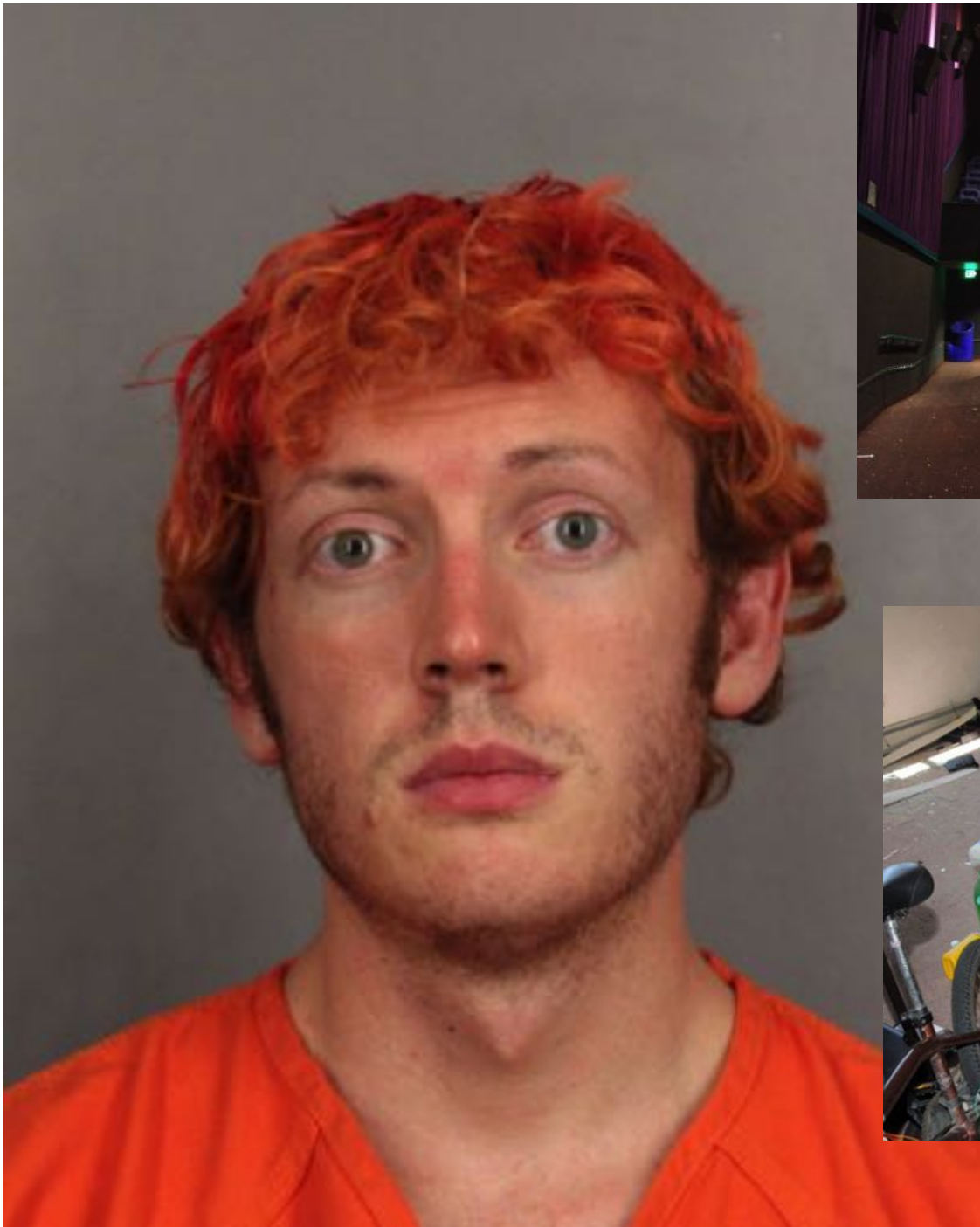


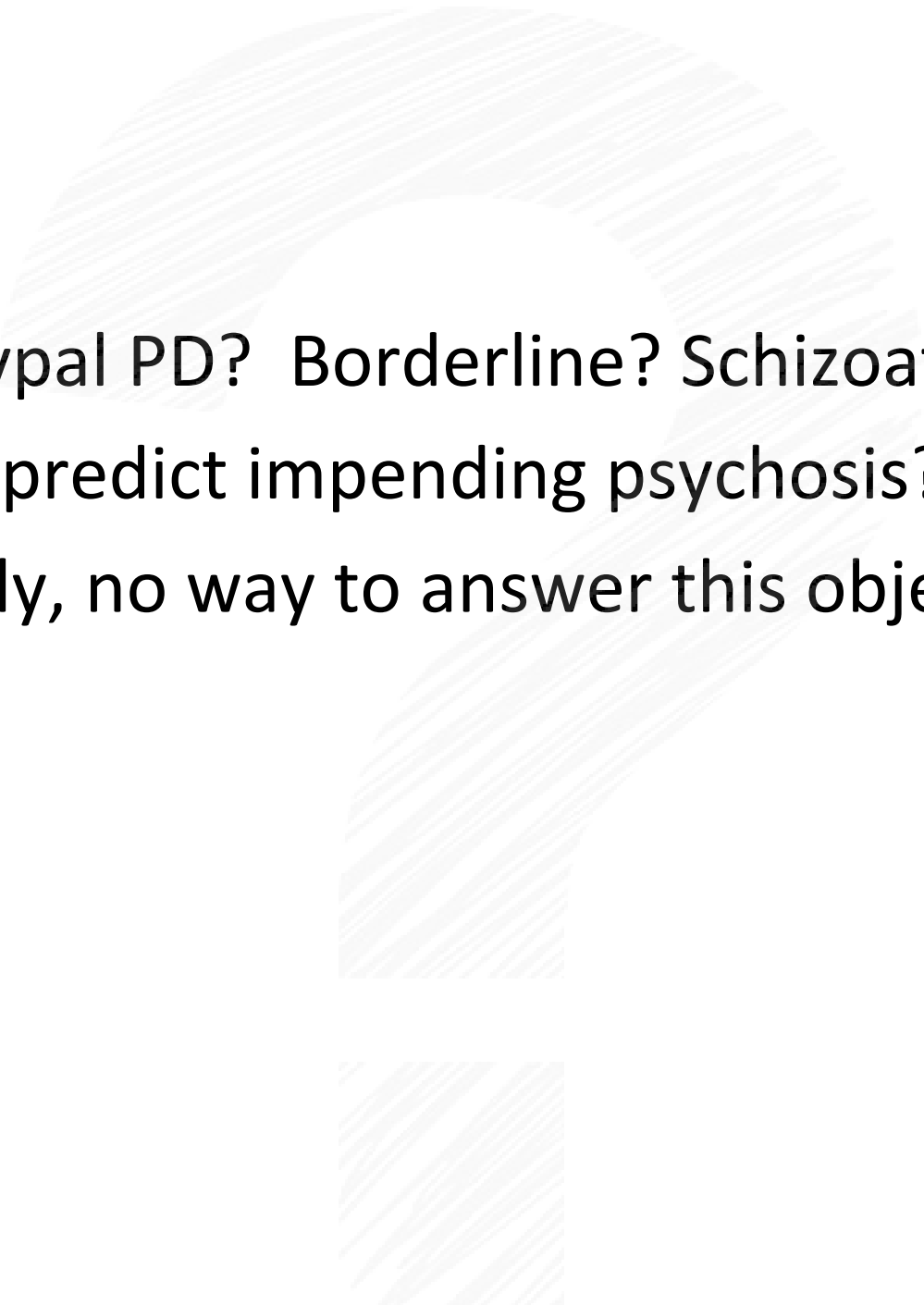
Visual perceptual disturbances as a window into the underlying pathophysiology of schizophrenia

Brian P. Keane

Rutgers—Robert Wood Johnson Medical School
Rutgers—University Behavioral HealthCare
Rutgers—University Center for Cognitive Science





- 
- Schizotypal PD? Borderline? Schizoaffective?
 - Can we predict impending psychosis?
 - Currently, no way to answer this objectively.

What we need is a biomarker

- “a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention” (NIH Definitions Working Group, 1998).
- Main claim: visual disturbances may provide a biomarker

Why look at visual disturbances in
schizophrenia?

Visual disturbances partly define the illness

They contribute to a DSM diagnosis.

VISUAL HALLUCINATIONS

Did you have visions or see things that other people couldn't see? (Were you awake at the time?)

Visual hallucinations

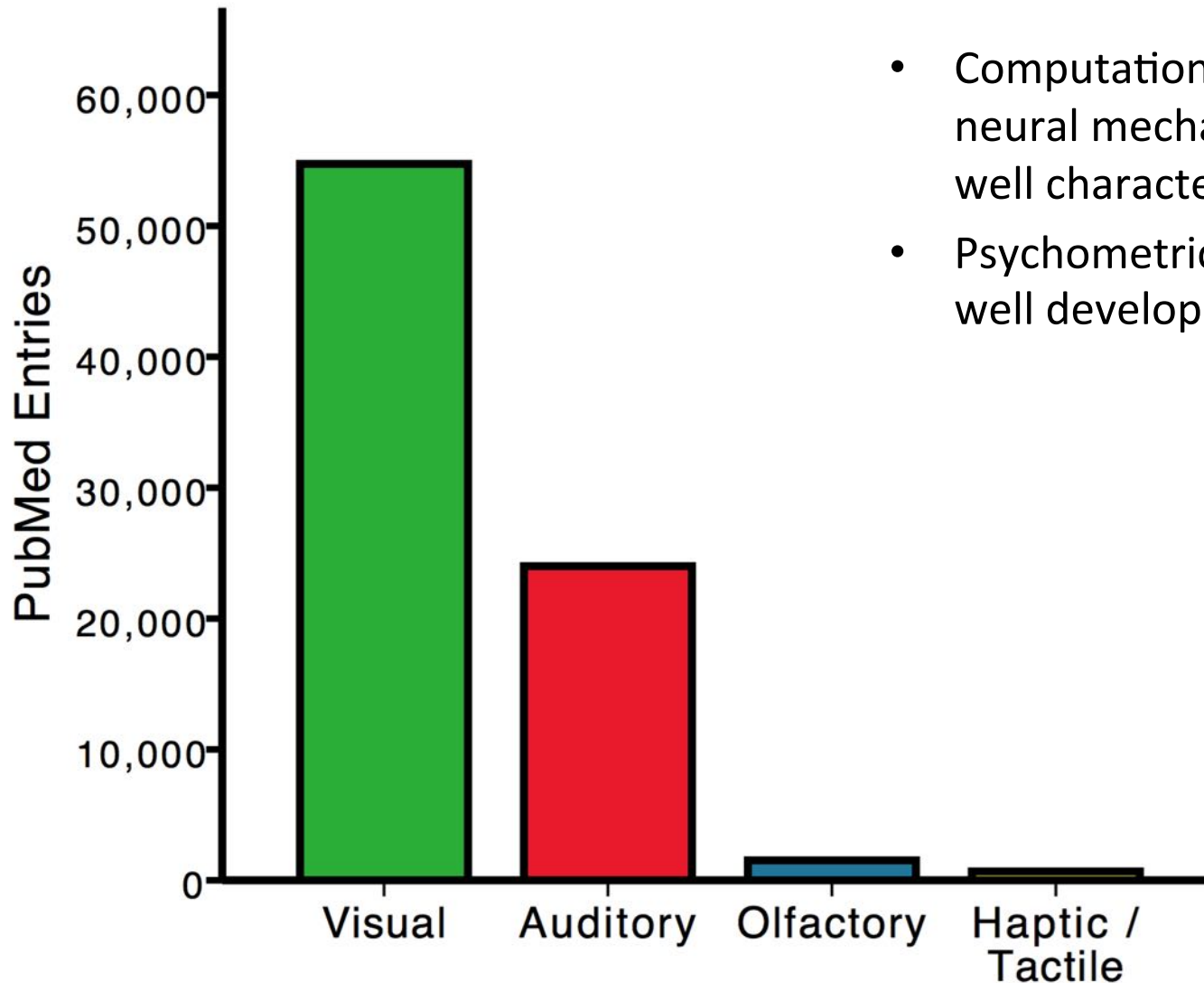
DESCRIBE:

NOTE: DISTINGUISH FROM AN ILLUSION, I.E., A MISPERCEPTION OF A REAL EXTERNAL STIMULUS



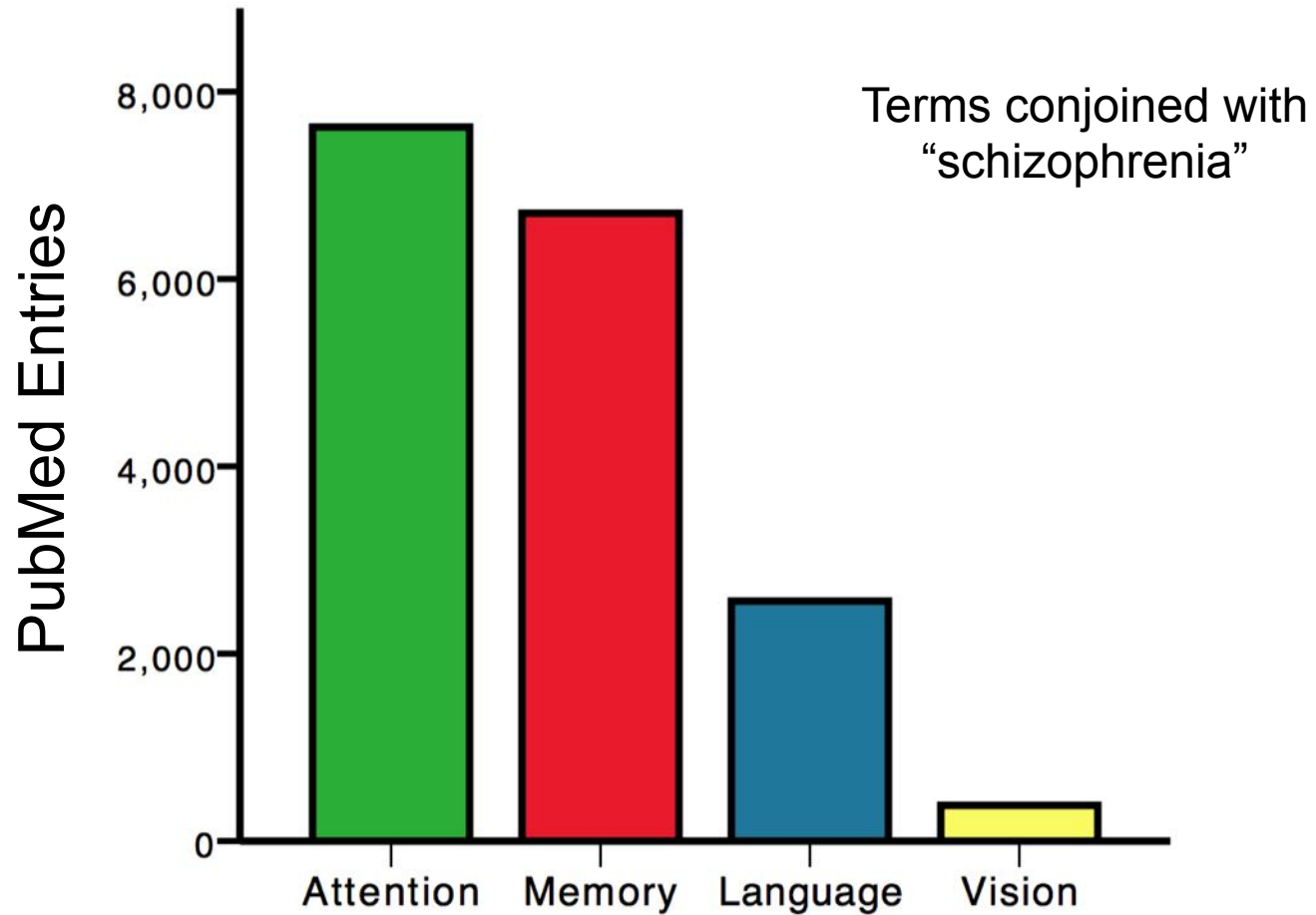
25-30% of SZ patients
(Waters et al., 2014)

Visual perception is the most studied sense modality



- Computational and neural mechanisms: well characterized
- Psychometric methods: well developed.

