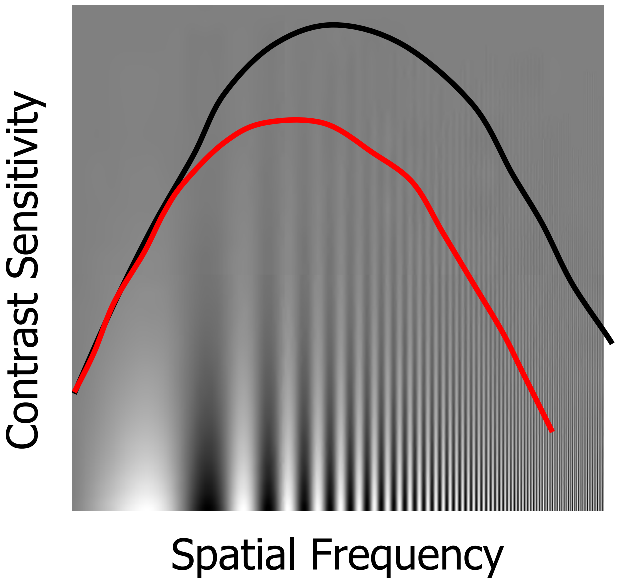
Human Amblyopia

- "Lazy Eye"
- Relatively common developmental visual disorder (~2%)
- Reduced visual acuity in an otherwise healthy and properly corrected eye
- Associated with interruption of normal early visual experience
- Most common cause of vision loss in children
- Well characterized behaviorally, not neurologically
- Treated by patching in children

Visual Deficits in Amblyopia

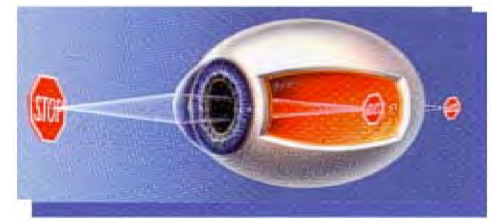
- Reduced monoc. visual acuity - defining feature
  - Usually 20/30 - 20/60
- Impaired contrast sensitivity
  - Prominent at high spatial frequencies
  - Central visual field is generally most affected



- Moderate deficits in object segmentation/recognition and spatial localization
- Severe deficits in binocular interactions

Subtypes of Amblyopia

- Anisometropic
  - Unequal refractive error between the two eyes



- Strabismic
  - Deviated eye that may or may not have unbalanced refraction

- Deprivation
  - Congenital cataract; corneal opacity; eyelid masses

Mechanisms of Amblyopia

1. Form deprivation
   - Sharp image is not formed at the retina

(deprivation of high sf)

2. Abnormal binocular vision
   - Binocularity is often changed or lost in amblyopia

(physiological suppression)

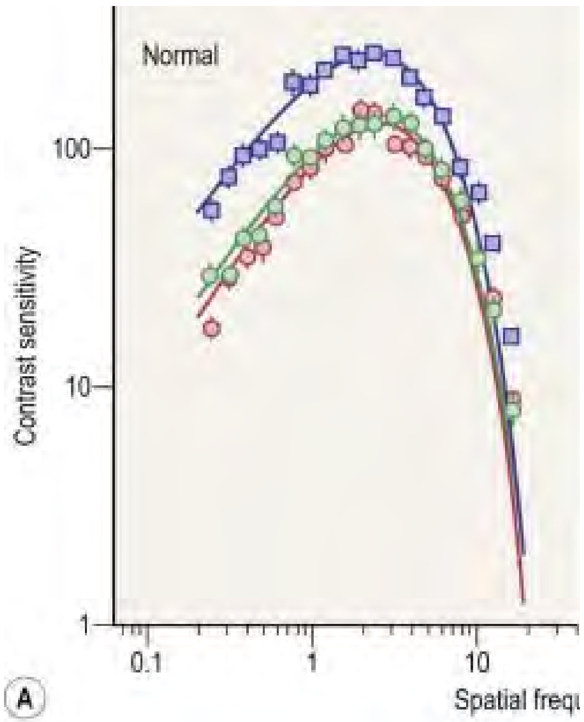
Suppression may be necessary to avoid 'double vision'

Models of Amblyopia

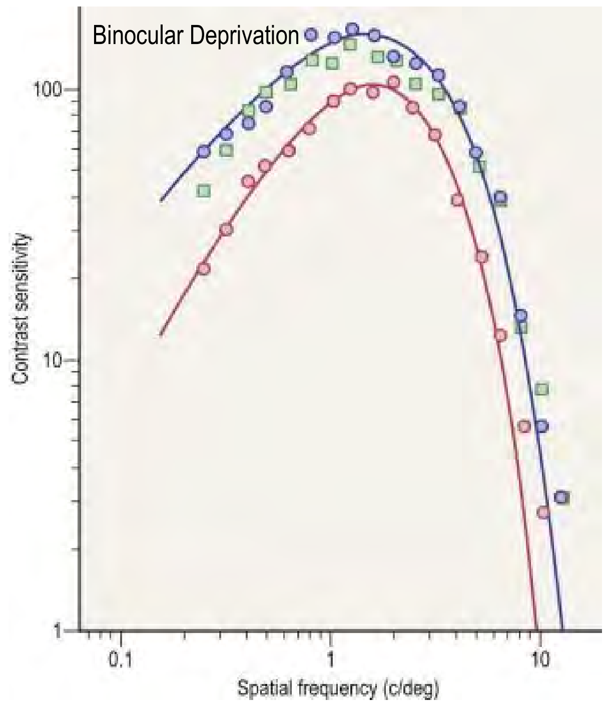
- Competition hypothesis originated with experiments in kittens in the 1960s by Hubel and Wiesel
- Monocular deprivation of retinal input during 'critical' developmental periods leads to striking abnormalities in the physiology of visual cortical neurons
- Binocular deprivation actually leads to *less* severe abnormalities
- Amblyopia may be a form of activity-dependent deprivation, modulated by competitive interactions.
- Sites of neural deficit? V1, + extrastriate, LGN?

Perceptual Effects of Deprivation

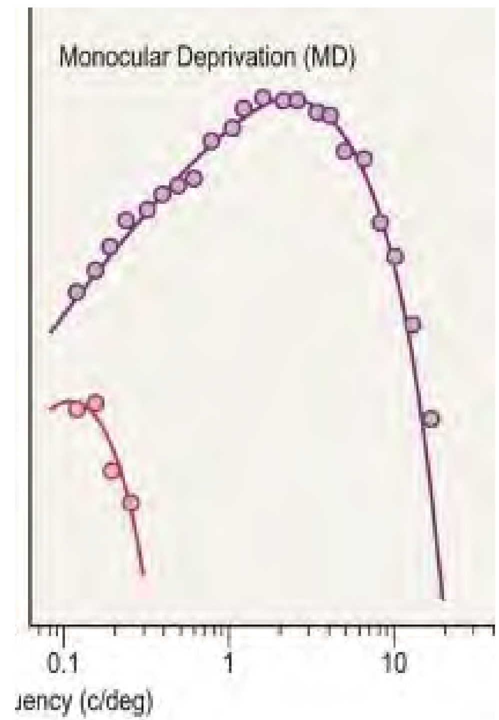
Primate



binocular
left
right



binocular
left
right

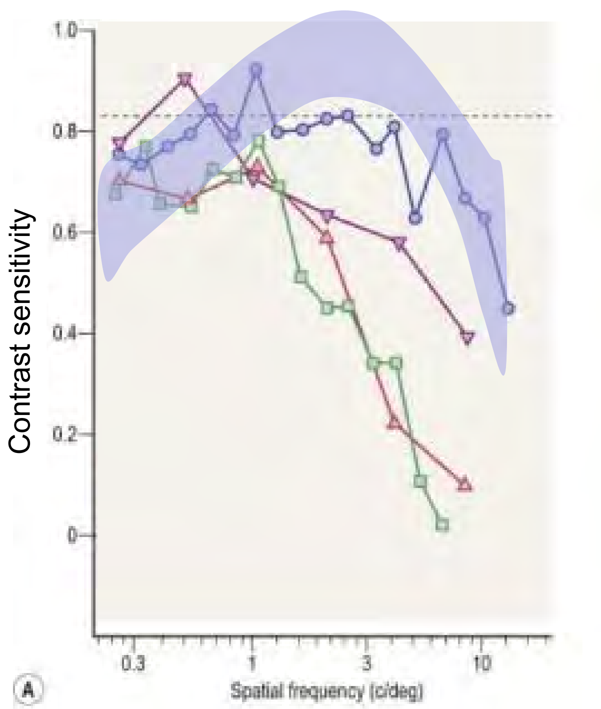


deprived
fellow

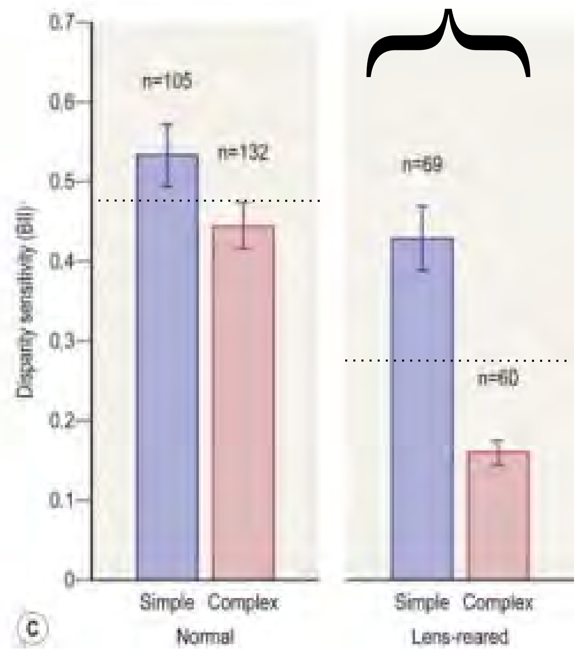
Perceptual Effects of Defocus

Primate

contrast sensitivity loss at high sf

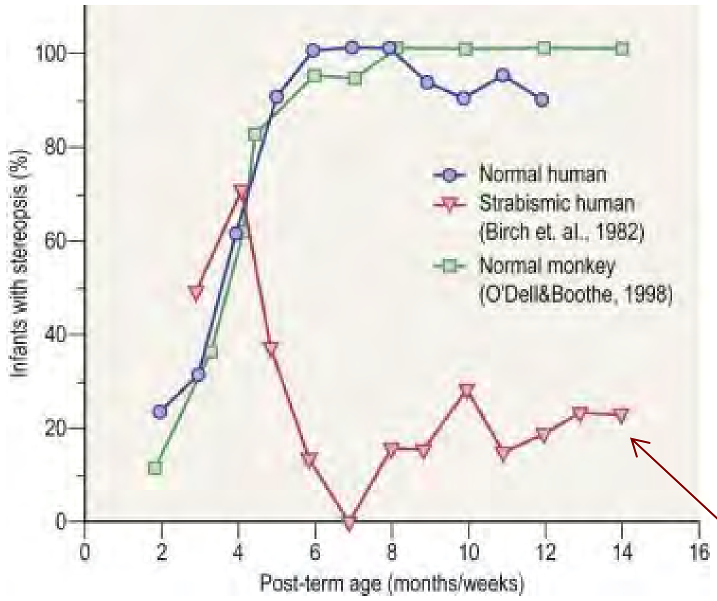


binocularity is diminished in V1



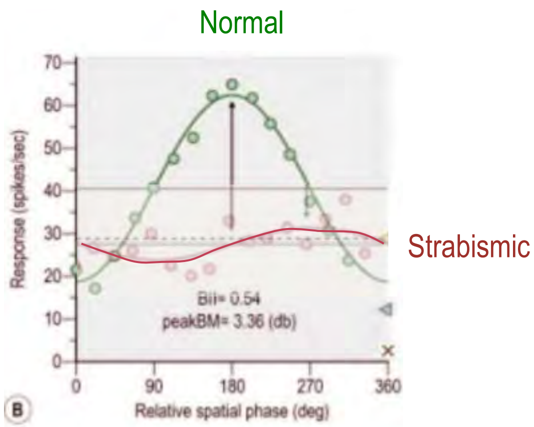
Perceptual Effects of Strabismus

Primate



1 human month = 1 monkey week

Severe loss of disparity tuning in V1



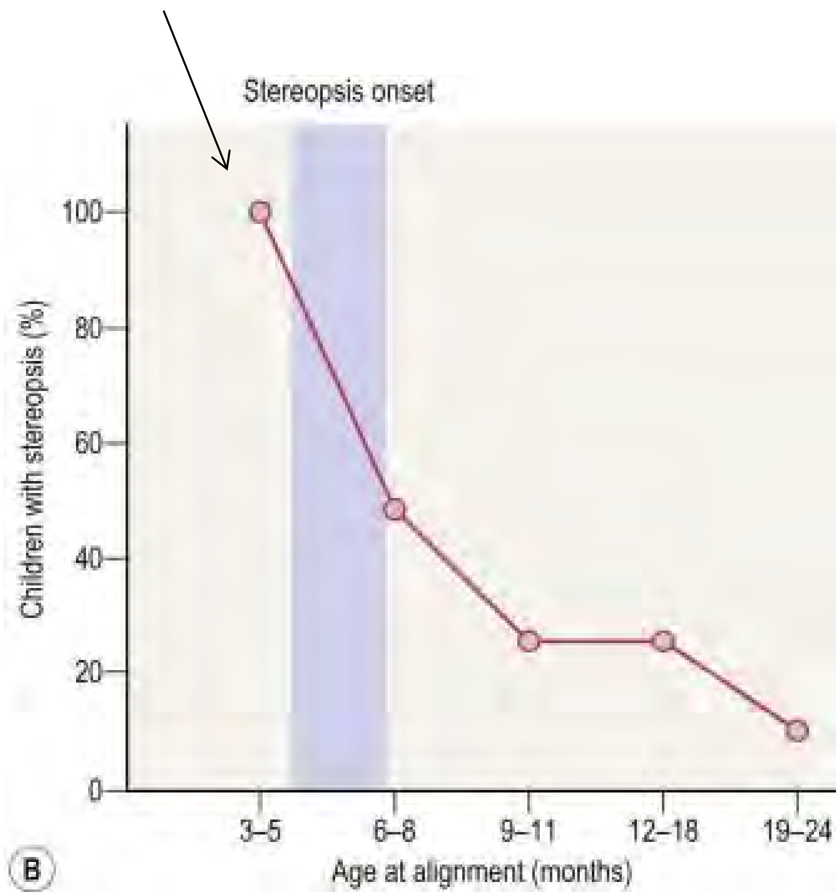
Stereopsis is devastated

Effects of Onset Age and Duration In Strabismus

Children:

Stereopsis onset is 4-6 months

Treatment before 4 months is best !



