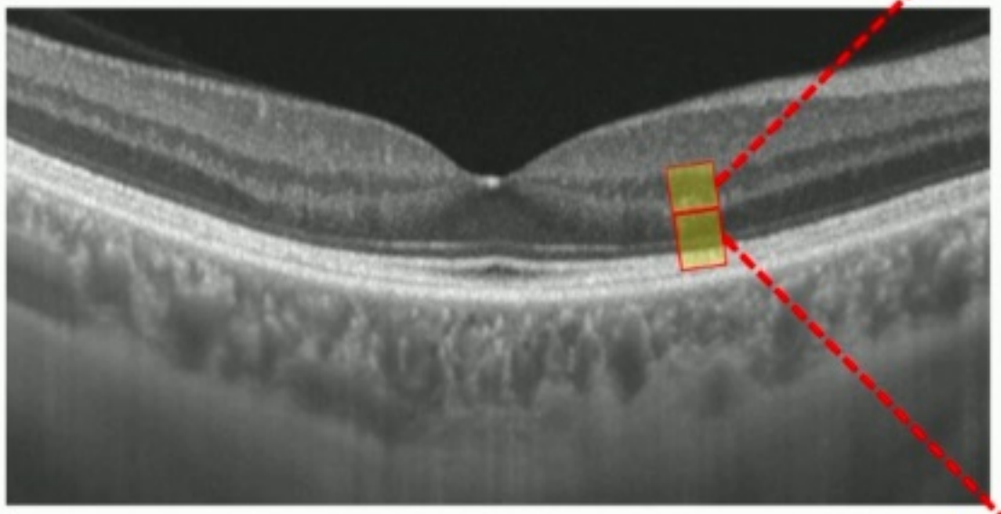
- Physiological Basis
- Prevalence in different cohorts
- Causes of electronegative ERGs
  - Inherited (bilateral, symmetric)
  - Non-genetic (unilateral/bilateral)
- Questions to ponder to make the diagnosis
- Additional protocols
- Concluding remarks

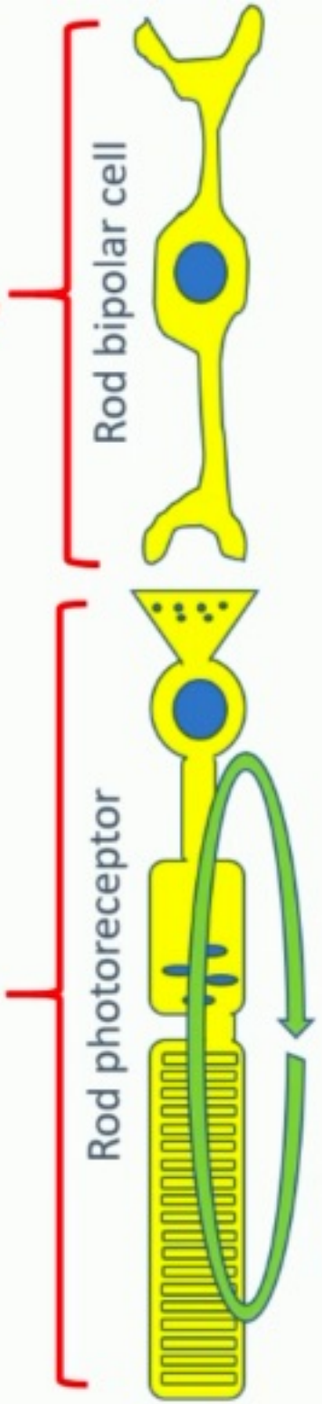




Dark-adapted bright-flash response







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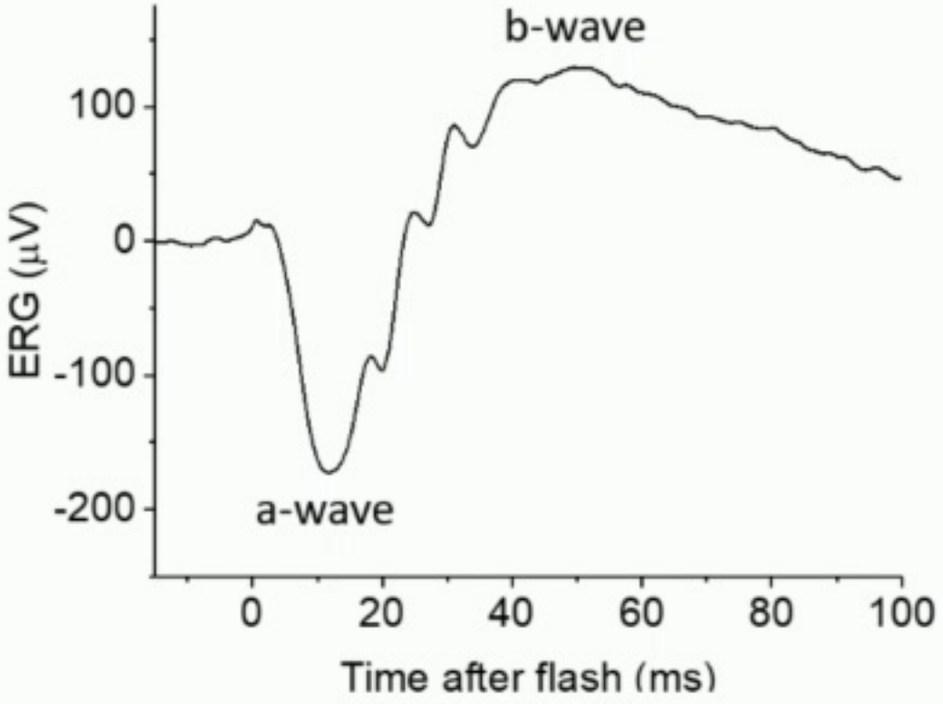

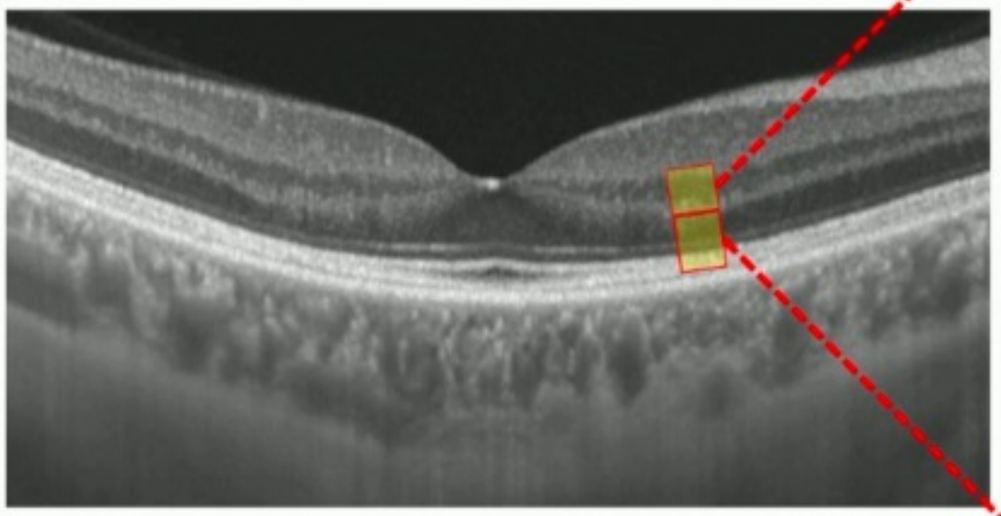

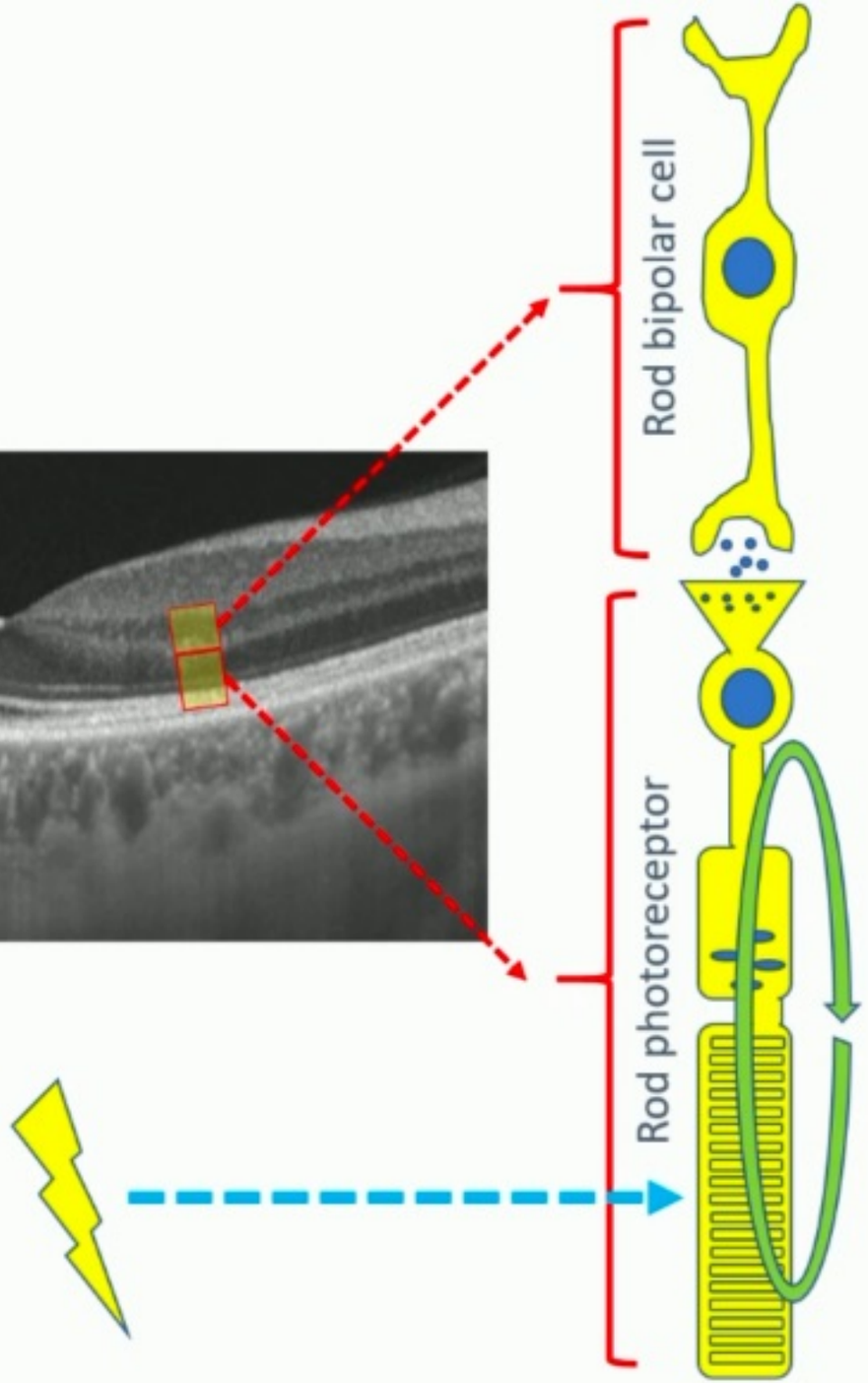

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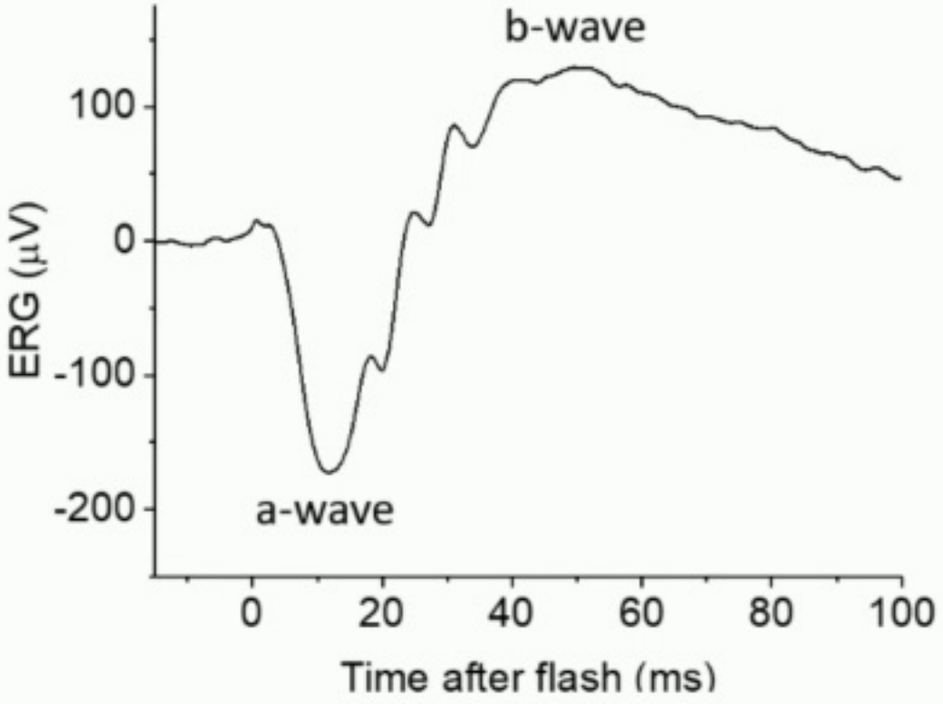

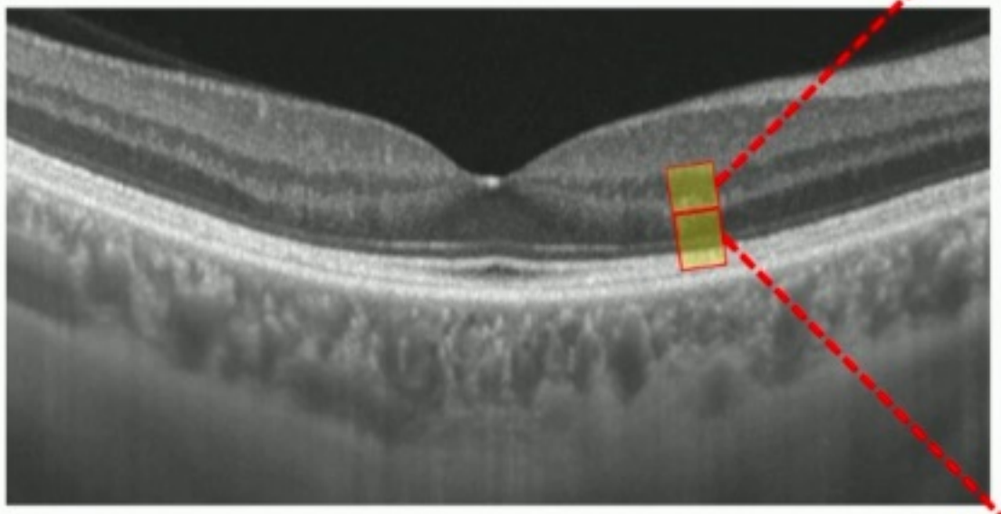

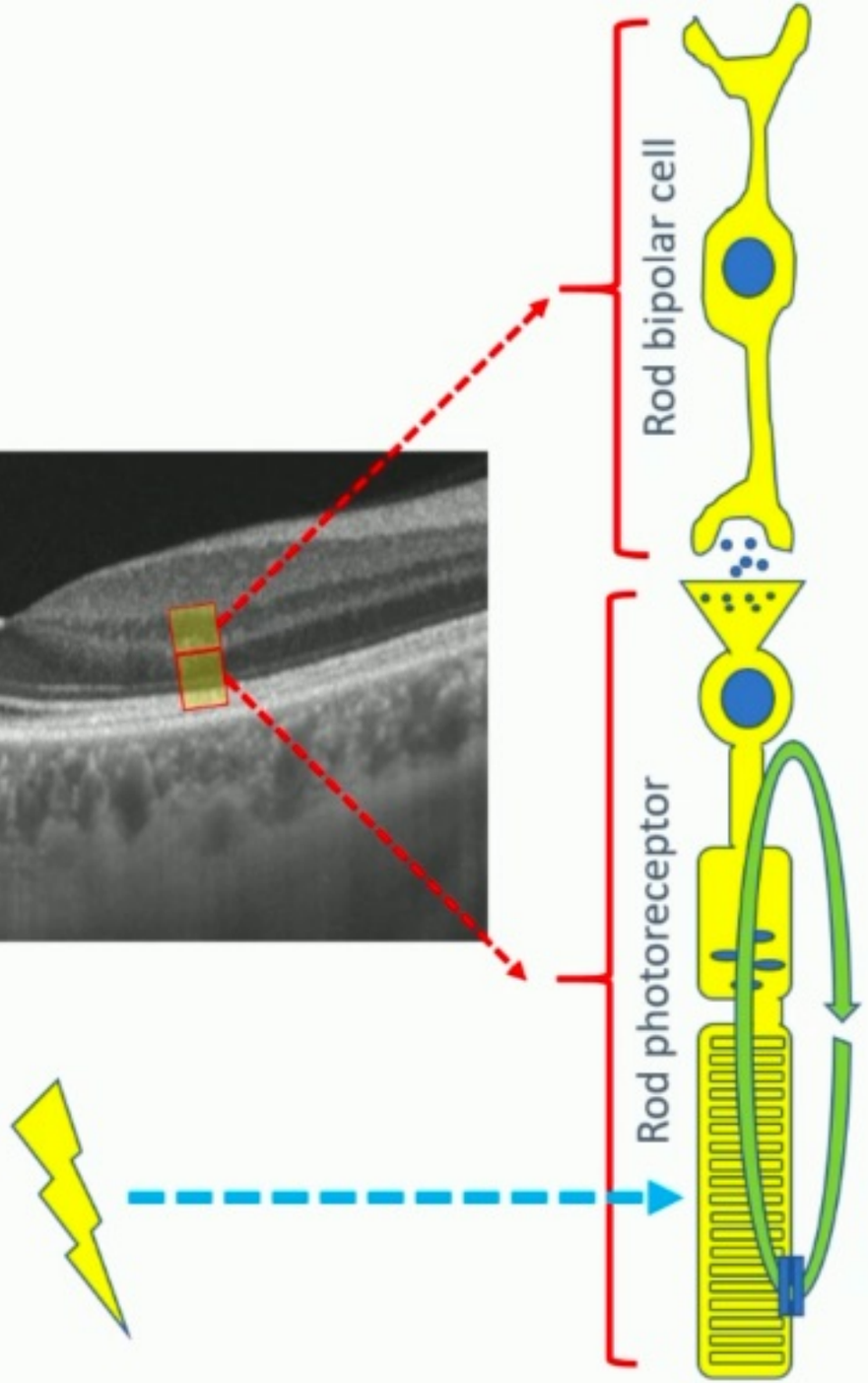

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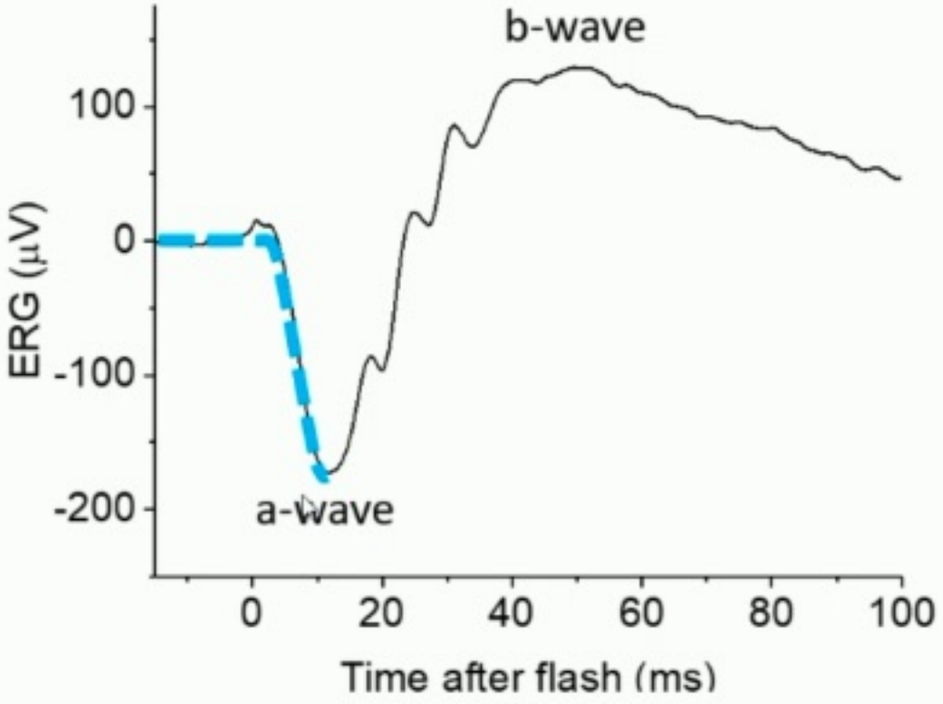

