# Uncovering Hidden Activation Using Model-Free Analysis


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# Declaration of Financial Interests or Relationships

Speaker Name: Javier Gonzalez-Castillo

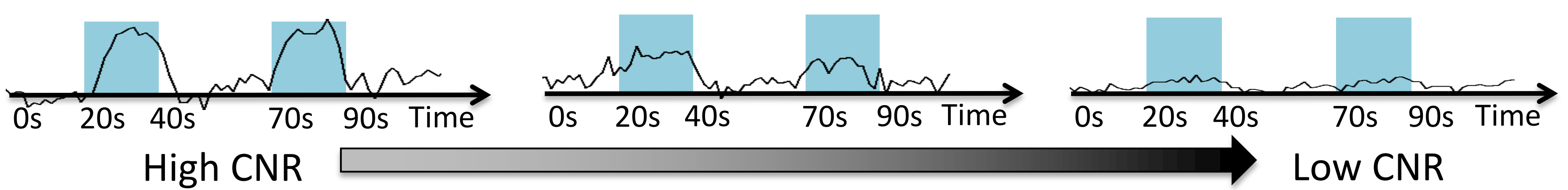
I have no financial interests or relationships to disclose with regard to the subject matter of this presentation.

- **BOLD fMRI time-series are noisy**

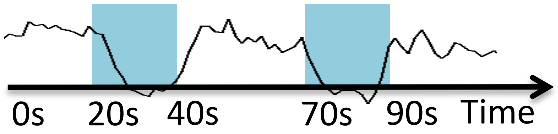
- Thermal Noise
- Signal Drift
- Intensity Inhomogeneity

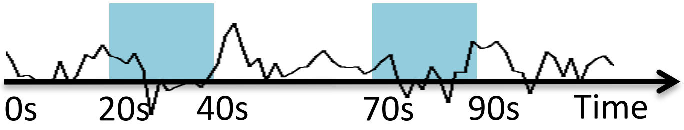
- Head Motion
- Physiological Noise
- Variable Compliance

- **BOLD responses are many times in the same order of magnitude as the noise**




- **BOLD responses vary regionally in shape and timing**

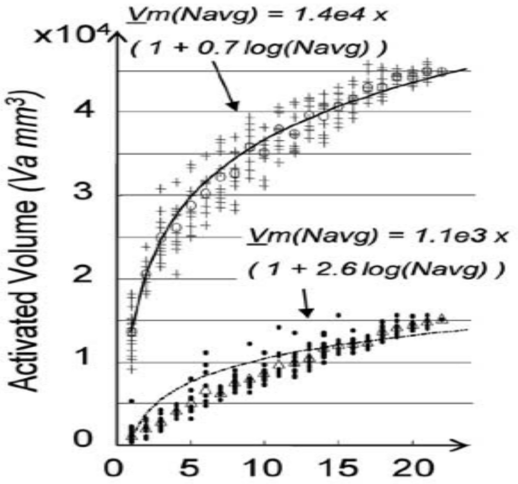



*Handwerker et al., NeuroImage* 2012

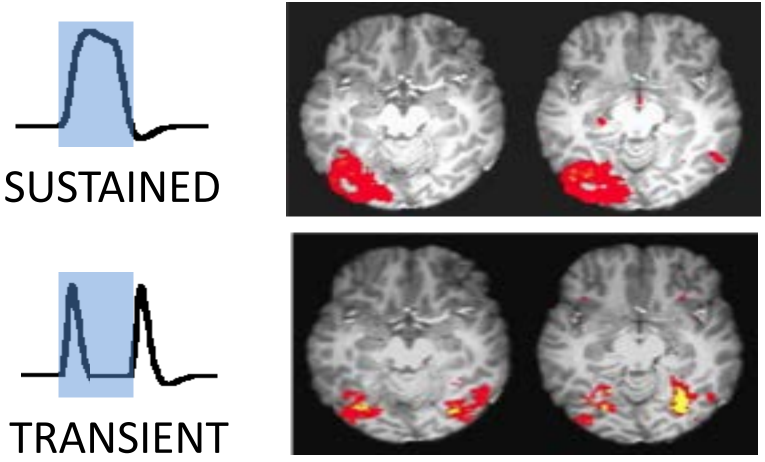
## fMRI Activation maps are highly dependent on:

- Available Temporal Signal-to-Noise
- Assumptions on Response Shape and Timing




**ACTIVATION VOLUME INCREASES LOGARITHMICALLY WITH NUMBER OF SCANS.**

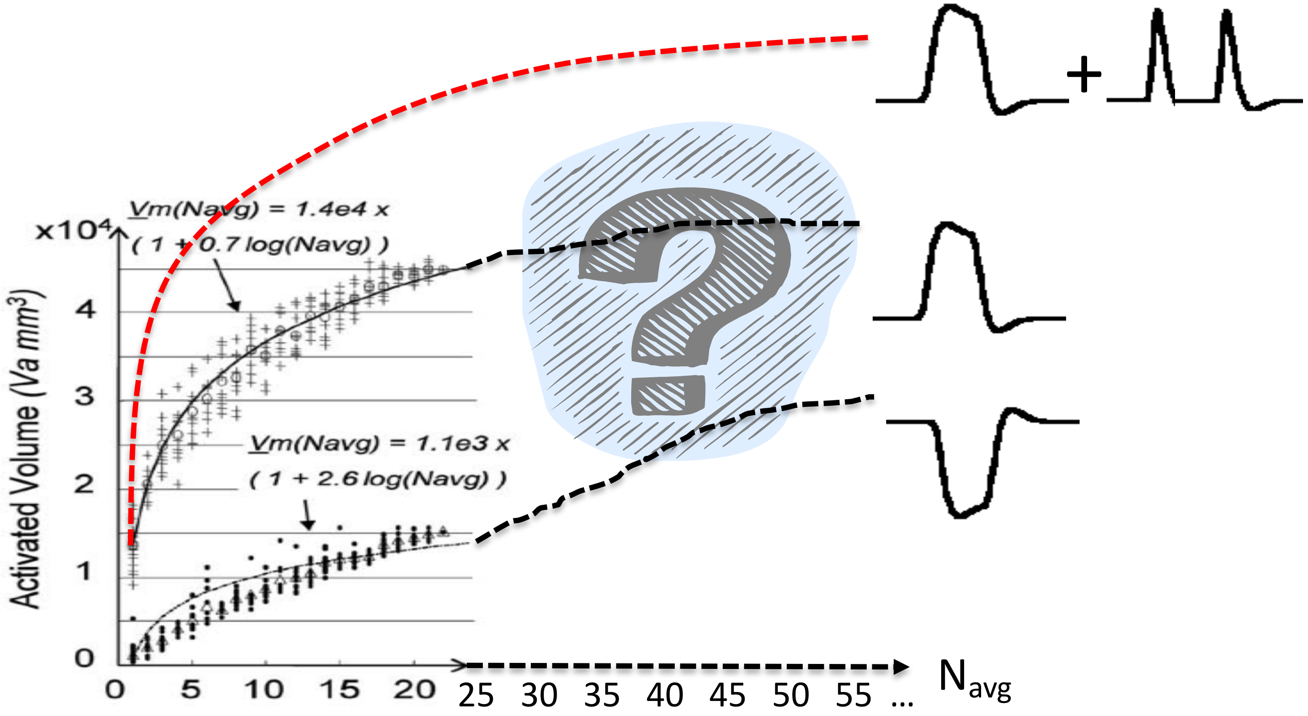
*Saad et al., NeuroImage 2003*




**CONSIDERATION OF ADDITIONAL RESPONSE SHAPES ALLOWS DETECTION OF NEW ACTIVATION SITES**

*Uludag et al., MRM 2008*

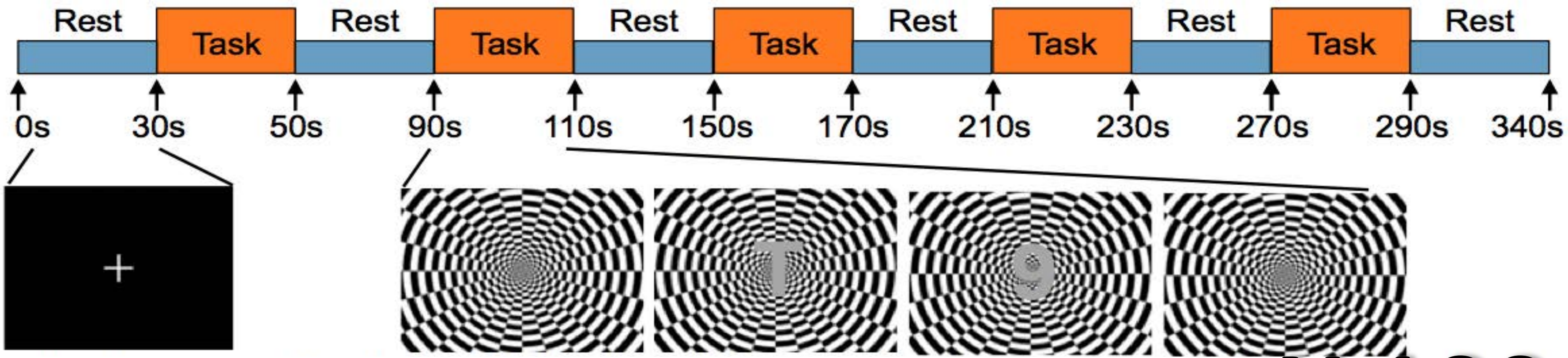
To what extent is the sparseness of task-based fMRI activation maps real or a result of noise levels (insufficient CNR) and/or modeling decisions?