Primates:

Stereopsis onset is 4-6 weeks

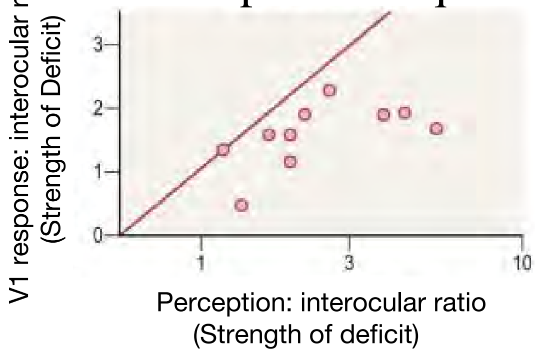
- At 4 weeks, only 3 days of induced deviation increases amount of binocular suppression in V1 measurably.

- At 4 weeks, only 2 weeks of induced deviation in monkeys fully reduces disparity tuning in V1

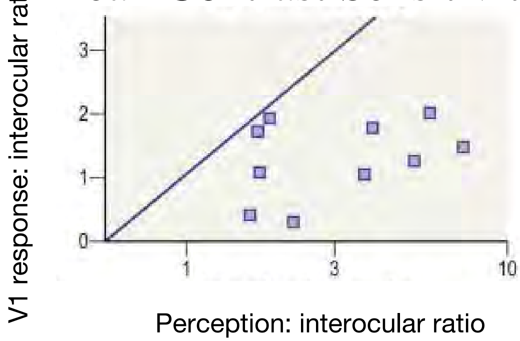
Physiology Related to Perception in Strabismic Amblyopic Monekys

Primates

Peak Spatial Frequency



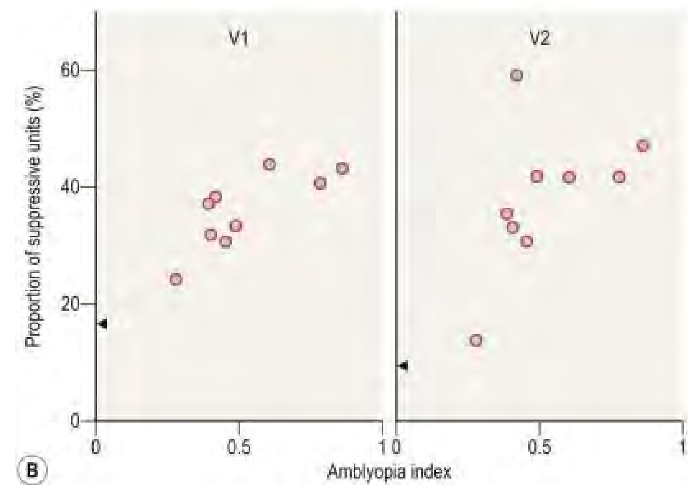
Peak Contrast Sensitivity



•Note: perceptual deficits are greater than seen in V1

* Strong implication of extrastriate!

Degree of amblyopia correlates with the amount of binocular suppression



* Is suppression an etiological factor?

Current Issues

- Abiding debate about how the *strabismic and anisometropic* subtypes differ from each other.
- Chicken and egg situation : Is amblyopia a consequence or a cause of strabismus/ anisometropia ?
- The *relationship* between performance on monocular versus binocular tests has not been well-studied.

Hypothesis

- Impairment in binocular functions may predict the pattern of monocular deficits, and thereby help explain the *mechanisms* (McKee, Movshon & Levi, 2003).

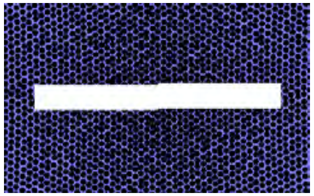
Experiments

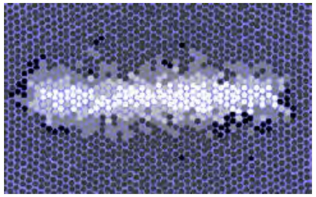
- *Monocular tests*
  - Snellen acuity
  - Grating acuity
  - Vernier acuity
  - Contrast sensitivity
- *Binocular tests*
  - Randot stereotest
  - Binocular motion integration

Results

- *<u>Monocular Tests:</u>* Amblyopic eyes showed a deficit for all the monocular functions tested; strabismic amblyopes are distinguished from anisometropic amblyopes by their severe loss of Vernier acuity.

- *<u>Binocular Tests:</u>* Stereopsis & Motion Integration
  – Very reduced in amblyopes, especially strabismics





• hyperacuity
• cortical processing

Can binocularity predict Vernier acuity?

Re-classification

- Reclassify amblyopes based on binocular properties. Subjects who passed both randot stereoacuity test and binocular motion integration were assigned "*binocular*." Those who couldn't pass were assigned "*non-binocular*"

- Deficits in Vernier acuity are much more severe in '*non-binocular*' group as compared to '*binocular*'.

- Vernier performance (and Snellen and crowding) in '*non-binocular*' subgroup can not be predicted the by grating acuities - suggesting additional factors (cortical).

Implications

- Vernier performance is better predicted by residual binocularity than by clinical subtype.

- Interocular suppression may be an important etiological factor in the development of amblyopia (e.g., Sireteanu, 1980; Agrawal et al., 2006).

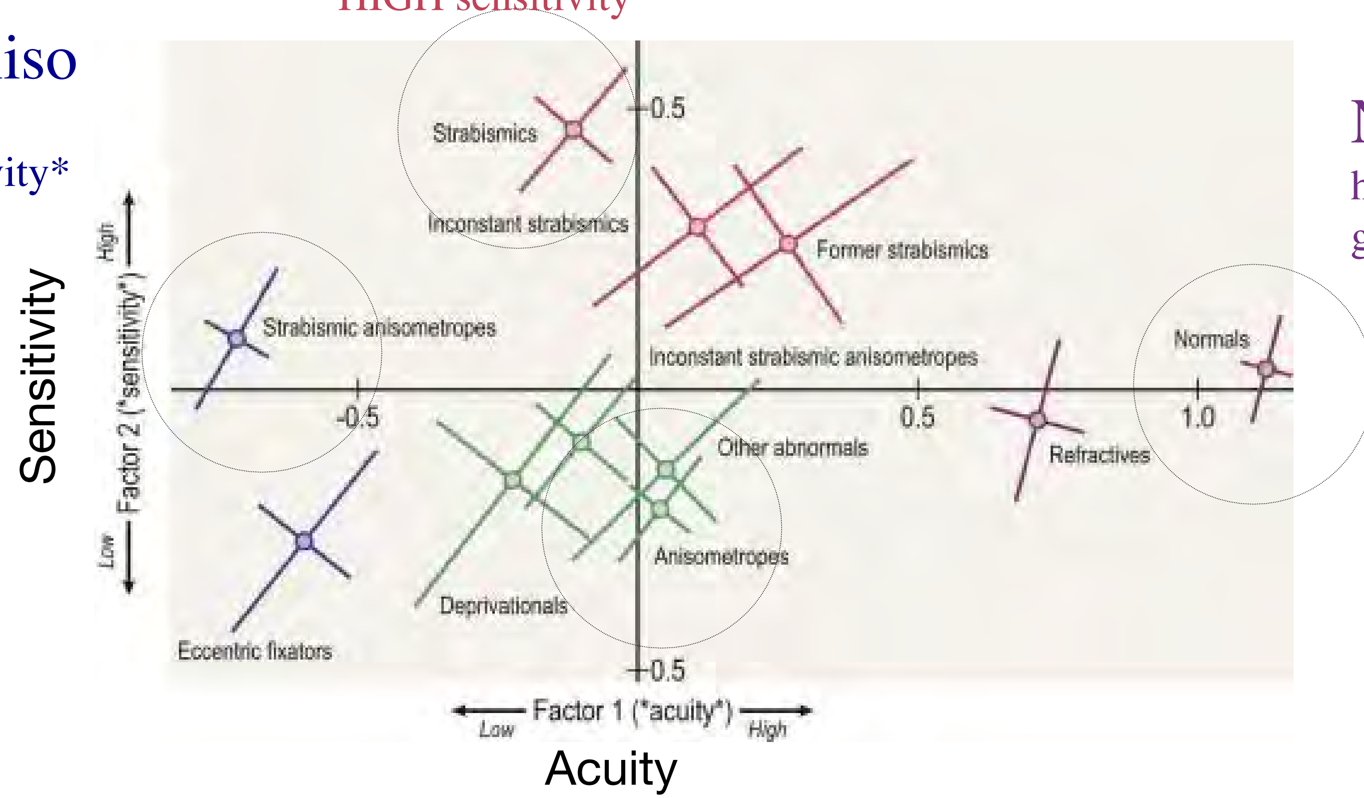
Amblyopia

*refers to relatively low level monocular tests

Strabismic
low acuity
HIGH sensitivity*

Strab Aniso
lower acuity
good sensitivity*

Normal
high acuity
good sensitivity

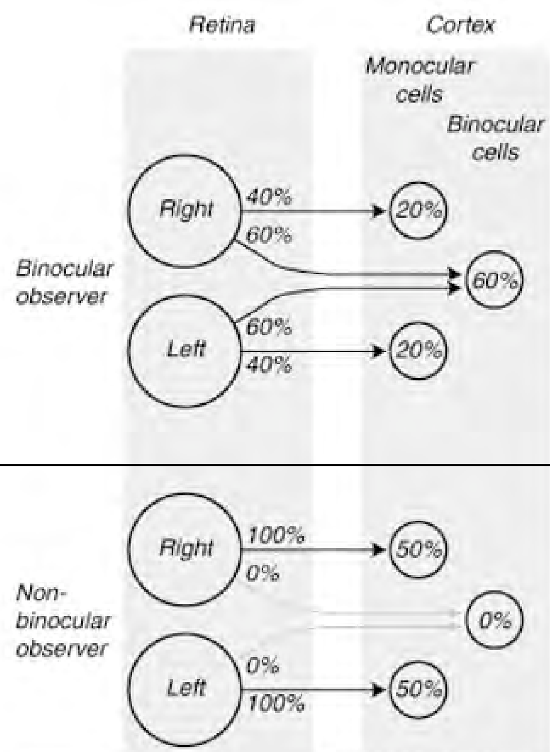


Anisometrope
low acuity
low sensitivity

McKee, Levi & Movshon, 2003

Amblyopia

The degree of binocularity is a better predictor of pattern of deficits than clinical diagnostic category. Non-binocular subjects can show relatively Superior sensitivity in combination with severe loss of acuity.

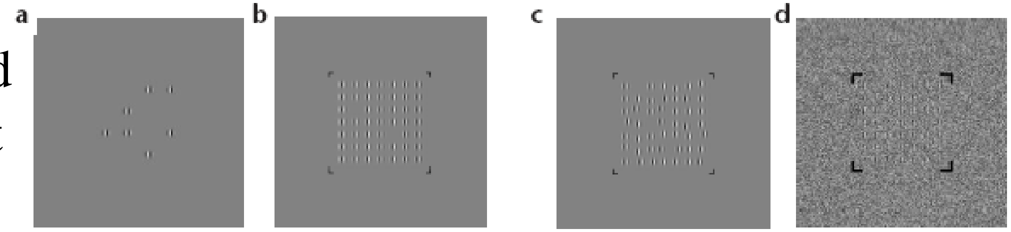


Possible explanation would be more monocular cells that contribute to superior monocular contrast sensitivity

McKee, Levi & Movshon, 2003

Amblyopia

Strabismics show loss that could seem to reflect acuity, but might be surprisingly ‘high-level’



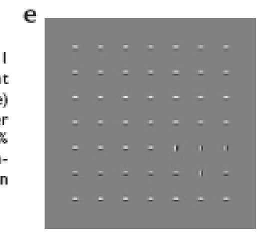
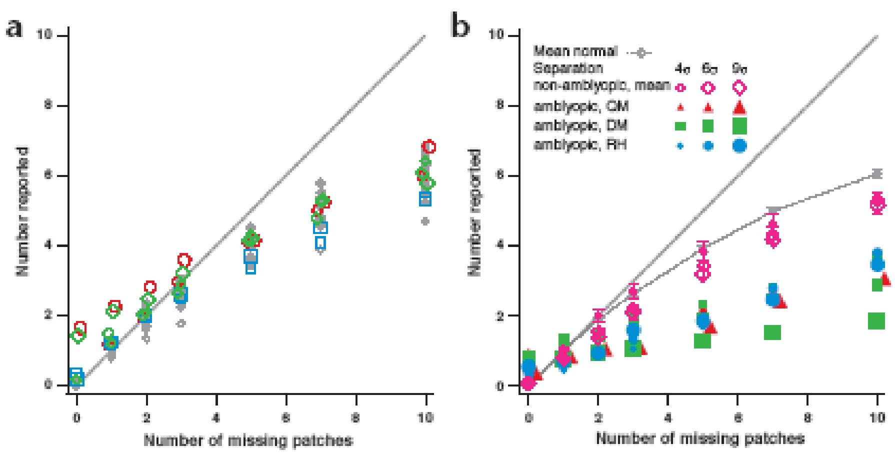


Fig. 1. Examples of stimuli. (a) Example of randomly arrayed Gabor patches used for experiment 1 (counting patches). (b) Example of the 7 × 7 matrix with $N = 2$ missing patches used in experiment 2 (counting missing patches). (c) Example of the 7 × 7 matrix (separation, 6σ of patch envelope) with $N = 2$ missing patches. The patches were subjected to random Gaussian positional jitter (jitter magnitude, 1.2σ). (d) Example of the 7 × 7 matrix with $N = 3$ missing patches. The patches had 50% contrast and were embedded in 50% root mean squared (rms)-contrast white noise. Each trial contained a new noise sample. (e) Example of the 7 × 7 matrix with $N = 4$ vertical patches used in experiment 3 (count vertical patches).

