Funkční zobrazování a mapování mozku fMRI

J. Kybic, J. Hirsch[1], J. Hornak[2], M. Bock, J. Hozman, a další[3]

January 9, 2008

[1] http://www.fmri.org

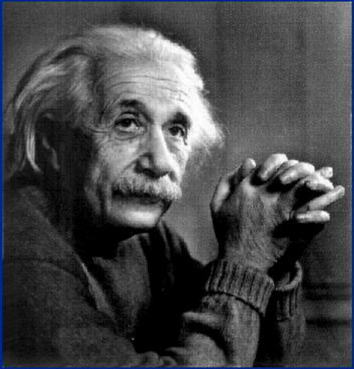
[2] http://www.cis.rit.edu/htbooks/mri/

[3] http://www.biac.duke.edu/education/courses/fall04/fmri/

Outline

1. Overview and Introduction - The Mind/Body Question
2. Historical Milestones
3. Principles and Methods of Brain Mapping
   - Methods to Measure Hemodynamic Variation
     - fMRI: functional magnetic resonance imaging
     - PET: positron emission tomography
   - Methods to Measure Electromagnetic Activity
     - MEG: magnetoencephalography
     - EEG: electroencephalography
4. Clinical Applications
5. Investigations of Human Brain Functions
6. Future Directions

A New View of Brain and Mind: Functional Neuroimaging

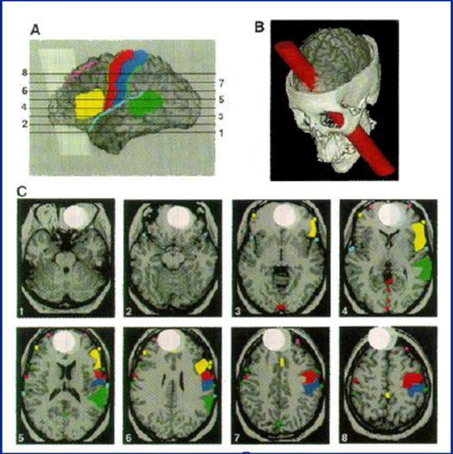


Důsledky zranění

Phineas Gage: Při nehodě v lomu mu v roce 1848 prolétl kus železné tyče hlavou, částí mozku. Přežil, ale jeho psychické vlastnosti se změnily — ztratil respekt, jeho slovník zhrubnul, stal se netrpělivým, náladovým, tvrdohlavým, nebyl schopen se rozhodnout. Zemřel v roce 1860, po několika epileptických záchvatech

Hypotéza: Každá část mozku je zodpovědná za určitou funkci.

Phineas P. Gage 1825-1861



Damasio, H., et al; Science 264: 1102-1105, 20 May 1994

Paul Broca (1861)
Observed language-related deficits following left frontal damage to the brain.

Karl Wernicke (1874)
Reported language-related deficits and motor deficits following left temporal damage to the brain.

Goal

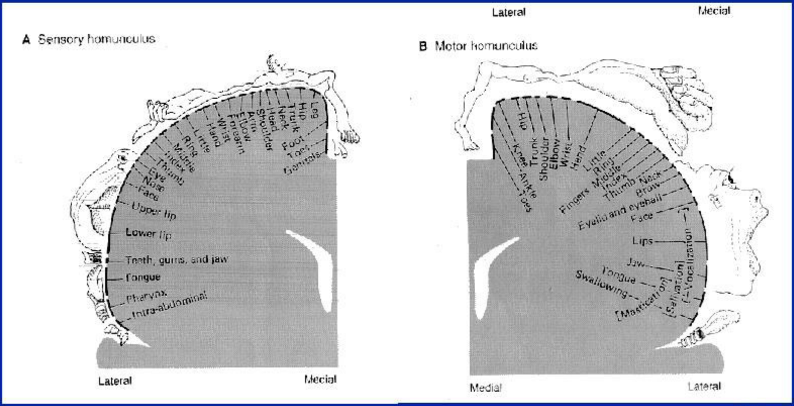
Brain Mapping → **Understanding the Brain**

Pomocí přímé stimulace mozkové kůry (s otevřenou lebkou) byla navržena předpokládaná korespondence mezi pozicí v mozku a částmi těla. . .

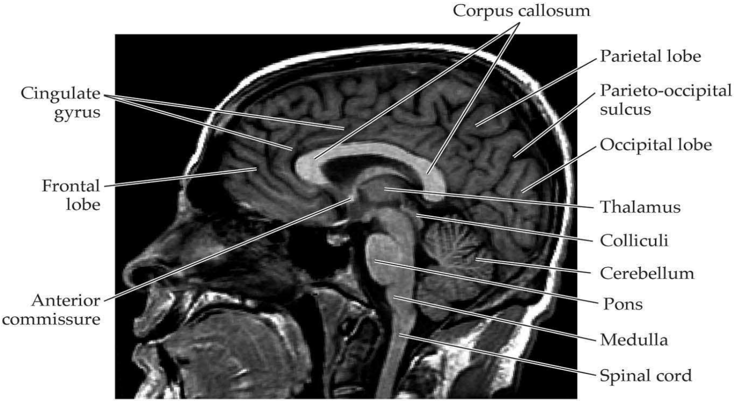
Dnes víme, že skutečnost je komplikovanější. . .

Wilder Penfield
(1937-1954)

Direct Cortical Stimulation



Columbia fMRI



FUNCTIONAL MAGNETIC RESONANCE IMAGING, **Figure 6.19**

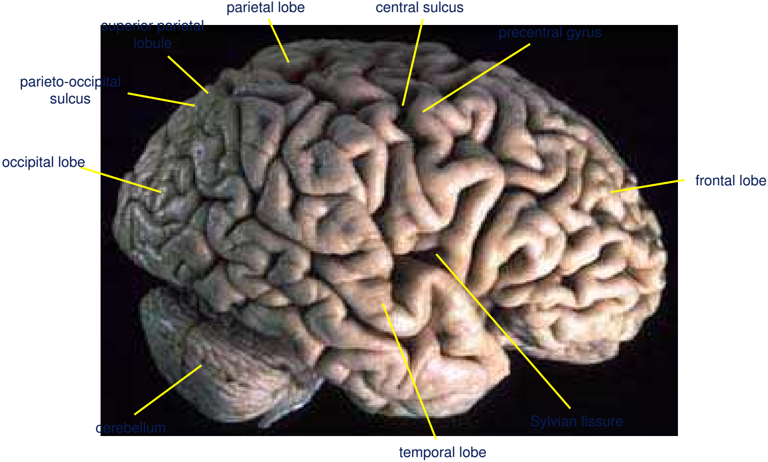

parietal lobe
central sulcus
superior parietal
lobule
precentral gyrus
parieto-occipital
sulcus
occipital lobe
frontal lobe
cerebellum
Sylvian fissure
temporal lobe

Fig 2.13

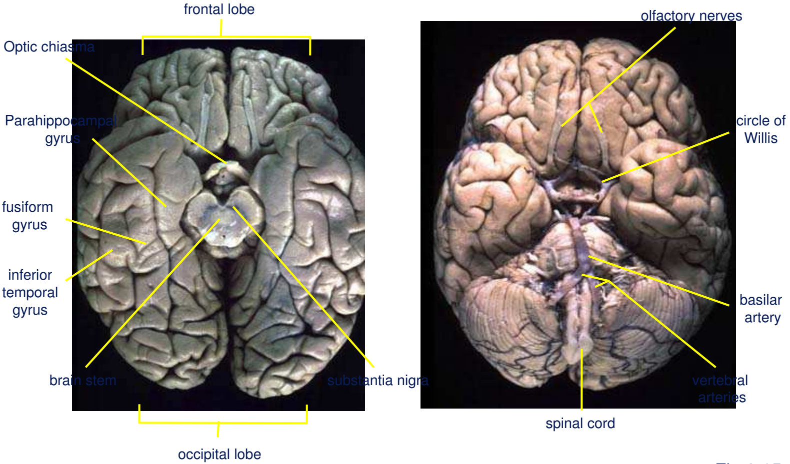
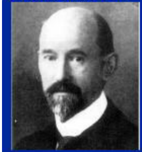

frontal lobe
Optic chiasma
Parahippocampal gyrus
fusiform gyrus
inferior temporal gyrus
brain stem
substantia nigra
occipital lobe
olfactory nerves
circle of Willis
basilar artery
vertebral arteries
spinal cord

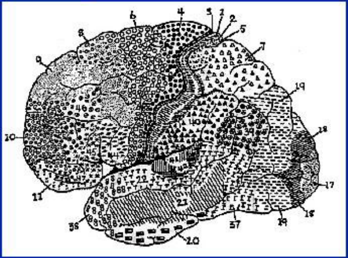
Fig 2.15

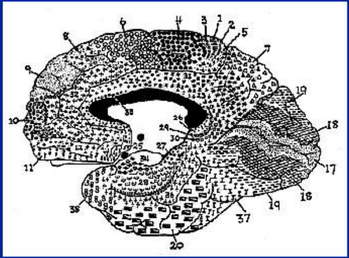
Mnoho navrhovaných dělení mozku do funkčních celků…

Korbinian
Brodmann 1909

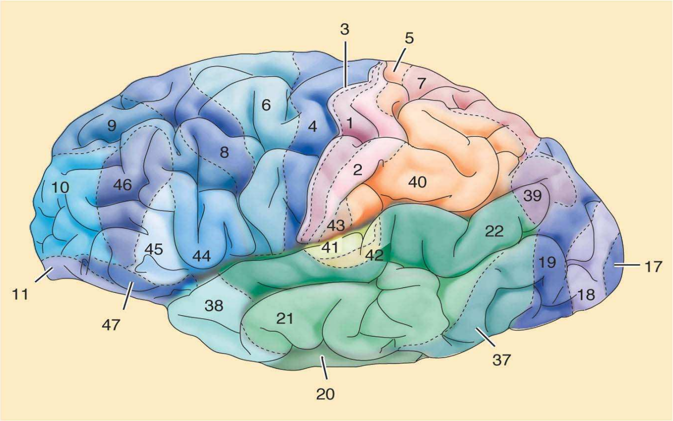


Cortical Cytoarchitecture



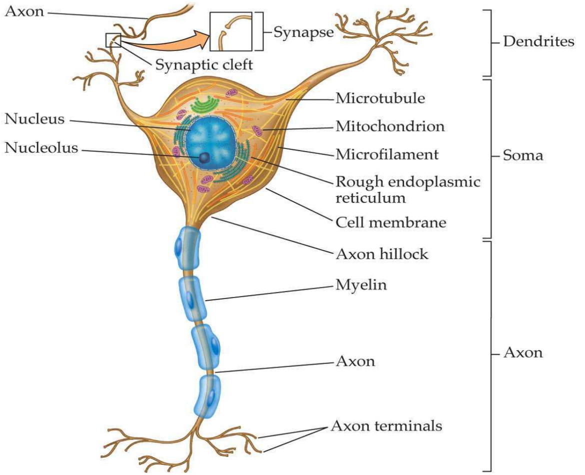


Cytoarchitectonic map, Brodman



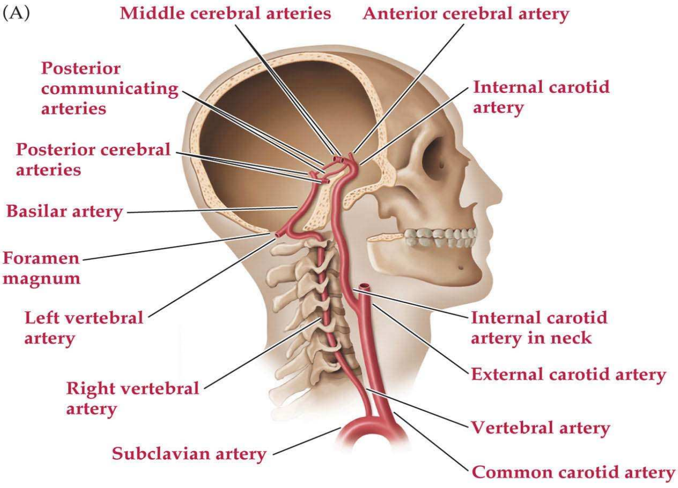
FUNCTIONAL MAGNETIC RESONANCE IMAGING, Figure 6.22 (Part 1)

Mikrostruktura

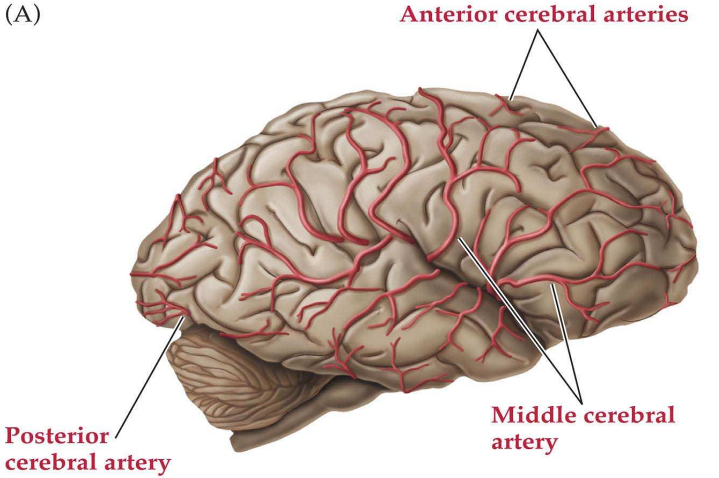


FUNCTIONAL MAGNETIC RESONANCE IMAGING, **Figure 6.2**

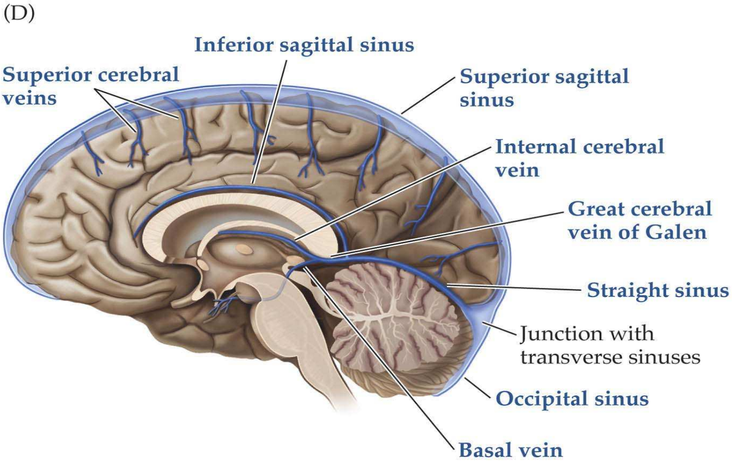
Zásobování mozku krví



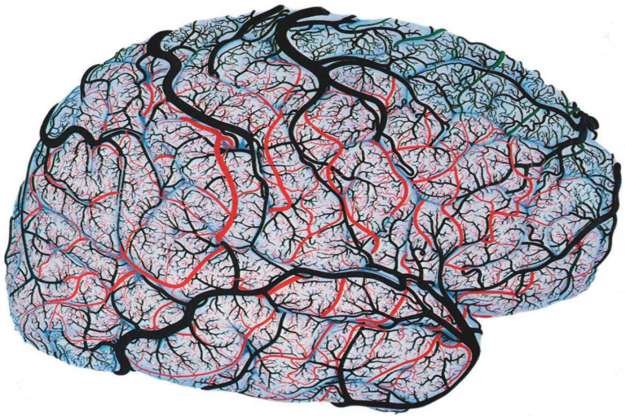
FUNCTIONAL MAGNETIC RESONANCE IMAGING, **Figure 6.10 (Part 1)**



FUNCTIONAL MAGNETIC RESONANCE IMAGING, Figure 6.11 (Part 1)



