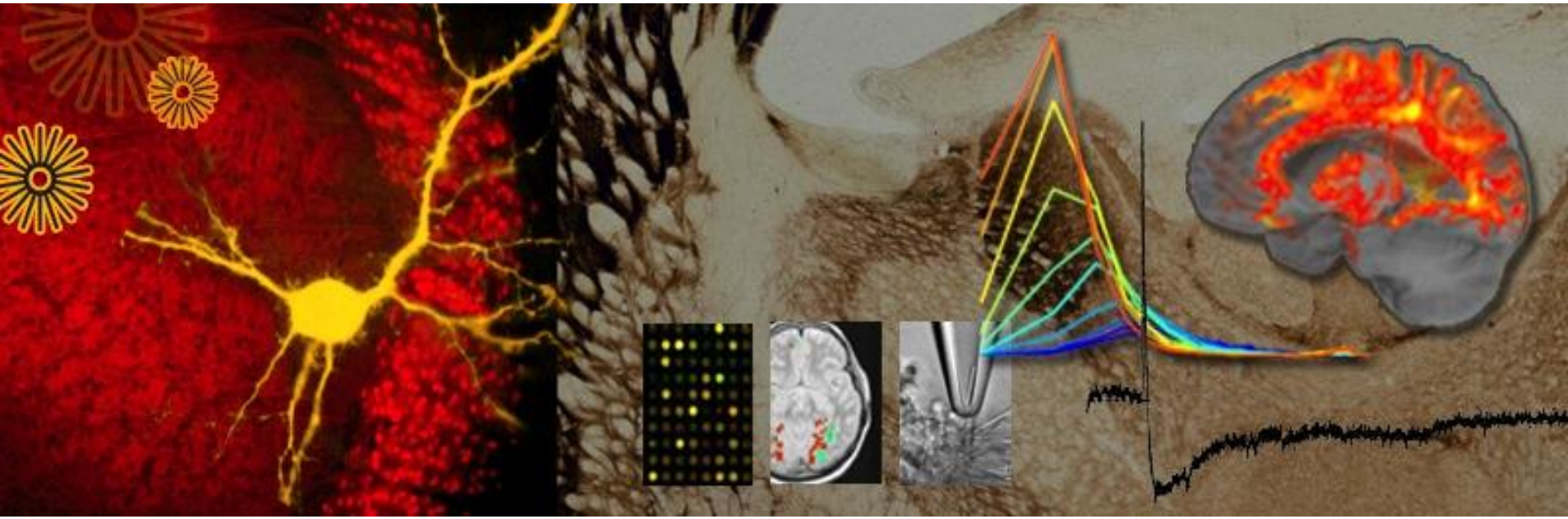
Cognitive Neuroscience at the Bedside
CNTRICS, CNTRACs and Beyond



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Disclosures

None

Overview

- CNTRICS and CNTRACS, principles and process
- Can the tools and constructs of cognitive neuroscience be used to enhance translational research and provide behavioral measures and imaging biomarkers in clinical trials and experimental medicine studies?

MATRICS

Measurement And Treatment Research to Improve Cognition in Schizophrenia

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Tools and Constructs of Cognitive Neuroscience: The Opportunities

- Measure specific deficits in discrete cognitive systems and component processes
- Linked to identifiable neural systems
- Functionally regulated by identifiable neuromodulatory systems
- Distinguish between specific deficits versus generalized deficits such as sedation, attention lapsing, dysphoria, poor test taking skills, etc.
- Bridge human and animal models of cognition, facilitate translational research

Tools and Constructs of Cognitive Neuroscience: The Challenges

- No general consensus regarding constructs from cognitive psychology that should be measured
- Uncertain psychometric properties and practicalities of administration
- No generally agreed upon standard versions of tasks for measuring specific mechanisms
  - Parameters, manipulations, etc.

cntrics.ucdavis.edu for ePrime task downloads, bibliography and pdf's of task and imaging biomarker recommendations

