Precision Psychiatry:
Biomarkers for major depression

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Mental Health and Wellness

Disclosures

- Advisory board member for One Mind Psyberguide
- Advisory board member for Laureate Institute for Brain Research
- Patents
  - Systems and methods for detecting complex networks in MRI image data.
    US Patent App. 16/921,388 of July 6, 2020.
    US Patent App. 16/368,774 of March 28, 2019; Patent No. US 10,702,232 B2 of July 7, 2020.
    US Patent App. 15/997,631 of June 4, 2018; Patent No. US 10,285,658.
    US Patent App. 15/830,338 of November 21, 2017; Patent No. US 10,034,645.

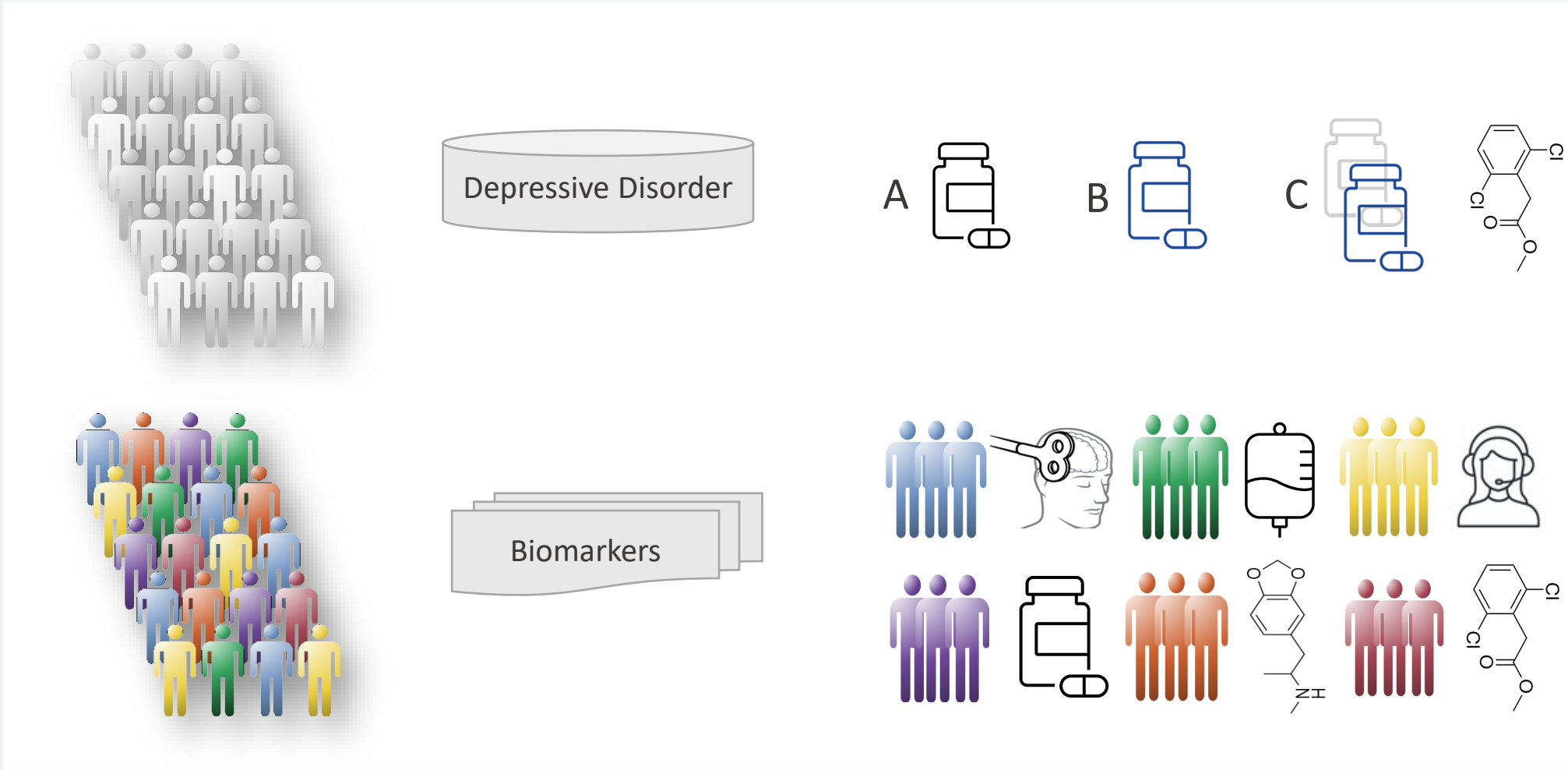
How do we advance precision medicine in depression using multimodal biomarkers?