...but understudied in SZ...



Adapted from: Silverstein & Keane, 2011, Schiz Bull

Three claims

- Visual assessments can:
 1. identify presence of schizophrenia
 2. reveal current stage or state of illness
 3. implicate specific brain regions/networks

Behavioral paradigms

1. Contour integration
2. Visual shape completion
3. Depth inversion illusions
4. Self-reported visual disturbances
(time pending)

Behavioral paradigms

1. Contour integration
2. Visual shape completion
3. Depth inversion illusions
4. Self-reported visual disturbances
(time pending)

1

2

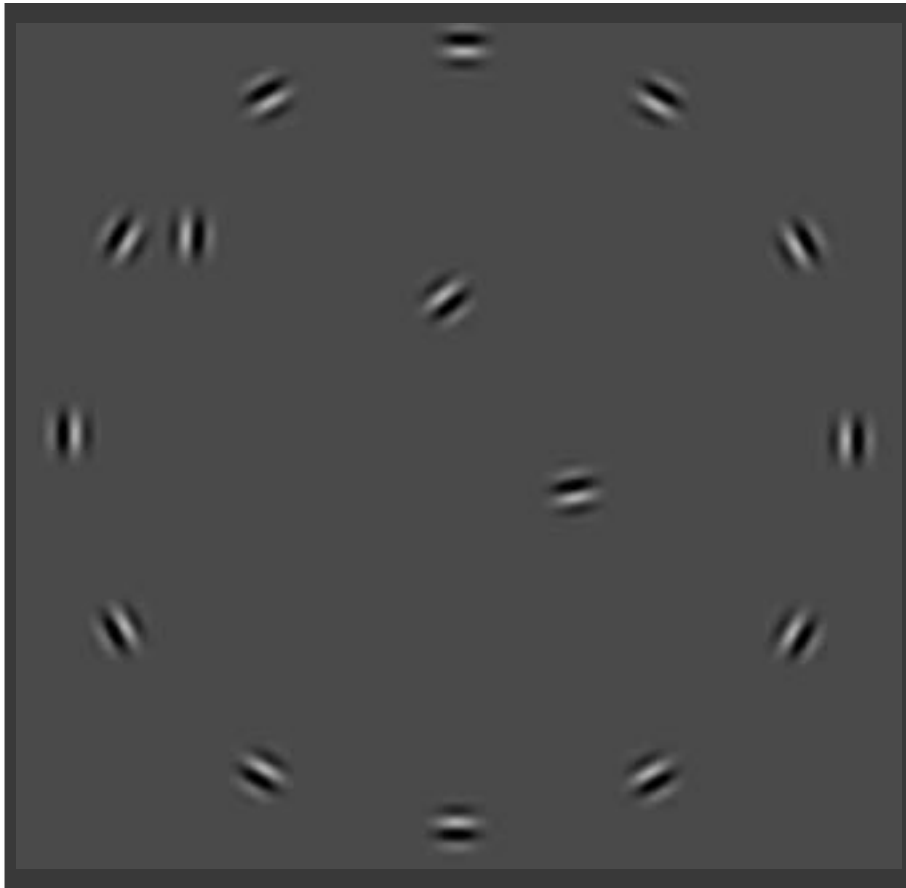
Task: Which quadrant
contains the circle?

3

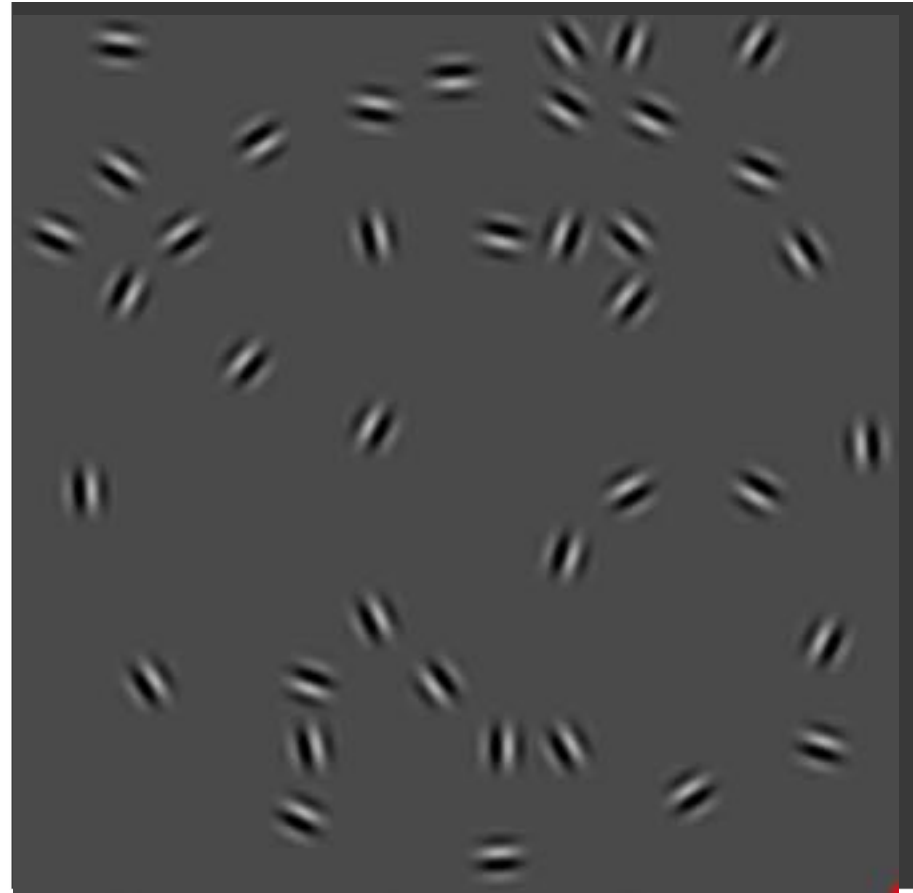
4

Difficulty depended on number of noise patches

Easier

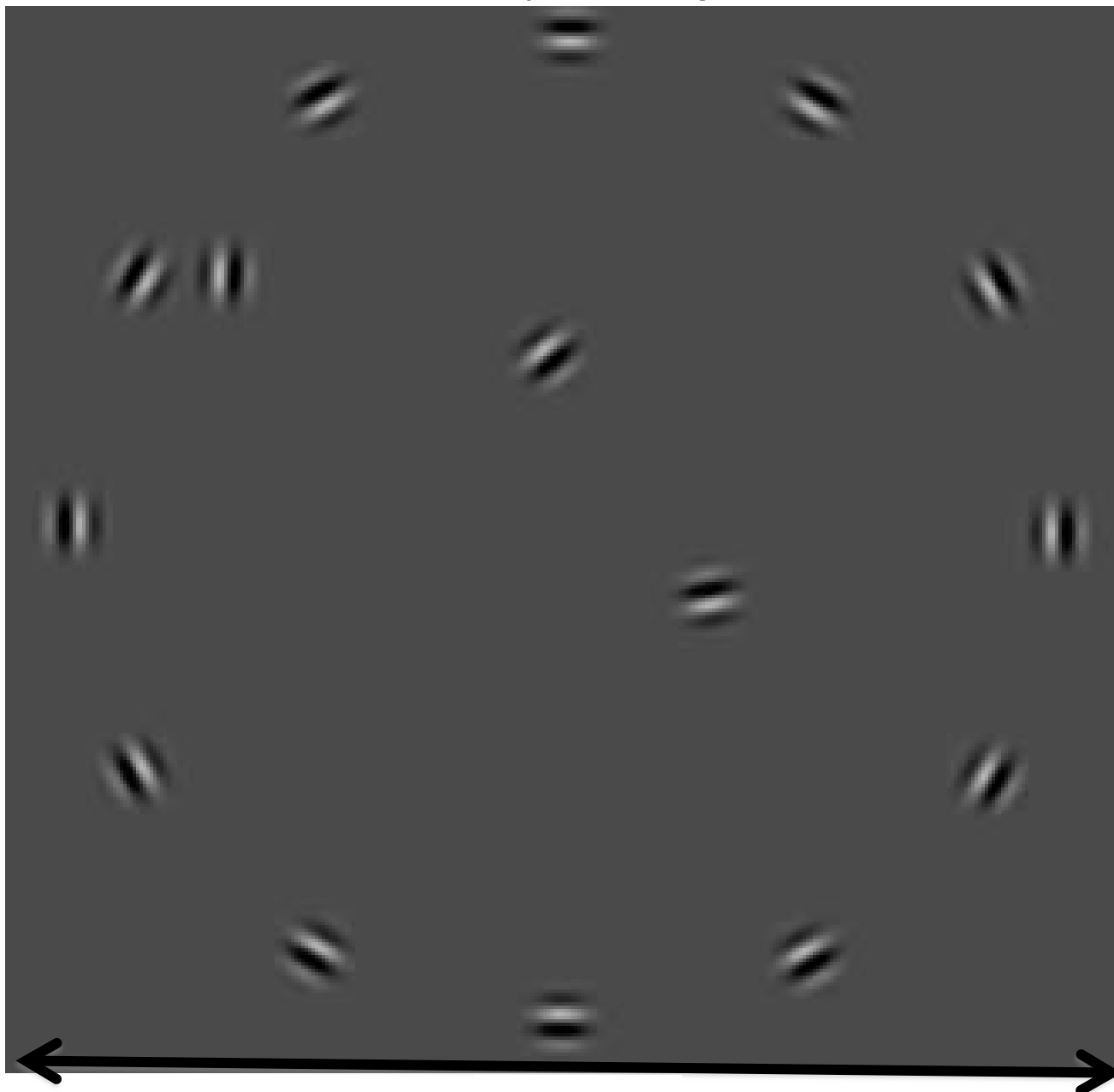


Harder



Threshold: Number of noise patches needed for 75% accuracy

4 cycles/deg



10.0 deg

12 cycles/deg



3.3 deg

Scaling:
Hess & Dakin (1997)



Catch trials = no noise

Contour integration in first episode and chronic schizophrenia

- Subject groups
 - 25 healthy controls
 - 22 first-episode (FE) patients
 - 24 chronic schizophrenia/schizoaffective (SZ) patients