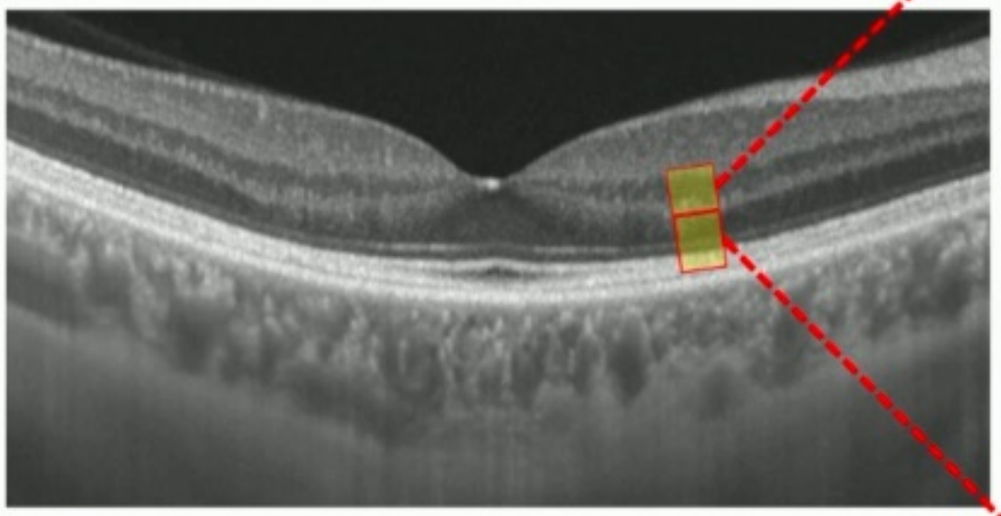

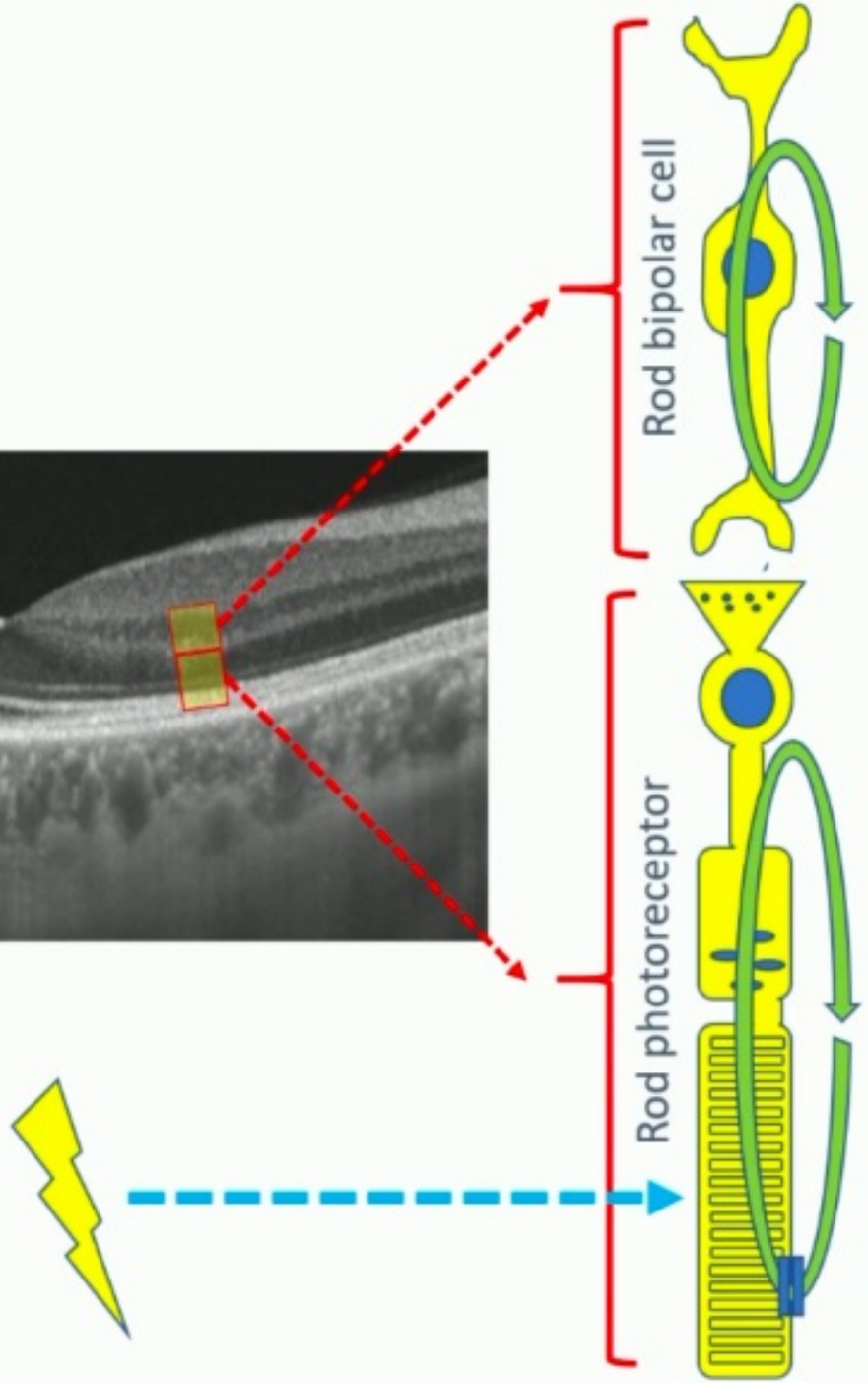

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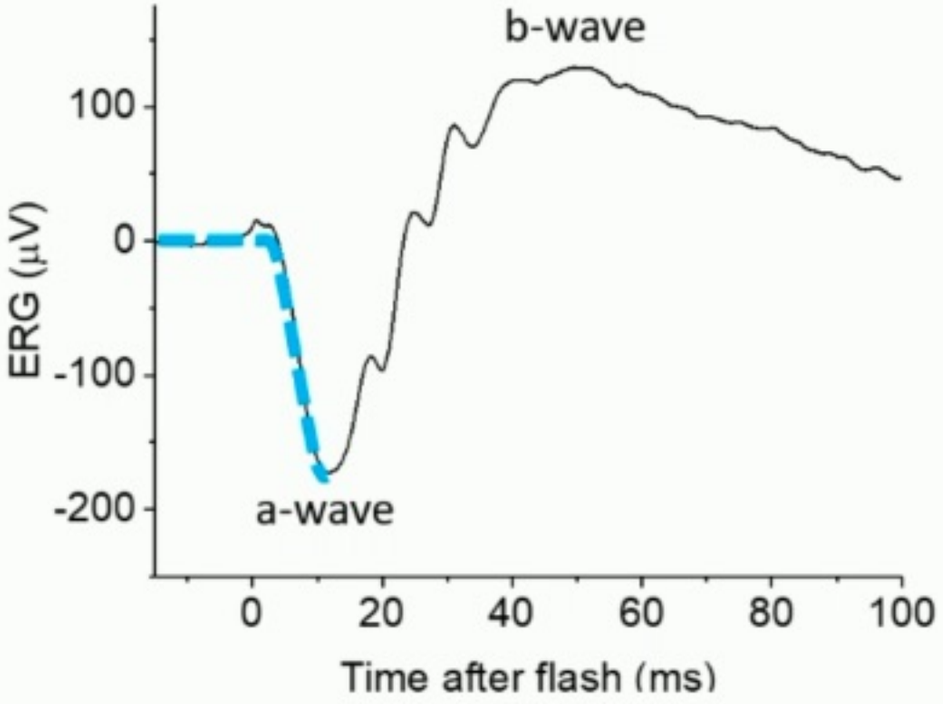

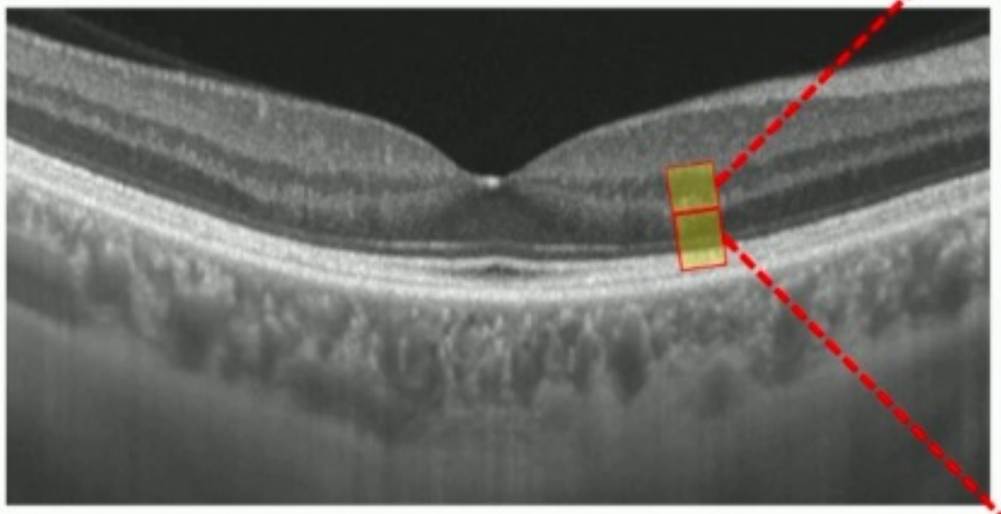

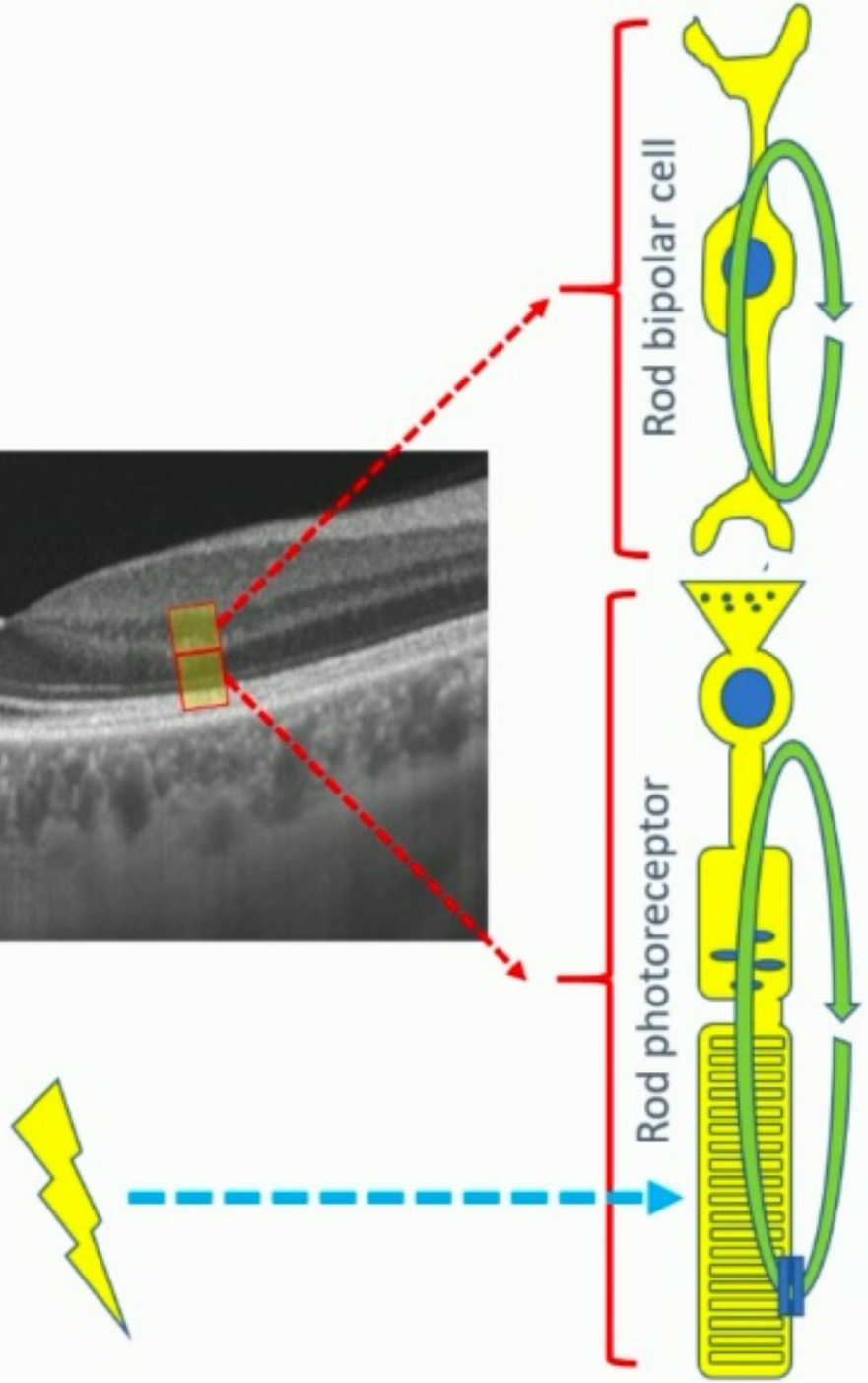

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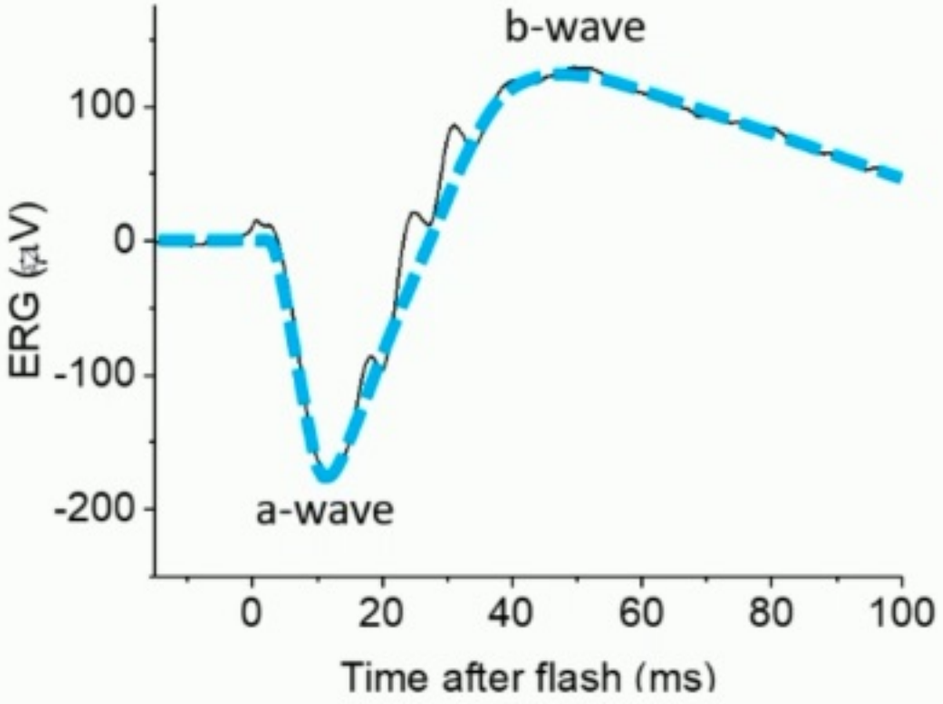

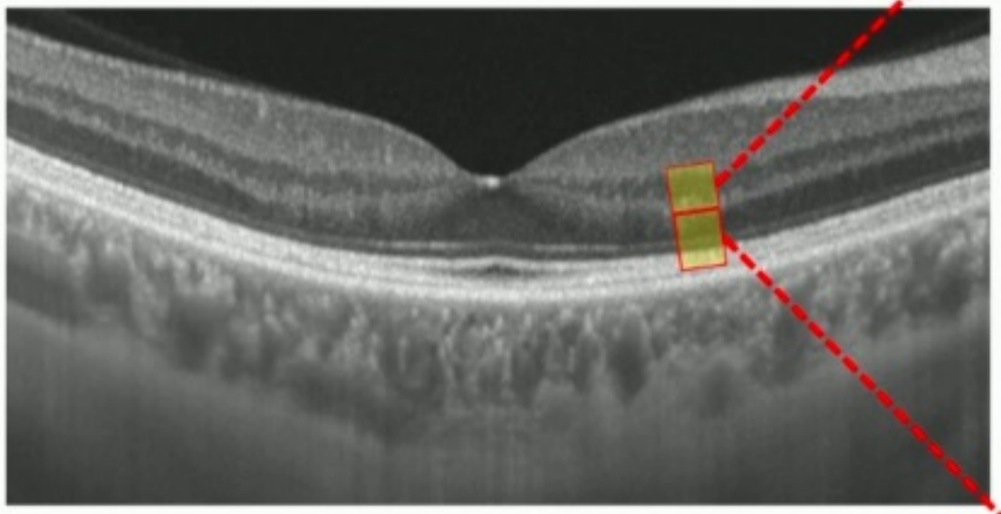

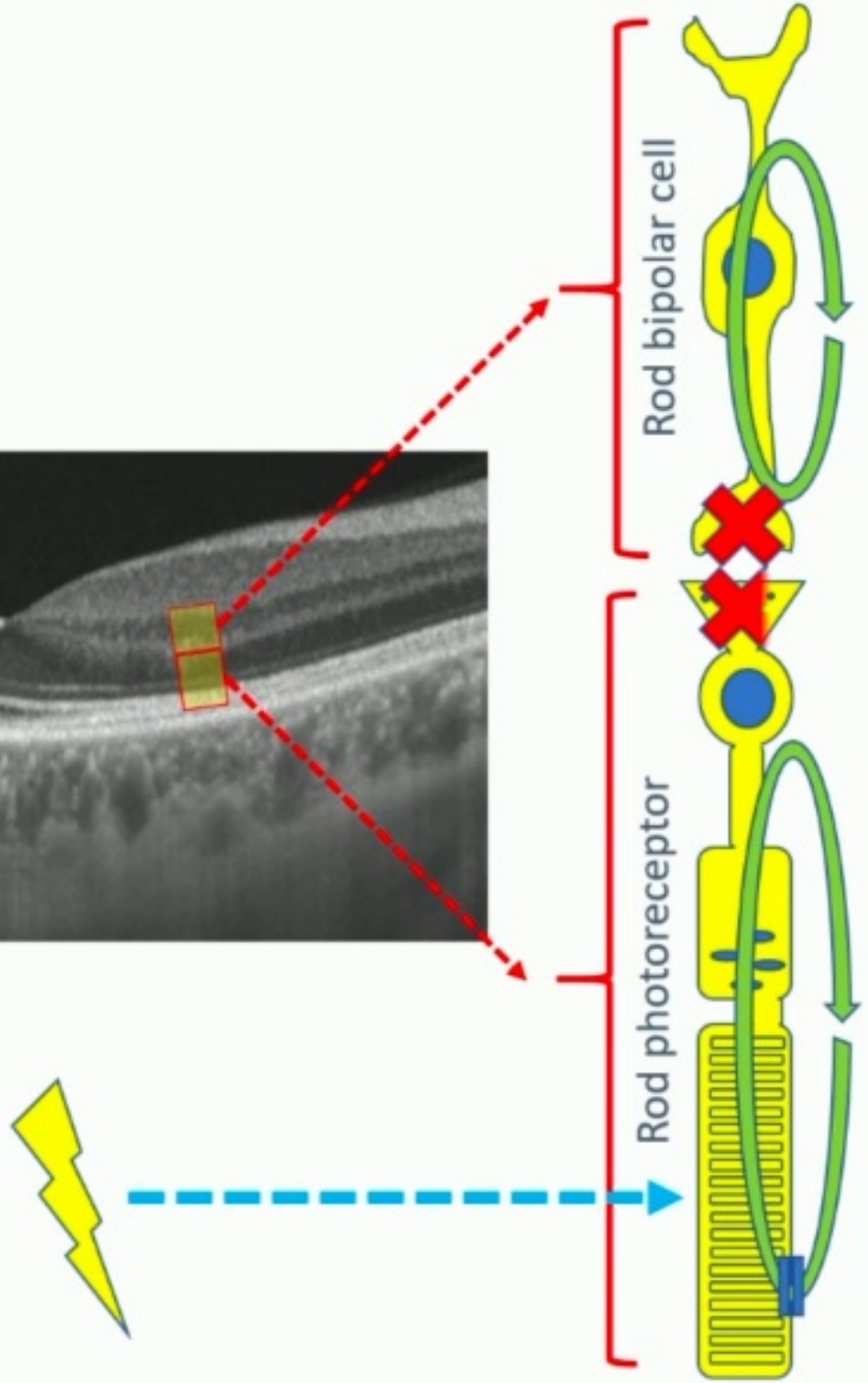

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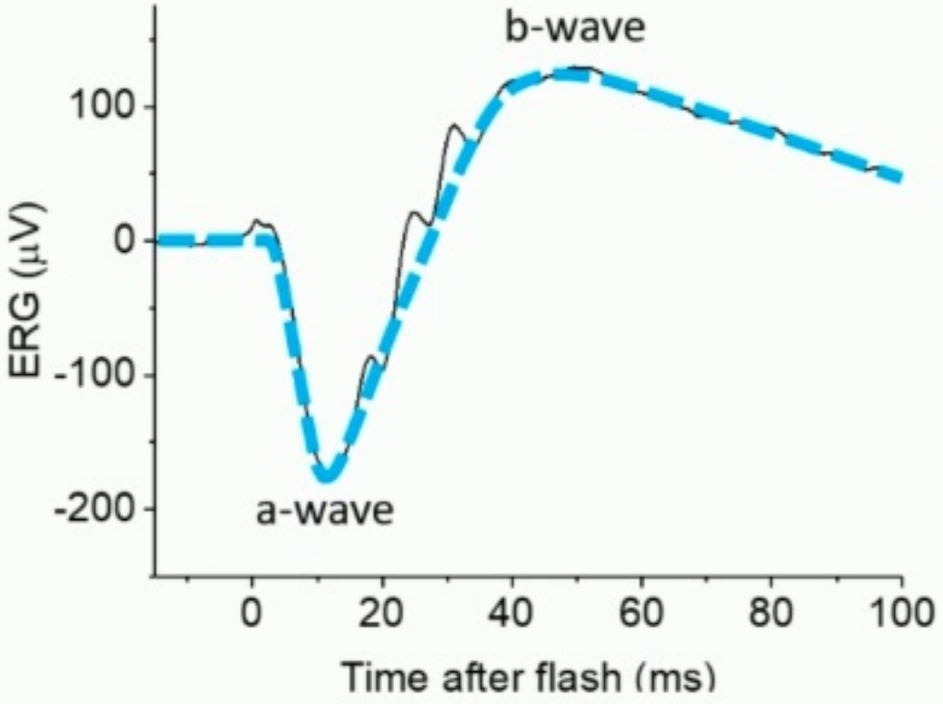