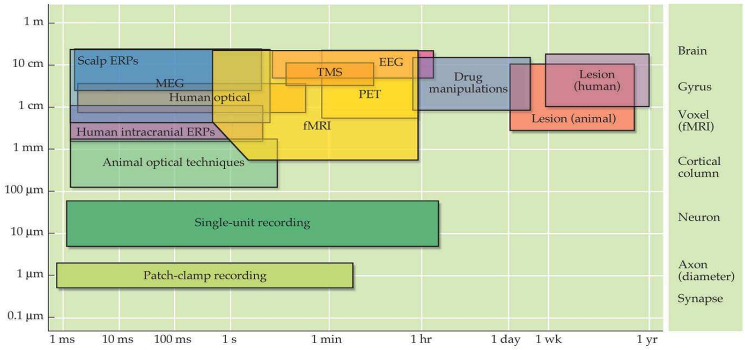
FUNCTIONAL MAGNETIC RESONANCE IMAGING, Figure 6.11 (Part 4)



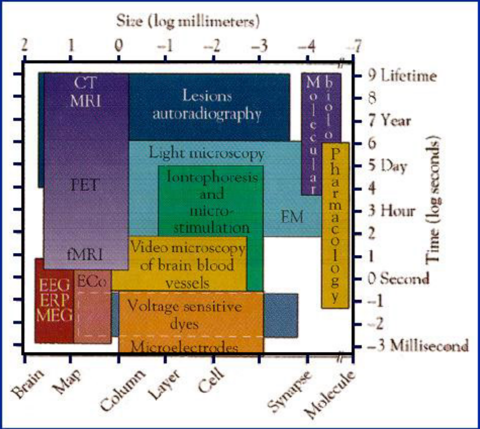
FUNCTIONAL MAGNETIC RESONANCE IMAGING, **Figure 6.8**

Jak lokalizovat funkci mozku
(Shrnutí a připomenutí)

- Invazivní
    - Následky zranění
    - Následky operací
    - Přímá stimulace (dnes jen na zvířatech)
    - Optické snímání (při otevřené lebce svítíme laserem, optické vlastnosti se mění s průtokem krve a s elektrickým polem)
- Neinvazivní
    - MEG, EEG
    - fMRI
    - PET



FUNCTIONAL MAGNETIC RESONANCE IMAGING, Figure 1.7

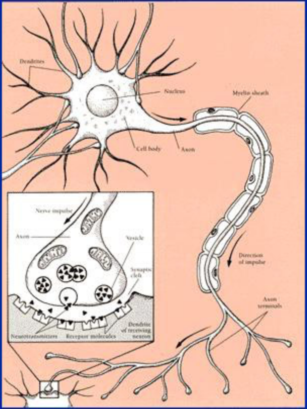


From: Images of Mind by Posner, M. and Raichle, M.
Scientific American Library, 1994, p. 24

EEG/MEG, opakování

Methods to Measure Electromagnetic Activity:

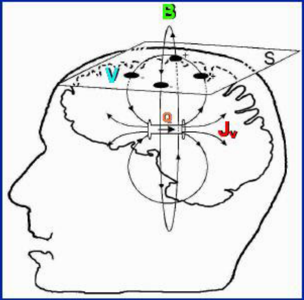
MEG (Magnetoencephalography) - EEC (Electroencephalography)



- **Signal Source: Electrical Activity of nerve cells.**
- **What is measured on the surface of the head is the result of mostly postsynaptic potentials (excitatory or inhibitory)**
- **Many nerve cells are aligned in palisades (e.g. pyramidal cells) and post-synaptic electrical fields sum with increasing area.**
- **Typically it is thought that 100,000 adjacent neurons acting in temporal synchrony are required to produce a measurable change in the magnetic field**

Relationship between currents in the brain and the magnetic field outside the head.

- Based on the discovery that electrical currents generate magnetic fields: Hans Christian Oersted, a Danish physicist (early 19th. century)
- A current source with strength Q causes a current flow Jv within the brain.

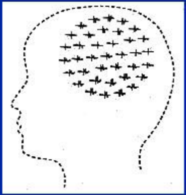


- The current flow produces a potential difference V on the scalp: (measured by EEG)
- And a magnetic field B outside of the head: (measured by MEG)

from:
www.Aston.ac.uk/psychology/meg/meg/intro/magfield.htm

Magnetoencephalography, MEG

Tiny magnetic fields produced by brain activity (10^{-13} Teslas) can be measured using Superconducting Quantum Interference Devices (SQUIDs).



SQUIDS operate at superconducting temperatures ($-269^{\circ}C$). Sensors are placed in a dewar containing liquid helium.

Stimulus – evoked neuromagnetic signals are recorded by an array of detectors.

The spatial location of the source is inferred by mathematical modeling of the magnetic field pattern.

Aplikace funkčního mapování mozku

- Porozumění struktuře mozku
- Porozumění procesům vnímání a myšlení
- Nové terapie
  - Porozumění fyziologickým příčinám duševních chorob
  - Porozumění fyziologickým příčinám bolesti a reakci na bolest
  - Porozumění účinkům drog
- Plánování operací
  - Identifikace nefunkčního centra
  - Omezení poškození důležitých center při chirurgické léčbě (epilepsie)

Clinical Uses of FMRI

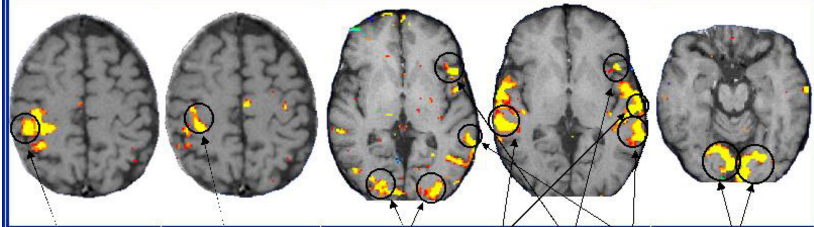
- Brain Tumors
  - Direct: Mapping of functional properties of adjacent tissue
  - Indirect: Understanding of likely consequences of a treatment
- Drug Abuse/Addiction
  - Understanding of brain effects of long-term use
  - Development of treatment strategies for abusers
- Drug Studies
  - What are the effects of a given medication on the brain?
  - How does a drug affect cognition? … our measures of cognition?
- Neuropsychological disorders
  - Understanding brain function may allow distinction among subtypes.
  - Identifying markers for a disorder may help in treatment

fMRI Task Battery for Cortical Mapping of Sensory, Motor, Language and Vision-Related Areas

1.	SENSORY Touch/hand	+	VISION Reversing Checkerboard
2.	MOTOR Finger/Thumb tapping	+	VISION Reversing Checkerboard
3.	LANGUAGE/active Picture Naming	+	VISION Pictures
4.	LANGUAGE/passive Listening to Words	+	AUDITION Spoken words

Standard Brain Mapping Tasks

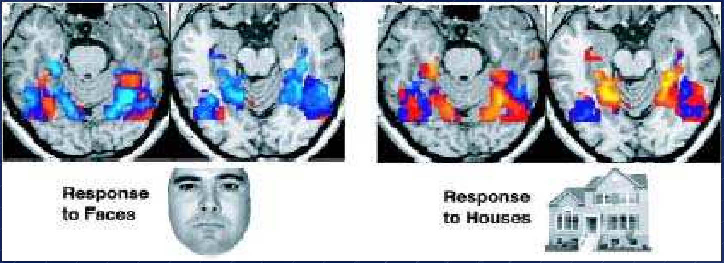
SENSORY	MOTOR	LANGUAGE		VISION
Touch (passive)	Finger Thumb Tapping (active)	Picture Naming (active)	Listening to Words (passive)	Reversing Checkerboard (passive)



GPoC	GPrC	GOi GTT GFi GTs	CaS

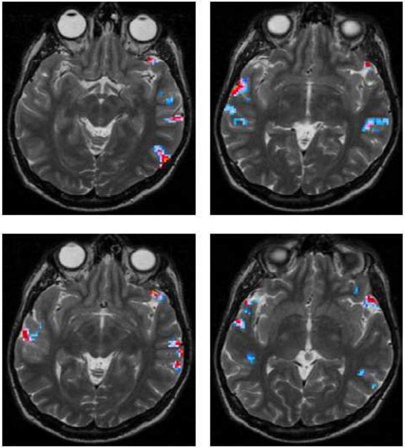
From Hirsch, J., et al; Neurosurgery 47: 711-722, 2000

Columbia fMRI

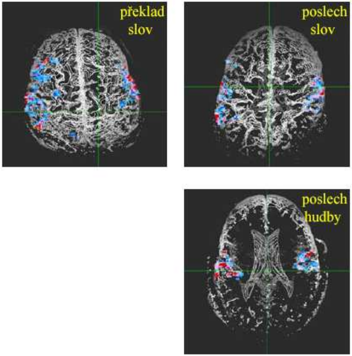

Response
to Faces
Response
to Houses

Funkční zobrazování (fMRI)

- Jsou vidět části mozku, které se používají při určité činnosti.
- Na obrázcích je činnost mozku při překladu slov.



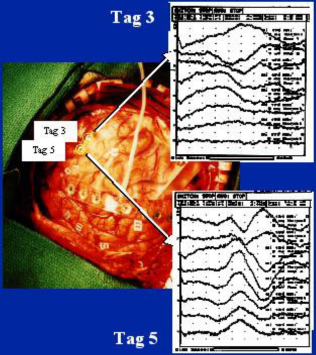
Funkční zobrazování (fMRI)



Sensory Motor Mapping

Craniotomy	SSEP	Direct Cortical Stimulation	Reference Image	fMRI Localization

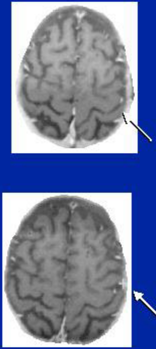
Tag 3

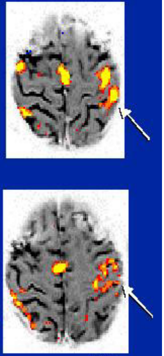


Tag 5

"Twitching of hand, focal seizure involving arm"

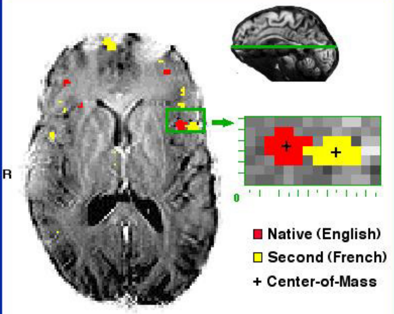
"Twitching in 1st three digits"





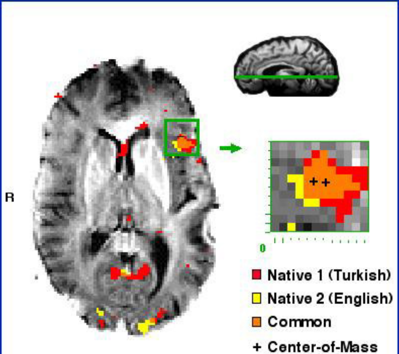
From Hirsch, J., et al; Neurosurgery 47: 711-722, 2000

"LATE" BILINGUAL (Subject A)
ANTERIOR Language Area



From Kim, et al, Nature, 388, 171-174, 1997

"EARLY" BILINGUAL (Subject G)
ANTERIOR Language Area

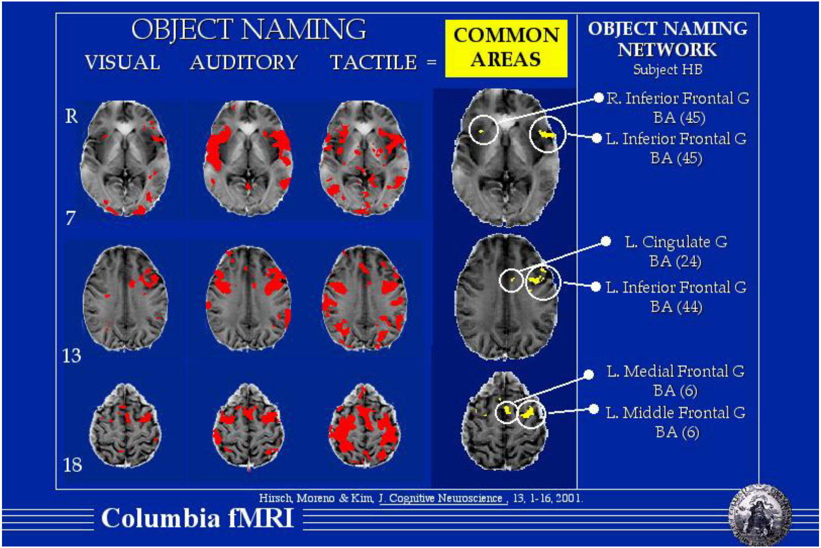


From Kim, et al, Nature, 388, 171-174, 1997

Global System Studies

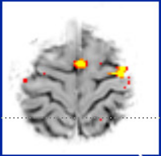
Hypothesis

Simple Cognitive tasks require the cooperation of multiple brain areas


OBJECT NAMING
VISUAL AUDITORY TACTILE =
COMMON AREAS
OBJECT NAMING NETWORK
Subject HB
R
7
13
18
R. Inferior Frontal G
BA (45)
L. Inferior Frontal G
BA (45)
L. Cingulate G
BA (24)
L. Inferior Frontal G
BA (44)
L. Medial Frontal G
BA (6)
L. Middle Frontal G
BA (6)
Hirsch, Moreno & Kim, J. Cognitive Neuroscience, 13, 1-16, 2001.
Columbia fMRI

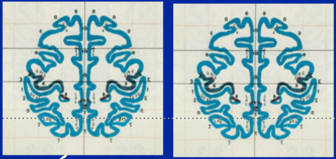
Labeling of Active Brain Areas

Functional Brain



activity

Atlas Brain



labels

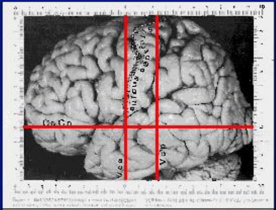
transfer

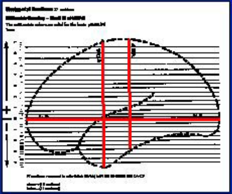
Name	BA	Sector
GPrC	4	c,E
GFs	6	b,E
GFd	6	a,E,60,-a
GFs	6	b,E,60
GRC	4	c,E,60
LPs	7	b,G,60

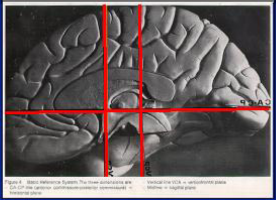
Co-Planar Stereotaxic Atlas of the Human Brain

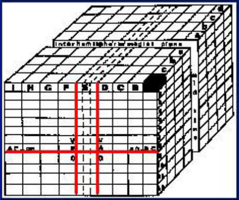
3-Dimensional Proportional System: An Approach to Cerebral Imaging

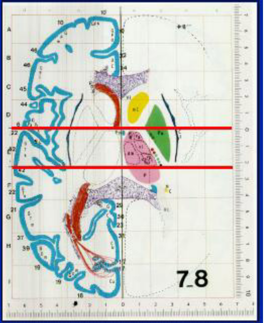
Jean Talairach
Pierre Tournoux
Translated by
Mark Rayport











