

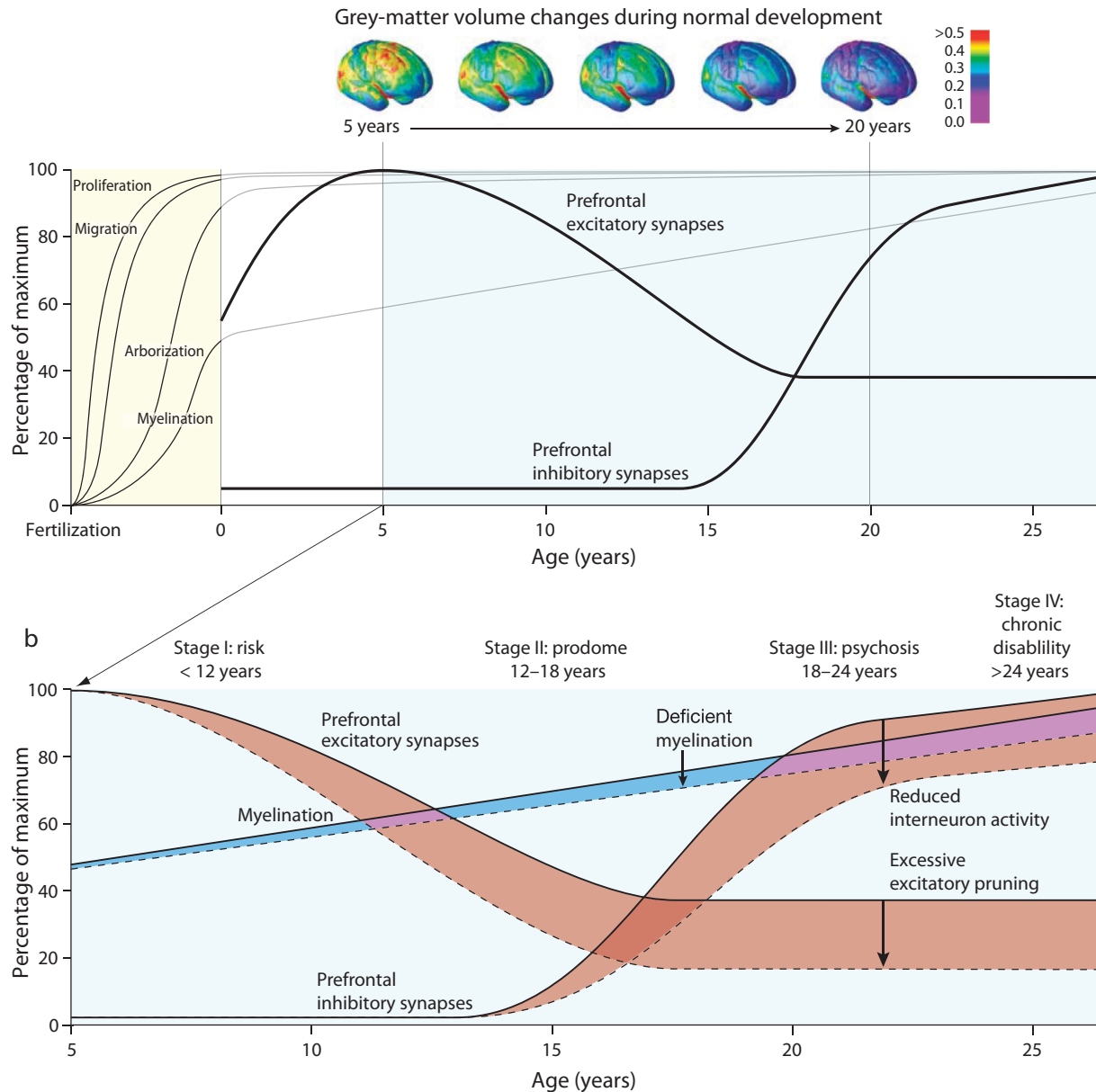


Early Course and Intervention in Youth At-Risk for Psychosis: Results from Longitudinal Studies

Raquel E. Gur, M.D. Ph.D.

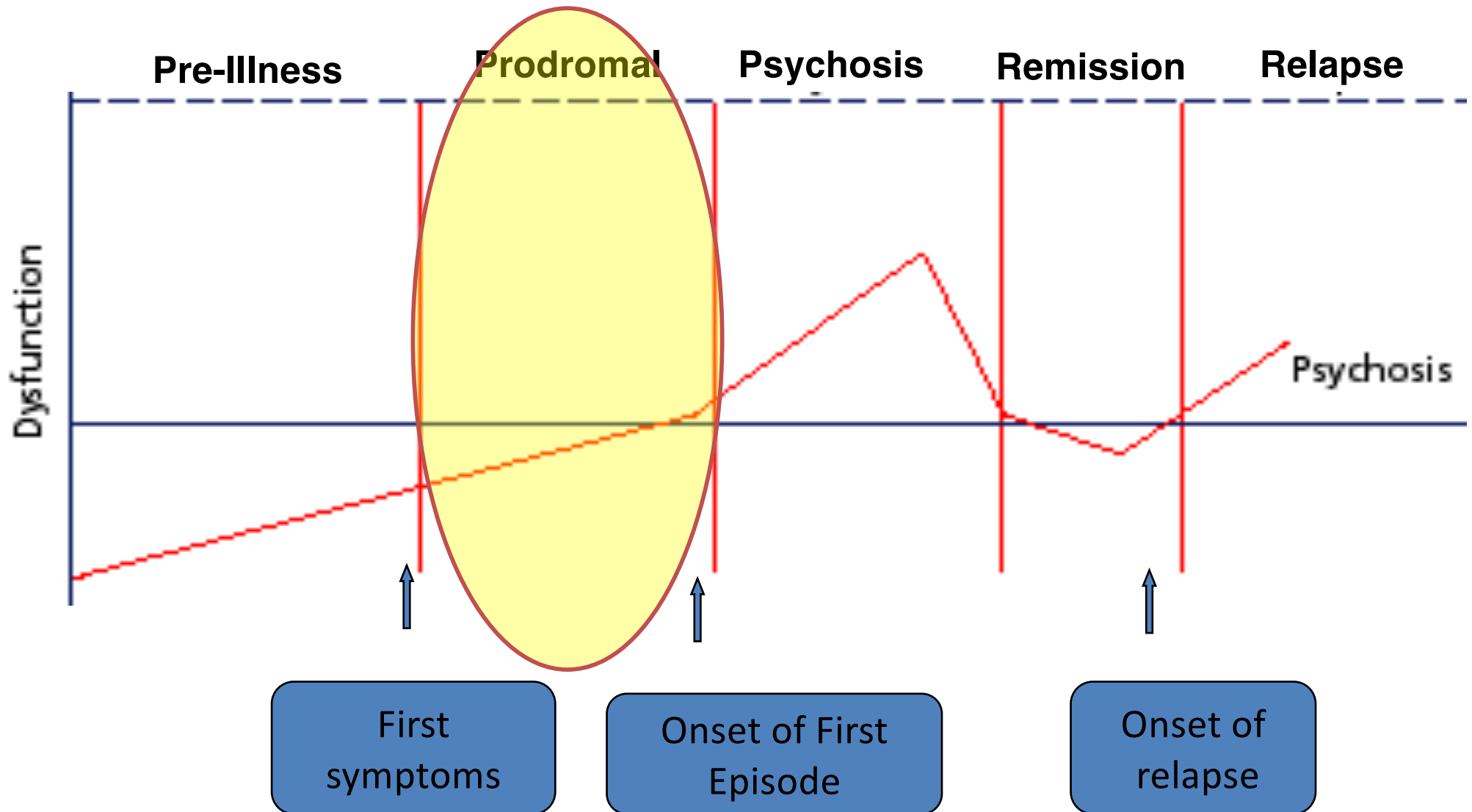
**ESCAP
Geneva,
July 11, 2017**

Schizophrenia: A Neurodevelopmental Disorder



From Insel

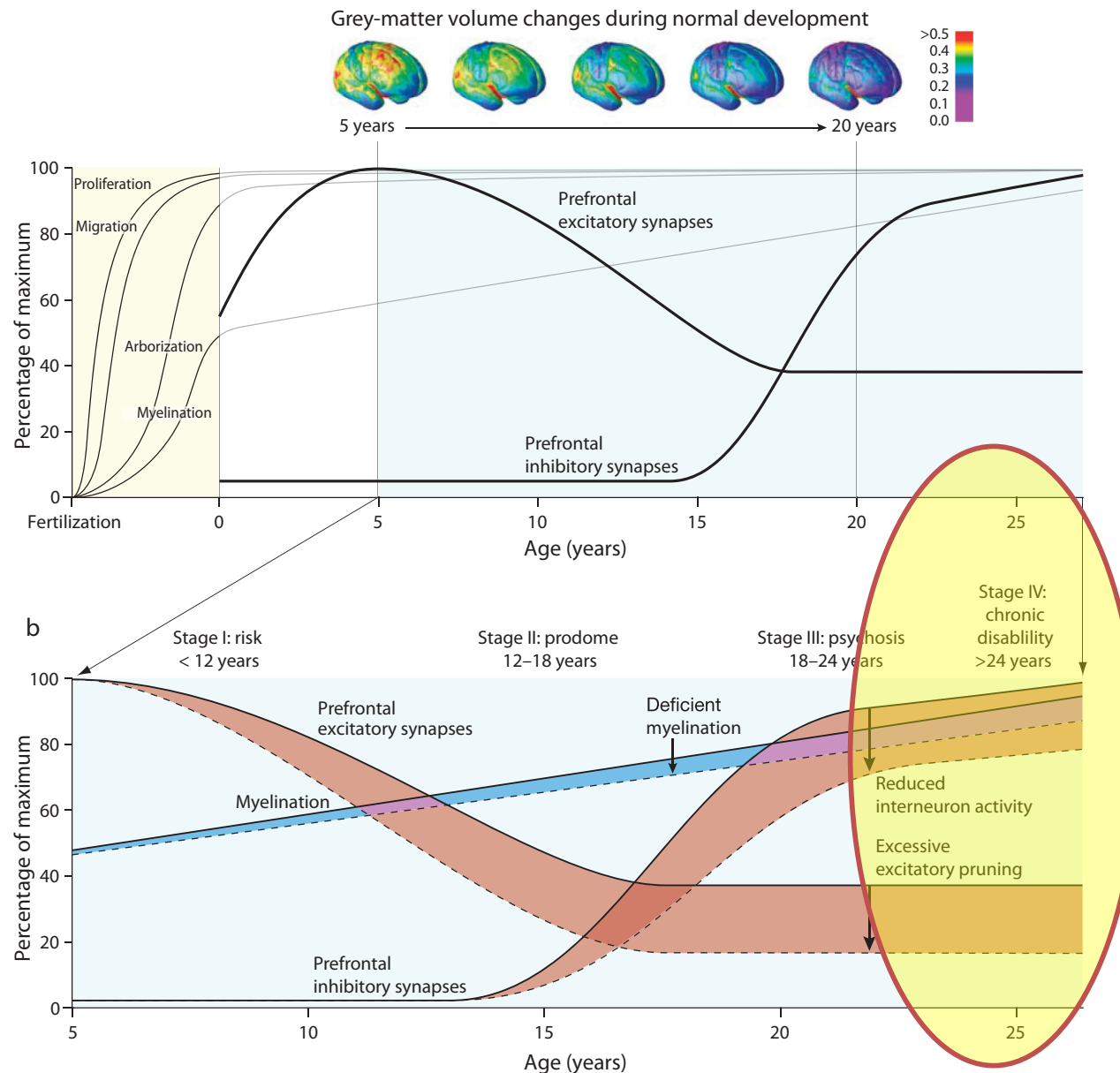
Paradigm Shift: Clinical Risk Strategy



Courtesy Monica Calkins

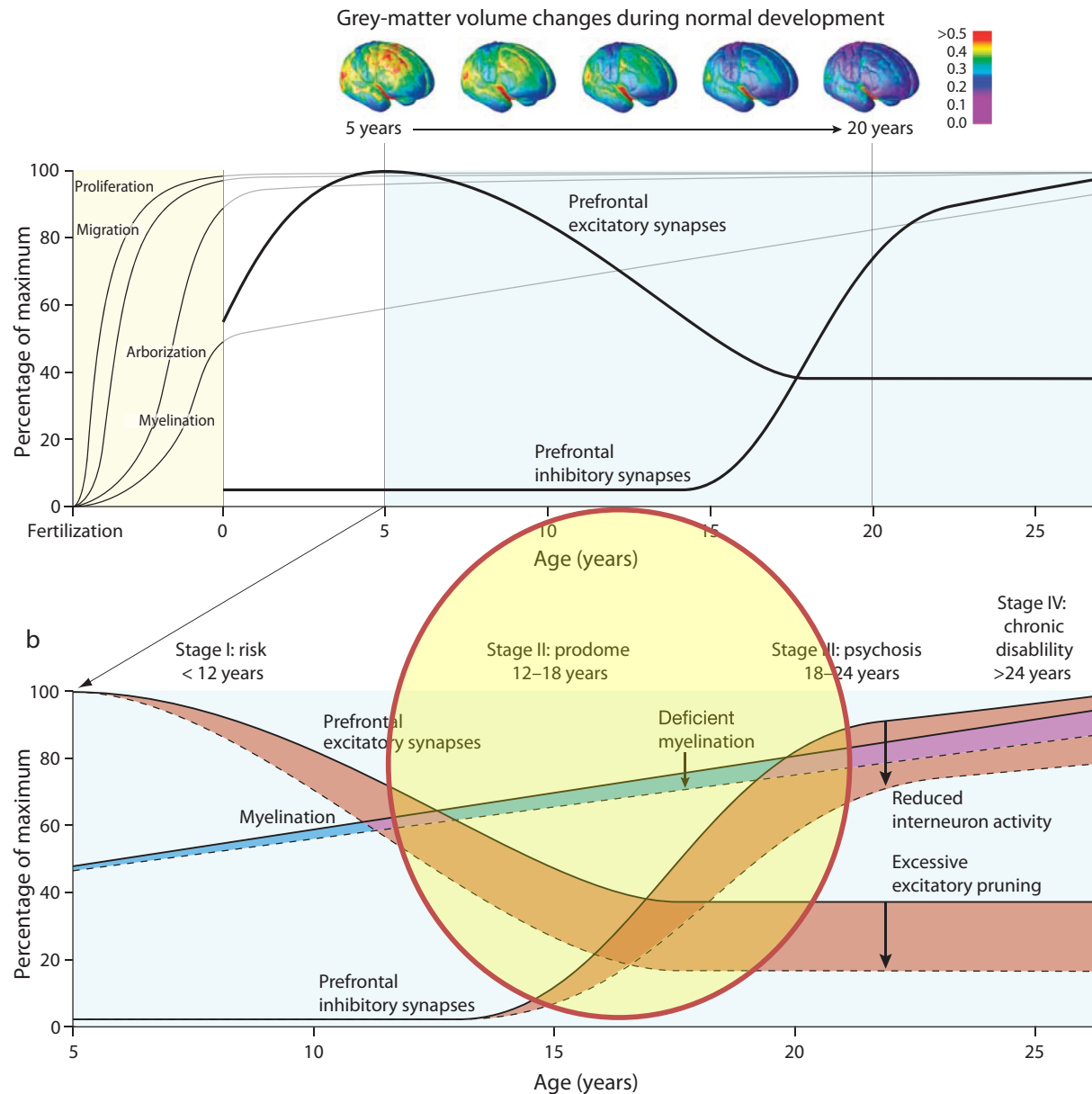
Adapted from Knowles, 2004

Traditional Strategy for Studying and Treating Psychotic Disorders



From Insel

Clinical Risk Strategy



From Insel

The paradigm shift mandates:

- **Bridging pediatrics and adult divide
establishing developmental trajectories**
- **Dissecting complex phenotypes
applying multi-dimensional levels of analysis**
- **Convergence
large samples, establishing common measures**
- **Integration with genomics**

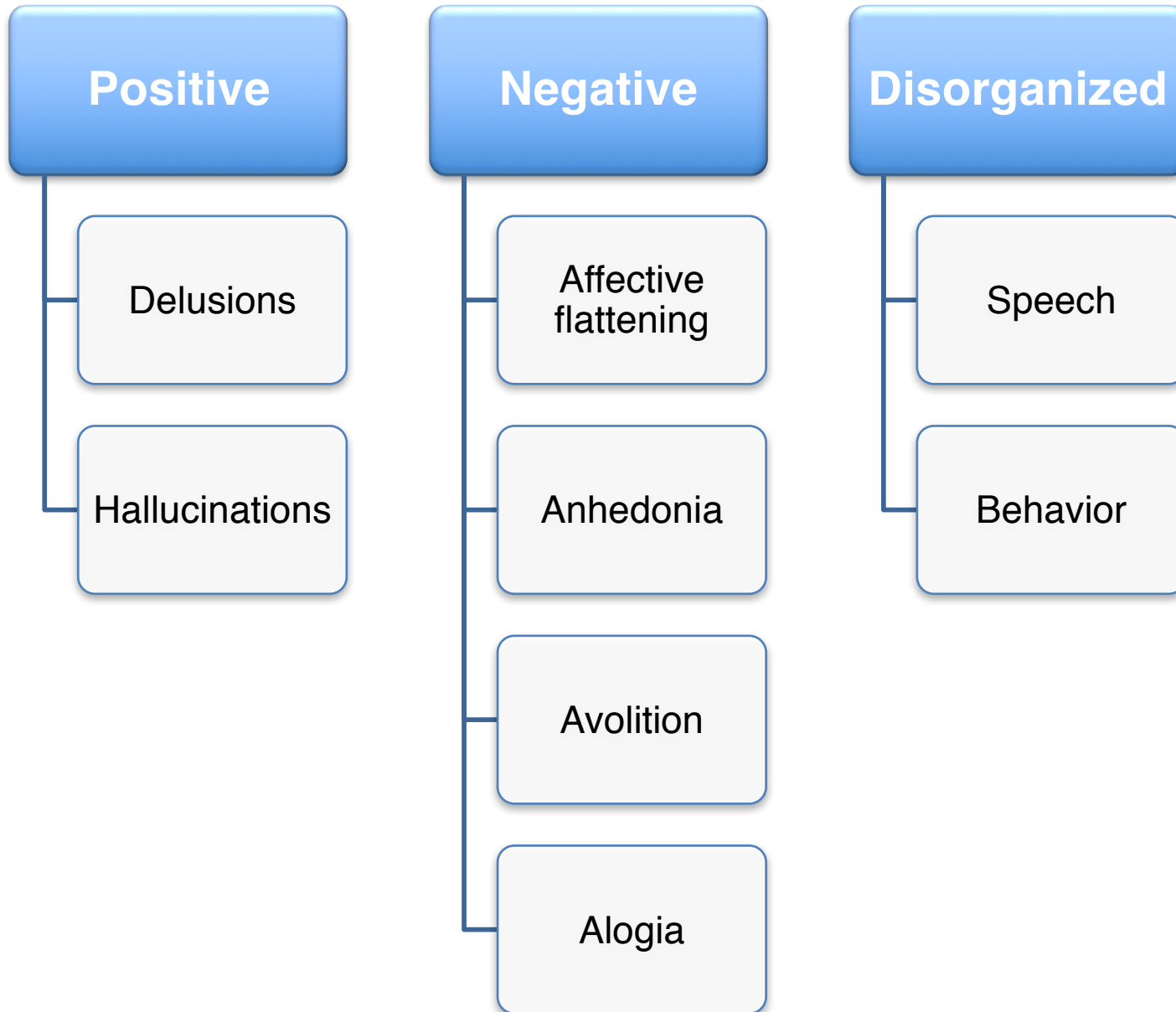
Why Identify Early?

