

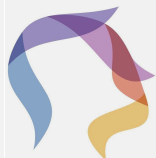
# Personalized Biomarkers for Treatment Selection

**Leanne Williams, PhD**

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Director of Center for Precision Mental Health and Wellness at Stanford

Director of Precision Medicine Core, MIRECC VA Palo Alto



**PMHW**

Stanford Center for Precision Mental  
Health and Wellness



**Stanford**  
**MEDICINE**



**MIRECC**

Mental Illness Research, Education and Clinical  
Center, VA Palo Alto

"We can envision a future in which clinical decision-making is complemented by tools and measures that help to diagnose individual clinical biotype profiles and tailor treatments to these profiles."



**PSYCHIATRIC NEWS**  
*Special Report*

## Precision Psychiatry: Are We Getting Closer?

*We are witnessing the emergence of precision medicine for psychiatry. This article discusses precision psychiatry as an integrative approach, one that pulls together the scientific foundation of the discipline and recent neuroscientific, technological, and computational advances and directs them at closing the gap between discovery and clinical translation. LEANNE M. WILLIAMS, PH.D.*

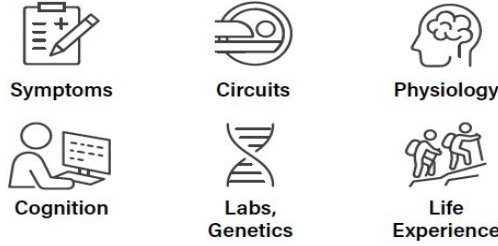


Leanne M. Williams, Ph.D., is a professor and associate chair of psychiatry and behavioral sciences at Stanford University School of Medicine. She directs the Stanford Center for Precision Mental Health and Wellness and the VA MIRECC Precision Medicine Core. She is the co-editor of *Precision Psychiatry: Using*

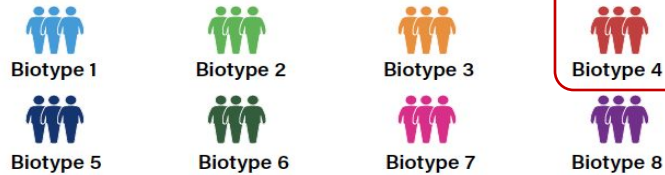
# Heterogenous Disorders



## Integrate Sources of Data



## New Stratifications: Clinical Biotypes



Cognitive type

## Personalized Treatment Options



# Diagnostic Criteria for Depressive Disorder



Low mood



Loss of interest, pleasure



Weight change



Sleep problems



Agitation or slowing



Fatigue



Problems concentrating,  
making decisions



Feeling worthless, guilty



Suicidal thoughts



## Why are these cognitive problems important for improving depression?

- They are a big contributor to poor social and occupational function
- They are not alleviated by current antidepressants
- They contribute to the recurrence of episodes of depression
- They increase risk of suicide
- They occur in younger people with depression, not just in later life

**Targeting improvement of cognitive impairments is an important goal for treatment for people to return to full function**

