

Hur ser prematurfödda barn när de blir äldre?

Eva Larsson

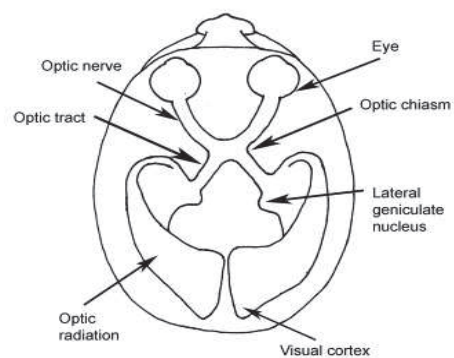
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Ögonkliniken, Akademiska sjukhuset

Uppsala

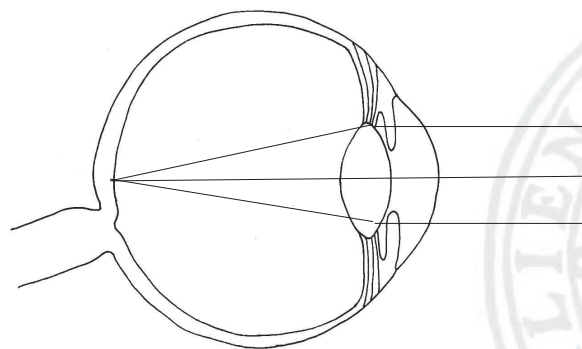
Vad skall fungera för att vi skall se?

- Ögat
- Synnerven
- Bakre synbanan
- Syncentrum
- Associativa bansystem



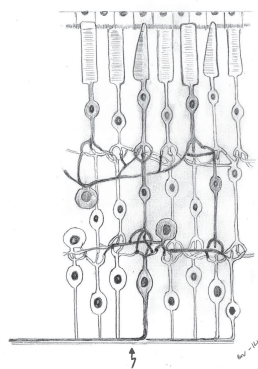
EN 2004

Optiskt organ med hornhinna och lins som bryter ljuset



EN 2014

Sinnesorgan med näthinnan och dess tappar och stavar



EN 2014



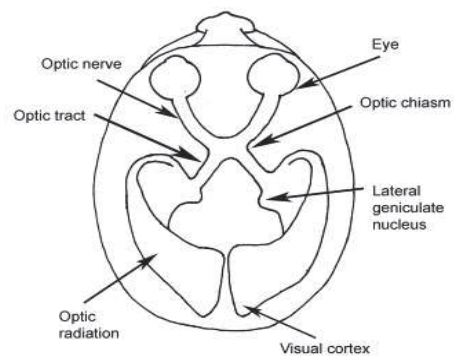
Bakre synbanan

Synnerven

Synkorsningen

Synstrålningen

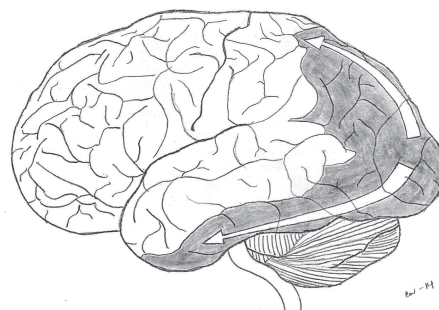
Syncentrum



Associativa banor

Visuell perception - Tolkning av synintryck

Vad och Var?



Prematuritet

För tidig födsel:
före 37(av 40) fullgångna gestationsveckor

och ögonproblem:

< 1500 gram

< 1250 gram

< 32 veckor

< 31 veckor

EL

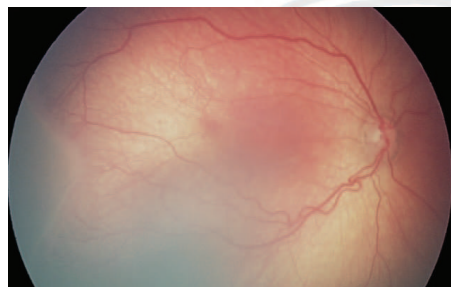
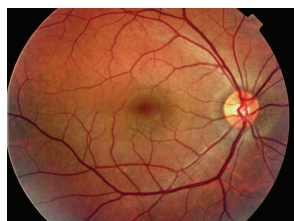
Prematuritet och ögonproblem

I nyföddhetsperioden:

Retinopathy of prematurity = ROP
=prematuritetsretinopati

Mild = stadium 1 och 2

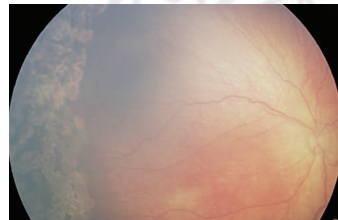
Svår = stadium 3, 4 och 5



Prematuritet och ögonproblem

Behandling:

Cryo = frysbehandling sedan slutet av 80-talet
Idag i första hand laserbehandling



Premature for Life

In 1988, the Academy published the findings of the multicenter Trial of Cryotherapy for Retinopathy of Prematurity (CRYO-ROP Study). From that time, it is widely read. The recommendations generated by that report, for the most part, have been followed. For the most part, the cryotherapy treatment has been effective for one of the major causes of childhood blindness. This issue of the Academy's newsletter the final results from the CRYO-ROP Study, which report the outcomes of those babies who were randomized to treatment in the 1980s and who are now teenagers or 15 years of age. This marks the end of the first for the CRYO-ROP study review in the literature and places back to review the impact of this study and see whether the hope to reduce retinopathy of prematurity (ROP) blindness has been realized in the long-term. With reports of outcomes at 3, 5, 10, and 15 years, the study provides a unique insight into the long-term ROP. As medical history, response to treatment, and its long-term sequelae of those treated and untreated and those that were not. The findings of the study are far too numerous to discuss in their entirety, but we have learned, for instance, that African American babies are less likely to develop ROP than white babies; that the extent, progression, and resolution of severe-phase ROP are all related more closely to gestational age than racial or ethnic, and that eyes in the same phase of ROP exhibit a high degree of interocular asymmetry. A particularly important aspect of the CRYO-ROP Study has been to identify the prognostic value of clinical signs, that the degree of retinal vascular development, the posterior zone of involvement, and plus disease¹ are all very strong predictors of poor outcome. The consensus is so strong as to suggest that this knowledge has all come from the CRYO-ROP Study.

See also page 311

Particularly pertinent to this retrospective are the long-term outcomes and complications that are unique to the CRYO-ROP Study. From, some of the details, Catherine et al² compared the outcome of partial retinal detachment at 3 months and 5 years and reported that partial retinal detachment present at 3 months has a poor visual prognosis and is generally associated with the rapid progression of disease at 5 years being the extent of detachment at 3 months. Particularly striking was the report of long-term follow-up of 50 patients (128 eyes) who developed total retinal detachment in one or both

eyes by 3 months after birth. Although 72 eyes of 54 patients had undergone retinal detachment procedures, only 1 eye had any evidence of posterior vision at 5 years. The CRYO-ROP Study has reported a wealth of information on retinopathy of prematurity. For instance, Quinn et al³ showed that the refractive status of children with mild ROP did not differ from those born prematurely but without ROP. The high refractive status with severe ROP is probably related to the disease process and is not influenced by cryotherapy per se.⁴ The prevalence of strabismic amblyopia in the CRYO-ROP Study population (more than 15%) has been strikingly different from previous reports in magnitude between 1 and 4.5% and 10 years.⁵ A very different refractive development compared with babies born at full term. Turning now to the final report, between the 10-year and 15-year assessments, some eye-developed new retinal lesions, and, surprisingly, as a consequence, developed eyes with late-onset or severe retinal vascularization, or macular ectopia at 10 years (10 and 12 control eyes).

