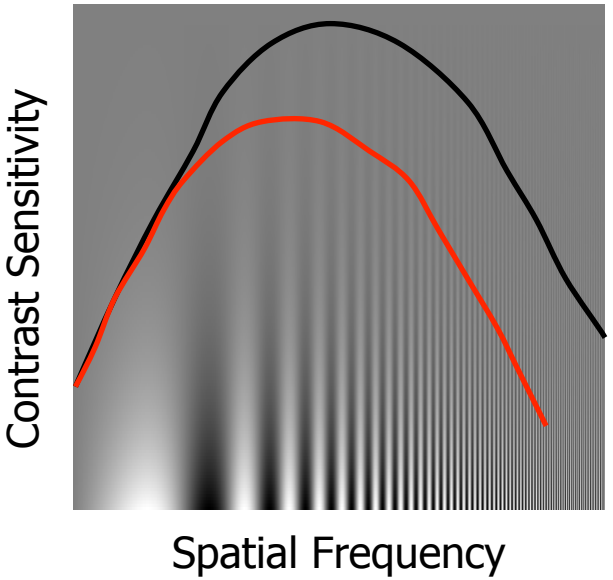
Human Amblyopia

- “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

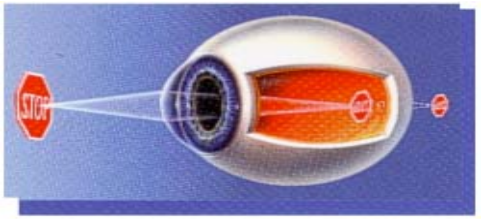
Visual Deficits in Amblyopia

- 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

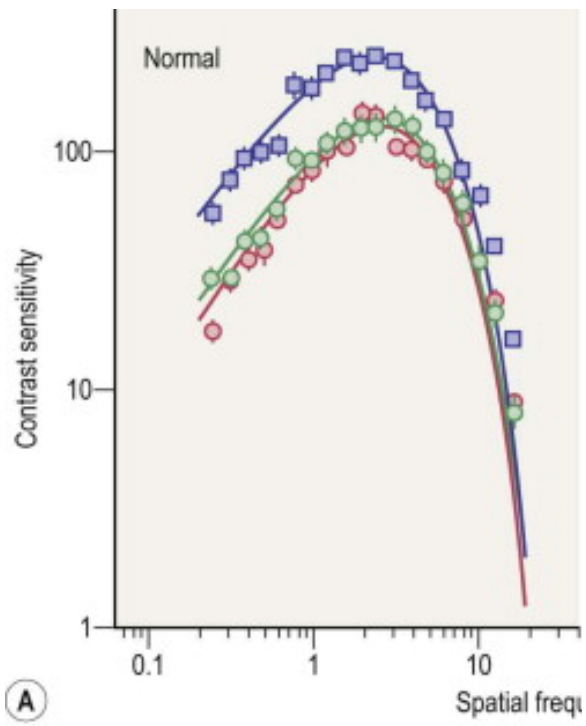
2. Abnormal binocular vision
   - Binocularity is often changed or lost in amblyopia

Models of Amblyopia

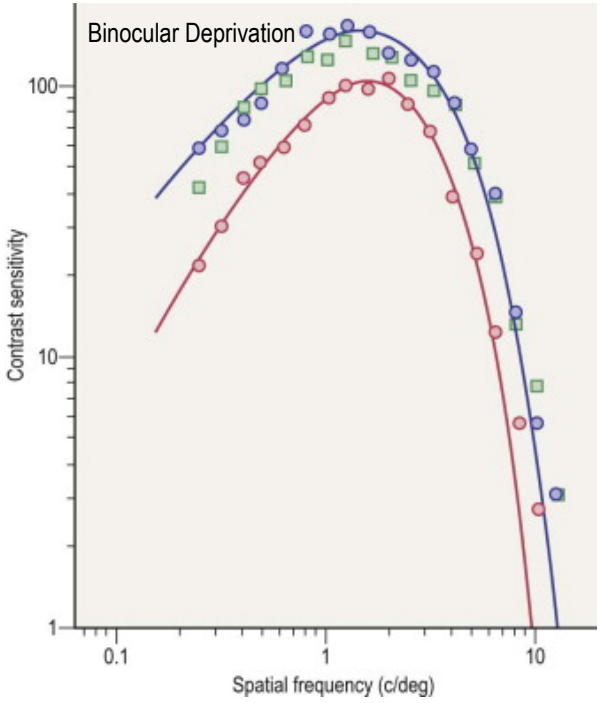
- Competition hypothesis originated with experiments in kittens in the 1960s by Hubel and Wiesel
- Monocular deprivation of retinal input during 'critical' developmental periods leads to striking abnormalities in the physiology of visual cortical neurons
- Binocular deprivation actually leads to *less* 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

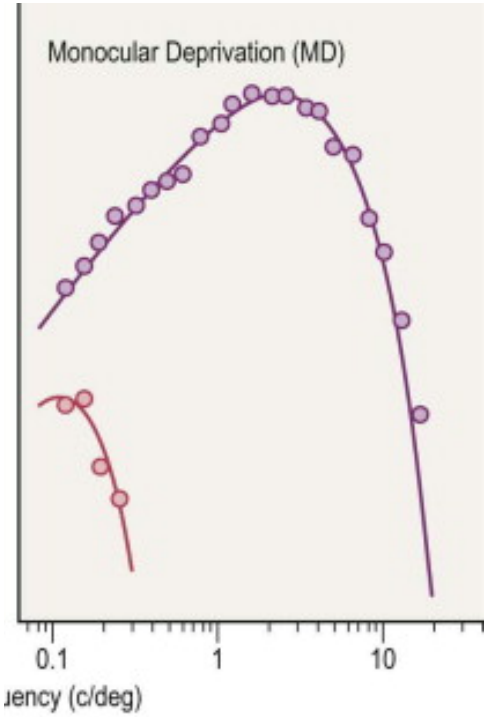
Primate



binocular
left
right



binocular
left
right

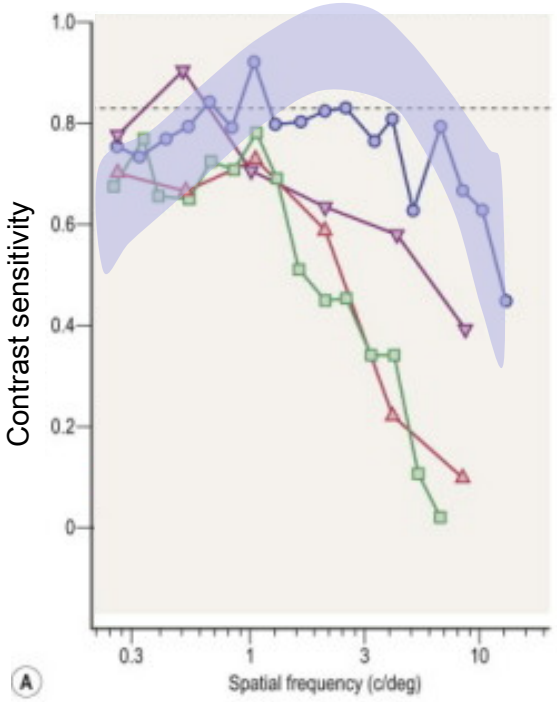


deprived
fellow

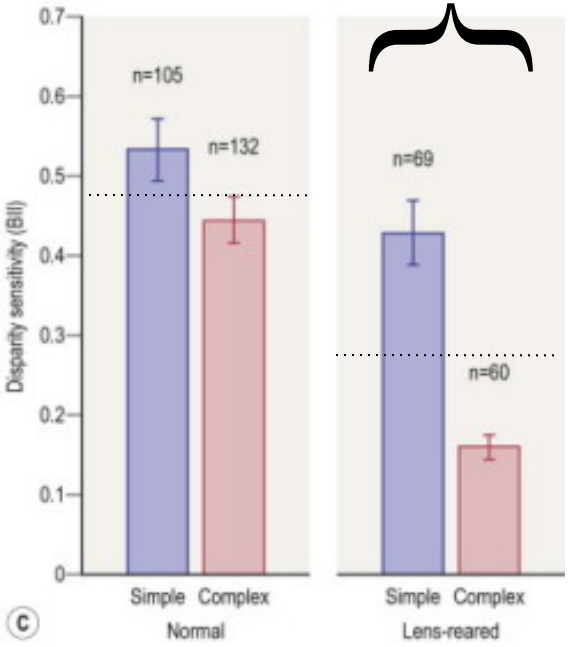
Perceptual Effects of Defocus

Primate

contrast sensitivity loss at high sf

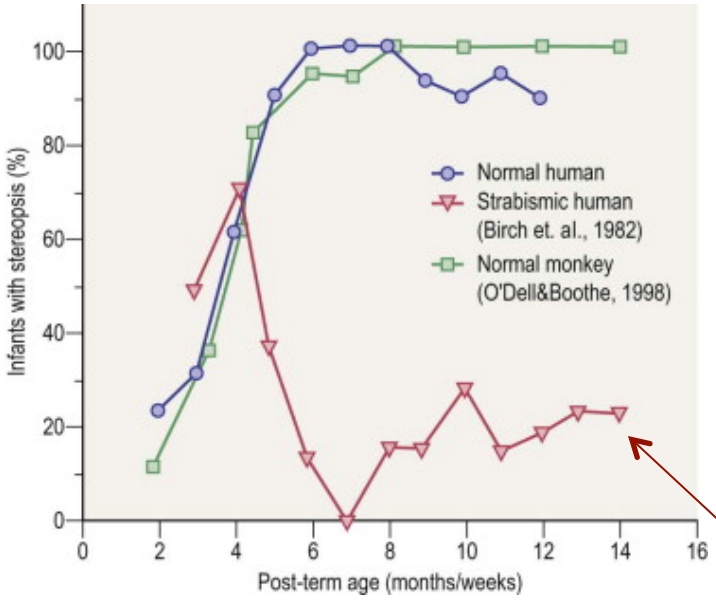


binocularity is diminished in V1



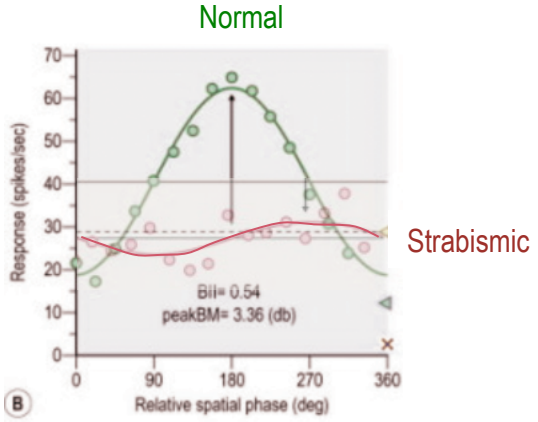
Perceptual Effects of Strabismus

Primate



1 human month = 1 monkey week

Severe loss of disparity tuning in V1



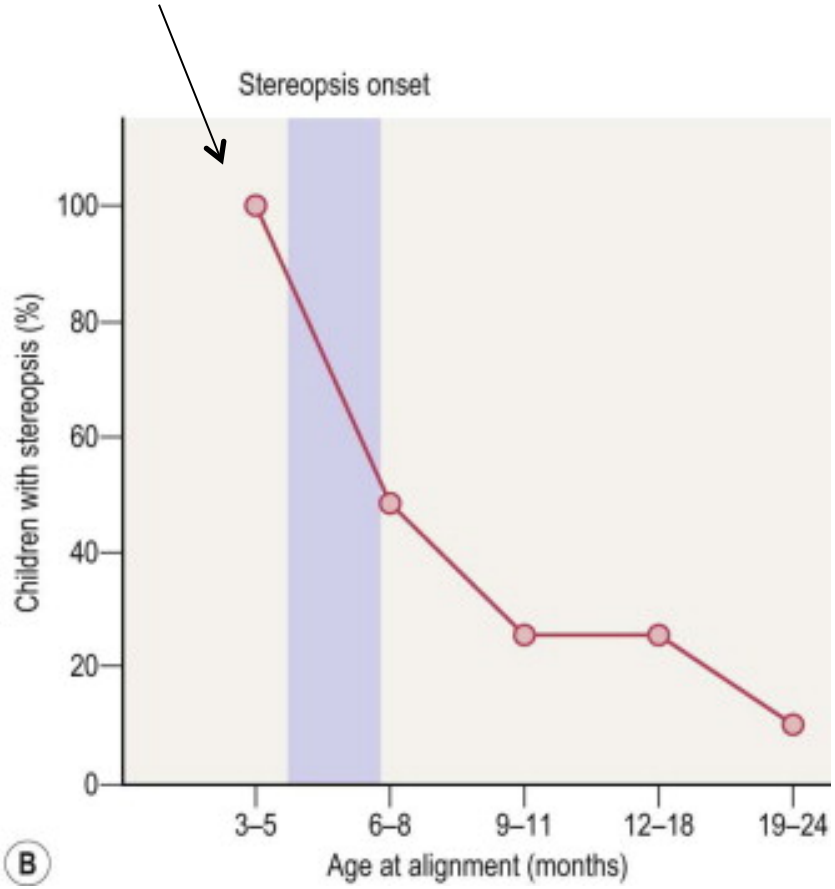
Stereopsis is devastated

Effects of Onset Age and Duration In Strabismus

Children:

Stereopsis onset is 4-6 months

Treatment before 4 months is best !