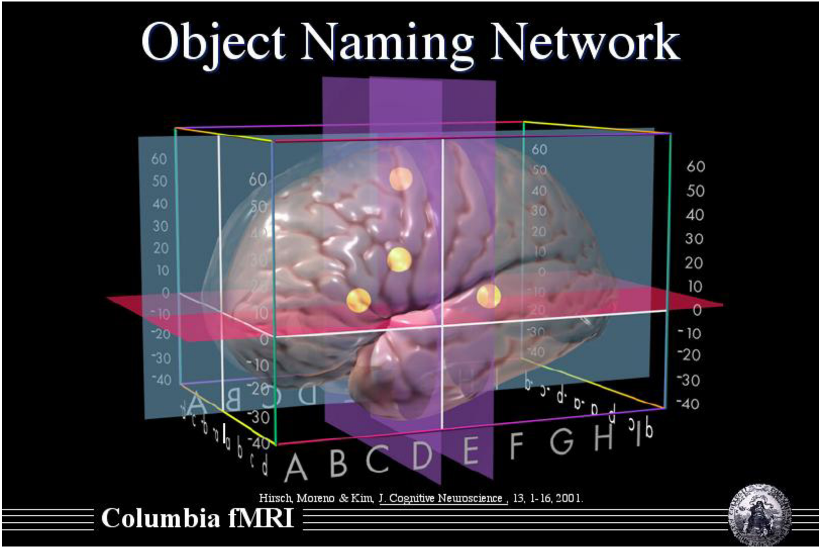
Columbia fMRI

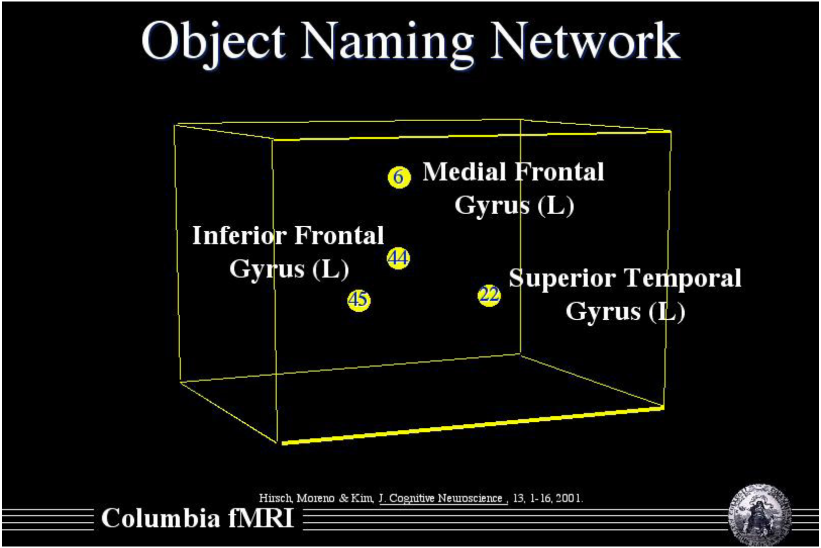
Object Naming

All Regions Activated
(one subject)

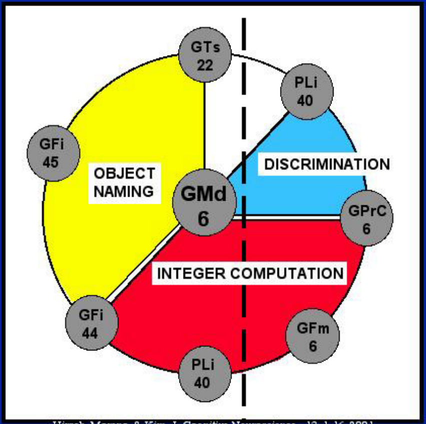
Common to
all subjects

Individually
Specific
Responses


Object Naming Network
60
50
40
30
20
10
0
-10
-20
-30
-40
A B C D E F G H
Hirsch, Moreno & Kim, J. Cognitive Neuroscience, 13, 1-16, 2001.
Columbia fMRI


Object Naming Network
6
Medial Frontal Gyrus (L)
Inferior Frontal Gyrus (L)
44
45
22
Superior Temporal Gyrus (L)
Hirsch, Moreno & Kim, J. Cognitive Neuroscience, 13, 1-16, 2001.
Columbia fMRI

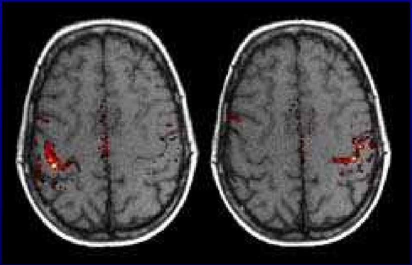
CORE NETWORKS FOR THREE PRIMARY COGNITIVE FUNCTIONS



Hirsch, Moreno & Kim, J. Cognitive Neuroscience, 13, 1-16, 2001.

Brain Mapping and Neurosurgery

Application: (Neuro)functional MRI



Volunteer

Patient w/ Glioblastoma

Surgery effect prediction

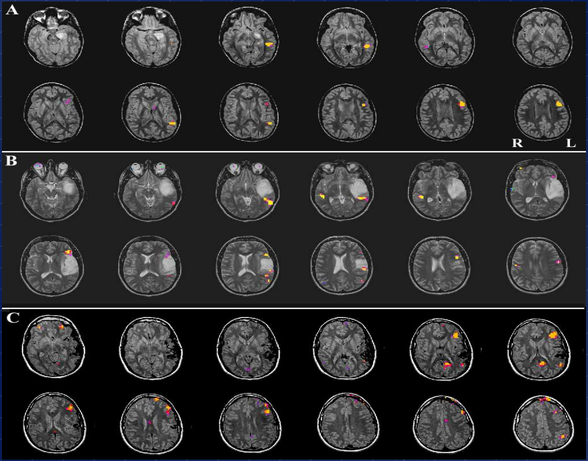
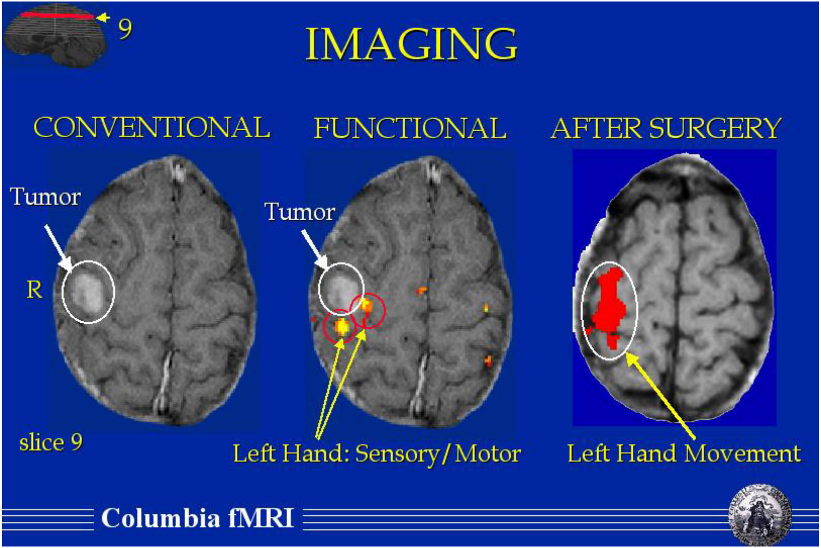
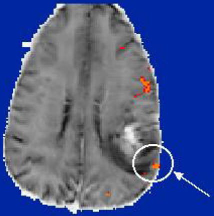


Image provided by Dr. James Voyvodic (Duke BIAC)

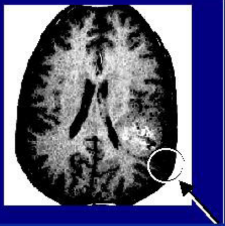

9
IMAGING
CONVENTIONAL
FUNCTIONAL
AFTER SURGERY
Tumor
R
Tumor
slice 9
Left Hand: Sensory/Motor
Left Hand Movement
Columbia fMRI

Intra-Operative Language Mapping

fMRI Map

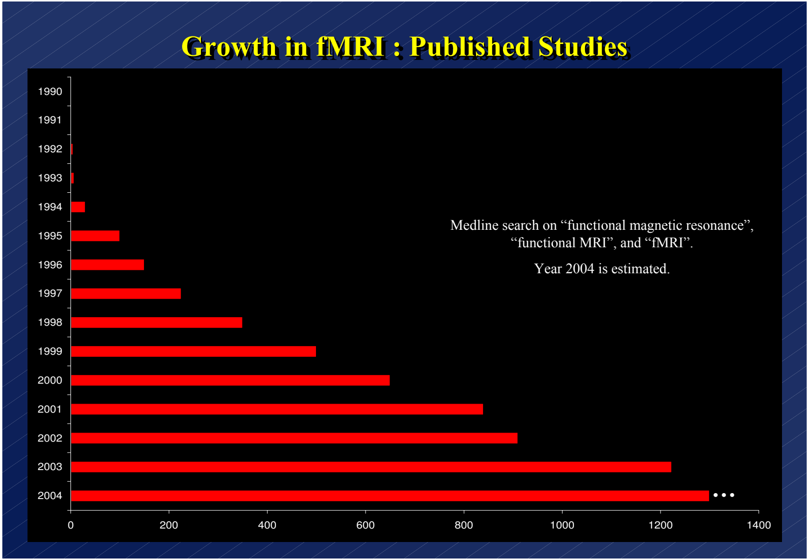


Cortical Stimulation



Word finding difficulty during picture naming

From Hirsch, J., et al; Neurosurgery 47: 711-722, 2000


Growth in fMRI : Published Studies
1990
1991
1992
1993
1994
1995
1996
1997
1998
1999
2000
2001
2002
2003
2004
0
200
400
600
800
1000
1200
1400
Medline search on “functional magnetic resonance”, “functional MRI”, and “fMRI”.
Year 2004 is estimated.

Essential Discoveries that enable PET and fMRI

Angelo Mosso

1881 Observed that blood flow changes were associated with mental activity

1890 Roy and Sherrington described an "intrinsic mechanism by which the vascular supply of the brain can be varied locally in correspondence with local variations in functional activity."

Linus Pauling

1936 Discovered the Magnetic Properties of Hgb

Siege Ogawa

1991 Discovered the Blood Oxygen Level Dependent (BOLD) Signal

PHYSIOLOGY

NEURAL ACTIVATION
IS ASSOCIATED WITH AN
INCREASE IN BLOOD FLOW

O2 EXTRACTION IS
RELATIVELY UNCHANGED

RESULT:
REDUCTION IN THE
PROPORTION OF DEOXY HGB
IN THE LOCAL VASCULATURE

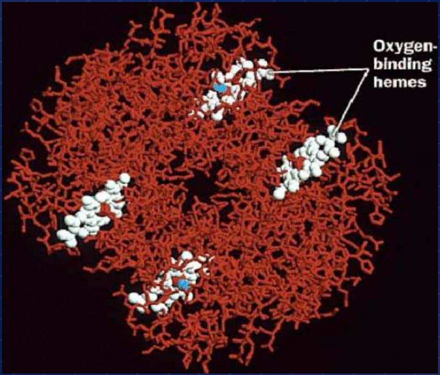
PHYSICS

DEOXY HGB
IS PARAMAGNETIC

AND DISTORTS THE LOCAL
MAGNETIC FIELD CAUSING
SIGNAL LOSS

RESULT:
LESS DISTORTION OF THE
MAGNETIC FIELD RESULTS IN
LOCAL SIGNAL INCREASE

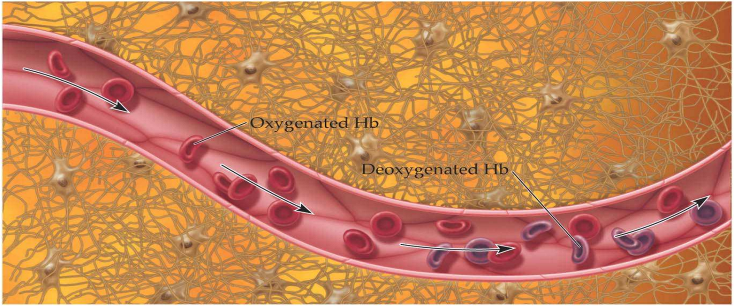
Hemoglobin Molecule



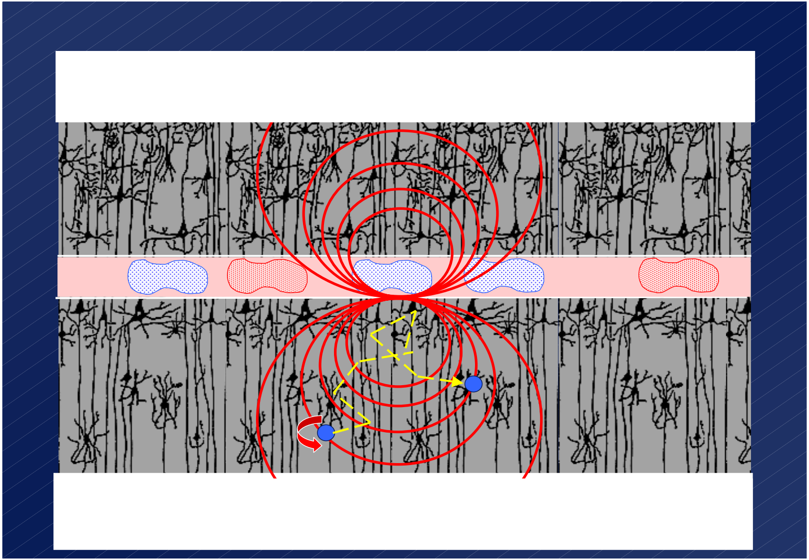
[illegible] Hb molecules per red blood cell

BOLD Signal Generation

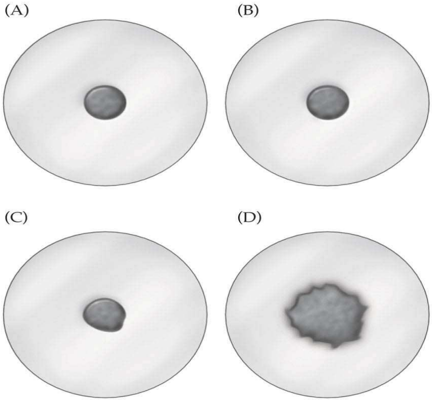
(B)



FUNCTIONAL MAGNETIC RESONANCE IMAGING, Figure 7.14 (Part 2)

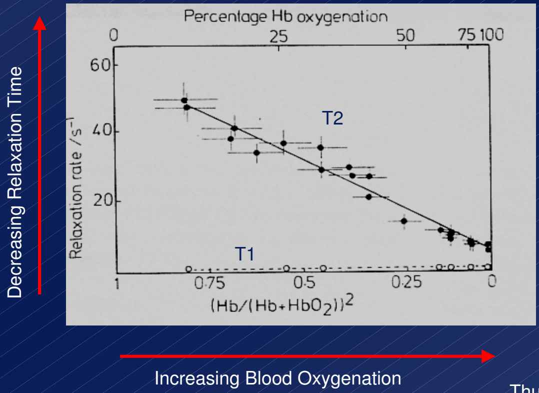


Oxy/deoxyhemoglobin (D)



FUNCTIONAL MAGNETIC RESONANCE IMAGING, **Figure 7.3**

Blood Deoxygenation affects T_2 Recovery

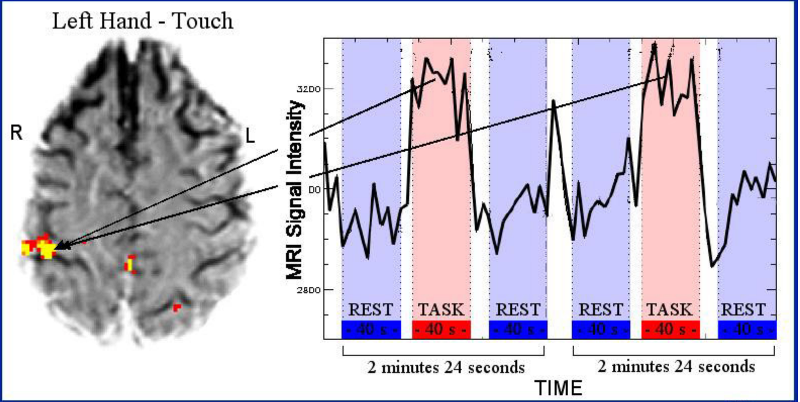


Thulborn et al., 1982

BOLD

- **B**lood **O**xygen **L**evel **D**ependent
- Gradient echo, EPI (kvůli rychlosti, lze i spin-echo)
- Paramagnetické vlastnosti deoxyhemoglobinu $\longrightarrow$ nehomogenita pole $\longrightarrow$ T_2^* efekt
- Velmi slabý signál (SNR ≈ 0.1)
- Průměrování:
  - Opakujeme např. 10 bloků (snímání) bez aktivity
  - . . . 10 bloků (snímání) s aktivitou