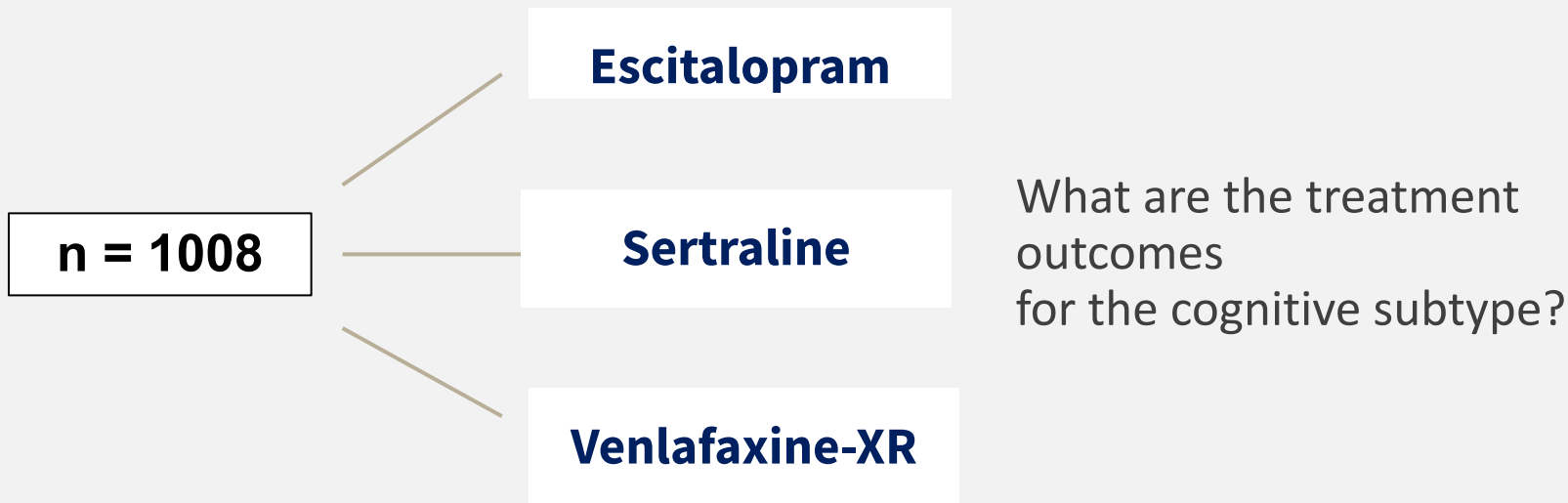
**STUDY PROTOCOL**

**Open Access**

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

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