Primates:

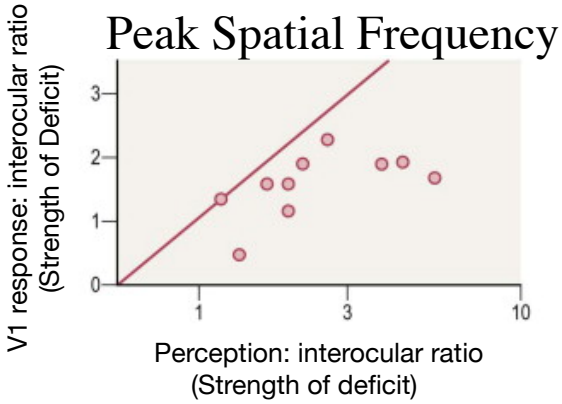
Stereopsis onset is 4-6 weeks

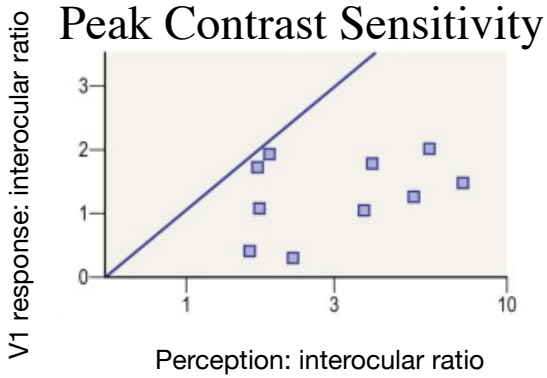
- At 4 weeks, only 3 days of induced deviation increases amount of binocular suppression in V1 measurably.

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

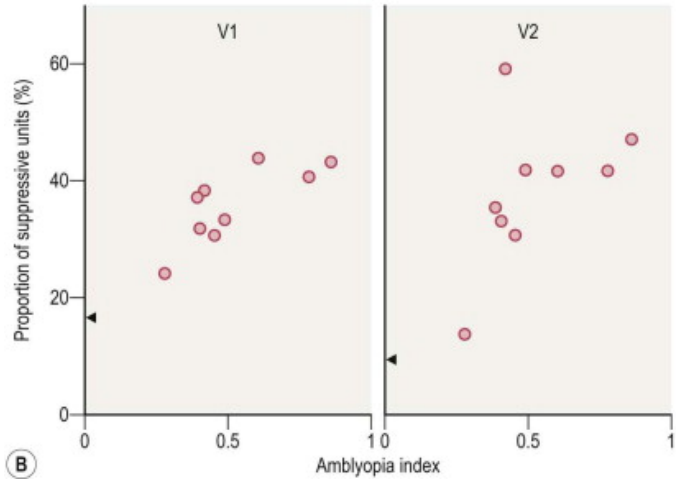
Physiology Related to Perception in Strabismic Amblyopic Monekys

Primates





Degree of amblyopia correlates with the amount of binocular suppression



* Is suppression an etiological factor?

- Note: perceptual deficits are greater than seen in V1

* Strong implication of extrastriate!

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).

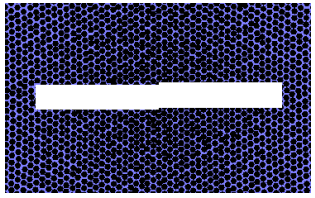
Experiments

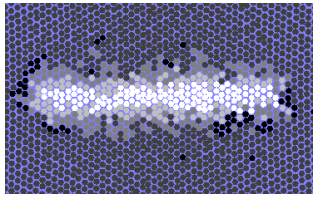
- *Monocular tests*
  - Snellen acuity
  - Grating acuity
  - Vernier acuity
  - Contrast sensitivity
- *Binocular tests*
  - Randot stereotest
  - Binocular motion integration

Results

- *Monocular Tests:* 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.

- *Binocular Tests:* 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

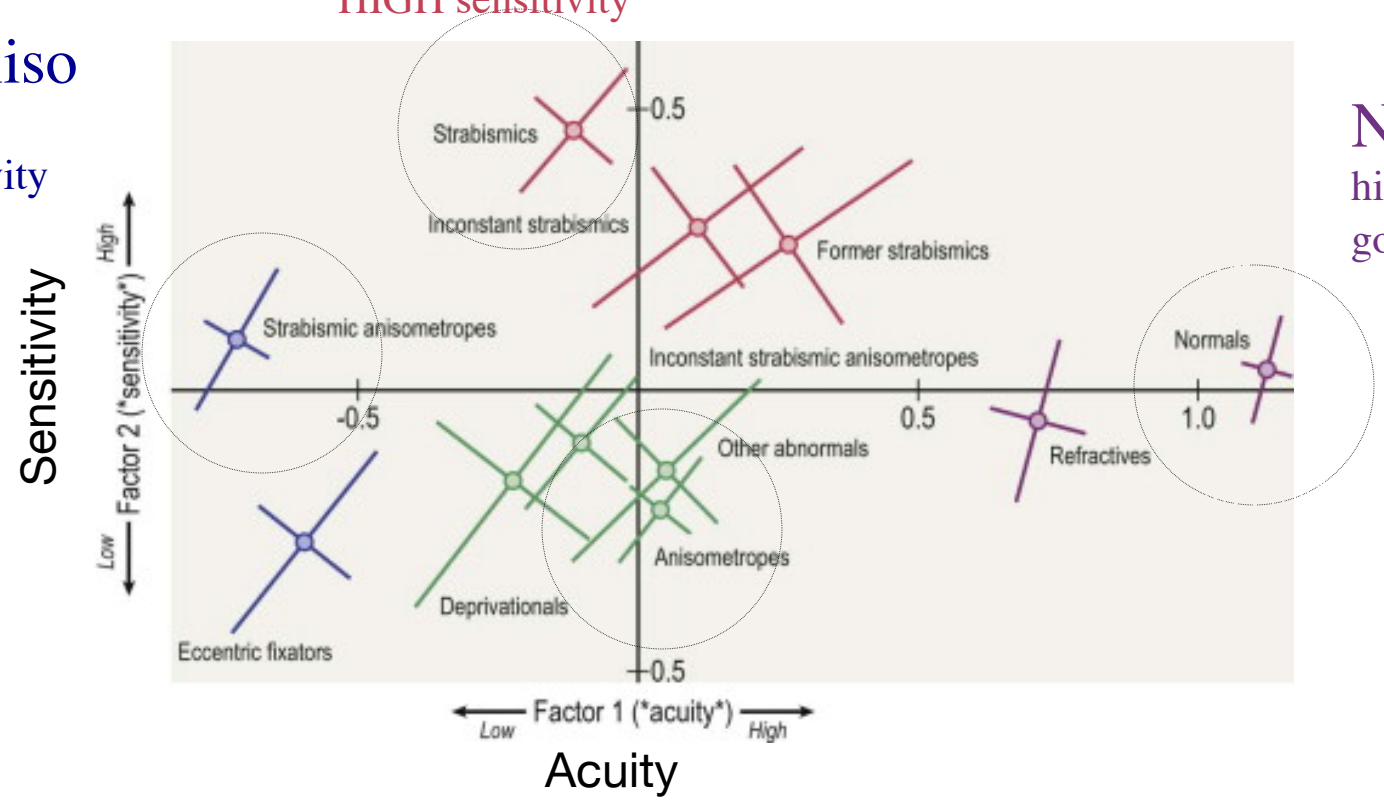
- Vernier performance is better predicted by residual binocularity than by clinical subtype.

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

Amblyopia

Strabismic
low acuity
HIGH sensitivity

Strab Aniso
lower acuity
good sensitivity



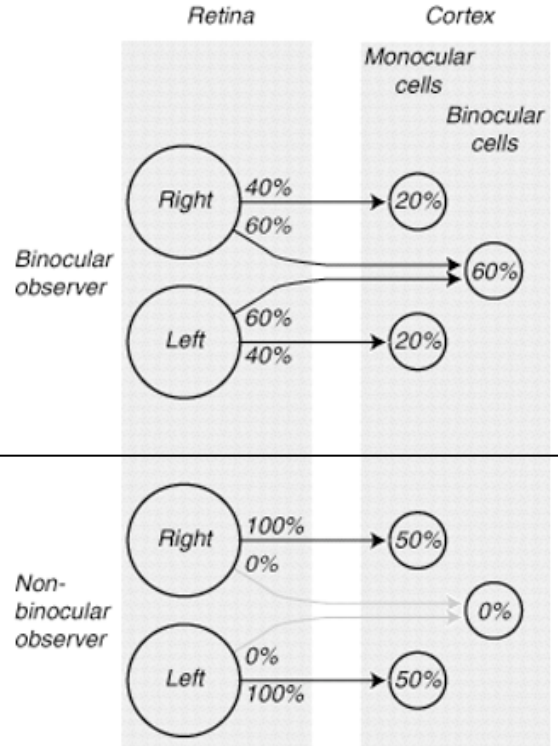
Normal
high acuity
good sensitivity

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'

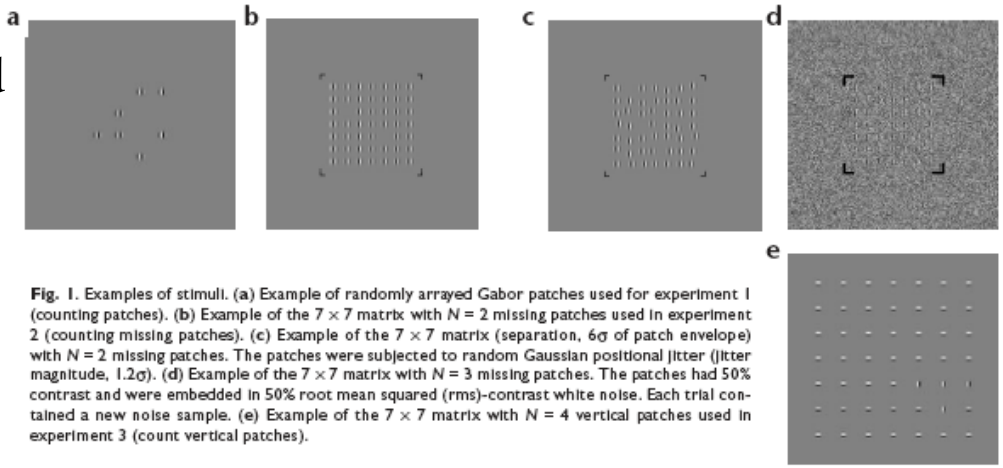
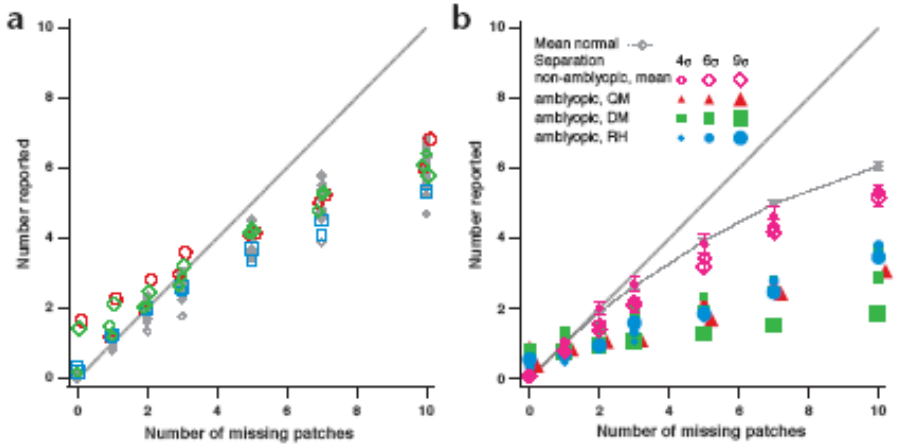


Fig. 1. Examples of stimuli. (a) Example of randomly arrayed Gabor patches used for experiment 1 (counting patches). (b) Example of the 7 × 7 matrix with $N = 2$ missing patches used in experiment 2 (counting missing patches). (c) Example of the 7 × 7 matrix (separation, 6σ of patch envelope) with $N = 2$ 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



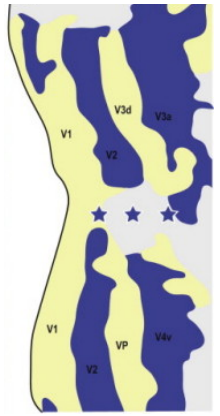
Suggests an attentional deficit, akin to neglect.