Counting Performance

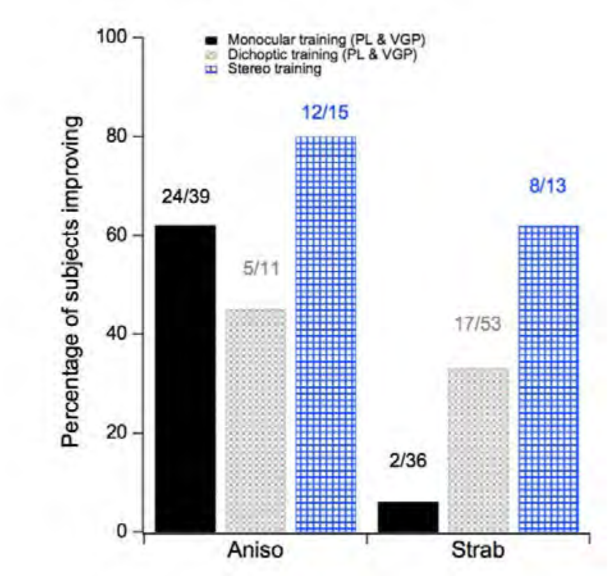


Suggests an attentional deficit, akin to neglect.

Sharma, Levi & Klein, 2000

Amblyopia Treatments

>200 subjects with wide range of ages.
Across all methods, more than one fourth of amblyopes with no measurable stereopsis prior to training showed at least some measurable stereopsis after training, and more than 50% of anisometropic and about 26% of strabismic amblyopes showed at least a 2-level improvement in visual acuity and stereoacuity of 160 arc s or better



Levi DM, Knill DC, Bavelier D. Stereopsis and amblyopia: A mini-review. Vision Res. 2015 Sep;114:17-30.

Amblyopia Treatments

94 **adults** and multiple training approaches, as post- vs. pre-training thresholds

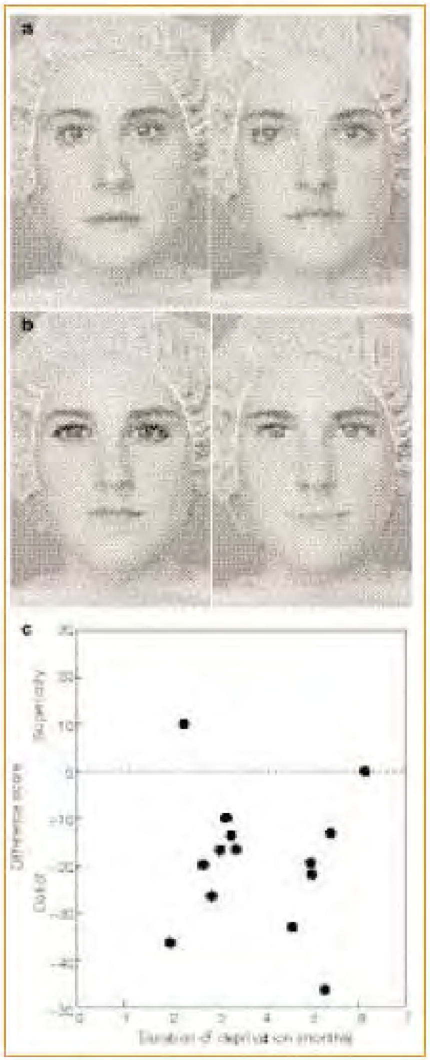
• Many more anisometropic than strabismic amblyopes improve after training.

• Many more strabismic (40/57 – 70%) than anisometropic (12/37 – 32%) amblyopes have no measurable stereopsis both before and after training.

• There are both anisometropic and strabismic amblyopes at all levels of pre-training stereoacuity (including no measurable stereopsis) who show improvements following training, some achieving stereoacuity of 140 arc s or better

• Despite the dogma, many adults with amblyopia can recover, at least partially, stereoacuity.

“Expert Configual Processing” In Adults after Congenital Cataracts



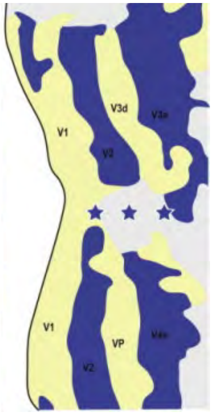
As little as 2 months of early deprivation leads to permanent deficits in certain global form configuration tasks, such as face discrimination.

Le Grand, R., Mondloch, C., Maurer, D., & Brent, H.P. Early visual experience and face processing. Nature , 2001, 410 , 890.

Visual Fields and fMRI

Adler's Physiology of the Eye 11th Ed.
Chapter 35 - by Johnson & Wall

http://www.mcgill.ca/mvr/resident/



Visual Fields

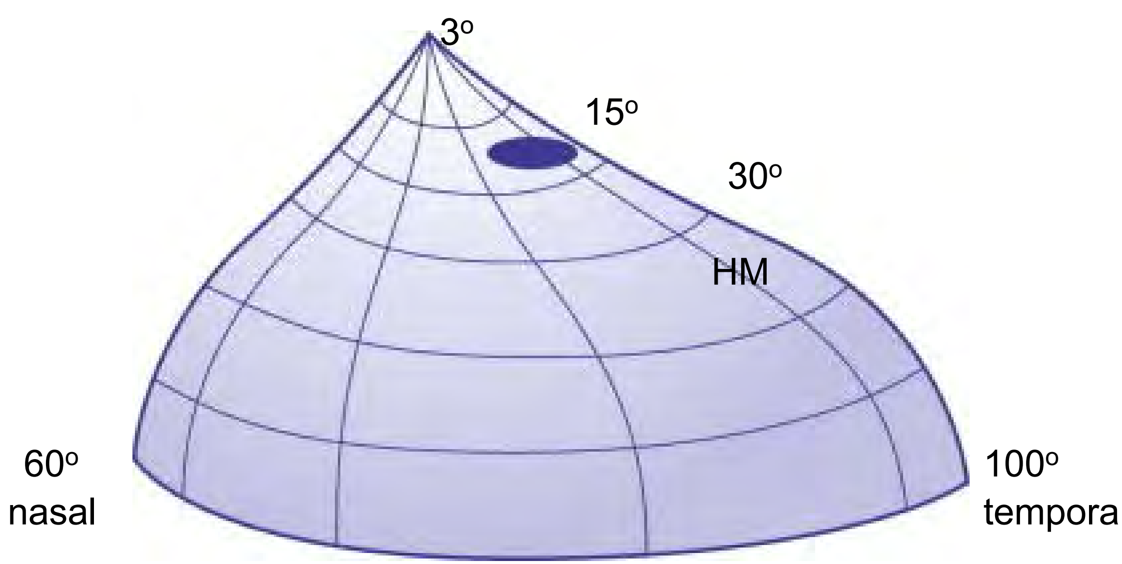
- Perimetry and visual field testing
  - detect functional losses
  - identify the location of a visual deficit
  - monitor the status of acute and chronic disease
  - evaluate efficacy of treatment

- Old technique, but continued improvements
  - automation
  - standardization
  - immediate statistical evaluation
  - greater efficiency

Visual Fields

Photopic adaptation, in normal eye, and visual system

Hill of Vision



Increment Detection Thresholds
(Weber's Law)

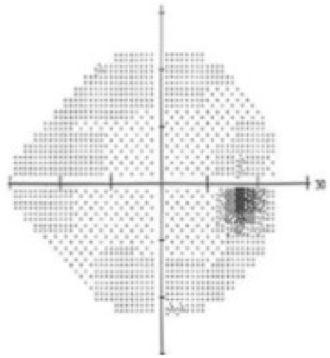
standard deviation
about 3dB

>300% more for damaged

Visual Fields

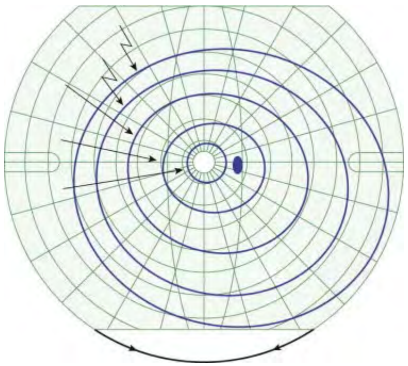
- Static Visual Fields

- most common, good standardization, and prediction
- immediate statistics, can monitor reliability, align. & fixation
- demanding for patient, high variability for low sensitivity



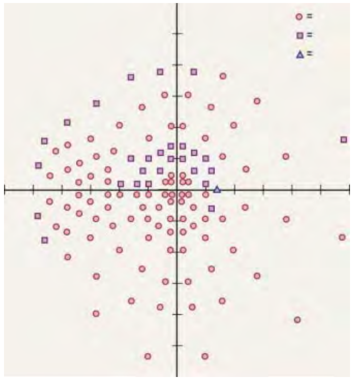
- Kinetic Visual Fields

- egg shaped isopters for a given target
- efficient & flexible method for center and periphery
- more variability, more expertise needed, less standards



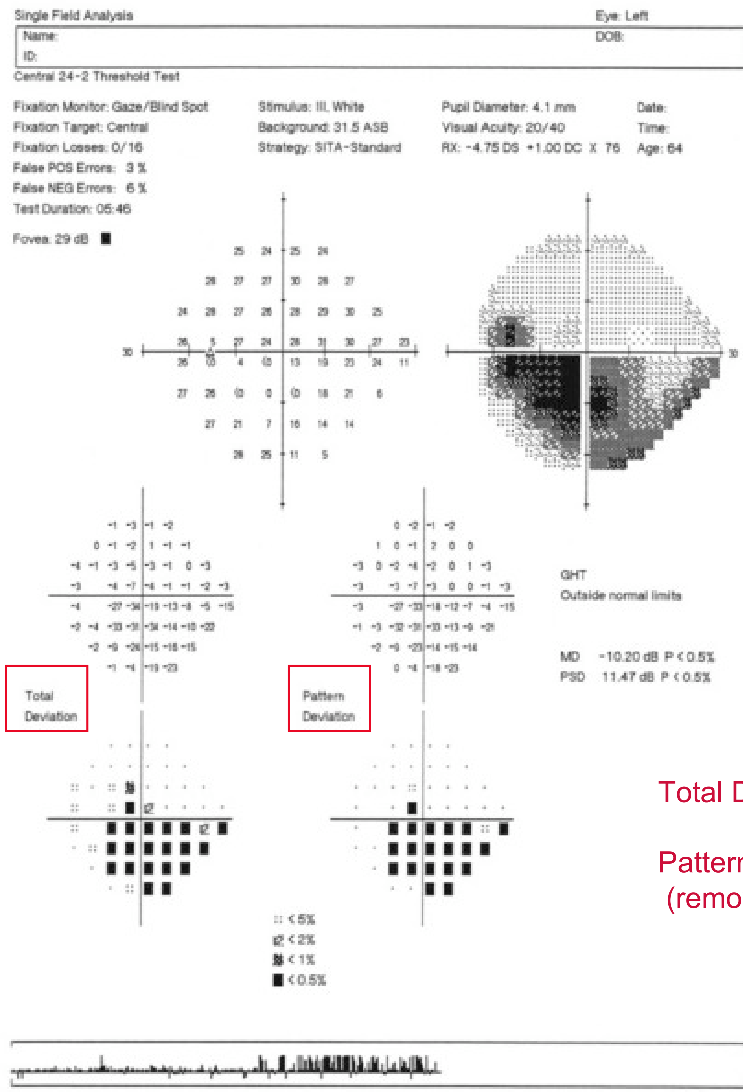
- Suprathreshold static perimetry

- rapid to detect field defects, over entire field
- limited quantification, lower sensitivity and specificity,
- less validation

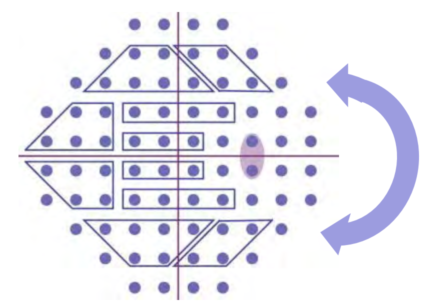


Visual Fields - Standard Automated Perimetry (SAP)

~1000 x dimmer than maximum



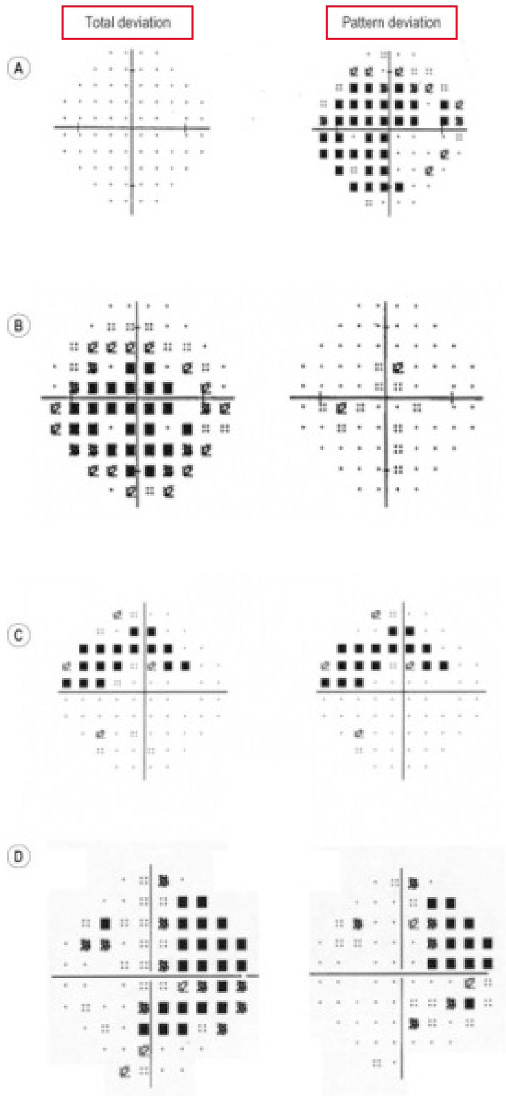
Glaucoma hemifield test
An index of symmetry for upper and lower field.



