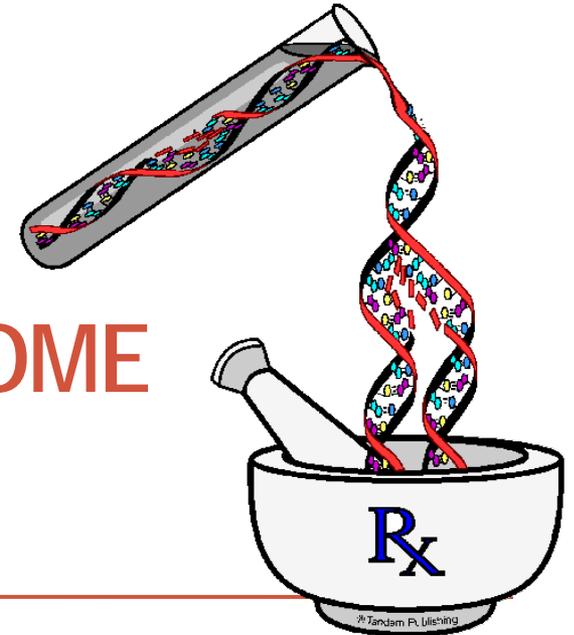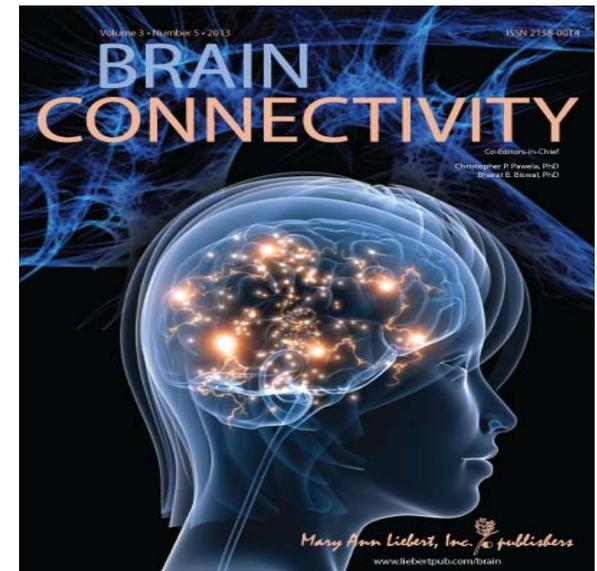# BIOMARKERS OF ANTIPSYCHOTIC DRUG RESPONSE: FROM THE GENOME TO THE CONNECTOME

Anil K. Malhotra, MD
Hofstra Northwell School of Medicine
Hempstead, New York
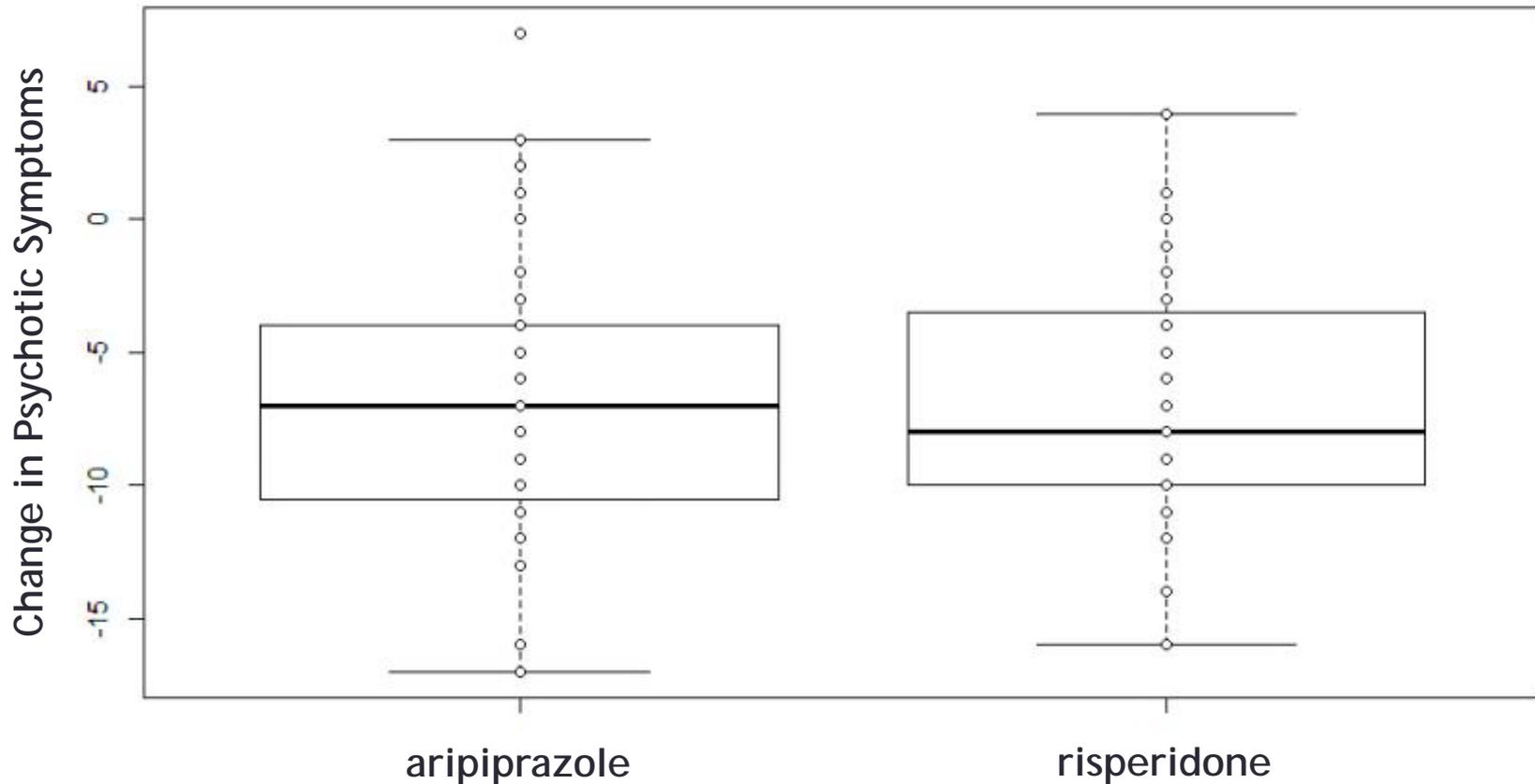
The Zucker Hillside Hospital
Glen Oaks, New York

