From Noise to Insight: Improving Neuroimaging Measurement for Credible and Reproducible Neuroscience

Ettore Ambrosini

About Me

I'm a researcher (better, a research worker) more than a Professor

I've 15 years of experience in designing experiments and collecting and analyzing data (and I still enjoy doing it)
→ I've tons of practical advices for you

I'm trying to use good research practices to do cumulative science

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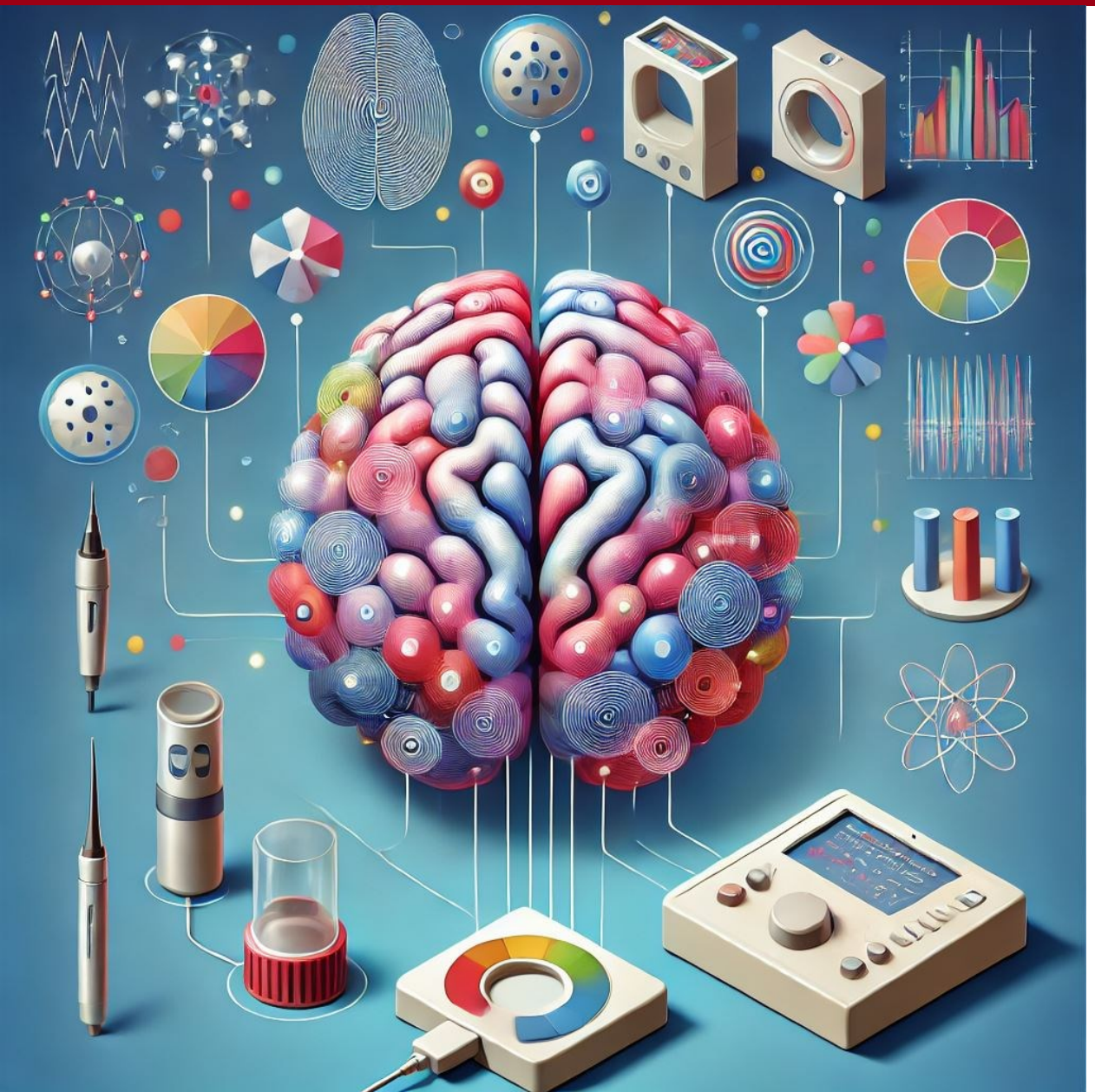
The Cornerstone of Credible (Neuro)science



Accurate and Precise Measurement

- Data interpretation
- Reproducibility of findings
- Cross-study comparisons
- Generalize results
- Creation of theoretical models

Scientific progress

From Noise to Insight: A (Neuro)scientist's Quest

The Promise:
We can unlock brain secrets!

vs.

The Reality:
It's messy…
very messy

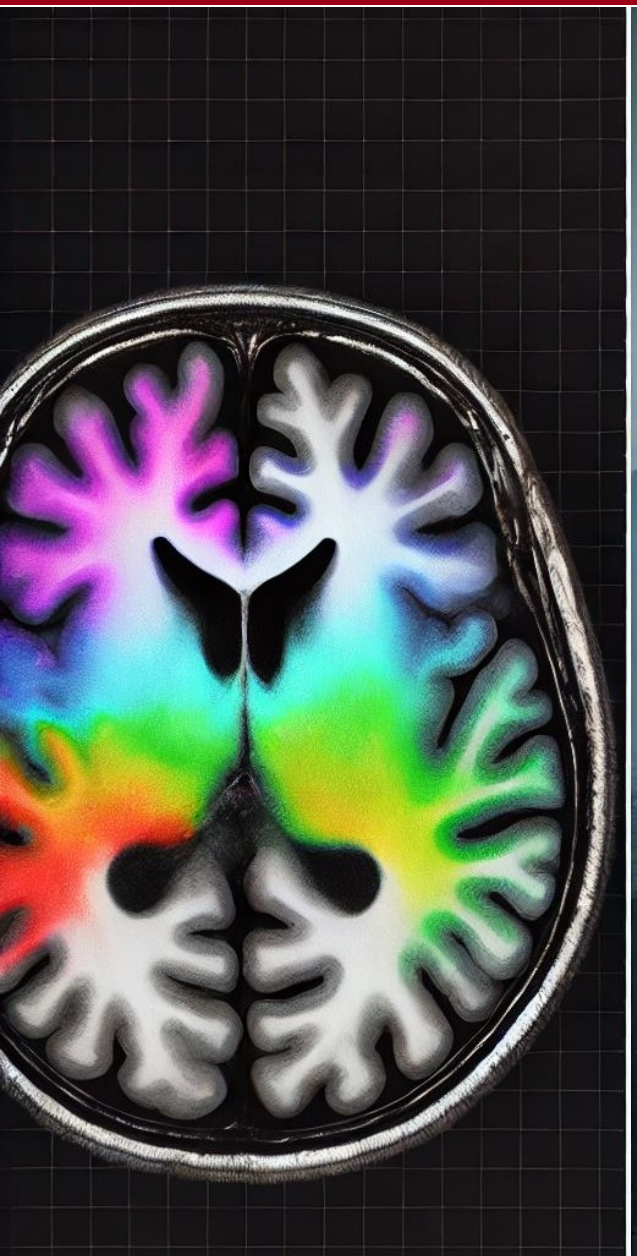
The Goal:
Credible, reproducible (neuro)science

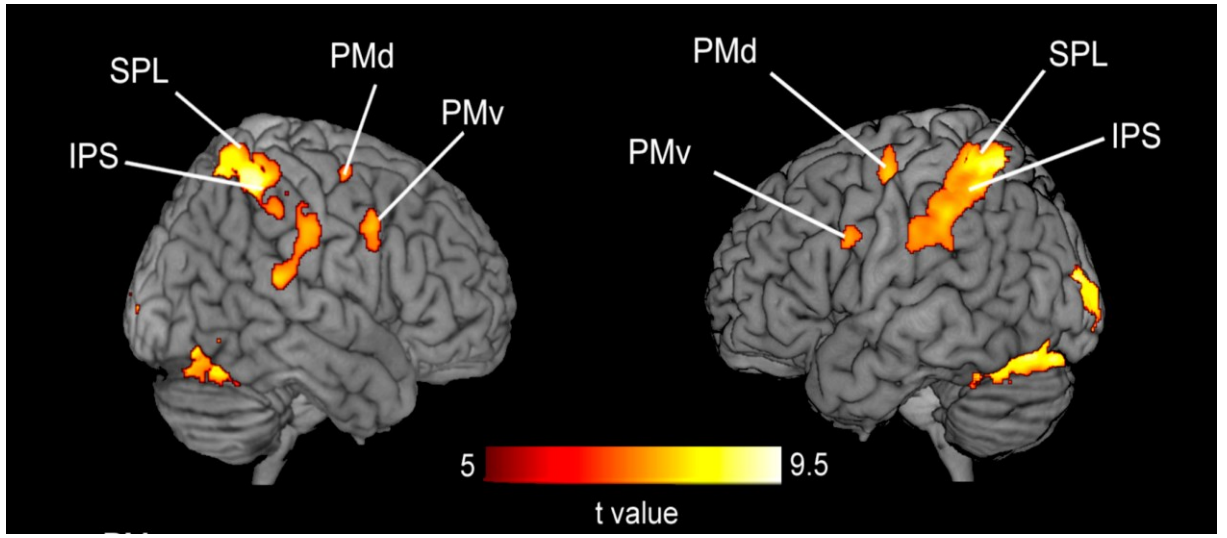
The Challenge:
Separate signal from noise

The Quest:
From messy data to reliable insights

What are we measuring?!?

fMRI Measures: Seeing the Lights, Missing the Action

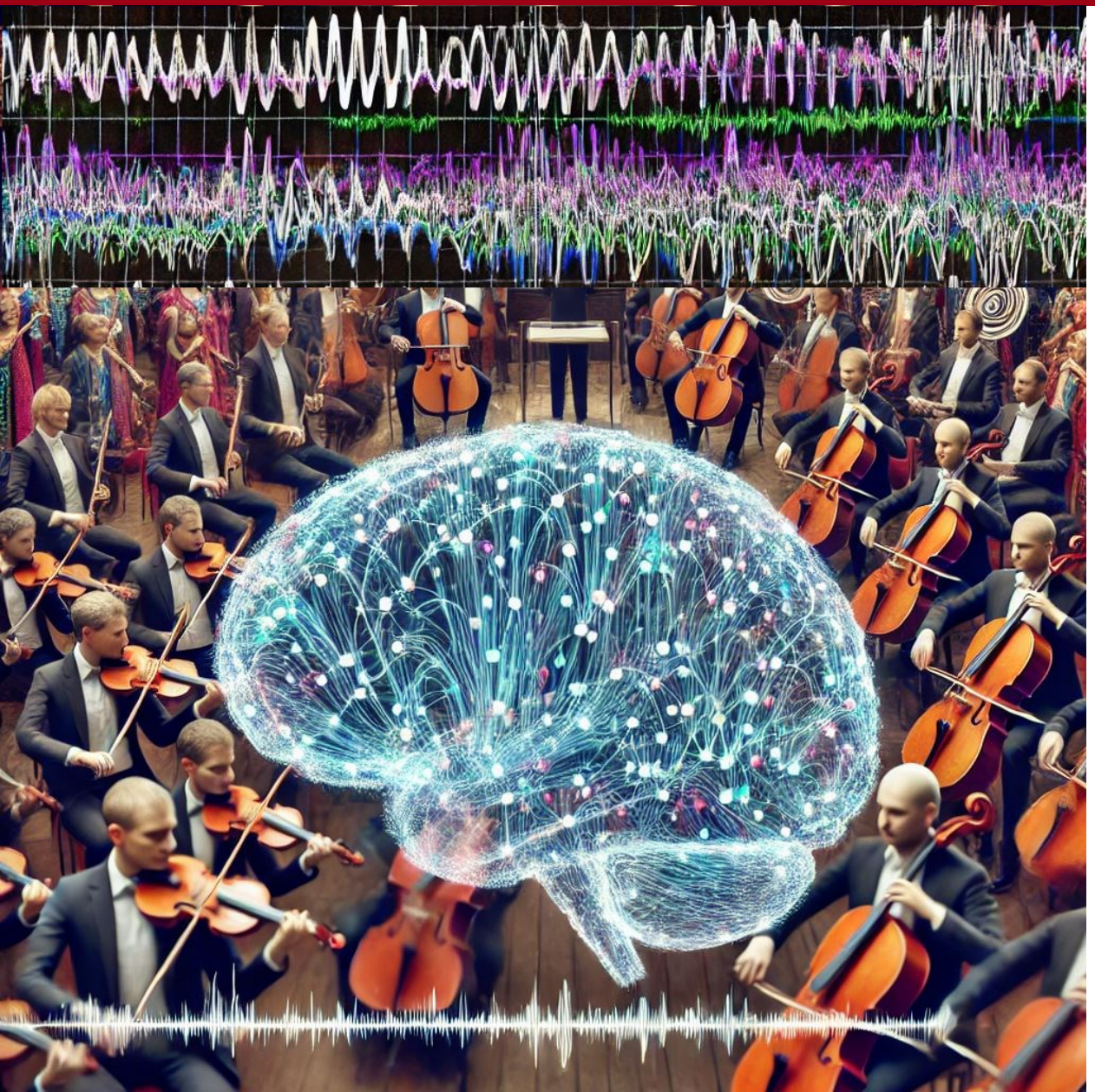


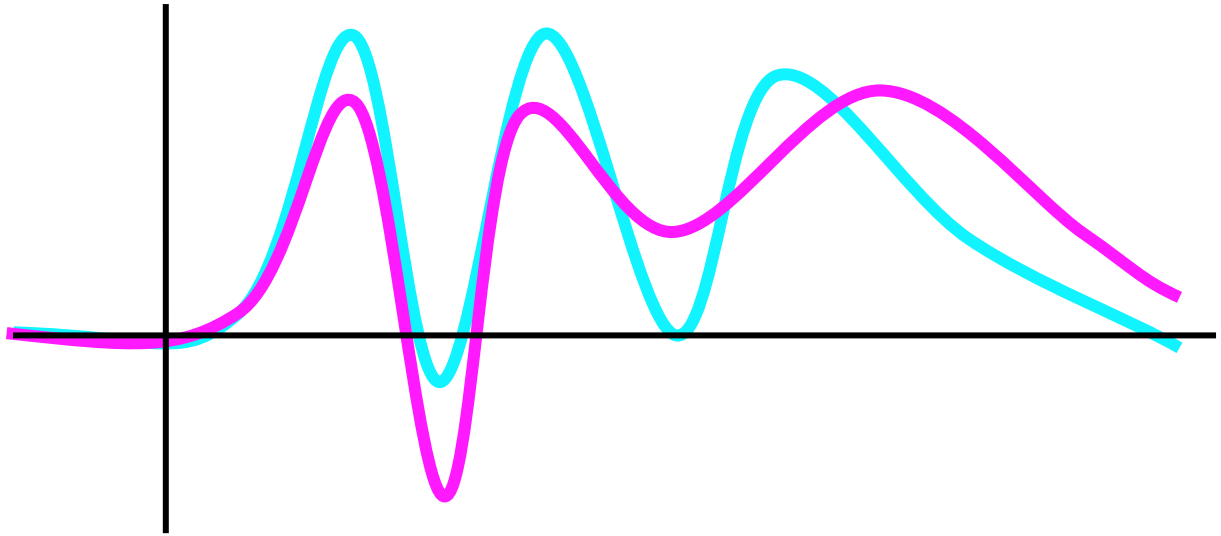


“Activation”
≠
Understanding function

We know something is happening…
…but not what’s going on!!!

The EEG Paradox: More Direct, yet More Ambiguous





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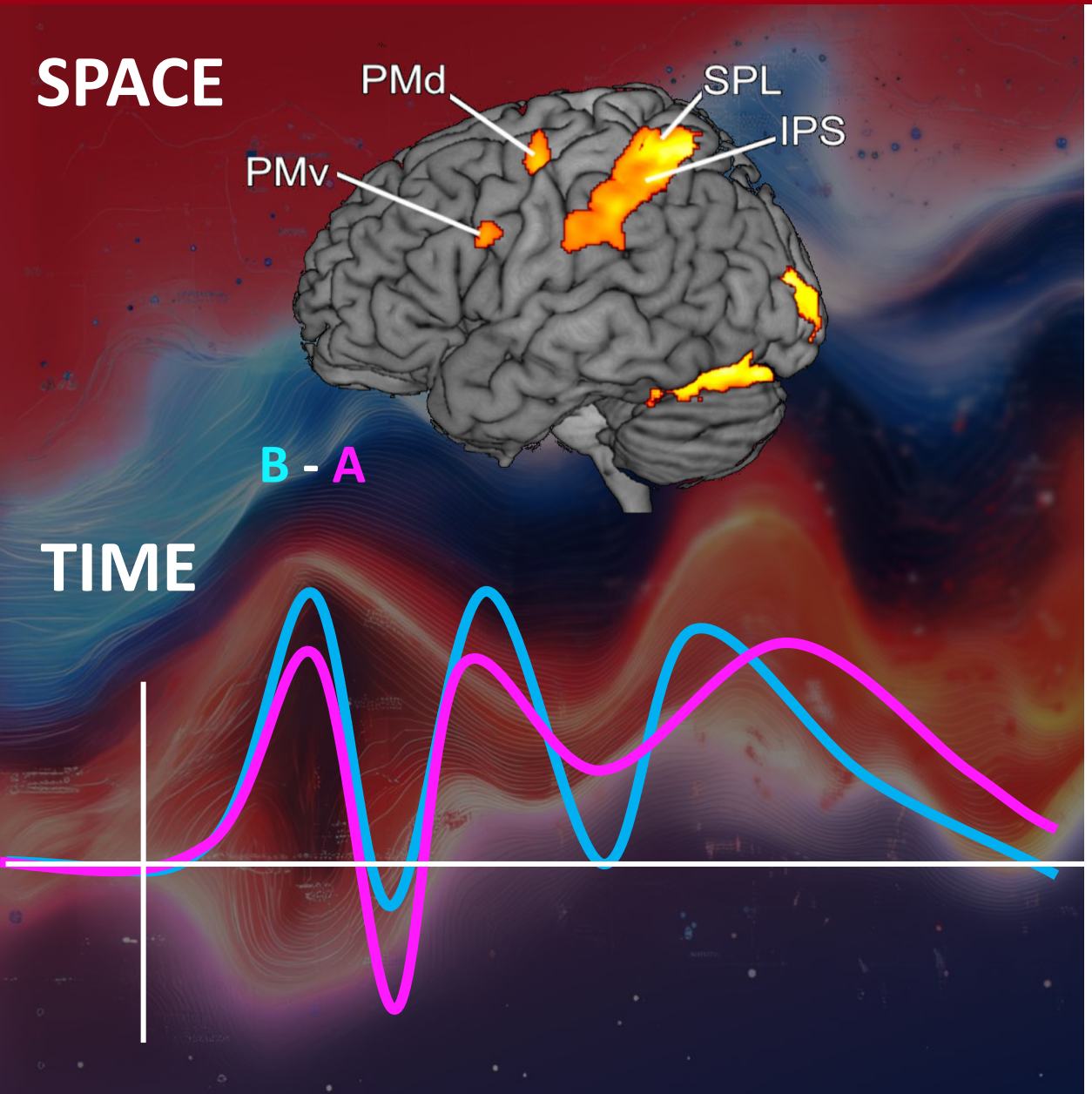
The Brain Signals Localization Problem(s)



