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Pragmatic Computational Psychiatry: Connecting Neuroscience with Clinical Care

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Outline

- Mental Health Challenges in 2016
- Applied Computational Psychiatry
- Deficits in inhibitory control in stimulant use disorder.
- Learning dysfunction in anxious individuals (Crane Huang)

Challenges to Mental Health

ESSAY

Why Most Clinical Research Is Not Useful

John P. A. Ioannidis[1,2]*

Table 1. Features to consider in appraising whether clinical research is useful.

Feature	Questions to Ask
Problem base	Is there a health problem that is big/important enough to fix?
Context placement	Has prior evidence been systematically assessed to inform (the need for) new studies?
Information gain	Is the proposed study large and long enough to be sufficiently informative?
Pragmatism	Does the research reflect real life? If it deviates, does this matter?
Patient centeredness	Does the research reflect top patient priorities?
Value for money	Is the research worth the money?
Feasibility	Can this research be done?
Transparency	Are methods, data, and analyses verifiable and unbiased?

Table 2. How often is each utility feature satisfied in studies published in major general medical journals and across all clinical research?*

Feature	Studies Published in Major General Medical Journals	All Clinical Research
Problem base	Varies a lot	Minority
Context placement	Varies per journal (uncommon to almost always)	Uncommon
Information gain	Majority	Rare
Pragmatism	Rare	Rare
Patient centeredness	Rare/uncommon	Rare
Value for money	Unknown, rare assessments	Unknown, rare assessments
Feasibility	Almost always	Majority
Transparency	Rare/uncommon (data sharing)**, almost always (trial registration), uncommon (other study registration)	Rare/uncommon, except for trial registration (still only a minority)

*Rare: satisfied in <1% of studies; uncommon: satisfied in 1%–20% of studies; minority: satisfied in 20%–50% of studies; majority: satisfied in 50%–80% of studies; very common: satisfied in 80%–99% of studies; almost always: satisfied in >99% of studies. For supporting evidence for these estimates, see references cited in the text.

**The situation is improving in recent years for clinical trials.

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Mental health research priorities for Europe

Wykes T, Haro JM, Belli SR, et al. The lancet. Psychiatry 2015;**2**(11):1036-42

- Research into mental disorder prevention, mental health promotion, and interventions in *children, adolescents, and young adults*
- Focus on the development and *causal mechanisms of mental health symptoms*, syndromes, and wellbeing across the lifespan
- Develop and maintain *international and interdisciplinary research networks* and shared databases
- Develop and *implement better interventions* using new scientific and technological advances
- *Reduce stigma and empower service users* and careers in decisions about mental health research
- Establish *health-systems and social-systems research* that addresses quality of care and takes into account sociocultural and socioeconomic contexts and approaches

The mental health challenges: Example - Depression

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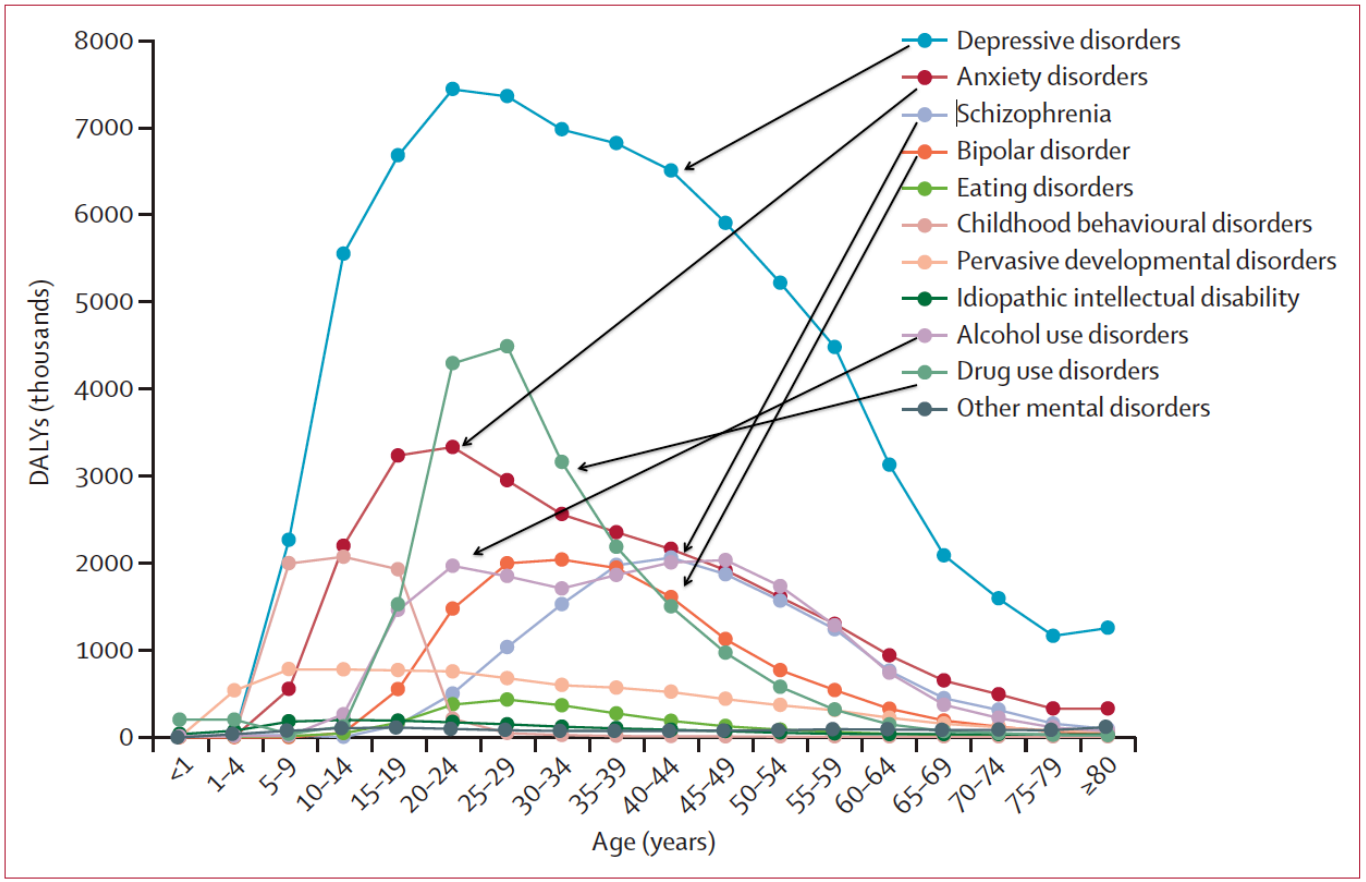
Depression:
Disability Adjusted Life Years (DALYs)