*Gonzalez-Castillo et al., PNAS 2012*

# Experimental Design / Methods

## 3 Subjects

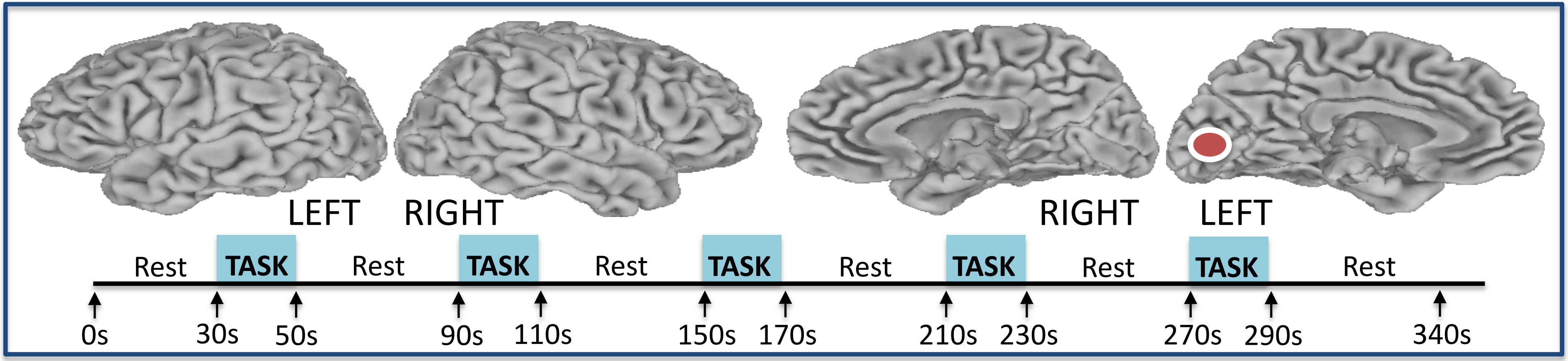



**X 100**

**9 HOURS OF FUNCTIONAL DATA PER SUBJECT**

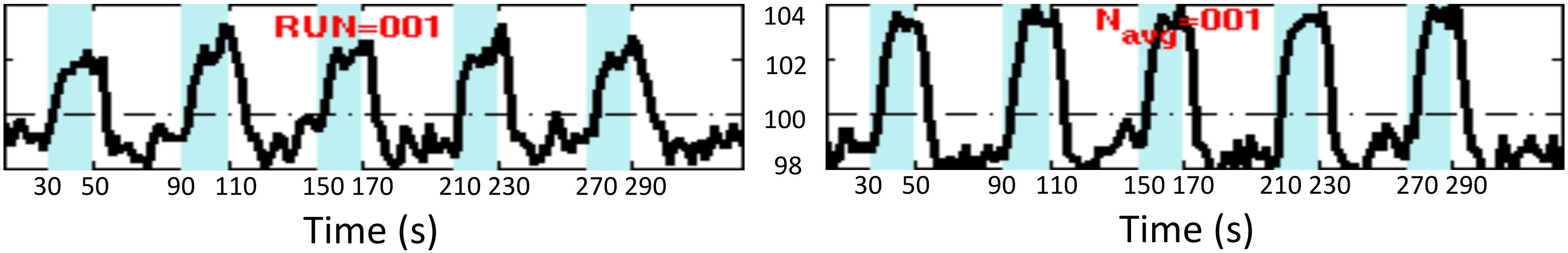
*Gonzalez-Castillo et al., PNAS 2012*

# Results: Primary Visual Cortex



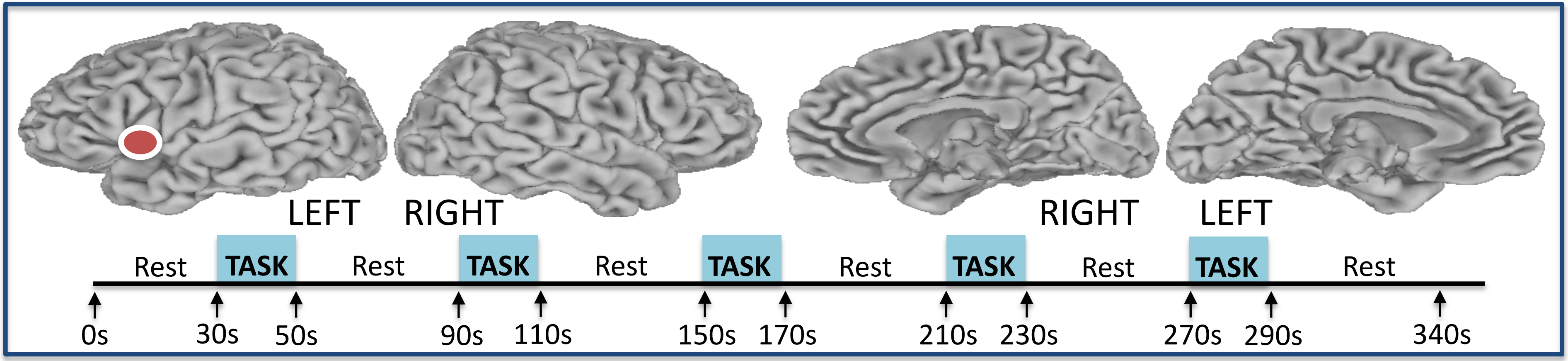

## INDIVIDUAL RUNS

## AVERAGING

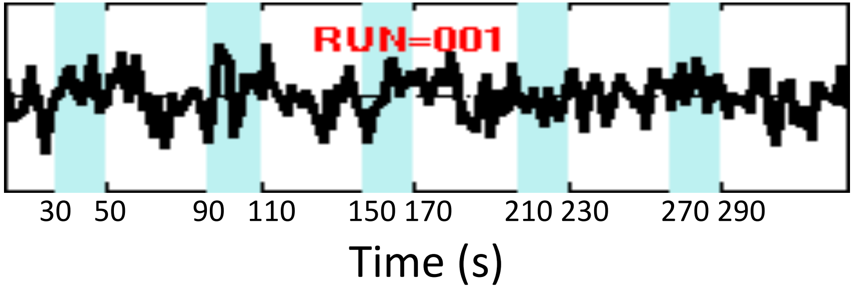



*Gonzalez-Castillo et al., PNAS 2012*

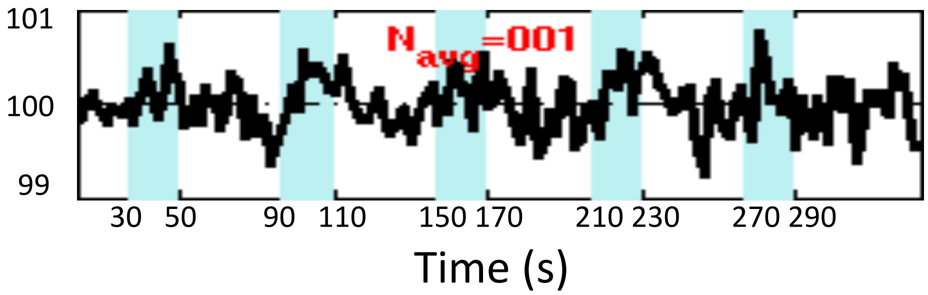
# Results: Anterior Insular Cortex




## INDIVIDUAL RUNS

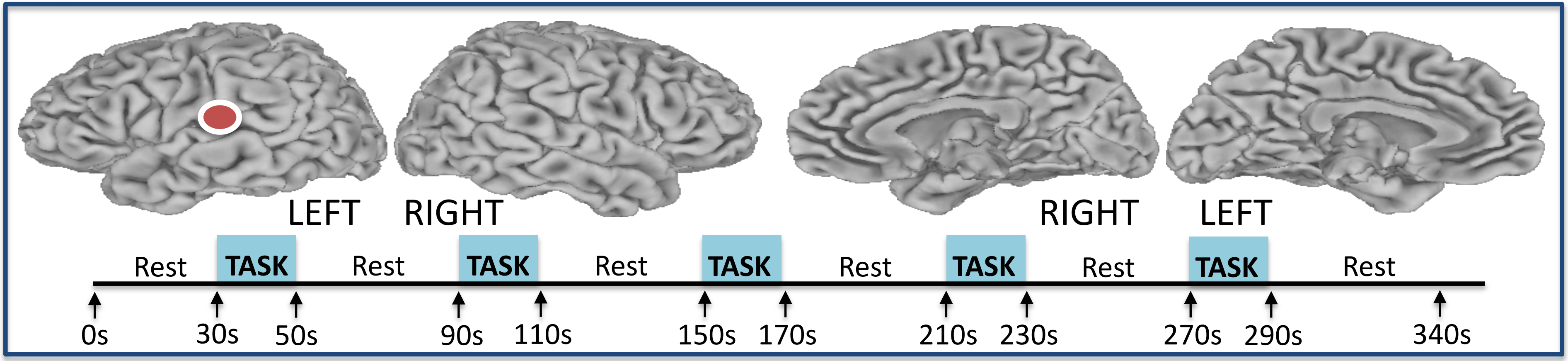



## AVERAGING

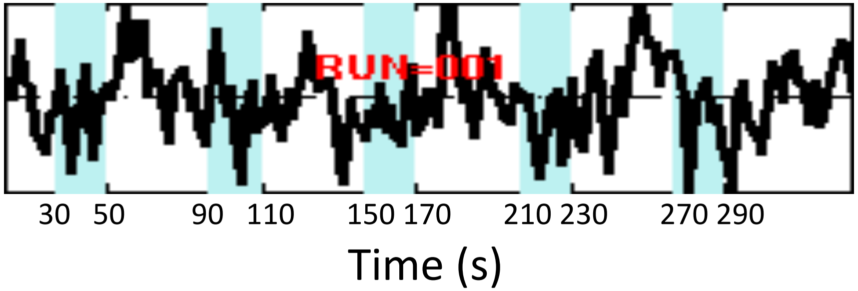



*Gonzalez-Castillo et al., PNAS 2012*

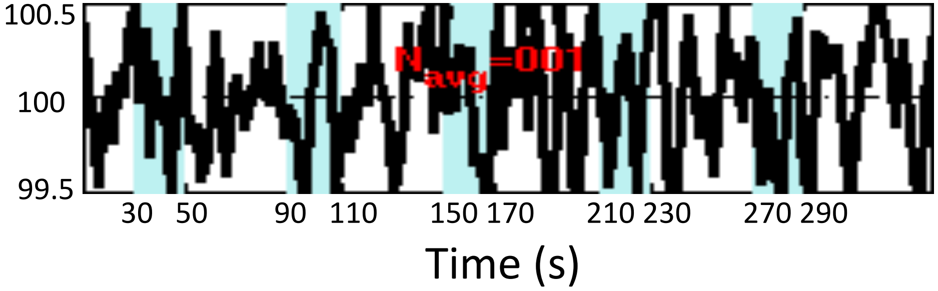
# Results: Primary Auditory Cortex




## INDIVIDUAL RUNS

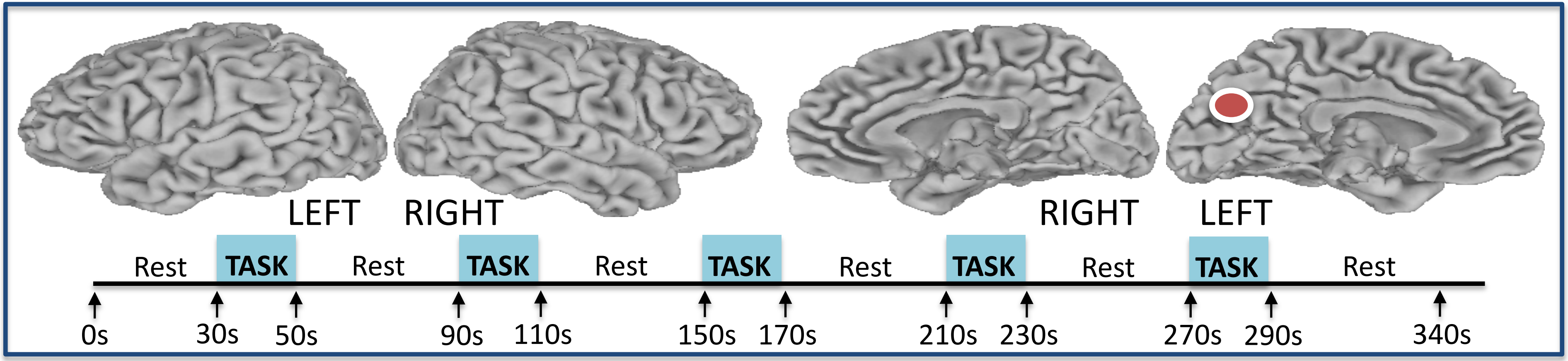



## AVERAGING

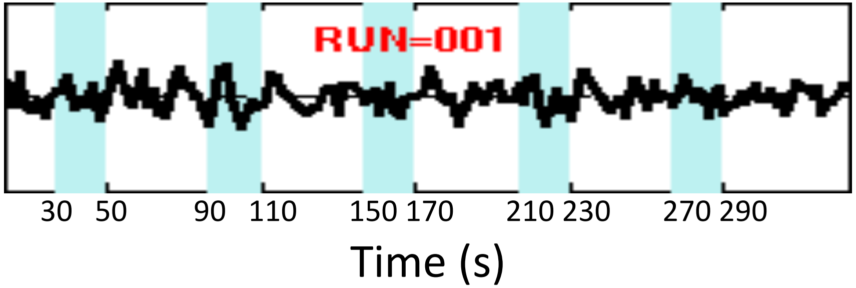



*Gonzalez-Castillo et al., PNAS 2012*

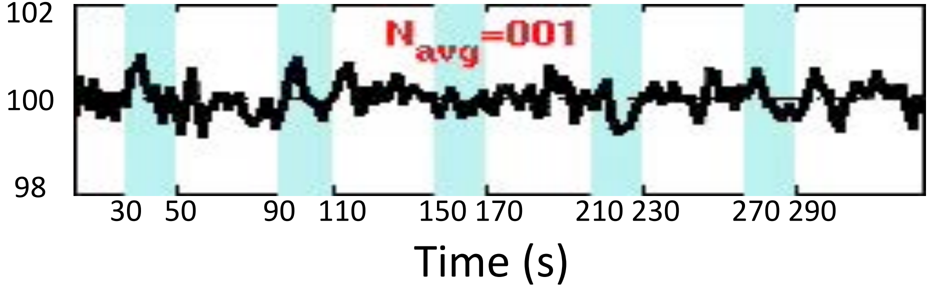
## *Results: Occipito-parietal Junction*




# INDIVIDUAL RUNS



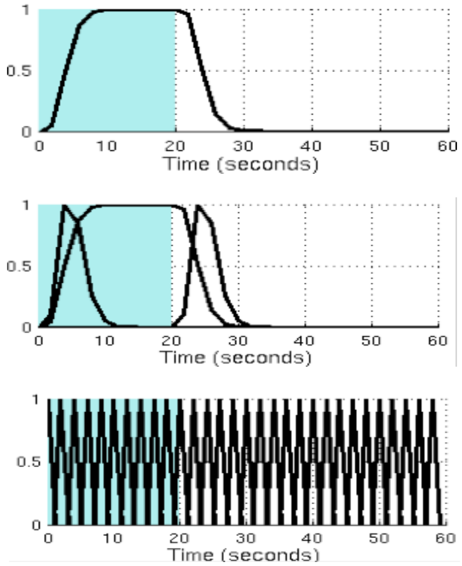

# AVERAGING




*Gonzalez-Castillo et al., PNAS 2012*

How does this observation translate in terms of volume of activation?