COND B - COND A

PROCESS/ABILITY X

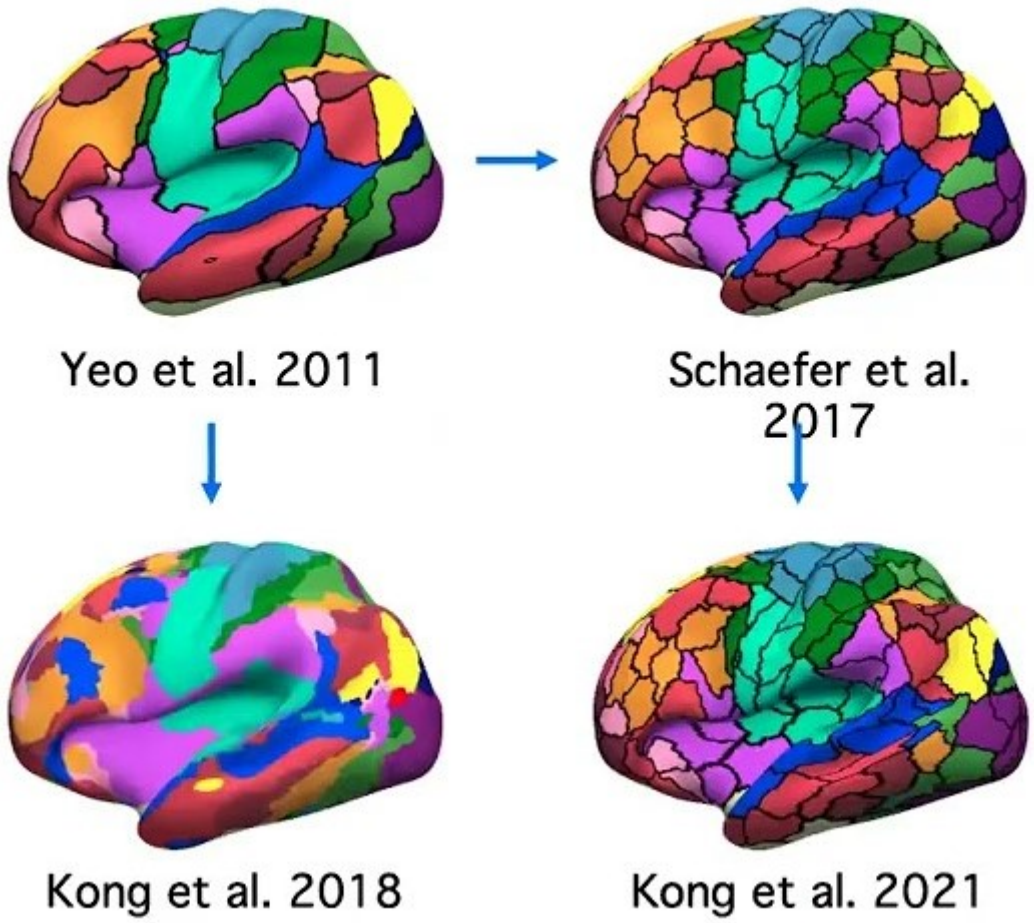
1) What's the function of that region/wave?

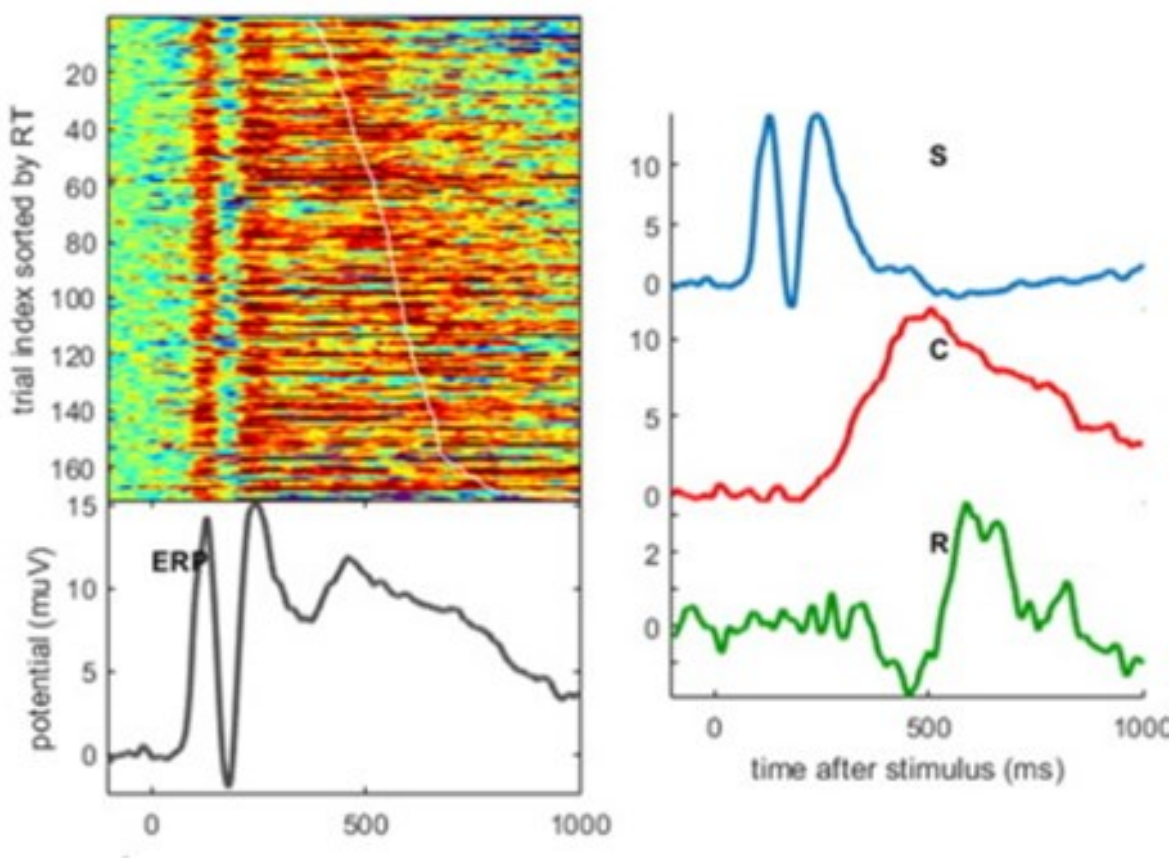
Where is the region X? (e.g., the Broca’s area)

When is the wave X? (e.g., the P3 ERP)

The Brain Signals Localization Problem(s)

We don’t even know how do define/isolate “regions” and “waves”!!!





Why do we have a brain?

INTERNAL WORLD

Memories
Goals

EXTERNAL WORLD

Senses

EXTERNAL WORLD

Actions
(Language)

List the cognitive functions that are important (to survive)

1.
2.
3.
4.
5.
6.
7.
8.
9.

Have you ever heard of Functional Connectivity Networks? What do they mean (functionally)? List them

1.
2.
3.
4.
5.
6.
7.
8.
9.

List the cognitive fu

that are important (to

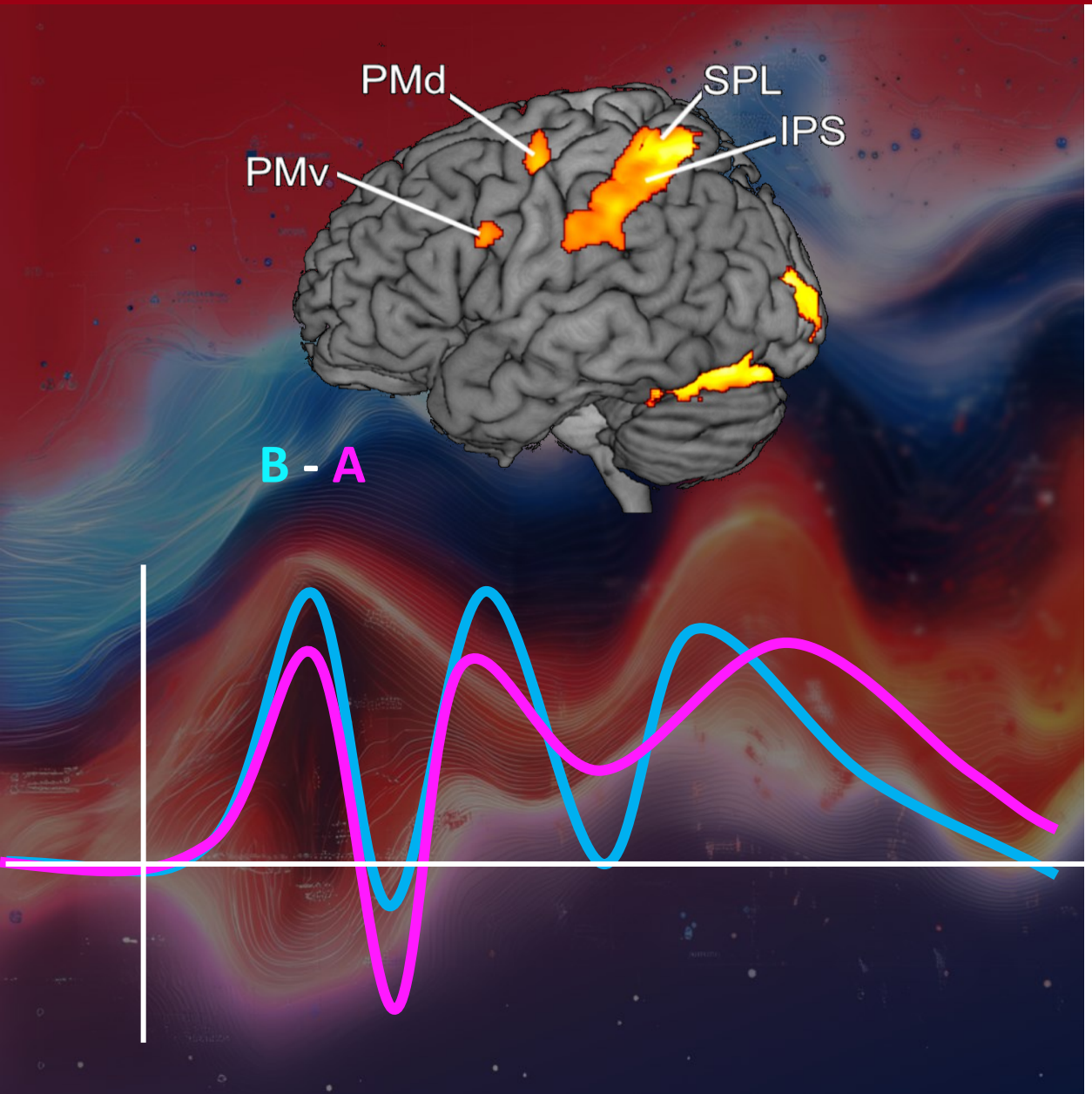
NOW CONNECT THEM!
SOMETHING STRANGE?

you ever heard of
Connectivity Networks?
What do they mean (functionally)?
List them

1.
2.
3.
4.
5.
6.
7.
8.
9.

1.
2.
3.
4.
5.
6.
7.
8.
9.

The Brain Signals Amplitude Problem



COND B - COND A

PROCESS/ABILITY X

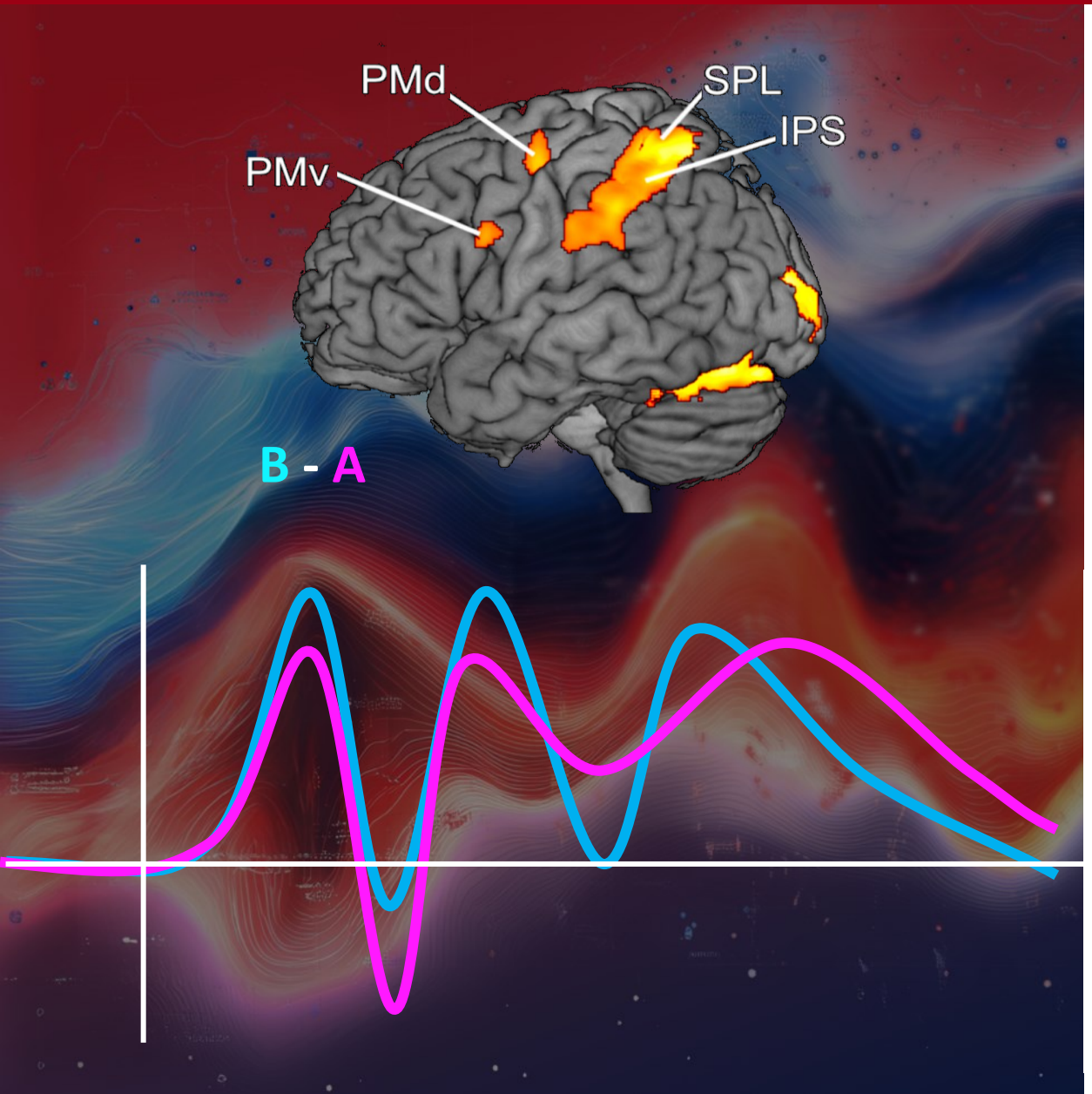
1) What's the function of that region/wave?

2) Larger signals not always mean stronger/better process/ability!


LET'S BEGIN, BUT FIRST
LET'S PLAY A GAME

Does it Measure Motor Inhibition? How/Why?

Interpretations Come with Implications!



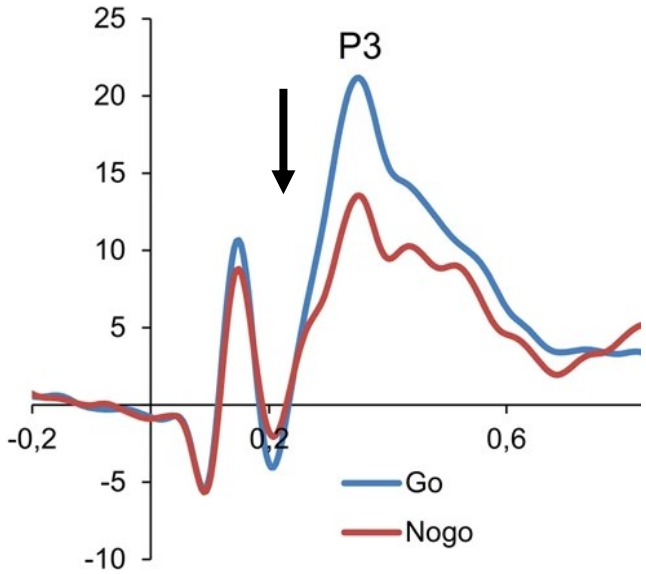
Test your interpretations!

NoGo - Go

Motor Inhibition

NoGo - Go

Motor Inhibition



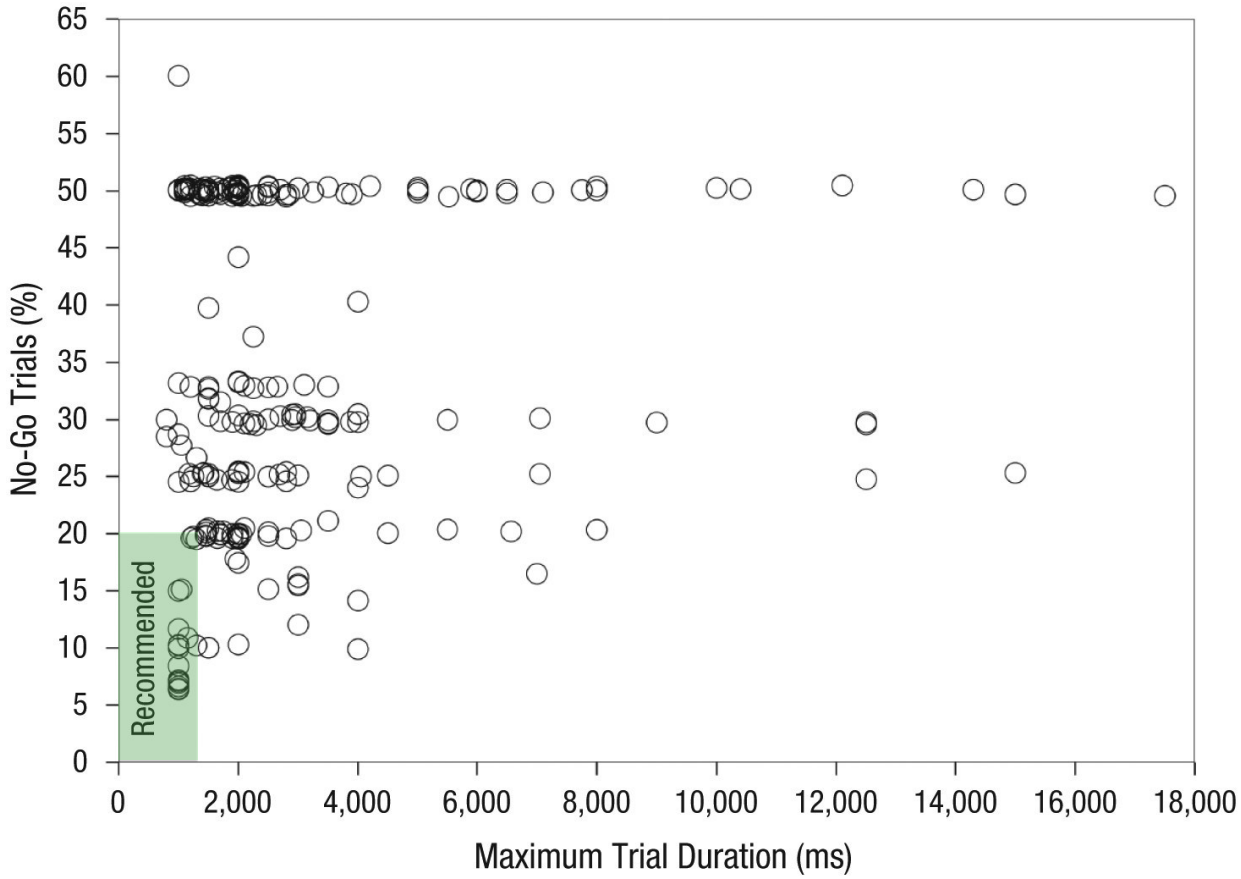
↓NoGo P3
=
↑Motor Inhib.

