



**Development of Complex Curricula for Molecular Bionics and Infobionics Programs within a consortial\* framework\*\***

Consortium leader

**PETER PAZMANY CATHOLIC UNIVERSITY**

Consortium members

**SEMMELWEIS UNIVERSITY, DIALOG CAMPUS PUBLISHER**

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# BEVEZETÉS A FUNKCIONÁLIS NEUROBIOLÓGIÁBA

# INTRODUCTION TO FUNCTIONAL NEUROBIOLOGY

By Imre Kalló

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# Functional imaging techniques

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*Pázmány Péter Catholic University, Faculty of Information Technology*

- I. Functional Magnetic Resonance Imaging (fMRI)  
Image acquisition, processing and analysis  
What fMRI can do and what it can not do?
- II. Investigation of  
Sensory processing  
Neural Plasticity  
Cognitive functions

## The MR system (1.5/3.0T )

*Main components:*  
external magnet  
gradient coils  
RF coils  
computers



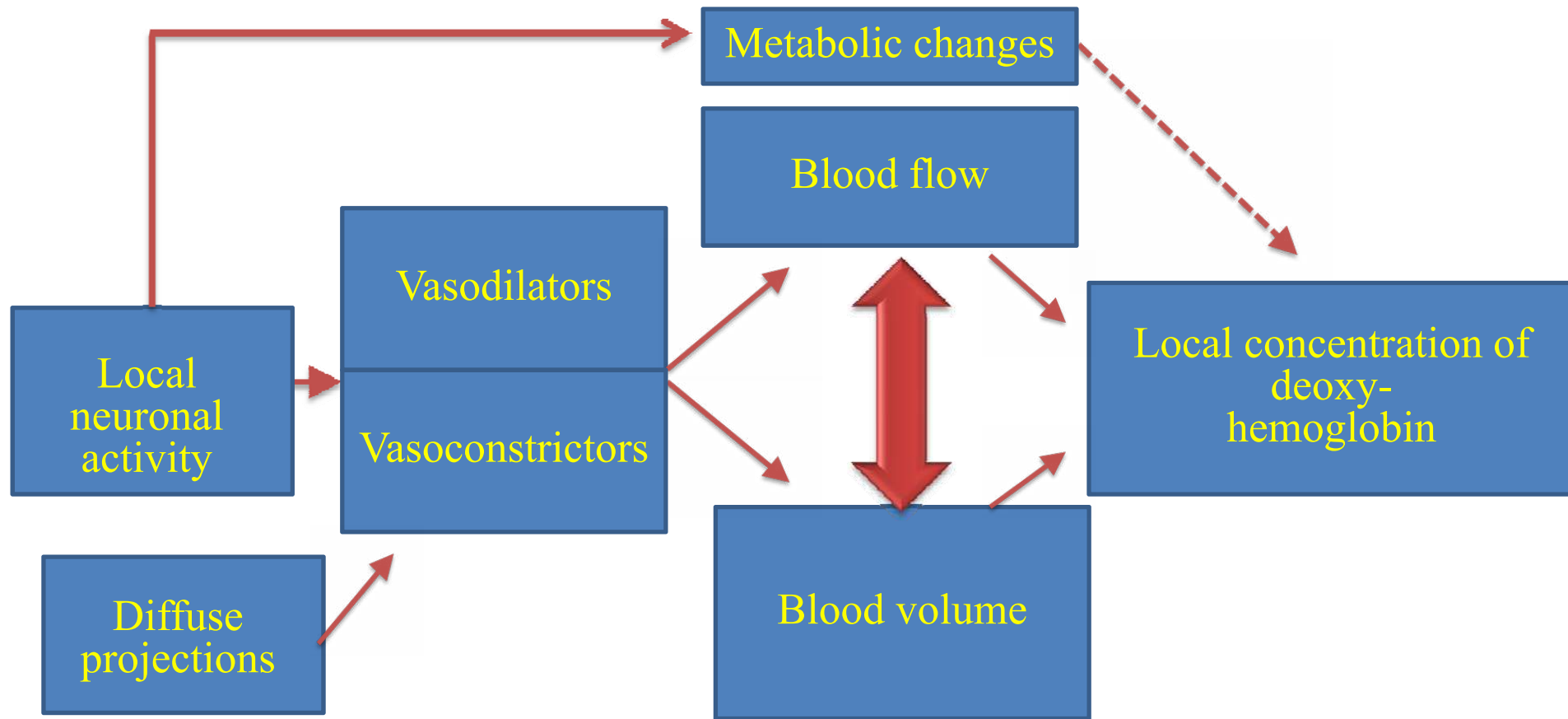
# Functional Magnetic Resonance Imaging (fMRI)

- **The Blood Oxygenation Level Dependent (BOLD, Ogawa et al, 1990 Magn. Reson.Med.)**

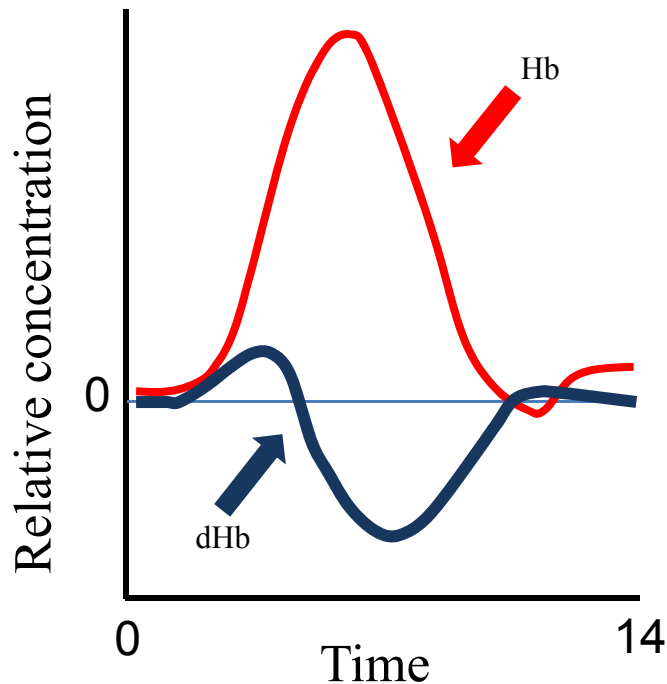
## Method:

- Magnetic resonance sequences that are based on the BOLD effect use the endogenous contrast agent deoxyhemoglobin as a source of contrast
- Deoxyhemoglobin is paramagnetic but Oxyhemoglobin is diamagnetic. Therefore magnetic resonance signal of blood is slightly different depending on the level of oxygenation.
- Higher BOLD signal intensities arise from relative decrease in the local concentration of Deoxyhemoglobin as a result of increased neural activity.

## Factors defining local deoxyhemoglobin-concentration



## Activity dependent changes in deoxy- and oxyhemoglobin levels



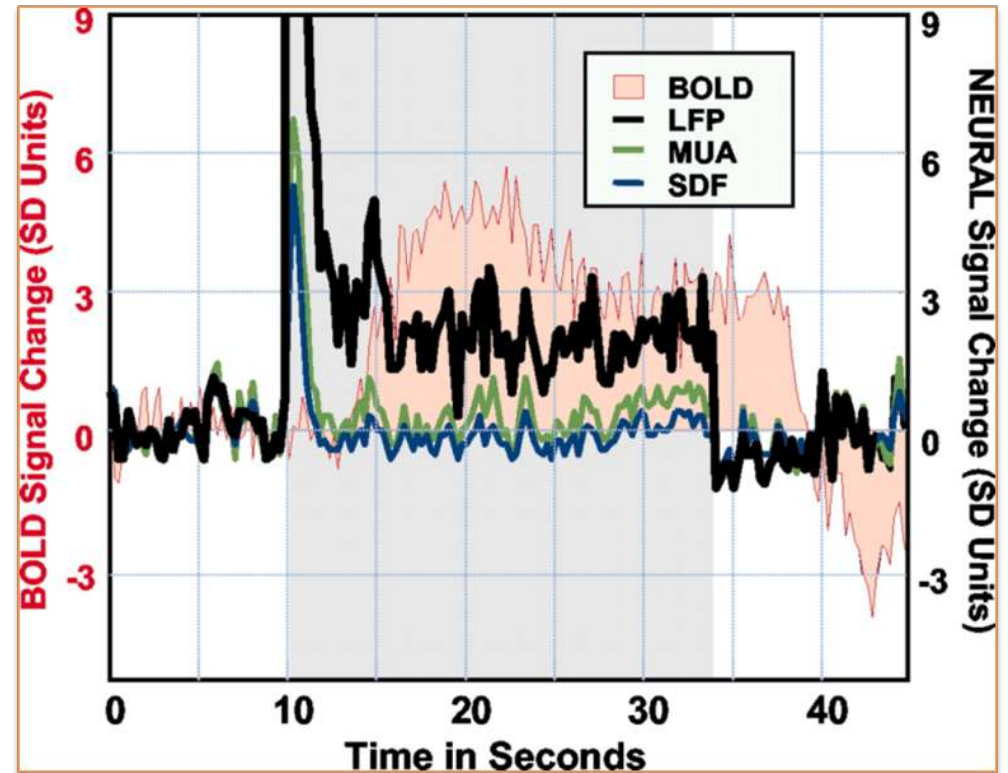
- Quite distinct changes in oxygenated(Hb) and deoxygenated hemoglobin(dHb) following neuronal activation.
- Unlike weak deoxygenated hemoglobin signal spatial pattern of oxygenated hemoglobin did not reflect the pattern of neuronal activity

# Functional Magnetic Resonance Imaging (fMRI)

**BOLD response correlates with the strength of the neural local field potentials (LFP)**

Spatial resolution of the BOLD method: 1-3 mm.

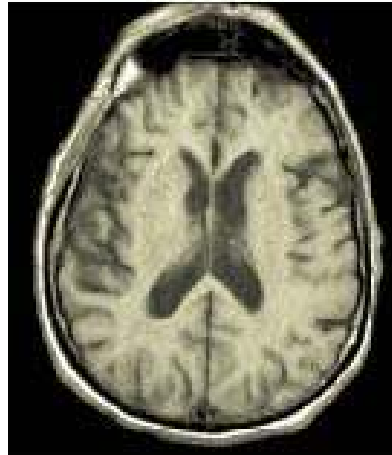
Temporal resolution of the BOLD method: seconds



Logothetis et al, Journal of Neuroscience, 2003,

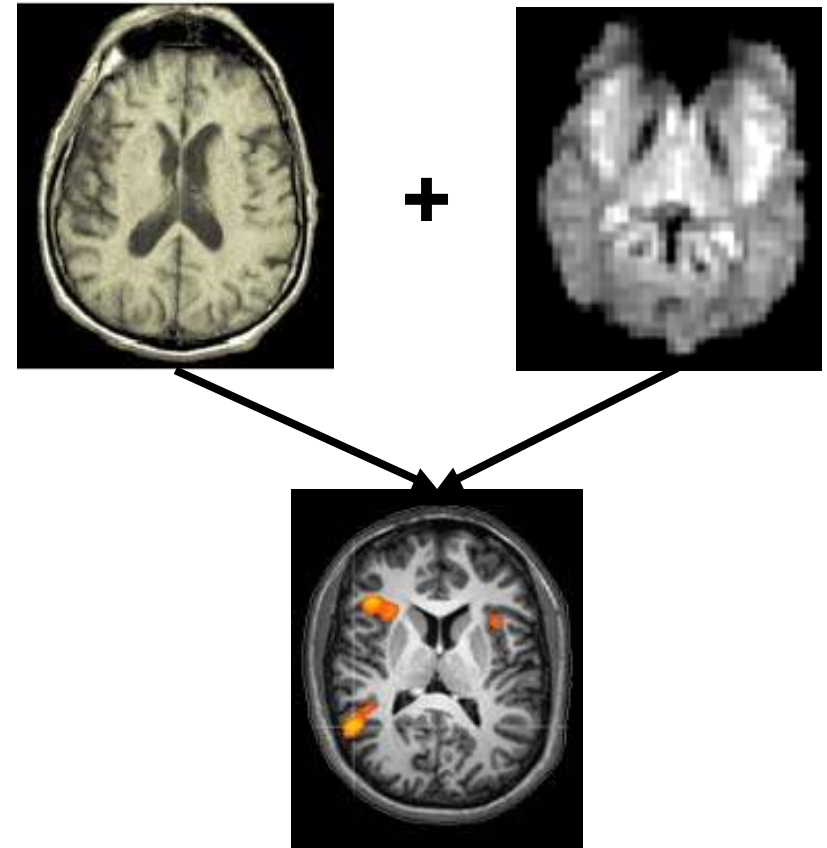
## Acquired Data

- 3D T1 anatomy
  - $1 \times 1 \times 1$  mm resolution
- 4D T2\* EPI images
  - 3D time series collected at each TR (1-2 s)
  - $\sim 4 \times 3.5 \times 3.5$  mm resolution



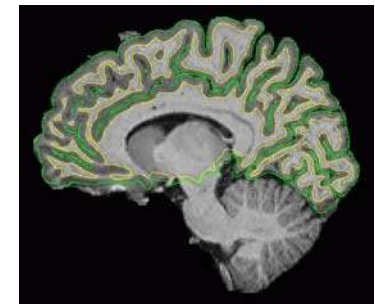
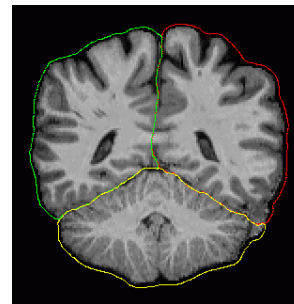
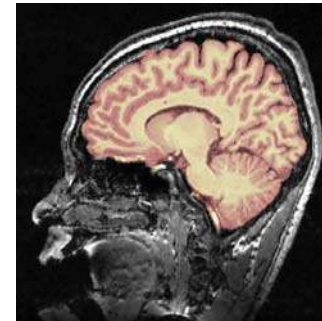
## Preprocessing and Processing Steps

- Anatomical images
  - Intensity normalization
  - Skull-stripping
  - 3D reconstruction
  - Normalization (MNI or Talairach)
- Functional images
  - Coregistration
  - 3D motion correction
  - Slice-time correction
  - Smoothing
  - Defining ROIs
  - Regression analysis



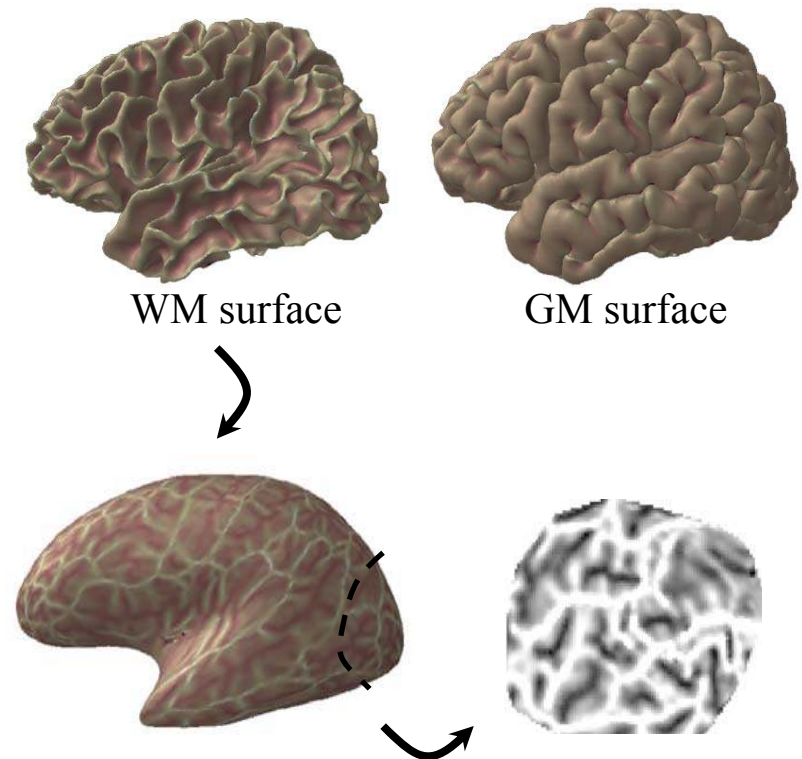
## Anatomical Preprocessing I.

