Generalized Psychophysiological Interactions: Theory and Applications (gPPI)

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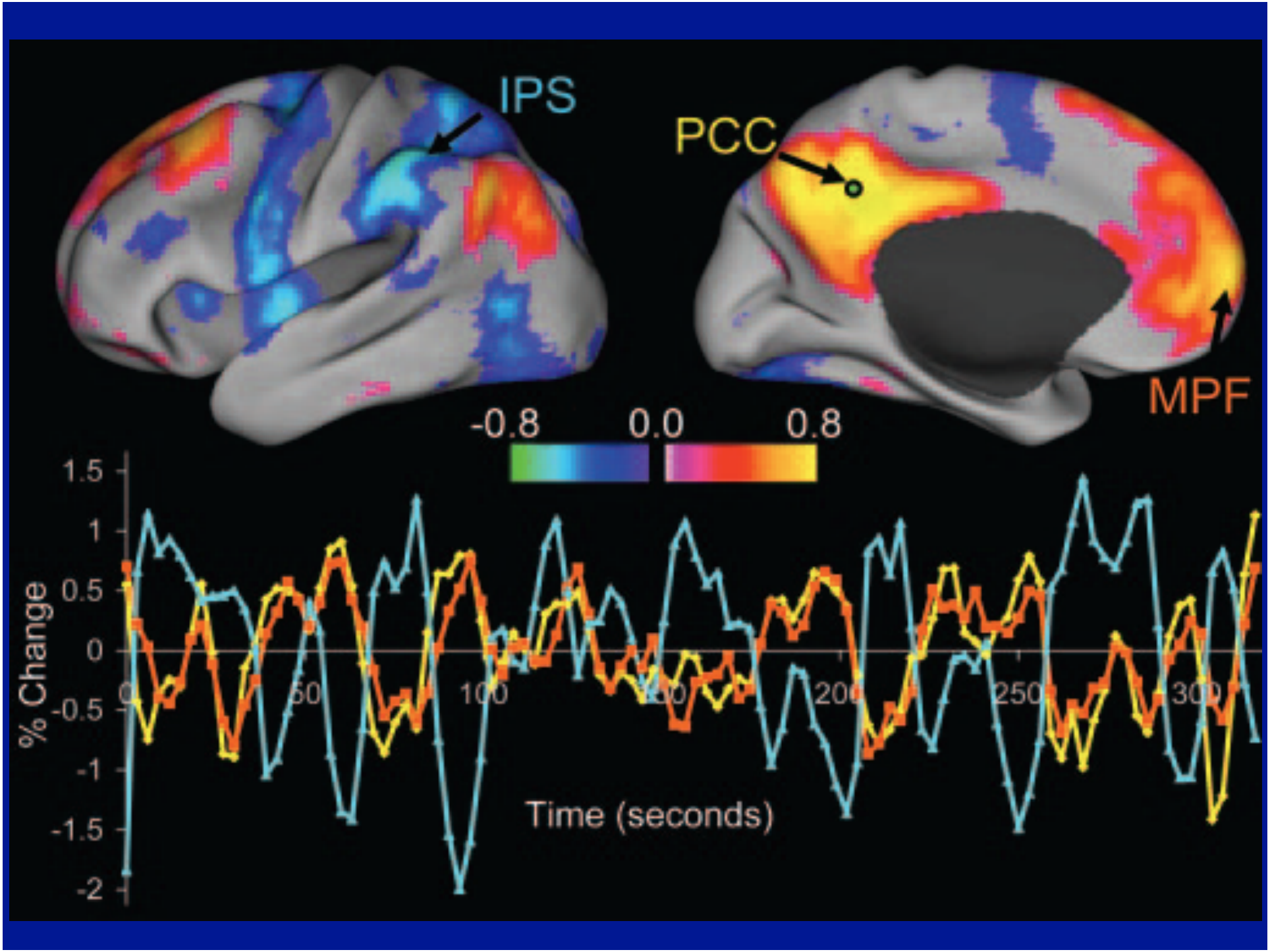
Financial Disclosures

- None related to this talk.

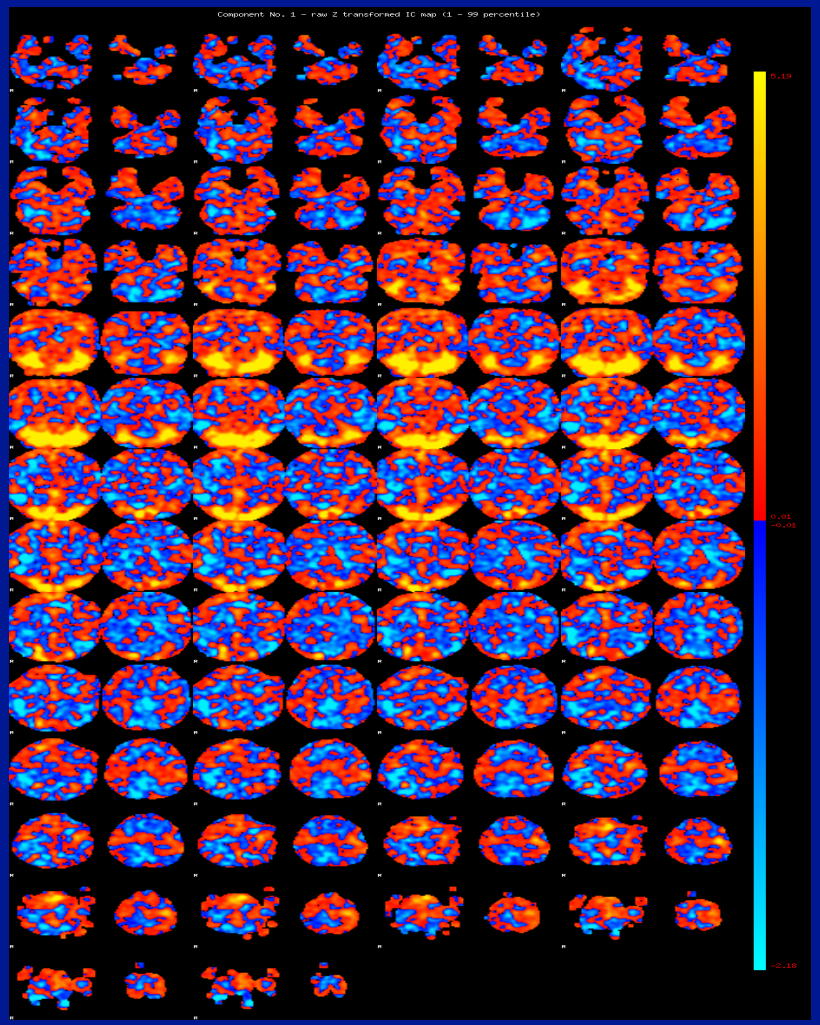
Resting State Connectivity


IPS
PCC
MPF
-0.8
0.0
0.8
1.5
1
0.5
0
-0.5
-1
-1.5
-2
% Change
Time (seconds)

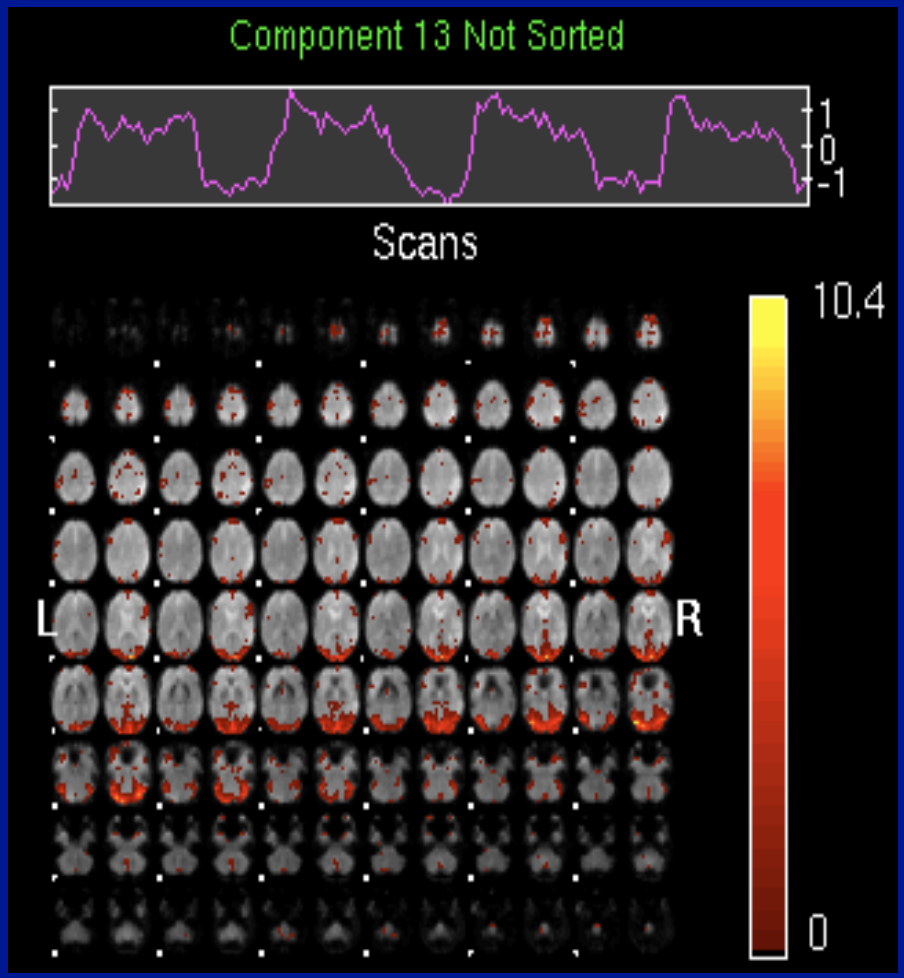
With This Method (and ICA)…

- I will show that 1 person scanned today and another person scanned next week doing a simple block design visual task have functional connected brains.

Melodic ICA

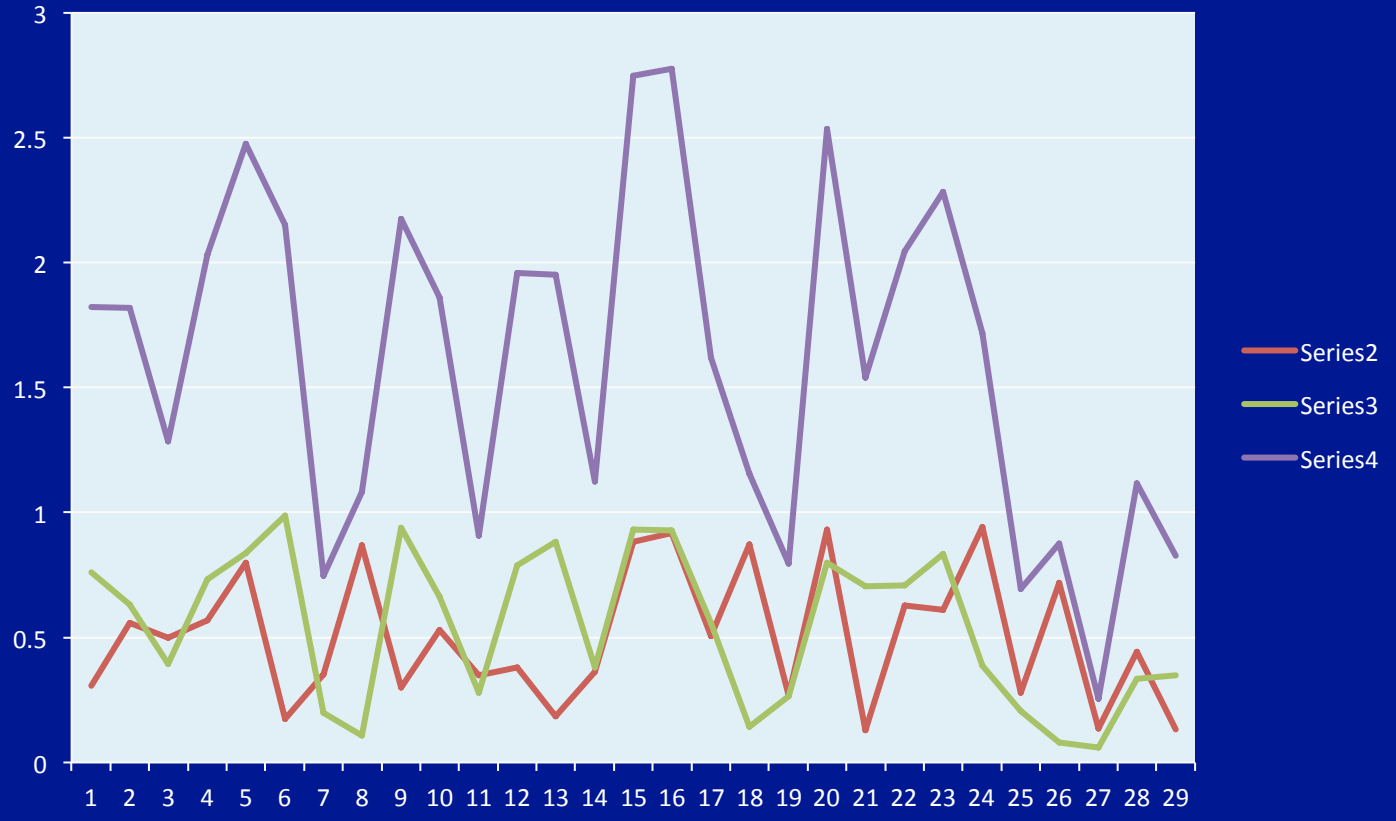


GIFT ICA



Resting Methods in Task Data: Pure Resting Data

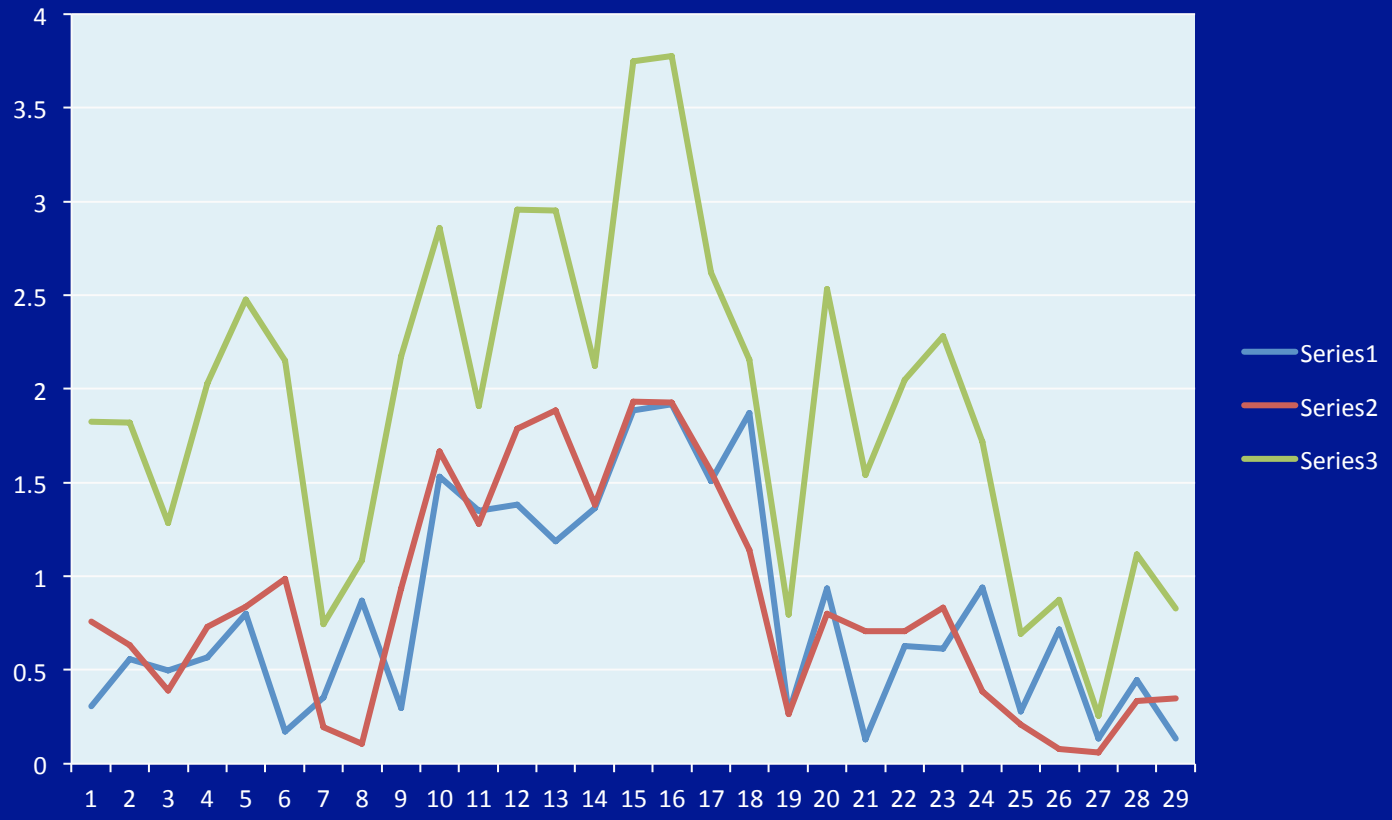
- ICA or Seed-Based (e.g. degree connectivity)



	voxel 2	voxel3
voxel1	0.067154913	0.456587852
voxel2	[redacted]	0.918332054
voxel3	[redacted]	[redacted]