In an overview, the CRYO-ROP Study confirmed that the benefit of cryotherapy for threshold ROP is maintained in the long-term—out to 15 years both with respect to retinal structure and functional outcomes, the former showing a decrease in retinal vascularization of more than 40% and the latter about 30%. There was a gradual decline in interocular asymmetry over the 10-year and 15-year assessments, and this is probably more apparent in comparison with control eyes, indicating that severe ROP is a lifelong condition affecting many components of the eye. One of the most interesting features of the CRYO-ROP Study was incorporating the measurement of retinal vessel flow age (year—the time medication study) to do so. This critical measurement component found that it is not the time to retinal vascularization, but rather it is now de regner. Nevertheless, around the 3.5-year publication, there was an interesting debate about the value of grading severity.⁶⁻⁸ The finding that a grading system score falls within the normal range at 1 year does not predict vision at 15 years. This is not the case and does not reflect the difference in the long-term prognosis, but it is a reflection of the developmental kinetics in the presence of ocular (and frequently additional developmental) pathologic factors. This process is complex and important for the clinical ophthalmologist to appreciate in pediatric clinical practice, including both structural and functional components added to the study, existing ocular stability to be continued in the long-term and analysis to

Vad händer senare i livet?

Prematur hela livet?

A Fielder, Editorial
Arch Ophthalmol 2005



Prematuritet och ögonproblem

Studier i tidig ålder kan påvisa grava skador

synnedsättning
blindhet
brytningsfel

Studier i senare ålder kan upptäcka mer subtila skador



Vad ser prematurfödda senare i livet?

Populationsbaserad långtidsuppföljning av prematurfödda barn som tidigare screenats för ROP

Nya Zeeland

Darlow et al-97

Danmark

Fledelius-98

Storbritannien

O' Connor, Fielder et al-02

Sverige



Vad ser prematurfödda senare i livet?

- 10-årsuppföljning av prematurfödda barn, tidigare inkluderade i en populationsbaserad studie över ROP- förekomsten
- Födda i Stockholmsområdet 1988-1990
- Födelsevikt 1500 gram eller mindre
Gestationsålder vid födelsen 24-35 veckor
- 40% hade ROP
- 11% var kryobehandlade



	0.5 år	1.5 år	2.5 år	3.5 år	10 år
Läkare	+		+		+
Ortopist	+	+	+	+	+
Visus				+	+
Strabism	+	+	+	+	+
Stereo	+	+	+	+	+
Cykloplegisk refraktion	+		+		+
Fundus	+		+		+
Kontrastkänslighet					+
Synfält					+
Färgsinne					+
Frågeformulär					+
Kontrollgrupp					+

Vid 10 år undersöktes

- 216 prematurfödda barn
- 217 barn födda i normal tid, födda i samma område och under samma tidsperiod
- 199 barn kom till samtliga 3 läkarundersökningar dvs 6 månader, 2,5 och 10 år

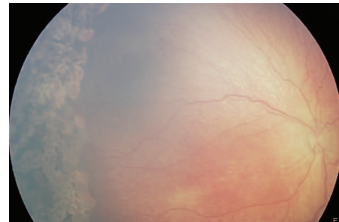
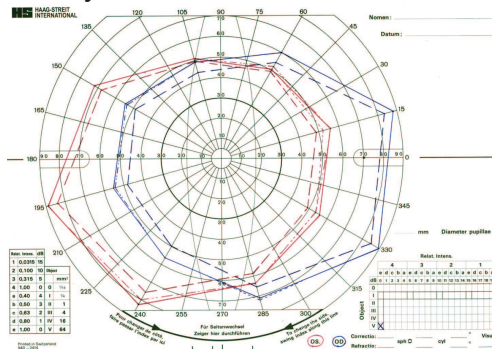
Synskärpan

	$\geq 20/200$ and $< 20/200$	$\geq 20/60$ and $< 20/60$	$\geq 20/60$ and $< 20/25$	$\geq 20/25$ and $< 20/20$	$\geq 20/20$ and $< 20/15$	$\geq 20/15$	Total
<i>Controls</i>	0 (0)	0 (0)	1 (0.5)	4 (1.8)	35 (16.1)	177 (81.6)	217
<i>Prematures (total group)</i>	3 (1.4)	1 (0.5)	6 (2.8)	21 (9.7)	70 (32.2)	116 (53.4)	217
No ROP	0 (0)	1 (0.7)	2 (1.4)	8 (5.6)	43 (30.3)	88 (62.0)	142
Mild ROP	0 (0)	0 (0)	1 (2.7)	4 (10.8)	16 (43.2)	16 (43.2)	37
Severe ROP, untreated	2 (14.3)	0 (0)	0 (0)	2 (14.3)	4 (28.6)	6 (42.9)	14
Cryotreated ROP	1 (4.2)	0 (0)	3 (12.5)	7 (29.2)	7 (29.2)	6 (25.0)	24

1.9% synskadade, hälften pga ROP och hälften pga synbaneskada

Arch Ophthalmol 2005;123:825-32.

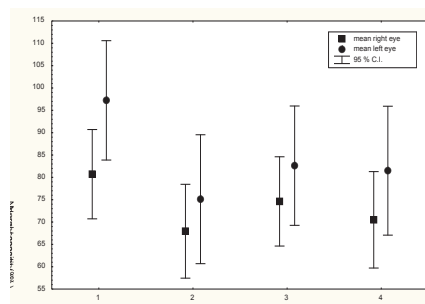
Synfält



Inskränkt synfält hos de behandlade barnen

J Pediatr Ophthalmol Strabismus 2004;41:39-45.

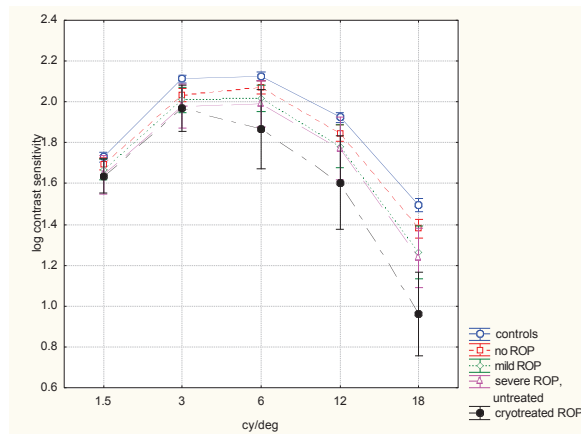
Synfält



Nedsatt neural kapacitet hos de prematura
(antalet fungerande kanaler till hjärnan)

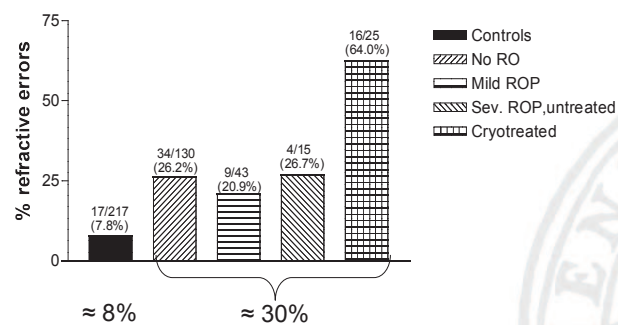
J Pediatr Ophthalmol Strabismus 2004;41:39-45.