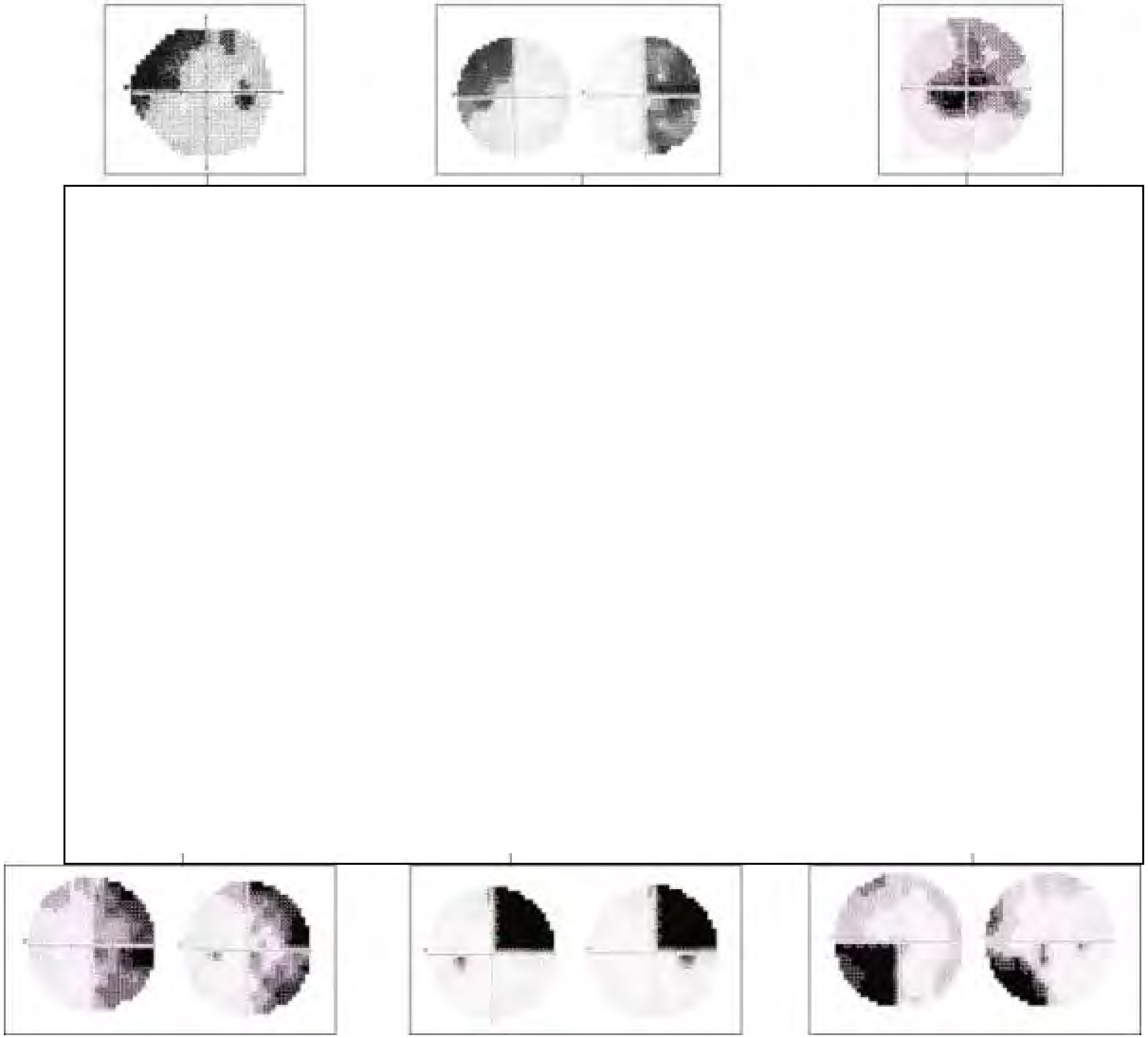
Total Deviation

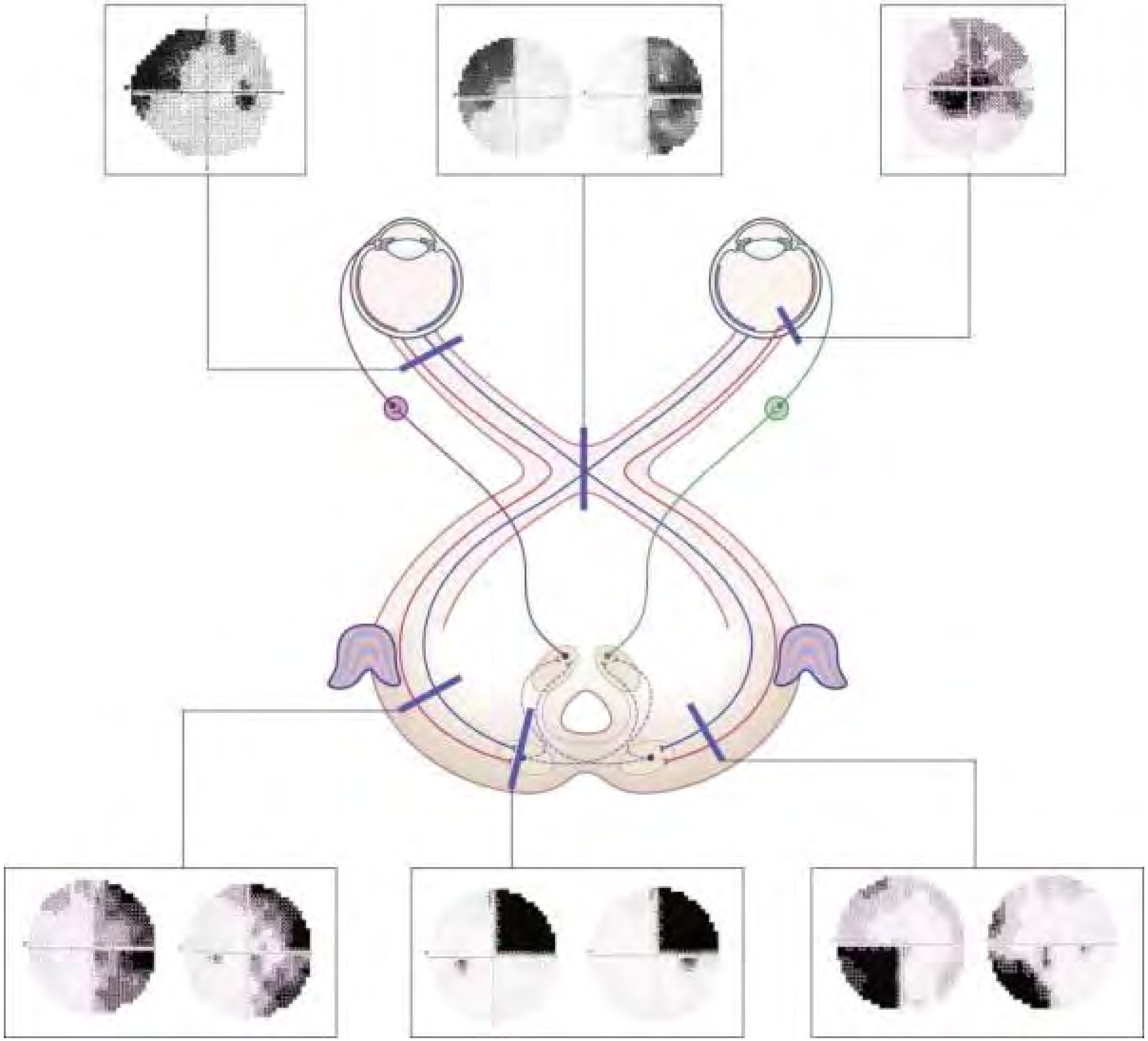
Pattern Deviation
(remove generalized sensitivity differences up to 85 percentile)

Visual Fields

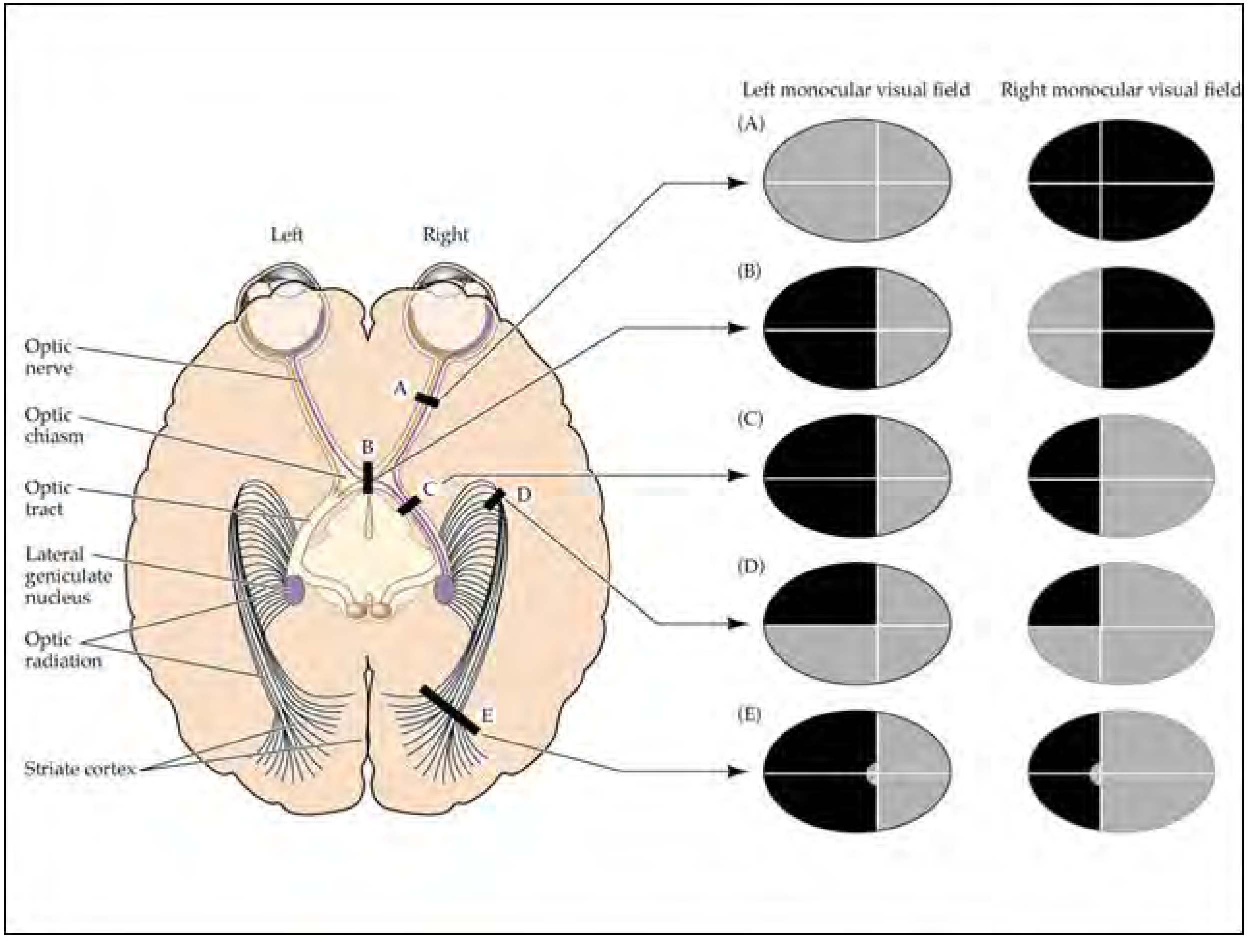


- Normal vision, but ‘trigger happy’
  - abnormally high sensitivity & false positives, hitting the button too often
- Generalized, widespread field loss
- Localized field loss
- Mixture of localized and widespread loss





Field Defects



New Perimetric Tests

Visual field test procedures

Contrast sensitivity and incremental light detection

- Standard Automated Perimetry (SAP) – A method of determining the eye's sensitivity to light at different locations throughout the field of view.

Spatial visual field tests

- High Pass Resolution Perimetry (HPRP) – A procedure that determines the minimum size of a low-contrast stimulus necessary for it to be detected.
- Rarebit Perimetry – A method of providing fine detail mapping of visual field locations by determining the detectability of tiny light dots.

Temporal visual field tests

- Flicker perimetry – A visual field procedure for determining the highest rate of flicker that can be detected (critical flicker fusion or CFF perimetry), the minimum amplitude (contrast) of flicker that can be detected (temporal modulation perimetry), or the minimum light increment needed to detect an illuminated target as flickering on a uniform background (luminance pedestal flicker perimetry).
- Motion perimetry – A method for determining sensitivity to motion throughout the visual field by determining the minimum displacement needed to detect motion (displacement threshold perimetry), the amount of directional coherence needed to detect motion among a collection of random dots (motion coherence perimetry) or the size of visual field area needed to detect motion of a subset of random dots.