VERSATILITY




**SUSTAINED RESPONSE ONLY (SUS)**

**ONSET + SUSTAINED + OFFSET RESPONSE (SUS)**

**UNCONSTRAINED MODEL (UNC)**

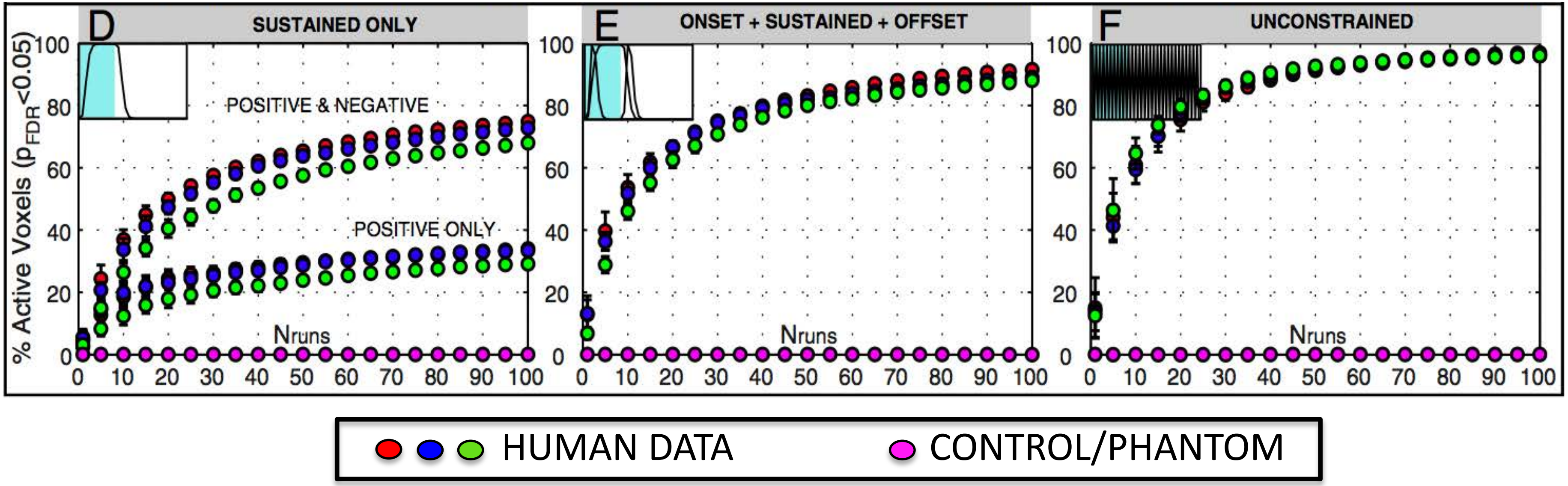
$N_{runs}$ = 1, 5, 10, 15, 20, 25, 30, 35 … 100

[10 Permutations per $N_{runs}$ level]

**TSNR**

*Gonzalez-Castillo et al., PNAS 2012*

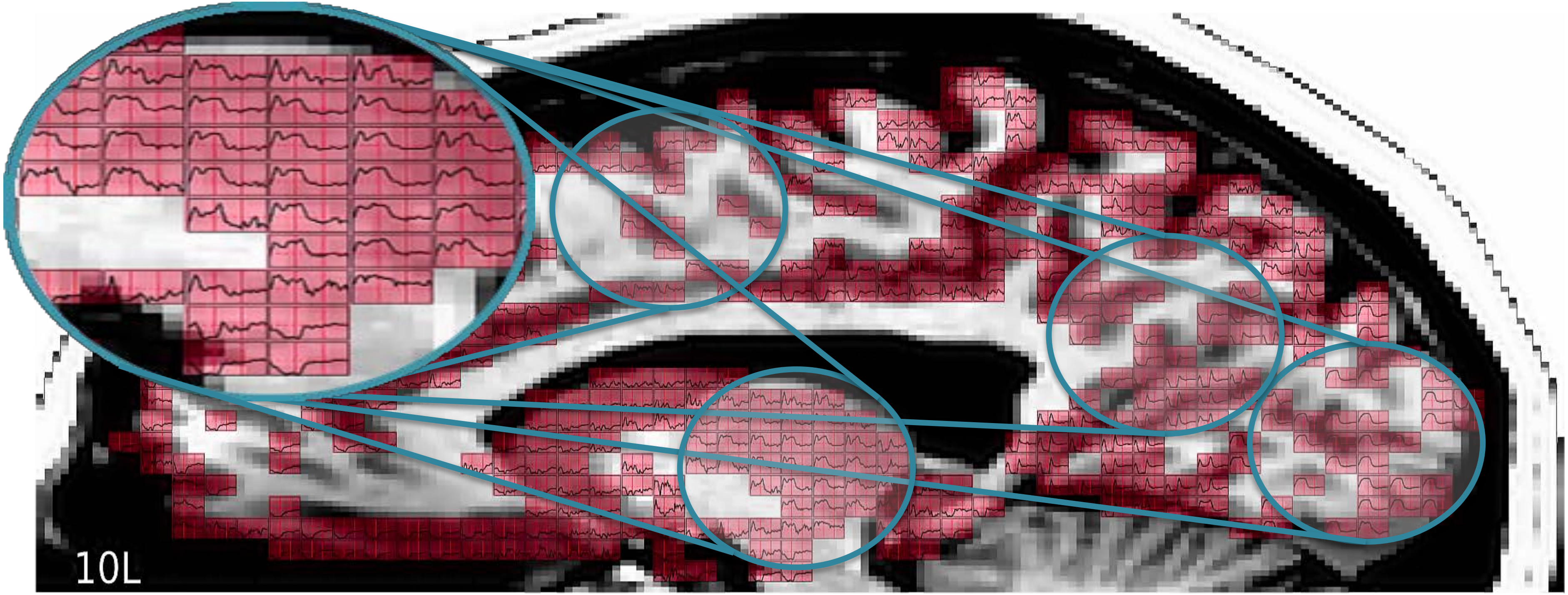
# Quantification / Dependence on TSNR & Response Model (II)




- Activation Volume increases considerably between $N_{runs}$=5-10 and $N_{runs}$=100
- Activation Volume increases with versatility of expected response models
- For $N_{runs}$=100, Unconstrained Model & pFDR<0.05 ➔ Active Volume ≈ 95%

*Gonzalez-Castillo et al., PNAS 2012*

# Biological/Neuronal Significance (I)




Are these additional responses biologically meaningful?