Groups well-matched

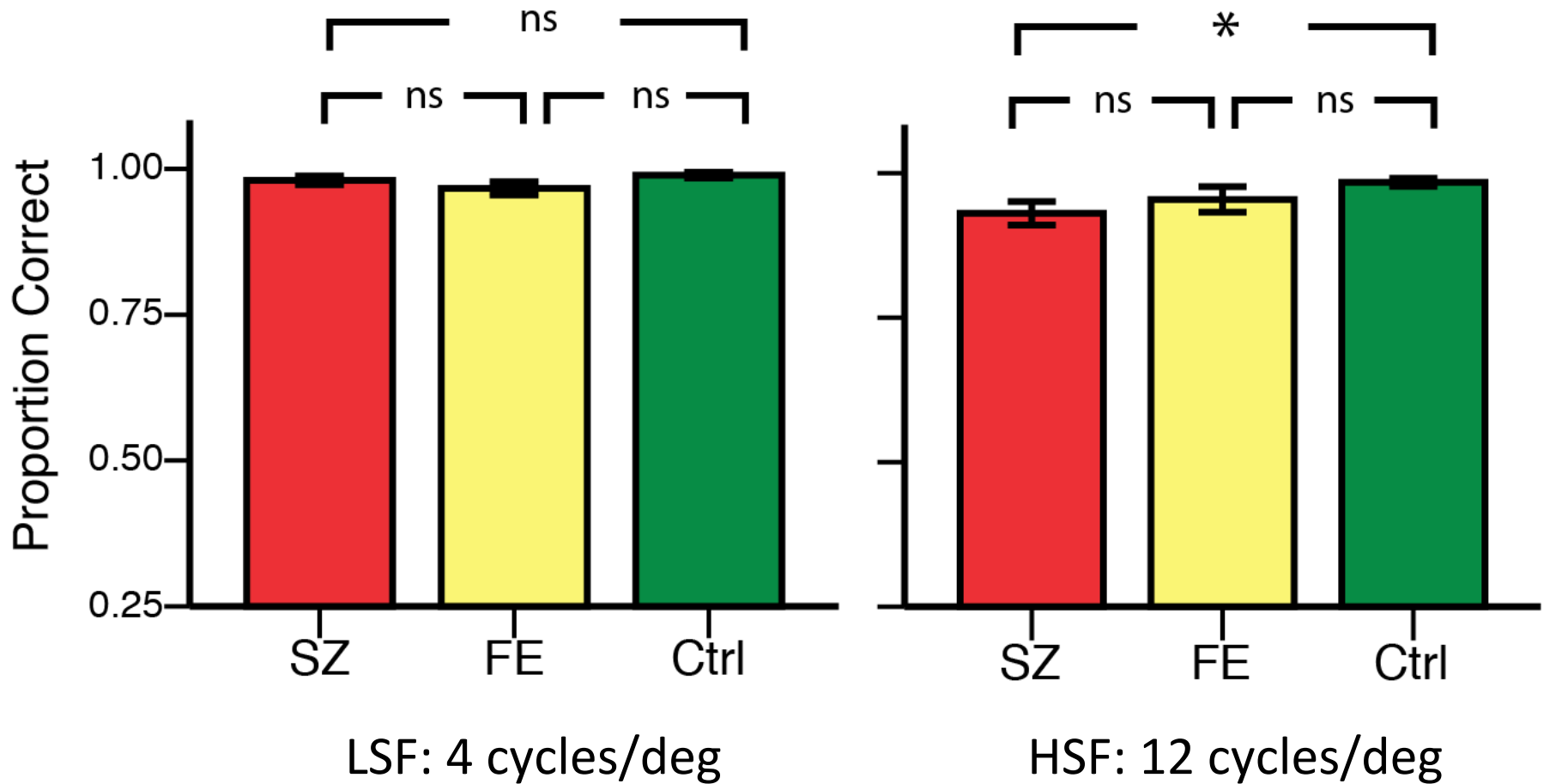
FEs & Ctrl

- Age
- Gender
- Parental Education

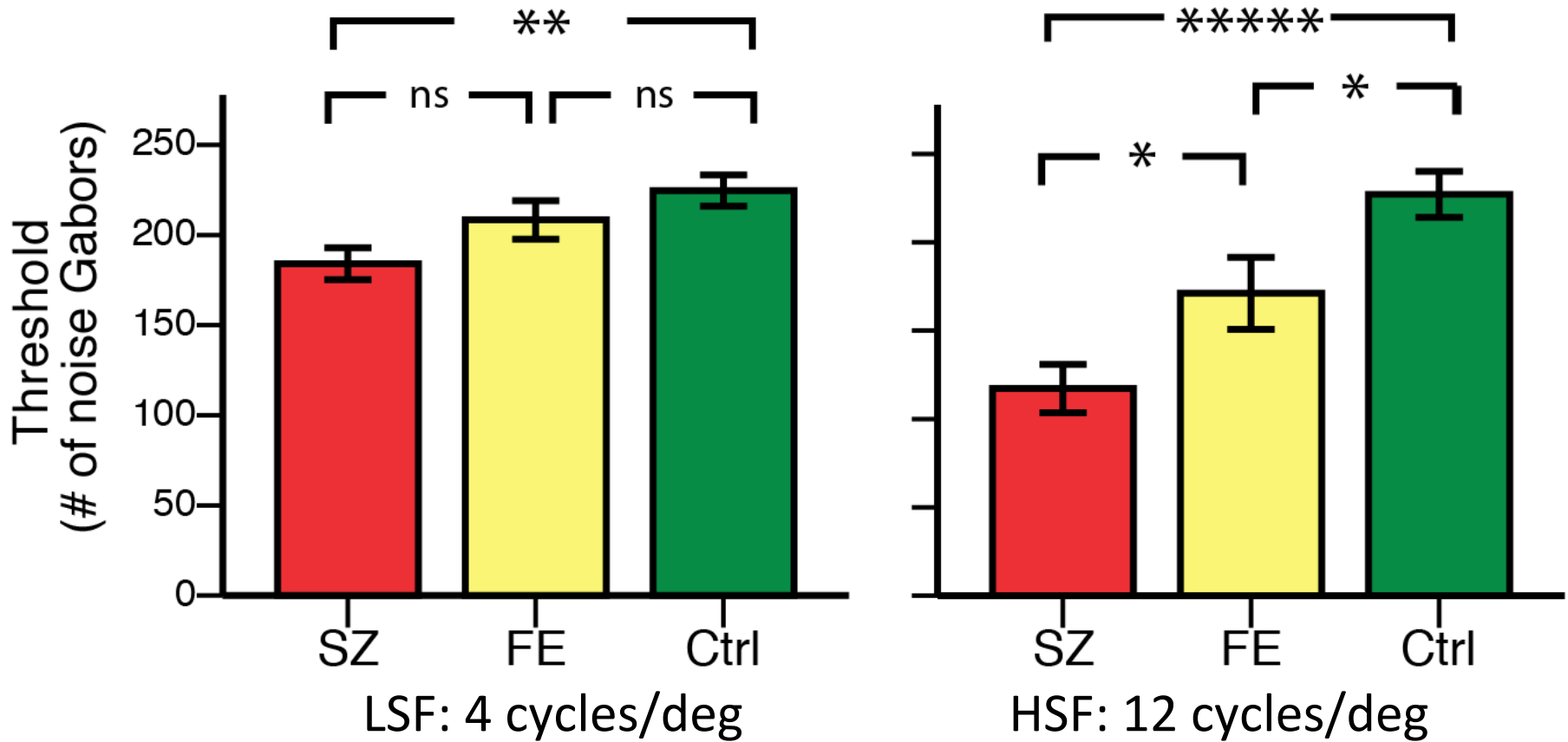
FEs & SZs

- Sex
- Parental education
- IQ
- Current level of functioning
- Premorbid functioning
- Age of onset
- PANSS symptoms
- Medication type/levels

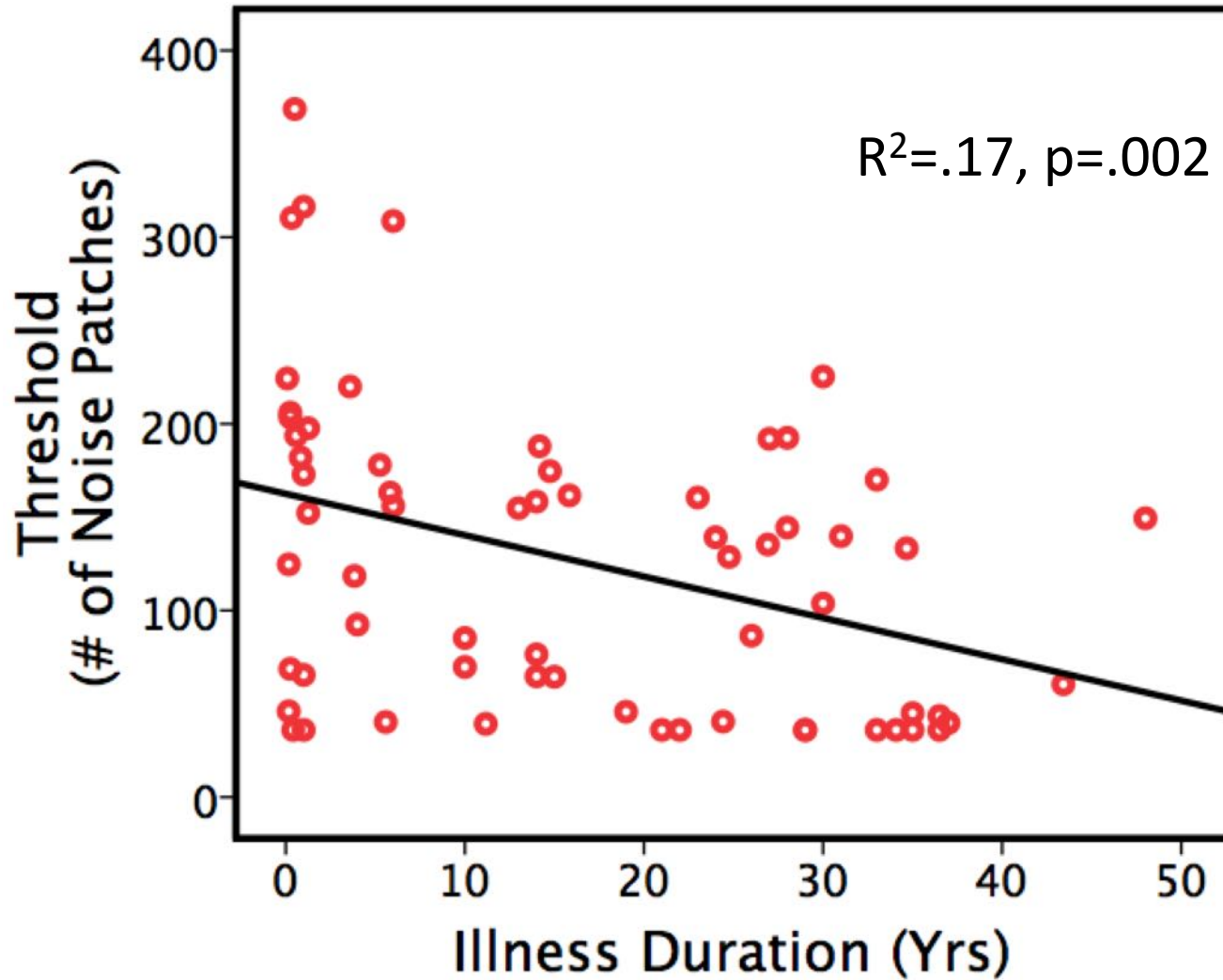
Catch trials



Regular trials



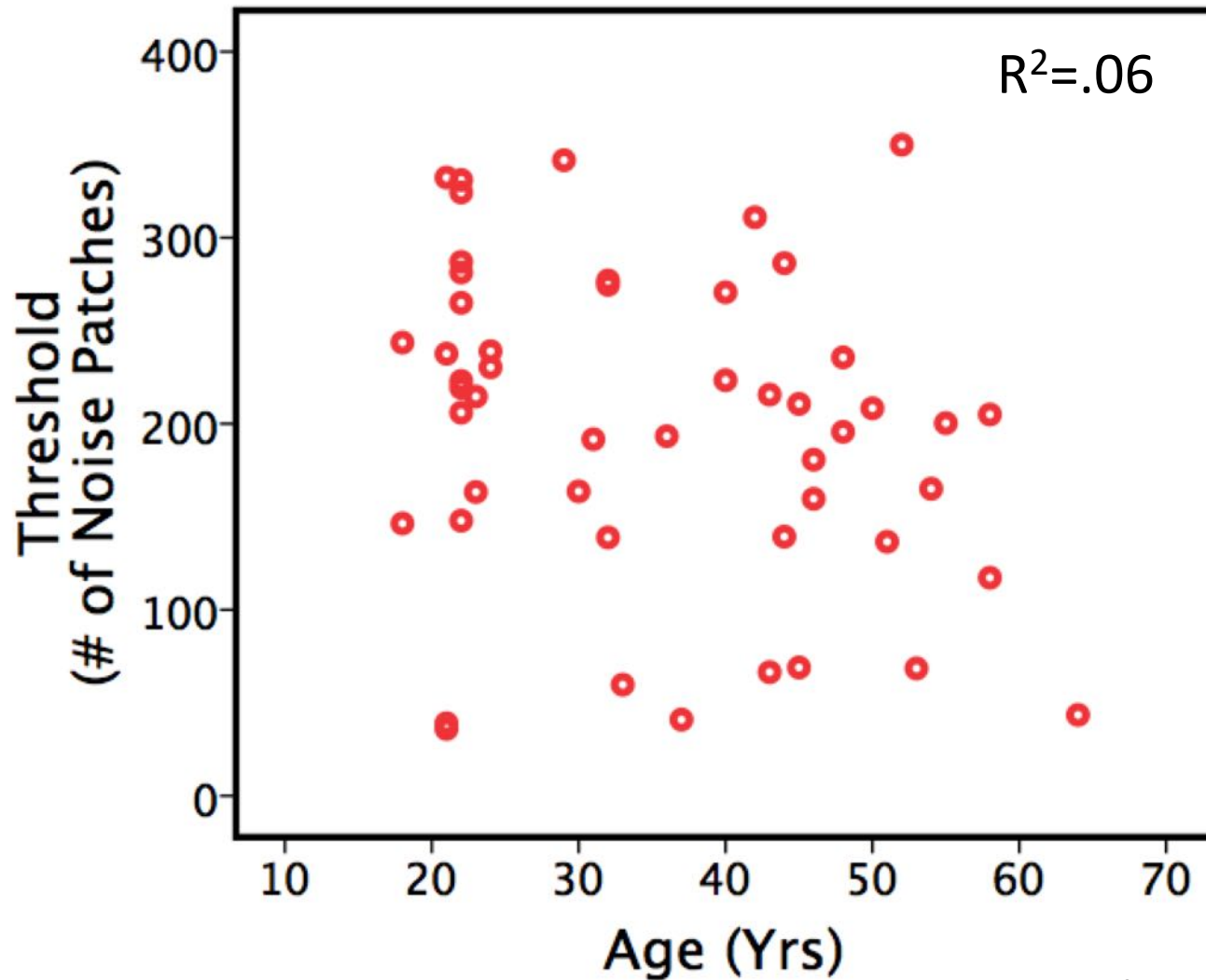
HSF correlation



Perhaps age is what worsens
integration?