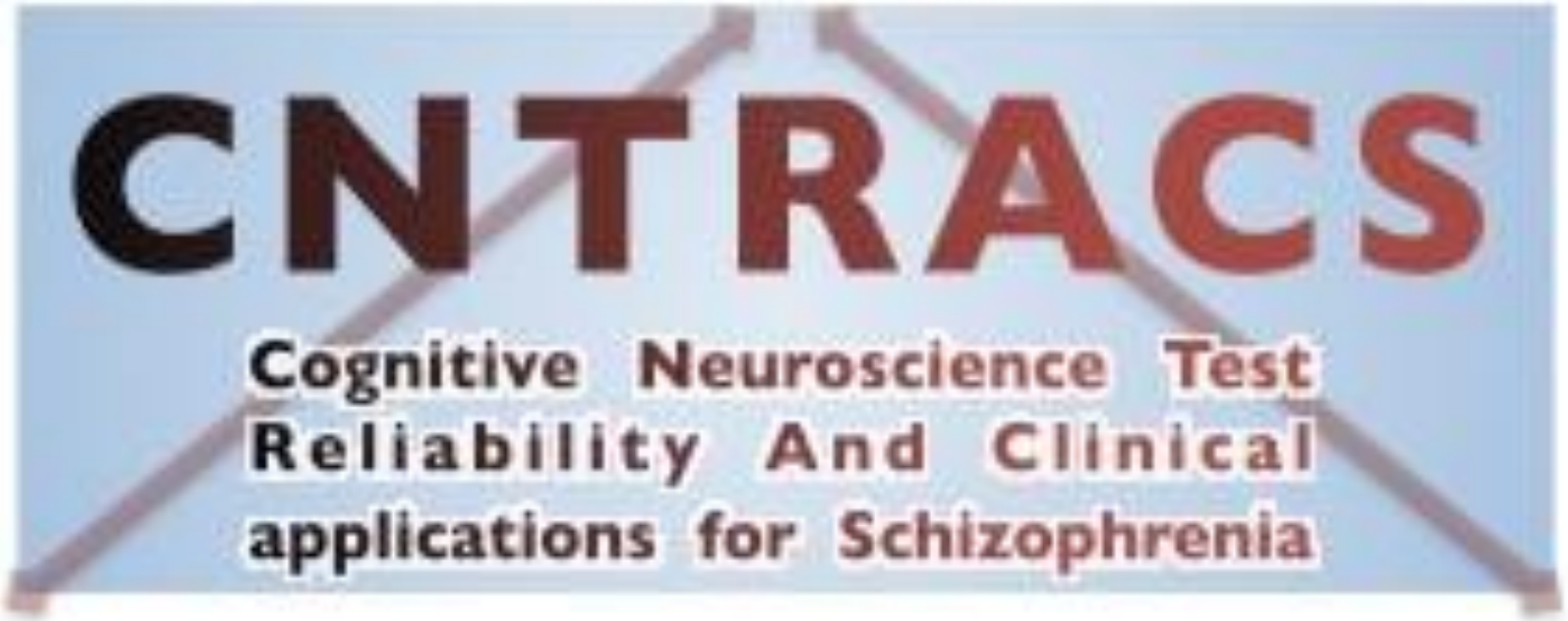
Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia

- Bring together individuals from academia, industry and government to facilitate translation from basic cognitive neuroscience to clinical neuroscience
  - A particular emphasis on translation for use in treatment research
  - Funded by R13 from NIMH
- Consensus Building Process
  - Pre-meeting surveys
  - Keynotes by basic scientists to frame breakout group process
  - Focused breakout groups
  - Products of Breakout group brought back to large group for consensus
  - Post meeting papers written and subjected to peer review

Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia

- Meeting 1: Constructs
- Meeting 2: Psychometrics
- Meeting 3: Tasks
- Meeting 4 Imaging Biomarkers
- Meeting 5 Animal Models
- Meeting 6 Imaging Biomarkers
- Meeting 7 Animal Models

– 30+ publications, Special Issues in Biological Psychiatry (2), Schizophrenia Bulletin (3), Neuroscience and Biobehavioral Reviews (1)
– 23 tasks, 20 imaging/electrophysiological biomarker paradigms
– Imaging and EEG/ERP candidate biomarkers
– Animal behavior paradigms



cntrics.ucdavis.edu for CNTRaCs bibliography, pdf's and downloadable Eprime scripts of optimized paradigms

Overarching Goals of CNTRaCS

- Assess cognitive mechanisms and neural systems that relate to fundamental components of human behavior
- Optimize tasks that have been developed to test cognitive neuroscience theories so that they can be used to improve clinical outcomes in schizophrenia, by
  - minimizing task length
  - simplifying and standardizing task administration across multiple sites ("idiot" proof)
  - maximizing sensitivity and selectivity in assessing the specific cognitive mechanisms of interest (address generalized deficit concerns, maximize effect sizes)
  - enhancing reliability and minimize floor and ceiling effects
- Bring together a collaborative translation team that represents significant expertise from the many fields necessary to achieve this optimization successfully
- Ensure that alterations in task parameters designed to enhance the psychometric properties of the task do not alter its construct validity