But Methodology is Key! You Must Know Your Stuff

Prepotent motor activity and inhibitory control demands in different variants of the go/no-go paradigm

Jan R. Wessel[1,2]

Paper



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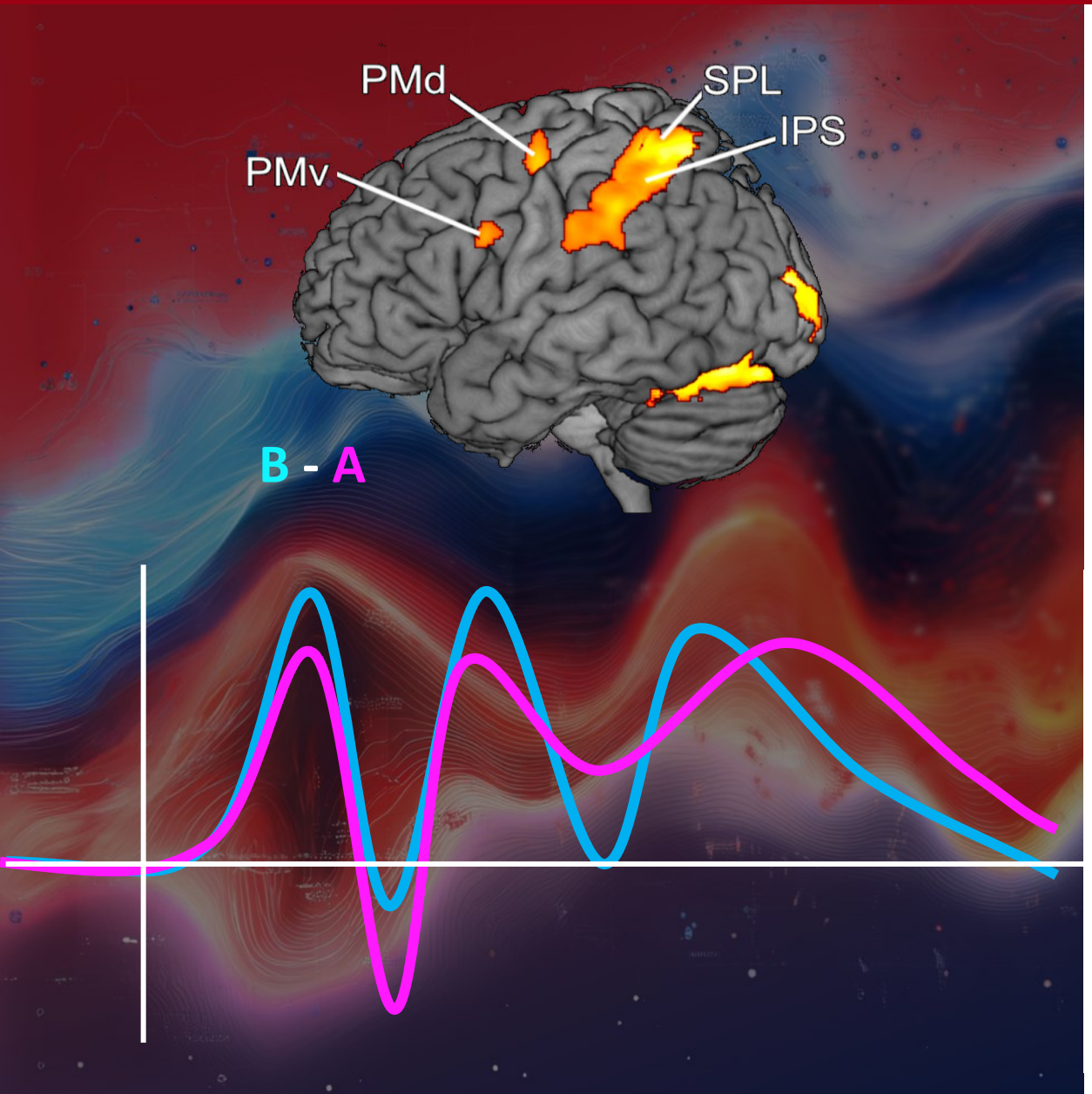

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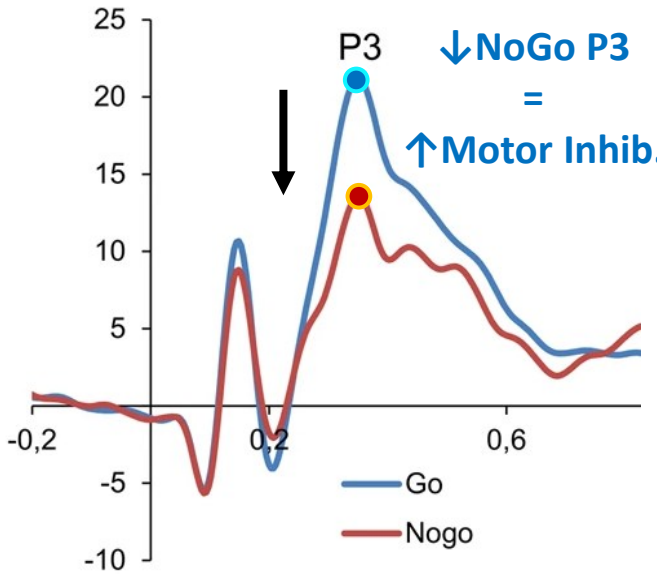

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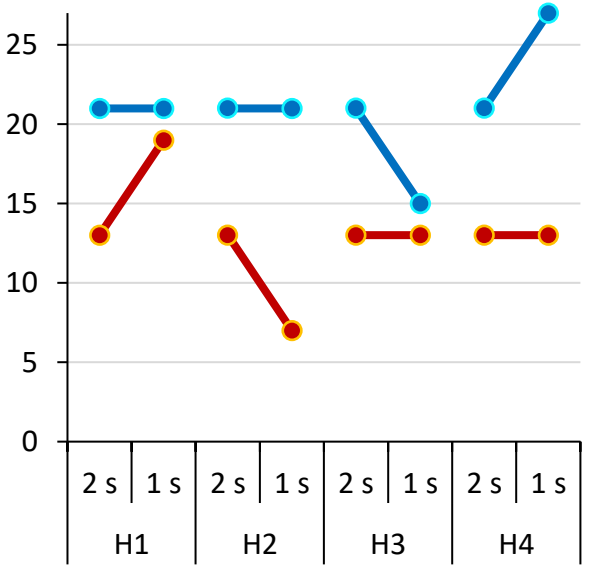
Motor Inhibition



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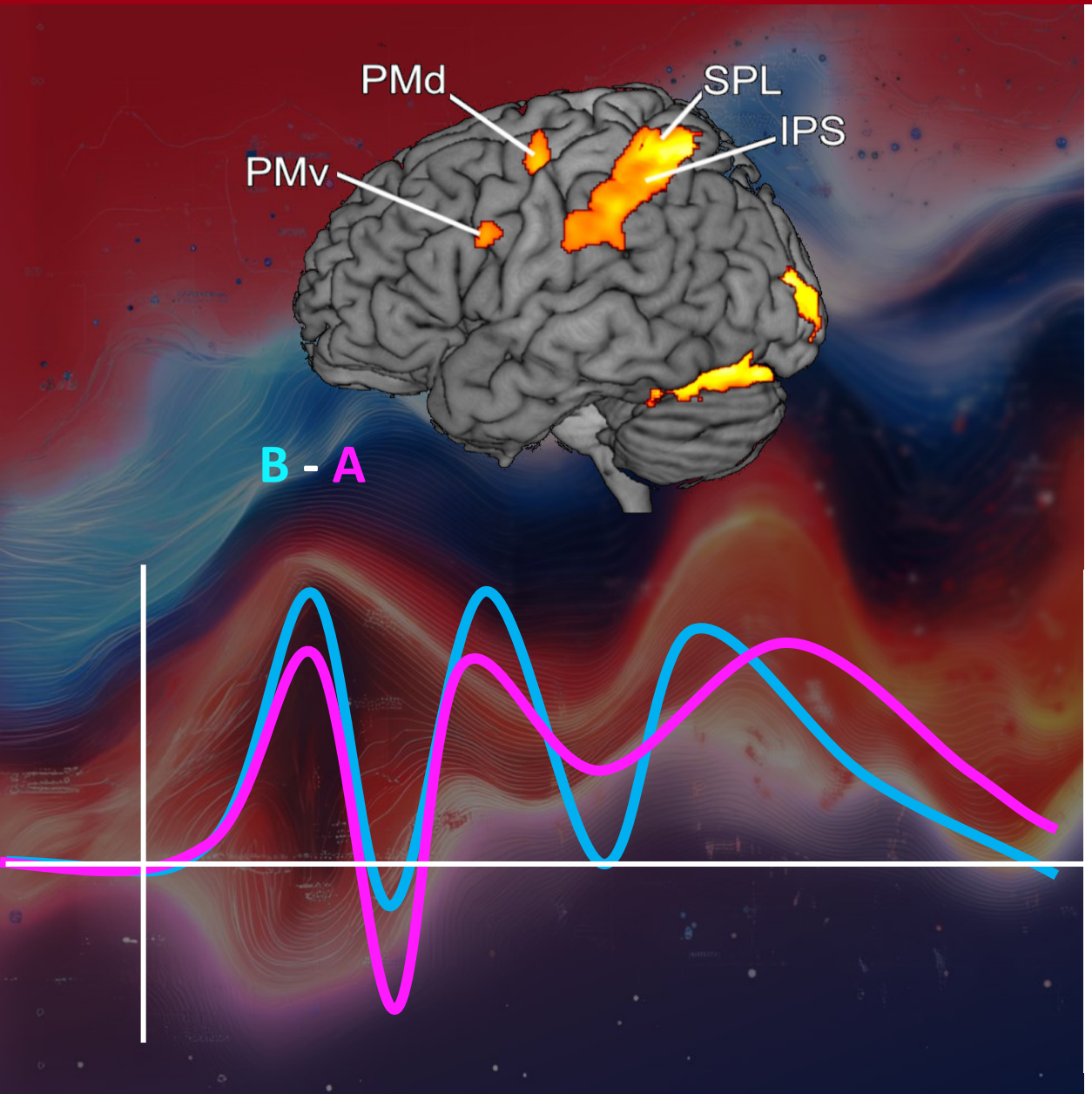

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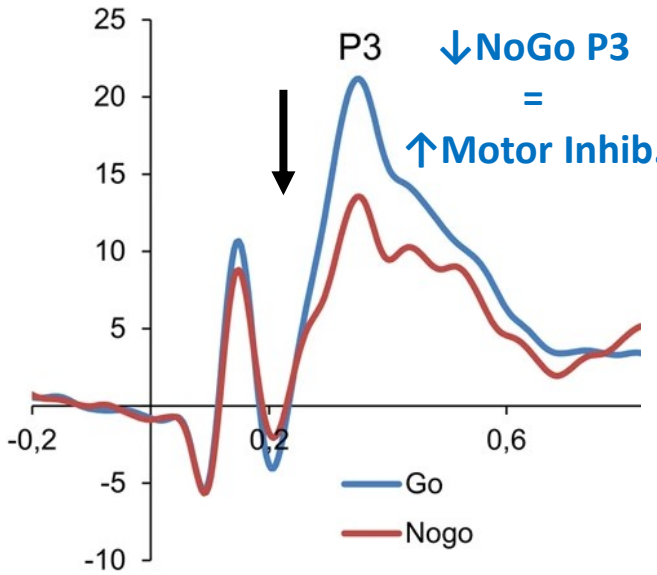

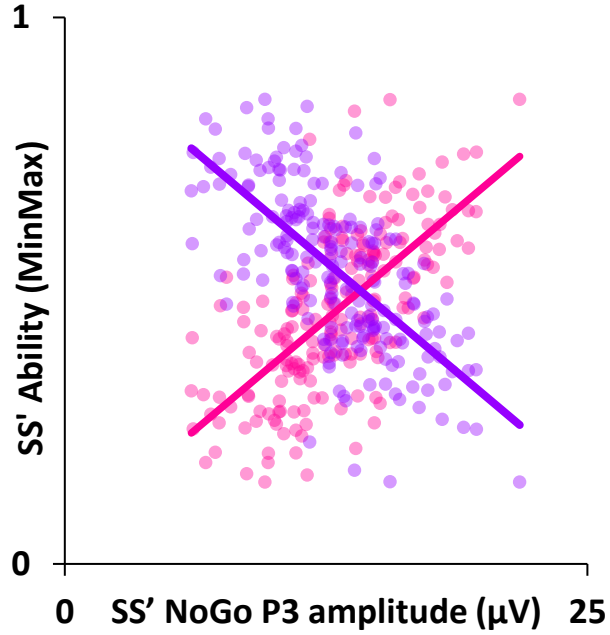

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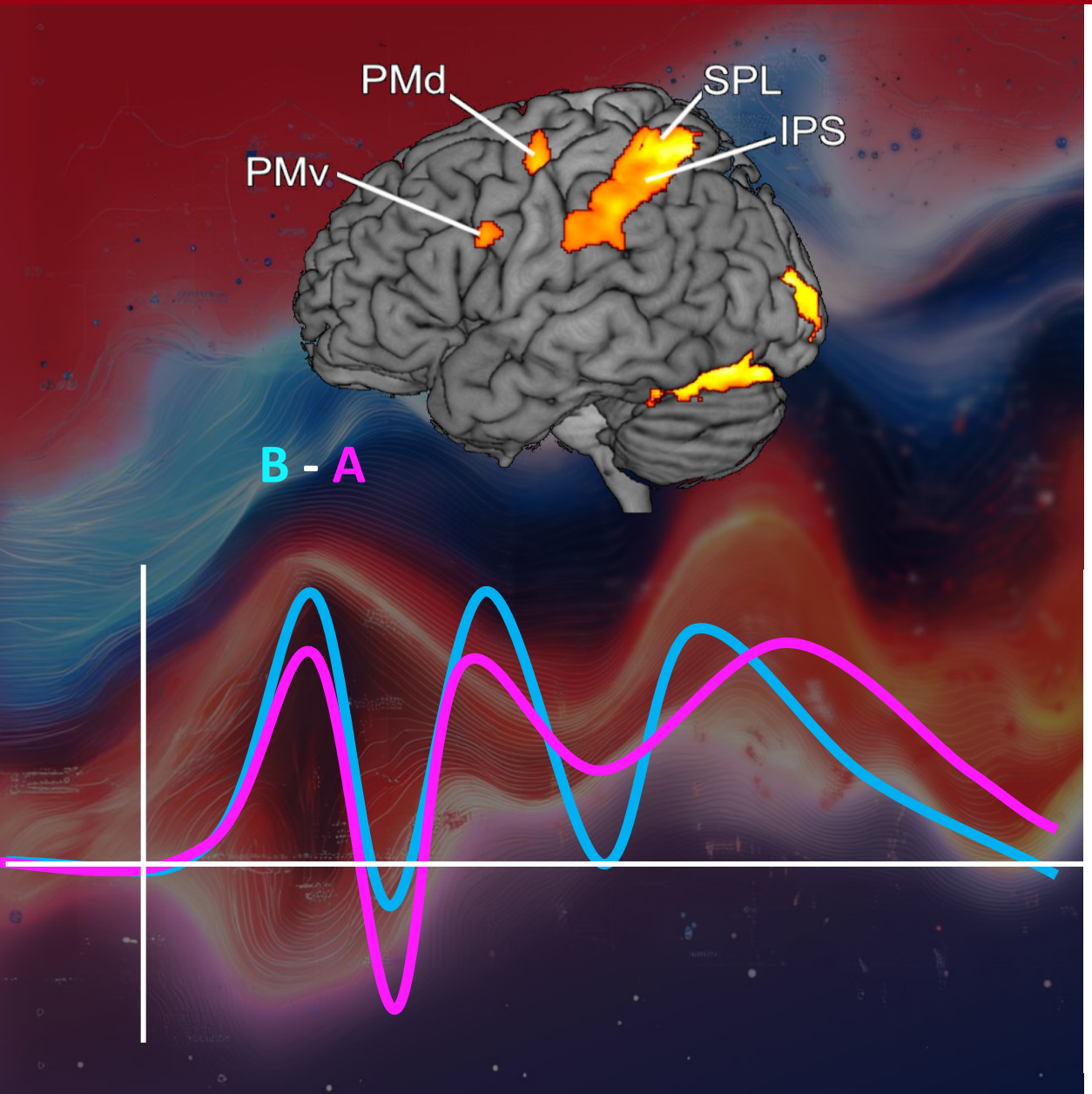
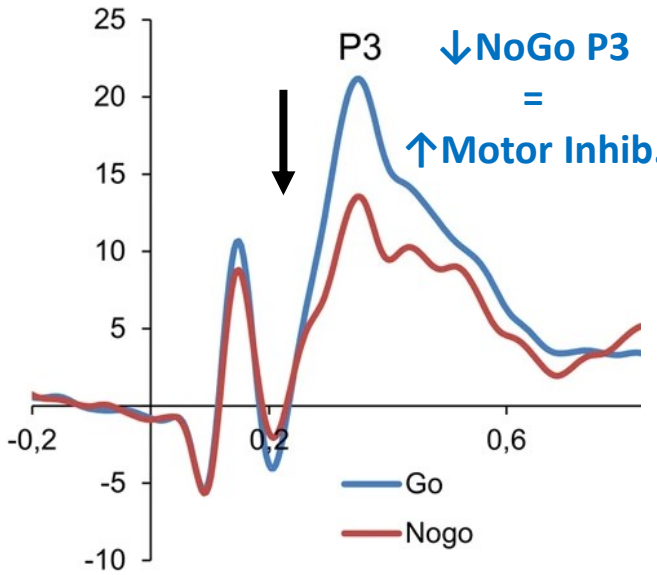


Test your interpretations!