Nedsatt kontrastkänslighet



Br J Ophthalmol 2006;90:87-90.

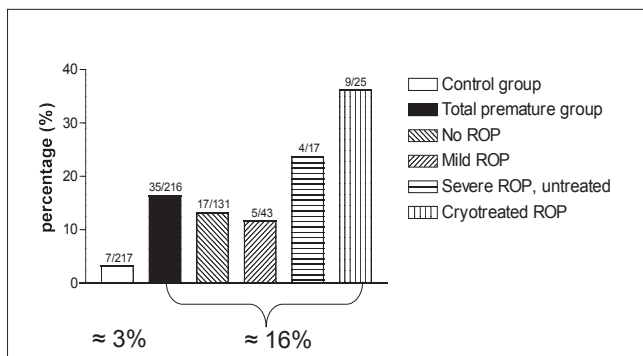
Högre prevalens av refraktionsfel



Refraktionsfel vid 2,5 år, men ej vid 6 mån, kunde predicera refraktionsfel vid 10 år

Arch Ophthalmol 2003;121:1430-1436.
Arch Ophthalmol 2005;123:1404-1411
Arch Ophthalmol 2006;124:1608-1614 .

Högre prevalens av skelning



J Pediatr Ophthalmol Strabismus. 2006;43:346-52.

Högre prevalens av skelning

	Lost cases	New cases	Total number of strabismus
6 months			18
18 months	10	5	13
30 months	0	4	17
42 months	2	6	21
10 years	0	14	35

J Pediatr Ophthalmol Strabismus. 2006;43:346-52.

Visuell dysfunktion vid 10 år

synskärpa ≤ 0.8 (≥ 0.1 logMAR)

skelning

subnormal kontrastkänslighet

25% hade visuell dysfunktion

J AAPOS 2008;12:157-162.

	Total cohort	"visual dysfunction"	no "visual dysfunction"	p-value
No.	199	49	150	
M/F	95/104	27/22	68/82	
GA (SD)	29.1 (2.3)	28.6 (2.3)	29.3 (2.3)	
BW (SD)	1163 (221)	1121 (224)	1177 (219)	
No ROP	118 (59.3%)	23 (46.9%)	95 (63.3%)	
Mild ROP	41 (20.6%)	9 (18.4%)	32 (21.3%)	
Severe ROP, untreated	16 (8.0%)	4 (8.2%)	12 (8.0%)	
Cryotreated ROP	24 (12.1%)	13 (26.5%)	11 (7.3%)	0.004
Neurological complications at 2.5 y	31 (15.6%)	15 (30.6%)	16 (10.6%)	<0.001
Schoolproblem at 10 y	76/192 (40.0%)	29/47 (64.4%)	47/147 (40.0%)	<0.001

J AAPOS 2008;12:157-162.



37% (18/49) av de med "visuell dysfunktion"
hade varken behandlad ROP eller neurologisk komplikation

Vad är orsaken?

Näthinnan?

Synbanan?



Vad ser prematurfödda senare i
livet?

Näthinnan?