Magnetic Resonance Signals to Location of Function

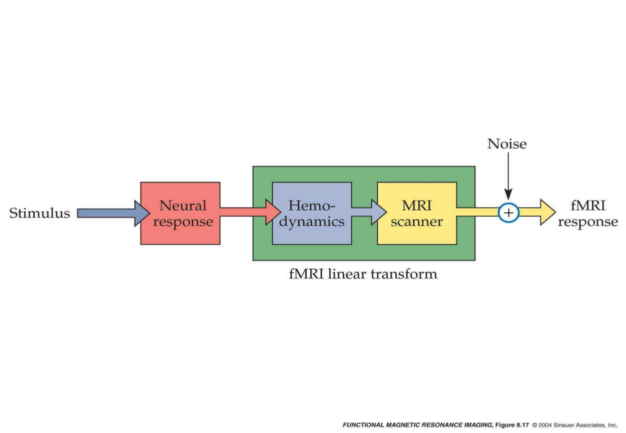


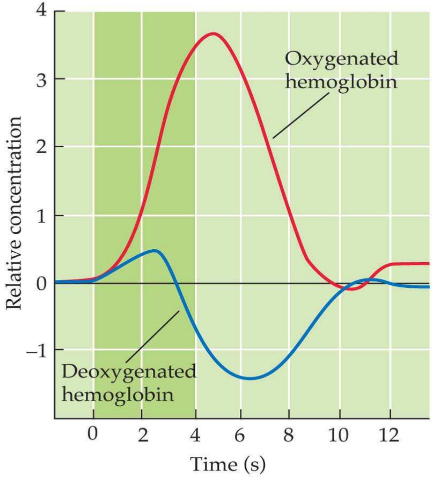
From Hirsch, J., et al; Neurosurgery 47: 711-722, 2000

Hemodynamická odezva
Hemodynamic response

- Nervová aktivita $\longrightarrow$ zásobování krví $\longrightarrow$ BOLD signál
- Reakce není okamžitá, impulzní charakteristika se nazývá **hemodynamická odezva**
- Odezva se liší mezi subjekty i v rámci jednoho subjektu

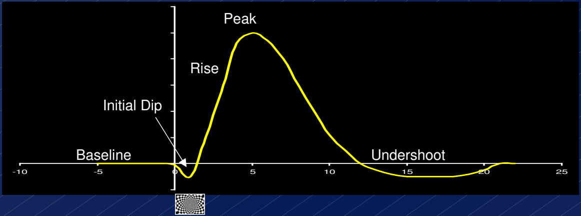
Hemodynamic response

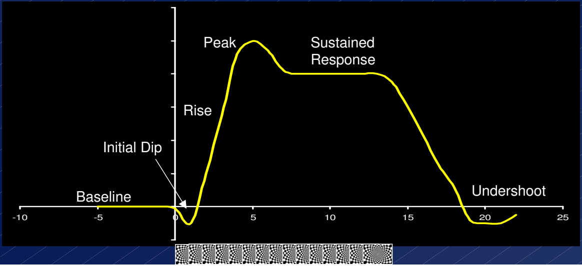




FUNCTIONAL MAGNETIC RESONANCE IMAGING, **Figure 7.5**

Basic Form of Hemodynamic Response

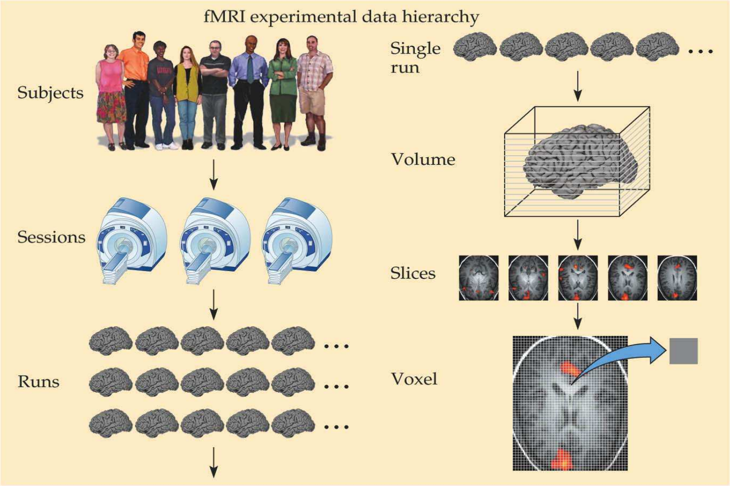




*f*MRI IMAGING PARAMETERS

SCANNER:	**GE Signa 1.5 T** **EPI Capability**
IN-PLANE RESOLUTION:	**1.5 mm x 1.5 mm**
SLICE THICKNESS:	**4.5 mm**
SLICE SEPARATION:	**0 mm**
NUMBER OF SLICES:	**21**
SLICE ORIENTATION:	**Axial on AC/PC Line**
RESONATOR:	**GE "bird cage"**
SEQUENCE:	**GRADIENT ECHO** **TR = 4000 msec TE = 60 msec** **Flip Angle = 60 deg**

Position of Headcoil and Mirror



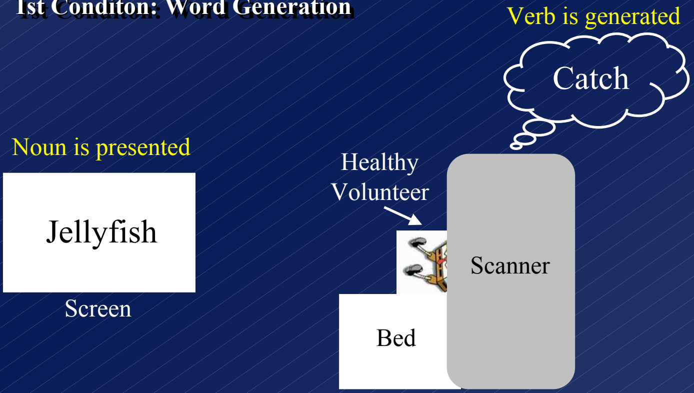
FUNCTIONAL MAGNETIC RESONANCE IMAGING, Figure 8.1

The Experiment:
fMRI adaptation of classic PET experiment

- **Three Conditions in 21 second epochs**
- **1st Conditon: Word Generation**

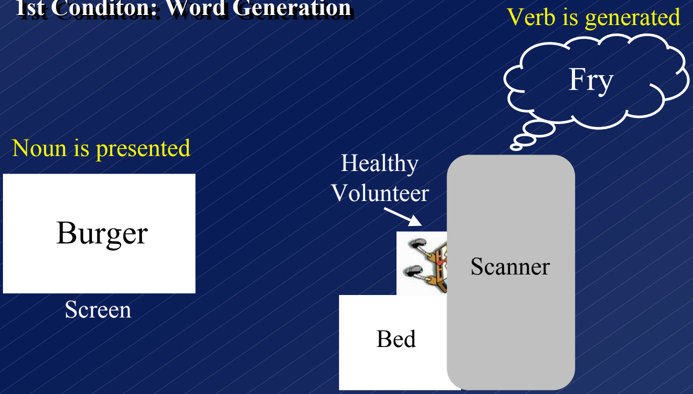
The Experiment:
fMRI adaptation of classic PET experiment

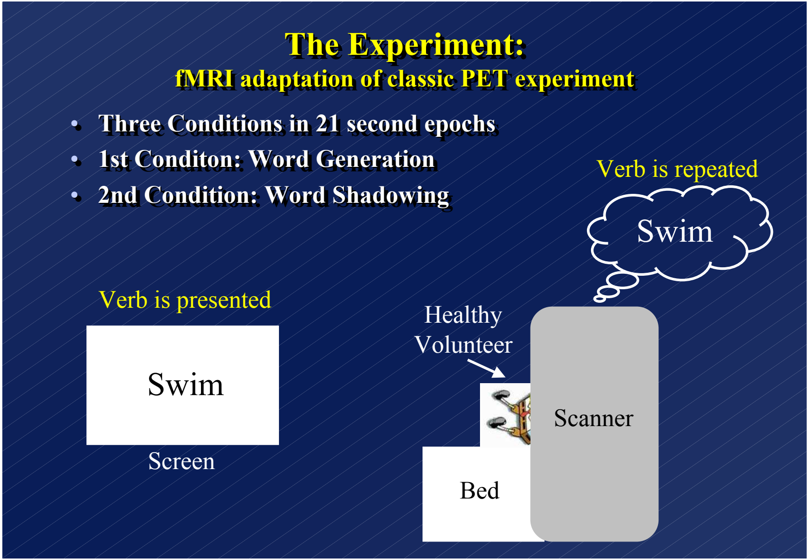
- Three Conditions in 21 second epochs
- 1st Conditon: Word Generation



The Experiment:
fMRI adaptation of classic PET experiment

- **Three Conditions in 21 second epochs**
- **1st Conditon: Word Generation**

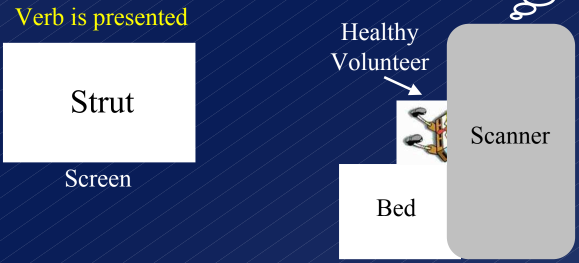



The Experiment:
fMRI adaptation of classic PET experiment
• Three Conditions in 21 second epochs
• 1st Conditon: Word Generation
• 2nd Condition: Word Shadowing
Verb is repeated
Swim
Verb is presented
Swim
Screen
Healthy Volunteer
Scanner
Bed

The Experiment:

fMRI adaptation of classic PET experiment

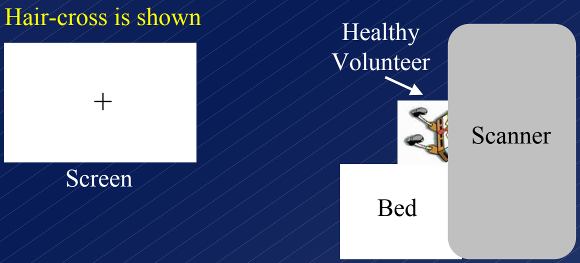
- Three Conditions in 21 second epochs
- 1st Conditon: Word Generation
- 2nd Condition: Word Shadowing



The Experiment:

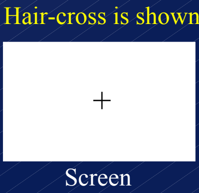
fMRI adaptation of classic PET experiment

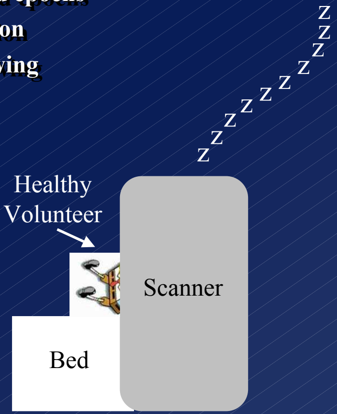
- Three Conditions in 21 second epochs
- 1st Conditon: Word Generation
- 2nd Condition: Word Shadowing
- 3rd Condition: Baseline



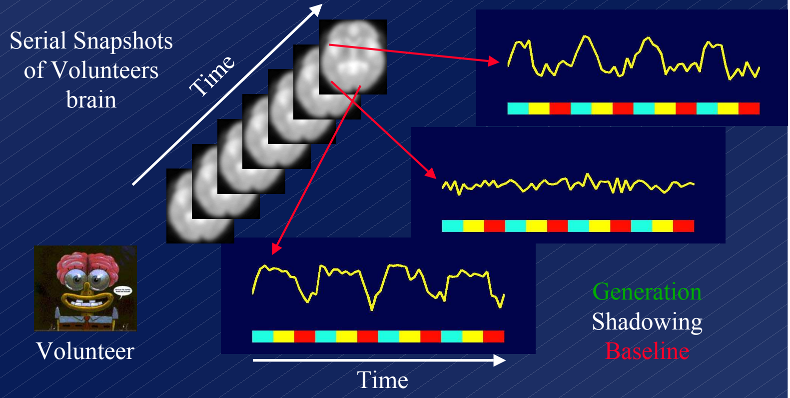
The Experiment:
fMRI adaptation of classic PET experiment

- **Three Conditions in 21 second epochs**
- **1st Conditon: Word Generation**
- **2nd Condition: Word Shadowing**
- **3rd Condition: Baseline**





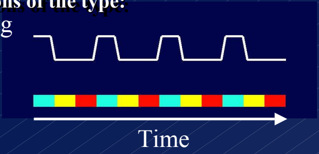
The Data:
Set of Volumes <u>or</u> Set of Time-series



The Model:
A Set of Hypothetical Time-series

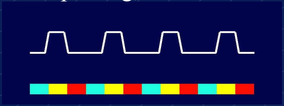
- **A model consists of a set of assumptions of the type:**

"I think a voxel that is into generating words might have a time-series looking like this"



- **and**

"A voxel that is into repeating, like this"



and

"A voxel that just doesn't care, like this"

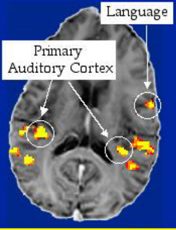
Generation Shadowing Baseline

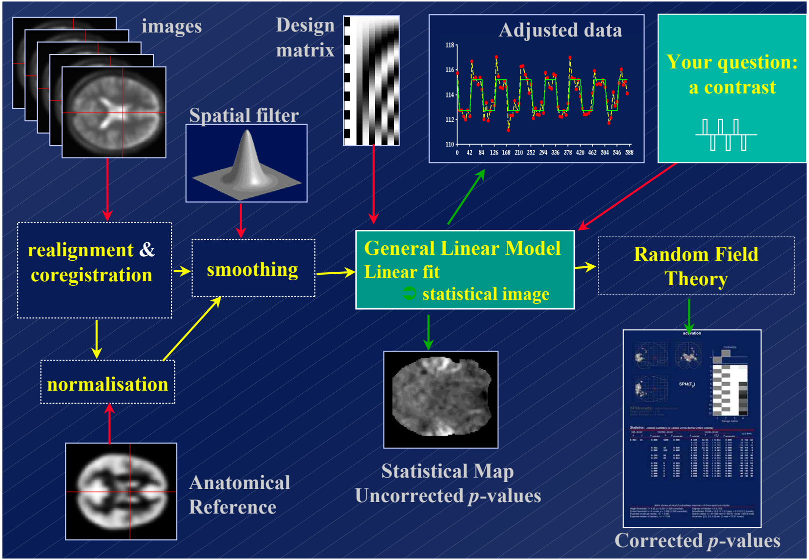
COMPUTATIONS FOR *f*UNCTIONAL IMAGE PROCESSING

Scanner

RECONSTRUCTION
ALIGNMENT
VOXEL BY VOXEL ANALYSIS
GRAPHICAL REPRESENTATION

Functional Brain Map





images
Design matrix
Adjusted data
Your question: a contrast
Spatial filter
realignment & coregistration
smoothing
General Linear Model
Linear fit
statistical image
Random Field Theory
normalisation
Anatomical Reference
Statistical Map
Uncorrected p-values
Corrected p-values

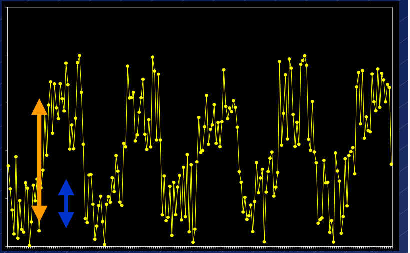
What is signal? What is noise?

- Signal, literally defined
  - Amount of current in receiver coil
- How can we control the amount of received signal?
  - Scanner properties (e.g., field strength)
  - Experimental task timing
  - Subject compliance (through training)
  - Head motion (to some degree)
- What can't we control (i.e., noise)?
  - Electrical variability in scanner
  - Physiologic variation (e.g., heart rate)
  - Some head motion
  - Differences across subjects

Signal-Noise-Ratio (SNR)

Task-Related
Variability

Non-task-related
Variability



What are typical SNRs for fMRI data?

