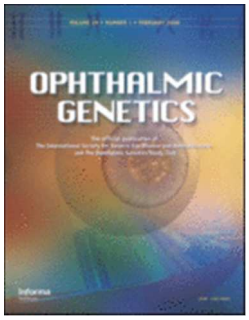

Retinitis pigmentosa and bilateral cystoid macular oedema in a patient heterozygous for the RIM1 mutation previously associated with cone-rod dystrophy 7

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RIM1, retinitis pigmentosa and macular oedema

Retinitis pigmentosa and bilateral cystoid macular oedema in a patient heterozygous for the *RIM1* mutation previously associated with cone-rod dystrophy 7

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Running title: *RIM1*, retinitis pigmentosa and macular oedema

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RIM1, retinitis pigmentosa and macular oedema

Abstract

Background
Autosomal dominant cone-rod dystrophy 7 (CORD7) has been previously associated with the *RIM1* c.2459G>A (Arg820His) mutation. Cystoid macular oedema (CMO) is a rare feature of CORD and has not been described in CORD7. We report a patient who was heterozygous for the *RIM1* mutation with bilateral CMO and who manifested a retinitis pigmentosa phenotype.

Materials and methods
The patient's medical notes were retrospectively reviewed over an 18-month period. Genetic testing was performed by next generation sequencing for a panel of 176 genes associated with retinal dystrophy.

Results
A 34-year old man presented with a five-year history of bilateral floaters and blurred vision. Visual acuity was 20/23 and 20/33 in the right and left eyes, respectively. Optical coherence tomography scans revealed bilateral CMO. Goldmann visual field tests detected mid-peripheral ring scotomas. Electrodiagnostic testing was overall consistent with a primary photoreceptor abnormality involving both rods and cones. Subsequent genetic testing identified heterozygosity for the *RIM1* c.2459G>A (Arg820His) mutation. Various treatments for CMO were trialled unsuccessfully. However at his latest clinic appointment the CMO had partially improved following topical brinzolamide therapy. Most recent visual acuity was 20/25 in the right eye and 20/24 in the left eye.

Conclusions
This is the first reported case of bilateral CMO in association with the *RIM1* mutation. Overall our findings were more consistent with a phenotype of retinitis pigmentosa. This could imply that the *RIM1* mutation causes diverse retinal dystrophies, or that the previously described CORD7 phenotype resulted from a different variant on the same haplotype.

Key words: cone-rod dystrophy 7, CORD7, RIM1, RAB3A-interacting molecule 1, cystoid macular oedema, retinitis pigmentosa

Comment [AW1]: Reviewer 3: In the Abstract add a coma between eyes and respectively (Results section on Line 26-27).

RIM1, retinitis pigmentosa and macular oedema

Introduction

The cone-rod dystrophies (CORD) are a group of inherited retinal disorders characterised by predominant loss of cone photoreceptors with a prevalence of 1 in 40,000.[1] This contrasts with the rod-cone dystrophies, ~~also known as~~of which the most common type is retinitis pigmentosa, where there is primary rod photoreceptor involvement and cones are affected later with more advanced disease with a prevalence of circa 1 in 4,000.[2] Patients with CORD therefore typically present with reduced central vision and photophobia by the second decade of life, although eventually rod dysfunction also causes loss of peripheral vision and night blindness.

CORDs are highly genetically heterogeneous and inheritance may be either autosomal dominant, autosomal recessive or X-linked. More than 30 genetic mutations have been associated with CORD to date,[3] including the G to A point mutation (c.2459G>A) in the Rab3A interacting molecule (*RIM1*) at chromosome locus 6q12-q13.[4, 5] This causes an Arg820His substitution in the RIM1 protein's highly conserved C_2A domain, previously associated with the autosomal dominant CORD7 phenotype. To date, the CORD7 phenotype has only been described for eight members of a four-generation, non-consanguineous British family, none of whom developed cystoid macular oedema (CMO).[6] We herein report the first case of an unrelated individual discovered to carry the Arg820His *RIM1* mutation, whose clinical features were more consistent with a phenotype of retinitis pigmentosa and associated CMO.

