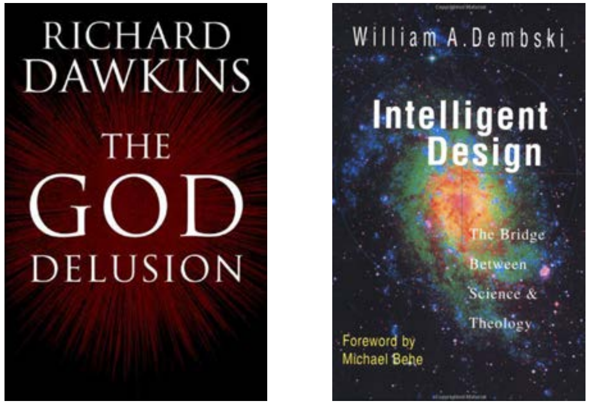
Donders Institute
for Brain, Cognition and Behaviour

Data analysis in experimental and clinical neuroscience, Ghent, April 14-18, 2014

Design and analysis of functional MRI experiments

Erno Hermans
erno.hermans@donders.ru.nl

Radboudumc
university medical center



Blood oxygenation level-dependent (BOLD) contrast

Proc. Natl. Acad. Sci. USA
Vol. 87, pp. 9868–9872, December 1990
Biophysics

Brain magnetic resonance imaging with contrast dependent on blood oxygenation

(cerebral blood flow/brain metabolism/oxygenation)

S. Ogawa, T. M. Lee, A. R. Kay, and D. W. Tank

Biophysics Research Department, AT&T Bell Laboratories, Murray Hill, NJ 07974

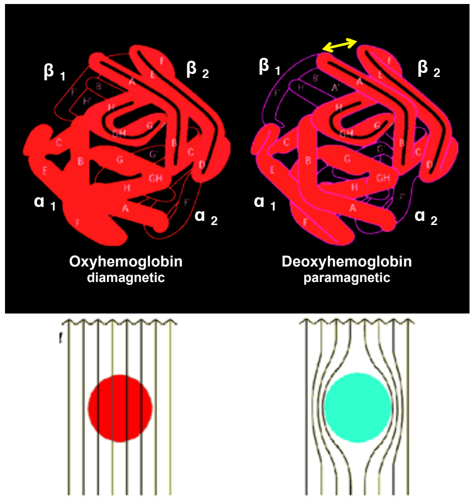
Communicated by Frank H. Stillinger, September 24, 1990 (received for review August 1, 1990)

ABSTRACT Paramagnetic deoxyhemoglobin in venous blood is a naturally occurring contrast agent for magnetic resonance imaging (MRI). By accentuating the effects of this agent through the use of gradient-echo techniques in high fields, we demonstrate *in vivo* images of brain microvasculature with image contrast reflecting the blood oxygen level. This blood oxygenation level-dependent (BOLD) contrast follows blood oxygen changes induced by anesthetics, by insulin-induced hypoglycemia, and by inhaled gas mixtures that alter metabolic demand or blood flow. The results suggest that BOLD contrast can be used to provide *in vivo* real-time maps of blood oxygenation in the brain under normal physiological conditions. BOLD contrast adds an additional feature to magnetic resonance imaging and complements other techniques that are attempting to provide positron emission tomography-like measurements related to regional neural activity.

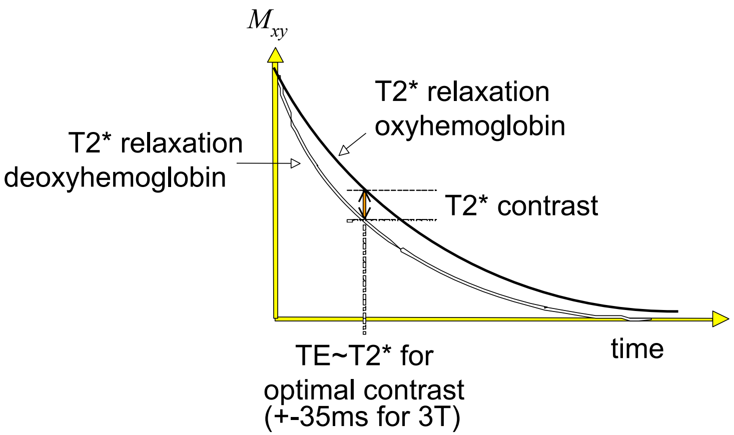
duced at the echo time. This dispersion reduces the signal intensity and the voxel appears dark in the image. These intensity losses, which at high magnetic fields (≥4 T) extend significantly beyond the boundary of the blood vessel, are the source of BOLD contrast. This form of contrast is not observed in spin-echo images. Through simulations (9), we have shown that vessels as small as 50 μm in diameter can be detected in images with a pixel size of 100 μm. We have also demonstrated that the size of the susceptibility-induced local field depends on (*i*) the concentration of paramagnetic deoxyhemoglobin and (*ii*) the orientation of the vessel relative to the main magnetic field (8, 9).

Since BOLD contrast depends on the state of blood oxygenation, physiological events that change the oxy/deoxyhemoglobin ratio should lend themselves to noninvasive detection through the accentuation of BOLD contrast in

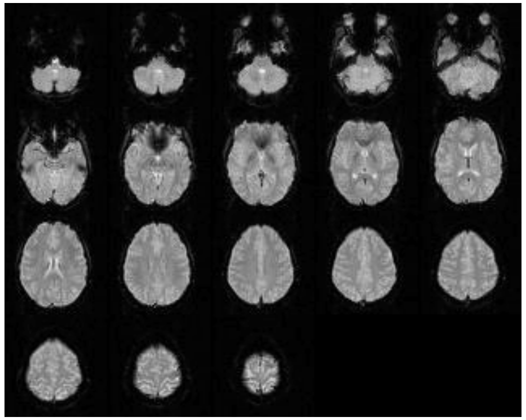
Blood oxygenation level-dependent (BOLD) contrast



Blood oxygenation level-dependent (BOLD) contrast

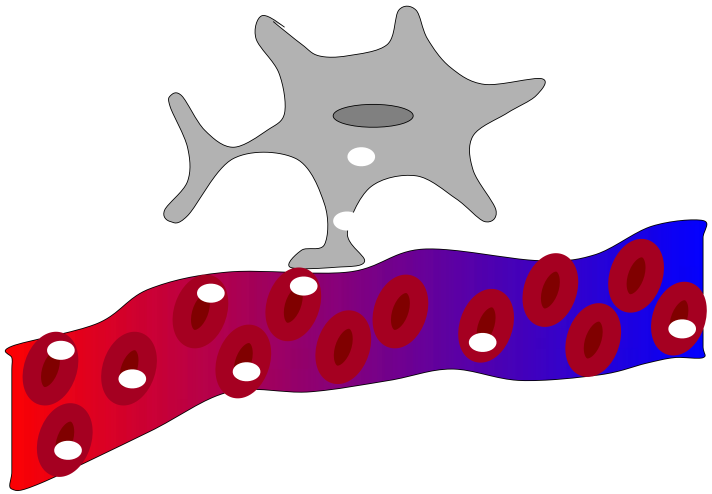


Echo-planar imaging (EPI)