Feinstein Institute for Medical Research
Manhasset, New York

A Randomized Comparison of Aripiprazole and Risperidone for the Acute Treatment of First-Episode Schizophrenia and Related Disorders: 3-Month Outcomes

Delbert G. Robinson*[1-4], Juan A. Gallego[1-3], Majnu John[1,2,5], Georgios Petrides[1-4], Youssef Hassoun[2,3], Jian-Ping Zhang[1-3], Leonardo Lopez[2,3], Raphael J. Braga[2,3], Serge M. Sevy[6], Jean Addington[7], Charles H. Kellner[8], Mauricio Tohen[9], Melissa Naraine[2], Natasha Bennett[2], Jessica Greenberg[2], Todd Lencz[1-4], Christoph U. Correll[1-4,10], John M. Kane[1-4,10,11], and Anil K. Malhotra[1-4,11]

Biomarkers of Antipsychotic Drug Response

- Multiple potential biomarkers that could relate to psychiatric clinical trial outcomes (CSF, plasma metabolites, cognitive or neurophysiologic measures etc...)

- Genetic biomarkers
  - Advantages – essentially immutable, easy to collect samples from blood or saliva, genotyping/sequencing technology well-developed and relatively inexpensive.

  - Disadvantages – power of the genetic association approach has been limited in complex traits such as psychiatric diagnoses.

- Neuroimaging biomarkers
  - Advantages – addresses the presumed site of action of psychiatric interventions, ability to assess specific regions/circuits within the brain, potential for multi-modal approaches.

  - Disadvantages – not always clear what is being measured, potential confounds of environmental factors (e.g. prior treatment), subject acceptance.

DRD2 -141C Ins/Del and Response to Atypical Antipsychotics

Log rank=5.0, df=1, *P* = 0.025.

Del- (n=31)

Del+ (n=30)

Lencz et al. 2006
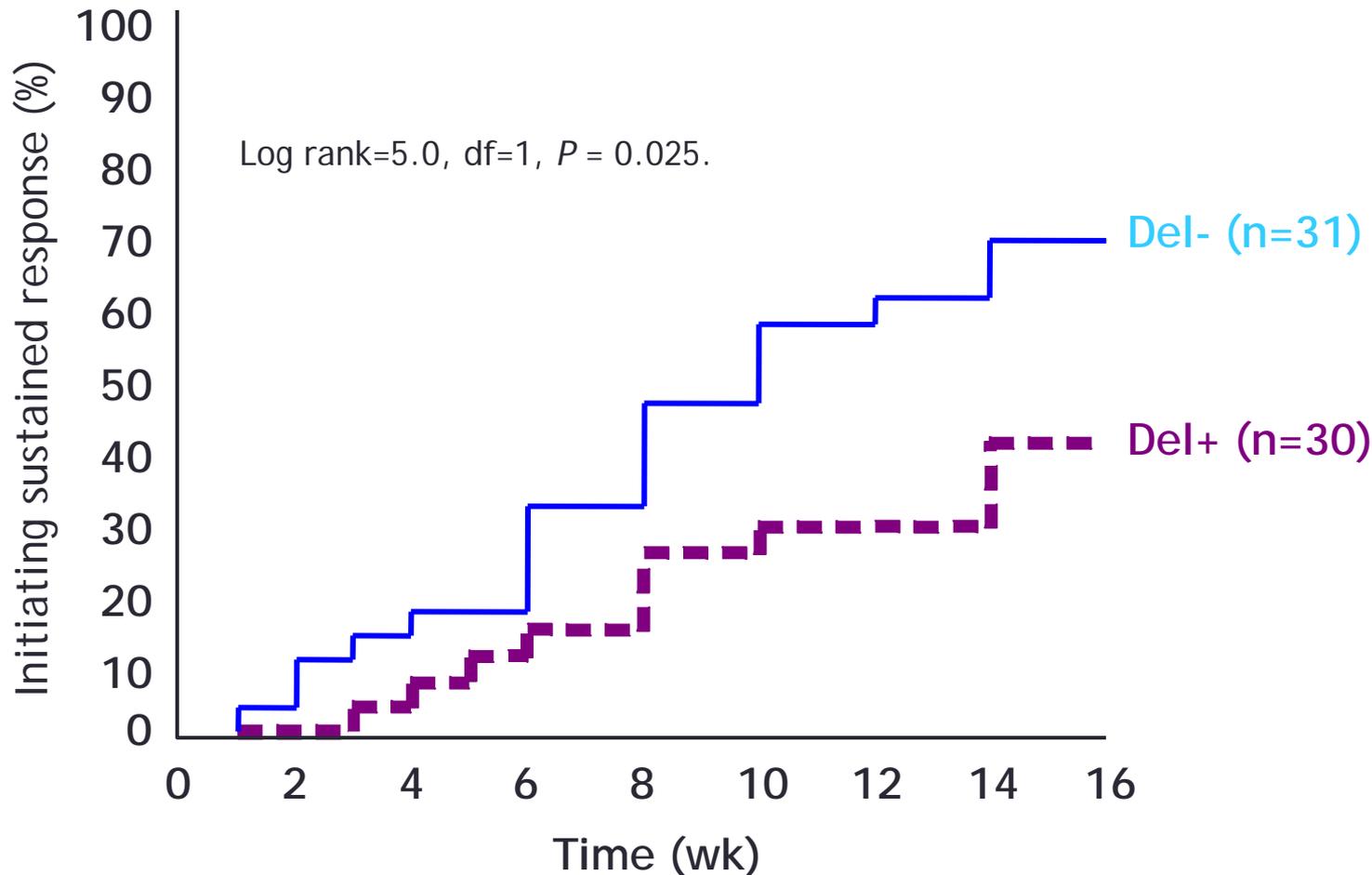
Neuroimaging Approaches to the Heterogeneity of Antipsychotic Response

- Structural CT or MRI: Assessments of morphology.

