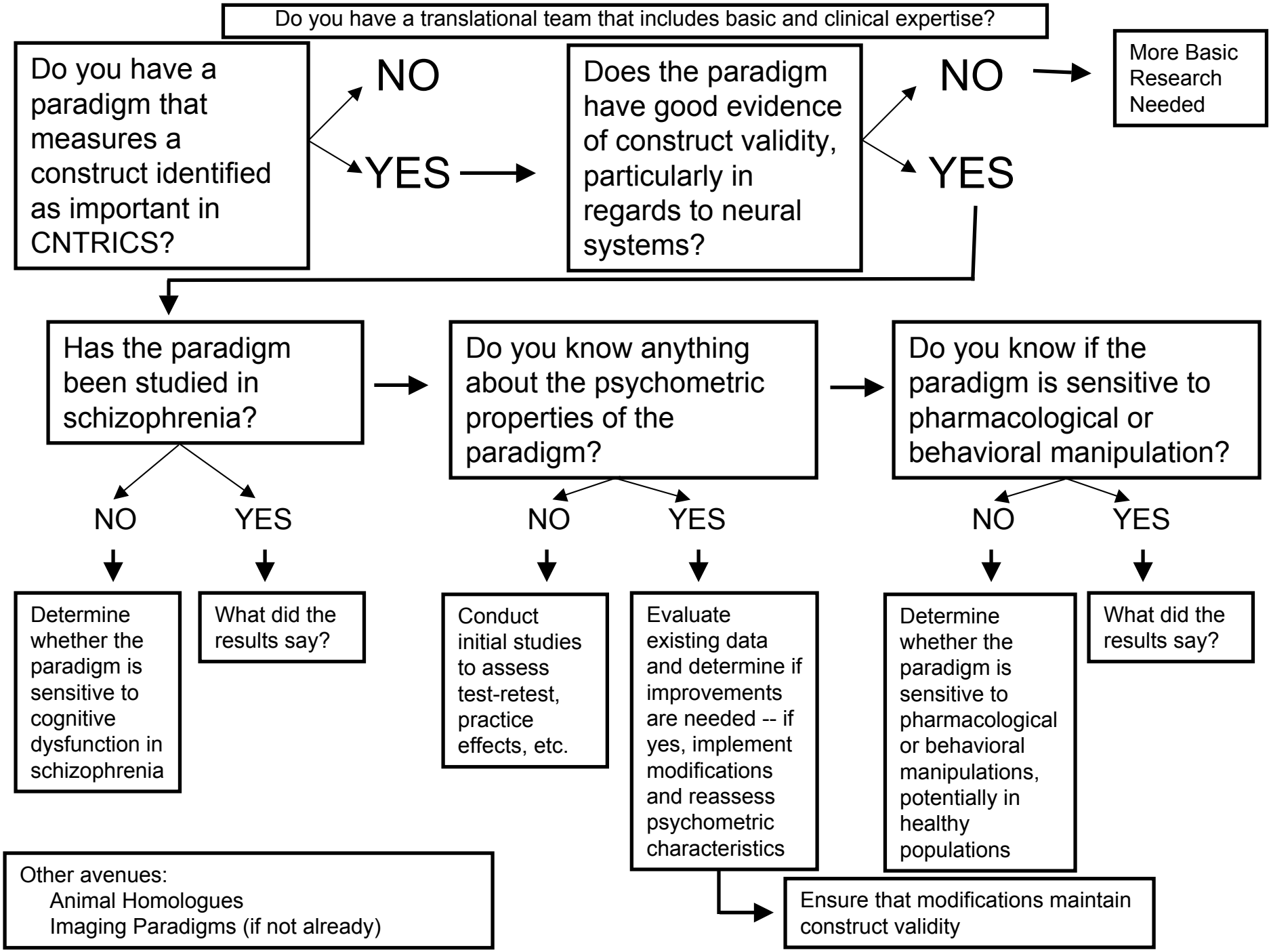

CNTRICS
Cognitive Neuroscience Treatment Research
to Improve Cognition in Schizophrenia

Goals

- Identify validated tasks from cognitive neuroscience that tap the targeted cognitive constructs of interest
  - Web based nomination portal
  - Emails to all people who have participated in any CNTRICS survey or meeting
  - Advertisements in SFN Nexus and CNS newsletter
- Collate materials for preview by individuals at this meeting
  - Summary documents sent to you by email
  - PDFs available on password protected site
- Consensus building discussions, based on data provided in summary documents and relevant published work
- Identify 1-2 most “promising” tasks to recommend for future development