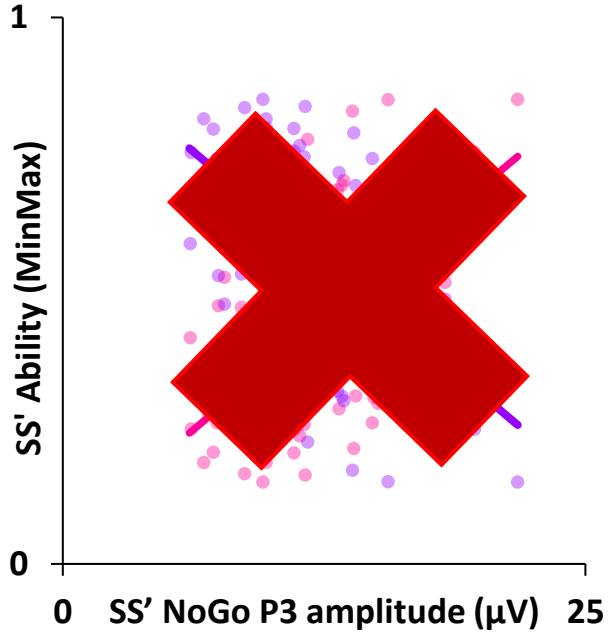
NoGo - Go

Motor Inhibition



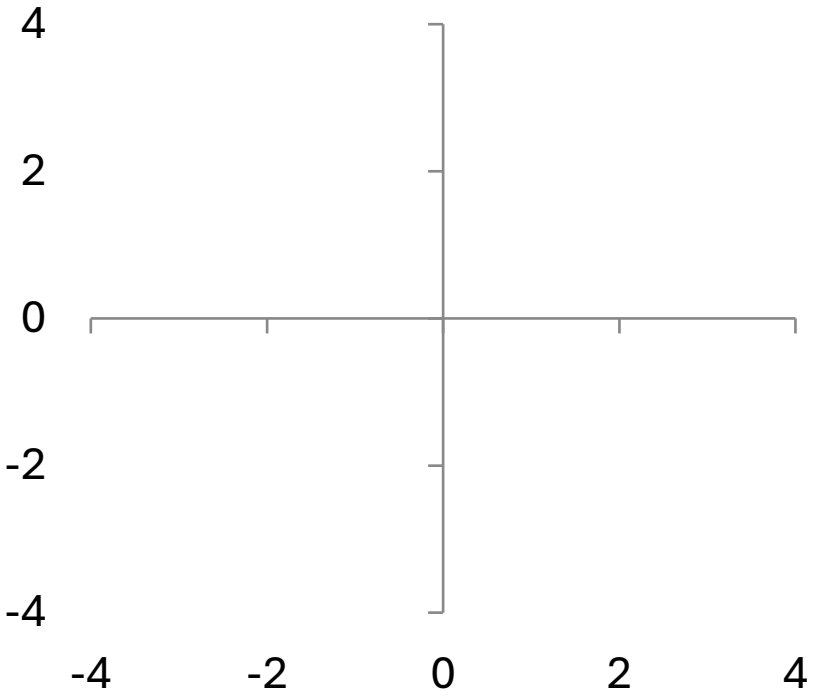
NoGo - Go

Motor Inhibition

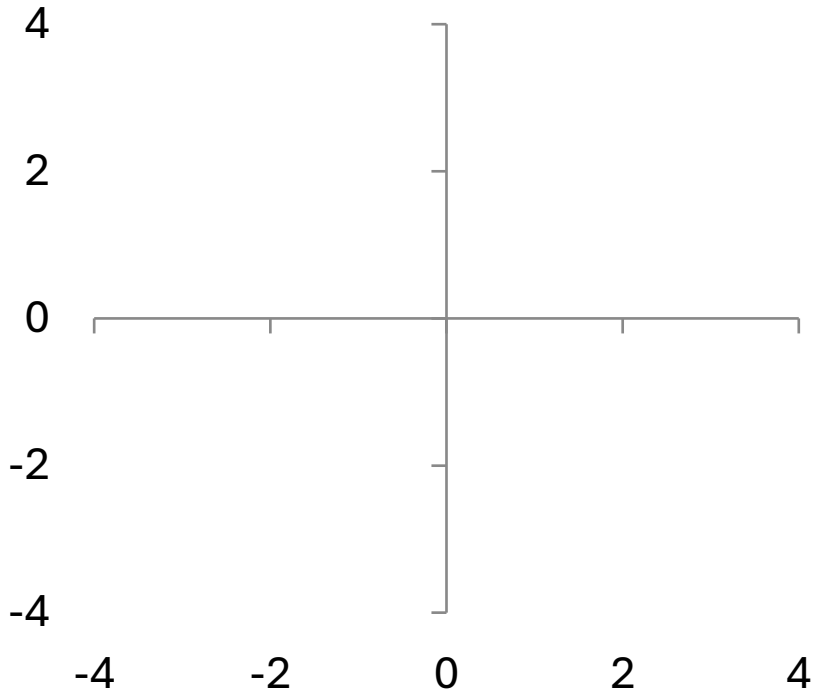


Guess the correlation!

Nearness to the equator and °C (U.S.A.)
N = 20000

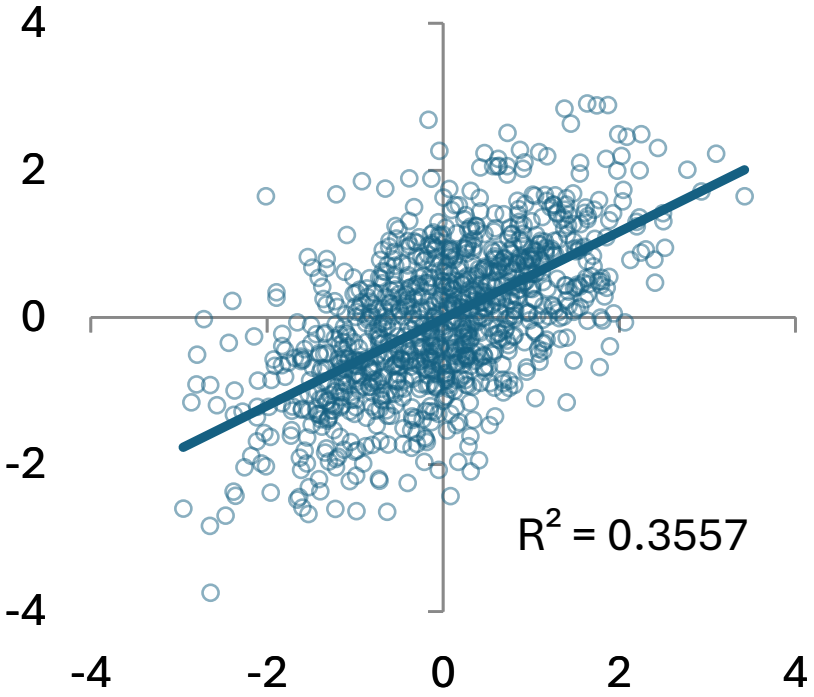


Weight and height for adults (U.S.A.)
N = 17000

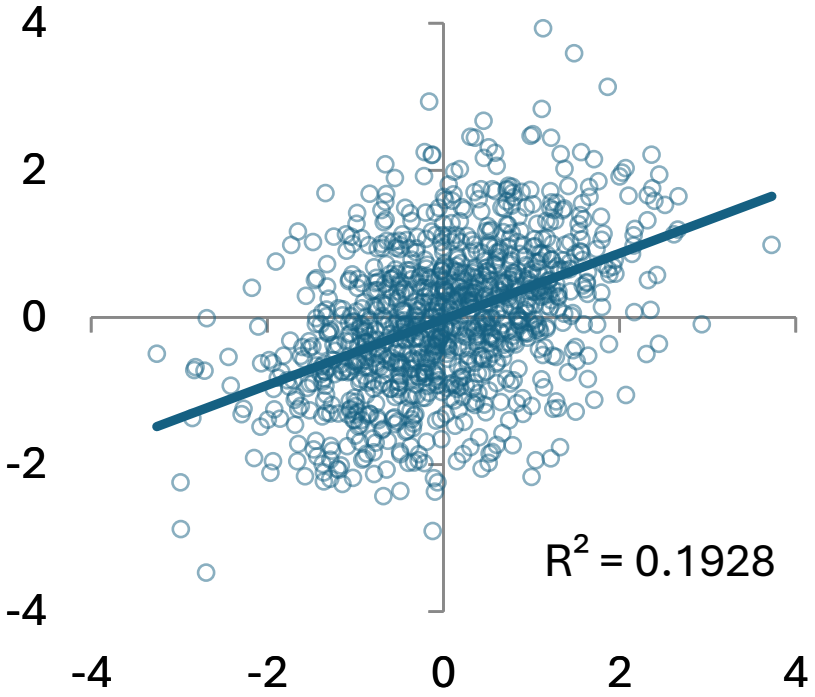


Guess the correlation!

Nearness to the equator and °C (U.S.A.)
N = 20000
r = .60

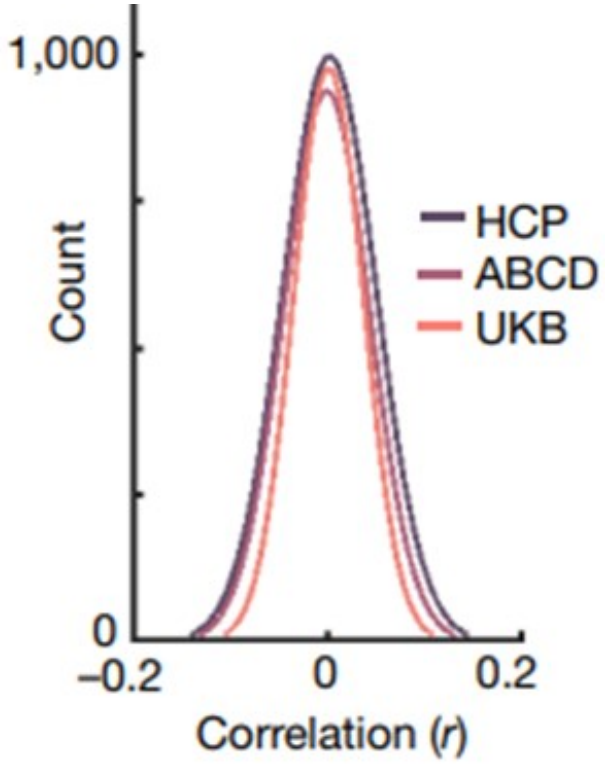


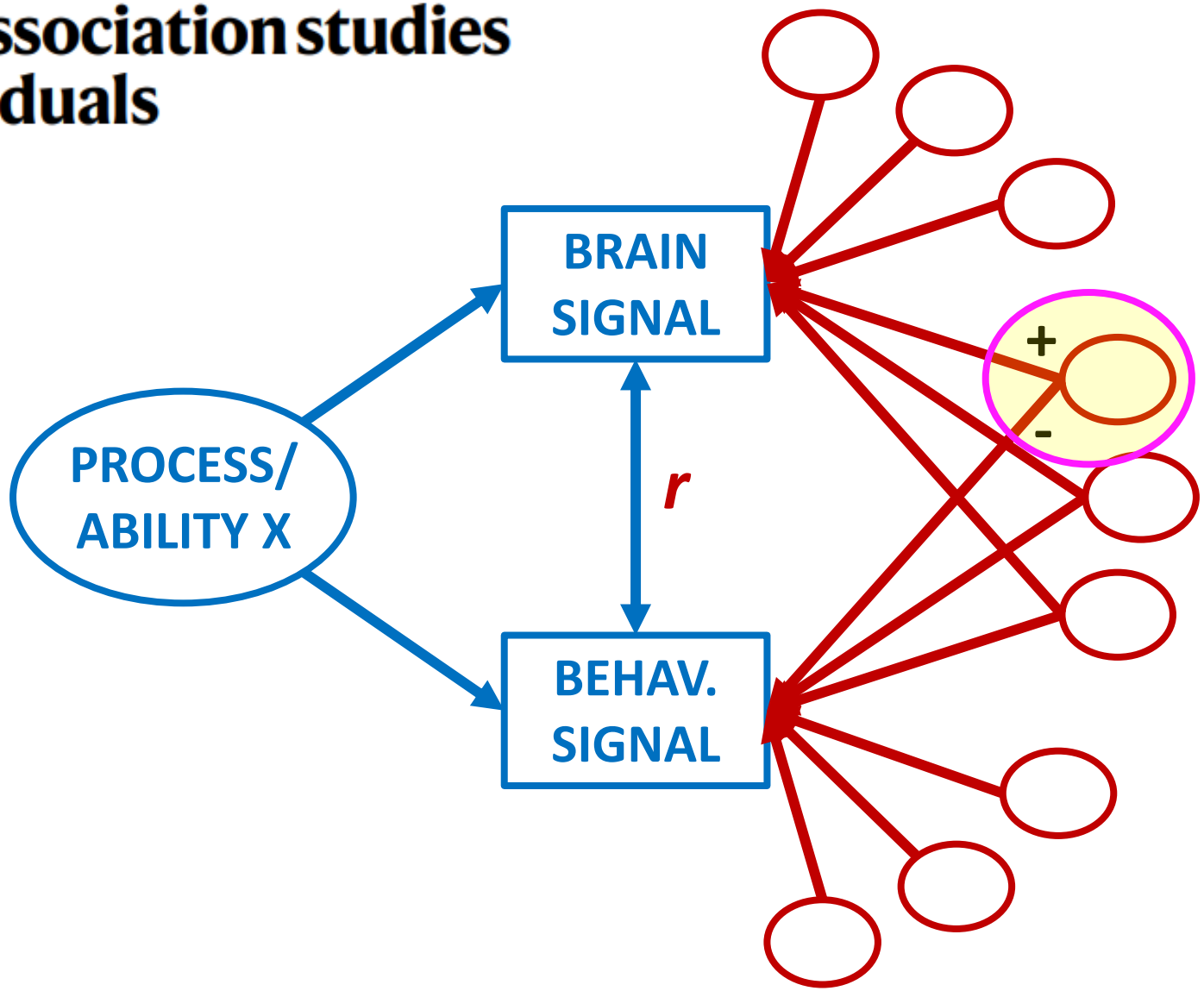
Weight and height for adults (U.S.A.)
N = 17000
r = .44



Lost in Translation: Brain-Behavior Predictions

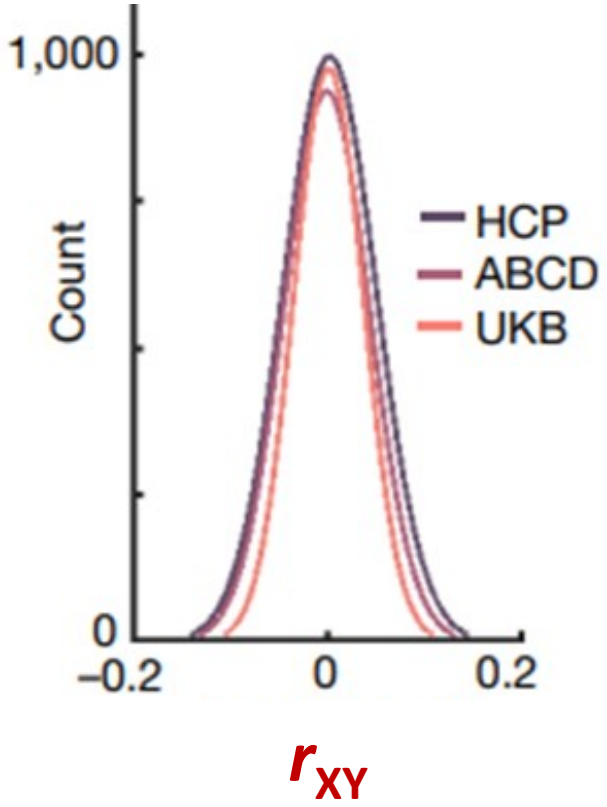
Reproducible brain-wide association studies require thousands of individuals



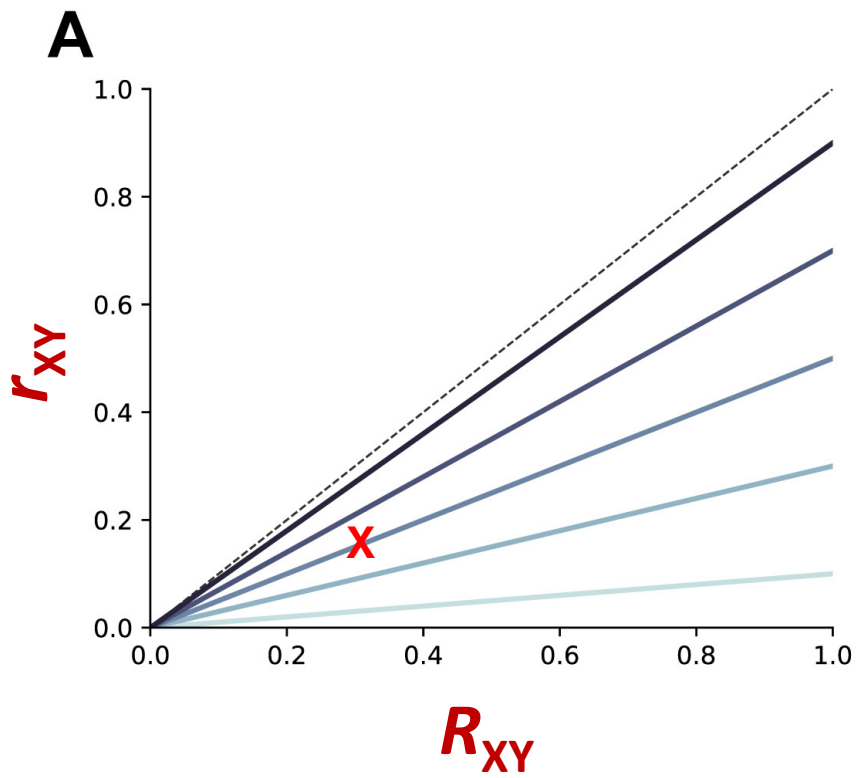


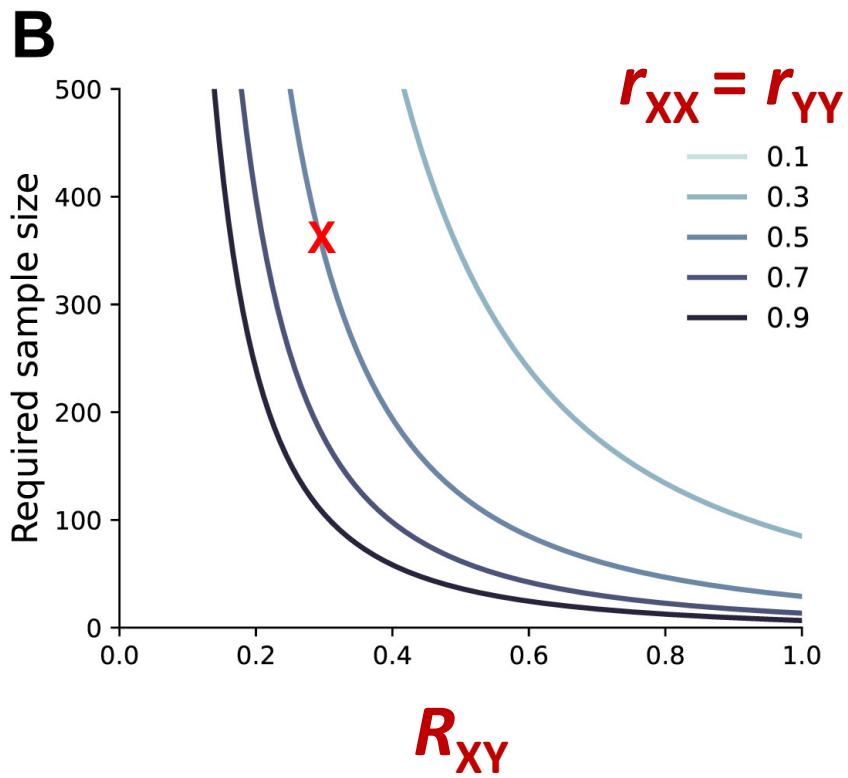
Brain-Behavior Predictions: Too Good to be True?