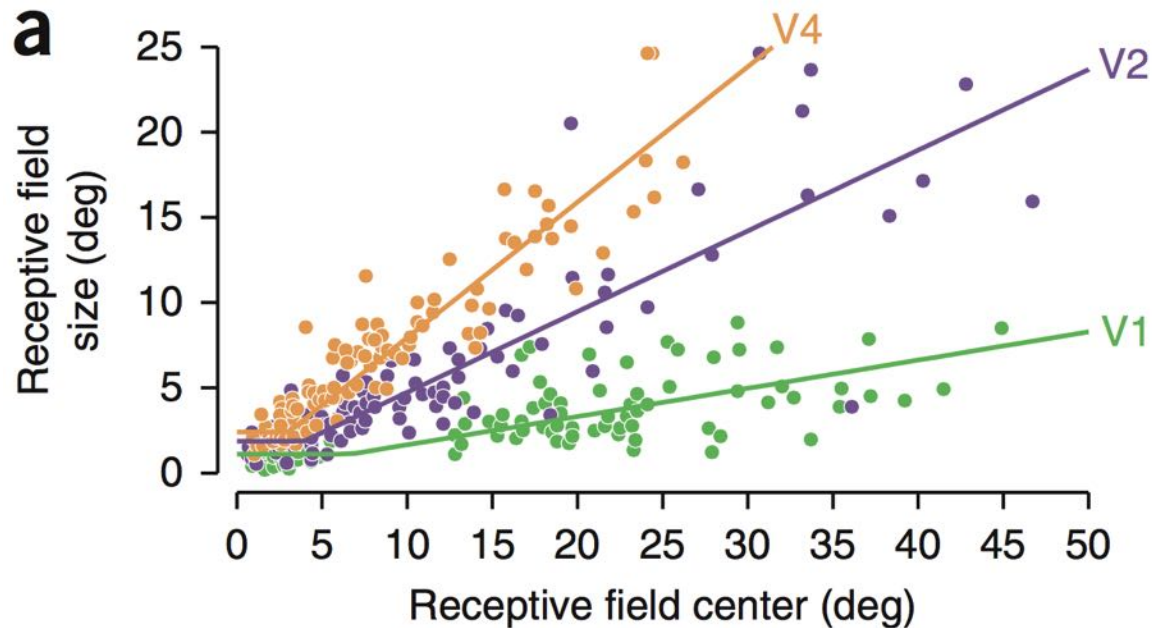
Unlikely.

Null effect of age for controls (HSF)



What is causing these effects?

- Visual acuity?
- Contrast sensitivity?



Freeman & Simoncelli,
2011, Nature Neuro

Neural basis of contour integration

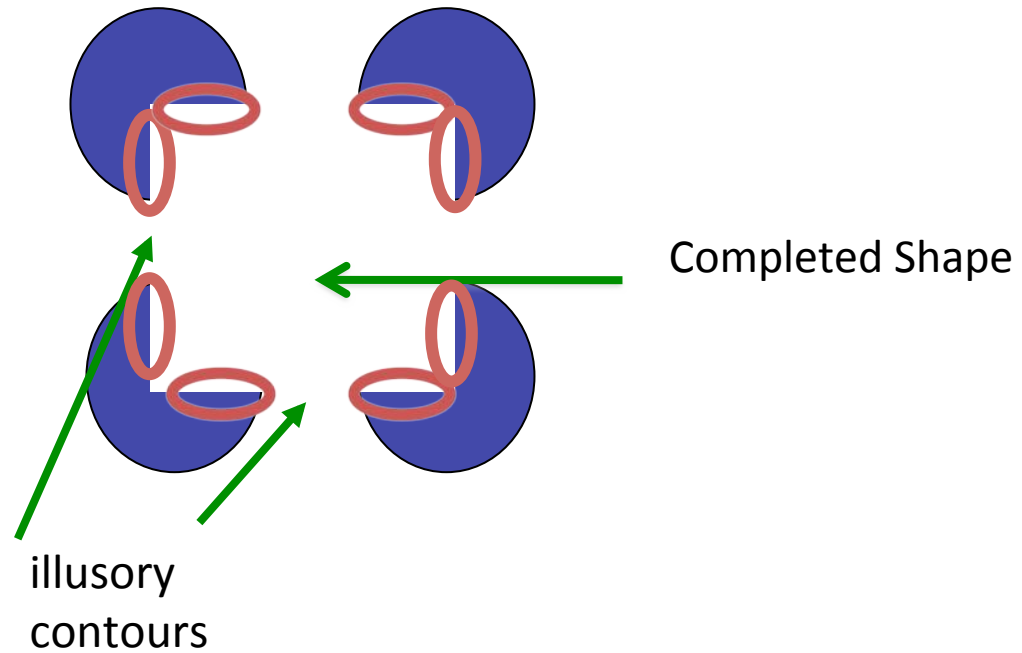
- V1, V2, V4, LOC
 - Single cell: Chen et al., 2014, *Neuron*
 - fMRI in healthy controls: Altmann et al., 2003, *Curr Bio*
 - fMRI in SZs: Silverstein et al., 2009, *J Integ Neuro*

Contour integration: Summary

- Deficits:
 - arise by 1st psychotic episode
 - worsen with illness duration
 - most apparent for HSF (smaller) stimuli
 - large effect size (Cohen's $D=1.7$)
 - cannot be explained by poor attention or advanced age
 - revealed with <8 min of testing
 - implicate cells with small receptive fields (V1)

1. Contour integration
2. **Visual shape completion**
3. Depth inversion illusions
4. Self-reported visual disturbances (time pending)

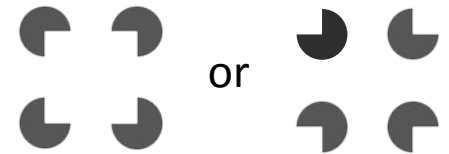
The process of interest...



Prior studies

- Electrophysiology
 - Oscillations: Spencer et al., 2004, PNAS
 - VEPs: Foxe et al., 2005, Cereb Cort
- Psychophysics
 - Keane et al., 2014a, Neuropsychologia
 - Keane et al., 2014b, Neuropsychologia

Task: Do
you see
square?

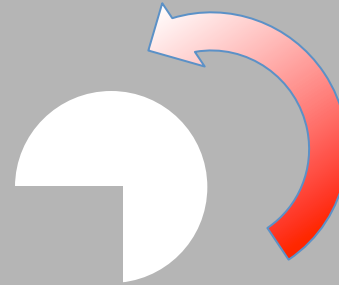


Are these specific to schizophrenia?

Visual shape completion

- Subject groups
 - 26 Bipolar patients
 - 23 SZ patients
 - 23 Healthy controls
- Matching: age, sex, parental education
- Subjects discriminated four sectored circles (“pac-men”) (Ringach & Shapley, 1996)
- Conditions: Illusory, Fragmented

Illusory



Fat



Thin



Fragmented



Left

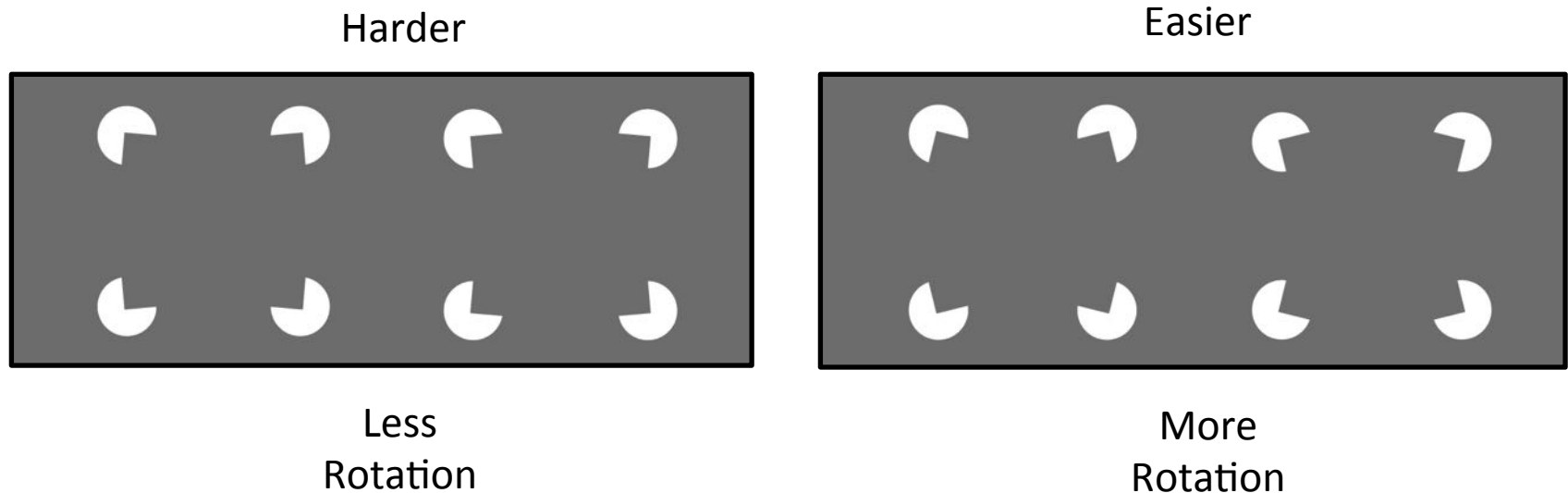


Right



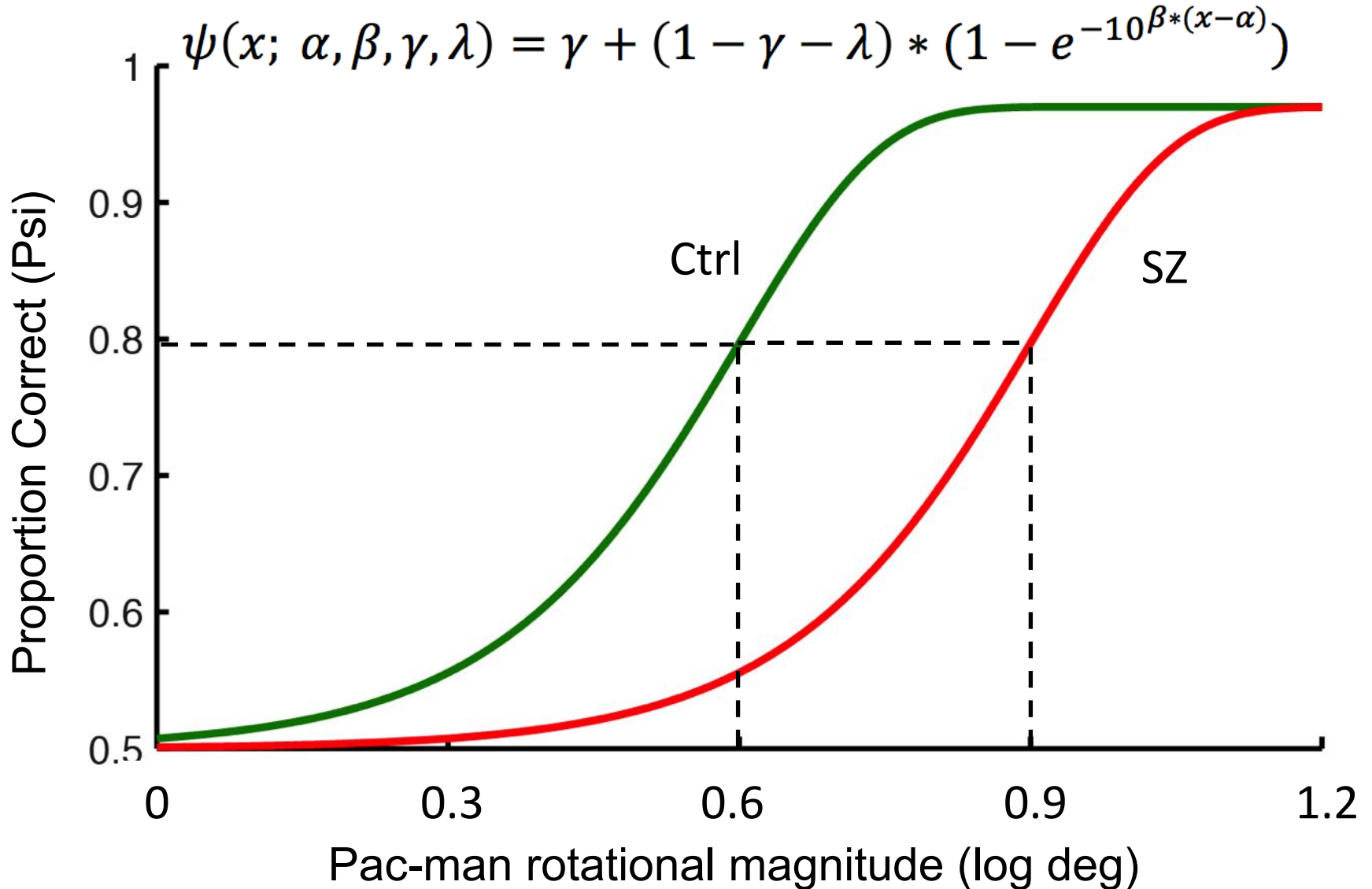
Measuring performance

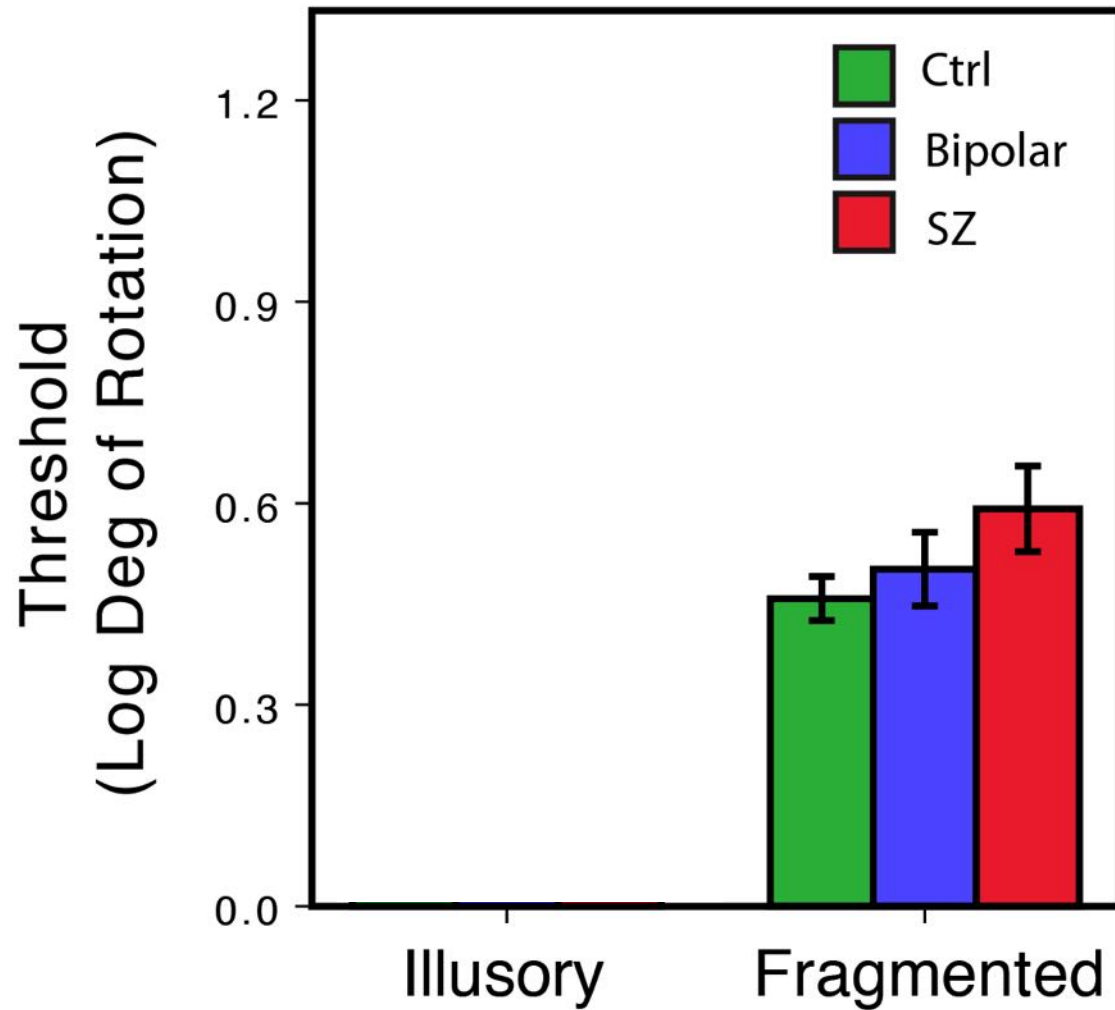
- Task difficulty depended on rotation



Threshold = amt of rotation for 80% accuracy (Psi Method)