Spatio-temporal visual field tests

- Frequency Doubling Technology (FDT) perimetry and Matrix perimetry – A method for presenting a low spatial frequency sinusoidal grating flickering at a high temporal frequency to determine the amount of contrast needed for detection.

Color perimetry

- Short Wavelength Automated Perimetry (SWAP) – A visual field technique that isolates and measures the sensitivity of short wavelength mechanisms.

Electrophysiological perimetry

- Multifocal Electroretinogram (mfERG) – A method of measuring electrical retinal signals for localized visual field regions.
- Multifocal visual evoked potentials (mfVEP) – A technique that measures the electrical activity from primary visual cortex for alternating stimuli presented to small regions of the visual field.

Magnetic Resonance Imaging

State of Affairs in 1990's

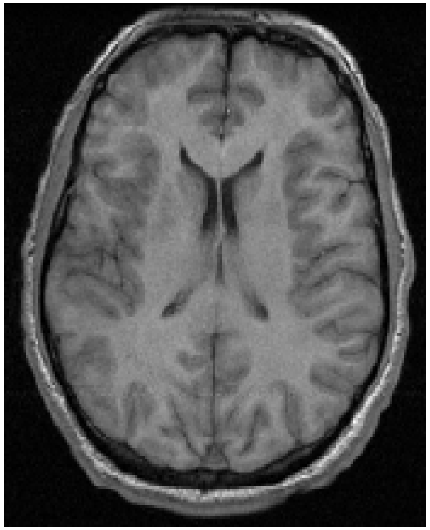
- **Monkey Visual Cortex – Highly complex wiring diagrams**
  Felleman & Van Essen, 1991

- **Human Visual Cortex – Only tedious postmortum techniques**
  Clarke & Miklossy, 1990; Horton & Hoyt, 1991

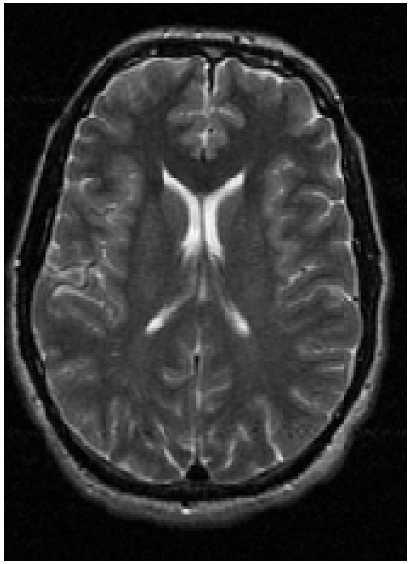
- **fMRI –Non-invasive measure with good resolution**
  Kwong et al., 1992; Ogawa et al., 1992

- **Cortical Surface Representation – Great facilitates interpretation**
  Dale & Sereno, 1993

Brain Images Showing T1 and T2 Contrast



T1 weighted



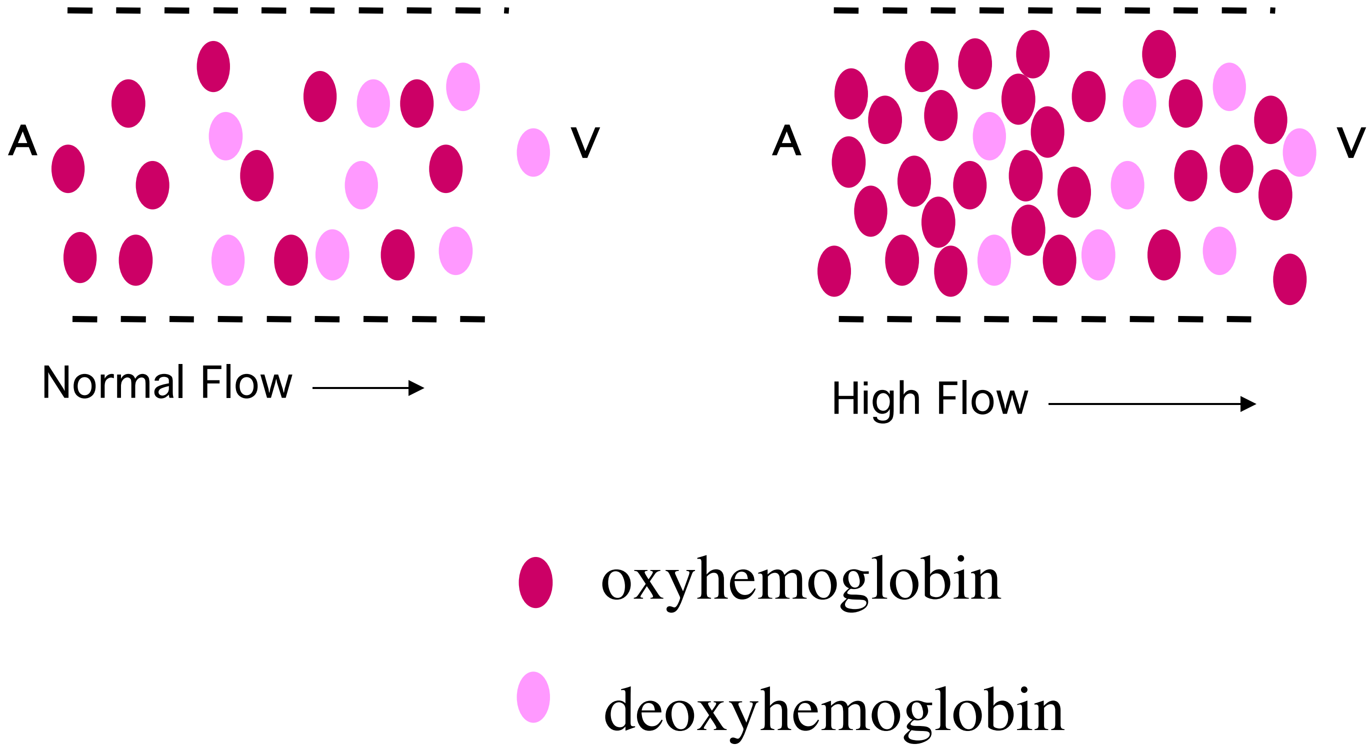
T2 weighted

By varying the timing of sending and receiving signals in the MR scanner, most **anatomical MR** images are either T1 weighted or T2 weighted. This is done to create contrast between different tissues types.

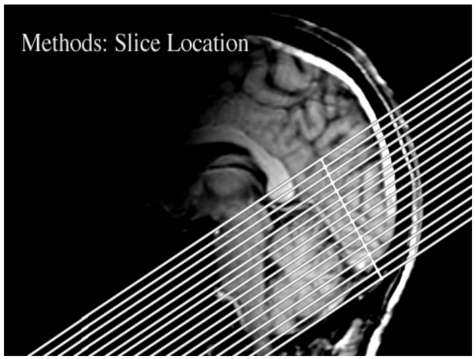
Functional MRI is a newer technique that detects the T2 difference between oxy-hemoglobin and deoxy-hemoglobin

The BOLD Effect

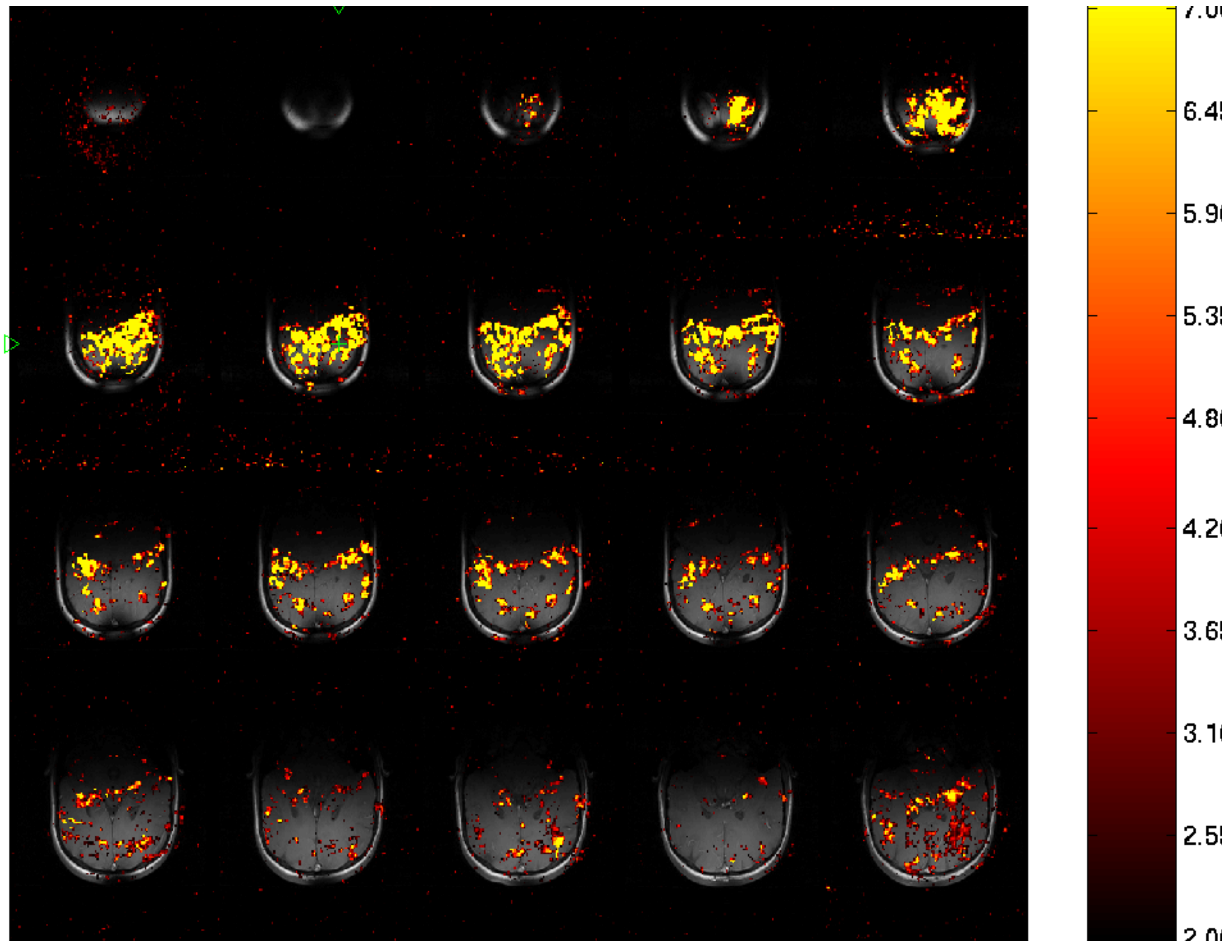
"Blood Oxygen Level Dependent"