Reproducible brain-wide association studies require thousands of individuals



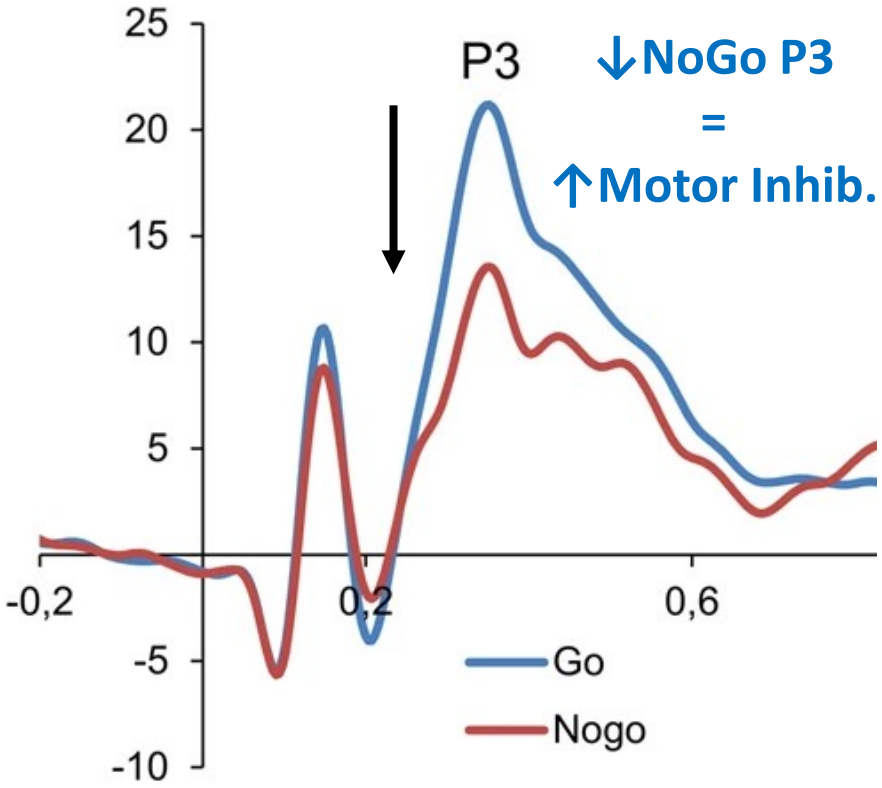
$$r_{XY} = R_{XY}\sqrt{r_{XX}\,r_{YY}}$$

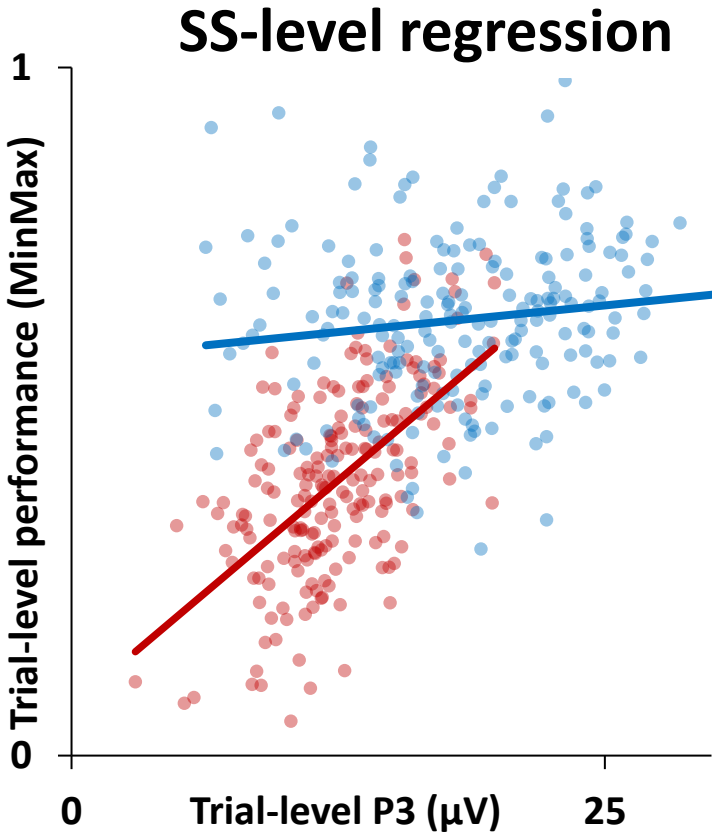


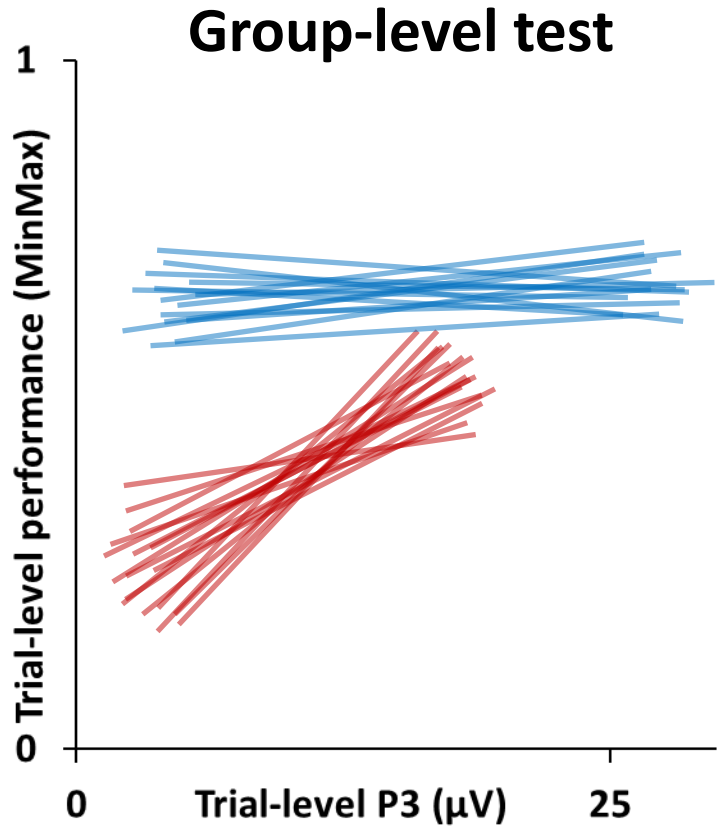


Interpretations Come with Implications!

Test your interpretations! (but do it better: multilevel modelling)







lmer(RTs ~ ERP*CONG + (ERP*CONG|SS)

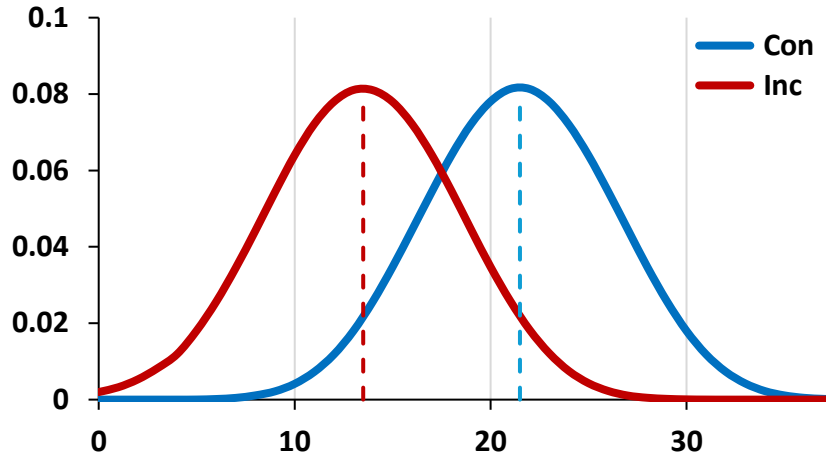
Let’s Start Again! How to Fix this Mess?!?

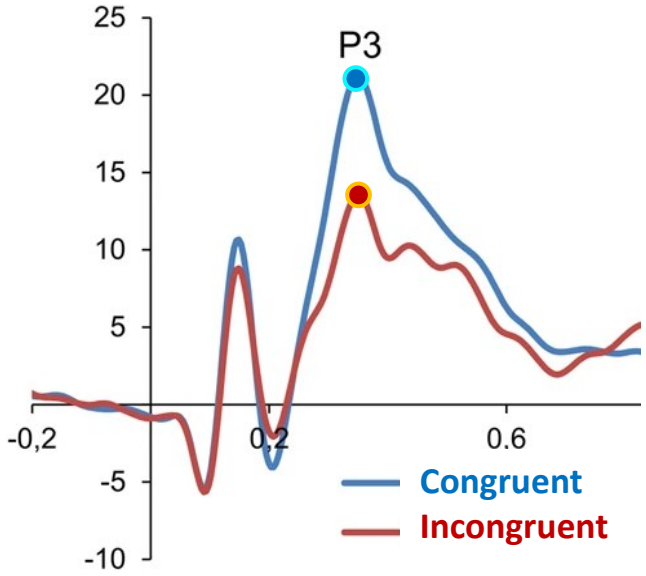
INCREASE SNR
(AND RELIABILITY)
(AND VALIDITY)
OF YOUR BRAIN AND BEHAVIOR MEASURES

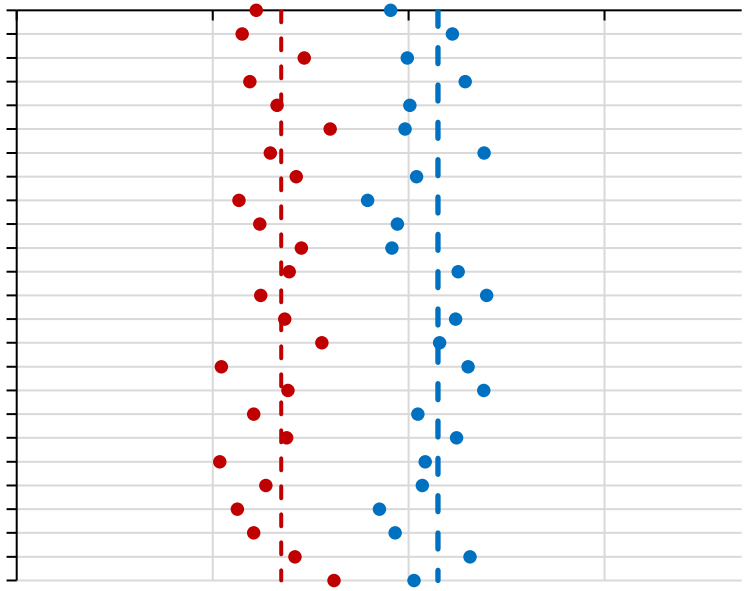
Let's Fix this Mess (1)

	P3 Con	P3 Inc	Con-Inc
SS01	20.20	10.46	9.74
SS02	17.39	24.49	-7.11
SS03	25.49	8.15	17.34
SS04	14.87	13.57	1.30
SS05	27.78	21.70	6.08
SS06	22.82	16.21	6.61
SS07	29.57	3.86	25.71
SS08	21.21	13.19	8.03
SS09	22.99	15.22	7.77
SS10	22.46	10.25	12.22
SS11	21.26	0.03	21.23
SS12	28.26	19.06	9.20
SS13	24.60	6.49	18.12
SS14	24.01	11.14	12.88
SS15	30.89	-2.54	33.42
SS16	21.80	8.41	13.39
SS17	40.22	3.90	36.32
SS18	26.99	-2.93	29.92
SS19	11.57	6.62	4.96
SS20	11.60	13.36	-1.76

Con-Inc	
M	8.02
SD	9.67
SE	2.01
t(19)	4.00
p	< 0.001
d	0.80







25 Exps
25 trials

Let's fix this Mess (1) – Increase Number of Trials

	P3 Con	P3 Inc	Con-Inc
SS01	20.20	10.46	9.74
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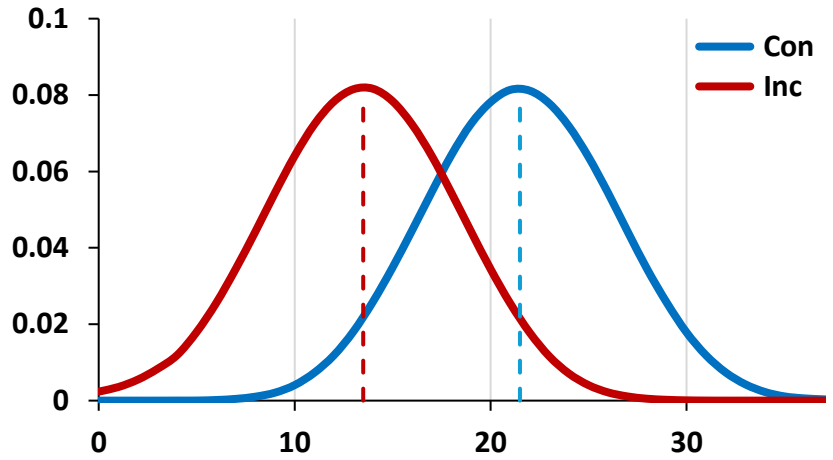

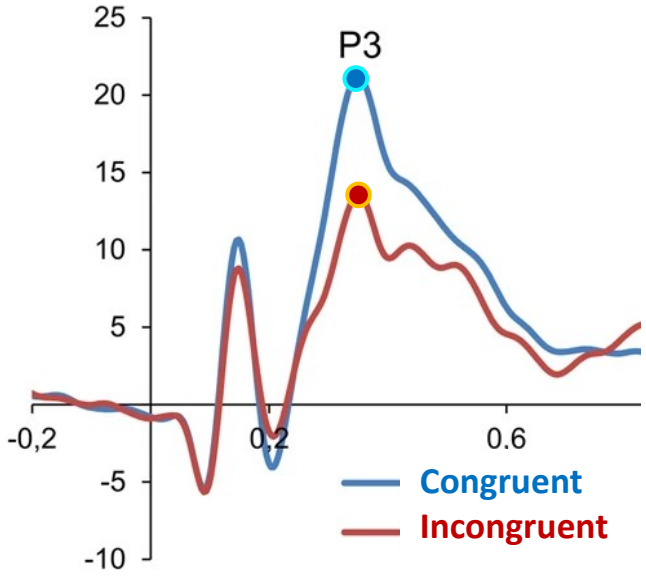

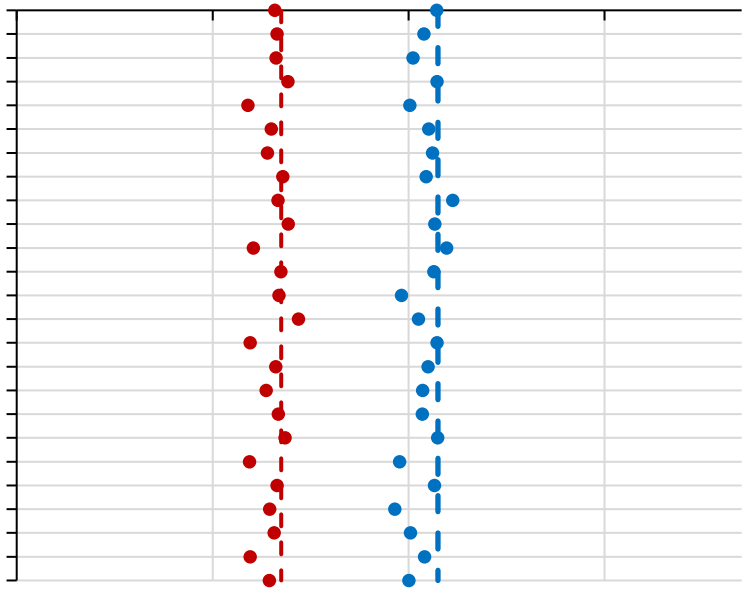

25 Exps
100 trials

Let's fix this Mess (1) – Increase Number of Trials

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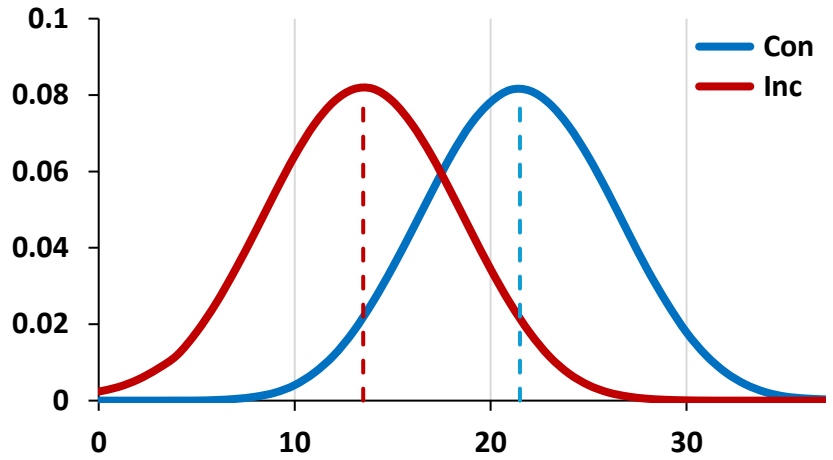
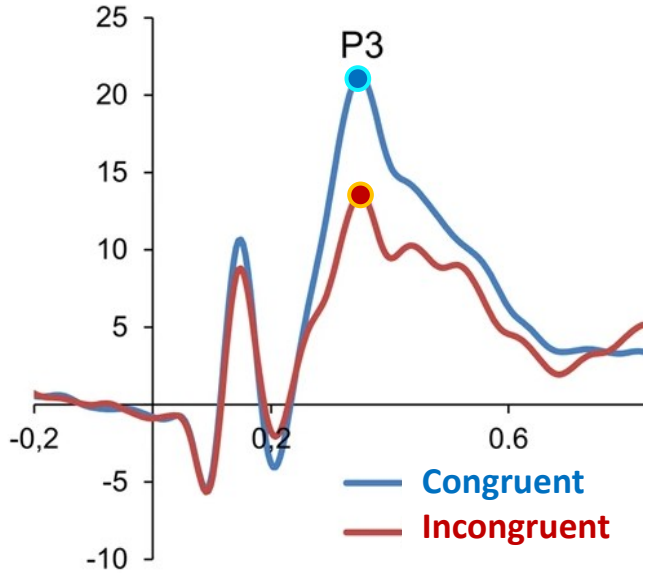




INCREASE SNR (AND RELIABILITY) BY REDUCING INTRA-INDIVIDUAL VAR BY INCREASING NUMBER OF TRIALS!