Resting Methods in Task Data: Task Added to All 3 Voxels

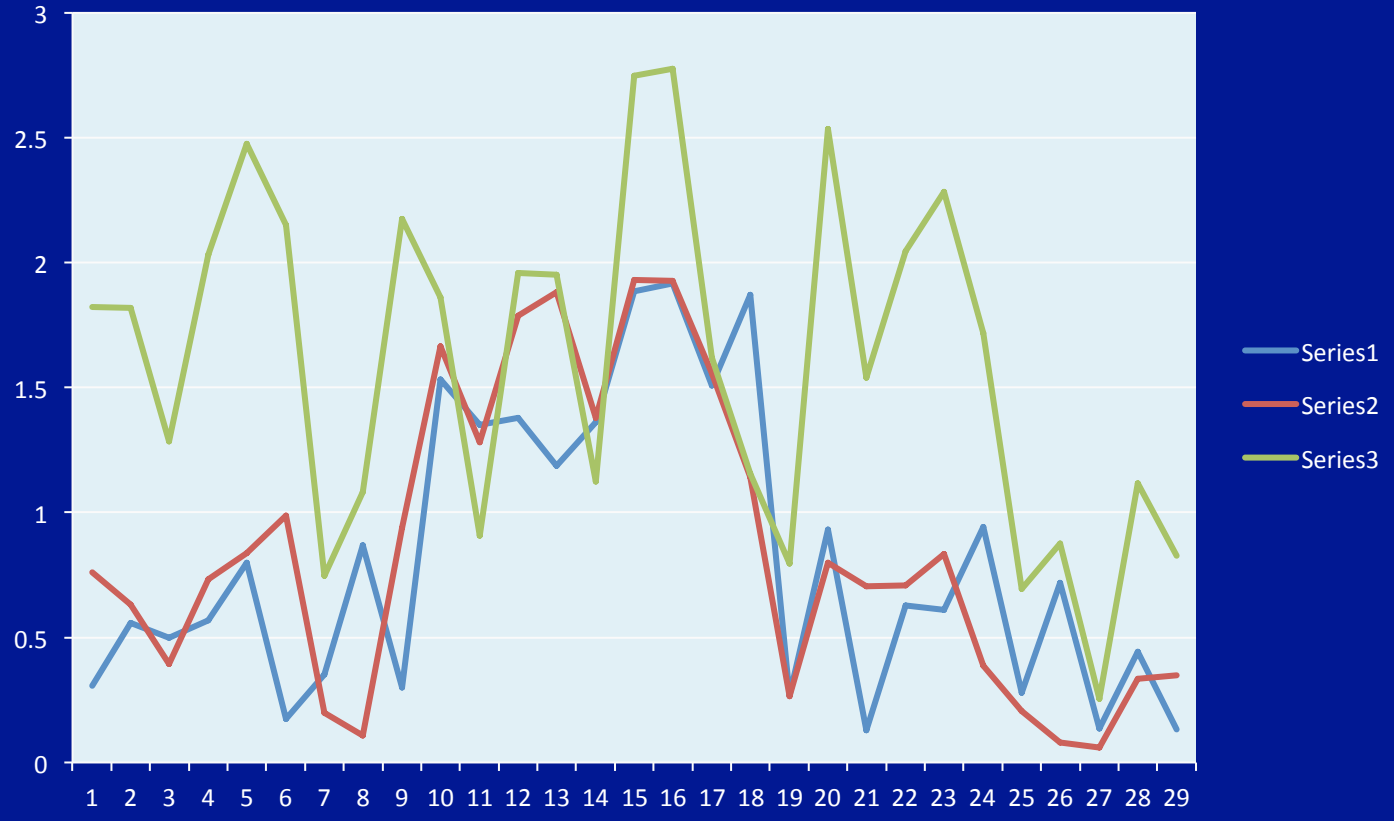
- ICA or Seed-Based (e.g. degree connectivity)



	voxel 2	voxel3
voxel1	0.77731657	0.74621643
voxel2		0.91991906
voxel3		

Resting Methods in Task Data: Task Added to 2 Least Correlated Voxels

- ICA or Seed-Based (e.g. degree connectivity)



	voxel 2	voxel3
voxel1	0.77731657	0.37278333
voxel2		0.61442407
voxel3		

Applying Resting Methods To Task Data

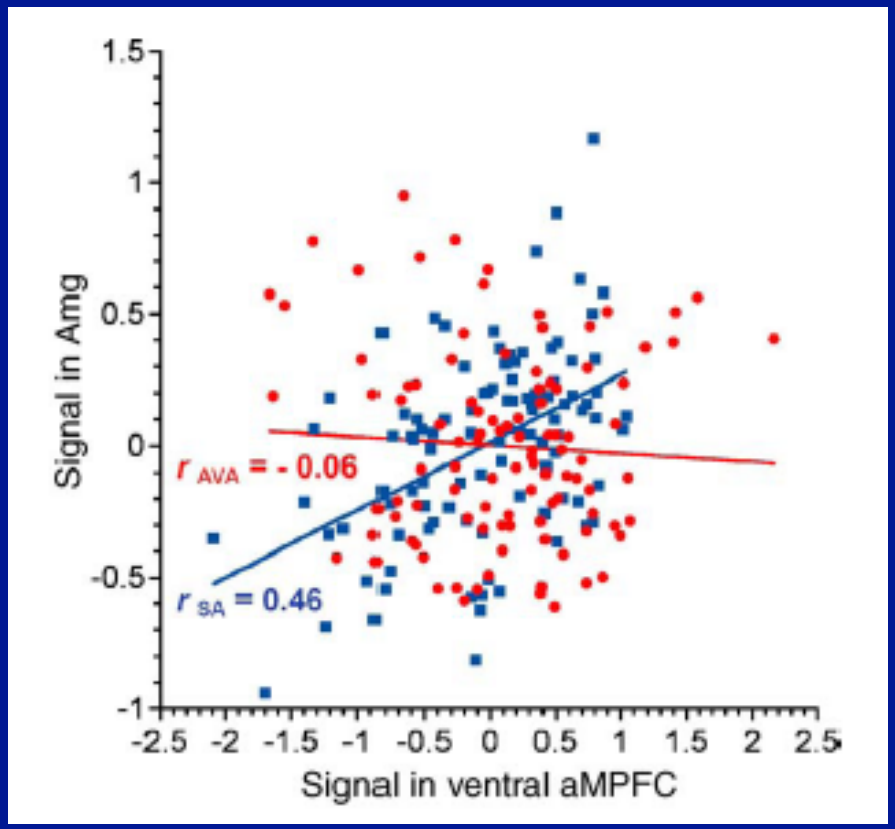
- While it can be done, the interpretation changes dramatically.
- We are interested in the connectivity during the task, which isn't being provided in most task designs – unless you have a 2-3+ minute block.
- Thus, we need another method.

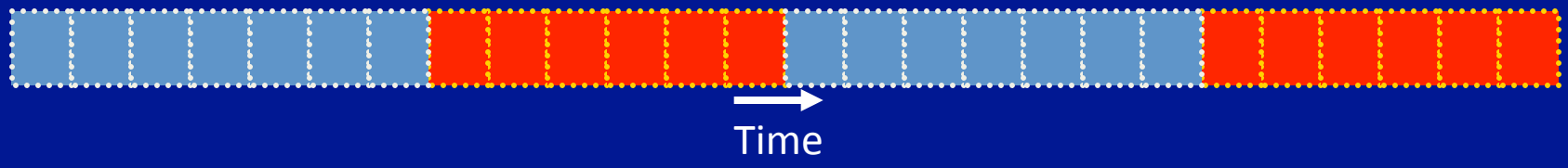
How Can We Identify Connectivity Differences (and Similarities)

Psychophysiological Interactions

Context-Dependent Connectivity

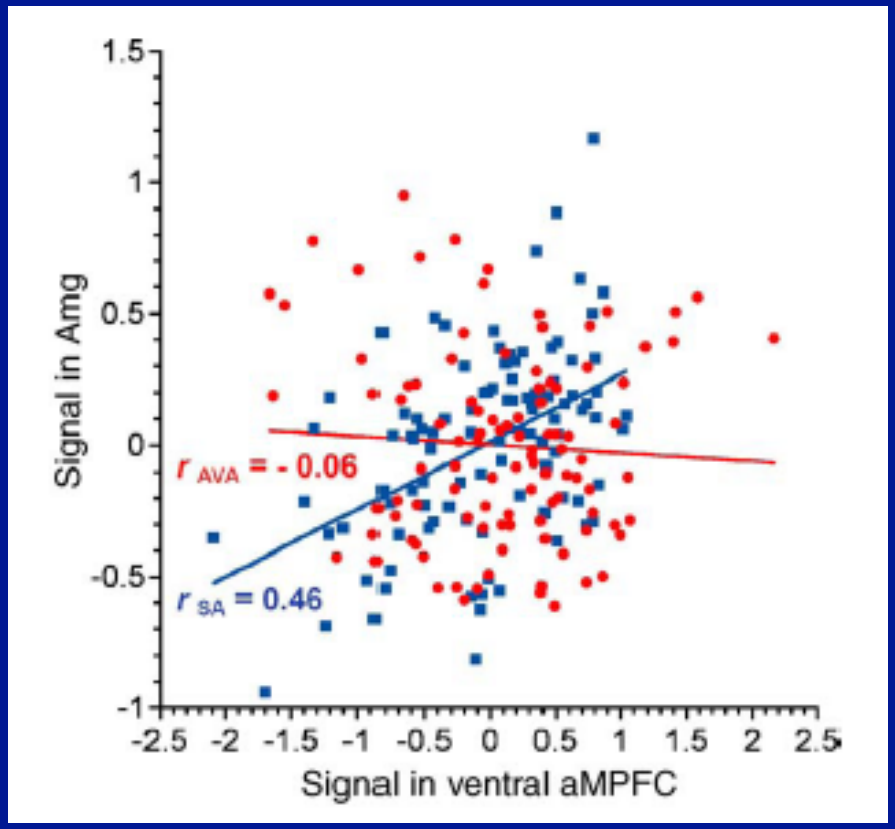
Context-Dependent Connectivity

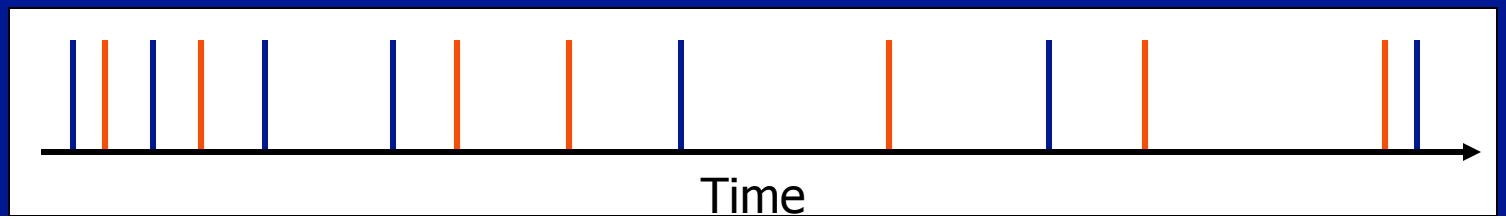




(Schmitz and Johnson 2006)

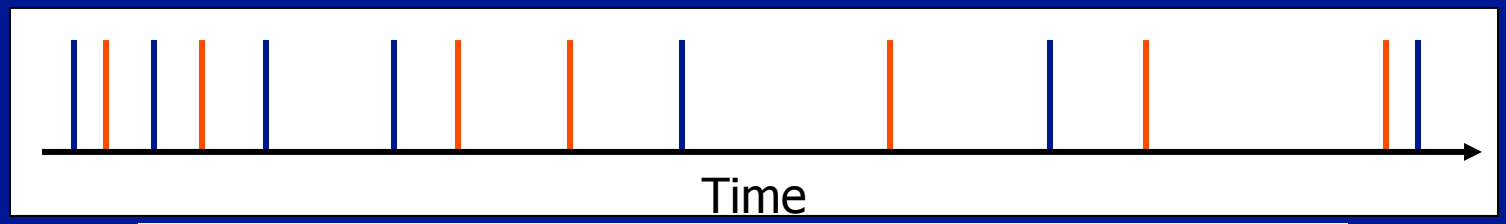
Context-Dependent Connectivity





Context-Dependent Connectivity

- Coincident (or nearly coincident) neural events (not BOLD) in different brain regions produce similar BOLD response profile shapes
  - X amount of neural stimulation will always lead to X BOLD response profile shape
- We assume in any fMRI analysis that the neural response (not BOLD) do not overlap.



$$Y_i = conv\left(deconv(Y_k) \times g_p\right) * \beta_i + \left[Y_k conv\left(g_p\right) G\right] * \beta_G + e_i$$

(Gitelman et al. 2003)