CNTRaCs Consortium

Wash U., U.C. Davis, MPRC, U. Minnesota, Rutgers

- 4 CNTRICS recommended tasks spanning domains of Cognitive Control (AX/DPX CPT, Episodic Memory (RISE) ,Perceptual Integration(JOVI) and Early Visual Perception (surround suppression, CCE)
- 2 large studies of 100+ subjects over 3 years
- Optimized tasks had:
- Moderate effect sizes
- Brief standardized administration (10-15 minutes)
- Good tolerability (comparable to MATRICS computerized tests)
- Adequate to moderate test –retest reliability
- Initial fMRI reliability data promising

CNTRaCS Studies

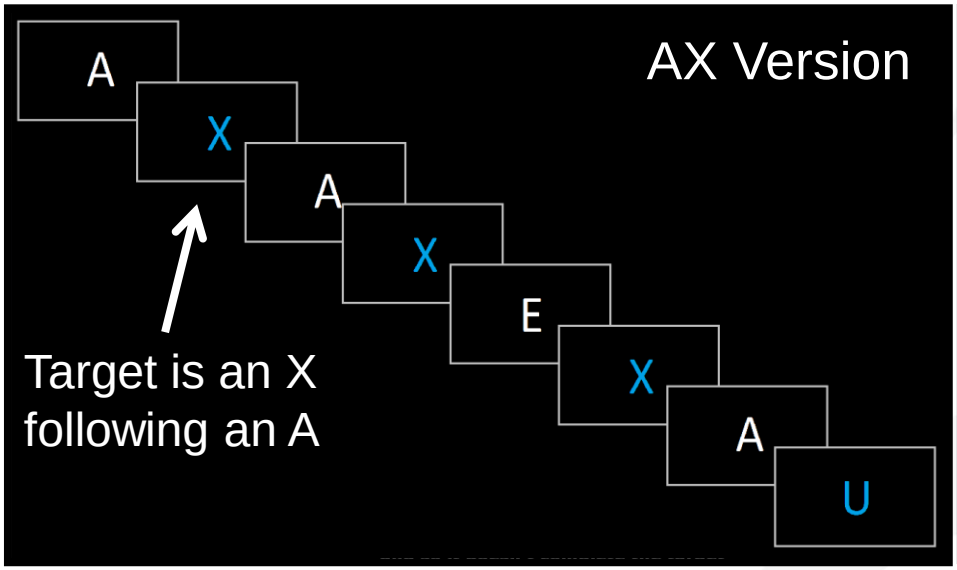
- Study 1 – Complete (~300 participants)
  - Generate standardized versions of each task in Eprime (easily available software)
  - Compare different versions of each task to identify ones that best meet the optimization goals
  - Used the data to modify, optimize and shorten tasks
    - http://cntracs.ucdavis.edu/publications.shtml
- Study 2 – Complete (~235 participants)
  - Test-retest reliability of optimized versions from Study 1
  - Relationship to functional outcome
  - Relationship to proxy measures of function
  - Relationship to subset of MATRICs battery tests
- Study 3 – Complete (~100 participants)
  - Imaging Biomarkers

