ISCTM
International Society for CNS Clinical Trials and Methodology

# Structure not just Severity


## Seth C. Hopkins, PhD

Sam Tomioka

Ken Koblan

Steven Szabo

# DISCLOSURES

employees of Sumitomo Pharma America, Inc.

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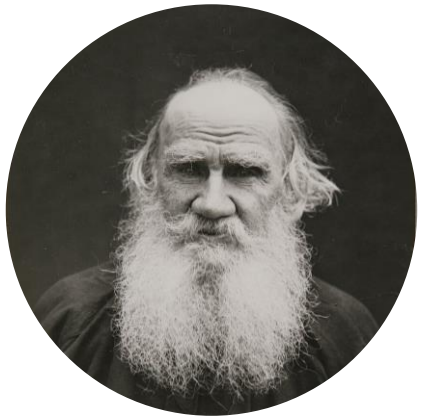
# Key concepts will be represented by historical figures

John F. Kennedy
1917-1963

Ludwig Boltzmann
1844-1906

James Clerk Maxwell
1831- 1879



Leo Tolstoy
1828-1910

Emil Kraepelin
1856-1926

Eugen Bleuler
1857-1939

# Can we flip the problem (of measurement)?

*Ask not what scale is best for your study...*
*...but what participants are best for your scale*

John F. Kennedy

PANSS

**The Positive and Negative Syndrome Scale (PANSS) for Schizophrenia**

***by Stanley R. Kay, Abraham Fiszbein, and Lewis A. Opler***

**Abstract**

The variable results of positive-negative research with schizophrenics underscore the importance of well-characterized, standardized measurement techniques. We report on the development and initial standardization of the Positive and Negative Syndrome Scale (PANSS) for typological and dimensional assessment. Based on two established psychiatric rating systems, the 30-item PANSS was conceived as an operationalized, drug-sensitive instrument that provides balanced representation of positive and negative symptoms and gauges their relationship to one another and to global psychopathology. It thus constitutes four scales measuring positive and negative syndromes, their differential, and general severity of illness. Study of 101 schizophrenics found the four scales to be normally distributed and supported their reliability and stability. Positive and negative scores were inversely correlated once their common association with general psychopathology was extracted, suggesting that they represent mutually exclusive constructs. Review of five studies involving the PANSS provided evidence of its criterion-related validity with antecedent, genealogical, and concurrent measures, its predictive validity, its drug sensitivity, and its utility for both typological and dimensional assessment.

MADRS

*Brit. J. Psychiat.* (1979), **134**, 382–9

A New Depression Scale Designed to be Sensitive to Change

By STUART A. MONTGOMERY and MARIE ÅSBERG

**SUMMARY** **The construction of a depression rating scale designed to be particularly sensitive to treatment effects is described. Ratings of 54 English and 52 Swedish patients on a 65 item comprehensive psychopathology scale were used to identify the 17 most commonly occurring symptoms in primary depressive illness in the combined sample.**

**Ratings on these 17 items for 64 patients participating in studies of four different antidepressant drugs were used to create a depression scale consisting of the 10 items which showed the largest changes with treatment and the highest correlation to overall change.**

**The inter-rater reliability of the new depression scale was high. Scores on the scale correlated significantly with scores on a standard rating scale for depression, the Hamilton Rating Scale (HRS), indicating its validity as a general severity estimate. Its capacity to differentiate between responders and non-responders to antidepressant treatment was better than the HRS, indicating greater sensitivity to change. The practical and ethical implications in terms of smaller sample sizes in clinical trials are discussed.**

# Visualize the key mathematical construct

symptom structure is inside the matrix

Variance-Covariance Matrix

**PANSS**

**acute schizophrenia**

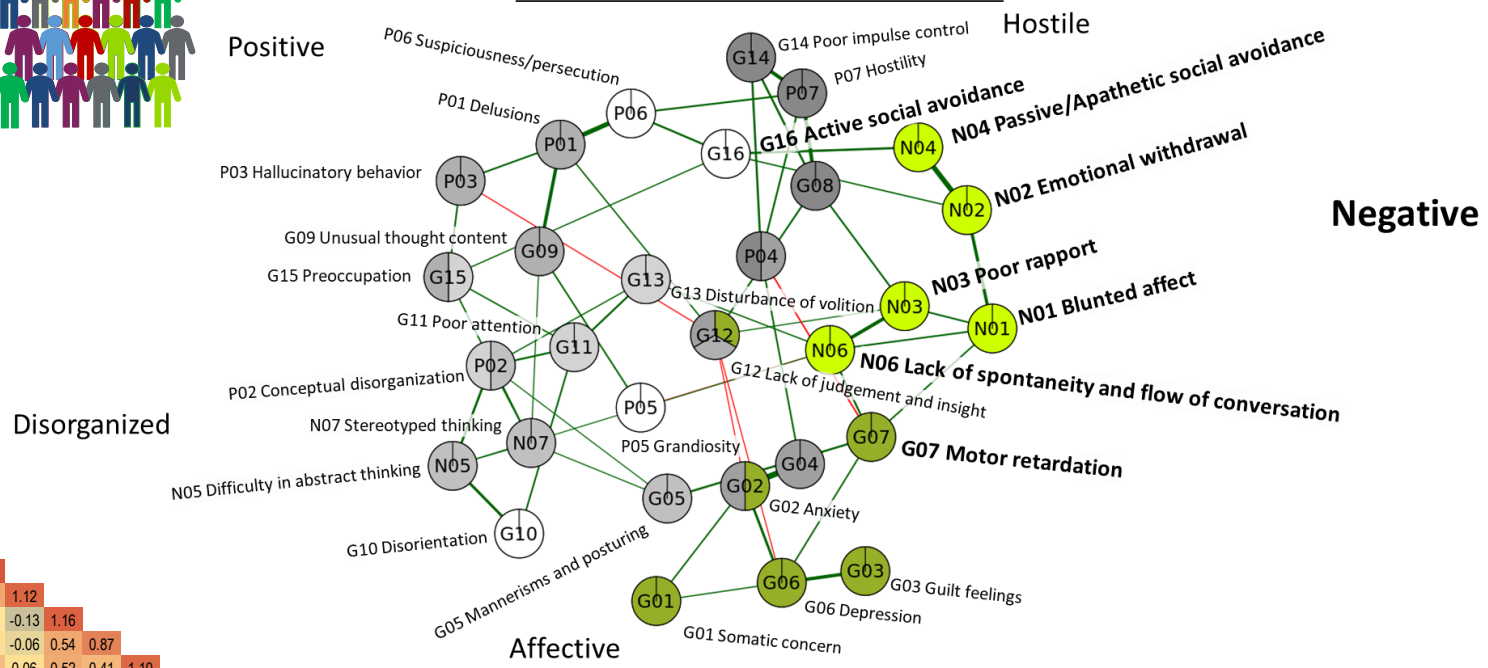
**13 trials**

**N=5,793**

| ITEM | P01 | P03 | P05 | P06 | N07 | G01 | G09 | G12 | P02 | N05 | G05 | G10 | G11 | G13 | G15 | P04 | P07 | G08 | G14 | N01 | N02 | N03 | N04 | N06 | G07 | G16 | G02 | G03 | G04 | G06 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| P01 DELUSIONS | 0.94 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| P03 HALLUCINATORY BEHAVIOR | 0.31 | 1.44 | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| P05 GRANDIOSITY | 0.30 | 0.18 | 2.03 | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| P06 SUSPICIOUSNESS/PERSECUTION | 0.48 | 0.23 | 0.09 | 1.04 | | | | | | | | | | | | | | | | | | | | | | | | | | |
| N07 STEREOTYPED THINKING | 0.17 | 0.05 | 0.20 | 0.04 | 1.03 | | | | | | | | | | | | | | | | | | | | | | | | | |
| G01 SOMATIC CONCERN | 0.10 | 0.06 | 0.16 | 0.09 | 0.18 | 1.70 | | | | | | | | | | | | | | | | | | | | | | | | |
| G09 UNUSUAL THOUGHT CONTENT | 0.44 | 0.20 | 0.40 | 0.17 | 0.28 | 0.18 | 1.03 | | | | | | | | | | | | | | | | | | | | | | | |
| G12 LACK OF JUDGEMENT AND INSIGHT | 0.24 | -0.10 | 0.02 | 0.05 | 0.25 | 0.02 | 0.28 | 1.36 | | | | | | | | | | | | | | | | | | | | | | |
| P02 CONCEPTUAL DISORGANIZATION | 0.12 | 0.00 | 0.12 | -0.06 | 0.38 | 0.11 | 0.27 | 0.33 | 1.14 | | | | | | | | | | | | | | | | | | | | | |
| N05 DIFFICULTY IN ABSTRACT THINKING | 0.01 | 0.10 | 0.09 | -0.05 | 0.29 | 0.06 | 0.11 | 0.25 | 0.46 | 1.40 | | | | | | | | | | | | | | | | | | | | |
| G05 MANNERISMS AND POSTURING | 0.02 | -0.02 | 0.10 | -0.05 | 0.30 | 0.14 | 0.14 | 0.18 | 0.32 | 0.14 | 1.22 | | | | | | | | | | | | | | | | | | | |
| G10 DISORIENTATION | 0.01 | 0.17 | 0.20 | 0.01 | 0.10 | 0.13 | 0.04 | 0.15 | 0.20 | 0.42 | 0.16 | 1.18 | | | | | | | | | | | | | | | | | | |
| G11 POOR ATTENTION | 0.05 | 0.06 | 0.07 | 0.00 | 0.25 | 0.08 | 0.13 | 0.23 | 0.42 | 0.31 | 0.28 | 0.29 | 0.97 | | | | | | | | | | | | | | | | | |
| G13 DISTURBANCE OF VOLITION | 0.07 | 0.03 | -0.08 | 0.00 | 0.27 | 0.09 | 0.14 | 0.26 | 0.37 | 0.23 | 0.30 | 0.12 | 0.38 | 0.99 | | | | | | | | | | | | | | | | |
| G15 PREOCCUPATION | 0.24 | 0.31 | 0.14 | 0.15 | 0.33 | 0.10 | 0.28 | 0.23 | 0.30 | 0.16 | 0.27 | 0.21 | 0.33 | 0.31 | 1.12 | | | | | | | | | | | | | | | |
| P04 EXCITEMENT | 0.19 | 0.10 | 0.32 | 0.19 | 0.20 | 0.16 | 0.16 | 0.03 | 0.20 | 0.07 | 0.12 | 0.06 | 0.20 | 0.07 | 0.16 | 1.14 | | | | | | | | | | | | | | |
| P07 HOSTILITY | 0.20 | 0.03 | 0.17 | 0.33 | 0.13 | 0.08 | 0.12 | 0.14 | 0.04 | -0.01 | 0.04 | 0.00 | 0.07 | 0.02 | 0.09 | 0.46 | 1.29 | | | | | | | | | | | | | |
| G08 UNCOOPERATIVENESS | 0.15 | -0.04 | 0.07 | 0.19 | 0.23 | 0.04 | 0.16 | 0.38 | 0.19 | 0.08 | 0.22 | 0.10 | 0.26 | 0.20 | 0.21 | 0.34 | 0.68 | 1.27 | | | | | | | | | | | | |
| G14 POOR IMPULSE CONTROL | 0.12 | 0.01 | 0.15 | 0.16 | 0.14 | 0.11 | 0.13 | 0.10 | 0.09 | 0.01 | 0.06 | 0.01 | 0.14 | 0.09 | 0.13 | 0.46 | 0.67 | 0.55 | 1.12 | | | | | | | | | | | |
| N01 BLUNTED AFFECT | -0.06 | 0.01 | -0.20 | -0.03 | 0.14 | 0.01 | -0.05 | 0.10 | 0.19 | 0.23 | 0.23 | 0.10 | 0.15 | 0.27 | 0.16 | -0.19 | -0.12 | 0.01 | -0.13 | 1.16 | | | | | | | | | | |
| N02 EMOTIONAL WITHDRAWAL | -0.01 | 0.06 | -0.16 | 0.03 | 0.10 | -0.01 | 0.00 | 0.10 | 0.15 | 0.18 | 0.12 | 0.09 | 0.11 | 0.21 | 0.16 | -0.12 | -0.02 | 0.07 | -0.06 | 0.54 | 0.87 | | | | | | | | | |
| N03 POOR RAPPORT | 0.01 | -0.04 | -0.19 | 0.02 | 0.21 | -0.04 | 0.05 | 0.35 | 0.26 | 0.25 | 0.29 | 0.08 | 0.28 | 0.31 | 0.23 | -0.01 | 0.16 | 0.37 | 0.06 | 0.52 | 0.41 | 1.10 | | | | | | | | |
| N04 PASSIVE/APATHETIC SOCIAL WITHDRAWAL | -0.01 | 0.05 | -0.18 | 0.02 | 0.13 | -0.01 | 0.00 | 0.12 | 0.15 | 0.19 | 0.14 | 0.09 | 0.11 | 0.24 | 0.18 | -0.13 | -0.02 | 0.09 | -0.08 | 0.51 | 0.64 | 0.42 | 1.14 | | | | | | | |
| N06 LACK OF SPONTANEITY AND FLOW OF CONVERSA | -0.11 | -0.01 | -0.33 | -0.06 | 0.23 | -0.06 | -0.04 | 0.26 | 0.28 | 0.36 | 0.31 | 0.16 | 0.28 | 0.42 | 0.23 | -0.14 | -0.01 | 0.22 | -0.04 | 0.62 | 0.47 | 0.71 | 0.51 | 1.40 | | | | | | |
| G07 MOTOR RETARDATION | -0.10 | 0.02 | -0.13 | -0.07 | 0.09 | 0.11 | -0.08 | -0.01 | 0.09 | 0.16 | 0.35 | 0.14 | 0.17 | 0.29 | 0.16 | -0.22 | -0.07 | 0.10 | -0.11 | 0.49 | 0.32 | 0.35 | 0.35 | 0.56 | 1.27 | | | | | |
| G16 ACTIVE SOCIAL AVOIDANCE | 0.18 | 0.17 | 0.00 | 0.34 | 0.08 | 0.01 | 0.08 | 0.01 | -0.01 | 0.05 | 0.08 | 0.08 | 0.06 | 0.18 | 0.26 | 0.04 | 0.16 | 0.20 | 0.13 | 0.19 | 0.33 | 0.20 | 0.41 | 0.22 | 0.19 | 1.12 | | | | |
| G02 ANXIETY | 0.09 | 0.23 | 0.17 | 0.26 | -0.03 | 0.39 | -0.04 | -0.38 | -0.14 | -0.10 | 0.01 | 0.11 | 0.02 | -0.02 | 0.07 | 0.25 | 0.11 | -0.05 | 0.12 | -0.08 | -0.05 | -0.17 | -0.03 | -0.20 | 0.01 | 0.23 | 1.45 | | | |
| G03 GUILT FEELINGS | -0.01 | 0.10 | 0.21 | 0.06 | 0.02 | 0.32 | 0.00 | -0.30 | -0.11 | -0.07 | 0.00 | 0.03 | -0.02 | 0.00 | -0.01 | 0.06 | 0.05 | -0.07 | 0.10 | -0.06 | -0.02 | -0.15 | -0.01 | -0.12 | 0.12 | 0.07 | 0.43 | 1.50 | | |
| G04 TENSION | 0.04 | 0.11 | 0.10 | 0.15 | 0.09 | 0.24 | 0.03 | -0.22 | 0.01 | 0.02 | 0.15 | 0.05 | 0.16 | 0.12 | 0.13 | 0.31 | 0.11 | 0.07 | 0.16 | -0.01 | 0.00 | -0.02 | 0.02 | 0.00 | 0.07 | 0.17 | 0.77 | 0.29 | 1.07 | |
| G06 DEPRESSION | -0.04 | 0.13 | 0.09 | 0.14 | -0.10 | 0.37 | -0.12 | -0.41 | -0.23 | -0.13 | -0.08 | 0.11 | -0.09 | -0.11 | -0.03 | 0.00 | 0.06 | -0.10 | 0.03 | -0.01 | 0.03 | -0.20 | 0.05 | -0.15 | 0.22 | 0.17 | 0.67 | 0.64 | 0.35 | 1.55 |