- Intensity normalization
  - make white matter (WM) homogenous to aid segmentation
- Skull-stripping
  - remove all non-brain tissues
  - caveat: shouldn't accidentally remove grey matter (GM)
- Segmentation
  - separate hemispheres, then separate GM from WM, so analysis can be restricted to GM



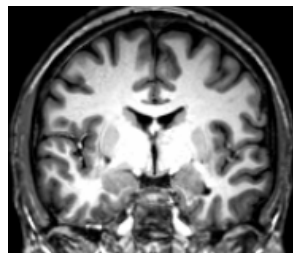
## Anatomical Preprocessing II.

- Surface creation
  - make surfaces out of the segmented GM and WM
- Inflation
  - inflate WM surface to better visualize activations in sulci
- Flattening
  - cut a patch and flatten or cut at predefined sulci to flatten the whole brain

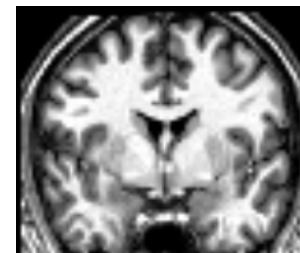
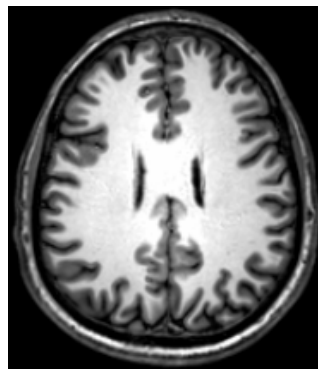


## Anatomical Preprocessing III.

- Normalization
  - transform each individual brain into a standard space by predefined algorithms so 2nd-level (group-level) analysis can be performed
  - standard spaces:
    - Talairach space based on one post-mortem brain
    - Montreal Neurological Institute (MNI) space based on a large series of MRI scans on normal controls



individual space

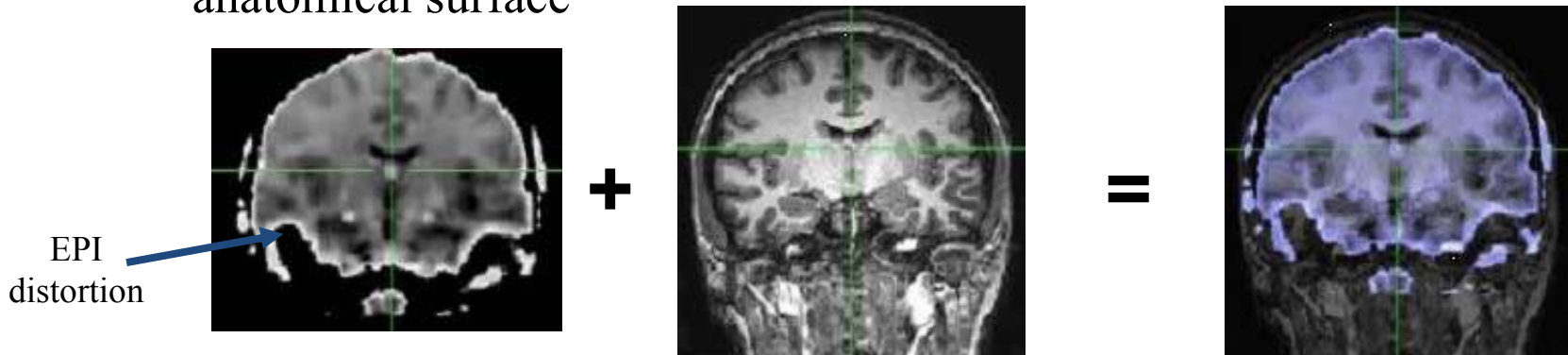


MNI space



## Functional Preprocessing I.

- Coregistration
  - 3D anatomy and the functional images are acquired in a different space; moreover the EPI sequence distorts the brain in the neighborhood of cavities
  - a linear (or non-linear) warping algorithm is required to register both in the same space so statistical activations can be projected to the anatomical surface



## Functional Preprocessing II.

- 3D Motion correction
  - align all functional images to a reference image (usually the first image or the image in the middle of the scan) since their location could have slightly changed due to subject motion and all statistical analyses assume that the location of a given voxel within the brain does not change over time
- Slice-timing correction
  - with a continuous descending EPI sequence, the bottom slice is acquired a TR later than the slice on the top, so there is a shift in the onset of the haemodynamic function. One solution to this problem is to interpolate the data during preprocessing as if the slices were acquired simultaneously
- Smoothing
  - spatially smoothing each of the images improves the signal-to-noise ratio (SNR), but will reduce the resolution in each image

## Statistical Analysis of Functional Images I.

- Aims:
  - find and describe the effect of stimulation if there is any
- Based on the spatial complexity of the signal, there are:
  - one-dimensional methods
    - doing the statistics separately on a voxel-by-voxel basis (classic GLM regression method)
    - averaging the time course of predefined voxels in a certain area (region-of-interest: ROI) and doing the statistics on that (increases signal-to-noise ratio (SNR))
  - multi-dimensional (multi-variate) methods
    - finding patterns in time *and* space

## Statistical Analysis of Functional Images II.

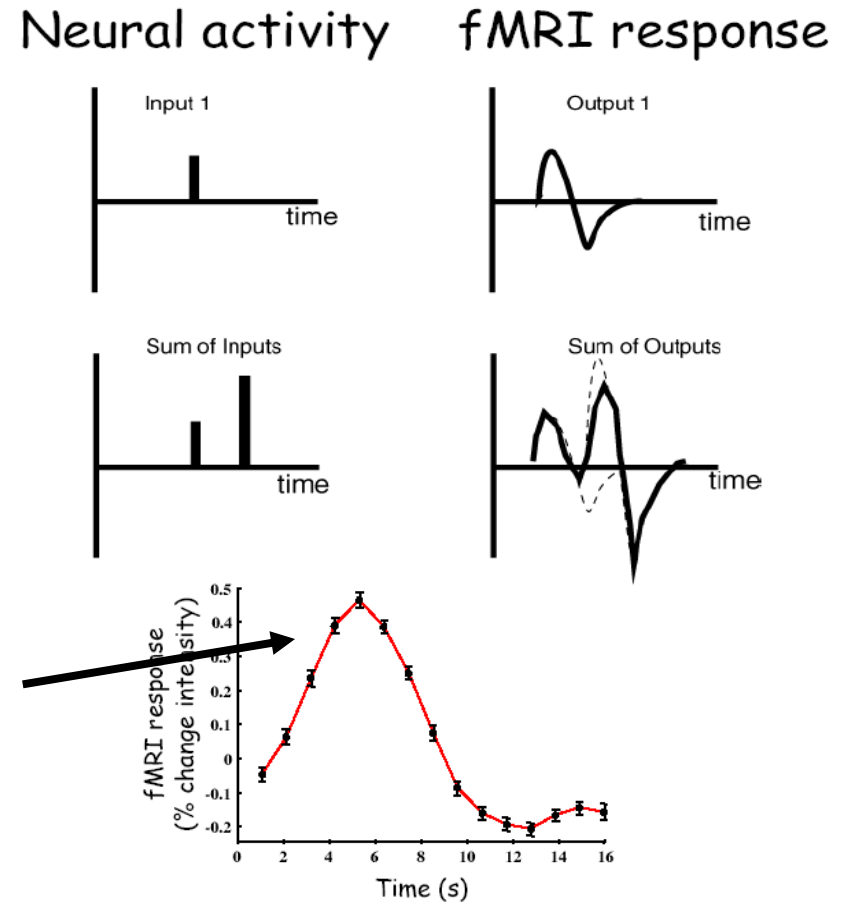
- Fitting models to the data:
  - find models that describe the signal and the noise and evaluate the fit
- Parametric models:
  - linear correlation
  - t-tests
  - event-related averaging
  - general linear models (GLM)
- Non-parametric models
  - bootstrap
  - Monte-Carlo simulations
  - multi-variate models

## Statistical Analysis of Functional Images III.

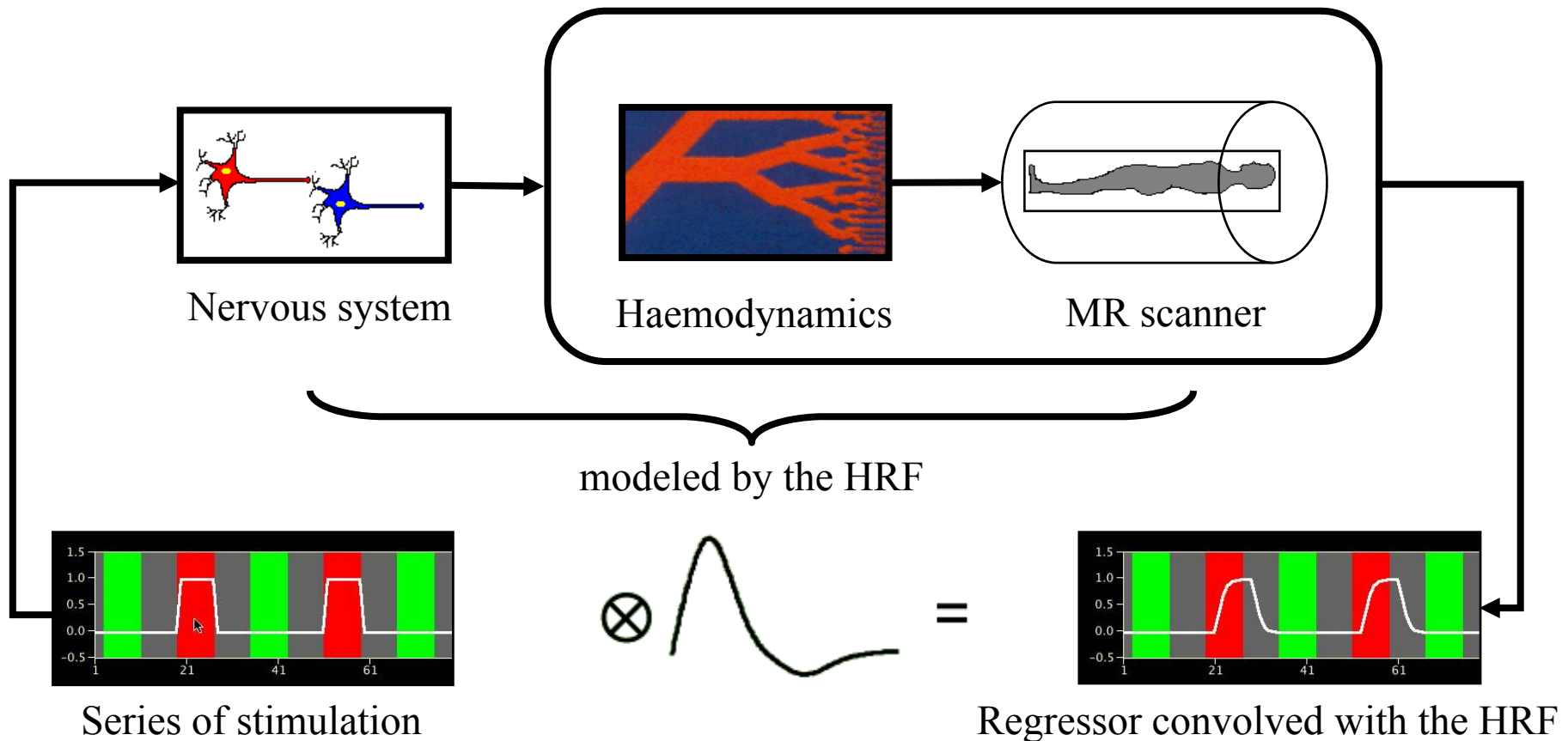
- Noise integration into models
  - models should take noise into account either as a separate term
  - there are models devoted to noise estimation (nuisance variability models) such as time autocorrelation or drift
- Univariate models treating each voxel separately need to be statistically corrected for
  - correction for the multiple comparison problem
- Group-level statistics model the population not particular individuals
  - Random effects models

# Linear Transform Hypothesis

- It is assumed that the processes from neuronal firing to BOLD response constitute a time-invariant linear system, so the fMRI signal is approximately proportion to a measure of local neural activity, averaged over a spatial extent of several millimeters and over a time of several seconds.
- *Haemodynamic impulse response function*: (HIRF or HRF) the measurable fMRI signal for a brief stimulus presentation.



# Haemodynamic Response Function



- Functional Contrast:
  - Blood volume
  - Blood flow/perfusion
  - Blood oxygenation
- Spatial resolution:
  - Typical: 3 mm<sup>3</sup>
  - Upper: 0.5 mm<sup>3</sup>
- Temporal resolution:
  - Typical: 2-3sec
  - Stimuli can be detected:
    - Minimum duration (single slice): < 16 ms
    - Minimum onset diff: 100 ms to 2 sec
- Interpretability:
  - Neurovascular coupling, vascular sampling, blood, physiologic noise, motion and other artifacts, etc.

## Overview of fMRI

## Why fMRI is so popular?

- **Powerful**
  - Improved ability to understand cognition
  - Better spatial resolution than PET
  - Allows new forms of analysis
- **High benefit/risk ratio**
  - Non-invasive (no contrast agents)
  - Repeated studies (multisession, longitudinal)
- **Accessible**
  - Uses clinically prevalent equipment
  - No isotopes required
  - Little special training for personnel

## Help in understanding healthy brain organization

- map networks involved with specific behavior, stimulus, or performance
- characterize changes over time (seconds to years)
- determine correlates of behavior (response accuracy, etc...)

## Current Clinical Applications

- presurgical mapping
- better understanding mechanism of pathology for focused therapy
- drug effect assessment
- assessment of therapy progress, biofeedback
- epileptic foci mapping
- neurovascular physiology assessment

## What fMRI Can Do

## Current Clinical Research

- assessment of recovery and plasticity
- clinical population characterization with probe task or resting state

## What fMRI Can't Do

- Too low SNR for routine clinical use (takes too long)
- Requires patient cooperation (too sensitive to motion)
- Too low spatial resolution (each voxel has several million neurons)
- Too low temporal resolution (hemodynamics are variable and sluggish)
- Too indirectly related to neuronal activity
- Too many physiologic variables influence signal
- Requires a task (BOLD cannot look at baseline maps)
- Too confined space and high acoustic noise.