Sharma, Levi & Klein, 2000

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

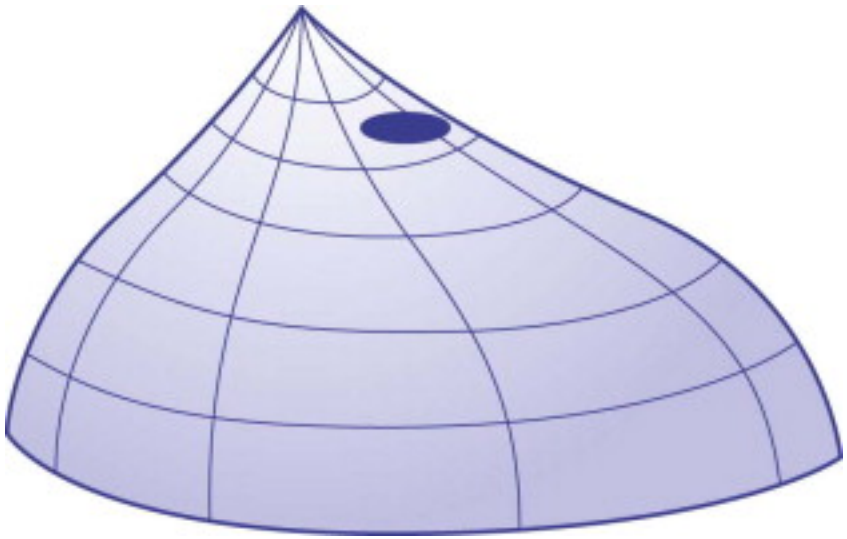
- Old technique, but continued improvements

- automation
- standardization
- immediate statistical evaluation
- greater efficiency

Visual Fields

Photopic adaptation, in normal eye, and visual system

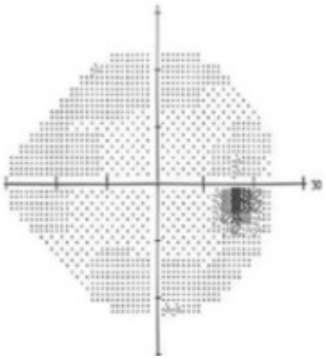
Hill of Vision



Visual Fields

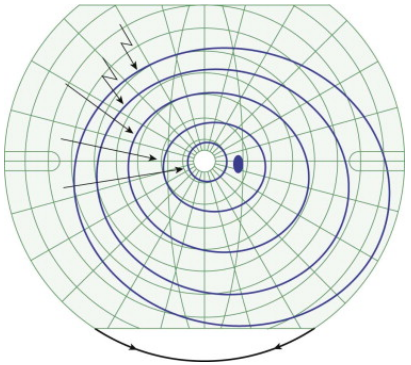
- Static Visual Fields

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



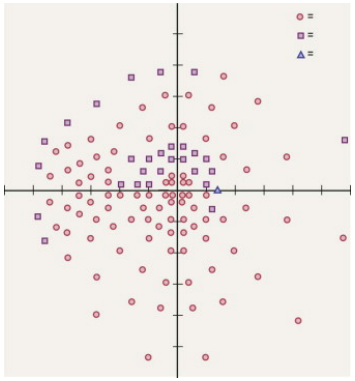
- Kinetic Visual Fields

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

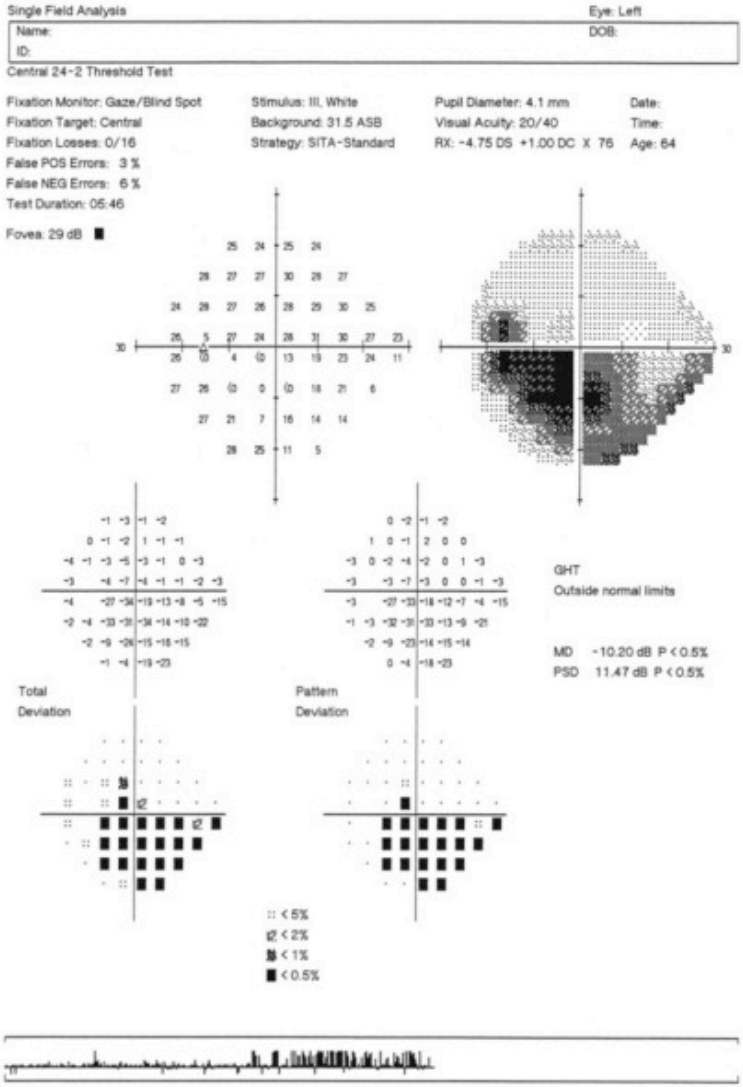


- Suprathreshold static perimetry

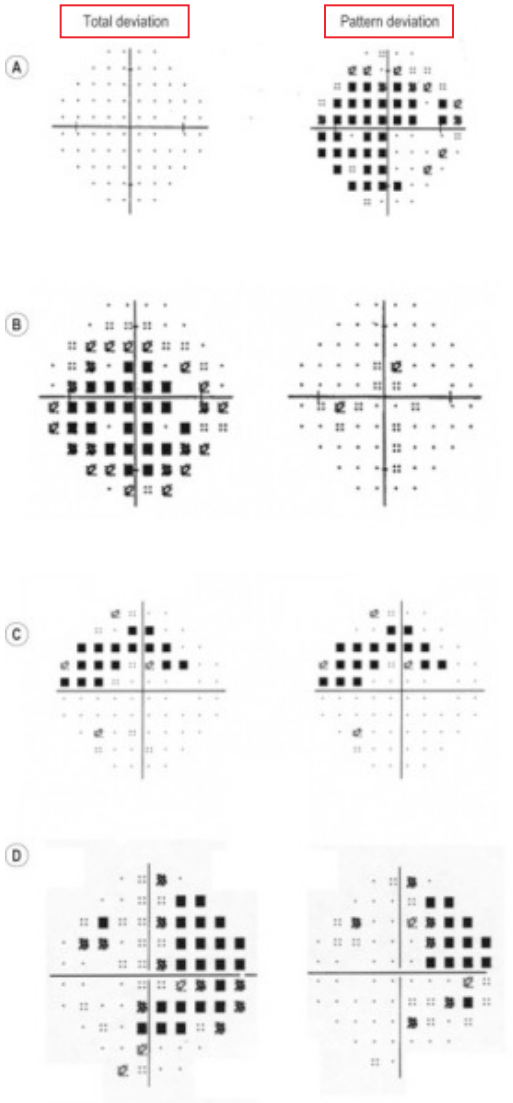
- rapid to detect field defects, over entire field
- limited quantification, lower sensitivity and specificity,
- less validation



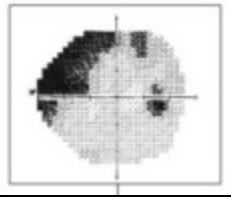
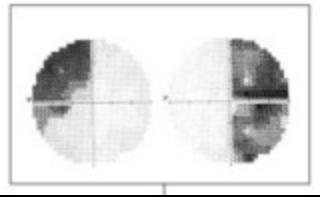
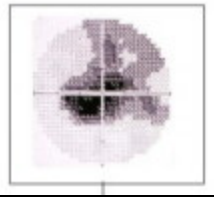
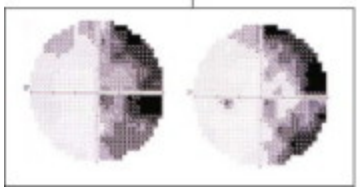
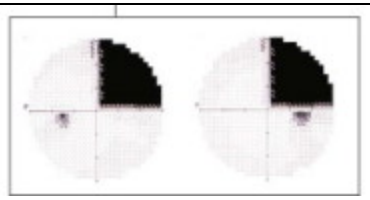
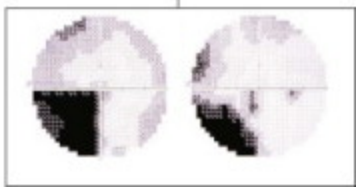
Visual Fields - Standard Automated Perimetry (SAP)