Funktionen – ERG

Strukturen – OCT = optical coherence tomography

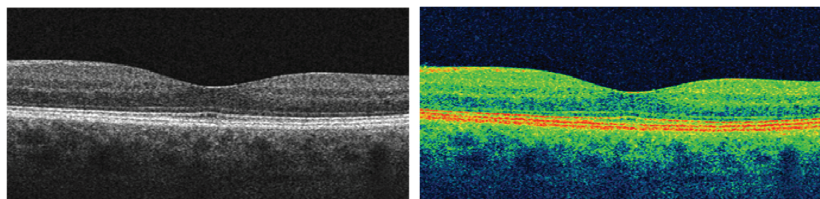
OCT

Optical coherence tomography

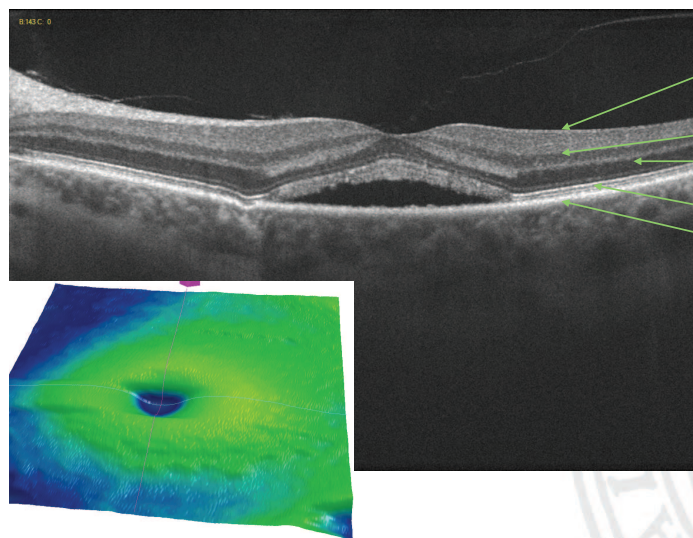
Liknar ultraljud

Kortvågigt nära infrarött ljus – mäter tiden för reflekterat ljus

Flera A-scan bygger upp en "pseudohistologisk" B-scan

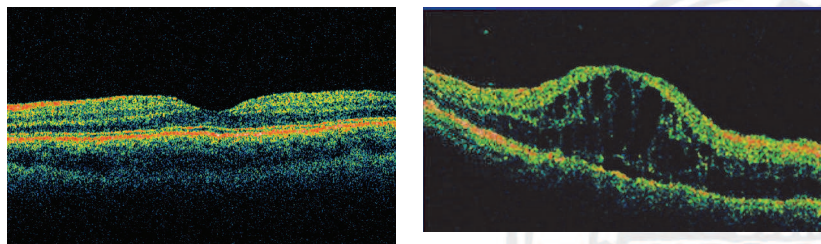


OCT

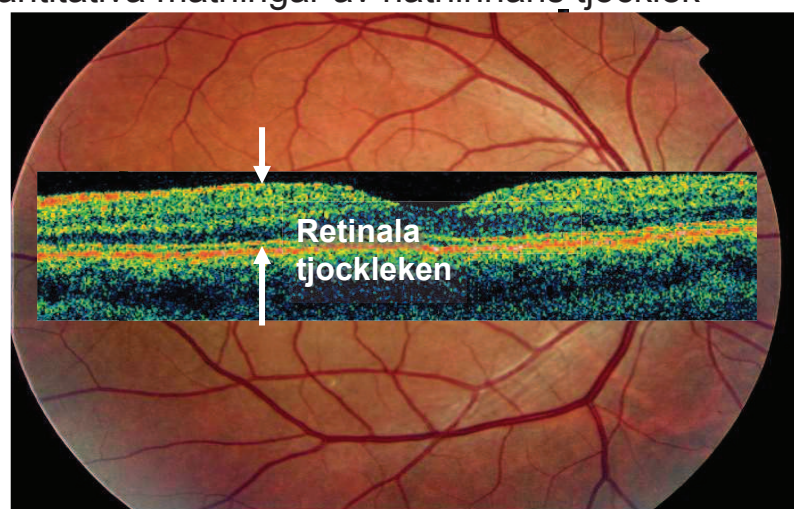


NFL
IPL
INL
OPL
ONL
ELM
Photorec
RPE

Kvalitativa mätningar av näthinnan



Kvantitativa mätningar av näthinnans tjocklek



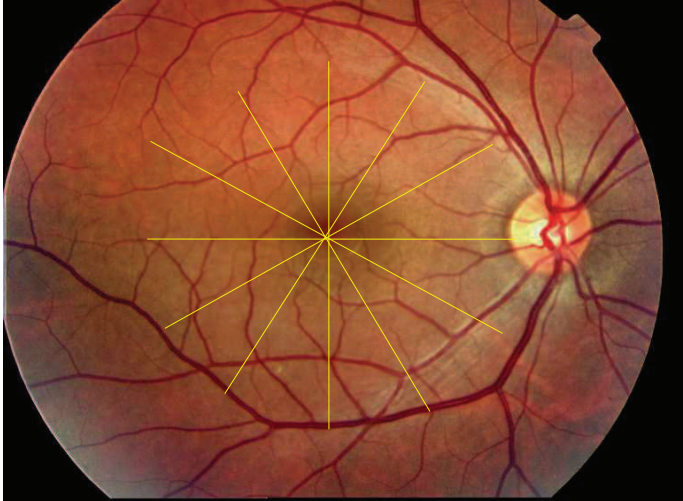
Courtesy
U Eriksson

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OCT-macula

Stratus OCT
6 B- scans
512 A-scans

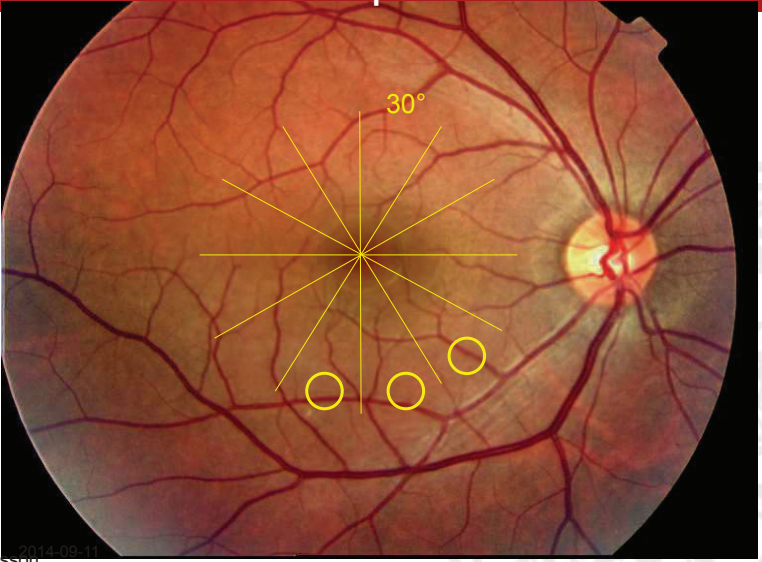
Fast protocol:
128 A-scans
1.92 sec



Courtesy U Eriksson

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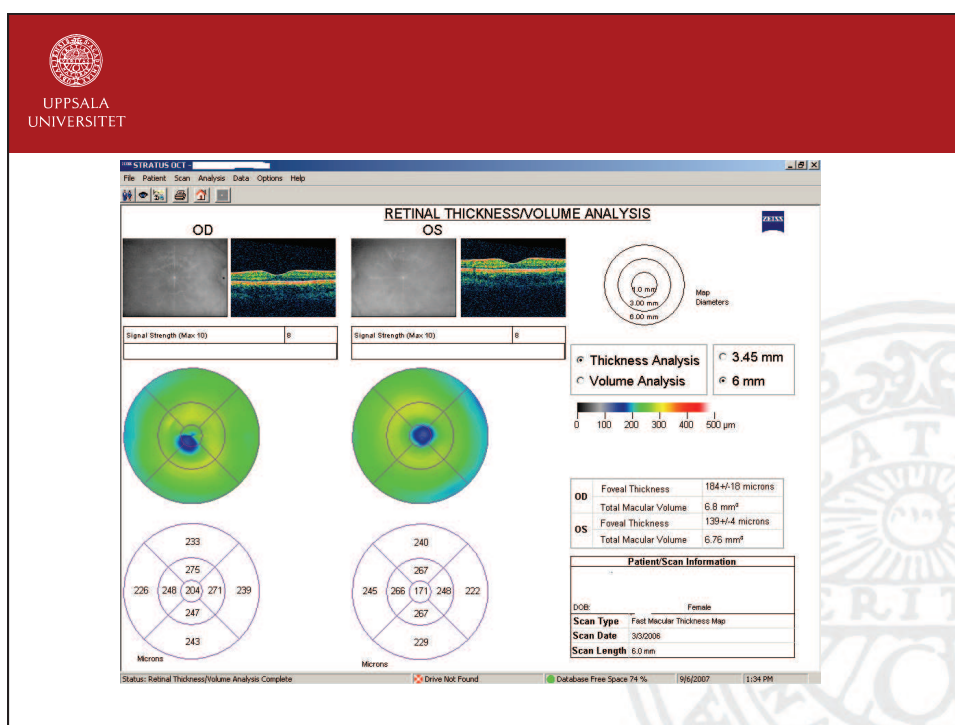
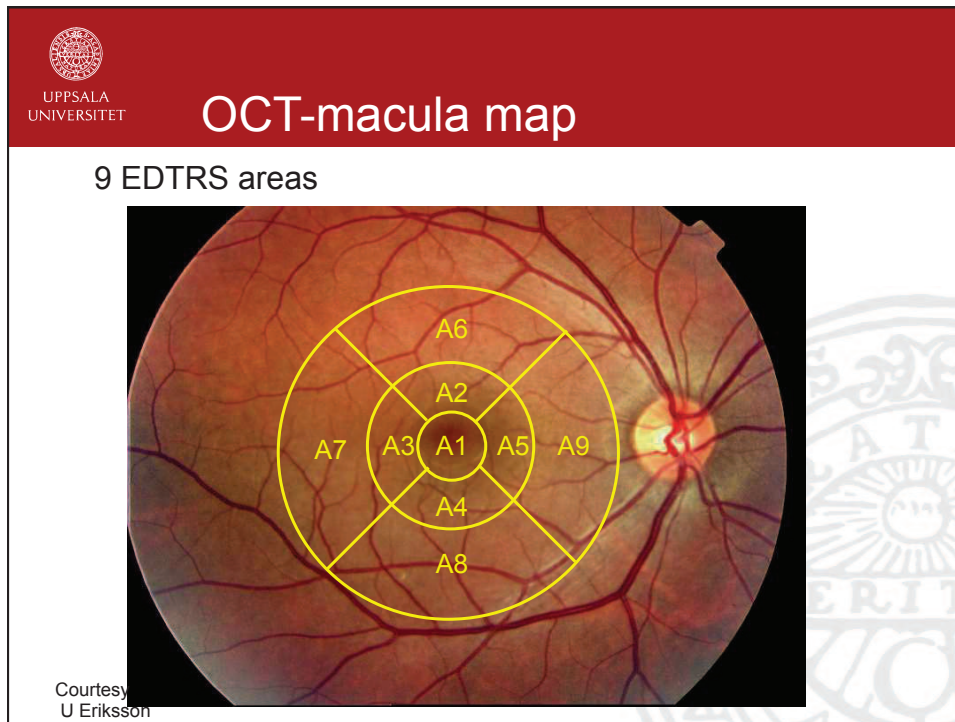
OCT-macula map