## Investigating Brain Functions with fMRI

- Sensory Processing
  - early level
  - higher-order
- Neural Plasticity
  - short-term plasticity
  - long-term cortical reorganization
  - developmental plasticity
- Cognitive Function
  - attentional network
  - decision making
  - memory

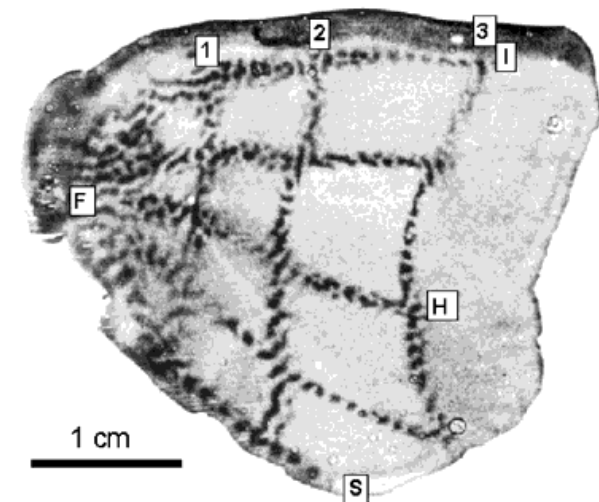
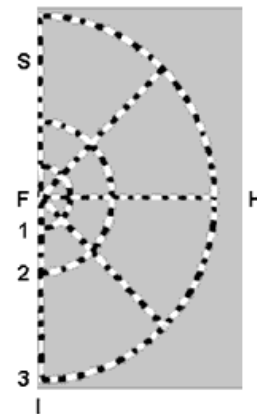
# Sensory Processing

# Retinotopical Mapping

Aim is to separate early and mid-level visual areas

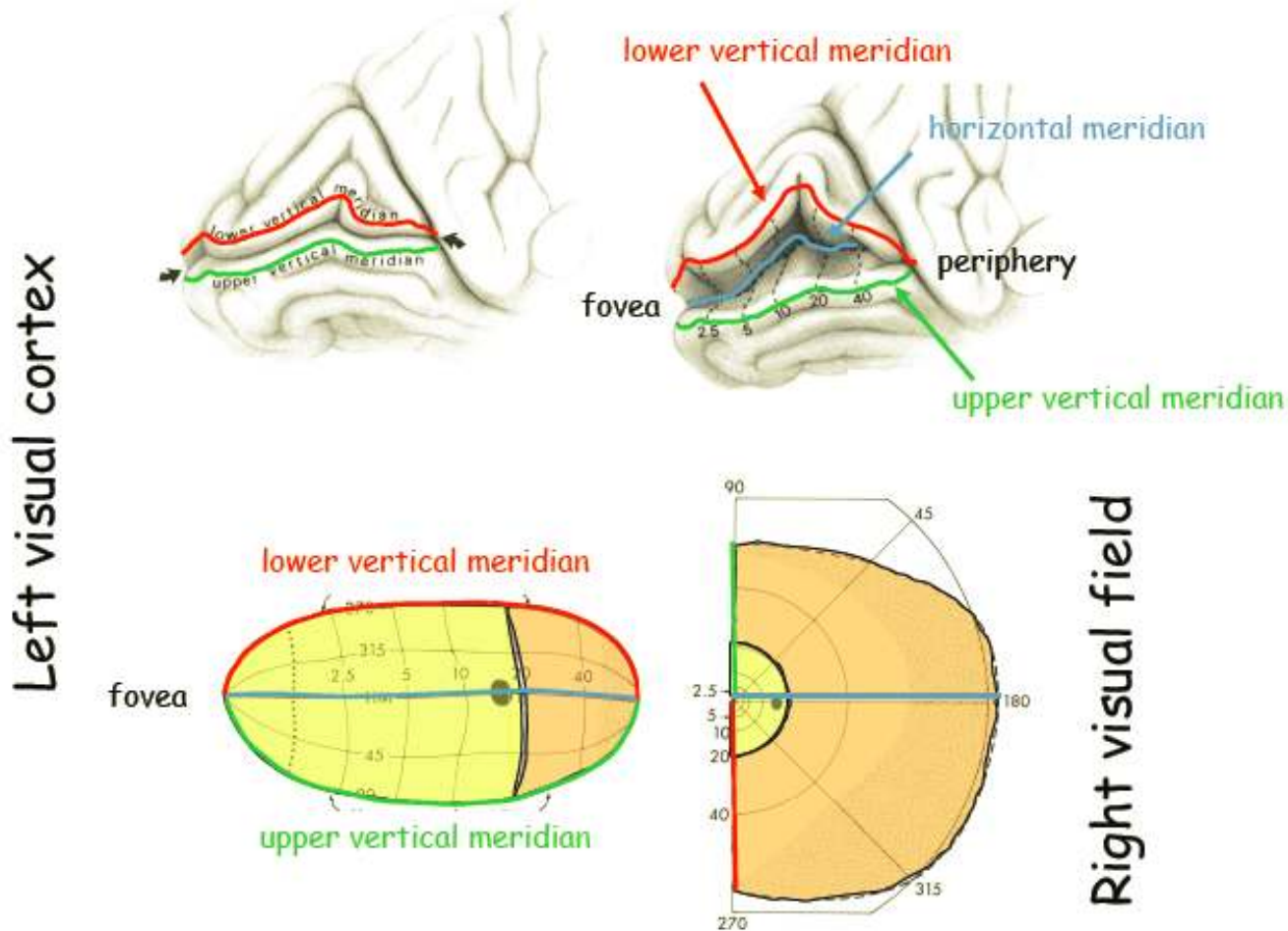
Visual areas in the brain are defined by

- Physiology
- Cellular architecture
- Connections to other areas
- **Topographical representation of the world**



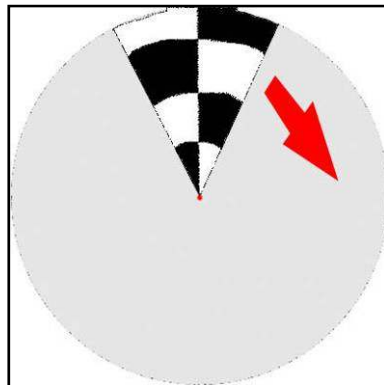
Neural representation of the stimulus in the primary visual cortex of a macaque monkey (Tootell et al. 1988, J Neurosci.).

## Visual field representation in human primary visual cortex (V1)

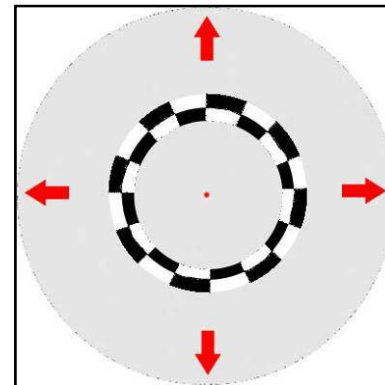


## Protocol for Retinotopy

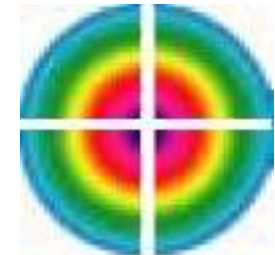
- Phase reversing checkerboard stimulus for strong excitation
- Aim is to probe the entire visual field:
  - Rotating wedge to get information about visual field quadrants
  - Contracting-expanding ring to get information about eccentricity



CW/CCW rotating wedge



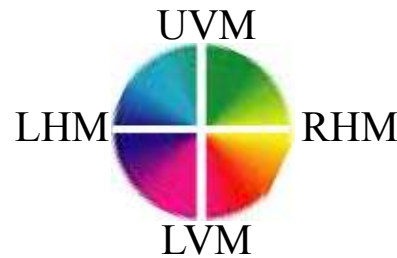
Contracting/expanding ring



# Defining visual areas on flattened cortex

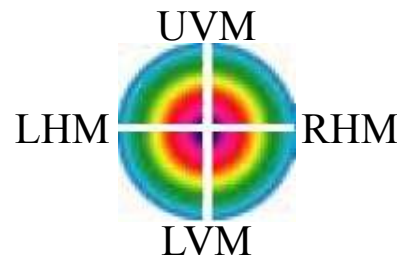
## Phase map

- Phase reversal delineates areas



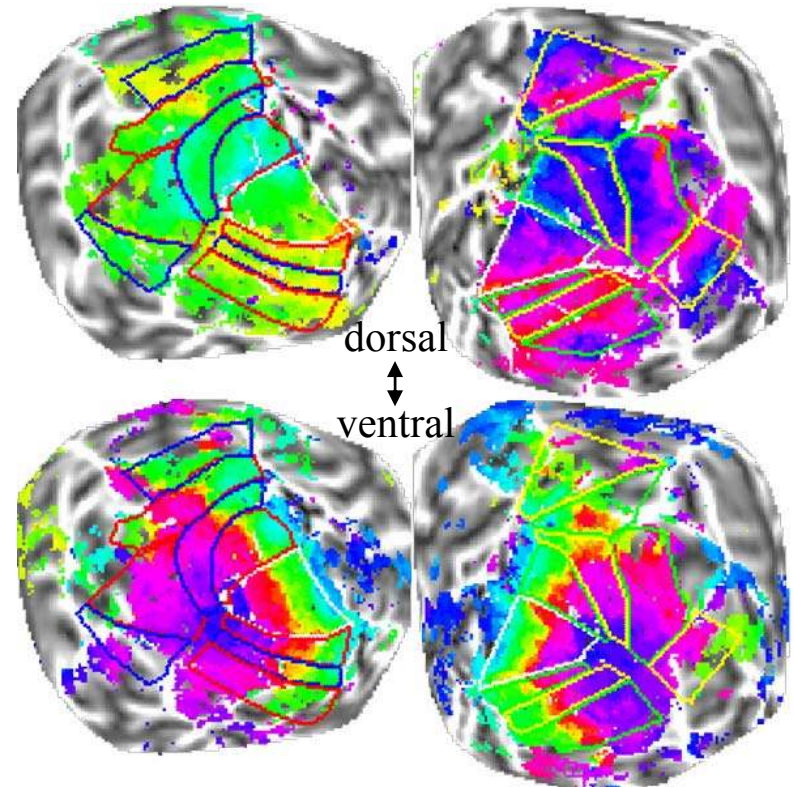
## Eccentricity map

- Tells about foveal and peripheral representation of each area



Left hemisphere

Right hemisphere

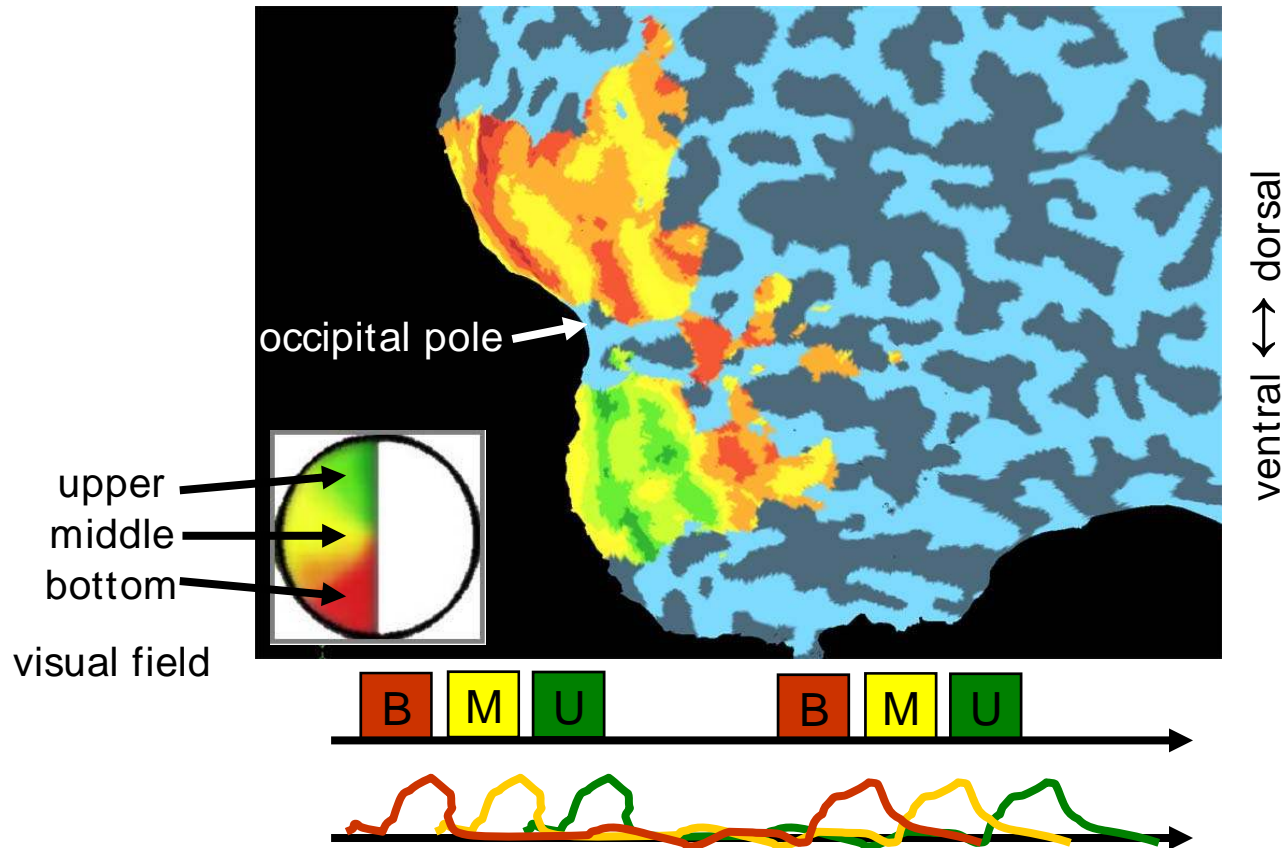


lateral ↔ medial

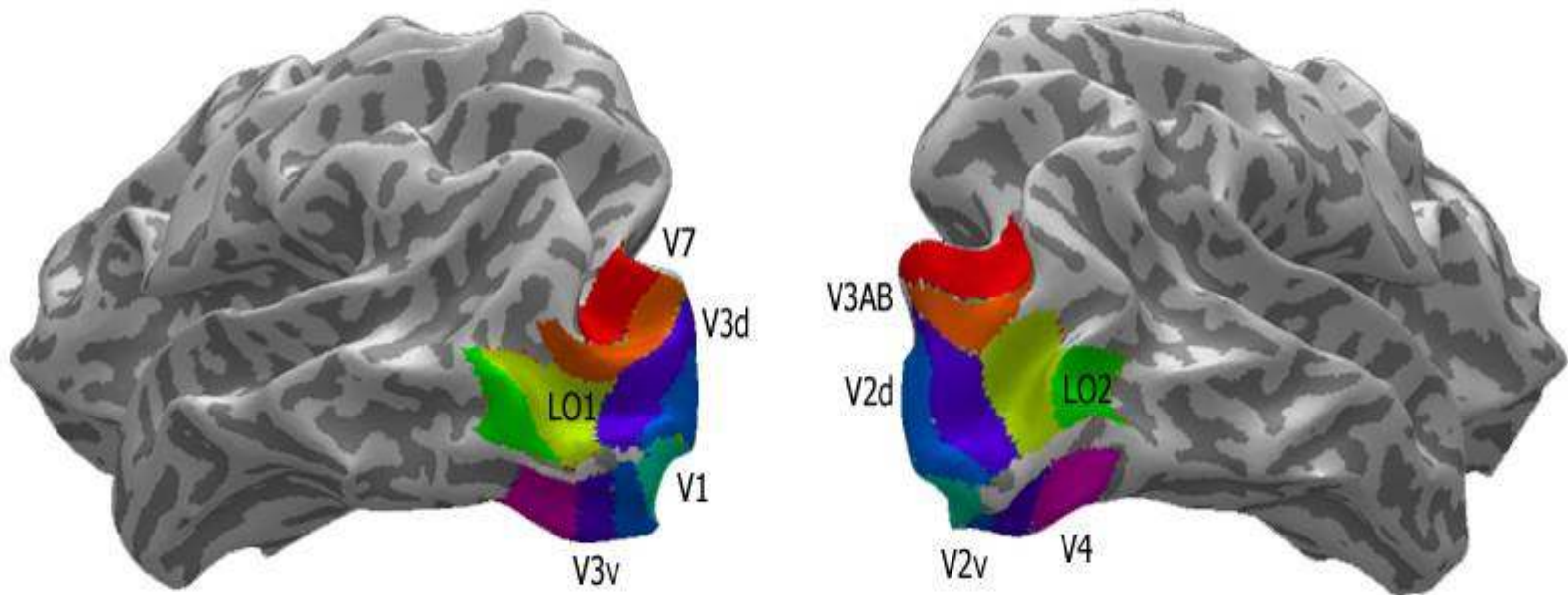
medial ↔ lateral

## Retinotopy Demo

Flattened right hemisphere, cut through the calcarine sulcus



- As a result the voxels are assigned to areas, so the activation pattern of each area in a specific experimental design can be studied separately.