pre-randomization data (screening and baseline)

## Negative symptom change is difficult to interpret (in standard trials of acute schizophrenia)



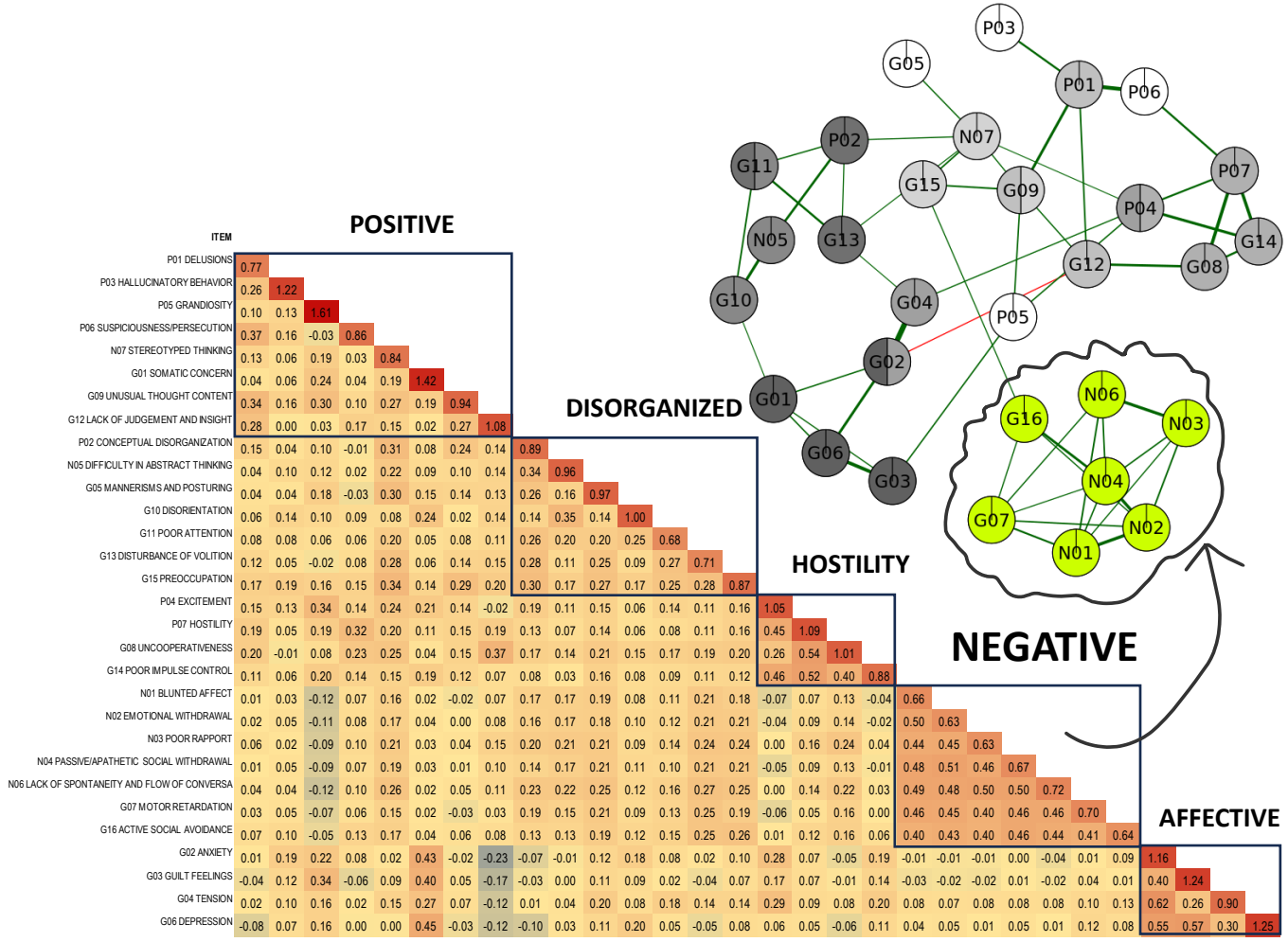

Total Score

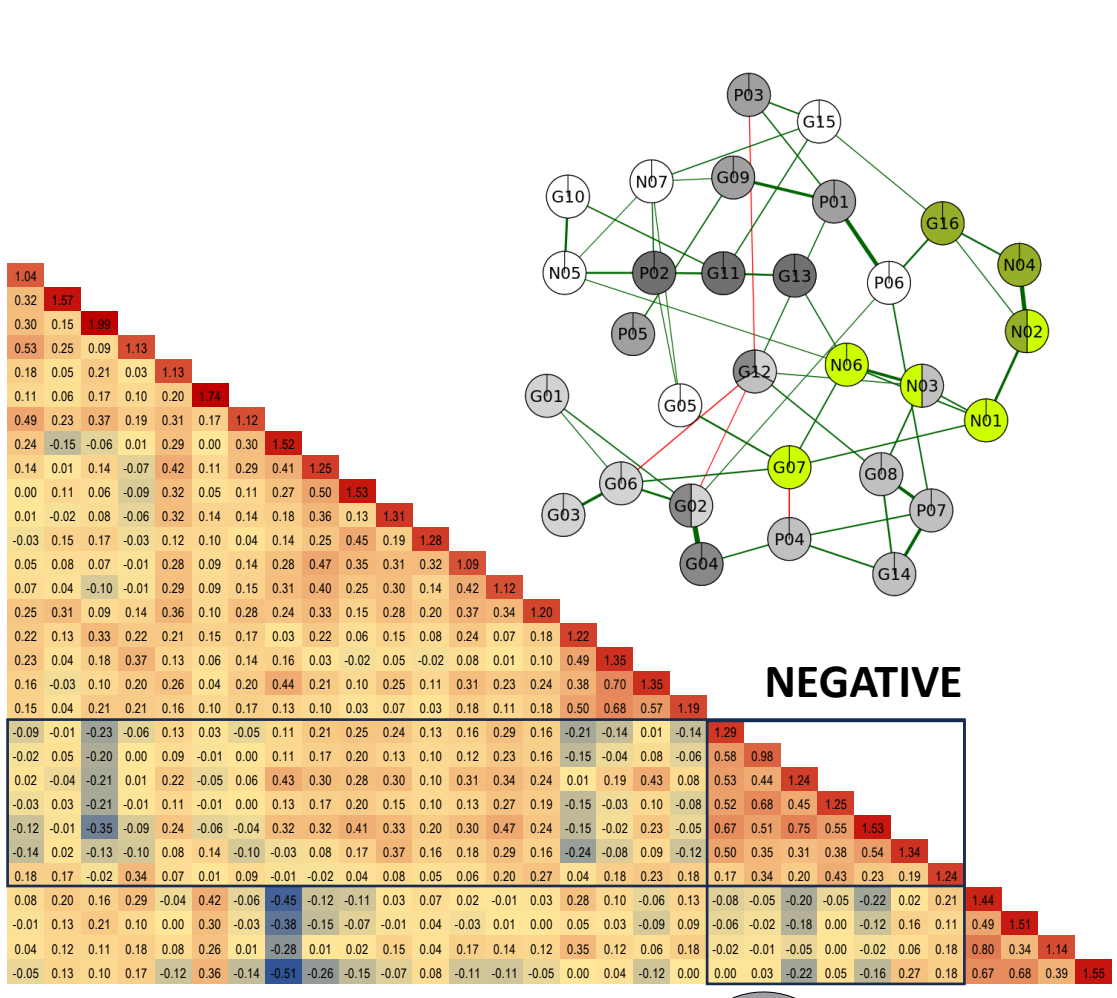


Hopkins SC, Tomioka S, Ogirala A, Loebel A, Koblan KS, Marder SR. *Assessment of Negative Symptoms in Clinical Trials of Acute Schizophrenia: Test of a Novel Enrichment Strategy.* Schizophrenia Bulletin Open, Volume 3, Issue 1, January 2022