- DTI: Putative measure of white matter integrity (see Chang et al. ACNP 2015).

- Task-based fMRI: Change in BOLD signal during conduct of cognitive/behavioral/emotional activation task.

- Resting State fMRI: Correlation in BOLD signal during "rest" (no task performance).

Resting State fMRI

- Brain activity continues in the absence of an externally prompted task. These spontaneous fluctuations demonstrate strong correlations across brain regions, defining functional networks.

- Advantages
  - Easy to obtain data e.g., ~ 5 minutes

- Disadvantages
  - No control over what individual is doing in the scanner
    - Can monitor performance in task-based studies
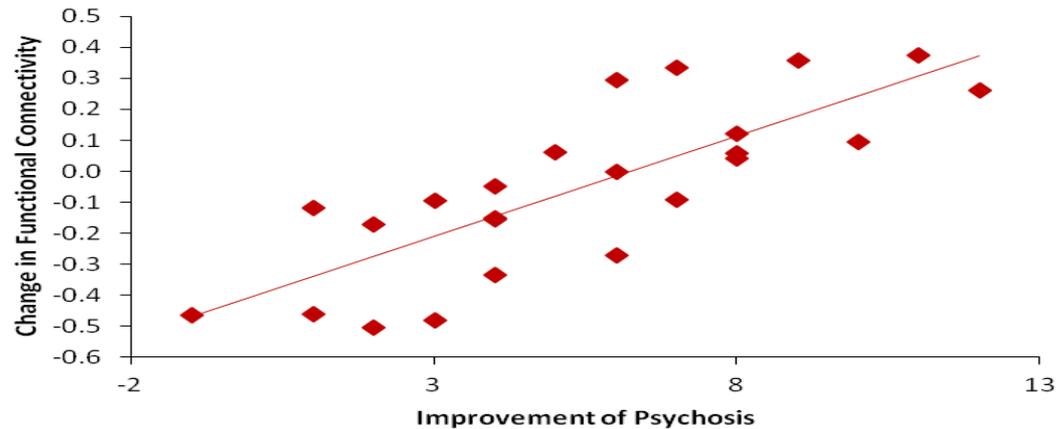   - Instructions do not guarantee compliance
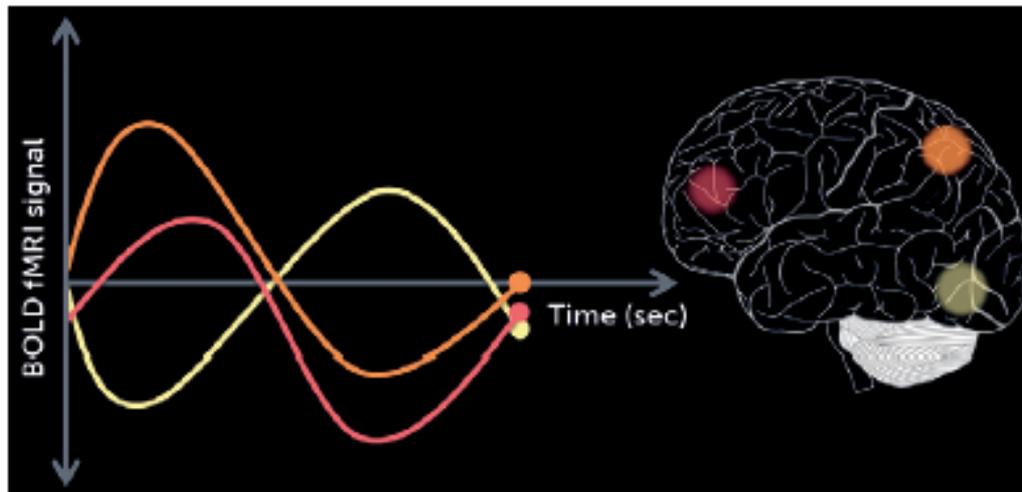
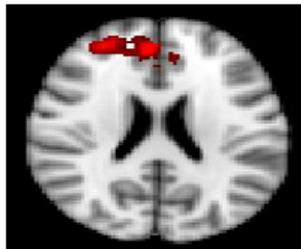# Antipsychotic Treatment and Striatal Functional Connectivity
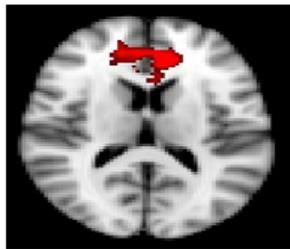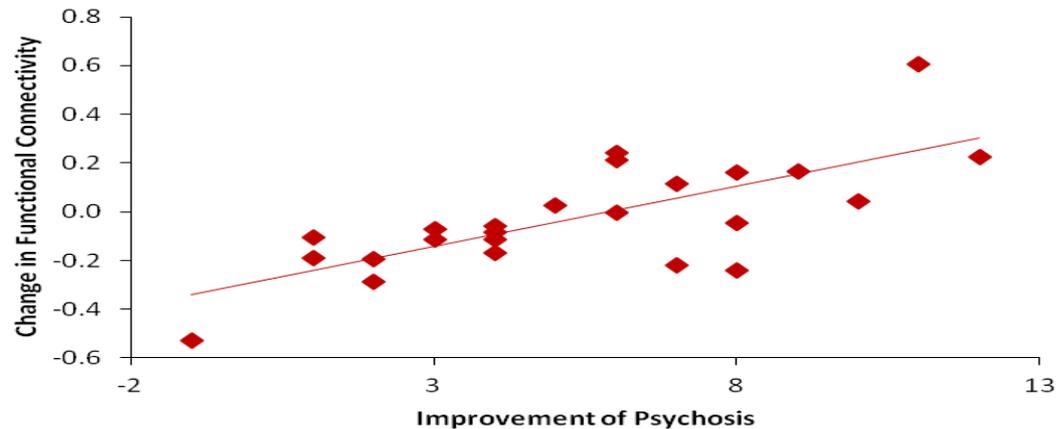
Baseline Striatal Functional Connectivity as a Predictor of Response to Antipsychotic Drug Treatment

Deepak K. Sarpal, M.D., Miklos Argyelan, M.D., Delbert G. Robinson, M.D., Philip R. Szeszko, Ph.D.,
Katherine H. Karlsgodt, Ph.D., Majnu John, Ph.D., Noah Weissman, B.A., Juan A. Gallego, M.D, M.S., John M. Kane, M.D.,
Todd Lencz, Ph.D., Anil K. Malhotra, M.D.