Enhance understanding of underlying neurobiology of psychosis

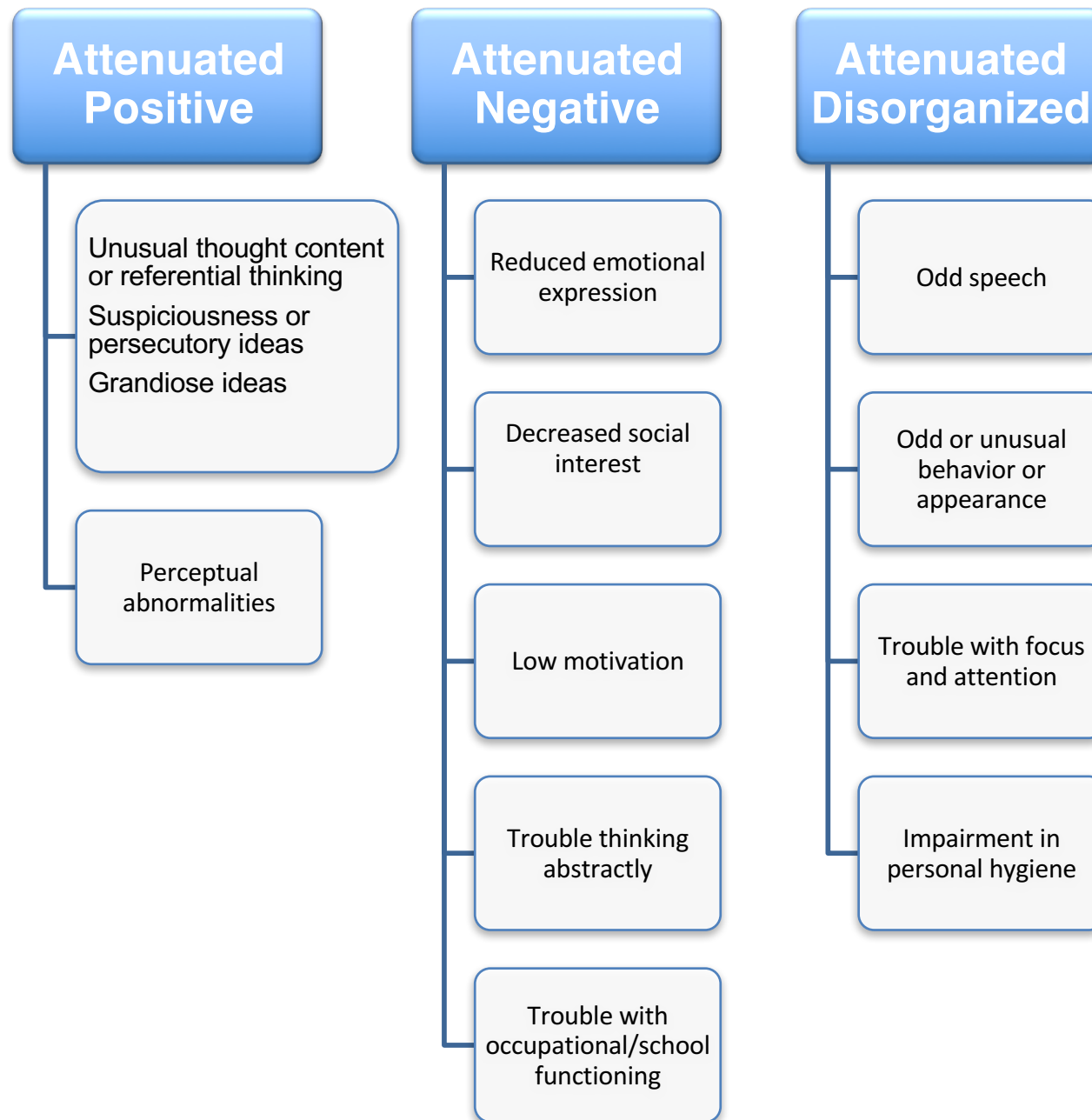
Early identification → timely treatment of psychosis

- The first episode of schizophrenia often goes untreated for an average of one year
- Longer duration of untreated psychosis is correlated with greater disability
- Early treatment can reduce relapse and deterioration
- Early response may prevent treatment resistance

Psychosis Symptoms



Subthreshold Psychosis Symptoms



Meta-analysis of Transition Outcomes in Individuals at High Clinical Risk

Paolo Fusar-Poli, MD, PhD; Ilaria Bonoldi, MD; Alison R. Yung, PhD; Stefan Borgwardt, PhD; Matthew J. Kempton, PhD; Lucia Valmaggia, PhD; Francesco Barale, PhD; Edgardo Caverzasi, PhD; Philip McGuire, PhD

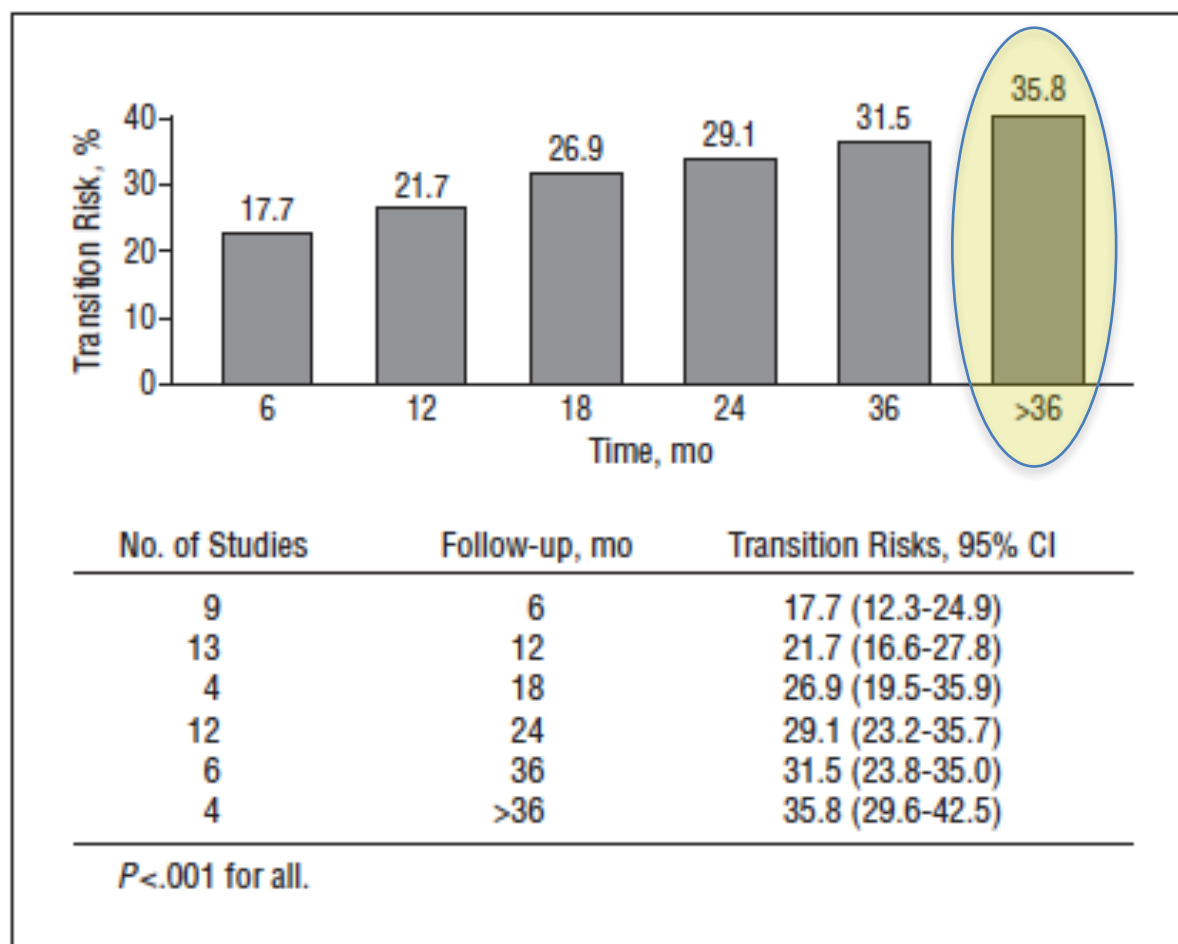


Figure 2. Meta-analyses of transition risks from clinical high risk to full psychosis at different time points of follow up.

Psychosis as a Continuum in the General Population

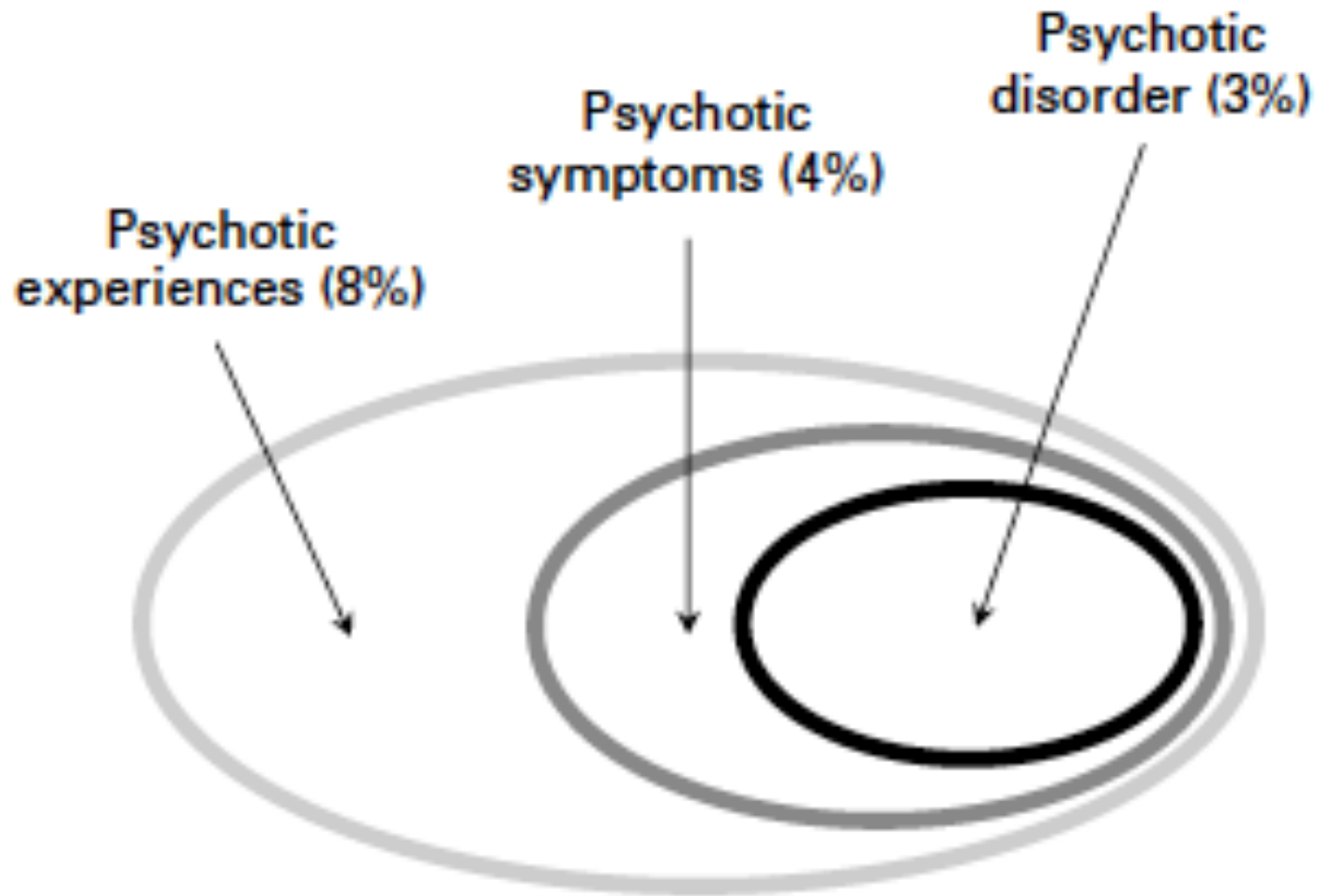


Fig. 4. Psychosis: variation along a continuum.

Psychosis: Complementary Lines of Research

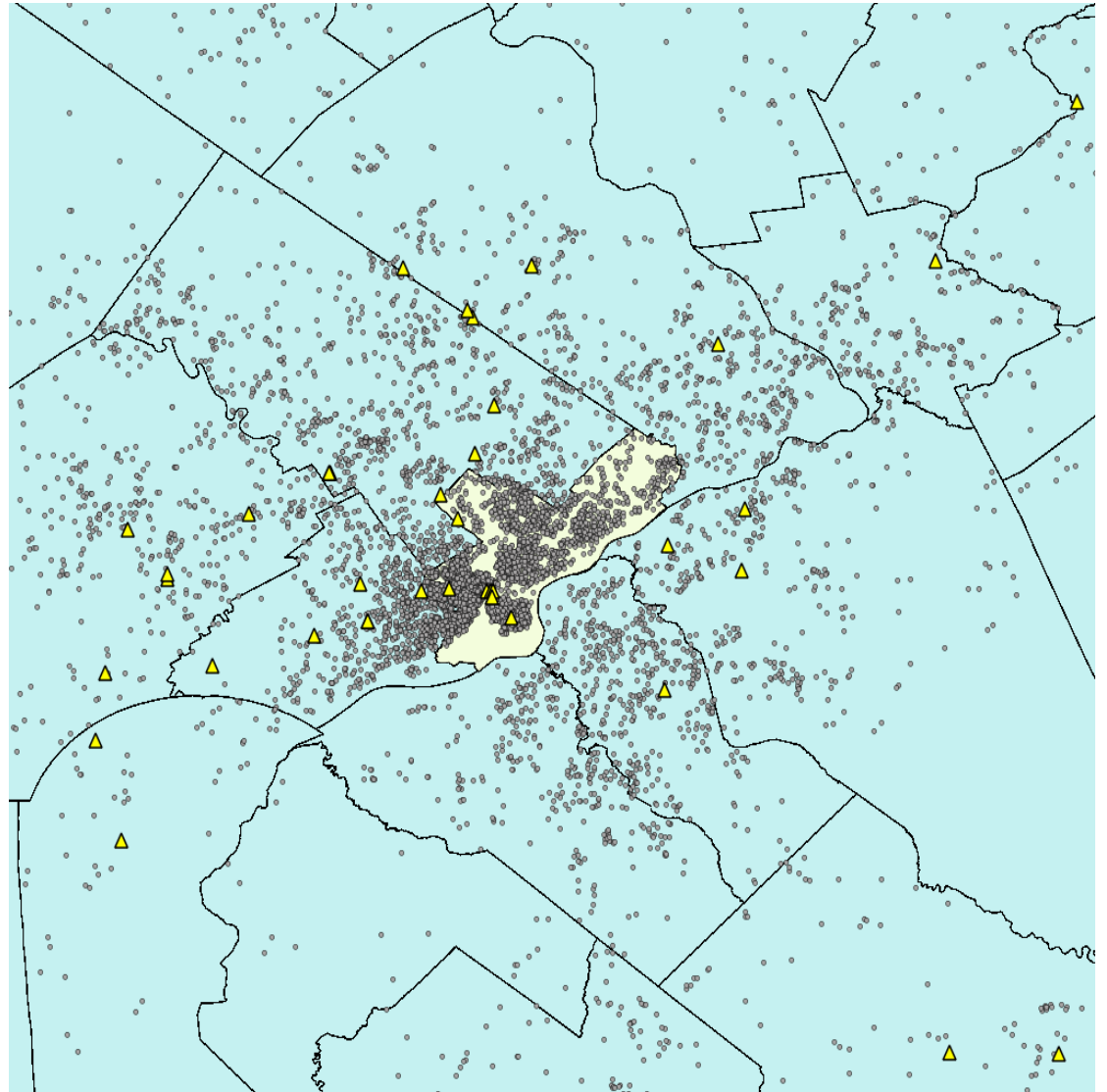
At-Risk, help-seeking

At-Risk, population-based

**Genetically informative – 22q11.2 Deletion
Syndrome**

The Philadelphia Neurodevelopmental Cohort

- Community based study of 9,500 children age 8-21.
- Goal of establishing national resource for investigation of relationships among genes, brain, and behavior in young people.
- Participants initially genotyped by the Center for Applied Genomics (CAG) and re-contacted.



Clinical Assessment:
GOASSESS

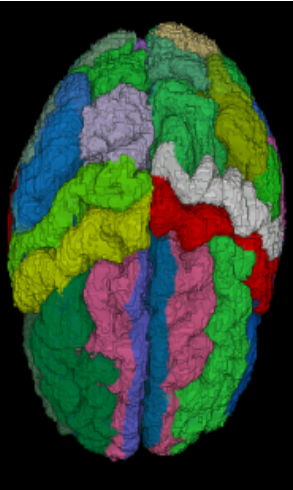
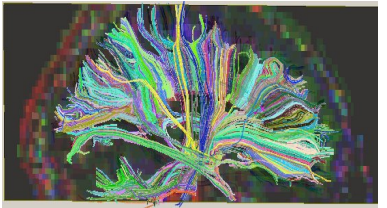
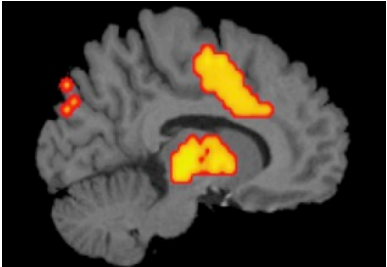
Computerized Neurocognitive Battery (CNB)

Neuroimaging:
sMRI, DTI, fMRI, ASL



<p>ABSTRACTION & MENTAL FLEXIBILITY (PCT)</p>	<p>WORD MEMORY</p> <p>REACTION</p>	<p>LANGUAGE REASONING (PVRT)</p> <p>Preparation is to concentrate on responses to the:</p> <ol style="list-style-type: none"> Answer Revised Final Start 	<p>SENSORIMOTOR (MP)</p>
<p>ATTENTION (CPT)</p> <p>FOK NUMBER LETTER</p> <p>TARGET</p>	<p>FACE MEMORY</p>	<p>SPATIAL (LOLO)</p> <p>Click on the lines where the red bar is the same position as the red bar of the fan.</p>	<p>MOTOR SPEED (TAP)</p> <p>TRIAL 2 USE YOUR "NON-WRITING HAND"</p> <p>This trial will begin in 7 seconds.</p> <p>USE THE CORRECT HAND POSITION WHEN PRESSING THE SPACEBAR</p>
<p>WORKING MEMORY</p> <p>0-BACK</p> <p>Press the space bar when you see the letter X</p> <p>F X N</p> <p>TARGET</p>	<p>SPATIAL MEMORY</p> <p>YES NO</p>	<p>EMOTION (ER20)</p> <p>Happy Sad Anger Fear No Emotion</p>	
<p>1-BACK</p> <p>Press the space bar when the letter that you see is the same as the previous letter</p> <p>D B B G</p> <p>TARGET</p>	<p>2-BACK</p> <p>Press the space bar when the letter you see is the same as the one before the previous letter</p> <p>D B G B</p> <p>TARGET</p>		

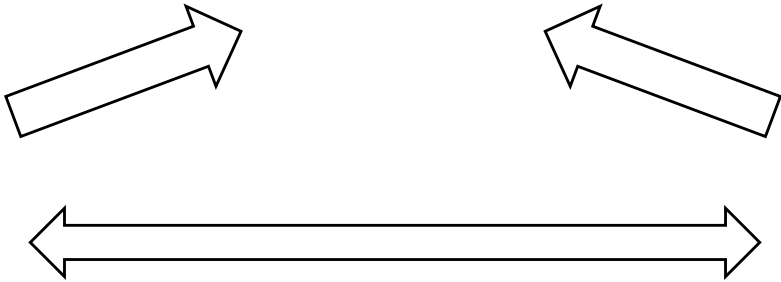
The computerized battery:
Illustration of test stimuli and procedures



