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

Consortium leader

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Consortium members

SEMMELWEIS UNIVERSITY, DIALOG CAMPUS PUBLISHER

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**Molekuláris bionika és Infobionika Szakok tananyagának komplex fejlesztése konzorciumi keretben

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BIOMEDICAL IMAGING

(Orvosbiológiai képalkotás)

fMRI – Neuroscience Applications

(fMRI alkalmazása a kutatásban)

ÉVA BANKÓ, ISTVÁN KÓBOR,
ZOLTÁN VIDNYÁNSZKY

Important Tool to Investigate Brain Function

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

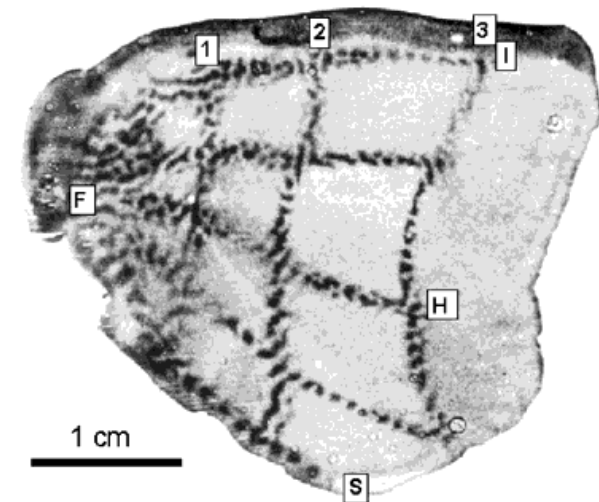
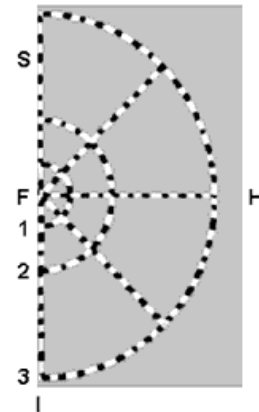
Sensory Processing

Retinotopical Mapping

Aim is to separate early and mid-level visual areas

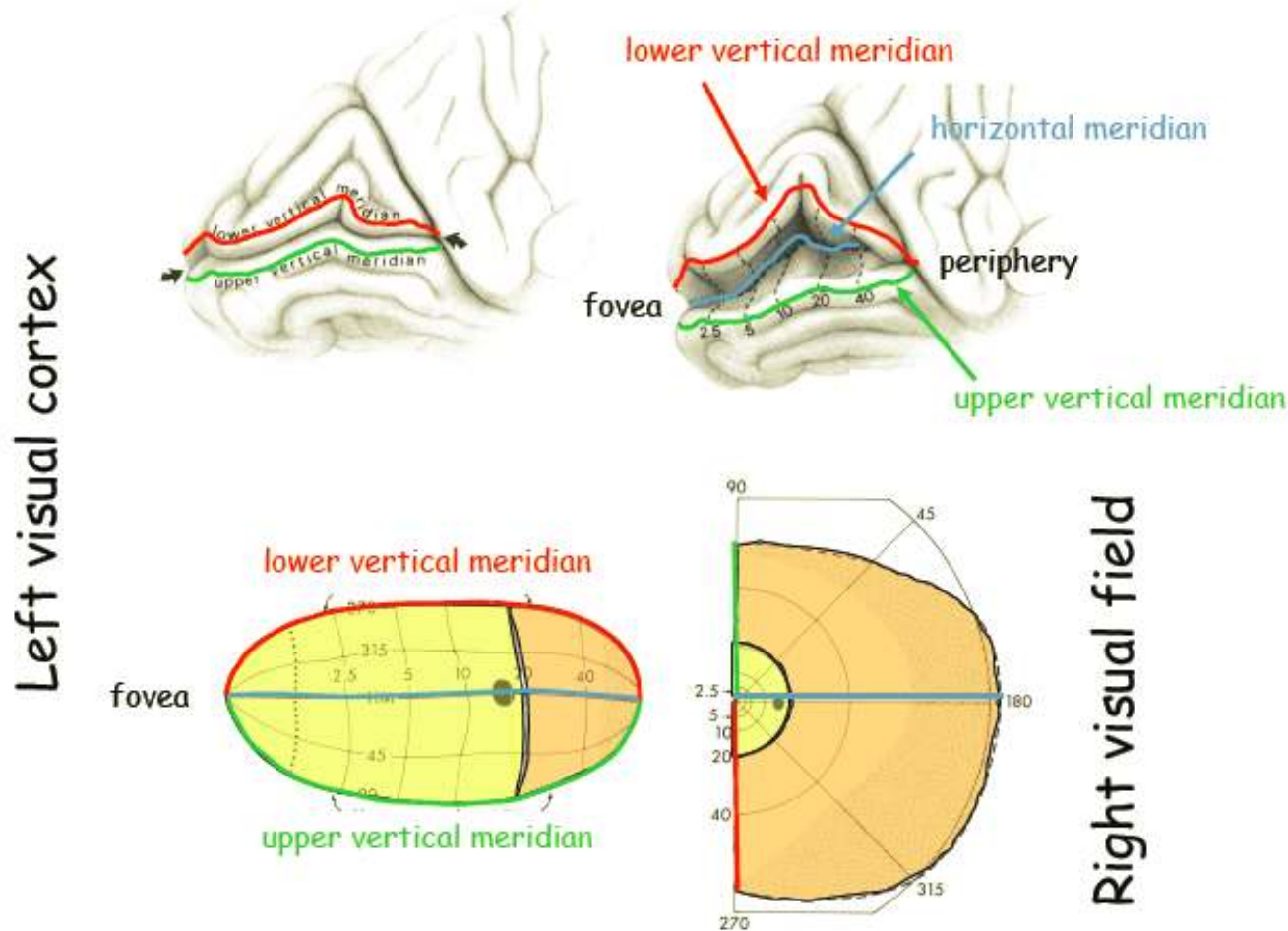
Visual areas in the brain are defined by

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



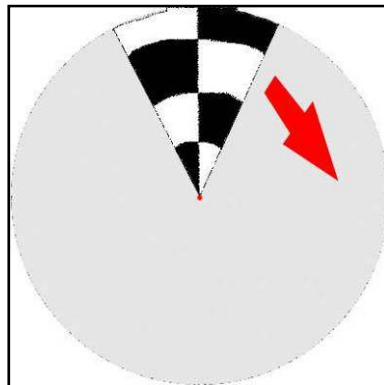
Neural representation of the stimulus in the primary visual cortex of a macaque monkey (Tootell et al. 1988, J Neurosci).

Visual field representation in human primary visual cortex (V1)

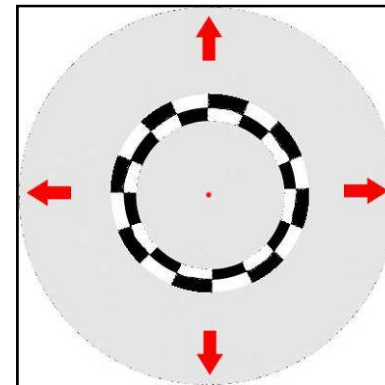


Protocol for Retinotopy

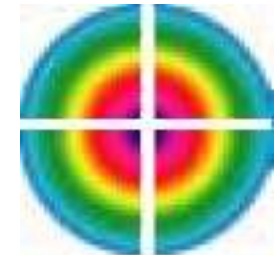
- Phase reversing checkerboard stimulus for strong excitation
- Aim is to probe the entire visual field:
 - Rotating wedge to get information about visual field quadrants
 - Contracting-expanding ring to get information about eccentricity



CW/CCW rotating wedge



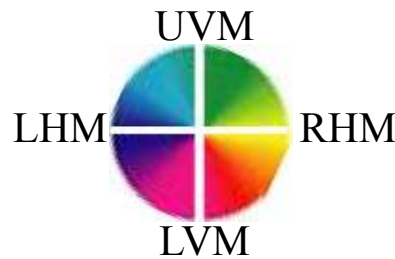
Contracting/expanding ring



Defining visual areas on flattened cortex

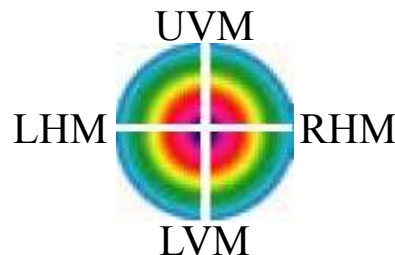
Phase map

- Phase reversal delineates areas



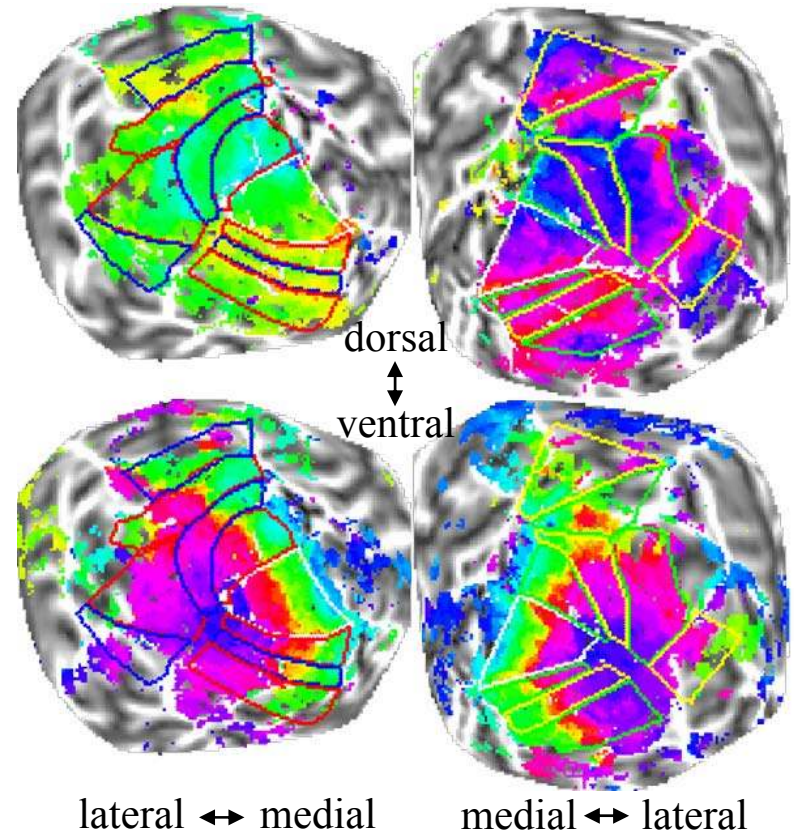
Eccentricity map

- Tells about foveal and peripheral representation of each area



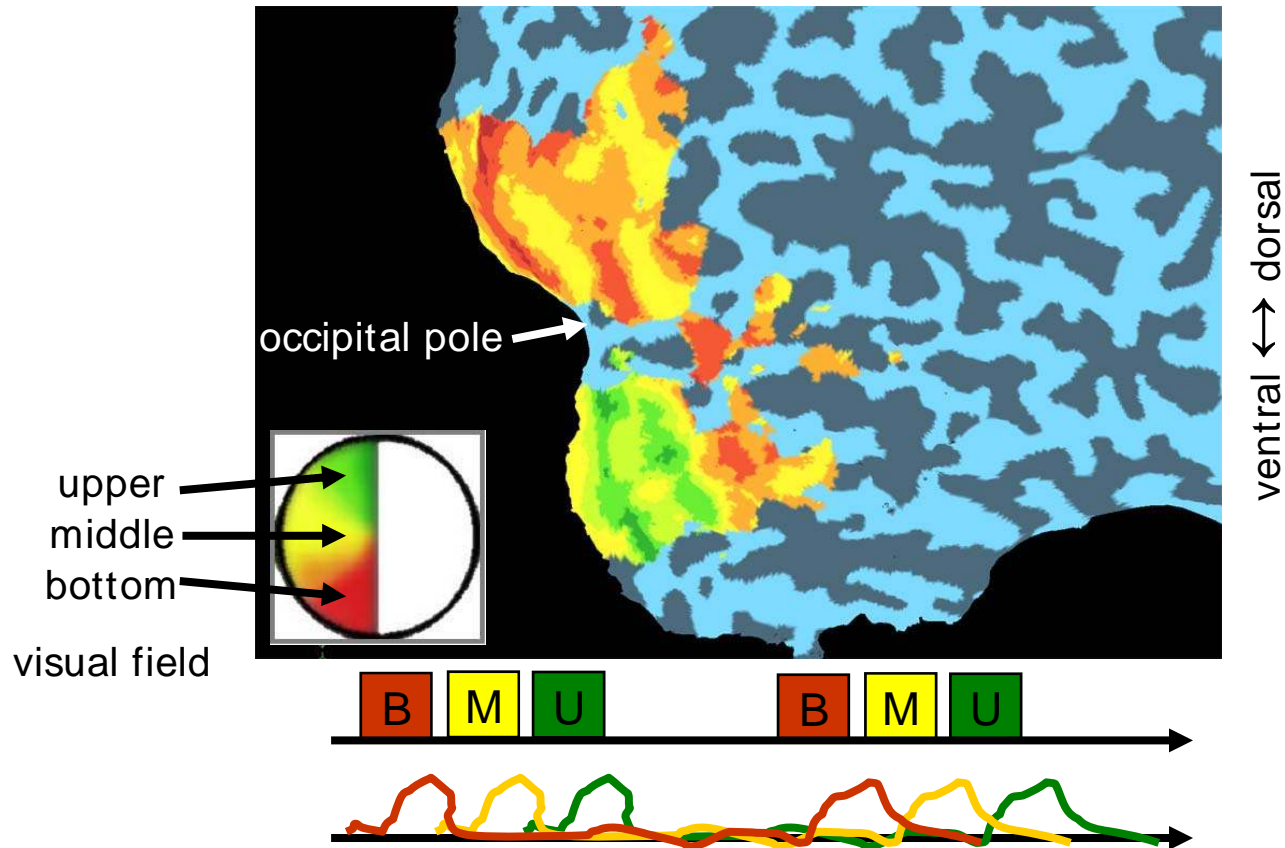
Left hemisphere

Right hemisphere

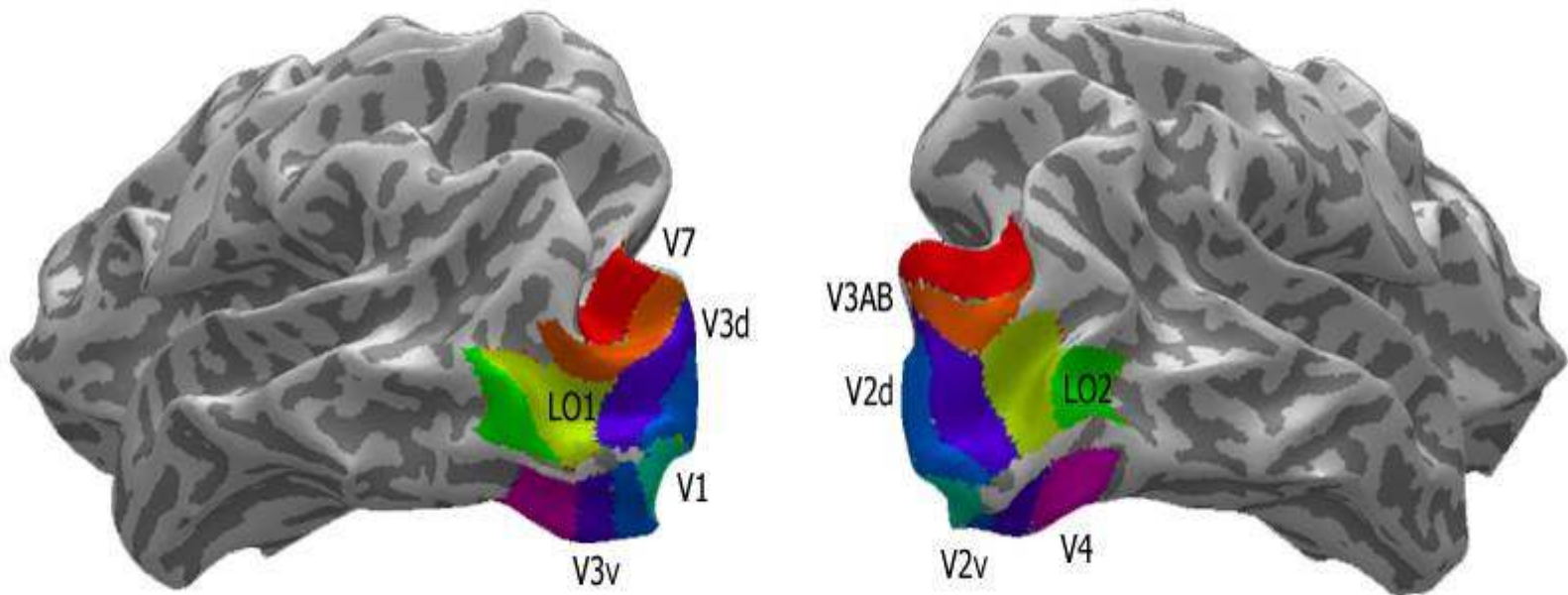


Retinotopy Demo

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.