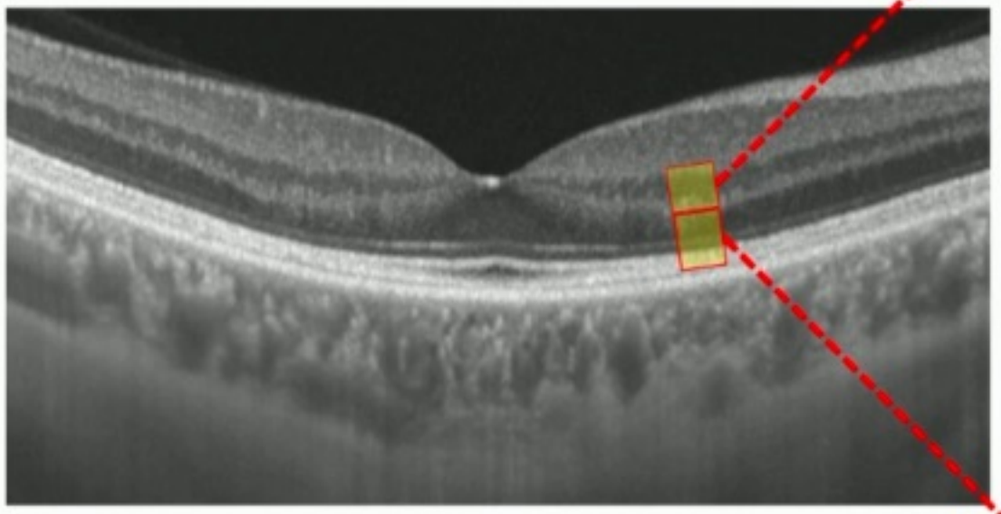

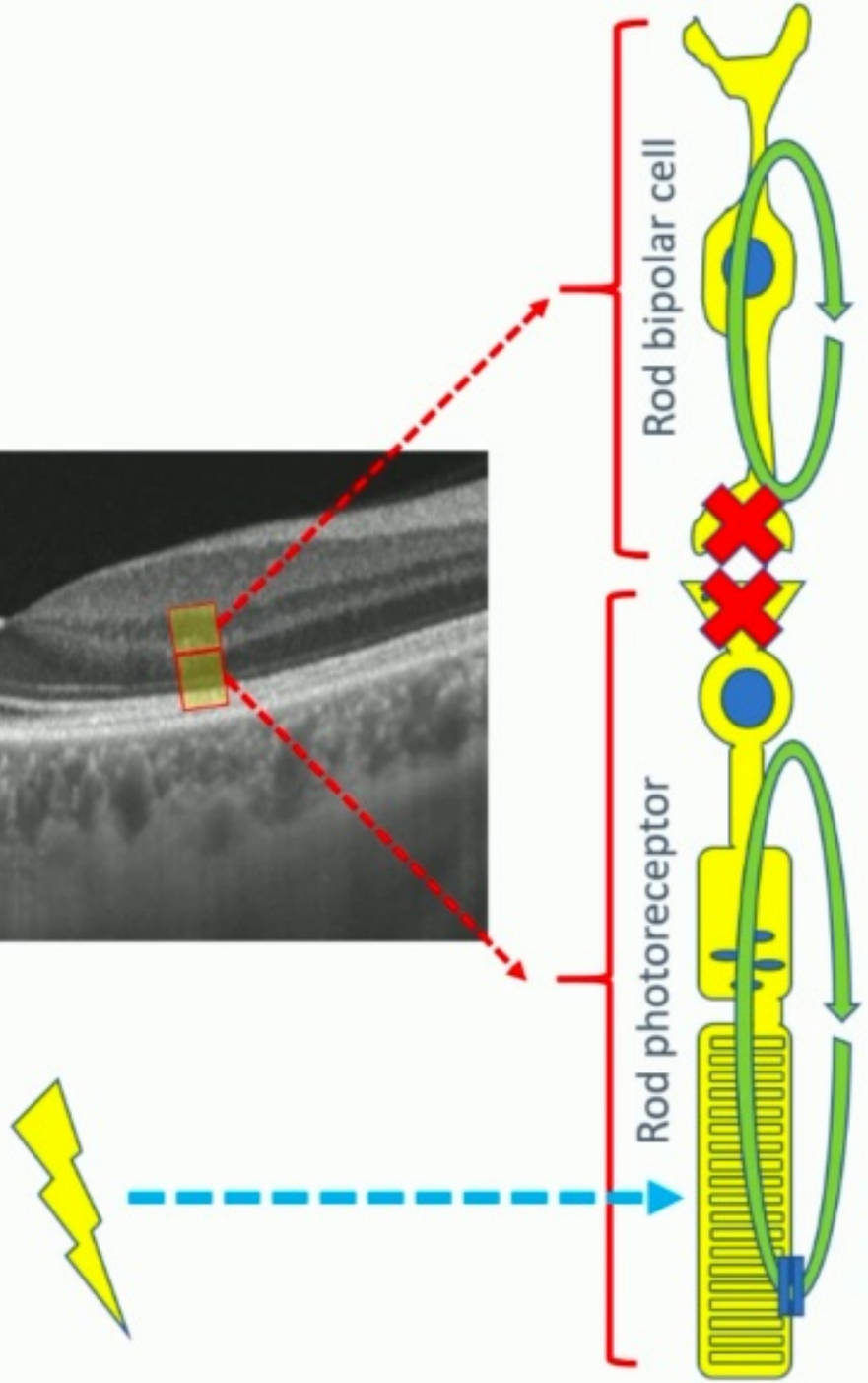

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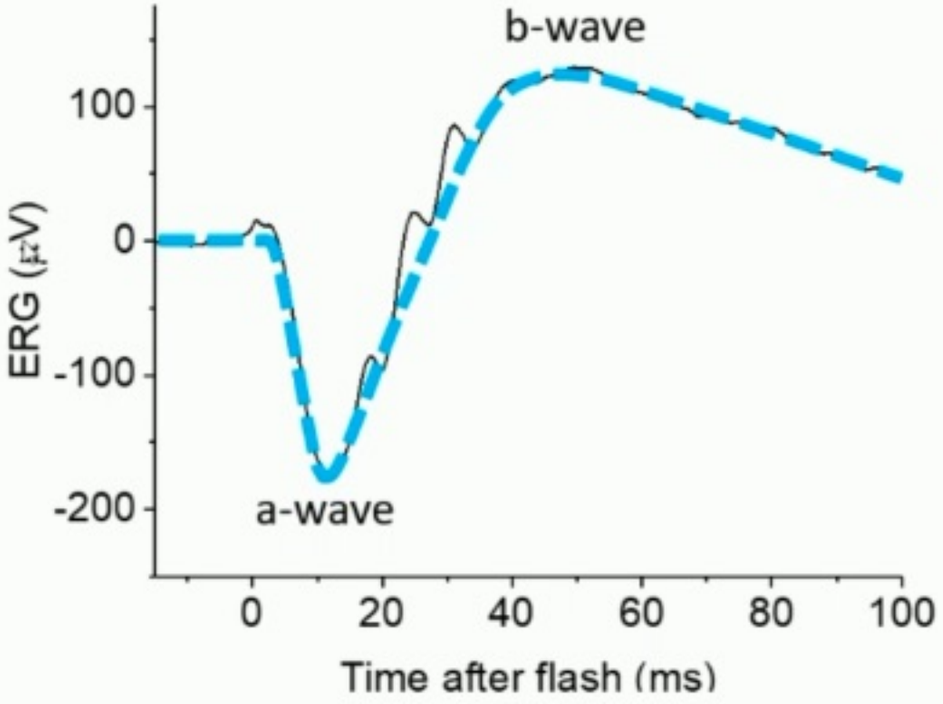

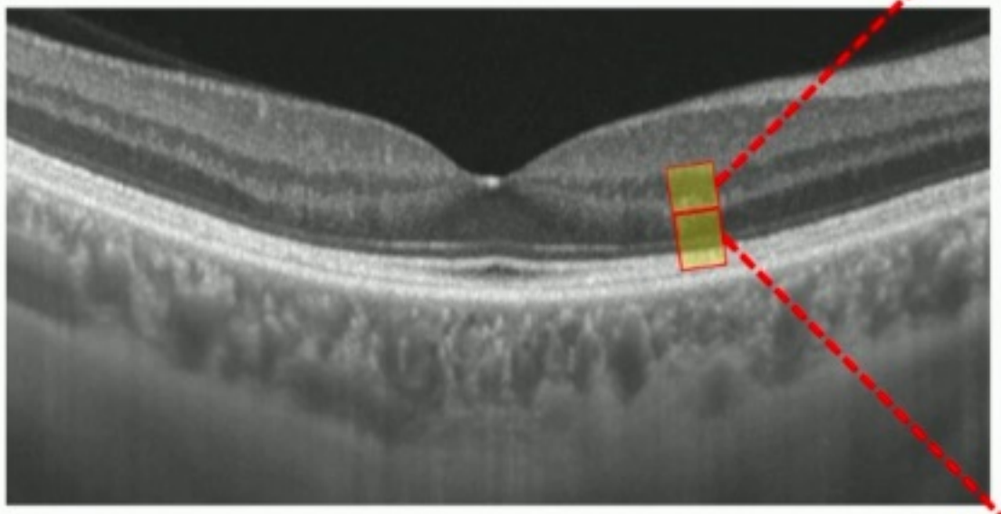

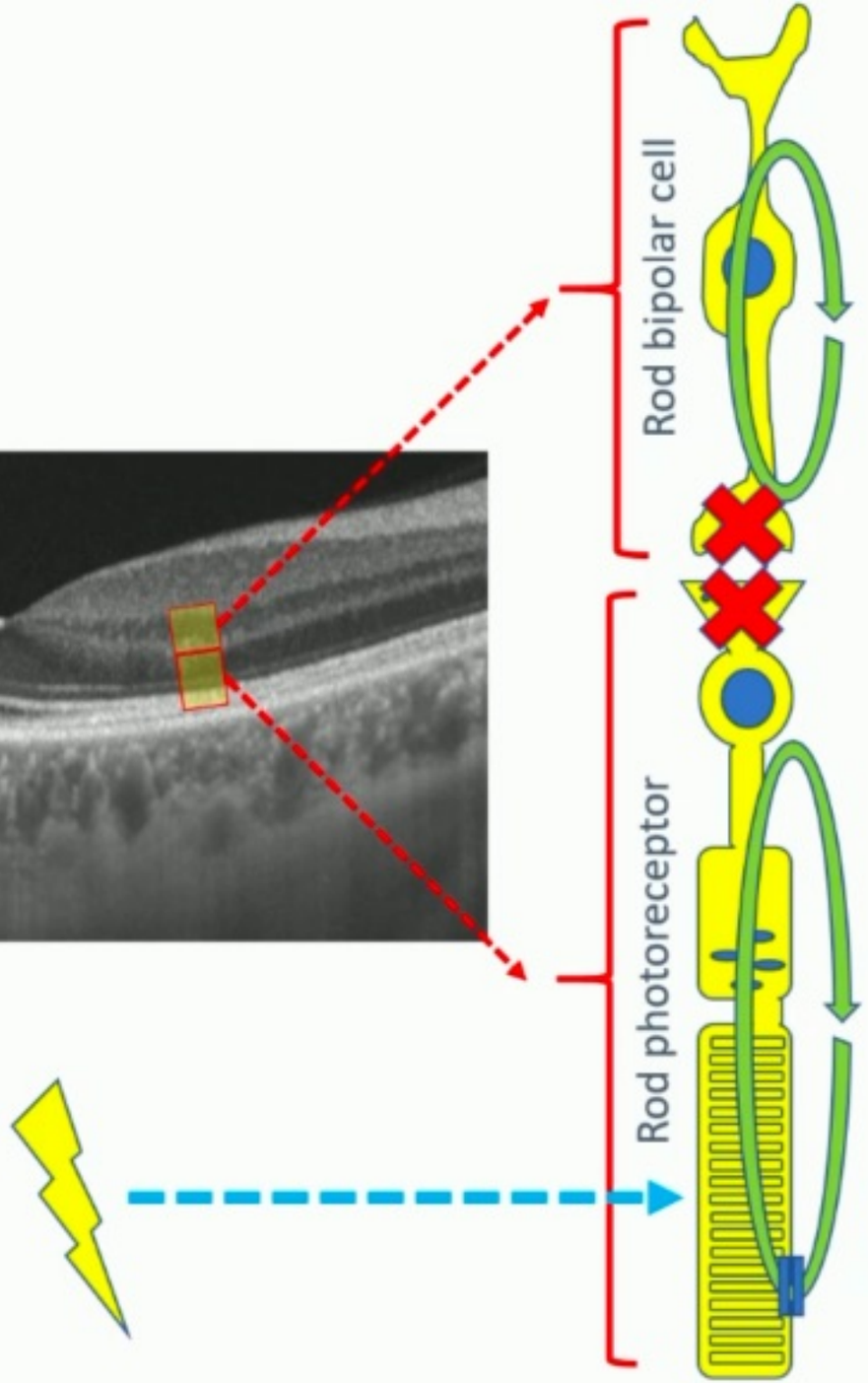

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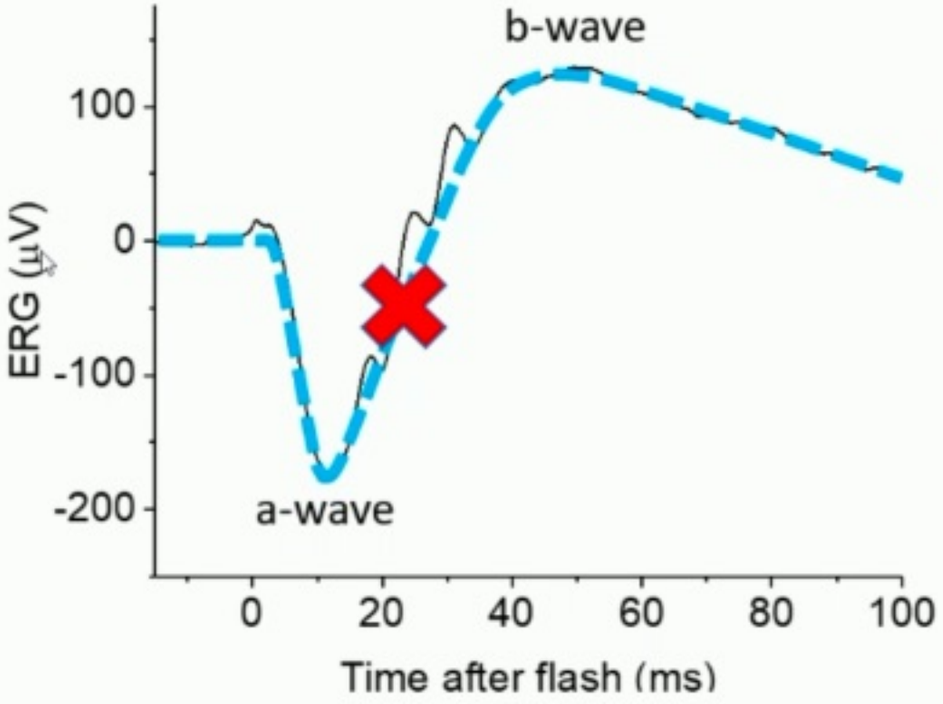


cone photo-transduction

synaptic transmission

ON bipolar cell response

OFF bipolar cell response

LA3 response

Light-adapted flash response

Light-adapted flash response

cone photo-transduction → synaptic transmission → ON bipolar cell response

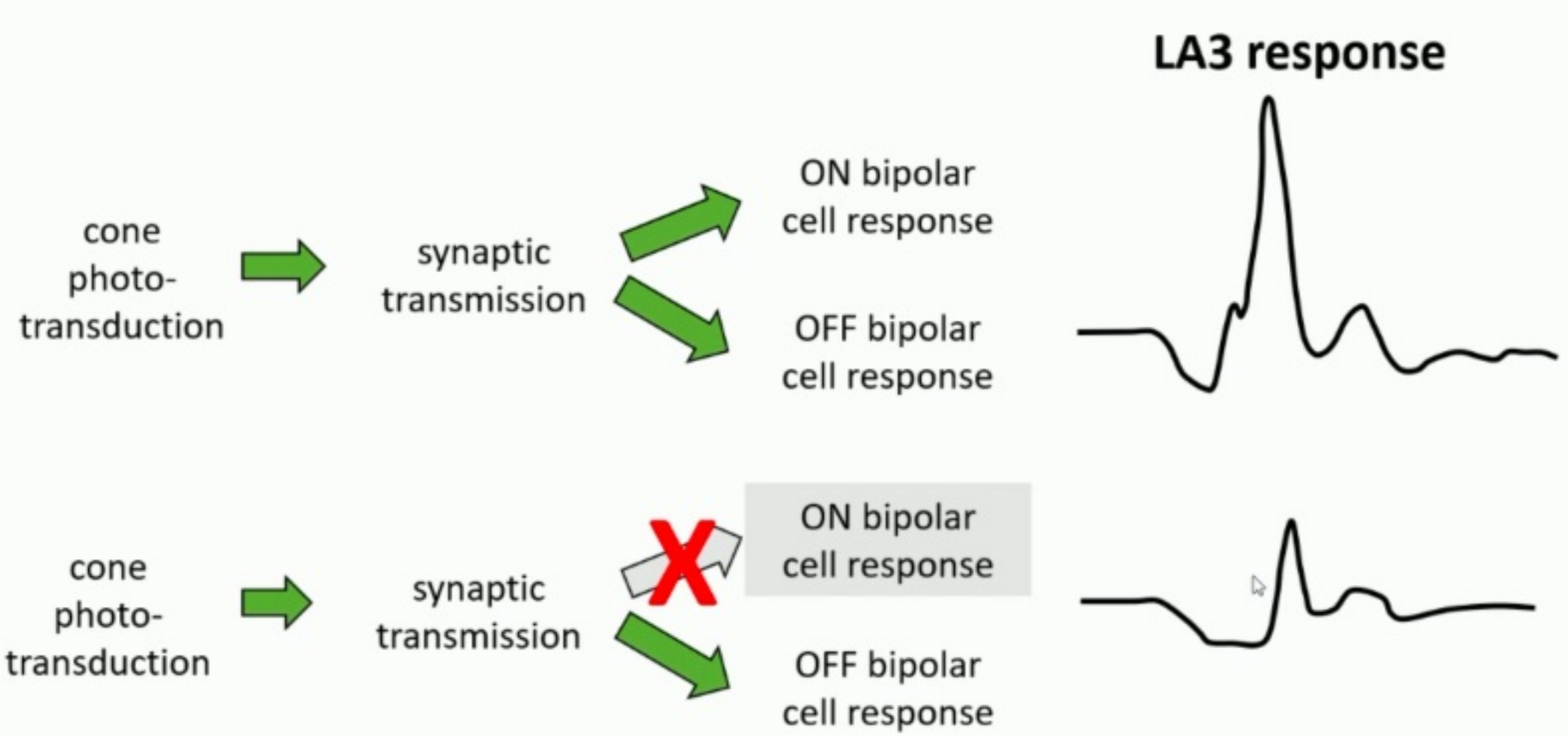
synaptic transmission → OFF bipolar cell response