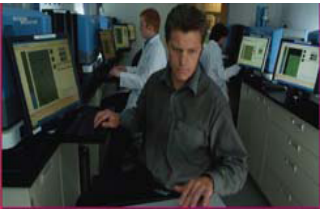
PHENOTYPING



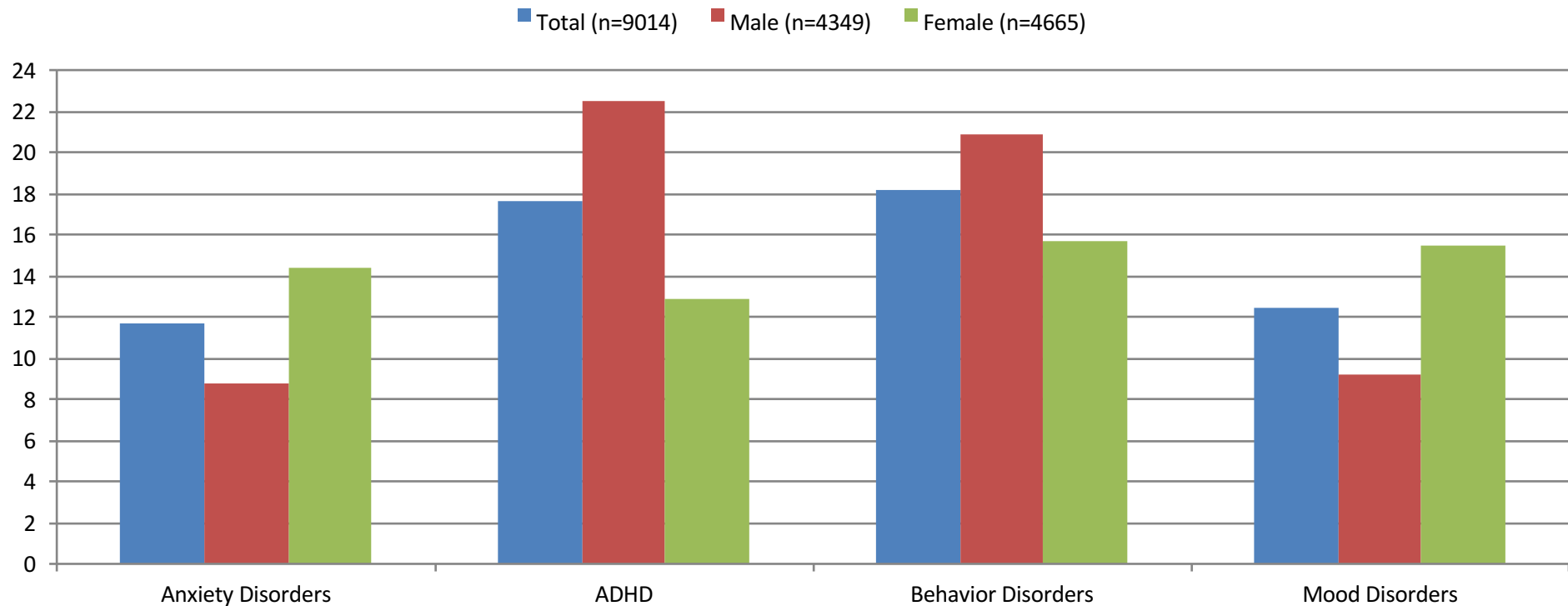
CAG



EMR

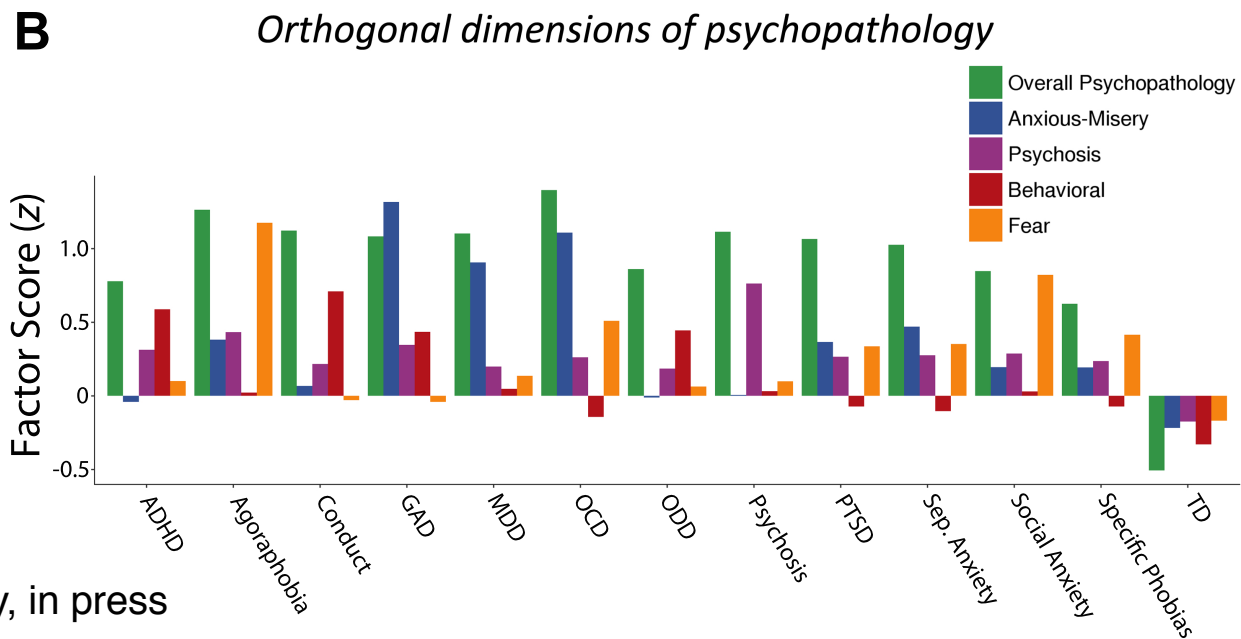
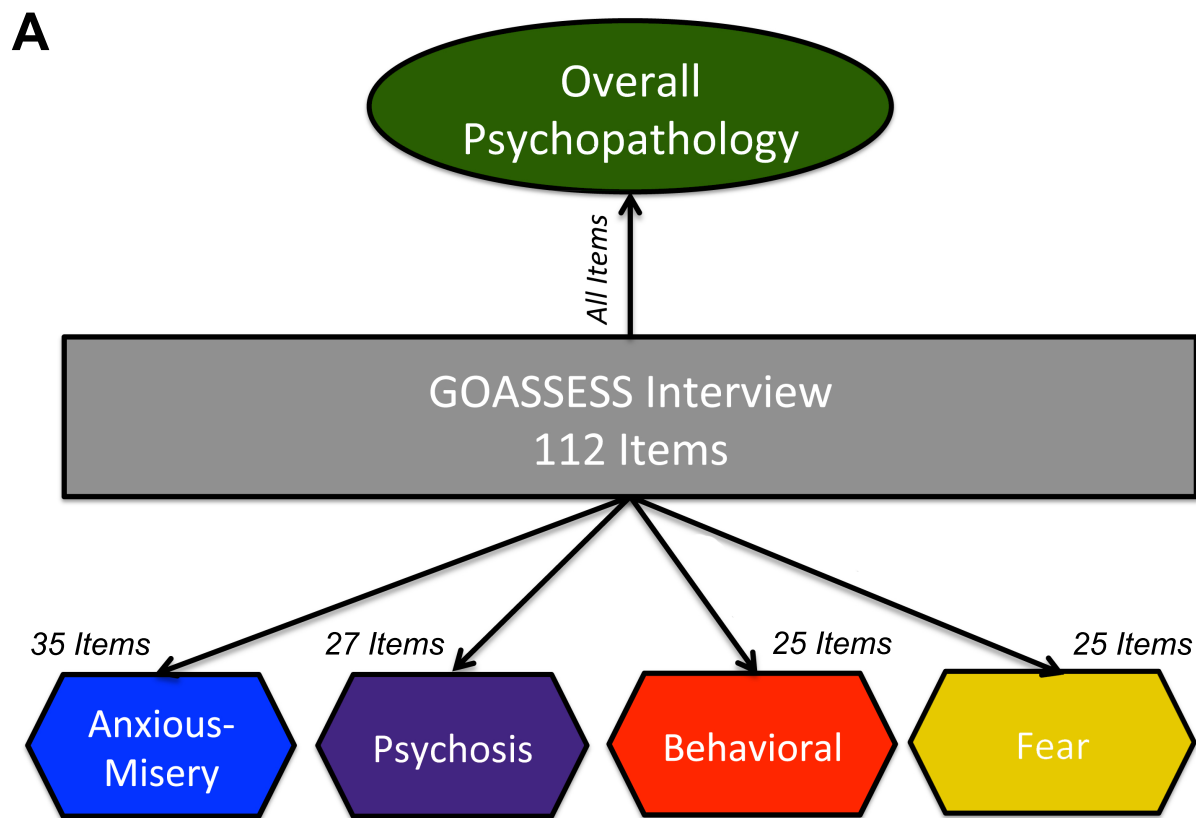


Psychopathology Prevalence



- Behavior disorders most frequent, followed by ADHD, mood and anxiety
- Males: greater rates of ADHD and behavior disorders
- Females: greater rates of anxiety and mood disorders

Adapted from Merikangas et al.



The psychosis spectrum in a young U.S. community sample: findings from the Philadelphia Neurodevelopmental Cohort

MONICA E. CALKINS¹, TYLER M. MOORE¹, KATHLEEN R. MERIKANGAS², MARCY BURSTEIN²,
THEODORE D. SATTERTHWAITE¹, WARREN B. BILKER¹, KOSHA RUPAREL¹, ROSETTA CHIAVACCI³,
DANIEL H. WOLF¹, FRANK MENTCH³, HAIJUN QIU³, JOHN J. CONNOLLY³, PATRICK A. SLEIMAN^{3,4},
HAKON HAKONARSON^{3,4}, RUBEN C. GUR¹, RAQUEL E. GUR¹
(World Psychiatry 2014;13:296-305)

- ~4% of youths reported psychotic symptoms
- 12.3% reported significant sub-psychotic symptoms
- Psychosis spectrum symptoms associated with
 - Reduced global functioning
 - Increased odds of depression, anxiety, behavioral disorders, substance use and suicidal ideation

PNC CNB Battery

Duration is ~1 hour

14 tests administered, measuring 5 domains

- Executive (Abstraction & Mental Flexibility, Attention, Working Memory)
- Episodic Memory (Verbal, Facial, Spatial)
- Complex Cognition (Language, Non-Verbal, Spatial)
- Social Cognition (Emotion Identification, Emotion Intensity Differentiation, Age Differentiation)
- Sensorimotor Speed (Praxis, Finger Tapping)

99% validity of CNB data within the PNC participants

CNB assessors blind to participant clinical data or diagnosis

The Computerized Battery: Illustration of Test Stimuli and Domains

WORKING MEMORY

0-BACK
Press the spacebar when you see the letter X

1-BACK
Press the spacebar when the letter you see is the same as the previous letter.

2-BACK
Press the spacebar when the letter you see is the same as the one before the previous letter.

TARGET X L X L D
TARGET P G G D P
TARGET P L G L D

ABSTRACTION & MENTAL FLEXIBILITY (PCET)

Click on the object that does not belong.

ATTENTION (CPT)

FOIL NUMBER TARGET
LETTER TARGET

EMOTION RECOGNITION (ER40)

Happy
Sad
Anger
Fear
No Emotion

WORD MEMORY (CPW)

REACTION

DEFINITELY YES PROBABLY YES PROBABLY NO DEFINITELY NO

FACE MEMORY (CPF)

DEFINITELY YES PROBABLY YES PROBABLY NO DEFINITELY NO

SPATIAL MEMORY (SVOLT)

DEFINITELY YES PROBABLY YES PROBABLY NO DEFINITELY NO

ATTENTION / INHIBITION (GNG150)

Remember - only press the SPACEBAR when you see the letter 'X' in the upper half of the screen.

Press X Don't Press Y
Don't Press X Don't Press Y

SPATIAL ABILITY (PLOT)

PRACTICE

Click the buttons to rotate the SLAT line. Click FINISHED when the line looks parallel.

FINISHED

LANGUAGE REASONING (PVRT)

Predicament is to carelessness as response is to...

- Answer
- Stimulus
- Effect
- Good

MOTOR SPEED (MOT)

TRIAL 2 USE YOUR
** NON-WRITING HAND **

This trial will begin in
7
seconds.

USE THE CORRECT HAND POSITION
WHEN PRESSING THE SPACEBAR

SENSORIMOTOR SPEED (SM)

Click on the green box

EMOTION DISCRIMINATION (MEDF)

Which face is more happy?

↑ This Face Equal This Face ↑

AGE DIFFERENTIATION (ADT)

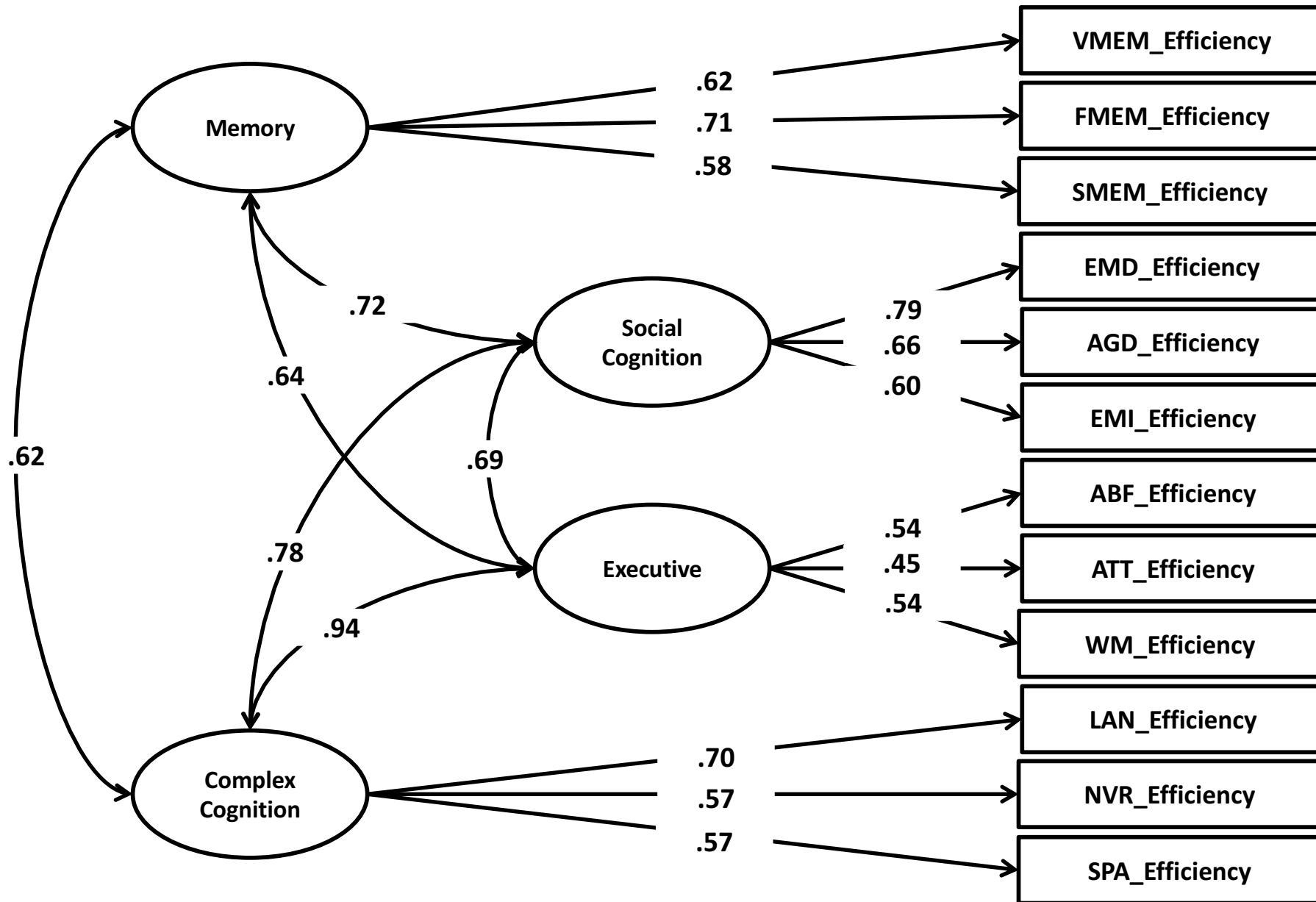
Which face is older?

↑ This Face Same Age This Face ↑

NONVERBAL REASONING (PMAT)

Gur et al., J Neuroscience Methods, 2010
Gur et al., Neuropsychology, 2012

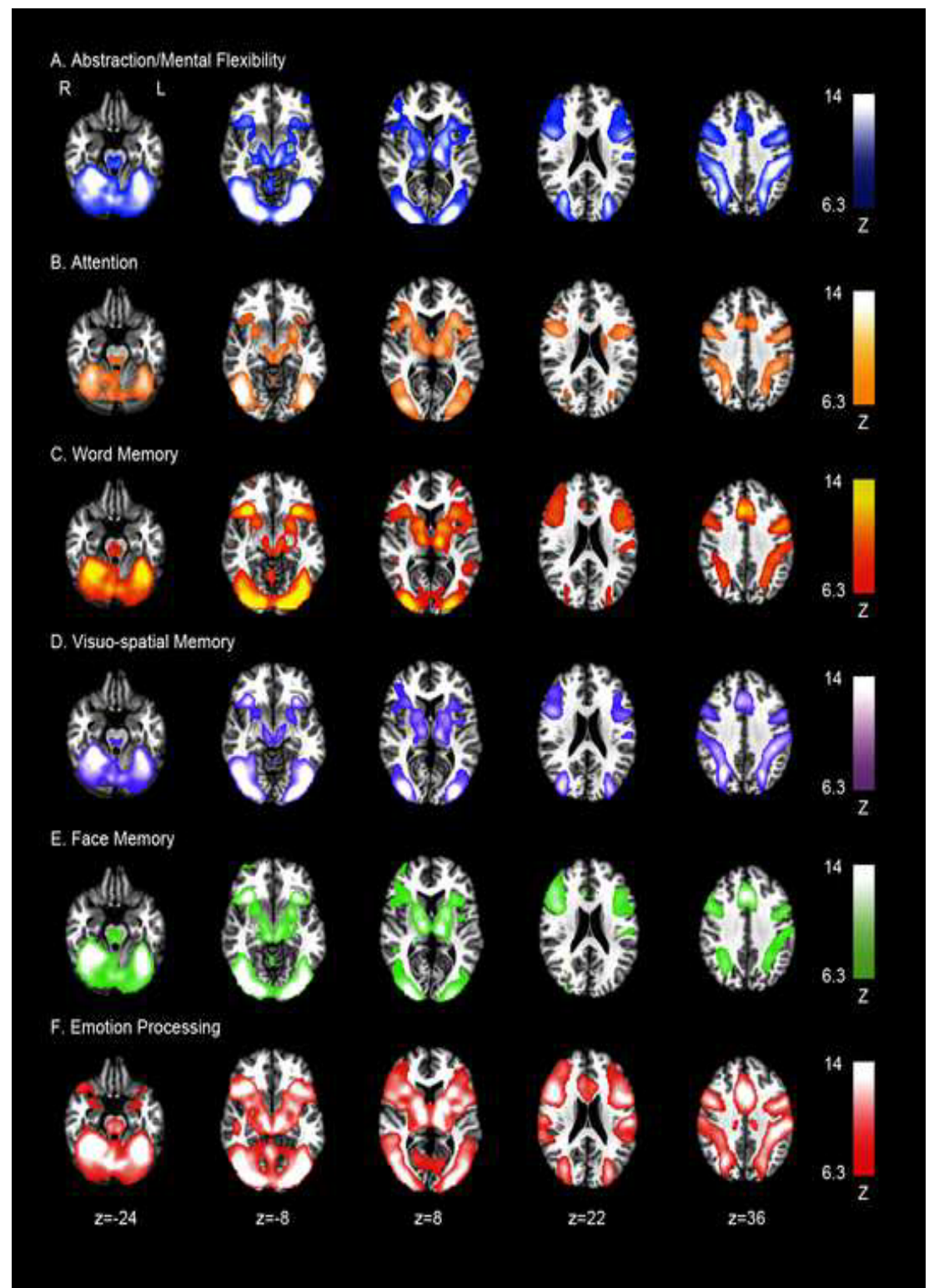
Factorial Structure of the CNB



Note. Results are standardized such that the variance of the latent variables is 1.00. All coefficient estimates are significant with standard errors of 0.01.