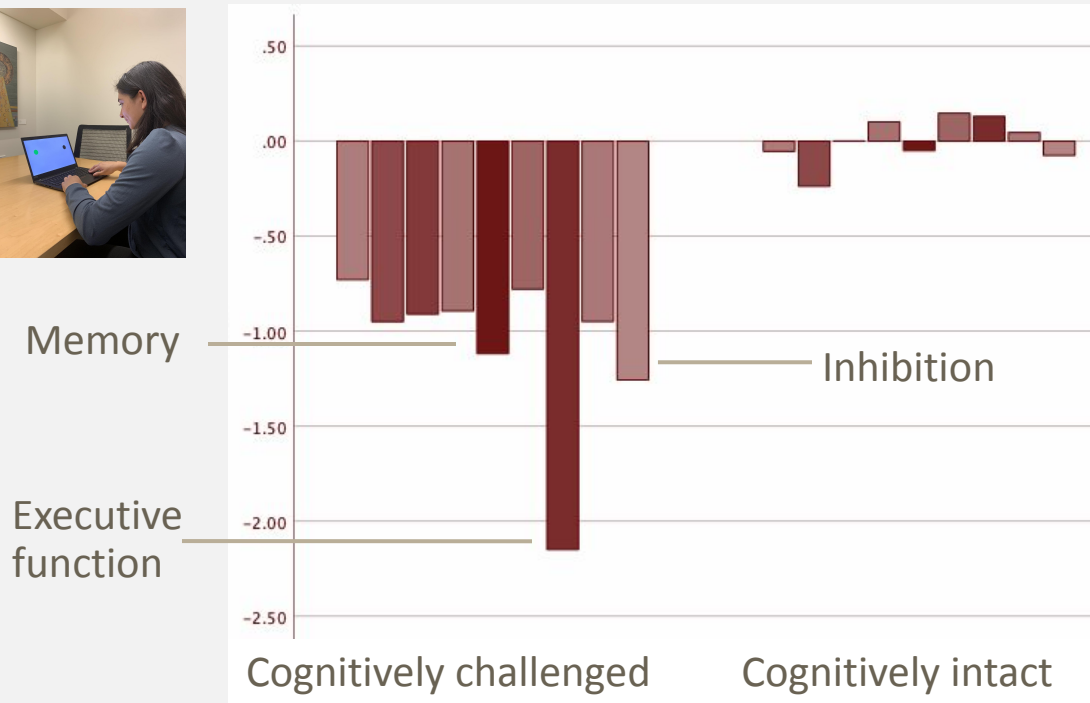








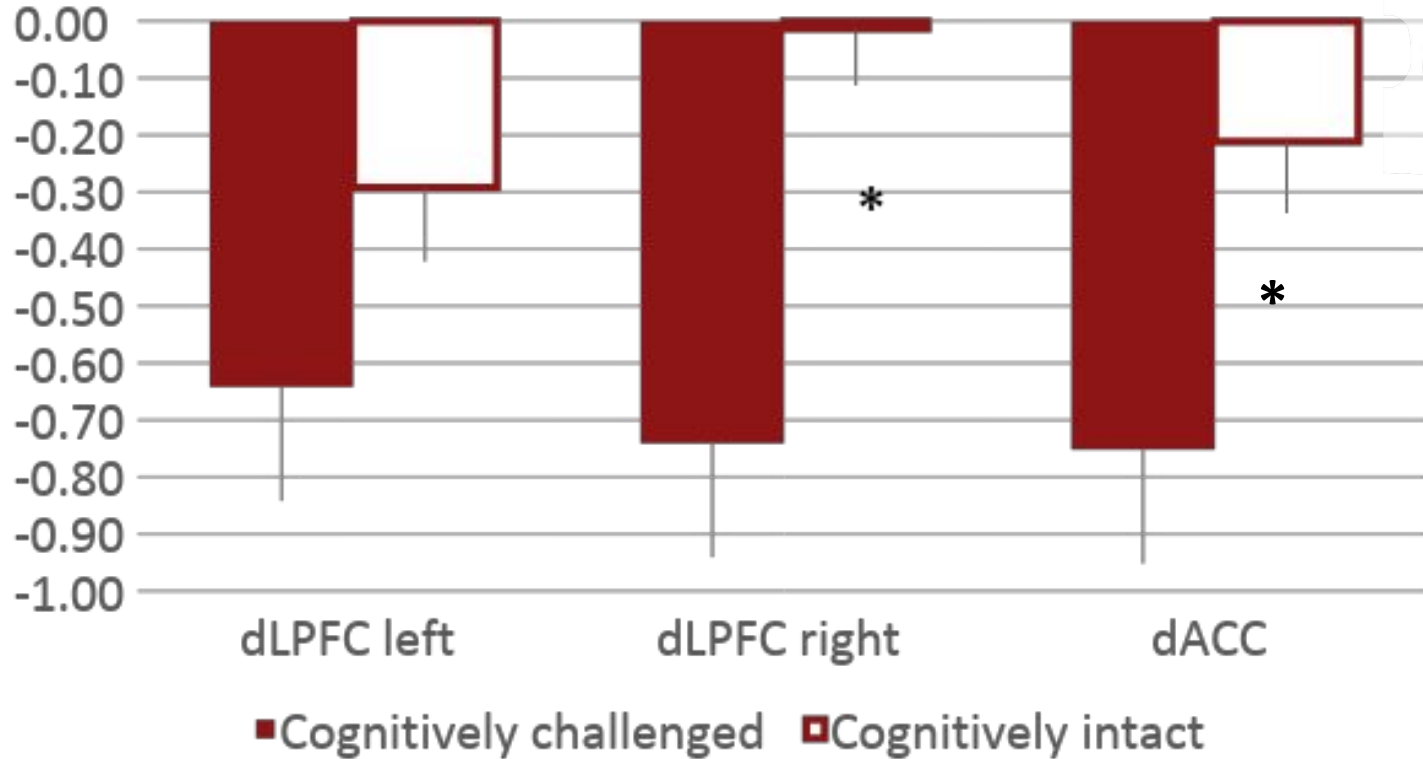
# Among major depressive disorder, **22% are cognitively challenged**