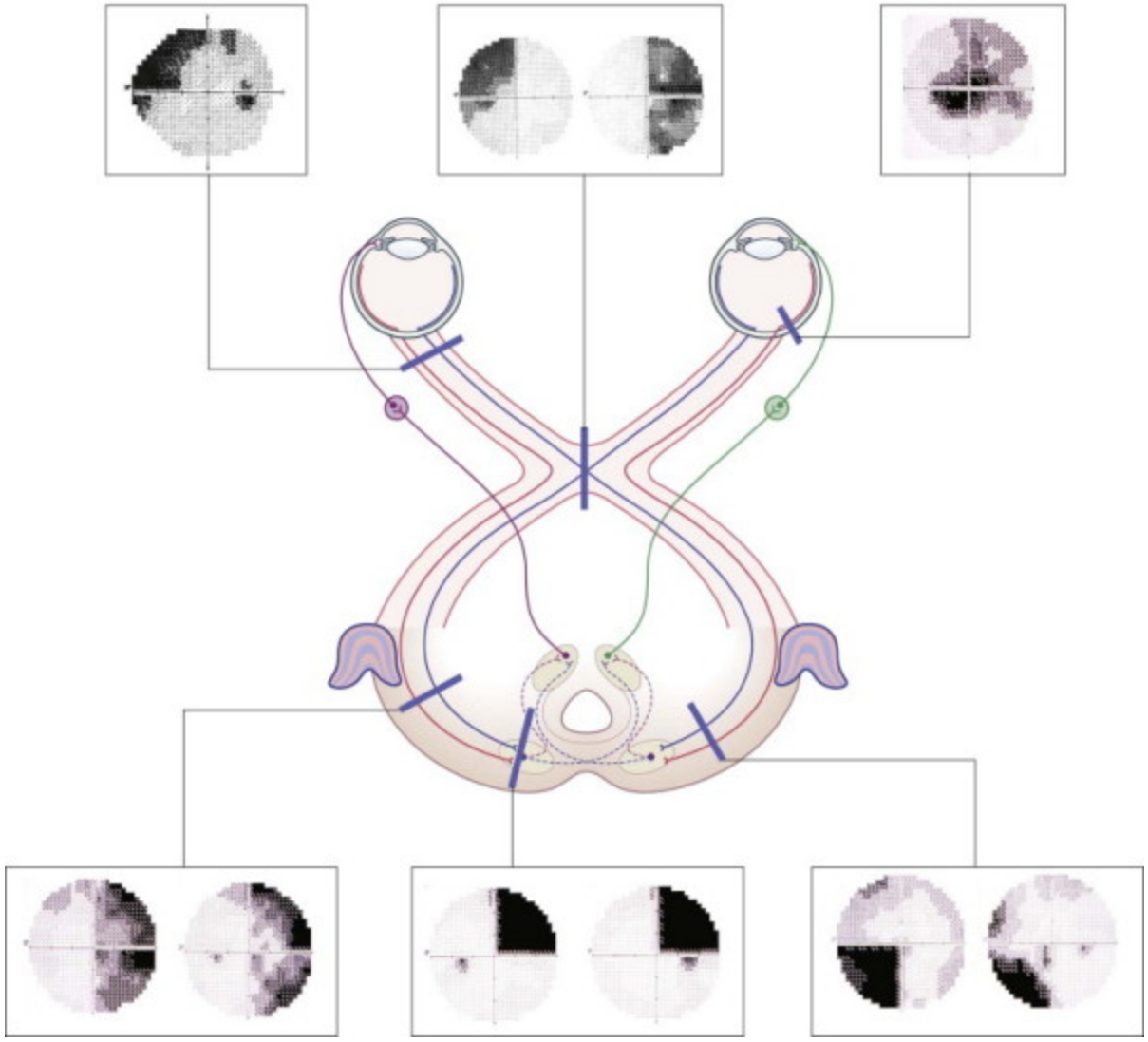


Visual Fields

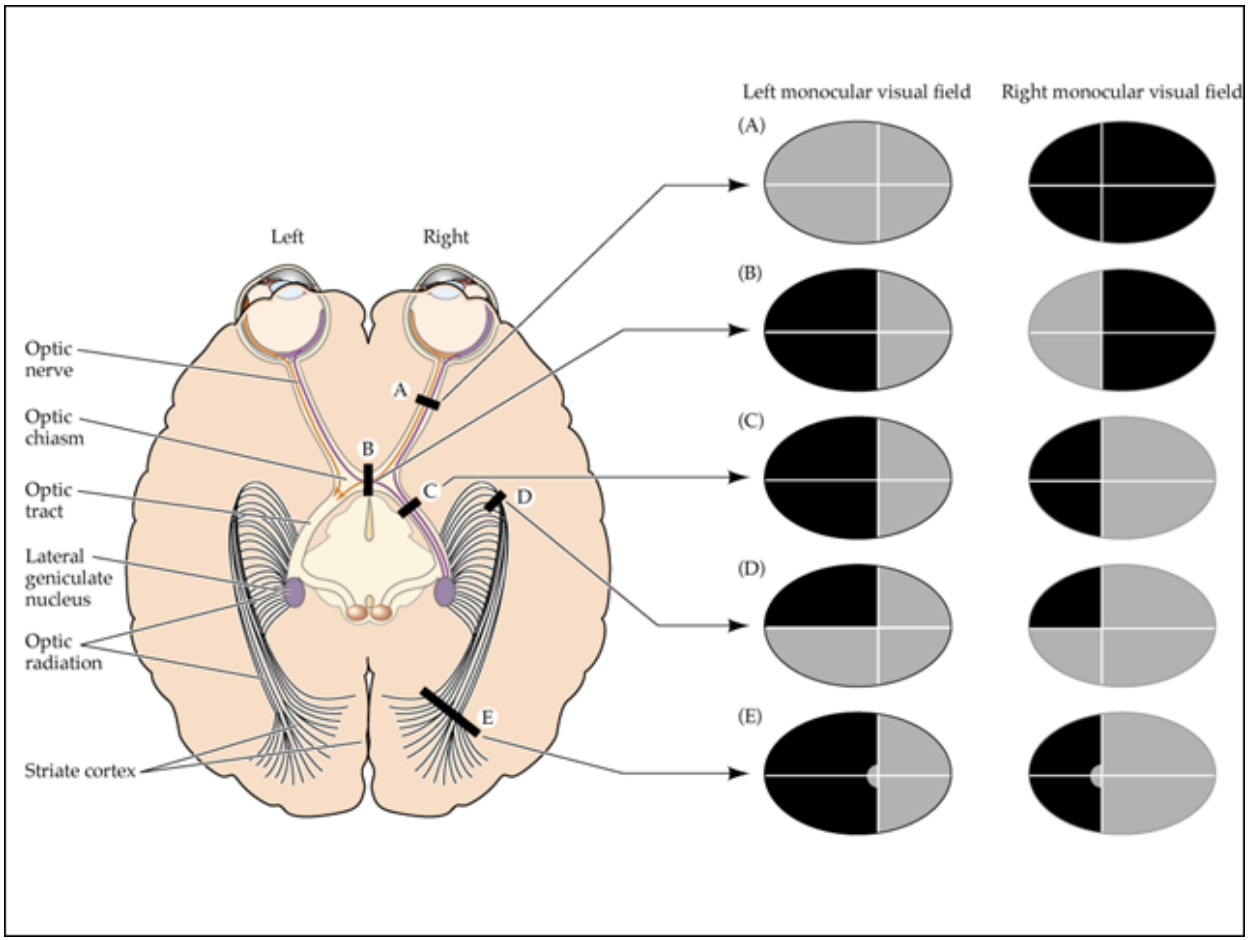


- Normal vision, but 'trigger happy'
  - abnormally high sensitivity & false positives, hitting the button too often
- Generalized, widespread field loss
- Localized field loss
- Mixture of localized and widespread loss



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**
  Felleman & Van Essen, 1991

- **Human Visual Cortex**
  Clarke & Miklossy, 1990; Horton & Hoyt, 1991

- **fMRI**
  Kwong et al., 1992; Ogawa et al., 1992

- **Cortical Surface Representation**
  Dale & Sereno, 1993

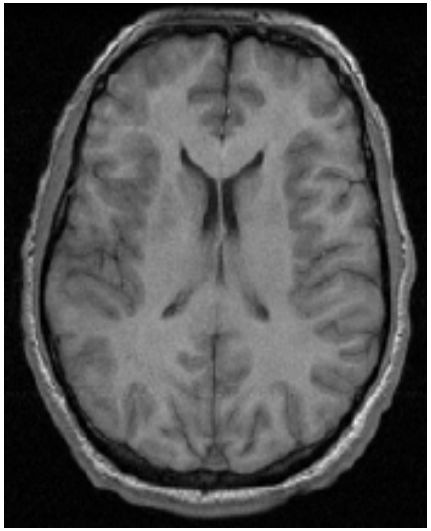
State of Affairs in 1990's

- **Visual Cortex Activation with PET**
  Fox et al., 1986

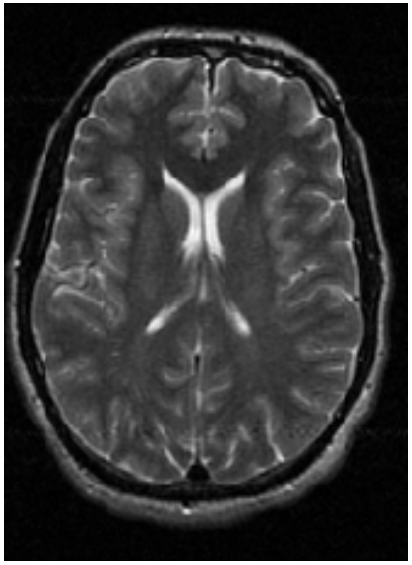
- **Idea of Phase-Encoded Stimuli & fMRI**
  Engel et al., 1994

- **Mapping Human Visual Cortex with fMRI**
  Sereno et al., 1995

Brain Images Showing T1 and T2 Contrast



T1 weighted



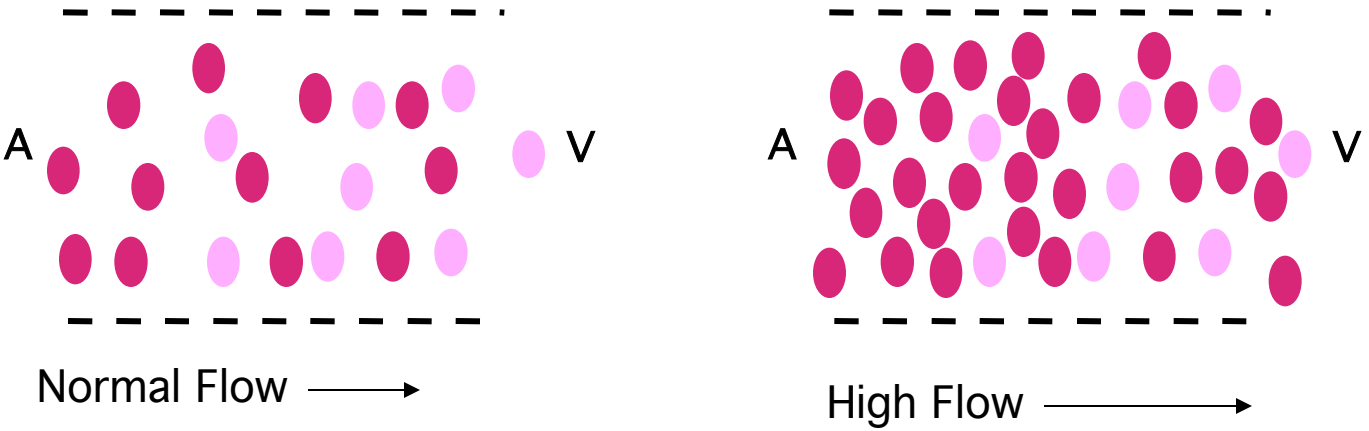
T2 weighted

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

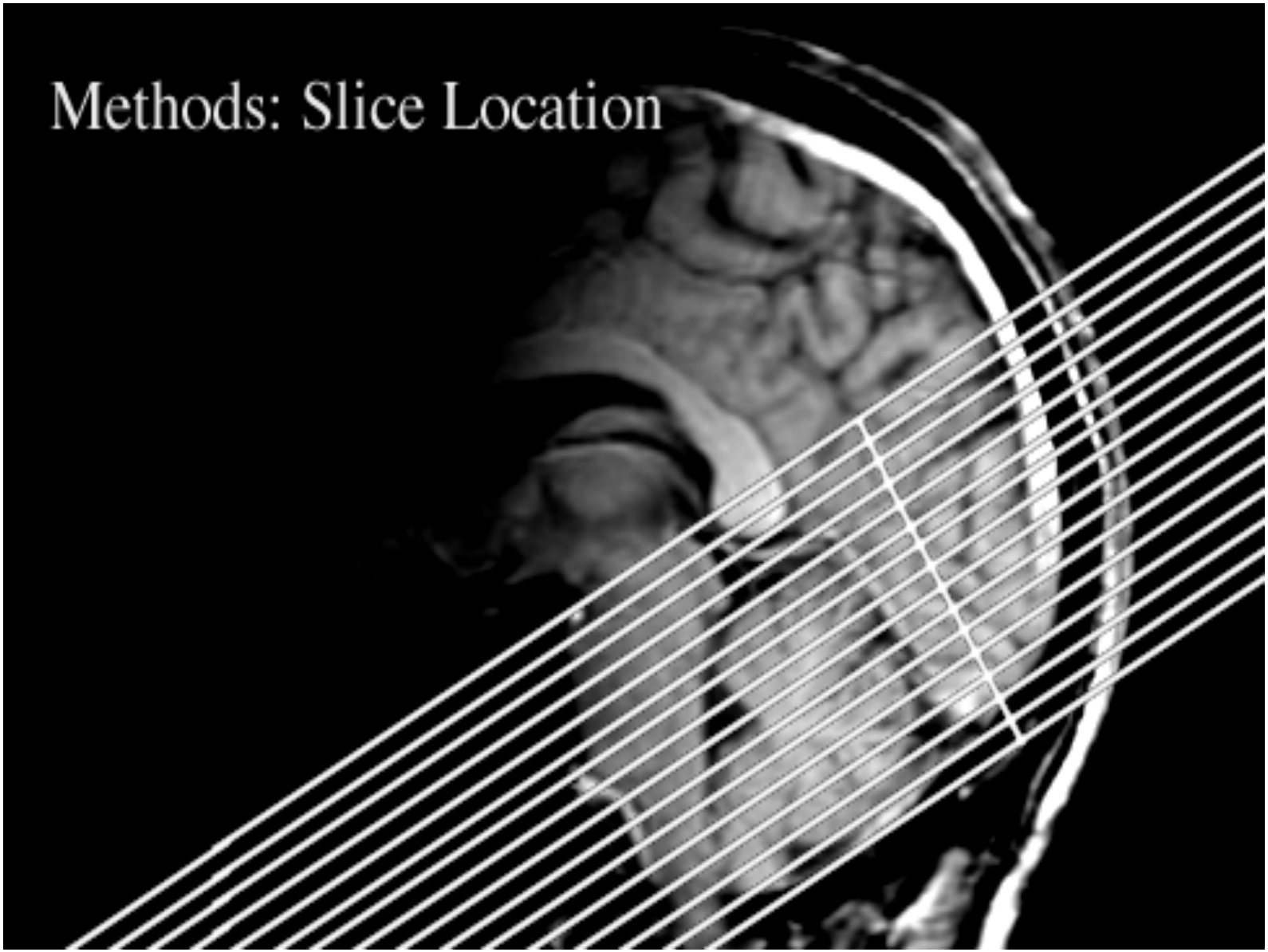
"Blood Oxygen Level Dependent"