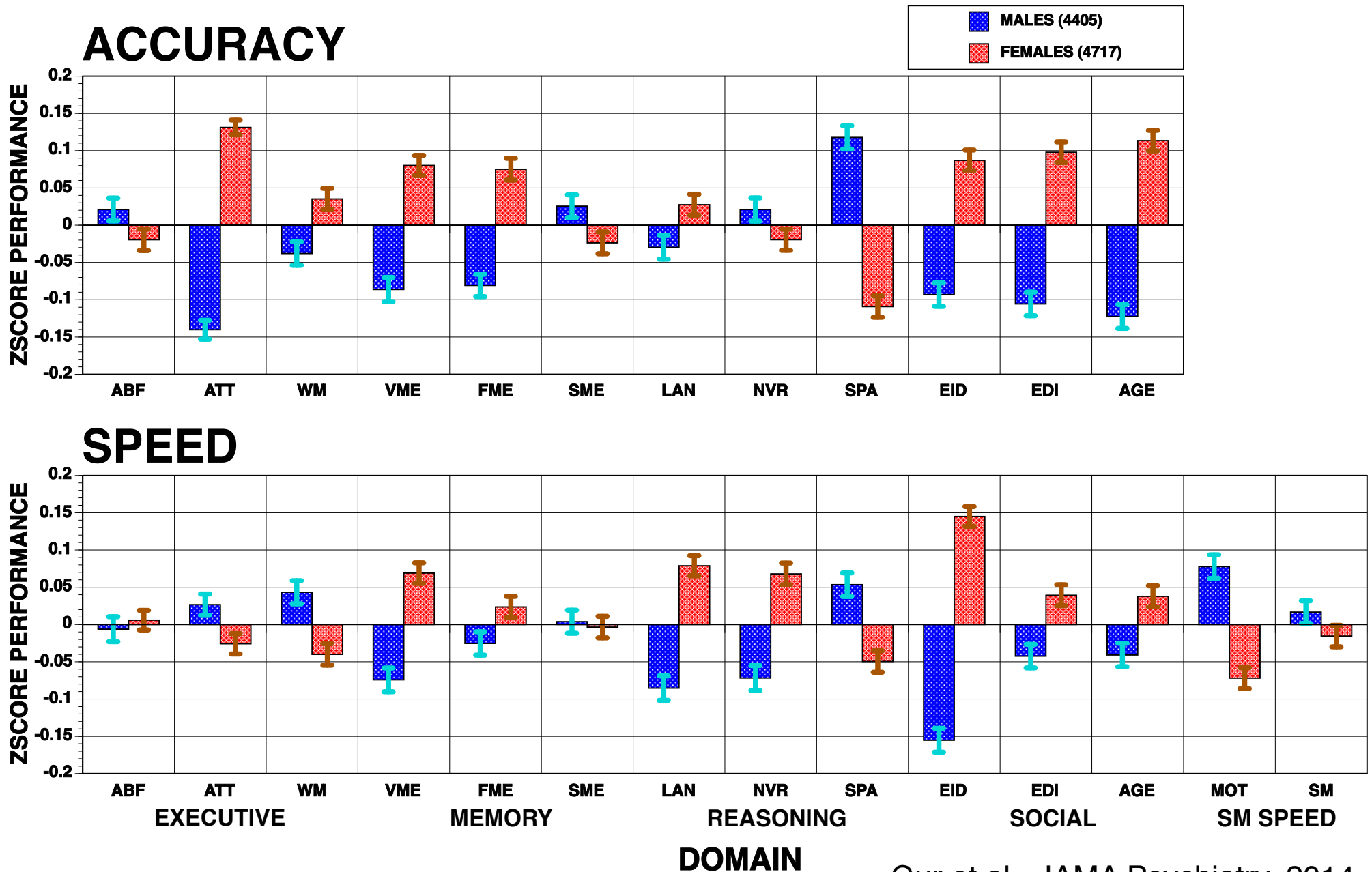
Brain Mapping with fMRI

In-Scanner CNB

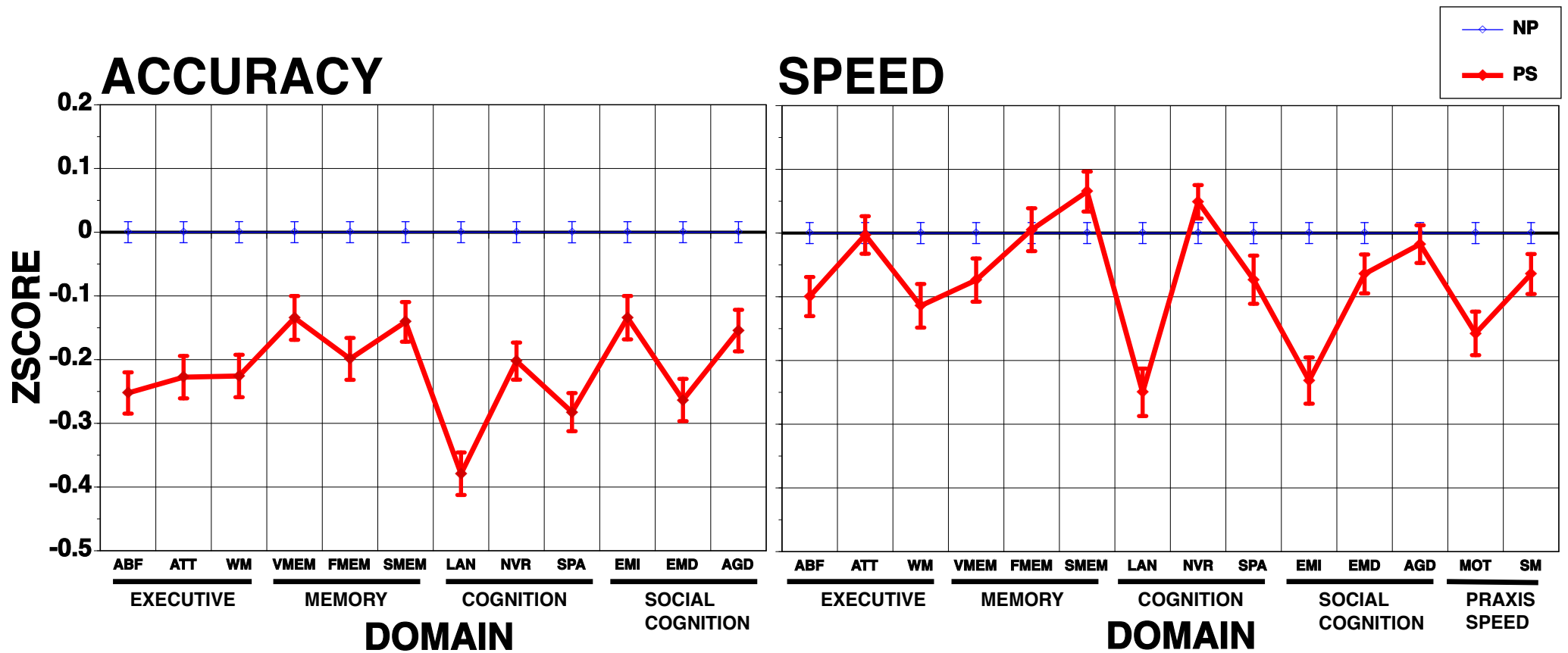


Roalf et al., Neuropsychology, 2013

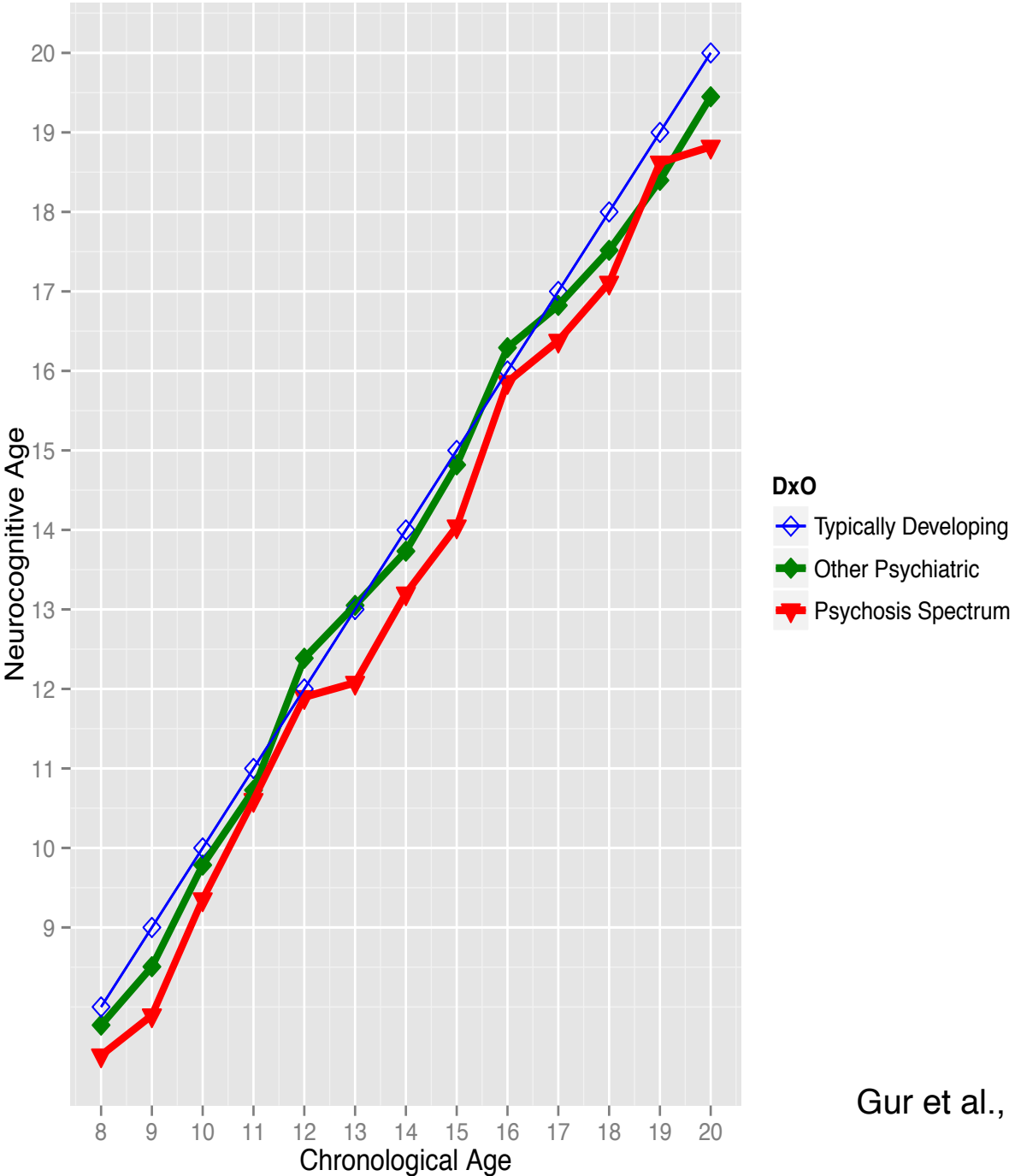
THE PHILADELPHIA NEURODEVELOPMENTAL COHORT: Sex differences in neurocognitive profile across age groups



Neurocognitive Profile of Psychosis Spectrum (PS, n=1171) Compared to No Psychosis (NP, n=3684) Age 11-21

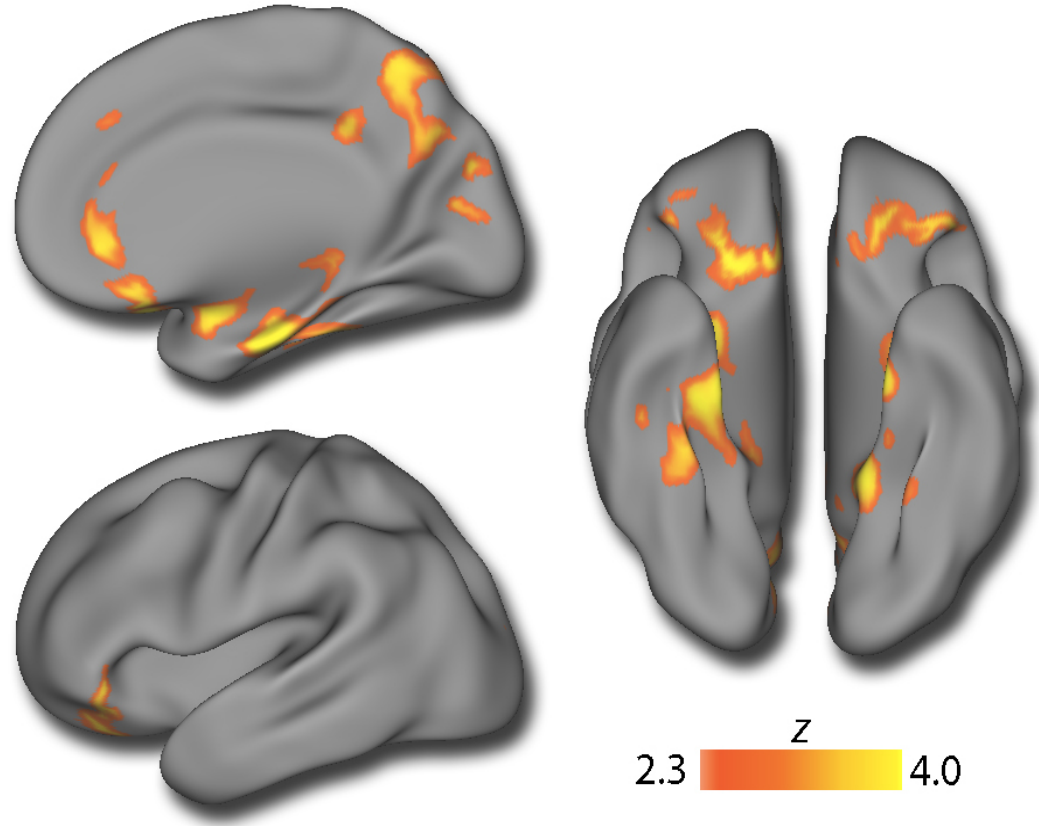
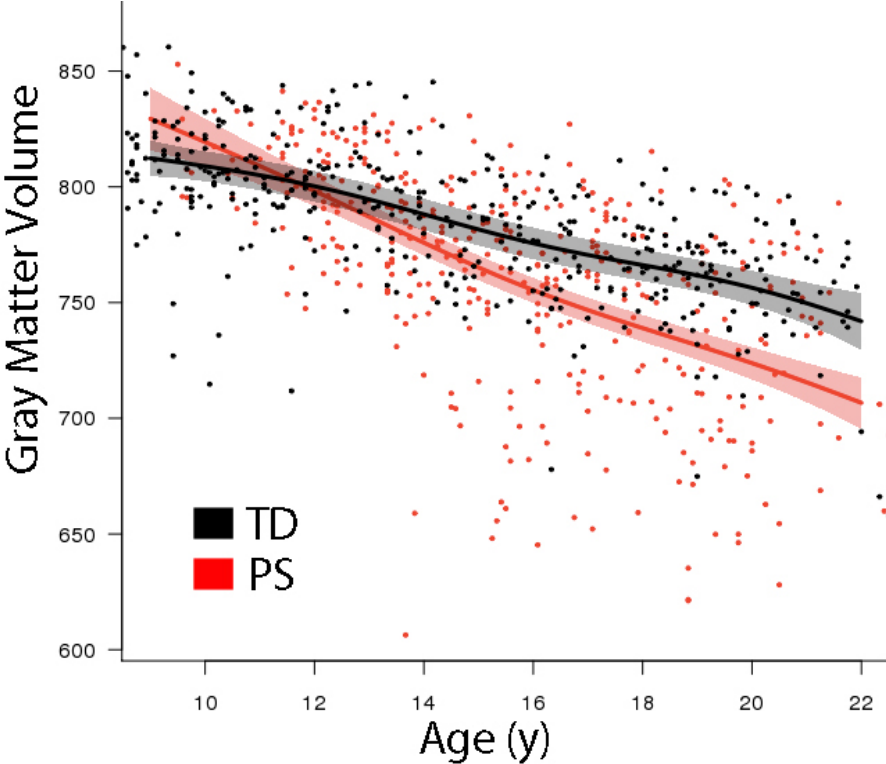