Light Activation Viewed on Brain Slices

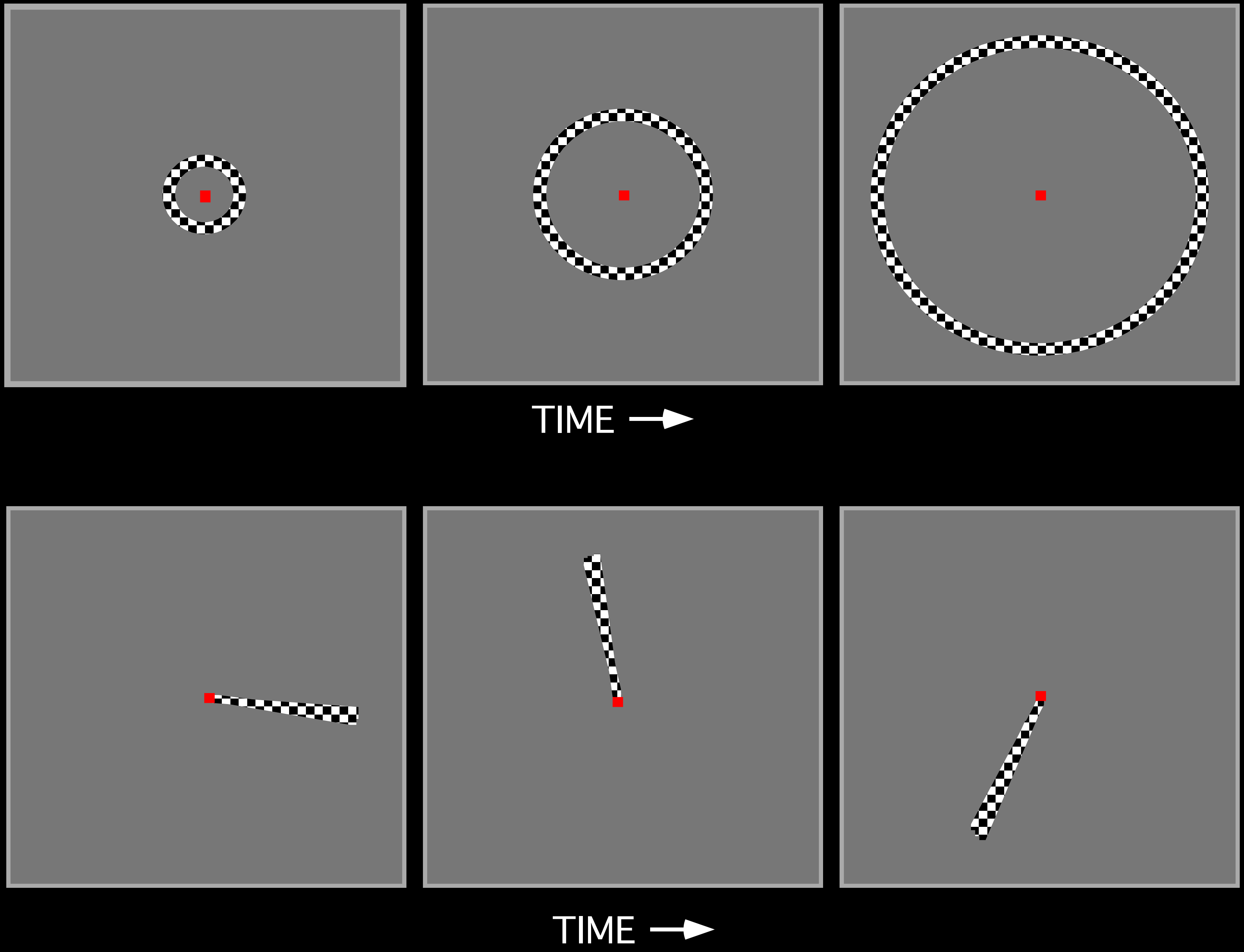


BOLD effect - fMRI

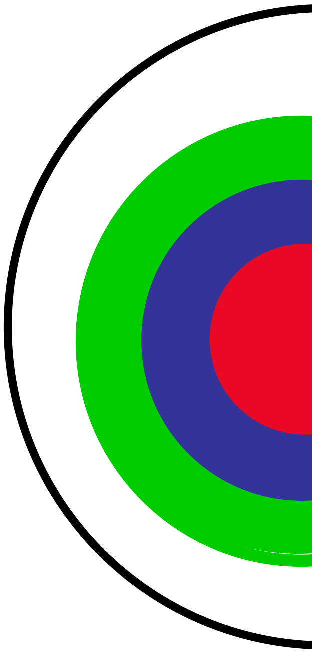


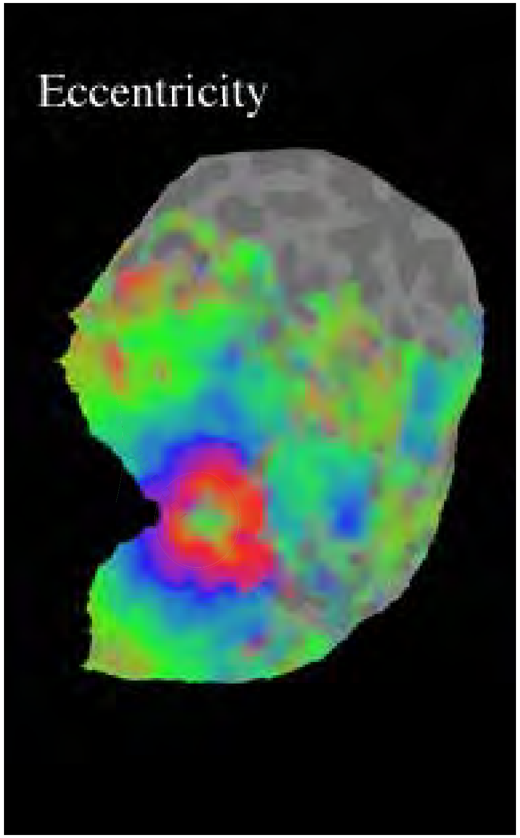
Mapping Visual Cortex

Eccentricity and Polar Angle Stimuli



Maps of Cardinal Axes on Flattened Cortical Surface





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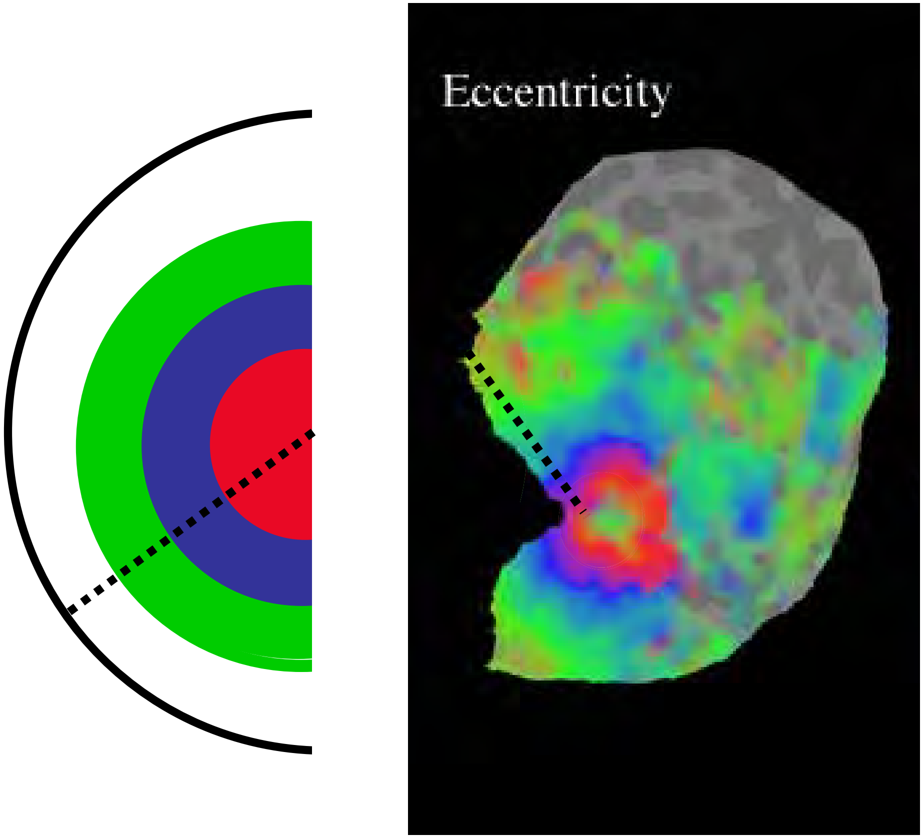

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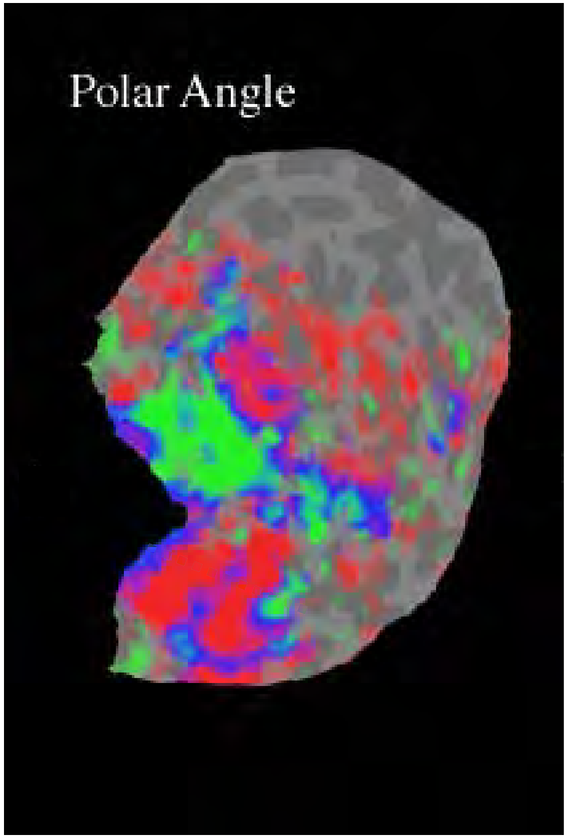

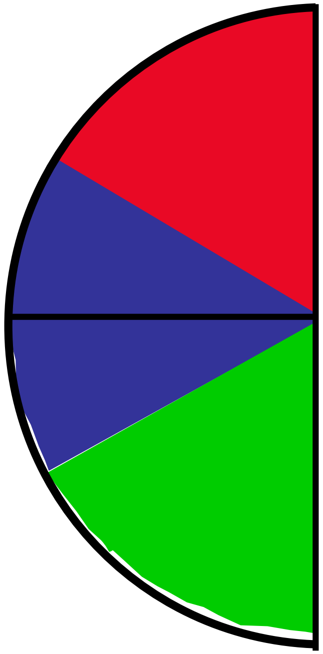

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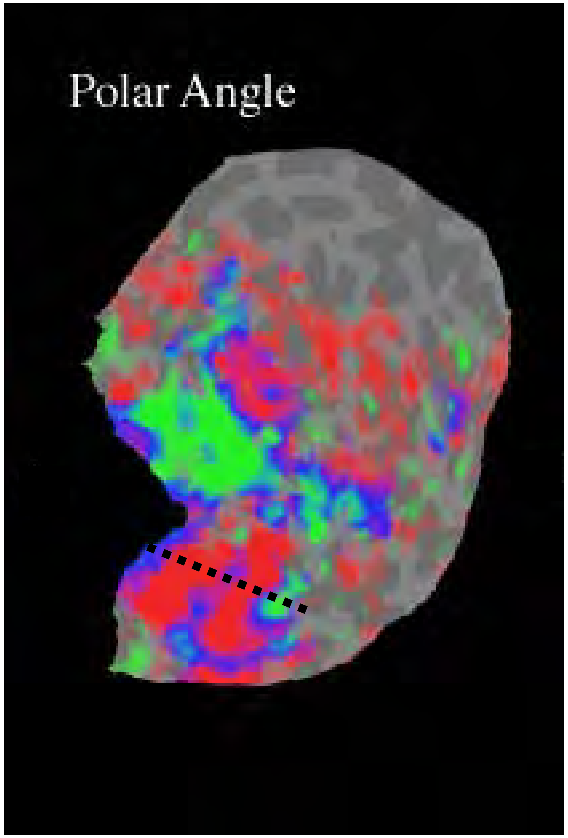
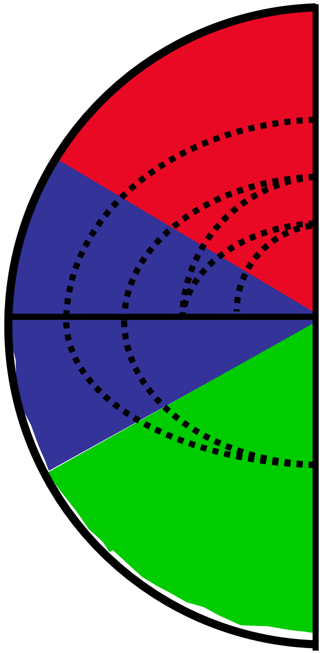
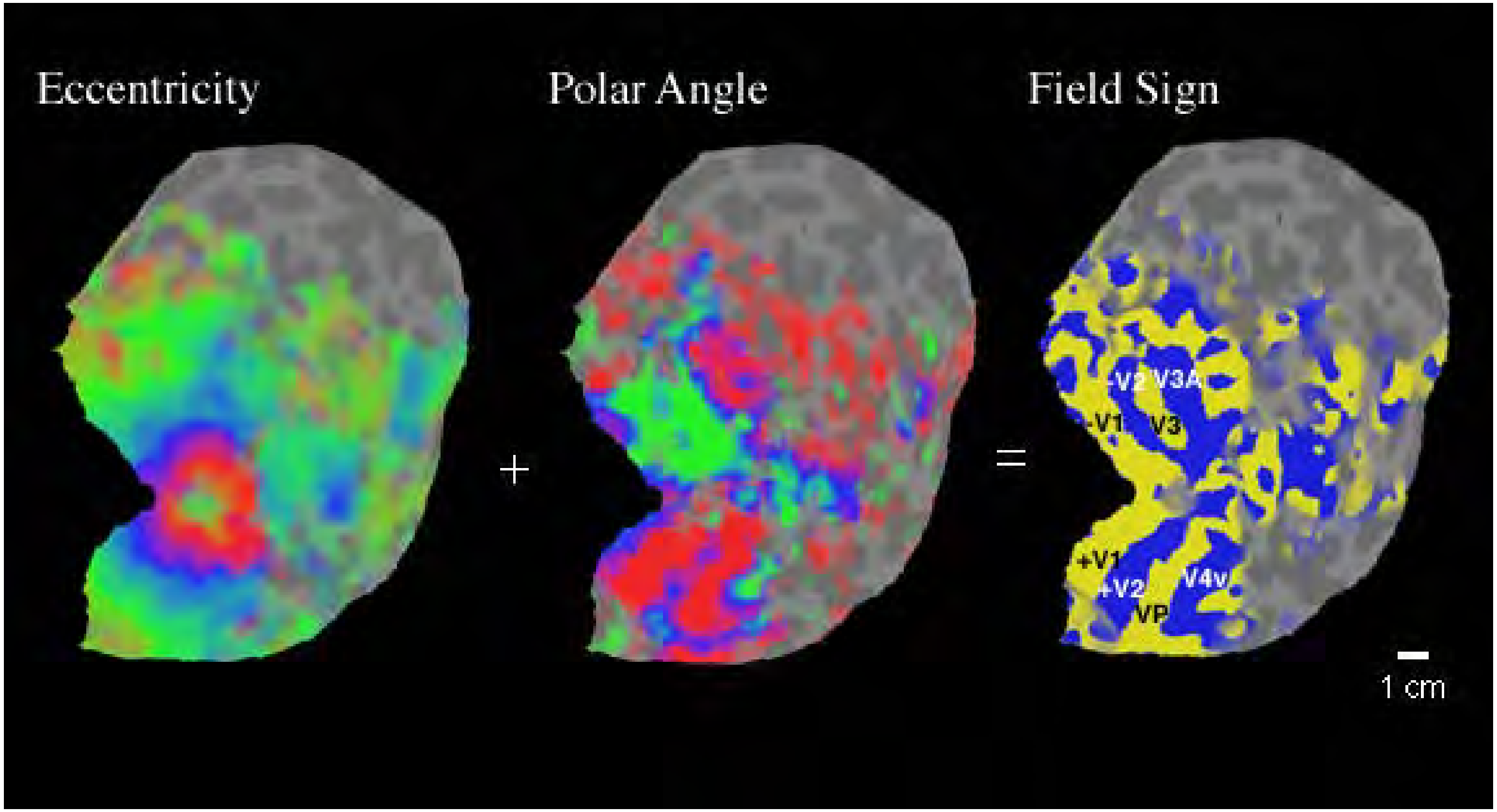
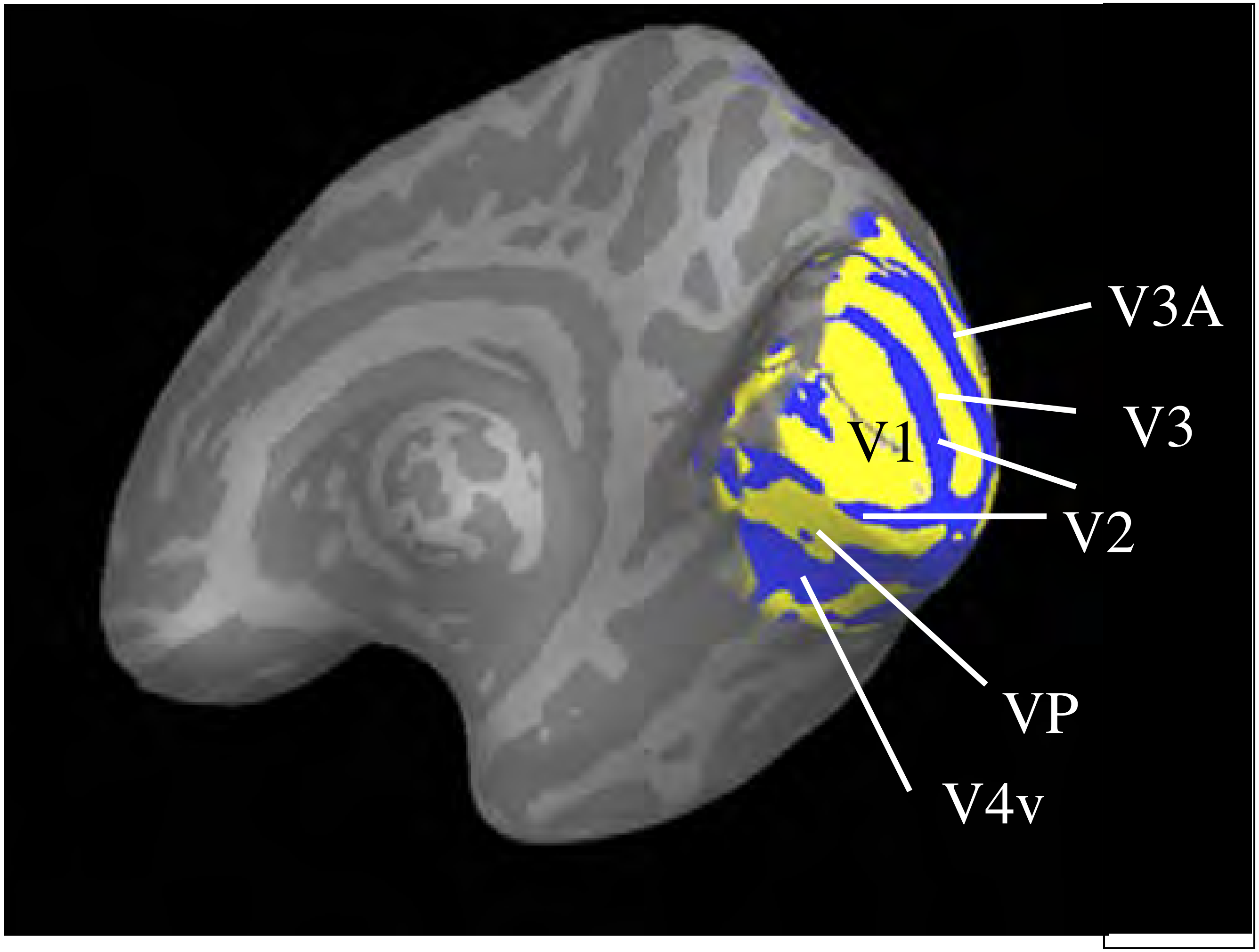