**13 trials**
**N=5,793**

# We can enrich on symptom structure




Subjects enriched for having MPNS construct (N=929)

**subjects having the most variance explained by a negative symptom construct**

Subjects de-enriched for MPNS construct (N=3,934)

**subjects whose symptom variance is NOT explained by a negative symptom construct**



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# Symptom structure is ergodic

**BETWEEN-SUBJECTS (FIXED IN TIME)**

"cross-section"

Variance-Covariance Matrix

ABSOLUTE SCORES

look a lot alike

=

**WITHIN-SUBJECTS (OVER TIME)**

"longitudinal"

Variance-Covariance Matrix

CHANGE SCORES

Ludwig Boltzmann

Ergodic Theory - that it is as good to observe a system over time as it is to make many independent observations of the same system



Hopkins SC, Ogirala A, Loebel A, Koblan KS. *Transformed PANSS Factors Intended to Reduce Pseudospecificity Among Symptom Domains and Enhance Understanding of Symptom Change in Antipsychotic-Treated Patients With Schizophrenia*. Schizophr Bull. 2018

# Two ways to reveal symptom structure

## BETWEEN-SUBJECTS (FIXED IN TIME)

"cross-section"

Variance-Covariance Matrix

ABSOLUTE SCORES

look a lot alike

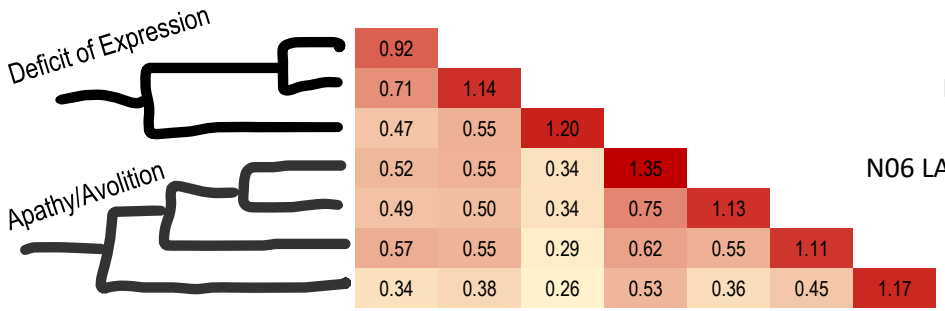
=

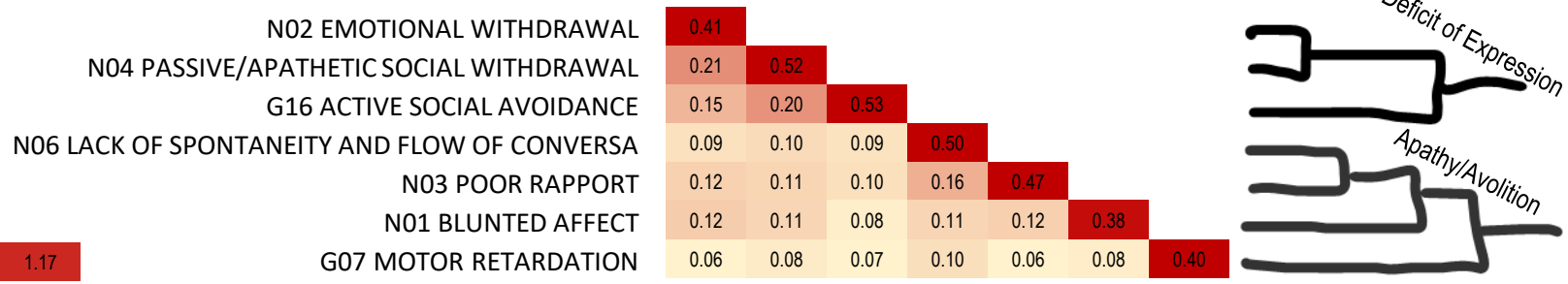
## WITHIN-SUBJECTS (OVER TIME)

"longitudinal"

Variance-Covariance Matrix

CHANGE SCORES






Hopkins SC, Ogirala A, Loebel A, Koblan KS. *Transformed PANSS Factors Intended to Reduce Pseudospecificity Among Symptom Domains and Enhance Understanding of Symptom Change in Antipsychotic-Treated Patients With Schizophrenia*. Schizophr Bull. 2018

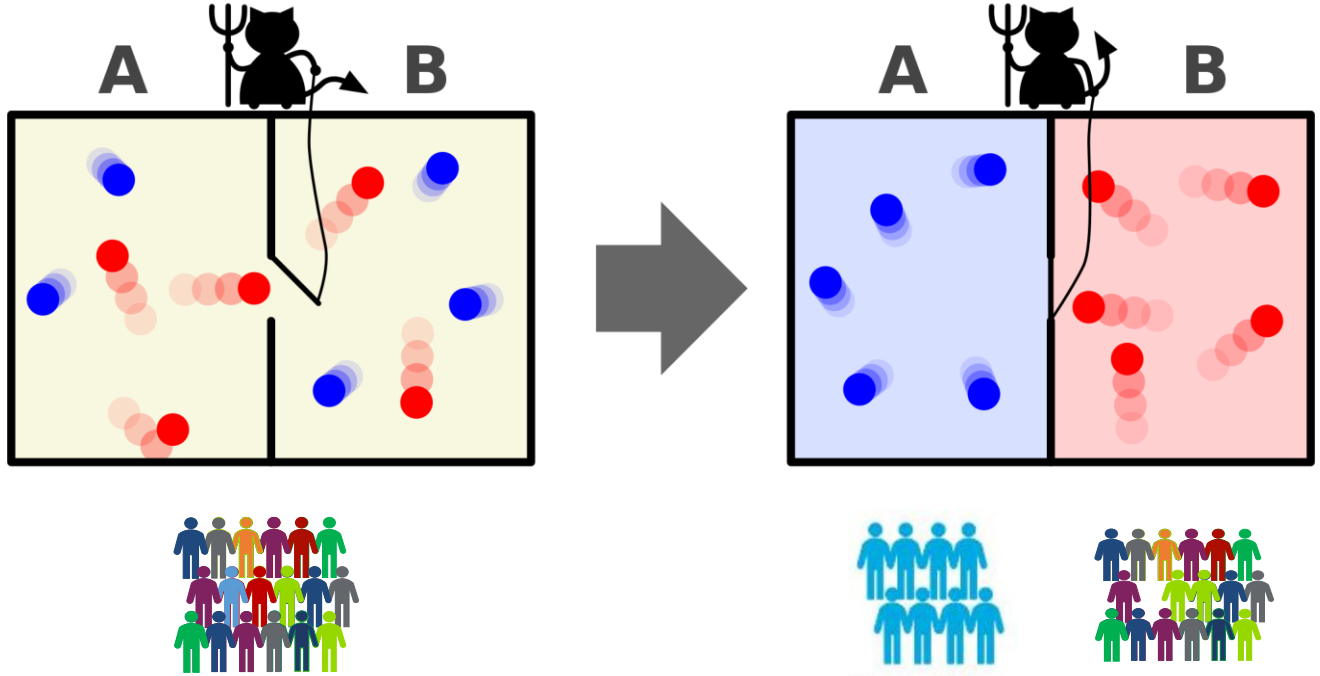
# We can measure symptom structure prior to study entry

**idea**: what if we could detect symptom structure in individual subjects?

**WE COULD DO ENRICHMENT**

James Clerk Maxwell

## Maxwell's Demon




subjects having the most variance explained by a negative symptom construct

subjects whose symptom variance is NOT explained by a negative symptom construct

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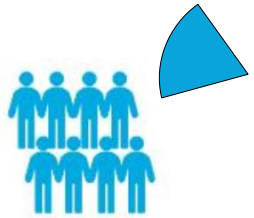
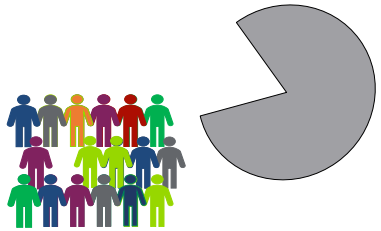
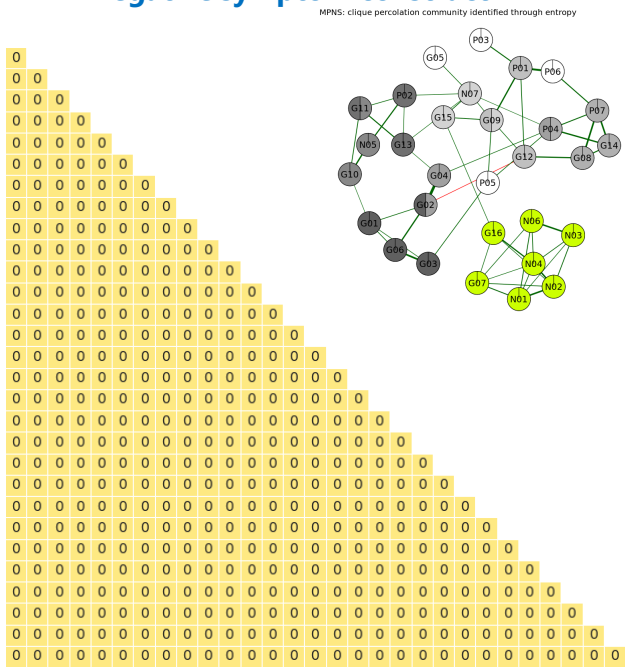
# SINGLE SUBJECTS' VECTORS

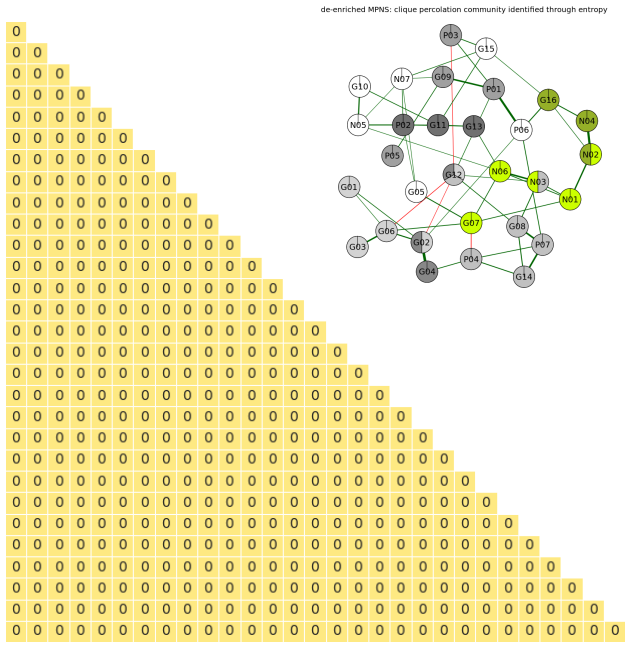


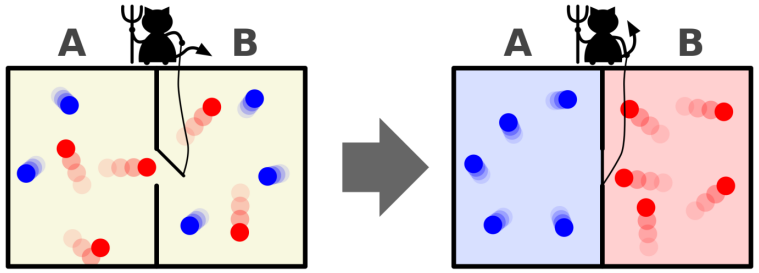
**subjects having the most variance explained by a negative symptom construct**