LA3 response

cone photo-transduction → synaptic transmission ✗ ON bipolar cell response

synaptic transmission → OFF bipolar cell response

Light-adapted flash response



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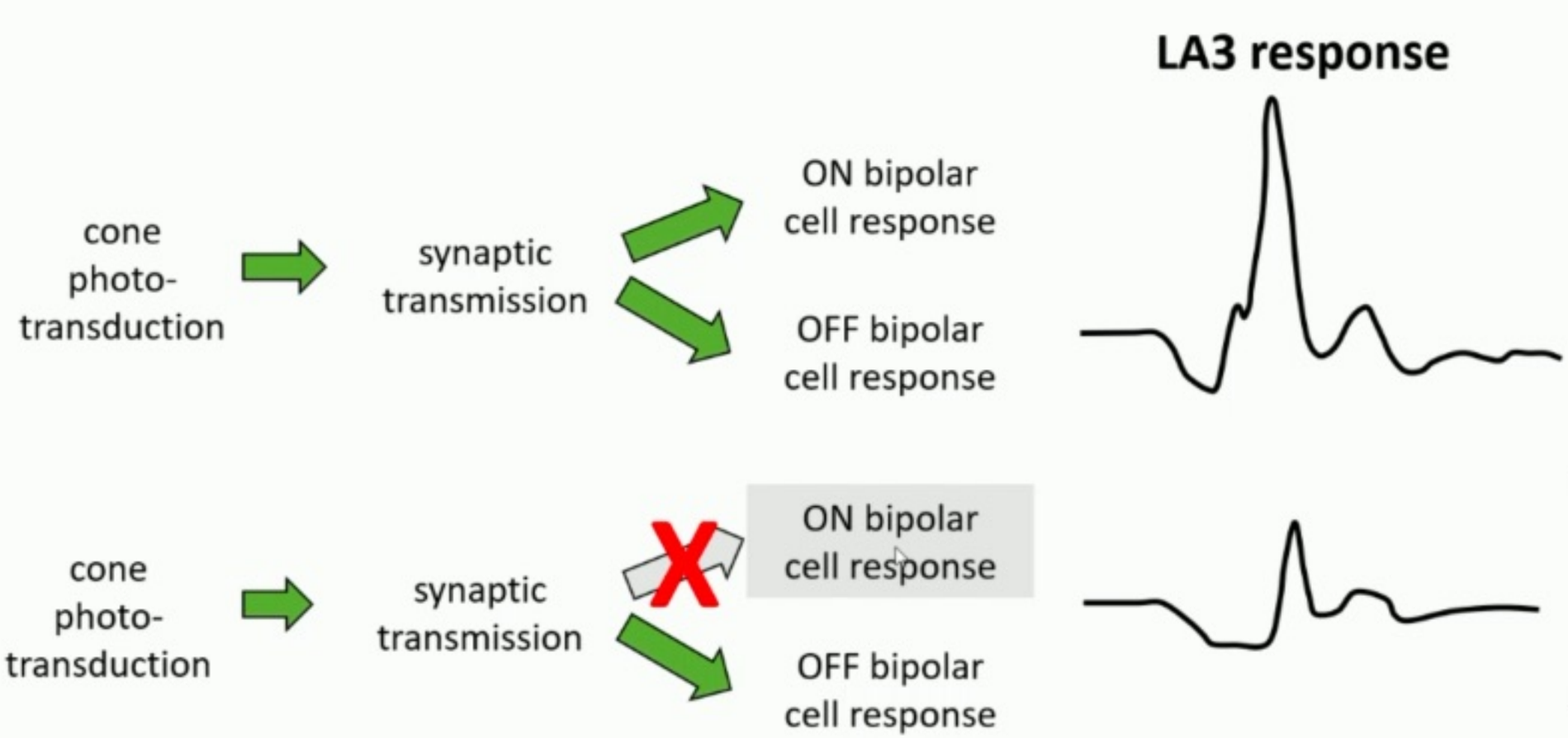
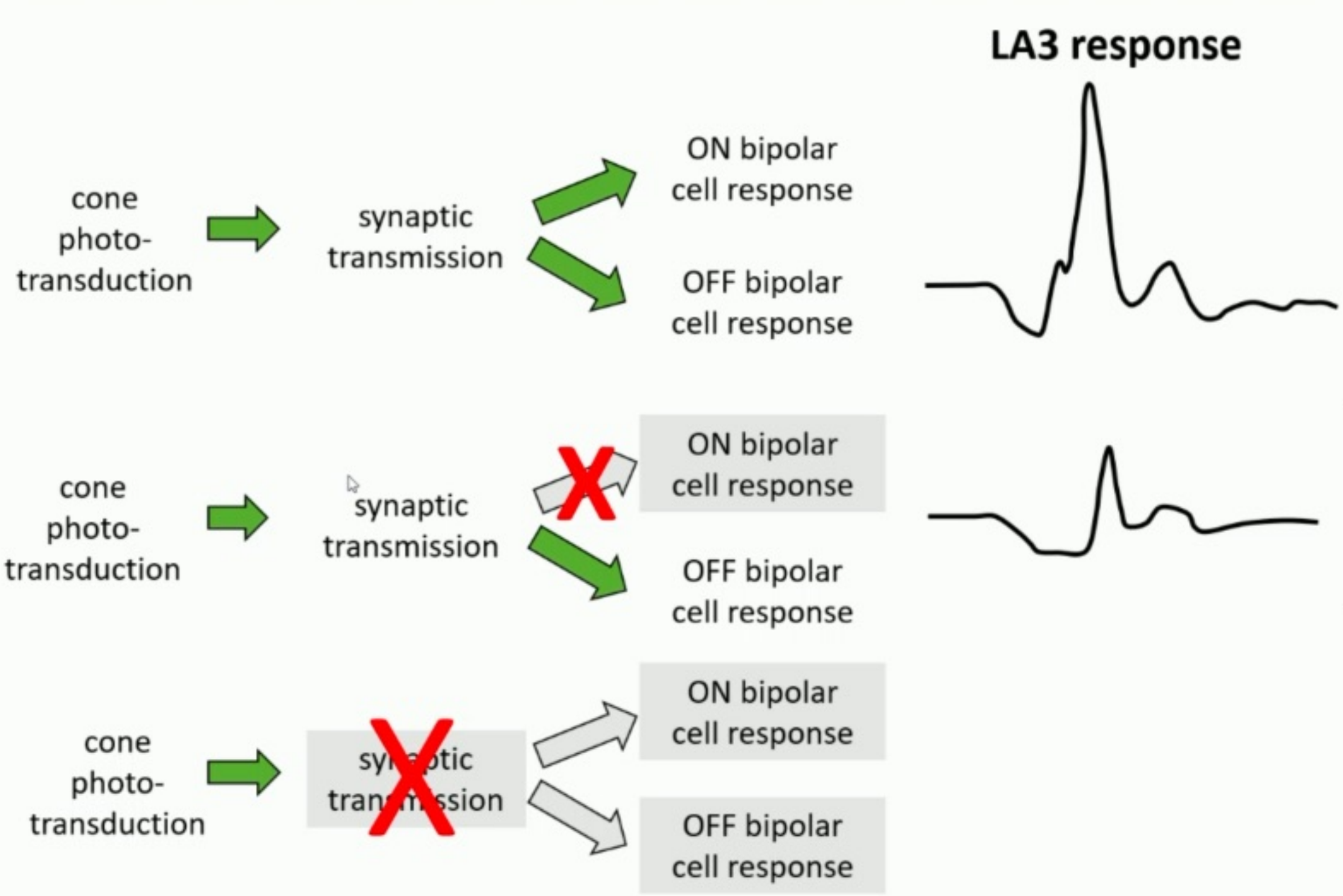


Selective loss of ON bipolar responses

Complete CSNB: *NYX*, *TRPM1*, *GRM6*, *GPR179*, *LRIT3*

Other causes include MAR

Light-adapted flash response



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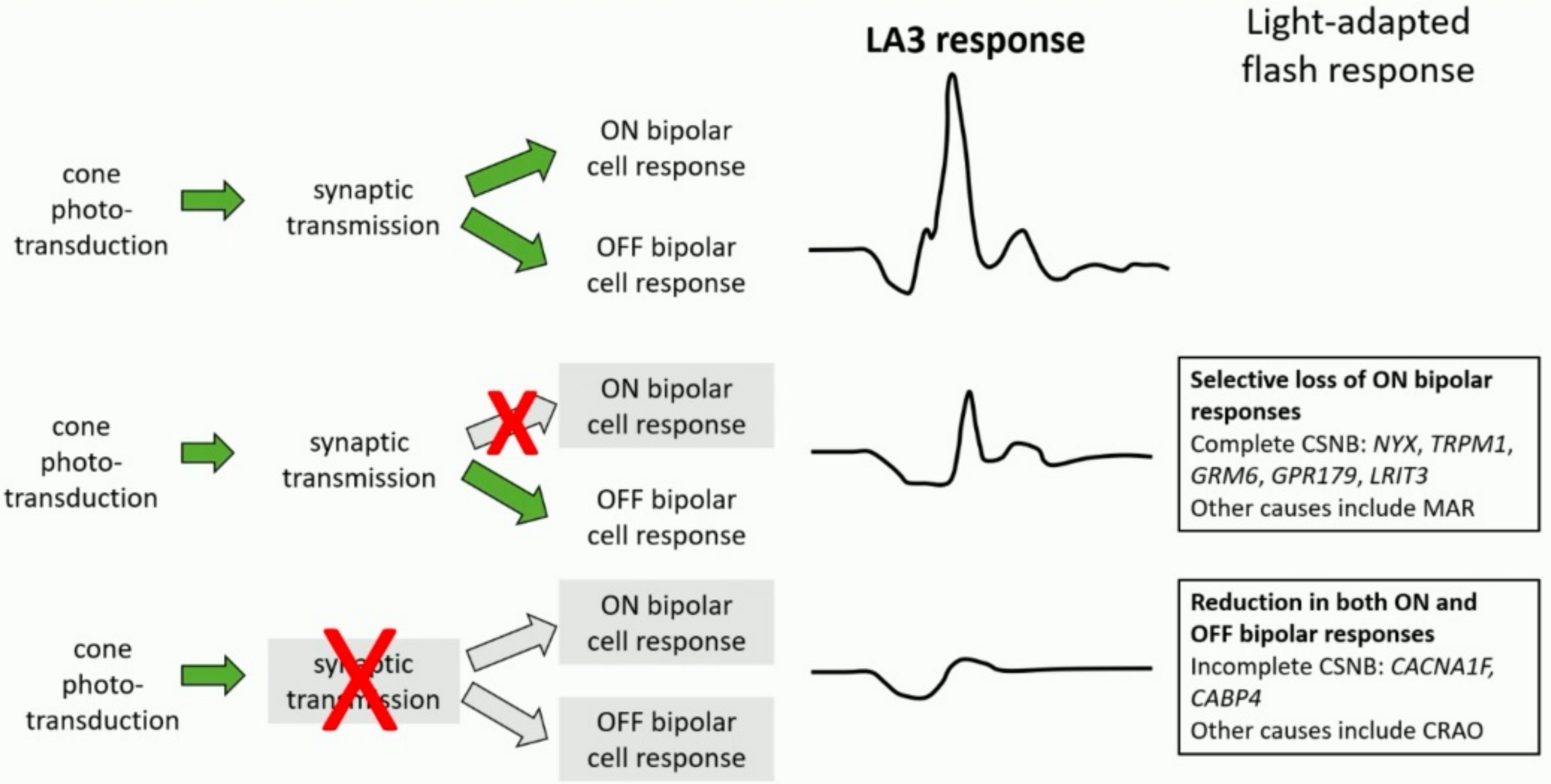
LA3 response
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cone photo-transduction
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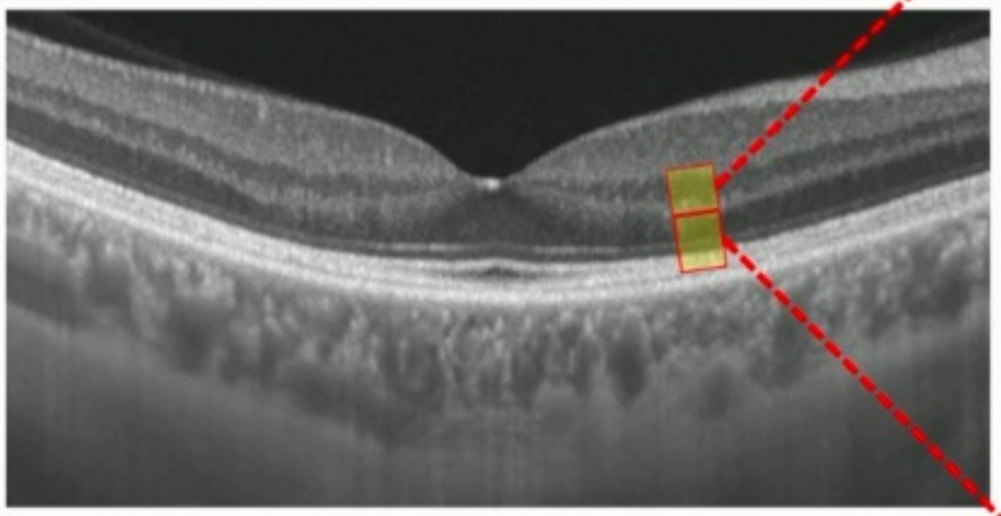
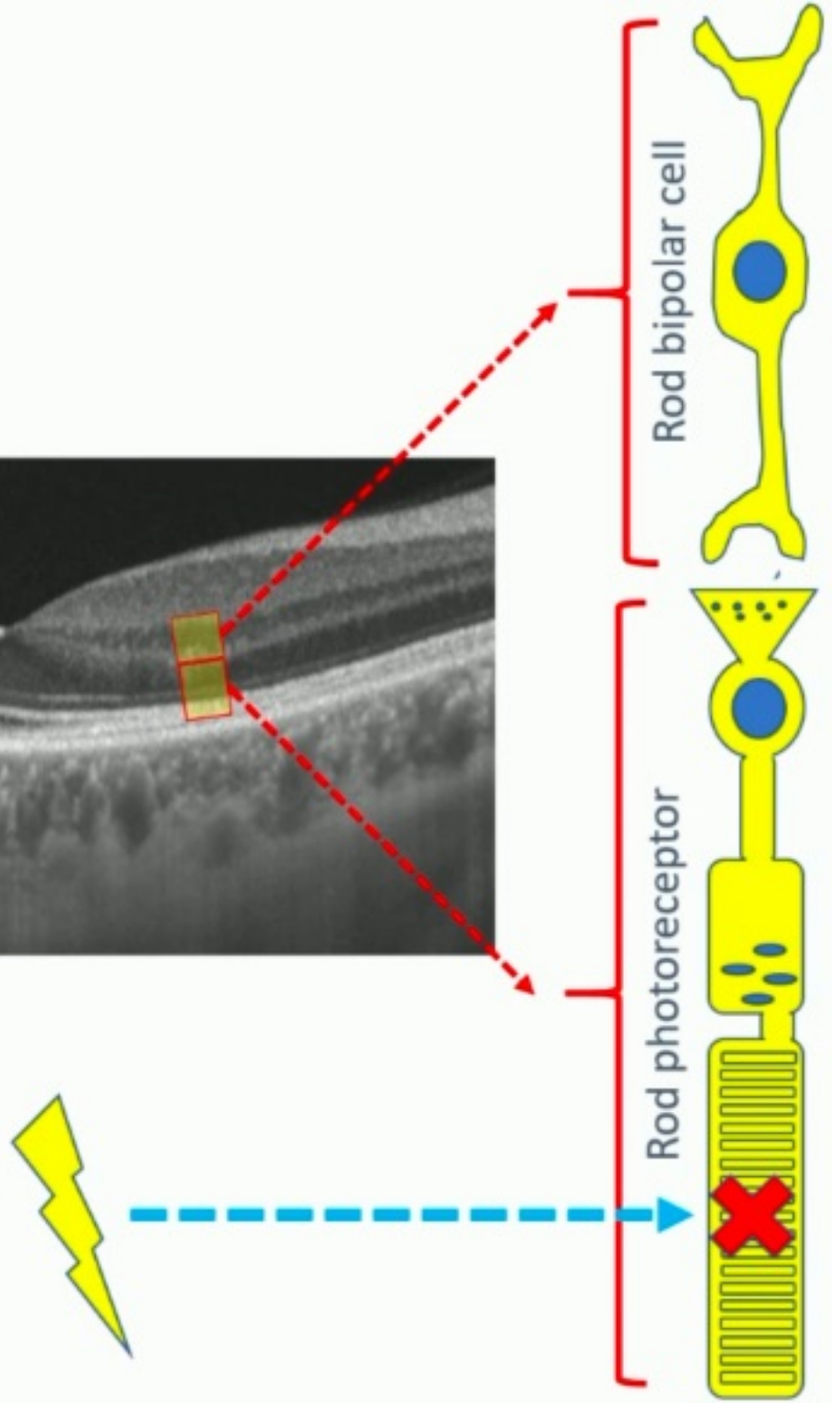
Selective loss of ON bipolar responses
Complete CSNB: NYX, TRPM1, GRM6, GPR179, LRIT3
Other causes include MAR
cone photo-transduction
synaptic transmission
ON bipolar cell response
OFF bipolar cell response
Reduction in both ON and OFF bipolar responses
Incomplete CSNB: CACNA1F, CABP4
Other causes include CRAO





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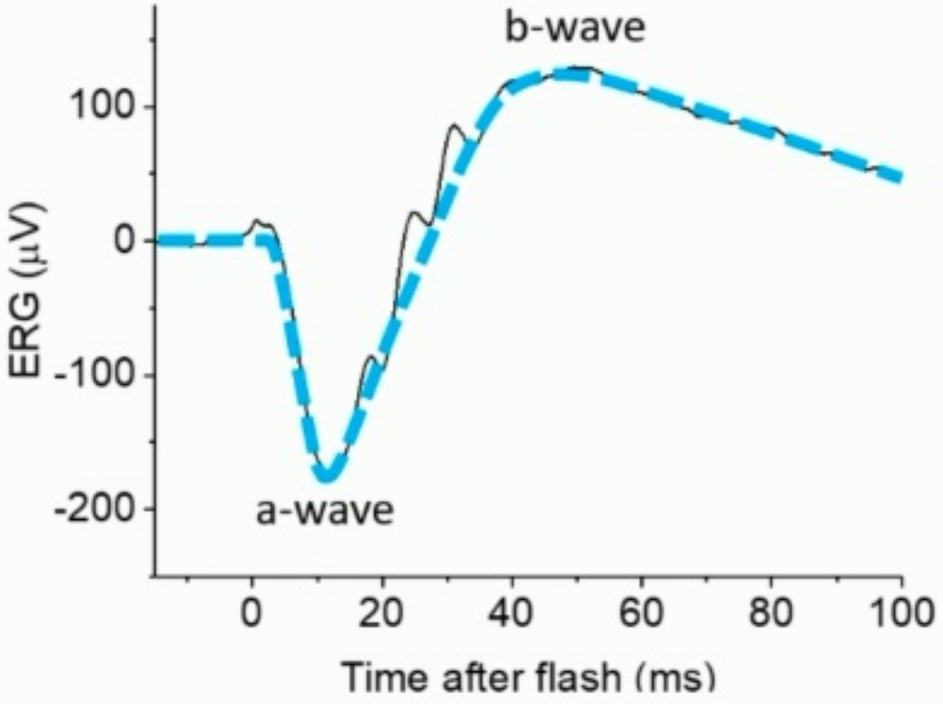