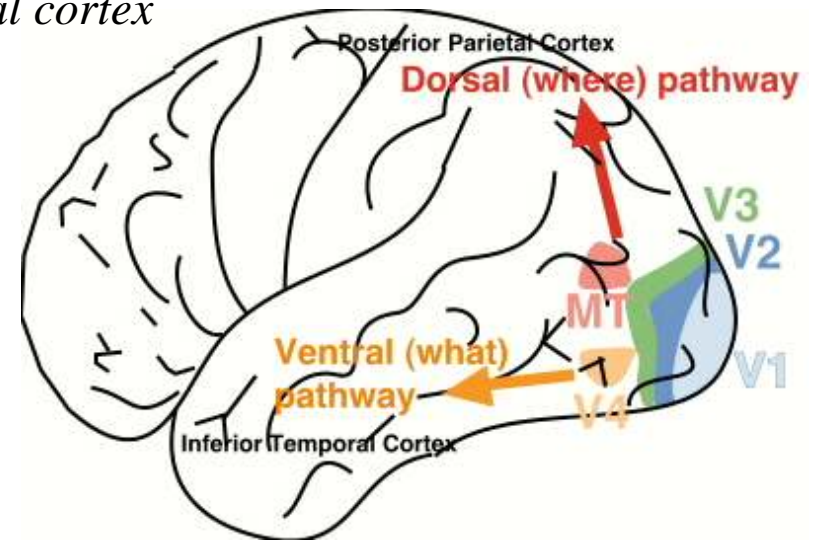


- Topographic mapping can also be done in somatosensory and auditory cortices.

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+*

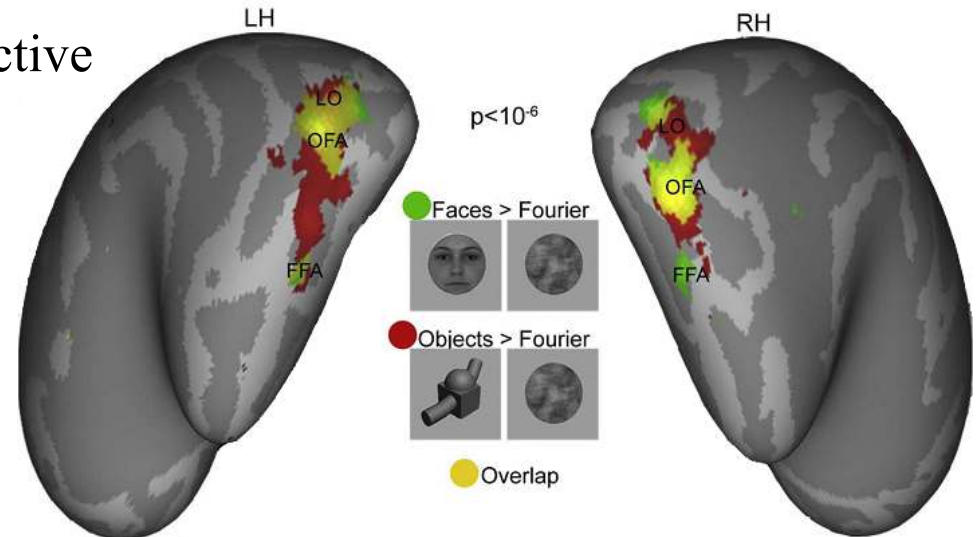


(Mischkin & Ungerleider 1983, Trends Neurosci)

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



(Kovács et al. 2008, Neuroimage)

Face processing network

Inferior occipital gyri
Early perception of facial features

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

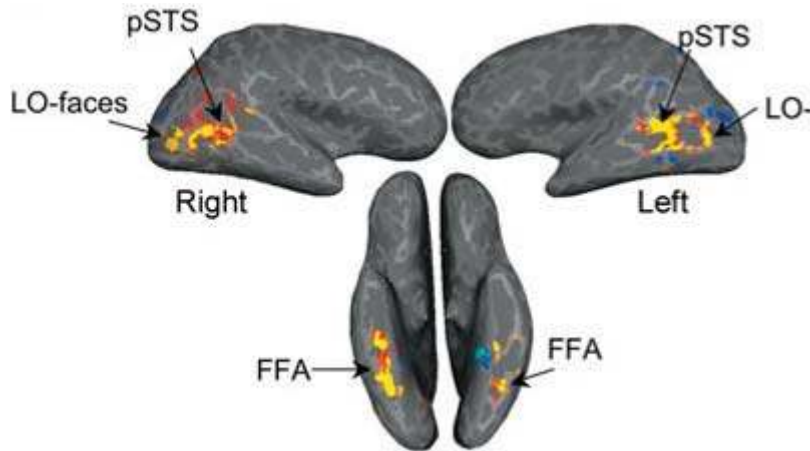
Superior temporal sulcus
Changeable aspects of faces – perception of eye gaze, expression and lip movement

Mainly the posterior part of STS (pSTS)

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

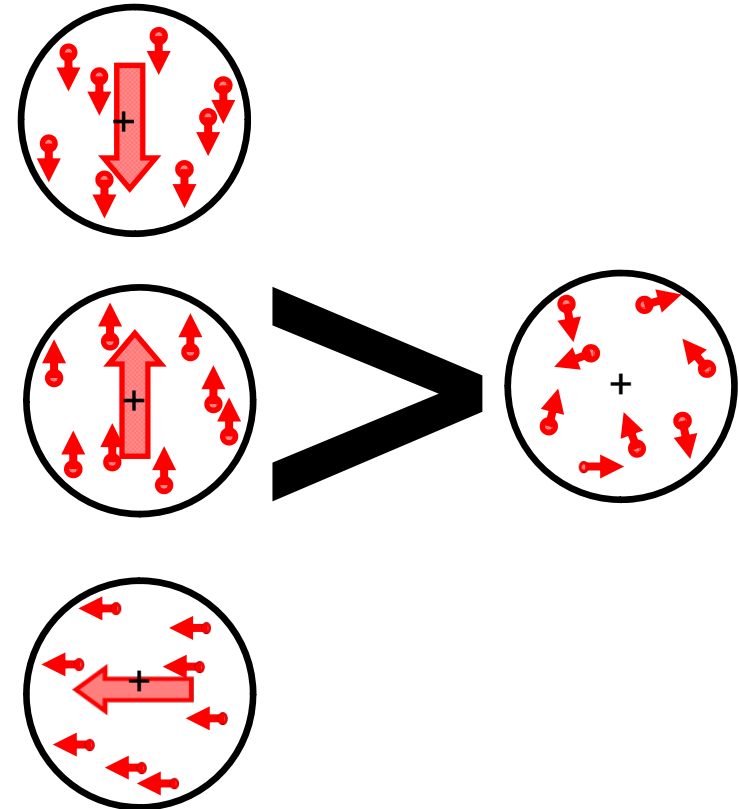
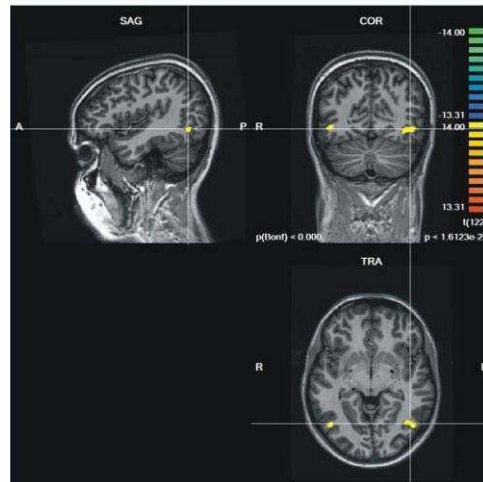
i.e. Fusiform Face Area, strongly right lateralized

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



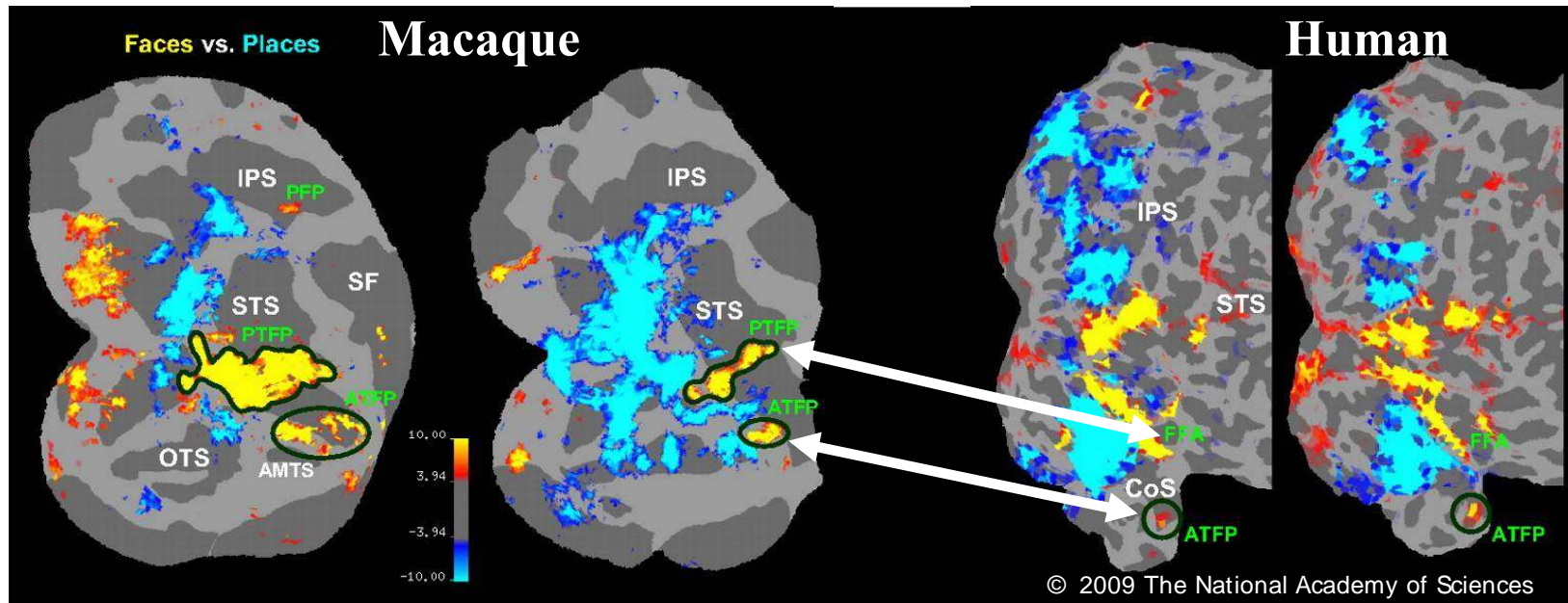
(Grill-Spector et al, 2004, Nature Neurosci) (Haxby et al, 2000, Trends Cog Sci)

- ***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

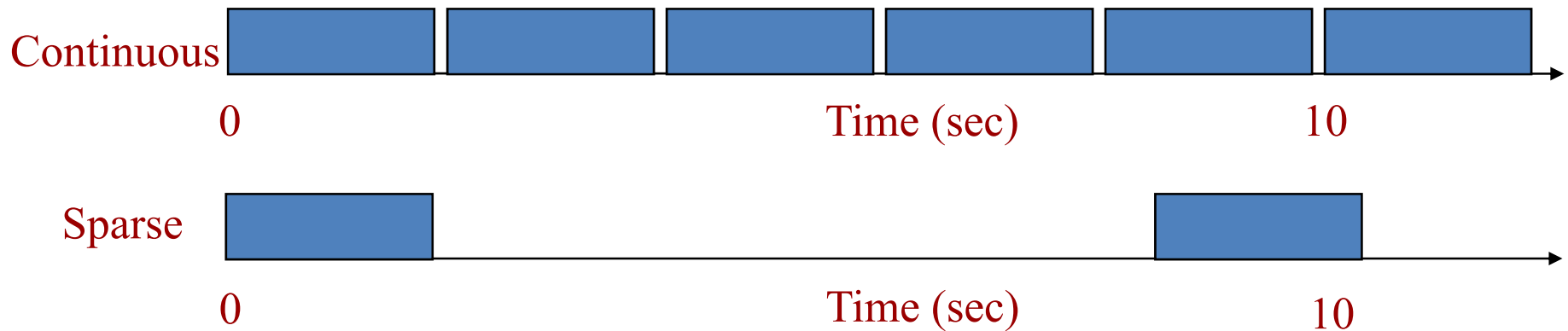
FFA: Fusiform Face Area

ATFP: Ant. Temp. Face Patch

(Rajimehr et al., 2009, PNAS)

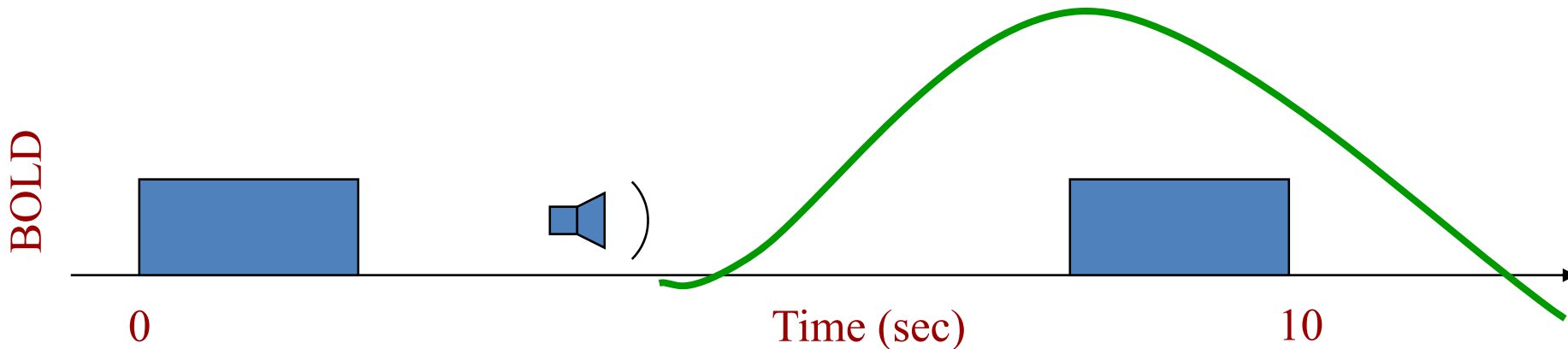
Studying the Auditory System

- Sparse fMRI:
 - To explore central auditory function may be compromised by the intense bursts of stray acoustic noise produced by the scanner whenever the magnetic resonance signal is read out
 - Sparse imaging includes a delay between each fMRI volume, so stimuli can be presented while scanner is silent.