25 Exps
100 trials

Let's Fix this Mess (1) – Increase Number of Trials

Using precision approaches to improve brain-behavior prediction

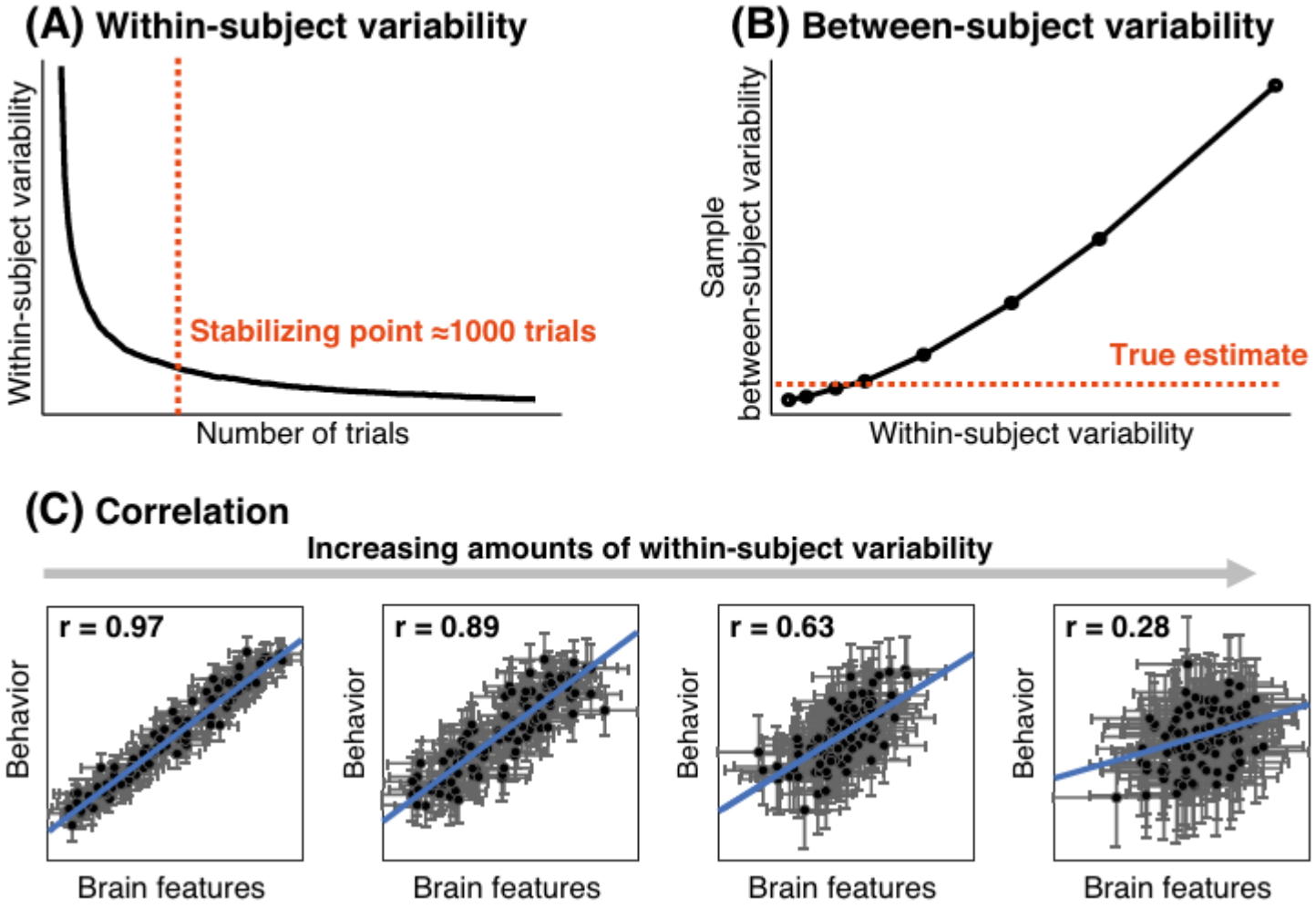
Hyejin J. Lee [1,2,*], Ally Dworetsky [1], Nathan Labora [1], and Caterina Gratton [1,2,*]

Paper

Aim for 80-120 trials/condition for w/in-SS studies

NB: Brain measures are way noisier!

→ Good preprocessing



Let's Fix this Mess (2) – Preprocess your Brain Measures

INCREASE SNR (AND RELIABILITY) OF YOUR EEG DATA WITH A GOOD PREPROCESSING

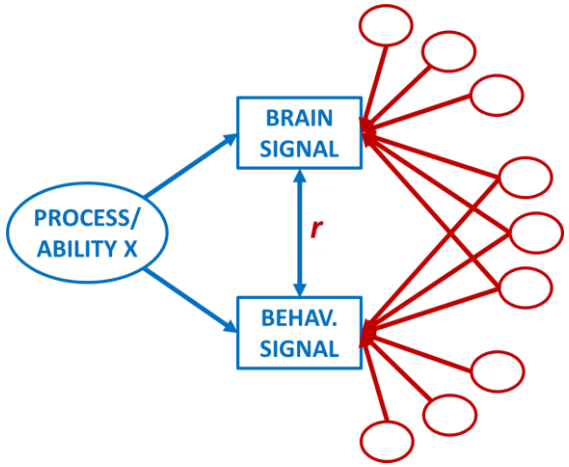
1) Use an evidence-based, reproducible preprocessing pipeline
sccn.ucsd.edu/wiki/Makoto's_preprocessing_pipeline

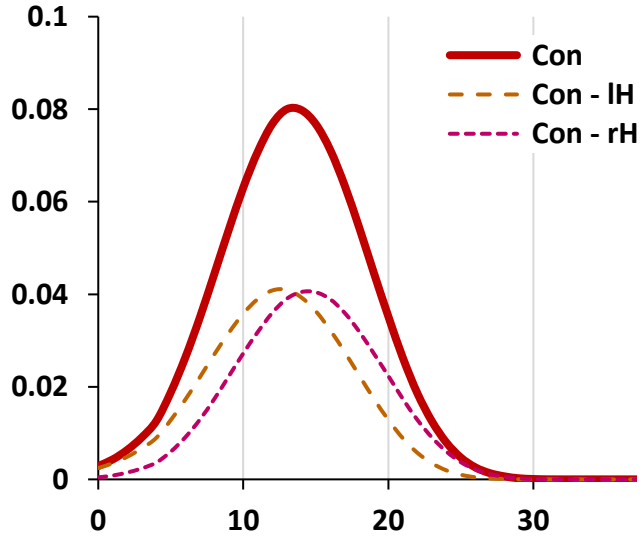
2) Perfect the art of ICA-based artifact removal
labeling.ucsd.edu/tutorial

3) Use the EEGLAB TBT plugin
(for Trial-By-Trial epoch rejection without losing trials)
github.com/mattansb/TBT

Let's Fix this Mess (3) – Control your Confounds

Brain and Behavior signals are affected by tens of confounds

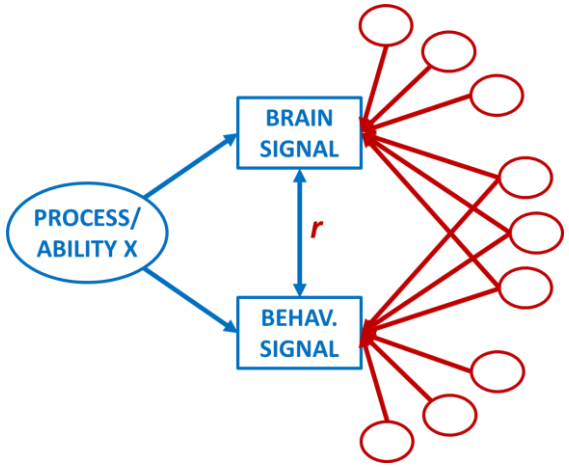


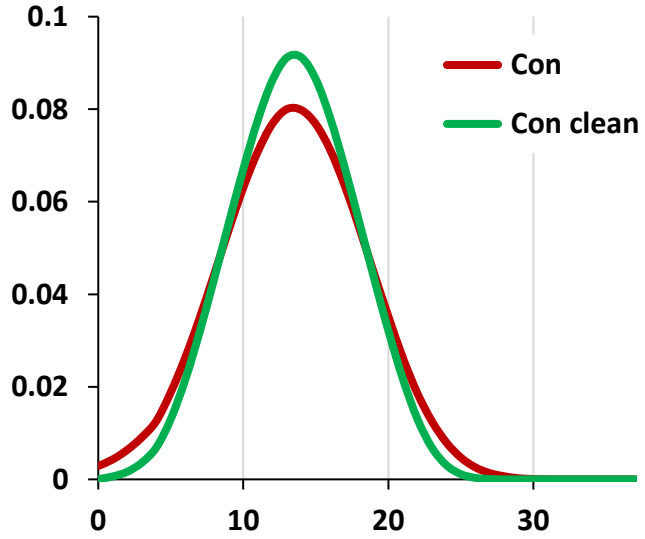


1) **Time-On-Task effects**
   (eg, fatigue/boredom, learning)
2) **Low-level Stimulus/Response features**
   (eg, visual hemifield, responding hand)
3) **Sequential effects of performance**
   (eg, post-error slowing, trial-by-trial autocorr)
4) **Sequential effects of low-level S/R features**
   (eg, Stimulus and/or Response repetition)
5) **Sequential effects of experimental conditions**
   (eg, condition repetition, priming)

Let's Fix this Mess (3) – Control your Confounds

Brain and Behavior signals are affected by tens of confounds





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Let's Fix this Mess (3) – Control your Confounds

INCREASE SNR (AND RELIABILITY/VALIDITY) OF YOUR MEASURES BY CONTROLLING CONFOUNDS

1) Balance your experimental design FOR EVERYTHING (methodological control)
2) Create your trial list to AVOID/BALANCE ANY SEQUENTIAL EFFECT (methodological control)

How do you decide the order of trials?

Let's Fix this Mess (3) – Control your Confounds

2.1a) Use MIX to avoid/balance sequential effects

2.1b) Use MATCH to balance covariates
(both here)

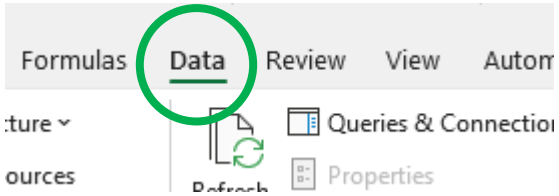
2.1c) Use Excel Solver to do both (evolutionary optimizer)
[File -> Options -> Add-ins -> Excel add-ins -> Solver]

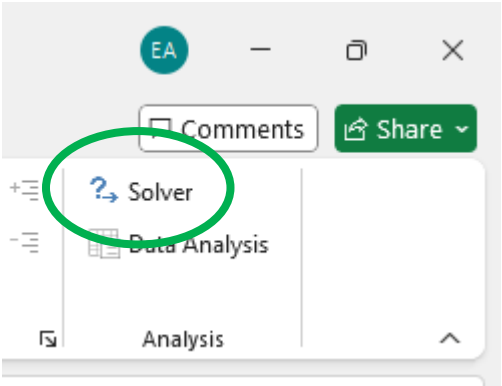
Mix, a program for pseudorandomization

MAARTEN VAN CASTEREN and MATTHEW H. DAVIS
MRC Cognition and Brain Sciences Unit, Cambridge, England

Match: A program to assist in matching the conditions of factorial experiments

MAARTEN VAN CASTEREN AND MATTHEW H. DAVIS
MRC Cognition and Brain Sciences Unit, Cambridge, England

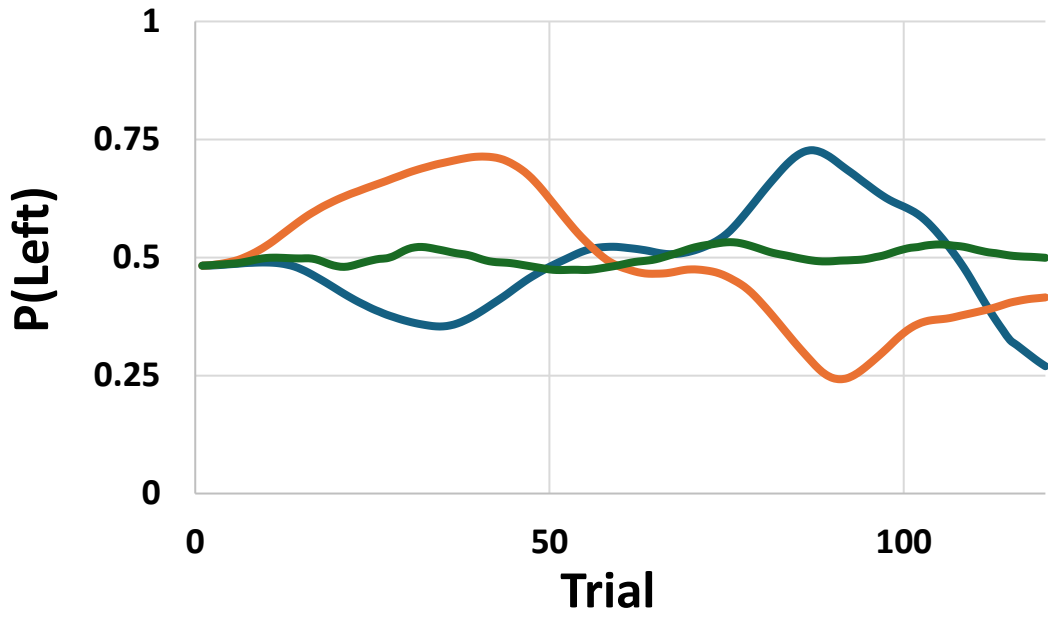




Let's Fix this Mess (3) – Control your Confounds

Trial	COND				
0	L				n
1	L	LL		L	10
2	L	LL		R	10
3	L	LL			
4	L	LL		LL	5
5	L	LL		LR	5
6	R	LR		RL	5
7	R	RR		RR	5
8	R	RR			
9	R	RR			
10	R	RR			
11	R	RR			
12	L	RL			
13	R	LR			
14	L	RL			
15	R	LR			
16	L	RL			
17	R	LR			
18	L	RL			
19	R	LR			
20	L	RL			

2.2) Compute trial-by-trial probabilities of experimental confounds (and effects)



Hierarchical Gaussian Filter (Bayesian observer)

github.com/translationalneuromodeling/tapas

Let's Fix this Mess (3) – Control your Confounds

INCREASE SNR (AND RELIABILITY/VALIDITY) OF YOUR MEASURES BY CONTROLLING CONFOUNDS

1) Try to balance your experimental design FOR EVERYTHING (methodological control)
2) Try to balance your trial list FOR EVERY SEQUENTIAL EFFECT (methodological control)
3) Include these confounds in your statistical model! (statistical control)

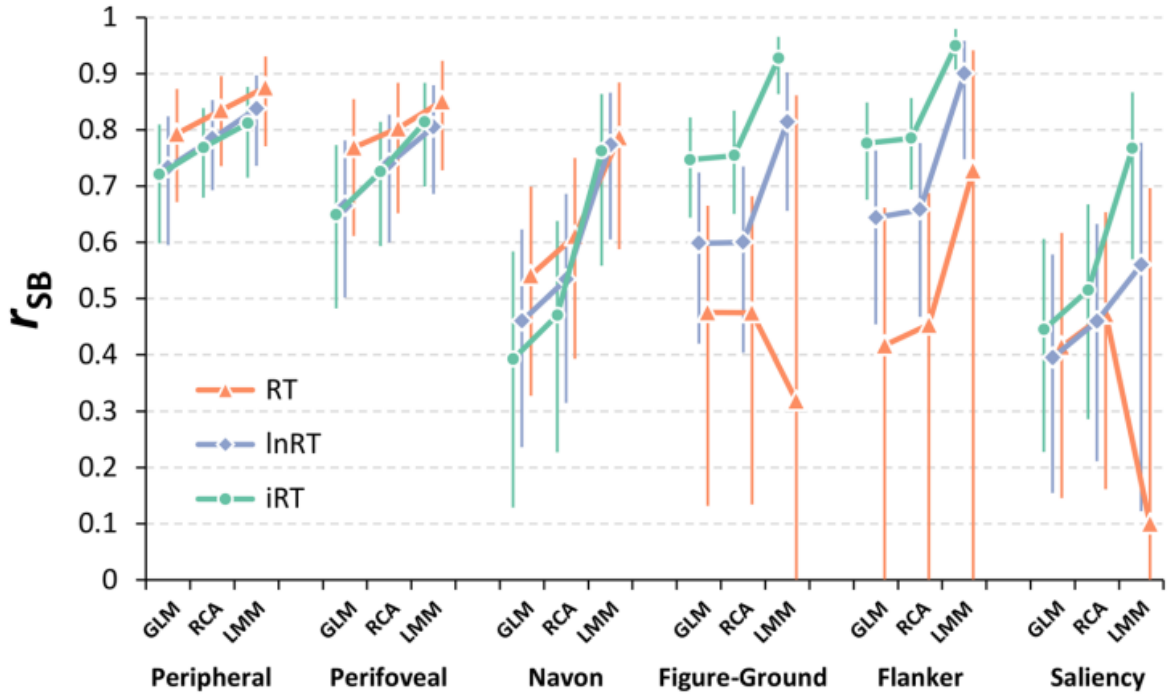
Let's Fix this Mess (3) – Control your Confounds

A comparison between different variants of the spatial Stroop task: The influence of analytic flexibility on Stroop effect estimates and reliability

Giada Viviani[1,2] · Antonino Visalli[1] · Livio Finos[2,3] · Antonino Vallesi[1,3] · Ettore Ambrosini[1,3,4]

Paper

RT ~ Trial*Block +
hStim + vStim + hResp + vResp +
preRT + PostERR +
P(Stim) + P(Resp) + P(Resp|Stim) +
P(Cong) +
Task∗Cong +
(Task∗Cong|SSID)



Let's Fix this Mess (4) – Increase Your Signal

INCREASE SNR (AND REL/VAL) OF YOUR MEASURES
BY IMPROVING YOUR MANIPULATIONS
→ Use good experimental paradigms

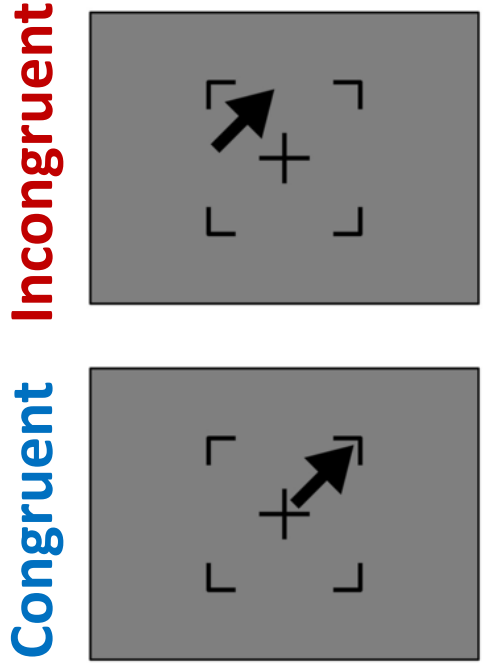
THEORY IS IMPORTANT!!!