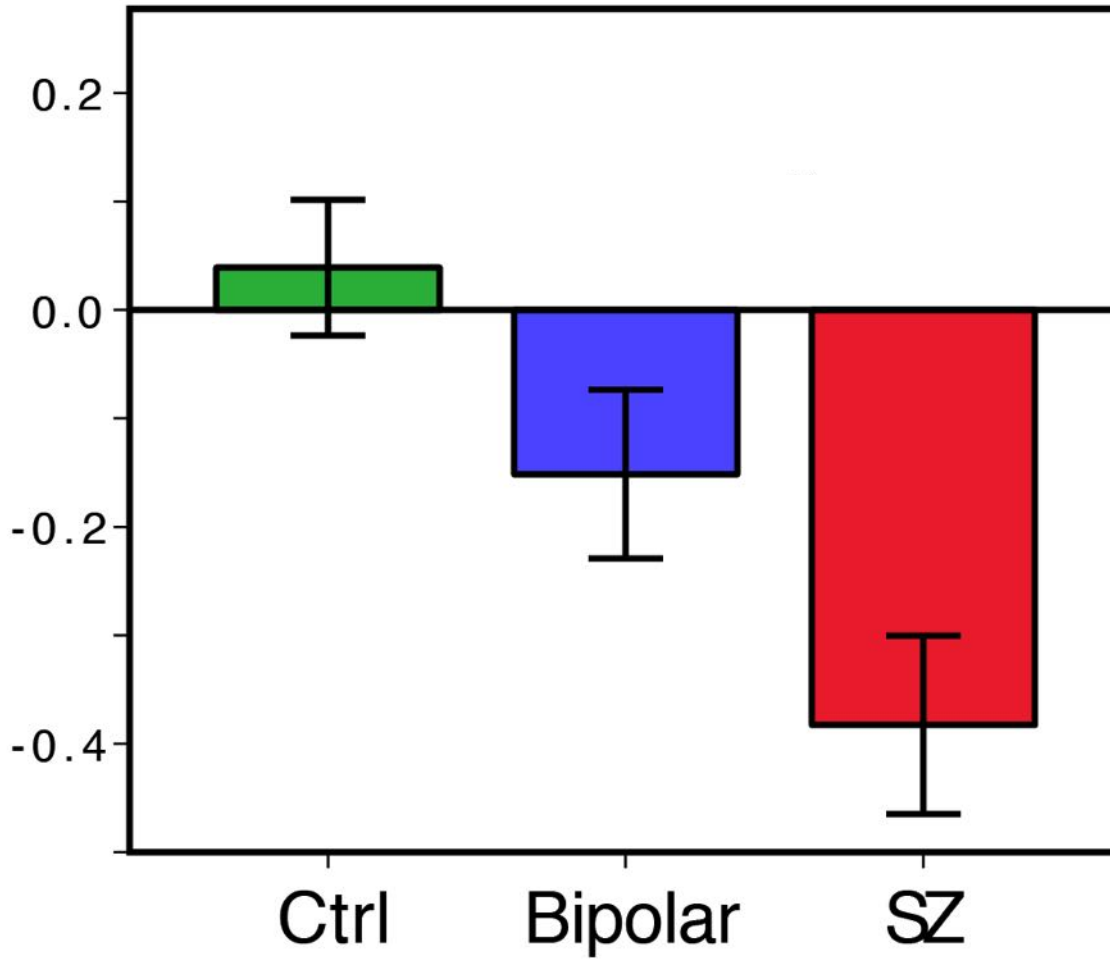
Hypothetical Psychometric Curves





Completion =
Fragmented
-
Illusory

Threshold Difference
(Fragmented - Illusory)

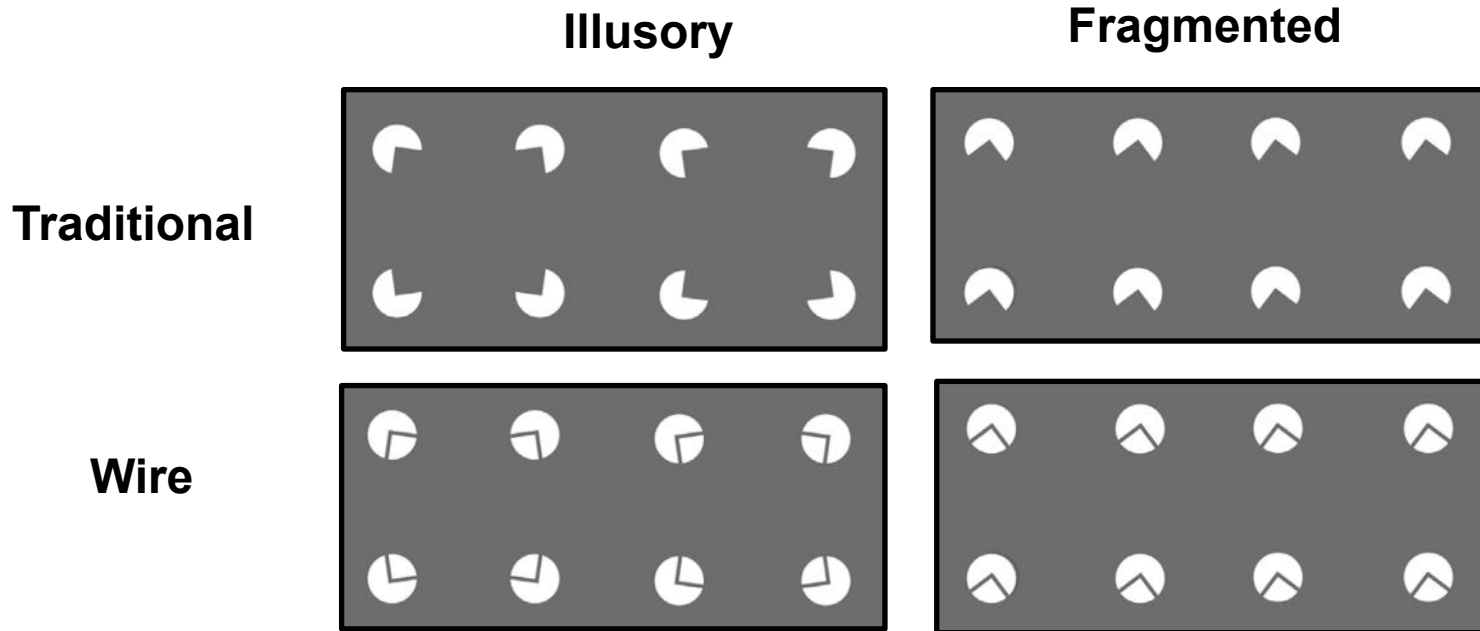


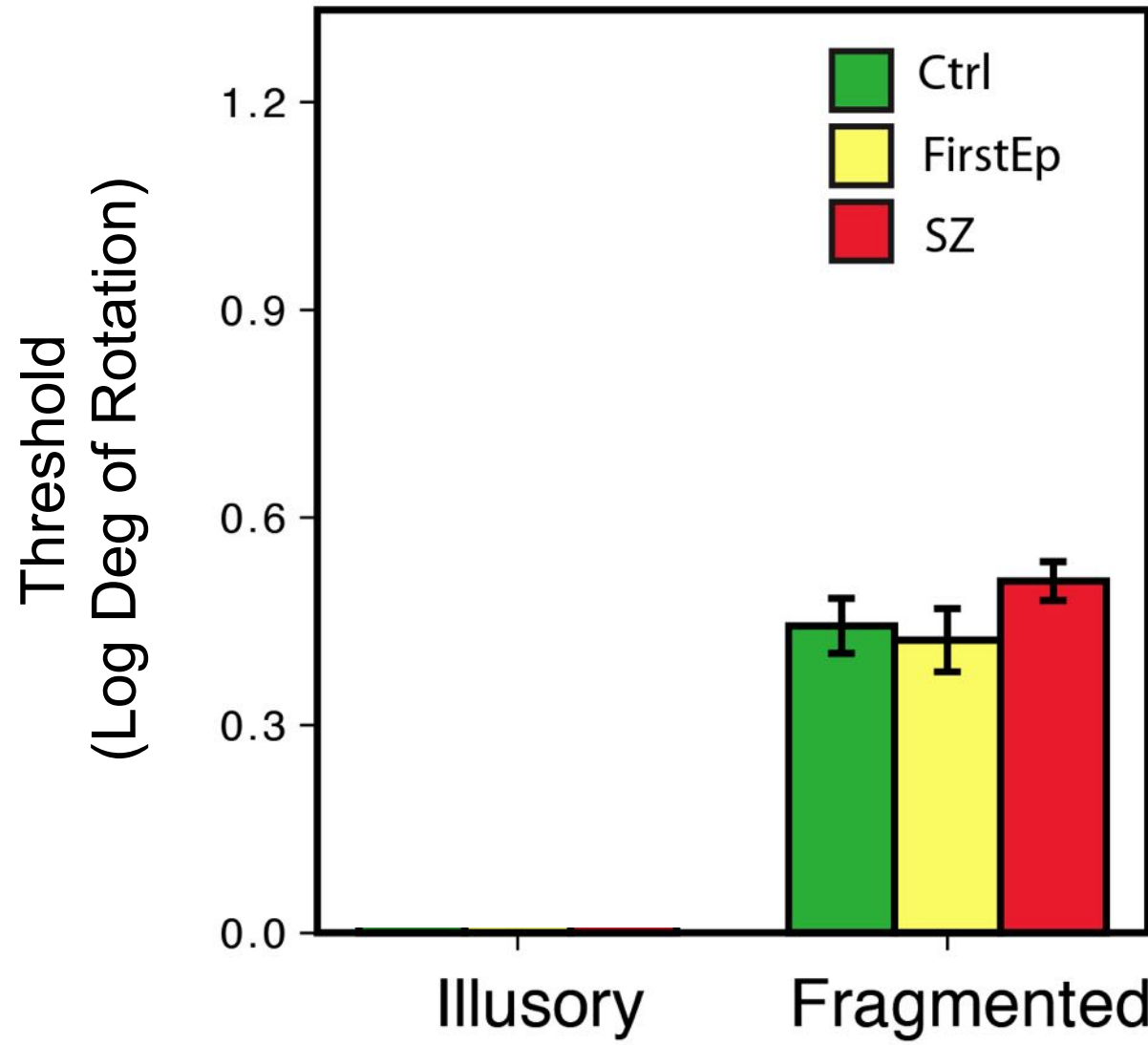
When do completion deficits emerge
and how do they change with illness
chronicity?