Materials and Methods

The patient's medical records were reviewed. Colour fundus photographs, optical coherence tomography (OCT) scans, fundus fluorescein angiography (FFA), fundus autofluorescence, Goldmann visual field (GVF) and electrodiagnostic testing were performed. Genetic testing was performed by next generation sequencing for a panel of 176 genes known to be associated with retinal dystrophy. This next generation sequencing was outsourced and performed as a fee for service test by the Manchester Centre for Genomic Medicine, Central Manchester University Hospitals NHS Foundation

Comment [AW2]: Reviewer 3: In terms of the Introduction I would suggest reconsidering the statement "rod-cone dystrophies, also known as retinitis pigmentosa." Instead, consider stating that the most common type of rod-cone dystrophy is retinitis pigmentosa as there are other types of rod-cone dystrophies (Page 3, Line 13-14).

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(http://www.mangen.co.uk/lab-services/).

Results

A 34 year-old man presented with a five-year history of bilateral floaters and blurred vision for fine detail. He denied any photophobia, nyctalopia, loss of peripheral vision or colour blindness. He had no past ocular or past medical history. There was no significant family history, including his only brother who had no visual symptoms. No other family members were available for examination. Visual acuity was 20/25 in the right eye and 20/32 in the left eye. Colour vision was not formally assessed. Intraocular pressure was 14mmHg bilaterally. On slit lamp examination he was noted to bilateral macular oedema,~~have bilateral~~ discrete white dots peripherally at the level of the retinal pigment epithelium, a peripapillary greyish hue to the retina, and arteriolar attenuation, suggesting a possible underlying retinal dystrophy (Figure 1A). The optic disc appeared pink with clear margins. Optical coherence tomography (OCT) confirmed bilateral moderate-severe CMO with a central macular thickness (CMT) of 625µm and 546µm in the right and left eyes respectively.~~and~~ ~~f~~Fluorescein angiography (FFA) ~~bilateral CMO~~ furthermore revealed active leakage at both maculae (Figure 1B and 1E(i)).

Fundus autofluorescence scans showed blocked autofluorescence centrally, presumably due to the cystoid macular oedema, increased paracentral ~~hyper~~autofluorescence and more peripheral puntcate ~~hyper~~ increased autofluorescence (Figure 1C). Goldmann Visual Field (GVF) tests detected mid-peripheral ring scotomas bilaterally (Figure 1D). Electrodiagnostic testing revealed significantly degraded rod and cone electroretinograms (ERG), with rods being more affected than cones (Figure 2). Interestingly, we observed a negative maximal mixed cone-rod flash ERG secondary to marked degradation of the responses, with an abnormally attenuated maximal a wave in association with an even smaller b wave. Pattern ERGs were also degraded and the 30 Hz flicker ERG was of diminished amplitude but normal implicit time. Subsequent genetic testing found the patient to be heterozygous for the RIM1 c.2459G>A mutation (OMIM *606629), known to cause CORD7.

Comment [AW3]: Reviewer 2: was colour vision tested?

Comment [AW4]: Reviewer 2: Since when has the patient been experiencing visual complaints? This is important – since CORD usually present in the 2nd decade with visual impairment with loss of color perception and light aversion. Was nyctalopia more prominent than photoaversion?

Comment [AW5]: Reviewer 2: Description of fundus on ophthalmoscopy should include description of the optic disc and the macula.

Comment [AW6]: Reviewer 2: There is no mention of central foveal thickness, pre and post treatment.

Reviewer 3: In the Results section I would recommend elaborating on your description of the CMO (mild, moderate, or severe) and the degree of reduction (for example, was the change in CMO considered significant in both eyes? What was the percentage of reduction?).

Comment [AW7]: Reviewer 2: Was IVFA performed? IVFA helps differentiate macular cysts due to schisis (no leak) from edema (leak).

Comment [AW8]: Reviewer 3: In the Discussion, I would use the terminology of increased or decreased autofluorescence instead of hypo- or hyperfluorescence (Page 5, Lines 32-35). The same applies for the Legend for Figure 1 (Page 7).

Comment [AW9]: Reviewer 2: The ERG shows greater rod affectation than the cones, with rod response almost flat.

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Topical nepafenac, ketorolac and dorzolamide, as well as oral acetazolamide were trialled for 2-4 months each with no success. However 18 months after initial presentation, the CMO had partially resolved following 4 months of topical brinzolamide therapy (Figure 1E(ii)). Central retinal thickness as measured by OCT had improved to 509µm in the right eye and 394µm in the left eye, corresponding to reductions of 19% and 28% respectively. ~~with v~~Most recent visual acuity ~~of~~ was 20/25 in both eyes.