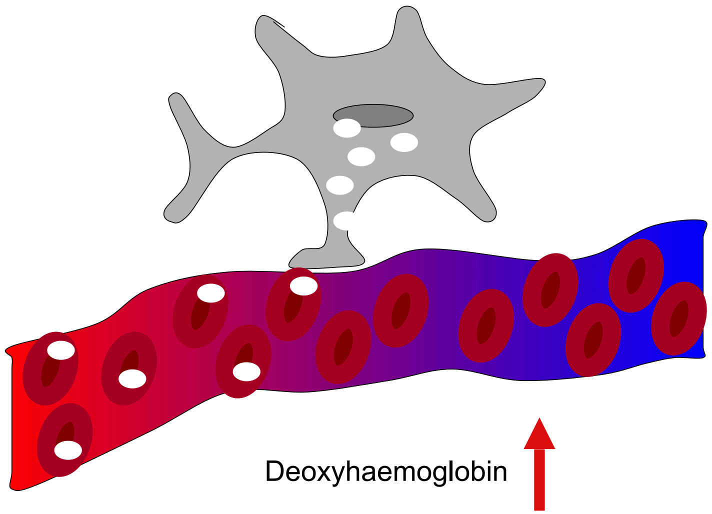


- 2 sec / volume
- +-3 mm resolution
- BOLD contrast

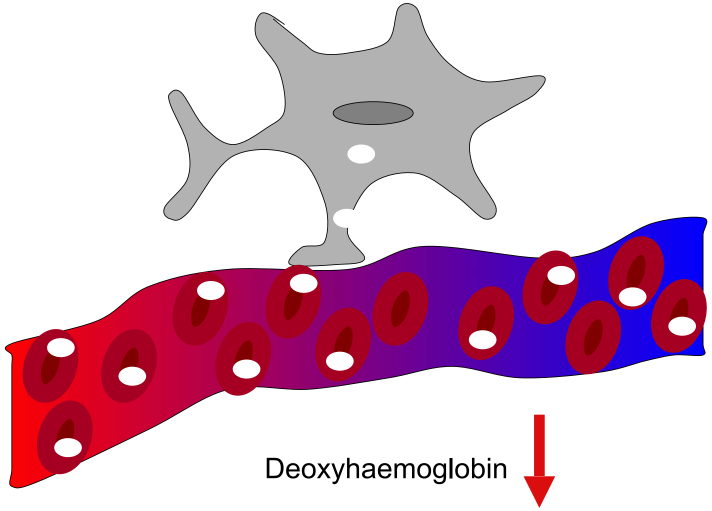
BOLD physiology: baseline



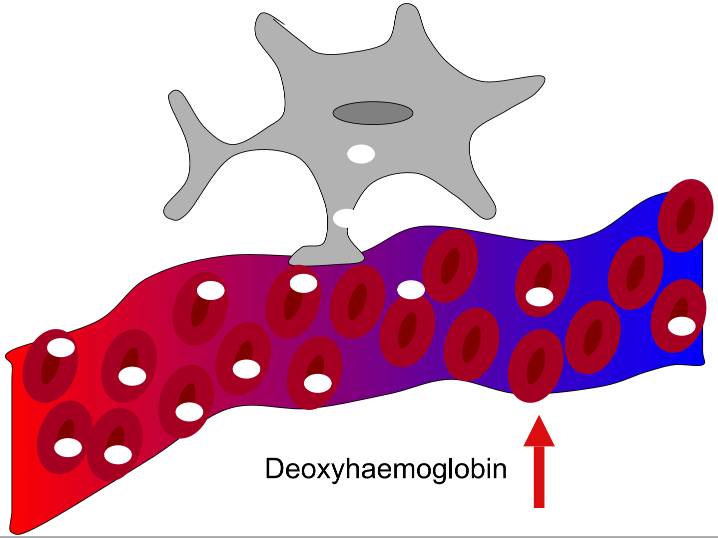
BOLD physiology: increase in oxygen use



BOLD physiology: increase in blood flow



BOLD physiology: increase in blood volume

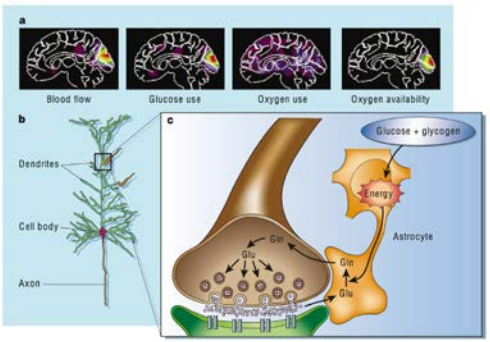


BOLD physiology: net effect

oxygen metabolism ↑ (deoxyHb ↑)

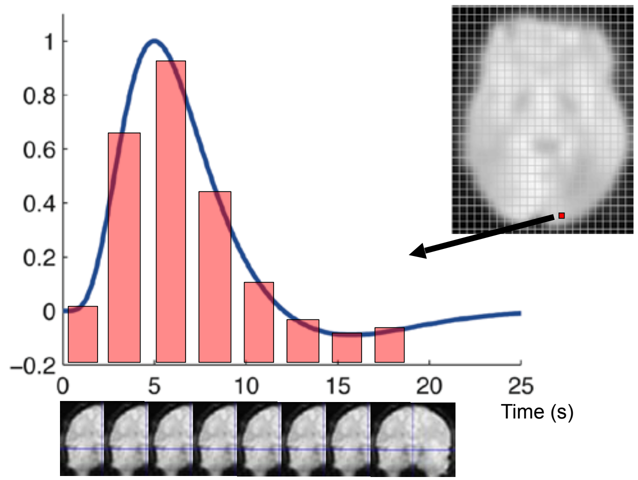
blood flow ↑ **(deoxyHb ↓)**

blood volume ↑ (deoxyHb ↑)