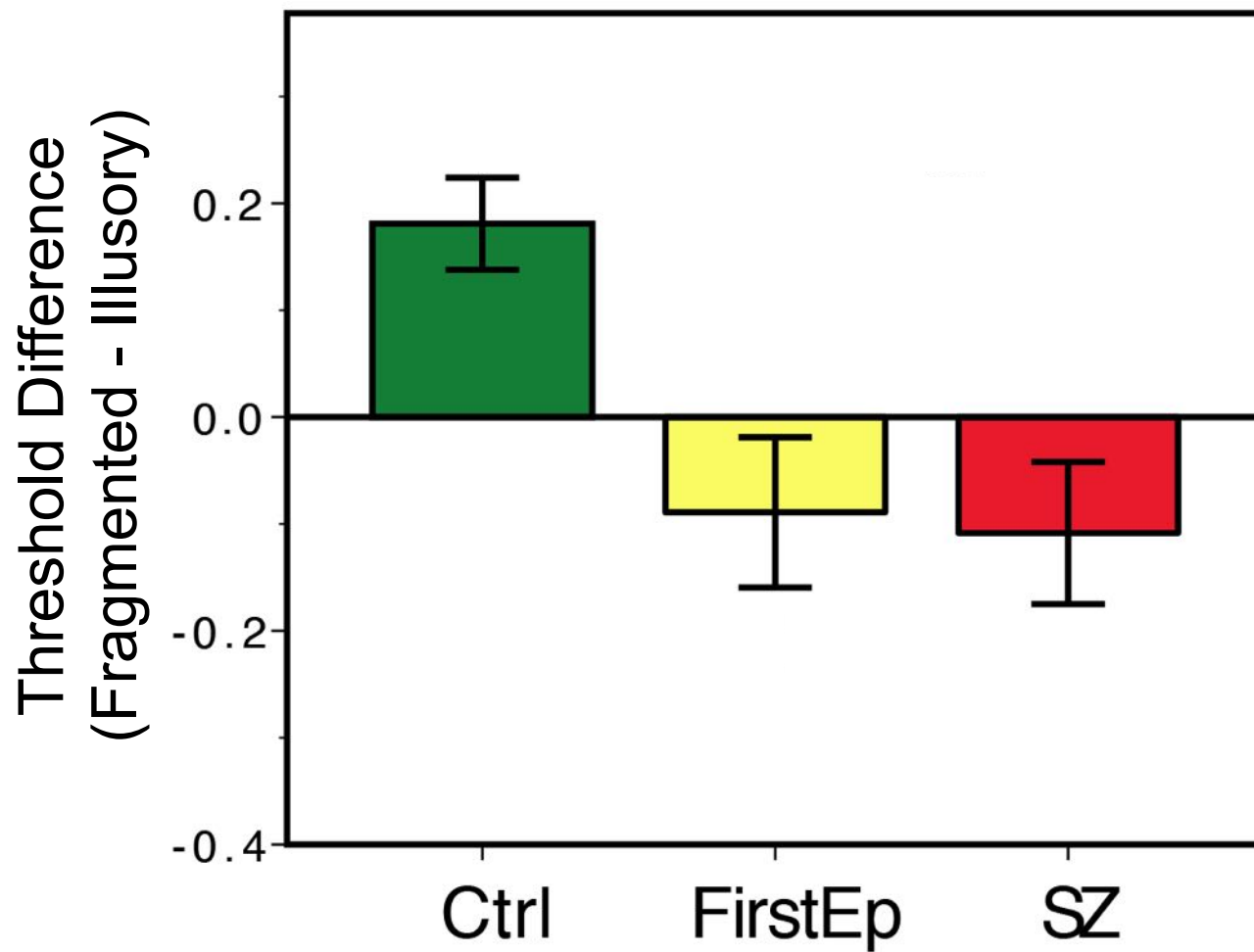
Visual shape completion in first episode and chronic schizophrenia

- Three subject groups
 - 18 first-episode patients
 - 37 chronic schizophrenia/schizoaffective patients
 - 50 healthy controls
- Patients performing poorly on the fragmented condition were excluded
- Matched on gender, parental education

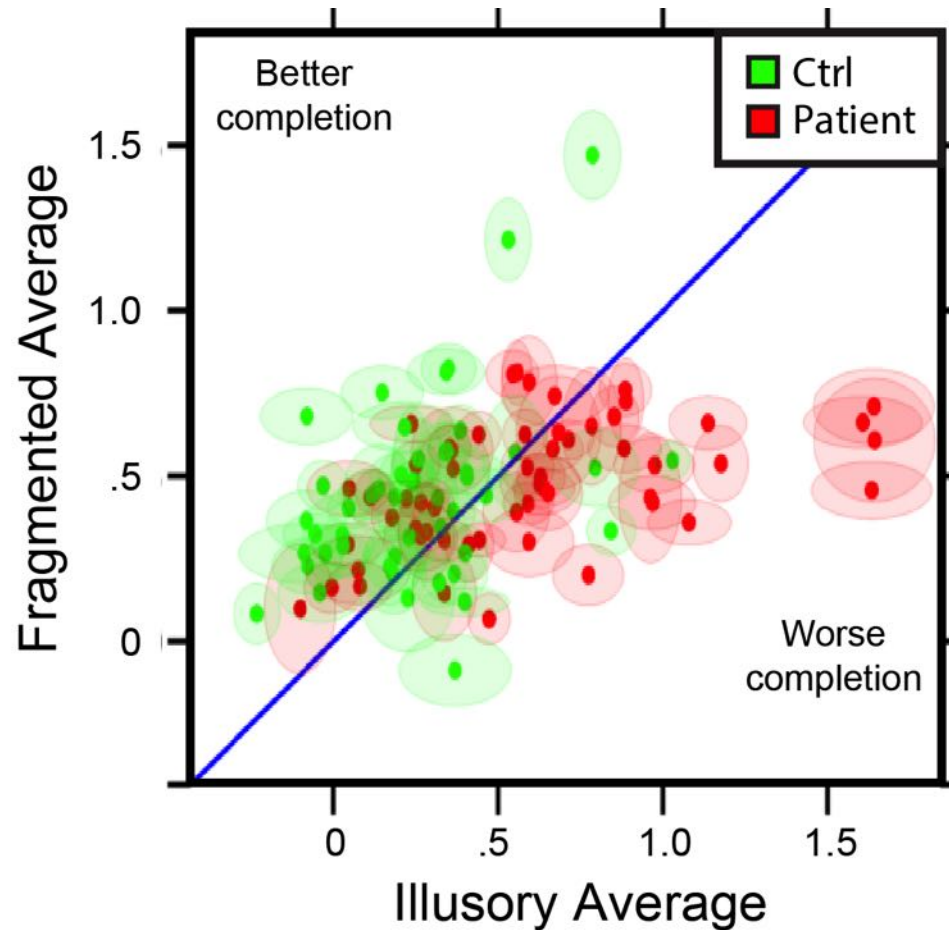
Experimental conditions







Another look



$d = 0.85$

Are deficits more pronounced in certain types of patients?

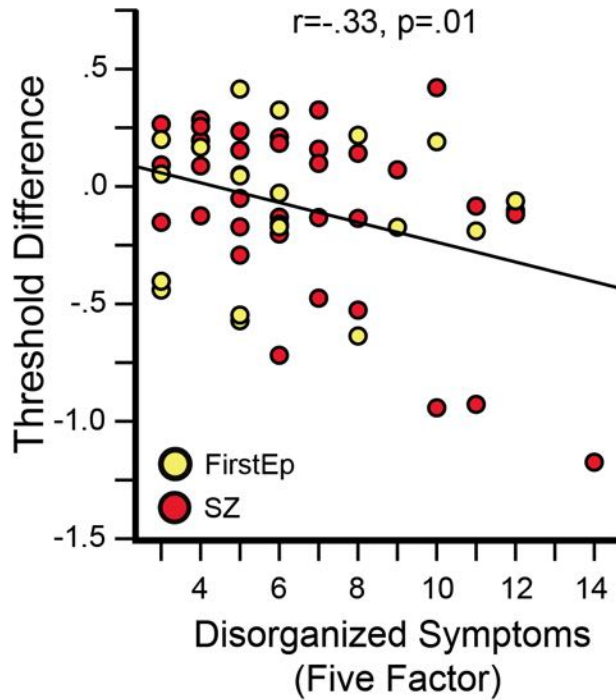
Yes

Disorganization (Thought disorder)

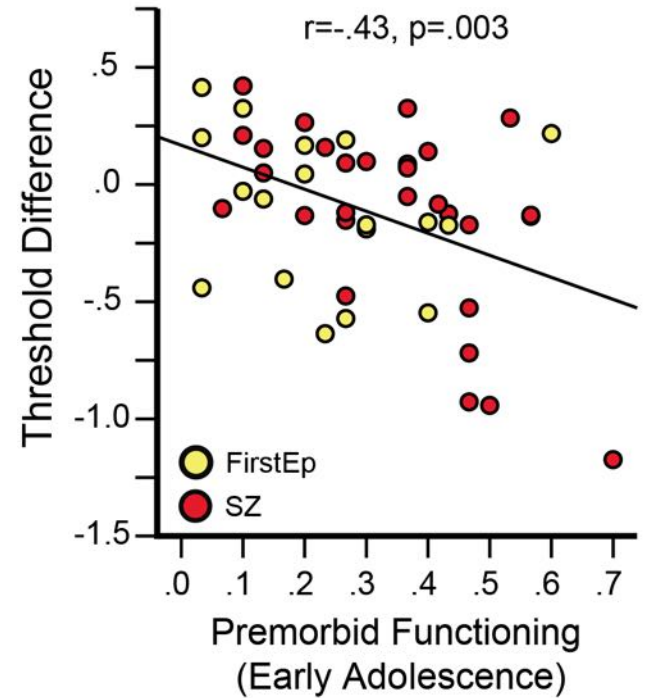
Previous completion studies:
Spencer et al., 2004; Keane et al., 2014a, 2014b



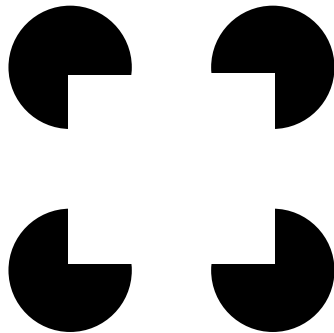
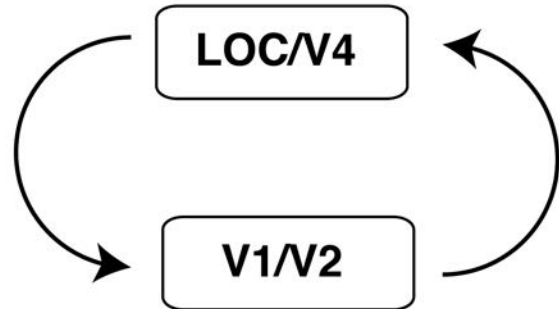
Completion deficits: Clinical correlates



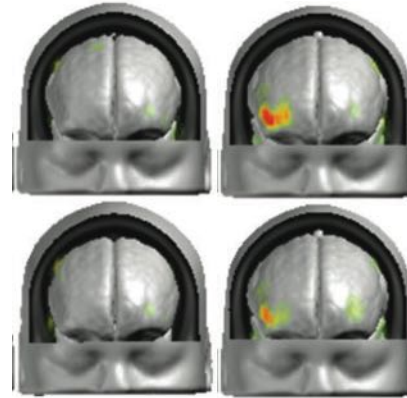
Worse Completion



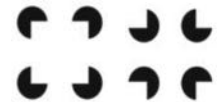
Neural mechanisms?



Foxe et al., 2005



Task:
Is square
present?



fMRI: Maertens et al., 2008
TMS: Wokke et al., 2013
Single-cell: Lee & Nguyen, 2001

fMRI: Halgren et al., 2003
EEG (SZ): Foxe et al., 2005
Psychophysics: Keane et al., 2012

Completion deficits: Summary

- worse in SZ compared to bipolar disorder
- arise by first psychotic episode but stable thereafter
- more severe for those with disorganization and poor premorbid functioning
- large effect sizes (Cohen's $d > .8$)
- cannot be attributed to poor attention or broad orientation tuning
- V1/V2, LOC, frontal regions implicated

3. Depth inversion illusions (DIIs)



Movie courtesy of Thomas V. Papathomas, Ph.D.

Reduced DII in schizophrenia

British Journal of Psychiatry 1989, 155 (suppl. 5), 37-39

A Three-Component-System Hypothesis of Psychosis
Impairment of Binocular Depth Inversion as an Indicator
of a Functional Dysequilibrium

HINDERK M. EMRICH

...and numerous others since...

Questions for DII

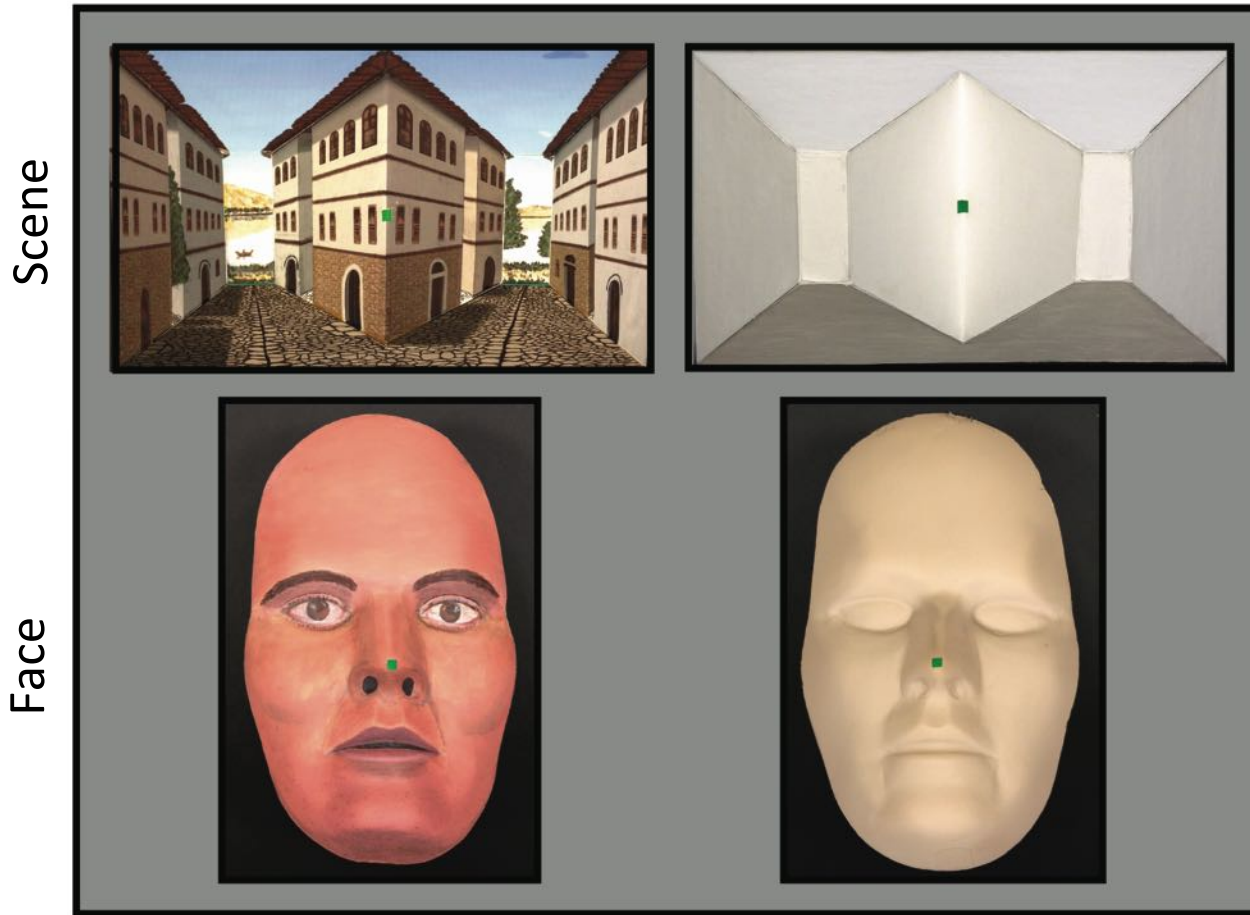
- Why are DIIs less common in schizophrenia?
- Do DII reductions vary with illness state?
- Are DII reductions specific to schizophrenia?
- Two studies...