Comment [AW10]: Reviewer 2: There is no mention of central foveal thickness, pre and post treatment.

Reviewer 3: In the Results section I would recommend elaborating on your description of the CMO (mild, moderate, or severe) and the degree of reduction (for example, was the change in CMO considered significant in both eyes? What was the percentage of reduction?).

Discussion

The RIM1 protein localises to the presynaptic active zone of chemical synapses in brain and retinal tissue, where it plays an important role in regulating synaptic vesicle release and presynaptic plasticity.[7] RIM1 is a large multidomain protein that interacts with a host of molecules at different regions. The *RIM1* Arg820His mutation associated with CORD7 affects the protein's highly conserved C_2A domain. This is thought to affect its affinity for either L-type Ca^{2+} channels or synaptotagmin, altering the rate of synaptic vesicle docking and fusion following a Ca^{2+} signal.[5, 8]

The c.2459G>A *RIM1* mutation was originally identified in a four generation, non-consanguineous British family.[4, 5]Michaelides subsequently provided a detailed study of the phenotype in eight members of this same family, reporting this as a cone-rod dystrophy (CORD7).[6] The majority of these individuals experienced progressive worsening of central vision, nyctalopia and peripheral visual field loss between the third and fourth decades. Visual acuity ranged between 20/20 and 20/400 while fundal changes varied from mild retinal pigment epithelium changes, as with our patient, to extensive atrophy and pigmentation. AF showed decreased central ~~hypo~~autofluorescence with a surrounding ring of increased ~~hyper~~autofluorescence in the majority of individuals.[6] The AF findings in our patient were similar, albeit more subtle. The electrodiagnostic results for our patient also resembled those found by Michaelides et al,[6] showing reduced pattern, cone and rod ERGs. However our patient additionally exhibited a negative ERG, suggesting inner retinal changes secondary to a primary photoreceptor abnormality. While a negative ERG was not described by Michaelides et al,[6]

Comment [AW11]: Reviewer 3: In the Discussion, I would use the terminology of increased or decreased autofluorescence instead of hypo- or hyperfluorescence (Page 5, Lines 32-35). The same applies for the Legend for Figure 1 (Page 7).

negative ERGs of this sort have been previously reported in CORDs.[9, 10] Perimetry showed localised central field loss and peripheral field loss in five individuals.[6] By contrast our patient showed mid-peripheral field loss with preserved central vision on GVF testing. None of these individuals developed CMO.[6] Overall, the phenotype in our case more closely resembled retinitis pigmentosa with CMO rather than CORD.

Macular oedema is a common complication of retinitis pigmentosa, affecting an estimated 27% of patients.[11] By contrast, CMO appears to be relatively rare in CORD.[12-14] The reason for this disparity is unknown. In our case, rods were significantly affected in addition to cones, therefore perhaps rod dysfunction is required for CMO in retinal dystrophy. However CMO has been reported in a case of clinically diagnosed CORD where rod-isolated ERG responses were within normal limits.[13] Treatment with carbonic anhydrase inhibitors, steroids, anti-vascular endothelial growth factor agents, photocoagulation and vitrectomy have been trialled with variable success in retinitis pigmentosa.[11] A recent case report of cone-rod dystrophy in a child with Alstrom syndrome found complete resolution of bilateral CMO following one month of treatment with topical dorzolamide.[15] By comparison, our patient showed no response to topical dorzalamide, nepafenac, ketorolac or oral acetazolamide, and only partial resolution of CMO after 4 months of topical brinzolamide therapy.

In conclusion, we report the only phenotypic description of the *RIM1* mutation outside the British family for which it was first described. This mutation has not been previously associated with either CMO or an electronegative ERG. The overall clinical picture was closer to retinitis pigmentosa with associated CMO rather than CORD. This could imply that the *RIM1* mutation causes diverse retinal dystrophies. Alternatively, it is possible that the previously described CORD7 phenotype may have resulted from a different variant on the same haplotype as *RIM1*.

Comment [AW12]: Reviewer 2: Recommend reviewing the paper…. Ophthalmic Genet. 2016 Feb 19:1-3. Topical carbonic anhydrase inhibitors in macular edema associated with Alström syndrome, wherein the authors report CME in a patient with CORD, and compare the findings with their patient.