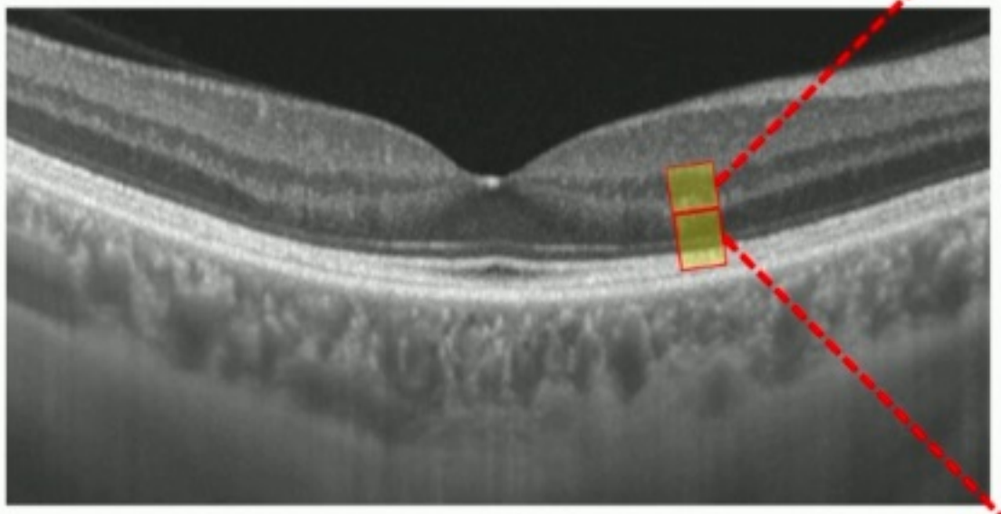

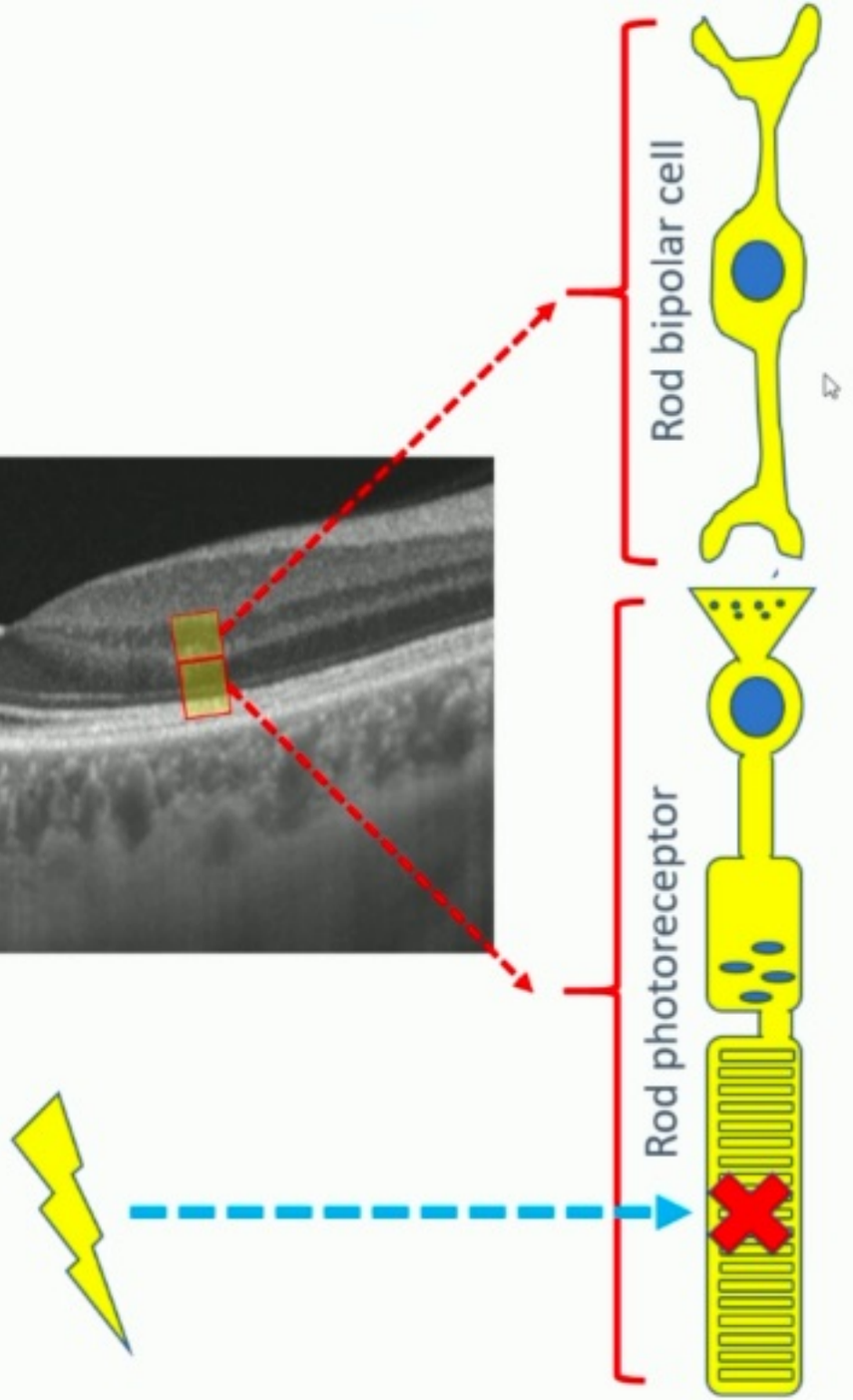

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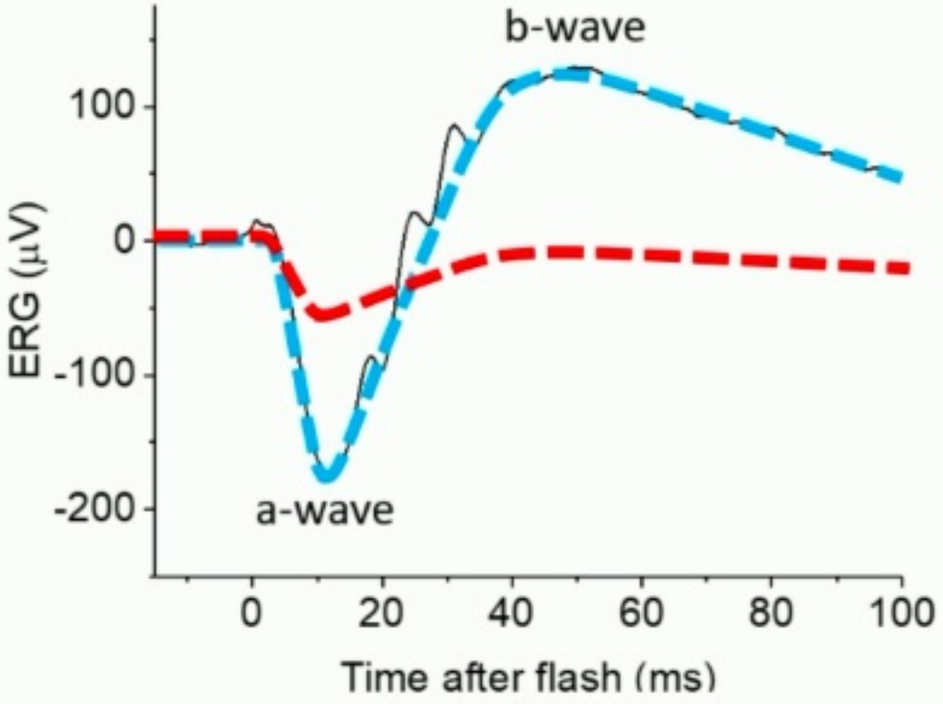
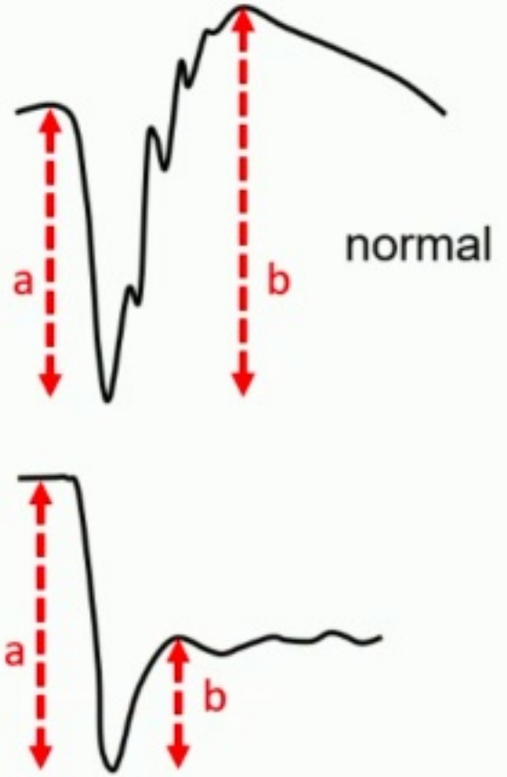


The electronegative ERG

- The b-wave is smaller than the a-wave (b:a ratio <1)
- Best seen in the dark-adapted bright flash
- The a-wave is of **normal** size
  - *If a-wave subnormal, indicates rod photoreceptor dysfunction*
  - *(Electronegativity could simply reflect dark-adapted cone system responses)*
- Indicates that dysfunction is *after* phototransduction



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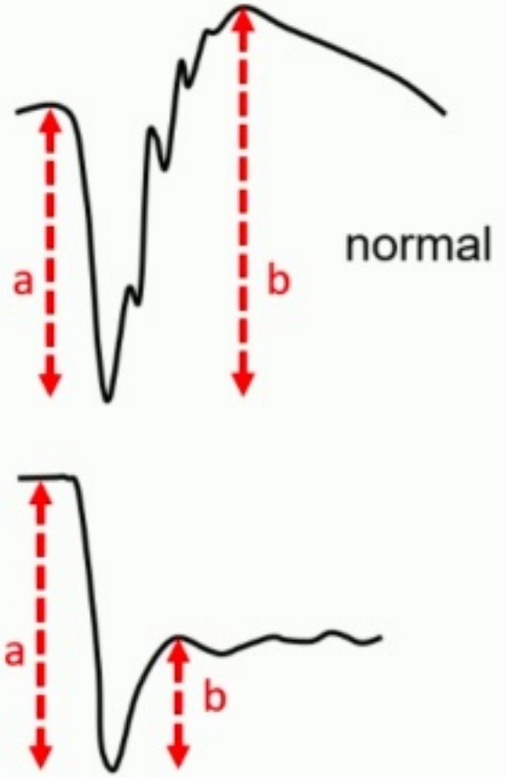

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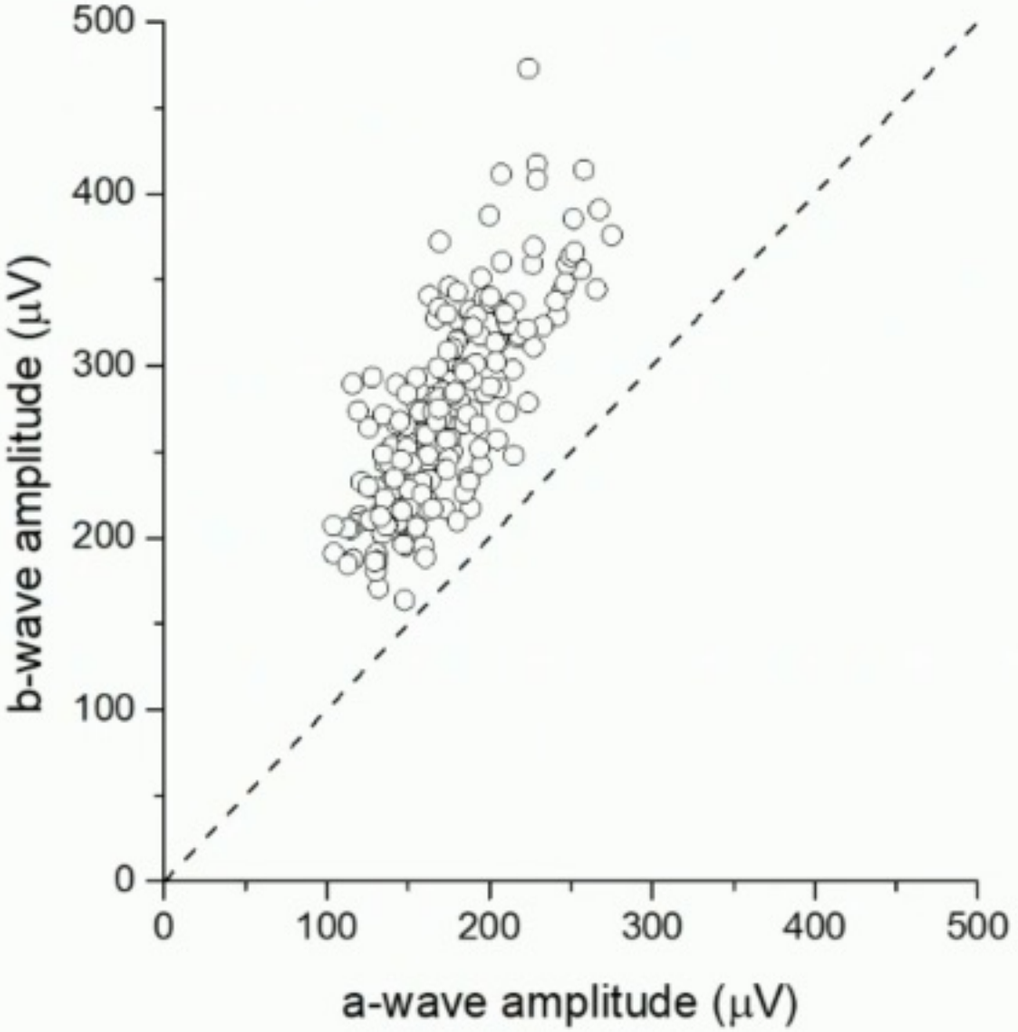
Scotopic bright flash (10 cd m^{-2} s): Data from TwinsUK (210 participants)



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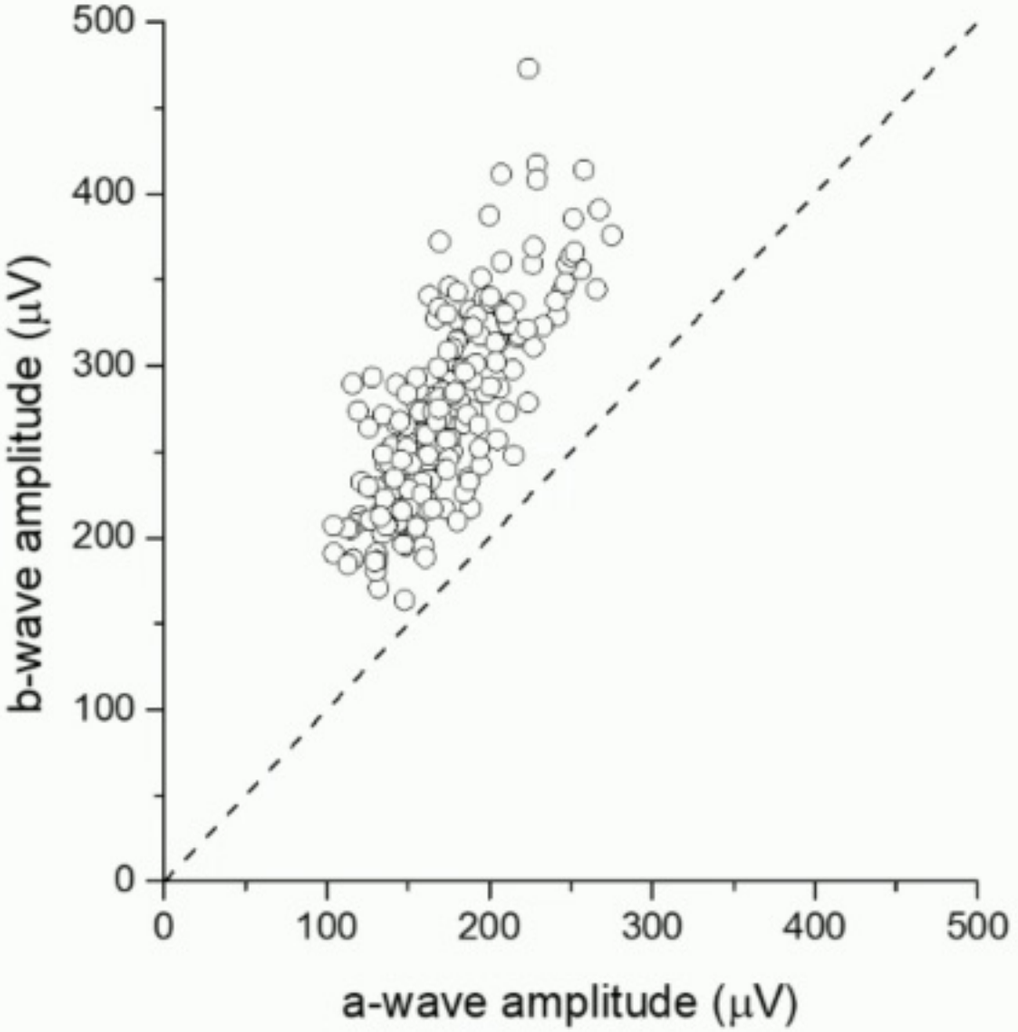