**subjects whose symptom variance is NOT explained by a negative symptom construct**




# POPULATION'S MATRIX

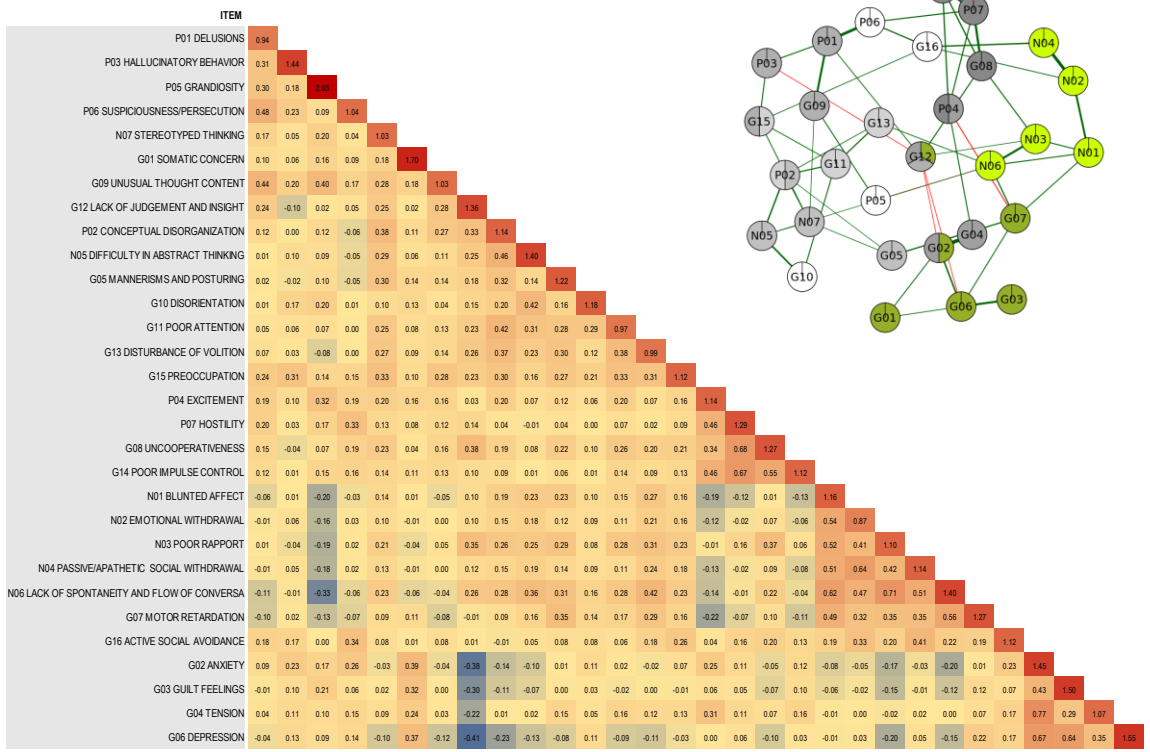
**13 trials**

**N=5,793**

Variance-Covariance Matrix

**PANSS**

**acute schizophrenia**

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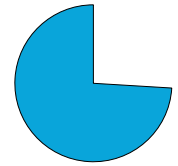
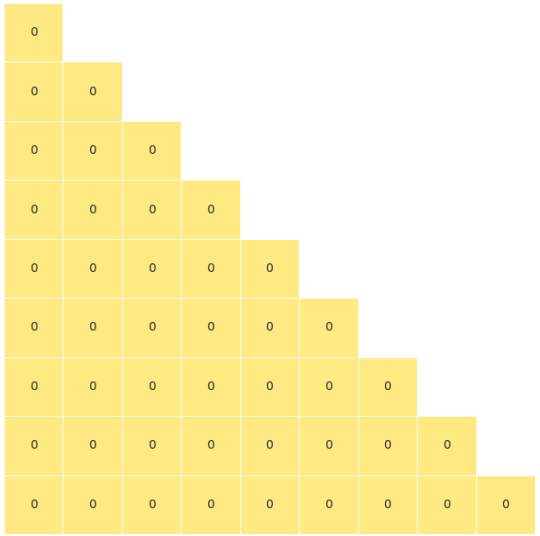
# SINGLE SUBJECTS' VECTORS

## CANONICAL SYMPTOMS

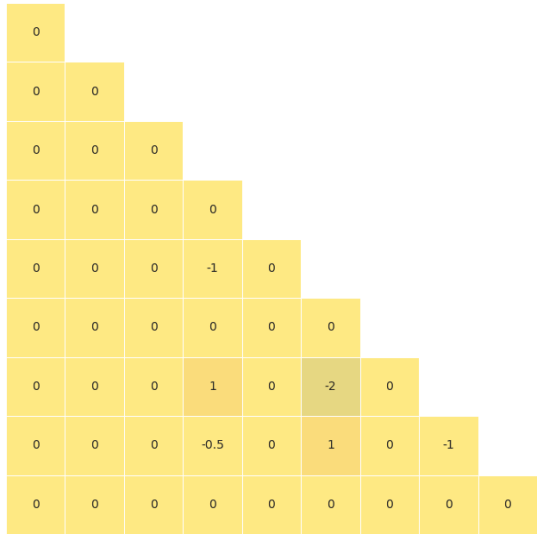


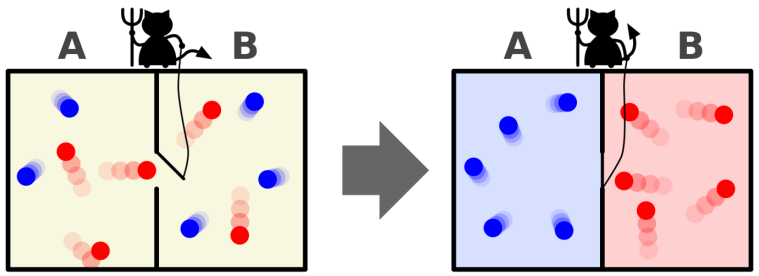
many vectors resemble each other




## ANOMALOUS SYMPTOMS

some look different, but each in their own way




# POPULATION'S MATRIX

Variance-Covariance Matrix

**MADRS**

**bipolar depression**

**5 trials**

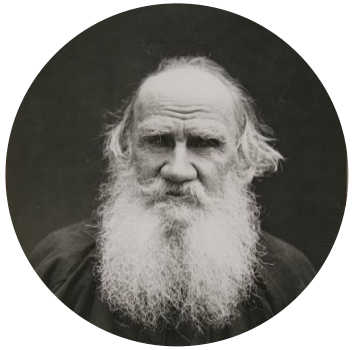
**N=2,026 subjects**

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Apparent Sadness | 0.63 | | | | | | | | | |
| Reported Sadness | 0.36 | 0.65 | | | | | | | | |
| Inner Tension | 0.13 | 0.13 | 1.21 | | | | | | | |
| Reduced Sleep | 0.19 | 0.14 | 0.11 | 1.92 | | | | | | |
| Reduced Appetite | 0.33 | 0.30 | 0.05 | 0.52 | 2.66 | | | | | |
| Concentration Difficulties | 0.17 | 0.18 | 0.23 | 0.16 | 0.20 | 1.02 | | | | |
| Lassitude | 0.21 | 0.21 | 0.10 | 0.12 | 0.31 | 0.26 | 0.89 | | | |
| Inability to Feel | 0.23 | 0.23 | 0.12 | 0.10 | 0.25 | 0.23 | 0.32 | 0.90 | | |
| Pessimistic Thoughts | 0.14 | 0.14 | 0.34 | 0.00 | 0.07 | 0.20 | 0.16 | 0.27 | 1.23 | |
| Suicidal Thoughts | 0.04 | 0.06 | 0.07 | 0.01 | 0.04 | 0.02 | 0.05 | 0.10 | 0.22 | 0.77 |


Hopkins SC, Tomioka S, Szabo ST, Koblan KS. *A clinical trial inclusion criteria to enrich for patients presenting with canonical symptom structure in bipolar depression*. In submission 2024

# Anomalous symptom structures are easily isolated

**Conjecture**: canonical symptom structures (*canonical vectors*) resemble each other, but every anomalous symptom structure is different in its own way (*anomalous vectors*).



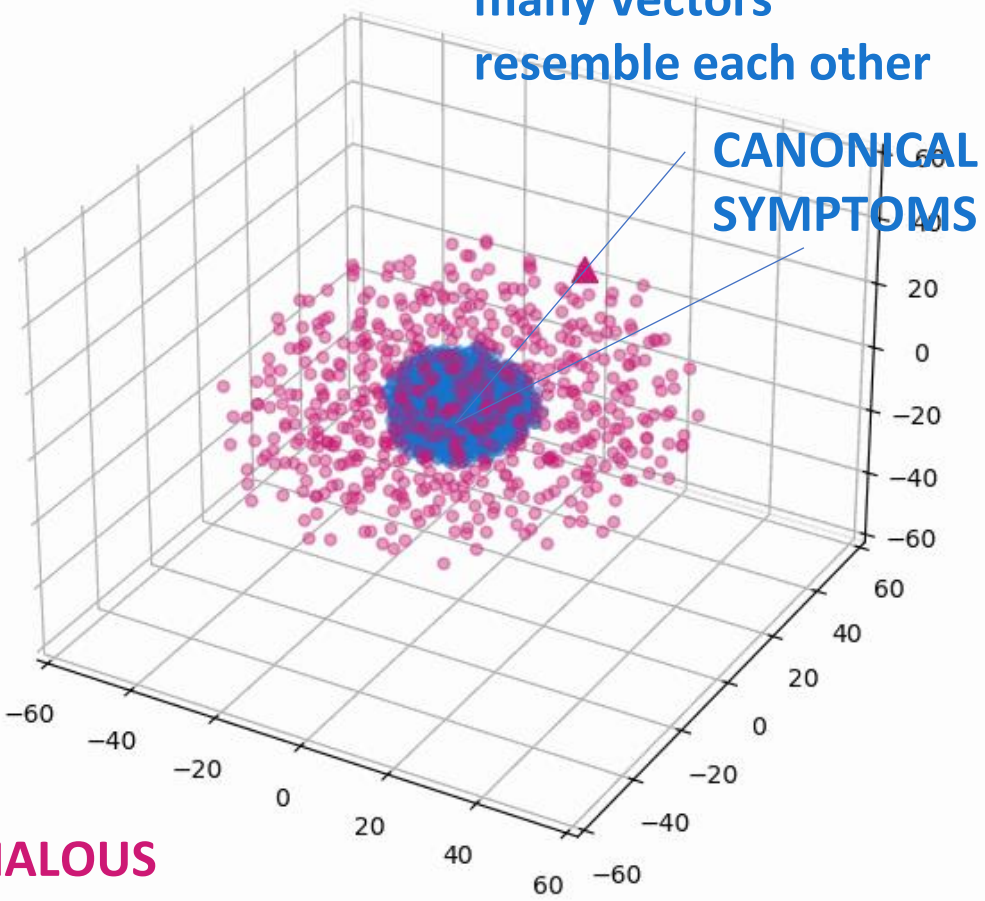
Leo Tolstoy

ANNA KARENINA

CHAPTER I

ALL happy families resemble one another; every unhappy family is unhappy in its own way.

