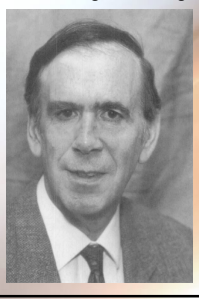
Amblyopia

Update?

Paul Harris, OD, FCOVD, FACBO, FAAO, FNAP
Professor, Southern College of Optometry

Background

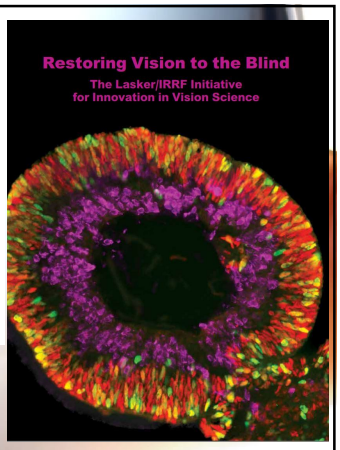
- Sue Barry invites Len Press and I to VSS in 2007
- We do a demo night – Brock String – Vectograms, etc.
- Whom do we meet?
- Nigel Daw, MD



The invite comes through

Woods Hole, MA – grounds of the NSF

Work Product from prior meetings



Restoring Vision to the Blind
The Lasker/IRRF Initiative for Innovation in Vision Science
December 2014

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http://www.laskerfoundation.org/programs/images/irrf_15.pdf

Steering Committee

- John E. Dowling, PhD – Prof of Neuroscience Harvard
- Nigel Daw, PhD – Prof of Ophthalmology & Visual Science & Neurobiology – Yale
- Larry Donoso, MD, PhD – Prof of Ophthalmology – Wills Eye Hospital and Jefferson Medical College
- Takao Hensch, PhD – Prof of Molecular and Cell Biology & Prof of Neurology – Harvard
- David Hunter, MD, PhD – Prof of Ophthalmology – Harvard
- Daphne Maurer, PhD, FRSC – Investigator – McMaster
- Donald Mitchell, PhD – Prof of Psychology and Neuroscience – Dalhousie University
- Michael Stryker, PhD – Prof Physiology, UCSF

Howard Hughes Medical Institute Janelia Farms - $18.2 Billion Endowment March 13-16, 2016

https://www.janelia.org/

Classification and Diversity of Amblyopia

Daphne Maurer and Suzanne McKee

What is amblyopia?

- DEFINITION: Abnormal best corrected monocular spatial vision associated with a history of abnormal visual experience.
- For practical purposes, a generally accepted marker is reduced visual acuity

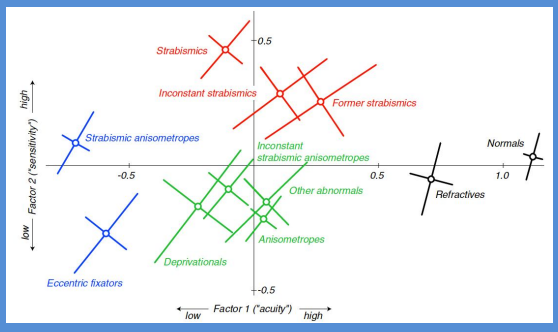
Why Classify?

- Based on PEDIG findings, classification by etiology is irrelevant to treatment outcome, as measured by improved acuity
- Is this because classification is inadequate or because outcome measures are too narrowly defined?

Working Classification

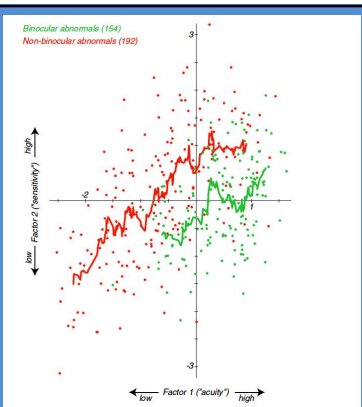
- Classification can be based on the presumed etiology (e.g. strabismus), modified by the history of treatment.
- However, etiology may be impossible to ascertain at presentation, because associated conditions may change over time.
- Nevertheless, classification of adults on the basis of quantitative behavioral measurements suggest functional differences among associated conditions
- These measurements include crowded acuity, contrast sensitivity, binocular function (stereopsis and suppression), oculomotor and manual movements

The Map



The groups are composed both amblyopes and 'at risk' individuals, e.g. all pure strabismics whether amblyopic or not.