Comment [AW13]: Reviewer 2: This is mere speculation. Are there any findings in their study to support this conclusion? If not suggest refraining from making this statement which is mere speculation.

Author response: as the clinical picture in our case more closely resembled retinitis pigmentosa than CORD, we have tried to provide speculative reasons which may explain this discrepancy with the earlier report by Michaelides et al.

Furthermore, this last sentence was added as per the previous suggestion from reviewer 3. We have therefore kept this in the manuscript.

RIM1, retinitis pigmentosa and macular oedema

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

Acknowledgements

None.

Figure legends

Figure 1

Title: Clinical imaging and Goldmann visual field findings

Legend: Fundus photographs (A) showing cystoid macular oedema, arteriolar attenuation, a peripapillary greyish hue to the retina, as well as scattered areas of nummular pigmentation and mottling of the peripheral retinal pigment epithelium with scattered white dots peripherally. The optic disc appears pink with clear margins. Wide field fluorescein angiography (B) demonstrates bilateral early mid-peripheral hyperfluorescence indicating leakage. Fundus autofluorescence imaging (C) showing blocked autofluorescence centrally, presumably due to the cystoid macular oedema, increased paracentral ~~hyper~~autofluorescence and more peripheral puntcate increased ~~hyper~~autofluorescence. Goldmann visual fields (D) reveals bilateral mid-peripheral ring scotomas. Optical coherence tomography (OCT) scans (E) showing bilateral cystoid macular oedema at presentation (i) and partial improvement at 18 months follow-up (ii). Central macular thickness measured with Heidelberg OCT reduced over 18 months from 625-µm to 509µm OD-, and from 546 µm ~~OS, to 509 µm OD and~~to 394-µm OS.

Figure 2

Title: Electrodiagnostic testing results

Legend: Electrophysiological tracings from the patient with normal traces for comparison. Pattern ERG (PERG), maximal mixed cone-rod flash ERGs and independent cone and rod ERGs were all markedly degraded, with rods being more affected than cones. The mixed cone-rod flash ERG was of negative configuration with an abnormal maximal a wave in association with an even smaller b wave, suggesting a primary photoreceptor abnormality with inner retinal changes secondary to photoreceptor dysfunction. The 30 Hz flicker ERG was of diminished amplitude but normal implicit time.

Comment [AW14]: Reviewer 2: Description of fundus on ophthalmoscopy should include description of the optic disc and the macula.

Comment [AW15]: Reviewer 2: Was IVFA performed? IVFA helps differentiate macular cysts due to schisis (no leak) from edema (leak)

Comment [AW16]: Reviewer 3: In the Discussion, I would use the terminology of increased or decreased autofluorescence instead of hypo- or hyperfluorescence (Page 5, Lines 32-35). The same applies for the Legend for Figure 1 (Page 7).

Comment [AW17]: Reviewer 2: There is no mention of central foveal thickness, pre and post treatment.

Reviewer 3: In the Results section I would recommend elaborating on your description of the CMO (mild, moderate, or severe) and the degree of reduction (for example, was the change in CMO considered significant in both eyes? What was the percentage of reduction?).

Comment [AW18]: Reviewer 2: The ERG shows greater rod affectation than the cones, with rod response almost flat.

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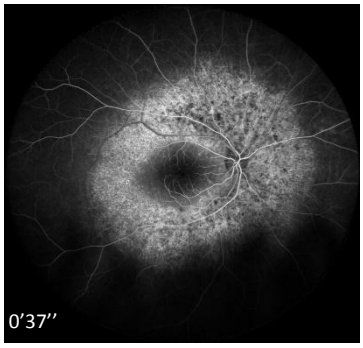
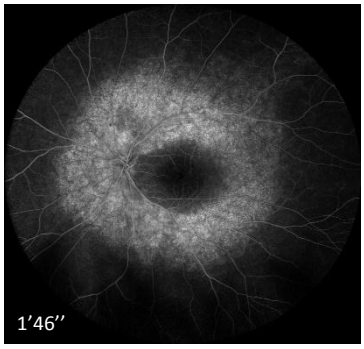
Right eye