Criteria

- **<u>Strong construct validity as a measure of the targeted cognitive construct</u>**
- **Clarity of the link to a specific neural circuit**
- **Clarity of the understanding of the cognitive system or mechanisms**
- **Availability of an explicit animal model**
- **Linked to neural systems through neuropsychopharmacology**
- **Practically amenable for use in human neuroimaging studies**
- **Strong evidence of impairment in schizophrenia:** Many nominated tasks may not have been studied in schizophrenia. Empirical evidence that a task elicits deficits in schizophrenia is not necessary if the task has good construct validity as a measure of one of the cognitive processes identified in the first CNTRICS meeting as being relevant to understanding the pathophysiology of schizophrenia. However, all else being equal, positive evidence that the task elicits deficits in schizophrenia, particularly if the design of the task allows a differential deficit interpretation, should be considered an advantage for a task.
- **Linked to functional outcome in schizophrenia:** The absence of evidence about links to functional outcome in schizophrenia should not be used to exclude tasks from consideration, as part of the goal of CNTRICS is to facilitate examination of such relationships in future research. However, all else being equal, positive evidence for a link to functional outcome in schizophrenia should be considered an advantage for a task.
- **Good psychometric properties:** The absence of evidence about psychometric characteristics such as test-retest reliability, practice effects, and floor-ceiling effects should not be used to exclude tasks from consideration, as part of the goal of CNTRICS is to facilities examination of such properties in future research. However, all else being equal, positive evidence for such characteristics should be considered an advantage for a task.


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
YES
Determine whether the paradigm is sensitive to cognitive dysfunction in schizophrenia
What did the results say?
Do you know anything about the psychometric properties of the paradigm?
NO
YES
Conduct initial studies to assess test-retest, practice effects, etc.
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
YES
Determine whether the paradigm is sensitive to pharmacological or behavioral manipulations, potentially in healthy populations
What did the results say?
Ensure that modifications maintain construct validity
Other avenues:
Animal Homologues
Imaging Paradigms (if not already)

Working Memory

- **Goal Maintenance:** The processes involved in activating task related goals or rules based on endogenous or exogenous cues, actively representing them in a highly accessible form, and maintaining this information over an interval during which that information is needed to bias and constrain attention and response selection.
    - **Nominated Tasks:**
        - ***AX-CPT/Dot Pattern Expectancy Task (selected)***
        - *Operation Span/Symmetry Span:*
            - » *Better measure of a different construct (Interference Control)*
            - » *Not clear what measure from Complex Span tasks reflect goal maintenance per se*
        - *Probabilistic Reversal Learning*
            - » *Better measure of a different construct (Reinforcement Learning)*
            - » *Not clear what measure from Complex Span tasks reflect goal maintenance per se*

AX-CPT/DPX

- Strengths:
  - Computational model suggesting cognitive and neural mechanisms
  - Convergent and divergent validity (correlates well with other putative measures of goal maintenance, correlates less well with measures of other constructs)
  - Functional neuroimaging data identifying activation of lateral PFC, dorsal parietal
  - Performance modulated by dopaminergic drugs in healthy individuals and in schizophrenia. Performance sensitive to MK-0777.
  - Performance modulated by cognitive interventions.
  - Strong evidence of impairment in schizophrenia, including medication naïve, chronic, relatives, schizotypal both behavior and neuroimaging
  - Animal Model
    - Killcross Bi-Conditional Discrimination
      - Further work is needed to establish homology

AX-CPT/DPX

- What needs to be done?
  - Links to functional outcome need to be studied
  - Psychometric Properties:
    - Needs to be shortened
    - Test-retest, practice, ceiling/floor effects need to be improved (though MK-0777 data does not suggest strong practice effects)

Working Memory

- **Interference Control:** The processes involved in protecting the contents of working memory from interference from either other competing internal representations or external stimuli.
    - **Nominated Tasks:**
        - ***Complex Span Tasks (Operation Span/Symmetry Span)***
        - ***Recent Probes Task***
        - *Ignore Suppress Task*
            - » *Hard to model in animals*
            - » *Links to neural systems less clear than in recent probes task (multicomponential)*
        - *Inhibition of Currently Irrelevant Memories Task*
            - » *Not clearly a measure of interference control in Working Memory*
            - » *Seemed to be a better measure of interference control in episodic memory (and was considered in long term memory group)*
            - » *Hard to model in animals*

Complex Span Tasks

- Strengths:
  - Fabulous construct validity as a measure of interference control in working memory
  - Has been shown to predict important outcomes in healthy population (strongly related to gF, other outcomes)
  - Already very well developed psychometrically
    - Excellent test-retest reliability
    - Ceiling/Floor effect dealt with in the older adults (analogous to schizophrenia?)
  - Some initial data (from reading span versions) of impairment in schizophrenia, optimistic that it might do a very nice job of predicting functional outcome
- What needs to be done?
  - Need more data about its neural circuitry
    - Some data on activation of lateral PFC
  - Needs to be more extensively studied in schizophrenia
  - Need to examine whether it is modulated by neuropharmacological or behavioral manipulations
  - Do we need alternative versions for clinical trials? How much practice effect with same stimuli?
  - Unlikely to be able to develop animal version that is reasonably homologous

Recent Probes

- Strengths:
  - Excellent construct validity as a measure of interference control
  - Good evidence for involvement of DLPFC and left inferior frontal cortex
    - Functional Imaging
    - Lesion models
    - Older adults
  - Can use both verbal and non-verbal versions (has been done)
  - Conceptually possible to develop a homologous animal model
- What needs to be done?
  - Needs to be studied in schizophrenia
  - Psychometric properties need to be examined
    - Do we need alternative versions for multi-session studies?
  - Need to determine whether it is amenable to pharmacological or behavioral intervention
  - Development of animal model