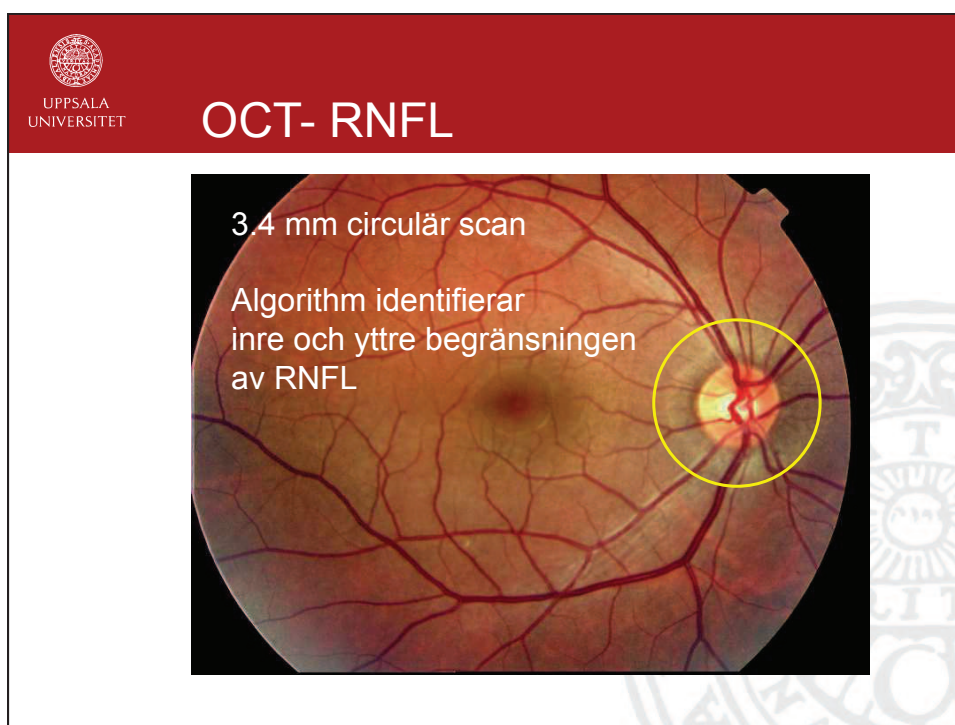
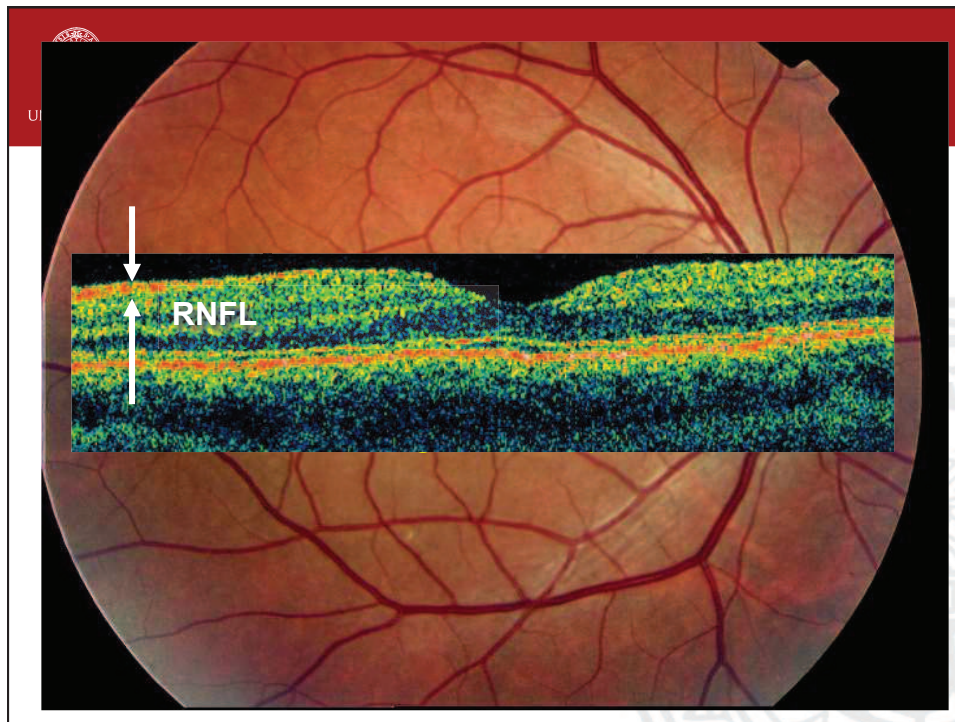


30°

2014-09-11

Courtesy U Eriksson

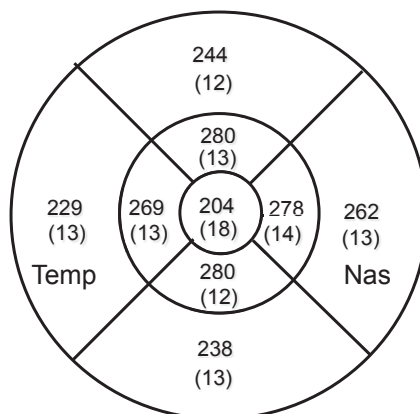




Kan med fördel användas på barn:

Icke invasivt
Ingen kontakt
Går fort

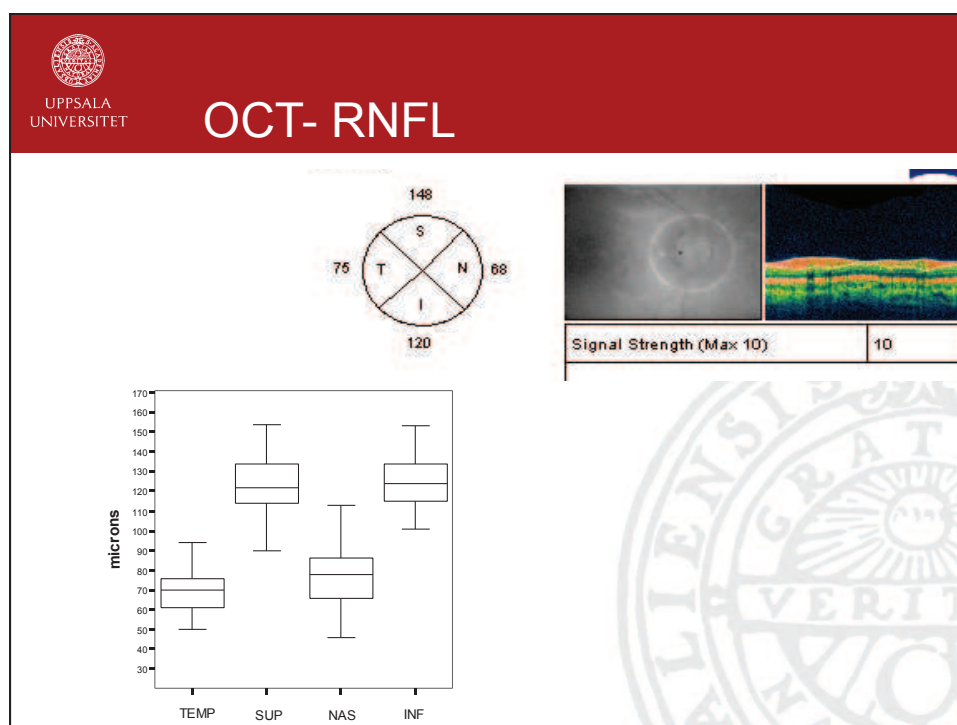
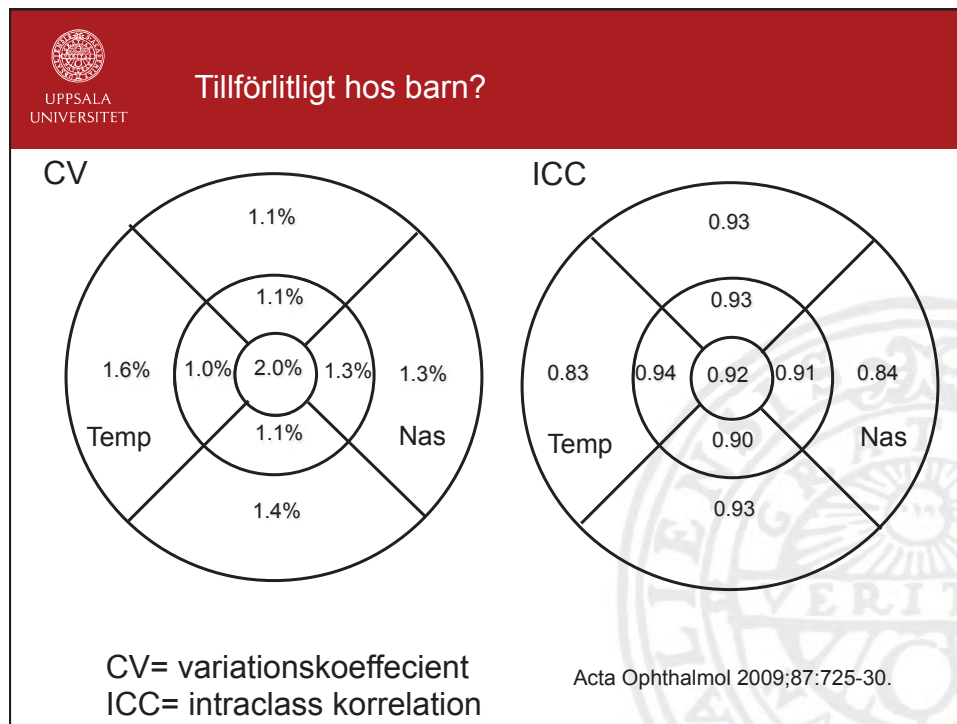
OCT-apparaten har inget
normalmaterial för barn!

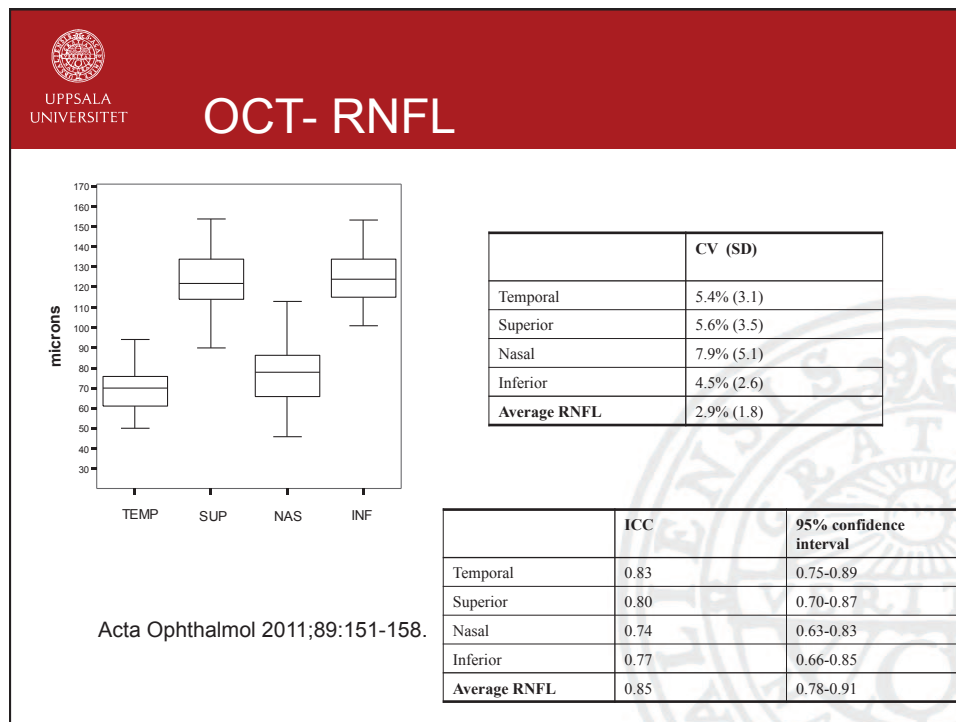


56 barn födda i normal tid (≥ 37 w) med
normal födelsevikt (≥ 2500 g)

5-16 år, medel 10.1 (SD 3.0)

Acta Ophthalmol 2009;87:725-30.