| Condition                                       | Intrinsic   | Intrinsic  | Intrinsic  | Evoked by Sad Stimuli  | Evoked by Threat Stimuli  | Evoked by Happy Stimuli                 | Evoked by NoGo Stimuli  |
|---|---|--|--|--|---|---|---|
| <b>Circuit</b>                                  | Default Mode  | Salience   | Attention  | Negative Affect - Sad  | Negative Affect - Threat  | Positive Affect                         | Cognitive Control   |
| <b>Identified Key Regions &amp; Connections</b> |   |  |  |  |   |   |   |
| <b>Quantifying Hypothesized Dysfunction</b>     |   |  |  |  |   |   |   |
| <b>Circuit Dysfunction Score</b>                | $\frac{(C_{D1,D2} + C_{D1,D3} + C_{D1,D4} + C_{D2,D4} + C_{D3,D4})}{5}$ | $\frac{(-C_{S1,S3} - C_{S2,S4} - C_{S1,S2})}{3}$ | $\frac{(-C_{A1,A4} - C_{A1,A5} - C_{A2,A4} - C_{A3,A5} - C_{A4,A6} - C_{A5,A7})}{6}$ | $\frac{(A_{N1} + A_{N2} + A_{N3} + A_{N4} + A_{N5} - C_{N1,N2} - C_{N1,N3} + C_{N1,N4} + C_{N1,N5})}{9}$ | $\frac{(-A_{T1} + A_{T2} + A_{T3} - C_{T1,T2} - C_{T1,T3})}{5}$ | $\frac{(-A_{P1} - A_{P2} - A_{P3})}{3}$ | $\frac{(-A_{C1} - A_{C2} - A_{C3} - C_{C1,C2} - C_{C2,C3})}{5}$ |