Whiteford HA, Degenhardt L, Rehm J, et al. Global burden of disease attributable to mental and substance use disorders: findings from the Global Burden of Disease Study 2010. *Lancet.* Nov 9 2013;382(9904):1575-1586.

Trends of DALYs for 2020

Rank	Worldwide			Developed regions			Developing regions		
	Disease or injury	DALYs ($\times 10^6$)	Cum %	Disease or injury	DALYs ($\times 10^6$)	Cum %	Disease or injury	DALYs ($\times 10^6$)	Cum %
- -	**All causes**	1388·8	- -	**All causes**	160·5	- -	**All causes**	1228·3	- -
1	Ischaemic heart disease	82·3	5·9	Ischaemic heart disease	18·0	11·2	Unipolar major depression	68·8	5·6
2	Unipolar major depression	78·7	11·6	Cerebrovascular disease	9·9	17·4	Road-traffic accidents	64·4	10·8
3	Road-traffic accidents	71·2	16·7	Unipolar major depression	9·8	23·5	Ischaemic heart disease	64·3	16·1
4	Cerebrovascular disease	61·4	21·1	Trachea, bronchus, and lung cancers	7·3	28·0	Chronic obstructive pulmonary disease	52·7	20·4
5	Chronic obstructive pulmonary disease	57·6	25·3	Road-traffic accidents	6·9	32·3	Cerebrovascular disease	51·5	24·6
6	Lower respiratory infections	42·7	28·4	Alcohol use	6·1	36·1	Tuberculosis	42·4	28·0
7	Tuberculosis	42·5	31·4	Osteoarthritis	5·6	39·5	Lower respiratory infections	41·1	31·4
8	War injuries	41·3	34·4	Dementia and other degenerative and hereditary CNS disorders	5·5	43·0	War injuries	40·2	34·6
9	Diarrhoeal diseases	37·1	37·1	Chronic obstructive pulmonary disease	4·9	46·0	Diarrhoeal diseases	37·0	37·6
10	HIV	36·3	39·7	Self-inflicted injuries	3·9	48·4	HIV	34·0	40·4

Murray CJ, Lopez AD. Alternative projections of mortality and disability by cause 1990-2020: Global Burden of Disease Study. Lancet. May 24 1997;349(9064):1498-1504.

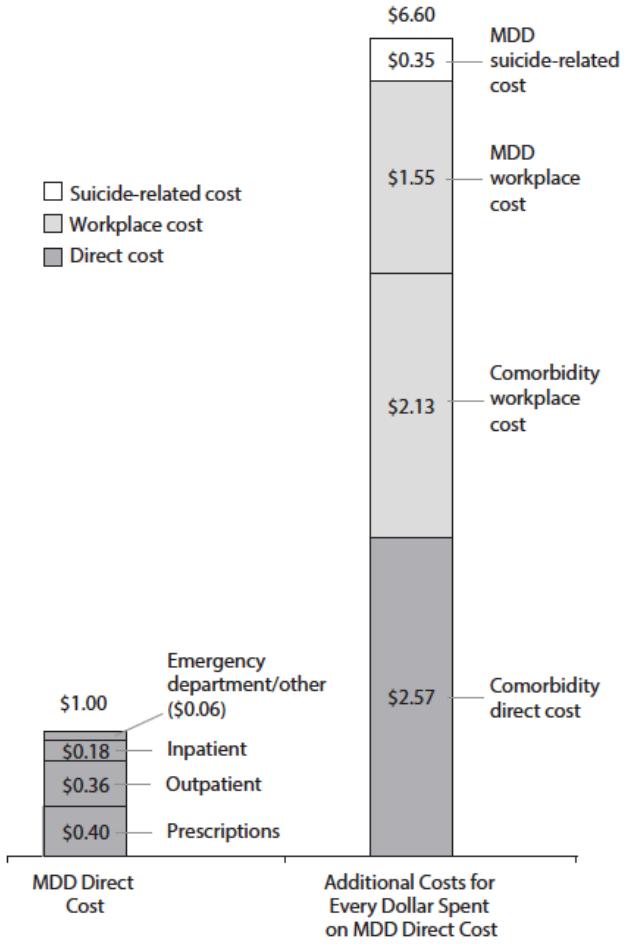
Eating disorders
Brain tumor
Neuromuscular disorders
Parkinsons disease
Epilepsy

Table 13: Mental illness costs expecte
Global cost of mental health

	Low- and Middle-Incor Countries		
	Direct Costs	Indirect Costs	To Cos Illn
2010	287	583	
2030	697	1,416	

Anxiety disorders
Psychotic disorders
Dementia
Mood disorders
0

Figure 2. Additional Costs of Individuals With Major Depressive Disorder (MDD) for Every Dollar Spent on MDD Direct Cost in 2010



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illions of 2010 US$

	World	
	Indirect Costs	Total Cost of Illness
	1,671	2,493
	4,051	6,046

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Applied Computational Psychiatry

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Applied Computational Psychiatry:

A Roadmap for the Development of Applied Computational Psychiatry

Martin P. Paulus, Quentin J.M. Huys, Tiago V. Maia

DOI: http://dx.doi.org/10.1016/j.bpsc.2016.05.001

Applied Computational Psychiatry

- Different **Model** Approaches:
  - biophysically based (e.g. channels and synpases)
  - connectionist and neural (e.g. PDP computational units)
  - Algorithmic (e.g. reinforcement)
  - Normative (e.g. Bayes-based)
- **Machine Learning:**
  - Random forest
  - Support Vector Machines
  - Deep Learning Nets

Goals

- Identify mechanistically interpretable parameters.
  - "how does the system work?"
- Integrate measurements across units of analysis.
  - "relate behavior to circuits"
- Classify individuals into different classes.
  - "separate health from pathology"
- Predict class membership (current and future)
  - "identify individuals at risk for bad outcomes"

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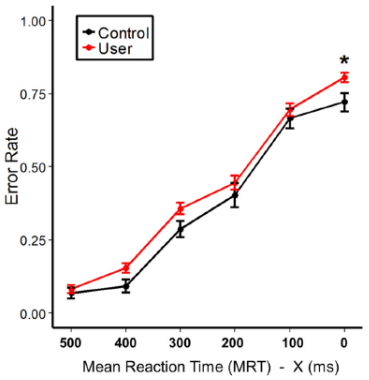
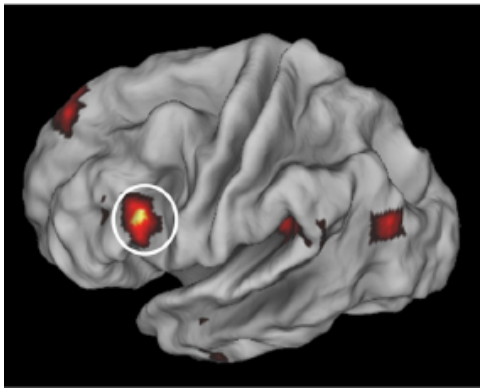
Computational Psychiatry

Old Approach:

Behavior

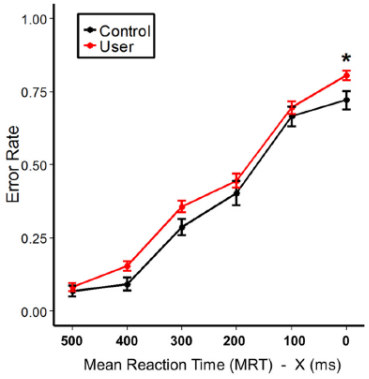


Brain Processing

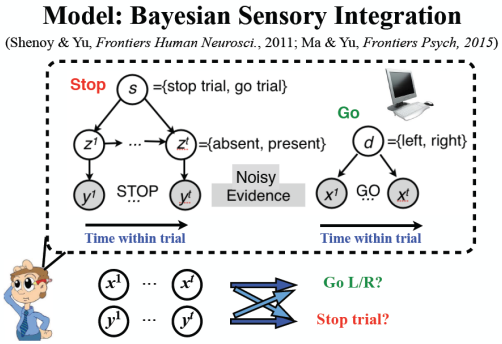


New Approach:

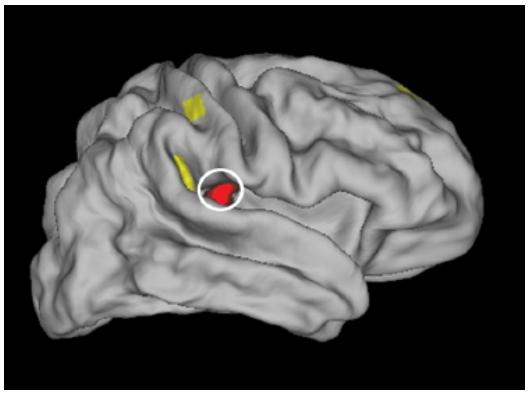
Behavior



Processing Model:



Model-derived Brain Processing



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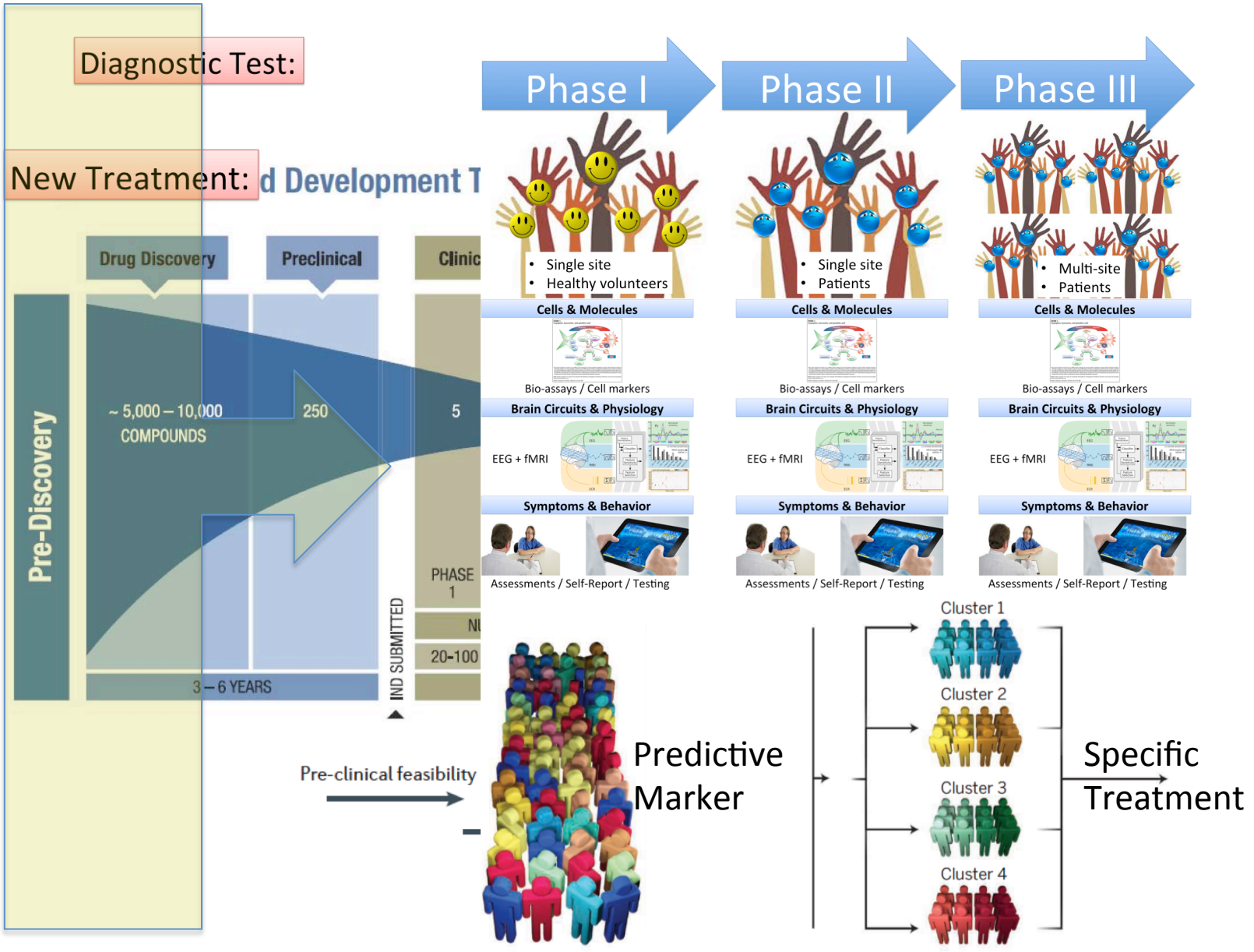
General Approach To Develop Tests And Interventions



Future Directions

- Implementation of Computational Approaches at all levels:

	Preclinical	**Phase I(a)**	**PhaseI(b)**	**Phase II**	**Phase III**	**Phase IV**
Drug Development Analog ORBIT(61)	Target (a) identification, (b) optimization	Safety / Tolerability Define	experimental medicine / target engagment Refine	Small Scale Efficacy Proof of Concept / Pilots	Large Scale Efficacy Efficacy Trial	Post-marketing Effectiveness
Time Line	Discovery (~ 6 years)		Development (~ 7 - 12 years)			
Goals	**"to identify probe(s) / measure(s) / model(s) / intervention(s)"**	**"to establish a reliable / robust probe(s) / measure(s) / model(s) / intervention(s)"**	**"to establish target process and engagement / model application / intervention engagement"**	**"to establish clinical efficacy and validity"**	**"to confirm clinical validity and demonstrate outcome improvement"**	**"new applications"**
Stages	Identification		Validation		Launch Readiness / Release	
Population	Healthy Volunteers (HV)	HV	HV, Target Population(s) TP	TP	TP	new TP
Study Type	cross-sectional (cs)	cs, longitudinal (l)	cs, l, experimental design(s)	Randomized Controlled Trial (RCT)	RCT	cs, l, RCT
Sites	single / few sites	single - multi-site	single / few sites	single - multi-site	multi-site	single / few sites
Study Size	small n	small to large n	medium n	large n	large n	small n

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Bayesian Adjustment of Inhibitory Control In Methamphetamine Dependence

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Stimulant Dependence

- Stimulants
  - Cocaine
  - Methamphetamine
  - Amphetamine
- 12 – 15% ever tried stimulants.
- 1-3% have stimulant dependence.
- Stimulants are the third most common cause for substance use treatment.

Figure 2.2 Past Month Use of Selected Illicit Drugs among Persons Aged 12 or Older: 2002-2008

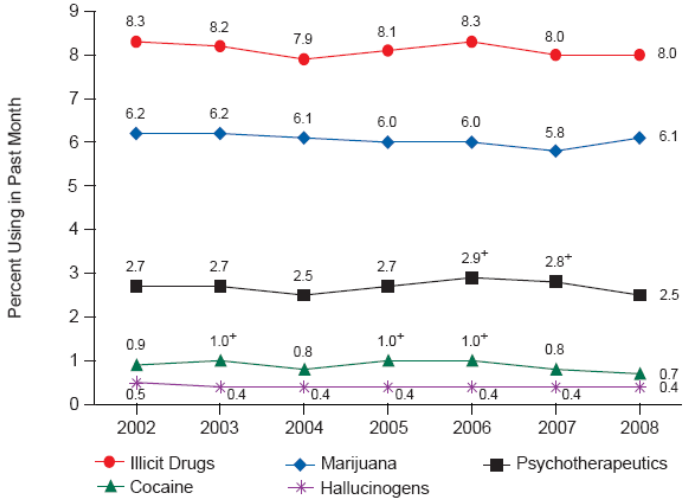


Figure 5.6 Past Year Methamphetamine Initiates among Persons Aged 12 or Older and Mean Age at First Use of Methamphetamine among Past Year Methamphetamine Initiates Aged 12 to 49: 2002-2008

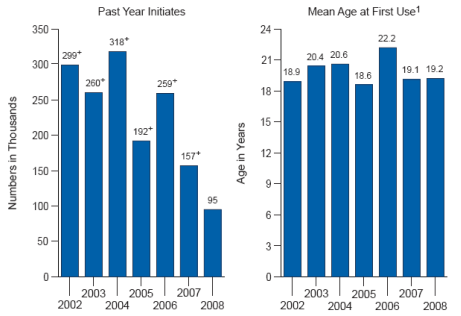
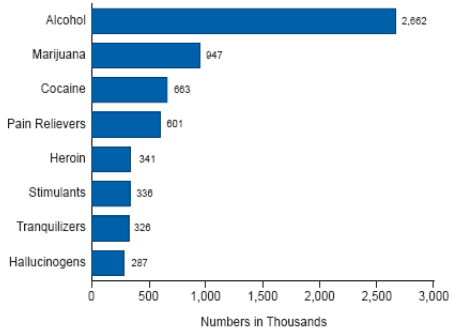