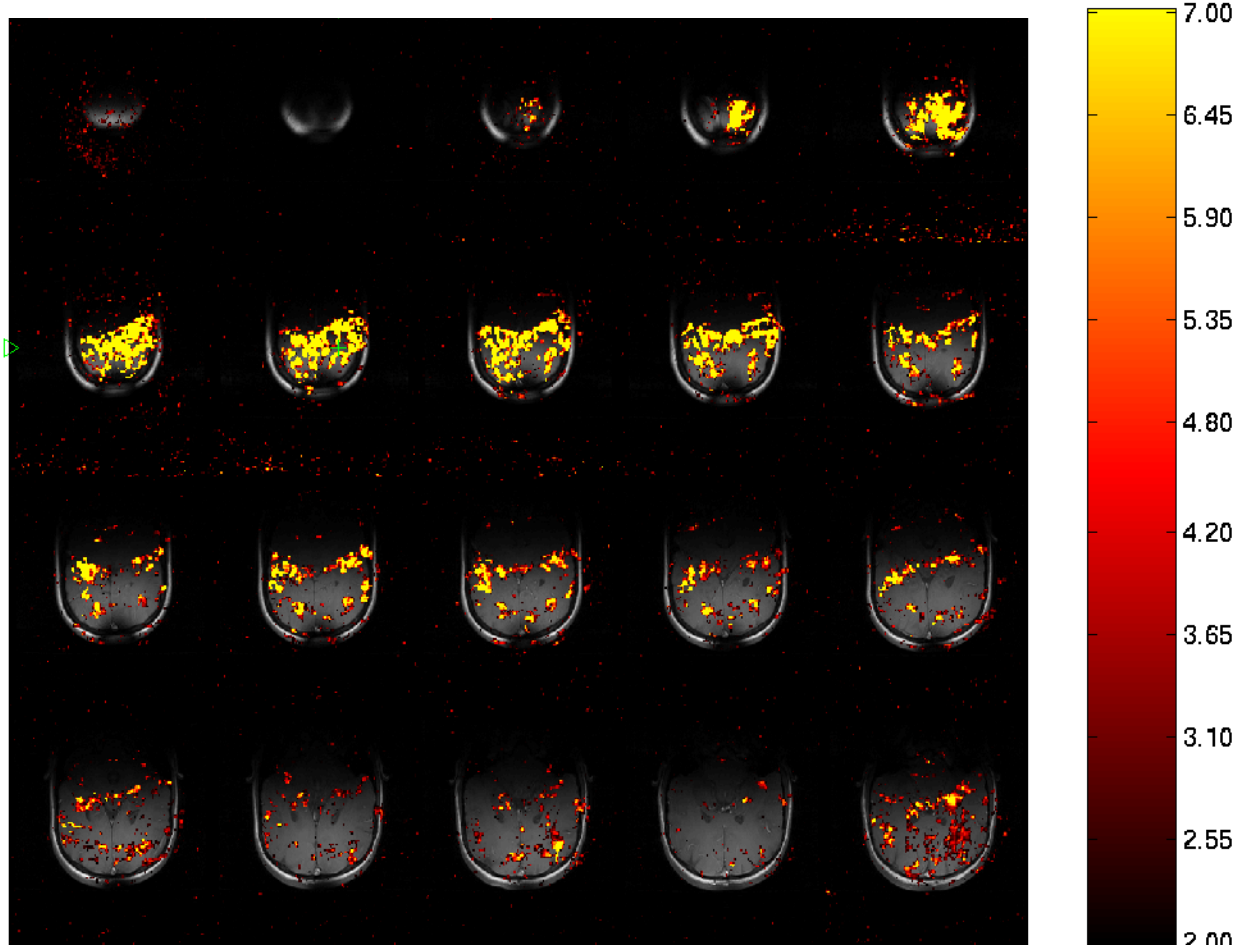
oxyhemoglobin

deoxyhemoglobin

Methods: Slice Location

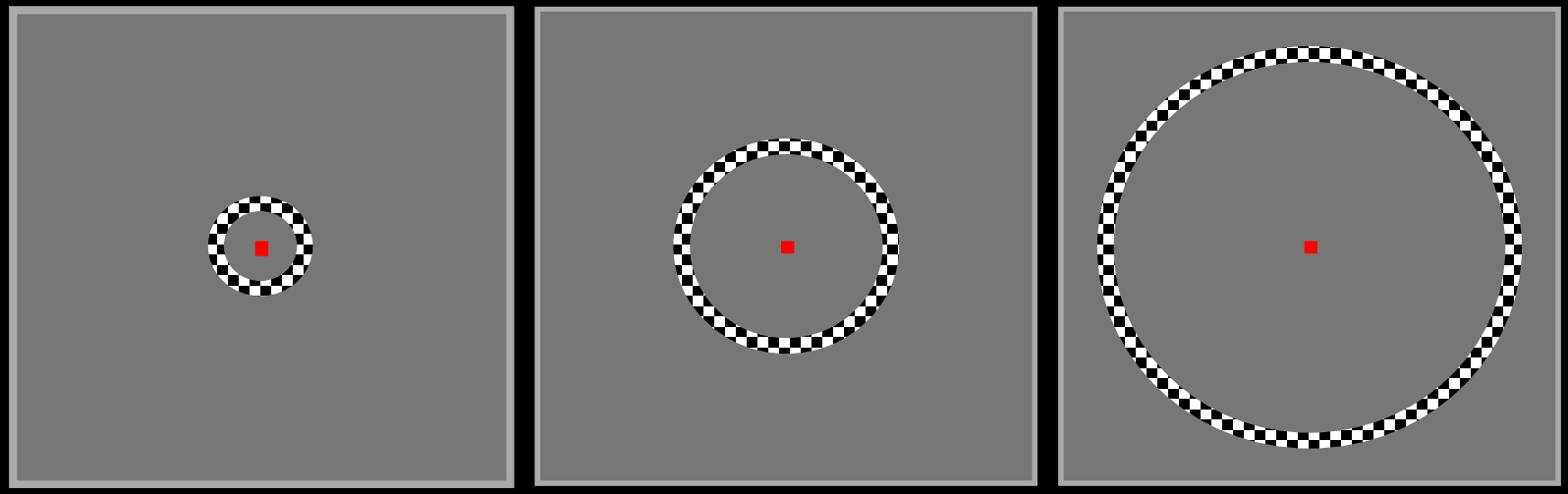


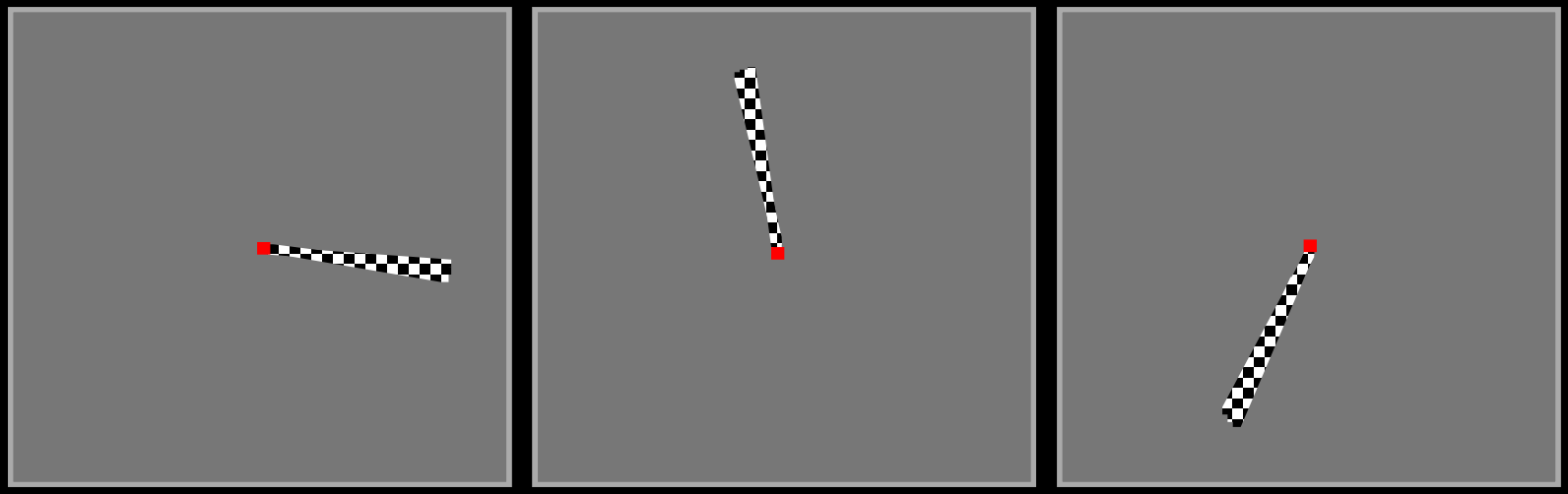
Light Activation Viewed on Brain Slices



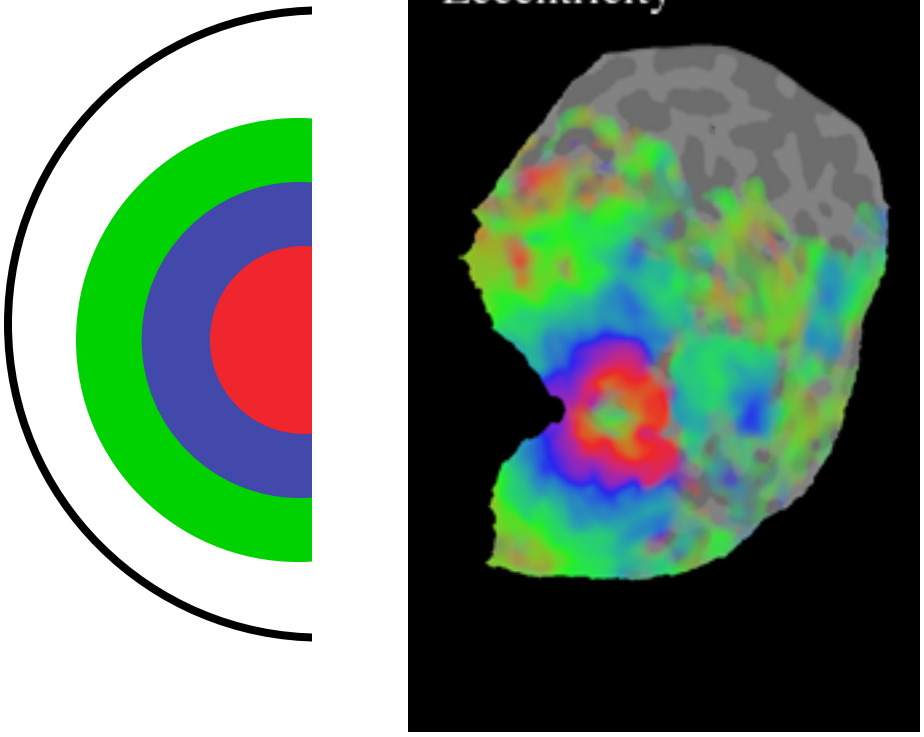
Mapping Visual Cortex

Eccentricity and Polar Angle Stimuli





Maps of Cardinal Axes on Flattened Cortical Surface



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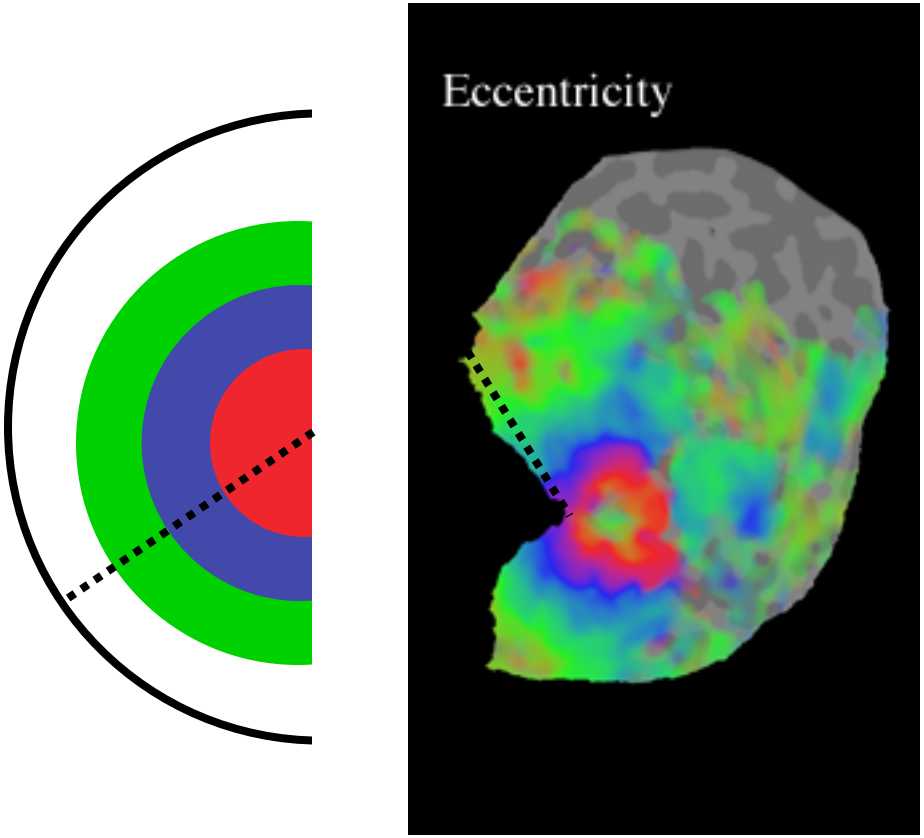