'Field-Sign' is Calculated from Cardinal Axes



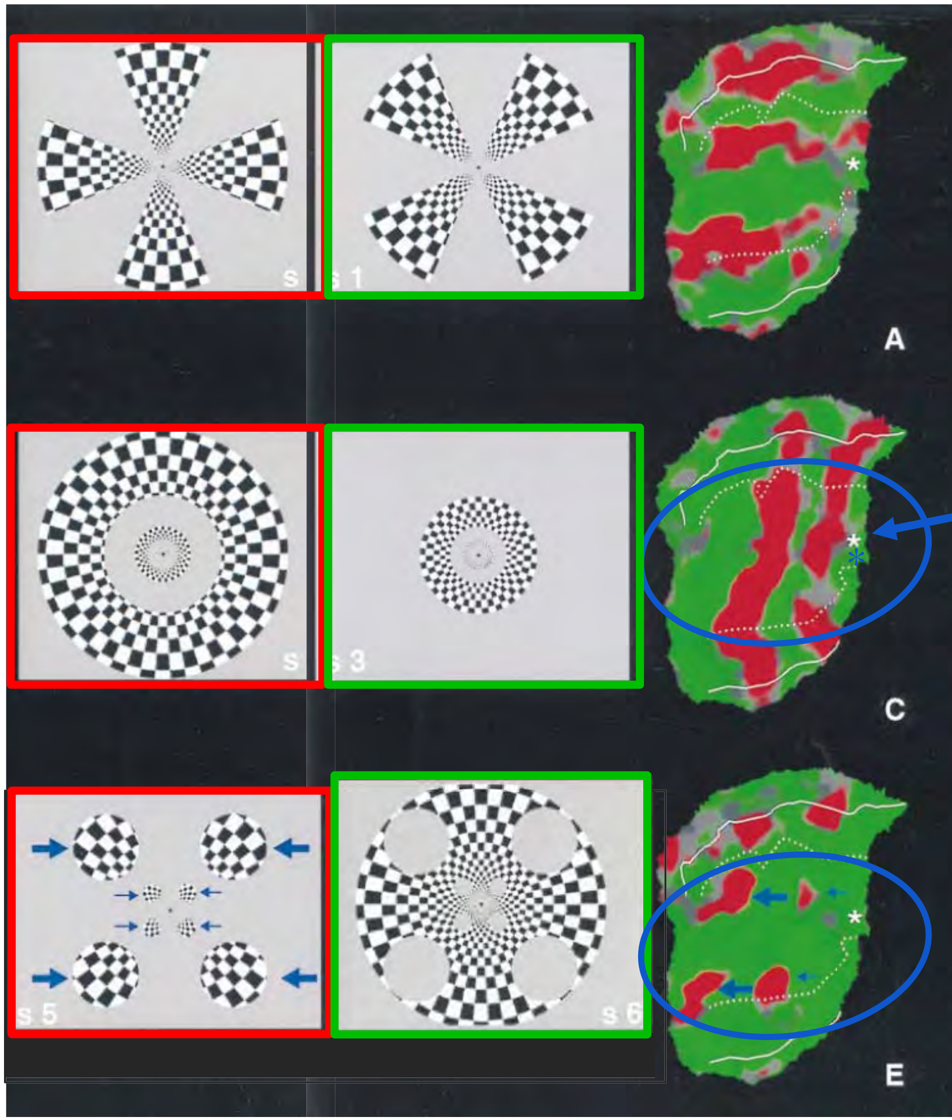
Inflated View of Areas

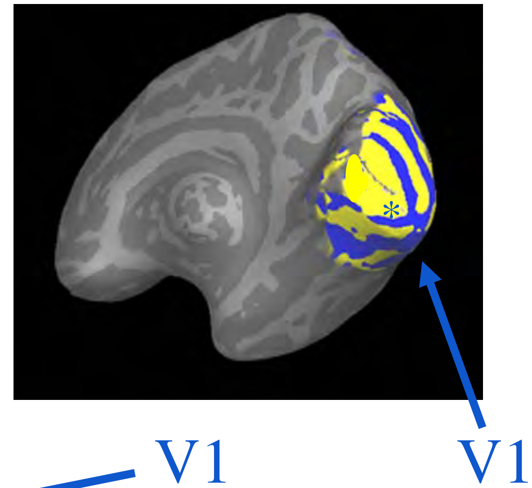


fMRI Demos

Cortical Magnification
Motion Sensitivity
Contrast Sensitivity
Amblyopic Suppression
Other Ophthalmic Conditions

Retinotopy & Cortical Magnification





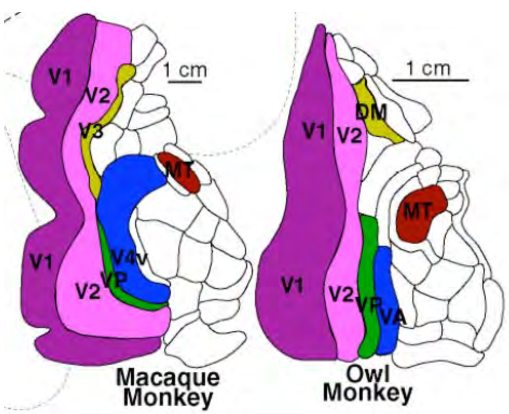
* = occipital pole
= foveal vision

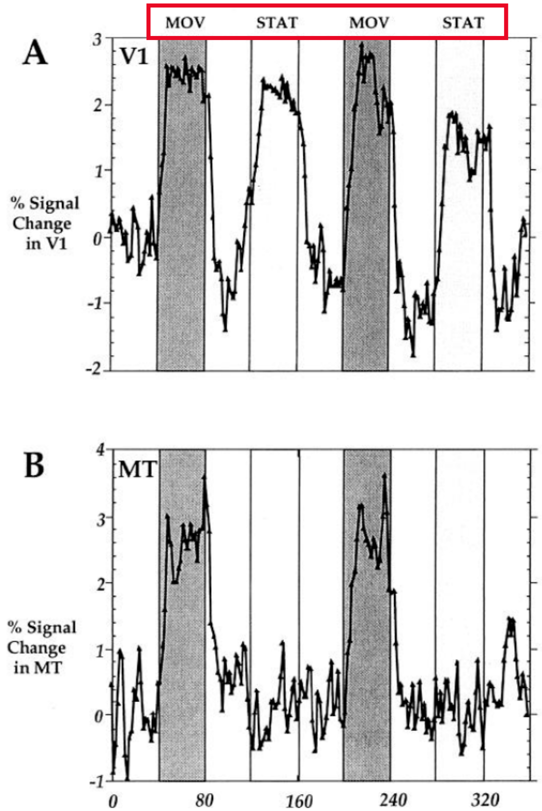
Red/green pseudo-color on flattened V1 shows cortex activated more by first or second stimulus respectively

Tootell et al., 1998b

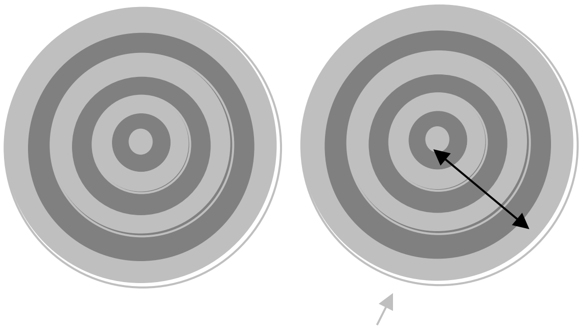
Human Cortical Area MT

Well studied in monkeys
Distinctive anatomy (myelin) and function –
motion direction selectivity
Present in all primates tested.

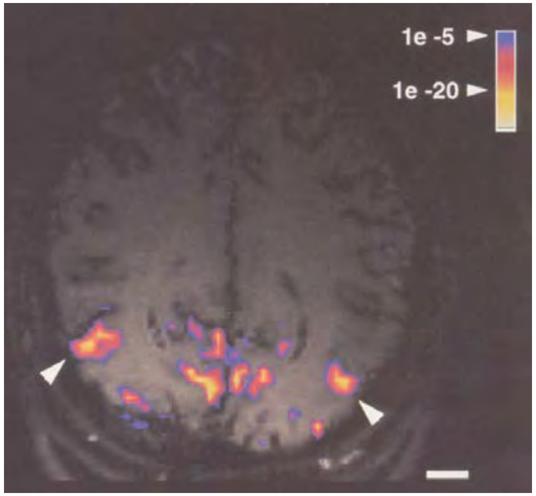




Localizing Stimuli

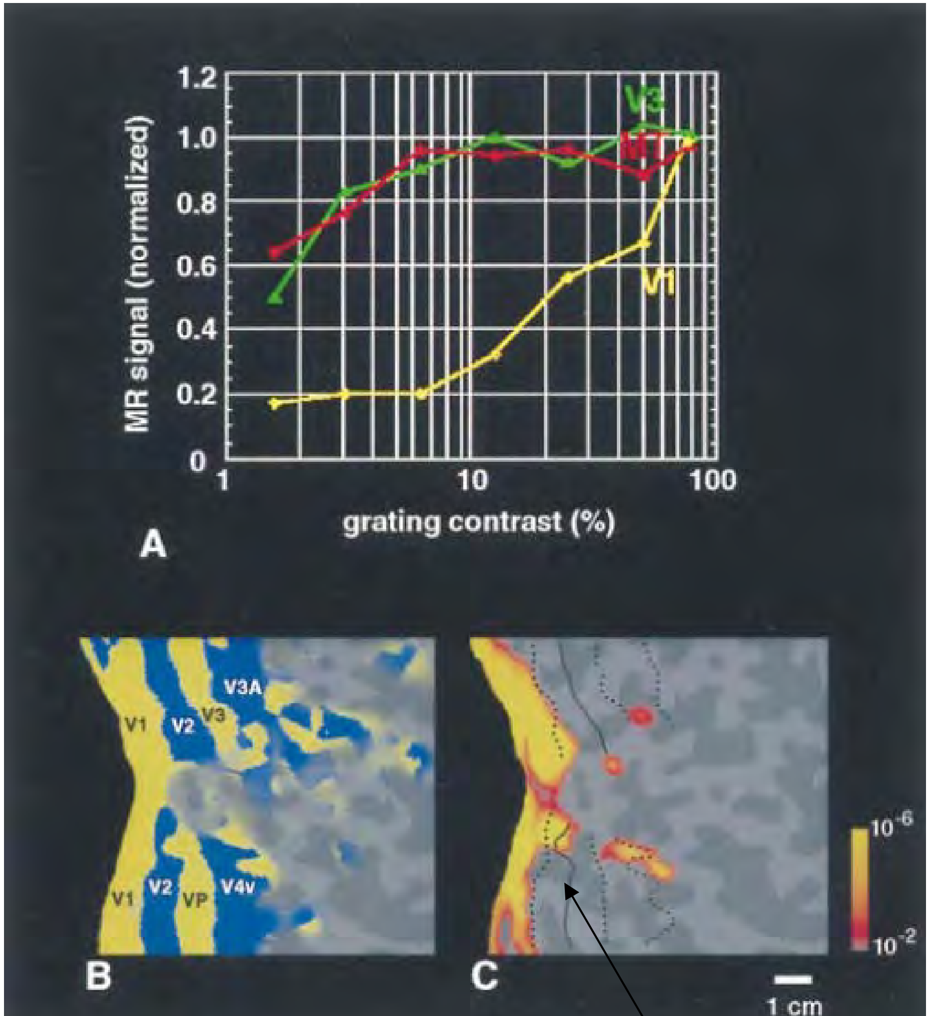


low-contrast motion vs.
low-contrast stationary



Tootell et al., 1995

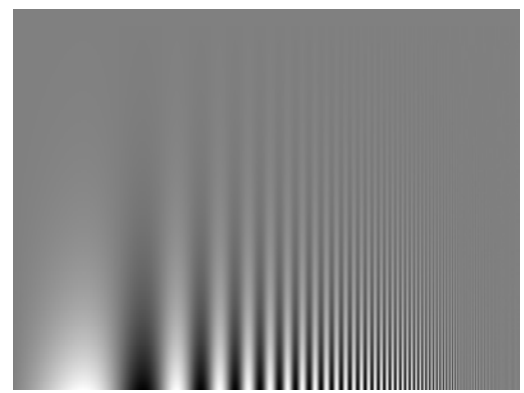
Contrast Sensitivity



Tootell et al., 1998b

MT has high contrast sensitivity
V1 has lower contrast sensitivity

MT good for low contrast *detection*
V1 good for medium contrast *discrimination*