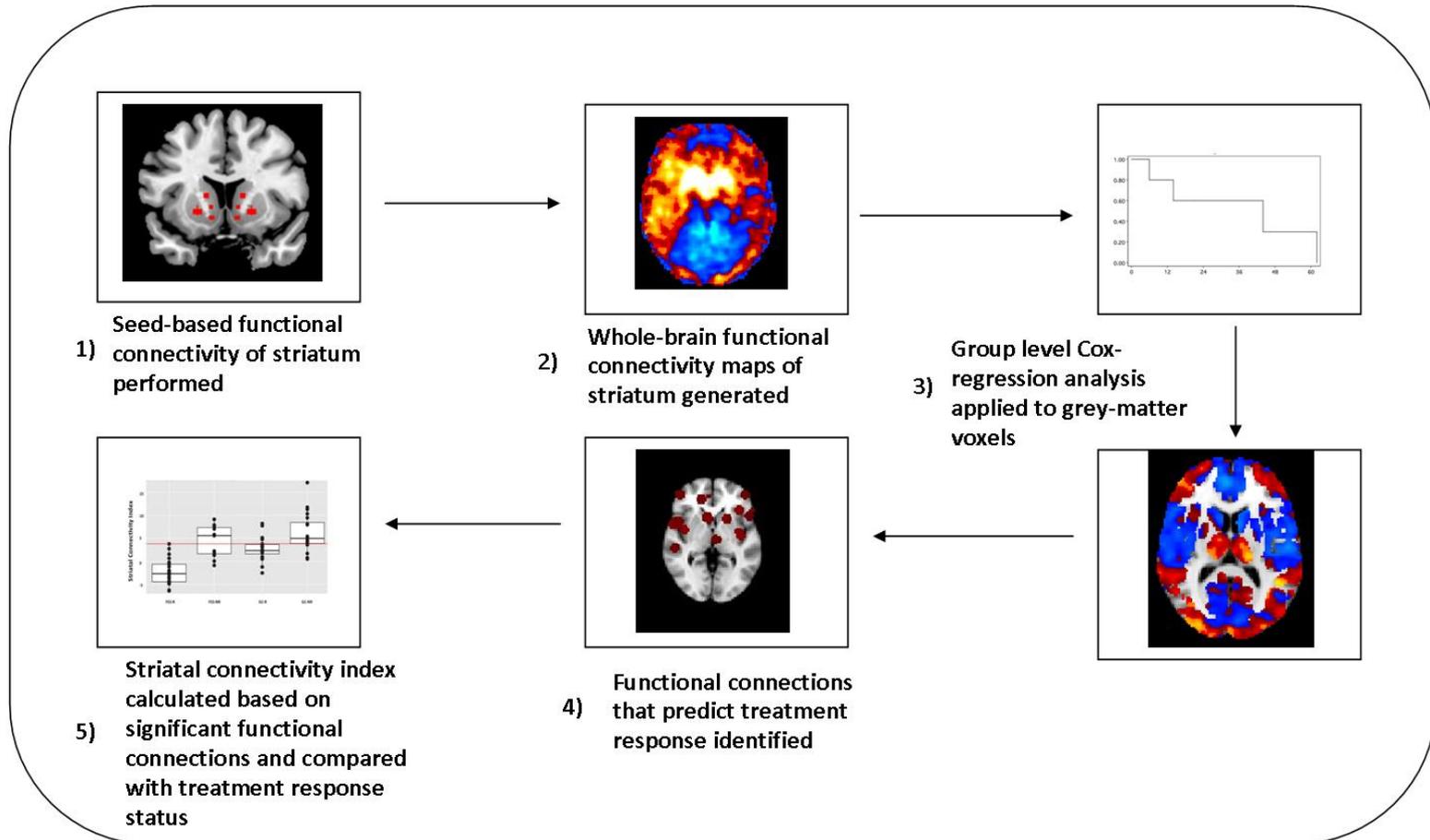|	
Age (years)	21.5 (5.5)
Sex (M/F)	29M/12F
Laterality quotient	.77 (.33)
Education (years)	12.2 (2.1)
Height (inches)	67.4 (3.6)
Weight (pounds)	154.3 (29.4)

Response defined as two consecutive ratings of:

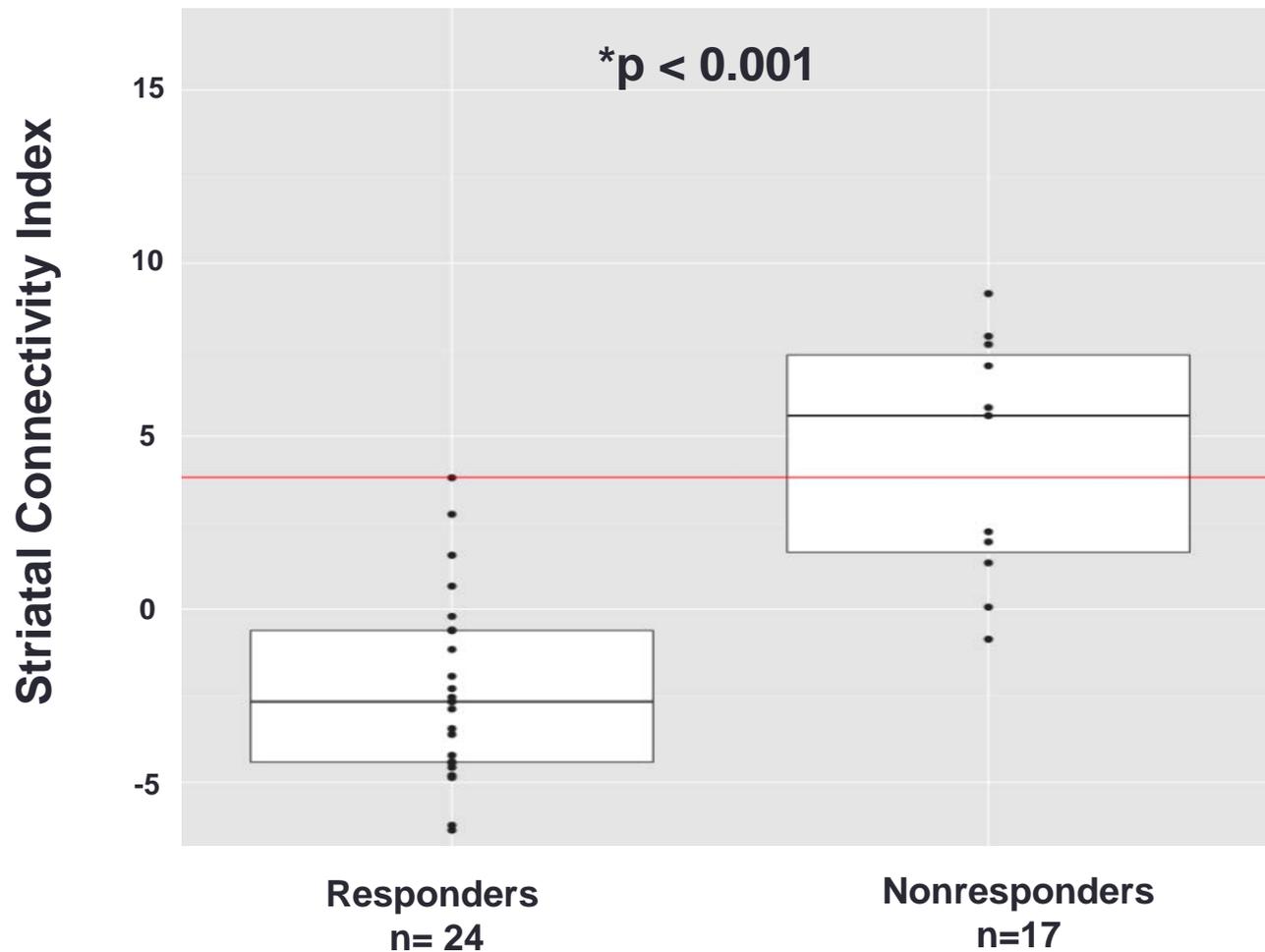3 or less on the following BPRS items:

1. Conceptual disorganization
2. Grandiosity
3. Hallucinatory behavior
4. Unusual thought content

CGI improvement score of "much" or "very much" improved

Methods

1) Seed-based functional connectivity of striatum performed

2) Whole-brain functional connectivity maps of striatum generated

3) Group level Cox-regression analysis applied to grey-matter voxels

4) Functional connections that predict treatment response identified

5) Striatal connectivity index calculated based on significant functional connections and compared with treatment response status
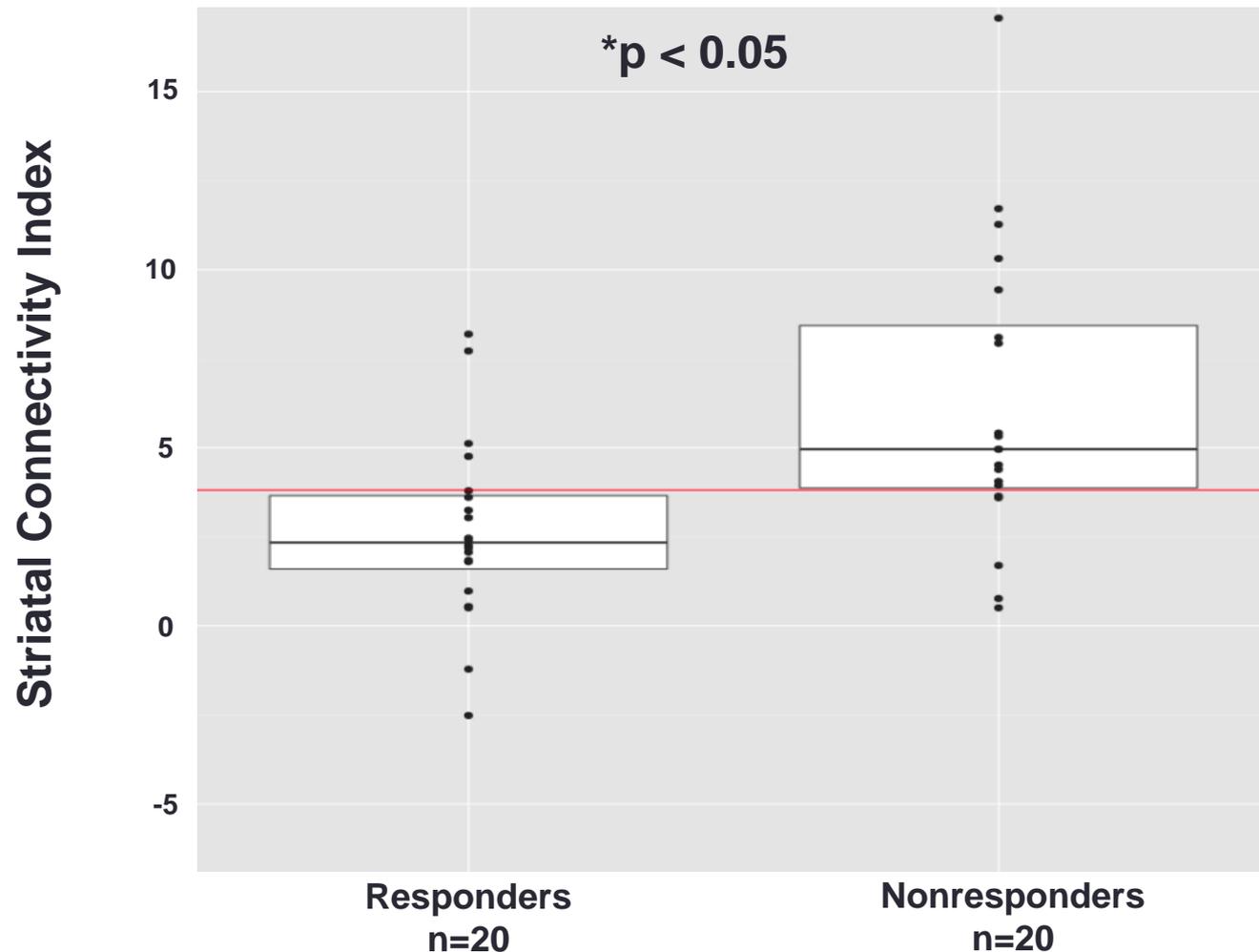
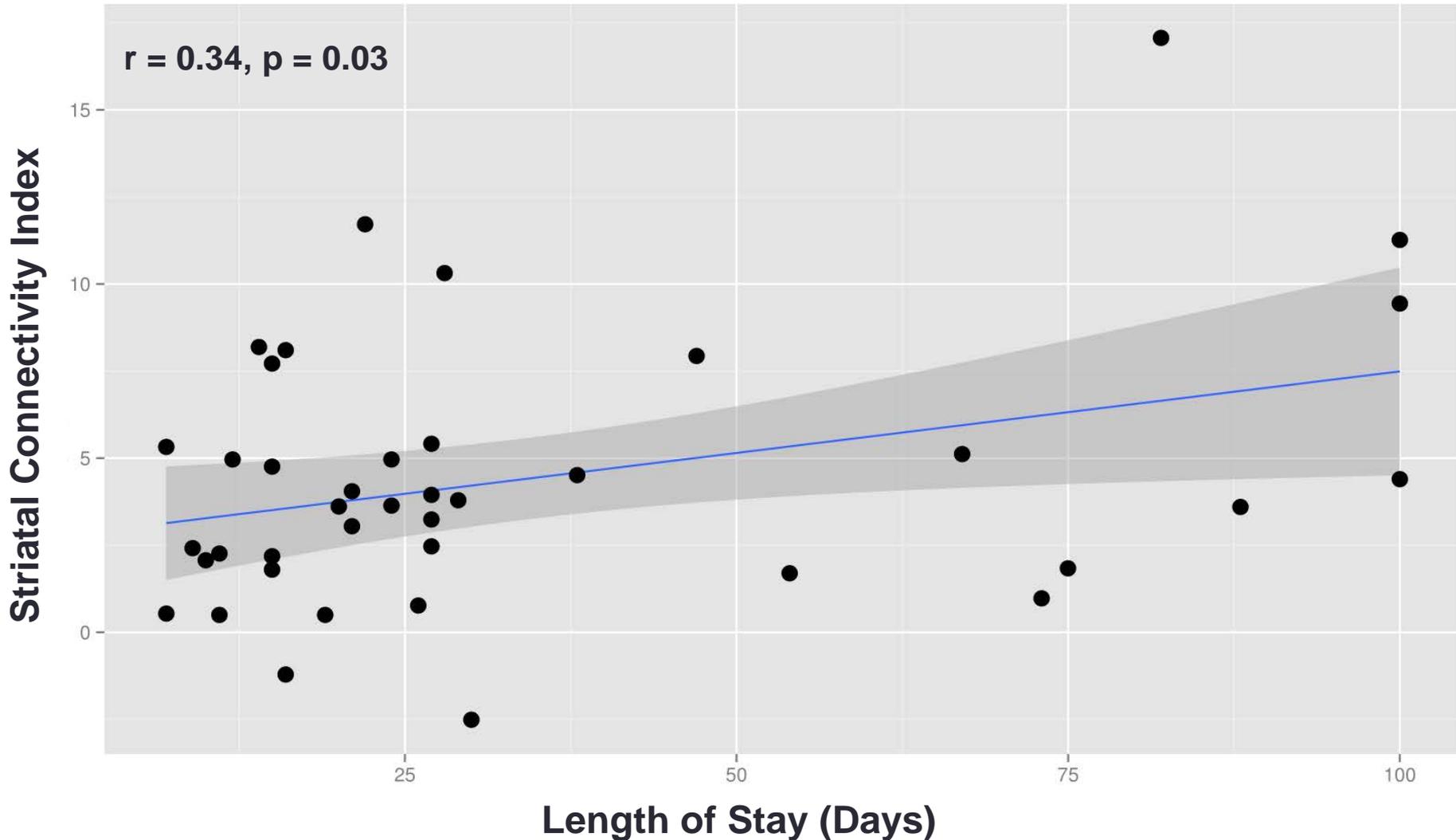# Predicting Response to Treatment in FE Schizophrenia

Predicting Response to Antipsychotic Treatment: Replication and Extension

- Patients with psychotic disorders hospitalized for psychotic symptoms

- 40 subjects
    - Mean age = 29 yrs
    - 29 Males, 11 Females

- Diagnoses: schizophrenia, schizophreniform disorder, schizoaffective disorder, bipolar disorder, psychotic disorder NOS

- Scanned at baseline, BPRS collected weekly during hospital stay; response = > 20% reduction in the 4 psychosis items