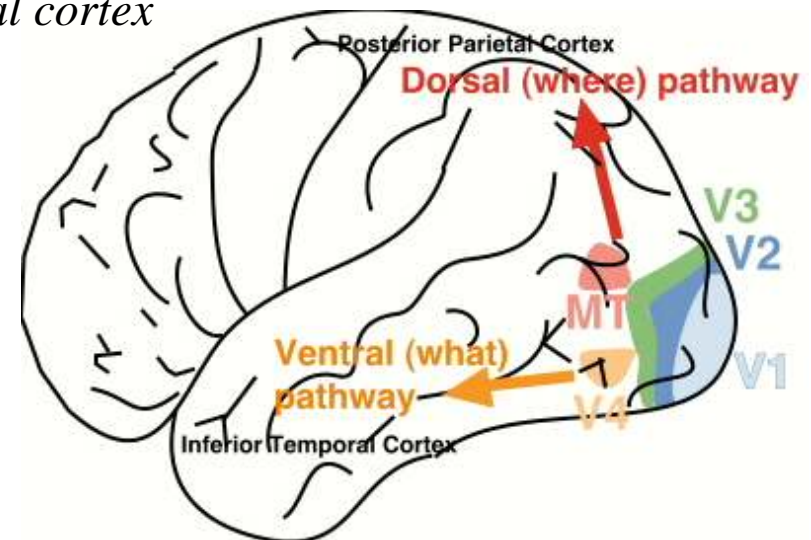


- Topographic mapping can also be done in somatosensory and auditory cortices.

## Category-specific higher-order cortical areas

There are two visual processing streams existing in the cortex for processing different visual percepts:

- **Ventral (“what”) pathway** – enables the visual identification of objects
  - main input from “slow and detailed” parvo system of LGN
  - ends in *object-selective inferior temporal cortex*
- **Dorsal (“where”) pathway** – spatial perception, visual location of objects
  - main input from “quick and dirty” magno system of LGN
  - ends in *posterior parietal cortex, comprises motion selective area MT+*



(Mischkin & Ungerleider 1983, Trends Neurosci)

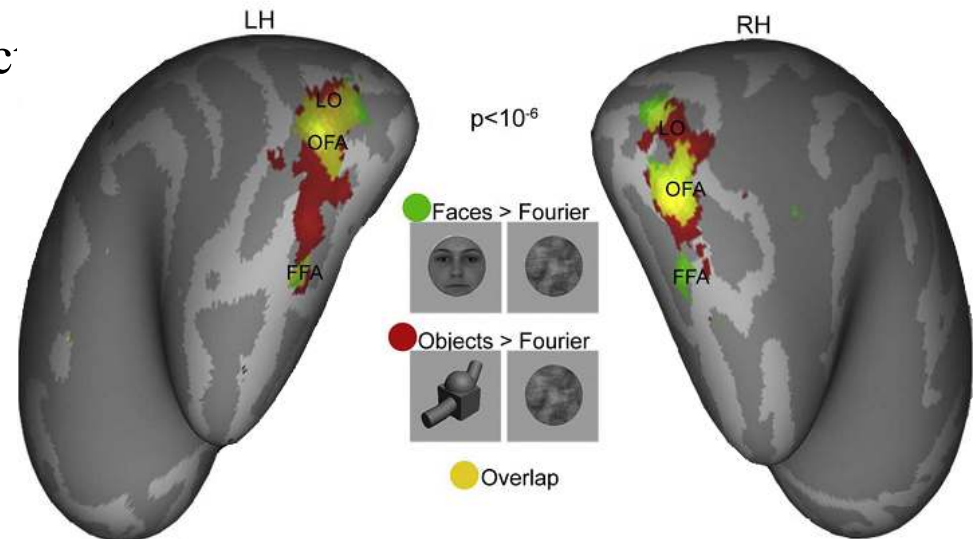
## Functional Localizers

- Higher-order cortical areas lacking topographical organization but being category-specific can still be determined based on functional contrasts
  - E.g. *Face-localizer*: probing the selectivity of object-selective inferotemporal cortex using the contrast of non-sense objects and faces

LO: Lateral Occipital Complex

OFA: Occipital Face Area

FFA: Fusiform Face Area



## Face processing network

**Inferior occipital gyri**  
Early perception of facial features

Activation due to presentation of faces w/ *emotional* expressions

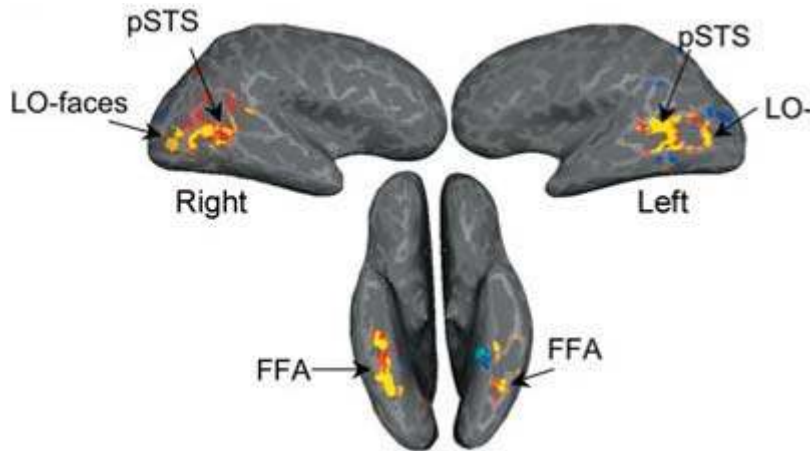
**Superior temporal sulcus**  
Changeable aspects of faces – perception of eye gaze, expression and lip movement

**Lateral fusiform gyrus**  
Invariant aspects of faces – perception of unique identity

Activation due to presentation of faces w/ both *emotional* and *neutral* expressions

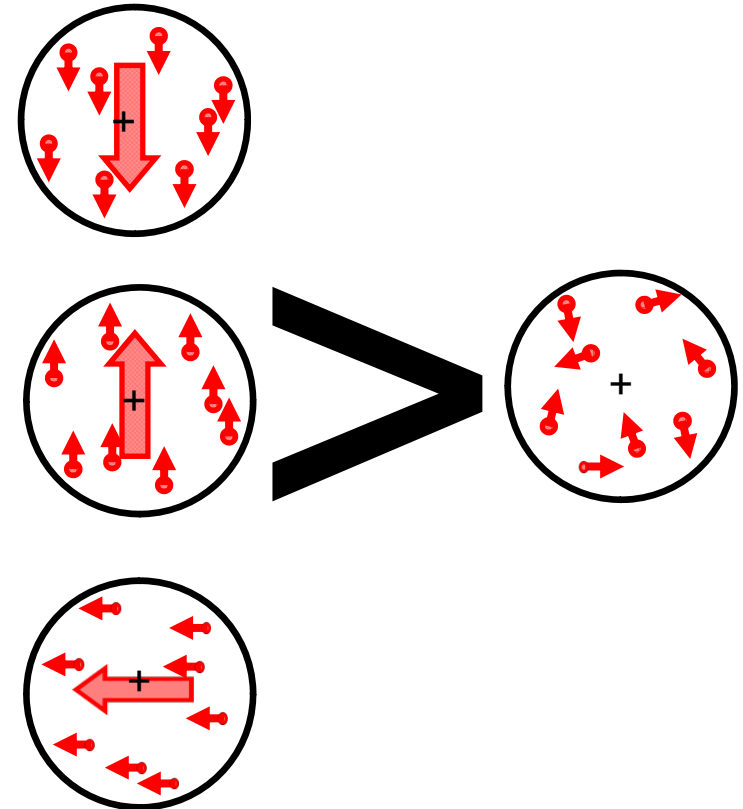
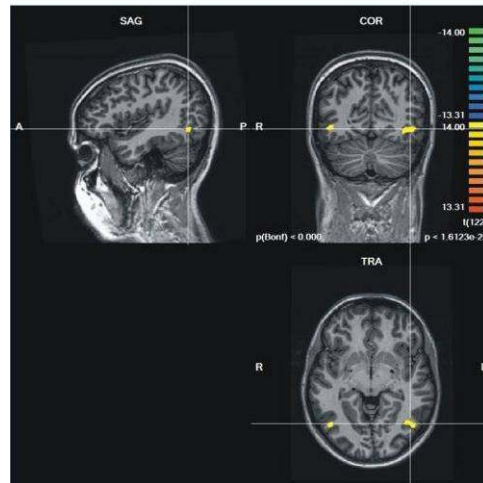
Mainly the posterior part of STS (pSTS)

i.e. Fusiform Face Area, strongly right lateralized



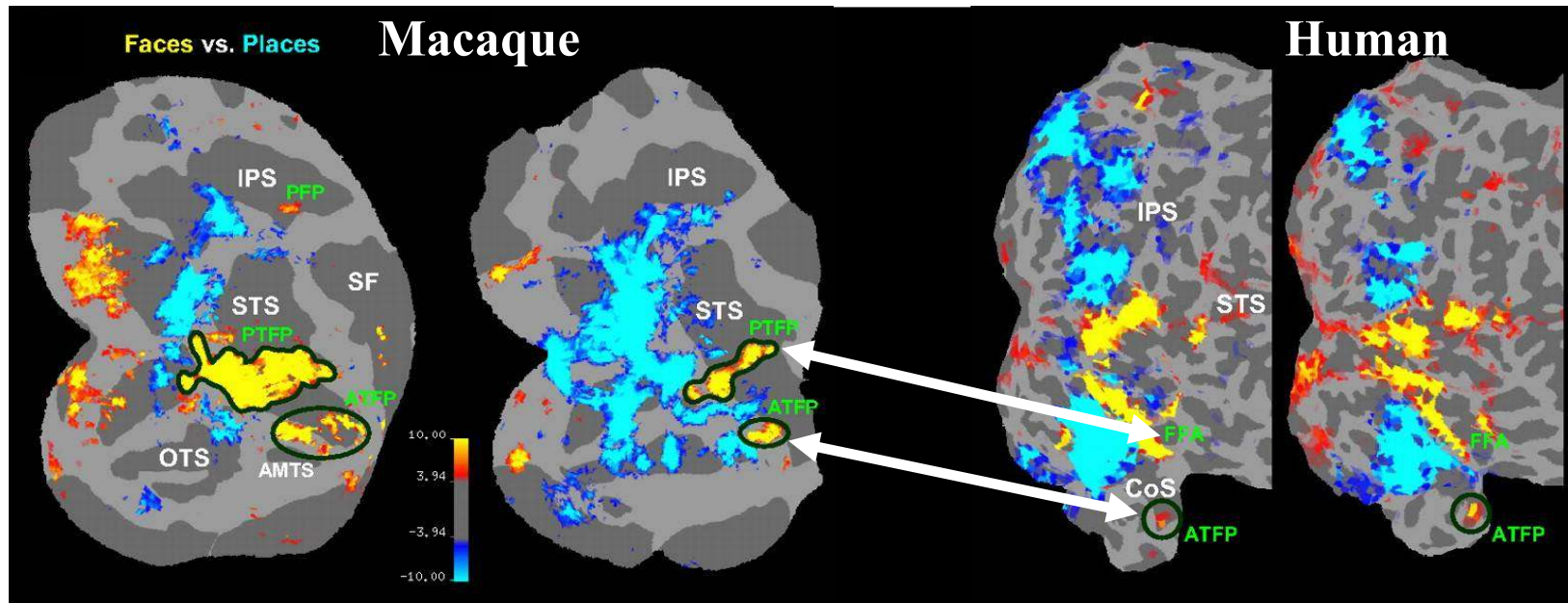
(Grill-Spector et al, 2004, Nature Neurosci) (Haxby et al, 2000, Trends Cog Sci)

- ***hMT+* (V5) localizer**: probing the motion-selectivity of the dorsal visual pathway
- specialized in the processing of visual motion information: its response to coherent motion is higher than to incoherent motion
- block design: coherently and incoherently moving dots are presented in interleaved order



## Localizers as means of studying homology between species

It was shown that both face-selective patches in macaque cortex (Tsao et al. 2003, Nat Neurosci; Pinsk et al. 2005, PNAS) correspond to existing structures in humans.