The premise of the Isolation Forest algorithm is that anomalous data points are easier to separate from the rest of the sample



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# BIPOLAR DATASET

**ANOMALOUS SYMPTOMS**

**CANONICAL SYMPTOMS**

**5 legacy trials**
**N=2,026 subjects**

# PROSPECTIVE USE

**1 trial**
**N=129 subjects, pre-randomization data**

Phase 3 trial

# RETROSPECTIVE USE

**1 trial**
**N=337 ITT**

Phase 2 trial

# DECOY TEST

**N=72,671 decoy subjects**

Hopkins SC, Tomioka S, Szabo ST, Koblan KS. *A clinical trial inclusion criteria to enrich for patients presenting with canonical symptom structure in bipolar depression*. In submission 2024

# BIPOLAR DATASET

**ANOMALOUS SYMPTOMS**

**5 legacy trials**
**N=2,026 subjects**

**CANONICAL SYMPTOMS**

# PROSPECTIVE USE

**1 trial**
**N=129 subjects, pre-randomization data**

Phase 3 trial

Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs
Guidance for Industry

**Enrichment Strategies for Clinical Trials to Support Determination of Effectiveness of Human Drugs and Biological Products**
**Guidance for Industry**

# RETROSPECTIVE USE

**1 trial**
**N=337 ITT**

Phase 2 trial

# DECOY TEST

**N=72,671 decoy subjects**

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# BIPOLAR DATASET

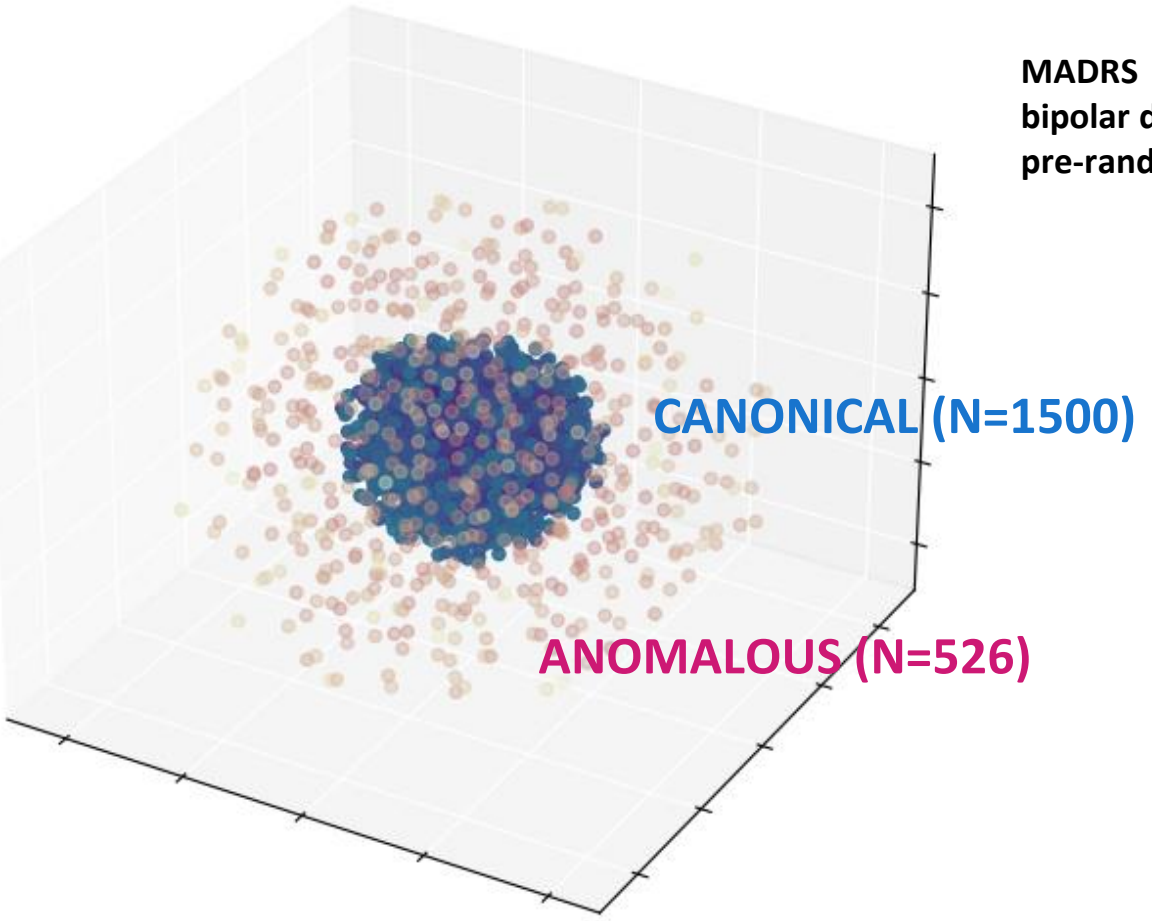
**5 legacy trials**
**N=2,026 subjects**

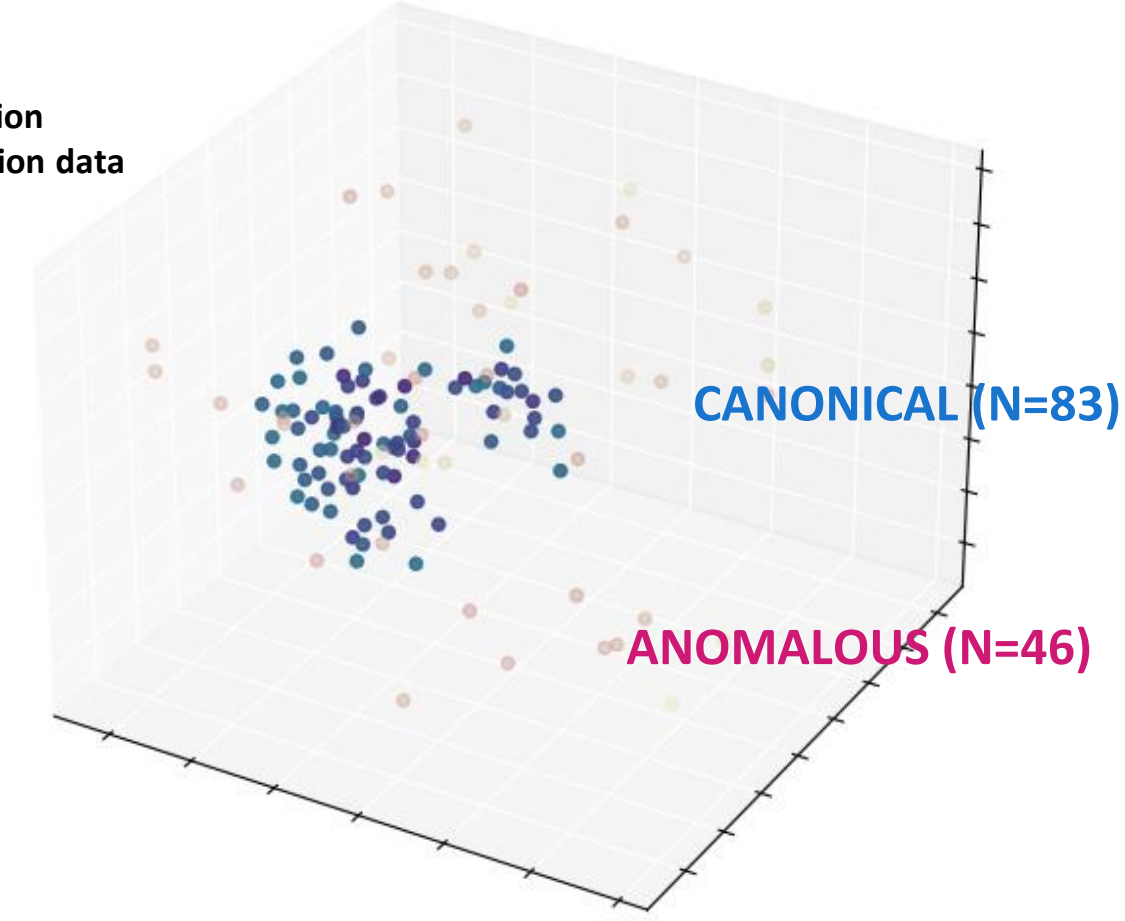
# PROSPECTIVE USE

**1 trial**
**N=129 subjects, pre-randomization data**

Dimension Reduction– each subject's 145-dimension vector is represented in 3-dimensions by t-SNE analysis

**MADRS**
**bipolar depression**
**pre-randomization data**

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# BIPOLAR DATASET

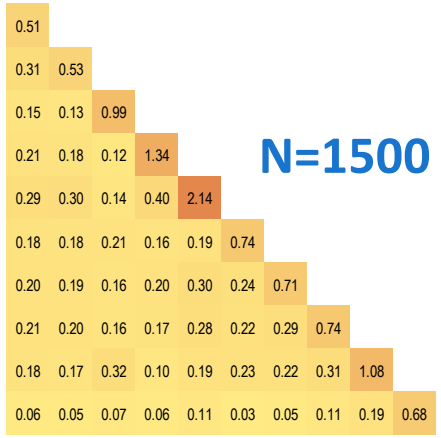
**5 legacy trials**
**N=2,026 subjects**

# PROSPECTIVE USE

**1 trial**
**N=129 subjects, pre-randomization data**

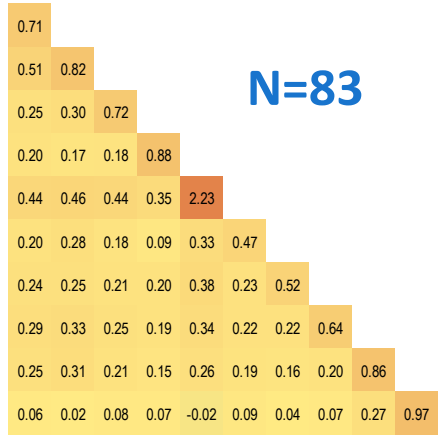
Variance-Covariance Matrix

## CANONICAL



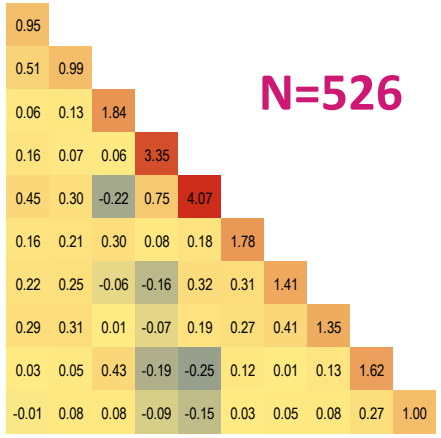

**N=1500**

**MADRS**
**bipolar depression**
**pre-randomization data**

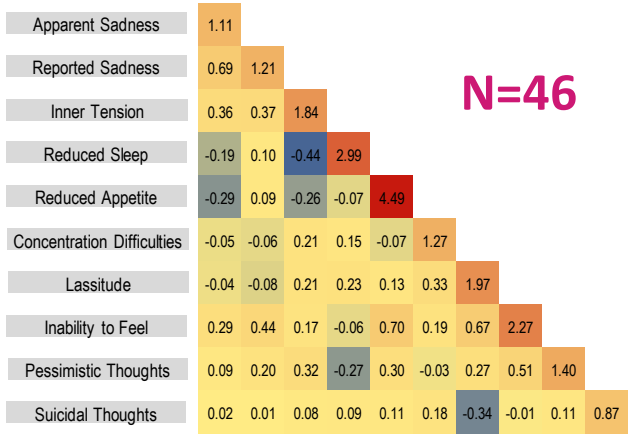



**N=83**

## ANOMALOUS




**N=526**




**N=46**


Hopkins SC, Tomioka S, Szabo ST, Koblan KS. *A clinical trial inclusion criteria to enrich for patients presenting with canonical symptom structure in bipolar depression*. In submission 2024