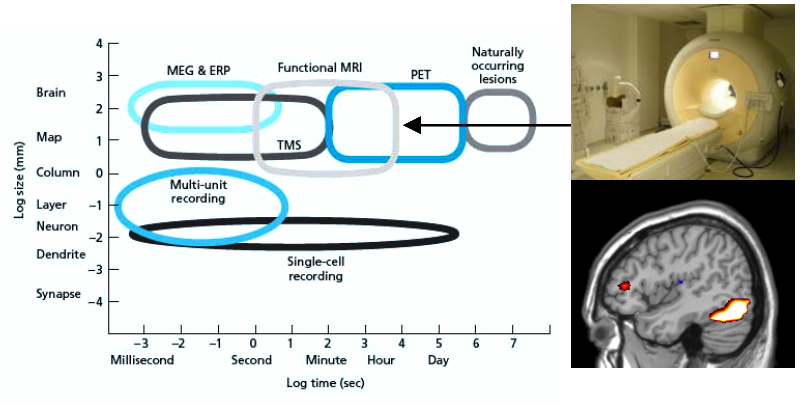


Raichle 2001 Nature

Hemodynamic response function

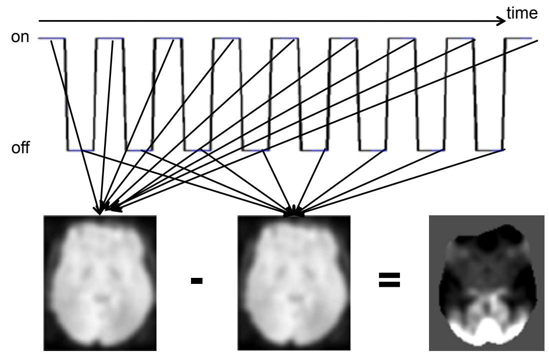


Spatial and temporal resolution of fMRI



Task design: Principle of cognitive subtraction

Franciscus Cornelis Donders
1818-1889



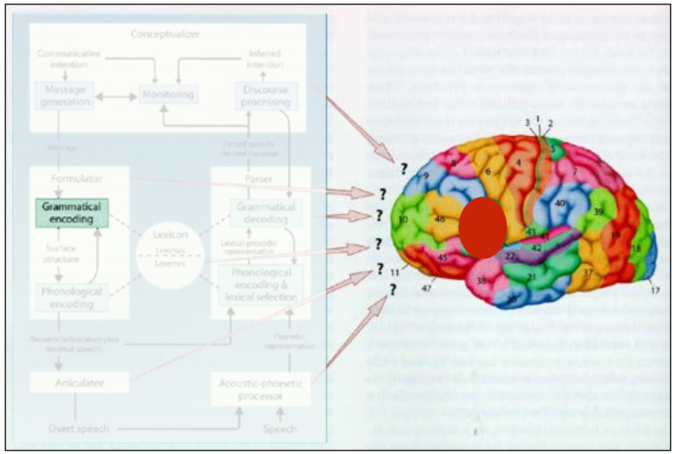
Task design: Assumptions underlying fMRI / cognitive subtraction

1. **Functional localization:**
   The brain is organized in separable cognitive modules.

2. **Pure insertion:**
   "Insertion" of a cognitive process into a set of other cognitive processes does not alter those.

3. **Linearity:**
   Increase in BOLD is linearly proportional to increase in neural activity

Task design: Forward inference



Task design: Reverse inference

OP-ED CONTRIBUTOR

You Love Your iPhone. Literally.

By MARTIN LINDSTROM
Published: September 30, 2011

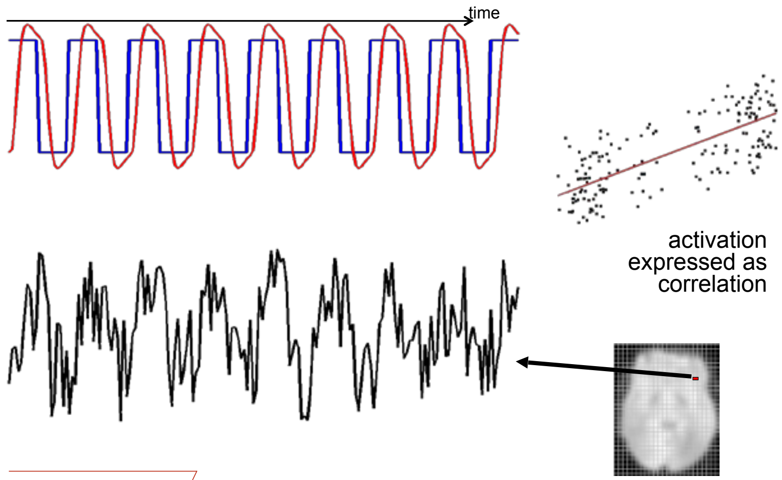
In conjunction with the San Diego-based firm MindSign Neuromarketing, I enlisted eight men and eight women…. Our 16 subjects were exposed separately to audio and to video of a ringing and vibrating iPhone.

… most striking of all was the flurry of activation in the insular cortex of the brain, which is associated with feelings of love and compassion. The subjects' brains responded to the sound of their phones as they would respond to the presence or proximity of a girlfriend, boyfriend or family member.

In short, the subjects ... loved their iPhones.

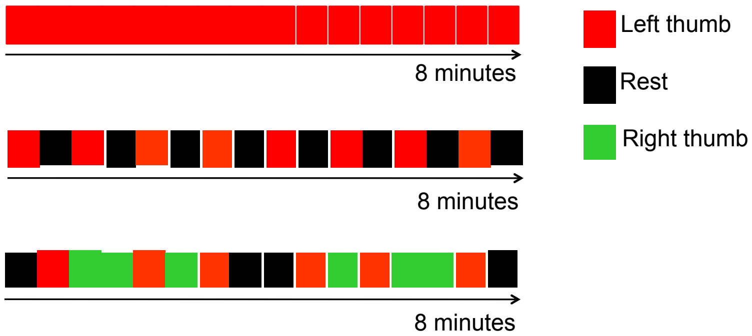
Task design: Hemodynamic convolution and regression

Example question: what region controls right thumb movement?