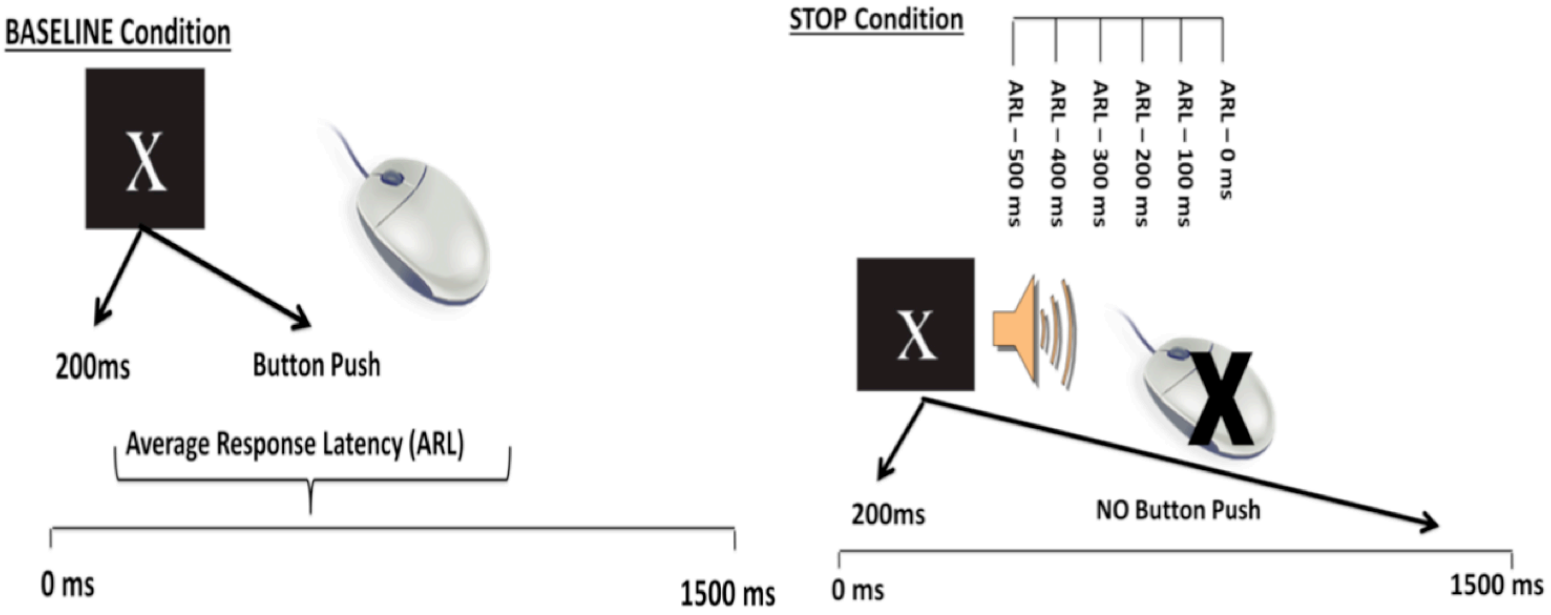
Figure 7.8 Substances for Which Most Recent Treatment Was Received in the Past Year among Persons Aged 12 or Older: 2008



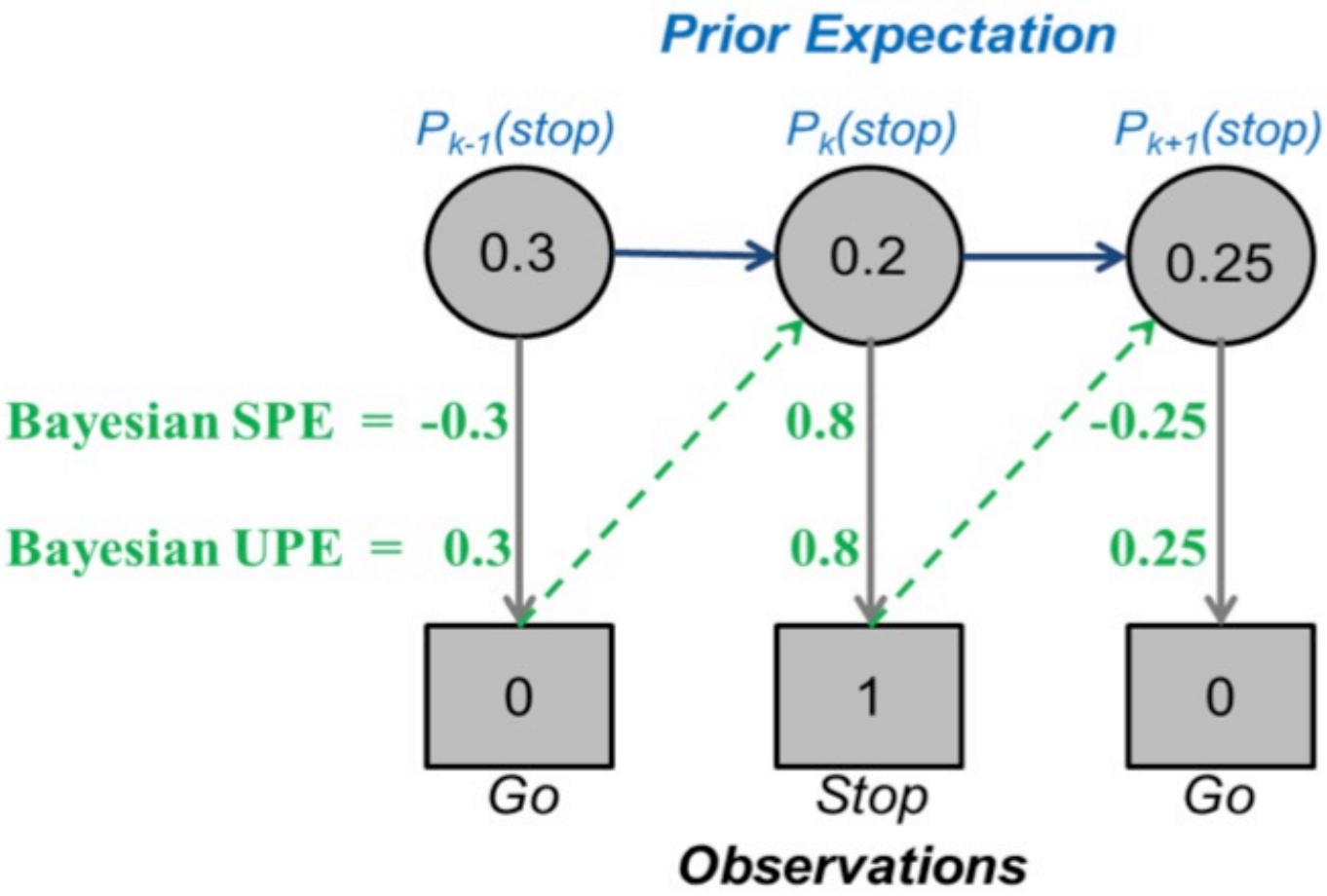
Goal of the Study:

- To identify any difference between methamphetamine dependent individuals (MDI) and healthy control subjects (CS) in their neural representation of
  - 1) **trial-wise expectations of inhibitory response**, and
  - 2) Bayesian prediction errors needed for updating those expectations.

Stop Signal Task

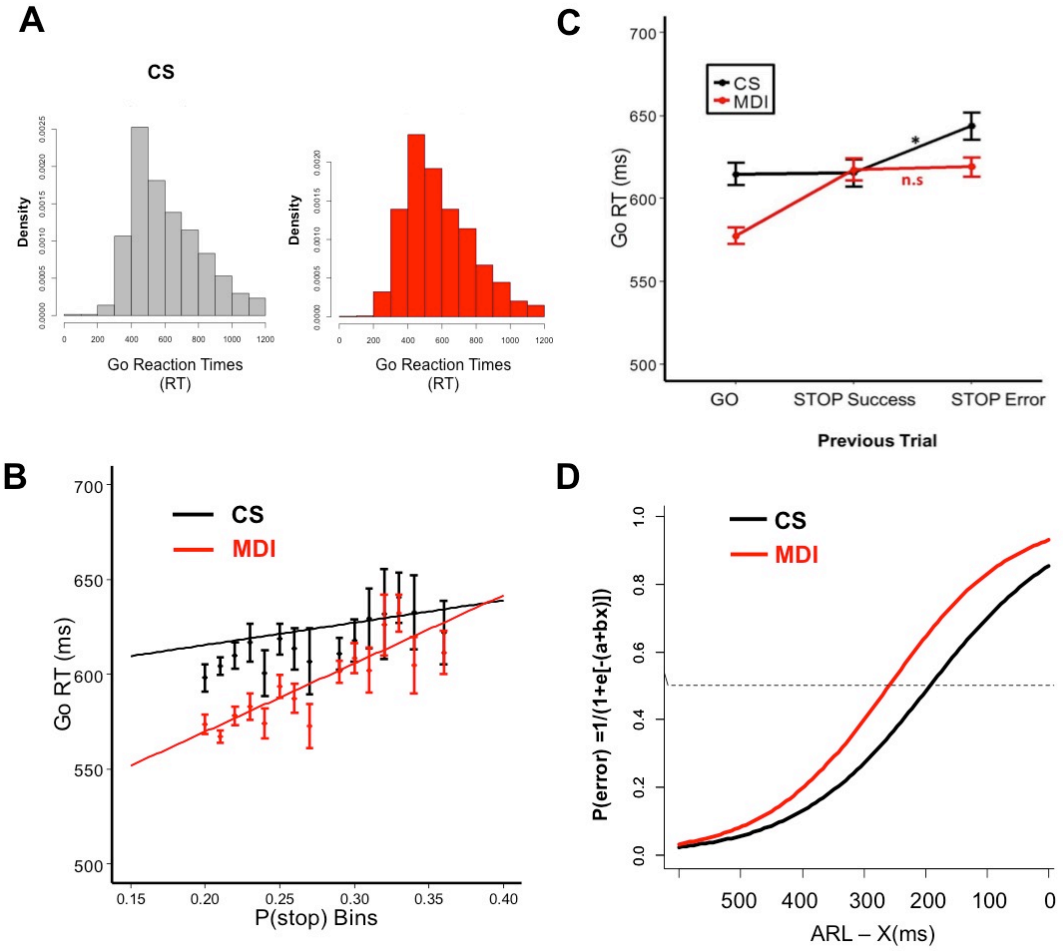


Bayesian Prediction Error:



Behavioral Effects

- MDI fail to adjust response latency as a function of prior stop error.