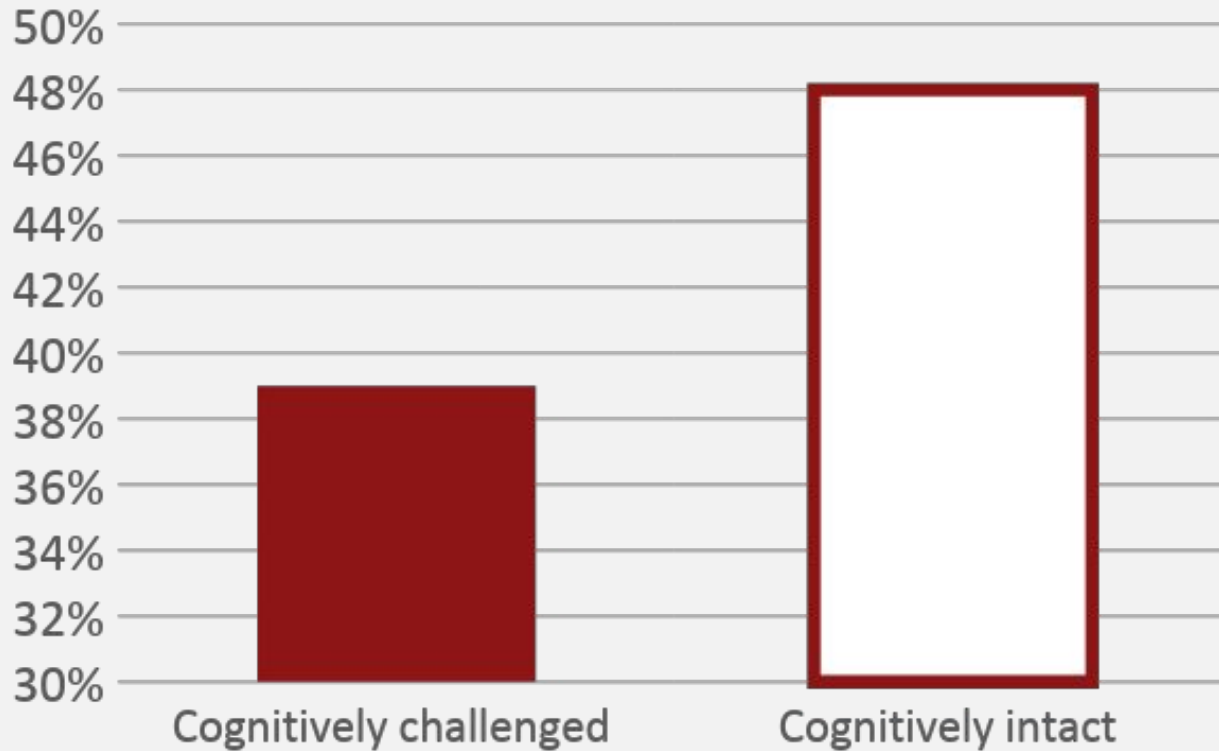
## Cognitive control activation



P=.003, p=.04

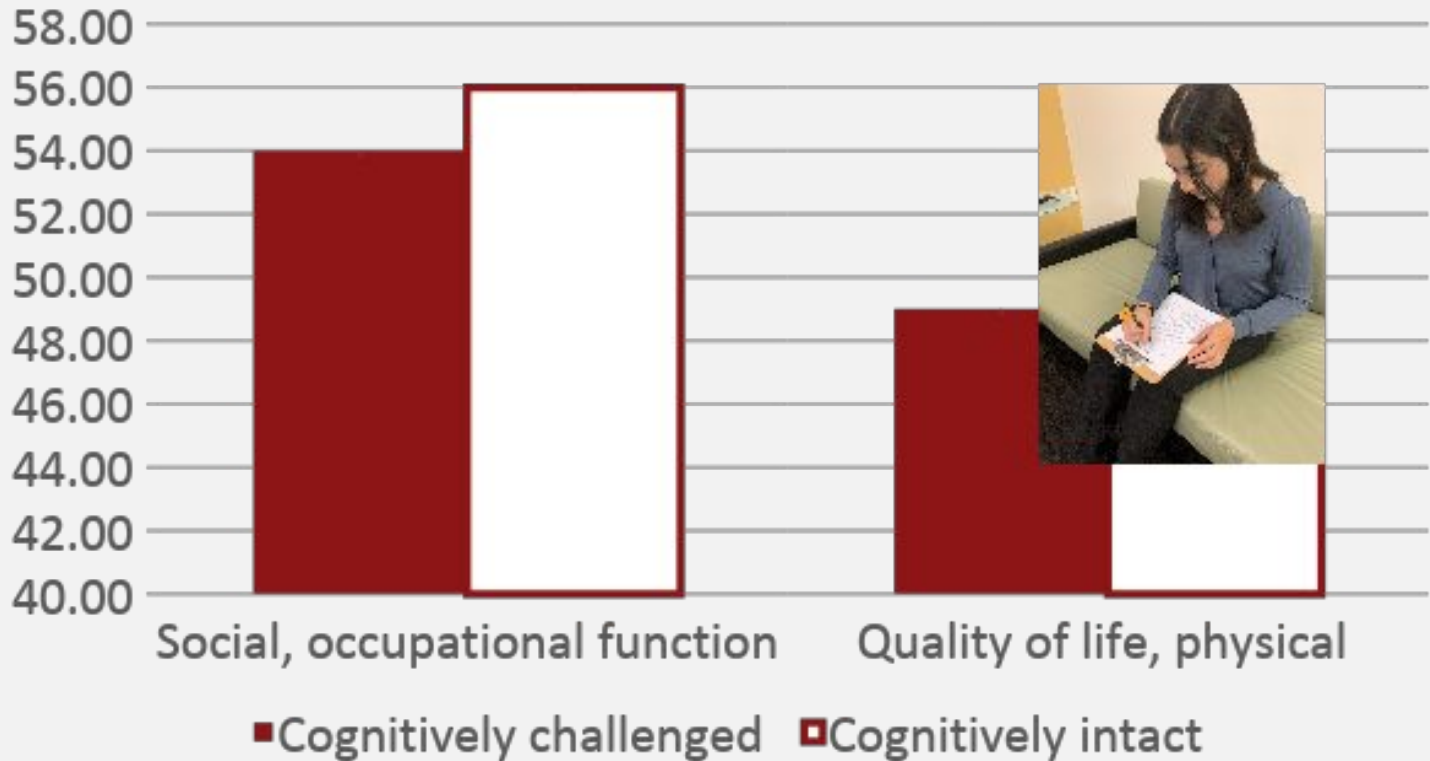
Does this cognitively challenged subtype  
respond to conventional antidepressants? **No**