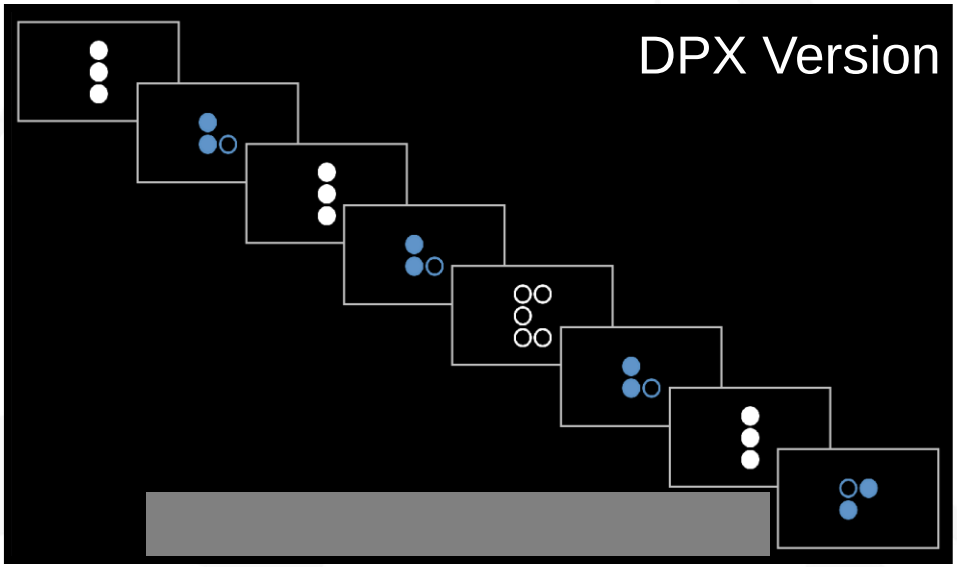
Goal Maintenance

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.

Goal Maintenance

Modified AX-Continuous Performance Test / Dot Probe Expectancy





- **Performance measures**
  - **BX Trials = Goal maintenance <u>reduces</u> interference**
  - **AY Trials = Goal maintenance <u>produces</u> interference**
  - **D'Context = Measure of Goal maintenance sensitivity**

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

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DPX Summary

- **Construct:** Goal Maintenance
- **Time Required**: 10’ running time + 4-5’ instructions and practice
- **Internal Consistency (ICC):**
  Patients: AX = .89, AY = .75, BX = .81, BY = .27
- **Effect Size of Interest (Cohen’s d):**
  D’-context = 1.12
  BX vs. AY = .43
- **Retest-Reliability:**
  - **Baseline to Day 7: ICC = .76**
  - **Day 7 to Day 21: ICC = .77**
  - **Baseline to Day 21: ICC = .70**
- **To read about task and download Eprime files:**
  - http://cntracs.ucdavis.edu/task_dpx.shtml

Relational Encoding and Retrieval

Relational and Item Specific Encoding (RiSE)

Item Specific Encoding

Living?
Yes or No

Relational Encoding

Inside?
Yes or No

Item Recognition

Relational Recognition

Adapted from: *Murray & Ranganath (2007) J Neurosci*

RISE Summary

- **Construct:** Item Specific & Relational Encoding & Retrieval
- **Time Required**: 20-25 minutes (less than ½ this if only do relational part)
- **Internal Consistency (ICC):**
  - Item Encoding, Item Recognition = .79
  - Relational Encoding, Item Recognition = .76
  - Relational Recognition = .62
- **Effect Size of Interest (Cohen's d):**
  - Item Encoding, Item Recognition = .62
  - Relational Encoding, Item Recognition = .84
  - Relational Recognition = .98
- **Retest-Reliability:**

	Relational Recognition	Item Recognition Item Encoding	Item Recognition Relational Encoding
• Baseline to Day 7:	ICC = .49	ICC = .71	ICC = .68
• Day 7 to Day 21:	ICC = .61	ICC = .62	ICC = .55
• Baseline to Day 21:	ICC = .54	ICC = .55	ICC = .51