- Signal amplitude
  - MR units: 5-10 units (baseline: ~700)
  - Percent signal change: 0.5-2%
- Noise amplitude
  - MR units: 10-50
  - Percent signal change: 0.5-5%
- SNR range
  - Total range: 0.1 to 4.0
  - Typical: 0.2 – 0.5

Types of Noise

- Thermal noise
  - Responsible for variation in background
  - Eddy currents, scanner heating
- Power fluctuations
  - Typically caused by scanner problems
- Variation in subject cognition
  - Timing of processes
- Head motion effects
- Physiological changes
- Differences across brain regions
  - Functional differences
  - Large vessel effects
- Artifact-induced problems

Why is noise assumed to be Gaussian?

- **Central limit theorem**
  - If $X_1 \ldots X_n$ are a set of independent random variables, each with an *arbitary* probability distribution, then the sum of the set of variables (probability density function) will be distributed normally.

Variability in Subject Behavior: Issues

- Cognitive processes are not static
  - May take time to engage
  - Often variable across trials
  - Subjects' attention/arousal wax and wane
- Subjects adopt different strategies
  - Feedback- or sequence-based
  - Problem-solving methods
- Subjects engage in non-task cognition
  - Non-task periods do not have the absence of thinking

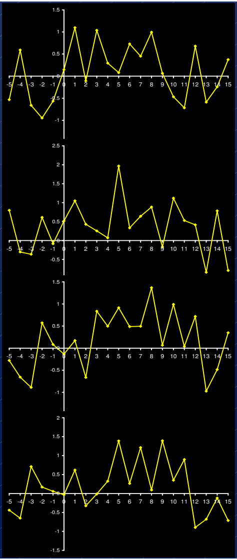
What can we do about these problems?

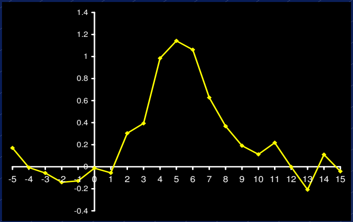
Trial Averaging

- **Static signal, variable noise**
  - Assumes that the MR data recorded on each trial are composed of a signal + (random) noise

- **Effects of averaging**
  - Signal is present on every trial, so it remains constant through averaging
  - Noise randomly varies across trials, so it decreases with averaging
  - Thus, SNR increases with averaging

Trial averaging

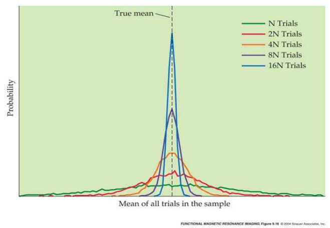




Average of 16 trials with SNR = 0.6

Fundamental Rule of SNR

For Gaussian noise, experimental power increases with the square root of the number of observations



Caveats

- Signal averaging is based on assumptions
  - Data = signal + temporally invariant noise
  - Noise is uncorrelated over time
- If assumptions are violated, then averaging ignores potentially valuable information
  - Amount of noise varies over time
  - Some noise is temporally correlated (physiology)
- Nevertheless, averaging provides robust, reliable method for determining brain activity

Signal, noise, and the General Linear Model

$$Y = \alpha M + \varepsilon$$

Measured Data

Amplitude (solve for)

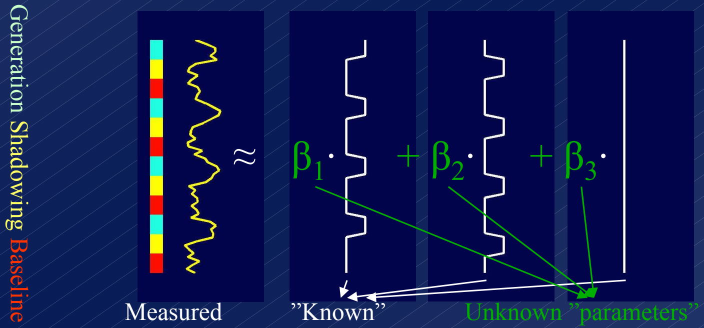
Design Model

Noise

Cf. Boynton et al., 1996

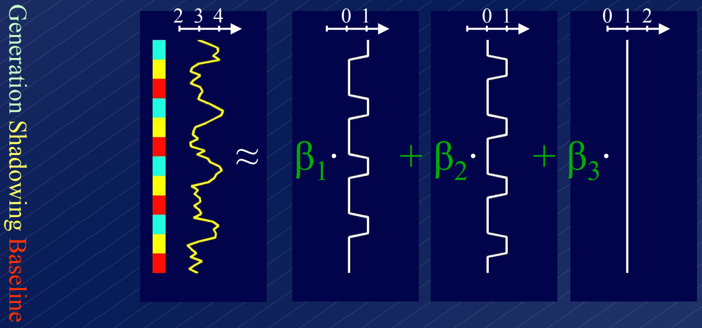
The Model:
A Set of Hypothetical Time-series

- For a given voxel (time-series) we try to figure out just what type that is by ”modelling” it as a linear combination of the hypothetical time-series.



The Estimation:
Finding the ”best” parameter values

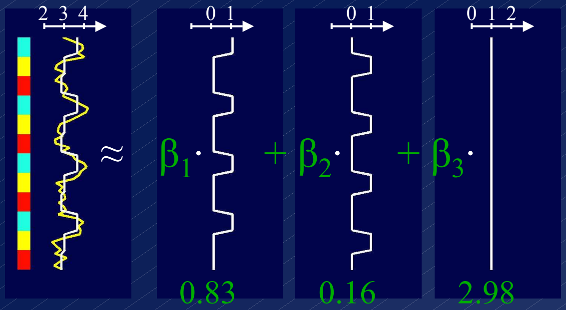
- The estimation entails finding the parameter values such that the linear combination ”best” fits the data.



The Estimation:
Finding the "best" parameter values

- **The estimation entails finding the parameter values such that the linear combination "best" fits the data.**

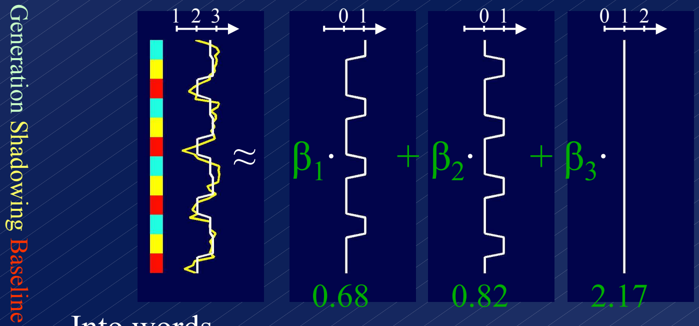
Generation Shadowing Baseline



Cool!

The Estimation:
Finding the ”best” parameter values

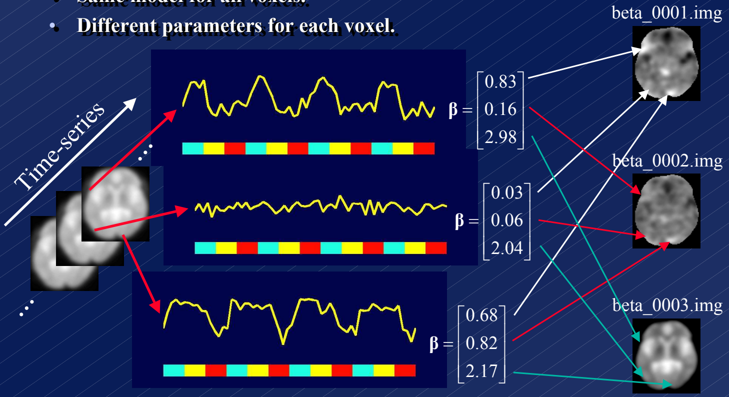
- And the nice thing is that the same model fits all the time-series, only with different parameters.



Into words

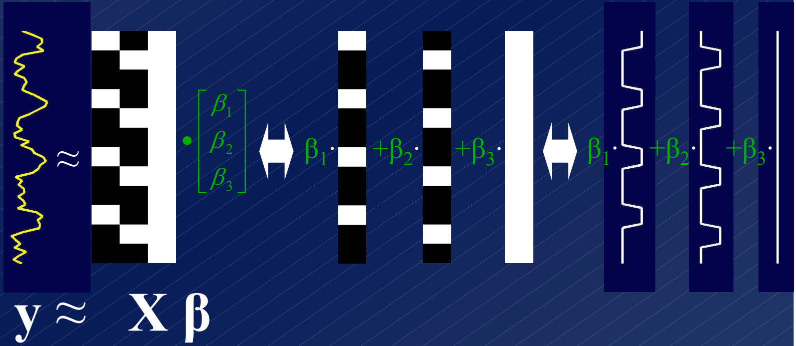
The Estimation:
The format of data, model and parameters

- Same model for all voxels.
- Different parameters for each voxel.



The model revisited.

- And, of course, the way we are used to see the model is like this.

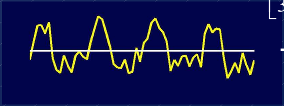


The estimation revisited
What do I mean by "best" fit

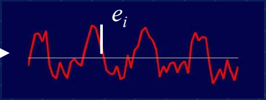
— Data

— Some fit

$$\boldsymbol{\beta} = \begin{bmatrix} 0 \\ 0 \\ 3.31 \end{bmatrix}$$



— Error



$$\sum_{i=1}^{n} e_i^2 = 17.16$$

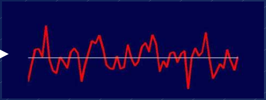
$$\sum_{i=1}^{n} e_i = 0$$

— Data

— Best fit

$$\boldsymbol{\beta} = \begin{bmatrix} 0.83 \\ 0.16 \\ 2.98 \end{bmatrix}$$

— Error

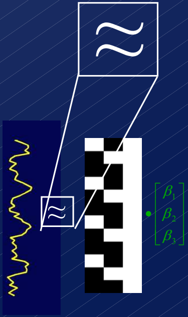


$$\sum_{i=1}^{n} e_i^2 = 9.47$$

$$\sum_{i=1}^{n} e_i = 0$$

Model revisited – again

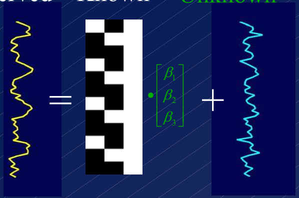
Now, what's that
all about?



Remember?

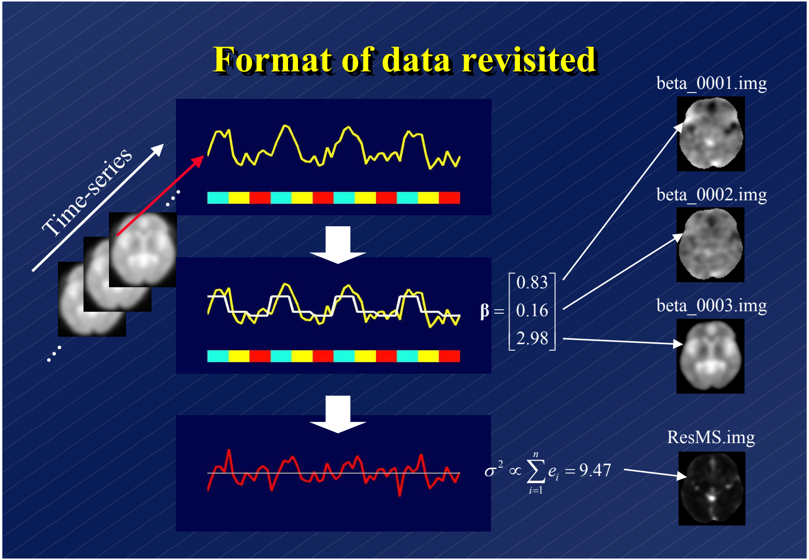
We need a model for the error!

Observed Known Unknown



$$\mathbf{y} = \mathbf{X\beta} + \mathbf{e}$$

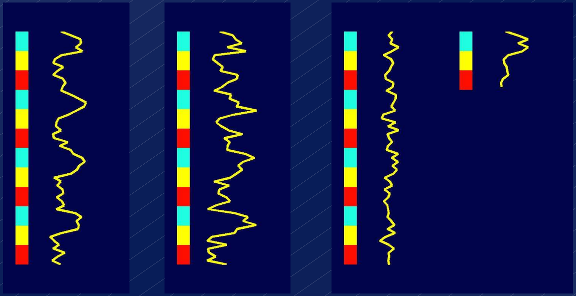
$$\mathbf{e} \sim N(\mathbf{0}, \sigma^2\mathbf{I})$$


Format of data revisited
Time-series
beta_0001.img
beta_0002.img
beta_0003.img
ResMS.img
$\beta = \begin{bmatrix} 0.83 \\ 0.16 \\ 2.98 \end{bmatrix}$
$\sigma^2 \propto \sum_{i=1}^{n} e_i = 9.47$

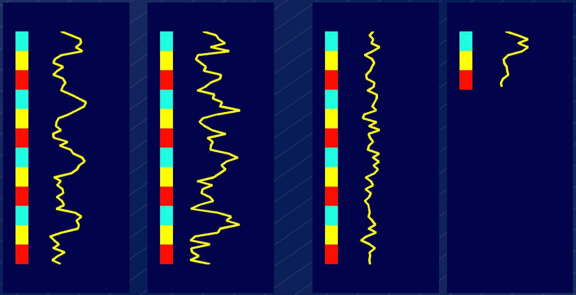
But why do we need the error?

It is about trust.

But why do we need the error?
Which sequence do you trust?



But why do we need the error?
Would you trust these?



β_1=1
σ=0.2
n=60

β_1=1
σ=0.5
n=60

β_1=0.3
σ=0.2
n=60

β_1=1
σ=0.2
n=15

But why do we need the error?
In conclusion:

- We trust long series with large effects and small error.

Effect size

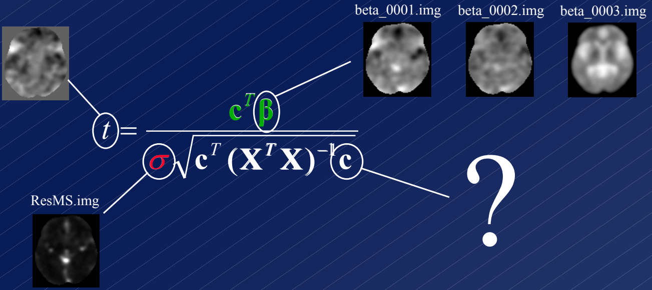
$$t = \frac{\mathbf{c}^T \boldsymbol{\beta}}{\sigma \sqrt{\mathbf{c}^T (\mathbf{X}^T \mathbf{X})^{-1} \mathbf{c}}}$$

Uncertainty of effect size

t-test

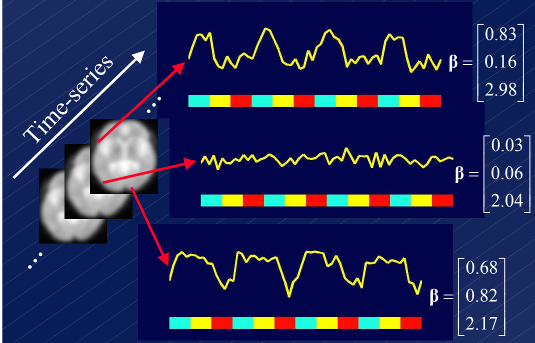
- We trust: Long series with large effects and small error.

$$t = \frac{c^T \beta}{\sigma \sqrt{c^T (X^T X)^{-1} c}}$$



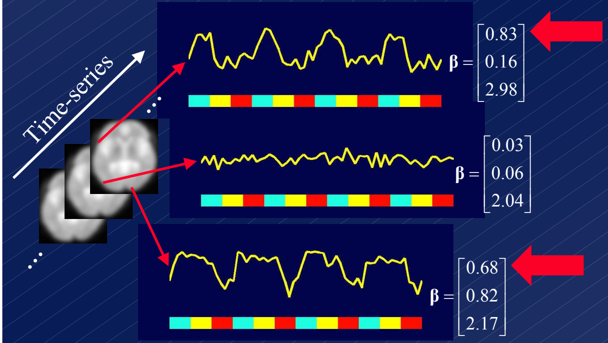
Asking questions of your data
t-contrasts

- Can we find voxels that are active in word-generation taks?