PTFP: Post. Temp. Face Patch

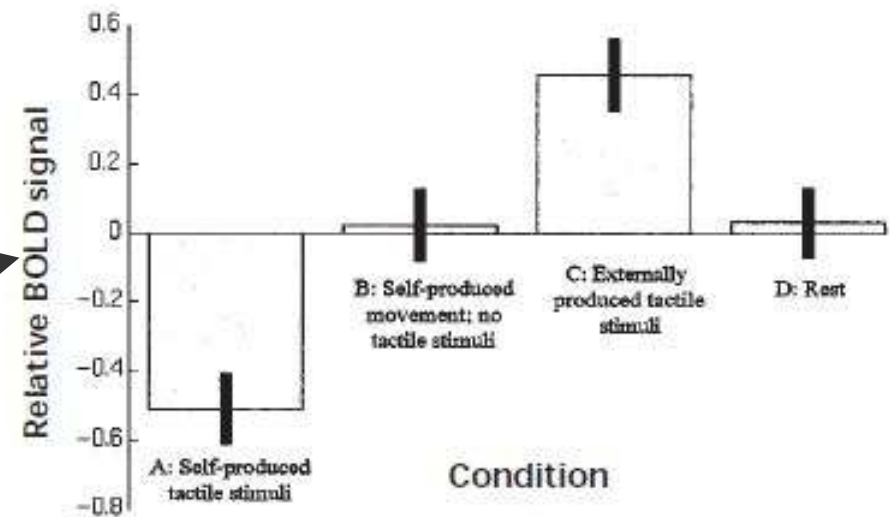
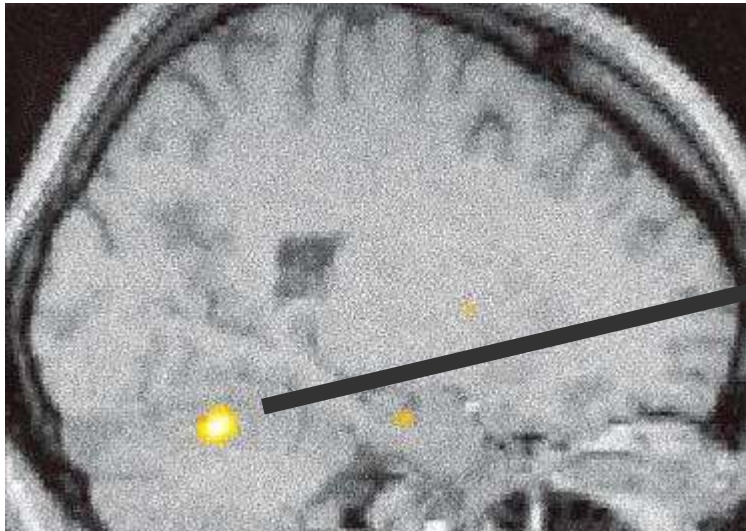
FFA: Fusiform Face Area

ATFP: Ant. Temp. Face Patch

(Rajimehr et al., 2009, PNAS)

## Somatosensory stimulation: self-produced or external?

- Somatosensory cortex: increased BOLD signal to baseline in the case of externally-produced tactile stimulation, while reduced BOLD signal compared to baseline in the case of self-produced tactile stimulation → mediated by the cerebellum



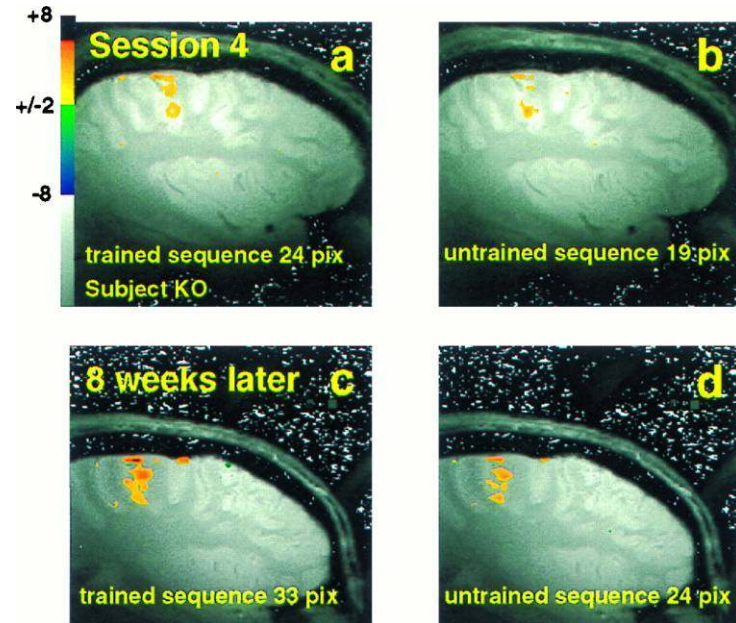
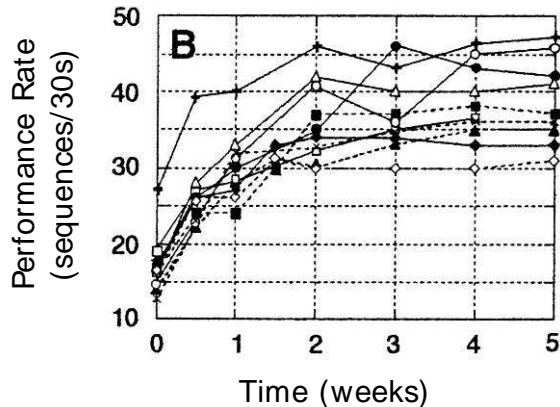
- Significantly decreased activity in right anterior cerebellar cortex associated with the interaction between the effects of self-generated movement and tactile stimulation (external input)  
(Blakemore et al., 1998, Nature Neurosci)

# Neuronal Plasticity

# Plasticity Underlying Short-term Learning

## Long-term practice on sequence performance (motor skill learning)

- In a complex finger moving paradigm after training improved rates of performance induced *increased activation of the primary sensorimotor cortex*, which did not generalize to the contralateral hand.

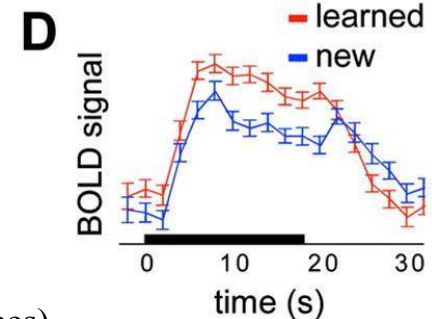
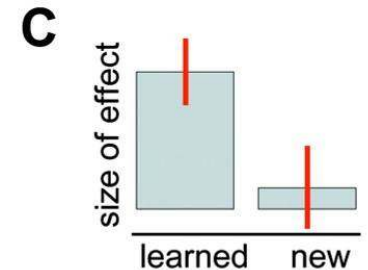
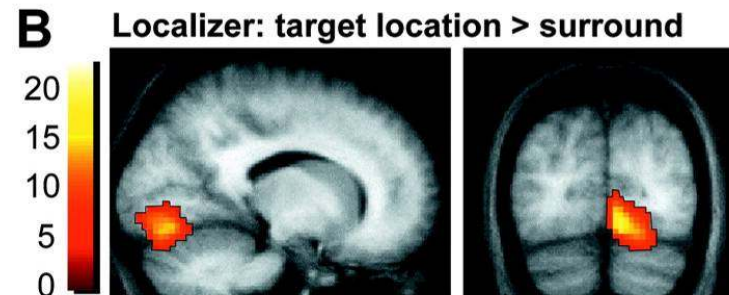


(Karni et al. 1998, PNAS)

## Enhancement of relevant information during perceptual learning

- *Perceptual learning* is defined as performance or sensitivity increase in a sensory feature as a result of repetitive training or exposure to the feature and is regarded as manifestation of sensory plasticity.
- Visual texture discrimination induces long-lasting behavioral improvement restricted to the trained eye and trained location in visual field. Within-subject comparisons between trained and untrained eye for targets presented within the same quadrant revealed higher activity in a corresponding retinotopic area of visual cortex.

→ learning leads to *enhanced perceptual and neural responses for the learned relevant stimulus*



(Schwarz et al. 2002, PNAS)

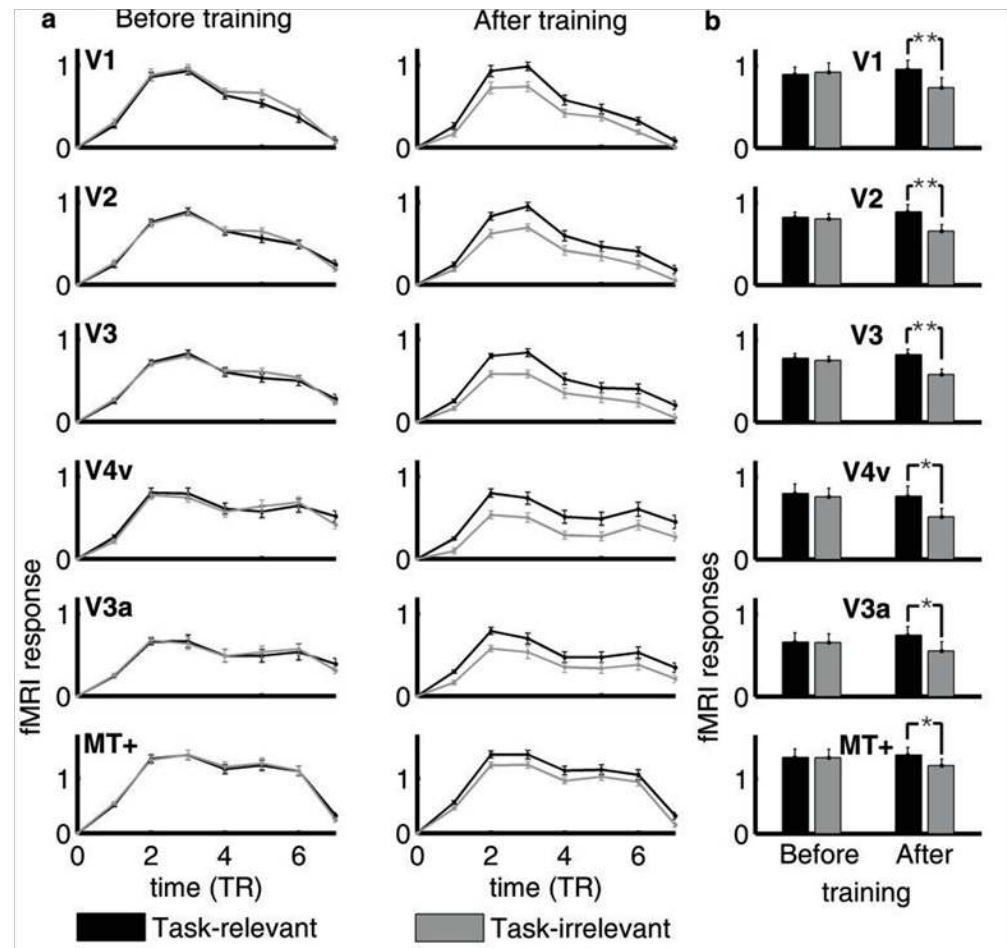
(©2002 The National Academy of Sciences)

## Learning to suppress irrelevant stimuli

- Before training: no difference between the fMRI responses evoked by the task-relevant and task-irrelevant motion directions
- After training: task-irrelevant direction (i.e. distractor stimulus) evoked significantly smaller fMRI responses than task-relevant direction

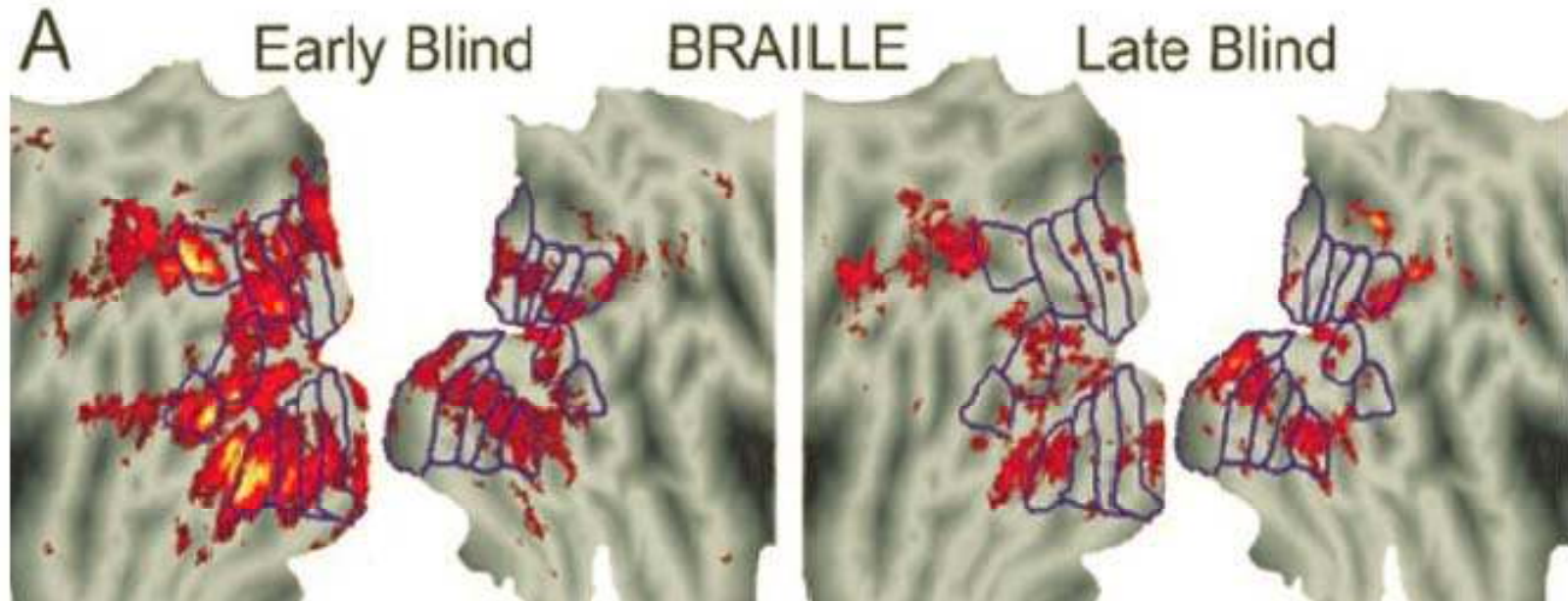
→ learning leads to *suppressed perceptual and neural responses for task-irrelevant information*, which competes with the processing of the task-relevant information during training

(Gál et al., 2009, E J Neurosci)



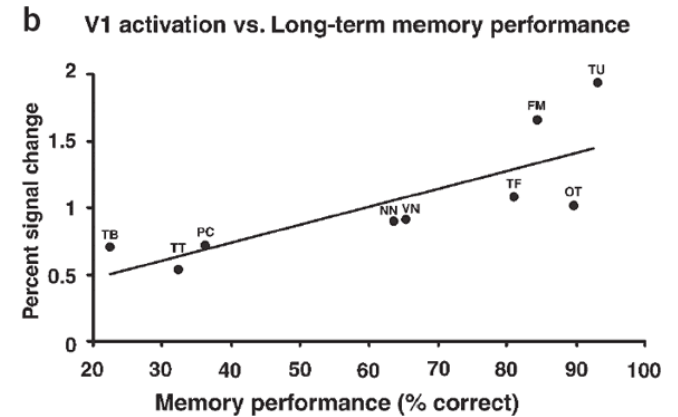
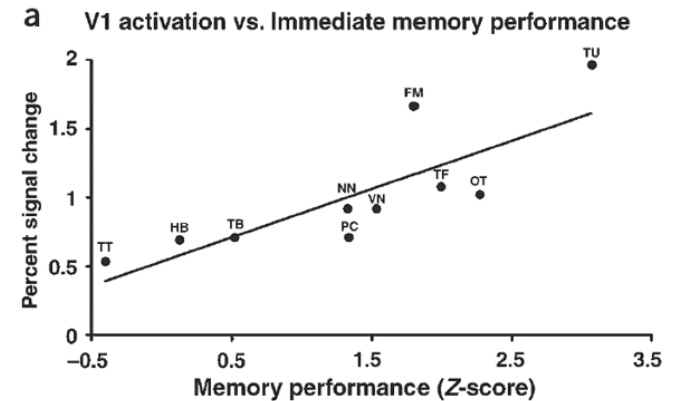
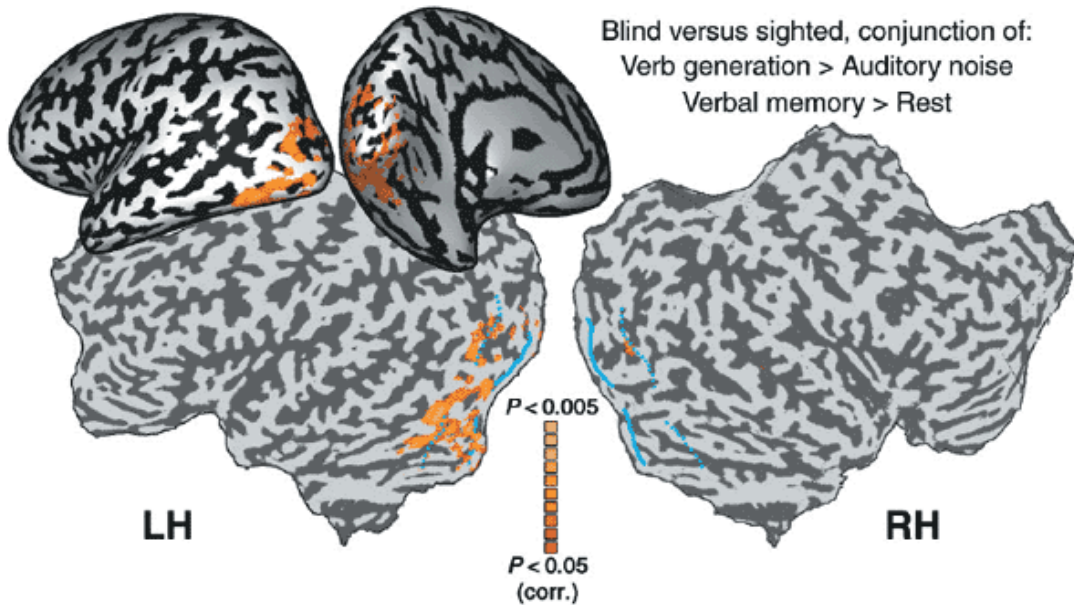
## Studying Long-Term Cortical Reorganization