A Statistical Thought To Consider…

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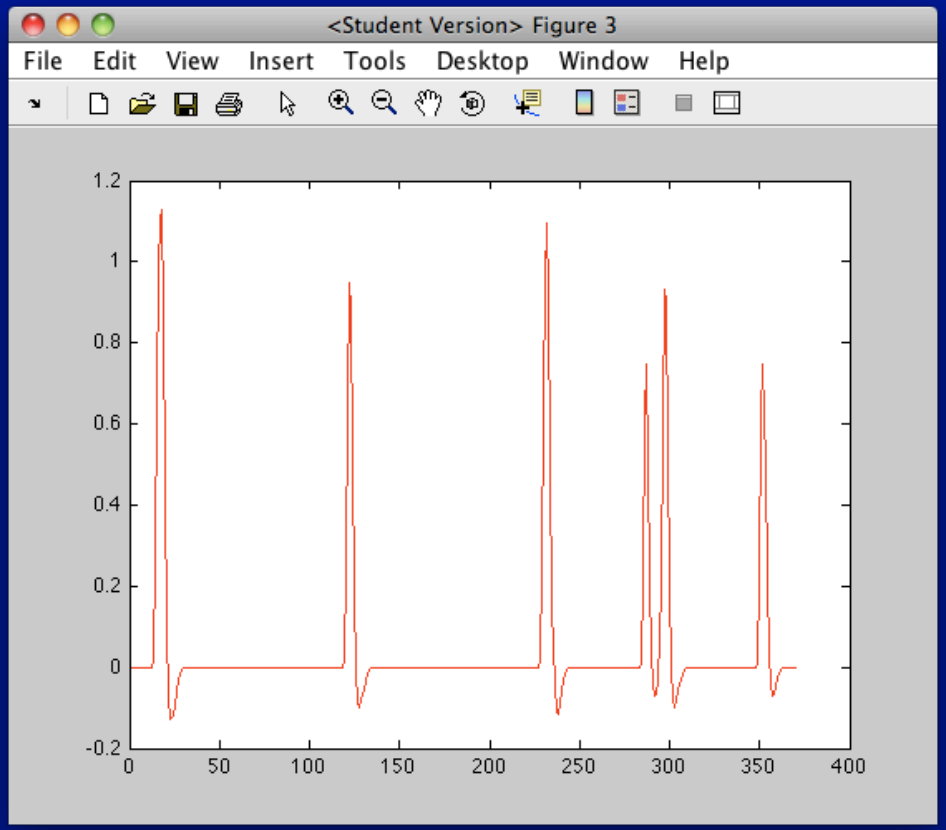
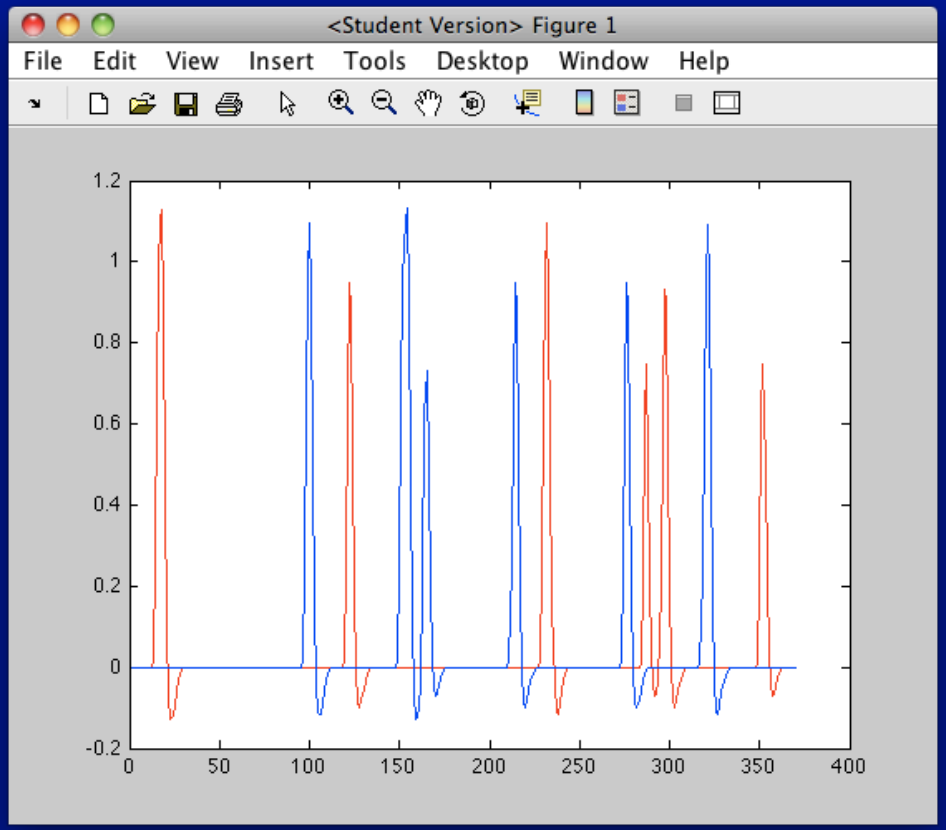
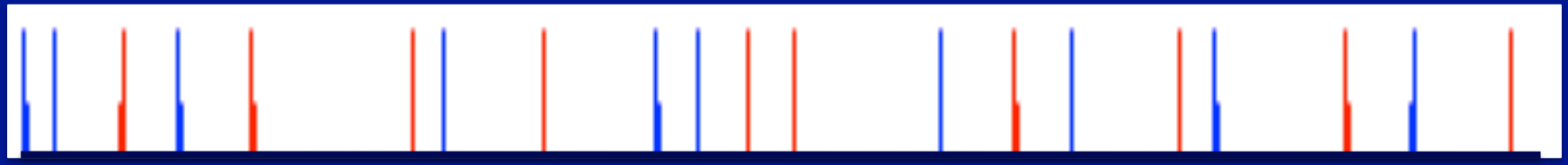
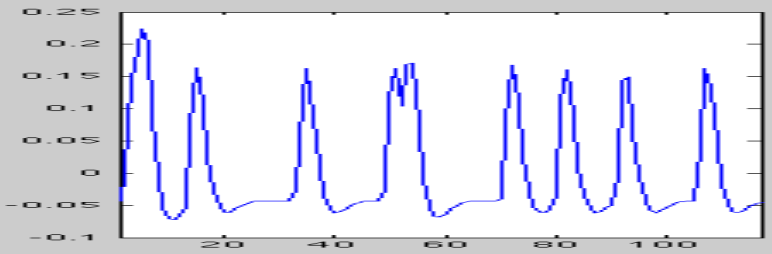


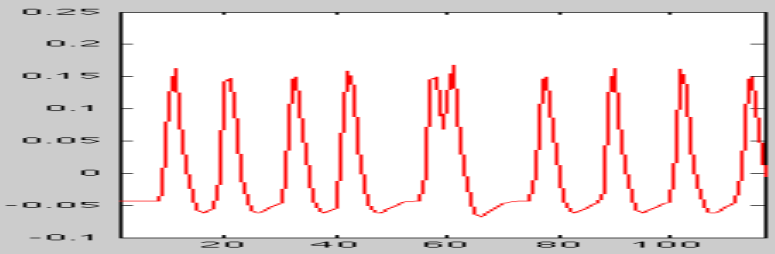
A Statistical Thought To Consider…

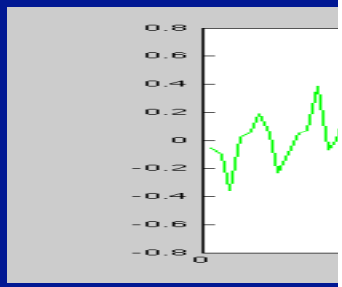


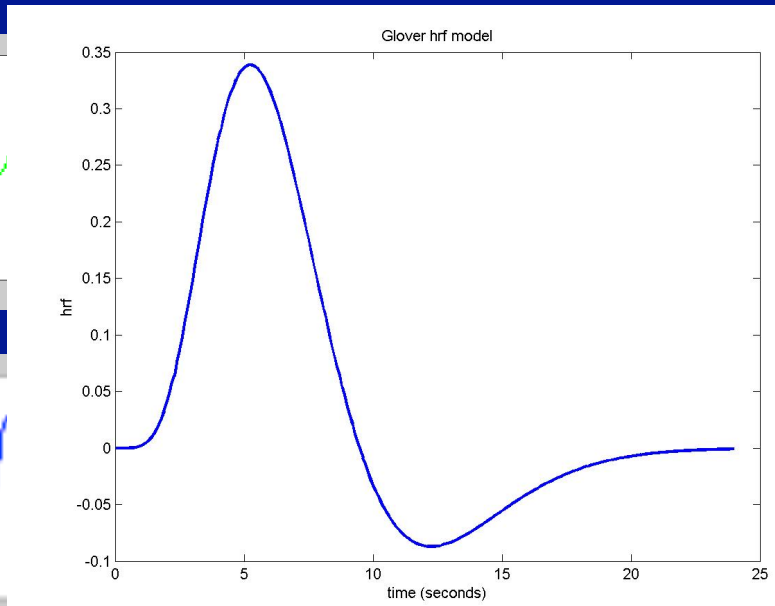
Context-Dependent Connectivity

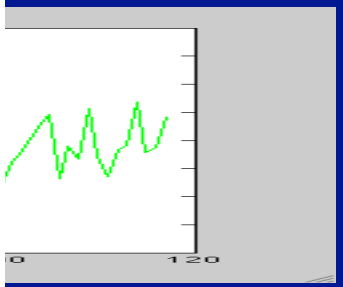


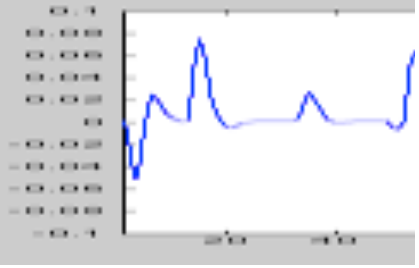


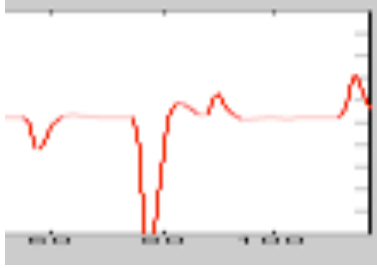




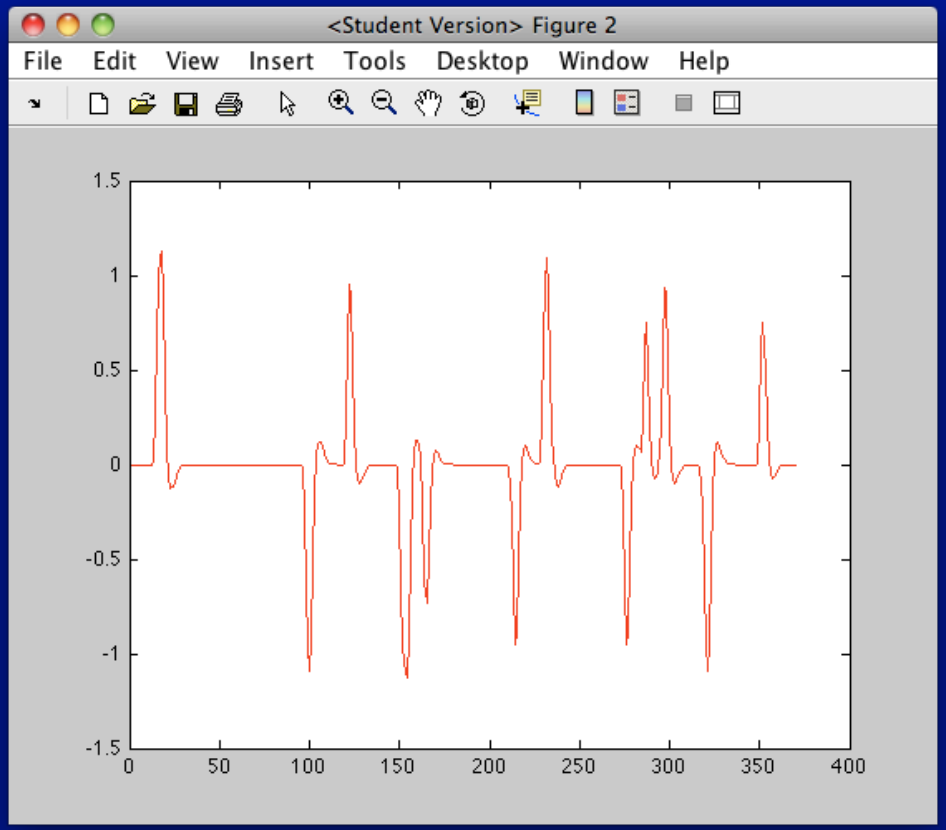




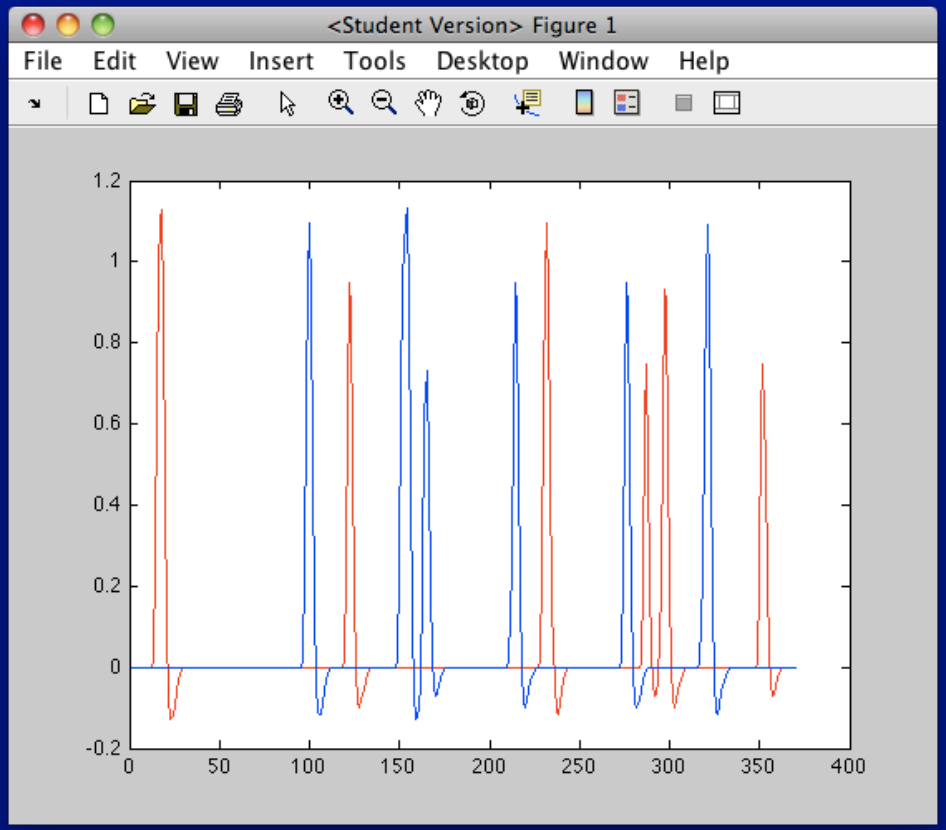




A Statistical Thought To Consider…

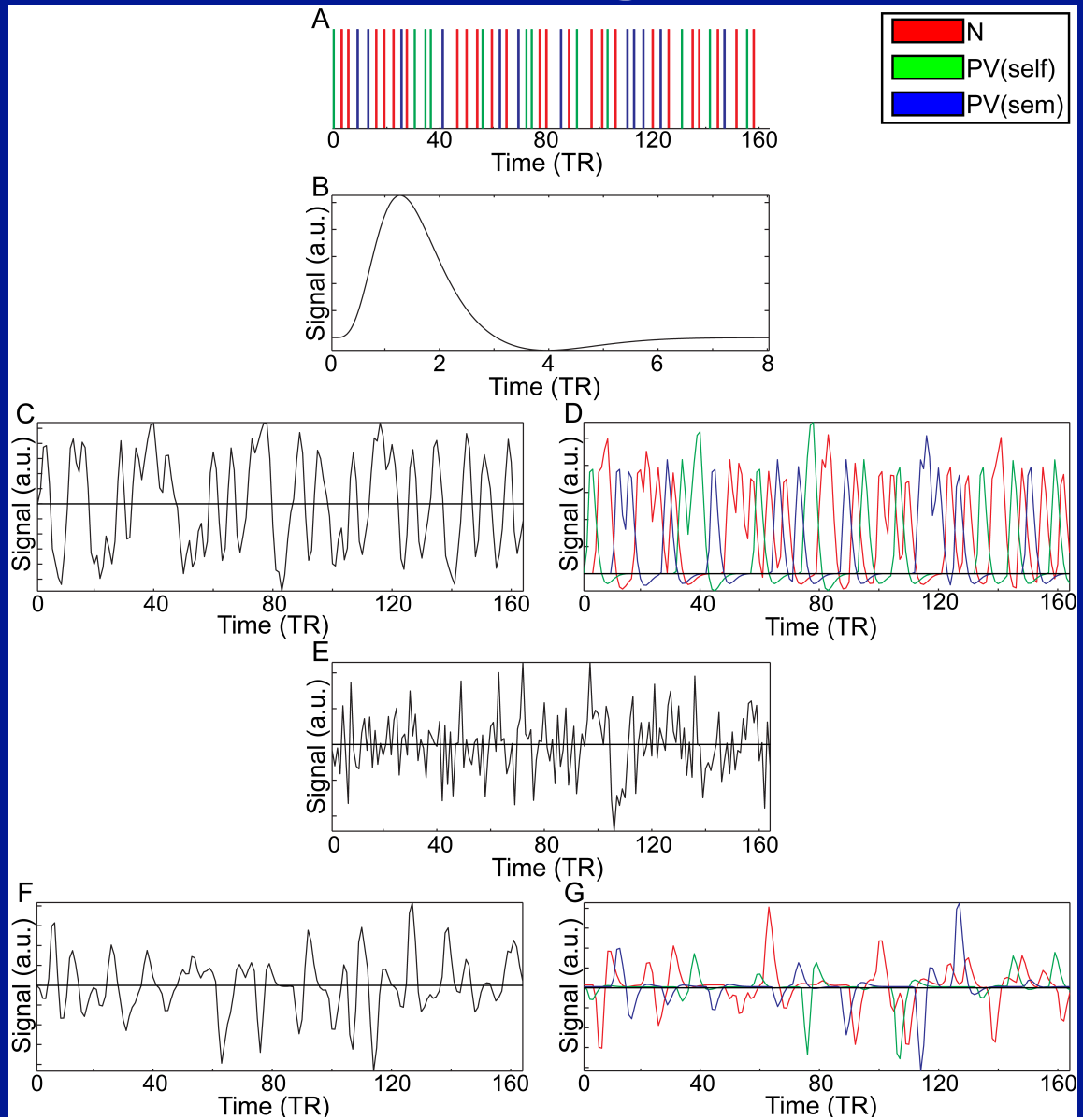


A Statistical Thought To Consider…



(McLaren et al. 2012)