NEUROCOGNITIVE AGE



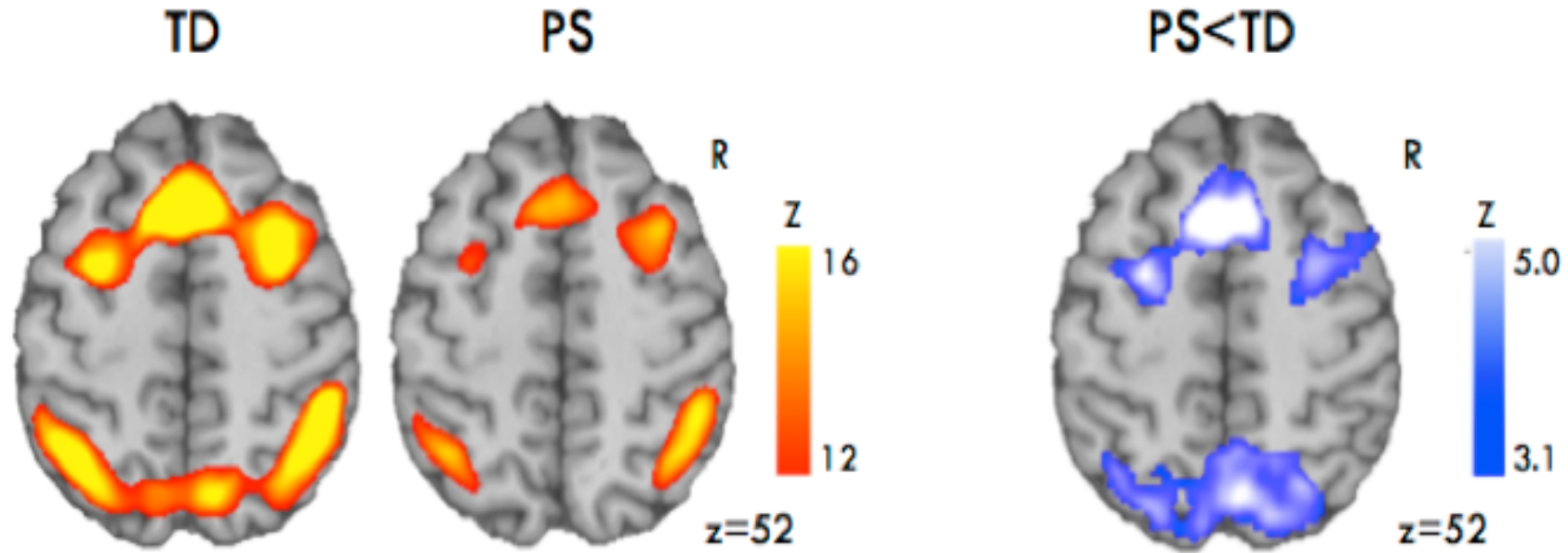
Gur et al., JAMA Psychiatry, 2014

Adolescents with Psychosis-Spectrum Symptoms have Reduced GM Volume

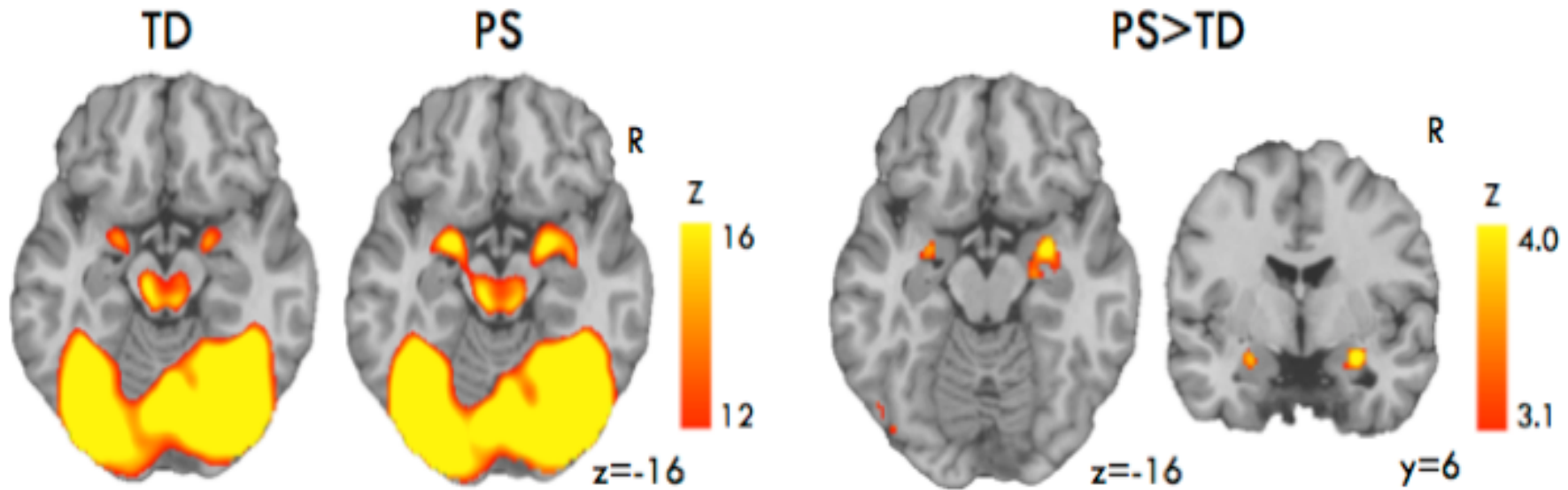


fMRI

Working Memory

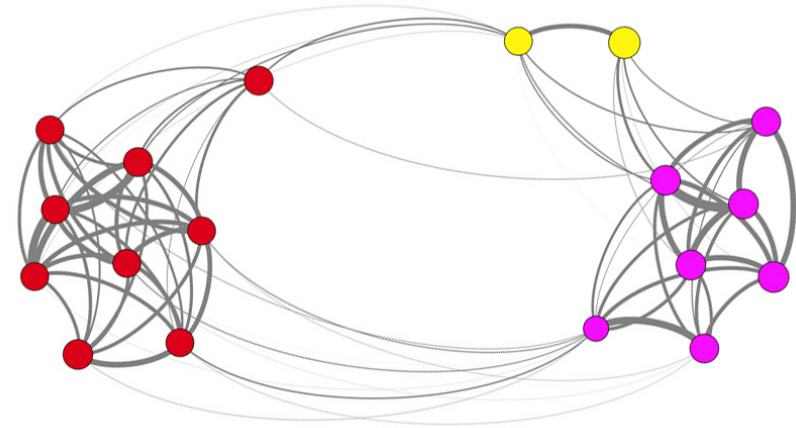
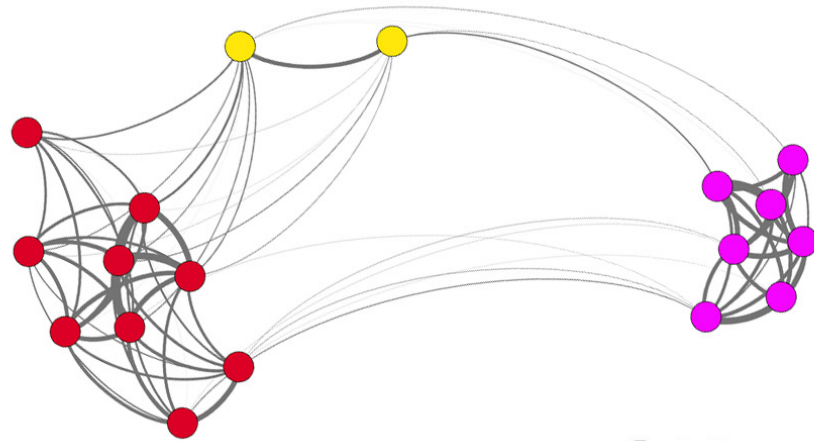


Emotion Identification



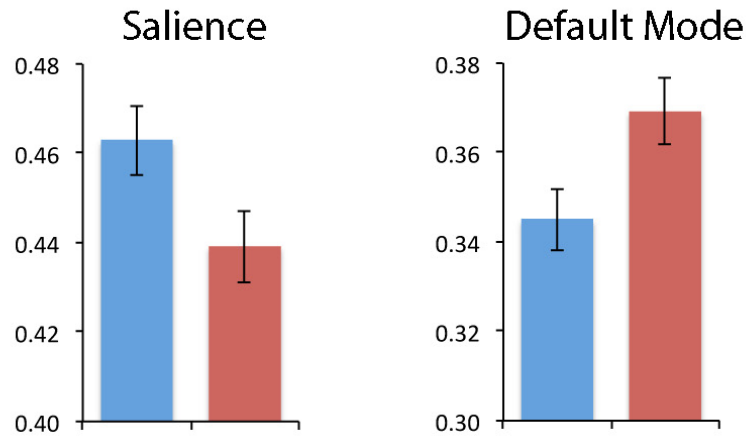
A Typically Developing

Psychosis Spectrum

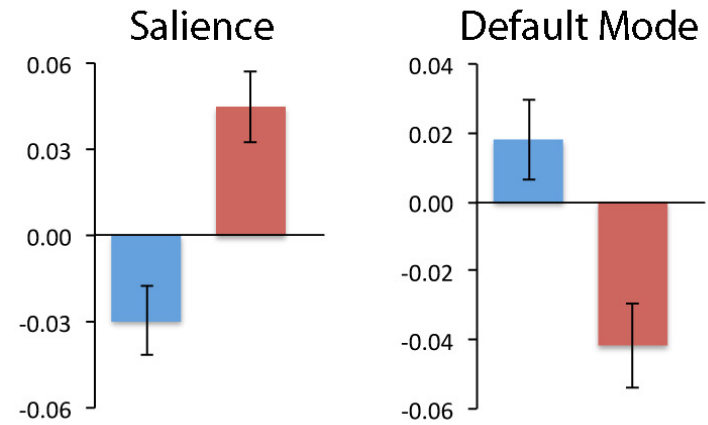


● Saliency / Ventral Attention
● Default Mode
● Frontal Pole

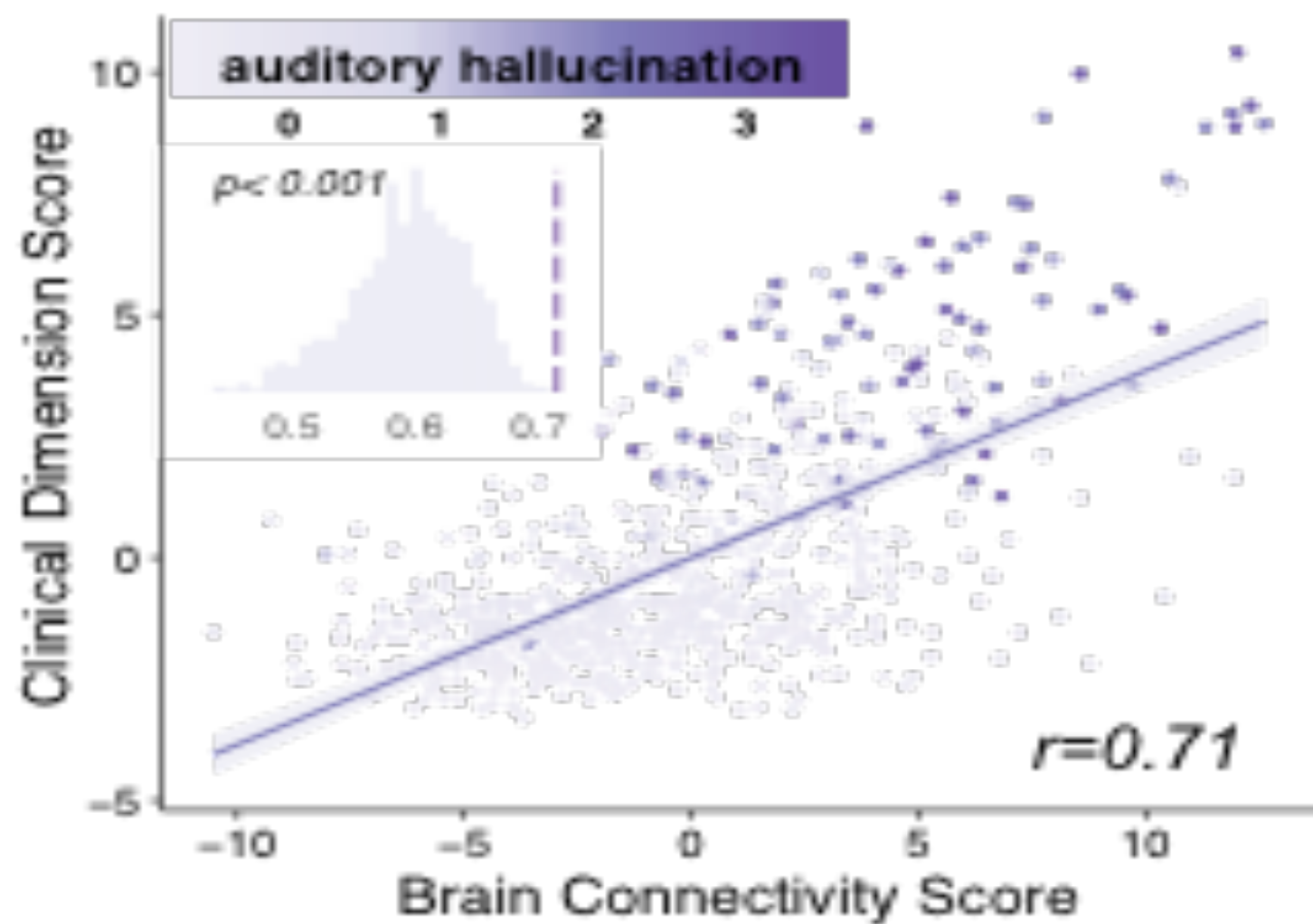
B Within Network Connectivity



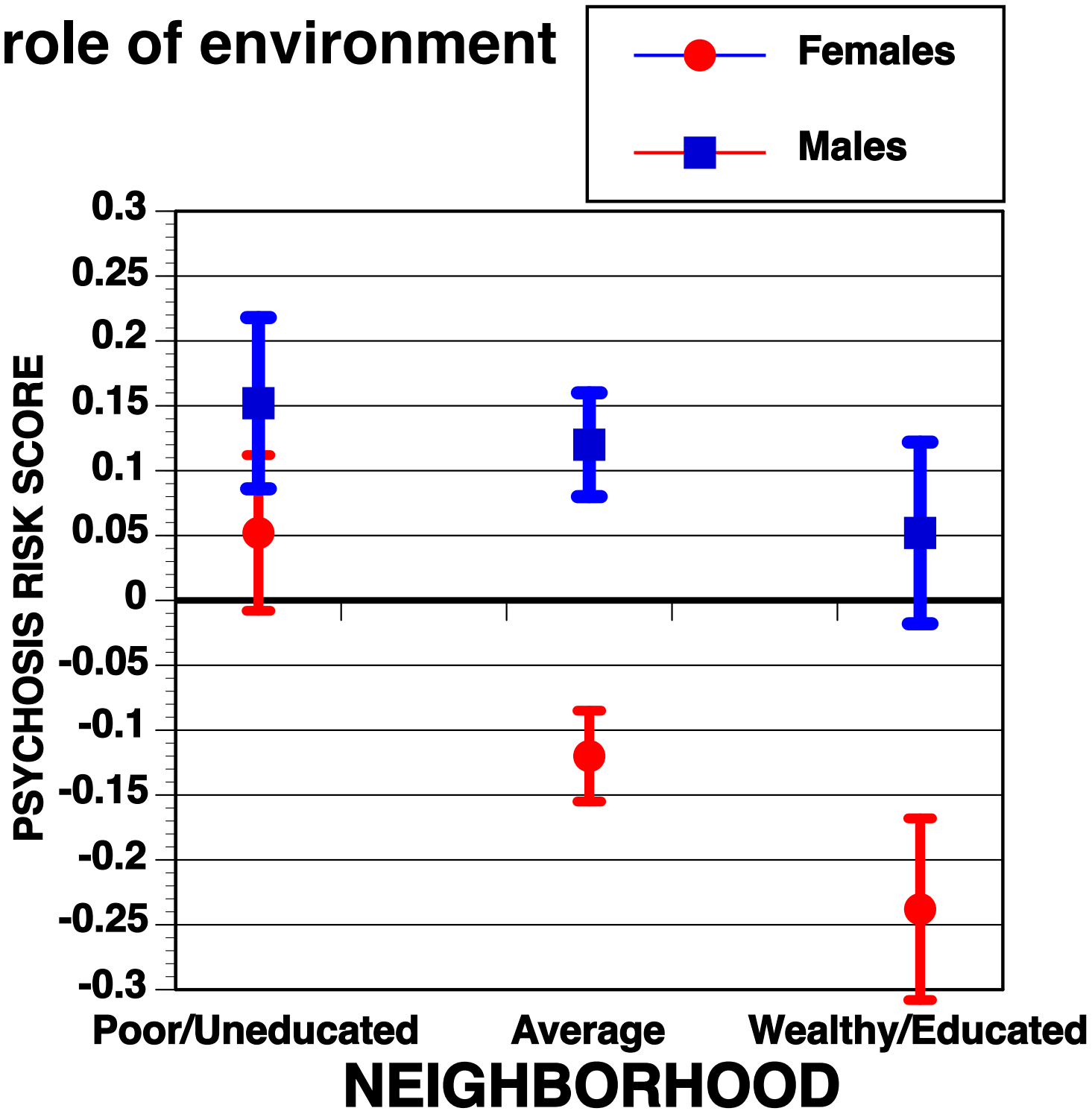
C Connectivity with Frontal Pole



■ Typically Developing ■ Psychosis Spectrum



The role of environment



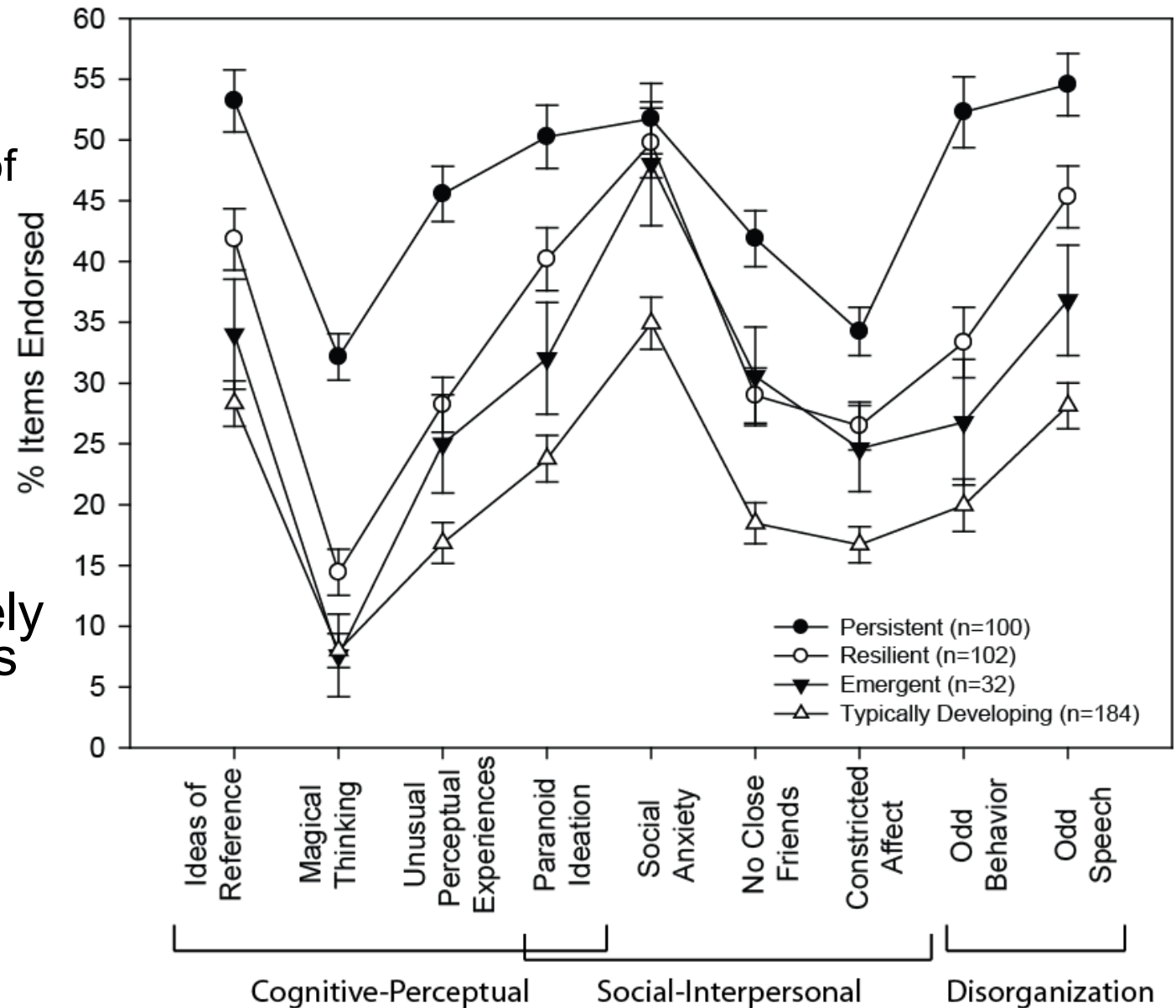
Persistence of psychosis spectrum symptoms in the Philadelphia Neurodevelopmental Cohort: a prospective two-year follow-up

Monica E. Calkins¹, Tyler M. Moore¹, Theodore D. Satterthwaite¹, Daniel H. Wolf¹, Bruce I. Turetsky¹, David R. Roalf¹, Kathleen R. Merikangas², Kosha Ruparel¹, Christian G. Kohler¹, Ruben C. Gur¹, Raquel E. Gur¹ *(World Psychiatry 2017;16:62-76)*

Symptom persistence predicted by baseline

- higher severity of subclinical psychosis
- lower global functioning
- prior psychiatric medication

Youths classified as resilient nonetheless exhibited comparatively higher symptom levels and lower functioning at both baseline and follow-up than TD