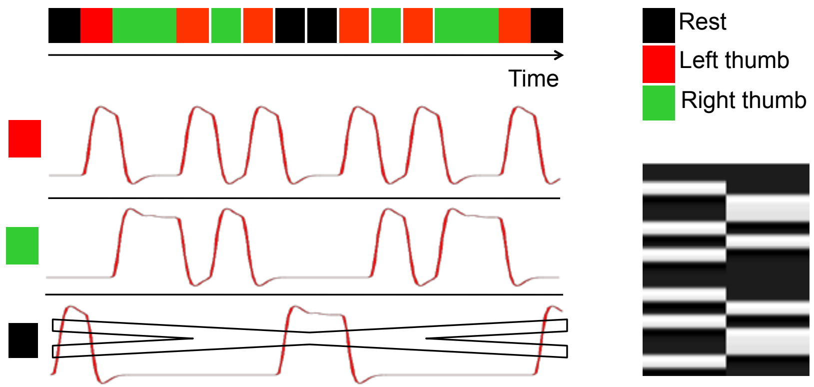
Task design: Multiple conditions

Example question: what region controls right thumb movement?



Task design: Multiple conditions

Example question: what region controls right thumb movement?



General linear model

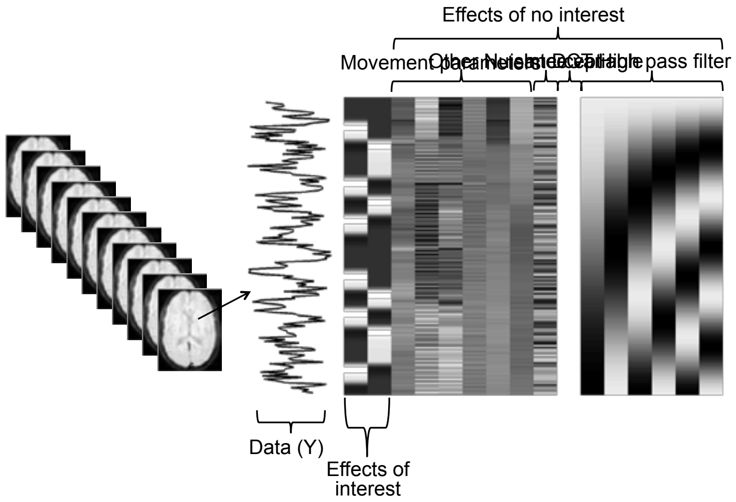
fMRI signal = task related signal changes + 'known artefacts' + random noise

Effects of interest | Effects of NO interest | ?

Effects of **no** interest : Predictable variations in the signal caused by effects other than the task

- Low-frequency drifts
- Movement
- Heart beat
- Respiration

General linear model: the design matrix



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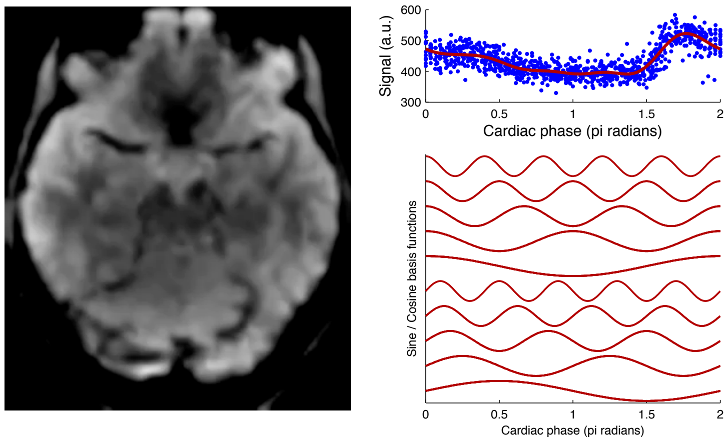
General linear model: cardiac noise modeling



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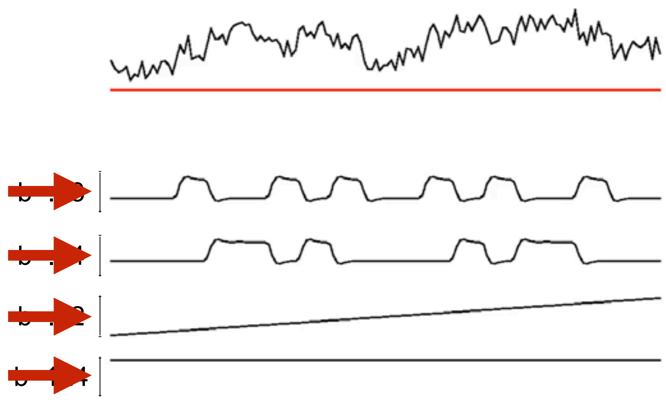
General linear model: fitting the model



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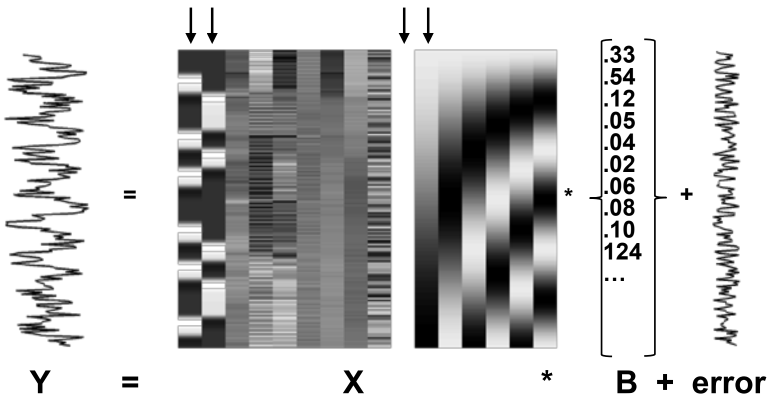
General linear model: fitting the model



General linear model: contrast specification

B = [.33, .54, .12, .05, .04, .02, .06, .08, .10, 124, …]

- *Contrast:* weighted sum of parameter estimates
  c' * B
- Left thumb movement relative to rest:
  c = [1 0 0 0 0 0 0 0 0 0]
- Right thumb movement relative to rest:
  c = [0 1 0 0 0 0 0 0 0 0]
- Right *more than* left thumb movement:
  c = [-1 1 0 0 0 0 0 0 0 0]

Statistical inference: null-hypothesis testing

Is my effect statistically *significant?*

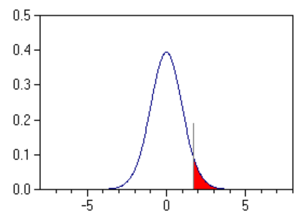
- *Classical inference*: What is the chance of observing this finding given H0? (*NOT* chance that H1 is false)
- If P < α, reject H0
- Null hypothesis: contrast of parameter estimates (c) = 0 (i.e., c'B = 0)
- The t-value is given by:

$$t = \frac{c'B}{\sqrt{MS_e c'(X'X)^{-1}c}} \qquad t = \frac{\text{explained variance}}{\text{unexplained variance}}$$

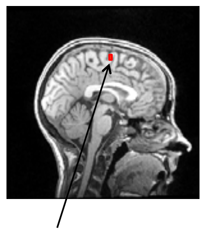
Statistical inference: null-hypothesis testing

What is the chance of observing this t-statistic under H0?