- **To read about task and download Eprime files:**

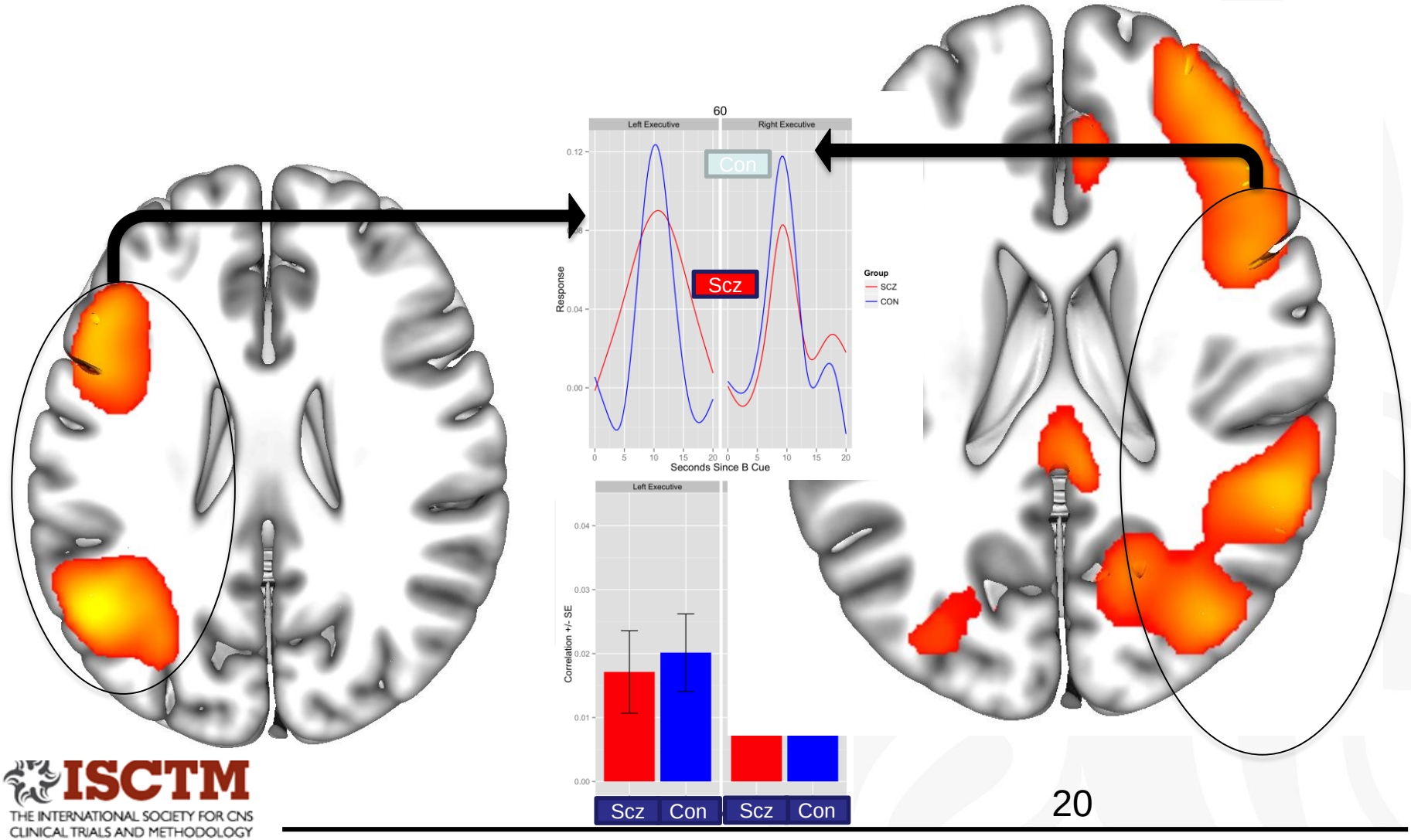
http://cntracs.ucdavis.edu/task_rise.shtml