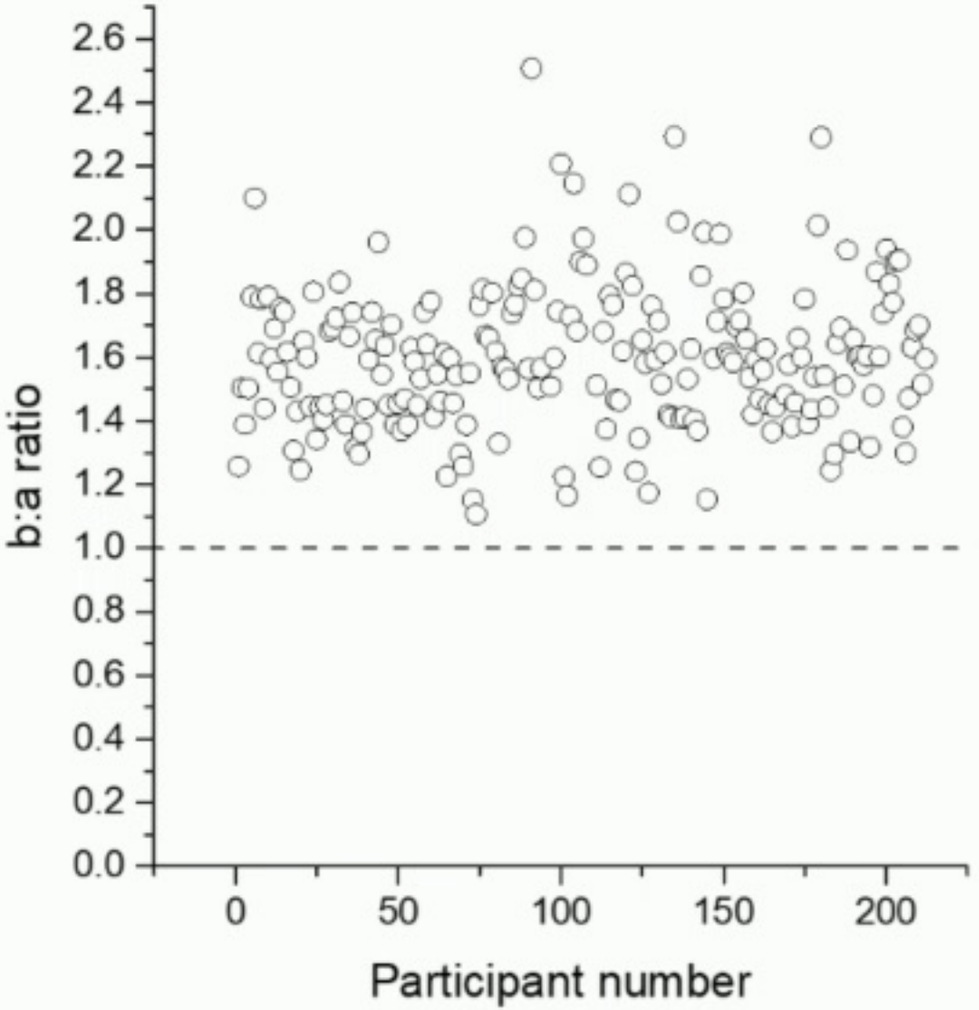

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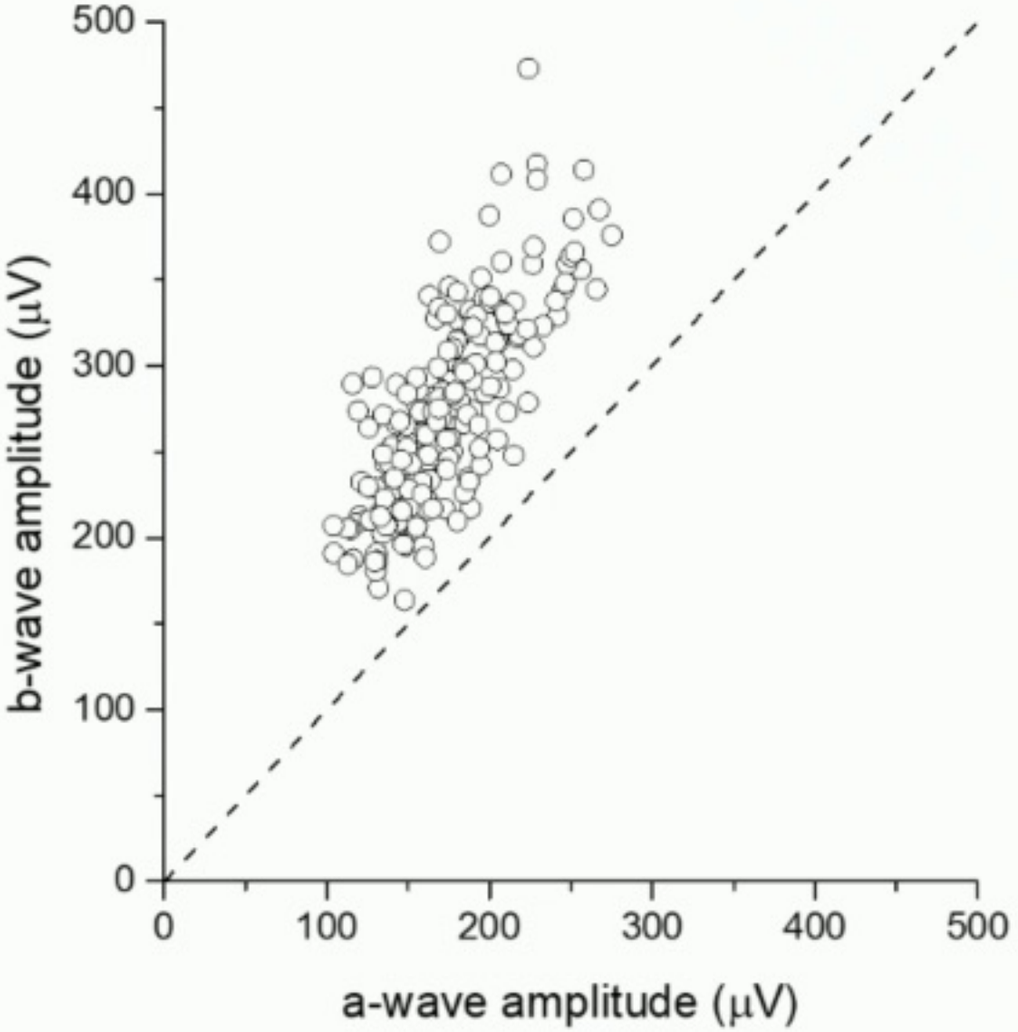

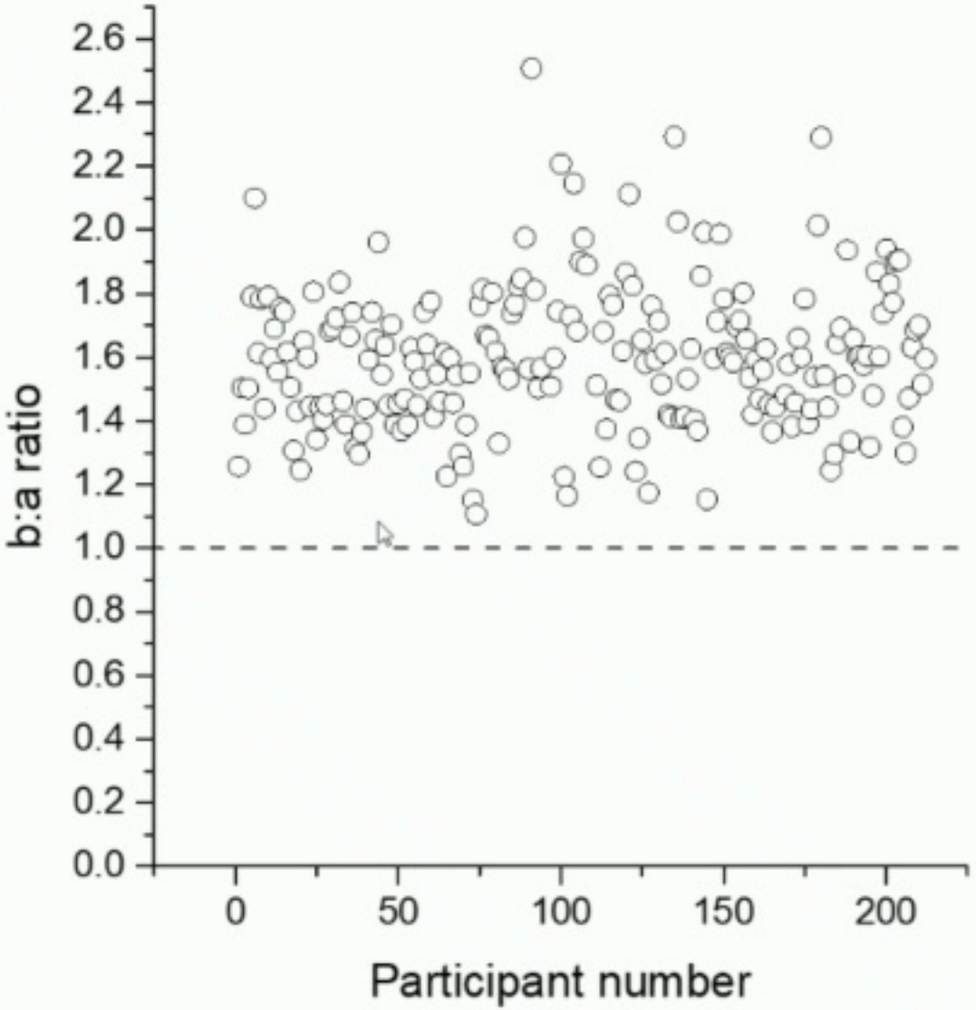

*Electronegative ERGs are **abnormal***

Electronegative ERGs in practice

- Koh, Hogg, Holder. *Doc Ophthalmol.* 2001
  - Retrospective review at Moorfields 1995-1997
  - Of 2640 ERGs, 128 showed negative ERGs

- Renner, Kellner, Cropp, Foerster. *Graefe's Arch Clin Exp Ophthalmol.* 2006
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4.8%

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2.9%

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4.0%

(2.5% adults
7.2% children)

Diagnostic categories	Patients in each category as proportion (%) of all patients with negative ERGs at each centre			
	London, UK (n=128) [1995-1997]	Berlin, Germany (n=47) [1992-2004]	Atlanta, Georgia (n=50) [1999-2008]	Sao Paolo, Brazil (n=41) [2004-2013]
X-linked retinoschisis	14.8	36.2	14	7.3
CSNB	13.3	12.8	58	2.4
CRAO	10.2	0	4*	0
Birdshot	5.5	0	0	0
Toxic	3.9	2.1	2	0
MAR	3.1	2.1	0	0
Batten	0.8	0	0	0
Inflammatory (unspecified)	2.3	0	2	12.2
Photoreceptor dystrophy**	26.6	27.7	8	58.5
Multisystem atrophy	0	0	2	0
Diabetic retinopathy	0	0	0	4.9
Undiagnosed	19.5	19.1	10	14.6

*CRAO: patients from Atlanta included those with vasculitis as well as vascular occlusions.

**In photoreceptor dystrophies, a-waves were also subnormal. Also applies to some other categories.

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Birdshot	5.5	0	0	0
Toxic	3.9	2.1	2	0
MAR	3.1	2.1	0	0
Batten	0.8	0	0	0
Inflammatory (unspecified)	2.3	0	2	12.2
Photoreceptor dystrophy**	26.6	27.7	8	58.5
Multisystem atrophy	0	0	2	0
Diabetic retinopathy	0	0	0	4.9
Undiagnosed	19.5	19.1	10	14.6

*CRAO: patients from Atlanta included those with vasculitis as well as vascular occlusions.

**In photoreceptor dystrophies, a-waves were also subnormal. Also applies to some other categories.

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- Additional protocols
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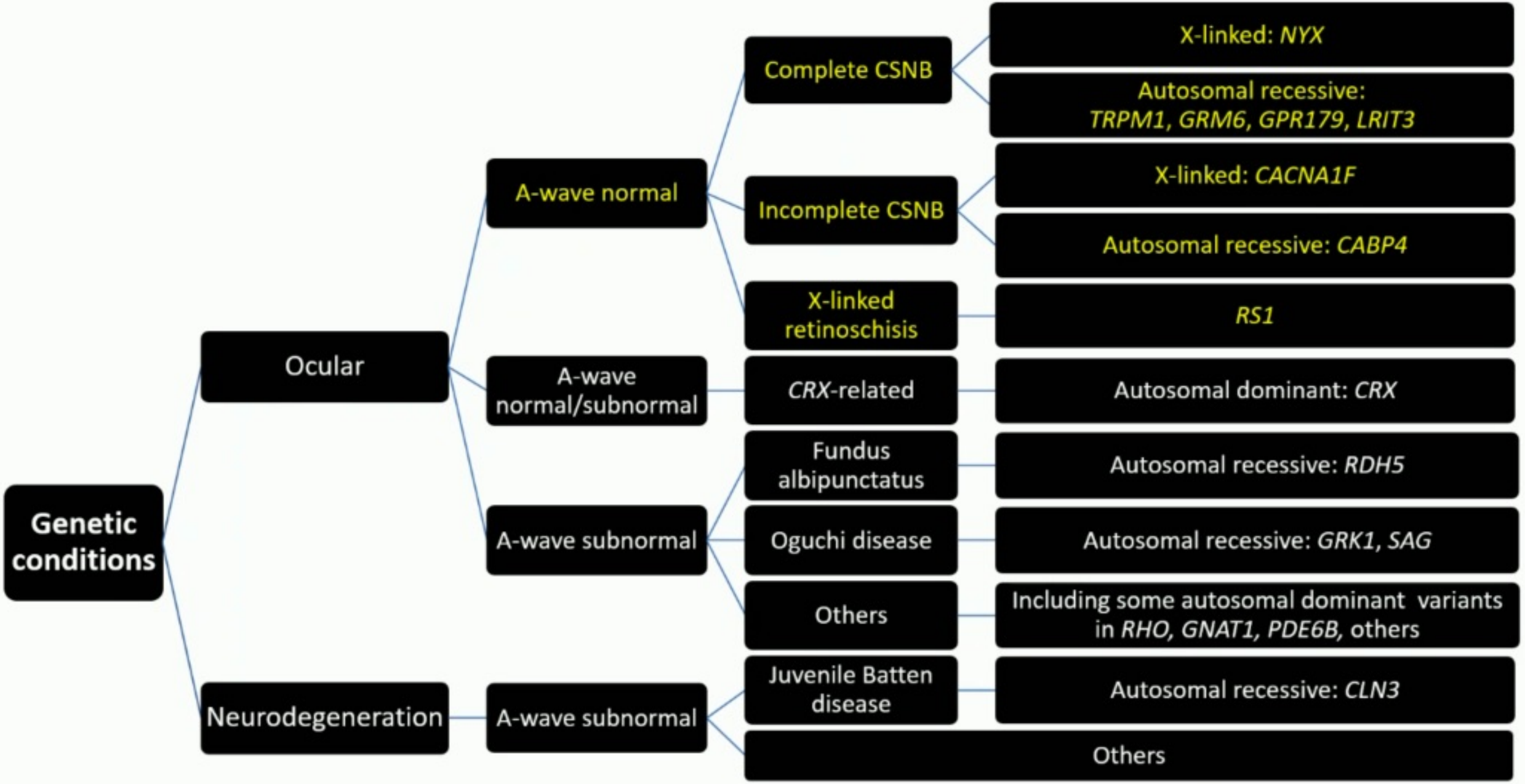
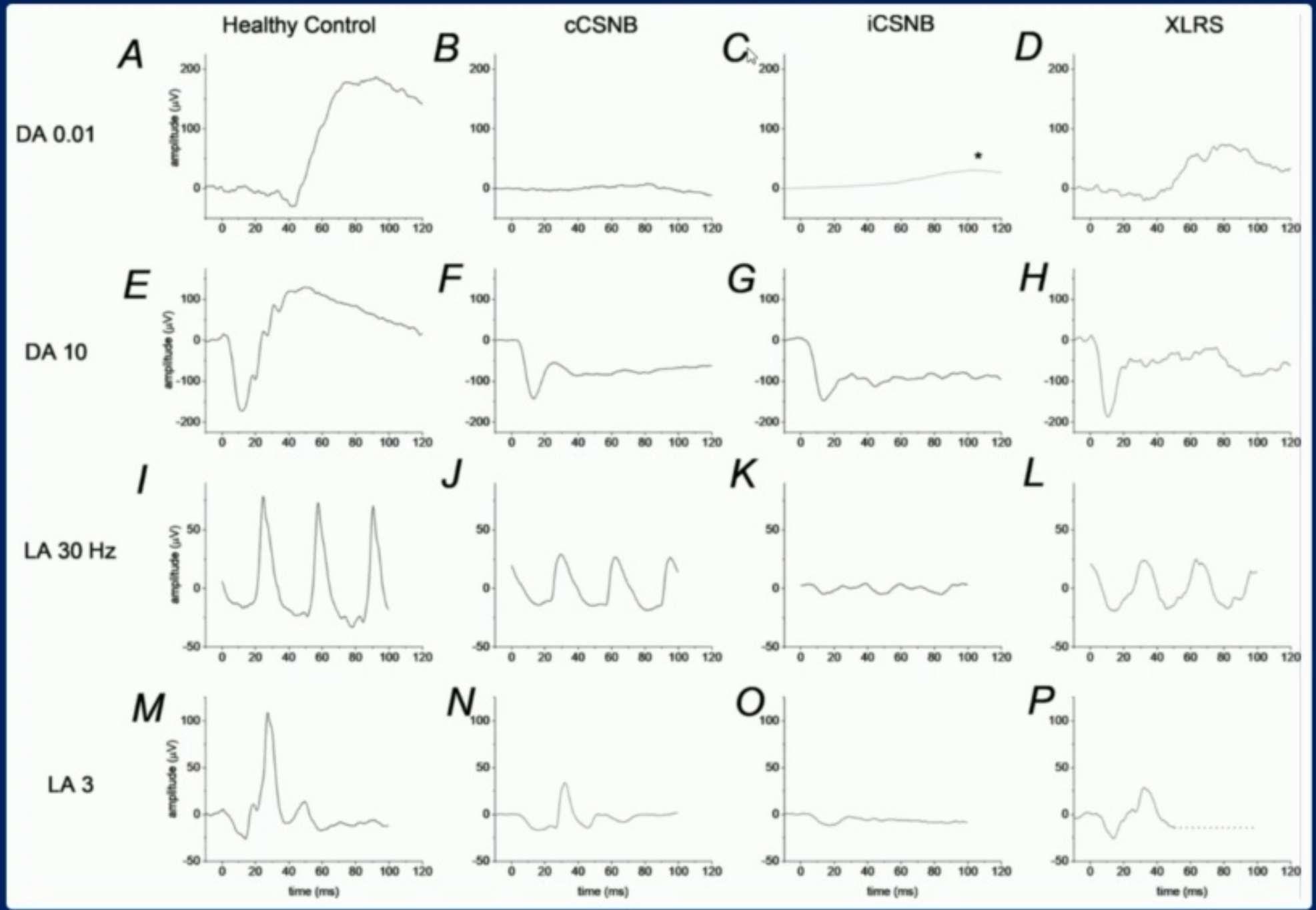
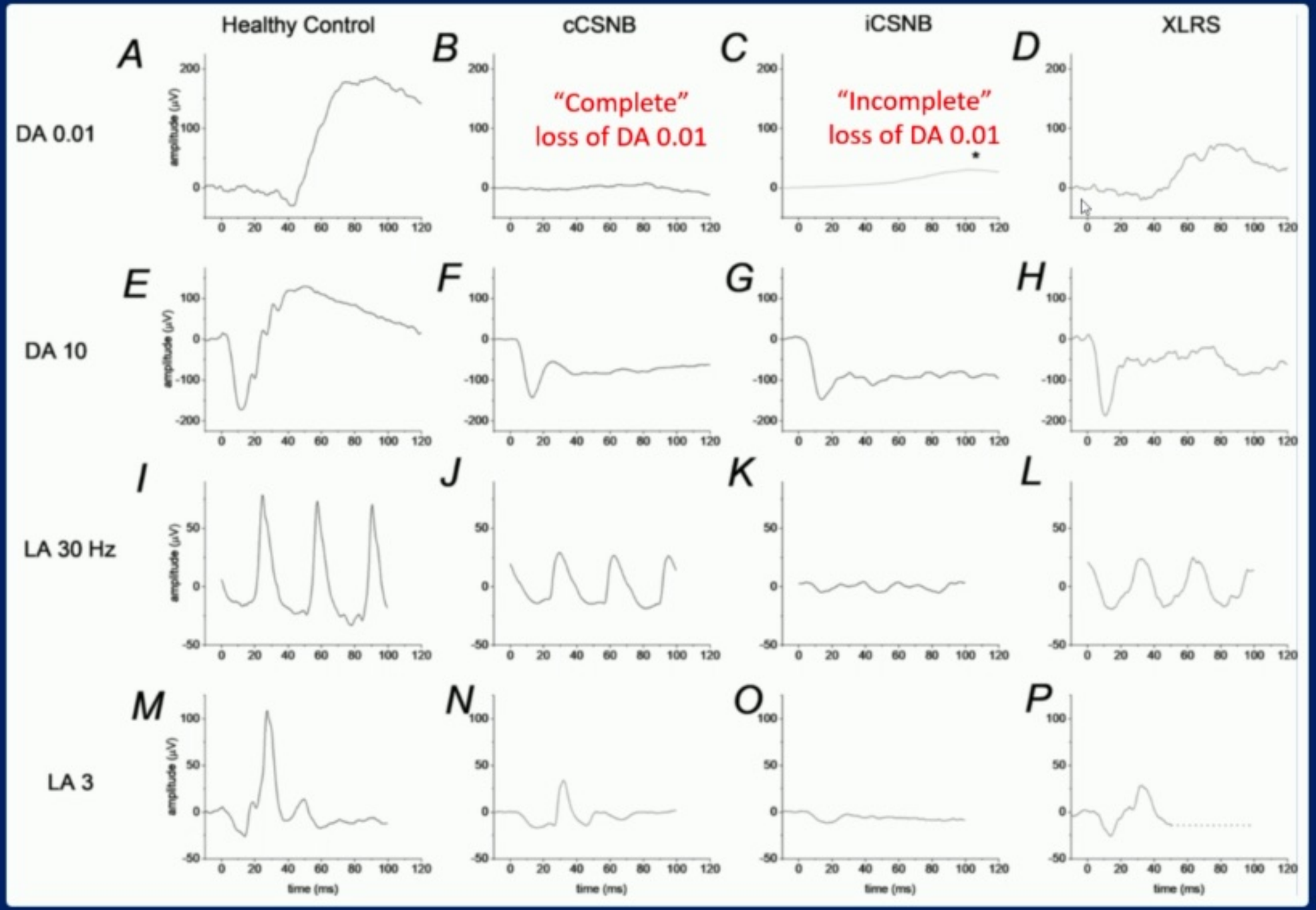

Genetic conditions
Ocular
A-wave normal
Complete CSNB
X-linked: NYX
Autosomal recessive: TRPM1, GRM6, GPR179, LRIT3
Incomplete CSNB
X-linked: CACNA1F
Autosomal recessive: CABP4
X-linked retinoschisis
RS1
A-wave normal/subnormal
CRX-related
Autosomal dominant: CRX
A-wave subnormal
Fundus albipunctatus
Autosomal recessive: RDH5
Oguchi disease
Autosomal recessive: GRK1, SAG
Others
Including some autosomal dominant variants in RHO, GNAT1, PDE6B, others
Neurodegeneration
A-wave subnormal
Juvenile Batten disease
Autosomal recessive: CLN3
Others