## Rate of remission (HDRS-17)



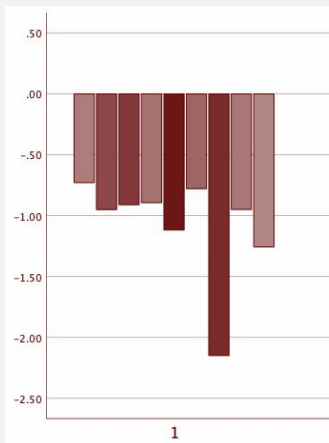
$\chi^2 = 4.4, p = 0.036$

## Function and Quality of Life



P<.001, p=.003

Cognitive problems are not improved by conventionally antidepressants.  
In fact, they **causally mediate** poorer symptom and quality of life outcomes



Less improvement in  
**Symptoms**  
**Quality of life**

The causal mediation effect is large: **0.70**

Could we treat this subtype in a more personalized way? **Yes**



# Problem-Solving Therapy

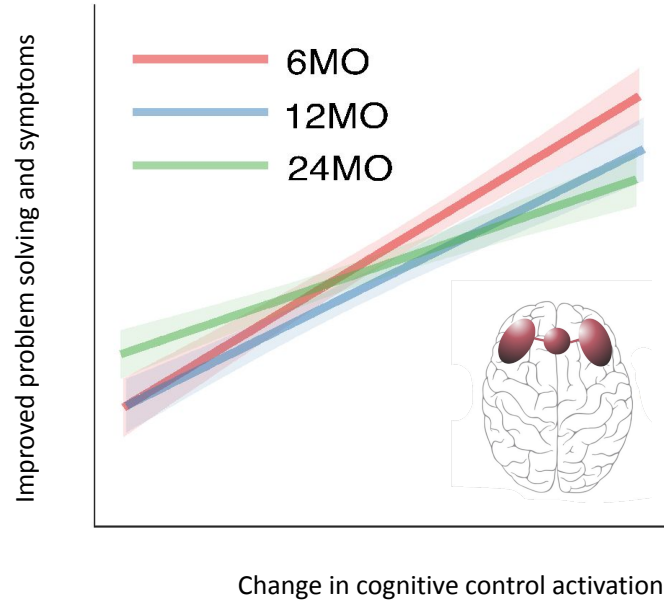


ENGAGE trial funded by NIH under the Science of Behavior Change initiative  
 Ma et al. JAMA, 2019; Williams et al., Behav. Res, Therapy, 2018.



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Ma et al. JAMA, 2019; Williams et al., Behav. Res, Therapy, 2018.

## Problem-Solving Therapy



Cognitive control circuit activation **increased** over 6, 12 and 24 months

# TMS



Stanford



Stanford



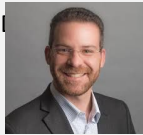
Palo Alto  
VA



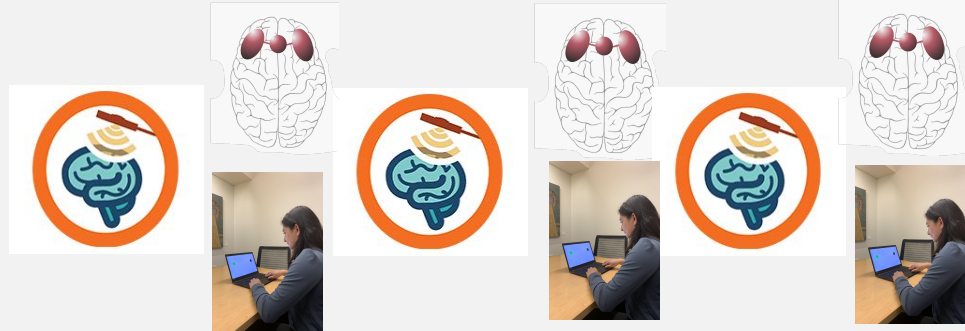
White River Jct  
VA



Minneapolis  
VA  
U Minnesota



Providence  
VA  
Brown

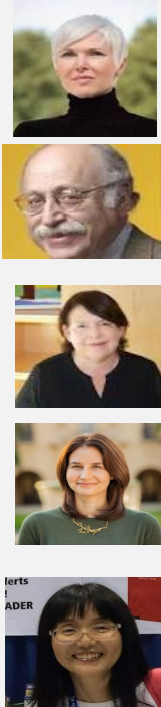


50 participants by end this year

Williams, L.M.. *et al.* Identifying response and predictive biomarkers for Transcranial magnetic stimulation outcomes. *BMC Psychiatry* **21**, 35 (2021).  
NIMH R01.