Remember: You Must Know Your Stuff

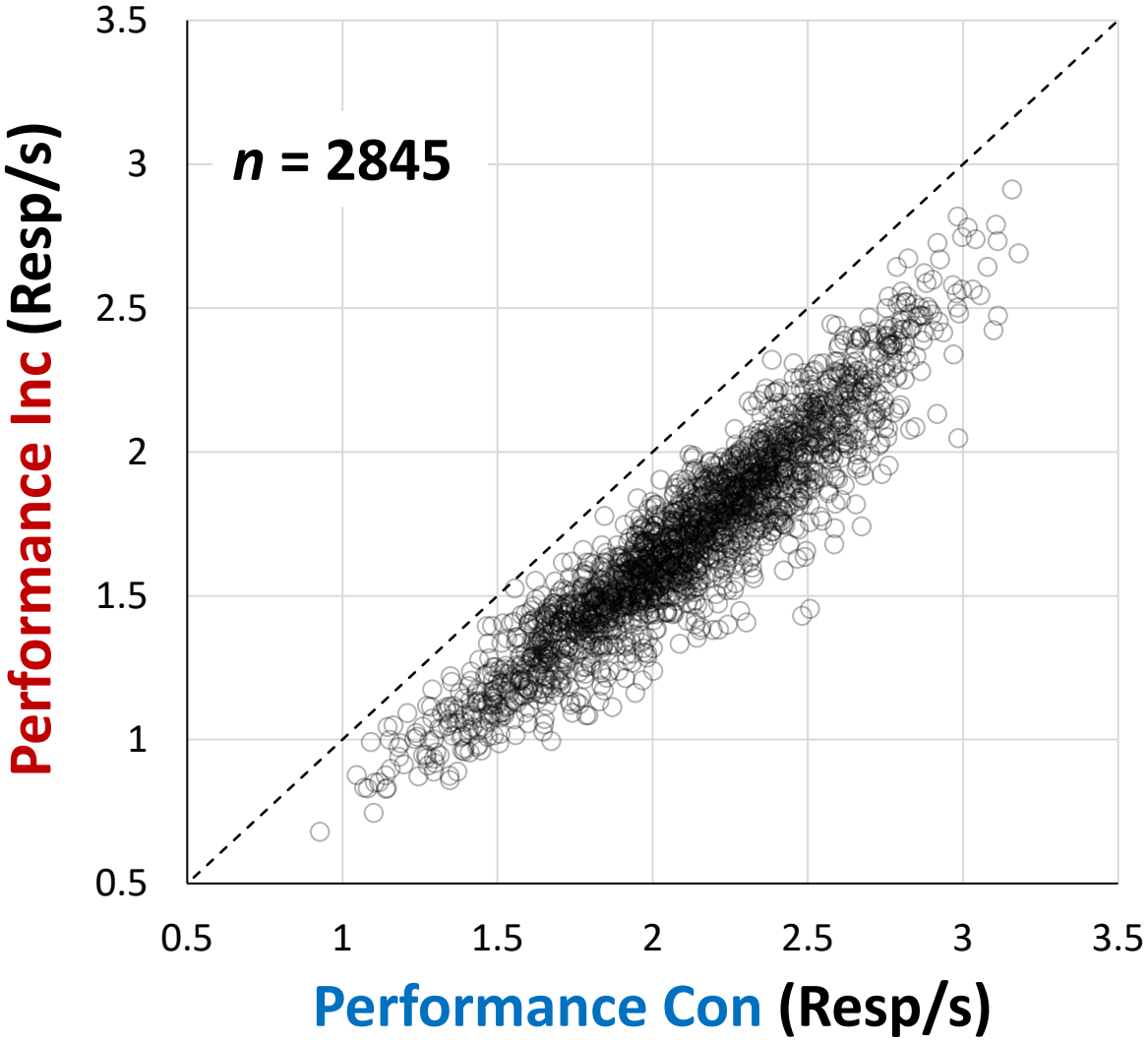
The Stroop legacy: A cautionary tale on methodological issues and a proposed spatial solution

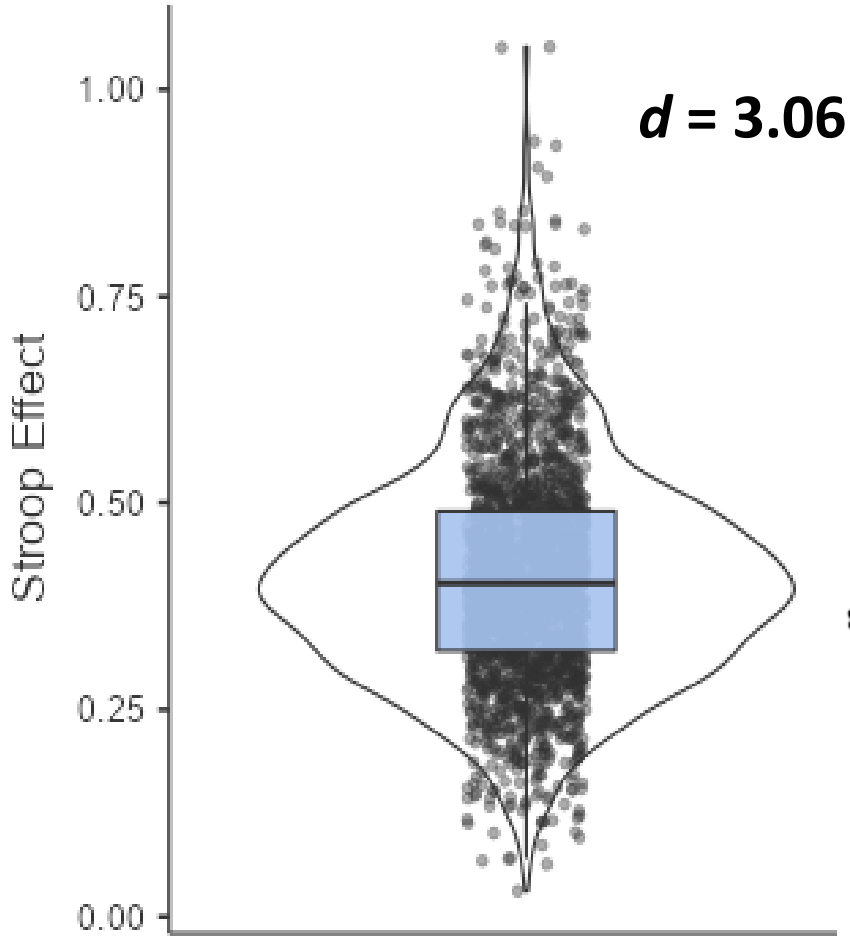
Giada Viviani[1,2] · Antonino Visalli[3] · Maria Montefinese[4] · Antonino Vallesi[1,2] · Ettore Ambrosini[1,2,5]

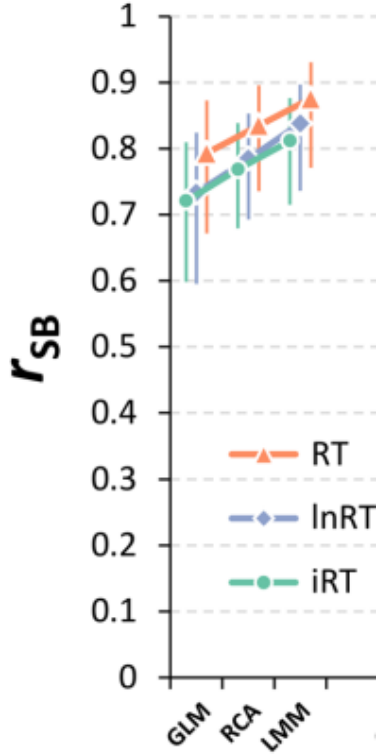
Paper



Let's Fix this Mess (4) – Increase Your Signal







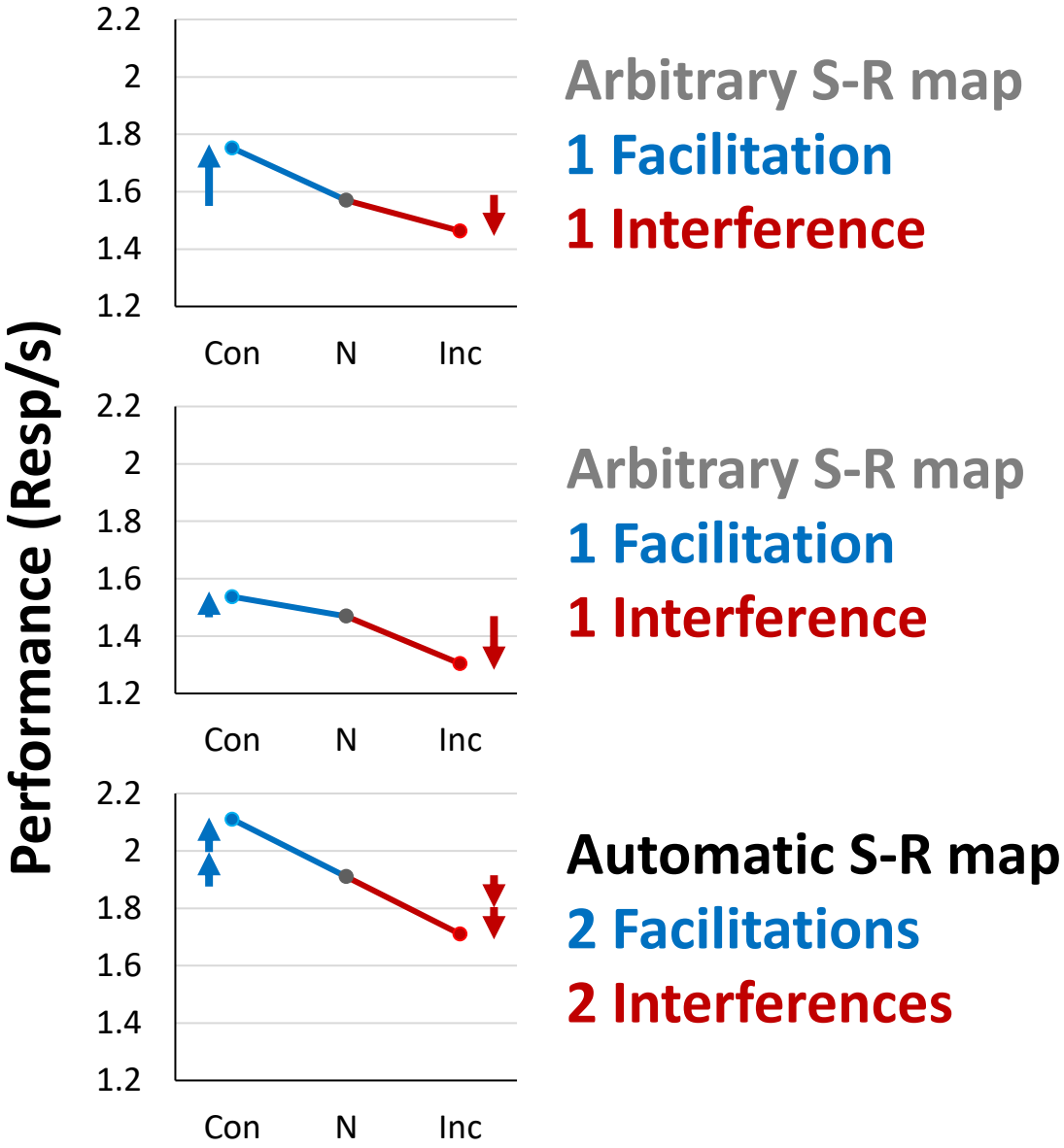
Let's Fix this Mess (4) – Increase Your Signal

THEORY IS IMPORTANT!!!

Remember: You Must Know Your Stuff

Cognitive control
Executive attention
Cognitive inhibition
Conflict resolution
Cognitive stability
Interference resistance
Task focus

→ Simon
→ Flanker
→ Stroop



Arbitrary S-R map
1 Facilitation
1 Interference

Arbitrary S-R map
1 Facilitation
1 Interference

Automatic S-R map
2 Facilitations
2 Interferences

Let's Fix this Mess (5) – Decompose Your Task/Beh Signal

THEORY IS IMPORTANT!!!

Remember: You Must Know Your Stuff

Analyze your task first, then your data!

Before asking where and when sth is happening in the BRAIN,
ask WHAT is happening in the MIND,
then verify your idea by looking at its effect on the BEHAVIOR

Mind → Behavior → Brain
Theory → Beh Exp → Brain Exp

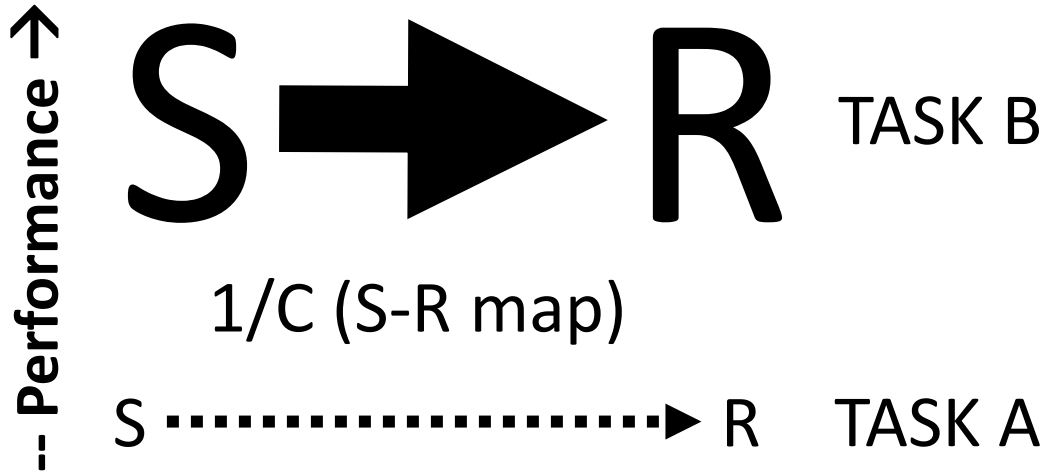
Let's Fix this Mess (5) – Decompose Your Task/Beh Signal

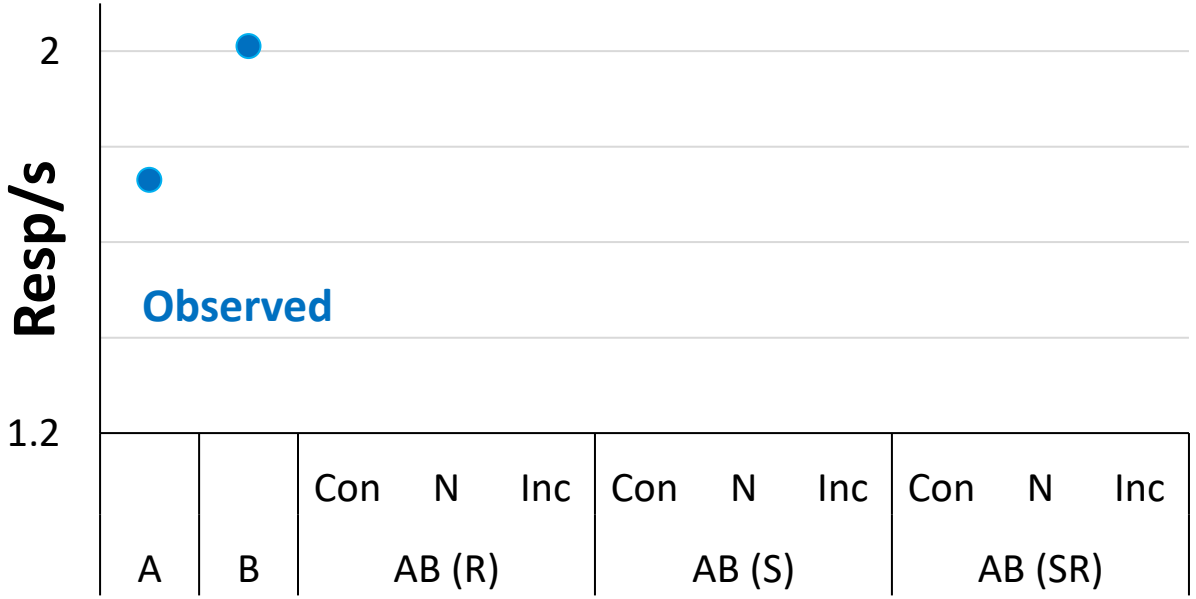
THEORY IS IMPORTANT!!!

Remember: You Must Know Your Stuff

Mind → Behavior → Brain

Theory → Beh Exp → Brain Exp





3 pre-registered studies: osf.io/jkq9n/

Let's Fix this Mess (5) – Decompose Your Task/Beh Signal

THEORY IS IMPORTANT!!!

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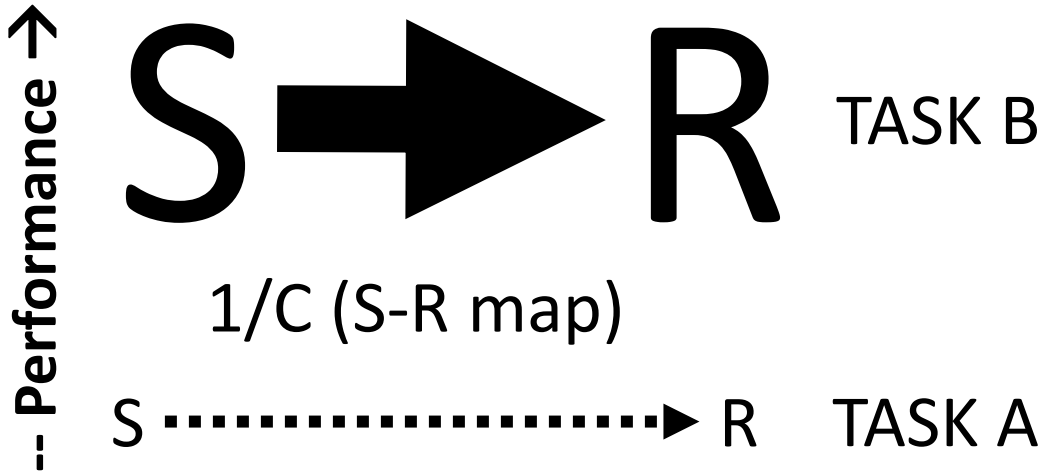
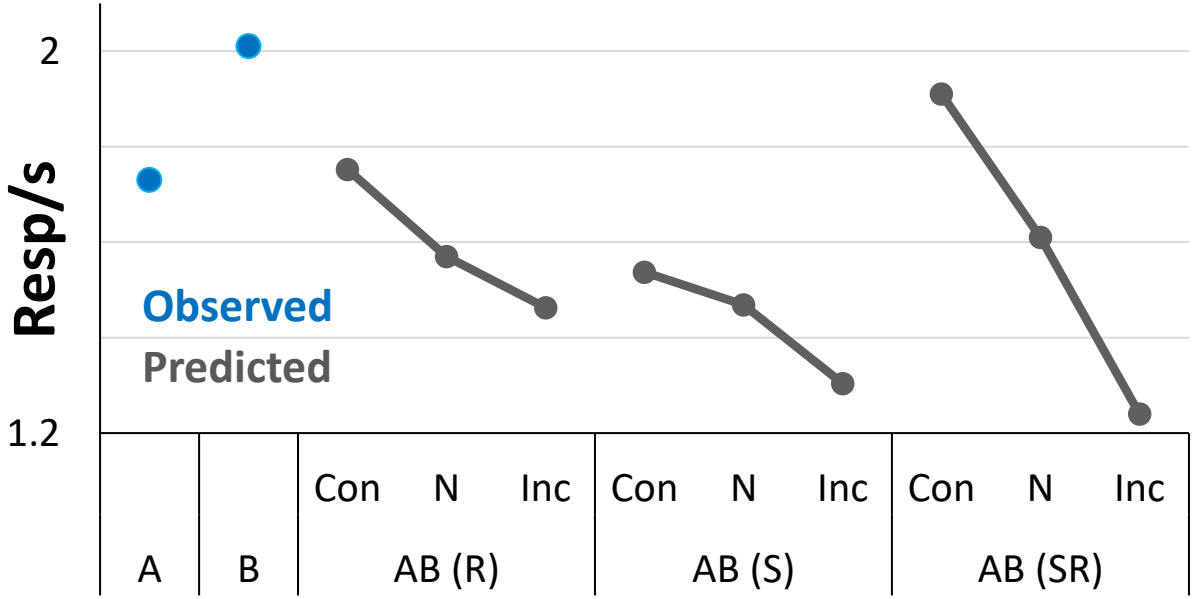
Mind → Behavior → Brain