sPPI vs gPPI



Simulations

- Using the gPPI framework, we simulated different interaction models.
  - PPI Term
  - Psychological/Task Term
  - Seed Term
  - Constant
- *[0.5 -0.5 0.5 -0.5 .25 100]*
- *[a a-1 0.5 -0.5 .25 100]*

Simulations=Accuracy

Table 1
Accuracy of psychophysiological interaction estimates: 2 conditions, no fixation.

Beta weights for simulated data						Models			
PPIA	PPIB	A	B	Seed	Constant	sPPI	sPPI + tasks	sPPIplus	gPPI2
0.5	−0.5	0.5	−0.5	0.25	100	0.50 (0.50)	0.50 (0.50)	0.50 (0.50)	1.00 (1.00)
a	*a*–1	0.5	−0.5	0.25	100	**0.00 (0.50)**	**0.03 (0.50)**	0.50 (0.50)	1.00 (1.00)
0.5	−0.5	*a*	*a*–1	0.25	100	**0.57 (0.50)**	0.50 (0.50)	0.50 (0.50)	1.00 (1.00)
a	*a*–1	*a*	*a*–1	0.25	100	**0.07 (0.50)**	**0.03 (0.50)**	0.50 (0.50)	1.00 (1.00)
a	−*a*	0.5	−0.5	0.25	100	−0.14 (−0.14)	−0.14 (−0.14)	−0.14 (−0.14)	−0.28 (−0.28)
0.5	−0.5	*a*	*a*	0.25	100	0.50 (0.50)	0.50 (0.50)	0.50 (0.50)	1.00 (1.00)
a	−*a*	*a*	*a*	0.25	100	−0.14 (−0.14)	−0.14 (−0.14)	−0.14 (−0.14)	−0.28 (−0.28)

Beta weights were multipled by a design matrix with the following regressors: PPI for condition A, PPI for condition B, HRF task regressor for condition A, HRF task regressor for condition B, seed voxel timecourse, and a constant. All datasets used 100 different values for a. Values represent the mean estimated interaction weight of A–B (the mean expected value of the interaction of A–B). **Bold** values indicate models where the model did not capture the true interaction. ***a*** is random number generated from the ***randn*** function in MATLAB®, which generates random numbers with a mean of 0 and a variance of 1.

(McLaren et al. 2012)

Simulations=Accuracy

Table 2
Accuracy of psychophysiological interaction estimates: 3 conditions, fixation.

Beta weights for simulated data								Models				
PPIA	PPIB	PPIC	A	B	C	Seed	Constant	sPPI	sPPI + tasks	gPPIplus	gPPI2	gPPI3
a	*a*−1	0	*a*	*a*−1	0	0.25	100	**0.441 (0.500)**	**0.487 (0.500)**	0.500 (0.500)	1.000 (1.000)	1.000 (1.000)
a	*a*−1	0.5	*a*	*a*−1	0.5	0.25	100	**0.259 (0.500)**	**0.297 (0.500)**	**0.313 (0.500)**	**0.625 (1.000)**	1.000 (1.000)
a	*a*−1	*a*−0.5	*a*	*a*−1	*a*−0.5	0.25	100	**0.663 (0.500)**	**0.719 (0.500)**	**0.729 (0.500)**	**1.457 (1.000)**	1.000 (1.000)
0.5	−0.5	0	*a*	*a*−1	0	0.25	100	**0.448 (0.500)**	0.500 (0.500)	0.500 (0.500)	1.000 (1.000)	1.000 (1.000)
0.5	−0.5	0.5	*a*	*a*−1	0.5	0.25	100	**0.267 (0.500)**	**0.310 (0.500)**	**0.313 (0.500)**	**0.625 (1.000)**	1.000 (1.000)
0.5	−0.5	0	*a*	*a*−1	*a*−0.5	0.25	100	**0.455 (0.500)**	0.500 (0.500)	0.500 (0.500)	1.000 (1.000)	1.000 (1.000)
a	*a*−1	0	0.5	−0.5	0	0.25	100	**0.493 (0.500)**	**0.487 (0.500)**	0.500 (0.500)	1.000 (1.000)	1.000 (1.000)
a	*a*−1	0.5	0.5	−0.5	0.5	0.25	100	**0.311 (0.500)**	**0.297 (0.500)**	**0.313 (0.500)**	**0.625 (1.000)**	1.000 (1.000)
a	*a*−1	*a*−0.5	0.5	−0.5	0	0.25	100	**0.708 (0.500)**	**0.719 (0.500)**	**0.729 (0.500)**	**1.457 (1.000)**	1.000 (1.000)
a	*a*	0	*a*	*a*	0	0.25	100	−0.110 (−0.110)	−0.110 (−0.110)	−0.110 (−0.110)	−0.220 (−0.220)	−0.220 (−0.220)
a	*a*	0.5	*a*	*a*	0.5	0.25	100	**−0.292 (−0.110)**	**−0.300 (−0.110)**	**−0.297 (−0.110)**	**−0.595 (−0.220)**	−0.220 (−0.220)
0.5	−0.5	0	*a*	*a*	0	0.25	100	0.500 (0.500)	0.500 (0.500)	0.500 (0.500)	1.000 (1.000)	1.000 (1.000)
0.5	−0.5	0.5	*a*	*a*	0.5	0.25	100	**0.318 (0.500)**	**0.310 (0.500)**	**0.313 (0.500)**	**0.625 (1.000)**	1.000 (1.000)
a	*a*	0	0.5	−0.5	0	0.25	100	−0.110 (−0.110)	−0.110 (−0.110)	−0.110 (−0.110)	−0.220 (−0.220)	−0.220 (−0.220)
a	*a*	0.5	0.5	−0.5	0.5	0.25	100	**−0.292 (−0.110)**	**−0.300 (−0.110)**	**−0.297 (−0.110)**	**−0.595 (−0.220)**	−0.220 (−0.220)
a	*a*	b	0.5	−0.5	0	0.25	100	**−0.083 (−0.110)**	**−0.080 (−0.110)**	**−0.081 (−0.110)**	**−0.162 (−0.220)**	−0.220 (−0.220)
a	*a*	b	0.5	−0.5	0.5	0.25	100	**−0.088 (−0.110)**	**−0.080 (−0.110)**	**−0.081 (−0.110)**	**−0.162 (−0.220)**	−0.220 (−0.220)

(McLaren et al. 2012)

Simulations=Significance

Table 3. Robustness of PPI Estimates and Significance=2 Conditions

			Models		
Model Parameters	*sPPI*	*sPPI+tasks*	*sPPIplus*	*gPPI2*	*Single Condition*
PPI Effect					
1 Condition plus fixation	**0.99 (0.01)**	**0.99 (0.01)**	**0.99 (0.01)**	**0.99 (0.01)**	**0.99 (0.01)**
2 Conditions (A-B)	**0.49 (0.01)**	**0.49 (0.01)**	**0.49 (0.01)**	**0.98 (0.02)**	**0.40 (0.01)**
2 Conditions (same data as 1 Condition model)	**0.88 (0.02)**	**0.88 (0.02)**	**0.49 (0.01)**	**0.98 (0.02)**	**0.99 (0.01)**
2 Conditions (effectively the same as 2 Conditions (A-B))	**0.49 (0.01)**	**0.49 (0.01)**	**0.49 (0.01)**	**0.98 (0.02)**	**0.40 (0.01)**
2 Conditions	**0.88 (0.02)**	**0.88 (0.02)**	**0.49 (0.01)**	**0.98 (0.02)**	**1.00 (0.01)**
2 Conditions plus fixation	**0.71 (0.03)**	**0.58 (0.03)**	**0.51 (0.01)**	**1.02 (0.01)**	**1.91 (0.01)**
No PPI Effect					
2 Conditions plus fixation	**0.15 (0.01)**	0.01 (0.01)	0.01 (0.01)	0.02 (0.1)	**0.06 (0.01)**

(McLaren et al. 2012)

Akaike Information Criterion

$$AIC = 2k + n[\log(\frac{RSS}{n})]$$

Simulations=Model Fit

Table S1. Simulation Model Fits=2 Conditions

	Model			
Simulated Data	*sPPI+tasks*	*sPPIplus*	*gPPI2*	*Single Condition*
PPI Effects				
1 Condition plus fixation	0.00	0.00	0.00	0.00
2 Conditions (A-B)	-10.17	-9.19	**-9.19**	18.63
	-1.77	-72.13	**-72.13**	-72.37
2 Conditions (same data as 1 Condition model)	-10.17	-9.19	**-9.19**	18.63
2 Conditions (effectively the same as 2 Conditions (A-B))	-7.28	-77.64	**-77.64**	-63.36
2 Conditions	-19.30	-264.42	**-264.42**	-112.01
2 Conditions plus fixation				
No PPI Effects				
2 Conditions plus fixation	-136.92	-137.57	**-137.57**	-29.95

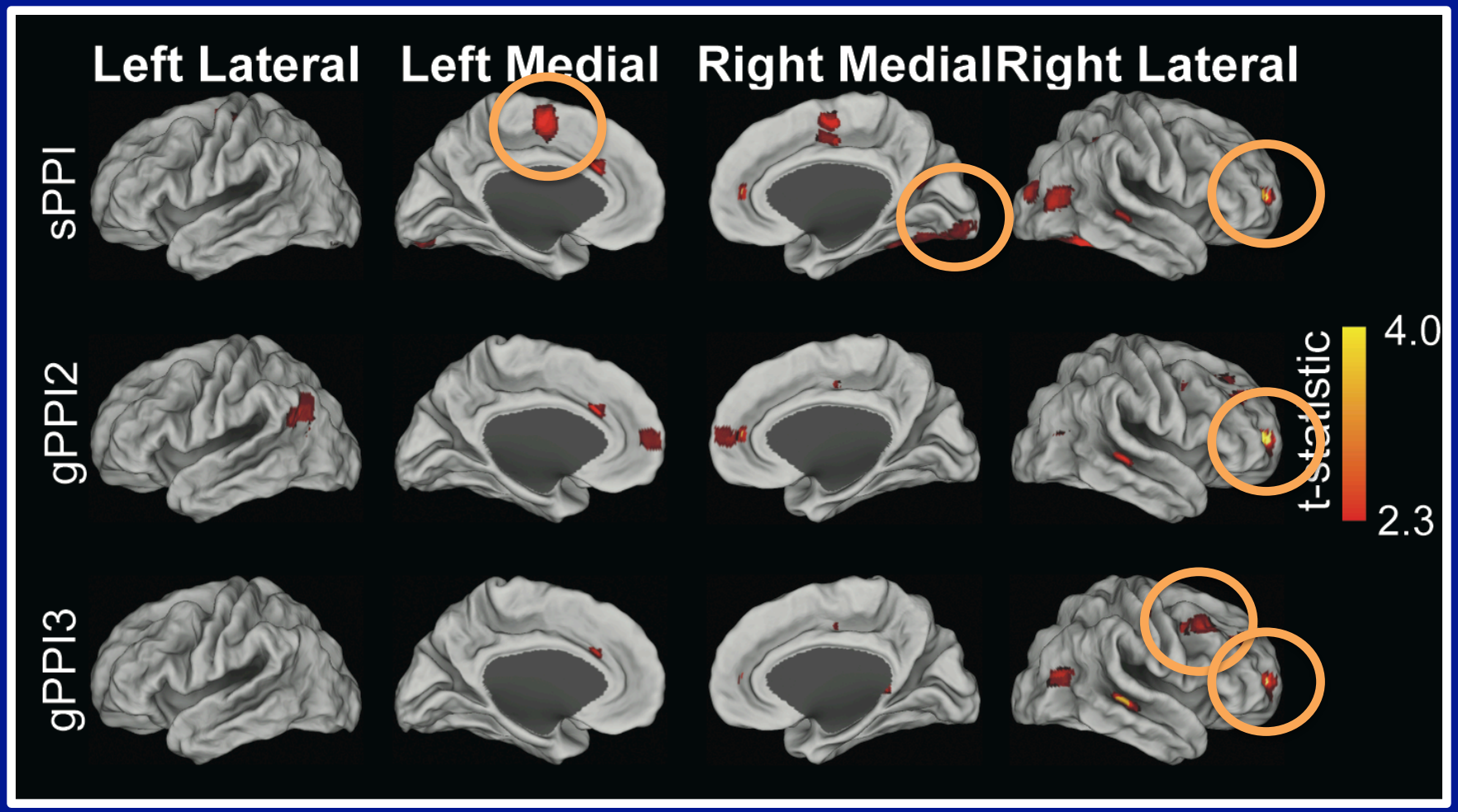
(McLaren et al. 2012)