Phase Specific Interventions

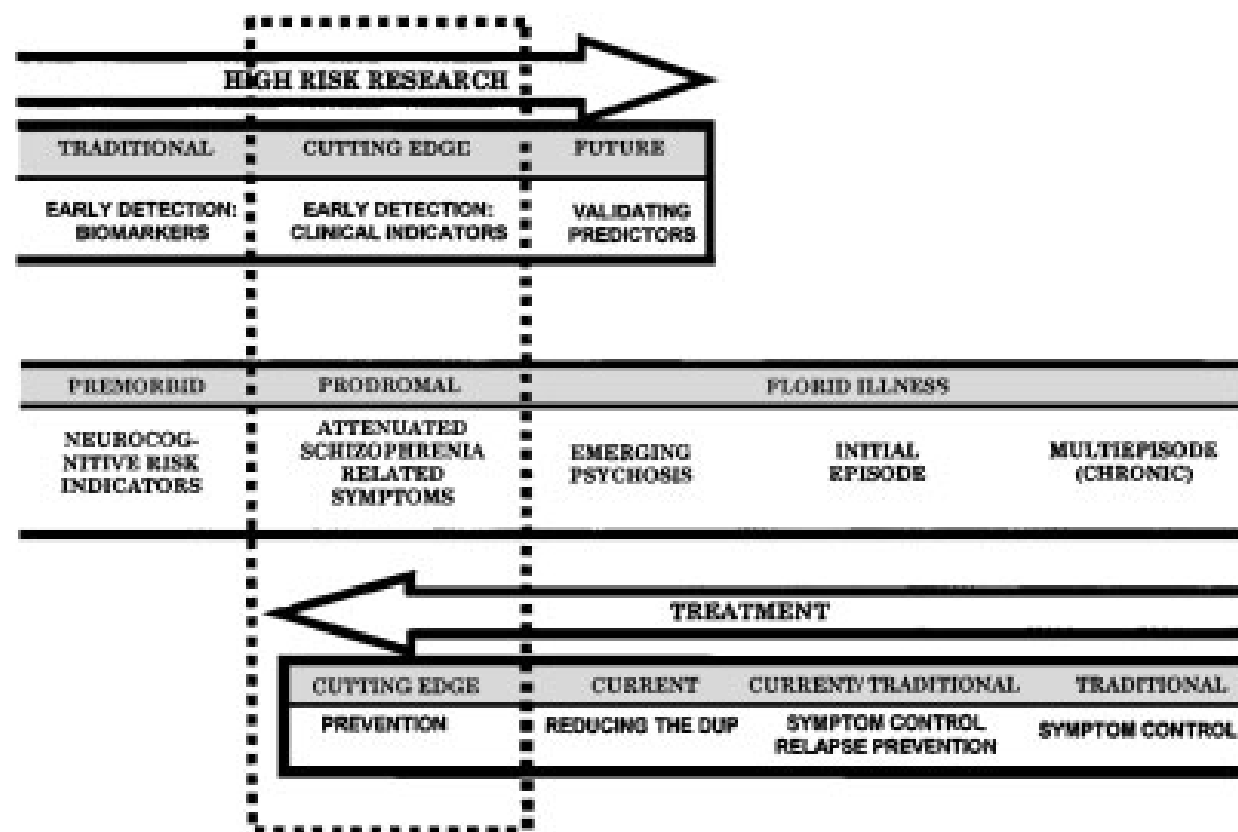


Fig. 1. Convergence of two research traditions—treatment and high risk—on the schizophrenia prodrome. Source: Cornblatt et al. [2002].

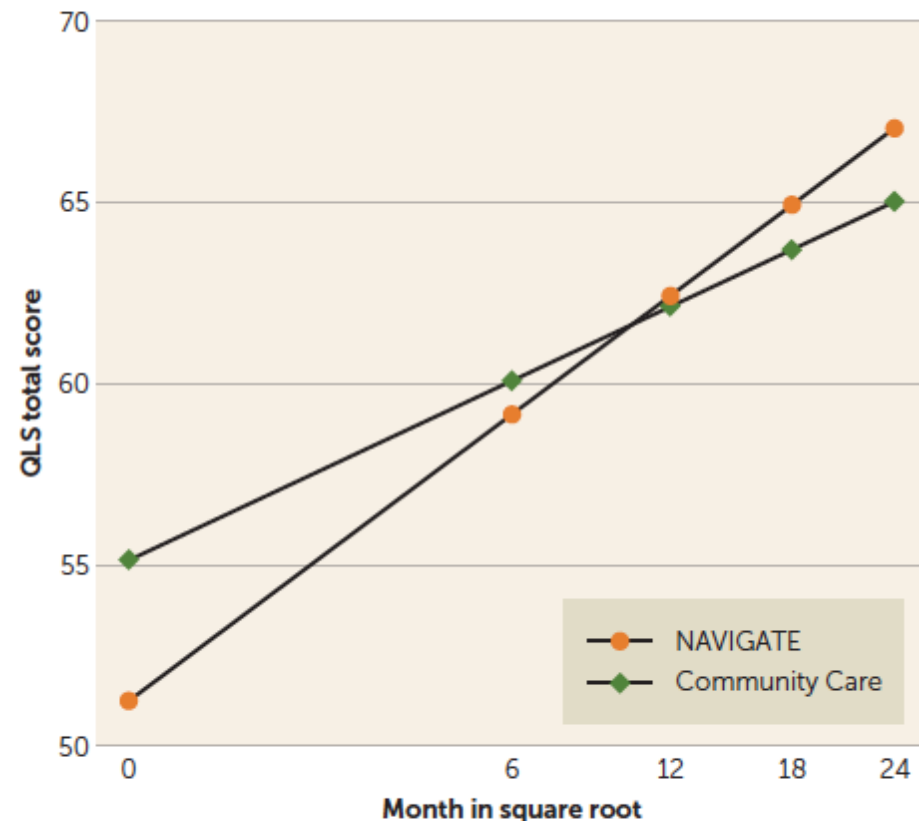
From Cornblatt et al., 2002 Am J Med Gen (Neuropsychiatric Genetics), 114: 956-966

Comprehensive Versus Usual Community Care for First-Episode Psychosis: 2-Year Outcomes From the NIMH RAISE Early Treatment Program

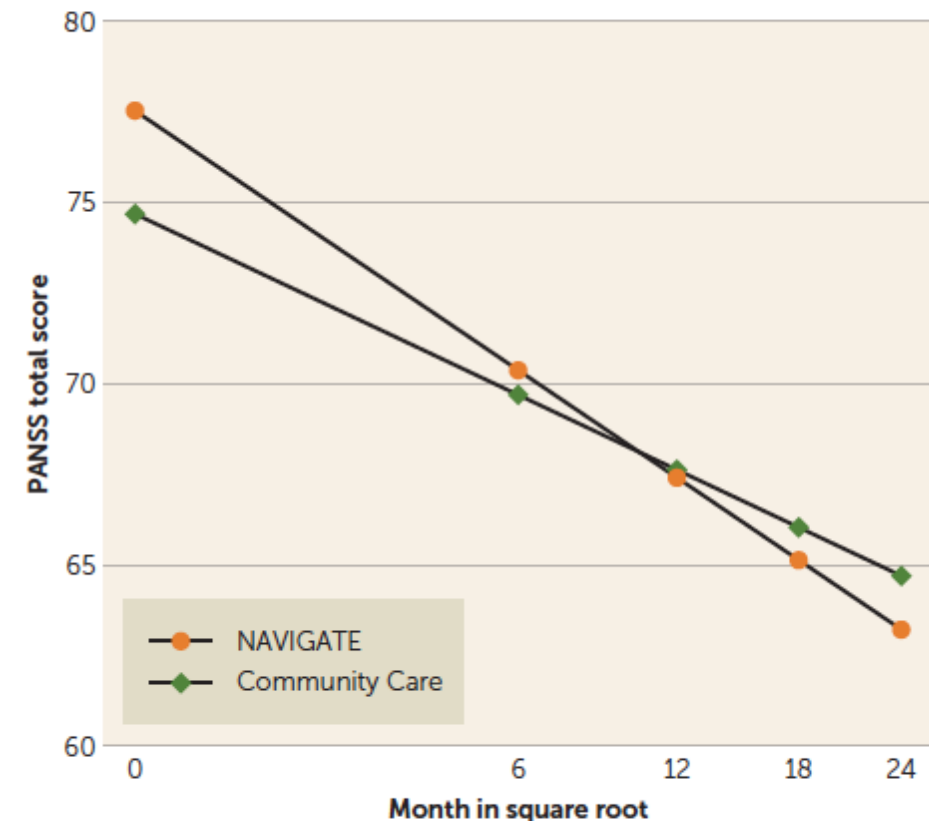
John M. Kane, M.D., Delbert G. Robinson, M.D., Nina R. Schooler, Ph.D., Kim T. Mueser, Ph.D., David L. Penn, Ph.D.,
AJP in Advance (doi: 10.1176/appi.ajp.2015.15050632)

FIGURE 2. Model-Based Estimates of Heinrichs-Carpenter Quality of Life (QLS) Total Score and PANSS Total Score^a

A. QLS total score^b



B. PANSS total score^c



^a PANSS=Positive and Negative Syndrome Scale.

^b Treatment by square root of time interaction, $p=0.015$.

^c Treatment by square root of time interaction, $p=0.016$.

Early psychosis: A unique opportunity for intervention

Decreasing duration of untreated psychosis is high priority

Prevention of chronic illness and disability

Specialized phase specific intervention services

- may improve symptoms and clinical course
- increase retention in treatment program
- improve outcome
- reduce cost of treatment

Christian Kohler, M.D.

Monica Calkins, Ph.D.

Paul Moberg, Ph.D.

Raquel Gur, M.D. Ph.D.

Anup Sharma, M.D.

Lyndsay Schmidt, M.A.

Kelly Peters, M.A.

Bridgette Patton, B.A.

Penn Behavioral Health
Penn Psychosis
Evaluation and Recovery Center
Penn PERC

Penn Medicine
Department of Psychiatry
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Hospital of the University of Pennsylvania
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Philadelphia, PA 19104
Tel: (215) 615-3292
Fax: (215) 615-7903
www.med.upenn.edu/perc

Fees/Insurance

Parts of this program may be covered by your insurance carrier. The program is further supported through Pennsylvania state funds for Pennsylvania residents. For Non-Pennsylvania residents, please contact us regarding other options. Individual parts of the comprehensive services are available on a fee for services basis.

Penn Psychosis

EVALUATION AND RECOVERY CENTER

Penn PERC



Eligibility



- Key Inclusion Criteria

- Early warning signs of psychosis or onset of psychosis within the past 3 years
- Males and females between the ages of 14-34

- Key Exclusion Criteria

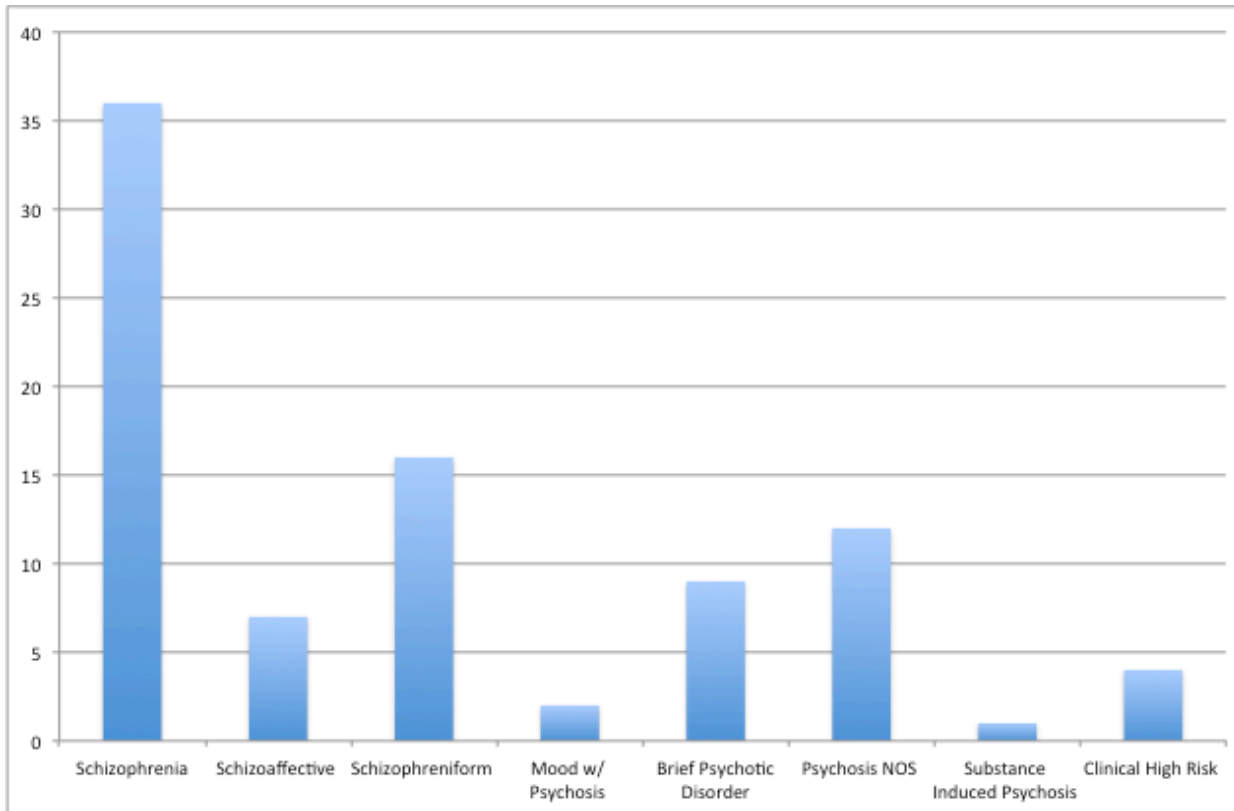
- Severe medical illness
- Diagnosis of intellectual disability
- Onset of psychotic disorder greater than 3 years
- Severe substance use disorder interfering with ability to complete study procedures, based upon clinician's review

Program Overview

- Community Outreach
- Assessment
- Recovery Planning
- Cognitive Behavioral Therapy (CBT)/Case Management
- Psychopharmacology
- Cognitive Remediation
- Multi-family Group Psychoeducation
- Occupational Intervention

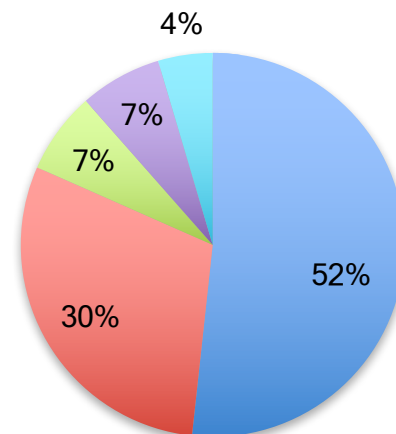
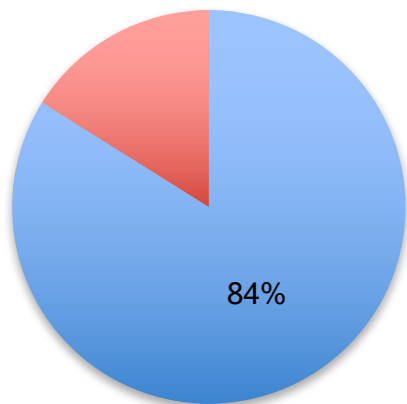
Patients Enrolled: 125

Age Range yrs 14-34
(Mean = 21.7)

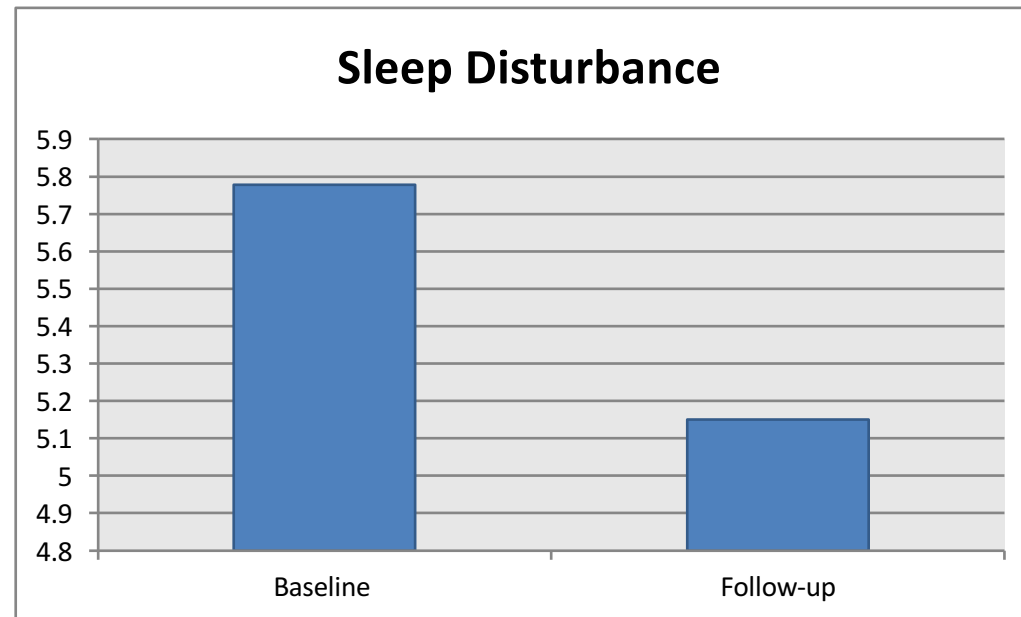
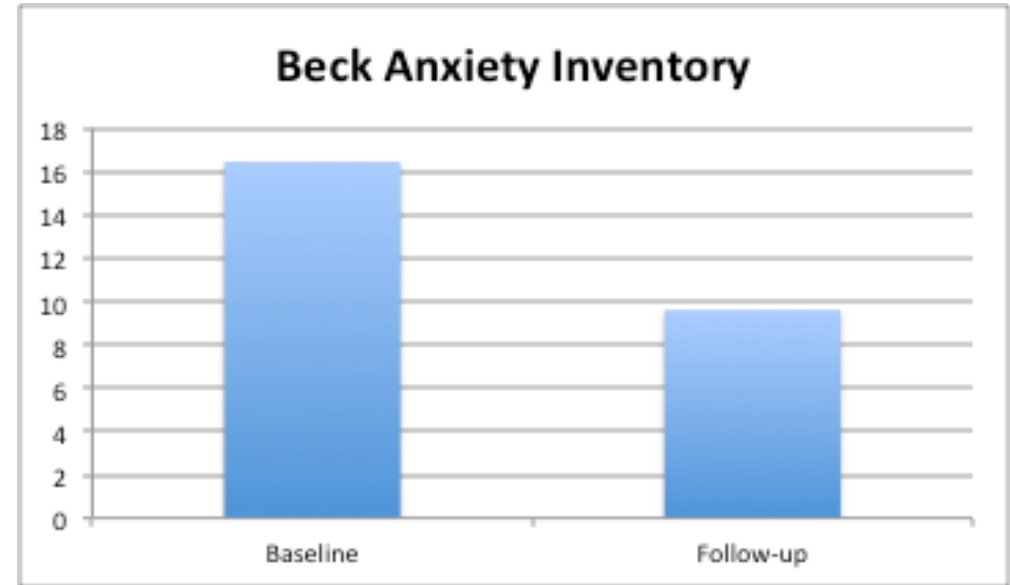
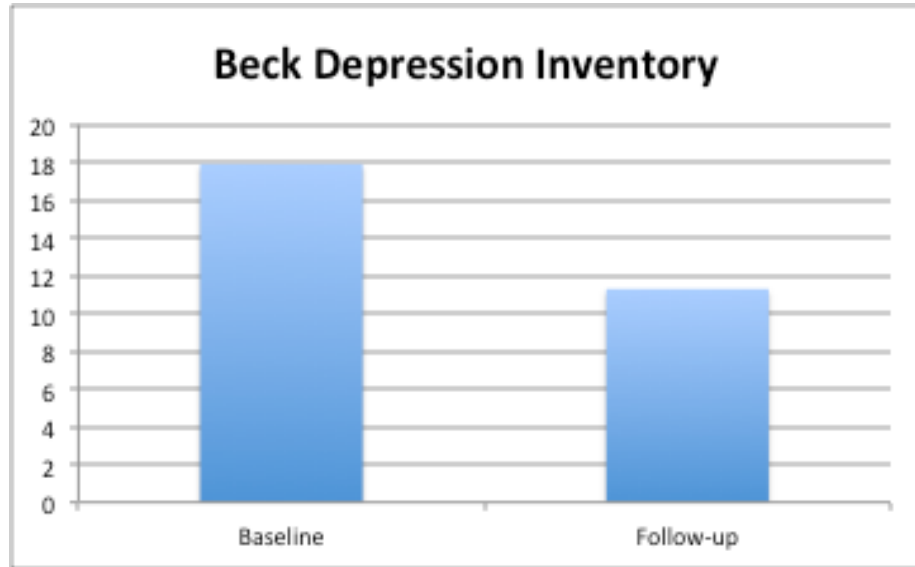