# BIPOLAR DATASET

**5 legacy trials**
**N=2,026 subjects**

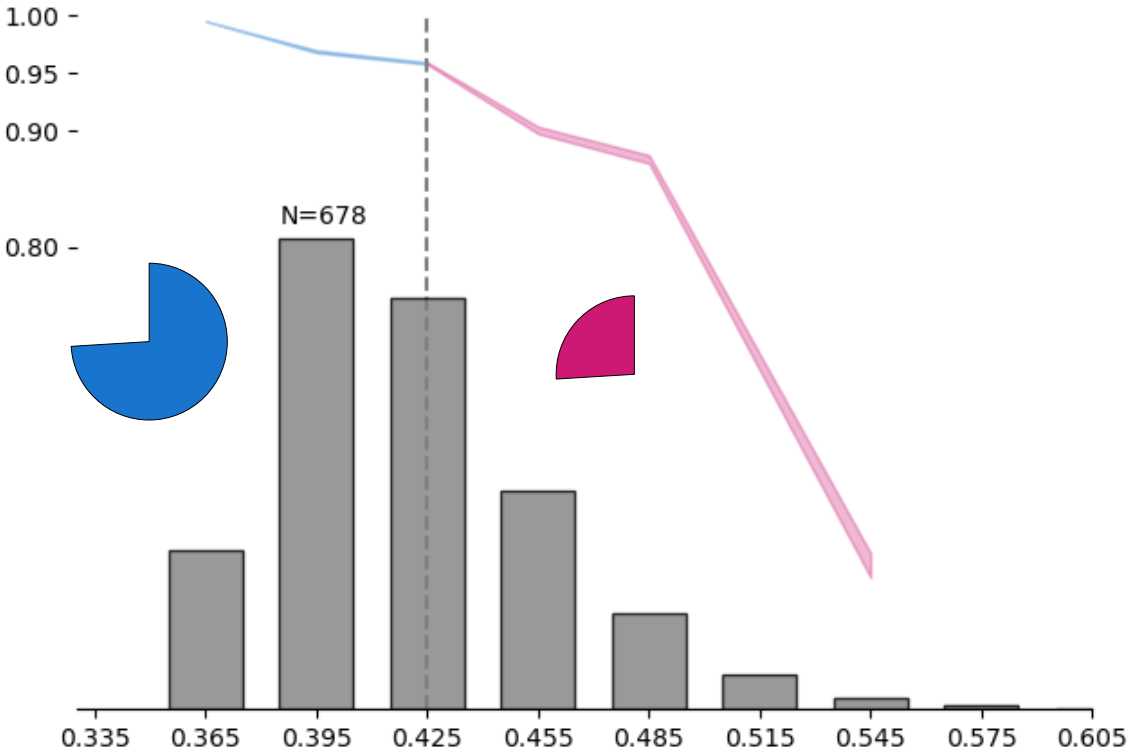
**MADRS**
**bipolar depression**
**pre-randomization data**

# PROSPECTIVE USE

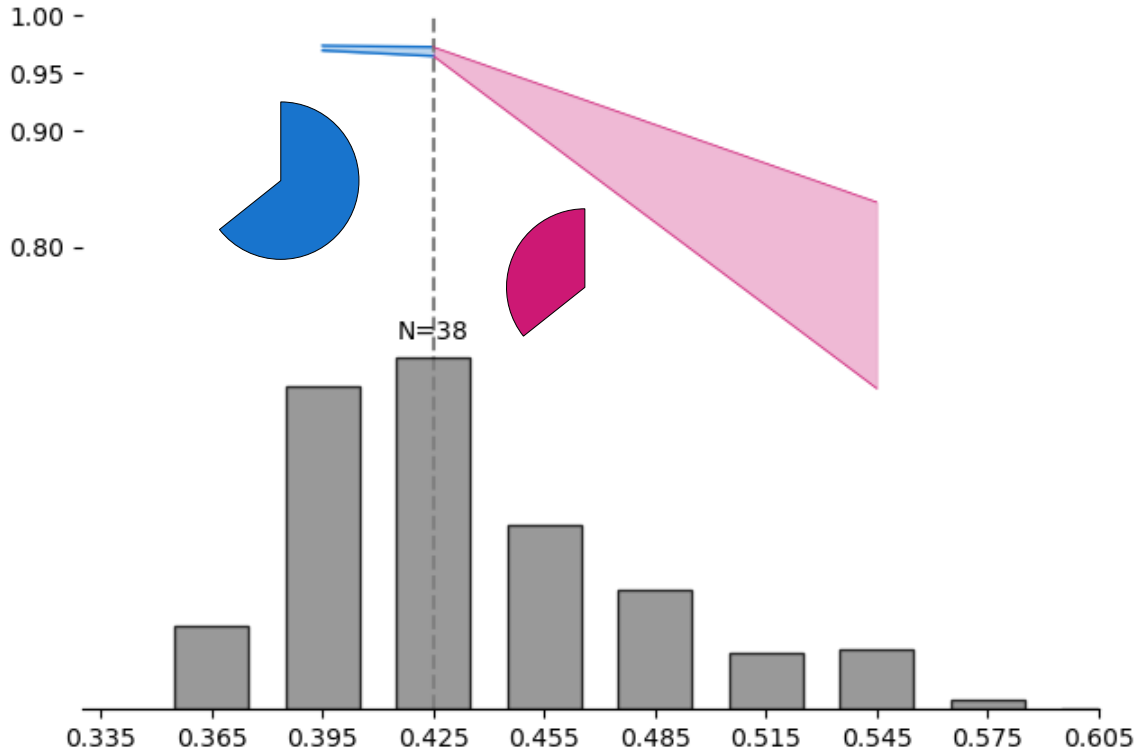
**1 trial**
**N=129 subjects, pre-randomization data**

Confirmatory Factor Analysis –goodness of fit and stability to 4-factor model

Comparative Fit Index (CFI)




Anomaly Score




Anomaly Score



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# BIPOLAR DATASET

**5 legacy trials**
**N=2,026 subjects**

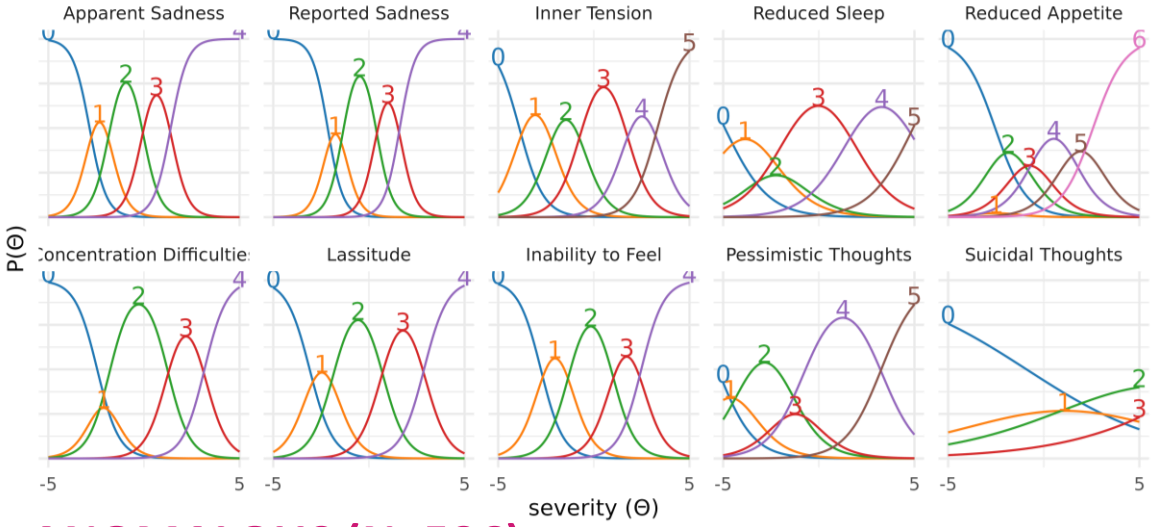
**MADRS**
**bipolar depression**
**pre-randomization data**

# PROSPECTIVE USE

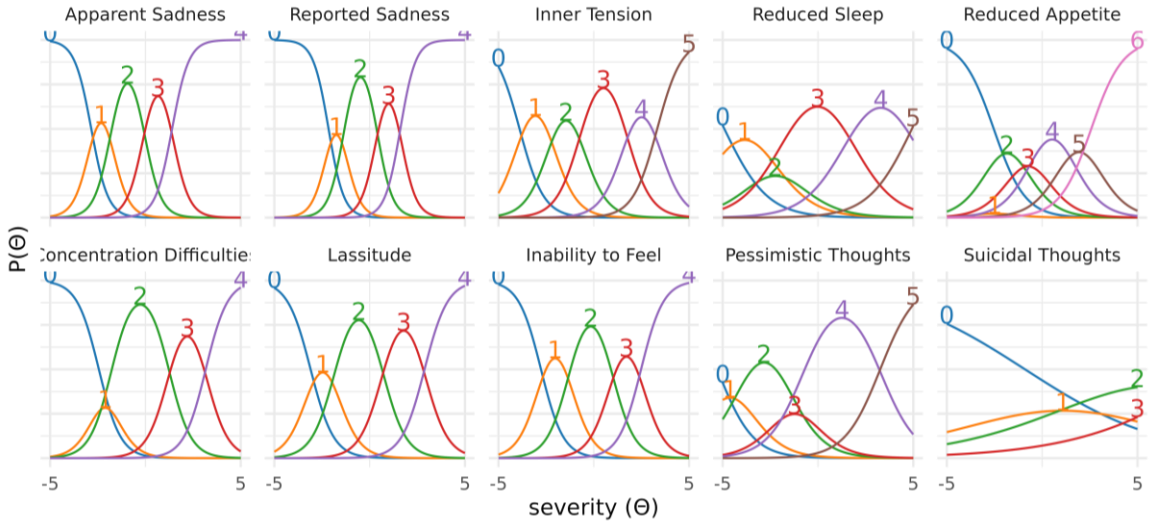
**1 trial**
**N=129 subjects, pre-randomization data**

Item Response Theory – curves are graded model outputs, where distinct peaks at different severity levels indicate each symptoms likelihood of being reported (y-axis) increases along defined gradations in overall depression severity (x-axis)

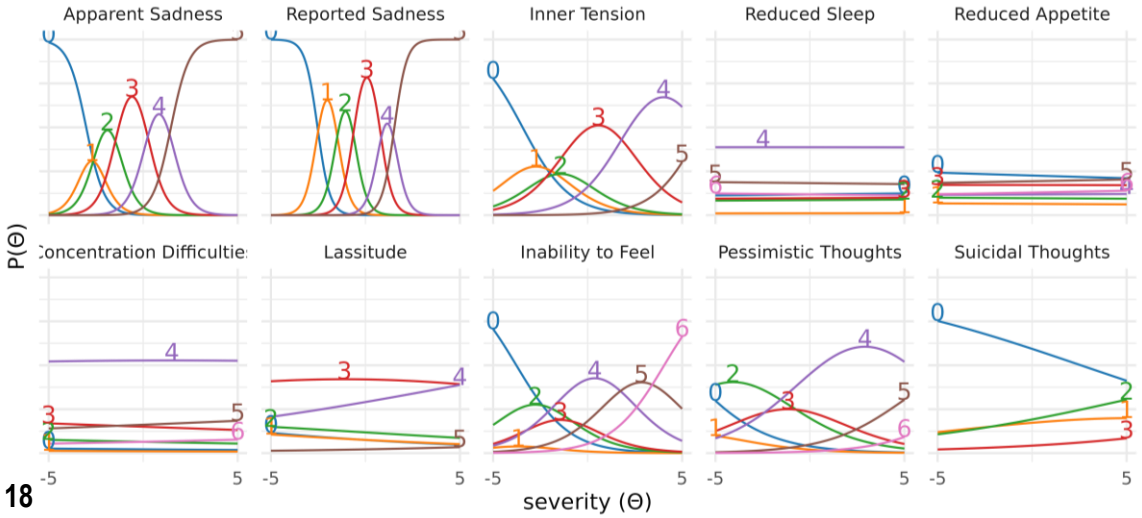
## CANONICAL (N=1500)