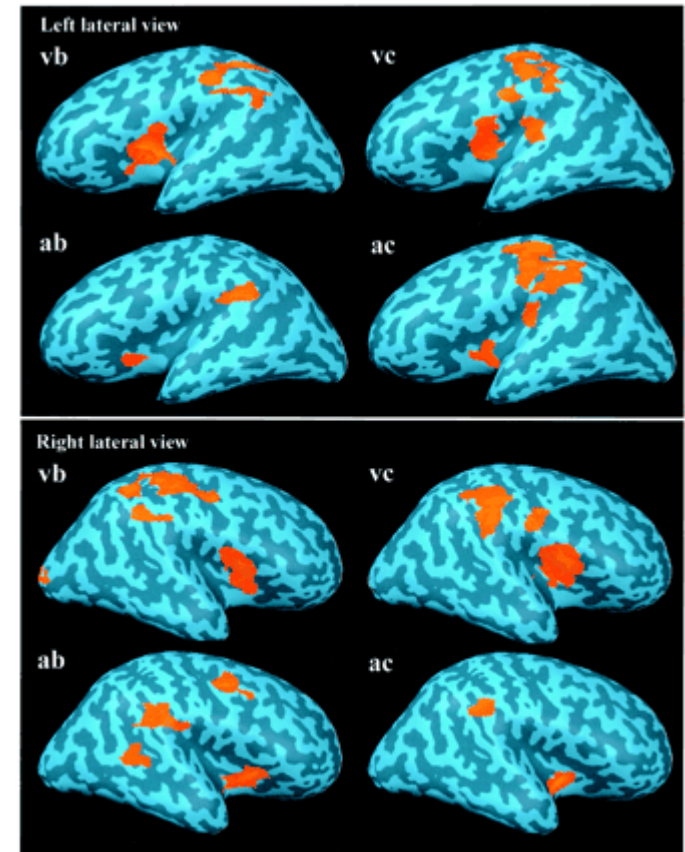
Sparse fMRI:

- Typically, sparse design like a block design – each acquisition measures effect of single stimuli.
- Stimuli must be presented ~5sec prior to acquisition.
- Sparse designs have less power than continuous designs, and it is difficult to estimate latency of BOLD response.
- Due to T1 effects, Sparse designs can still have good power.



Continuous fMRI: The functional neuroanatomy of target detection

- When performing both auditory and visual oddball task significant increases in fMRI signal for target versus non-target conditions were observed in the supramarginal gyrus, frontal operculum and insular cortex bilaterally, and in further circumscribed parietal and frontal regions corresponding to the P300 component.
- The effects were consistent over various stimulation and response modalities and can be regarded as specific for target detection in both the auditory and the visual modality. These results therefore contribute to the understanding of the target detection network in human cerebral cortex and impose constraints on attempts at localizing the neuronal P300 generator

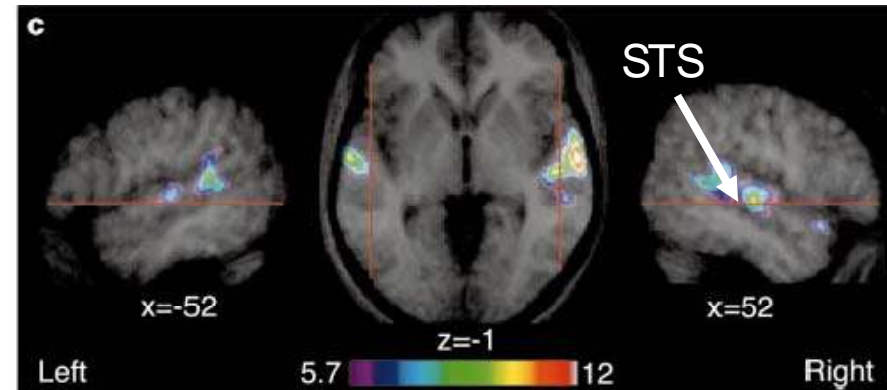


(Linden et al. 1999, Cereb Cortex)

Sparse fMRI: Voice-selective areas in human auditory cortex

- Voice-selective regions can be found bilaterally along the upper bank of the superior temporal sulcus (STS):

- greater neuronal activity when subjects listened passively to vocal sounds, than to non-vocal environmental sounds
- high degree of selectivity (central STS) – responding significantly more to vocal sounds than to matched control stimuli, including scrambled voices and amplitude-modulated noise

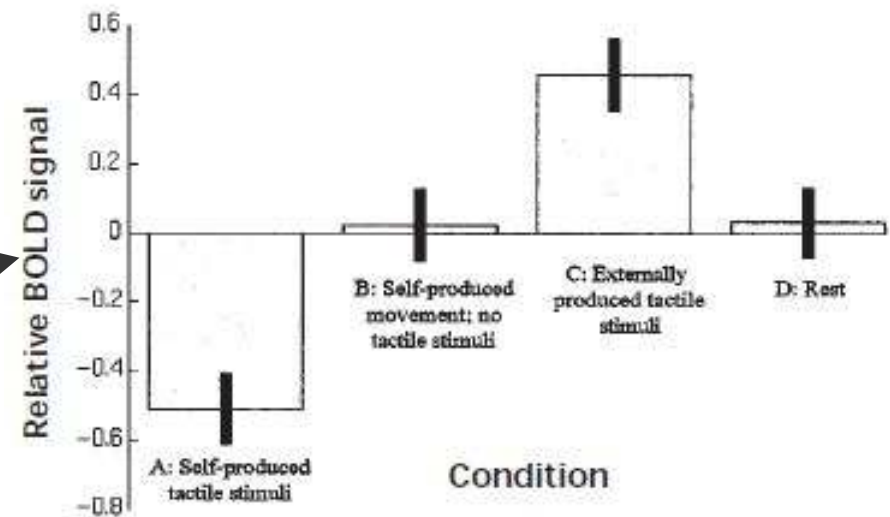
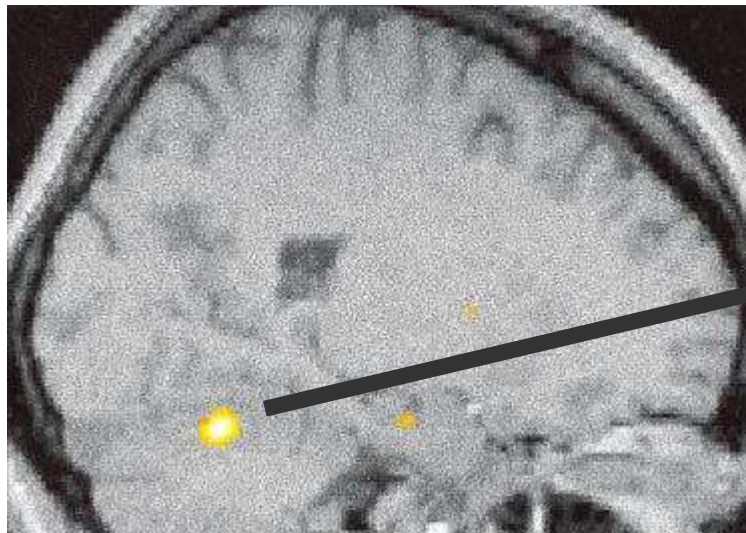


- The voice-selective areas in the STS may represent the counterpart of the face-selective areas in human visual cortex.

(Belin et al. 2000, Nature)

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)

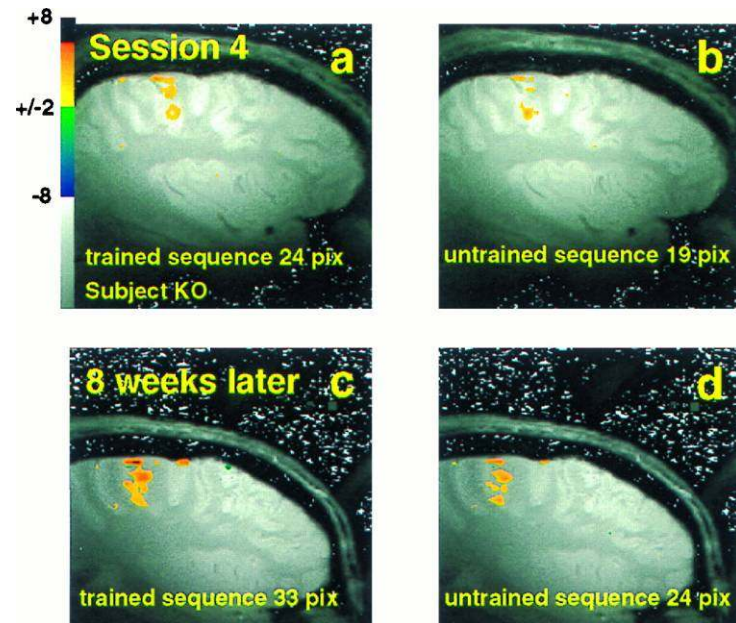
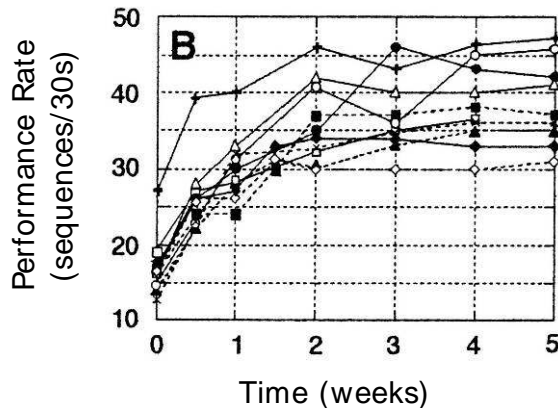


Neuronal Plasticity

Plasticity Underlying Long-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)

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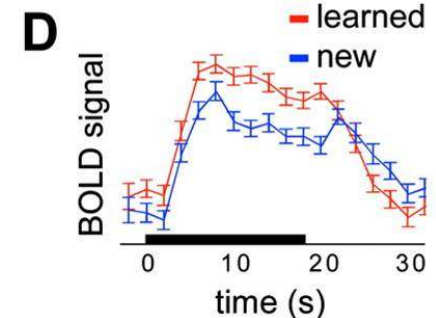
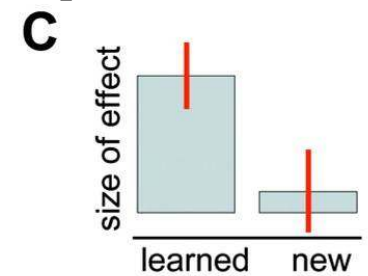
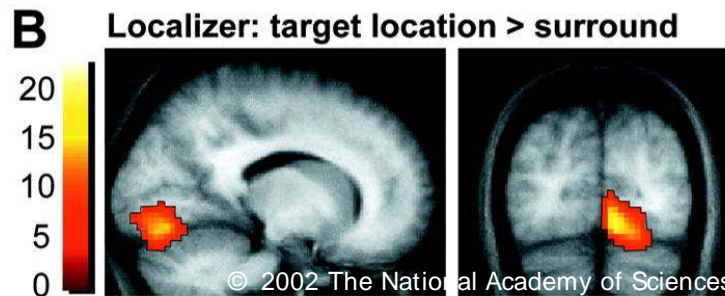
Enhancement of relevant information during perceptual learning

- *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)