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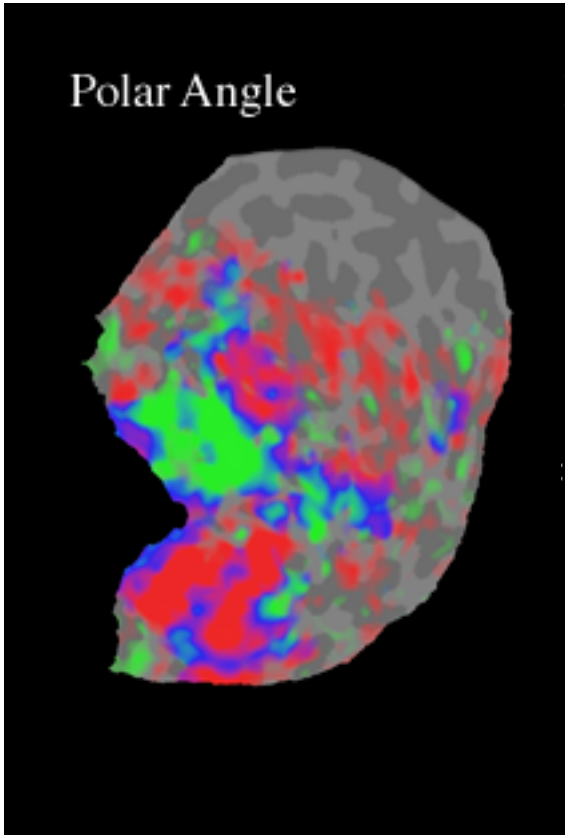

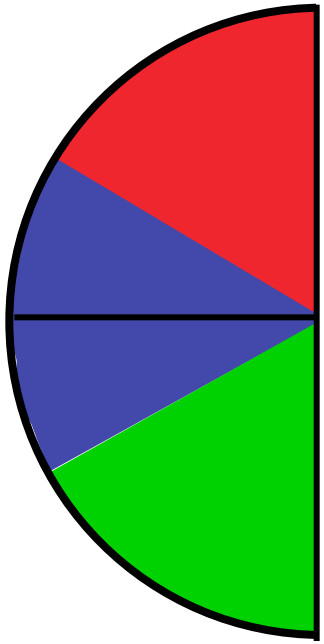

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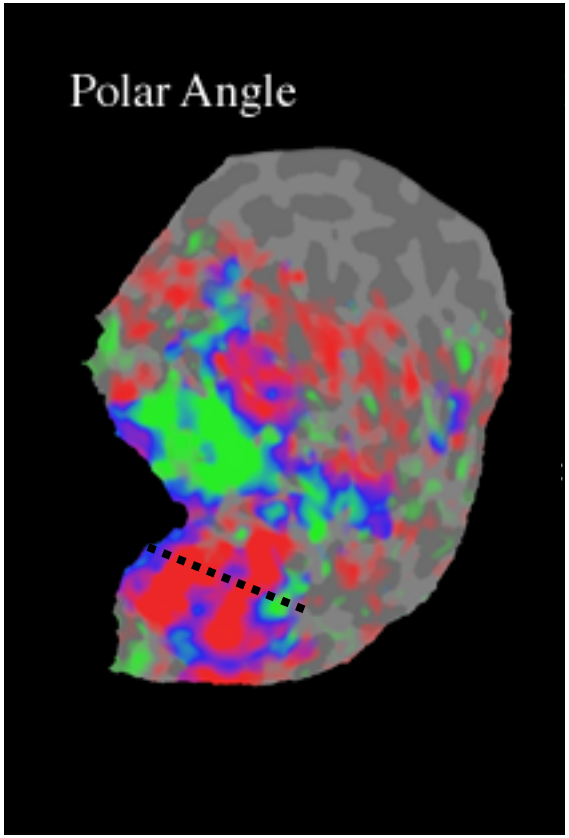
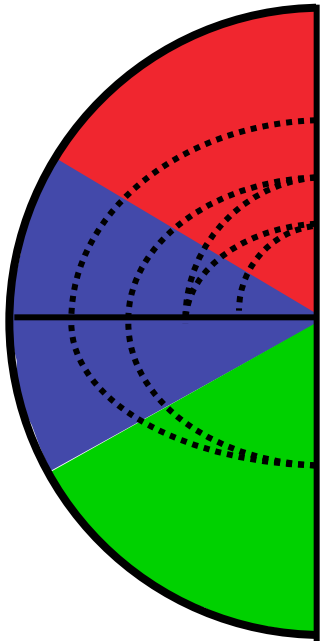
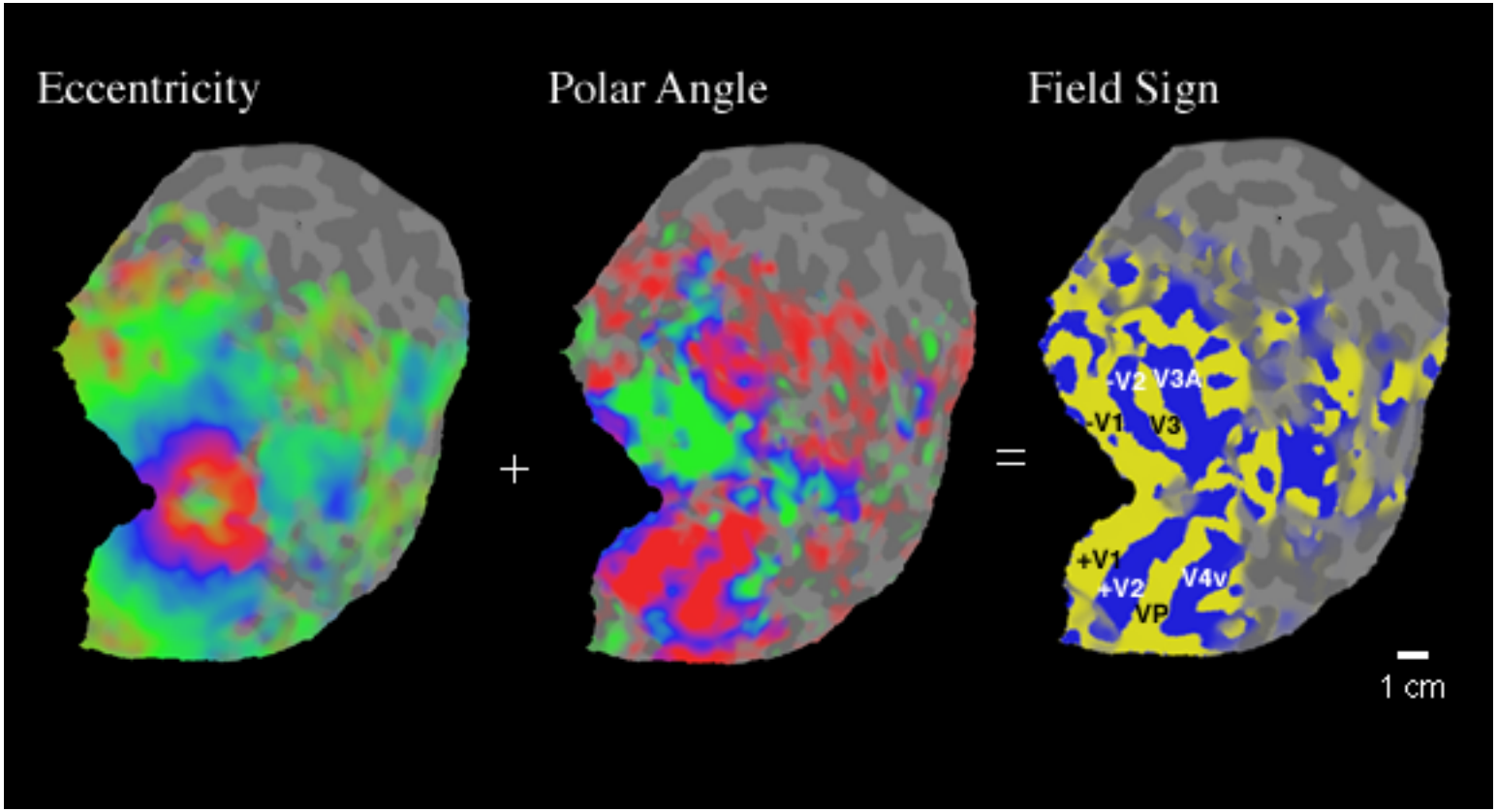
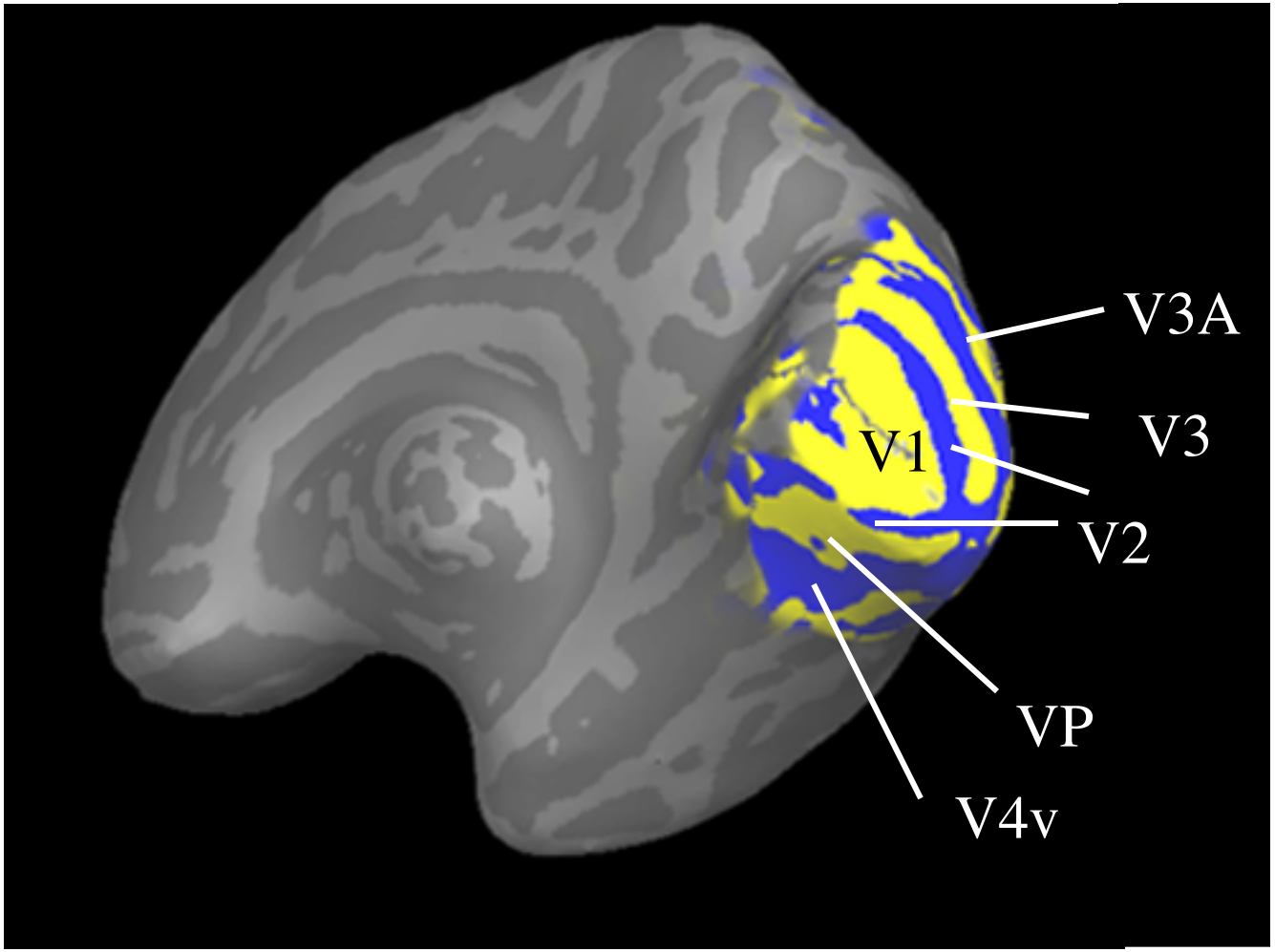




