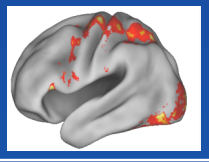
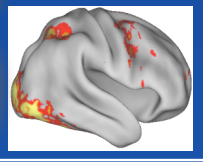


CNTRICS



Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia

Anatomy of A Translation: A Proposed Framework for Optimizing a Cognitive Task for Use in a Clinical Trial

or

“how the heck would we actually do this”

How to get out of here!

4:44P
4:49P
4:54P
4:59P
5:04P
5:09P
5:14P
5:19P
5:24P
5:29P
5:34P

5:39P
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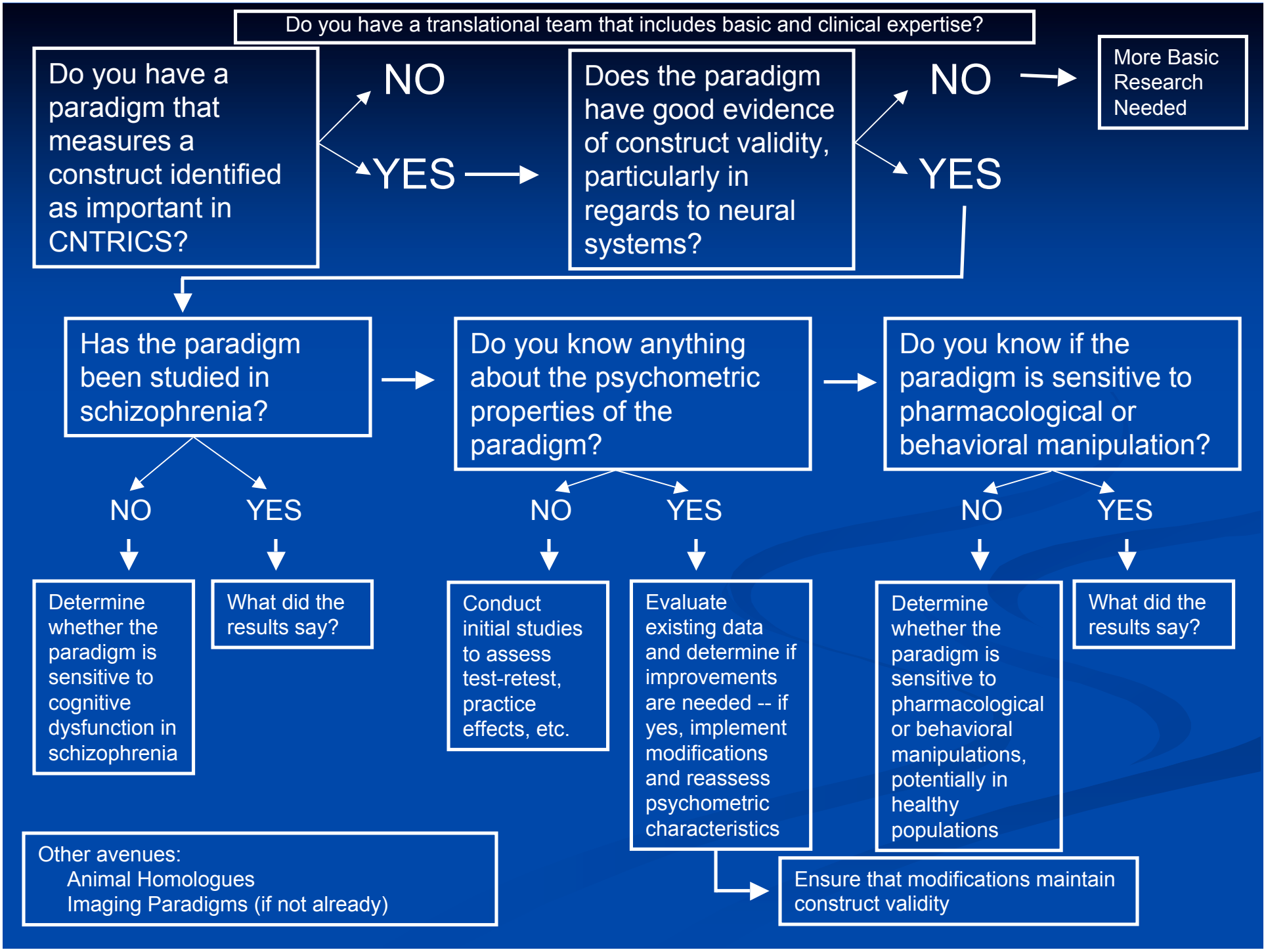
Thanks to CNTRICS Executive Board Team for development of ideas


Do you have a translational team that includes basic and clinical expertise?
Do you have a paradigm that measures a construct identified as important in CNTRICS?
NO
YES
Does the paradigm have good evidence of construct validity, particularly in regards to neural systems?
NO
More Basic Research Needed
YES
Has the paradigm been studied in schizophrenia?
NO
Determine whether the paradigm is sensitive to cognitive dysfunction in schizophrenia
YES
What did the results say?
Do you know anything about the psychometric properties of the paradigm?
NO
Conduct initial studies to assess test-retest, practice effects, etc.
YES
Evaluate existing data and determine if improvements are needed -- if yes, implement modifications and reassess psychometric characteristics
Do you know if the paradigm is sensitive to pharmacological or behavioral manipulation?
NO
Determine whether the paradigm is sensitive to pharmacological or behavioral manipulations, potentially in healthy populations
YES
What did the results say?
Other avenues:
Animal Homologues
Imaging Paradigms (if not already)
Ensure that modifications maintain construct validity

Who should be on a translation team?