The Importance of Binocularity in Classification



~80% of abnormals could be classified as either have some binocular function or none

What is needed

- **We need to agree on a common set of sensitive tests that are used clinically and in research**
- **Normative data need to be collected for these measures across different age ranges.**

Lasker/IRRF Initiative: Amblyopia 2016

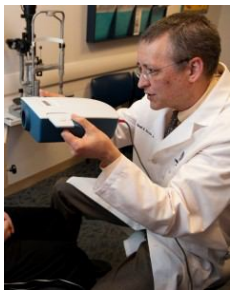
Early Diagnosis of Amblyopia and New Approaches

Co-chairs: David Hunter, Sue Cotter

Participants: Jan Atkinson, Peter Bex, Eileen Birch, Dennis Levi, Sjoukje Loudon, Hugo Marx, Paul Sieving, Herb Simonsz, Earl Smith, Al Sommer, Larry Tychsen

Disclosures:

David Hunter



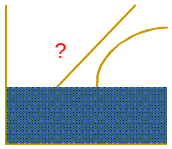
REBIScan
Pediatric Vision Scanner (PVS)

Slide 15

1 I find black letters on a textured, blue background hard to see. What to you think about this theme?
David G. Hunter, 3/15/2016

At what age can we reliably make a diagnosis?

Factors:
- Tools (Teller vs Optotypes)
- Training of examiner



For amblyopia?
- 2 years – soft (Fixation preference)
- 3 years – reliably measure acuity/stereo
- 4 years – solid (Optotype acuity)

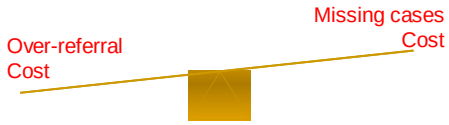
How much earlier should we be diagnosing amblyopia?

For strabismus?
- <1 year, but can arise any time
  - Periodic screening

How frequently should we be screening?

Who should be screening?

Ophthalmologists/Optometrists
Pediatricians/Nurses/Medical Assistants/Lay Persons



Lessons from Europe

Frequent screenings: well child visits
> Low cost for screening
Stereo: high sensitivity, low specificity for amblyopia

How are we diagnosing/screening?

Refractive error
- Hyperopia/Astigmatism > Myopia

Strabismus
- Photoscreeners for large angles only
- Enough to rely on family?

Risk Factors

Acuity (with crowding)
- Clinical basis, minimum 3 years

Stereo
- More comprehensive, minimum 3 years

VEP/Anatomic correlates
- Practical/Available

Disease

New biomarkers: which infants > amblyopia?

Serve as the Gold standard for establishing …

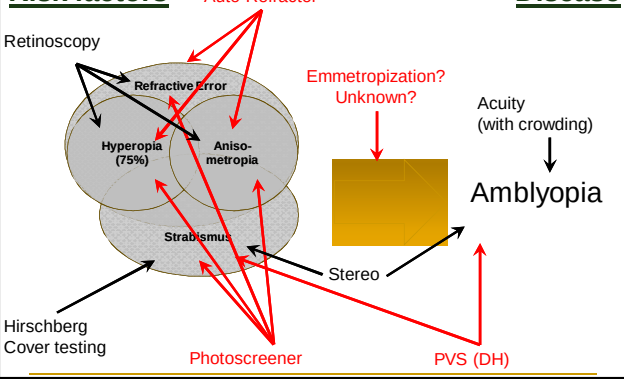
Diagnostic Tools | **Screening Tools**

Guide referral for evaluation using…

Makes Diagnosis:	**Performs Screening:**
MDs, ODs, Orthoptists (Regional differences)	Community/Family Pediatrician/Nurses/Technicians
Diagnostic Tools:	**Screening Tools:**
Visual acuity (with crowding) Stereopsis Fixation	Visual Acuity/Stereopsis Autorefractor/photoscreener Fixation instability detector