ISCEV Standard ERGs



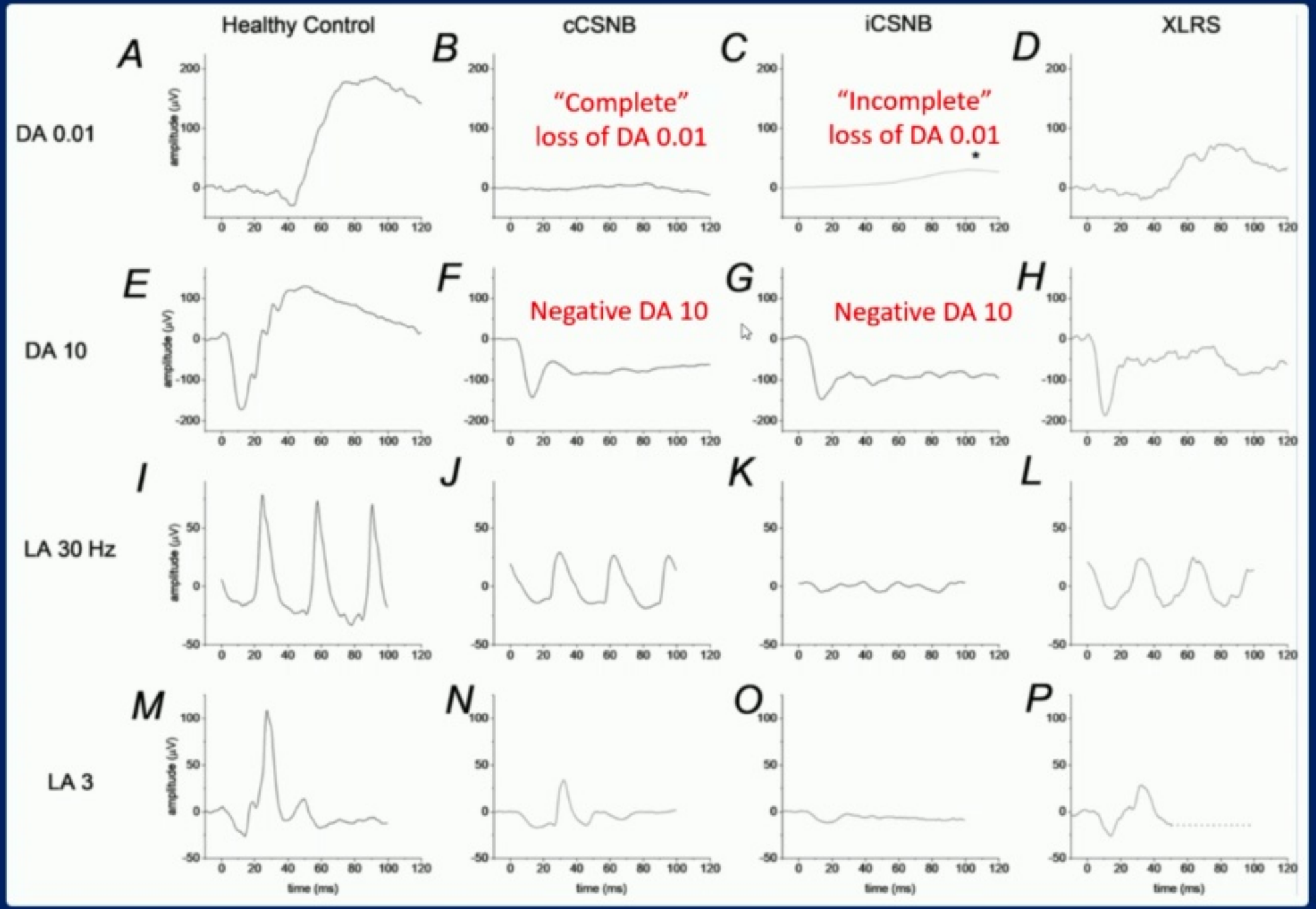
Jiang & Mahroo.
Eye, 2021

ISCEV Standard ERGs



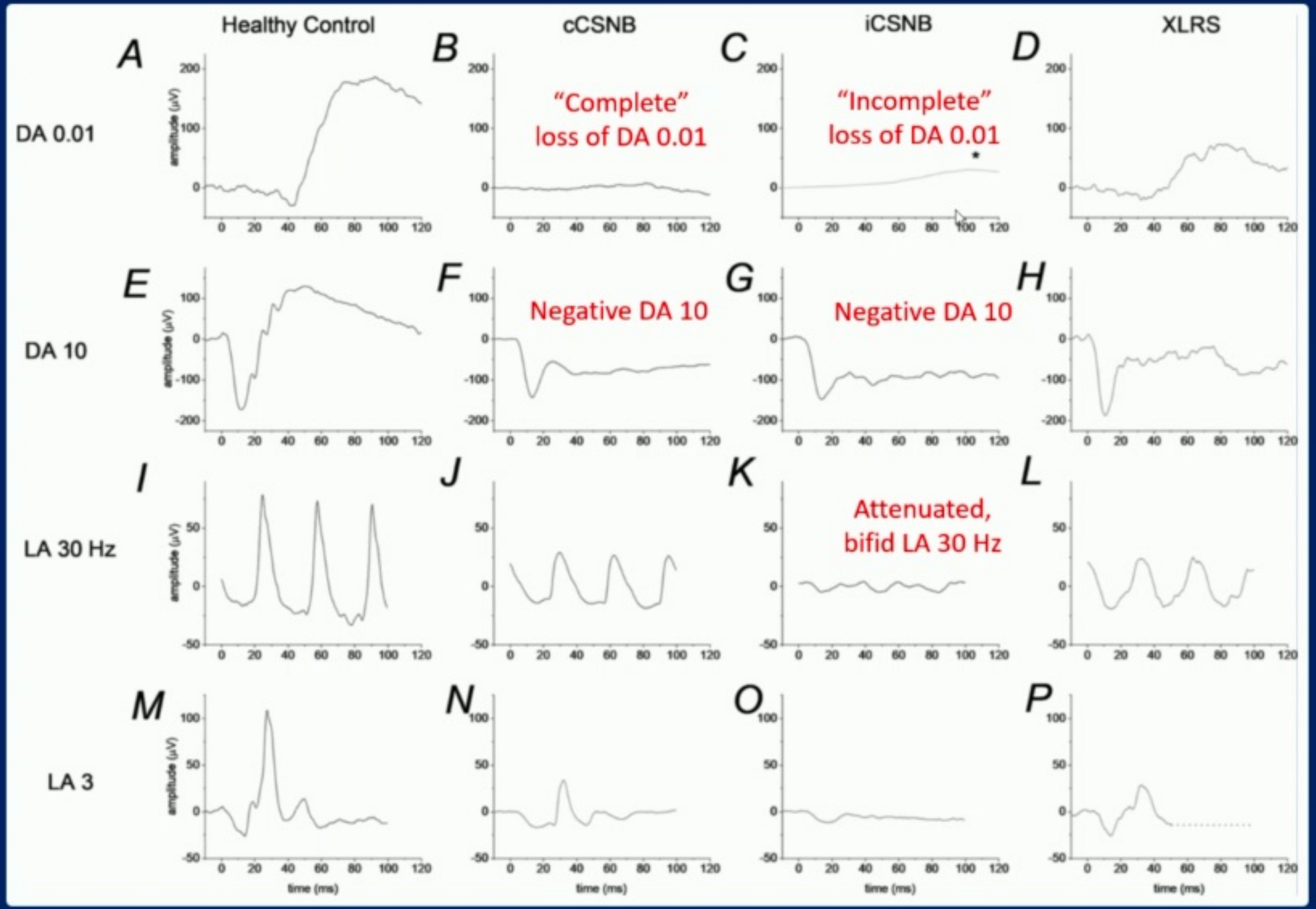
Jiang & Mahroo.
Eye, 2021

ISCEV Standard ERGs



Jiang & Mahroo.
Eye, 2021

ISCEV Standard ERGs



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Eye, 2021

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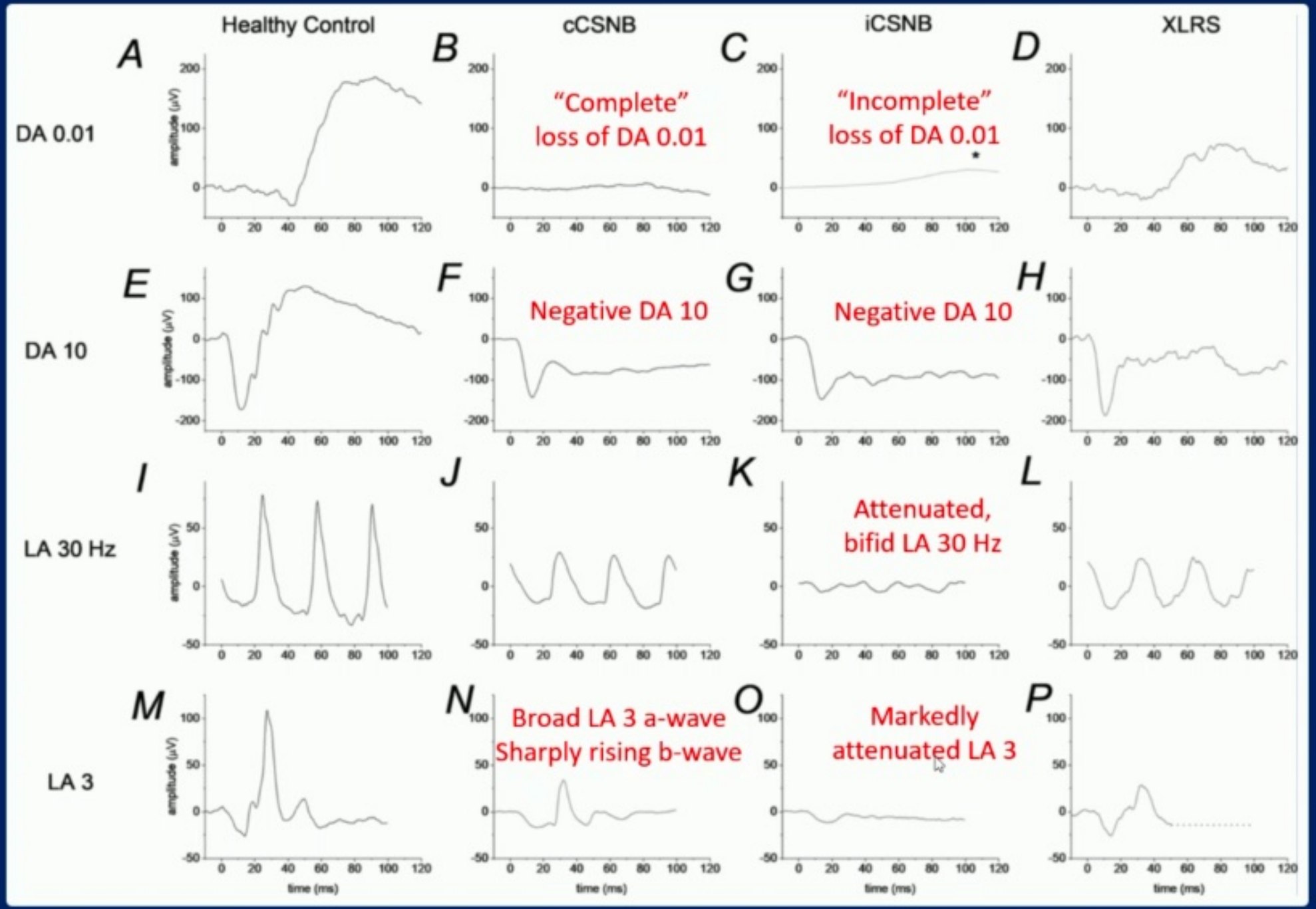

Jiang & Mahroo.
Eye, 2021

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Congenital stationary night blindness: An analysis and update of genotype–phenotype correlations and pathogenic mechanisms

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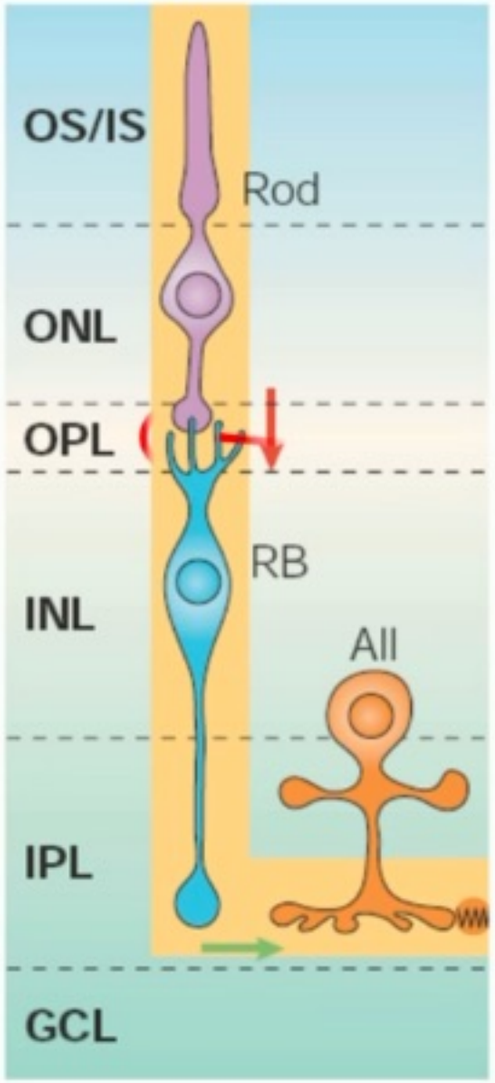

OS/IS
Rod
ONL
OPL
RB
INL
AII
IPL
GCL

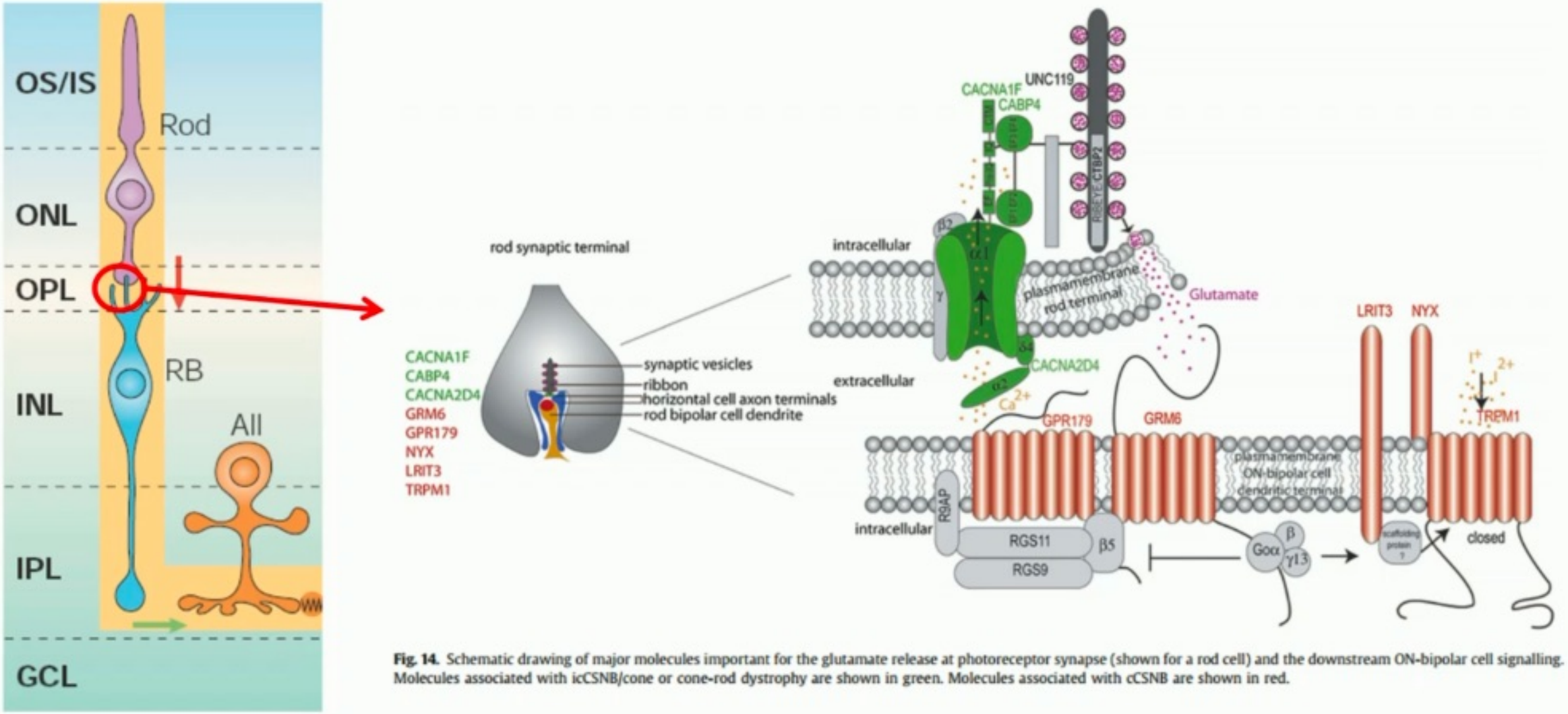
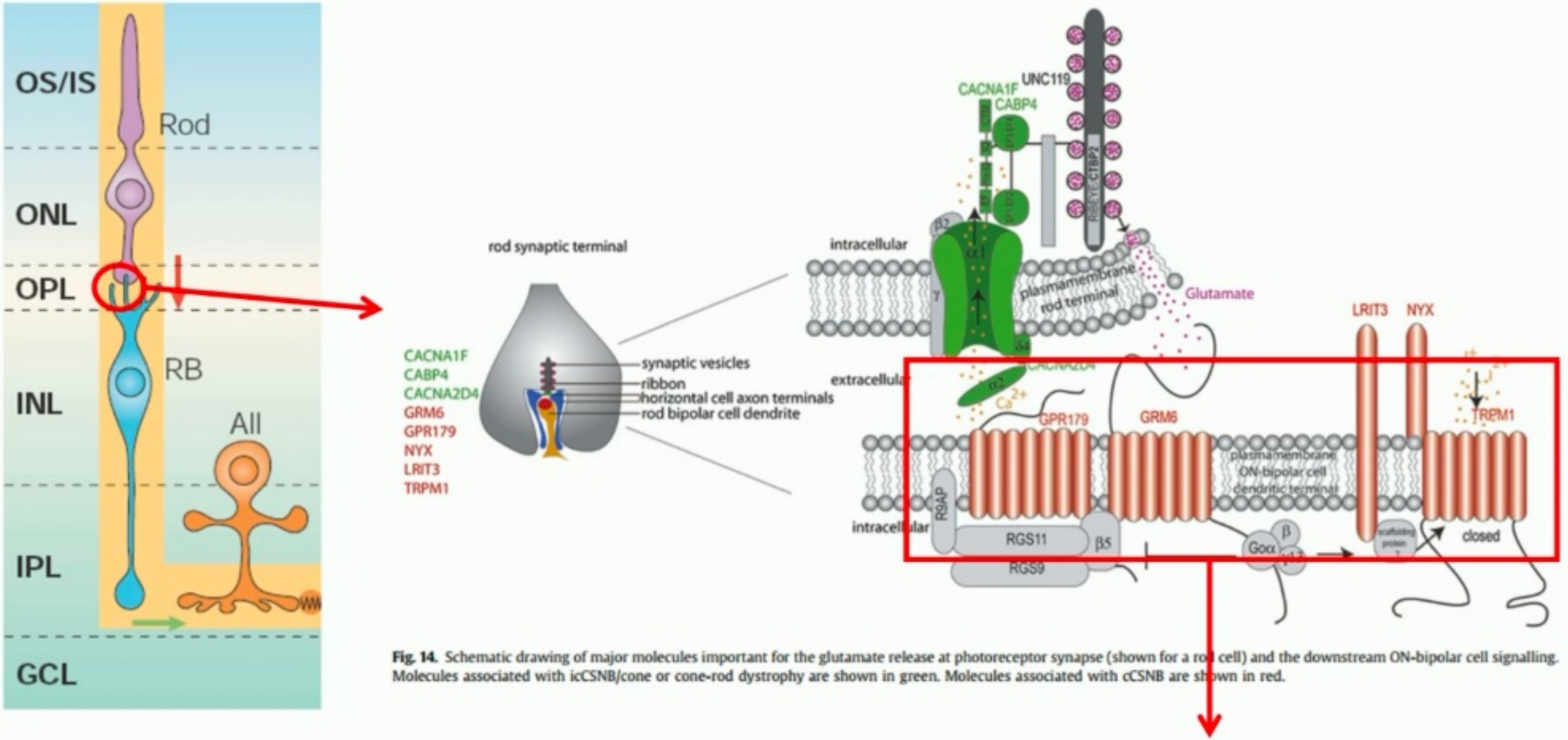


Fig. 14. Schematic drawing of major molecules important for the glutamate release at photoreceptor synapse (shown for a rod cell) and the downstream ON-bipolar cell signalling. Molecules associated with icCSNB/cone or cone-rod dystrophy are shown in green. Molecules associated with cCSNB are shown in red.