Relationship To Function

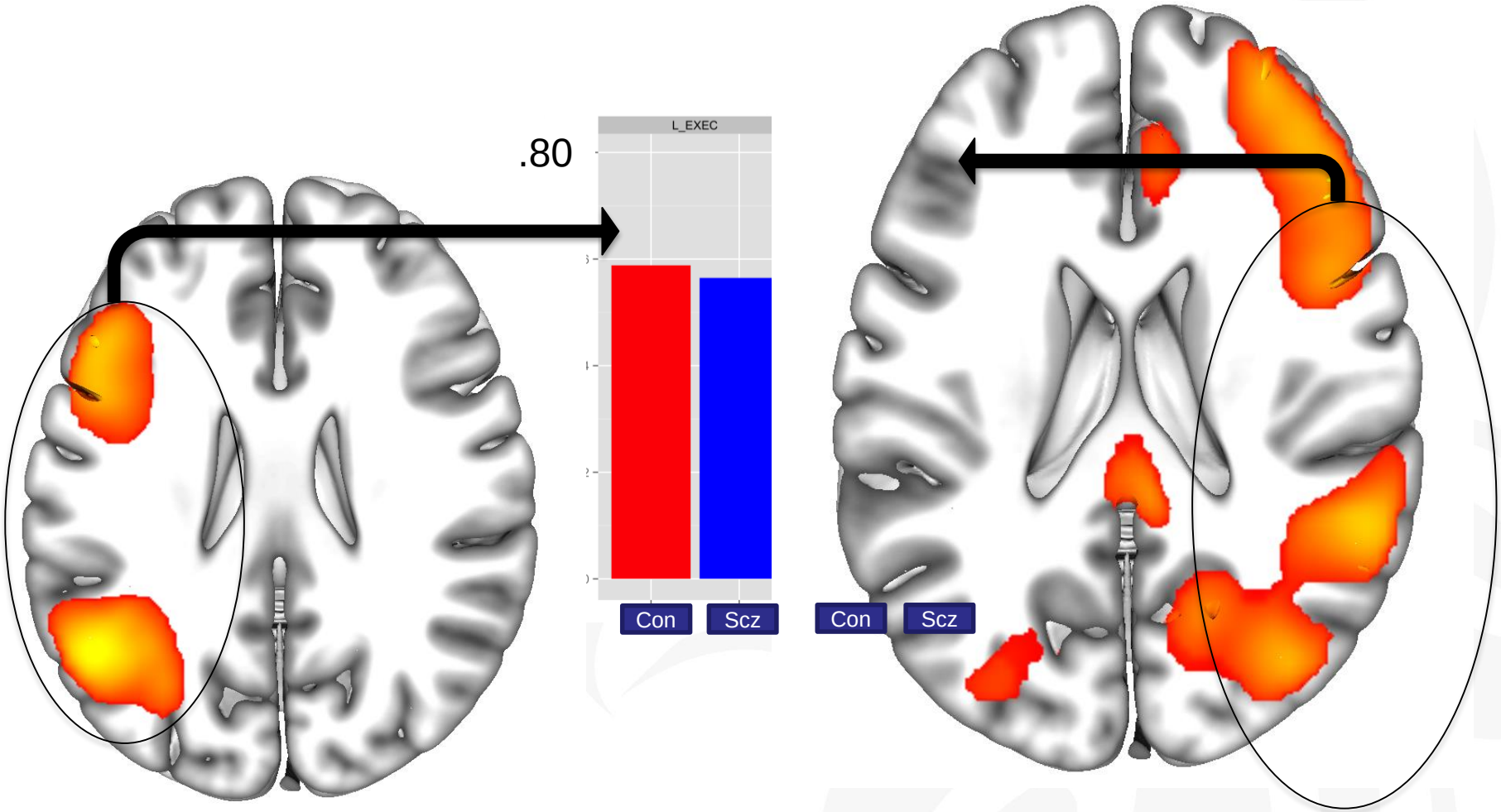
Task	UPSA-B (Proxy Function Measure)		SLOF Informant Report	
	Study 1	Study 2	Study 1	Study 2
RISE Item Encoding / Item Retrieval	0.28**	0.22*	0.07	0.18
RISE Relational Encoding / Item Retrieval	0.34**	0.30**	0.09	0.23
RISE Relational Retrieval	0.21*	0.21*	0.08	0.06
DPX	0.20**	0.29**	0.20*	0.26*
JOVI	0.13	0.20	0.04	0.04