Diagnostic/Screening Targets

Risk factors Auto-Refractor **Disease**



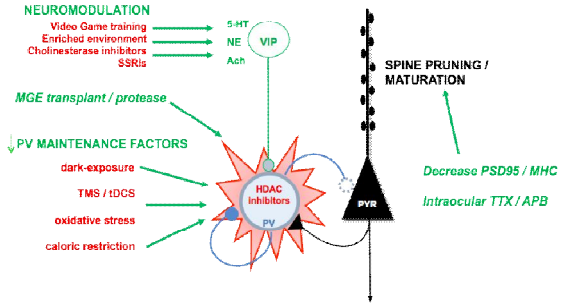
Critical Periods

Co-chaired by Takao Hensch and Elizabeth Quinlan

Critical Period

1. Nature of 'plasticity' changes with age:
   -- loss of deprived eye response / acuity (juvenile) vs open eye response gain (adult)
2. Mouse work suggests critical period timing is malleable
   -- the 'alphabet soup': regulating E-I balance / silent synapses across the lifespan
   -- inspires novel ways to lift the ceiling on plasticity in adults (beyond L-Dopa)
3. Pilot human trials informed by critical period biology:
   -- training / neuromodulation (Aricept, SSRI, TMS), dark exposure, repurposing drugs (VPA)
4. Need to model complete *recovery* vs initial *vulnerability* to deprivation
   -- how much recovery is possible, given the distorted starting point in V1?
   -- test recovery across deprivation, anisometropic, strabismic amblyopia?
   -- is functional recovery possible in V2 and beyond, if V1 remains distorted?
5. Path forward – better models
   -- primates: plot biochemical correlates of critical period across age to inform trial timing
   -- humans: examine late onset cataracts, plasticity in ADHD / SZ populations
   -- mouse: improve assays to better approximate human condition (stereopsis), genetics / individual differences in recovery

Novel therapeutic approaches



Cortical Correlates

Nigel Daw | Lynne Kiorpes

Suppression

- Suppressive mechanisms are present in normal animals
  - Recorded in V1 – bidirectional and dependent on presence of stimulus
- Is suppression in amblyopia using the same suppressive mechanisms?
  - Do signatures of suppression differ by cortical area?
  - Is removing stimulus sufficient in amblyopic suppression?

Stereo Acuity

- What are the areas that encode stereoacuity?
  - Relative retinal disparity information is necessary for stereo acuity
  - Not present in V1
- Will refining our knowledge of which areas encode stereo acuity be helpful in recovering function?
  - Better to focus energy on how to recover stereopsis?
    - fMRI of patients with and without recovery
  - Locating a brain area could give insights into development/plasticity of this region – target treatment

High-level deficits

- Despite “fixing” V1 monocular acuity/contrast sensitivity, high-level deficits are present in patients and animal models
  - Object recognition and global form deficits – not explained by acuity loss
  - Oculomotor deficiencies (fixation instability, pursuit abnormalities) – sensory and motor contributions?

Hierarchical processing and plasticity(?)

- High-order visual areas do not function in isolation – cascade of processing
  - Identify points of information breakdown
- Is development, and vulnerability, of cortical areas also sequential?
  - Differential plasticity at time of insult or therapy
- How to measure sequential maturation?
  - Molecular markers from primary areas
  - Anatomical projections (feed-forward and feedback)
  - High density EEG across visual areas in infants and young children given relevant stimuli

Fellow eye deficits

- Not present when testing low level visual functions
  - Deficits in fellow eye in monkey and human amblyopes – object recognition, global form and motion
- Binocular vision trains monocular vision
  - Individuals with worse binocular vision have worse monocular vision
  - Monocular visuomotor control in individuals with one eye is no better than in normal individuals

Sensorimotor integration

- Oculomotor deficits – are they central to amblyopic phenotype or correlates of visual deficits?
  - Saccade frequency, fixation instability, pursuit abnormalities
  - Need information on motor and sensory systems

Conclusions

- Recurring theme – importance of areas other than V1 (extrastriate, motor)
- Are we treating to the wrong standard?
  - Binocular deficit, high-order deficit
  - Monocular acuity
- Does treating to monocular standard exacerbate high order perceptual and oculomotor deficits?