Subjects for DII

- 25 healthy controls (age=46, 13 female)
- 30 chronic schizophrenia patients (age=47, 9 female)
- Three patient subgroups (for heterogeneity):
 - 10 *acute* partial hospital patients
 - 10 *extended* partial hospital patients
 - 10 *outpatients*
- Groups matched on 8 variables (IQ, education, etc)

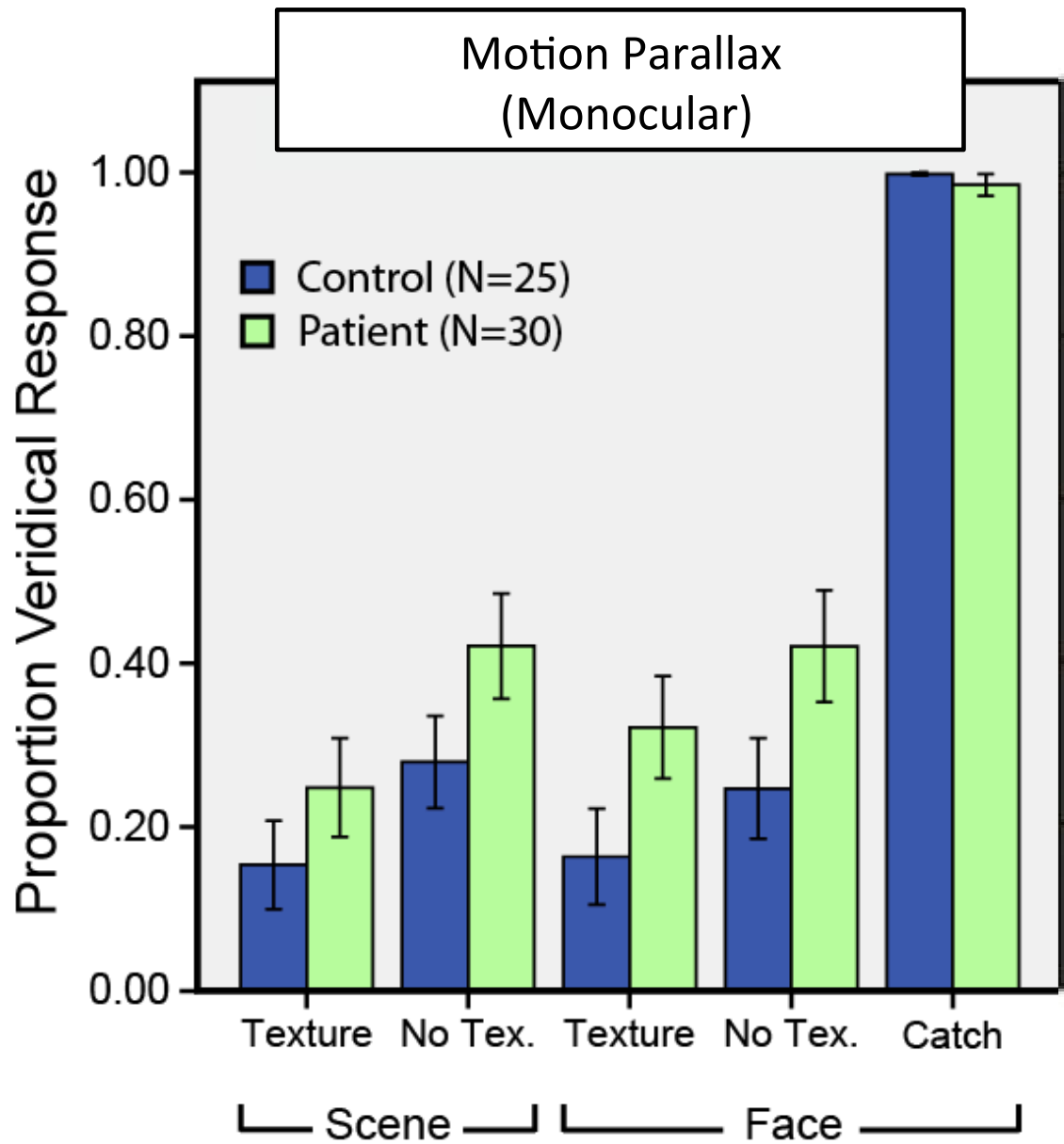
Stimuli

Illusory Stimuli

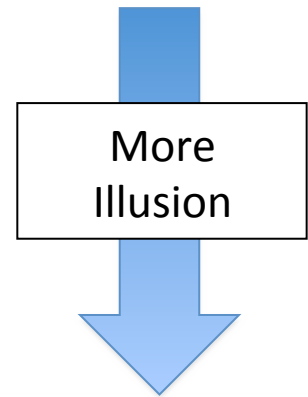
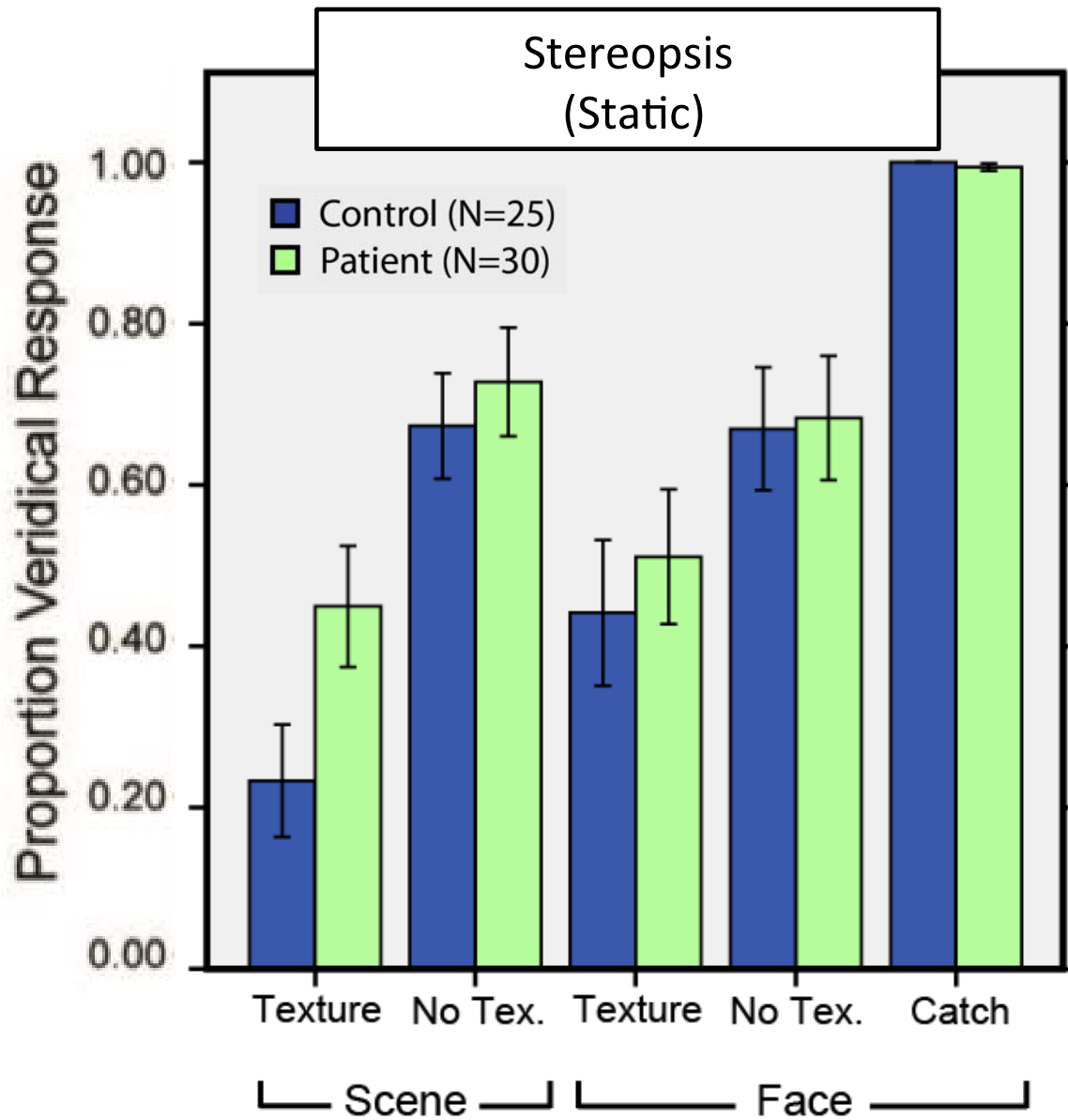


Procedure

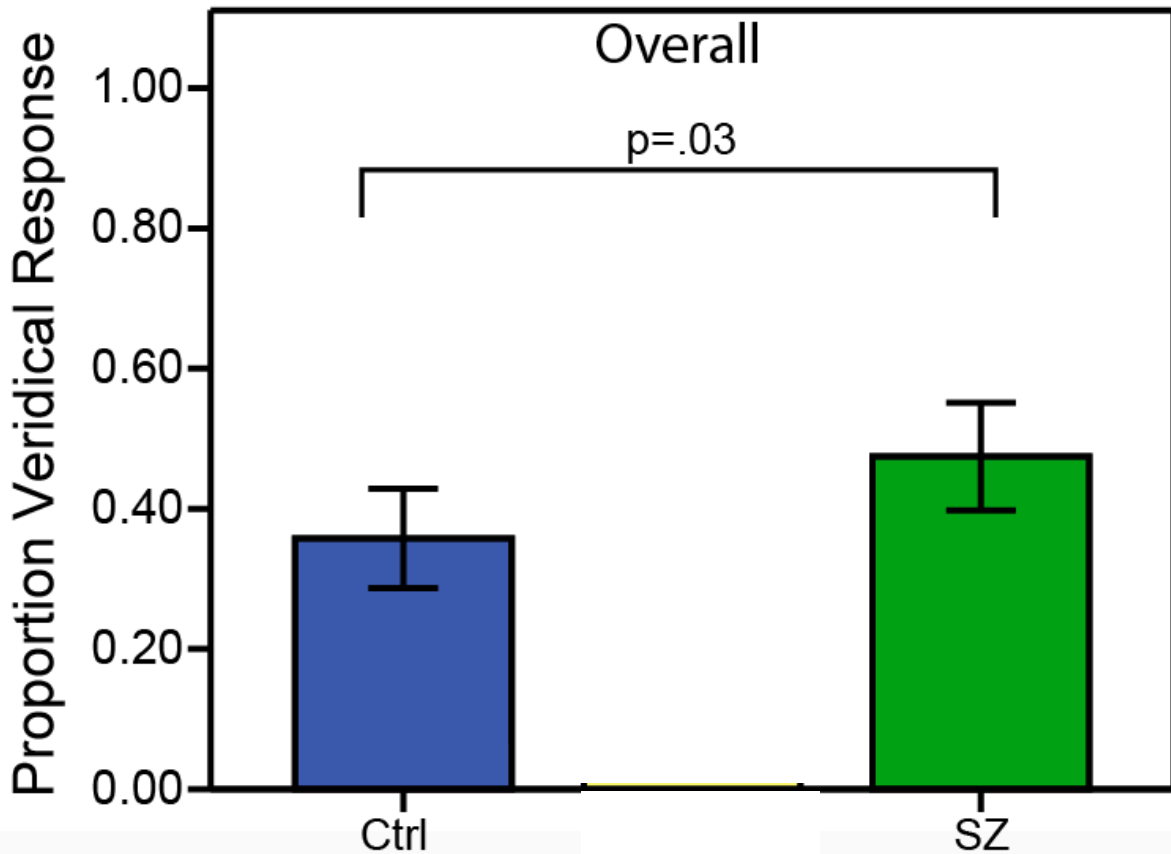
- Each object viewed twice for two minutes:
 1. Motion parallax (monocular)
 2. Stereoscopic (static)
- For each viewing, subjects judged whether an object appeared convex or concave every 12 seconds.
- Performance = proportion of time that subjects reported seeing true shape (veridical response).



More
Illusion



DII results, collapsed

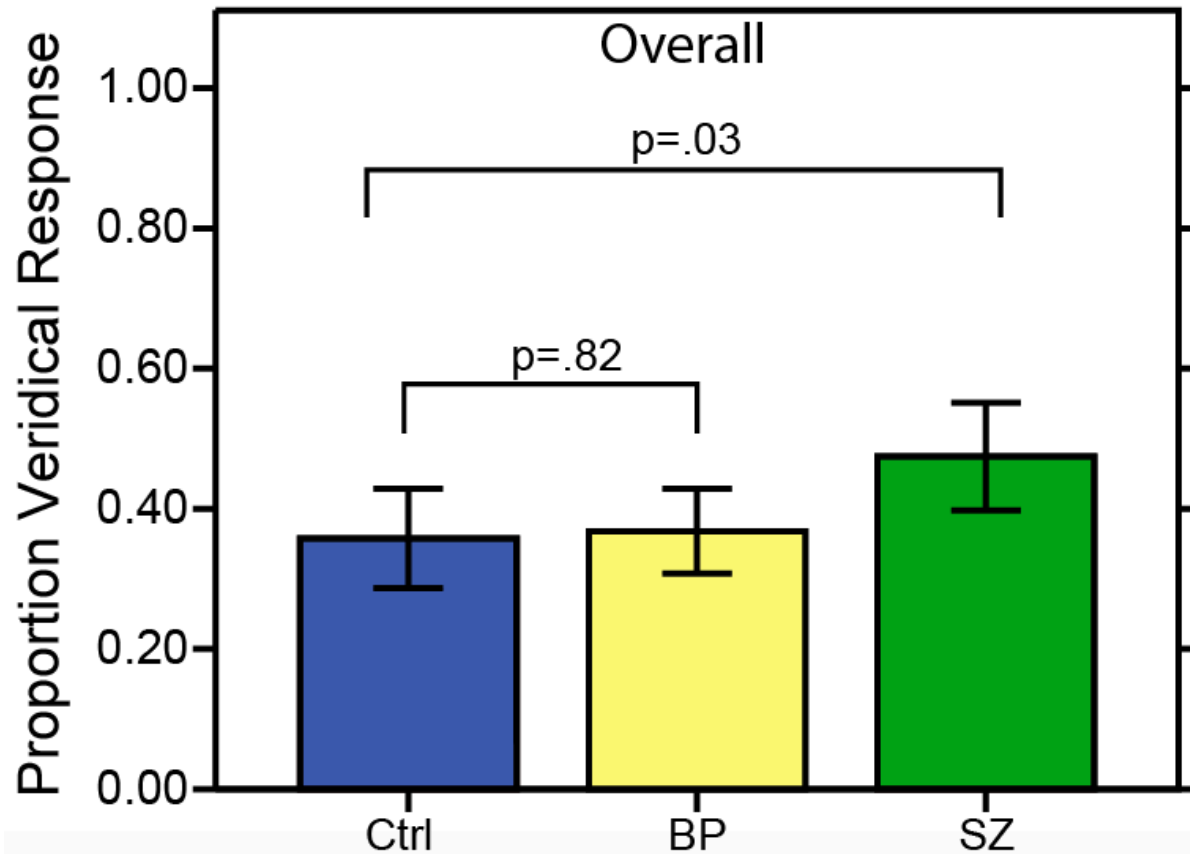


No interactions with viewing condition or object type

Were these effects specific to schizophrenia?