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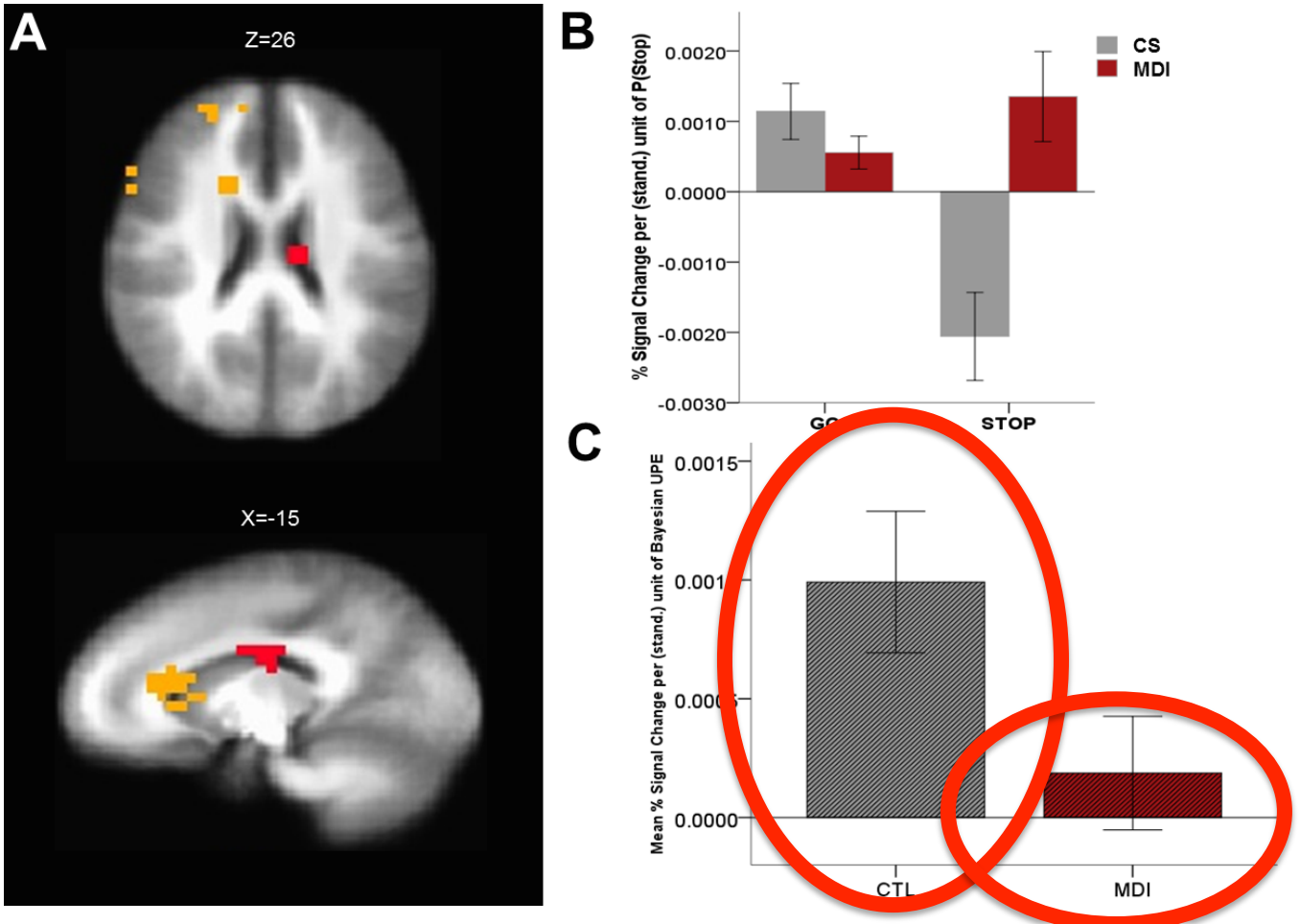
Group difference in sensitivity to surprising trials: Caudate



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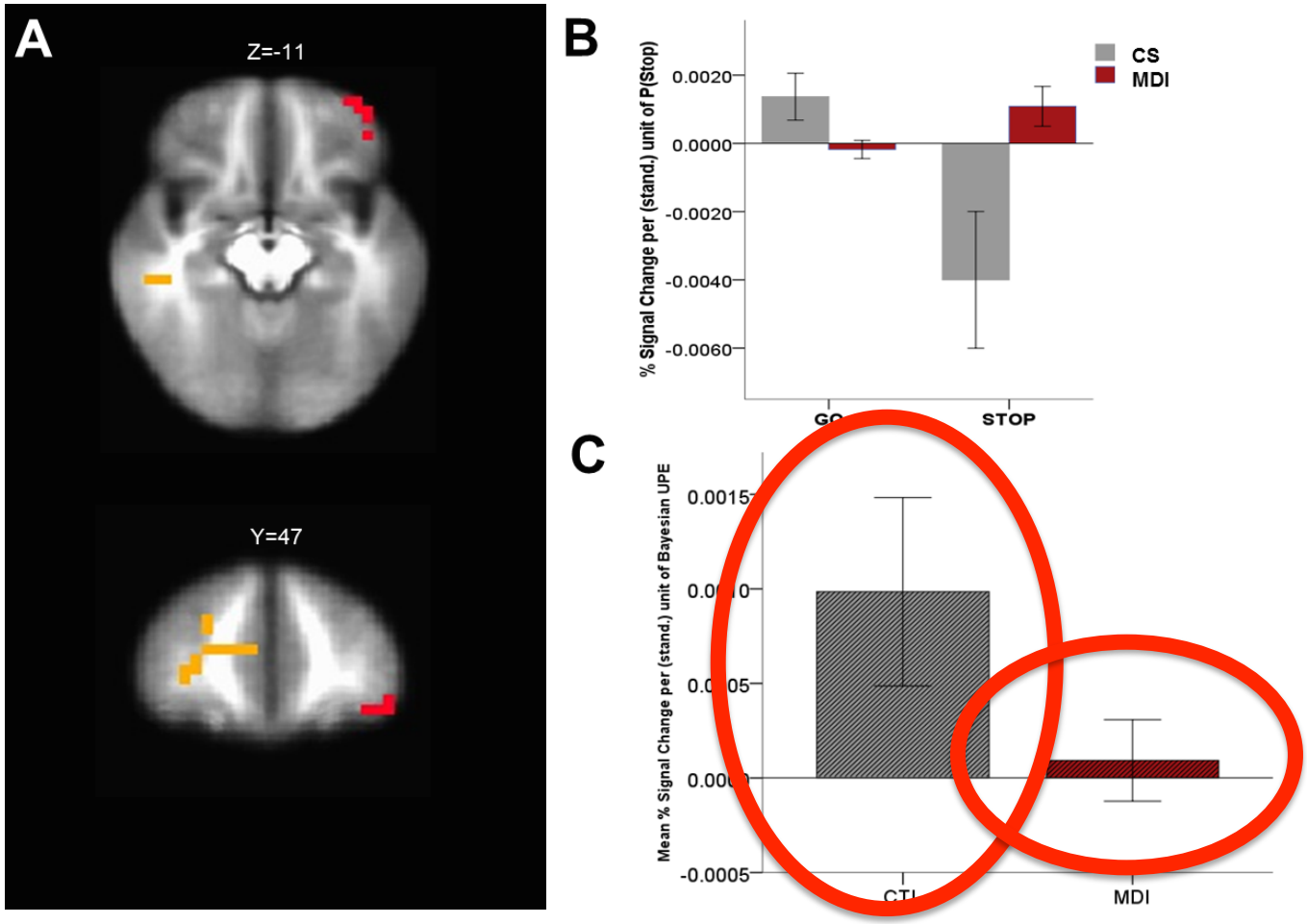
Group difference in sensitivity to surprising trials: IFC & DLPFC