Animal Models

Donald Mitchell | Frank Sengpiel

Points of consensus

- **Information from all species is valuable**
- Proposals to improve comparisons across species
- Pipeline for application of animal model research to therapeutics

Understand "performance space" for each species

- What is the behavioral and perceptual repertoire of each species?
- Reassessment of acuity across species
  - Grating, vernier and optotype acuity – can hyperacuity measurements be done in rodents? What is the value compared to grating acuity?
- Lack of understanding of high order visual areas and their deficits in amblyopic individuals
  - Do V1 findings apply to other areas? Cascading deficit
  - Some models such as rodents could be useful for these experiments – can mice do high order visual behaviors?

Common assessment technique across species

- EEG and evoked potentials, potentially done under light anesthesia, are applicable across species and behavioral/stimulus paradigms

Conversion of developmental timeline across species

- Match ages for manipulations and treatments across species
  - Are we hitting the sweet spot for all species – do we know how to convert between species?
    - Some timelines are based on results from a single study without replication
  - Is this nice data versus essential data?
- Understand the difference in development of response properties or behavior and sensitive periods (to perturbation or recovery)
  - "sleeper effects"

Pipeline to therapeutics

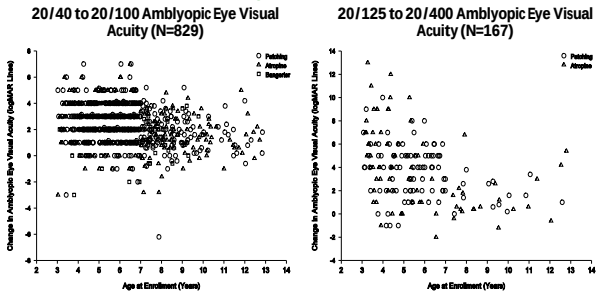
- Rule of two species (from morning sessions)
  - In what cases should one species always be a primate?
- Can we proceed straight from mouse to human with approved drugs?
  - Dosage differences in new application
  - Problematic in children

Treatment as a function of age

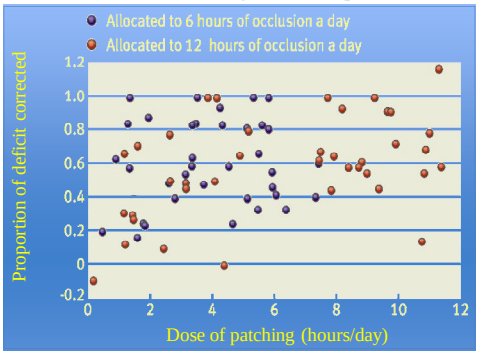
Co-chairs: Dennis Levi, Jonathan Holmes

Participants: Jan Atkinson, Peter Bex, Eileen Birch, Alistair Fielder, David Hunter, Sjoukje Loudon, Herb Simonsz, Al Sommer, Ben Thompson, Larry Tychsen, Sue Cotter

Variability of treatment response in which age is one factor



Response to patching and individual variability of response



Some children respond well to 1 or 2 hrs/d – others poorly to 10+ hrs/d

Current treatment modalities with considerations for age:

(Pre-)School children vs Adults

1. Optical correction
   - Recent data > worth doing among adults
     - Minimal drawback
     - Adults still responsive?
   - Among adults, is it "amblyopia"?
   - Is there ever a true (no treatment) control group? Delayed treatment?

What is the effect of optical correction then patching among amblyopic adults? Full correction?

Current treatment modalities with considerations for age: (continued)

2. Patching
   - Factors: Age, duration of patching, compliance
   - Compliance monitoring: importance and pitfalls
   - Easier in children with 2 hour dosing (PEDIG)
   - Basis for comparison moving forward

3. Atropine/Penalization
   - Drawbacks:
     - Necessary full correction for school
     - Reverse amblyopia

Ways to predict response? Classification (Age is ONE of many biomarkers)

Current treatment modalities with considerations for age: (continued)

4. Goggles/Shutter
   - Studies underway, promising results
   - Similar advantages/drawbacks to patching

5. Monocular/Binocular tasks: iPad games and movies
   - Advantages:
     - More appealing than patching
     - We know how to incentivize play
   - Drawbacks:
     - Dedicated time: 1 hr/day
     - High minimum age?