<https://www.mirecc.va.gov/visn21/>

# Selective therapies to target the cognitive control circuit



Assessments



Circuit biomarker  
guided treatment

Guanfacine -IR



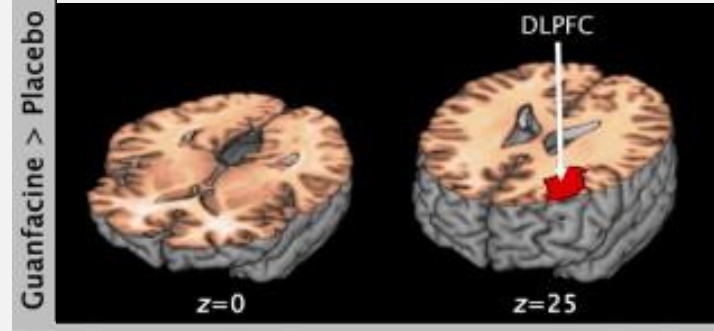
Outcomes



**Stanford Innovative Medicine Accelerator (IMA)**  
Biomarker imaging guided trial, 'BIG'

# Guanfacine targets cognitive control

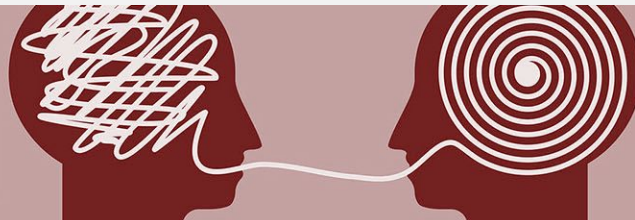
- Guanfacine-immediate release
- Selective for  $\alpha_2$  receptors in prefrontal brain regions
- Increases activation in the cognitive control circuit
- Improves cognition
- Meets safety/availability criteria



e.g., McAllister et al. Int J Psychophysiol 2011; Arnsten et al. Science 1985; Jarrott et al. Br J Pharmacol 1982; Kim et al. Psychopharmacol 2012

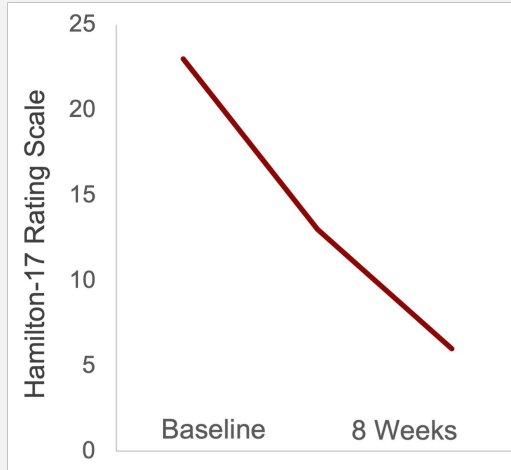
## Illustrative case: Ms. A

- 52 yo female
- *“I haven't been able to concentrate on work for a month now. I haven't put out anything productive...I find myself be easily distracted.”*
- Guanfacine 1 mg daily for one week, then 2 mg daily