- in congenitally and early blind people retinotopic visual cortex is activated when reading Braille, as opposed to late blind people who show much less activation



Burton 2003, J Neurosci

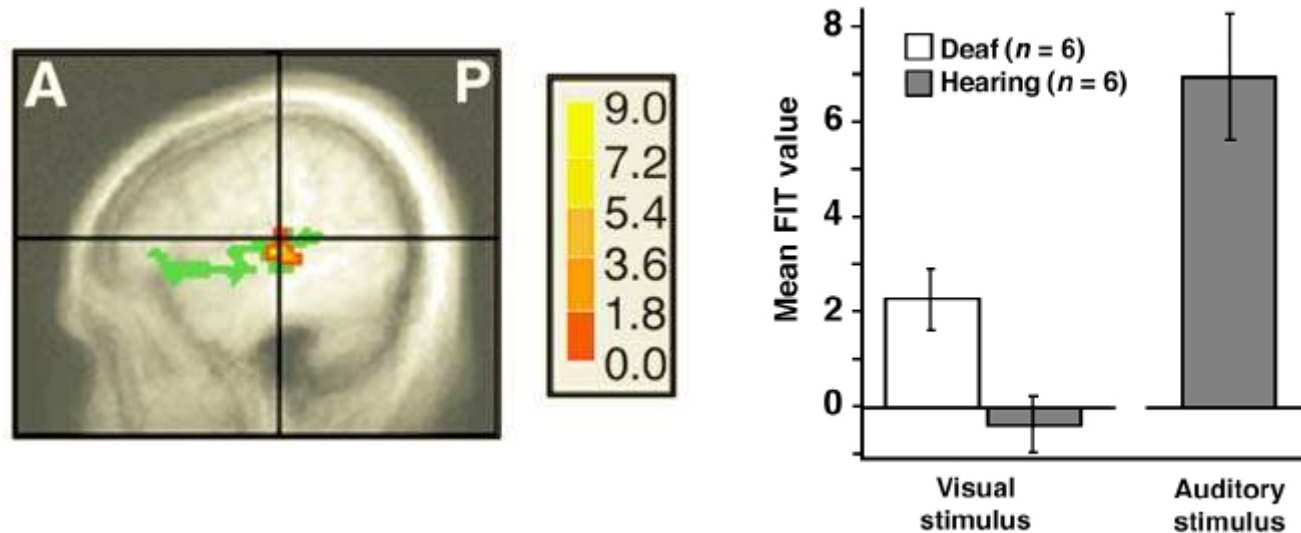
- Visual cortex activation in verbal tasks in blind people also correlates with verbal memory performance



(Amedi et al, 2003, Nature Neurosci)

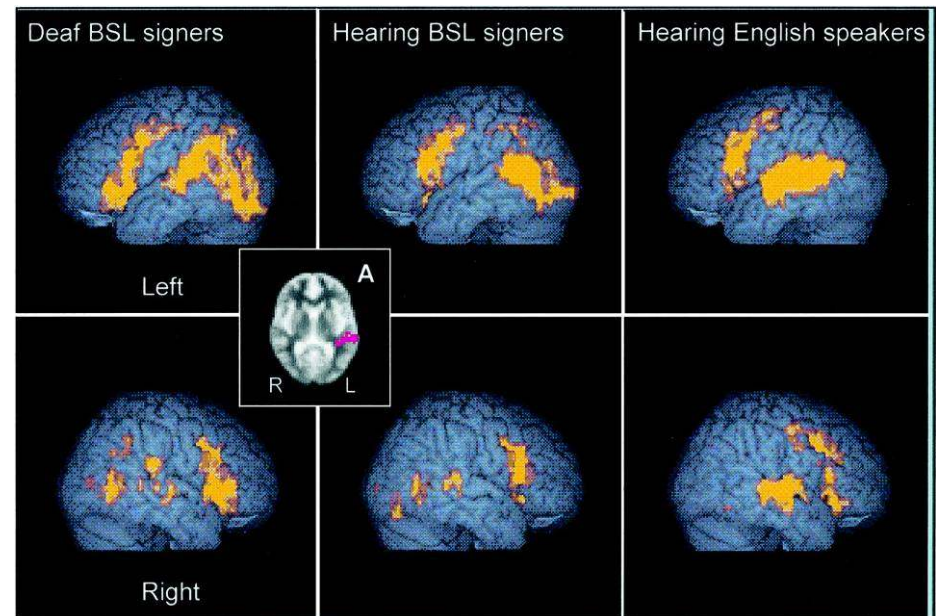
## Cross-modal plasticity in congenitally deaf:

- Auditory cortex activates for simple visual stimuli (moving dot pattern) in early deaf subjects, demonstrating that early deafness results in the processing of visual stimuli in primary auditory cortex.



(Finney et al. 2001, Nature Neurosci)

- Both bilateral inferior prefrontal regions (including Broca's area) and bilateral superior temporal regions (including Wernicke's area) were activated by viewing sign language (BSL) in congenitally deaf signers. Deaf native signers also demonstrated greater activation in the left superior temporal gyrus in response to BSL than hearing native signers (A), which suggests that left temporal auditory regions may be privileged for processing heard speech even in hearing native signers. However, in the absence of auditory input this region can be recruited for visual processing.



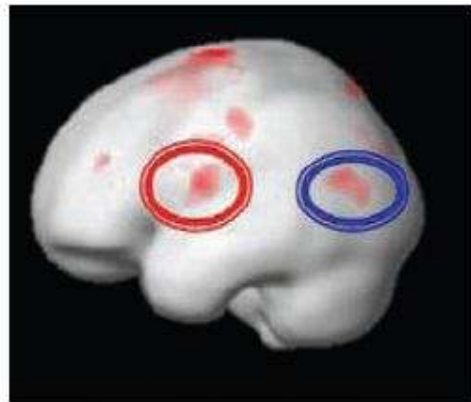
(MacSweeney et al. 2002, Brain)

## Studying Developmental Plasticity

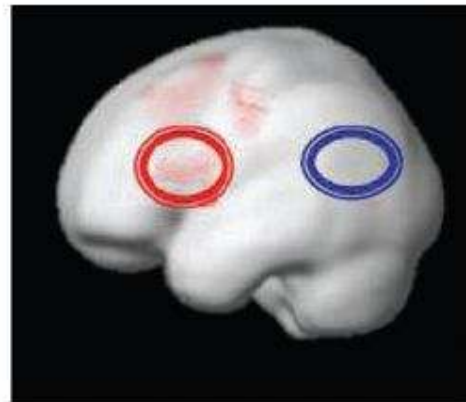
### Dyslexia, a developmental disorder

- Functional neuroimaging studies have revealed differences in brain function and connectivity that are characteristic of dyslexia, e.g.
  - children and adults with dyslexia exhibit reduced or absent activation in the left temporo-parietal cortex
  - left temporo-parietal region supports the cross-modal relation of auditory and visual processes during reading
  - atypical activations in left middle and superior temporal gyri associated with receptive language, and left occipito-temporal regions associated with visual analysis of letters and words

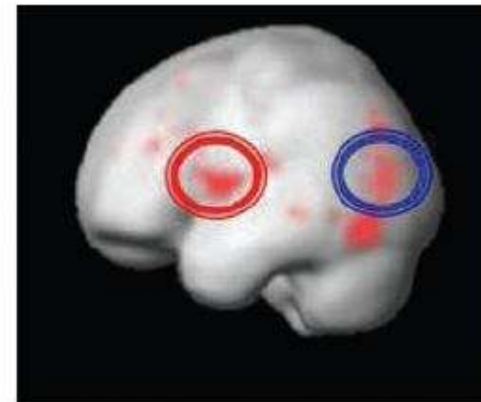
## Brain Plasticity Associated with Treatment



Typically reading children



Children with dyslexia before remediation



Children with dyslexia after remediation

During phonological processing there is a marked frontal (red circles) and temporoparietal (blue circles) hypoactivation in dyslexic readers compared to typically developing readers, which became more active after remediation.

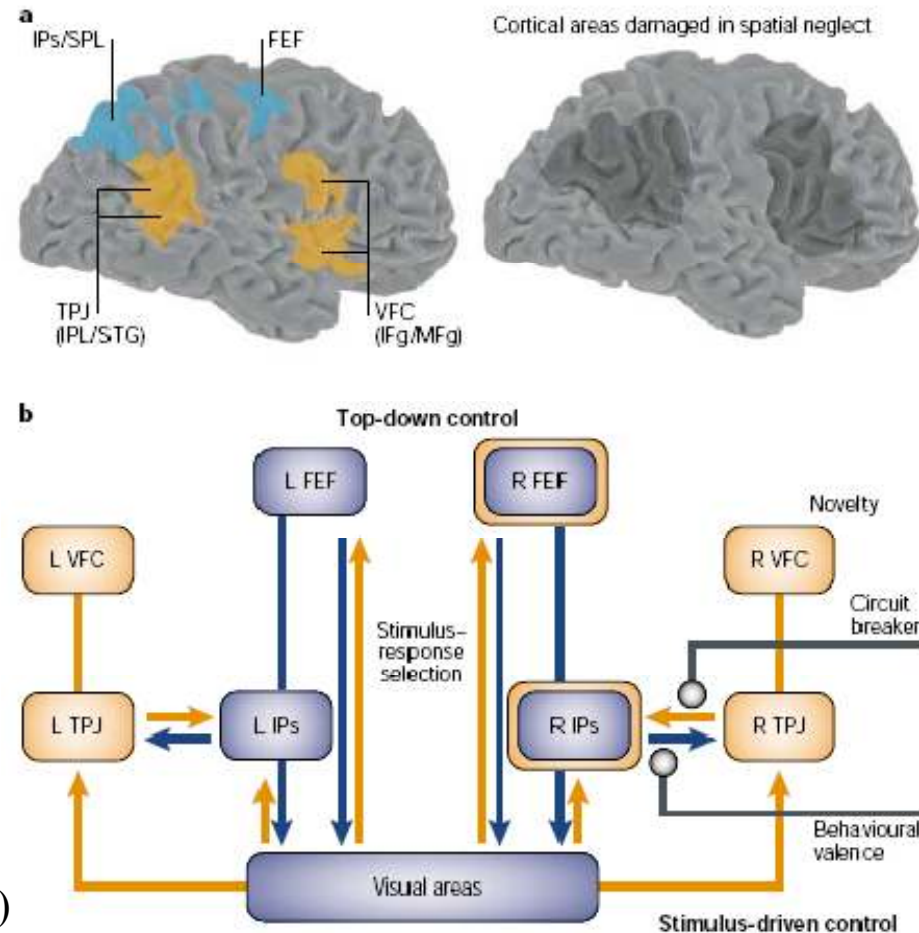
# Cognitive Functions

# Studying the Organization of Attention System

## Attention systems:

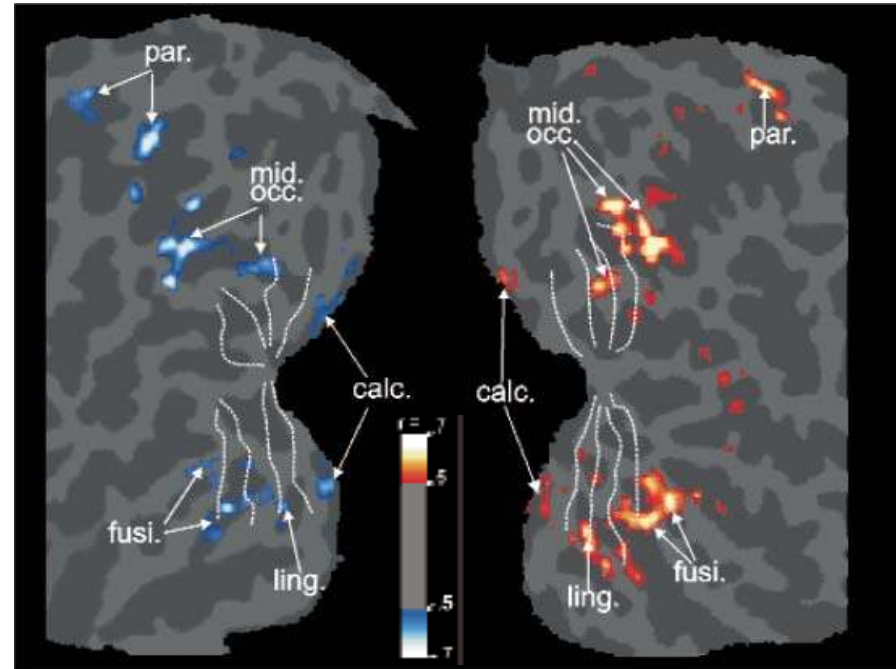
- **Dorsal goal-directed attentional network** (blue) is involved in preparing and applying goal-directed (top-down) selection for stimuli and responses. (rightward bias)
- **Ventral stimulus-driven attentional network** (orange) is not involved in top-down selection. Instead, this system is specialized for the detection of behaviourally relevant stimuli, particularly when they are salient or unexpected. (reorienting deficit)

(Corbetta and Shulman, 2002, Nature Rev Neurosci)



