



**Cognitive Neuroscience Treatment
Research
to Improve Cognition in Schizophrenia**

<http://cntrics.ucdavis.edu>

Translational Neuroscience

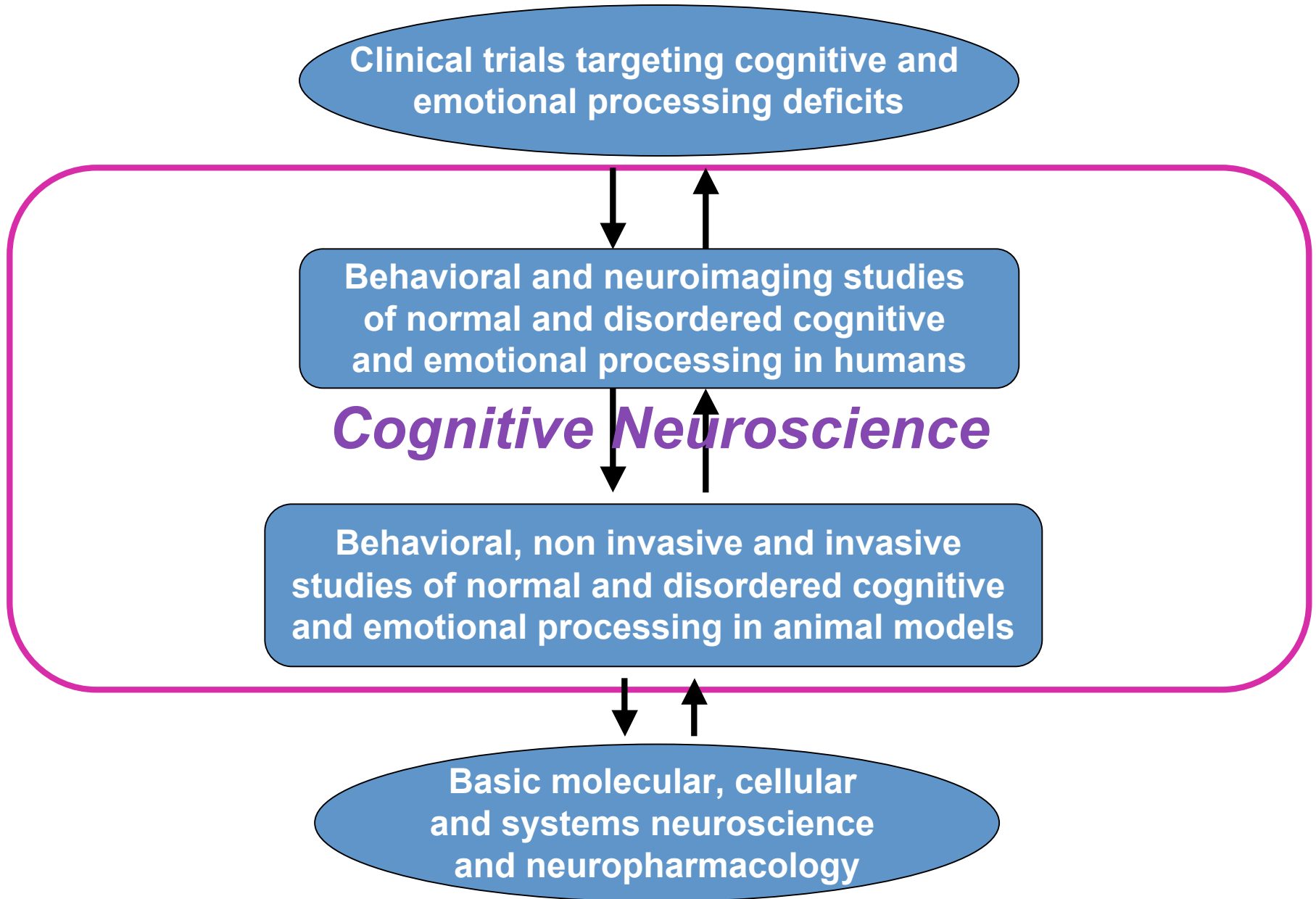
Clinical trials targeting cognitive and emotional processing deficits