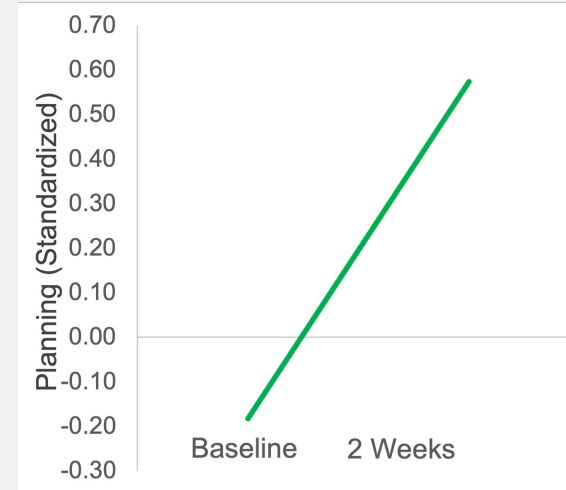


# After 8 weeks of Guanfacine

## Depression Score

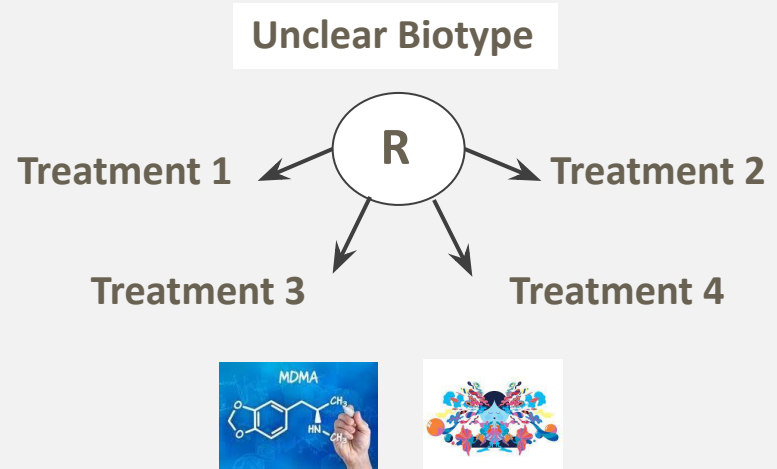
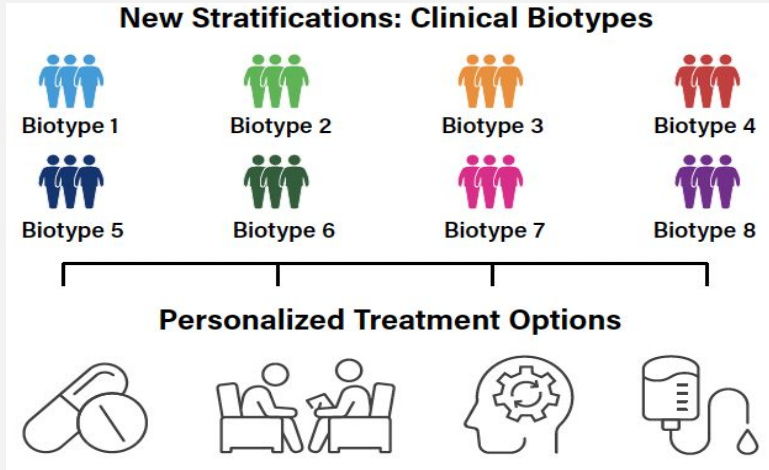


## Cognitive function



- Had the motivation to return to work during pandemic.
- Able to focus on projects; started planning ahead





The vision is for a bay area-wide precision mental health trial that evaluates **biotype matching with multiple treatment options in parallel**

We invite your research participation  
We welcome your partnership

**Grateful thanks to our supporters,  
collaborators and participants**

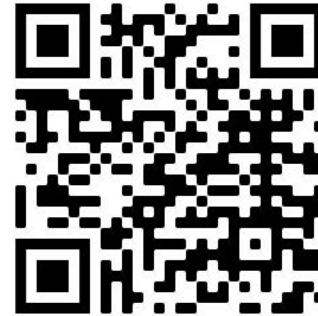


PMHW  
Stanford Center for Precision  
Mental Health and Wellness



**Stanford**  
MEDICINE

# To participate in our personalized mental health research



**Project information:** <https://med.stanford.edu/pmhw/clinic-project>

**Contact:** [pmhw\\_admin@stanford.edu](mailto:pmhw_admin@stanford.edu)



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