## Basis of Attentional Selection: *Location*

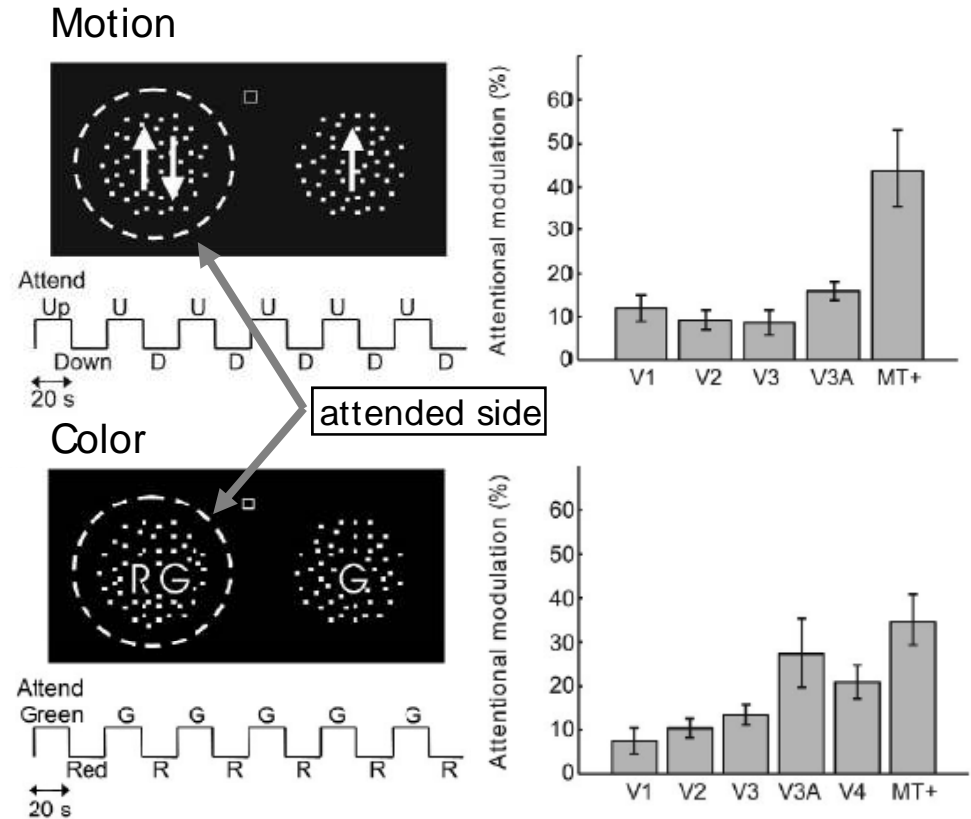
Spatial attentional selection:  
When subjects are cued to shift their attention between two locations of the visual field, striate and extrastriate cortex responses modulate with the alternation of the attentional cue: responses are greater when the subjects attend to the stimuli in the contralateral hemifield.



(Matrinez et al., 1999, Nature Neurosci)

## Basis of Attentional Selection: *Features*

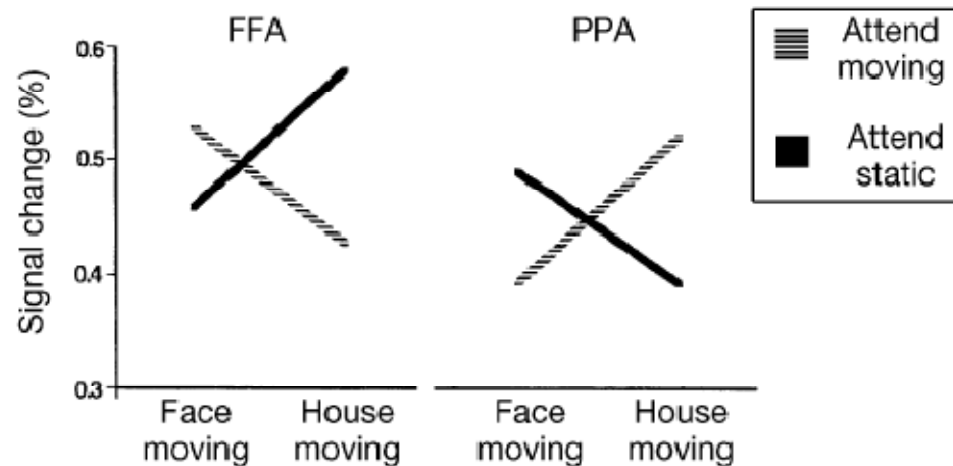
Global attentional selection: attention to a stimulus feature (color or direction of motion) increased the response of cortical visual areas not only to the stimuli at the attended location but also to a spatially distant, ignored stimulus that shared the same feature.



(Saenz et al., 2002, Nature Neurosci)

## Basis of Attentional Selection: *Objects*

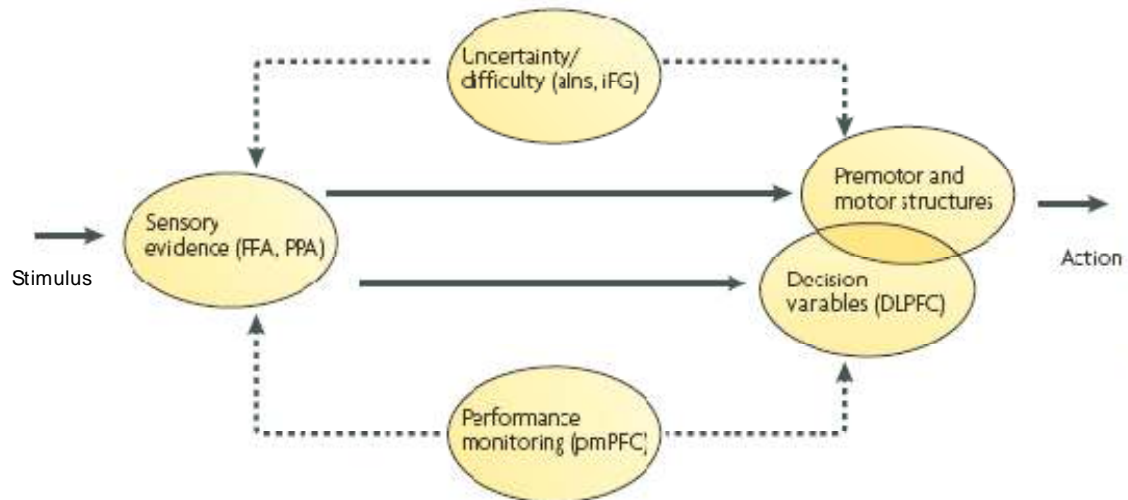
With stimuli consisting of a face transparently superimposed on a house, with one moving and the other stationary or vice versa, attending to the moving object resulted in higher activation not only in motion processing area MT but also in the cortical area selective for the moving object. This provides physiological evidence that whole objects are selected even when only one visual attribute is relevant, instead of locations or feature being the units of attentional selection.



(O'Craven et al., 1999, Nature)

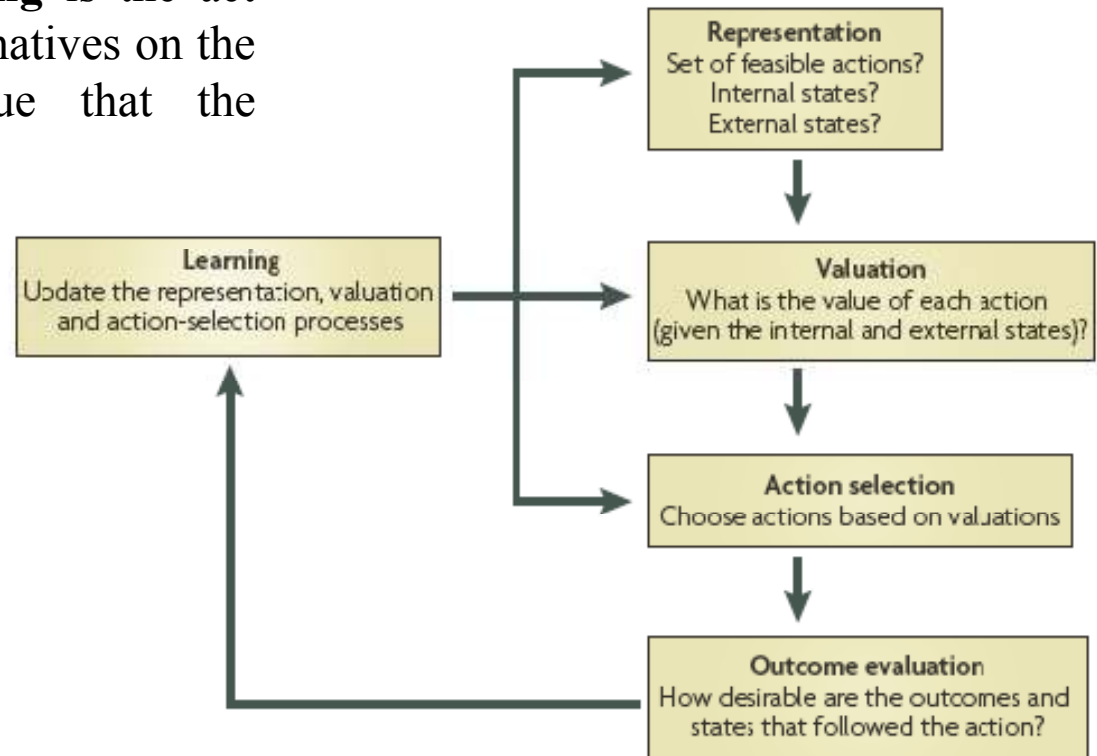
## Studying Areas Involved in Decision Making

• **Perceptual decision making** is the act of choosing one option or course of action from a set of alternatives on the basis of available sensory evidence. The cortical areas involved i) represent sensory evidence ii) accumulate and compare sensory evidence to compute a decision variable iii) monitor performance detecting errors to signal for adjustment of decision strategies.



(Heekeren et al. 2008, Nature Rev Neurosci)

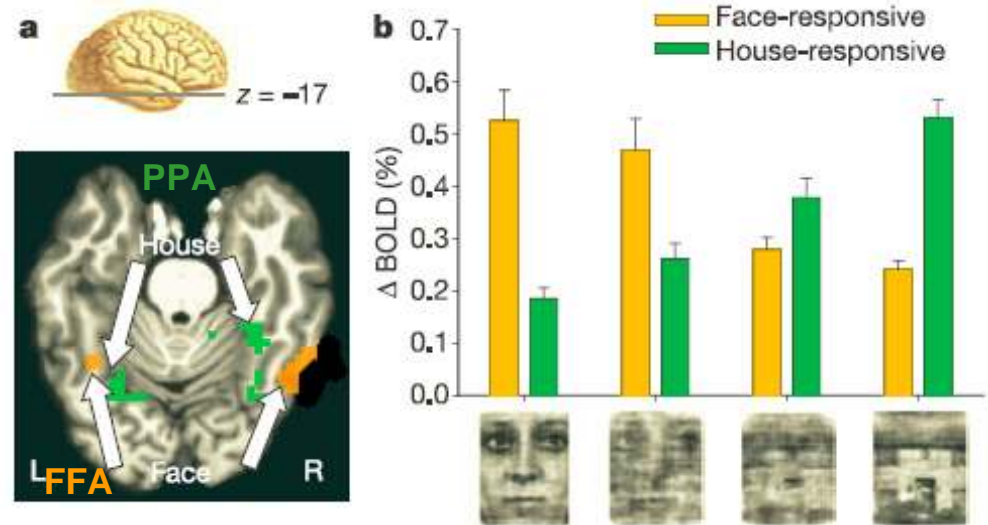
• **Value-based decision making** is the act of choosing from several alternatives on the basis of a subjective value that the individual places on them.



(Rangel et al. 2008, Nature Rev Neurosci)

## Sensory evidence representation in perceptual decision making

• For the preferred category, both face- (FFA) and house-selective regions (PPA) responded more to suprathreshold than to perithreshold images whereas the opposite was true for the non-preferred category, indicating that face- and house-selective regions in inferotemporal cortex represented the sensory evidence for the two respective categories.



(Heekeren et al., 2004, Nature)

# Studying the Neural Network Associated with Memory

## Long-term memory systems:

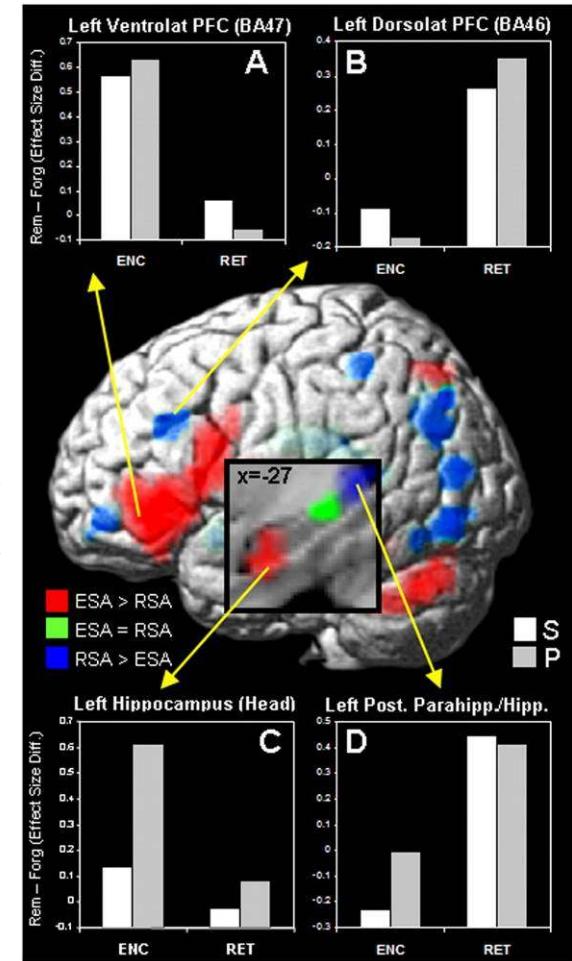
- Declarative (explicit) memory affords the capacity for conscious recollections about facts and events
  - subtypes: semantic memory; episodic memory
  - structures involved are medial-temporal lobe, prefrontal cortex, diencephalon and basal forebrain
- Non-declarative (implicit) memory, a heterogeneous collection of nonconscious abilities that includes the learning of skills and habits, priming and some forms of classical conditioning.