Simulations=Significance

Table 4. Robustness of PPI Estimates and Significance=3 Conditions, Fixation

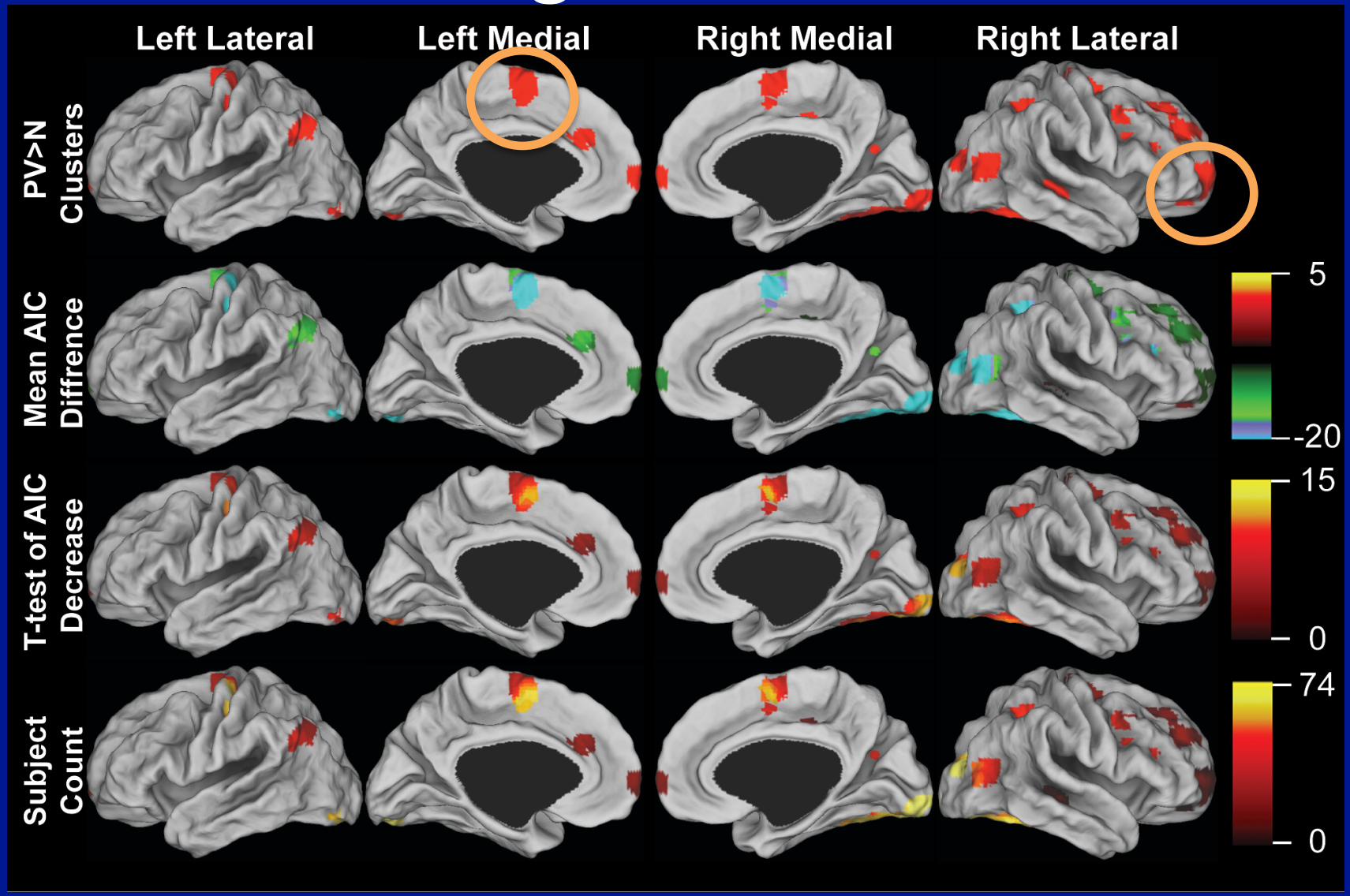
			Models		
Model Parameters	*sPPI*	*sPPI+tasks*	*sPPIplus*	*gPPI2*	*gPPI3*
PPI Effect					
PPIA=1;PPIB=0.75; PPIC=0	**0.15 (0.02)**	**0.12 (0.02)**	**0.12 (0.01)**	**0.24 (0.01)**	**0.25 (0.01)**
PPIA=1;PPIB=0.75; PPIC=0.5	-0.02 (0.02)	-0.06 (0.02)	-0.06 (0.01)	-0.12 (0.02)	**0.25 (0.01)**
PPIA=0.125; PPIB=-0.125;PPIC=0	**0.15 (0.01)**	**0.12 (0.01)**	**0.12 (0.01)**	**0.24 (0.01)**	**0.25 (0.01)**
PPIA=0.125; PPIB=-0.125;PPIC=0.5	-0.03 (0.01)	-0.06 (0.01)	-0.06 (0.01)	-0.13 (0.02)	**0.25 (0.01)**
No PPI Effect					
PPIA=0;PPIB=0; PPIC=0	**0.02 (0.01)**	-0.01 (0.01)	-0.01 (0.01)	-0.01 (0.01)	0.00 (0.01)
PPIA=0;PPIB=0; PPIC=0.5	**-0.16 (0.01)**	**-0.19 (0.01)**	**-0.19 (0.01)**	**-0.38 (0.02)**	0.00 (0.01)
PPIA=0;PPIB=0; PPIC=-0.5	**0.20 (0.01)**	**0.18 (0.01)**	**0.18 (0.01)**	**0.35 (0.01)**	0.00 (0.01)

sPPI vs. gPPI=Contrasts



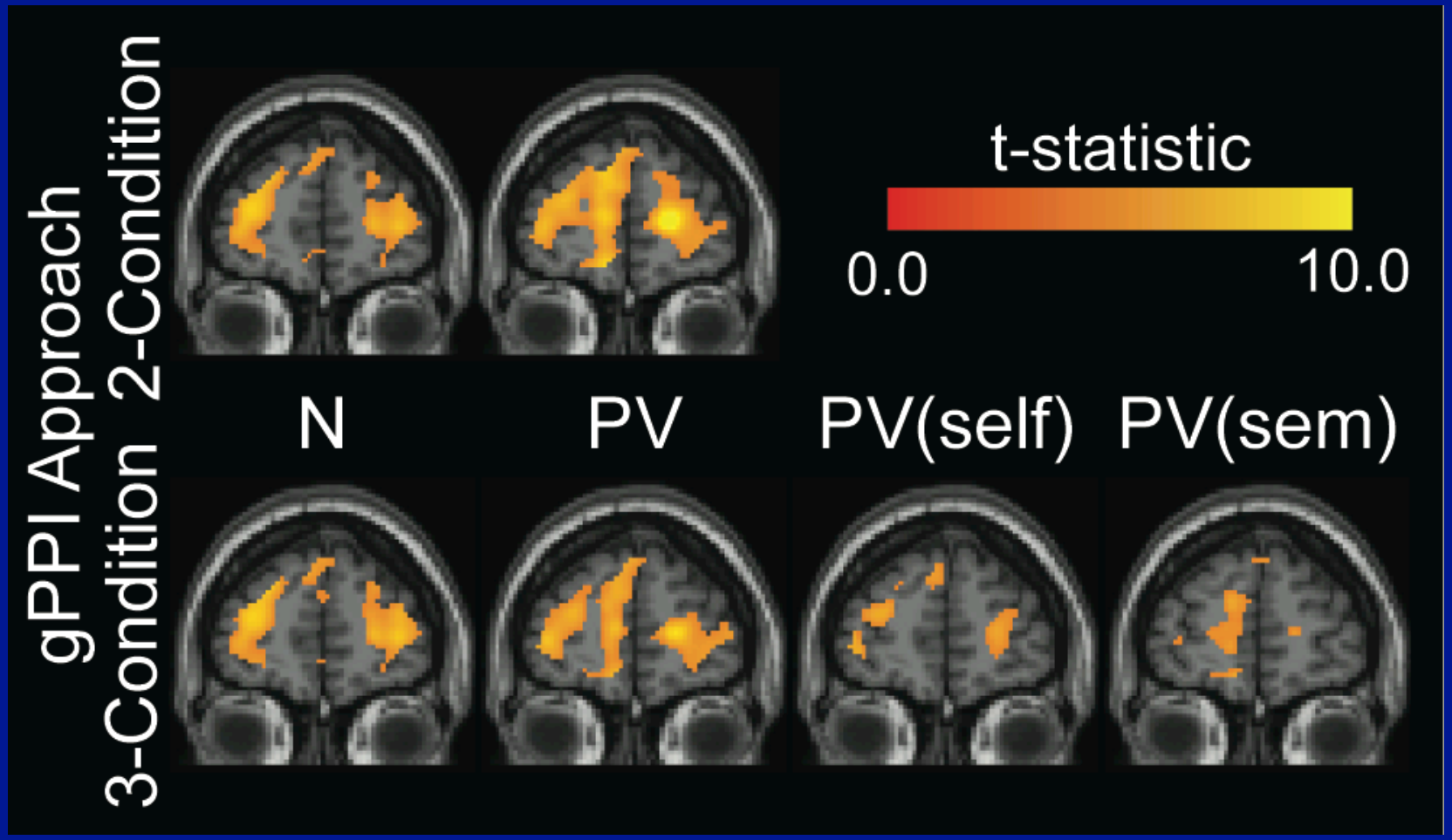
(McLaren et al. 2012)

sPPI vs gPPI=Model Fit



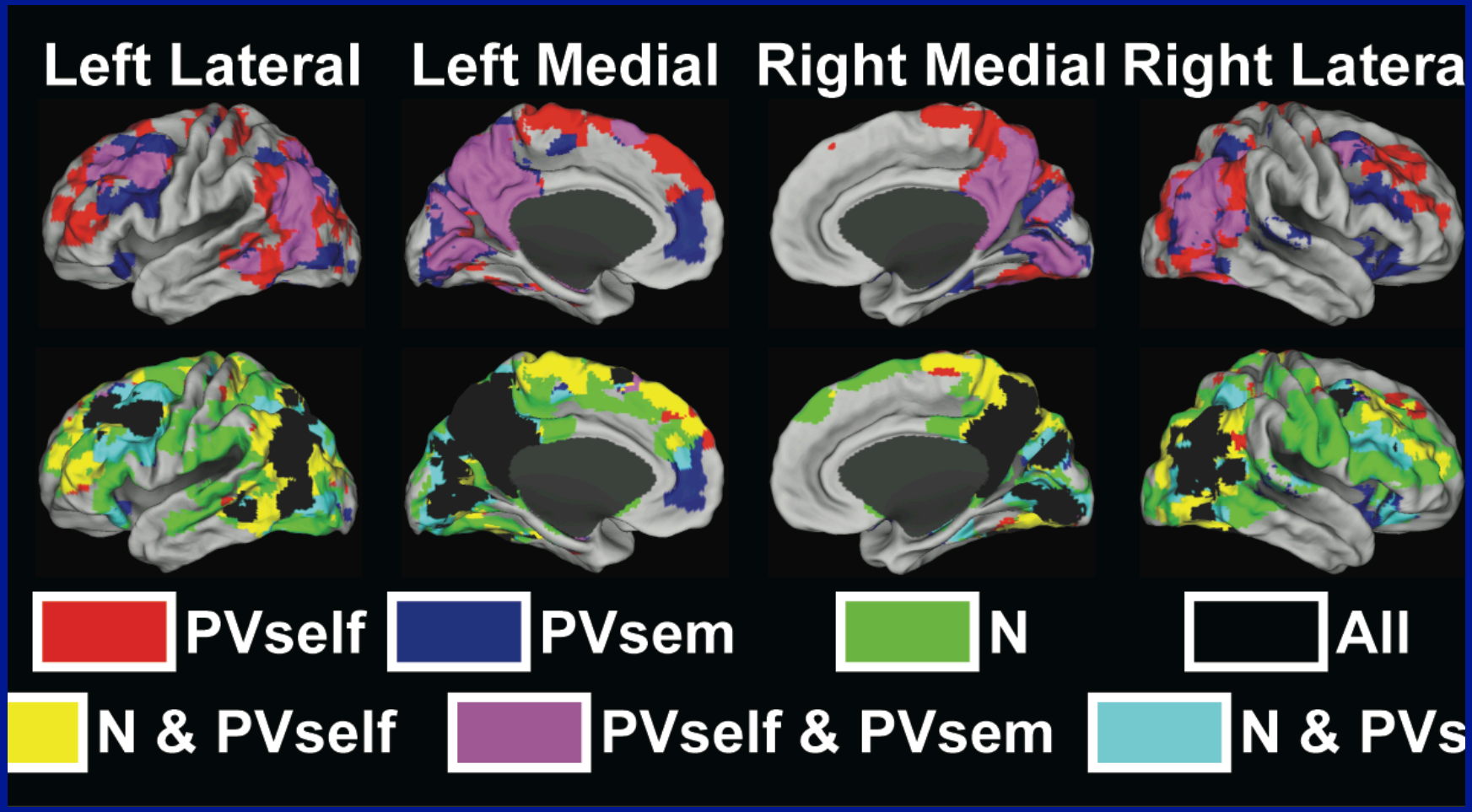
(McLaren et al. 2012)

Flexibility of gPPI



(McLaren et al. 2012)

Conjunctions – Where Are Tasks Similar



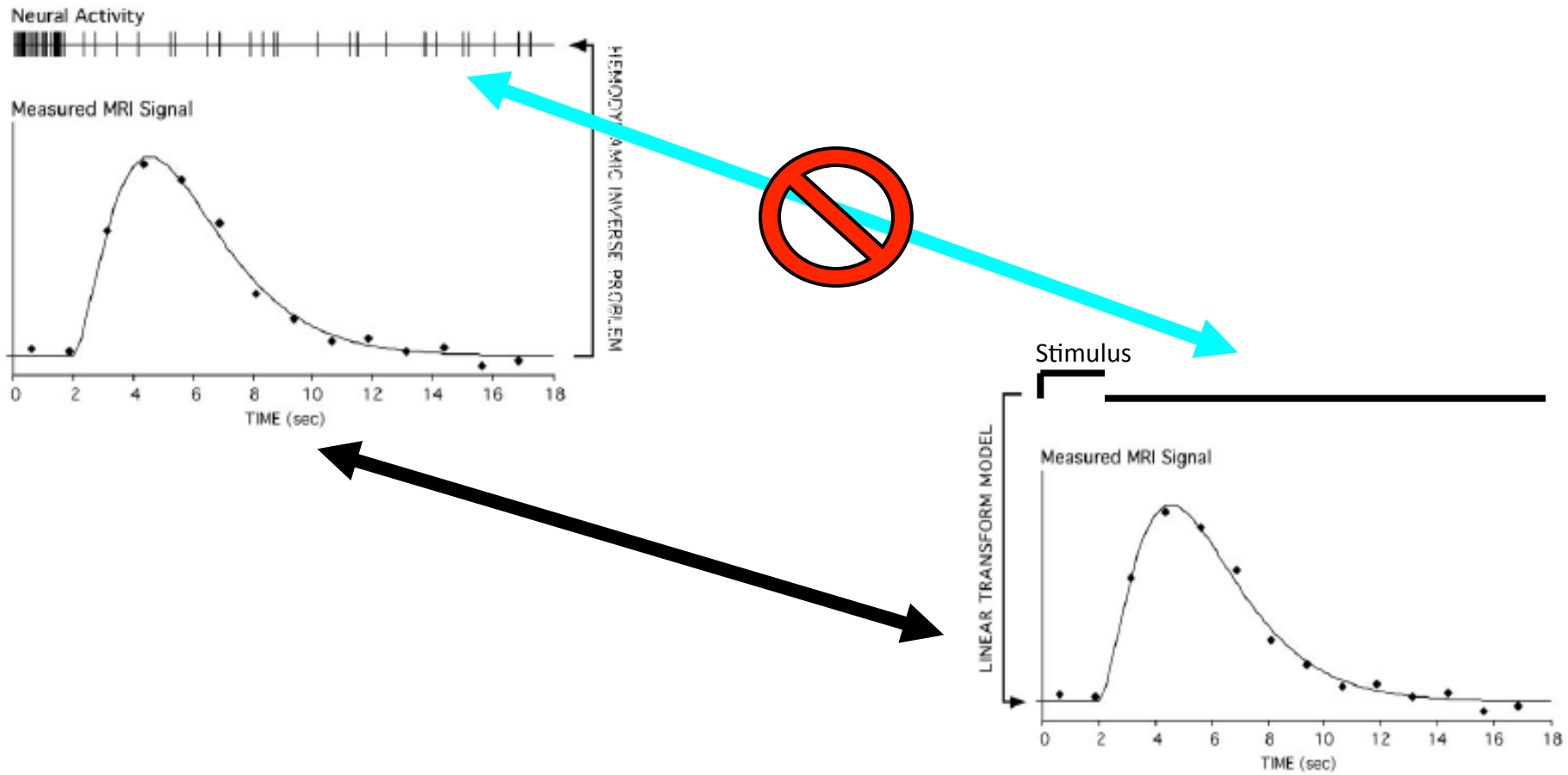
(McLaren et al. 2012)