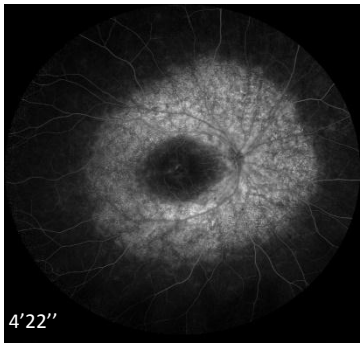
Left eye

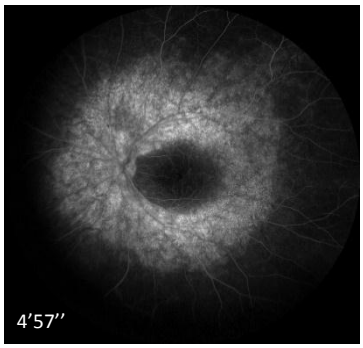
A

B









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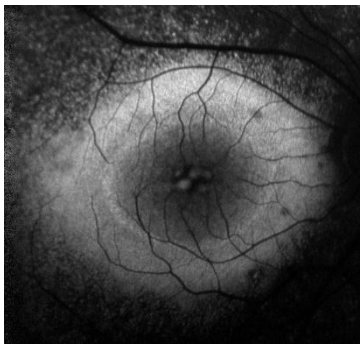

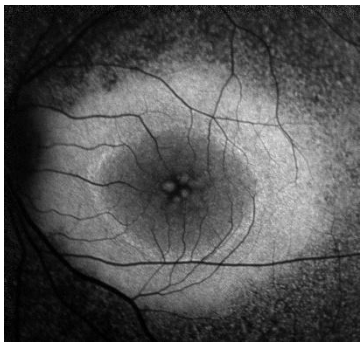

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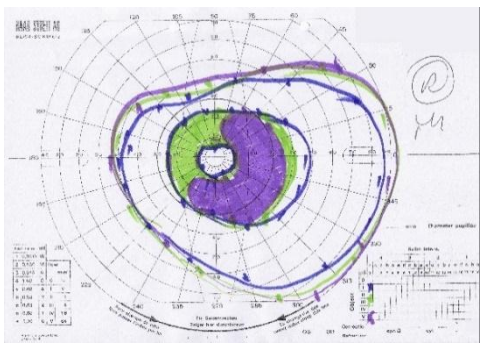

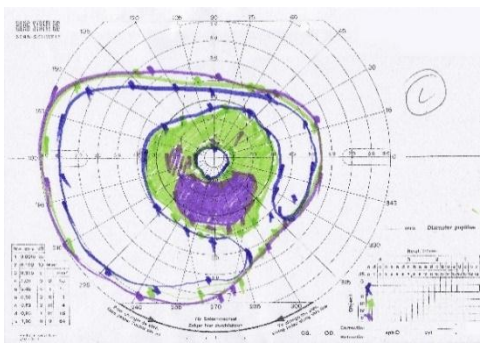

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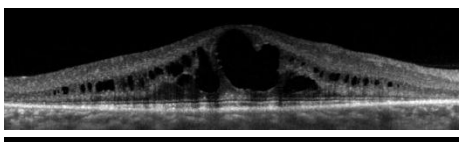

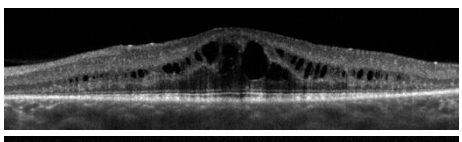

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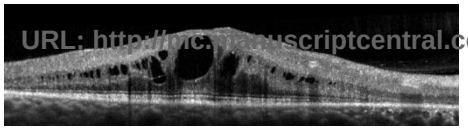