- Set an acceptable chance of type 1 error (alpha)
- Use the null distribution (e.g., Student's T):

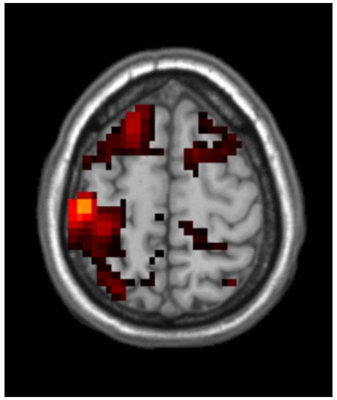


DF = 25



If significant, we have…

Statistical inference: the multiple comparisons problem



Threshold: alpha=.05

Peak t value: 7.68

P = .000008

Statistical inference: the multiple comparisons problem

If α = .05, then:

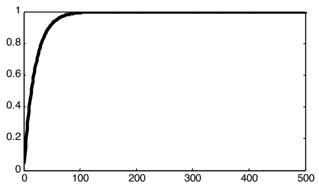
$P_{\text{type I error}}$ = .05

With a *family* of two tests: trouble

$P_{\text{family wise error}}$ = 1-(1-α)^2 = .095

With a *family* of >20.000 tests: big trouble!

$P_{\text{family wise error}}$ = 1-(1-α)^20000 =~ 1



Statistical inference: the multiple comparisons problem

- Proper multiple comparisons corrections are essential

  As illustrated in this study:

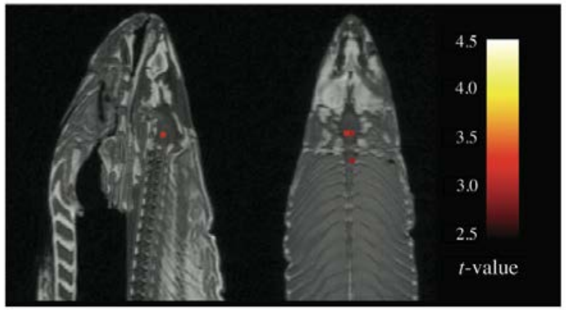
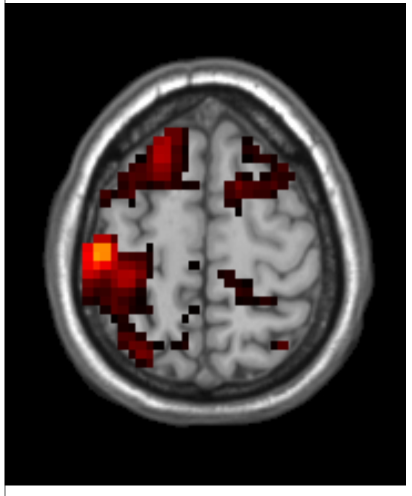


Fig. 1. Sagittal and axial images of significant brain voxels in the task > rest contrast. The parameters for this comparison were t(131) > 3.15, p(uncorrected) < 0.001, 3 voxel extent threshold. Two clusters were observed in the salmon central nervous system. One cluster was observed in the medial brain cavity and another was observed in the upper spinal column.

Bennett et al 2010 JSUR

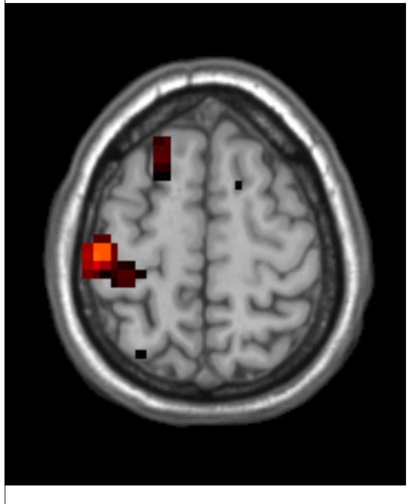


Alpha=.05
(t>1.65)

Statistical inference: the multiple comparisons problem

Alpha=.01
(t>2.33)

Statistical inference: the multiple comparisons problem



Alpha=.001
(t>3.09)

Statistical inference: the multiple comparisons problem

Alpha=.0001
(t>3.72)

Statistical inference: the multiple comparisons problem

Alpha=.00001
(t>4.26)

Multiple comparisons corrections

- **Bonferroni correction**
- **Gaussian Random Field Theory - based corrections**
  Voxel-level
  Cluster-level
  Set-level
- **False discovery rate**
- **Region-of-interest analysis**

Multiple comparisons corrections: Bonferroni

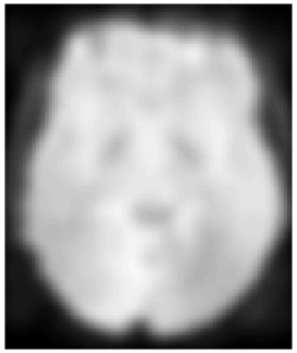
Bonferroni correction:

If $P^{\text{family wise error}}$= 1-(1-α)^n
And we want: .05 chance of a *single* false positive
Or: $P^{\text{family wise error}}$= .05

$\alpha^{\text{corrected}} = \alpha / n$
α =.05 / 23914 = .00000209 (pretty small!)
(or Z>4.60)

Bonferroni is overly conservative
because tests are not independent

Multiple comparisons corrections: Random Field Theory

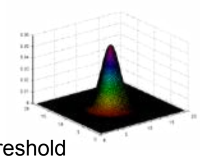


Sources of spatial correlation:
- The spatial resolution of the underlying signal
- Blurring due to resampling during preprocessing
- Smoothing that is often deliberately applied.

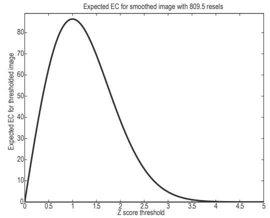
So: correct for estimated number of true independent tests instead of number of voxels!