Conclusions

- Increased accuracy of the connectivity model
- Increased sensitivity and specificity
- Get the connectivity for each task
- Only requires a single model
- Fully Automated

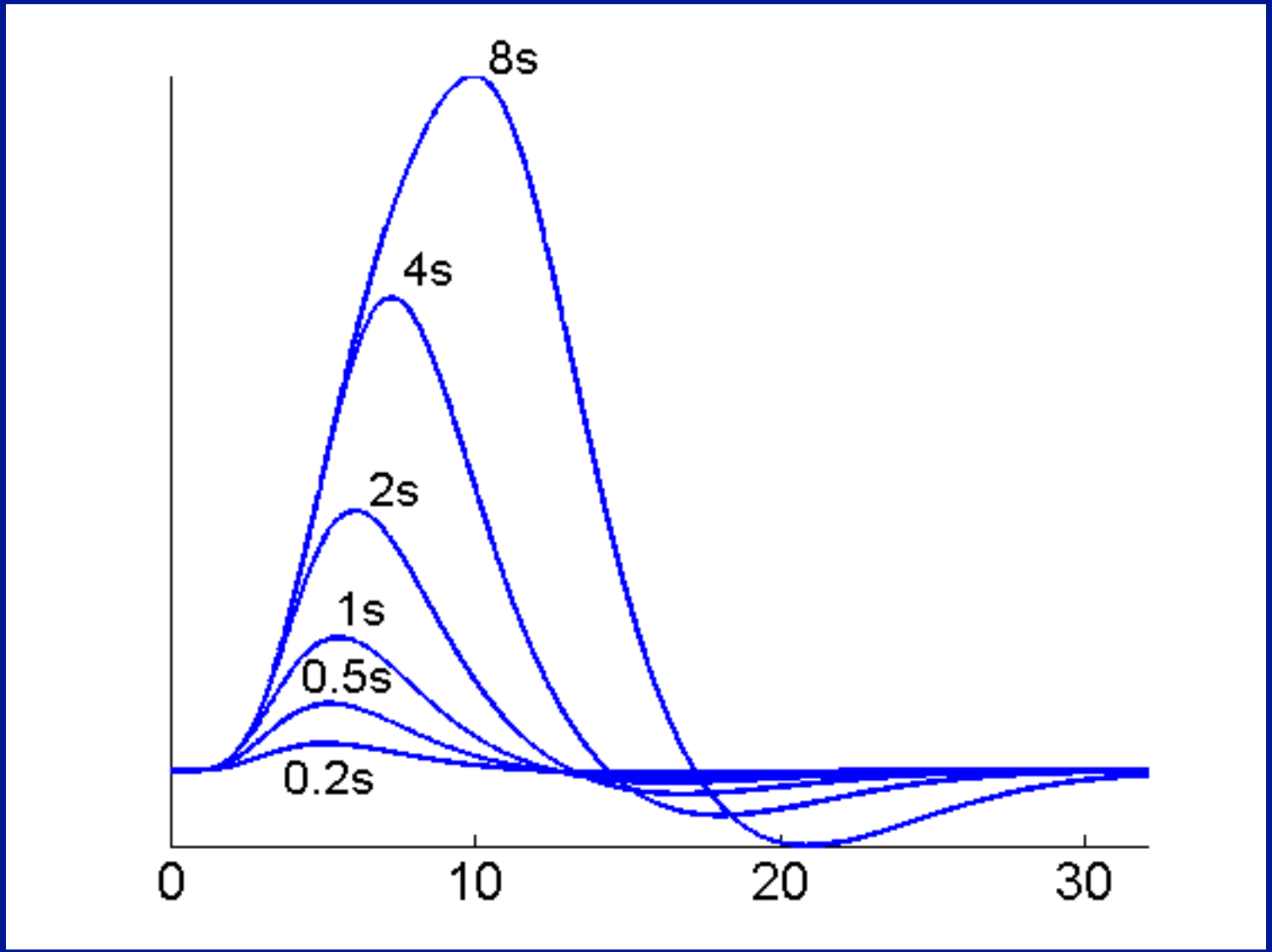
Practical

Caveat 1: The Inverse Problem

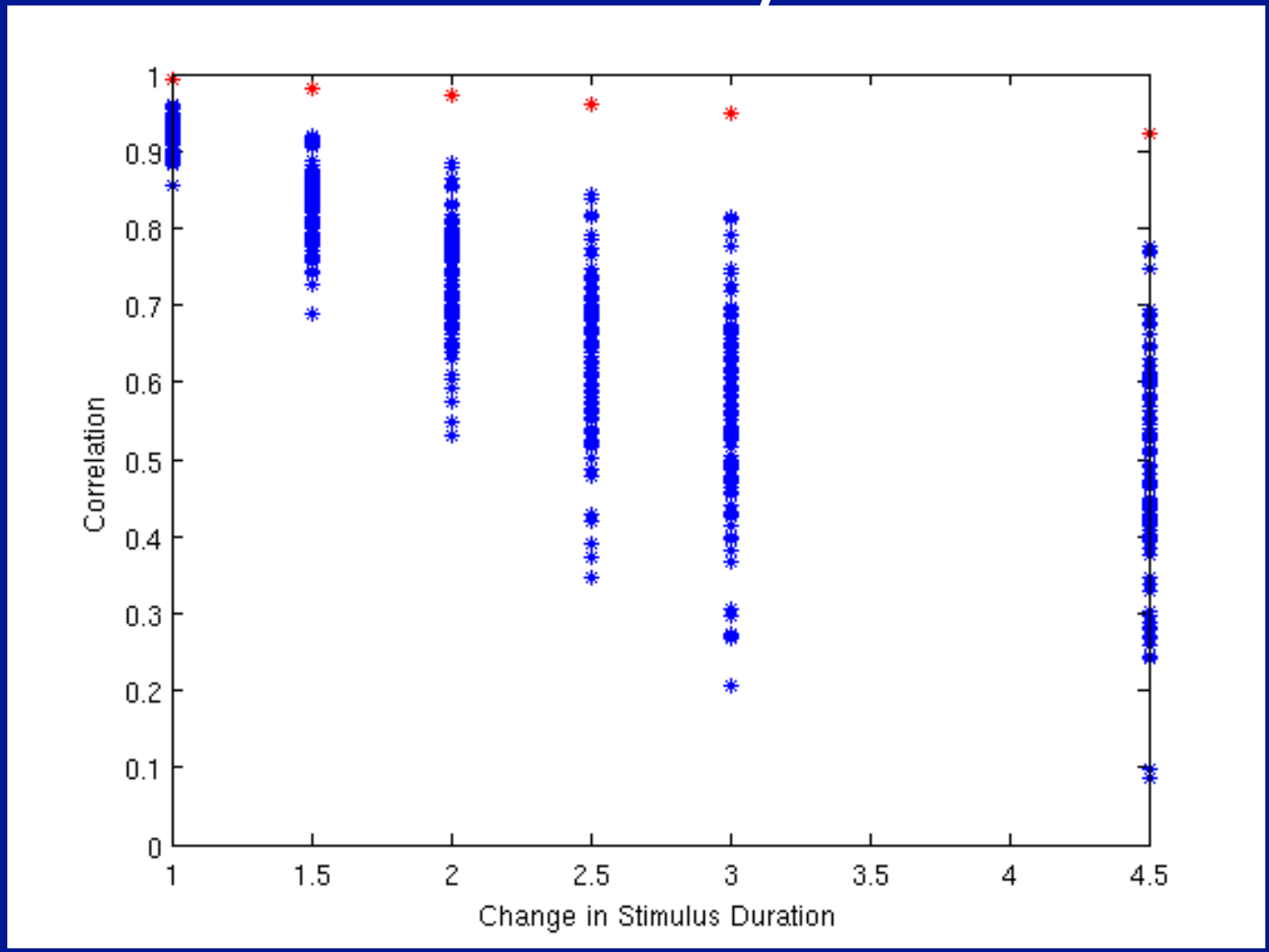


(Adapted from Bucker 2003)

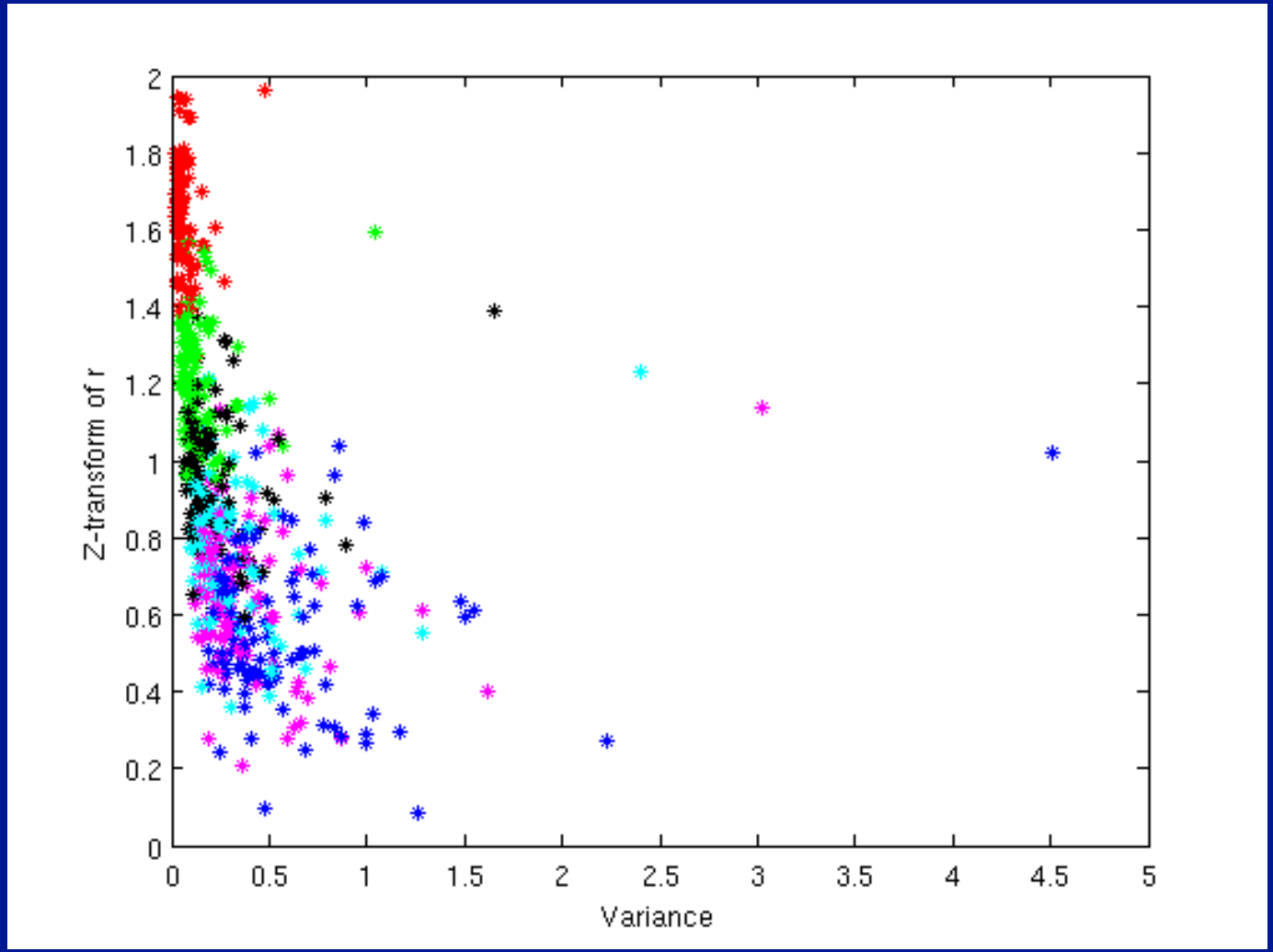
The Inverse Problem: Task Duration



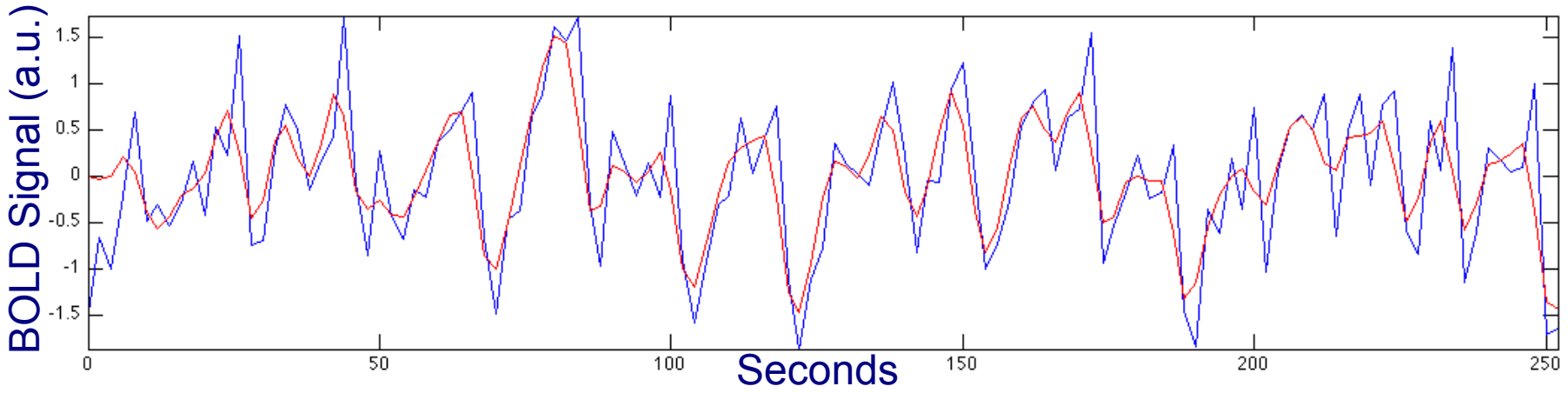
The Inverse Problem: Neuronal Activity and PPI