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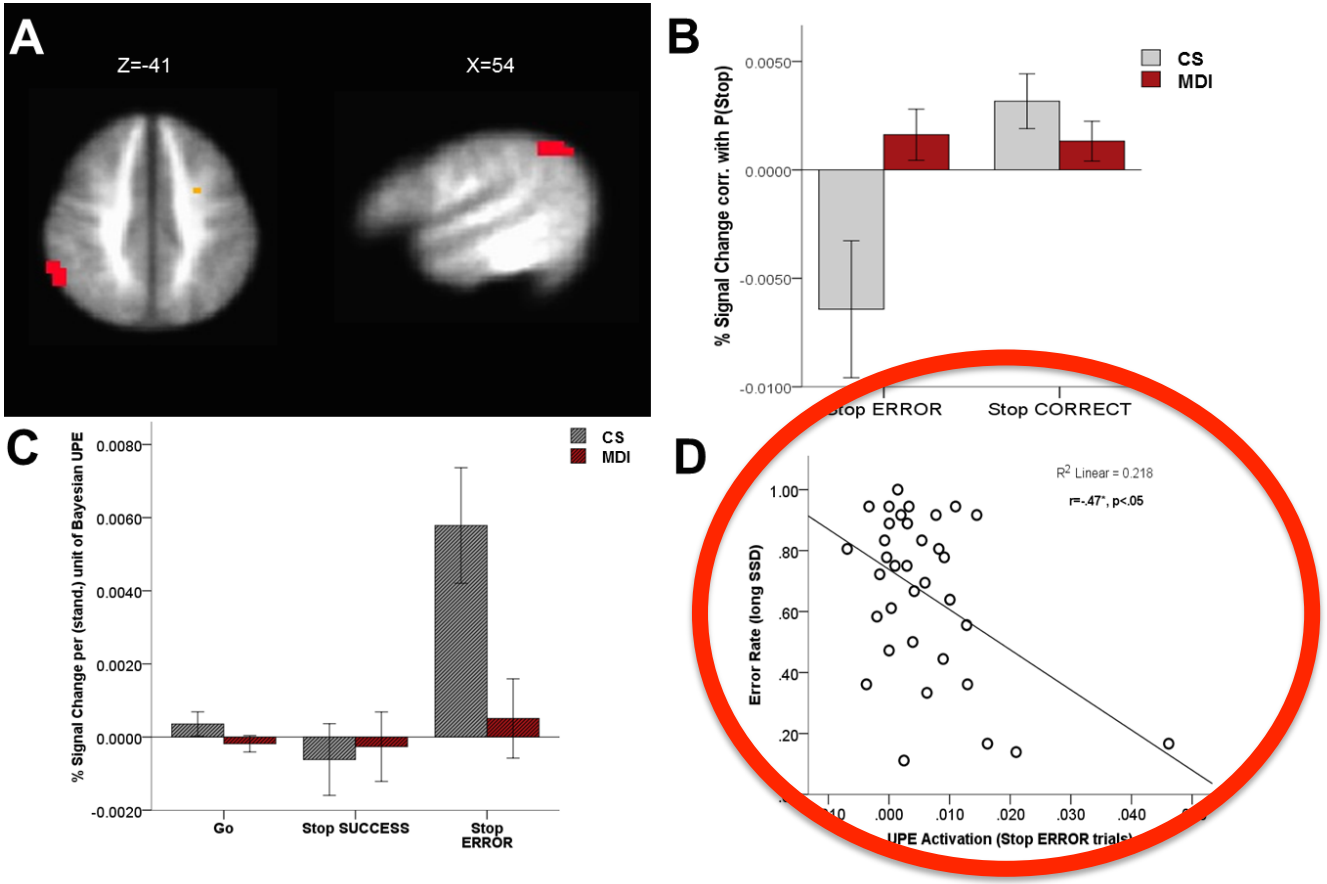
Modulation Of Neural Activation And P(stop): Relation To Inhibitory Success



Summary

- MDI: **reduced neural activation** associated with
  - Higher error likelihood on more challenging stop trials (i.e., longer SSD)
  - No RT slowing following Stop error trials
  - Trial-level Bayesian prediction error signals in frontal, parietal, and subcortical areas.

Implication

- Methamphetamine dependence:
  - **Poorer tracking of expectancy violation, i.e., weaker sensitivity to surprising task events.**
  - Less prepared for switching strategy in response to significant changes in the environment (e.g., sudden change in reward rate).

- Can we develop “computational cognitive control coaches”?

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Learning Dysfunctions Anxious Individuals