- Basic Cognitive Scientist(s) with expertise in the domain of interest and with the cognitive paradigm of interest
- Clinical Cognitive Neuroscientist(s) with expertise in studying cognitive deficits in the domain of interest in schizophrenia
- Drug Development Expert(s) with expertise in conducting early and/or late phase clinical trials
- Psychometrician(s) with expertise task design and analysis
- Animal Cognitive Neuroscientist(s) with expertise in the development of animal models in the cognitive domain of interest

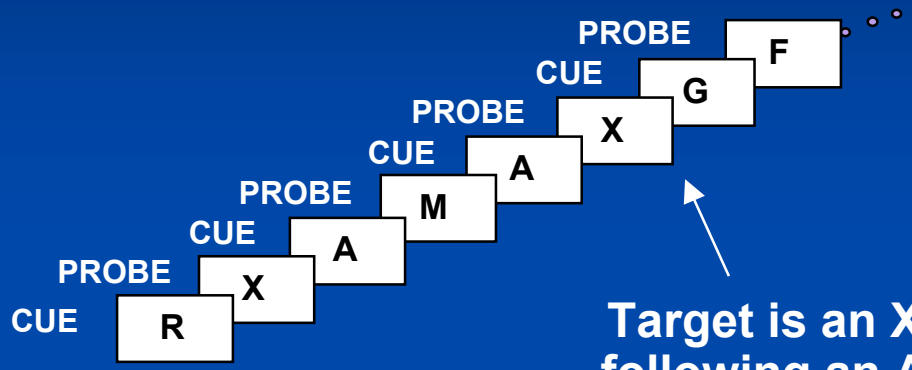
Has the paradigm been studied in schizophrenia?

- If similar task has been used, and found to elicit deficits, may be “close enough”
- If not, may want to do a pilot study to see if the paradigm is sensitive to the cognitive deficits present in schizophrenia
  - May wish to compare to other tasks in the same domain already known to tap the cognitive deficit of interest

Do we know anything about its psychometric properties?

- Two potentially dissociable areas:
  - Nature of the task
    - Length
    - # of critical trials
    - Ease of administration, understandability of instructions
    - Can it be done in the same way at multiple sites?
  - Classic Psychometric
    - Reliability
    - Practice Effects
    - Ceiling/Floor Effects

Nature of the Task - AX-CPT Example



		CUE	
		VALID	INVALID
PROBE	TARGET	A-X (70%)	"B-X" (10%)
	NONTARGET	"A-Y" (10%)	"B-Y" (10%)

- Correct responding requires maintenance of prior context (i.e. cue)
- Response biases manipulated through target frequency
- Maintenance demand manipulated through cue-probe delay

Nature of the Task - AX-CPT Example

- "Standard Version"
  - Long (20-30 minutes):
    - 200 trials
    - short and long delays between cues and probes
  - Small # of "critical" trials (10%)
- Potential Modifications:
  - Only long delay trials
  - Does long delay need to be 5 seconds?
  - Increase number of critical trials

How would you validate that you are maintaining construct validity?

- Compare directly to performance on original version:
  - Convergent Validity - relationship to other measures of same construct
  - Same pattern across conditions if that is predicted ("signature of that process")
  - Group discrimination - sensitivity to cognitive deficit present in schizophrenia
  - Interpretability - differential versus generalized deficit
  - Relationships to clinical symptoms, course, etc.
  - Change sensitivity - pharmacological or behavioral
  - Neural systems - functional imaging

Classic Psychometrics

- Examine test-retest, practice and ceiling effects:
  - Can multiple baselines help reduce practice effects (same day, subsequent days?)
    - Get person in “trained” state
  - Short term and longer term test-retest
    - 2 weeks
    - 4 weeks
    - Months
  - Run longer versions, compare parameters for different task lengths
    - e.g., run 200 trials, see if reliability is as good with 100
  - Multiple sites -- how easy it is to train, get quality data

AND!!!

- Measure relationship to other tests that you might use in later “phases”

Is there any evidence this paradigm might be sensitive to cognitive change?

- Start small, work up?
  - Start with drug/technique known to elicit some improvement
    - Single dose
    - Modafinil, Amphetamine (only in certain folks), etc.
- Measure effect of “nuisance” variables:
  - Nicotine
  - Caffeine
  - Sleep amount and cycle
  - Fatigue

And …

- Compare to existing measures (MATRICS, BACS, etc.)

Will the paradigm work in imaging?

- Imaging measures could serve as useful biomarkers
  - Did the drug/technique get in and change anything, even if you can't see it in behavior?
  - Do baseline individual differences in functional activation predict responsivity to drug/technique
  - Do initial changes in functional activation predict responsivity to drug/technique

Is there any animal version, or can we develop one?

- Would vastly add preclinical testing to have viable animal homologues that predict performance on human versions
- Not nearly enough explicit parallel development
- Need the unique expertise of human and animal people to work together to develop paradigms that meet the needs and constraints of both worlds

Other Ideas?

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