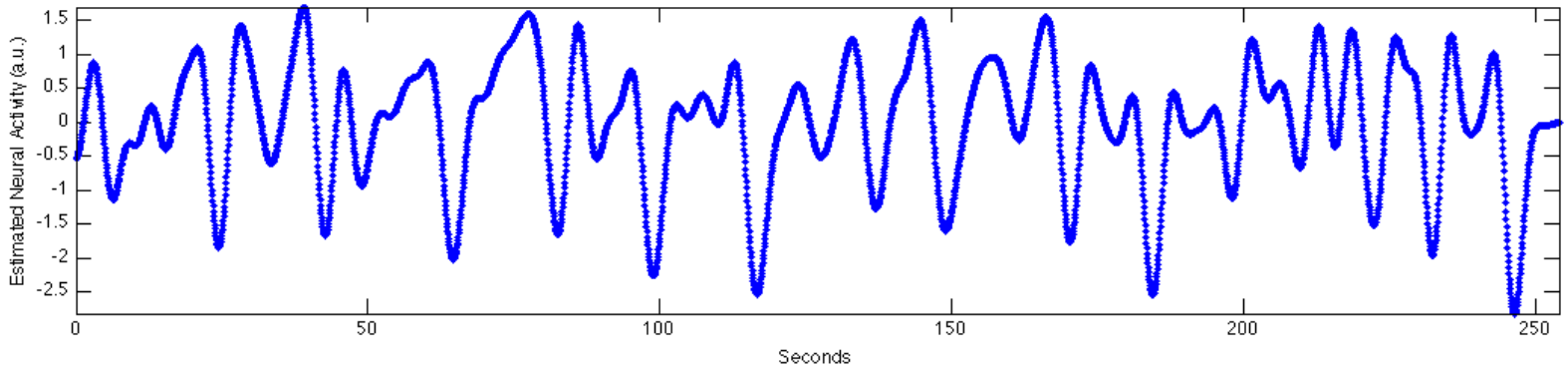


Caveat 1=Neuronal Activity

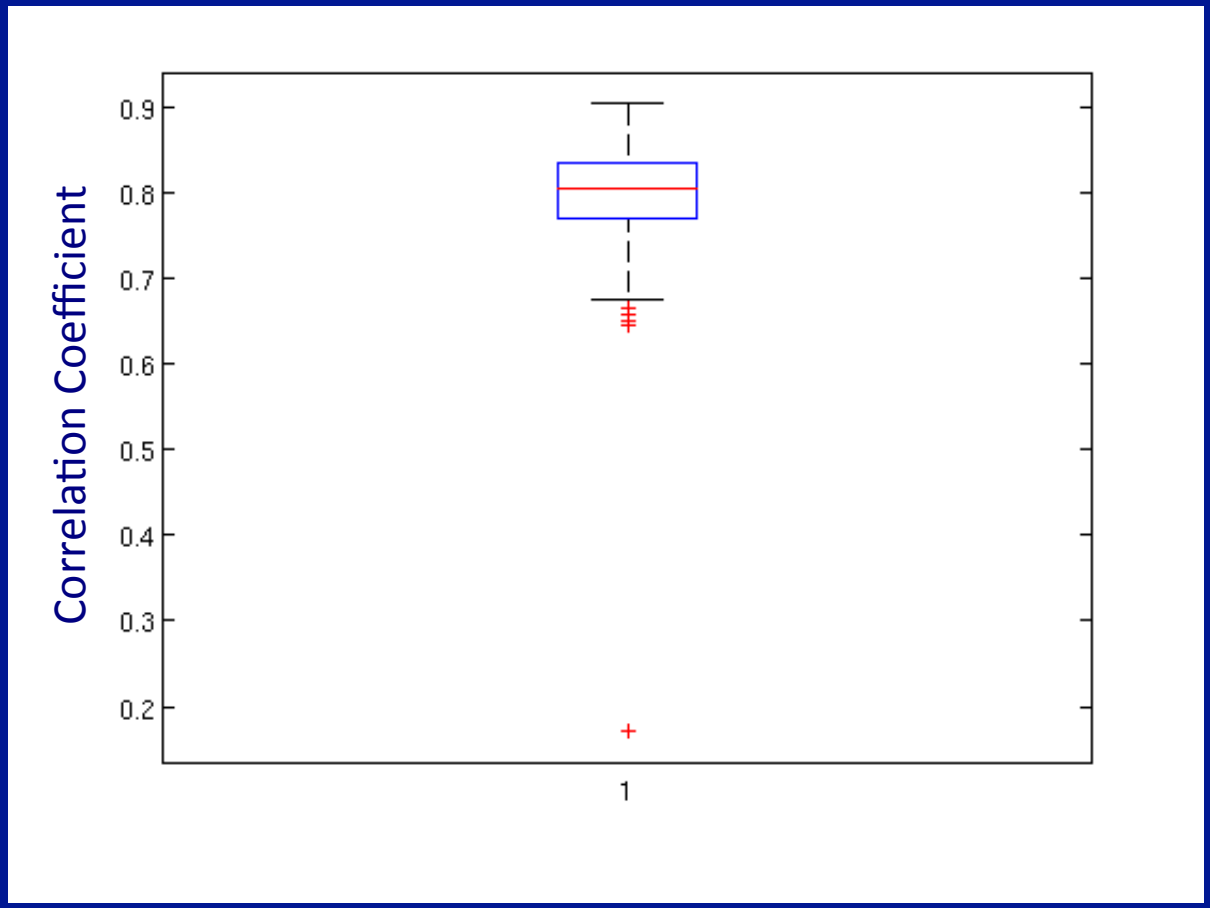


Estimated Neural Activity





Estimated Neural Activity



Analysis in progress

- QC of deconvolution and trial duration

Caveat 2

- PPI is only as good as your model

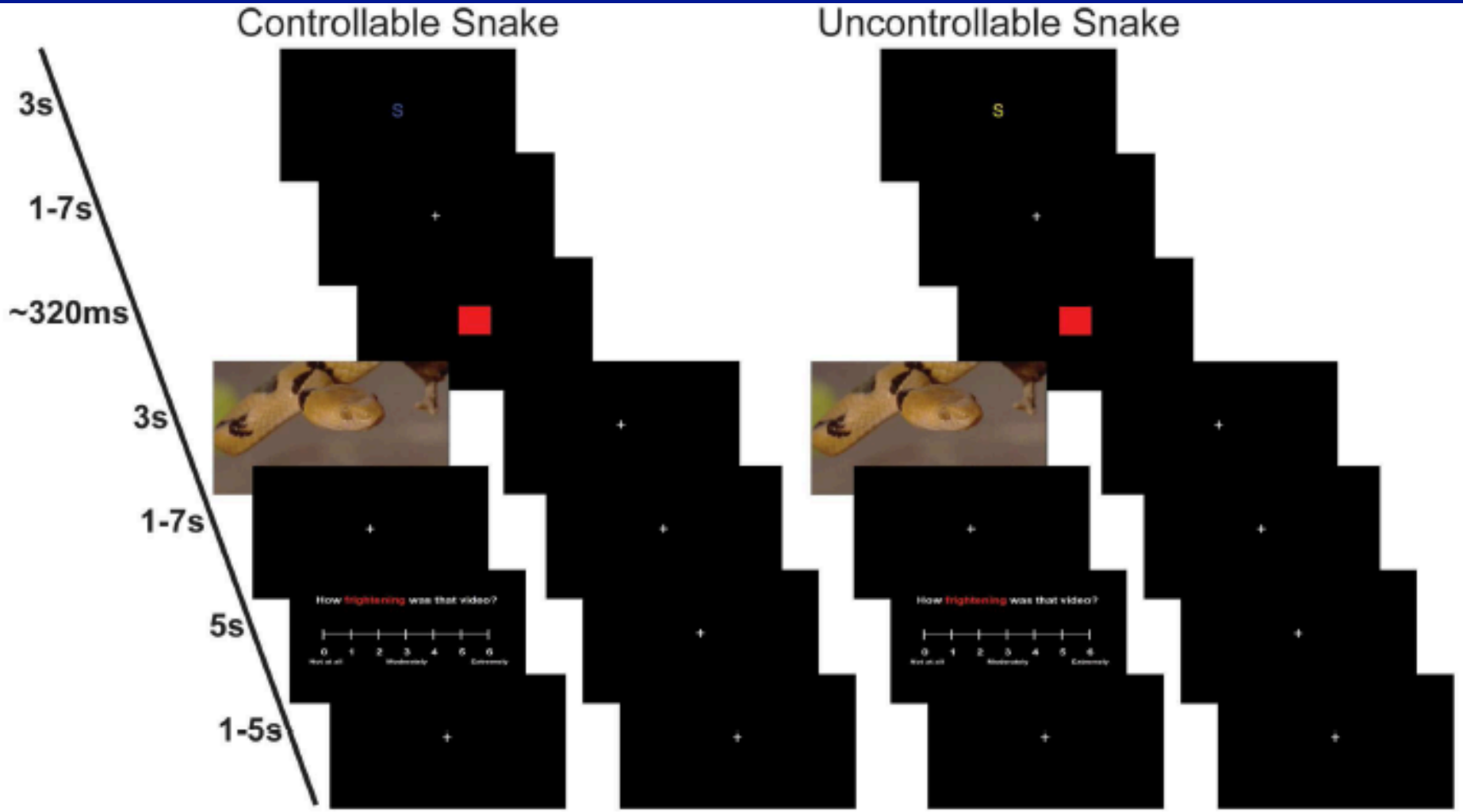
Caveat 3: Collinearity due to few trials

- Analysis in progress to show these effects and concatenation as a solution

Applications

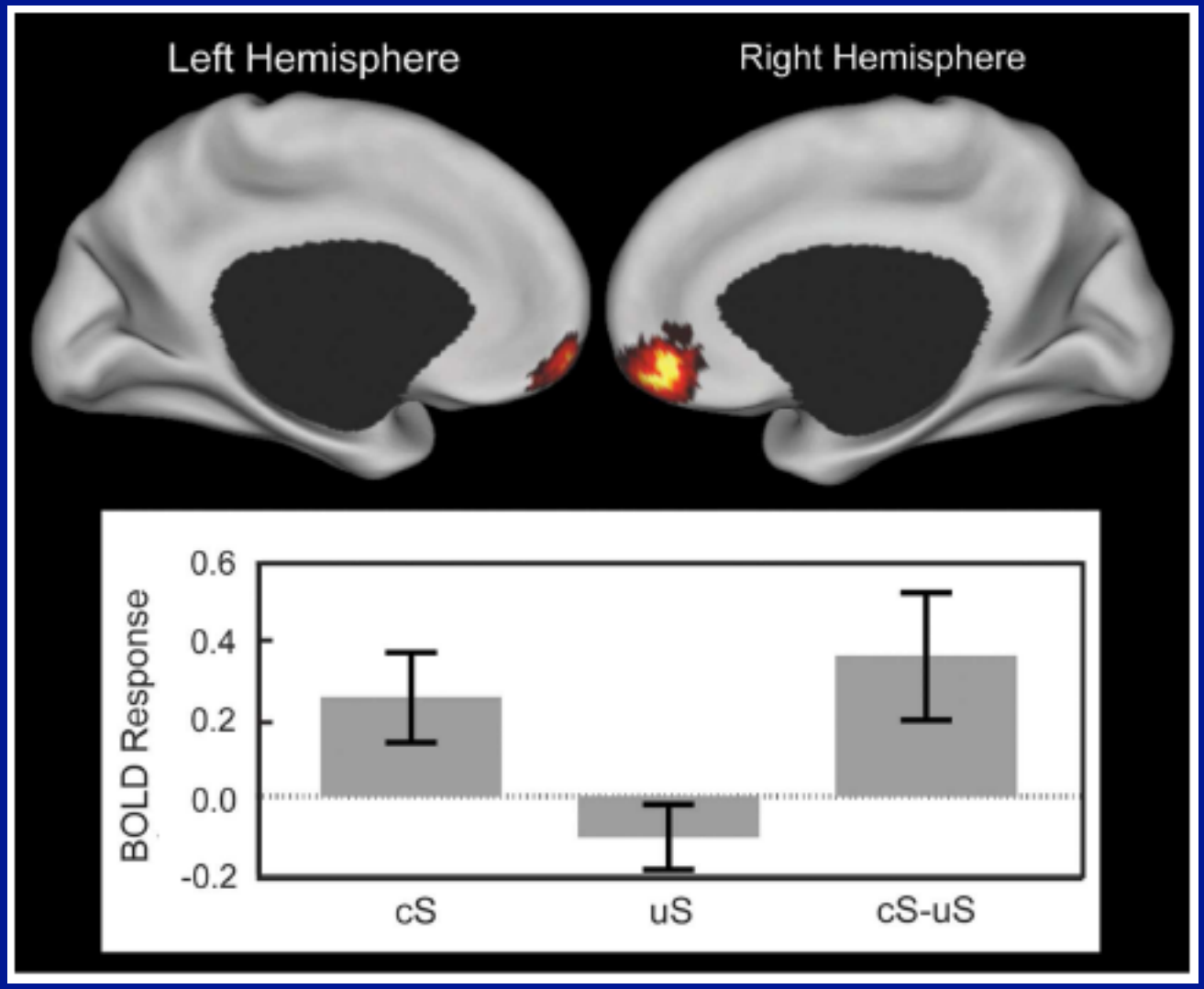
- Snake Phobia
- Swallowing
- Brain-Behavior Correlations
- Pharmacology

Controllability in Snake Phobics



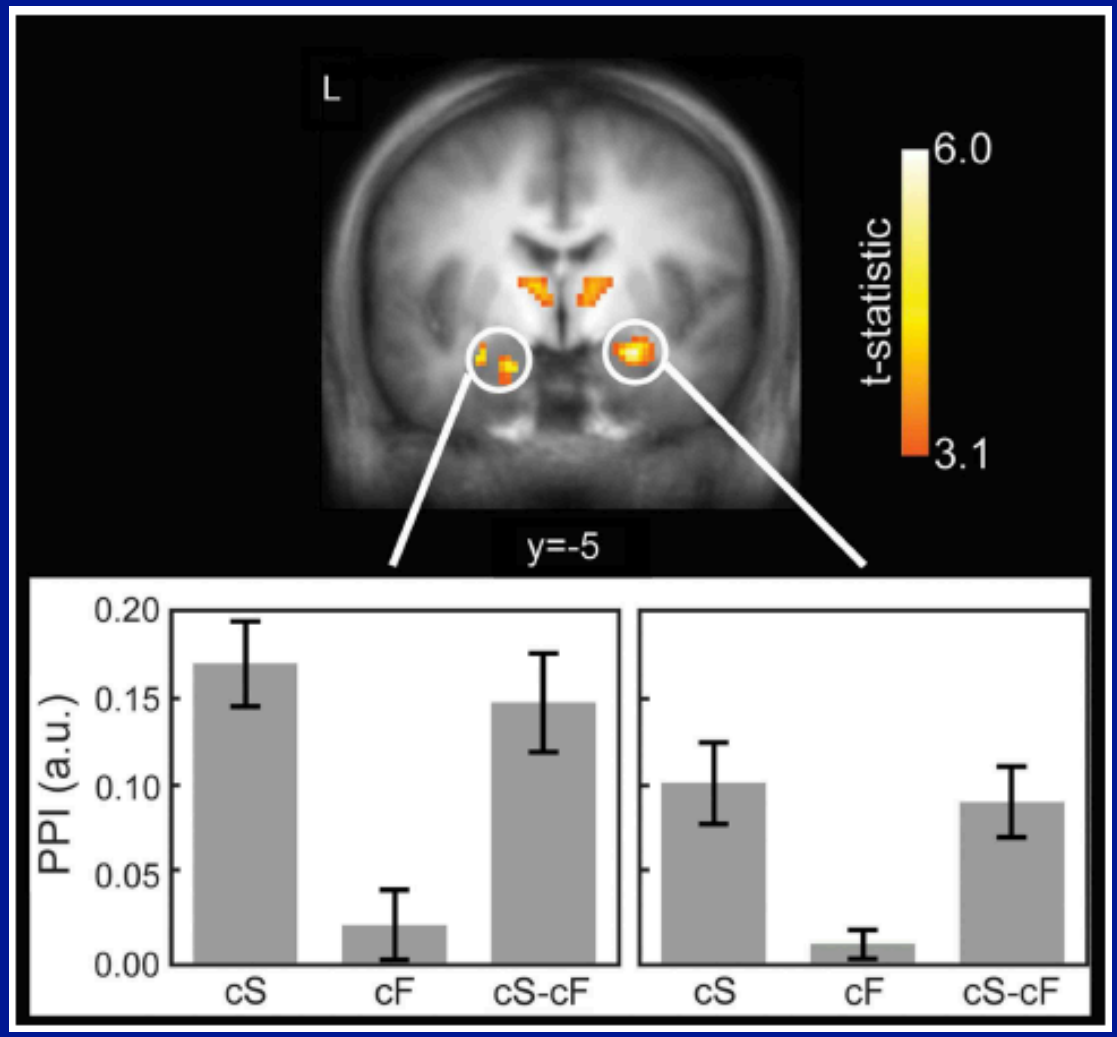
(Kerr et al. 2012/3)