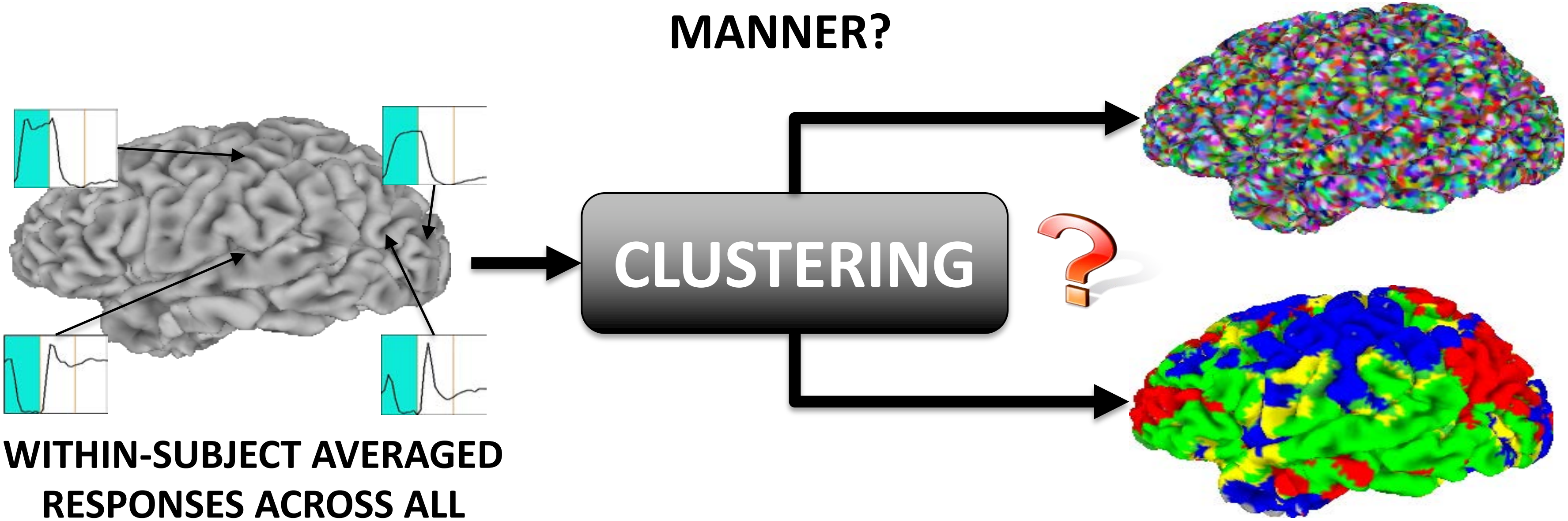
Gonzalez-Castillo et al., PNAS 2012

# Biological/Neuronal Significance (II)

**ARE RESPONSE SHAPES RANDOMLY DISTRIBUTED ACROSS THE BRAIN**

**OR**

**DO THEY CLUSTER IN A FUNCTIONALLY/ANTOMICALLY MEANINGFUL MANNER?**

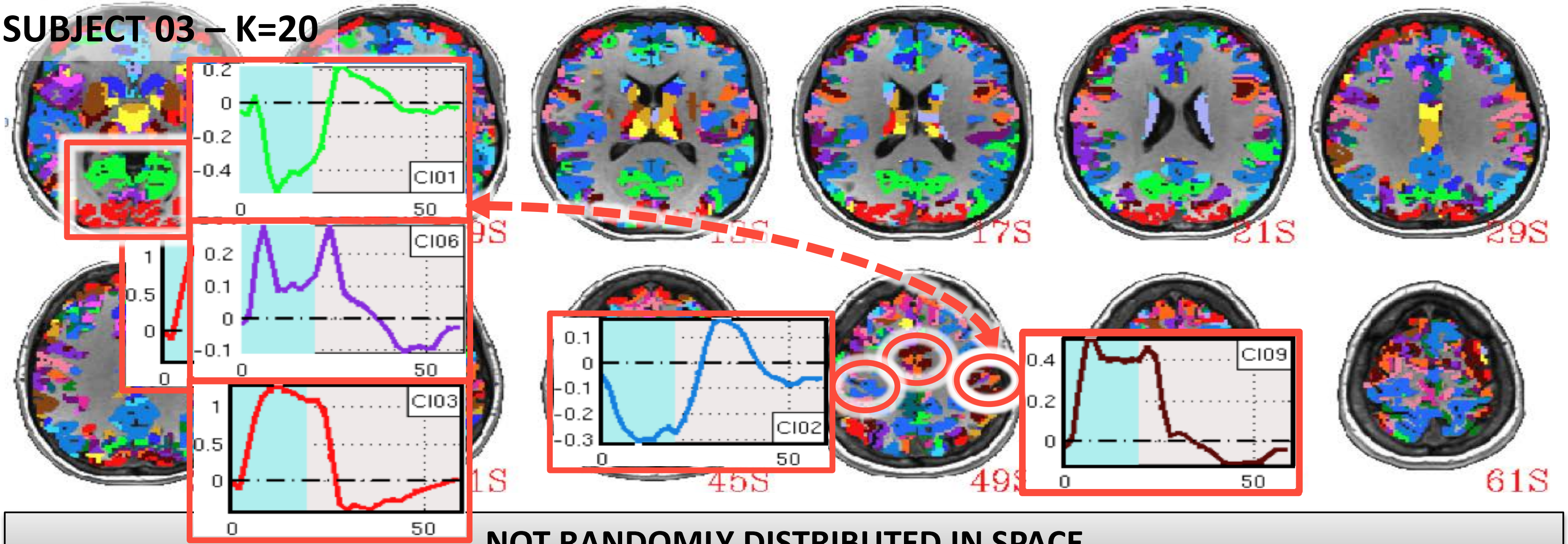



**WITHIN-SUBJECT AVERAGED RESPONSES ACROSS ALL RUNS AND TRIALS**

*Gonzalez-Castillo et al., PNAS 2012*

# Biological/Neuronal Significance (III)

**SUBJECT 03 – K=20**




NOT RANDOMLY DISTRIBUTED IN SPACE

SYMETRICAL ACROSS HEMISPHERES

FUNCTIONALLY & ANATOMICALLY MEANINGFUL

REPRODUCIBLE PARCELLATION ACROSS SUBJECTS

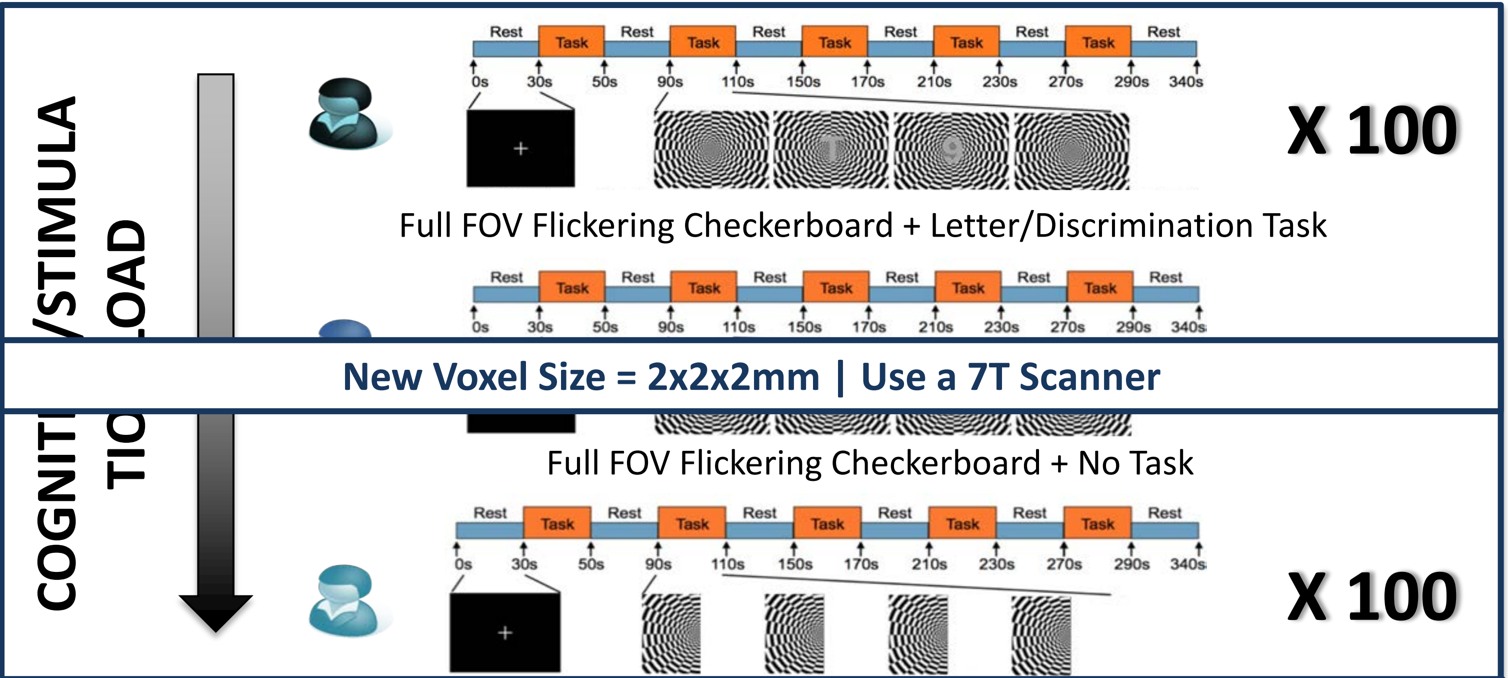
*Gonzalez-Castillo et al., PNAS 2012*

# Follow-Up Experiments @ 7T

- Advance our understanding of the biological/neuronal significance of the original observation.
  - ➪ Vary Cognitive/Stimulation Load across subjects