## Short-term memory:

- Working memory

## Encoding and retrieval of semantic and perceptual associations

- Encoding and retrieval differences were found within the:
  - medial temporal lobes (MTLs): encoding (ESA) induced greater activity in the anterior hippocampus, while retrieval (RSA) was associated with greater activity in the posterior parahippocampal cortex/hippocampus (encoding-retrieval gradient along the longitudinal MTL axis).
  - prefrontal cortex (PFC): encoding induced greater activity in ventrolateral PFC, while retrieval was associated with greater activity in dorsolateral and anterior PFC.
- Only the left hippocampus was associated with relational memory in general (i.e., for both semantic and perceptual encoding and retrieval)

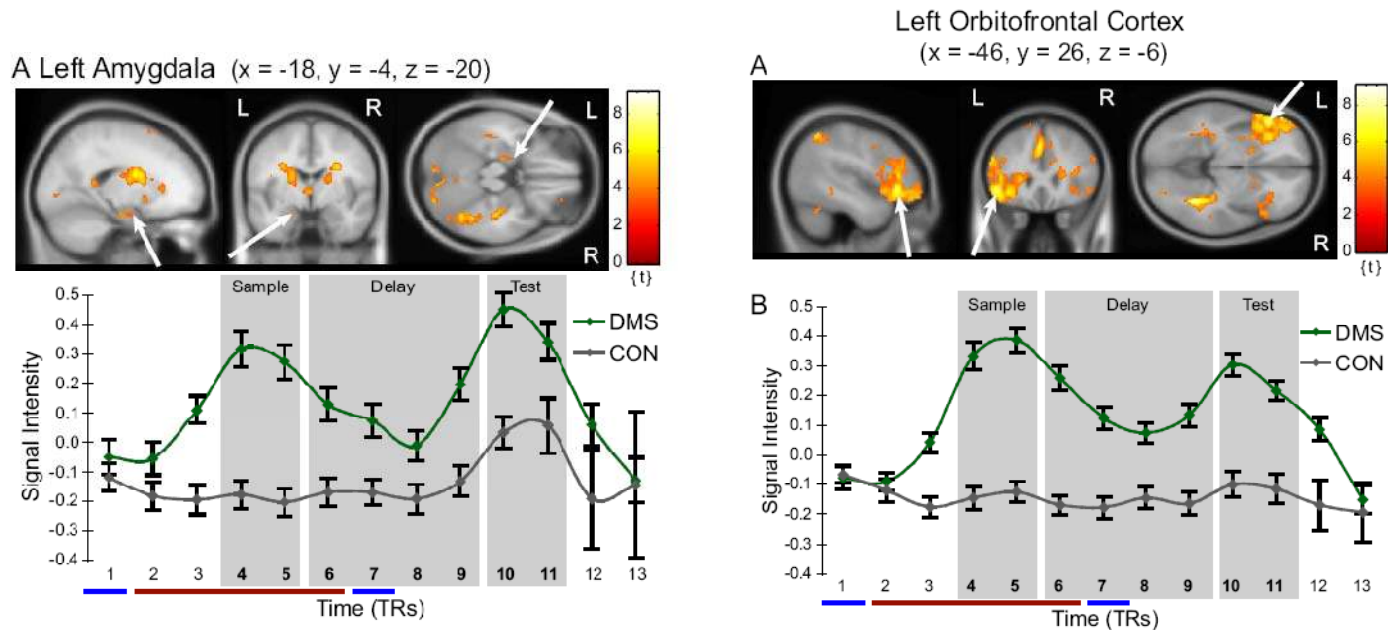


(Prince et al., 2005, J Neurosci)

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## Working memory for emotional expressions

- Although initial processing of emotion and identity is accomplished in anatomically segregated temporal and occipital regions, active maintenance of both facial emotions and identity is associated with a sustained delay-period activity in orbitofrontal cortex (OFC), amygdala and hippocampus.

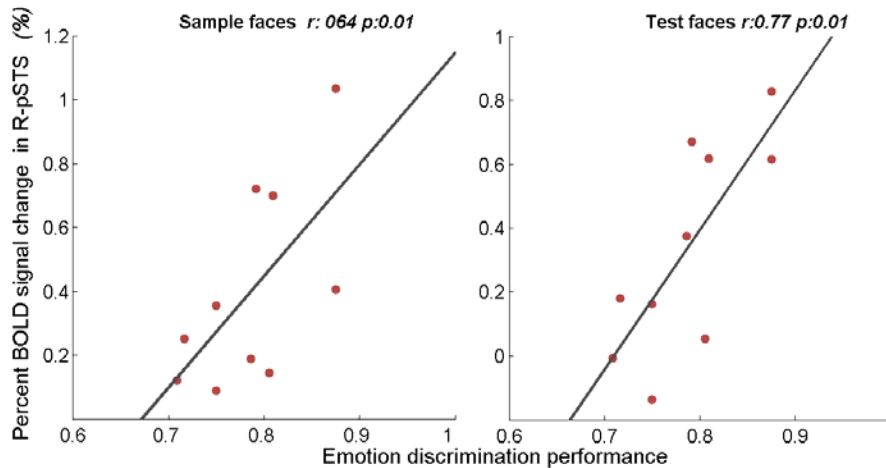


(LoPresti et al., 2008, J Neurosci)

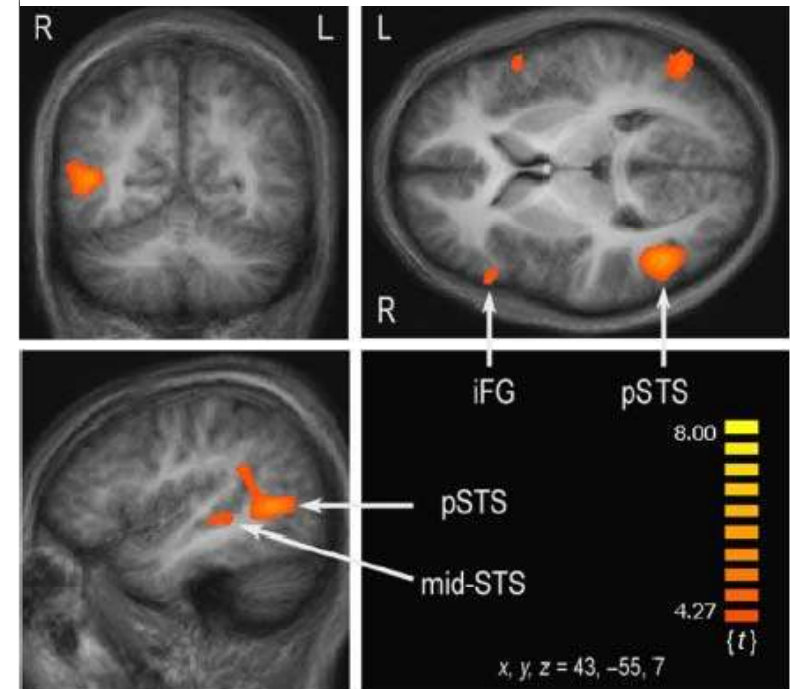
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## Working memory for emotional expressions II

- Short-term encoding and retrieval of facial expressions depend on the activation level of right pSTS, which predominantly processes changeable facial features such as facial expressions
- Correlation only existed if expression was attended and disappeared when identity was relevant



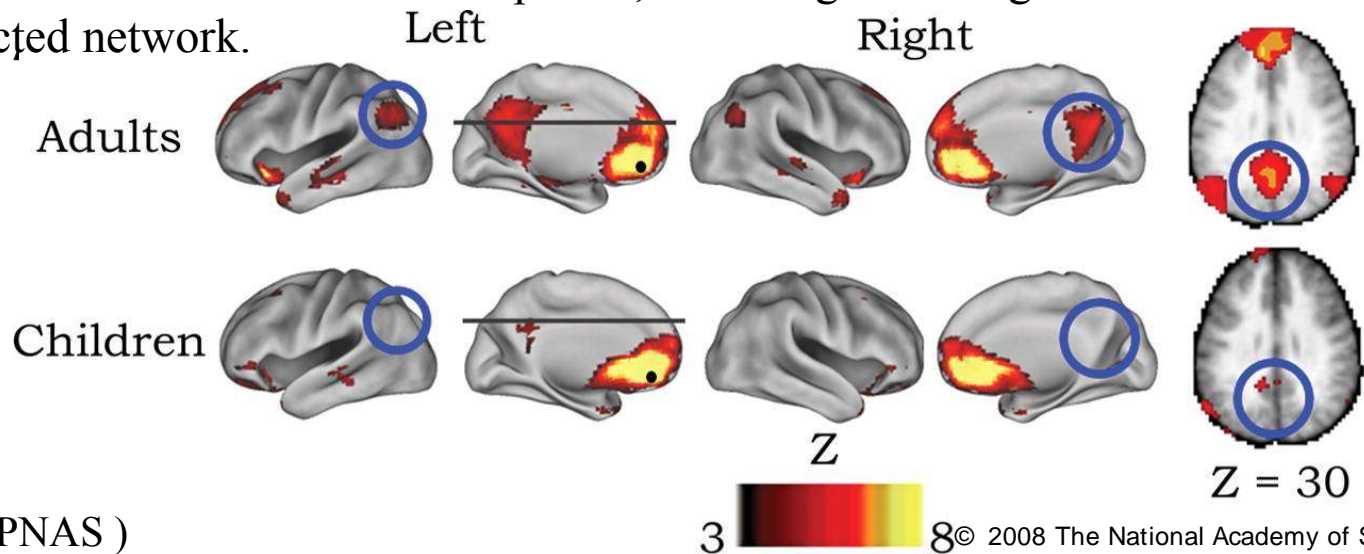
Attend to emotion > attend to identity



(Bankó et al., 2009, J Vision)

## Resting State fMRI – Default Network

- A baseline or control state is fundamental to the understanding of most complex systems.
- Default network: areas that consistently exhibit decreases from this baseline, during a wide variety of goal-directed behaviors. These decreases suggest the existence of an organized, baseline default mode of brain function that is suspended during specific goal-directed behaviors. Over development, these regions integrate into a cohesive, interconnected network.



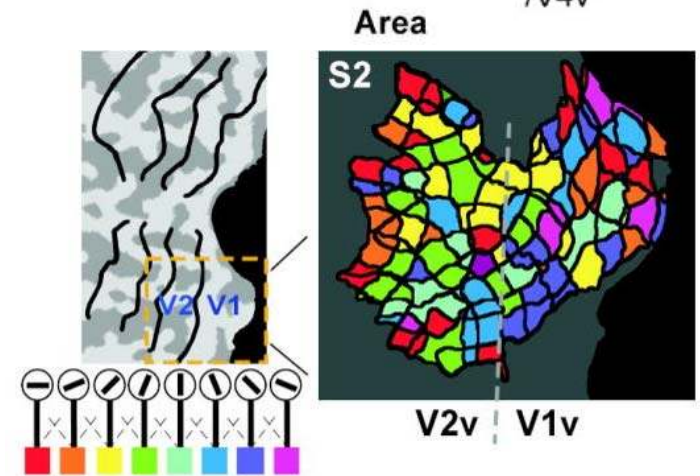
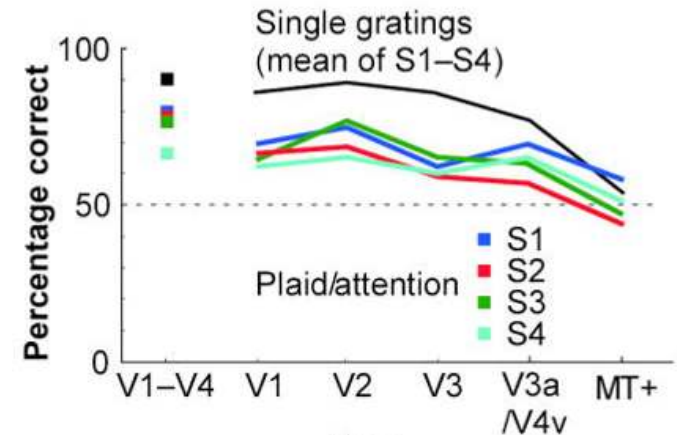
(Fair et al. 2008, PNAS )

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# Other fMRI applications

# “Mindreading” – Decoding Cortical Activity

- Ensemble fMRI signals in early visual areas can reliably predict on individual trials which of eight stimulus orientations the subject was seeing.
- Feature-based attention strongly biased ensemble activity towards the attended orientation
  - fMRI activity patterns in early visual areas, including primary visual cortex (V1), contain detailed orientation information that can reliably predict subjective perception.

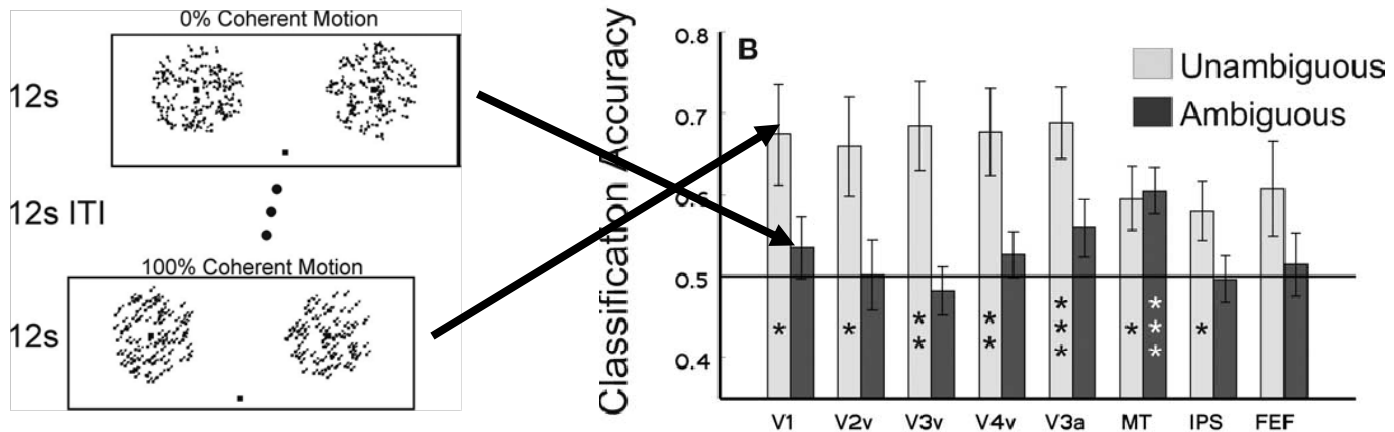


(Kamitani and Tong, 2005, Nature Neurosci)

## “Mindreading” – Decoding Cortical Activity II

### Representation of Behavioral Choice for Motion in Human Visual Cortex

- Multivoxel pattern analysis (MVPA) enables to discriminate with 60-70% accuracy between leftward and rightward motion in the case of 100% motion coherence in all areas regardless of its motion selectivity. However only motion sensitive area hMT+ was able to discriminate between perceived direction of motion (ambiguos stimulus) making this area the candidate which the conscious experience is based on.



(Serences and Boynton, 2007, J Neurosci)

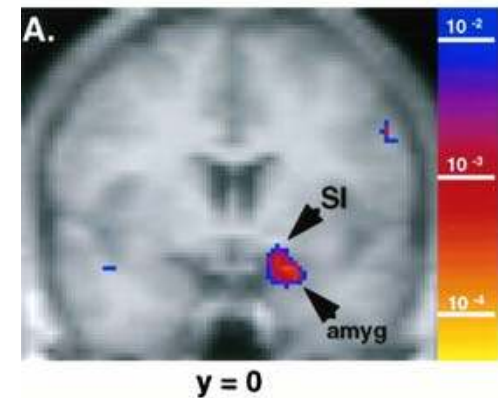
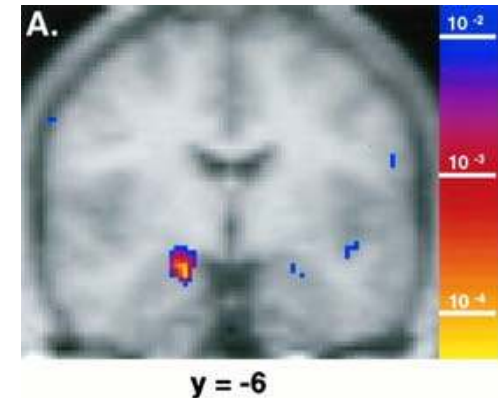
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## “Mindreading” – Perception w/o awareness

fMRI is a useful tool to investigate perception without awareness, because the neural locus of any activation that occurs outside of awareness provides some information about the nature of the information represented:

- The presentation of fearful faces masked with neutral faces elicits a stronger amygdala response than when happy faces are presented before neutral faces, even though subjects failed to see any expressive faces.

→ amygdala responds to nonconscious stimuli



(Whalen et al. 1998, J Neurosci)

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