The **heterogeneity** of clinical depression is a major **challenge and opportunity**

- 1. Depressed mood
- 2. Anhedonia
- 3. Feeling worthless and guilty
- 4. Cognitive problems
- 5. Weight changes
- 6. Appetite changes
- 7. Sleep problems
- 8. Psychomotor changes
- 9. Suicidal thinking

- Must cause significant impairment in **important areas of functioning**

Treatment of major depression proceeds by trial-and-error, and we lack **biomarkers for** more **precise** and **personalized treatment selection**



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One way to make progress is to focus on **biomarkers for subtypes** underserved by current treatment approaches

- I aim to illustrate opportunities, challenges, successes and lessons learned through an illustrative example, the **cognitive subtype**
- Cognitive problems are a major contributor to disability and suicidality and do not respond to current antidepressants

- 1. Depressed mood
- 2. Loss of interest and pleasure
- 3. Feeling worthless and guilty
- **4. Cognitive problems**
- 5. Weight changes
- 6. Appetite changes
- 7. Sleep problems
- 8. Psychomotor changes
- 9. Suicidal thinking

- 1. Depressed mood
- 2. **Anhedonia**
- 3. Feeling worthless and guilty
- 4. Cognitive problems
- 5. Weight changes
- 6. Appetite changes
- 7. Sleep problems
- 8. Psychomotor changes
- 9. Suicidal thinking

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Lam et al. Can J Psychiatry, 2014; Schussler-Fiorenza Rose et al. J Psychiatry Res, 2021.

Multimodal data from the international biomarker trial, iSPOT-D: n=1008

Williams *et al. Trials* 2011, **12**:4
http://www.trialsjournal.com/content/12/1/4

TRIALS

STUDY PROTOCOL **Open Access**

International Study to Predict Optimized Treatment for Depression (iSPOT-D), a randomized clinical trial: rationale and protocol

Leanne M Williams[1,2*], A John Rush[3], Stephen H Koslow[1,4], Stephen R Wisniewski[5], Nicholas J Cooper[6], Charles B Nemeroff[7], Alan F Schatzberg[8], Evian Gordon[2,6]

1.

- Symptoms
- Daily function
- Brain circuits - fMRI
- Behavior
- Genes

2.

A B C

3.

Symptom outcomes
Functional outcomes

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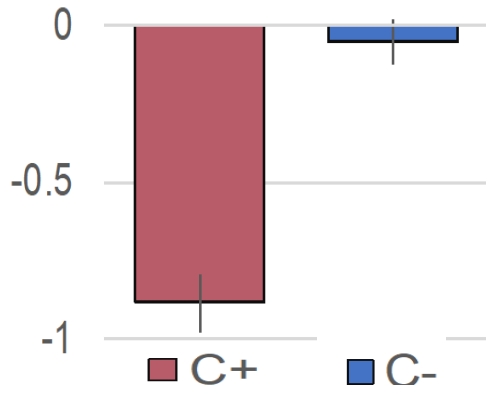
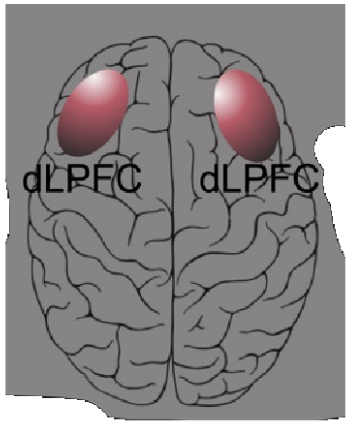
Williams et al. Trials, 2011; Grieve, et al. Trials, 2013

Cognitive biomarker illustration: Identifying a C+ subgroup

1. Behavior
27% of patients were C+.
Marked cognitive impairment.



2. Brain circuits
C+ had reduced cognitive control circuit activity.



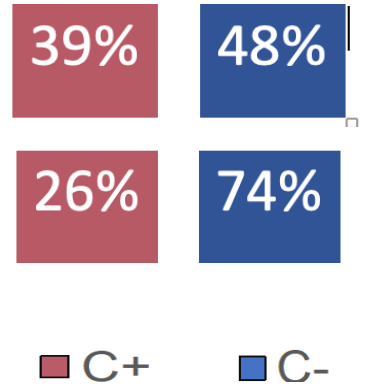
3. Symptoms
C+ had specific symptoms.