Pelli-Robson Chart

How could V1 be activated selectively?

high-contrast stationary vs.
low-contrast stationary

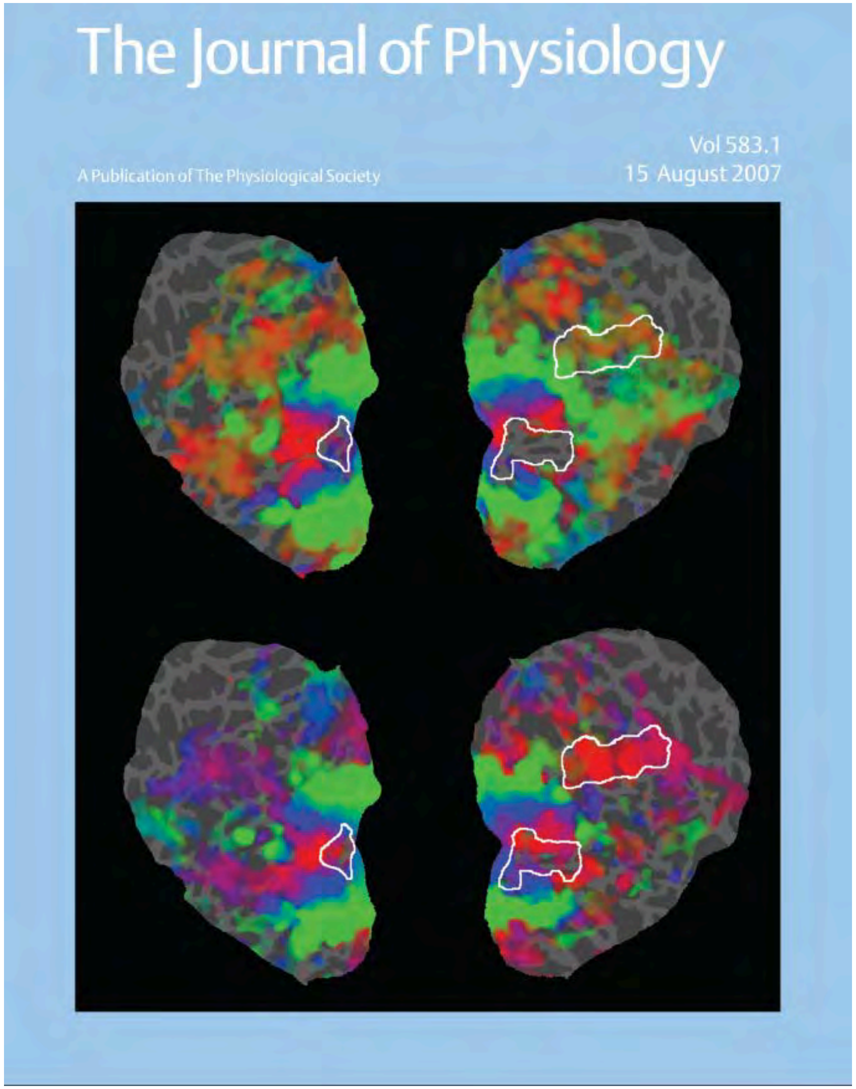
Visualizing Interocular Suppression

Eccentricity Map from Amblyopic Eye

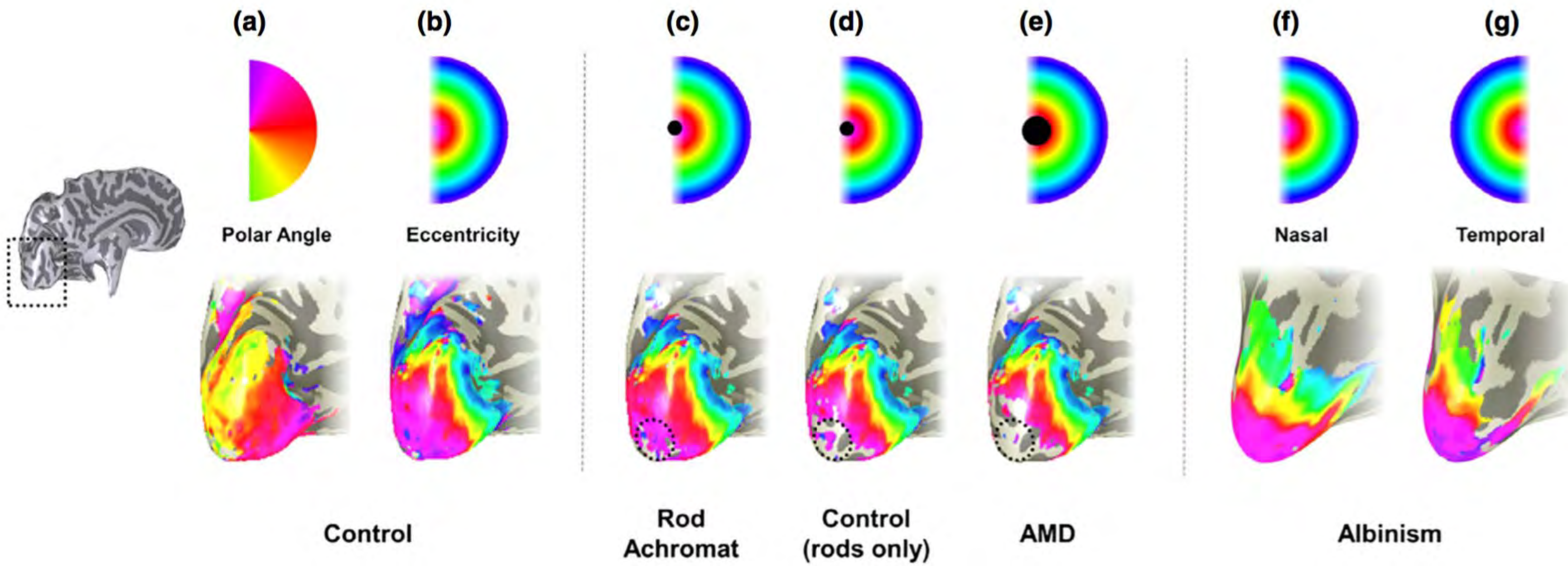
Early onset strabismic subject

good eye open
(interocular suppression)

good eye closed
(more foveal activity)

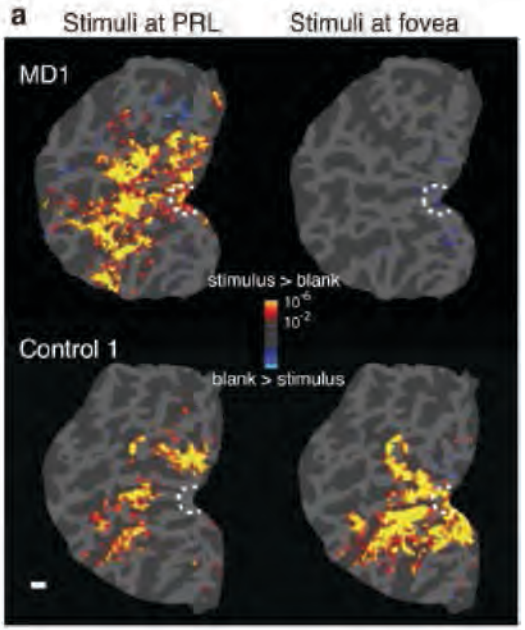


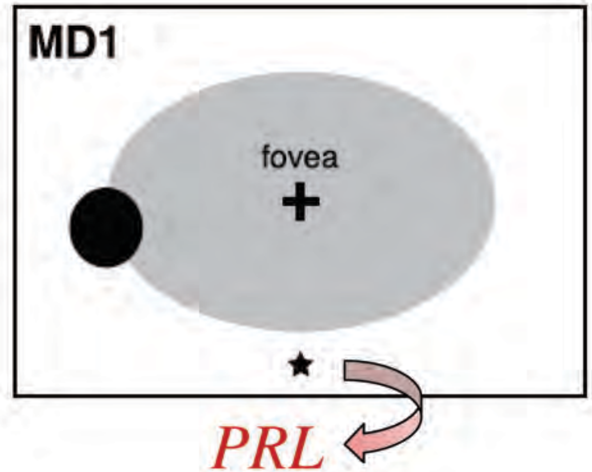
Review of fMRI in Ophthalmology



Brown et al., (2016)
Ophthalmic & Physiological Optics

Cortical Reorganization in AMD



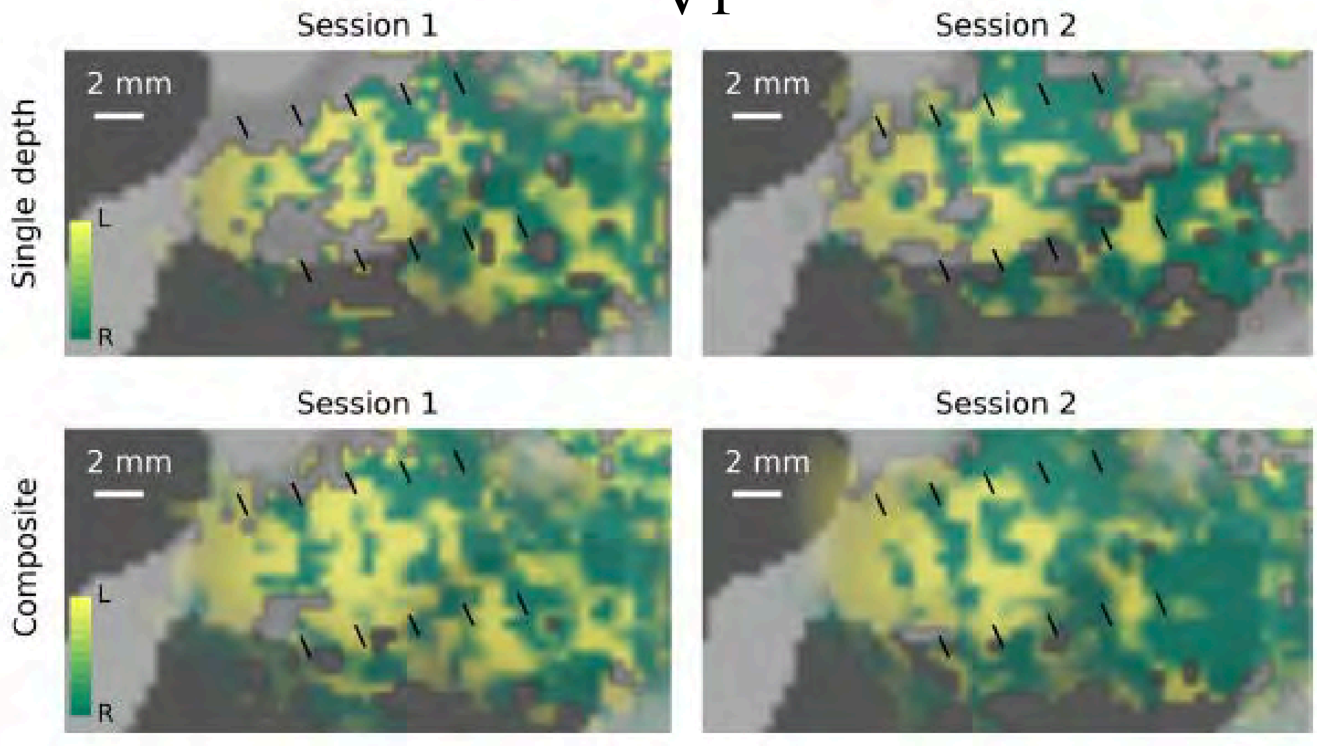


In at least a few case studies, preferred retina location (PRL) (star) seems to drive greater cortical territory than normal.

Baker CI, Peli E, Knouf N, Kanwisher NG. Reorganization of visual processing in macular degeneration. J Neurosci. 2005; 25(3):614-8.

Cortical Reorganization in Achiasma

V1



Olman et al., (2017) Hemifield columns co-opt ocular dominance column structure in human Achiasma. Neuroimage