Behavioral and neuroimaging studies of normal and disordered cognitive and emotional processing in humans

Cognitive Neuroscience

Behavioral, non invasive and invasive studies of normal and disordered cognitive and emotional processing in animal models

Basic molecular, cellular and systems neuroscience and neuropharmacology



CNTRICS

- Traditional clinical neuropsychological tests do not isolate specific cognitive processes that are associated with discrete neural systems
- Clinical neuropsychological tests are not amenable for incorporation into neuroimaging paradigms
- Most mammalian species used in screening pharmacological agents cannot perform clinical neuropsychological tests
- Translational research needs tools and constructs from cognitive neuroscience

The Challenges for CNTRICS I: cognitive task development

- Develop consensus regarding constructs from cognitive neuroscience that should be measured
- Need to optimize psychometric properties and practicalities of administration
- Identify tasks that provide valid measurement of relevant mechanisms

CNTRICS I

- 3 consensus building meetings over 2 years
- Identify cognitive systems and component processes with strong construct (and neural) validity *Biological Psychiatry July 2008 Vol 64 (1)*
- Identify measurement and pragmatic issues related to developing cognitive neuroscience measures into translational research tools *Schizophrenia Bulletin July 2008 34(4)*
- Identify a set of tasks for translation *Schizophrenia Bulletin 2009 35(1)*
- RFA MH-08-090 “Adapting Basic Cognitive Measures for Clinical Assessment in Schizophrenia” and ensuing RO1’s

Mechanisms Selected For Translation

- Perception
 - Gain control and perceptual integration
- Attention
 - Control of attention
- Executive Control
 - Rule generation and selection, Dynamic adjustments of control
- Working Memory
 - Goal Maintenance and Interference Control
- Long Term Memory
 - Relational encoding and retrieval
 - Item encoding and retrieval
 - Reinforcement learning
- Social and Emotional Processing
 - Affect Recognition and Evaluation

Next Steps: CNTRICS II

- Now that we are on the path towards having a set of efficient tasks that will measure key cognitive mechanisms targeted for treatment in schizophrenia how can this be leveraged to enhance translational research
- Imaging Biomarkers
- Animal Models

Imaging Biomarkers

- Meeting 4 (this one)
 - What is the physiological basis of the signals and how are they related to neural activity
 - What are the pragmatic and measurement issues related to developing these measures for use as biomarkers
- Meeting 6 (fall 2010)
 - Identifying specific imaging biomarkers for development

Animal Models

- Meeting 5 (April 2010)
 - What is homology
 - Issues related to the measurement of CNTRICS constructs in different species
 - Issues related to the use of animal models of putative pathophysiology in cognitive treatment development
- Meeting 7 (Spring 2011)
 - Identifying specific novel animal models for development

Biomarker

- “a characteristic that is objectively measured and evaluated as an index of a pathogenic process or a response to a therapeutic intervention”
- Validity- does it really reflect the pathogenic process of interest?
- Reliability- does it have the necessary measurement properties?

Utility of Imaging Biomarkers

- Leverages 50 years of progress in biomedical engineering and cognitive and systems neuroscience
- Allows us to conceptualize and measure the target of an intervention as a discrete neural system supporting the impaired cognitive and emotional processes that we seek to remediate
- In proof of concept and first into human studies
 - Can provide proof of pharmacodynamic effect in the brain
 - Can provide proof of mechanism of action
- In Phase II
 - Early effects in brain may predict clinical effects occurring later
 - Individual differences in brain activity or response may predict clinical effects-personalized medicine

Challenges to Address in this Meeting

- What is the physiological basis of the signal we measure with different potential biomarker method and how are they related to neural activity and potential pathophysiological mechanisms?
- How do the direct effects of drugs on the coupling between neural activity and our signal of interest confound their use as biomarkers and how can this be controlled for?
- What is the reliability of each method and how can it be better measured and optimized?
- What are the unique challenges of using each method in multi-site studies and how can these be overcome?
- What are the pragmatic issues related to using each method during the treatment development process (early vs later phases)?