■ Male ■ Female

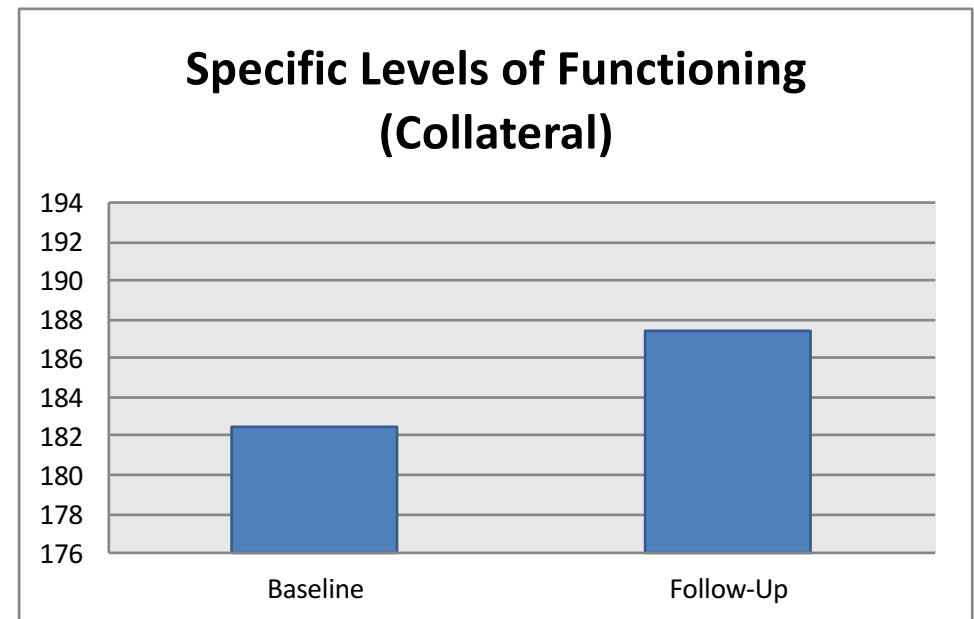
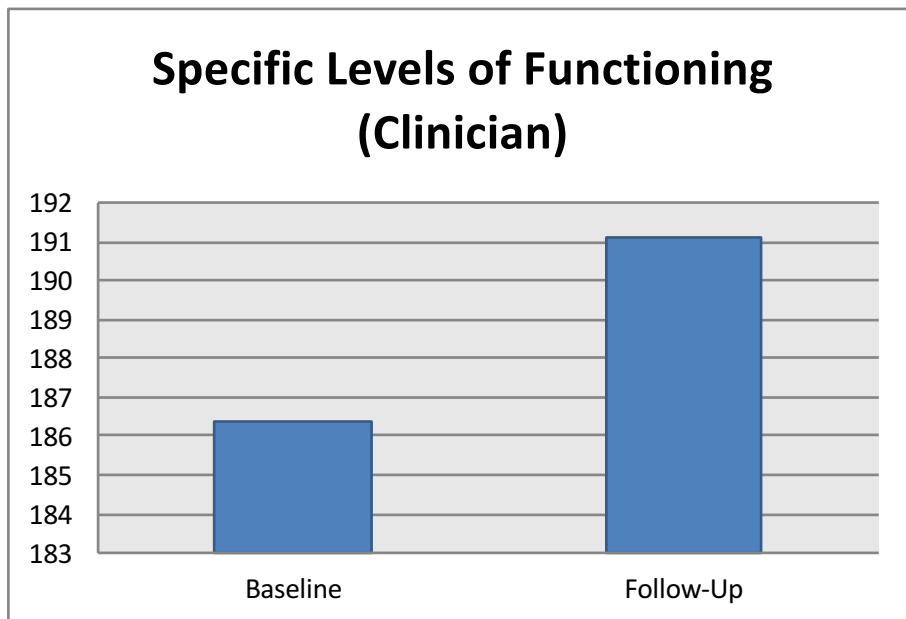
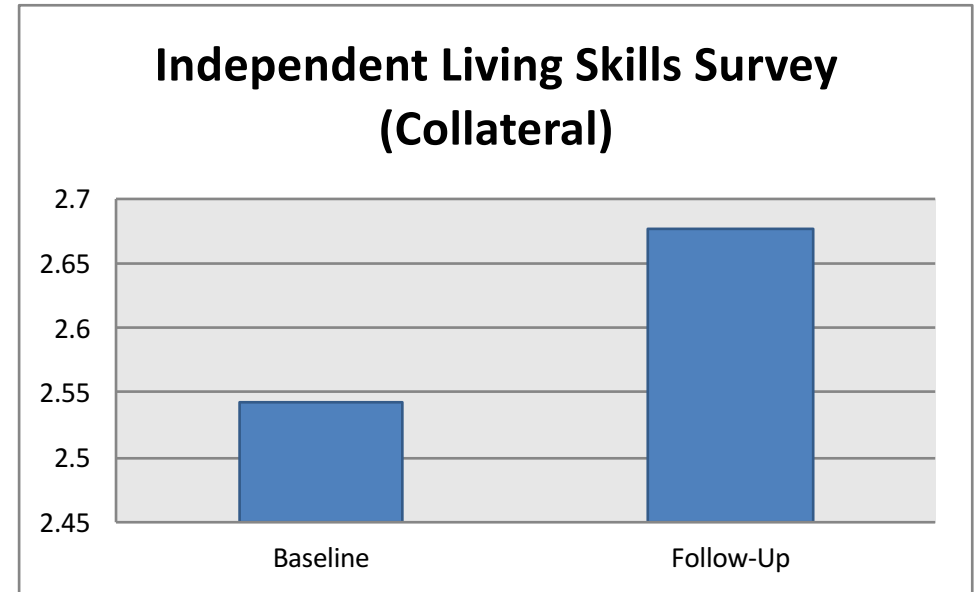
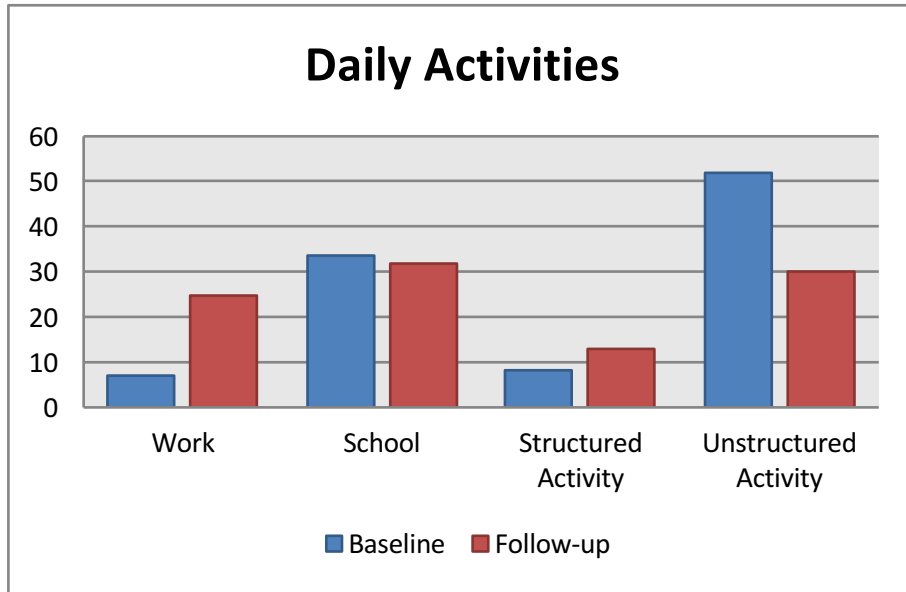
■ Caucasian ■ African American ■ Asian ■ Hispanic/Latino ■ Other



Symptom Improvement



Functional Improvement



Social Cognition in Psychosis Risk

- Evidence for impairment in this domain
- Associated with negative symptoms and poorer functional outcome

EMOTION RECOGNITION



- Happy
- Sad
- Angry
- Fearful
- No Emotion

EMOTION DISCRIMINATION

Which face is more happy?



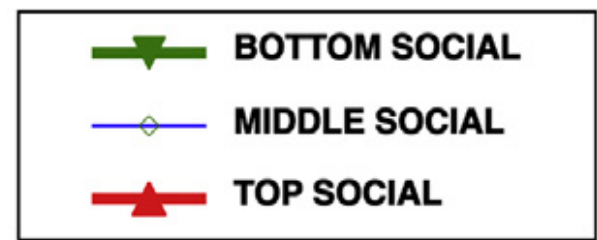
- ↑ This Face
- Equal
- This Face ↑

AGE DIFFERENTIATION

Which face is older?

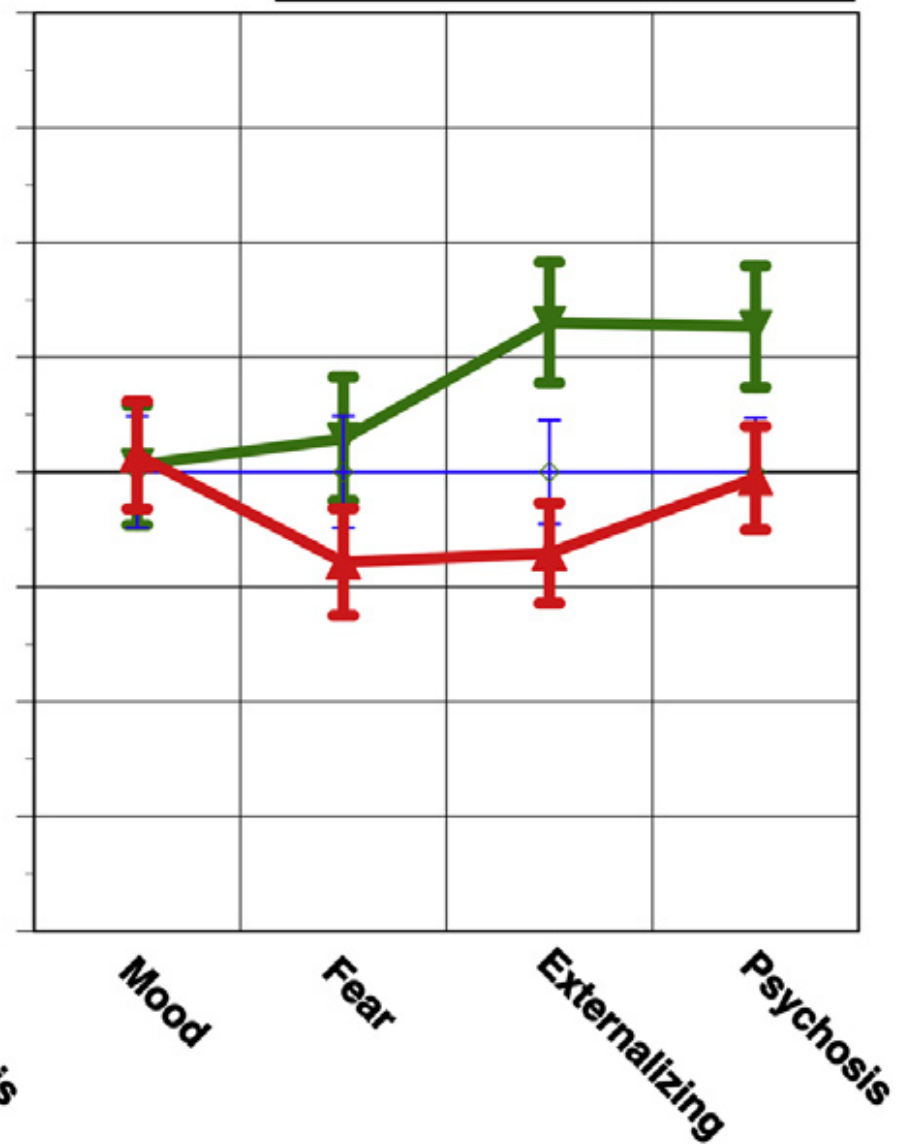
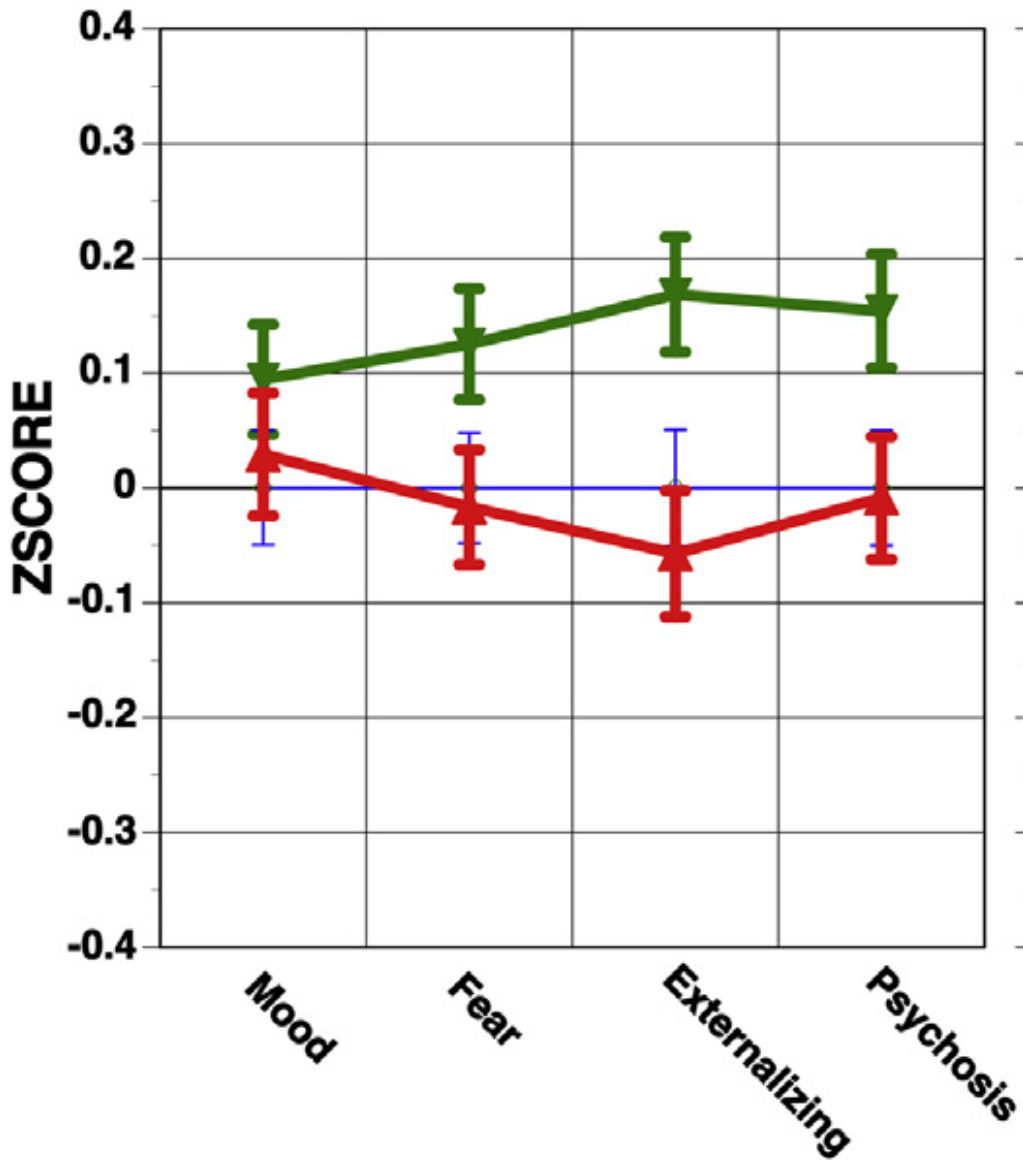


- ↑ This Face
- Same Age
- This Face ↑



Males

Females



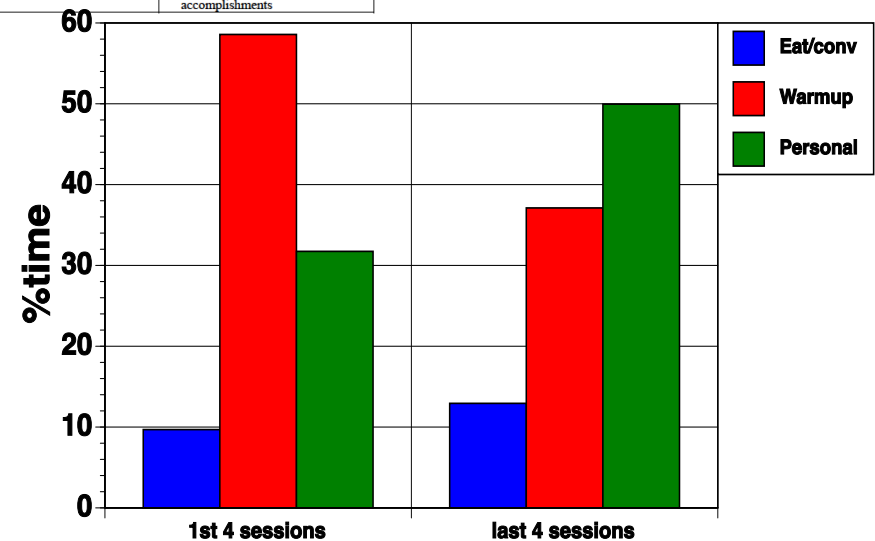
SYMPTOM DOMAINS

SYMPTOM DOMAINS

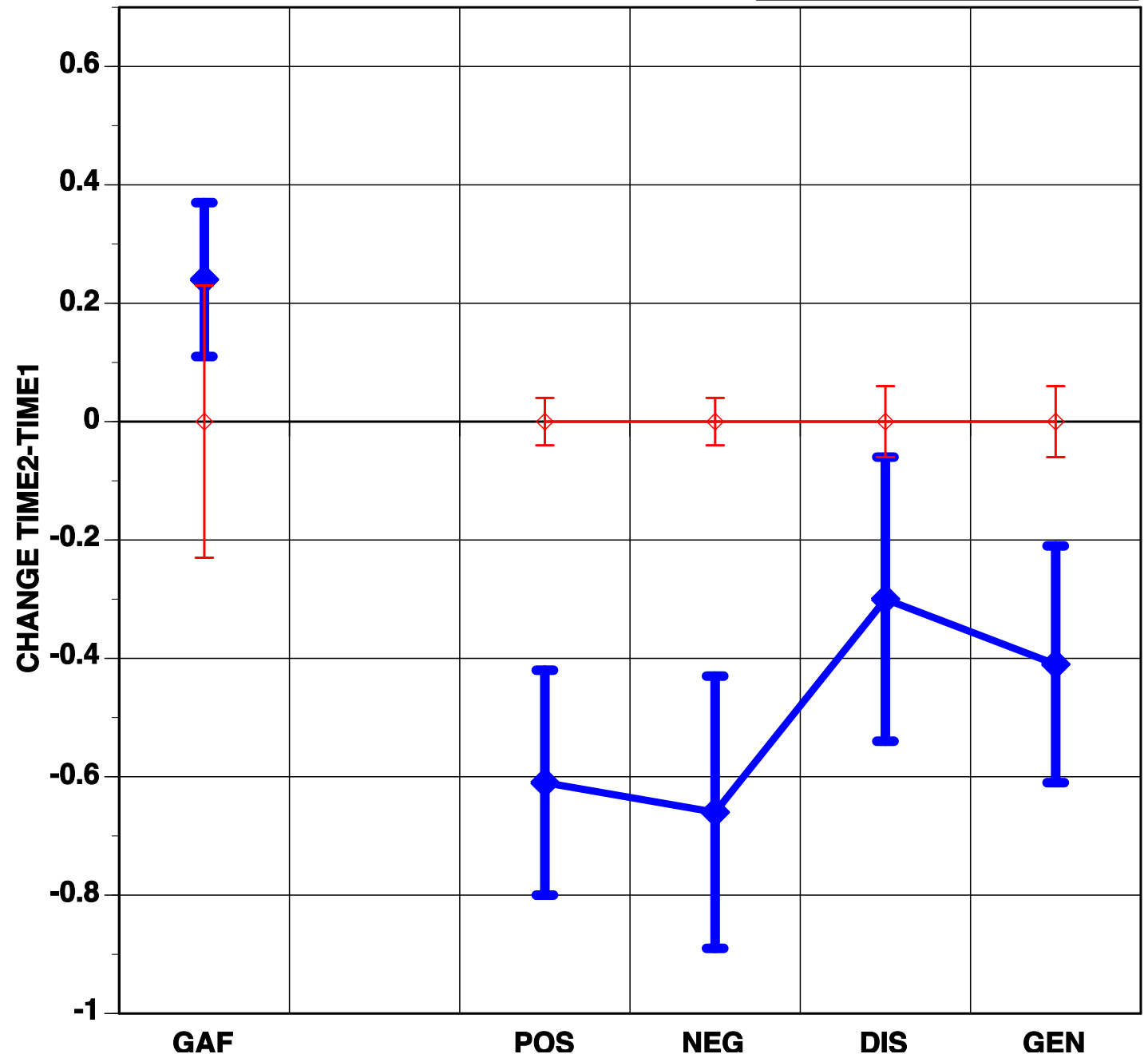
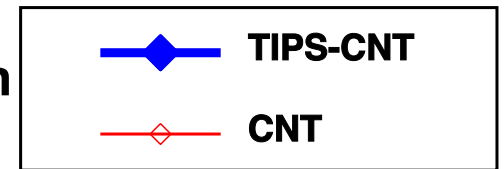
CBT-informed social enactment training curricula for CHR youth