Current treatment modalities with considerations for age: (continued)

6. Pharmacology/Treadmills/TMS/TDCS
   Use in children?
   Masking problem

7. Light deprivation/retinal silencing
   Promising effects
   Future
   Adults

Summary of Future Directions

Current Treatment
- Expand the effect of optical correction
- Further innovation and investigation
- Predict treatment response; improve classification

What studies are needed?
- Ways to predict outcomes: response to treatment, compliance
- Function measures of amblyopia (QOL)

Ongoing Challenges
- New methods for monitoring compliance
- Appropriate controls; delay treatment?
- Recruitment (especially in adults)

New Molecular / Pharmacological Environmental Approaches

Co-chaired by Michael Stryker and Siegrid Löwel

1. What pharmacological (in humans) or genetic treatments (in animals) show avenues for amblyopia therapy?

- Targeting the neuromodulatory systems
  - Studies in animals suggest that VIP cells, inhibitory cells important for adult plasticity, respond to both acetylcholine and serotonin (Stryker)
  - Ongoing clinical trials with SSRIs (Thompson) and cholinesterase inhibitors (Hensch)
- HDAC inhibitors: VPA may lead to specific plasticity (perfect pitch; Werker, Hensch)
- PSD-95/PSD-93 and AMPA-silent synapses (Löwel, Schlüter)
- tDCS/TMS (Ben Thompson)

2. What behavioral treatments for amblyopia demonstrably work in humans? What behavioral treatments in animals are successful?

- Environmental Enrichment (EE)
  - At any age, environmentally enriched (EE) mice never lose sensitivity to monocular deprivation (Löwel)
  - Adult amblyopic rats can recover from long-term MD following transfer into enriched environment (Sale)
  - Can we translate EE to a treatment protocol?
  - What is EE for humans?
- Extensive visual training with many tasks that involve active hand-eye coordination
- Recommendation to stop patching (continue penalizing)
- Short-term dark exposure (Quinlan)

Emerging Themes and Approaches

Co-chaired by Tony Movshon and Mark Bear

Heritability and genetics of amblyopia

- The dream
  - genetic profile to understand/predict
    - individual response to amblyopia risk factors
    - Individual response to treatment
- The consensus
  - Prior to large-scale genetic study, good-quality, consistent phenotyping is essential
  - Any large-scale genetic study must occur in concert with accurate phenotyping

"Plasticity"

- A catch-all phrase
- Plasticity that renders cortex vulnerable to MD may be qualitatively different from plasticity that promotes recovery from deprivation
- We must be explicit about the type of plasticity we are targeting

Therapeutic approaches

Retinal inactivation

Dark exposure

Systemic drugs

Vergence/motor training

Binocular therapies/games

Perceptual learning

Therapeutic approaches - consensus

- New/adjunct therapy should confer some benefit over the current common standard (EFFICACY)
  - Better sensory/motor/QOL outcomes
  - Recovery later in life
  - Better adherence/tolerance; shorter duration
  - More cost effective
- New treatments have unknown risks that must be considered/evaluated (SAFETY)
  - Role of animal studies

Therapeutic approaches - consensus

- Risk vs benefit must be considered
  - what gains are we hoping to achieve, and are they worth the expected harms or potential risks?
  - differential risks for adults vs. children
- Reasonable people might differ on what is and is not a worthwhile goal of treatment; risk/benefit analysis may be culturally specific

Therapeutic approaches - an open question

- What role should “higher-level” perceptual deficits, oculomotor, and visuomotor performance play in evaluating new therapies?

Therapeutic approaches - consensus

- Need for high-quality scientific evidence (e.g. RCTs) before accepting or dismissing ANY promising new interventions
  - Local or systemic drugs
  - Dark exposure
  - Binocular games / perceptual learning
  - Vision therapy

Therapeutic approaches - consensus

Need to improve large-scale coordination between different eye care groups to rationally assess new therapies for amblyopia

Publication

- 8 reports to committee members for critical feedback
- Then, all 8 reports to all meeting participants for feedback
- Publication in first quarter 2017

Thank you to SCO leadership for making it possible for me to contribute.