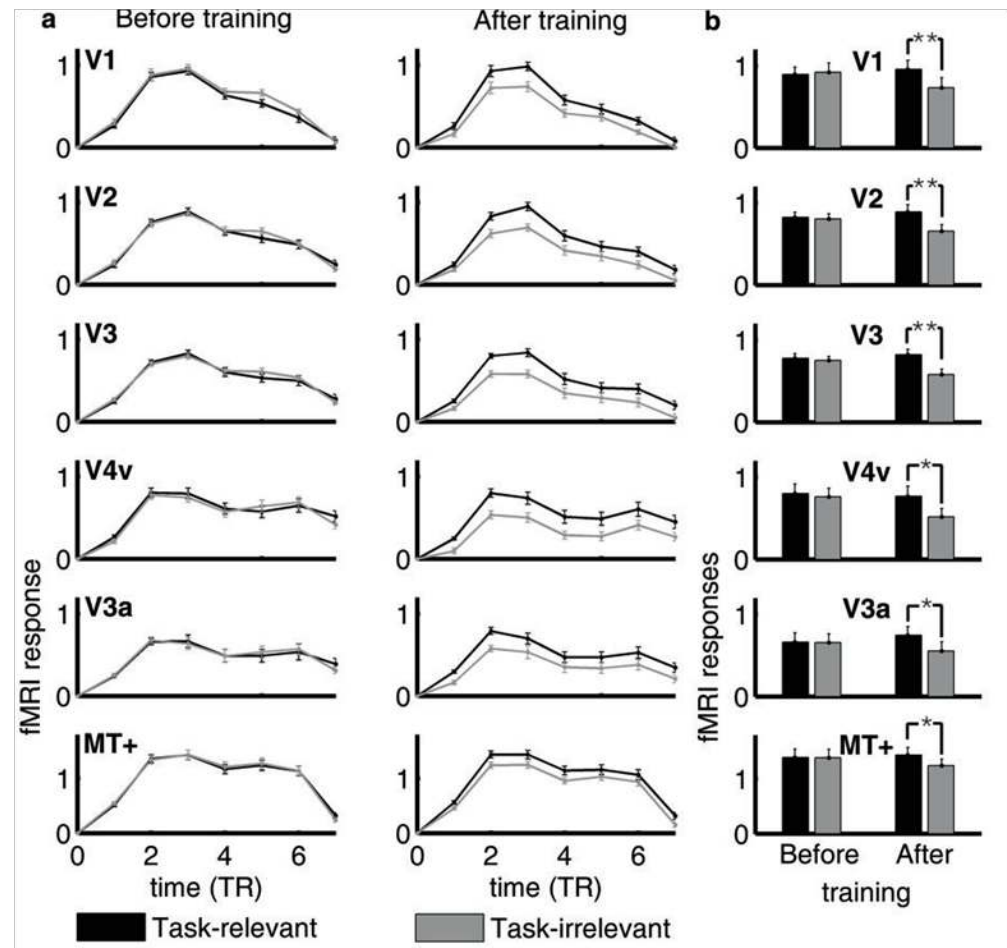


Learning to suppress irrelevant stimuli

- 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

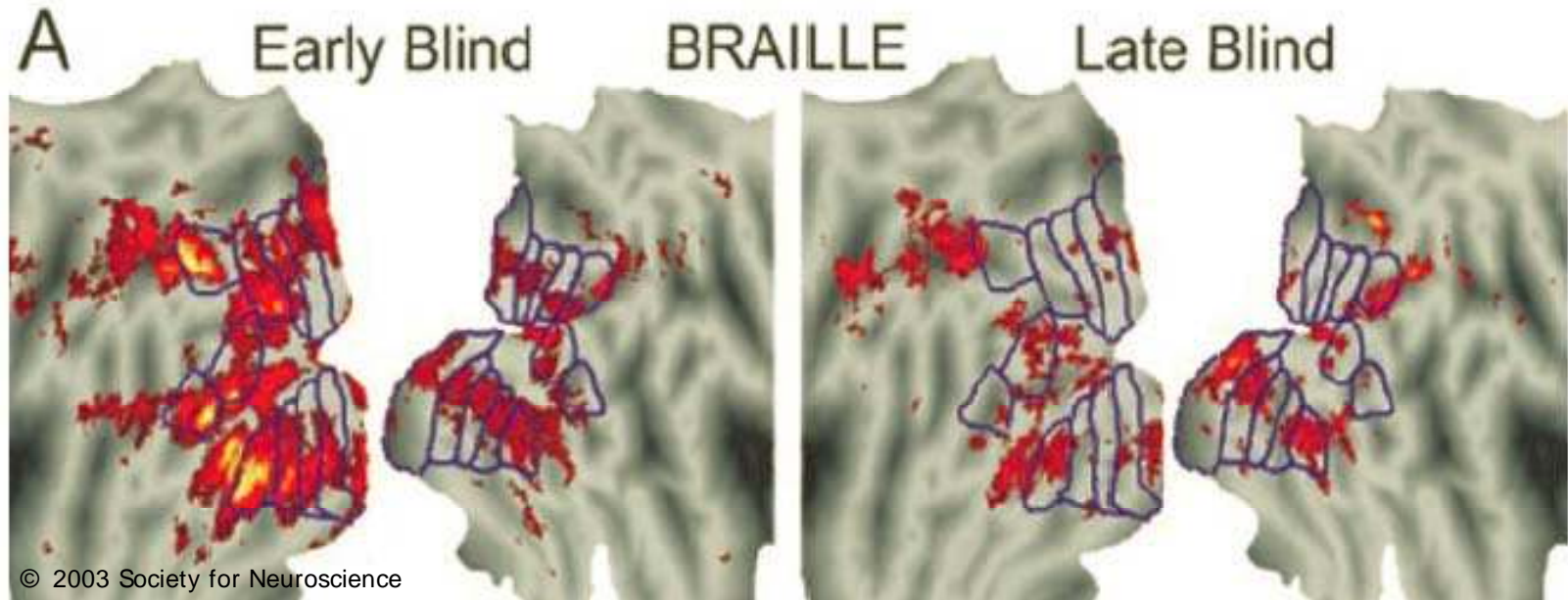
→ learning leads to *suppressed perceptual and neural responses for task-irrelevant information*, which competes with the processing of the task-relevant information during training

(Gál et al., 2009, E J Neurosci)



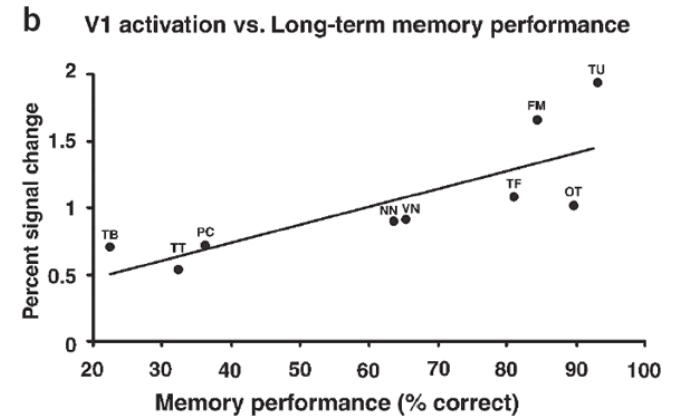
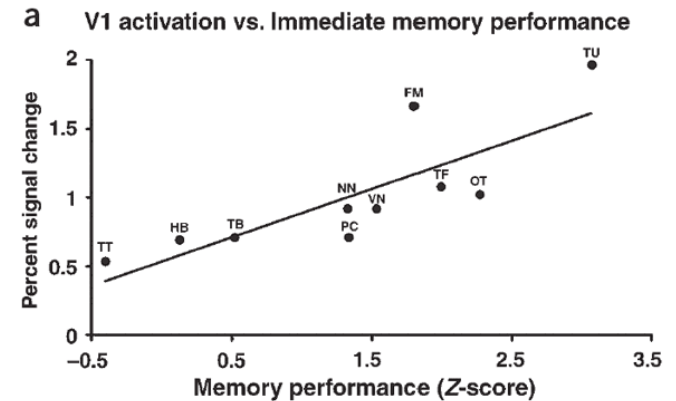
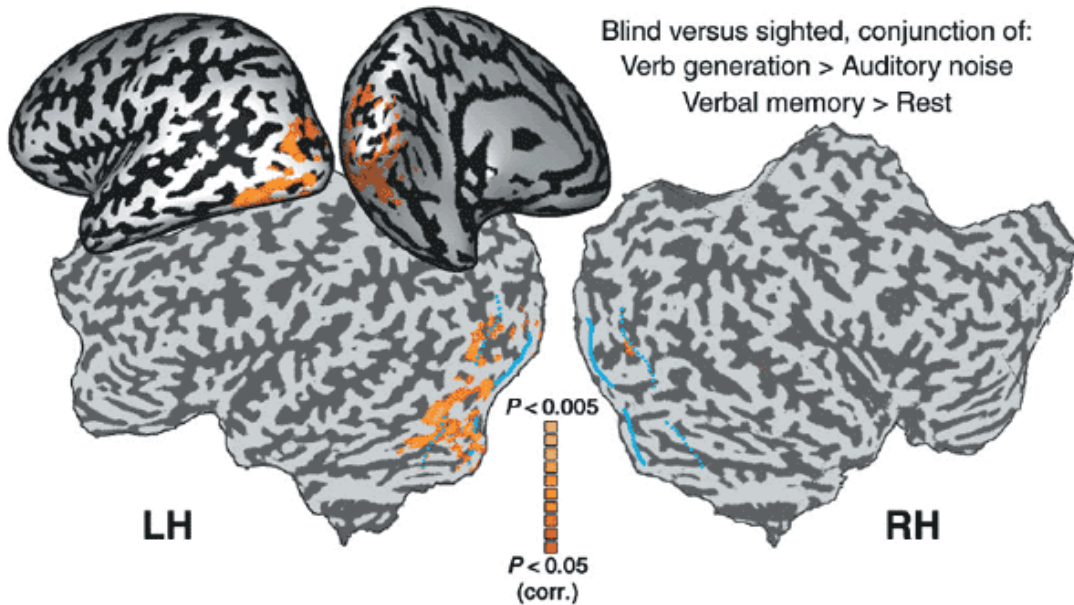
Studying Long-Term Cortical Reorganization

- 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)

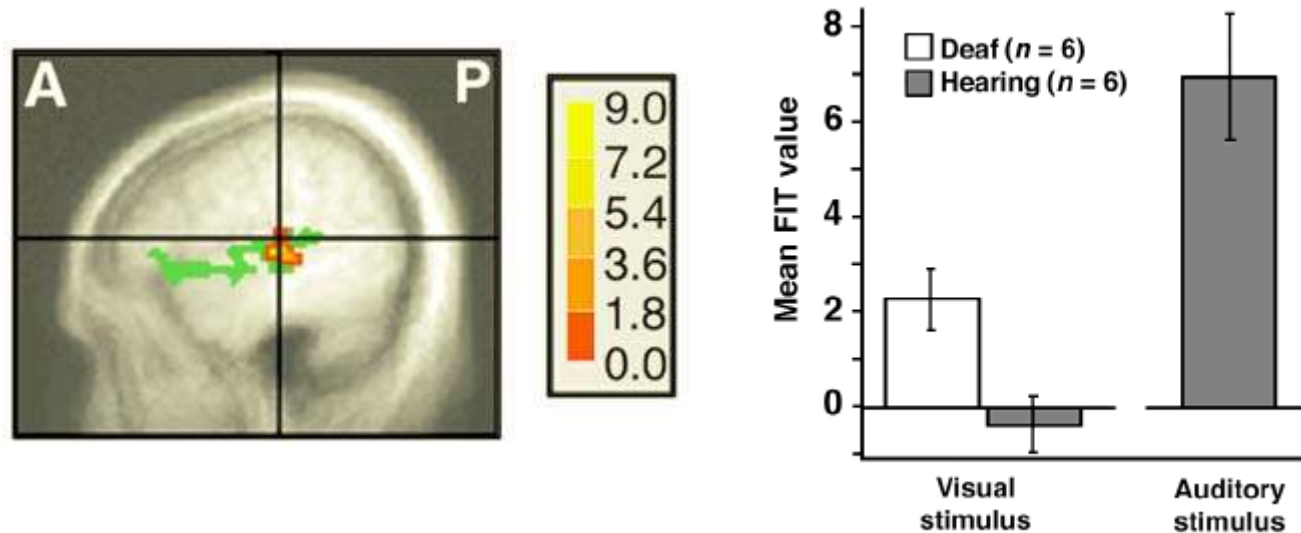
- Visual cortex activation in verbal tasks in blind people also correlates with verbal memory performance



(Amedi et al, 2003, Nature Neurosci)

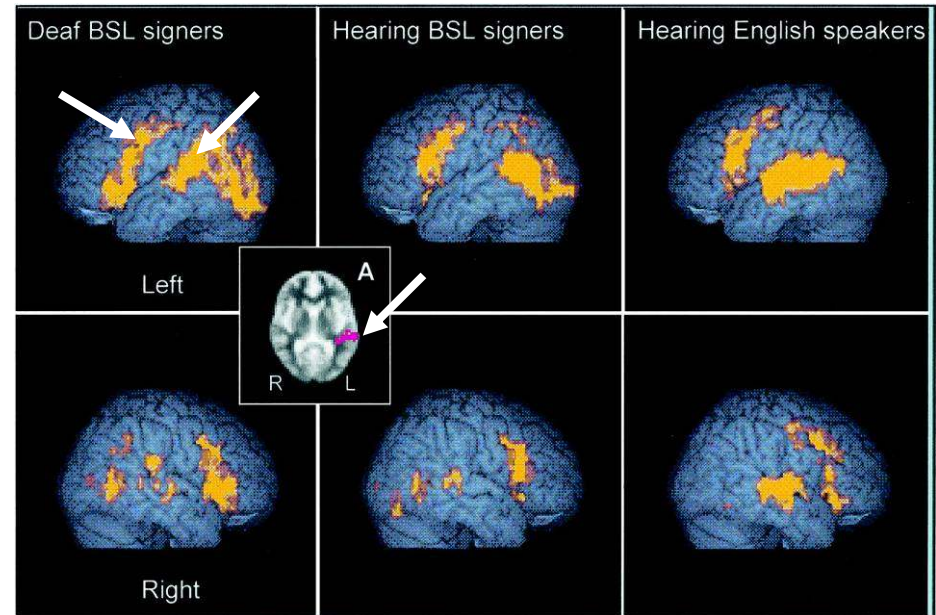
Cross-modal plasticity in congenitally deaf:

- 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.



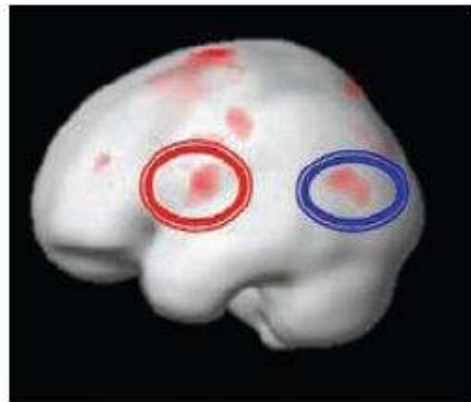
(MacSweeney et al. 2002, Brain)

Studying Developmental Plasticity

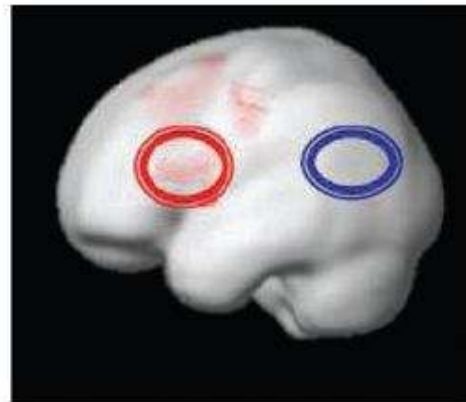
Dyslexia, a developmental disorder

- 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

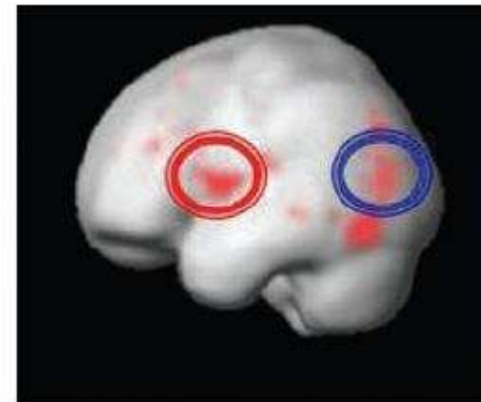
Brain Plasticity Associated with Treatment



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.

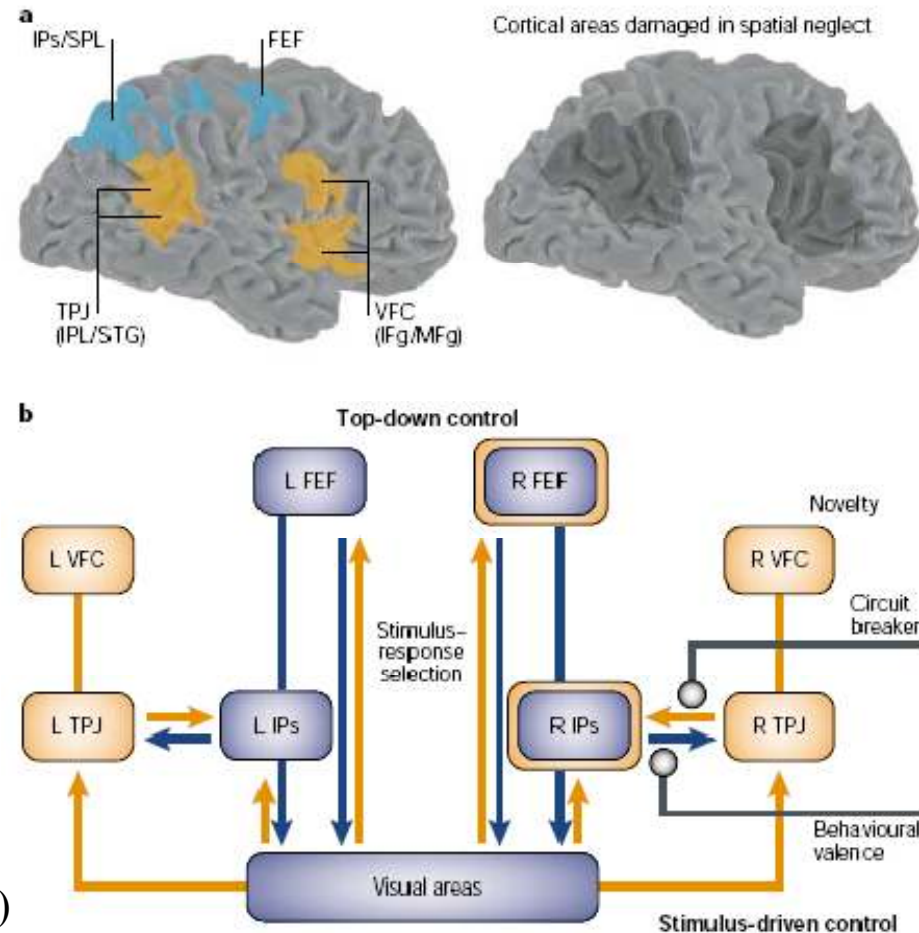
Cognitive Functions

Studying the Organization of Attention System

Attention systems:

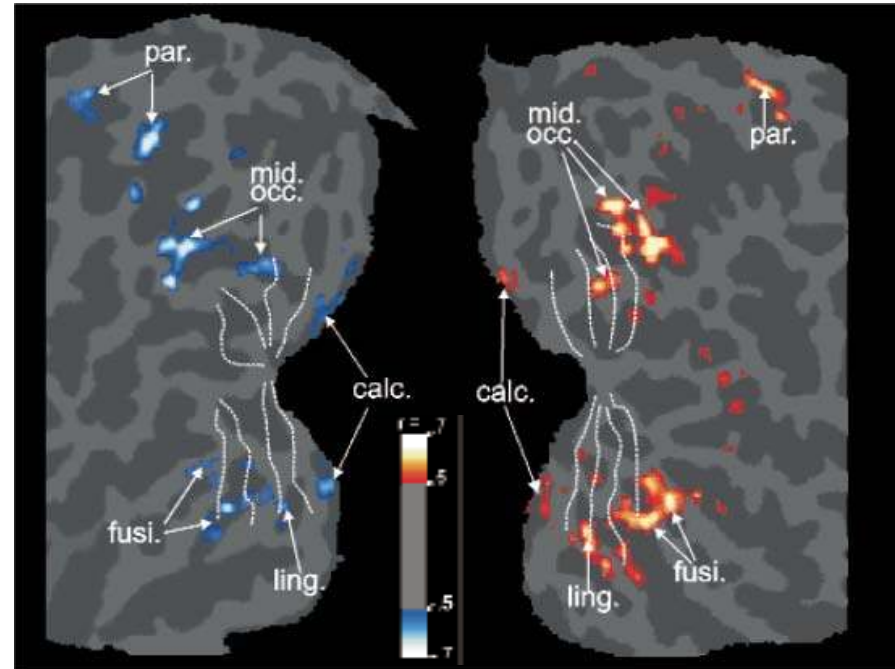
- **Dorsal goal-directed attentional network** (blue) is involved in preparing and applying goal-directed (top-down) selection for stimuli and responses. (rightward bias)
- **Ventral stimulus-driven attentional network** (orange) is not involved in top-down selection. Instead, this system is specialized 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*

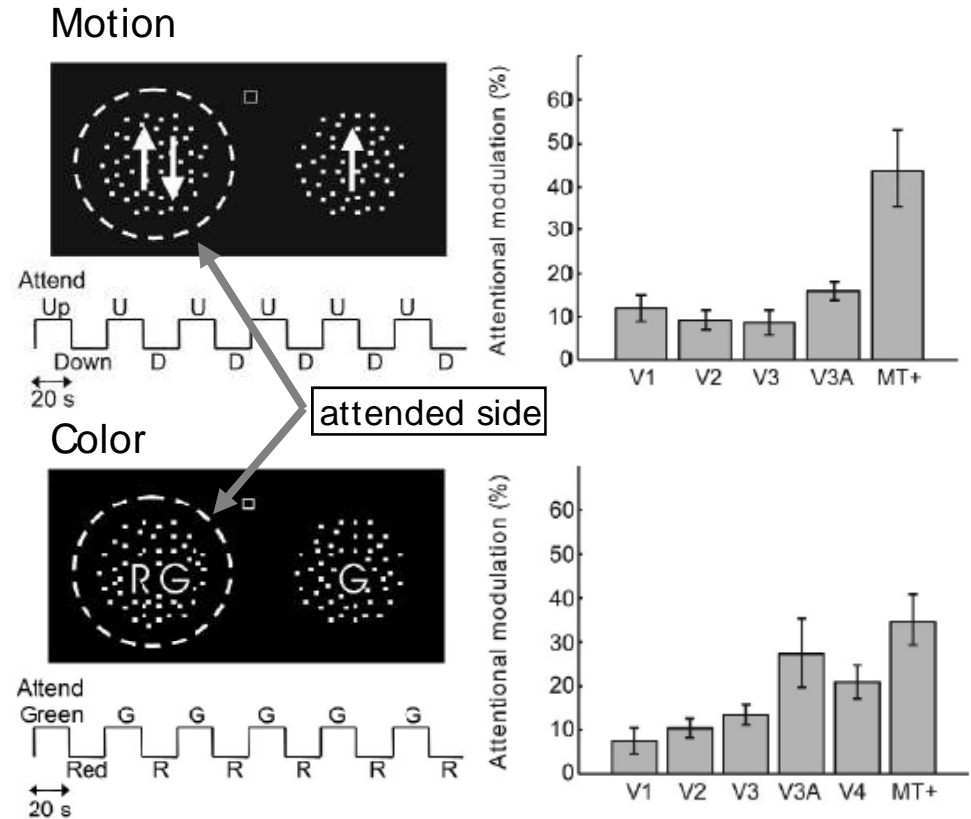
Spatial attentional selection:
When subjects are cued to shift their attention between two locations of the visual field, striate and extrastriate cortex responses modulate with the alternation of the attentional cue: responses are greater when the subjects attend to the stimuli in the contralateral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



(Matrinez et al., 1999, Nature Neurosci)

Basis of Attentional Selection: *Features*

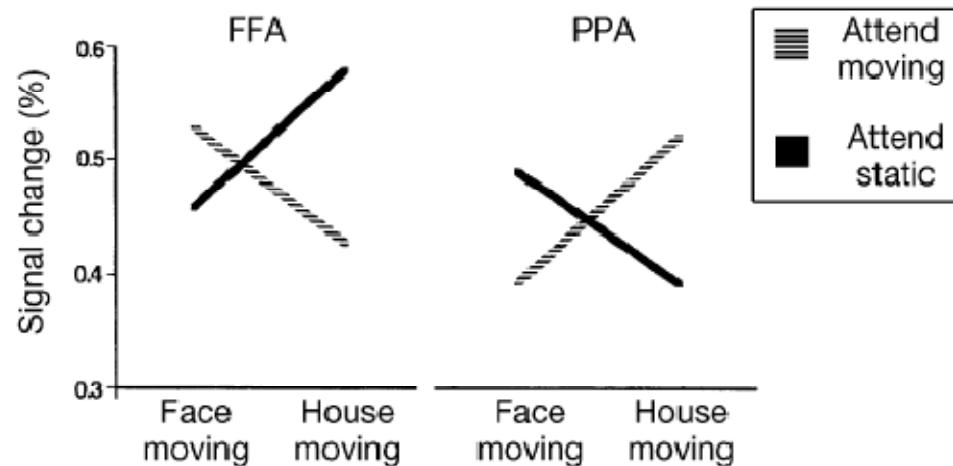
Global attentional selection: attention to a stimulus feature (color or direction of motion) increased the response of cortical visual areas not only to the stimuli at the attended location but also to a spatially distant, ignored stimulus that shared the same feature.



(Saenz et al., 2002, Nature Neurosci)

Basis of Attentional Selection: *Objects*

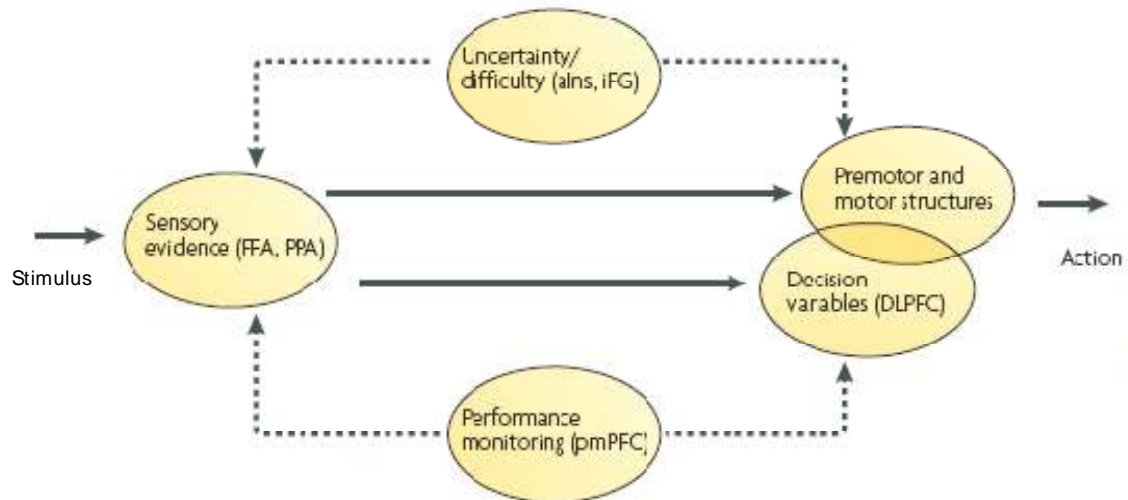
With stimuli consisting of a face transparently superimposed on a house, with one moving and the other stationary or vice versa, attending to the moving object resulted in higher activation not only in motion processing area MT but also in the cortical area selective for the moving object. This provides 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)

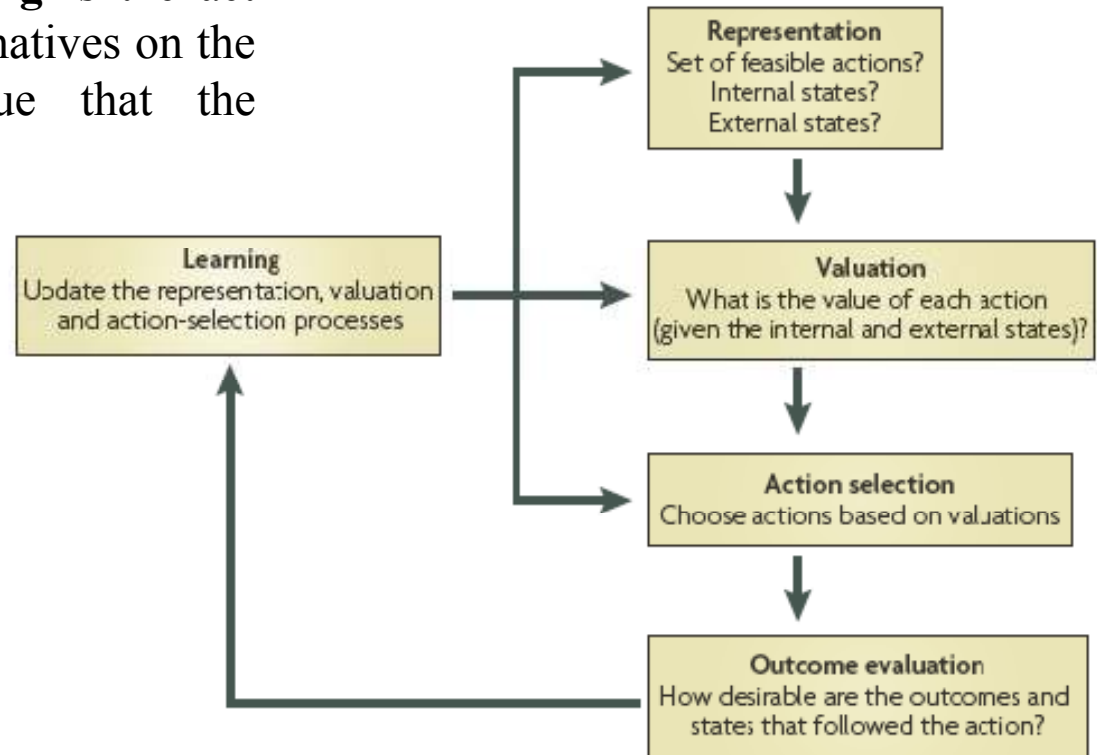
Studying Areas Involved in Decision Making

• **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)

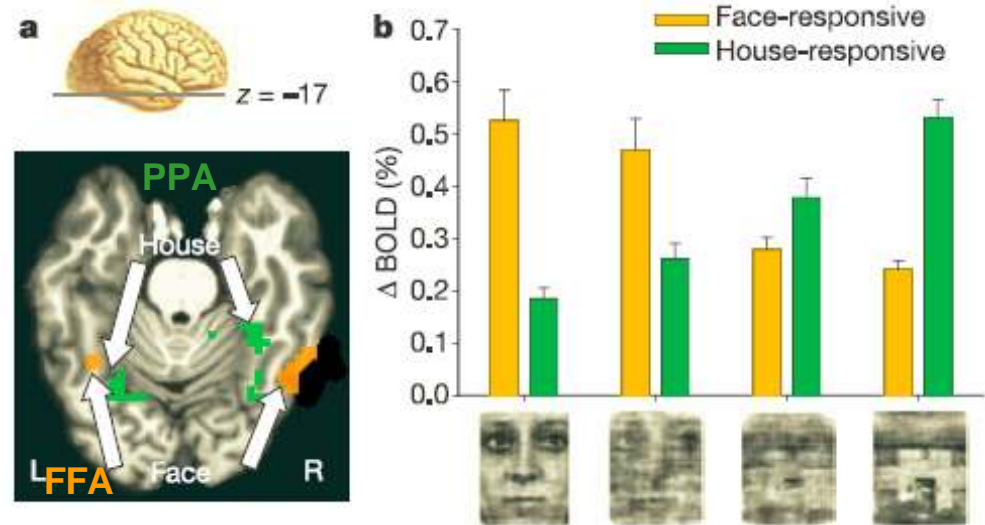
- **Value-based decision making** is the act of choosing from several alternatives on the basis of a subjective value that the individual places on them.



(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.