Theater Improvisation Training to Promote Social Cognition (TIPS)

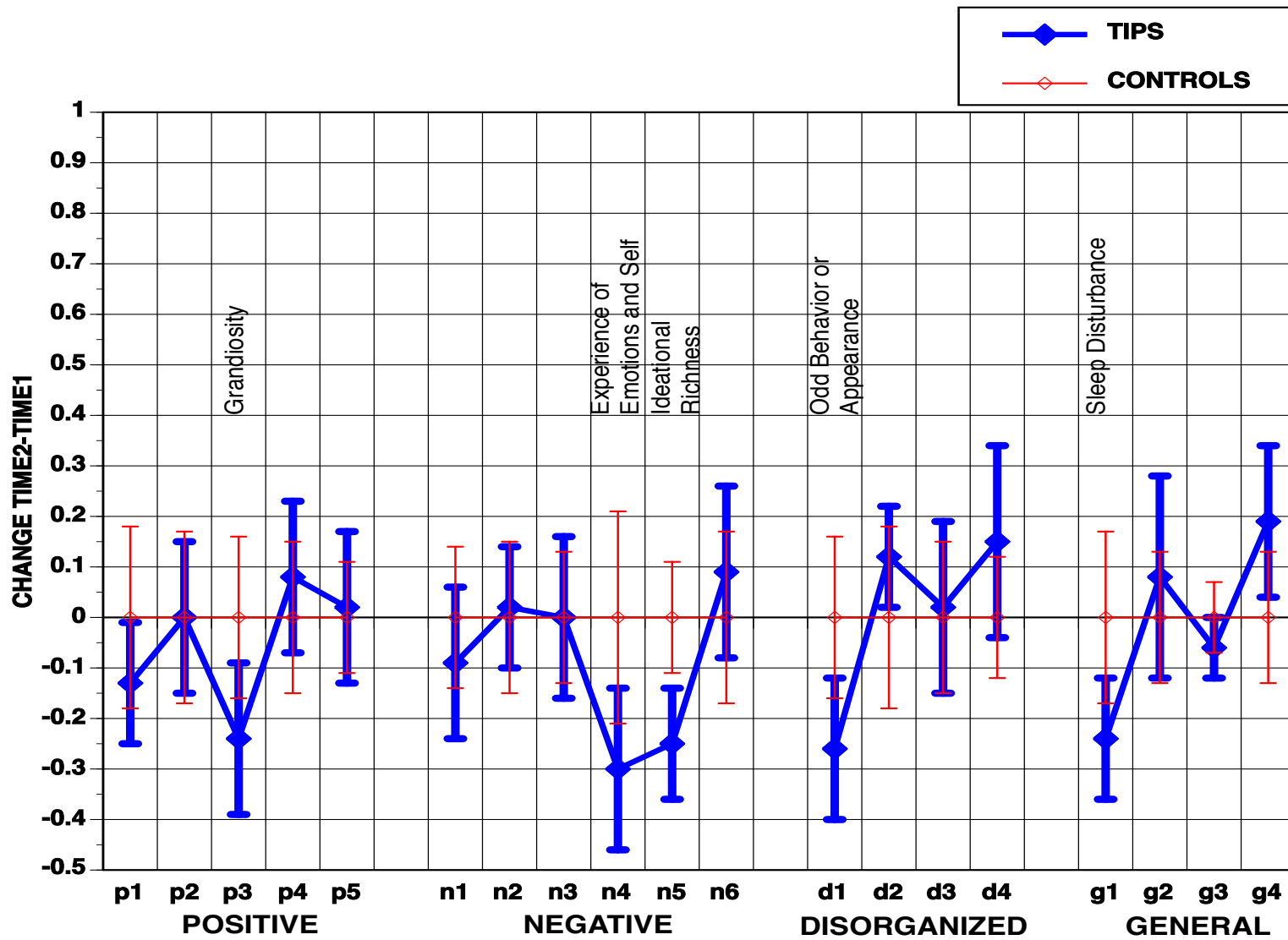
<p>Week 1 INTRODUCTION</p> <ul style="list-style-type: none"> • Introduction – both to each other and to course • Improvisational exercises to get people comfortable with one another • Acting/improv games designed specifically to open people up and banish embarrassment • Create class ritual together (a ritual that, from this point onward, will begin each class) 	<p>Week 2 CHARACTER & BODY</p> <ul style="list-style-type: none"> • Class ritual • Improv games designed to open people up and banish embarrassment • Introduce idea of character • Improv exercise dealing with character development • Begin working on body, and how we use our bodies to reveal our character • ASSIGNMENT: Go to a park, a shopping mall, or somewhere else there are a lot of people. Look at how they move and see if how they move reveals anything about who they are and what they want. 	<p>Week 3 CHARACTER, BODY & BODY LANGUAGE</p> <ul style="list-style-type: none"> • Class ritual • Improv games designed to open people up and banish embarrassment • Improv exercise that is completely physical • Continue working on physicalization, in particular how we can use our bodies to communicate without speaking. • ASSIGNMENT: Go out with a fellow classmate to where there are a lot of people. Look at how people move; see if how they move reveals anything about who they are and what they want. Compare notes afterward to see if you are drawn to the same kind of people or different ones. 	<p>Week 7 CHARACTER, INTENTION & TENSION</p> <ul style="list-style-type: none"> • Class ritual • Continue to learn about INTENTION - how actors to use their minds, bodies and voices to get what their characters want • Learn how actors figure out what other character want by decoding their intentions • Negotiate tension – when two characters intentions are in conflict • Explore what conflict feels like and discovers tactics to resolve the conflict • Explore what makes a good story 	<p>Week 8 CHARACTER, STATUS, CONFLICT & STORY</p> <ul style="list-style-type: none"> • Class ritual • Continue to learn about intention, how intention can sometimes cause conflict and how to use tactics to either raise or lessen tension • Learn how actors figure out what other character want by decoding their intentions • Do status exercises and play improv games that explore status • Explore how status changes a character's body, voice, intention and tactics • Explore what makes a good story • ASSIGNMENT: Fieldtrip – see a play with instructor and classmates at a professional theatre. 	<p>Week 9 STORY BUILDING</p> <ul style="list-style-type: none"> • Class ritual • Use structured long form improv to generate our own stories • Use props and costumes to generate improvised story • Write two brief scenes together based on improv experience • Put that scene up on its feet • ASSIGNMENT: Get together with partner outside of class and write a 2 character scene
<p>Week 4 CHARACTER, BODY LANGUAGE & VOICE</p> <ul style="list-style-type: none"> • Class ritual • Improv games designed to open people up and banish embarrassment • Explore our voices and how to use them • Improv games that focus on vocal work • Exploration of how voice can reveal character and intention • ASSIGNMENT: Go to a place where there are a lot of people. Listen to how they talk and discover if how they sound reveals anything about who they are and what they want. 	<p>Week 5 CHARACTER, VOICE & INTENTION</p> <ul style="list-style-type: none"> • Class ritual • Improv games designed to open people up and banish embarrassment • Explore our voices and how to use them • Learn about INTENTION - how actors to use their minds, bodies and voices to get what their characters want • Script work using intention • ASSIGNMENT: Write a character sketch 	<p>Week 6 CHARACTER & INTENTION</p> <ul style="list-style-type: none"> • Class ritual • Share character sketches • Continue to learn about INTENTION - how actors to use their minds, bodies and voices to get what their characters want • Learn how actors figure out what other character want by decoding their intentions • Script work using intention • ASSIGNMENT: Write more detailed character sketch 	<p>Week 10 MASK WORK & SCRIPT SHARING</p> <ul style="list-style-type: none"> • Class ritual • Read new scenes out loud for each other • Discuss what works and what doesn't • Pick on scene to develop briefly • Introduction to mask work • ASSIGNMENT: Write a scene on your own 	<p>Week 11 MASK WORK & SCRIPT SHARING</p> <ul style="list-style-type: none"> • Class ritual • Read new scenes outloud • Discuss what works and what doesn't • Delve further into mask work and how developing a character in a mask opens you up for new discoveries • ASSIGNMENT: Write a scene on with a partner 	<p>Week 12 MASK WORK & SCRIPT SHARING</p> <ul style="list-style-type: none"> • Class ritual • Read new scenes outloud • Discuss what works and what doesn't • Decide what our play will be • Delve further into mask work and how developing a character in a mask opens you up for new discoveries
			<p>Week 13 REHEARSAL</p> <ul style="list-style-type: none"> • Class ritual • First read-through of our original play • Do table work and discuss what characters want, who has high status, where are the conflicts • ASSIGNMENT: Start to memorize your part 	<p>Week 14 REHEARSAL</p> <ul style="list-style-type: none"> • Class ritual • Start blocking the play and getting it up on its feet • Improv games and workshop exploration as necessary to support actors and text • ASSIGNMENT: Memorize your part 	<p>Week 15 REHEARSAL</p> <ul style="list-style-type: none"> • Class ritual • Finish blocking the play and getting it up on its feet • Improv games and workshop exploration as necessary to support actors and text • ASSIGNMENT: Memorize your part
			<p>Week 16 REHEARSAL</p> <ul style="list-style-type: none"> • Class ritual • Do a full run through of the play • Work on play and problem spots • ASSIGNMENT: Work your part 	<p>Week 17 DRESS REHEARSAL</p> <ul style="list-style-type: none"> • Class ritual • Do a full run through of the play with costumes and props • ASSIGNMENT: Work your part 	<p>Week 18 SHARING</p> <ul style="list-style-type: none"> • Class ritual • Perform our play for family members and friends • Host a reception to celebrate our accomplishments



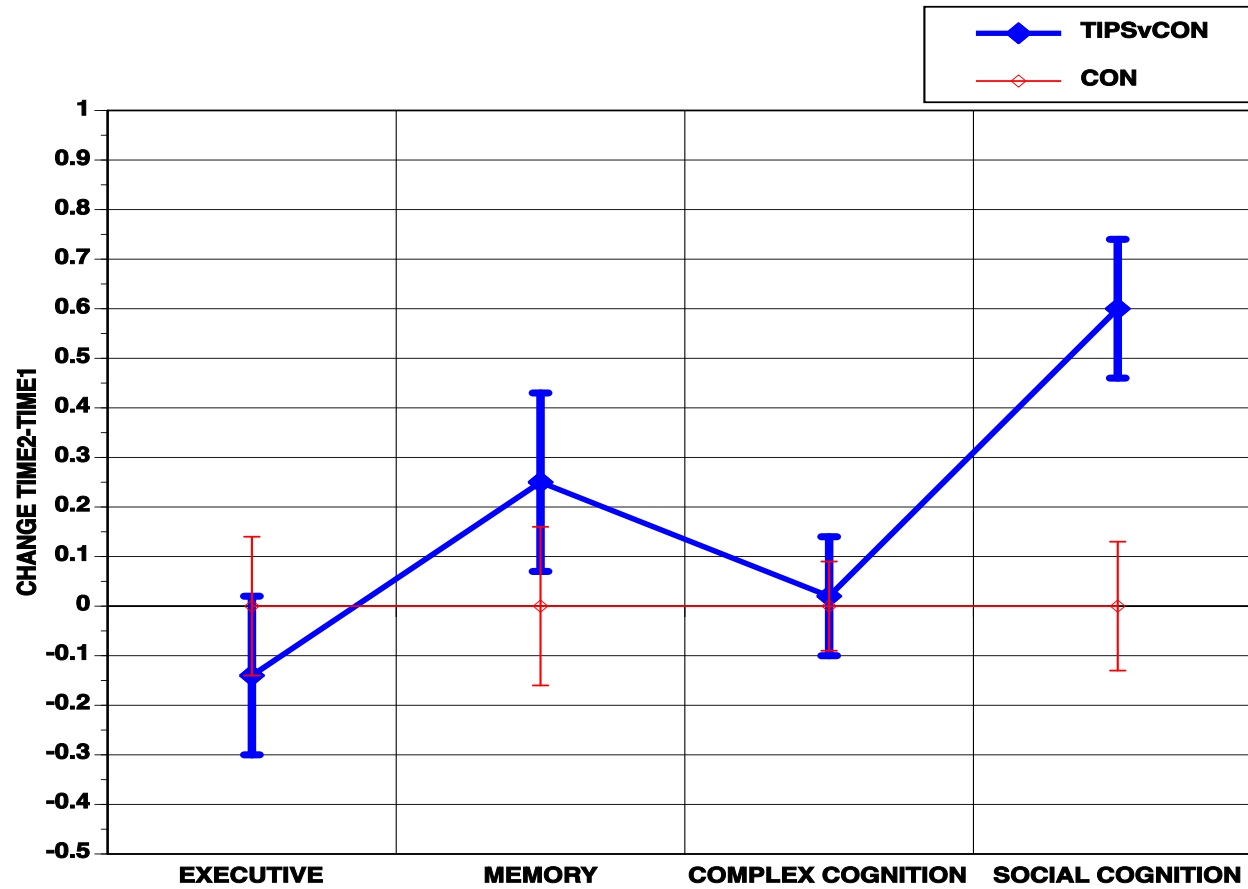
Symptom severity change following intervention

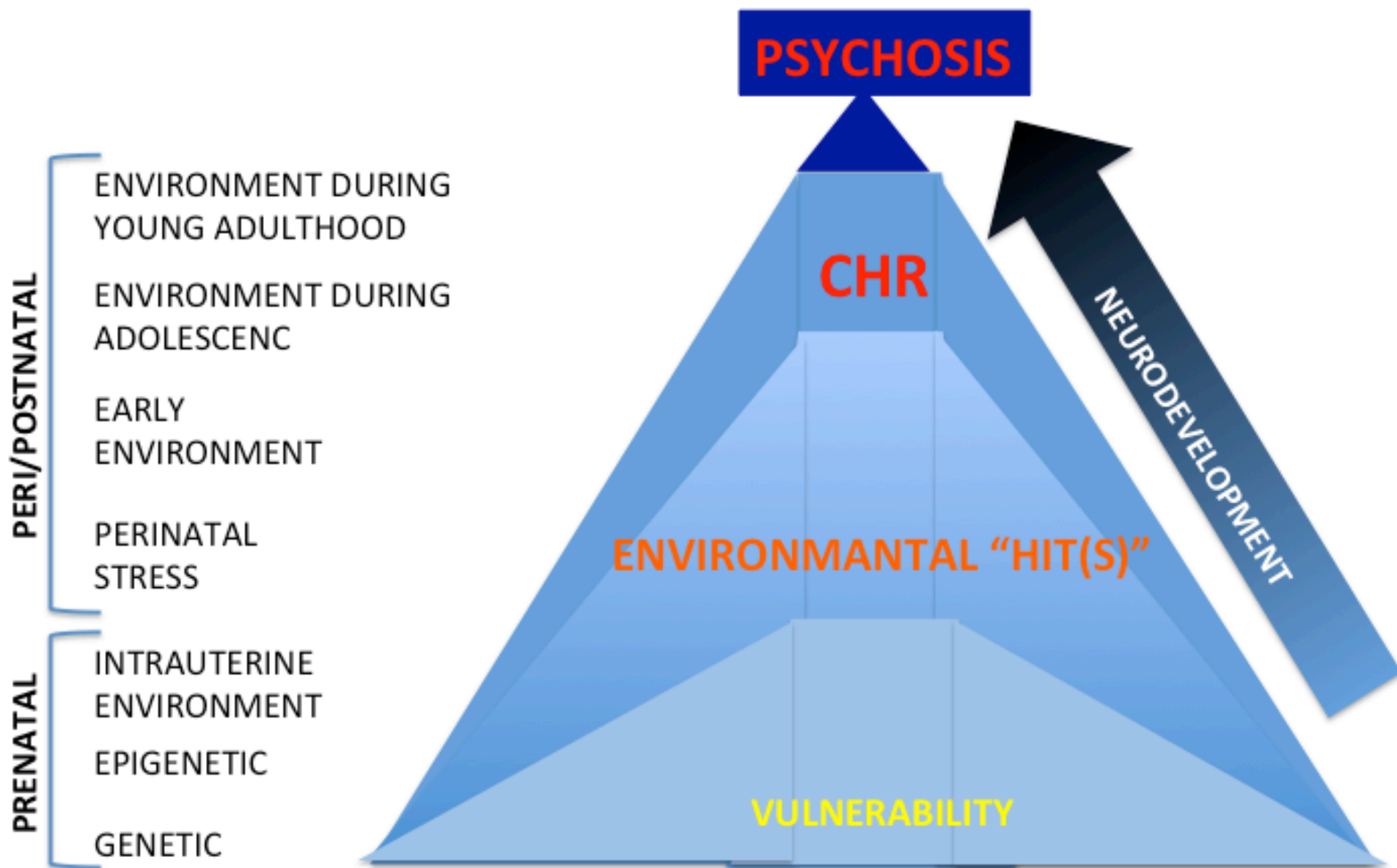


Symptom severity change following intervention



Neurocognitive performance change following intervention





Strategies for Early Detection and Intervention

- **Screening, education**
- **Establishing programs nationwide**
- **Complementary concomitant approaches**
 - **Cognitive remediation**
 - **Social cognition**
 - **Psychotherapy – CBT**
 - **Parents and family support**
 - **Medications**
- **Collaborative evidence-based studies**

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SUPPORTED BY NIMH