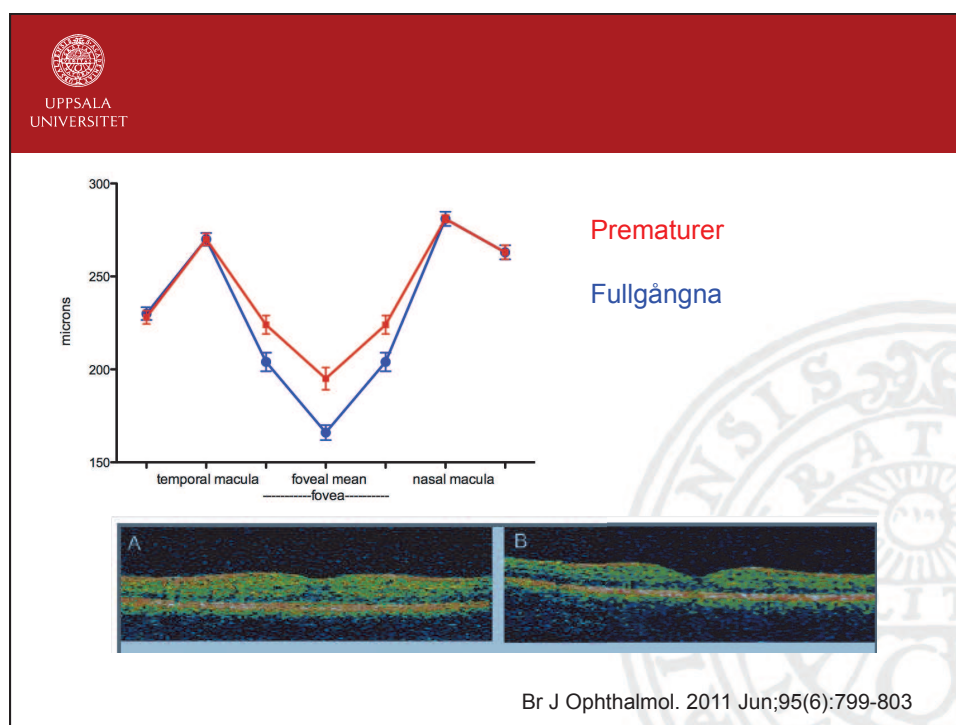
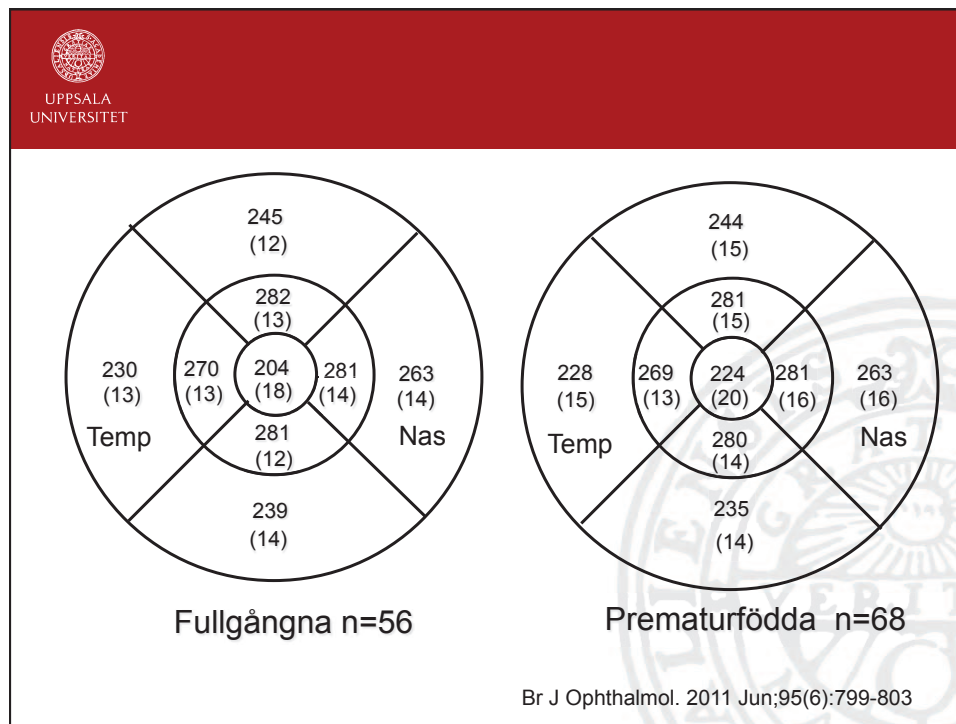
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Vad ser prematurfödda senare i livet?

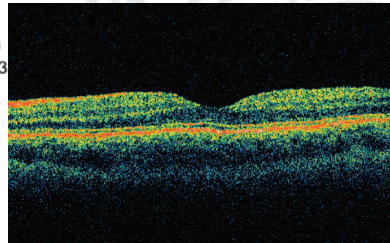
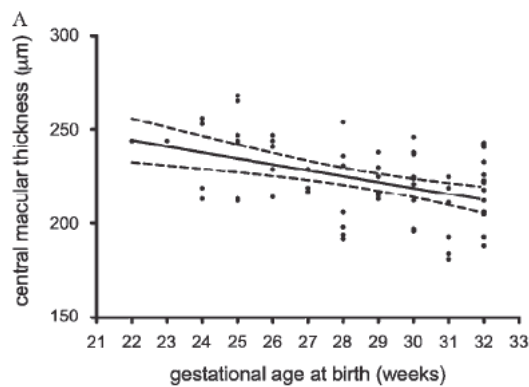
68 för tidigt födda barn undersöktes vid 5-15 års ålder

Gestationsålder (GA) $\leq$ 32 veckor

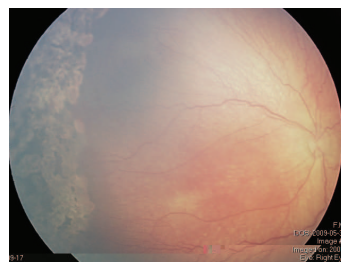
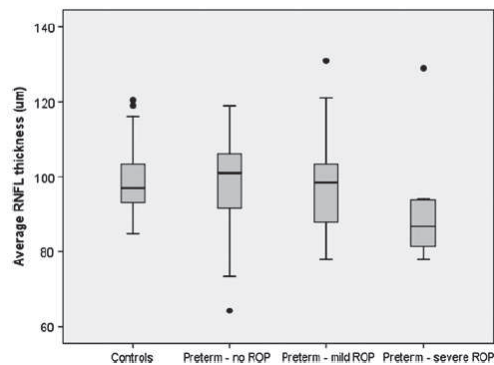
Medelvärde 28 veckor (range 22-32)
Medelfödelsevikt (BW) 1274 grams (range 453-2510)



Vad ser prematurfödda senare i livet?



Br J Ophthalmol. 2011 Jun;95(6):799-803

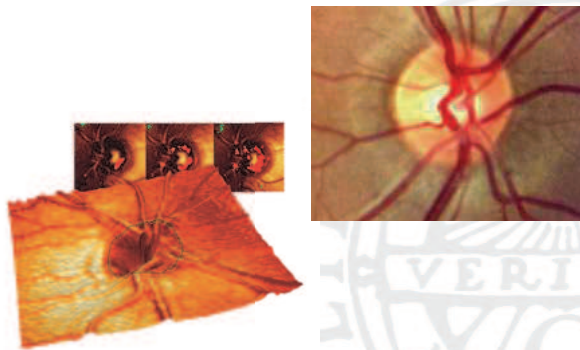


Br J Ophthalmol 2012;96:956-60.

Heidelberg Retina Tomograph HRT



Scanninglaser som bygger upp 3-dimensionella bilder av synnervshuvudet



HRT – Synnervshuvudet och RNFL

Synnervshuvudets kontur ritas ut

Manuellt

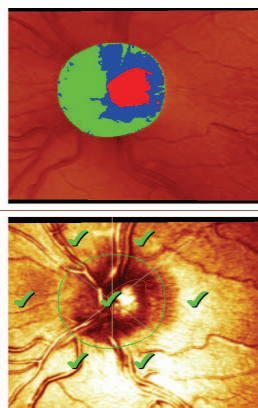
Disc area (DA)

Cup area (CA)

Rim area (RA)

Rim disc ratio (RDr)

RNFL





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Table 1. Mean values of topographical parameters of the optic nerve head, and the repeatability expressed as coefficient of variance (CV) and intraclass correlation (ICC) in 54 randomized eyes, assessed with Heidelberg retina tomography.