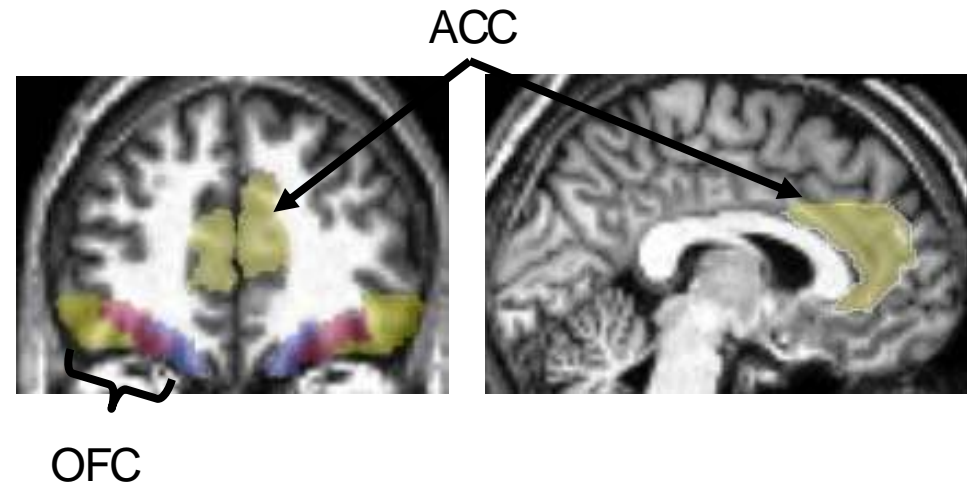


(Heekeren et al., 2004, Nature)

Facets of value-based decision making uncovered by fMRI:

Value representation

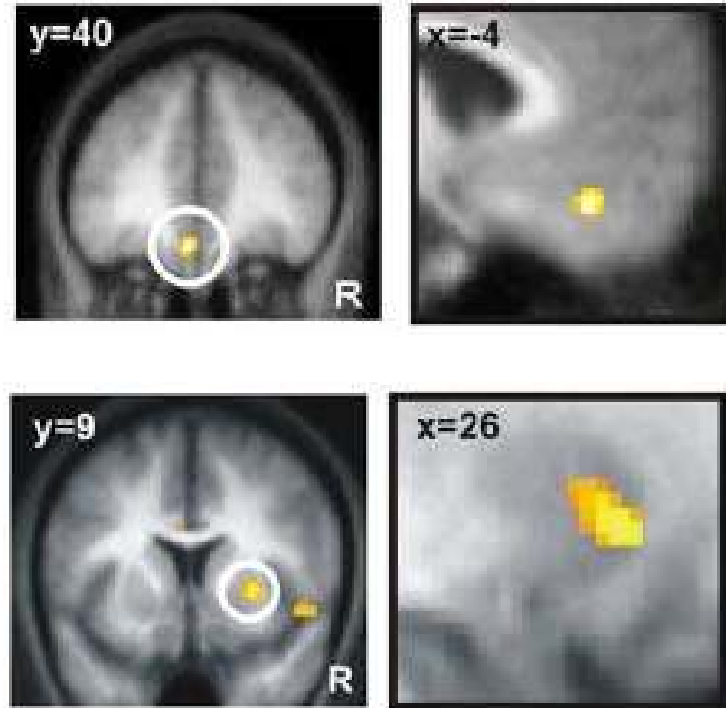
- *Orbitofrontal cortex (OFC)* – primary involved in representing the reinforcement value of objects and value expectations
- *Anterior Cingulate cortex (ACC)* – primary involved in representing the reinforcement value of actions



(Rushworth et al., 2007, Trends Cog Sci)

Reference-dependent value computation

- *Orbitofrontal cortex (OFC)* and *Dorsal Striatum* – track parameters such as expected value indicating the computation of reference-independent value.
- *Ventral Striatum* – indexes the degree to which stated prices are distorted with respect to a reference point (framing effect).

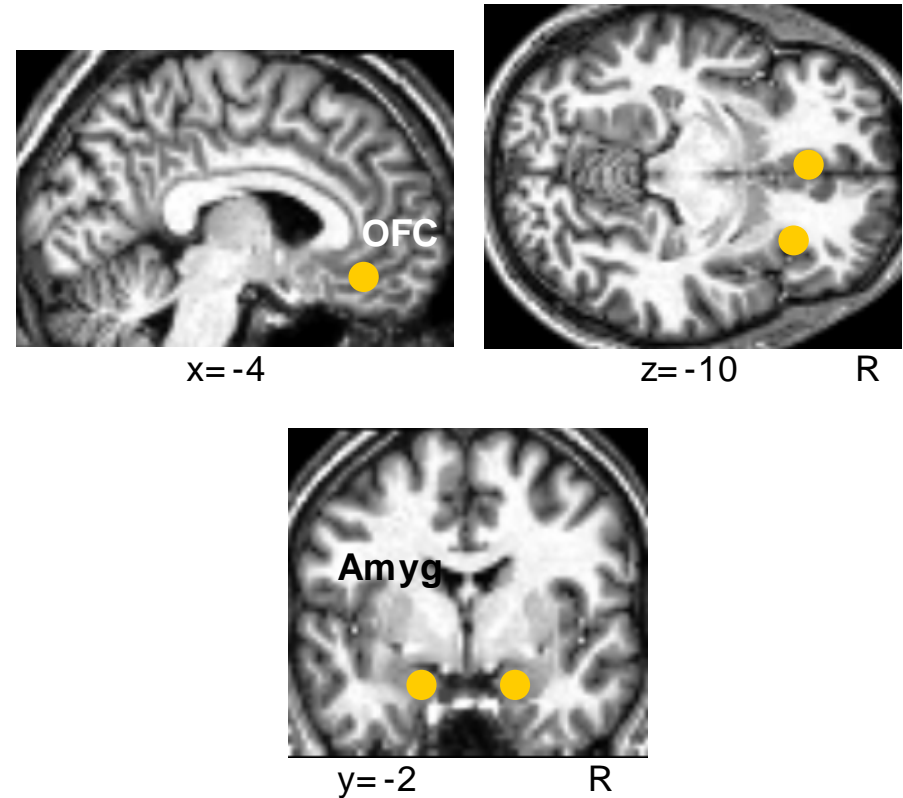


(De Martino et al. 2009, J Neurosci)

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Role of emotions in decision making

- *Orbitofrontal cortex (OFC)* – has higher activation in the case of rational decisions.
- *Amygdala* – has higher activation in the case of irrational decisions (loss-aversion).



(De Martino et al. 2006, Science)

Studying the Structures Associated with Memory

Long-term memory systems:

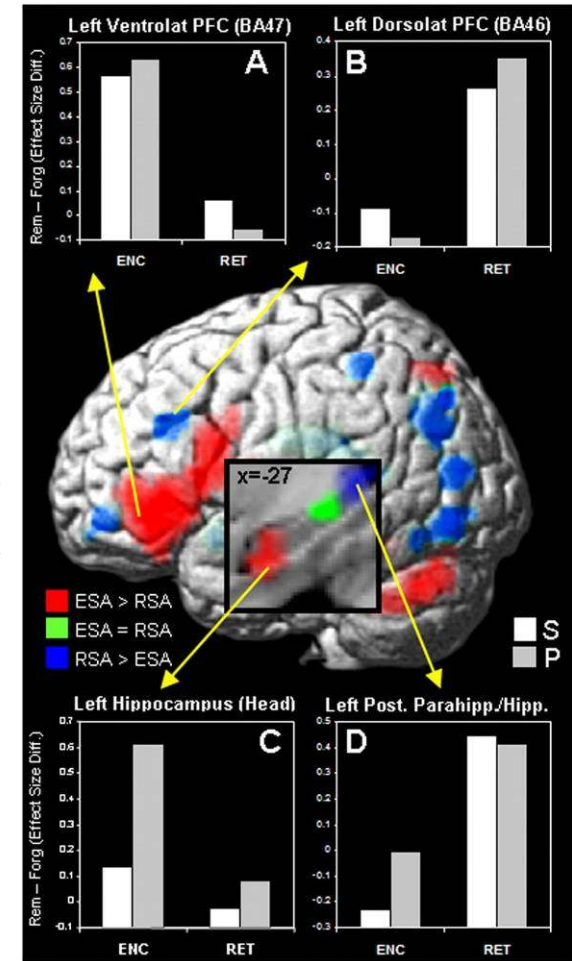
- Declarative (explicit) memory affords the capacity for conscious recollections about facts and events
 - subtypes: semantic memory; episodic memory
 - structures involved are medial-temporal lobe, prefrontal cortex, diencephalon and basal forebrain
- Non-declarative (implicit) memory, a heterogeneous 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)

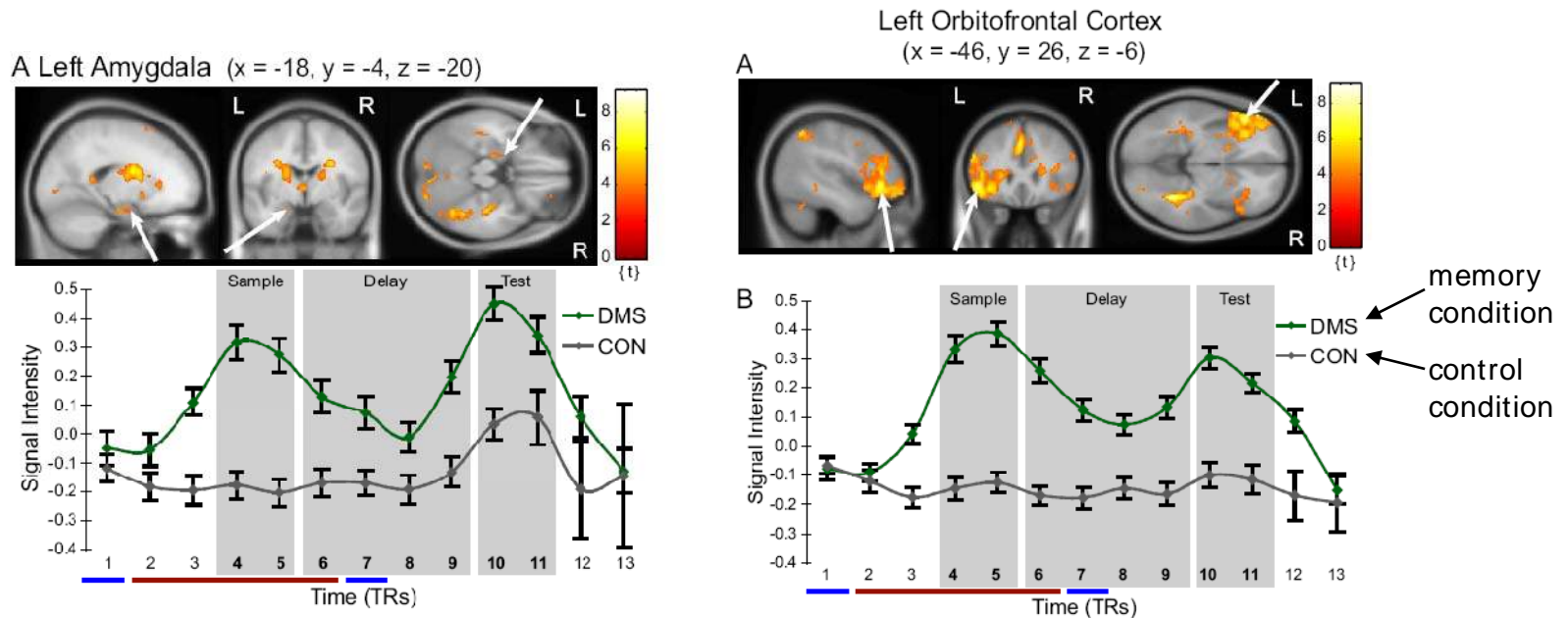


(Prince et al., 2005, J Neurosci)

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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.

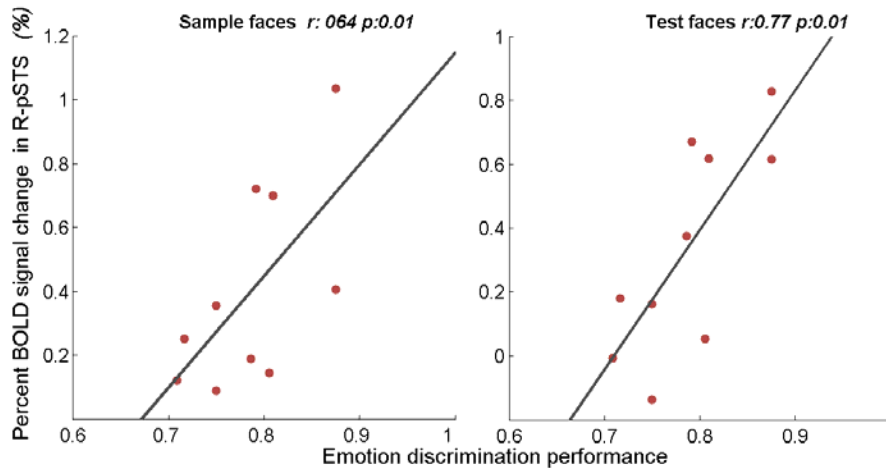


(LoPresti et al., 2008, J Neurosci)

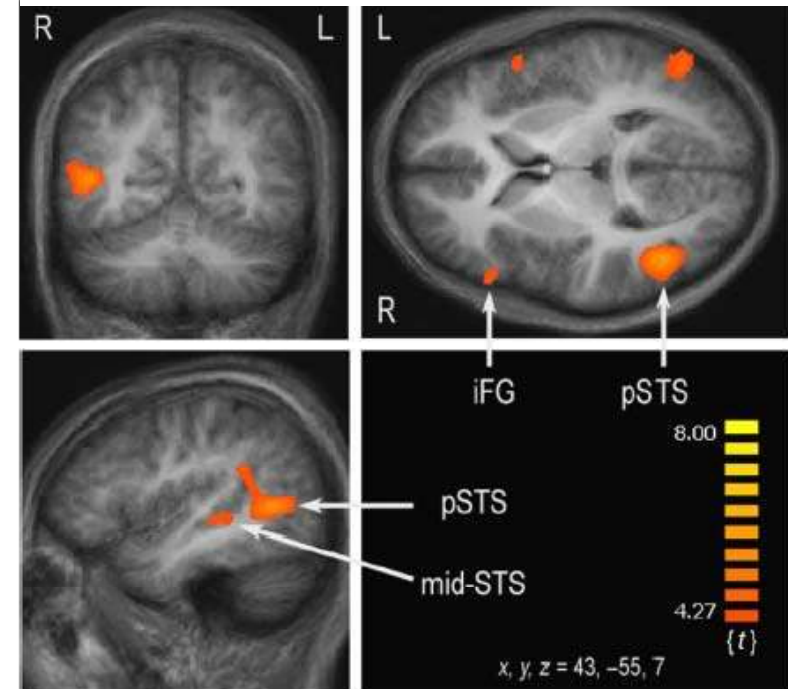
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Working memory for emotional expressions II

- 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



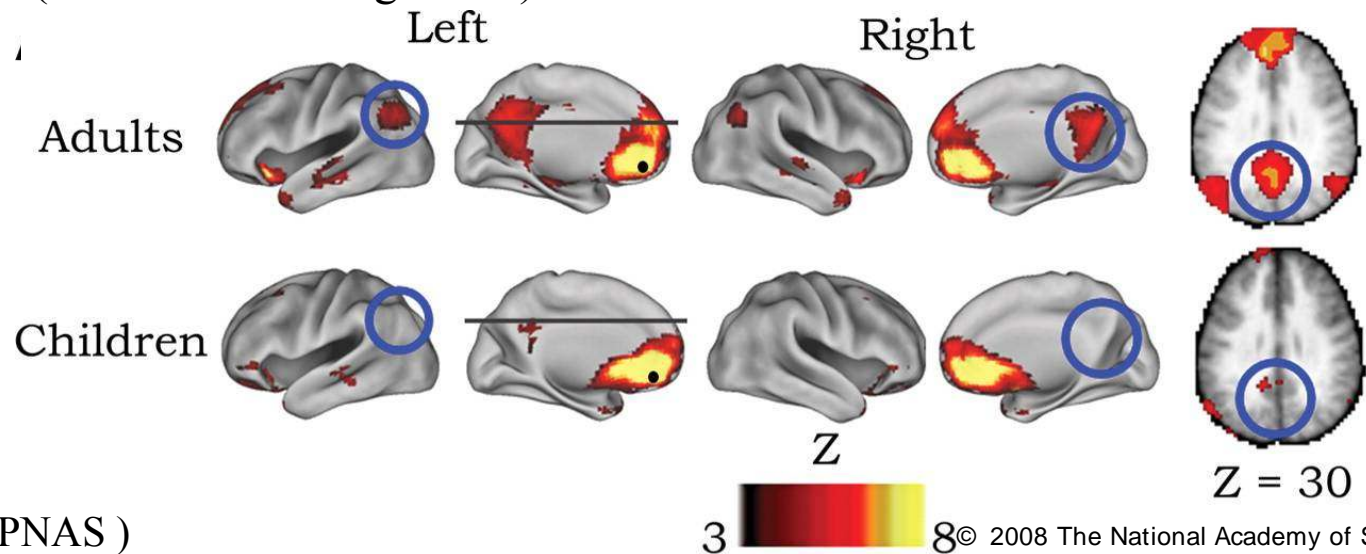
Attend to emotion > attend to identity



(Bankó et al., 2009, J Vision)

Resting State fMRI – Default Network

- Default network: areas that consistently exhibit decreases from baseline activity, 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. However, its specific function is debated.
- Imaging can be difficult, since there is no standard way of measuring the brain in its resting state (i.e. what is resting state?).