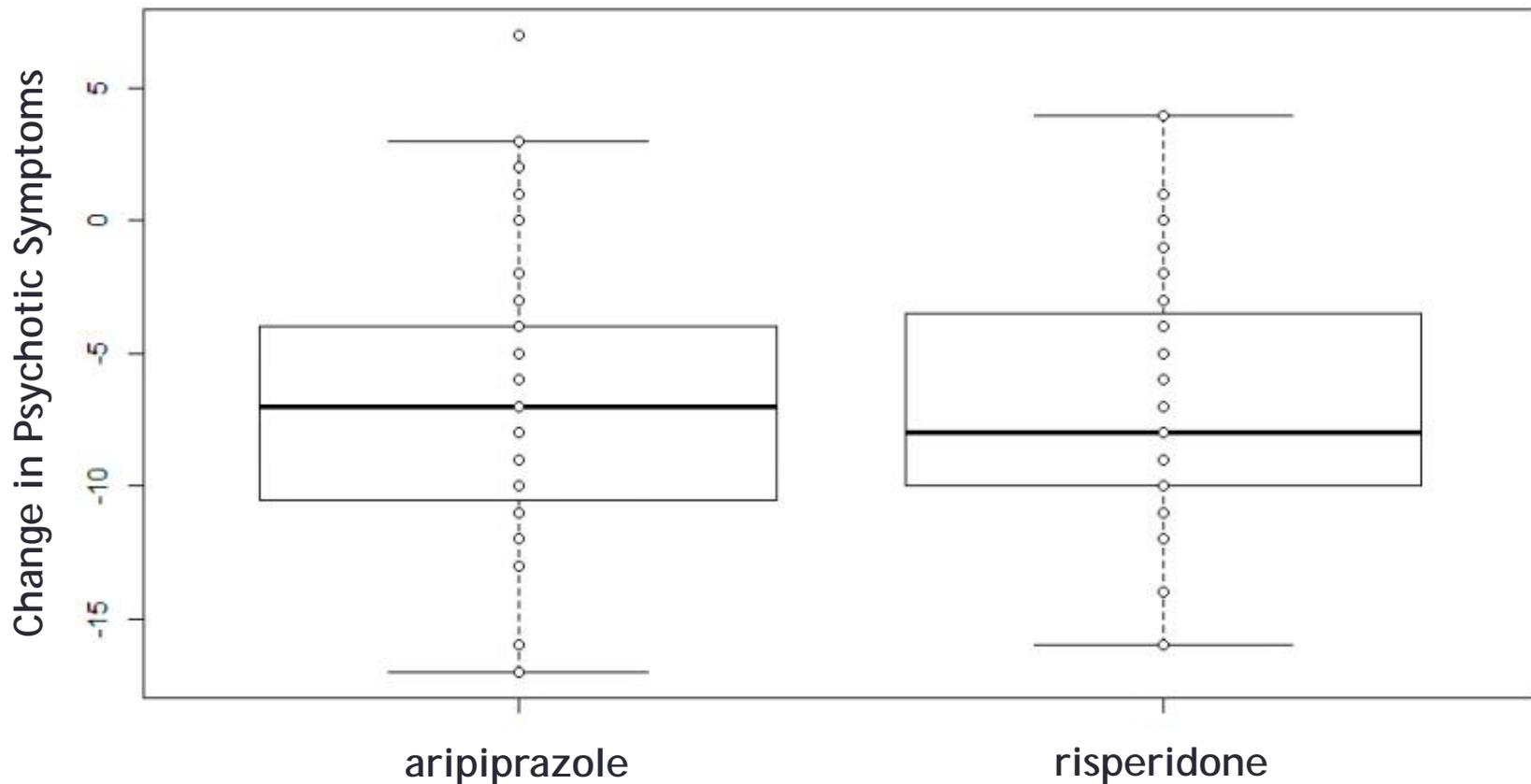# Predicting Response to Antipsychotic Treatment: Replication and Extension

Predicting Response to Antipsychotic Treatment: Clinical Implications?

A Randomized Comparison of Aripiprazole and Risperidone for the Acute Treatment of First-Episode Schizophrenia and Related Disorders: 3-Month Outcomes