Trouble concentrating

4. Function
C+ had more disability.

Function < 25th percentile

5. Remission rates
C+ poorer outcomes.



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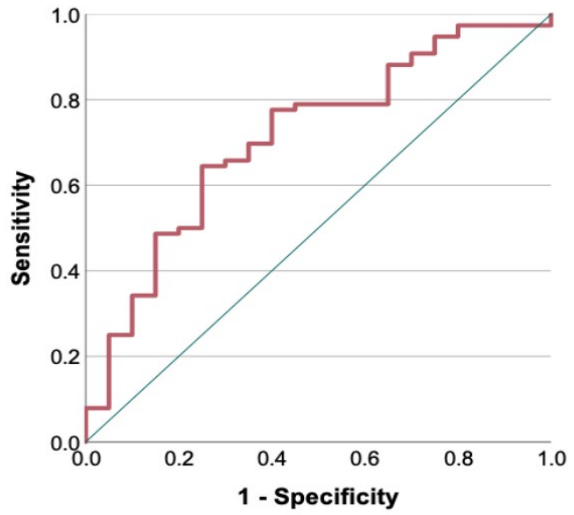
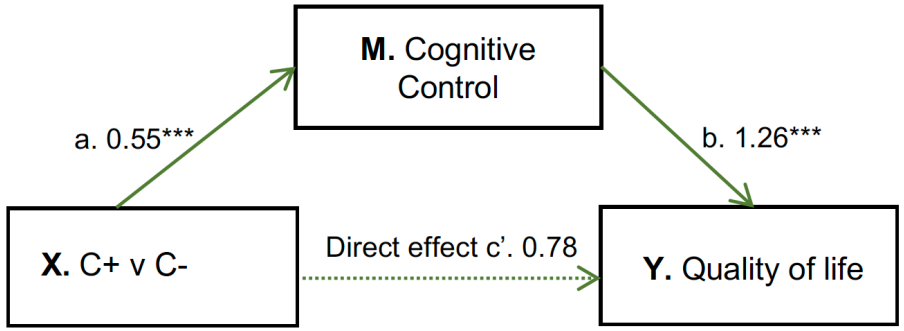
Hack, Tozzi et al. in submission