‘Field-Sign’ is Calculated from Cardinal Axes



Inflated View of Areas



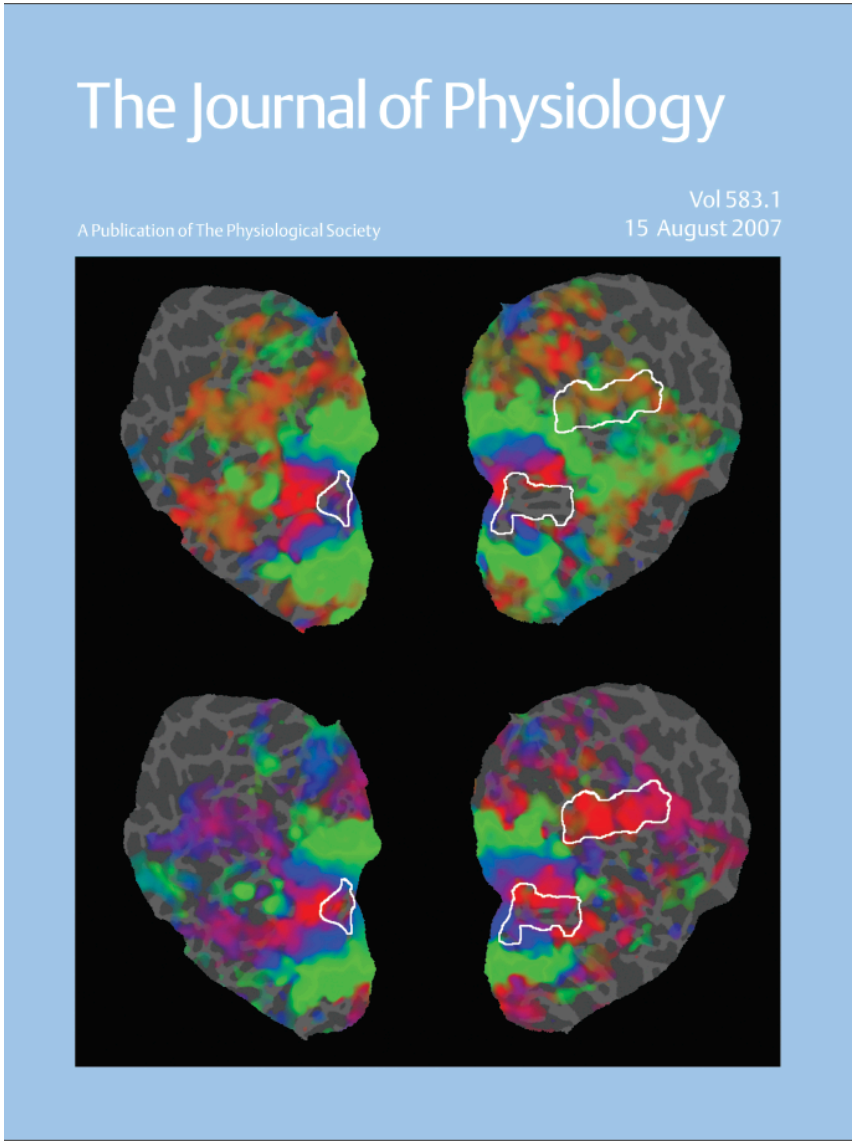
fMRI Demos

Amblyopic Suppression
Ipsilateral (bilateral) representation
Cortical Magnification
Ocular Dominance
Contrast Sensitivity
Motion Sensitivity

Eccentricity Map from Amblyopic Eye

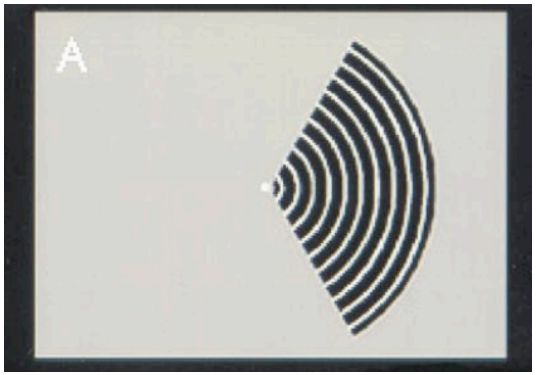
Good eye open
(interocular suppression)

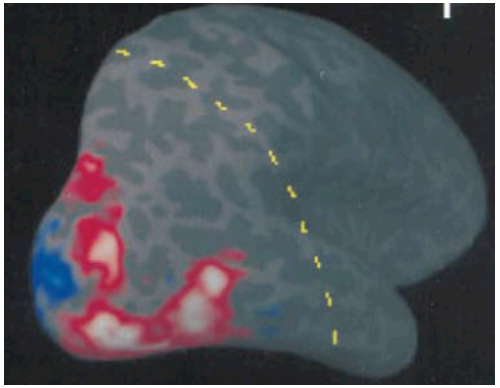
Good eye closed
(more foveal activity)

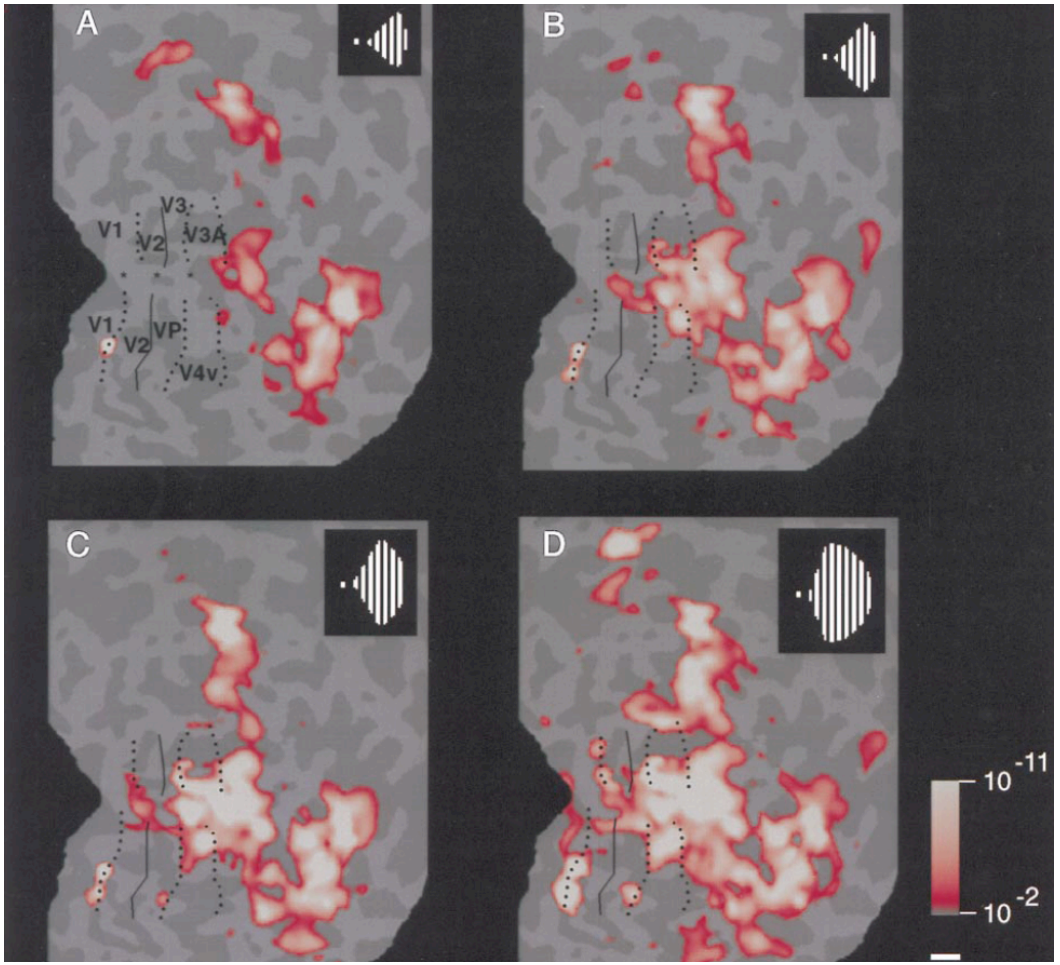


Human Ipsilateral Visual Field Representation

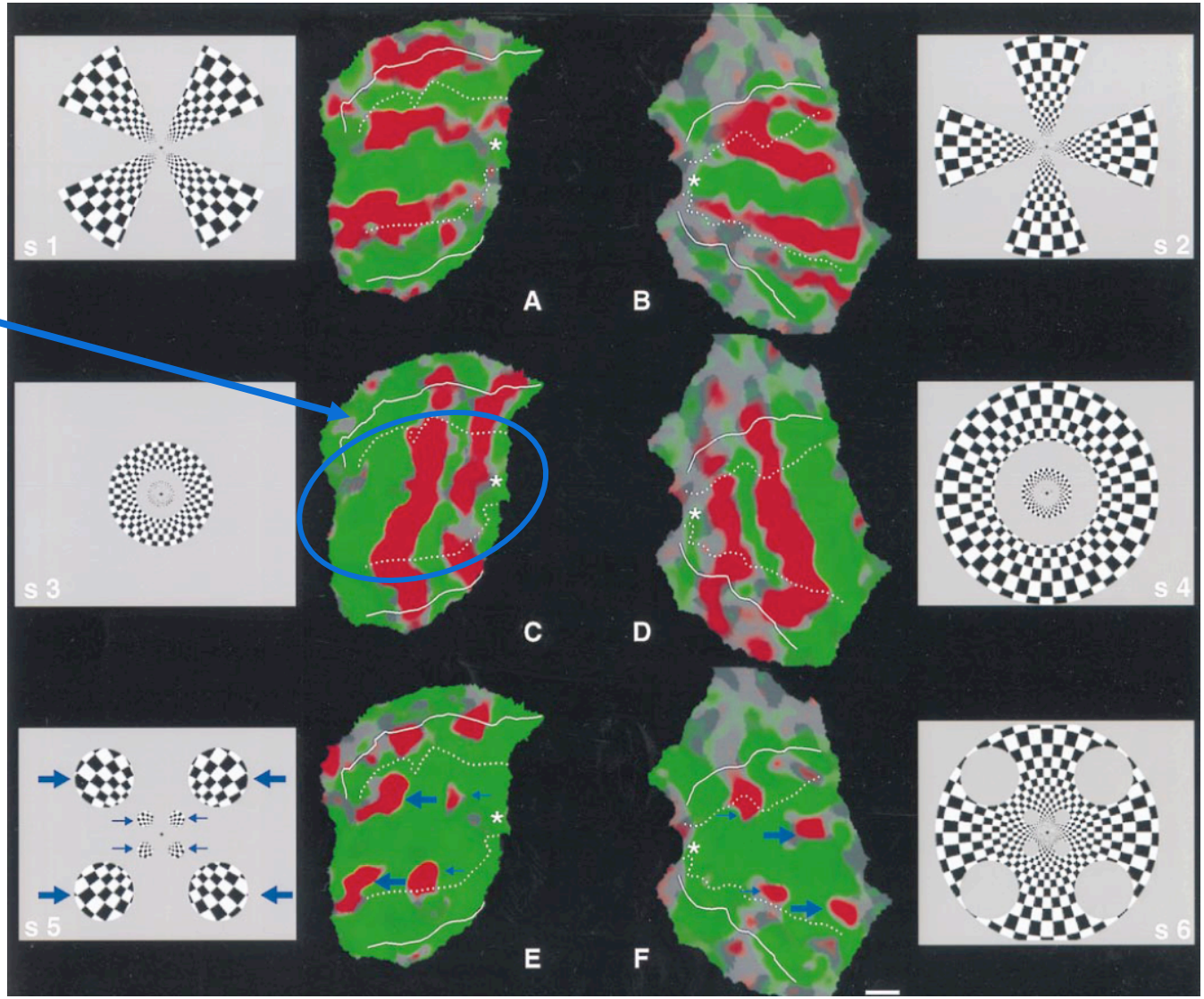
Moving stimulus confined to hemifield







Retinotopy & Cortical Magnification



Tootell et al., 1998b

Ocular Dominance (blind spot)