- Redu
  - ➪ Re
  - ➪ M

- Stud
  - ➪ Po
  - ➪ Ne
  - ➪ Or

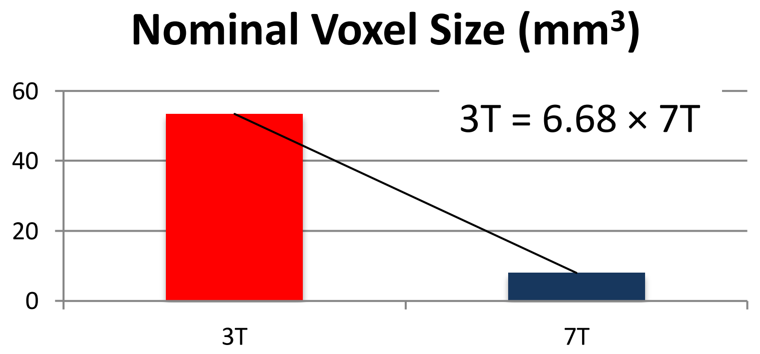


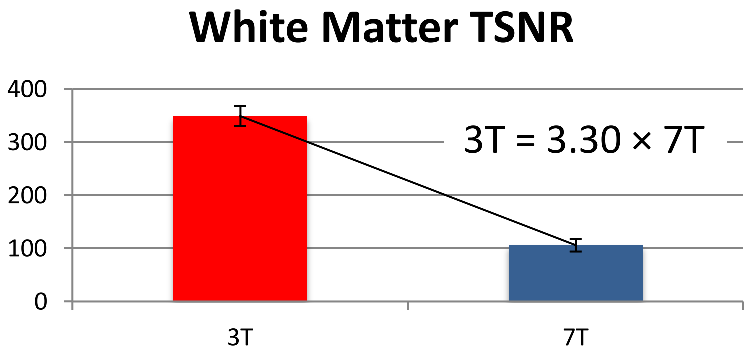

**New Voxel Size = 2x2x2mm | Use a 7T Scanner**

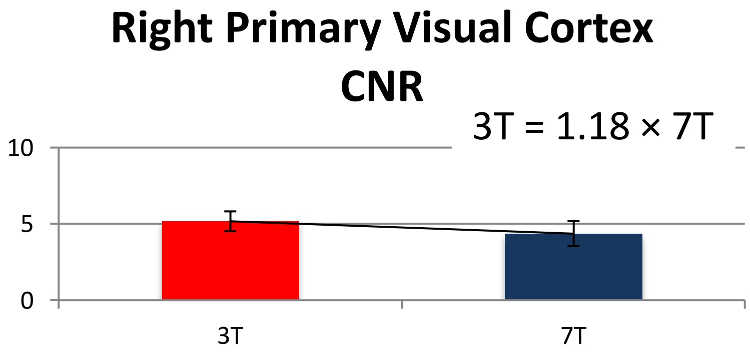
**Use a modified version of Harms & Melcher (2003) waveshape index (w) that accounts for negatively sustained responses**