Controllability in Snake Phobics



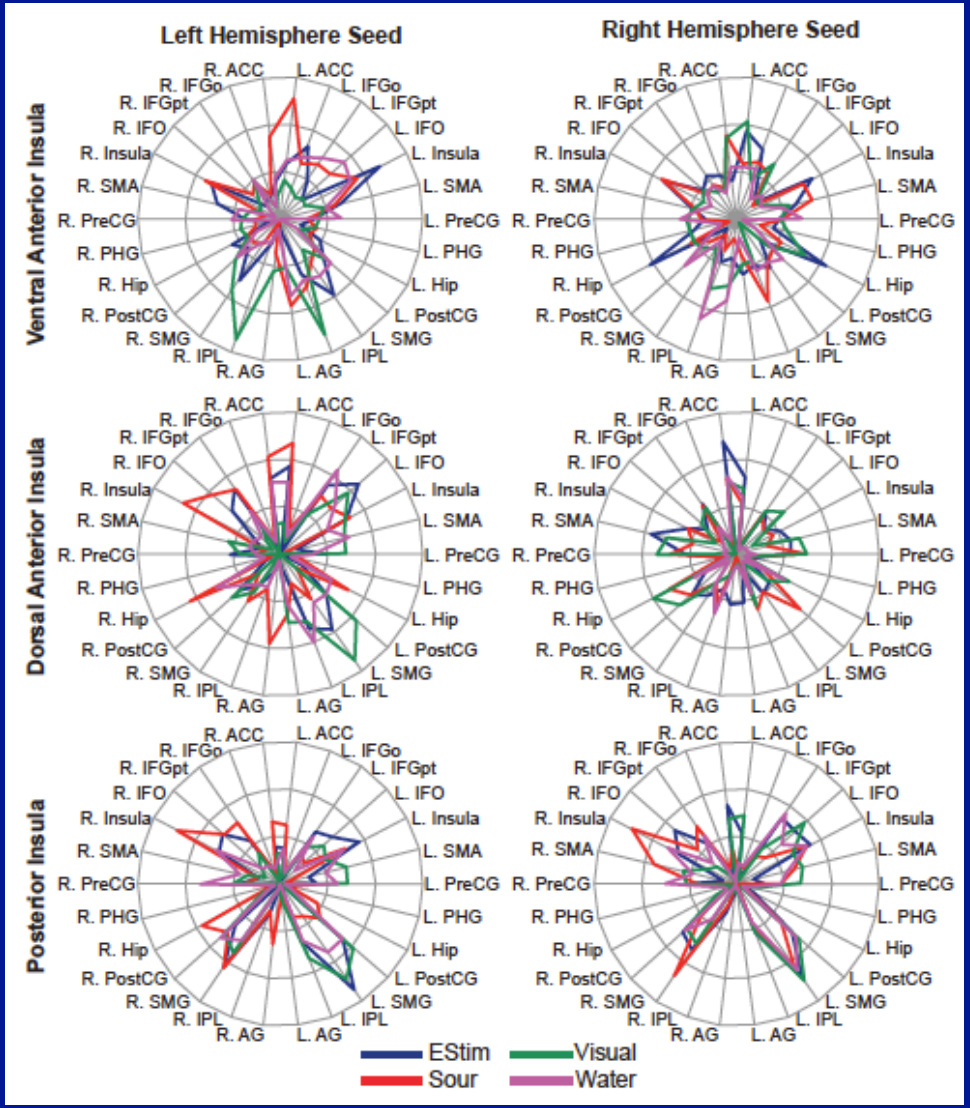
(Kerr et al. 2012/3)

Controllability in Snake Phobics



(Kerr et al. 2012/3)

Swallowing



(Humbert and McLaren, *in prep*)

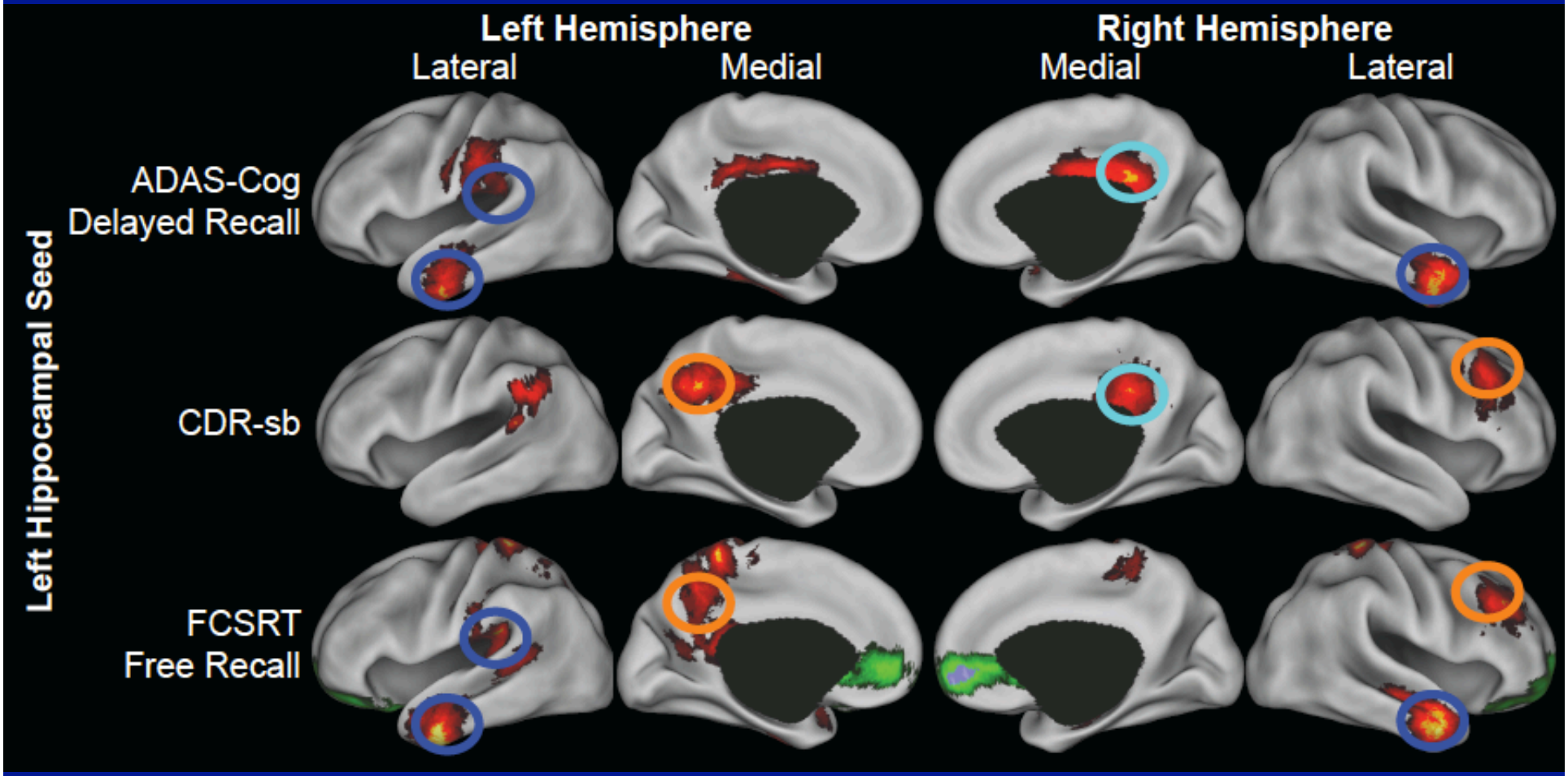
Correlations with Cognition in AD

(McLaren et al., *in prep*)

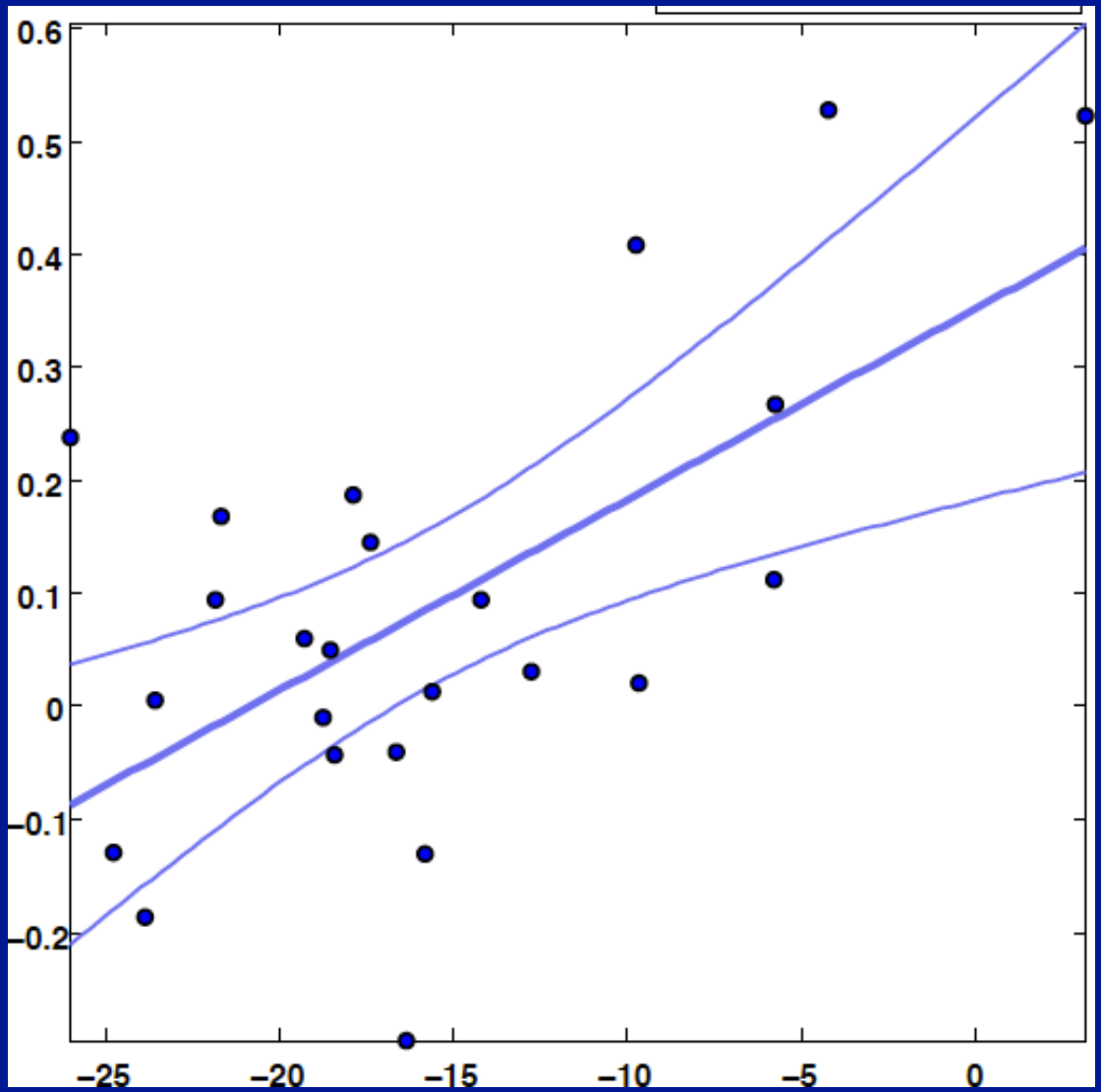
Task Stimuli

Task Stimuli

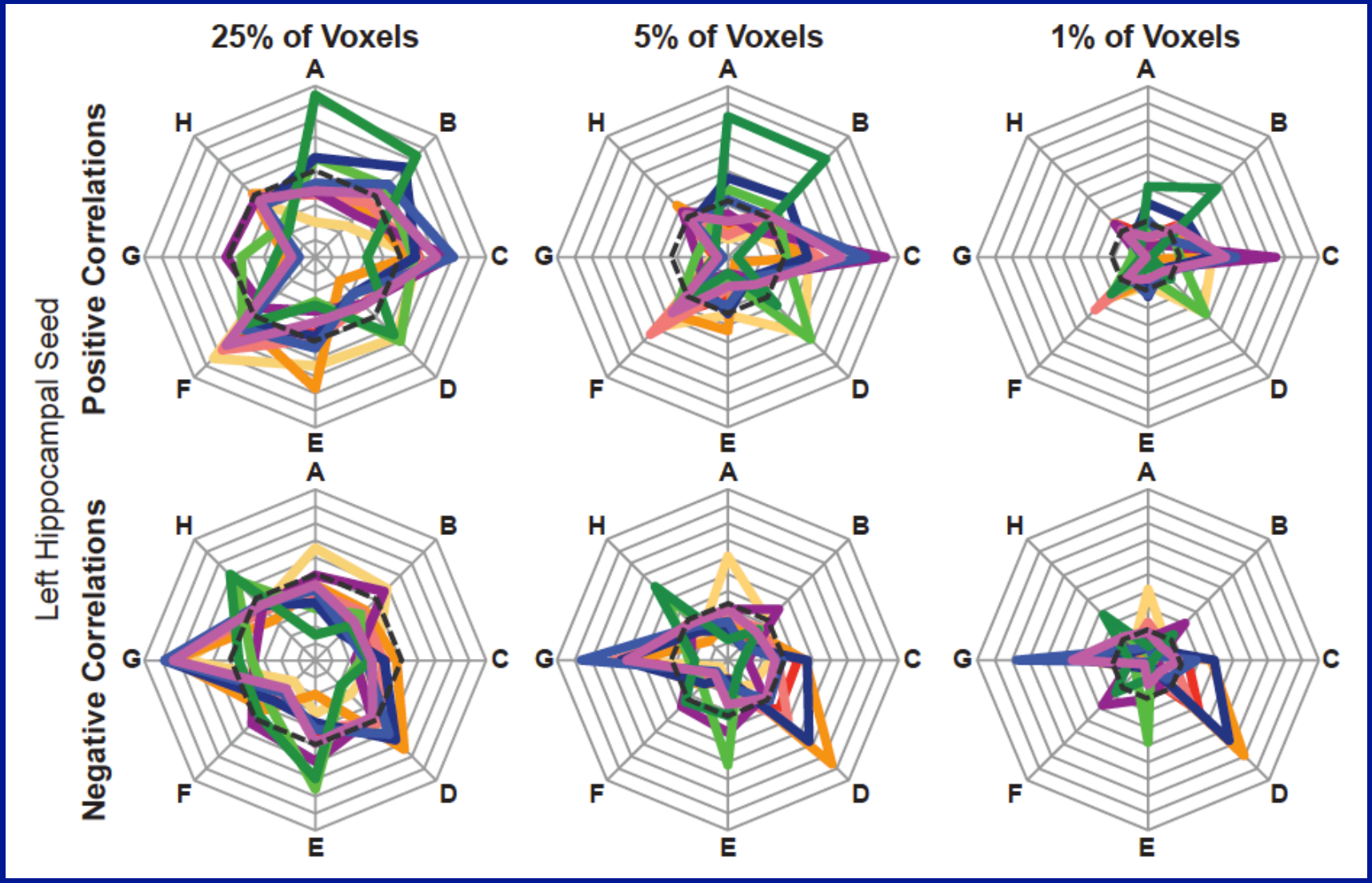
Correlations



Correlations



Correlations



Future Directions

- Integrate fMRI task, gPPI, and CBF into our understanding of the brain
- Develop graph theory for gPPI
- Develop gPPI for the resting state
- Develop gPPI as a biomarker of cognitive function in preclinical AD

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