Theory → Beh Exp → Brain Exp





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Let's Fix this Mess (5) – Decompose Your Task/Beh Signal

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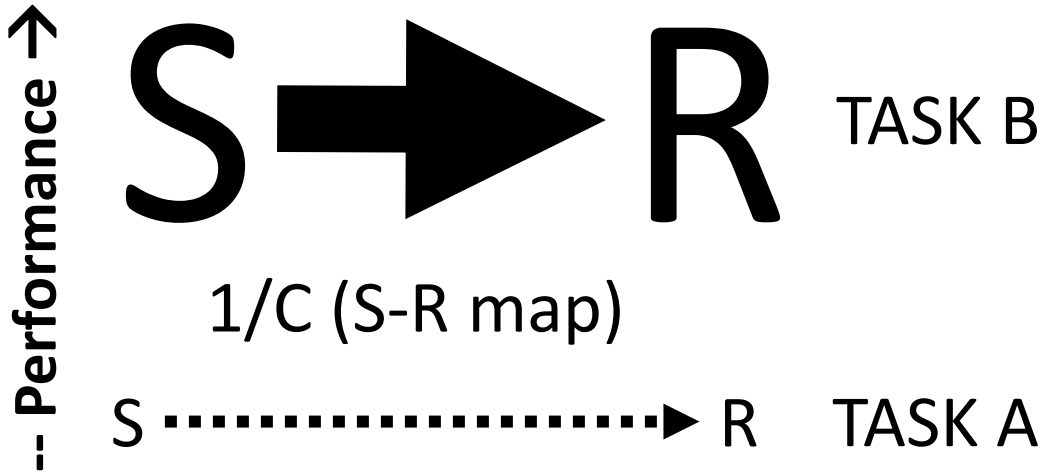

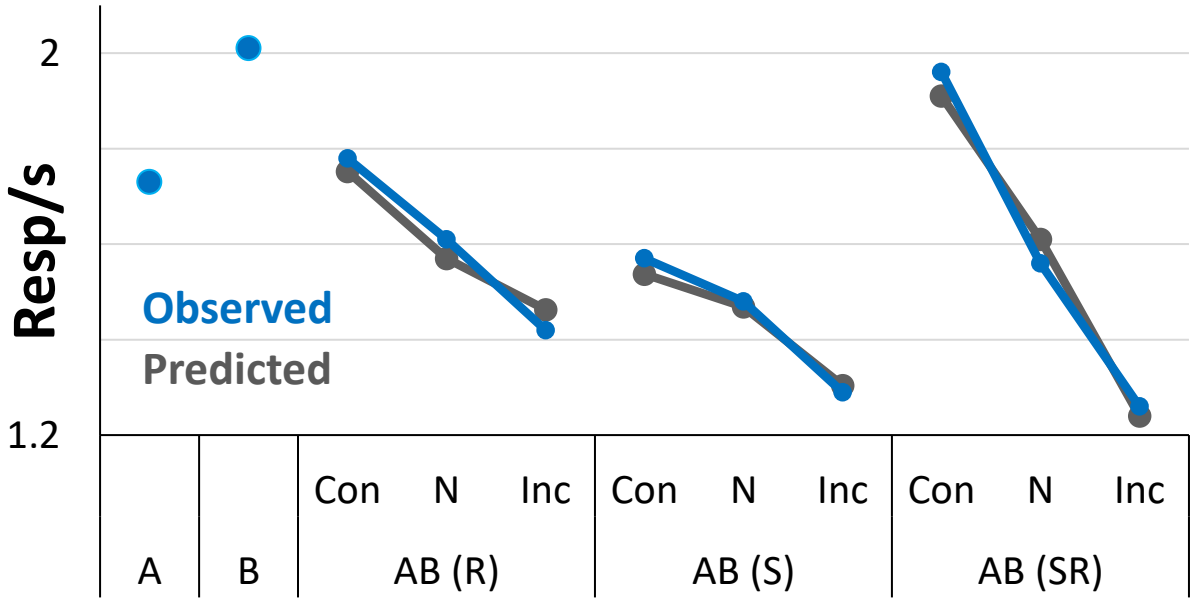

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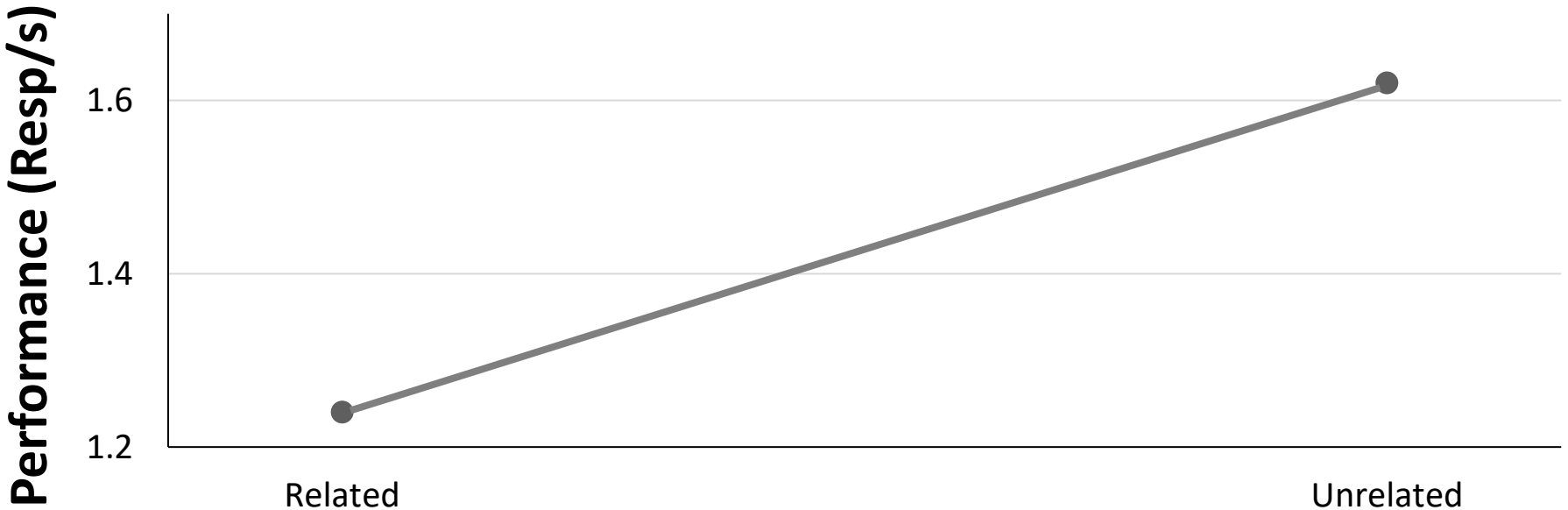
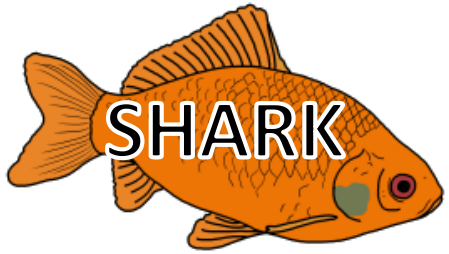
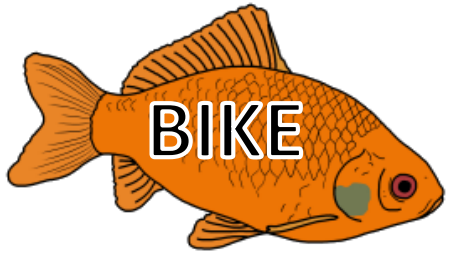
Let's Fix this Mess (6) – Use Better Manipulations

Test your hypotheses (but do it better! Fine-grained effects)



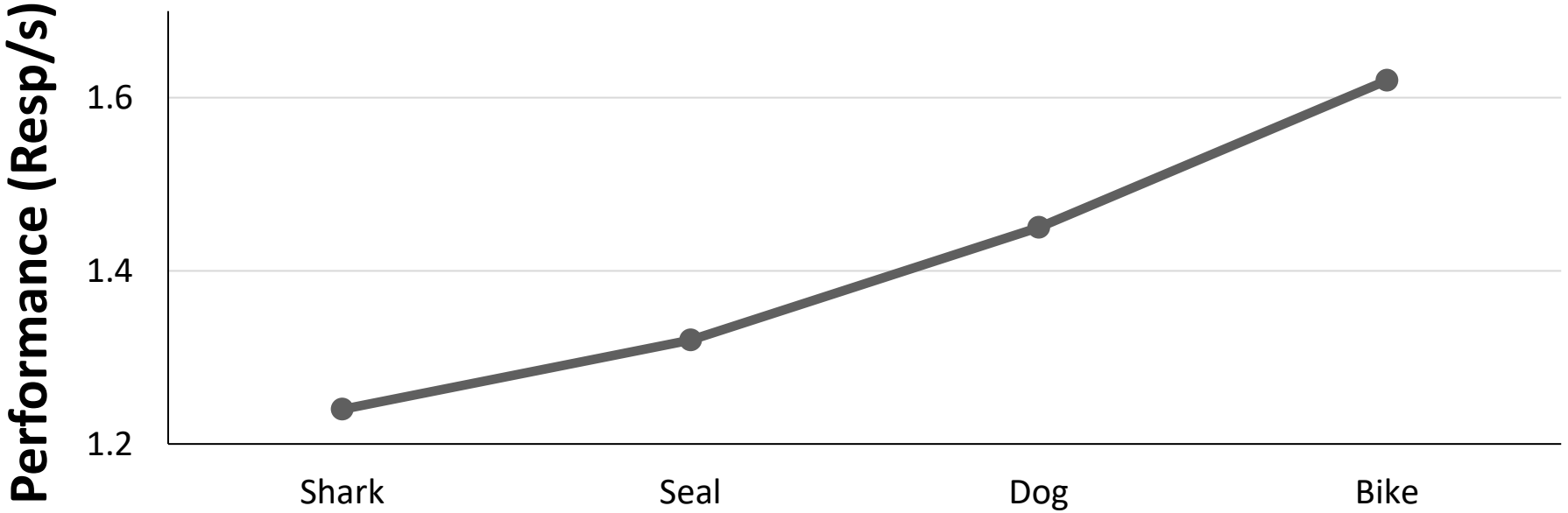


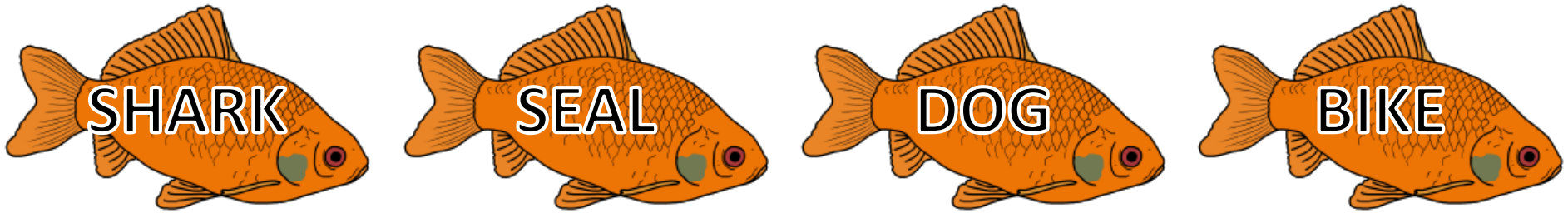


Semantic distance (?)

Let's Fix this Mess (6) – Use Better Manipulations

Test your hypotheses (but do it better! Fine-grained effects)





Semantic distance (!)

Let's Fix this Mess (6) – Use Better Manipulations

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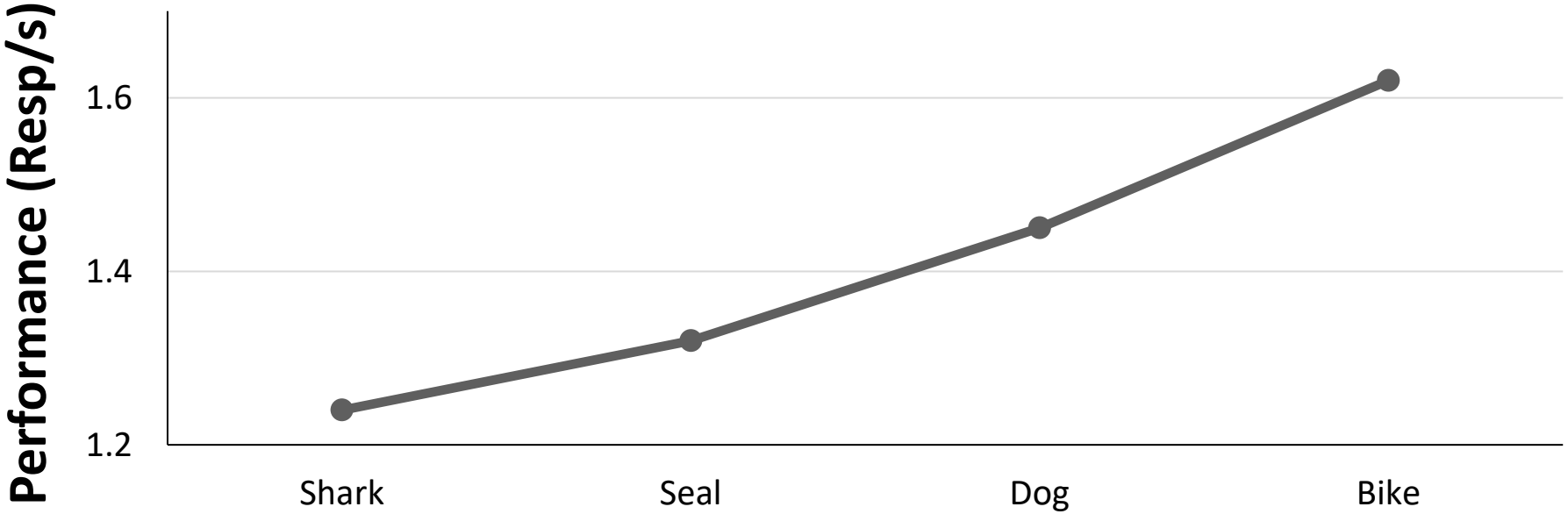
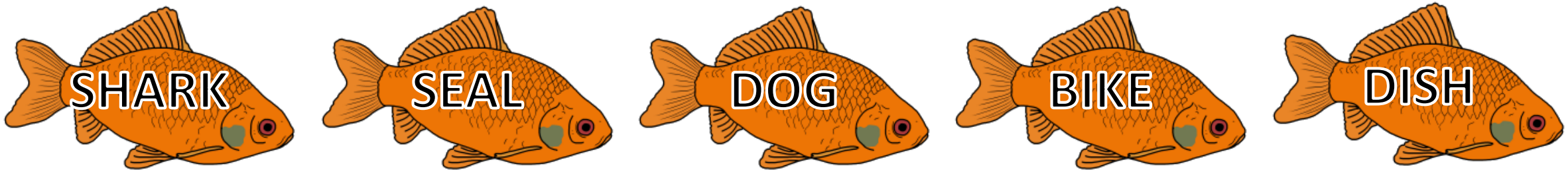


?



Semantic distance (!)

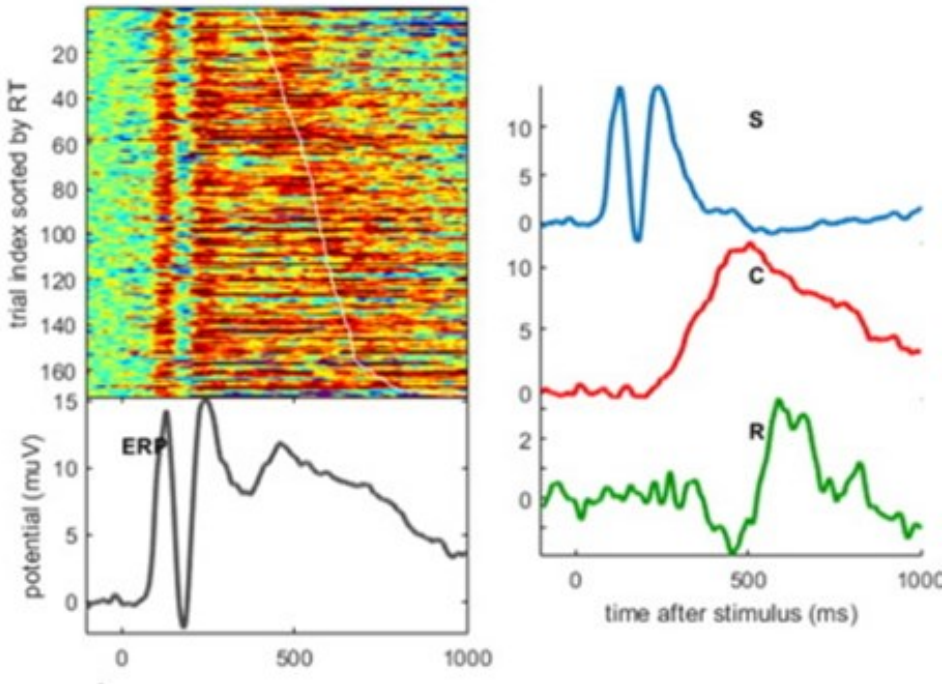
Let's Fix this Mess (7) – Now… the Brain!

INCREASE SNR (AND RELIABILITY/VALIDITY) OF YOUR MEASURES BY

1) USING STRONG, THEORY-DRIVEN, FINE-GRAINED MANIPULATIONS

2) WHILE CONTROLLING CONFOUNDS → MLM

BUT… Remember the EEG localization problem?



Single-trial ERPs: high spatio-temporal variability

→ **It's hard to distinguish process-specific ERPs**

→ **It's hard to define spatio-temporal ROIs**

(but see this)

Do whole-brain (mass-univariate) analyses!

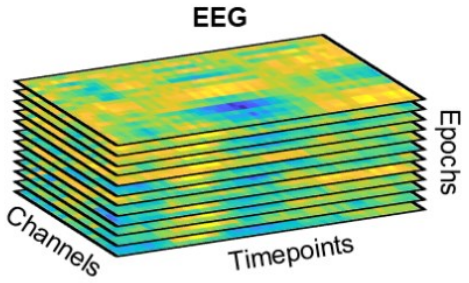
But correct them for multiple comparisons

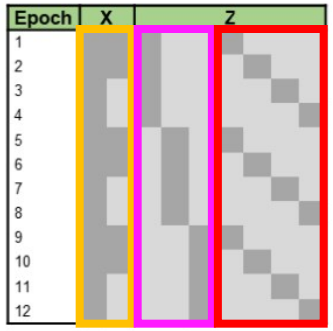
github.com/Mensen/ept_TFCE-matlab

Let's Fix this Mess (7) – Now… the Brain!

Do whole-brain (mass) MLM analyses!

But correct them for multiple comparisons





Fixed

Random, by-SS

Random, by-Item

But it takes forever to run 10^7 complex MLM models!

Use lmeEEG! (PrePrint, GitHub, OSF, Slides)

lmeEEG: Mass linear mixed-effects modeling of EEG data with crossed random effects

Antonino Visalli [a,*], Maria Montefinese [b], Giada Viviani [c,d], Livio Finos [d,e], Antonino Vallesi [c,d], Ettore Ambrosini [c,d,f]

What's the take-home message?

THANKS!

osf.io/rgku3

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