*Gonzalez-Castillo et al., Cerebral Cortex 2015*

# Results (I): Data Quality Comparison across studies

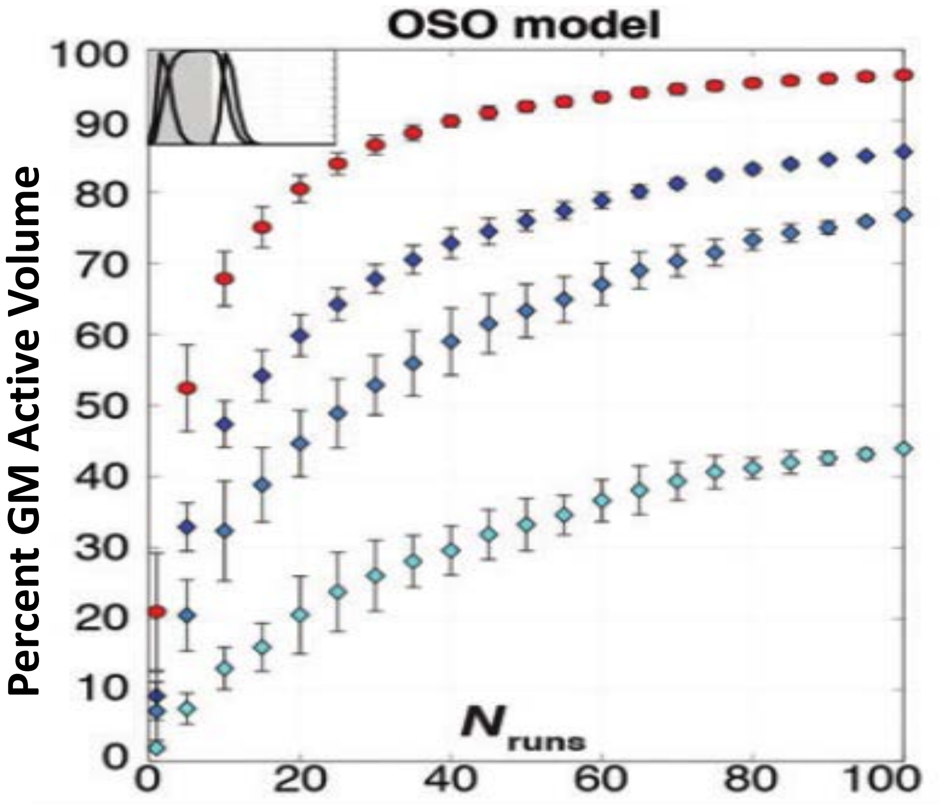



*Gonzalez-Castillo et al., Cerebral Cortex 2015*

# Results (II): Activation Volume vs. Cognitive/Stimulation Demands




3T: fFOV + Task 7T: fFOV + Task 7T: fFOV 7T: hFOV

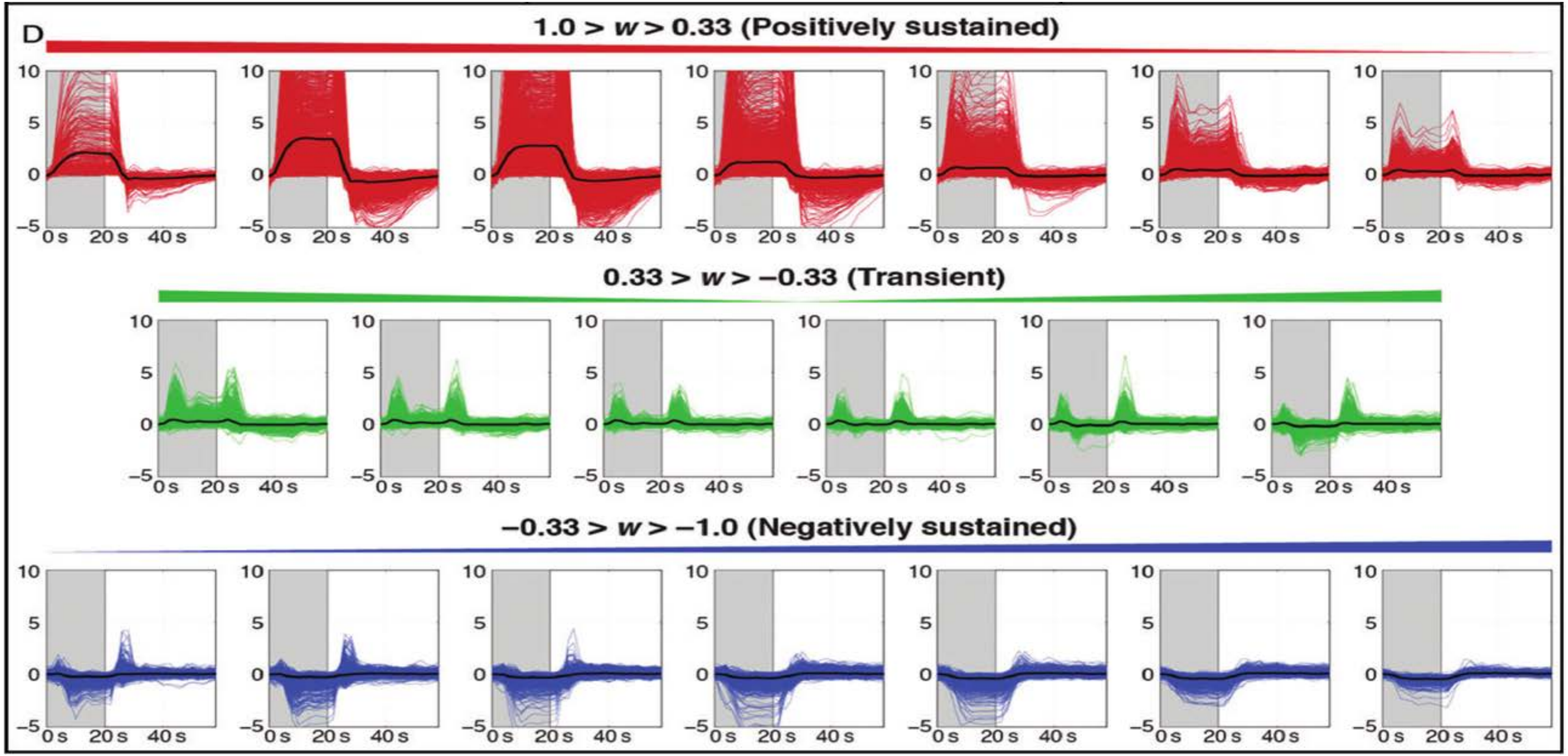
*Gonzalez-Castillo et al., Cerebral Cortex 2015*

# Results (III): Contribution of the three primary response types

**Waveshape Index:**

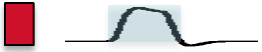
$$w = \frac{\beta_{\mathrm{SUS}}}{|\beta_{\mathrm{SUS}}| + |\beta_{\mathrm{ON}}| + |\beta_{\mathrm{OFF}}|}$$

$\beta_{xx}$ = Effect size of OSO model for $N_{runs}$=100



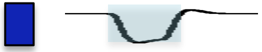

*Gonzalez-Castillo et al., Cerebral Cortex 2015*

# Results (III): Contribution of the three primary response types



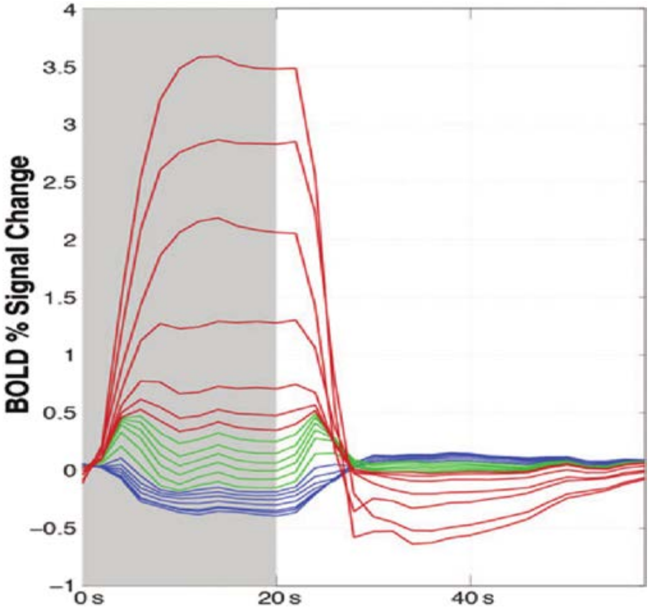
pSUS [0.33<w<1]

TRAN [-0.33<w<0.33]



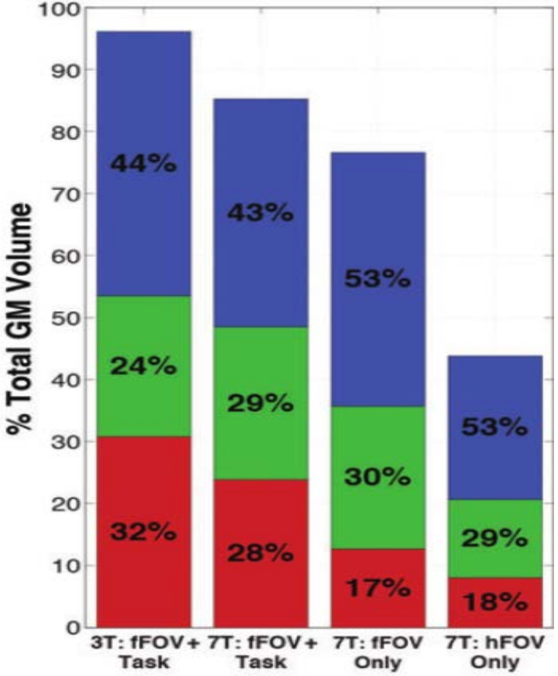
nSUS [-1<w<-0.33]

## Average Percent Change vs. Response Type




Positively sustained responses have the highest SPC, are the easiest to detect.

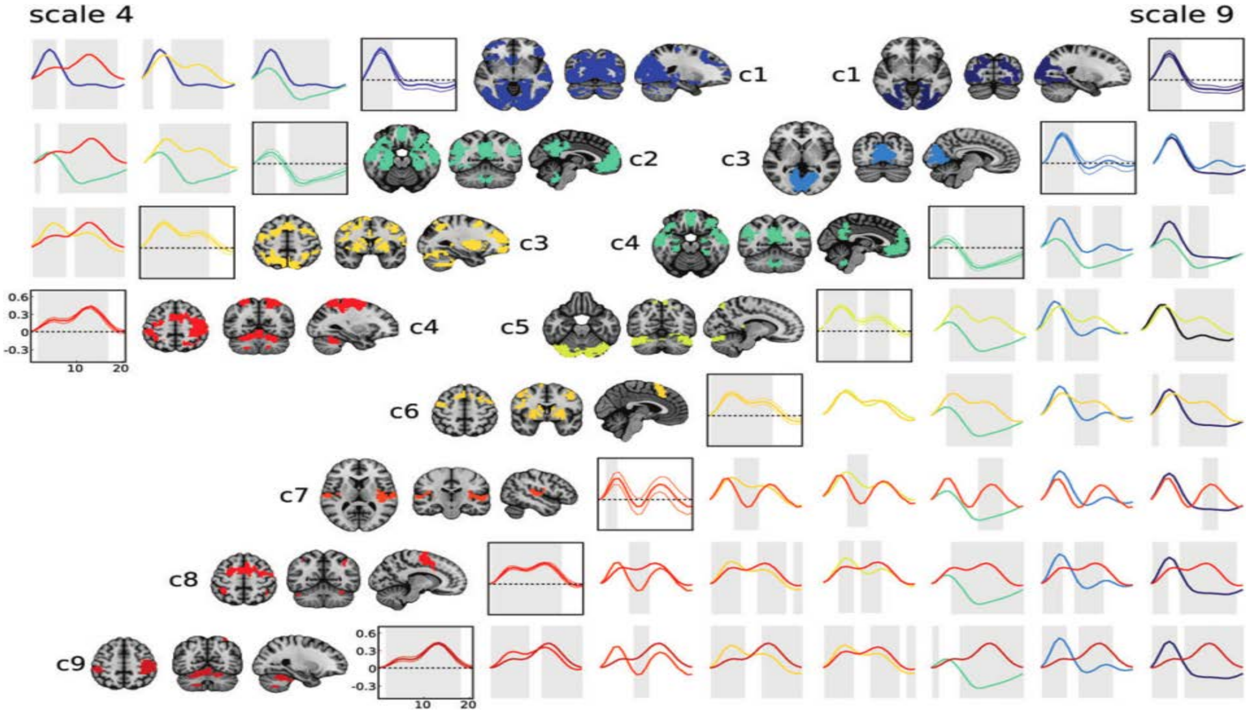
## Contribution of each response to activation volume