Multiple comparisons corrections: Random Field Theory

Random Field Theory:



- Estimate the smoothness of the images in FWHM
- Calculate the number of resolution elements (ResEls)
- Calculate the expected *number* of clusters at given threshold in a *random field* (H0) with this smoothness
- Calculate the expected *size* of clusters at given threshold in a *random field* (H0) with this smoothness



Euler characteristic

Multiple comparisons corrections: RFT-based corrections

Levels of topological inference:

1. *Voxel* level:

   determinine a threshold where the expected number of clusters under H0 is .05

2. *Cluster* level: Control type I error by:

   fix a voxel threshold, and determine the cluster extent with a .05 chance of arising under H0

3. *Set level:* Control type I error by:

   fix a voxel threshold and an extent threshold, and determine the number of clusters that has a chance of .05 of arising under H0

Multiple comparisons corrections: RFT-based corrections

Voxel level (little smoothing):
Smoothness FWHM: 3*3*2.9 voxels
23914 voxels > 809.5 ResEls

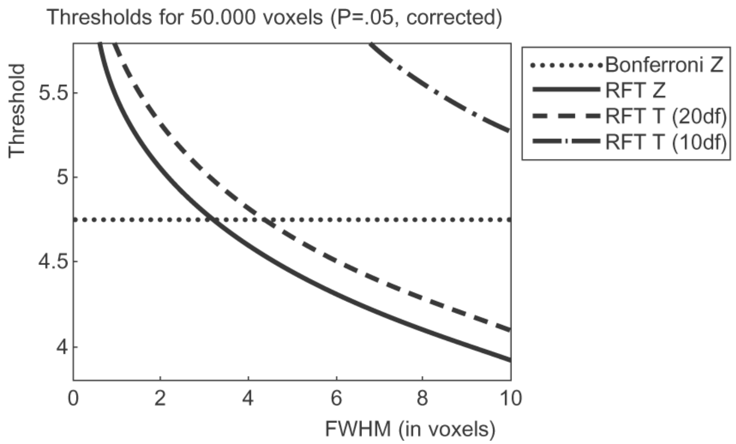
T threshold: 4.68; 335 degrees of freedom
P threshold: .00000209

Multiple comparisons corrections: RFT-based corrections

Voxel level (more smoothing):
Smoothness FWHM: 5.7*5.9*5.2 voxels
23914 voxels > 124.3 ResEls

T threshold: 4.24; 335 degrees of freedom
P threshold: .0000145

Multiple comparisons corrections: RFT-based corrections



Worsley 2003 Human Brain Function 2nd ed.

Multiple comparisons corrections: False discovery rate

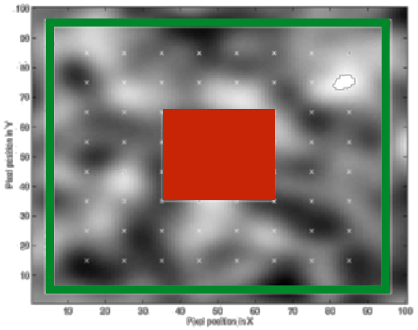
False discovery rate:

- Instead of controlling *chance* of false positives, now control the *proportion* of false positives
- Now control number of *false discoveries:* *Proportion* of false positives = .05
- Order all P values in the volume:
  P1<=P2 <=P3 <= … <=Pn
  Cutoff = largest value with:
  Pk < α k / n
- This changes the inferences you can make.

Reduction of multiple comparisons: region-of-interest analyses

Region-of-interest analysis:

- A priori hypotheses about the search area.
- Correct only for number of independent tests in this area.



Small volume correction :

number of resels may vary with the shape of a small volume

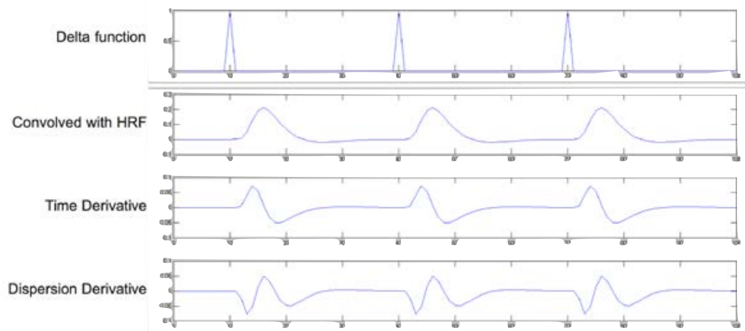
Brett et al 2003 Human Brain Function 2nd ed.

Variations of first-level designs

Example variations of first-level analyses:

- Event-related designs:

  Is the response to oddball stimuli greater than normals?

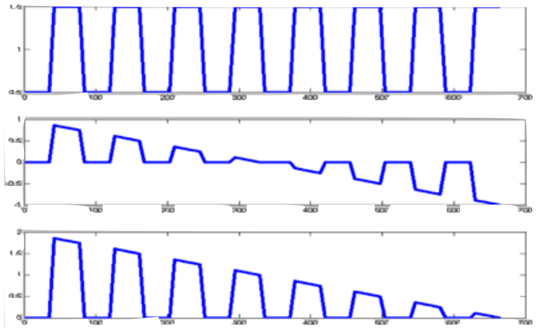


Variations of first-level designs

Example variations of first-level analyses:

- Parametric designs:

  Does the amygdala response to facial expressions habituate over time?



Optimizing first-level designs

Block designs:

- Use block designs whenever possible
- Optimal block length ~20 s.
- Include rest blocks.

Event-related designs:

- Trade off between ability to separate BOLD responses (better with larger ITIs) and number of trials within a given task duration.
- Rapid event-related (2-3 s ITI) designs are very efficient.
- Jitter ITIs with respect to TRs.

Statistical analysis of group data

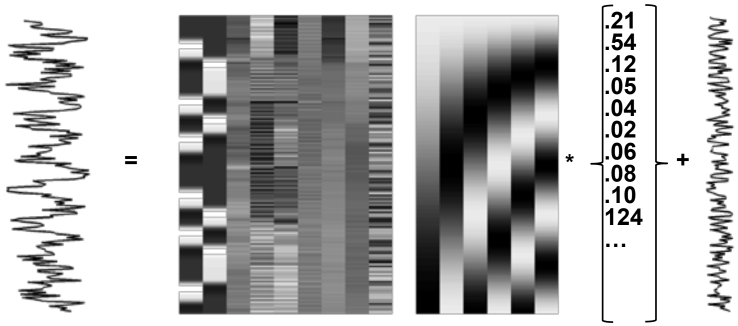
Why?

- Is my effect consistent across a group of subjects?
- Generalize beyond your subjects

How?