Asking questions of your data
t-contrasts

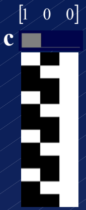
- **Can we find voxels that are active in word-generation taks?**

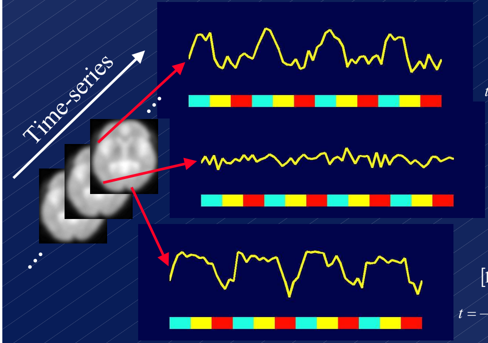


Hmm, seem to have large values for β_1

Asking questions of your data
t-contrasts

- **Can we find voxels that are active in word-generation taks?**





$$t = \frac{\begin{bmatrix}1 & 0 & 0\end{bmatrix}\begin{bmatrix}0.83\\0.16\\2.98\end{bmatrix}}{0.41*0.32} = \frac{0.83}{0.41*0.32} = 6.42^{**}$$

$$t = \frac{\begin{bmatrix}1 & 0 & 0\end{bmatrix}\begin{bmatrix}0.03\\0.06\\2.04\end{bmatrix}}{0.19*0.32} = \frac{0.03}{0.19*0.32} = 0.44$$

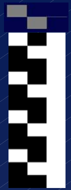
$$t = \frac{\begin{bmatrix}1 & 0 & 0\end{bmatrix}\begin{bmatrix}0.68\\0.82\\2.17\end{bmatrix}}{0.40*0.32} = \frac{0.68}{0.40*0.32} = 5.41^{**}$$

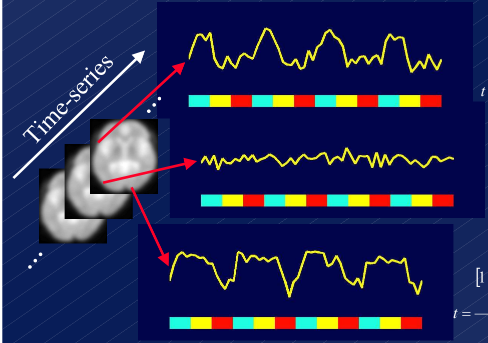
Asking questions of your data
t-contrasts

- Voxels that are <u>more</u> active in generation than shadowing?

$[1 \quad -1 \quad 0]$

c



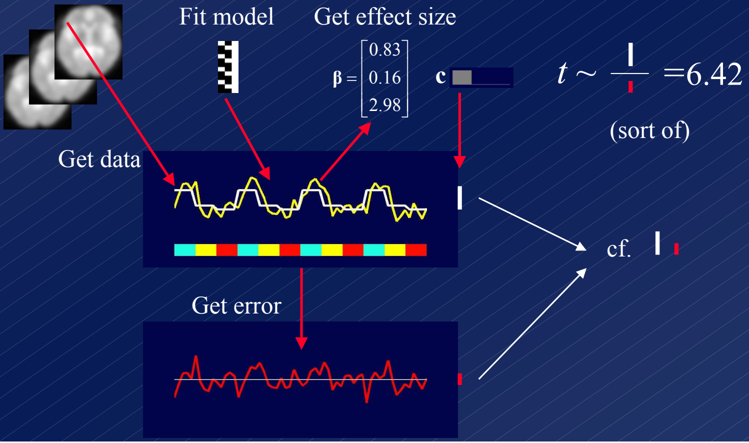


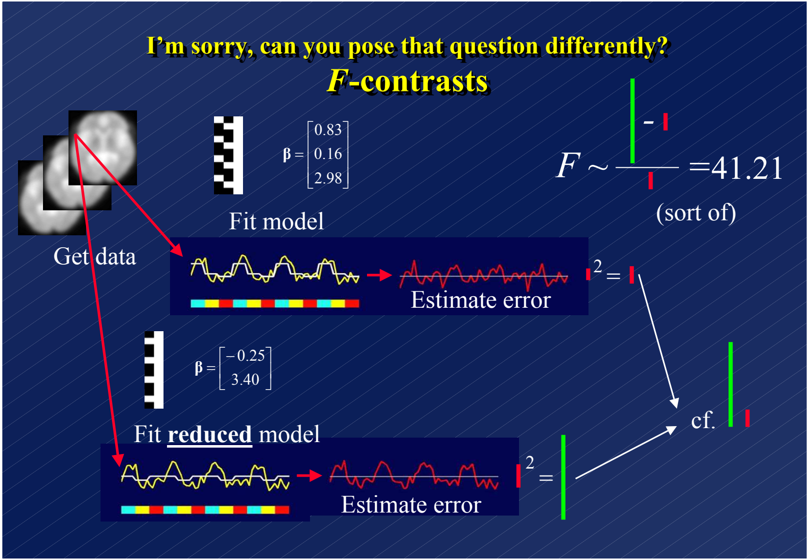
$$t = \frac{[1 \quad -1 \quad 0]\begin{bmatrix}0.83\\0.16\\2.98\end{bmatrix}}{0.41*0.32} = \frac{0.67}{0.41*0.32} = 5.16^{**}$$

$$t = \frac{[1 \quad -1 \quad 0]\begin{bmatrix}0.03\\0.06\\2.04\end{bmatrix}}{0.19*0.32} = \frac{-0.03}{0.19*0.32} = -0.58$$

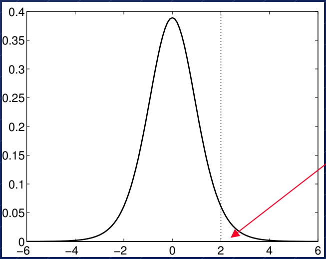
$$t = \frac{[1 \quad -1 \quad 0]\begin{bmatrix}0.68\\0.82\\2.17\end{bmatrix}}{0.40*0.32} = \frac{-0.14}{0.40*0.32} = -1.12$$

t-contrasts revisited




I'm sorry, can you pose that question differently?
F-contrasts
Get data
Fit model
β = [0.83, 0.16, 2.98]
Estimate error
2 =
F ~ =41.21
(sort of)
β = [−0.25, 3.40]
Fit reduced model
Estimate error
2 =
cf.

Inference at a single voxel



u=2

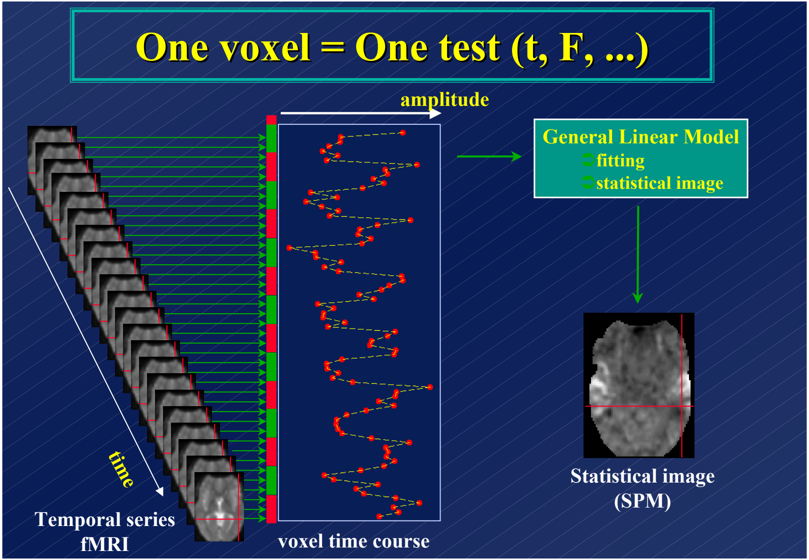
t-distribution

NULL hypothesis, H: activation is zero

$\alpha = p(t>u|H)$

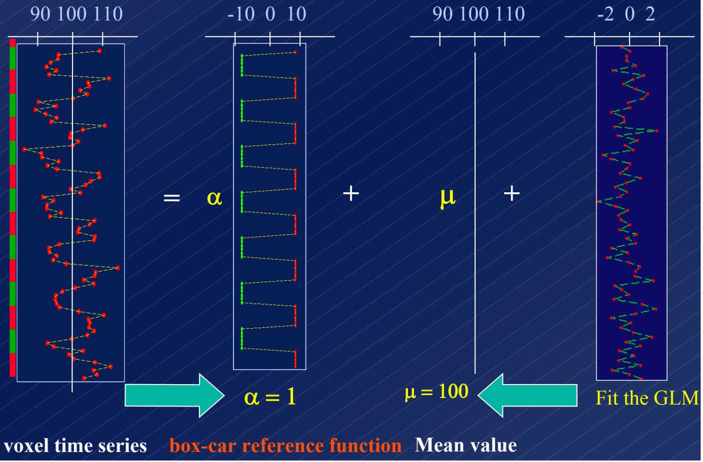
p-value: probability of getting a value of t at least as extreme as u. If α is small we reject the null hypothesis.

u=(effect size)/std(effect size)

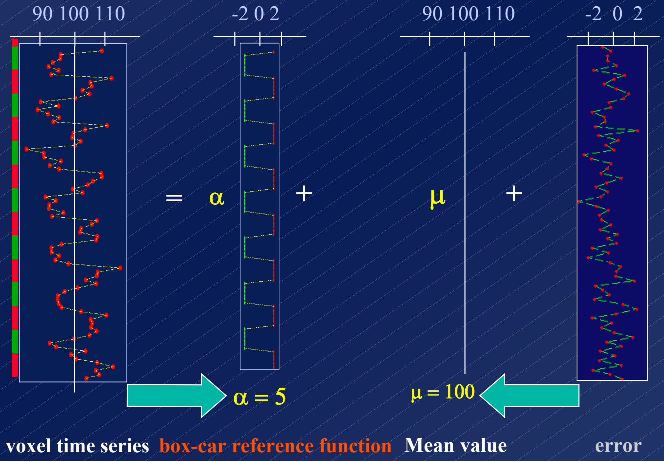


One voxel = One test (t, F, ...)
amplitude
General Linear Model
fitting
statistical image
time
Temporal series
fMRI
voxel time course
Statistical image
(SPM)

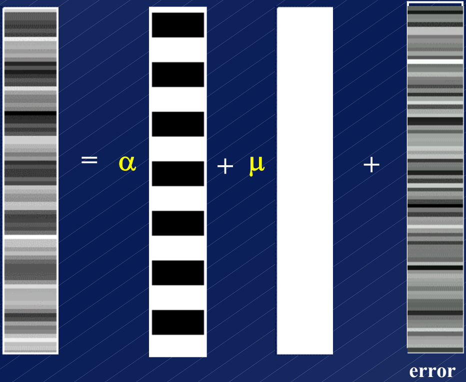
Regression example…



Regression example…

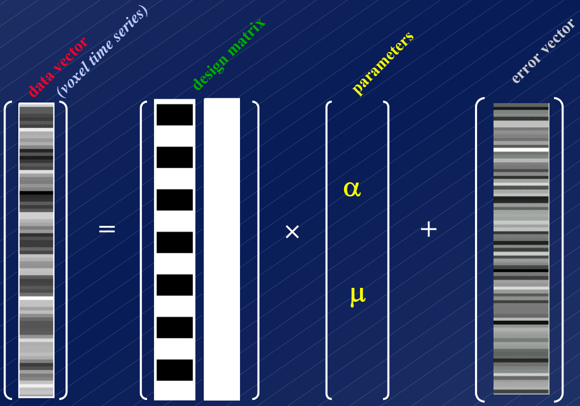


…revisited : matrix form



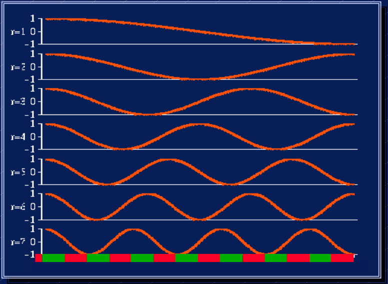
$$Y_s = \mu \times \mathbf{1} + \alpha \times f(t_s) + \varepsilon_s$$

Box car regression: design matrix…

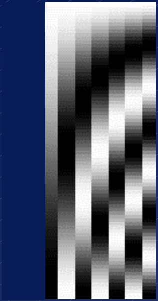


$$\underline{Y} = X \times \underline{\beta} + \underline{\varepsilon}$$

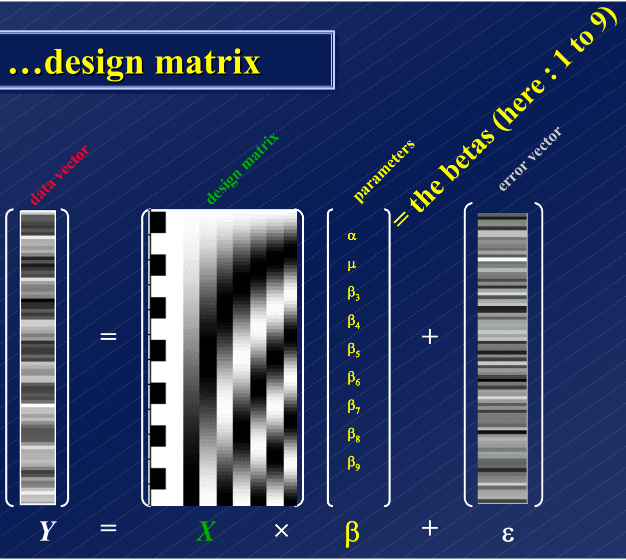
Add more reference functions ...



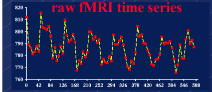
Discrete cosine transform basis functions

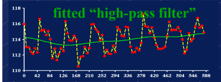


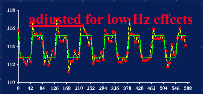
…design matrix



Fitting the model = finding some estimate of the betas = minimising the sum of square of the residuals S^2

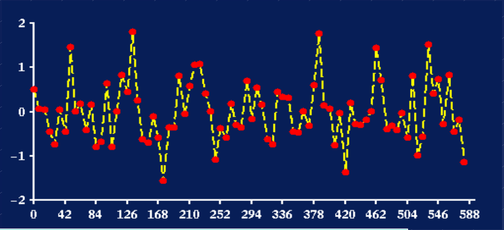






fitted box-car

residuals



$$\frac{\sum \text{the squared values of the residuals}}{\text{number of time points minus the number of estimated betas}} = s^2$$

Summary ...

- *We put in our model regressors (or covariates) that represent how we think the signal is varying (of interest and of no interest alike)*

- *Coefficients (= parameters) are estimated using the Ordinary Least Squares (OLS) or Maximum Likelihood (ML) estimator.*

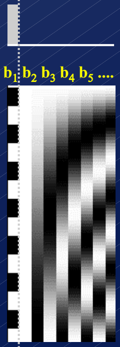
- *These estimated parameters (the "betas")* ***depend*** *on the scaling of the regressors.*

- *The residuals, their sum of squares and the resulting tests (t,F),* ***do not*** *depend on the scaling of the regressors.*

T test - one dimensional contrasts - SPM{t}

A contrast = a linear combination of parameters: $c' \times \beta$

$c' = 1\ 0\ 0\ 0\ 0\ 0\ 0\ 0$



box-car amplitude > 0 ?

=

$\beta_1 > 0$?