*Gonzalez-Castillo et al., Cerebral Cortex 2015*

# Similar Observations for Motor Task

## Extension to group level in the context of a delayed sequential motor task

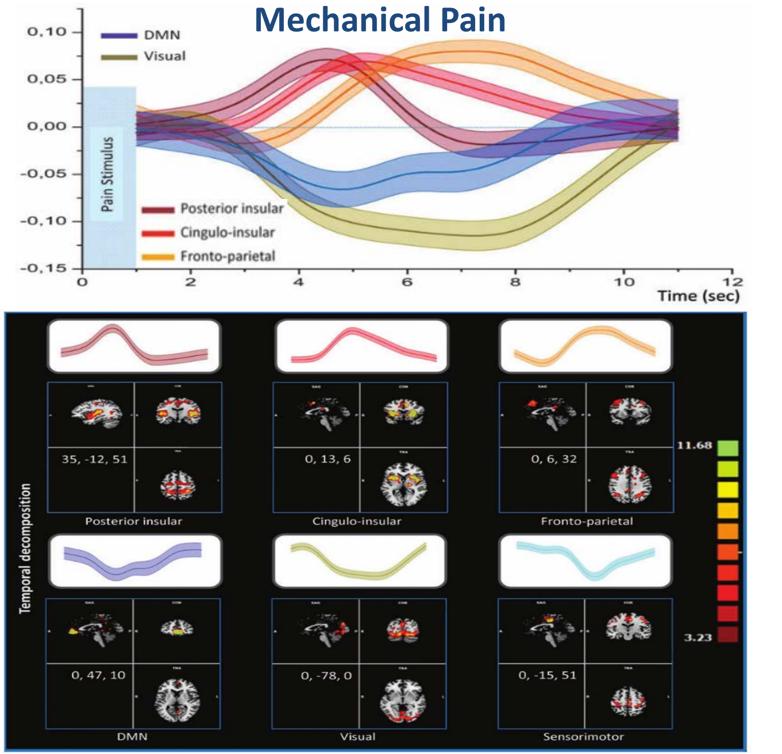



*"…rich variety of hemodynamic responses elicited by a motor task is systematic enough to decompose the whole human brain into stable task-evoked networks at the group level."*

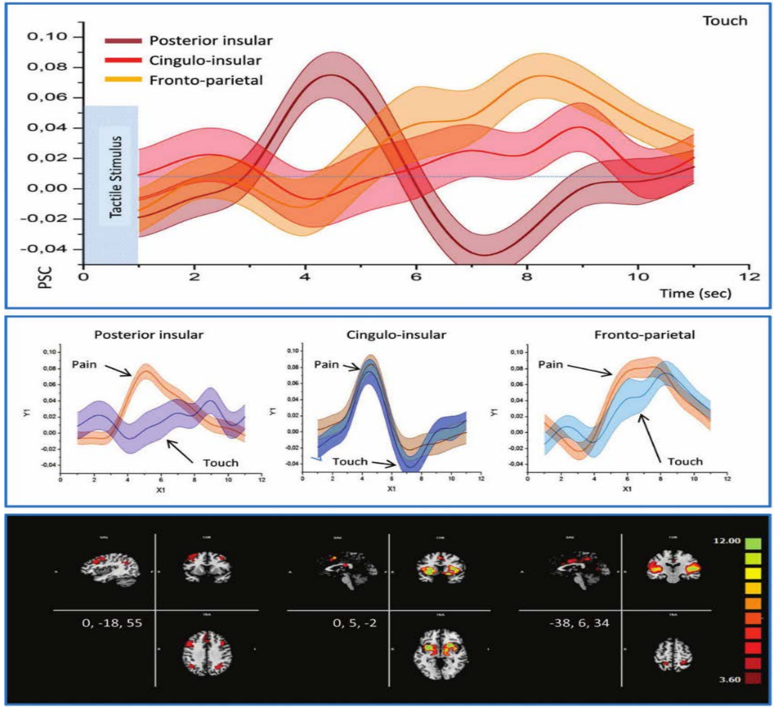
*Orban et al., Cerebral Cortex 2014*

# Unhidden Activation – Study of Pain

## Mechanical Pain




## Tactile Stimuli




*"Our findings suggest that the areas that respond with stimulus-locked activation to painful stimuli are likely to reflect the activity of different networks, each having different temporal behavior, and possibly, subserving different cognitive functions."*

*Cauda et al. Cerebral Cortex 2014*

# Other ways to uncover "hidden activations"…

frontiers in NEUROSCIENCE
OPINION ARTICLE
published: 27 August 2013
doi: 10.3389/fnins.2013.00154

## Spatial ICA reveals functional activity hidden from traditional fMRI GLM-based analyses

*Jiansong Xu*[1]*, *Marc N. Potenza*[1,2,3] *and Vince D. Calhoun*[1,4,5]

[1] Department of Psychiatry, Yale School of Medicine, Yale University, New Haven, CT, USA
[2] Child Study Center, Yale School of Medicine, Yale University, New Haven, CT, USA
[3] Department of Neurobiology, Yale School of Medicine, Yale University, New Haven, CT, USA
[4] The Mind Research Network, Albuquerque, NM, USA
[5] Department of Electrical and Computer Engineering, The University of New Mexico, Albuquerque, NM, USA
*Correspondence: jiansong.xu@yale.edu

ELSEVIER
NeuroImage
www.elsevier.com/locate/ynimg
NeuroImage 25 (2005) 527–538

## Semi-blind ICA of fMRI: a method for utilizing hypothesis-derived time courses in a spatial ICA analysis

…C. Stevens,[a,b] K.A. Kiehl,[a,b] and J.J. Pekar[e,f]

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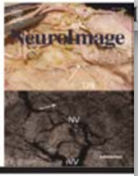
Contents lists available at SciVerse ScienceDirect
NeuroImage
journal homepage: www.elsevier.com/locate/ynimg



## Contributive sources analysis: A measure of neural networks' contribution to brain activations

Ewa Beldzik [a,b,d,*], Aleksandra Domagalik [a,d], Sander Daselaar [c], Magdal…
Wojciech Froncisz [b], Halszka Oginska [a], Tadeusz Marek [a,d]

ELSEVIER
Available online at www.sciencedirect.com
ScienceDirect
MAGNETIC RESONANCE IMAGING
Magnetic Resonance Imaging 25 (2007) 860–868

## Dissecting cognitive stages with time-resolved fMRI data: a comparison of fuzzy clustering and independent component analysis

Alain Smolders[a], Federico De Martino[b], Noël Staeren[b], Paul Scheunders[b],
Jan Sijbers[b], Rainer Goebel[b], Elia Formisano[b,*]

[a] *Vision Lab (Department of Physics), University of Antwerp, Universiteitsplein 1, B-2610 Antwerpen, Belgium*
[b] *Department of Cognitive Neuroscience, Faculty of Psychology, Maastricht University, 6200 MD Maastricht, The Netherlands*

## Conclusions

- Simple tasks can significantly modulate on-going BOLD fluctuations across large portions of the brain.
- Traditional analyses can miss more than half of locations affected by task performance.
- Subtle interregional differences in BOLD response contain sufficient information to produce functional parcellations of the whole brain “in action”, which can deviate in some instances from connectivity patterns measured at rest.
- A simple Active/Inactive dichotomy does not capture all information present in the data.

## Limitations / Additional Questions

- First, and foremost, the impossibility to unquestionably claim a neuronal origin for all detected hemodynamic responses.

**Statistical Significance <<<< Biological Significance <<<< Neuronal Significance**

- Need to better understand “non-traditional” hemodynamic responses.
- Differentiating task-essential regions from task-accessory regions.
- Distinguishing hemodynamic events tightly co-localized to neuronal activity from those that only manifest as a vascular-driven distant echo of true neuronal modulation at a different location.
- How to optimally visualize, interpret and report all this information.

# Acknowledgements


## Section on Functional Imaging Methods

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Ziad S. Saad
Daniel Glen
Richard Reynolds
Gang Chen

## Advanced MRI

Catie Chang

Advanced MRI
LFMI, NINDS,
National Institutes of Health