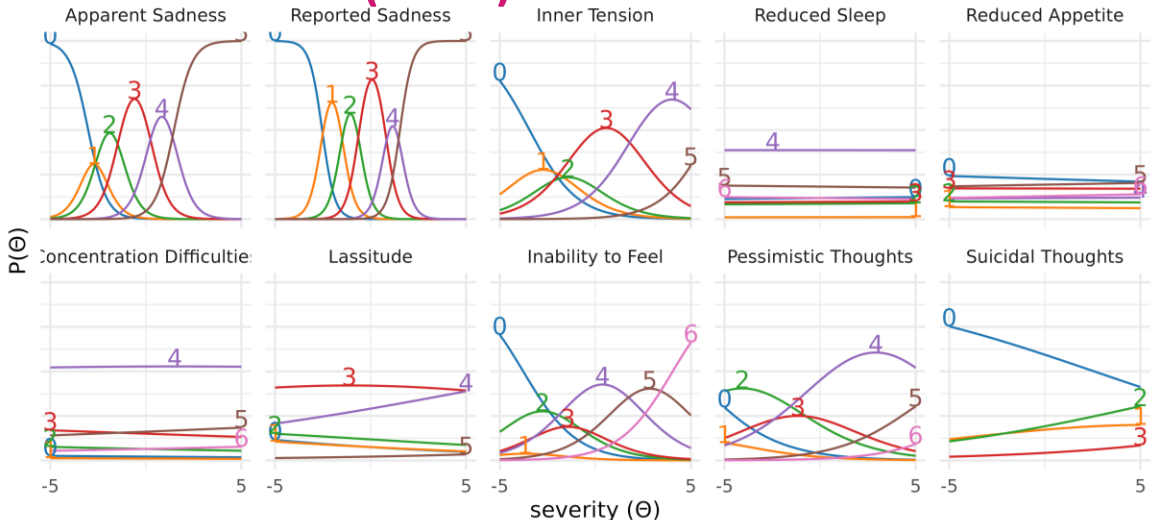

## CANONICAL (N=83)




## ANOMALOUS (N=526)




## ANOMALOUS (N=46)



# BIPOLAR DATASET

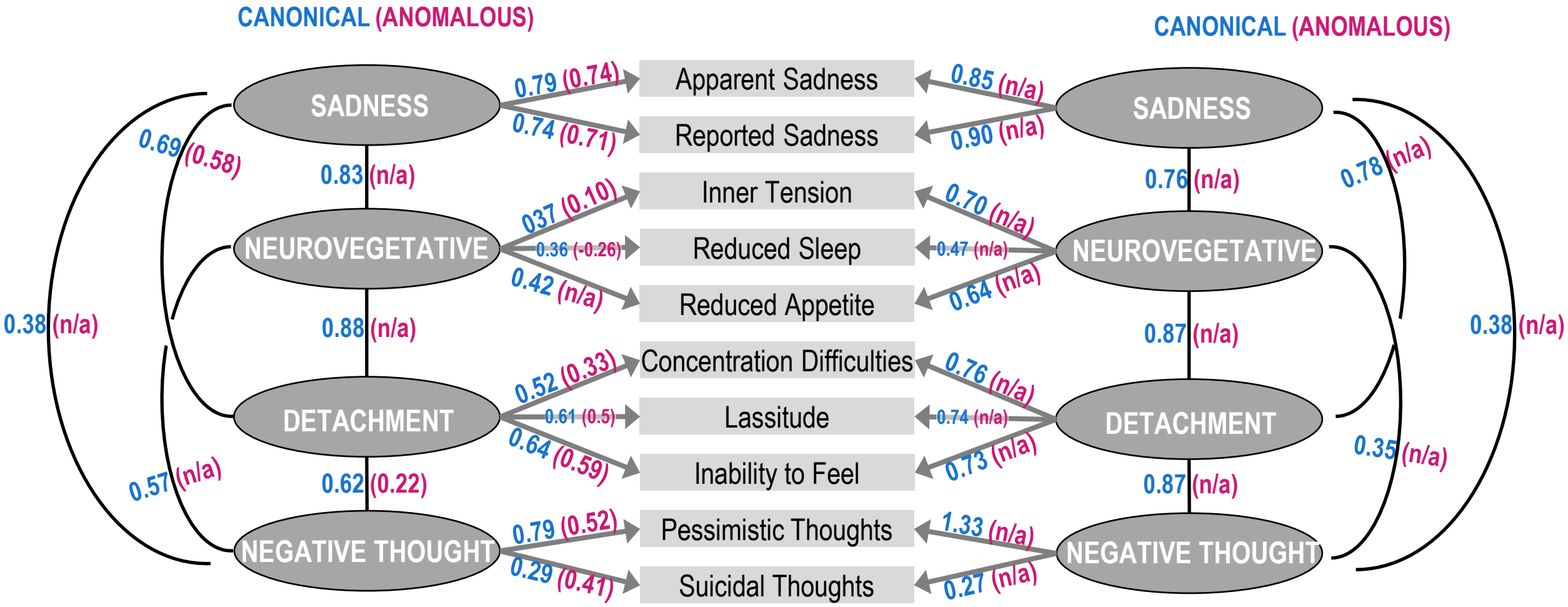
**5 legacy trials**
**N=2,026 subjects**

**MADRS**
**bipolar depression**
**pre-randomization data**

# PROSPECTIVE USE

**1 trial**
**N=129 subjects, pre-randomization data**

Confirmatory Factor Analysis– path diagrams with arrows label the significant factor loadings and black lines label significant model correlations



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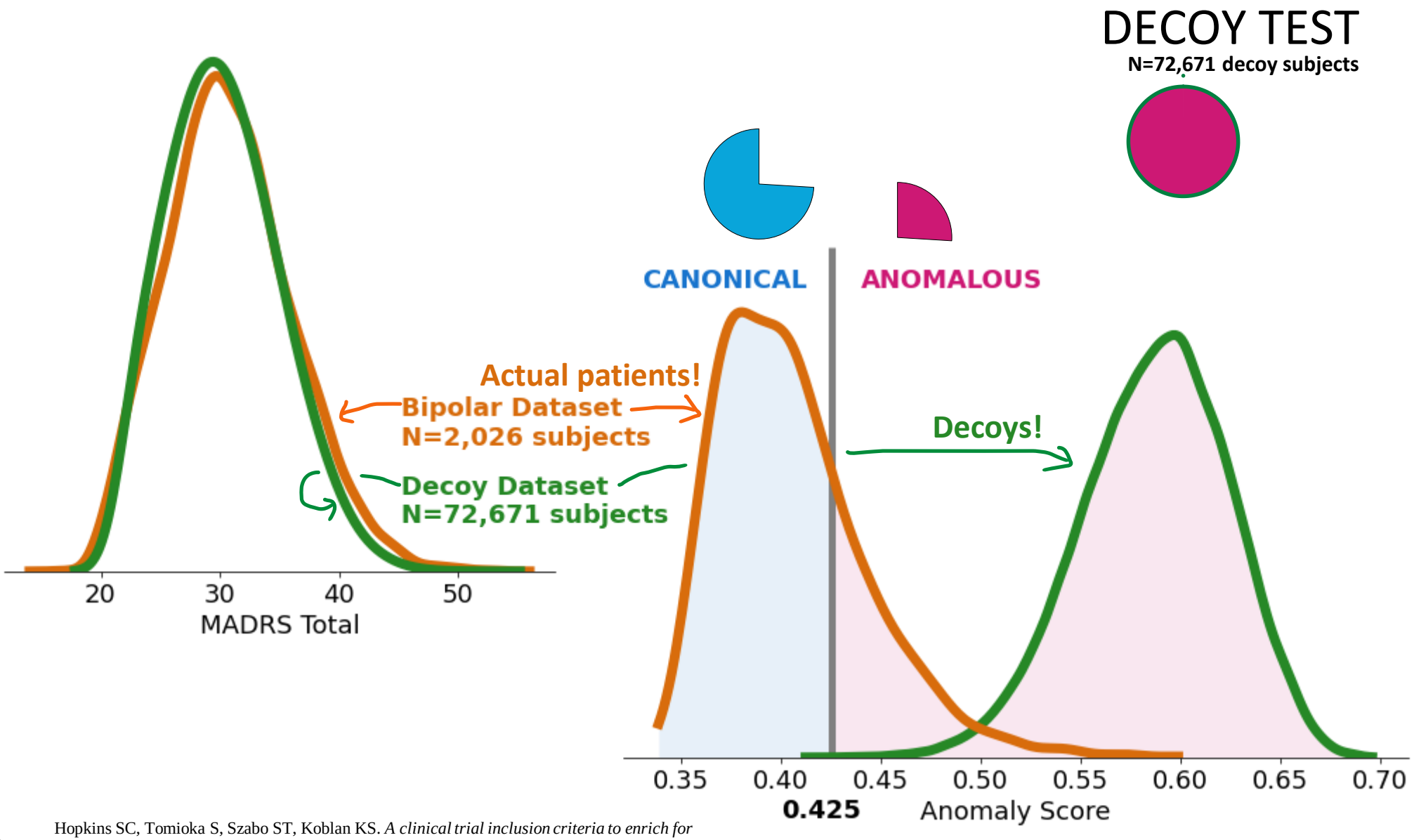
# Anomaly Score detects DECOY subjects

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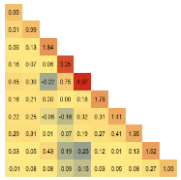
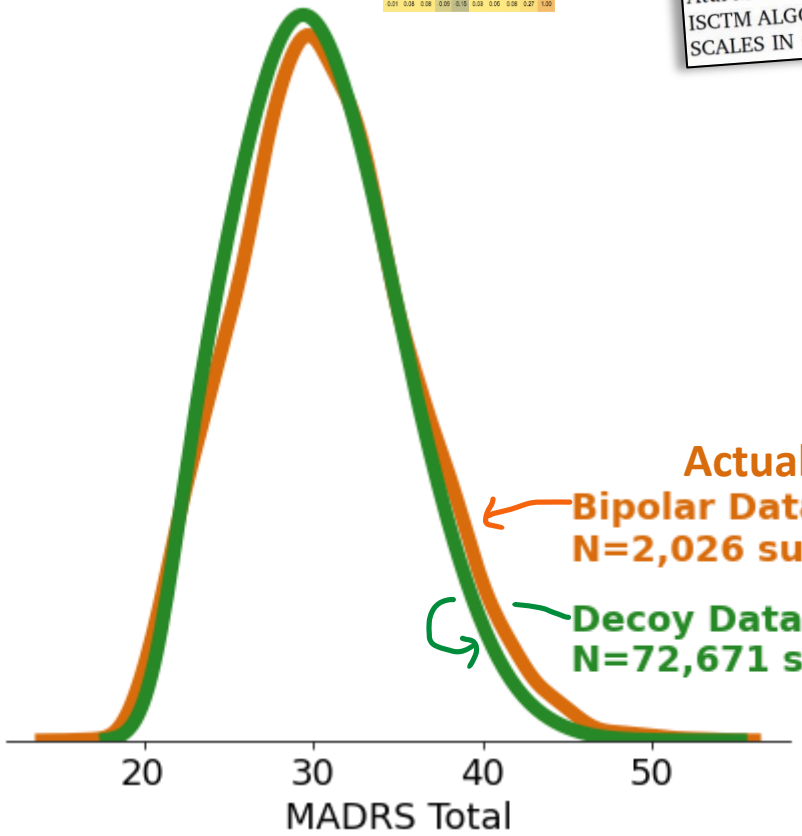
# Anomaly Score versus ISCTM expert working group