=>

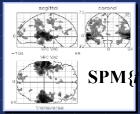
Compute $1 \times b_1 + 0 \times b_2 + 0 \times b_3 + 0 \times b_4 + 0 \times b_5 + \ldots$

and

divide by estimated standard deviation

$$T = \frac{\textit{contrast} \text{ of estimated parameters}}{\sqrt{\text{variance estimate}}}$$

$$T = \frac{c'b}{\sqrt{s^2 c'(X'X)^+ c}}$$

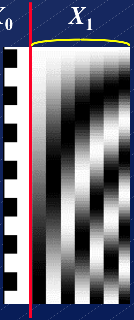


F-test (SPM{F}) : a reduced model or ...

Tests multiple linear hypotheses : Does X1 model anything ?

H_0: True (reduced) model is X_0

X_0 X_1



$\longrightarrow$ S^2

This (full) model ?

X_0

$\longrightarrow$ S_0^2

Or this one?

$$F = \frac{\text{additional variance accounted for by tested effects}}{\text{error variance estimate}}$$

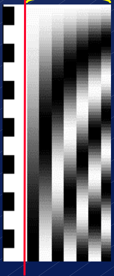
$$F \sim (S_0^2 - S^2) / S^2$$

F-test (SPM{*F*}) : a reduced model or ... multi-dimensional contrasts ?

tests multiple linear hypotheses. Ex : does DCT set model anything?

H_0: True model is X_0 H_0: $\beta_{3\text{-}9} = (0\ 0\ 0\ 0\ ...)$ test H_0 : $c' \times b = 0$?

X_0 X_1 $(\beta_{3\text{-}9})$

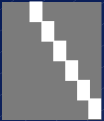


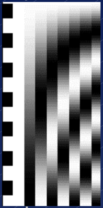
This model ?

X_0

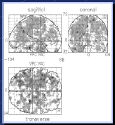
Or this one ?

$$c' = \begin{matrix} 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 \end{matrix}$$



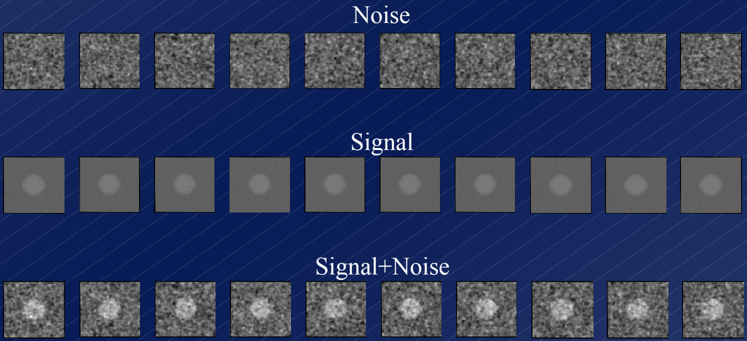


SPM{*F*}

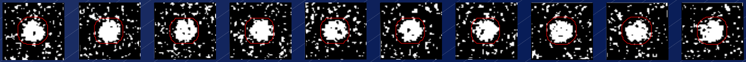


Bonferroni correction

Inference for Images



Use of ‘uncorrected’ p-value, α=0.1



11.3%   11.3%   12.5%   10.8%   11.5%   10.0%   10.7%   11.2%   10.2%   9.5%

Percentage of Null Pixels that are False Positives

Using an ‘uncorrected’ p-value of 0.1 will lead us to conclude on average that 10% of voxels are active when they are not.

This is clearly undesirable. To correct for this we can define a null hypothesis for images of statistics.

Family-wise Null Hypothesis

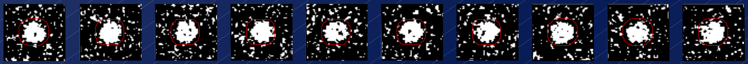
FAMILY-WISE NULL HYPOTHESIS:
Activation is zero everywhere

If we reject a voxel null hypothesis
at *any* voxel, we reject the family-wise
Null hypothesis

A FP **anywhere** in the image
gives a Family Wise Error (FWE)

Family-Wise Error (FWE) rate = ‘corrected’ p-value

Use of ‘uncorrected’ p-value, α=0.1



Use of ‘corrected’ p-value, α=0.1

FWE

The Bonferroni correction

The Family-Wise Error rate (FWE), α, for a family of N **independent** voxels is

$$\alpha = Nv$$

where v is the voxel-wise error rate. Therefore, to ensure a particular FWE set

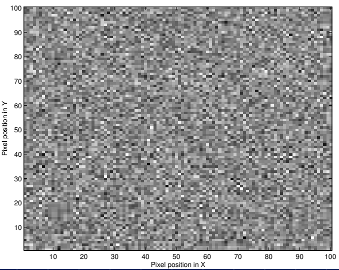
$$v = \alpha / N$$

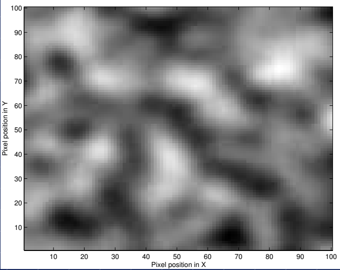
BUT ...

The Bonferroni correction

Independent Voxels

Spatially Correlated Voxels





Bonferroni is too conservative for brain images

Applied Smoothing

Smoothness

smoothness » voxel size

practically

$FWHM \geq 3 \times \texttt{VoxDim}$

Typical applied smoothing:

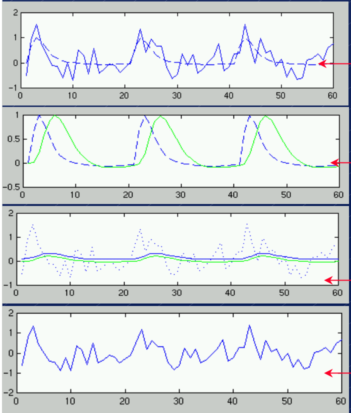
Single Subj fMRI: 6mm

PET: 12mm

Multi Subj fMRI: 8-12mm

PET: 16mm

A bad model ...



True signal and observed signal (---)

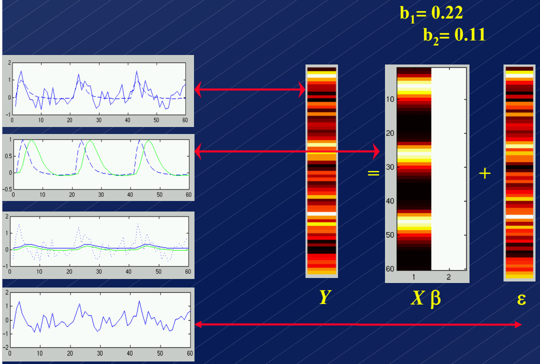
Model (green, pic at 6sec)
TRUE signal (blue, pic at 3sec)

Fitting (b1 = 0.2, mean = 0.11)

Residual (still contains some signal)

=> Test for the green regressor not significant

A bad model ...

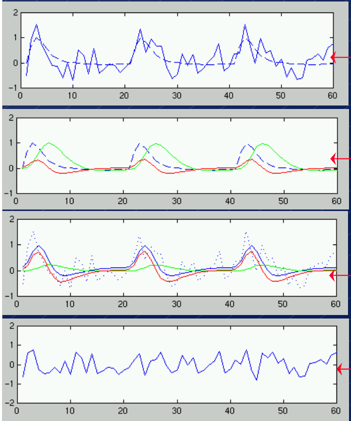


Residual Variance = 0.3

$P(Y|\ \beta_1 = 0)$ =>
p-value = 0.1
(t-test)

$P(Y|\ \beta_1 = 0)$ =>
p-value = 0.2
(F-test)

A « better » model ...



True signal + observed signal

Model (green and red)
and true signal (blue ---)
Red regressor : temporal derivative of the green regressor

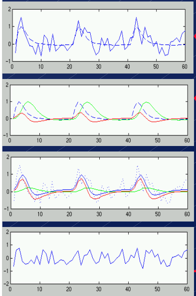
Global fit (blue)
and partial fit (green & red)
Adjusted and fitted signal

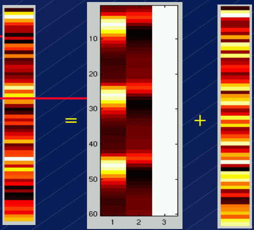
Residual (a smaller variance)

=> t-test of the green regressor significant
=> F-test very significant
=> t-test of the red regressor very significant

A better model ...

$b_1 = 0.22$
$b_2 = 2.15$
$b_3 = 0.11$





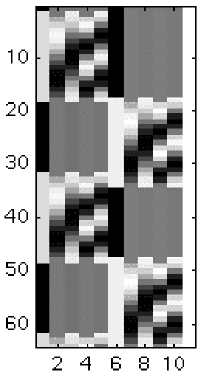
Y   *X* β   ε

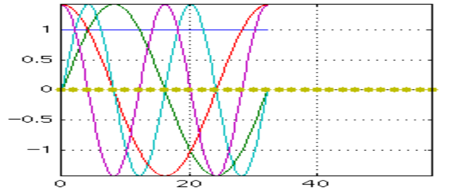
Residual Var = 0.2

$P(Y|\ \beta_1 = 0)$
p-value = 0.07
(t-test)

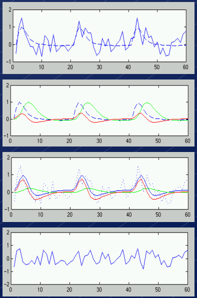
$P(Y|\ \beta_1 = 0, \beta_2 = 0)$
p-value = 0.000001
(F-test)

Flexible models :
Fourier Transform Basis



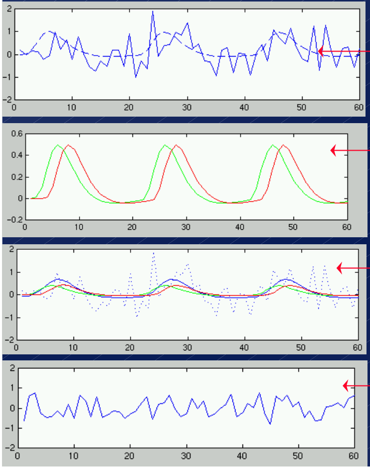


Summary ... (2)



- *The residuals should be looked at ...(non random structure ?)*
- *We rather test flexible models if there is little a priori information, and precise ones with a lot a priori information*
- *In general, use the F-tests to look for an overall effect, then look at the betas or the adjusted data to characterise the response shape*
- *Interpreting the test on a single parameter (one regressor) can be difficult: cf the delay or magnitude situation*

Correlation between regressors



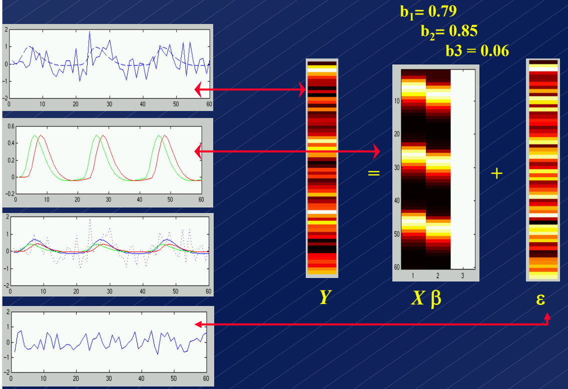
True signal

Model (green and red)

Fit (blue : global fit)

Residual

Correlation between regressors



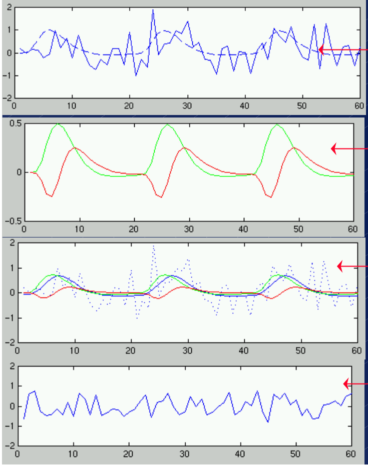
Residual var. = 0.3

$P(Y|\ \beta_1 = 0)$
p-value = 0.08
(t-test)

$P(Y|\ \beta_2 = 0)$
p-value = 0.07
(t-test)

$P(Y|\ \beta_1 = 0, \beta_2 = 0)$
p-value = 0.002
(F-test)

Correlation between regressors - 2



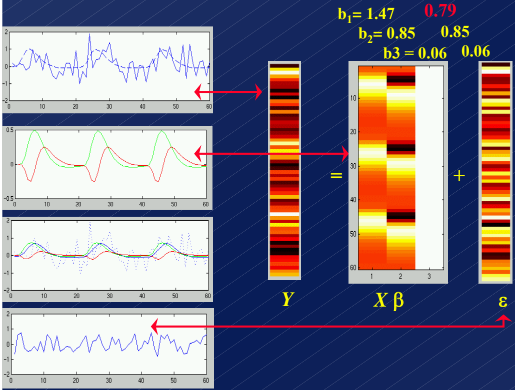
true signal

Model (green and red)
red regressor has been orthogonalised with respect to the green one
⇔ remove everything that correlates with the green regressor

Fit

Residual

Correlation between regressors -2



Residual var. = 0.3

$P(Y|\ \beta_1 = 0)$
p-value = 0.0003
(t-test)

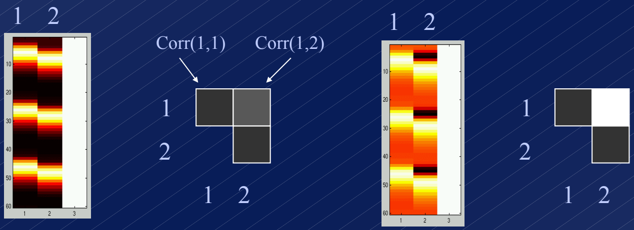
$P(Y|\ \beta_2 = 0)$
p-value = 0.07
(t-test)

$P(Y|\ \beta_1 = 0, \beta_2 = 0)$
p-value = 0.002
(F-test)

See « explore design »

Design orthogonality : « explore design »

Black = completely correlated   White = completely orthogonal



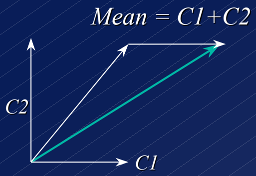
Beware: when there are more than 2 regressors (C1,C2,C3,...), you may think that there is little correlation (light grey) between them, but C1 + C2 + C3 may be correlated with C4 + C5

"completely" correlated ...

$$Y = Xb + e$$

$$X = \begin{matrix} 1 & 0 & 1 \\ 0 & 1 & 1 \\ 1 & 0 & 1 \\ 0 & 1 & 1 \end{matrix}$$

Cond 1 *Cond 2* *Mean*



Parameters are not unique in general ! Some contrasts have no meaning: NON ESTIMABLE

Summary ... (3)

- *We implicitly test for an additional effect only, so we may miss the signal if there is some correlation in the model*
- *Orthogonalisation is not generally needed - parameters and test on the changed regressor don't change*
- *It is always simpler (if possible!) to have orthogonal regressors*
- *In case of correlation, use F-tests to see the overall significance. There is generally no way to decide to which regressor the « common » part should be attributed to*
- *In case of correlation and if you need to orthogonolise a part of the design matrix, there is no need to re-fit a new model: change the contrast*

What is fMRI Experimental Design?

- Controlling the timing and quality of cognitive operations (IVs) to influence resulting brain processes (DVs)

- What can we control?
  - Experimental comparisons (what is to be measured?)
  - Stimulus properties (what is presented?)
  - Stimulus timing (when is it presented?)
  - Subject instructions (what do subjects do with it?)