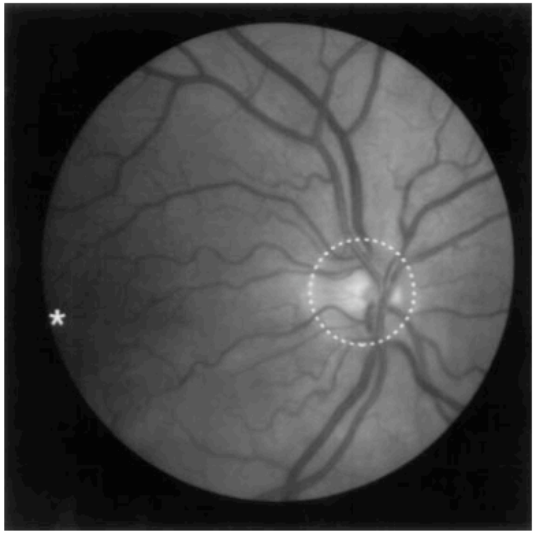
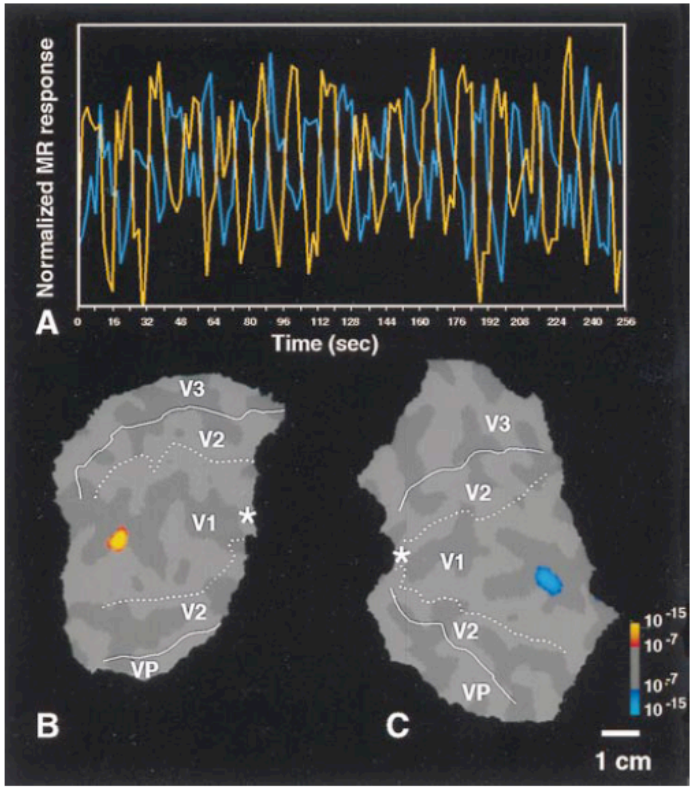


FIG. 3. Ophthalmological view of the normal retina, including the fovea (asterisk) and the optic nerve head ("blind spot," delineated by the dashed white line). In each retina, the blind spot is located nasally, and slightly superior to, the fovea. The blind spot comprises a significant region in the retina. However, its relative contribution to the cortical retinotopic map is minimized by its relatively peripheral location, convolved by the cortical magnification factor (see Fig. 4).

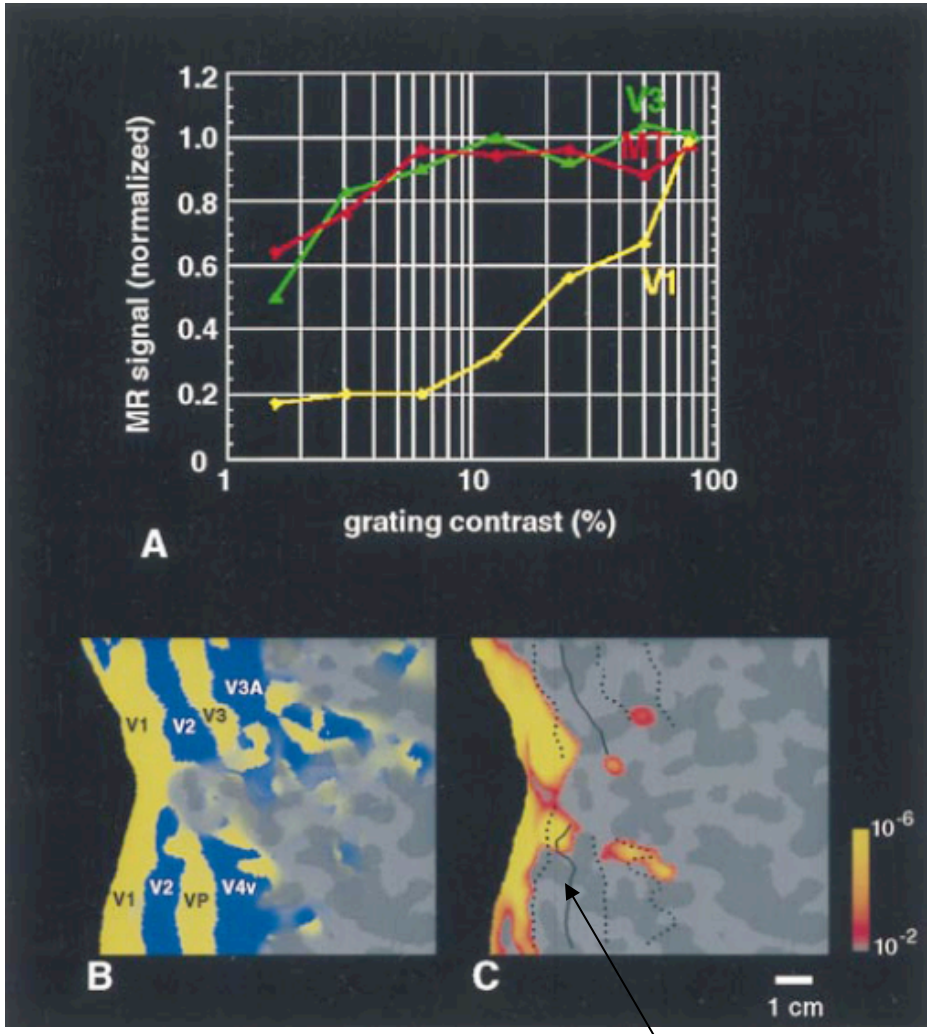


The representation of the blind spot was straightforward to demonstrate in V1, by treating it as an extra-large ocular dominance column. Subjects were instructed to fixate the center of a field of scaled, black-and-white flickering checks.

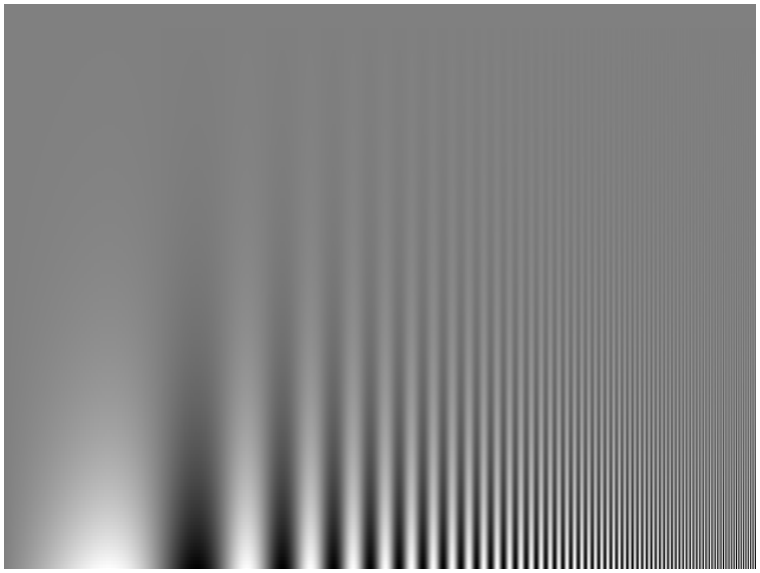
when subjects viewed the stimulus *monocularly*, using either left or right eye in alternating 16-sec epochs, the representation of the monocular "blind" spot was clearly revealed (see yellow–red vs. blue–cyan spots near the middle of the left vs. right hemispheres, respectively, in Fig. 4). The monocular crescent was beyond the limits of the stimulus, so it was not activated in these experiments.

Tootell et al., 1998a

Contrast Sensitivity



MT has high contrast sensitivity
V1 has lower contrast sensitivity



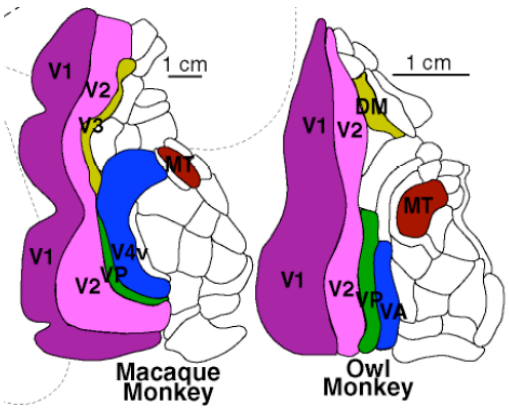
Pelli-Robson Chart

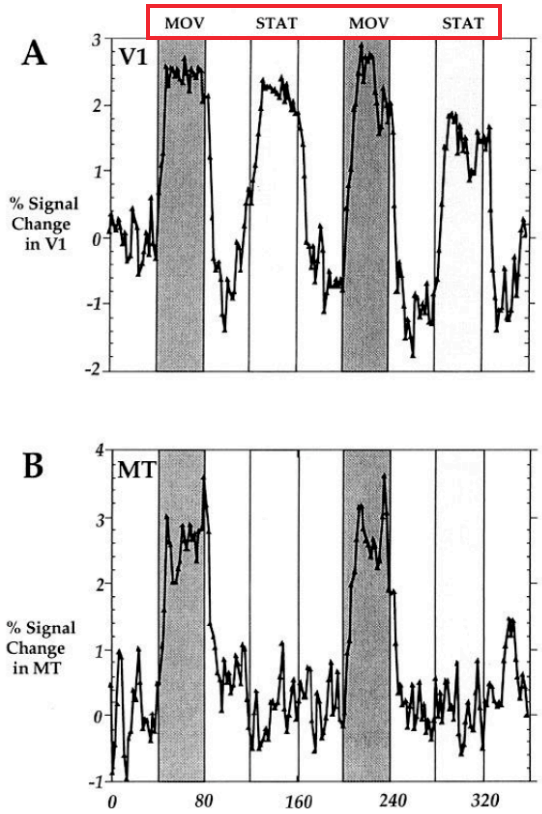
How could V1 be activated selectively?

Tootell et al., 1998b

Human Cortical Area MT

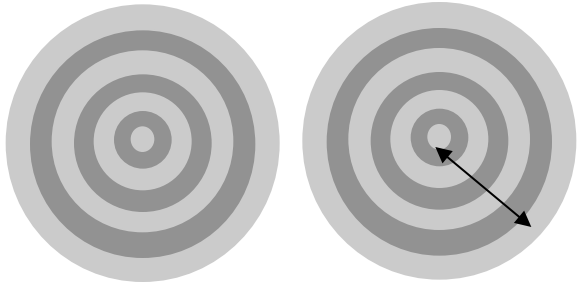
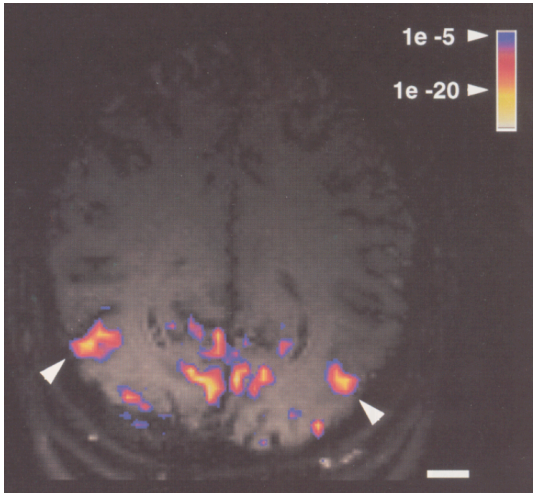
Well studied in monkeys
Distinctive anatomy (myelin)
and function direction selectivity
Present in all primates tested.





Tootell et al., 1995

Localizing Stimuli



low-contrast motion compared to low-contrast stationary