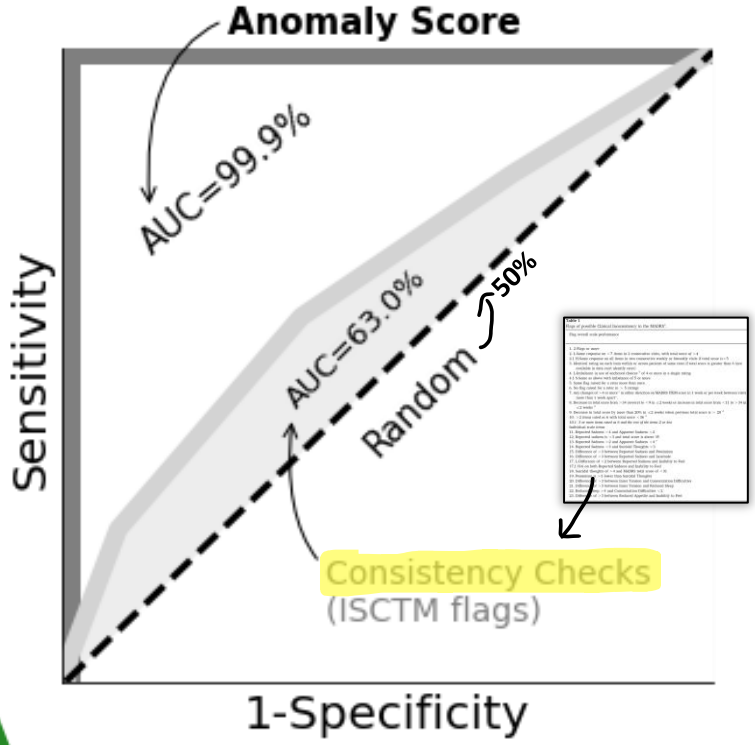


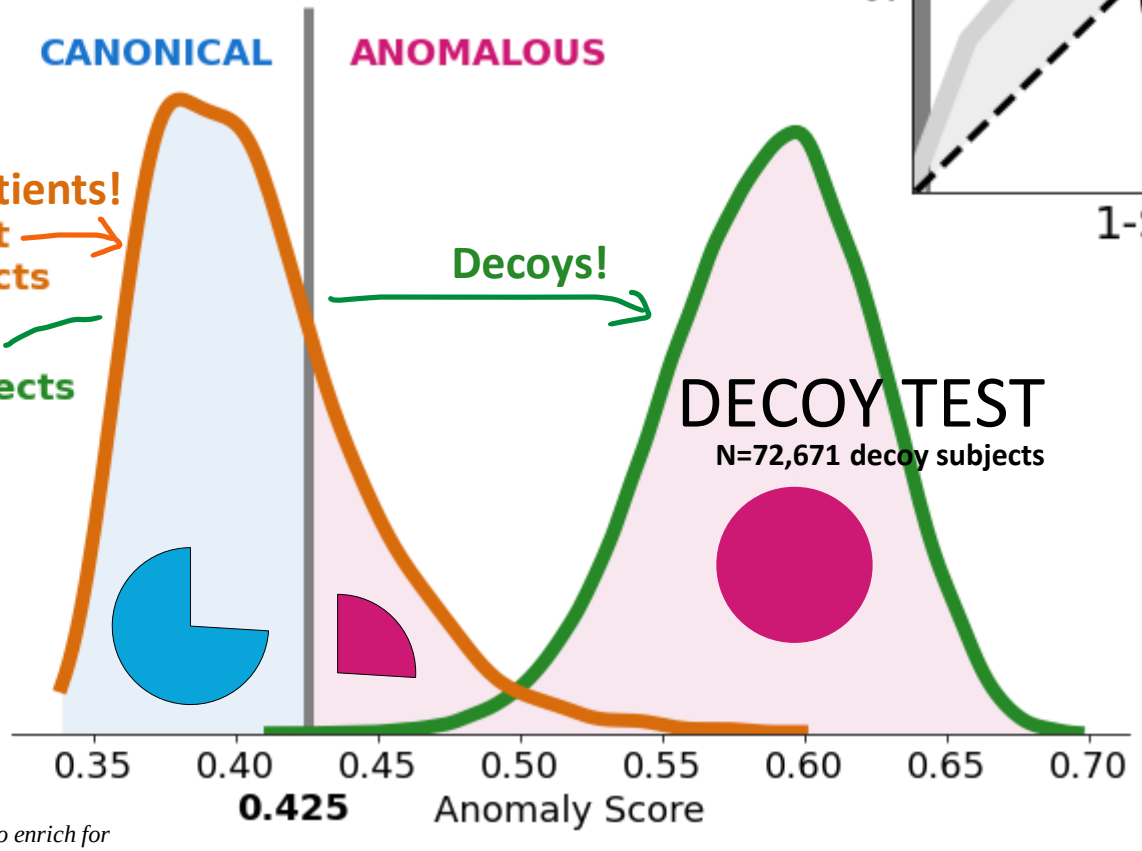
vs.

Consistency checks to improve measurement with the Montgomery-Asberg Depression Rating Scale (MADRS)

Jonathan Rabinowitz[a,1,*], Nina R Schooler[b,1], Brianne Brown[c,1], Mads Dalsgaard[d], Nina Engelhardt[e], Gretchen Friedberger[f], Bruce J Kinon[g], Daniel Lee[h], Felice Ockun[i], Atul Mahableshwarkar[j], Joyce Tsai[k], Janet B.W. Williams[l], Colin Sauder[m,n], Christian Yavorsky[o], ISCTM ALGORITHMS/FLAGS TO IDENTIFY CLINICAL INCONSISTENCY IN THE USE OF RATING SCALES IN CNS RCTs working group members

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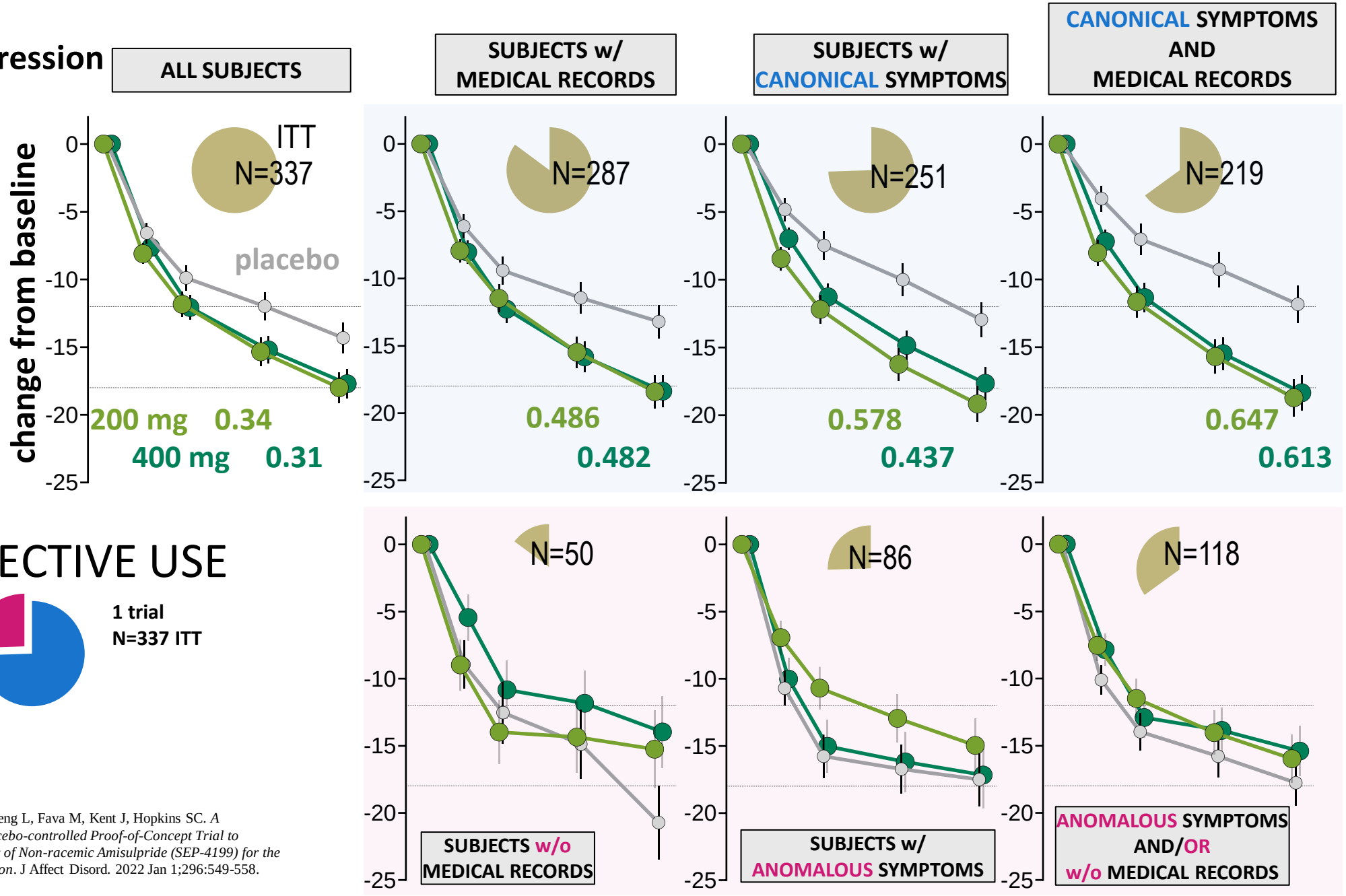
# MADRS
# bipolar depression




Loebel A, Koblan KS, Tsai J, Deng L, Fava M, Kent J, Hopkins SC. *A Randomized, Double-blind, Placebo-controlled Proof-of-Concept Trial to Evaluate the Efficacy and Safety of Non-racemic Amisulpride (SEP-4199) for the Treatment of Bipolar I Depression*. J Affect Disord. 2022 Jan 1;296:549-558.

Hopkins SC, Tomioka S, Szabo ST, Koblan KS. *A clinical trial inclusion criteria to enrich for patients presenting with canonical symptom structure in bipolar depression*. In submission 2024

# Let’s use structure to measure severity better

**The Positive and Negative Syndrome Scale (PANSS) for Schizophrenia**

***by Stanley R. Kay, Abraham Fiszbein, and Lewis A. Opler***


**Abstract**

The variable results of positive-negative research with schizophrenics underscore the importance of well-characterized, standardized measurement techniques. We report on the development and initial standardization of the Positive and Negative Syndrome Scale (PANSS) for typological and dimensional assessment. Based on two established psychiatric rating systems, the 30-item PANSS was conceived as an operationalized, drug-sensitive instrument that provides balanced representation of positive and negative symptoms and gauges their relationship to one another and to global psychopathology. It thus constitutes four scales measuring positive and negative syndromes, their differential, and general severity of illness. Study of 101 schizophrenics found the four scales to be normally distributed and supported their reliability and stability. Positive and negative scores were inversely correlated once their common association with general psychopathology was extracted, suggesting that they represent mutually exclusive constructs. Review of five studies involving the PANSS provided evidence of its criterion-related validity with antecedent, genealogical, and concurrent measures, its predictive validity, its drug sensitivity, and its utility for both typological and dimensional assessment.

Emil Kraepelin

Eugen Bleuler

| Typological | Dimensional |
|---|---|
| classify<br>DSM, SCID | measure<br>PANSS, MADRS |
| Structure<br>pattern recognition | Severity<br>common symptoms |
| Variance-Covariance Matrix | Total Score |