	Mean (SD)	Range	CV mean (SD)	ICC (CI)
Disc area (mm ²)	2.16 (0.47)	1.15–3.09	0	1.0
Cup area (mm ²)	0.41 (0.33)***	0.00–1.37	8.9% (10)	0.99 (0.99–1.0)
Rim area (mm ²)	1.75 (0.39)***	0.92–2.59	1.8% (2.6)	0.99 (0.99–1.0)
Cup/disc area ratio	0.18 (0.12)*	0.00–0.49	9.3% (10)	0.98 (0.97–0.99)
Rim/disc area ratio	0.82 (0.12)**	0.51–1.00	1.8% (2.7)	0.98 (0.97–0.99)
Cup volume (mm ³)	0.09 (0.12)***	0.00–0.58	21% (41)	0.98 (0.97–0.99)
Rim volume (mm ³)	0.41 (0.17)**	0.12–1.01	6.2% (7.3)	0.95 (0.92–0.97)
Mean cup depth (mm)	0.16 (0.08)**	0.04–0.41	4.4% (3.8)	0.99 (0.98–0.99)
Maximum cup depth (mm)	0.49 (0.21)**	0.10–0.88	4.6% (3.6)	0.99 (0.98–0.99)
Height variation (mm)	0.32 (0.09)	0.17–0.56	7.8% (15)	0.90 (0.84–0.94)
Cup shape measure (mm)	–0.24 (0.08)	–0.43 to 0	–12% (24)	0.92 (0.87–0.95)
Mean RNFL thickness (mm) [†]	0.21 (0.05)	0.13–0.34	5.7% (8.1)	0.88 (0.82–0.93)

Correlation with disc area.

* $p < 0.05$; ** $p < 0.01$ and *** $p < 0.001$.

[†] Larsson et al. 2009.

SD = standard deviation; CI = confidence interval and RNFL = retinal nerve fibre layer.

Acta Ophthalmol 2011 Dec;89(8):755-8

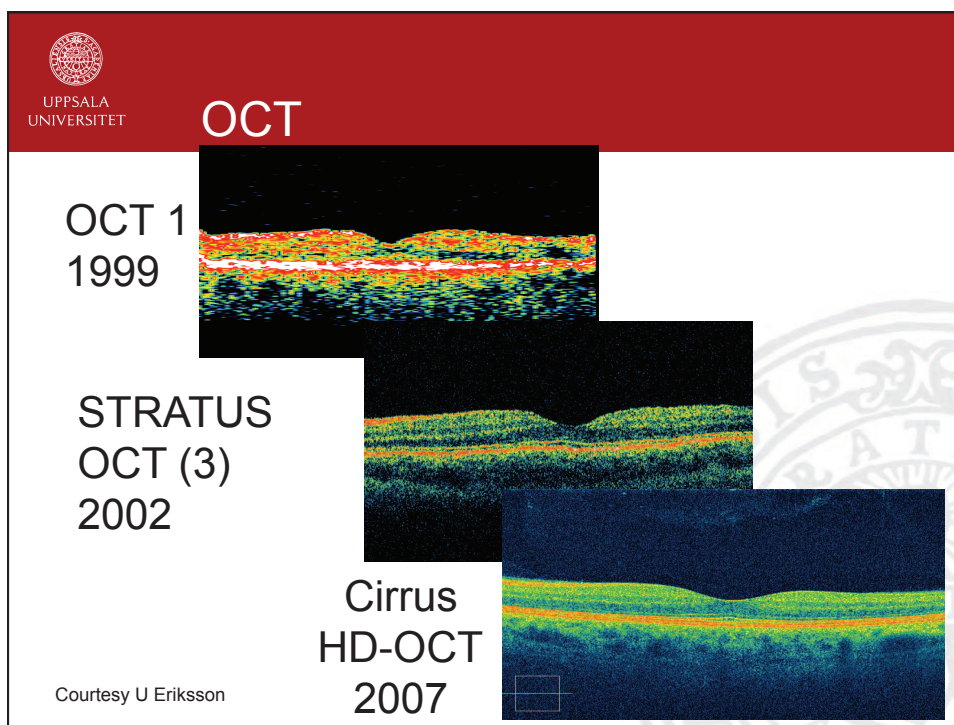


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Vad ser prematurfödda senare i livet?

Trots strukturella skillnader uppmätt med OCT och HRT fanns ingen säker korrelation med synskärpan

Funktionen i tappar och stavar?

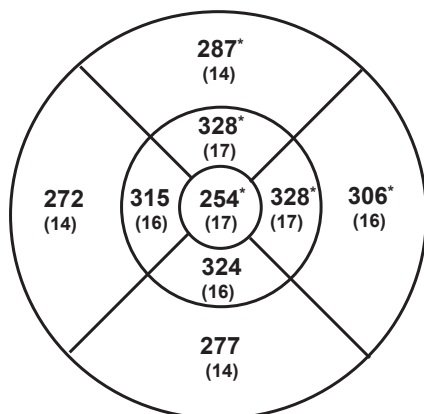


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	Right eye Mean values (SD) μm no = 14		Left eye Mean values (SD) μm no = 11	
	Cirrus	Stratus	Cirrus	Stratus
A1	258 (13)	200 (12)	258 (10)	201 (8.1)
A2	328 (17)	283 (13)	330 (17)	282 (12)
A3	316 (18)	269 (14)	314 (16)	267 (13)
A4	325 (17)	280 (14)	324 (18)	280 (15)
A5	330 (16)	280 (12)	330 (18)	279 (13)
A6	288 (16)	247 (14)	290 (18)	249 (14)
A7	271 (17)	233 (14)	271 (17)	229 (14)
A8	278 (18)	243 (16)	276 (17)	242 (15)
A9	306 (17)	264 (15)	306 (17)	264 (15)

SD=standard deviation
no=number

Cirrus mäter ca 30% tjockare makula



58 fullgångna barn födda i
normal tid

5-15 år

Tillförlitligheten

Samma undersökare

Area	CoV (%)	SD (%)	ICC	CI (LB - UB)
A1	1.01	0.91	0.968	0.948 - 0.981
A2	0.84	0.78	0.956	0.931 - 0.973
A3	0.86	0.87	0.952	0.925 - 0.970
A4	1.20	2.85	0.953	0.925 - 0.970
A5	0.74	0.72	0.968	0.950 - 0.980
A6	1.19	0.90	0.923	0.882 - 0.953
A7	0.98	0.83	0.949	0.920 - 0.969
A8	1.15	0.88	0.929	0.890 - 0.956
A9	0.66	0.59	0.975	0.961 - 0.985
CV	0.63	0.54	0.968	0.948 - 0.981
CAT	0.62	0.52	0.970	0.961 - 0.985

Olika undersökare

Area	CoV (%)	SD	ICC	CI (LB - UB)
A1	0.92	0.78	0.973	0.954 - 0.984
A2	1.20	0.86	0.916	0.861 - 0.950
A3	1.05	0.82	0.935	0.892 - 0.961
A4	1.23	1.49	0.857	0.769 - 0.914
A5	0.99	0.75	0.948	0.913 - 0.969
A6	1.37	1.05	0.872	0.791 - 0.923
A7	1.21	0.92	0.917	0.863 - 0.951
A8	1.18	1.02	0.904	0.840 - 0.943
A9	1.12	0.90	0.925	0.875 - 0.955
CV	0.84	0.70	0.936	0.892 - 0.963
CAT	0.84	0.68	0.939	0.896 - 0.964



Vad ser prematurfödda senare i livet?

De flesta ser och fungerar bra, men det finns en skillnad mot barn födda i normal tid

Finns kommande studier där allt mer prematura barn undersöks

Framtiden?



Tack till medarbetare!

BOSS-gruppen i Uppsala