**p<.05, **p<.01*

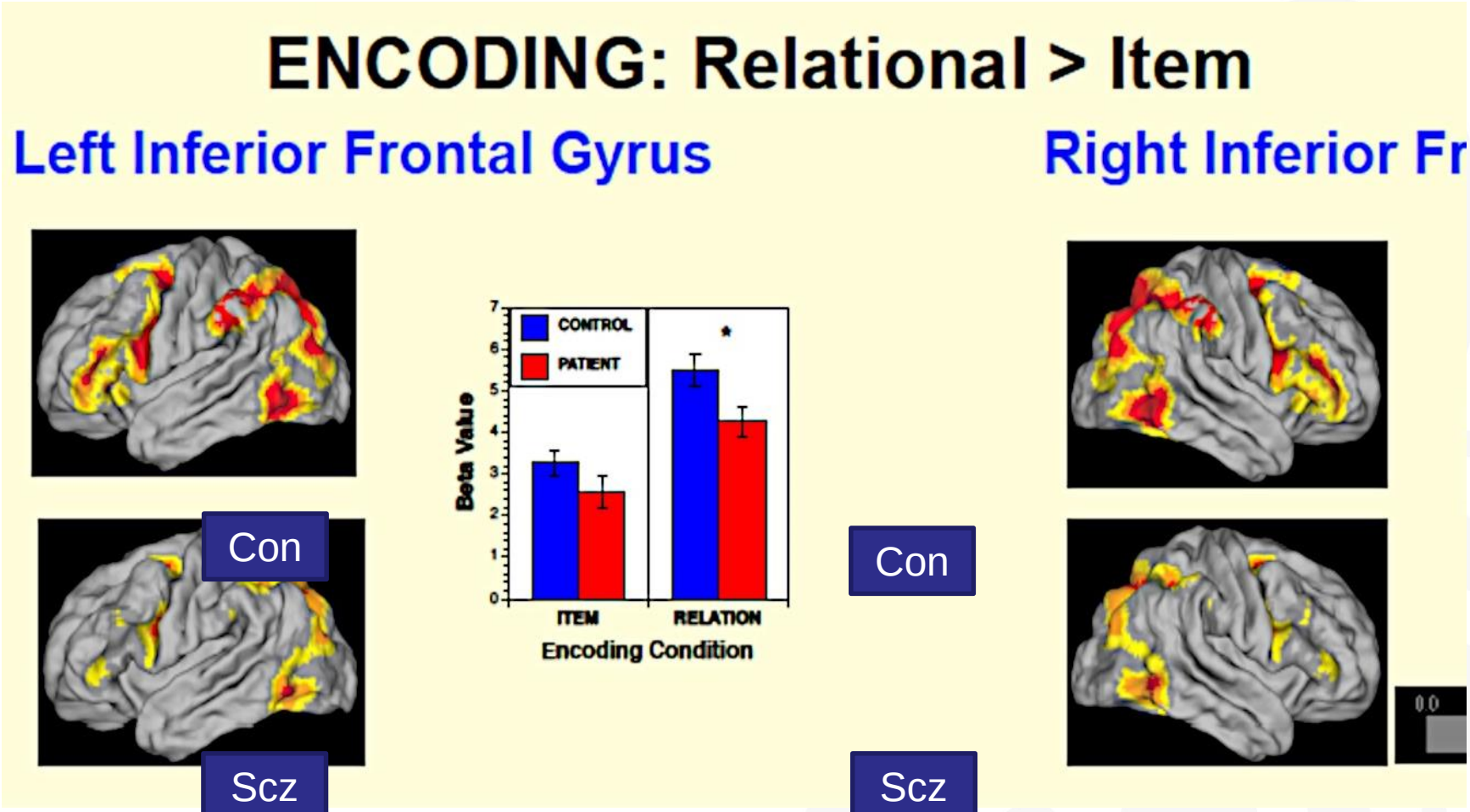
ICA: Group Effects in Task-related Networks