Cognitive biomarker illustration: Validating a C+ subgroup

Cross-validated accuracy for cognitive biomarker is 79%



Extent of change in cognition mediated symptom and function outcomes



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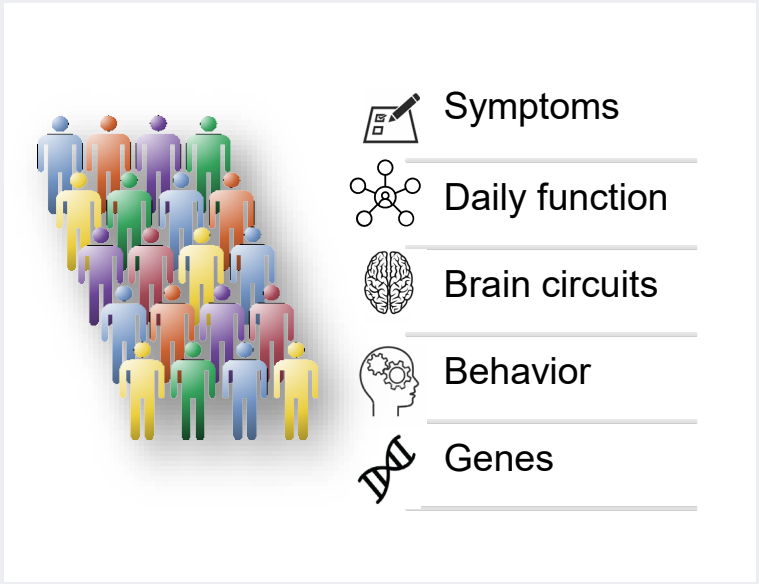
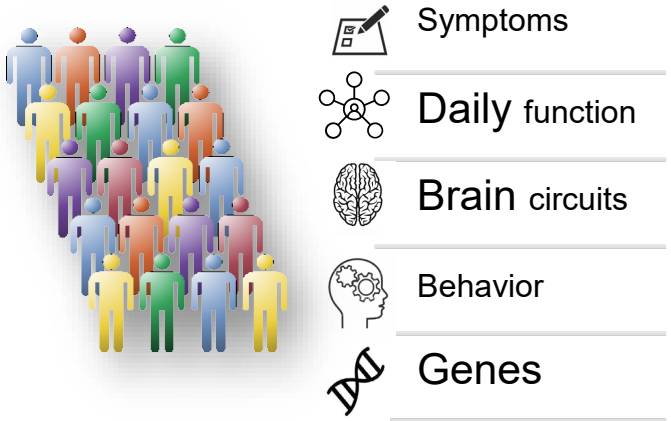
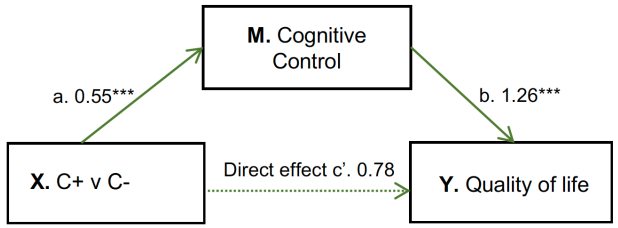
Hack, Tozzi et al. in submission

#1 Lesson learned: Symptoms alone are insufficient to identify subgroups with precision. We need biomarkers that connect brain, behavior and experience.



#2 Lesson learned: We need functional as well as symptom endpoints





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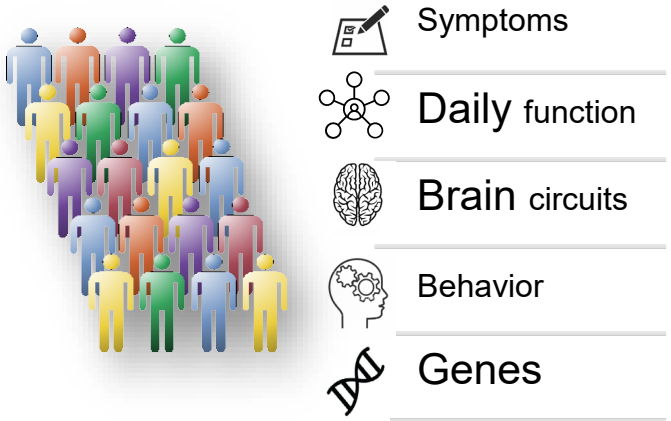
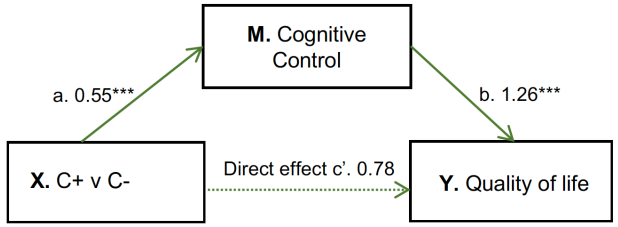
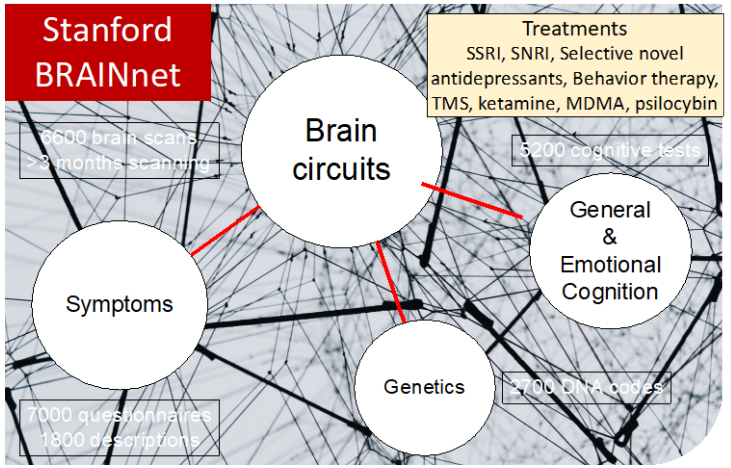
#3 Lesson learned: We need standardized measures.