Refractory Periods

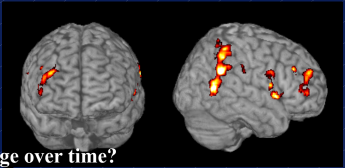
- **Definition: a change in the responsiveness to an event based upon the presence or absence of a similar preceding event**
  - **Neuronal refractory period**
  - **Vascular refractory period**

Goals of Experimental Design

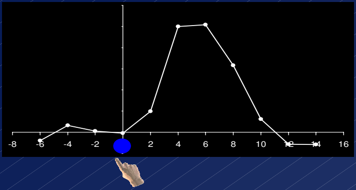
- To maximize the ability to test hypotheses
- To facilitate generation of new hypotheses

Detection vs. Estimation

- **Detection: What is active?**



- **Estimation: How does activity change over time?**



fMRI Design Types

1) Blocked Designs
2) Event-Related Designs
   a) Periodic Single Trial
   b) Jittered Single Trial
   c) Staggered or Interleaved Single Trial
3) Mixed Designs
   a) Combination blocked/event-related
   b) Variable stimulus probability

fMRI Design Types

1) Blocked Designs
2) Event-Related Designs
    a) Periodic Single Trial
    b) Jittered Single Trial
    c) Staggered or Interleaved Single Trial
3) Mixed Designs
    a) Combination blocked/event-related
    b) Variable stimulus probability

What are Blocked Designs?

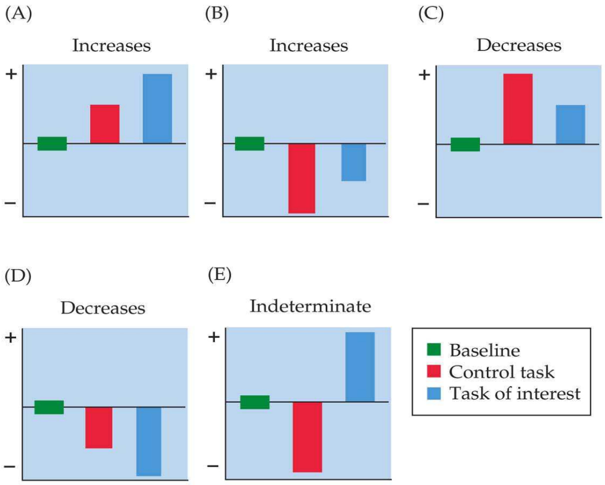
- Blocked designs segregate different cognitive processes into distinct time periods

Task A	Task B	Task A	Task B	Task A	Task B	Task A	Task B

Task A	REST	Task B	REST	Task A	REST	Task B	REST

What baseline should you choose?

- Task A vs. Task B
  - Example: Squeezing Right Hand vs. Left Hand
  - Allows you to distinguish differential activation between conditions
  - Does not allow identification of activity common to both tasks
    - Can control for uninteresting activity
- Task A vs. No-task
  - Example: Squeezing Right Hand vs. Rest
  - Shows you activity associated with task
  - May introduce unwanted results



Adapted from Gusnard & Raichle (2001)

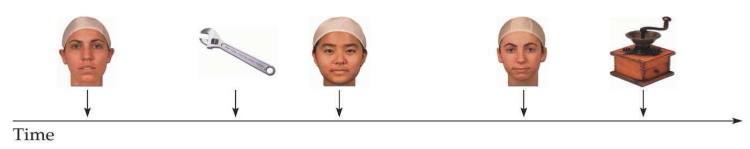
FUNCTIONAL MAGNETIC RESONANCE IMAGING, Figure 11.12

Limitations of Blocked Designs

- Very sensitive to signal drift
  - Sensitive to head motion, especially when only a few blocks are used.
- Poor choice of baseline may preclude meaningful conclusions
- Many tasks cannot be conducted repeatedly
- Difficult to estimate the HDR

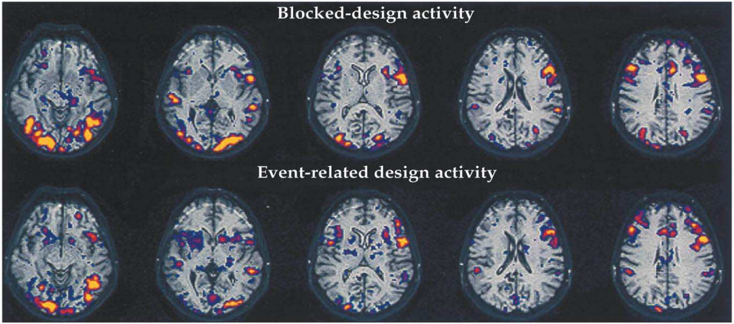
What are Event-Related Designs?

- Event-related designs associate brain processes with discrete events, which may occur at any point in the scanning session.



Some tasks are suitable for both block and event related designs.

(A)



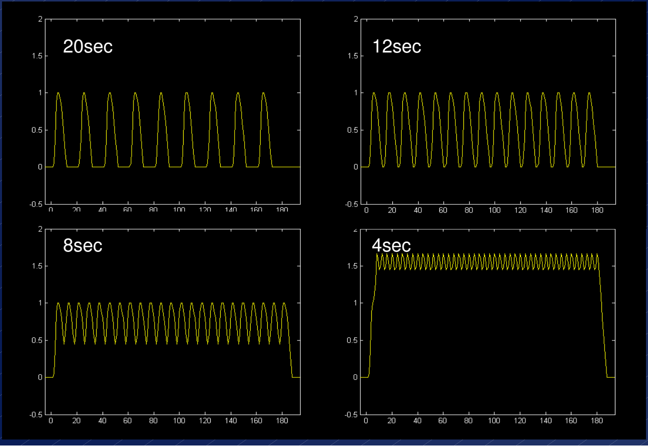
Word-stem completion task. Blocked design: 30s on/off. Event-related design: 15s ISI.

Buckner et al., (1996)

2a. Periodic Single Trial Designs

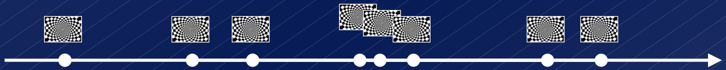
- **Stimulus events presented infrequently with long interstimulus intervals**

Trial Spacing Effects: Periodic Designs

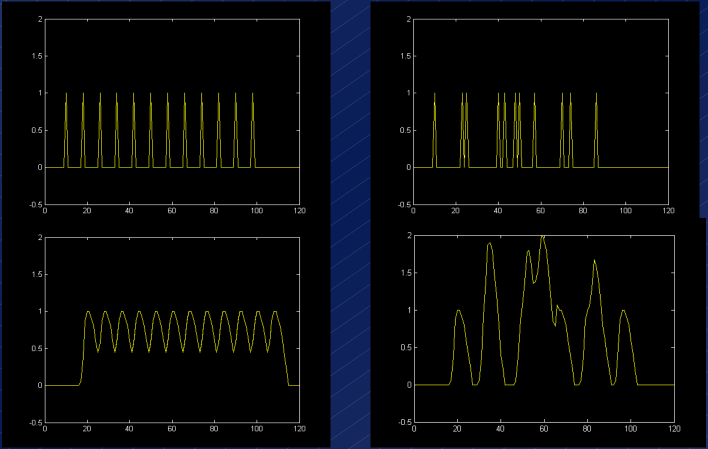


2b. Jittered Single Trial Designs

- Varying the timing of trials within a run
- Varying the timing of events within a trial



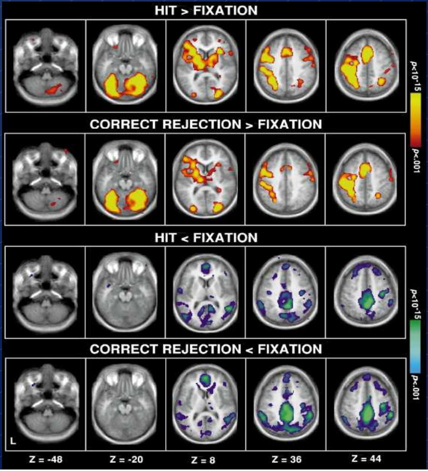
Effects of Jittering on Stimulus Variance

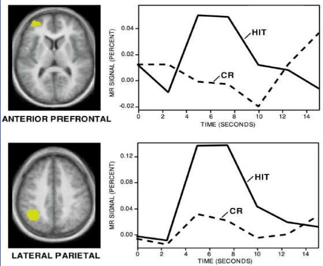


Post-hoc sorting
Dodatečné třídění

- Rozhodneme se až dodatečně (podle výsledku experimentu), do které kategorie pokus zařadíme.
- **Typický příklad:** Subjekt odpověděl správně/špatně.

Post-Hoc Sorting of Trials





Data from old/new episodic memory test.

From Konishi, et al., 2000

Limitations of Event-Related Designs

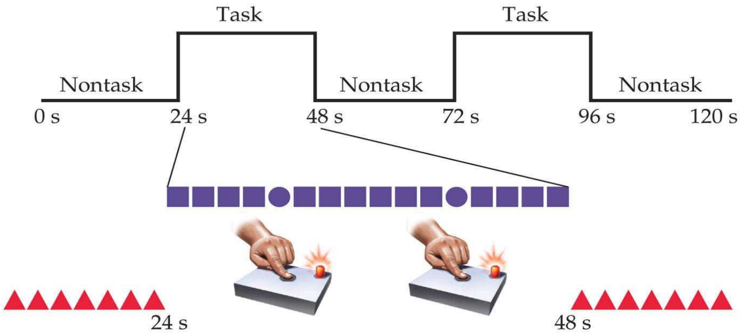
- **Differential effects of interstimulus interval**
  - **Long intervals do not optimally increase stimulus variance**
  - **Short intervals may result in refractory effects**

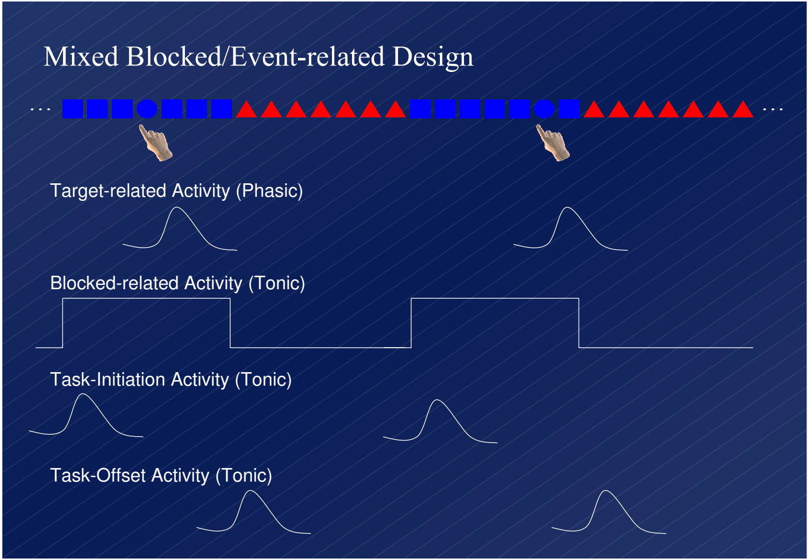
- **Detection ability dependent on form of HDR**

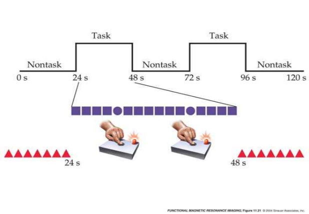
- **Length of “event” may not be known**

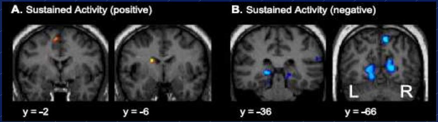
3a. Combination Blocked/Event

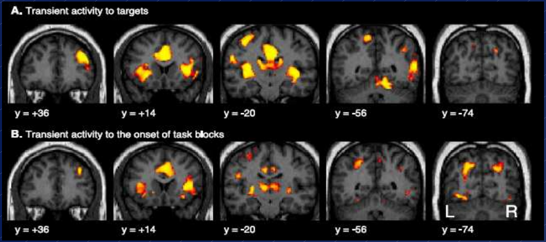
- **Both blocked and event-related design aspects are used (for different purposes)**
  - **Blocked design is used to evaluate *state-dependent* effects**
  - **Event-related design is used to evaluate *item-related* effects**
- **Analyses are conducted largely independently between the two measures**
  - **Cognitive processes are assumed to be independent**


Task
Task
Nontask
Nontask
Nontask
0 s
24 s
48 s
72 s
96 s
120 s
24 s
48 s


Mixed Blocked/Event-related Design
Target-related Activity (Phasic)
Blocked-related Activity (Tonic)
Task-Initiation Activity (Tonic)
Task-Offset Activity (Tonic)


Task
Task
Nontask
Nontask
Nontask
0 s
24 s
48 s
72 s
96 s
120 s
24 s
48 s

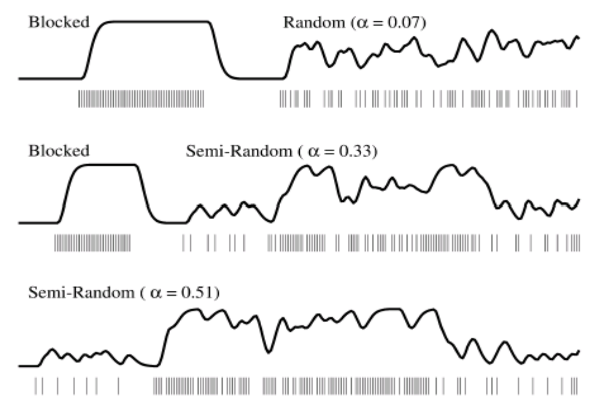

A. Sustained Activity (positive)
B. Sustained Activity (negative)
L
R
y = -2
y = -6
y = -36
y = -66


A. Transient activity to targets
y = +36
y = +14
y = -20
y = -56
y = -74
B. Transient activity to the onset of task blocks
L
R
y = +36
y = +14
y = -20
y = -56
y = -74

3b. Variable Stimulus Probability

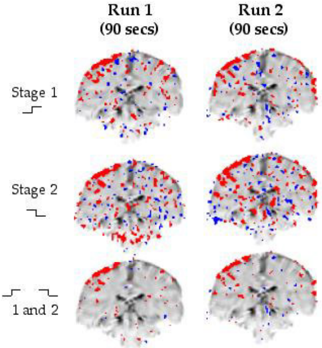
- Stimulus probability is varied in a blocked fashion
  - Appears similar to the combination design
- Mixed design used to maximize experimental power for single design
- Assumes that processes of interest do not vary as a function of stimulus timing
  - Cognitive processing
  - Refractory effects

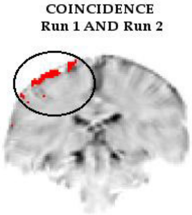
Random and Semi-Random Designs

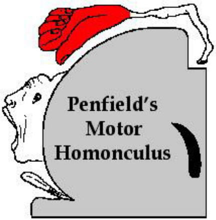


From Liu et al., 2001

MULTI-STAGE ANALYSIS WITH COINCIDENCE







Left Hand: Finger Thumb Tapping

Summary of Experiment Design

- Main Issues to Consider
  - What design constraints are induced by my task?
  - What am I trying to measure?
  - What sorts of non-task-related variability do I want to avoid?

- Rules of thumb
  - Blocked Designs:
    - Powerful for detecting activation
    - Useful for examining state changes
  - Event-Related Designs:
    - Powerful for estimating time course of activity
    - Allows determination of baseline activity
    - Best for post hoc trial sorting
  - Mixed Designs
    - Best combination of detection and estimation
    - Much more complicated analyses

MRI — závěr

- 3D zobrazování
- Výborné prostorové rozlišení
- Neinvazivní
- Obrovská variabilita — nejuniverzálnější ze zobrazovacích technik

MRI — závěr

- ⊕ 3D zobrazování
- ⊕ Výborné prostorové rozlišení
- ⊕ Neinvazivní
- ⊕ Obrovská variabilita — nejuniverzálnější ze zobrazovacích technik
- ⊖ Cena
- ⊖ Silná (elektro)magnetická pole — opatrnost nutná
- ⊖ Nepohodlí — hluk, stísněný prostor

fMRI — závěr

- ⊕ Lze zjistit, kde mozek pracuje
- ⊕ In-vivo
- ⊕ Neinvazivní
- ⊕ Relativně dobré prostorové rozlišení
- ⊖ Špatné časové rozlišení
- ⊖ Nutnost průměrování (nelze snímat ojedinělé jevy)