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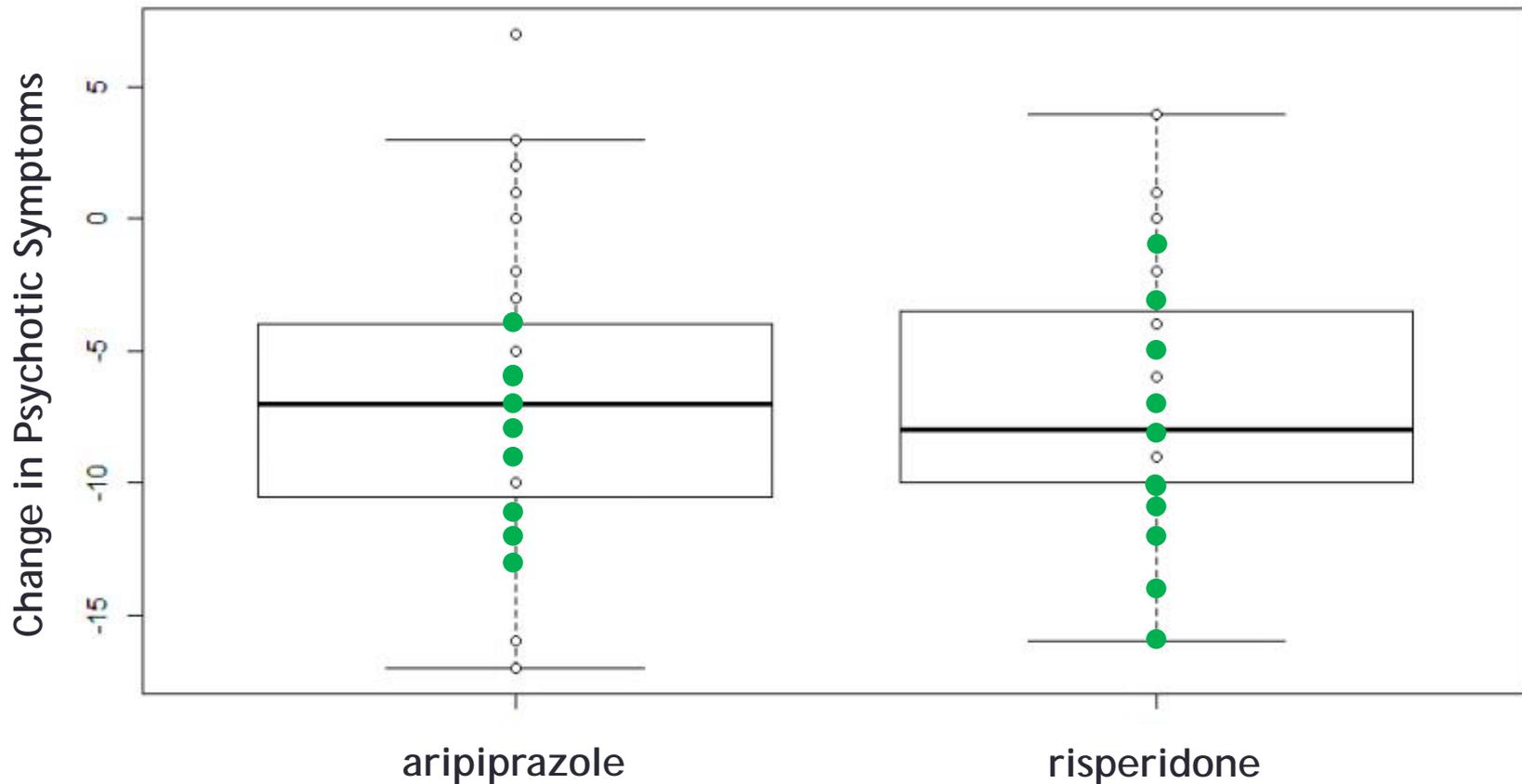
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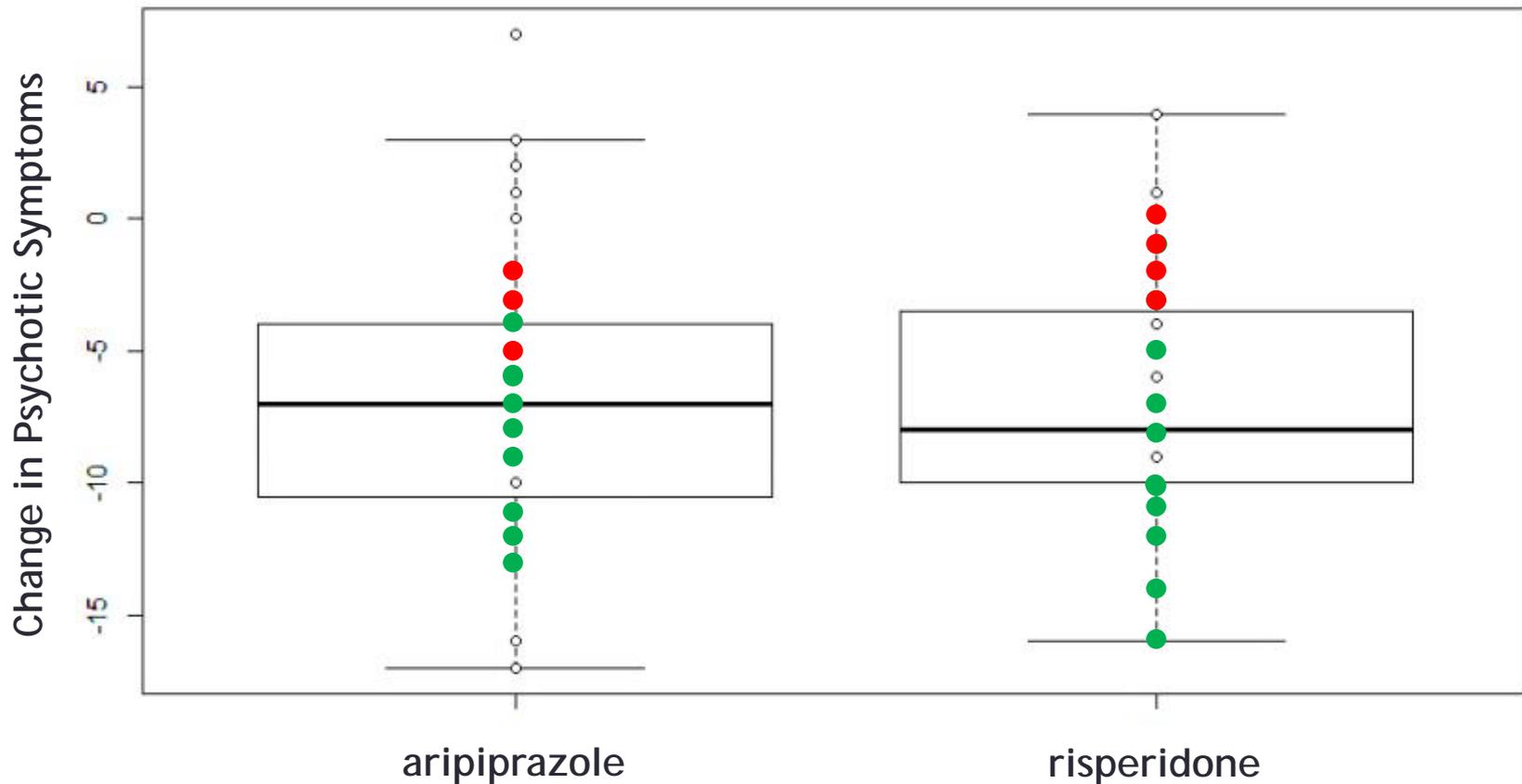
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Conclusions

- *DRD2* genotype predicts clinical response to antipsychotic drug treatment in first episode and other cohorts of patients with schizophrenia.

- Corticostriatal connectivity changes with antipsychotic drug treatment correlate with antipsychotic efficacy.

- Baseline striatal connectivity predicts response to treatment in two independent cohorts of subjects.

- Future directions: Multimodal neuroimaging + more comprehensive genotypic information

Acknowledgements

- Miklos Argyelan
- Deepak Sarpal
- Todd Lencz
- Philip Szeszko
- Delbert Robinson
- John Kane
- Katie Karlsgodt
- Juan Gallego