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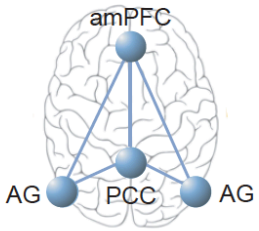
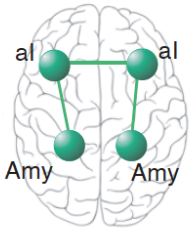
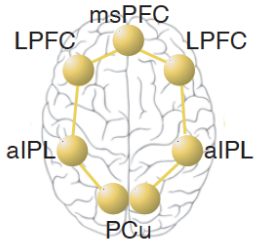
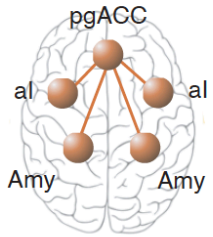
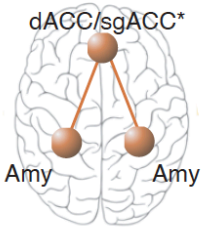
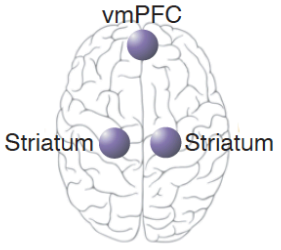
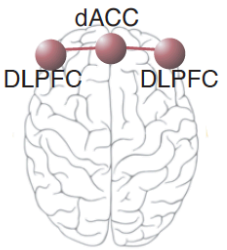
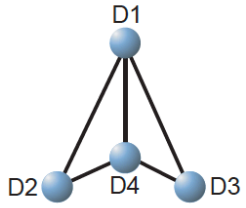
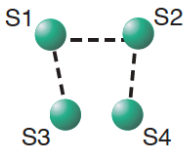
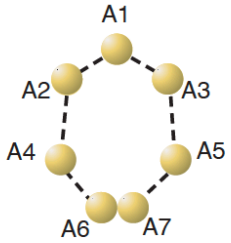
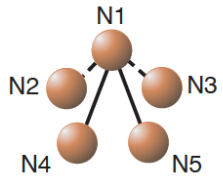
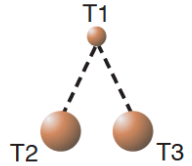
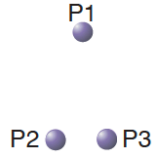
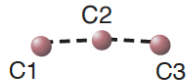
To advance precision medicine, how can we move beyond group averages to **subject-level** biomarkers and targeted treatments?

Illustration of a subject-level circuit quantification platform for functional MRI

Circuit	Default Mode	Salience	Attention	Negative Affect - Sad	Negative Affect - Threat	Positive Affect	Cognitive Control
Standardizing Regions & Connections							
Quantifying Regional Circuit Clinical Scores							
Computing Global Circuit Clinical Scores	$(C_{D1,D2} + C_{D1,D3} + C_{D1,D4} + C_{D2,D4} + C_{D3,D4})/5$	$(-C_{S1,S3} - C_{S2,S4} - C_{S1,S2})/3$	$(-C_{A1,A2} - C_{A1,A3} - C_{A2,A4} - C_{A3,A5} - C_{A4,A6} - C_{A5,A7})/6$	$(A_{N1} + A_{N2} + A_{N3} + A_{N4} + A_{N5} - C_{N1,N2} - C_{N1,N3} + C_{N1,N4} + C_{N1,N5})/9$	$(-A_{T1} + A_{T2} + A_{T3} - C_{T1,T2} - C_{T1,T3})/5$	$(-A_{P1} - A_{P2} - A_{P3})/3$	$(-A_{C1} - A_{C2} - A_{C3} - C_{C1,C2} - C_{C2,C3})/5$