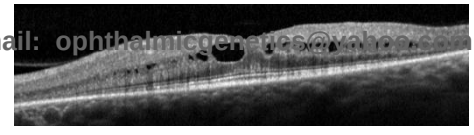

Patient

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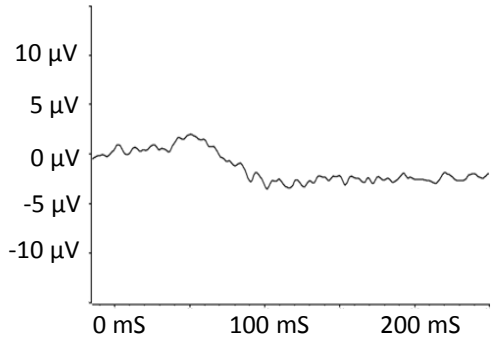
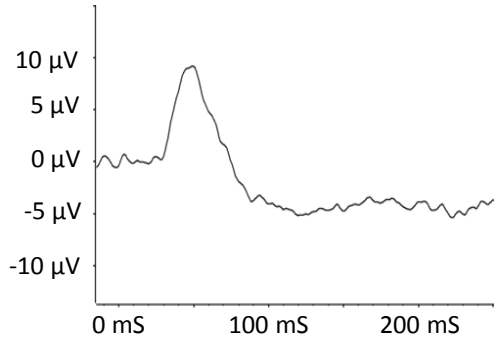
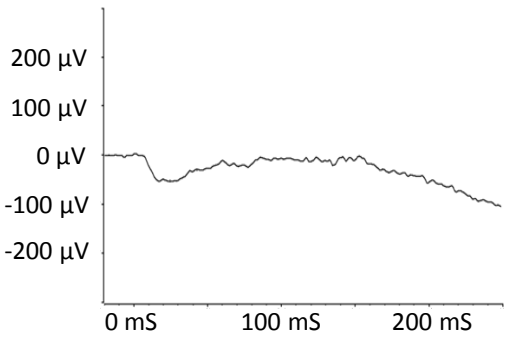
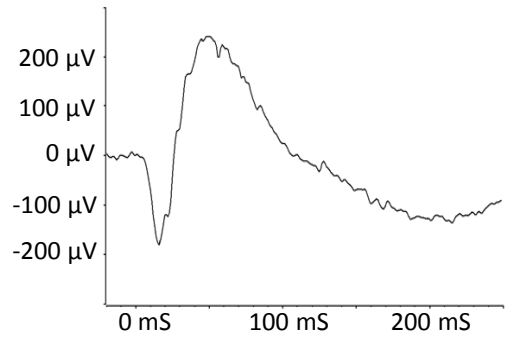


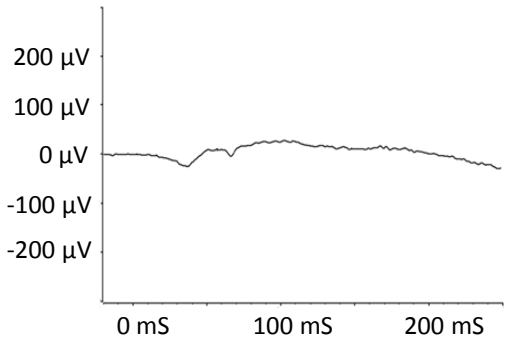


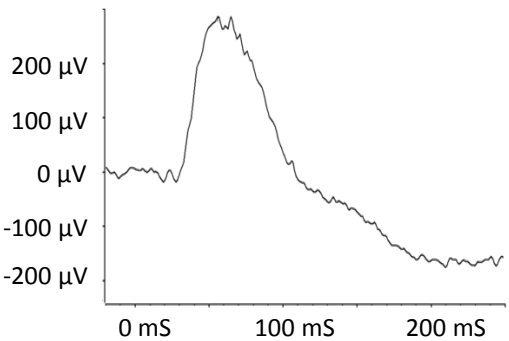
Maximal mixed cone/rod ERG



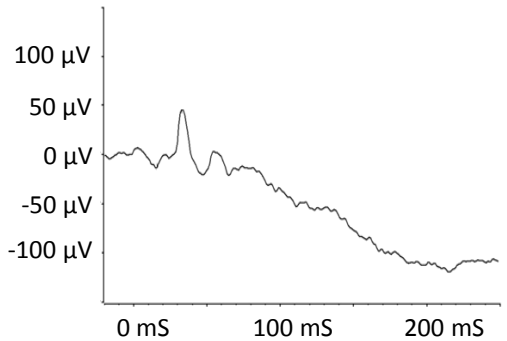


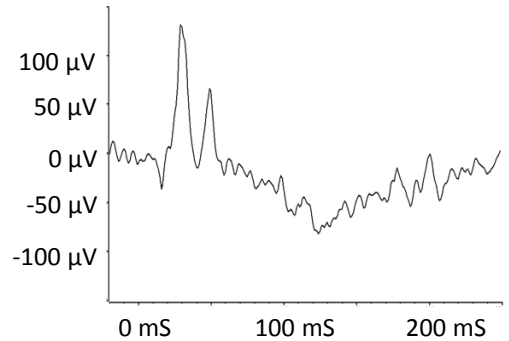
Scotopic rod ERG





Photopic cone ERG





30 Hz flicker