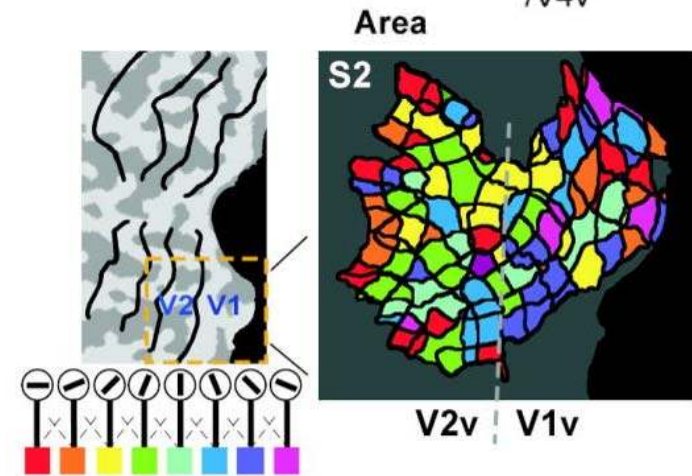
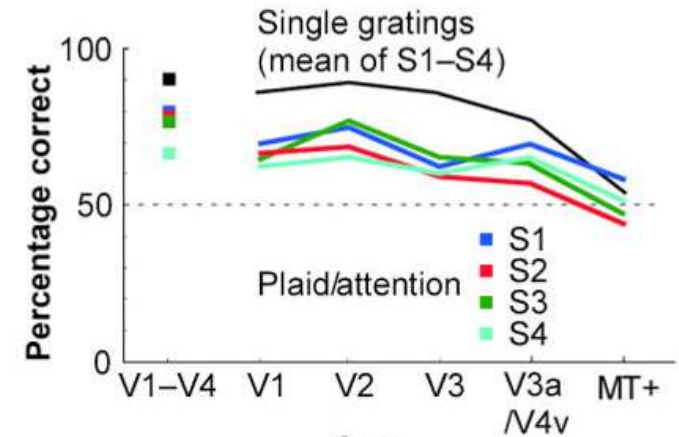
(Fair et al. 2008, PNAS)

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Other 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.

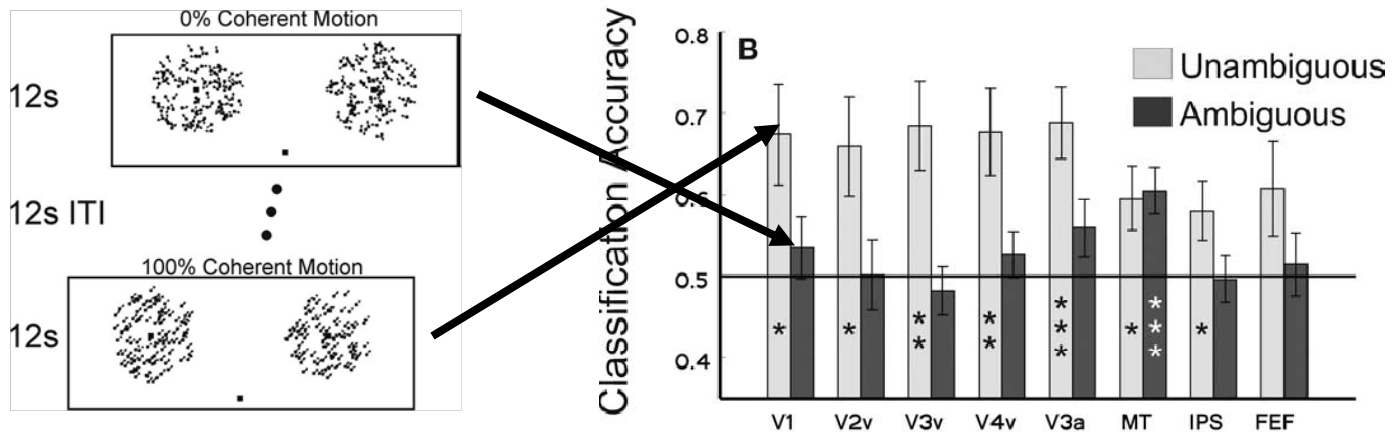


(Kamitani and Tong, 2005, Nature Neurosci)

“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)

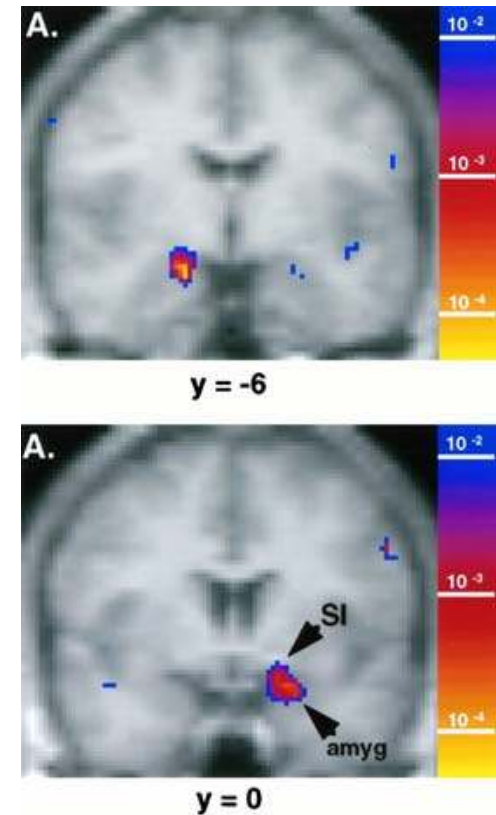
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“Mindreading” – Perception w/o awareness

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)

© 1998 Society for Neuroscience

Voluntary Regulation of Brain Activity

Real-time fMRI (rtfMRI): evidence show that voluntary regulation of brain activity can be achieved by training led by on-line (direct or indirect) feedback of BOLD signal

➤ Delayed:

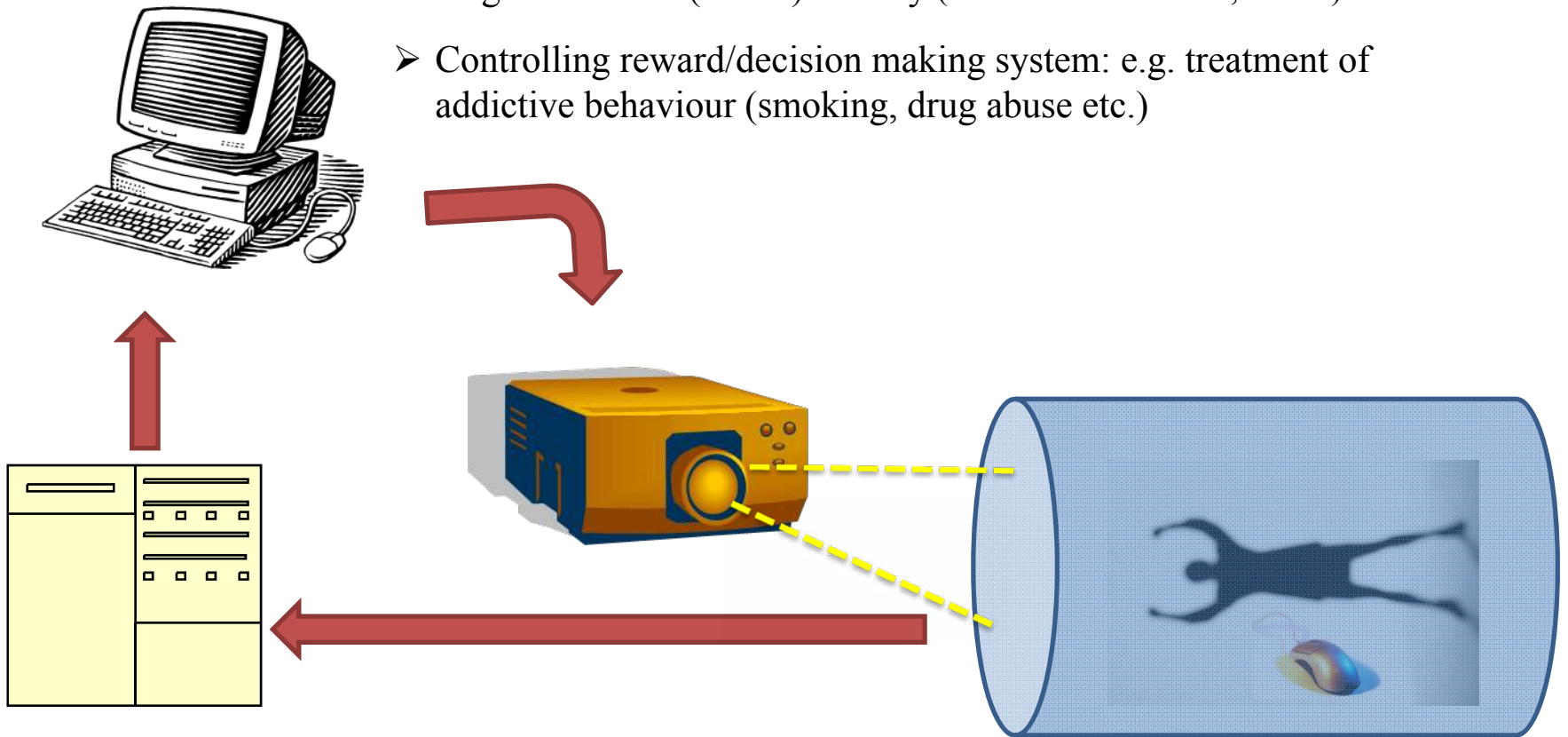
- Adjusting motor behavior in order to expand activation in the motor and somatosensory cortex (Yoo and Jolesz 2002 Neuroreport)
- Effects related to the visual presentation of facial expressions could not be separated from the effects of the feedback from amygdala–hippocampal area (Posse et al 2003 NeuroImage)

➤ Quasi-realtime

- Regulation of anterior cingulate and anterior insular cortex (Weiskopf et al 2003 Neuroimage, Caria et al. 2007, NeuroImage)

Prospective clinical/industrial consequences of rtfMRI:

- Pain perception reduced via rtfMRI training based on rostral anterior cingulate cortex (rACC) activity (deCharms et al. 2005, PNAS)
- Controlling reward/decision making system: e.g. treatment of addictive behaviour (smoking, drug abuse etc.)



Combined Methodologies

Pros and Cons of Imaging (fMRI/PET)

- high spatial resolution
- sluggish and temporally blurred:
temporal scale is on the order of
seconds

Pros and Cons of Electrophysiology (EEG/MEG)

- limited spatial resolution
- excellent millisecond order temporal
resolution, which enables studying
sequential processing steps as they take
place in the brain

Combining the two methodologies can be used to address questions for which
neither method would be appropriate alone!

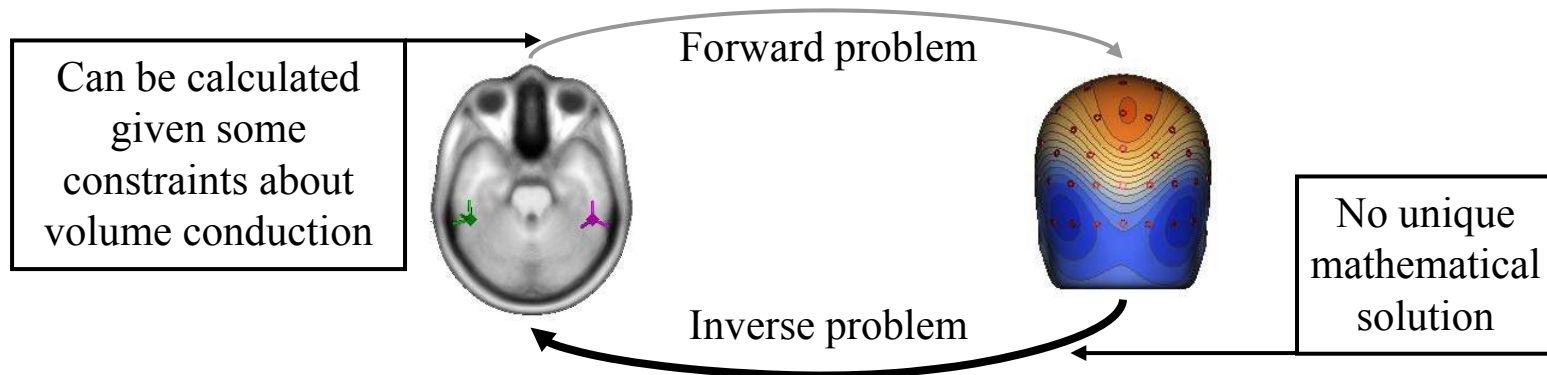
Theoretical considerations

To confidentially correlate haemodynamic and electrophysiologically based measurements of neural activity one must have:

- common sensory frame (identical stimuli)
- common biological reference (identical subjects)
- common experimental frame (identical paradigms)
- appropriate spatial frame (individual dipole modeling of ERP scalp topography i.e. *source localization*)
 - to establish an approximate location of the ERP-generating dipole of interest, which has strong correspondence with the foci of haemodynamic activity

Source localization

- aim is to infer the underlying source location from the obtained scalp potential maps

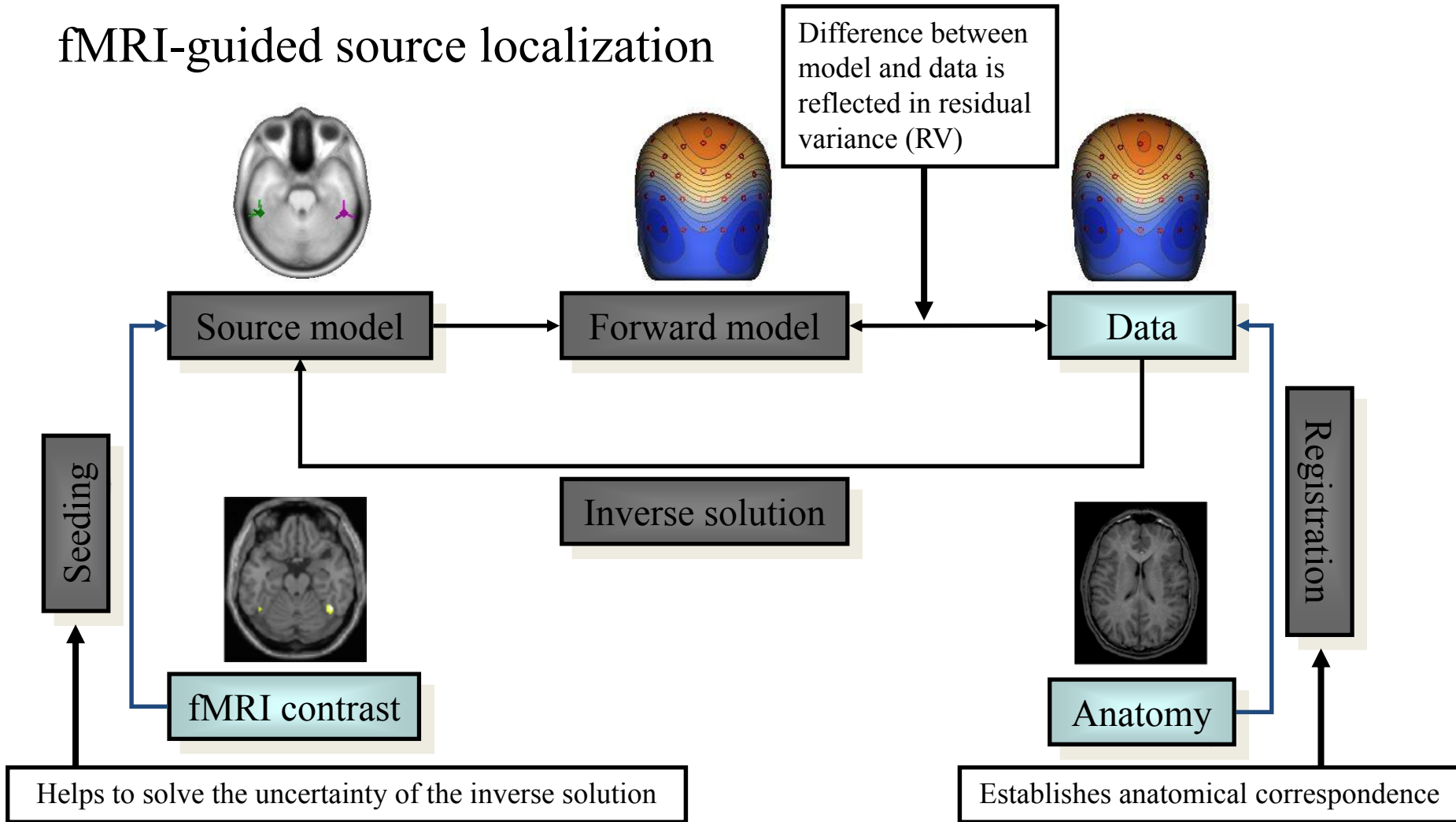


... however, any field potential vector could be consistent with an infinite number of possible dipoles