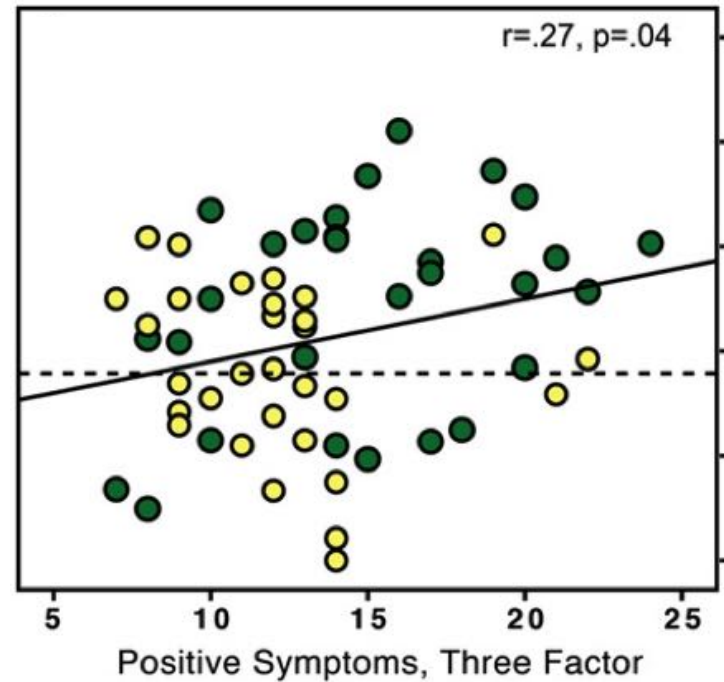
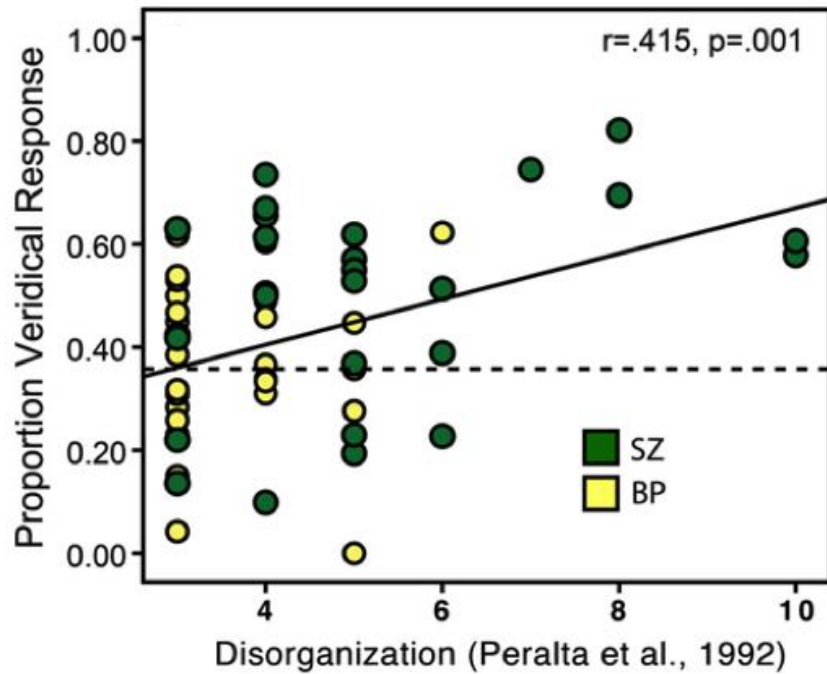
- The same task, but with 30 bipolar disorder patients.
- Groups matched: age, IQ, education, ethnicity, handedness

DII results, collapsed



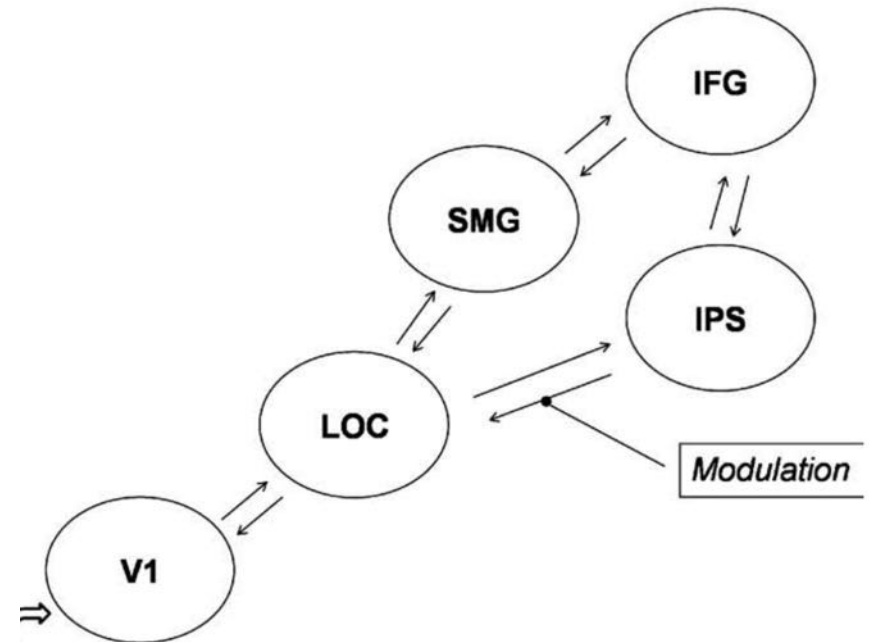
As before:
No interactions

DII and illness state



Explaining reduced DIIs in SZ

- Objects are typically convex
- The visual system internalizes this fact
- DII occurs when the prior *overrules* contrary depth information (stereo or motion)
- Psychosis weakens the prior, but how?



Dima et al., 2009, Neuroimage

Depth inversion illusions: Summary

- Reduced DII:
 - specific to schizophrenia
 - linked to more positive and disorganized symptoms
 - cannot be explained by poor motivation/attention
 - arises from a lessened reliance on a convexity prior
 - may arise from reduced top-down feedback from IPS → LOC

1. Contour integration
2. Visual shape completion
3. Depth inversion illusions
4. Self-reported visual disturbances (time pending)

Subjective visual disturbances are linked to illness features

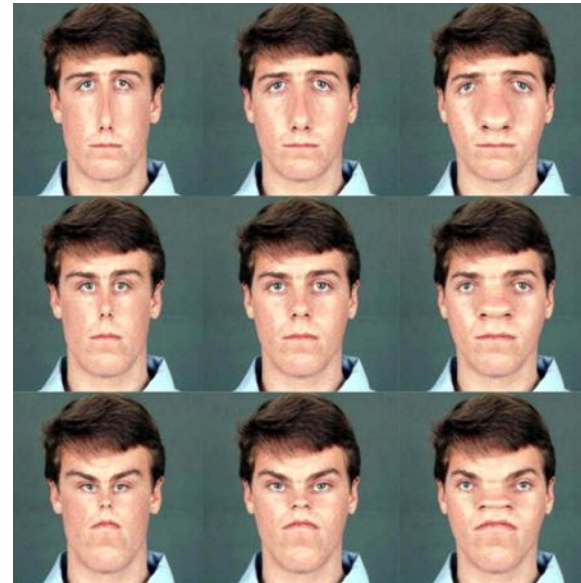
Instrument: Bonn Scale for the Assessment of Basic Symptoms



Pseudomovement



Double vision



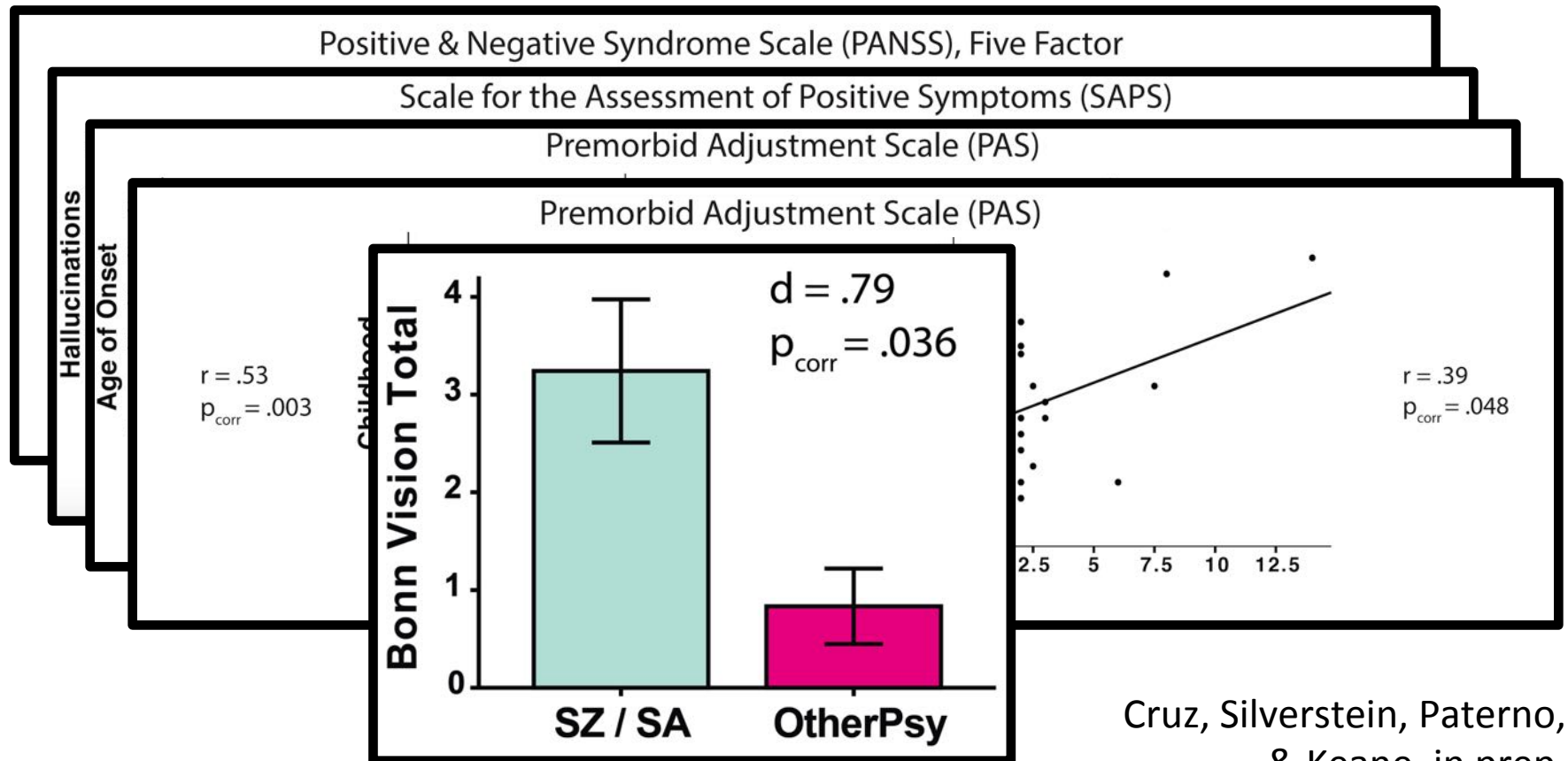
Distorted faces

...and 14 others...

Cruz, Silverstein, Paterno, & Keane, in prep.

Subjective visual disturbances linked to illness features

Subjects: 22 chronic SZ/SA patients and 21 first episode psychosis patients (9 with SZ/SA) assessed with the “Bonn Scale”.



Cruz, Silverstein, Paterno,
& Keane, in prep.

Conclusion: Visual perception as a biomarker

- The search for biomarkers is an active and important area of investigation in schizophrenia research.
- Certain biomarkers are obvious to consider.
- But so far none predict the presence, stage, or state of the illness with a high degree of accuracy.
- Behavioral analyses from vision tasks hold promise in this regard.

Take home message: Don't forget about visual processing!

- Visual assessments:
 - are fast, easy to implement, non-invasive and inexpensive
 - can help tell us whether a person has schizophrenia
 - tell us about likely symptoms
 - tell us the likely stage of illness
 - can implicate specific brain circuits
 - don't (usually) require the patient to be good at divulging facts about his/her own subjective experience
 - can complement standard clinical interviews

Supported by...



National Institute
of Mental Health

F32MH094102 & K01MH10873 to BPK

Acknowledgements

Rutgers, Division of Schizophrenia Research

Lisa Cruz

Danielle Paterno

Steve Silverstein, PhD

Yushi Wang

Rutgers, Department of Biomedical Engineering

Thomas Papathomas, PhD

Princeton, PNI, Psychology

Sabine Kastner, MD, PhD

THANK YOU!