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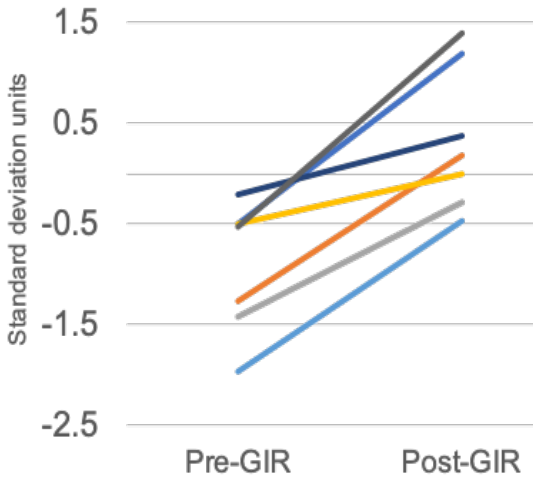
Goldstein-Piekarski et al. Biological Psychiatry, 2022

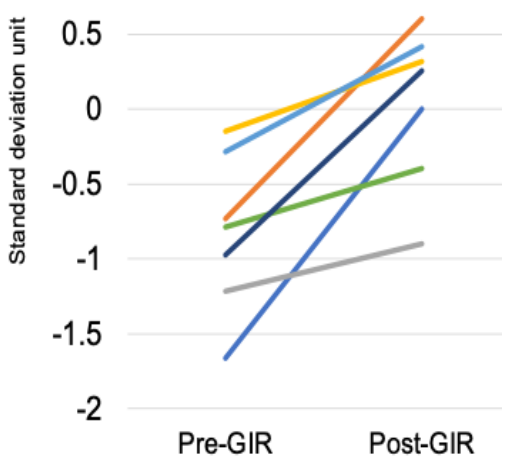
Using multimodal biomarkers to **target subtypes with selective interventions**:

Targeting the cognitive subtype with alpha 2a receptor mechanism of immediate release guanfacine (GIR)

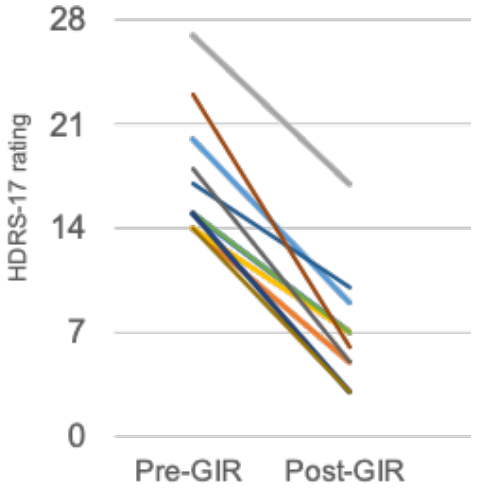
1. Behavior
GIR improved cognition in C+



2. Brain circuits
GIR improved cognitive control circuit activity in C+



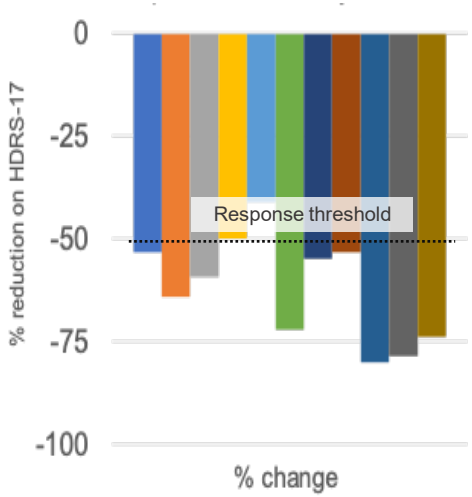
3. Symptoms
GIR improved symptoms in C+



4. Function
GIR improved function in C+

20%

5. Treatment response
GIR produced high rates of response in C+



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Williams, Hack et al. in prep

Using multimodal biomarkers to **target subtypes with selective treatments**

Targeting anhedonia prospectively with brain-behavior biomarkers and selective interventions

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Pizzagalli circuit-behavior https://www.statnews.com/2023/01/24/predictive-biomarkers-antidepressants-depression-ssri/

How do we advance precision medicine in depression using multimodal biomarkers?

By disentangling heterogeneity, connecting brain-behavior-symptom units of analysis, including functional endpoints, enabling standardization and subject level quantification, and enriching samples to target more selective interventions

I welcome discussion in the panel session

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