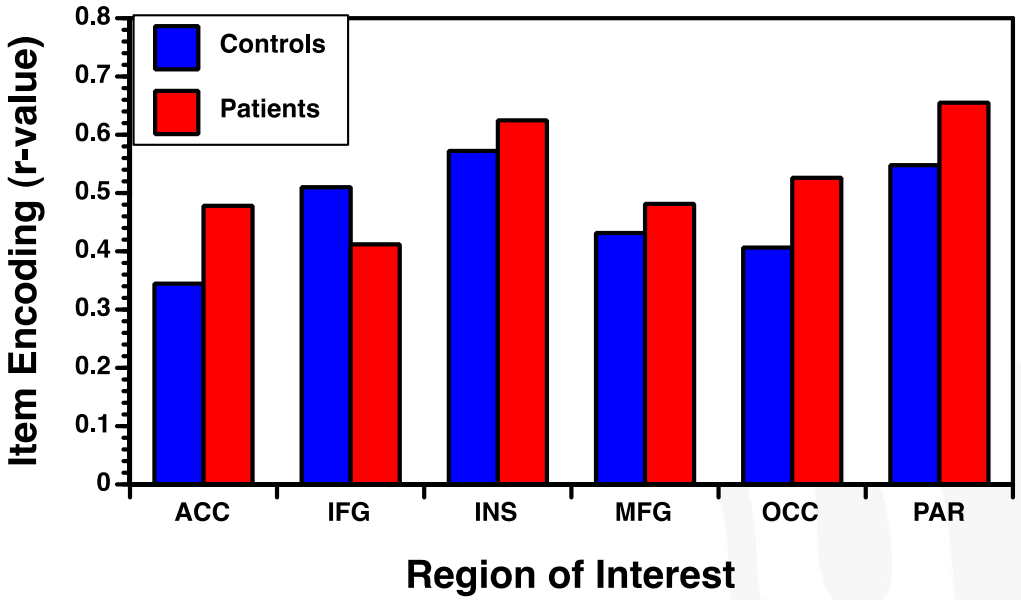
ICA: Reliability of Networks

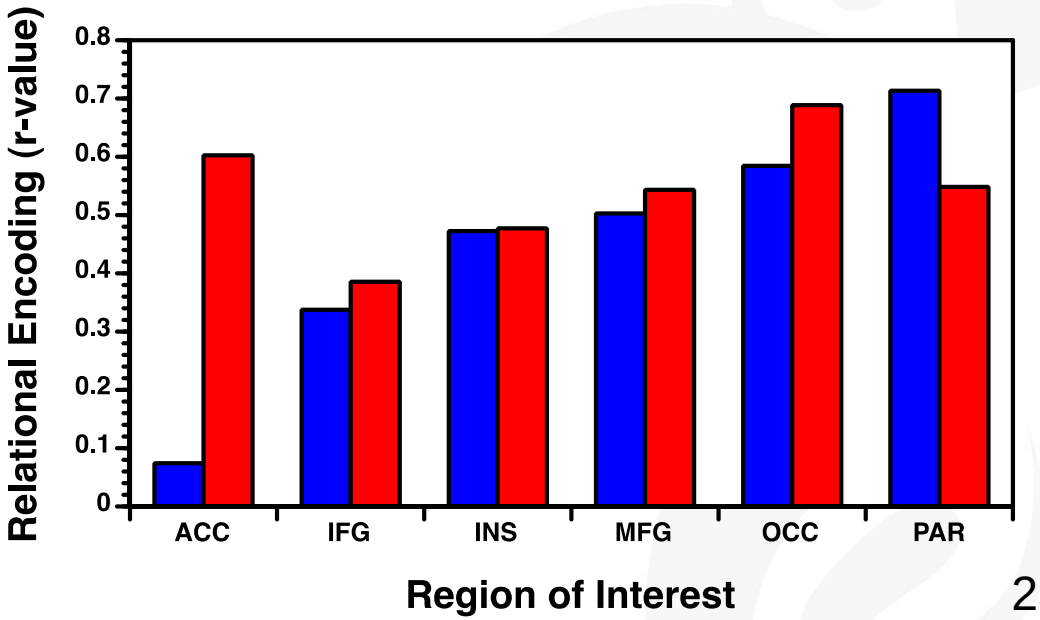


RISE Imaging Biomarker Development



Time 1 – Time 2 Reliability





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FAST-FS

- 3 Site experimental medicine method development study
- Columbia, Yale, U.C. Davis
- Ketamine model of psychosis
- Placebo controlled iv bolus and infusion
- Glutamate MRS, fMRI (resting and RiSE)
- MR Imaging Biomarker based platform for evaluating target engagement for glutamate based therapies

Conclusions

- Experimental cognitive measures engaging specific cognitive and neural systems can be adapted for use in clinical trials and experimental medicine studies (ease of administration, length, tolerability, internal and test re-test reliability)
- These measures can also be implemented as imaging biomarkers and used in multisite experimental medicine studies (e.g. FAST-FS)
- An initial set of paradigms is publically available and can be downloaded at cntrics.ucdavis.edu

The CNTRaCS Consortium

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Table 3 Correlations between the CNTRACS tasks, MATRICSsub tasks, and WTAR

	Healthy Controls			Schizophrenia Patients		
	HVLT–R	BACSsc	WTAR	HVLT–R	BACSsc	WTAR
RISE IRIE	0.19*	0.39***	0.41***	0.28**	0.14	0.16
RISE IRAE	0.20*	0.44***	0.33***	0.23*	0.16	0.12
RISE AR	0.26**	0.40***	0.39***	0.37** *	0.38***	0.22*
AX-CPT D'-context	0.29**	0.32***	0.24**	0.36***	0.31***	0.23*
DPX D'-context	0.34***	0.36***	0.22*	0.40***	0.35***	0.23*
JOVI threshold	−0.20*	−0.26**	−0.14	−0.03	−0.19	−0.16

WTAR Wechsler Test of Adult Reading, *HVLT–R* Hopkins Verbal Learning Task–Revised, *BACSsc* Brief Assessment of Cognition in Schizophrenia, *RISE* Relational and Item-Specific Encoding Task, *IRIE* item recognition for items following item-specific encoding item recognition for items following item-specific encoding, *IRAE* item recognition for items following relational encoding, *AR* associative recognition for item pairs from the relational encoding condition, *AX-CPT* AX-Continuous Performance Task, *DPX* Dot Probe Expectancy Task, *JOVI* Jittered Orientation Visual Integration Task