- there is *no* way to know which one is correct... we can only guess which is better than the other one, but only out of those solutions considered

→ source localization is an ill-defined problem and requires imaging

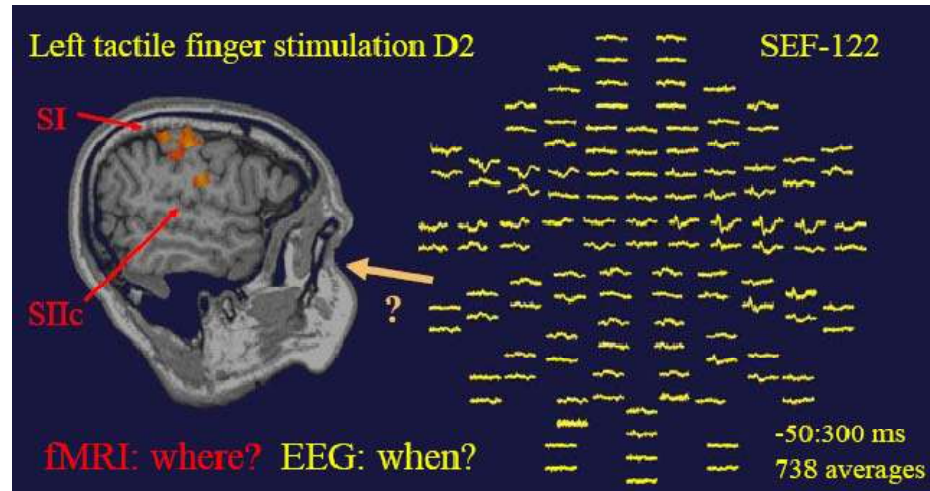
fMRI-guided source localization



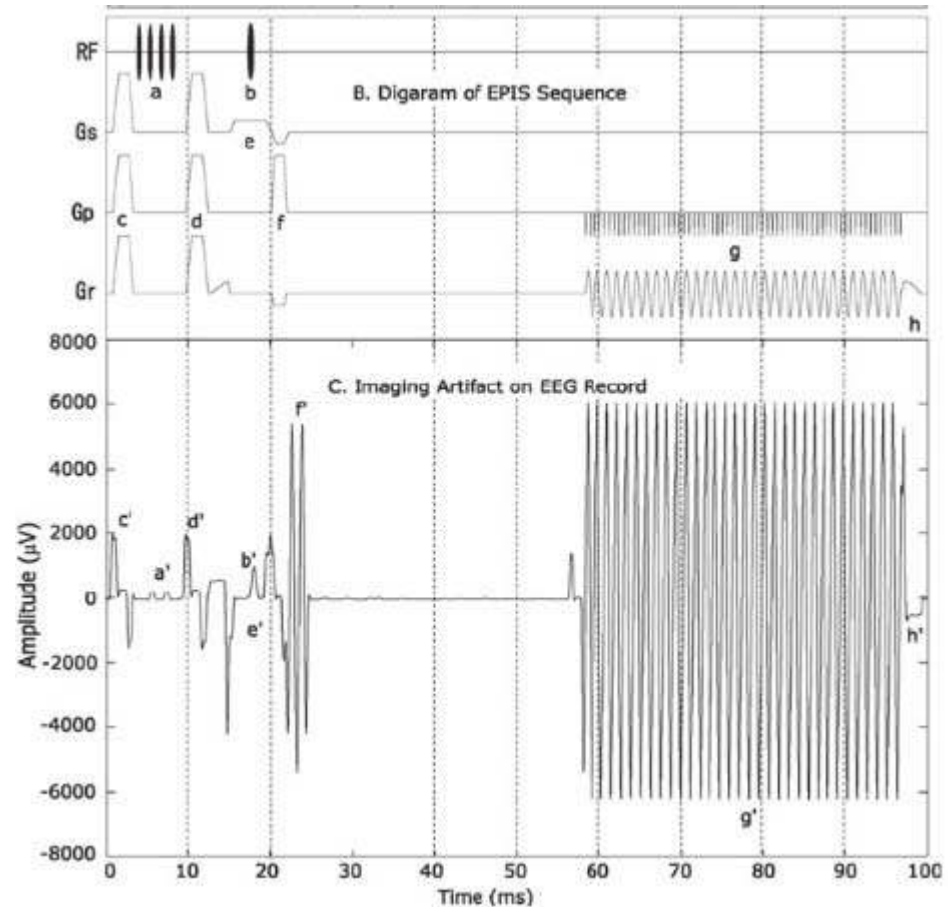
Procedure

- a model-fitting procedure for estimating intracranial sources underlying ERPs (not for ongoing EEG – too many sources)
- Estimation:
 - define a source model → calculate the corresponding potential map (forward model) → compare the fit of the forward model to the actual data: if model fits (the residual variance between model and data is low), then data is consistent with these sources; yet there is no unique solution
- Imaging helps:
 - to confine sources to anatomically plausible places after registration with 3D anatomy
 - helps to know the exact locations of electrodes relative to the individuals' brain
 - how to: define fiducial positions in MRI slices to match up EEG/MEG and MRI coordinate systems
 - result is an individual head model

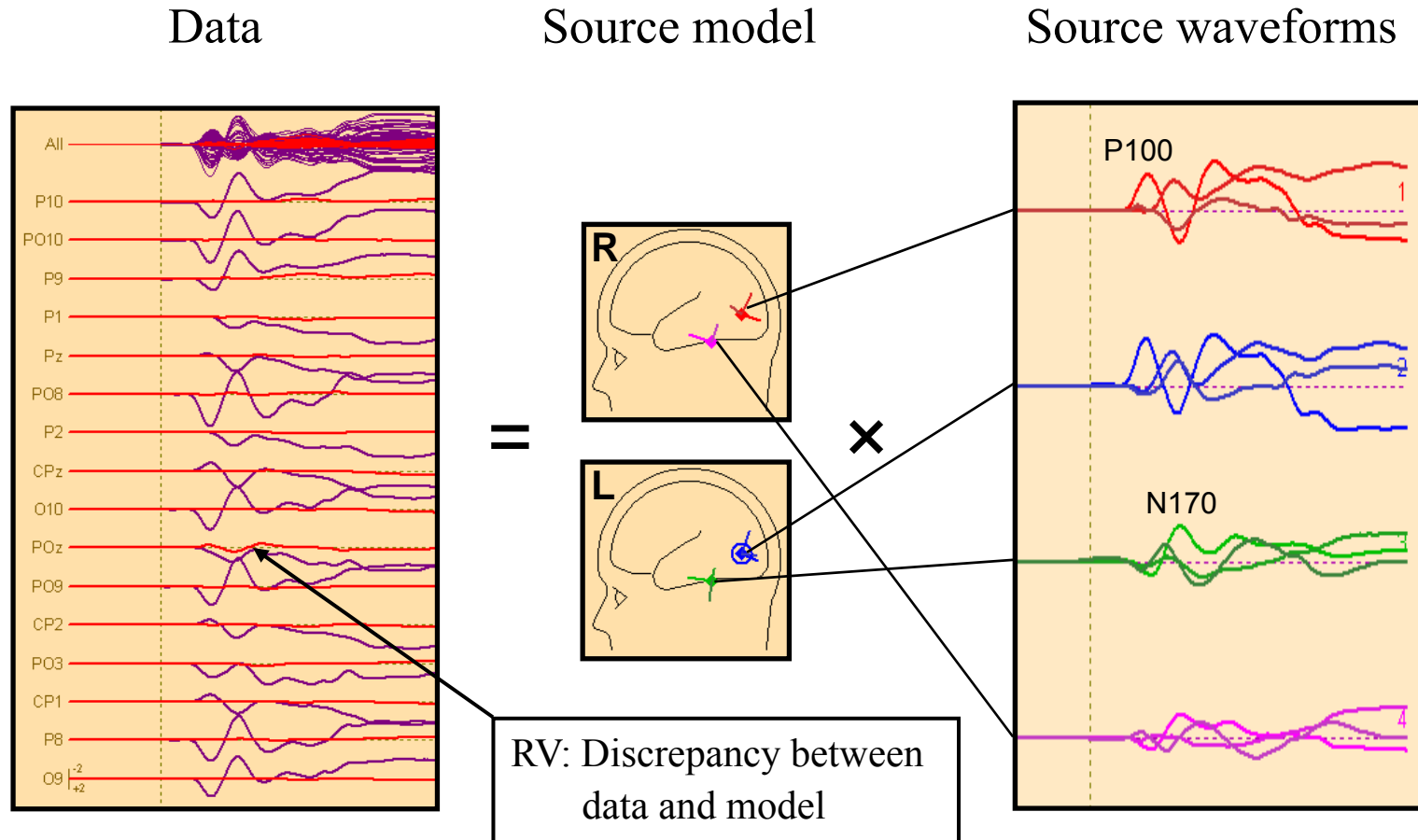
- Imaging helps:
 - to seed from fMRI activations
 - Orientation and temporal evolution computed from EEG/MEG
 - Inaccuracy of localization not critical for regional source



- Imaging helps:
 - Best results are obtained if measuring EEG/fMRI concurrently
 - However, simultaneous EEG/fMRI registration introduces fMRI acquisition artefacts, which need to be eliminated (big challenge: the artefact can be more than two orders of magnitude higher than the physiological EEG signal)
 - Possible solution is using interleaved EEG-fMRI protocols or doing sequential EEG and fMRI sessions



Linear superposition of source activities at scalp



Mathematically speaking...

- Decompose the reference-free data of ERPs $U_{E \times n}$ into a set of sources $S_{S \times n}$ and a set of attenuation coefficients $c_{S \times E}$, so that

$$U_{E \times n} = c_{S \times E} \times S_{S \times n}$$

E: number of channels + reference channel

n: number of timepoints

S: number of sources

- Decomposition results in:
 - an electroanatomical time-independent matrix c that reflects that anatomical substrates do not move around in the head
 - a time-variant dipole source potential matrix S that represents the change in activity of each source over time

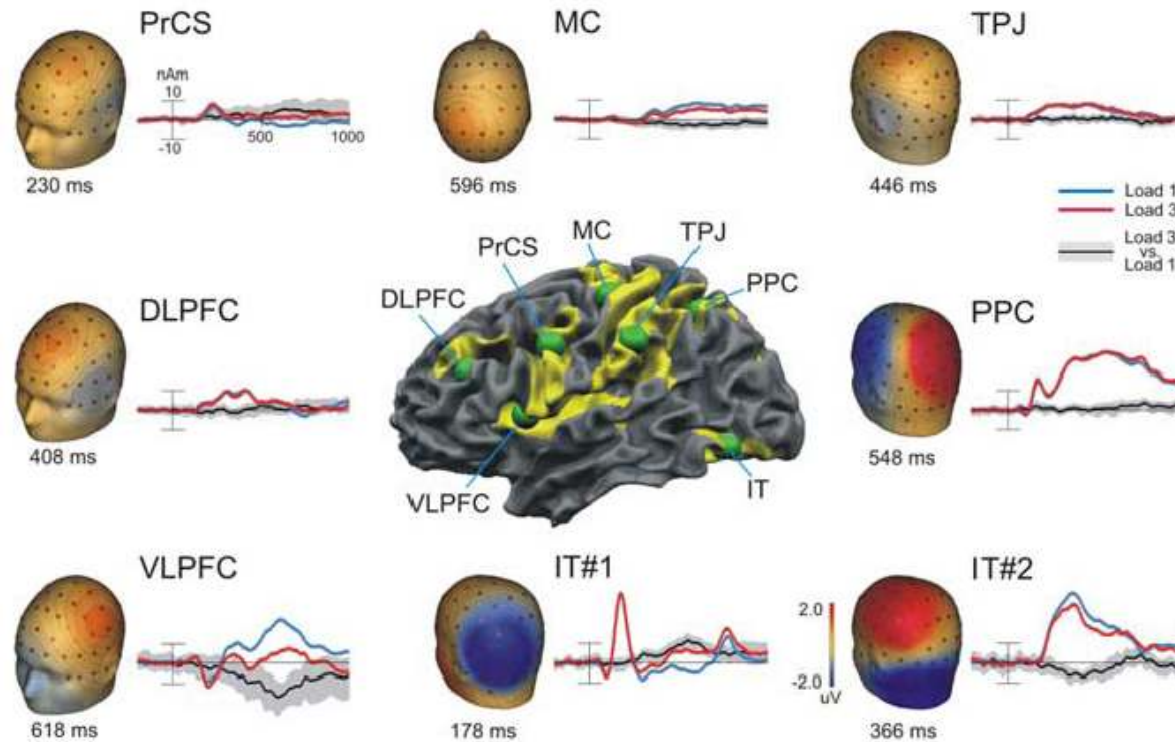
The attenuation matrix c is determined by:

- the geometry between the source and the electrodes (the head model)
- the nature of the conductance of the three-layer head model (Brain, Skull, Scalp);
 - the skull is less conductive than the layers on either side this results in a spatial smearing of potentials as they cross the skull

Solutions are constrained by:

- the geometry of the head
- the volume conduction of the dipoles
- the anatomical constraints dictated by the user (e.g., inside the head, symmetrical, not in the ventricles, etc...)

Application – MR guided localization



By using MR guided source localization the authors were able to decompose the processing stages of working memory retrieval

Possible problems of combined methodologies

- Coregistration of EEG electrodes with MRI ~ 5 mm
- Inaccuracy of head model (even for realistic model!) ~ 10 mm
- Coregistration of MRI and fMRI (distortions) ~ 5 mm
- Location of center of gravity of neuronal activity versus BOLD effect, e. g. influence of venous signal ~ 10 mm

→ fMRI clusters provide only rough localization of neuronal activation. Systematic differences (~ 15 mm) between EEG and fMRI are likely. However, source waveform topography is rather *insensitive to small variations* in source location.