- Take (contrasts of) parameter estimates (not T-maps)
- Put these into a *second level* model
- Treat subjects as *random effects*

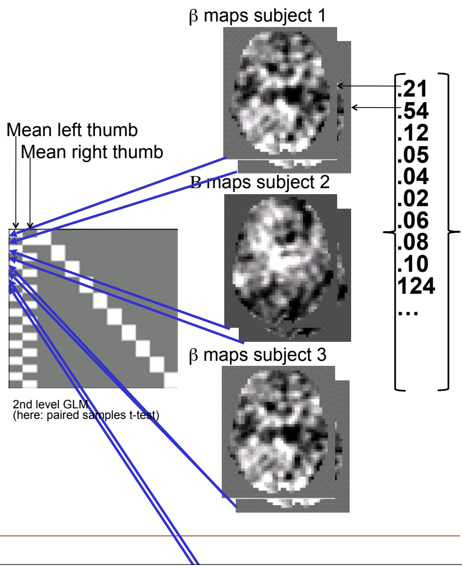
Statistical analysis of group data



Statistical analysis of group data

.23
.51
.32
.41
.36
.21
.22
.35
.40
.32
.45
.31

\> -.23 + .51 = .28

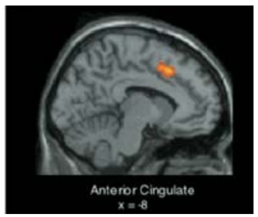


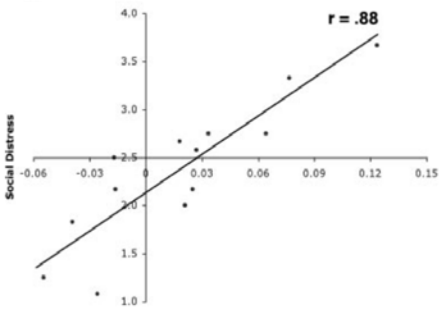
Statistical analysis of group data

Example variations of group analyses:

- Paired samples t-tests:
  Is activity in condition A greater than B across subjects?
- Two-sample t-tests:
  Do patients respond more than controls?
- Factorial ANOVAs:
  Does effect of emotion interact with working memory load?
- ANCOVAs:
  Is the difference in response to condition A vs. B correlated with a personality trait?

Example of ANCOVA / correlational study





- r = .88 means that $r^2 = .77$; thus 77% of variance in questionnaire data is explained by brain data.
- Problem: test-retest reliability hardly ever reaches this!

Example of ANCOVA / correlational study of correlational study

Puzzlingly high ~~Voodoo~~ **Correlations in** ~~Social Neuroscience~~ Emotion, Personality, and Social Cognition [1]

Edward Vul[1], Christine Harris[2], Piotr Winkielman[2], & Harold Pashler[2] *
[1]Massachussetts Institute of Technology
[2]University of California, San Diego
*to whom correspondence should be addressed: hpashler@ucsd.edu

In Press, Perspectives on Psychological Science
Dec. 23, 2008

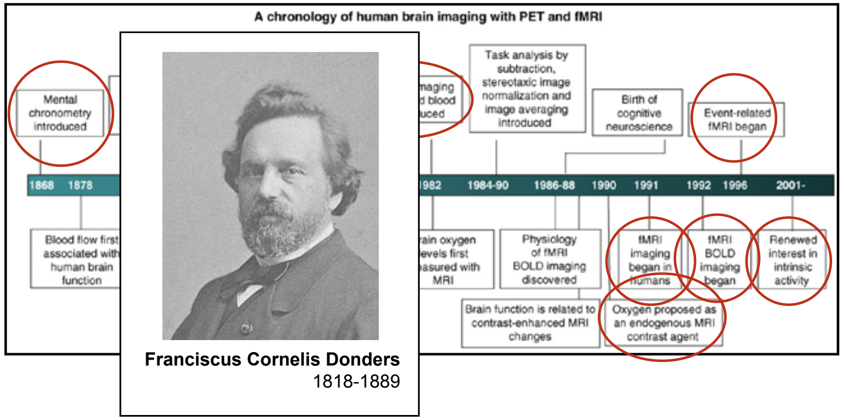
[1]This article was formerly known as "Voodoo Correlations in Social Neuroscience."

Historical perspective

A brief history of human brain mapping

Marcus E. Raichle

Raichle 2009 TINS



Measuring intrinsic activity using fMRI

Functional Connectivity in the Motor Cortex of Resting Human Brain Using Echo-Planar MRI

Bharat Biswal, F. Zerrin Yetkin, Victor M. Haughton, James S. Hyde

An MRI time course c
human brain obtain
signal intensity in ea
Regions of the sens
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(<0.1 Hz) fluctuation
a high degree of tem
regions and also wit
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arise from fluctuatio
manifestation of fun
Key words: function

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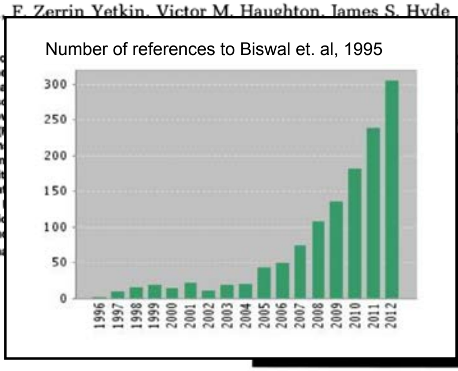
fluctuations observed in
are of a similar nature,



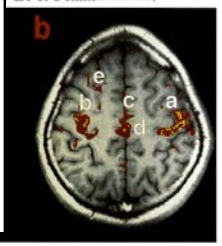
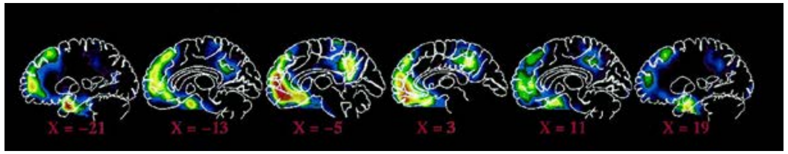


FIG. 3. (Left) FMRI task-activation response to bilateral left and right finger movement, superimposed on a GRASS anatomic image. (Right) Fluctuation response using the methods of this paper. See text for assignment of labeled regions. Red is positive correlation, and yellow is negative.