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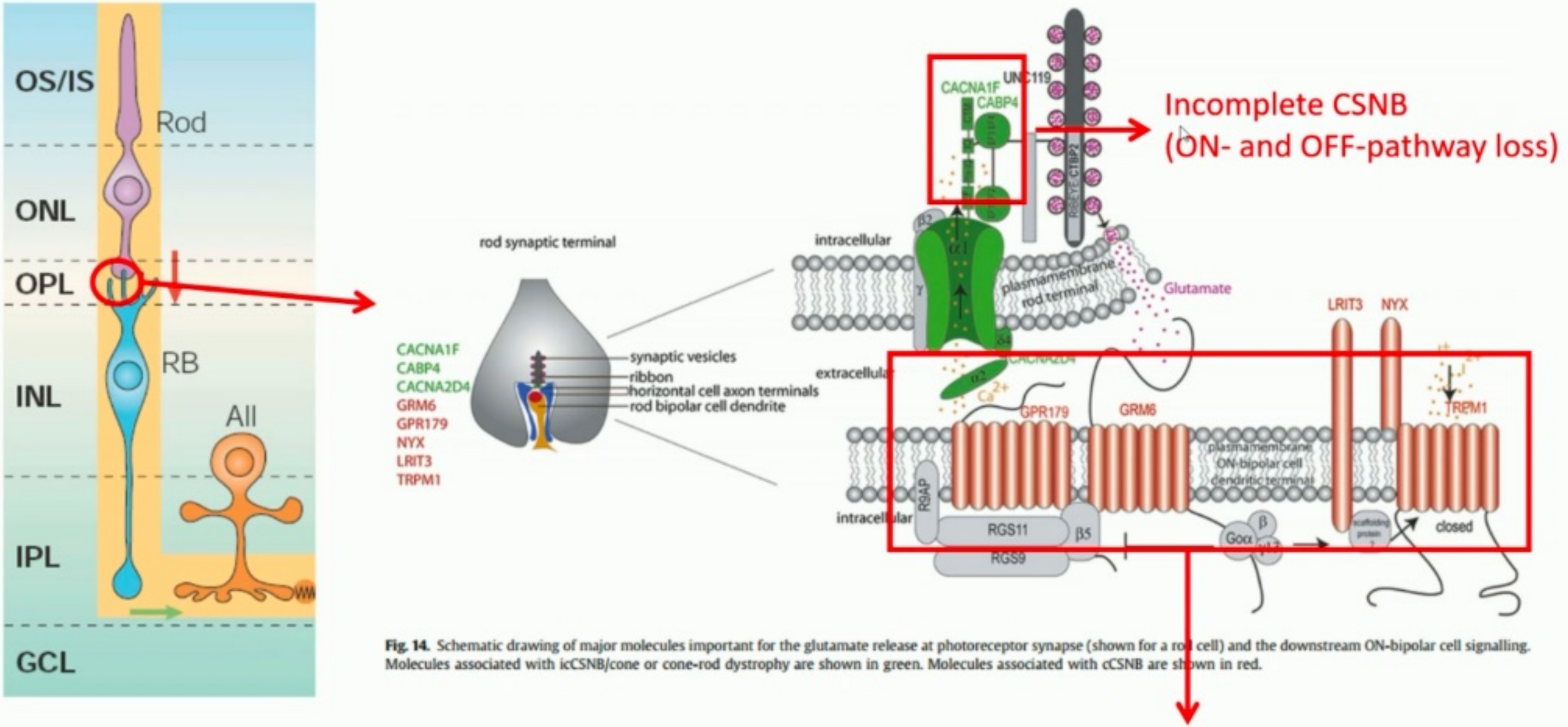
Complete CSNB (ON-pathway loss)



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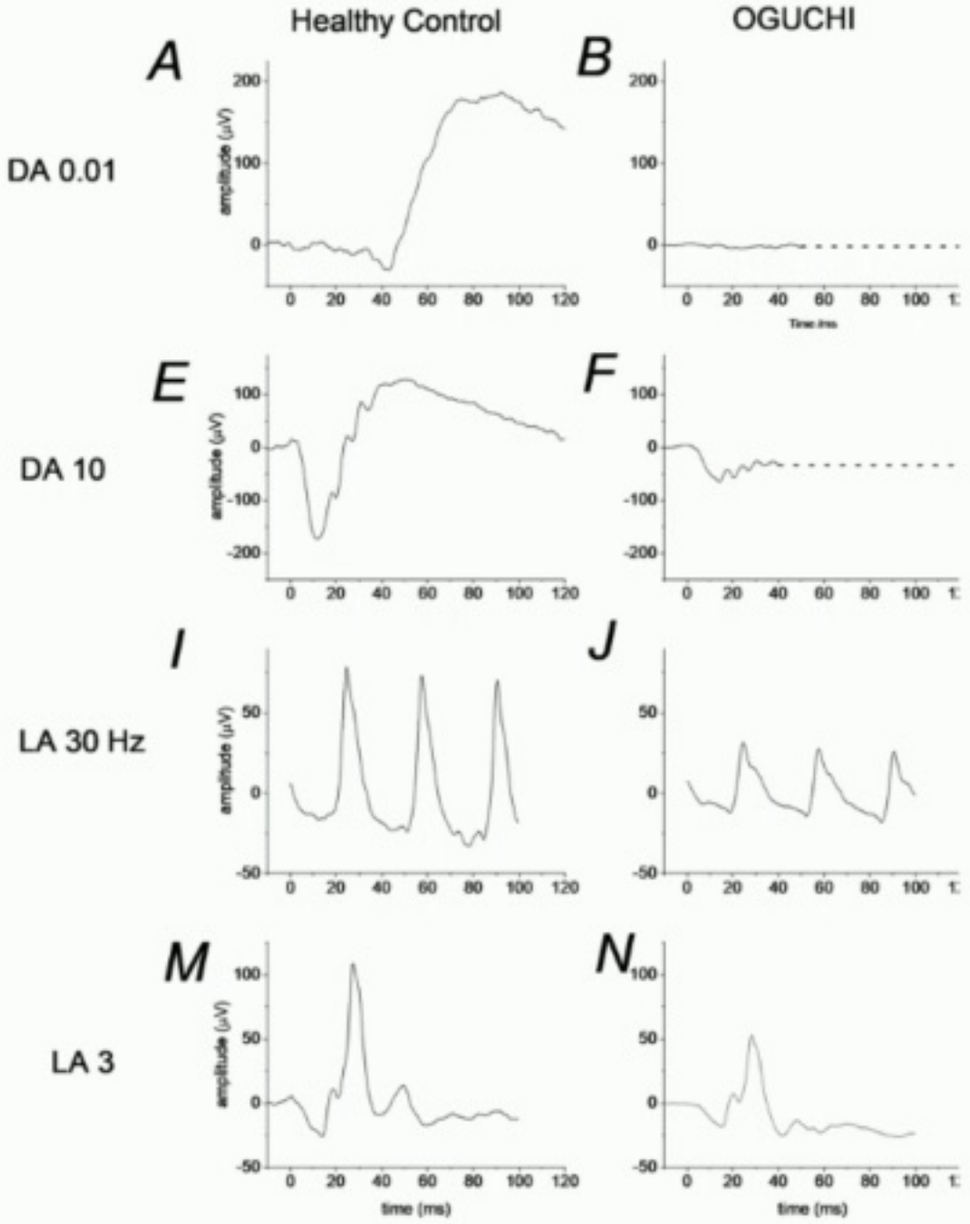
Healthy Control
OGUCHI
A
B
DA 0.01
E
F
DA 10
I
J
LA 30 Hz
M
N
LA 3
amplitude (μV)
time (ms)

Outline

- Physiological Basis
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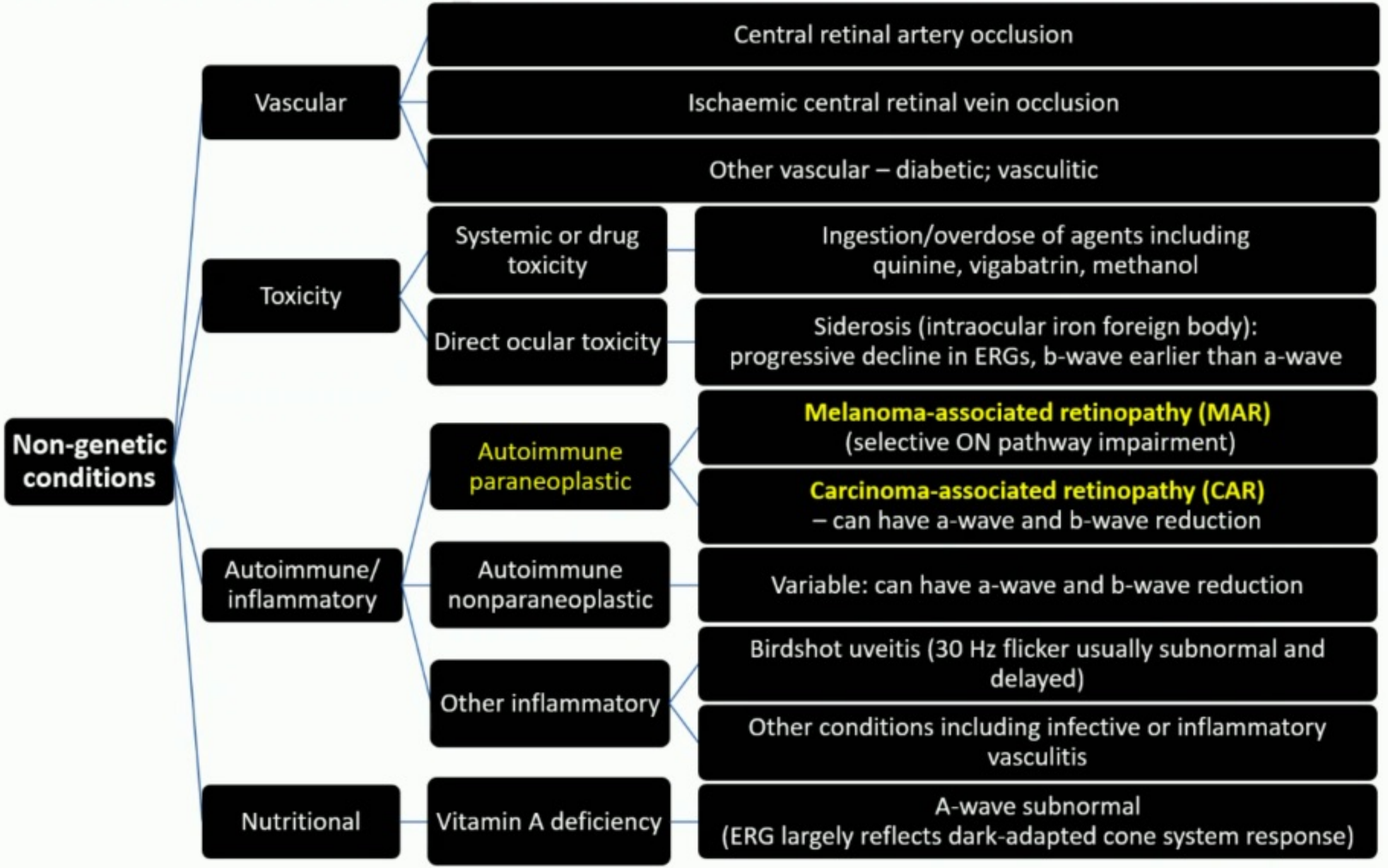
Non-genetic conditions
Vascular
Central retinal artery occlusion
Ischaemic central retinal vein occlusion
Other vascular – diabetic; vasculitic
Toxicity
Systemic or drug toxicity
Ingestion/overdose of agents including quinine, vigabatrin, methanol
Direct ocular toxicity
Siderosis (intraocular iron foreign body): progressive decline in ERGs, b-wave earlier than a-wave
Autoimmune/ inflammatory
Autoimmune paraneoplastic
Melanoma-associated retinopathy (MAR) (selective ON pathway impairment)
Carcinoma-associated retinopathy (CAR) – can have a-wave and b-wave reduction
Autoimmune nonparaneoplastic
Variable: can have a-wave and b-wave reduction
Other inflammatory
Birdshot uveitis (30 Hz flicker usually subnormal and delayed)
Other conditions including infective or inflammatory vasculitis
Nutritional
Vitamin A deficiency
A-wave subnormal (ERG largely reflects dark-adapted cone system response)

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Questions to ask

- ERG-related
  - Unilateral or bilateral? Symmetrical?
  - Is the *a*-wave normal?
  - Is there a rod-specific (dim-flash) *b*-wave?
  - What is the shape of the photopic responses?

Questions to ask

- ERG-related
  - Unilateral or bilateral? Symmetrical?
  - Is the *a*-wave normal?
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  - What is the shape of the photopic responses?

- Symptoms?
- Other investigations: visual fields, imaging (OCT, autofluorescence)
- Ocular and medical history

Features in patient history	
Ocular history	• CSNB patients have stationary, congenital visual impairment, and are associated with myopia. • XLRS usually presents in childhood. • Rapidly progressive visual loss aged 4 to 8 can be seen in juvenile Batten disease. • Acquired conditions usually much later onset of symptoms. • More acute/subacute onset of symptoms in adult (e.g. photopsia, night blindness) could reflect autoimmune (including paraneoplastic) disorders or inflammatory/vascular disorders. Some genetic conditions can present as adult. • History of IOFB or penetrating injury may point towards siderosis.
General medical history	• Specific neurological/neuromuscular/metabolic systemic diagnoses. • Medication history to include quinine, vigabatrin (and methanol). • Known diagnosis or symptoms suggestive of cancer or melanoma. • Dietary insufficiency or intestinal or liver disease that could result in VAD.
Family history	• Male with X-linked pedigree suggests X-linked genes (*RS1*, *NYX*, *CACNA1F*) • Other generations not affected in autosomal recessive diseases (unless pseudodominance/consanguinity). • Dominant family history in CRX-related disease.

Features on retinal imaging

Colour fundus imaging, OCT, AF	• Myopic changes in CSNB. • Schisis in XLRS (sometimes macular outer retinal atrophy in adult). • Bull's eye maculopathy and progressive degeneration in Batten disease. • Range of changes possible in *CRX*-related retinopathy, but symmetric. • Sheen in Oguchi disease; small white dots in fundus albipunctatus and in VAD. • Outer retinal abnormalities, nonspecific thinning, pigmentary changes possible in autoimmune and inflammatory retinopathies, often asymmetric. • Typical pale depigmented lesions in Birdshot chorioretinopathy. Inflammatory conditions may have cystoid macular oedema. • Inner retinal OCT hyper-reflectivity and swelling in CRAO followed by loss of inner retinal layers over weeks months. Widespread haemorrhages in CRVO. • Evidence of trauma or IOFB in siderosis.
FFA, ICG	• FFA can delineate ischaemia/leakage in retinovascular/inflammatory disease • ICG can help in choroidal diseases; hypofluorescent lesions in Birdshot.

Features relating to ERGs	
Are the abnormalities bilateral and symmetric?	• Genetic diseases, systemic drug toxicities, and Vitamin A deficiency should give symmetric abnormalities. • Ocular siderosis and central retinovascular occlusions are usually unilateral • Paraneoplastic, inflammatory, autoimmune conditions may be unilateral or bilateral, and can be asymmetric.
Is the DA10 a-wave normal-sized or subnormal?	• Normal-sized in CSNB, XLRS. • Normal-sized in CRAO and CRVO and certain drug toxicities. • May be normal-sized in MAR, but can be variable in other inflammatory and autoimmune retinopathies (including CAR) • Can be normal or subnormal in *CRX*-related disease. • A-wave usually subnormal in fundus albipunctatus, Oguchi disease, Batten disease and other diseases affecting photoreceptors. • A-wave subnormal in VAD.
What is the shape of the LA responses?	• Shape may reflect selective ON pathway dysfunction (cCSNB, MAR) or combined ON and OFF dysfunction (other conditions) – see Figures 2 and 3. • LA response may be normal when cone system function normal (and DA responses reflect intact cone function)

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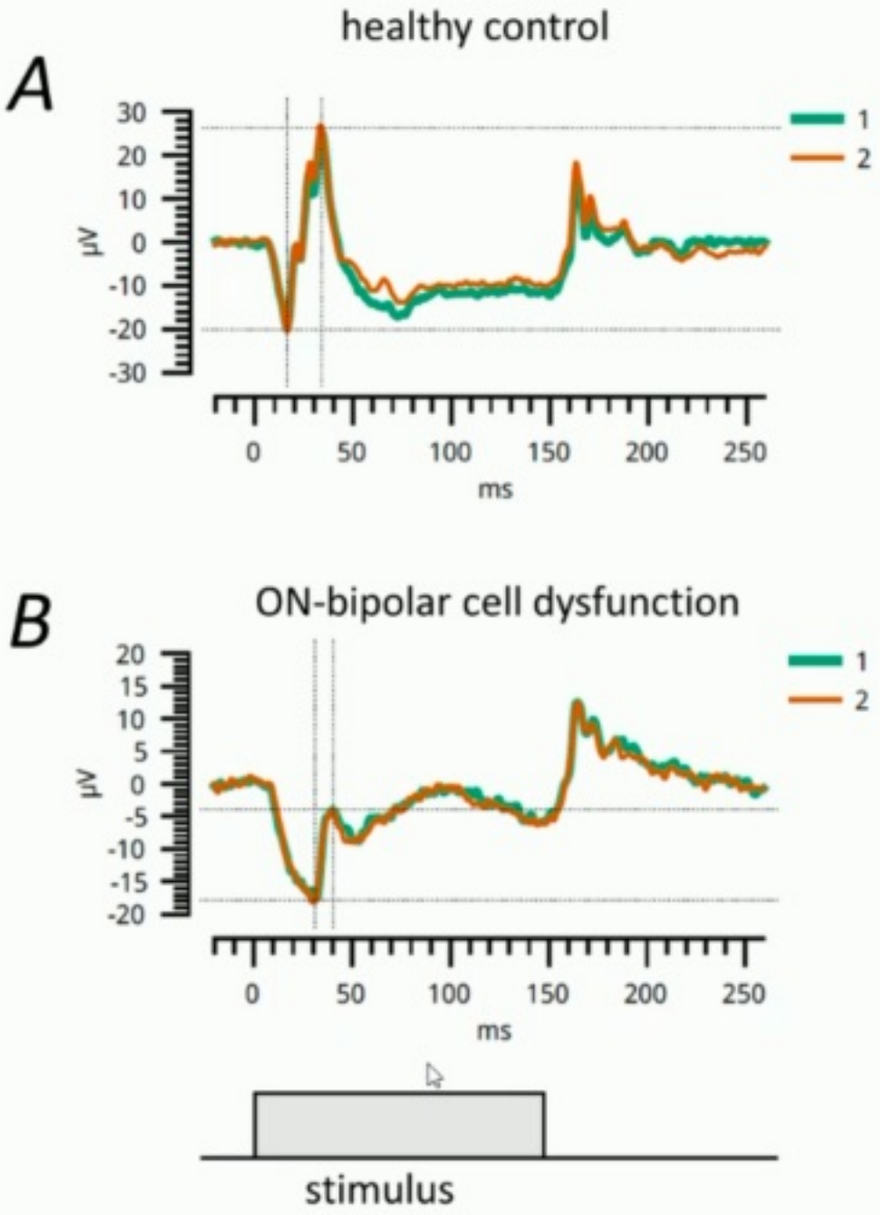
Sustar M, Holder GE, Kremers J, Barnes CS, Lei B, Khan NW, Robson AG.

ISCEV extended protocol for the photopic On-Off ERG.

Doc Ophthalmol. 2018 Jun;136(3):199-206.


A
healthy control
30
20
10
0
-10
-20
-30
µV
1
2
0
50
100
150
200
250
ms
B
ON-bipolar cell dysfunction
20
15
10
5
0
-5
-10
-15
-20
µV
1
2
0
50
100
150
200
250
ms
stimulus

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Concluding Remarks

- The electronegative ERG is an important finding

- Genetic diseases
  - Narrows differential of likely associated genes.
  - Can guide gene screening (and its interpretation)

- Non-genetic disease
  - May point to particular diagnoses including paraneoplastic retinopathy
  - In some cases of MAR, visual dysfunction and electrophysiological findings might ***precede*** melanoma diagnosis