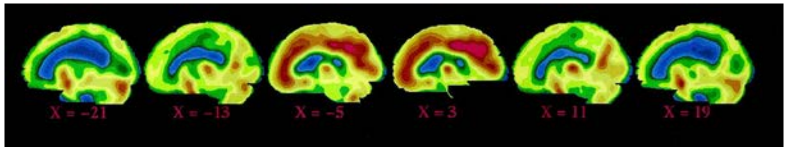
Biswal et al., 1995 MRM

Default mode network

Brain regions that are deactivated during a task



Quantitative perfusion measurements of the brain at rest

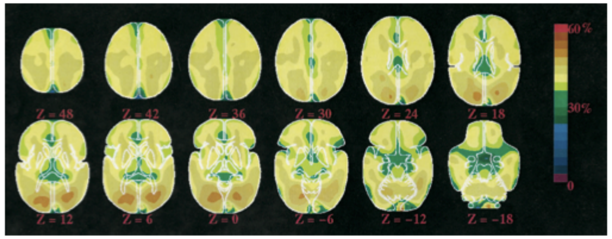


Resting brain uses 20% of energy (evoked changes: <5% increase)

Raichle et al, PNAS 2001

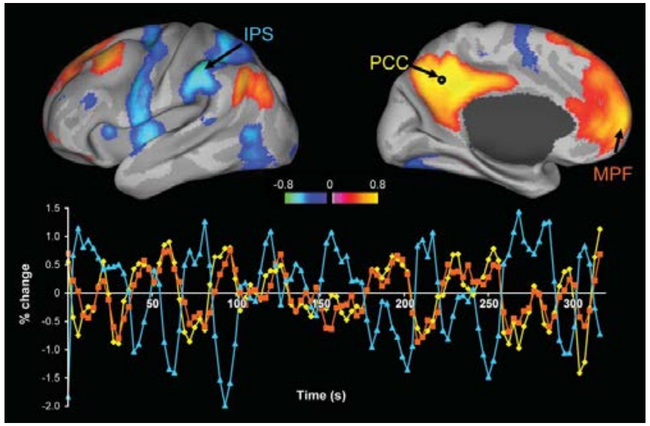
Default mode network

Uniformity of oxygen extraction factor (OEF):



- Activity increases > oversupply of oxygenated blood > decrease in OEF
- Baseline defined as (homeostatic) state with stable OEF
- Suggest existence of organized “**default mode**” of brain function

Multiple anti-correlated networks

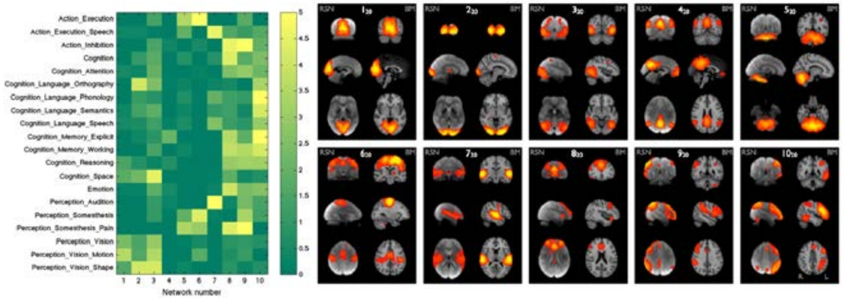


Anticorrelation of task-positive and task-negative (default mode) networks

Fox et al, PNAS 2005

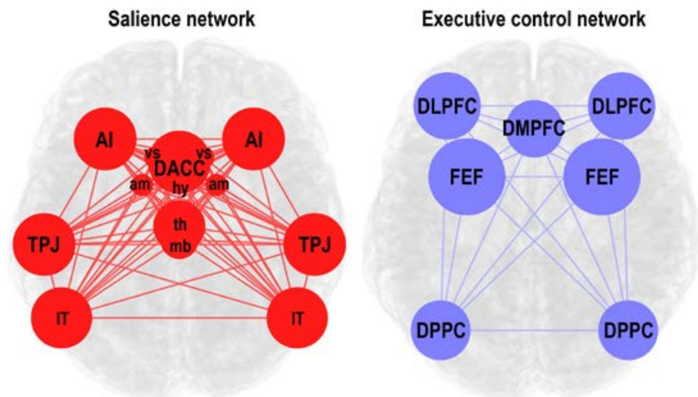
Measuring intrinsic activity using fMRI

Multiple resting state networks, overlap with task activation



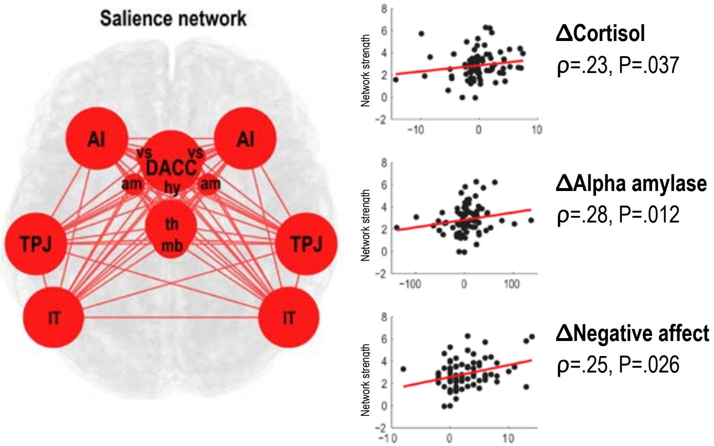
Smith et al 2009 PNAS

Large-scale networks in the human brain



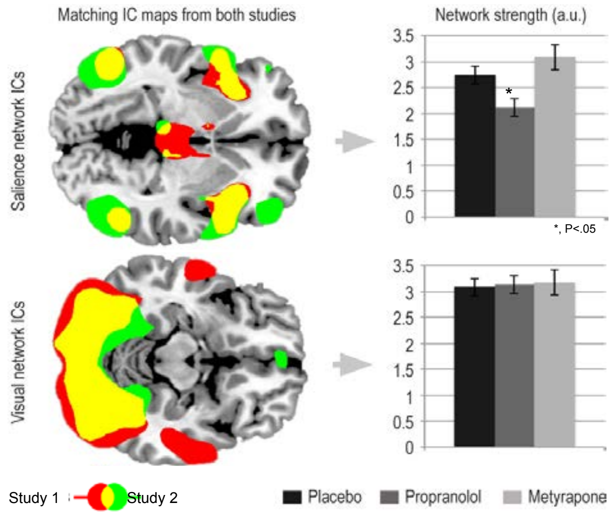
Hermans et al TiNS in press; Menon 2011 TiNS

Salience network strength: correlations with stress measures



Hermans et al, Science 2011

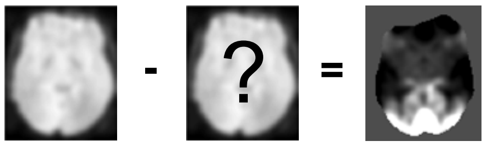
Pharmacological manipulation of network activity



Hermans et al, Science 2011

Donders revisited

Franciscus Cornelis Donders
1818-1889



Pure insertion?

Thank you

erno.hermans@donders.ru.nl