

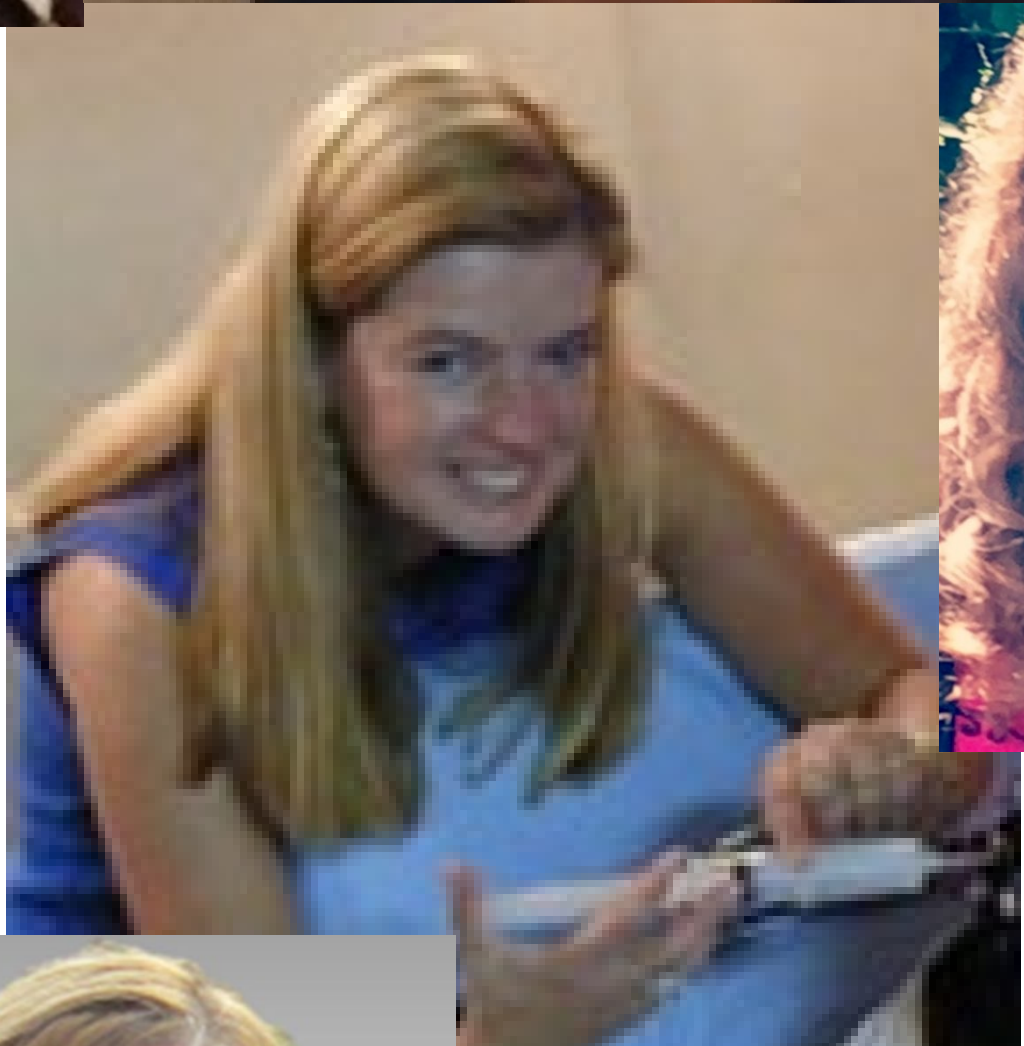
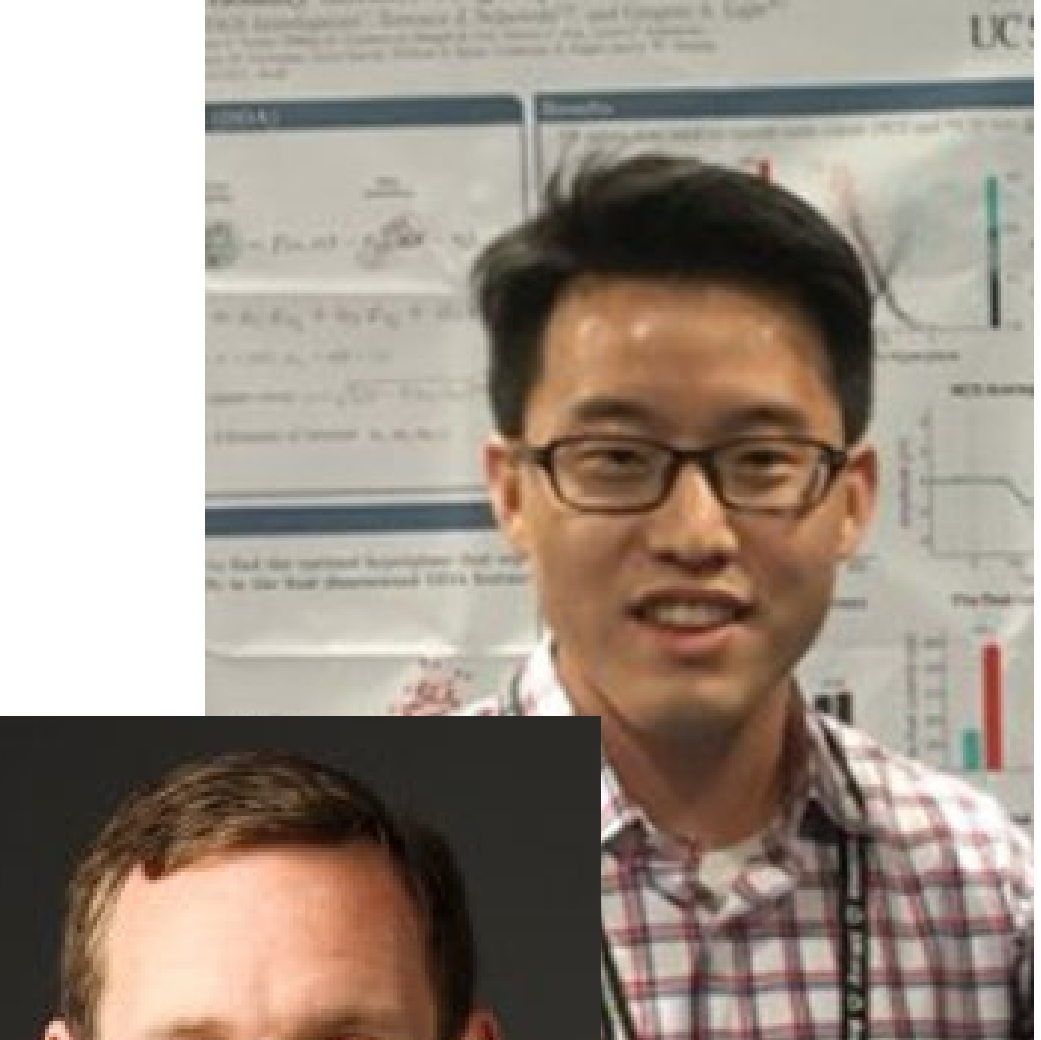
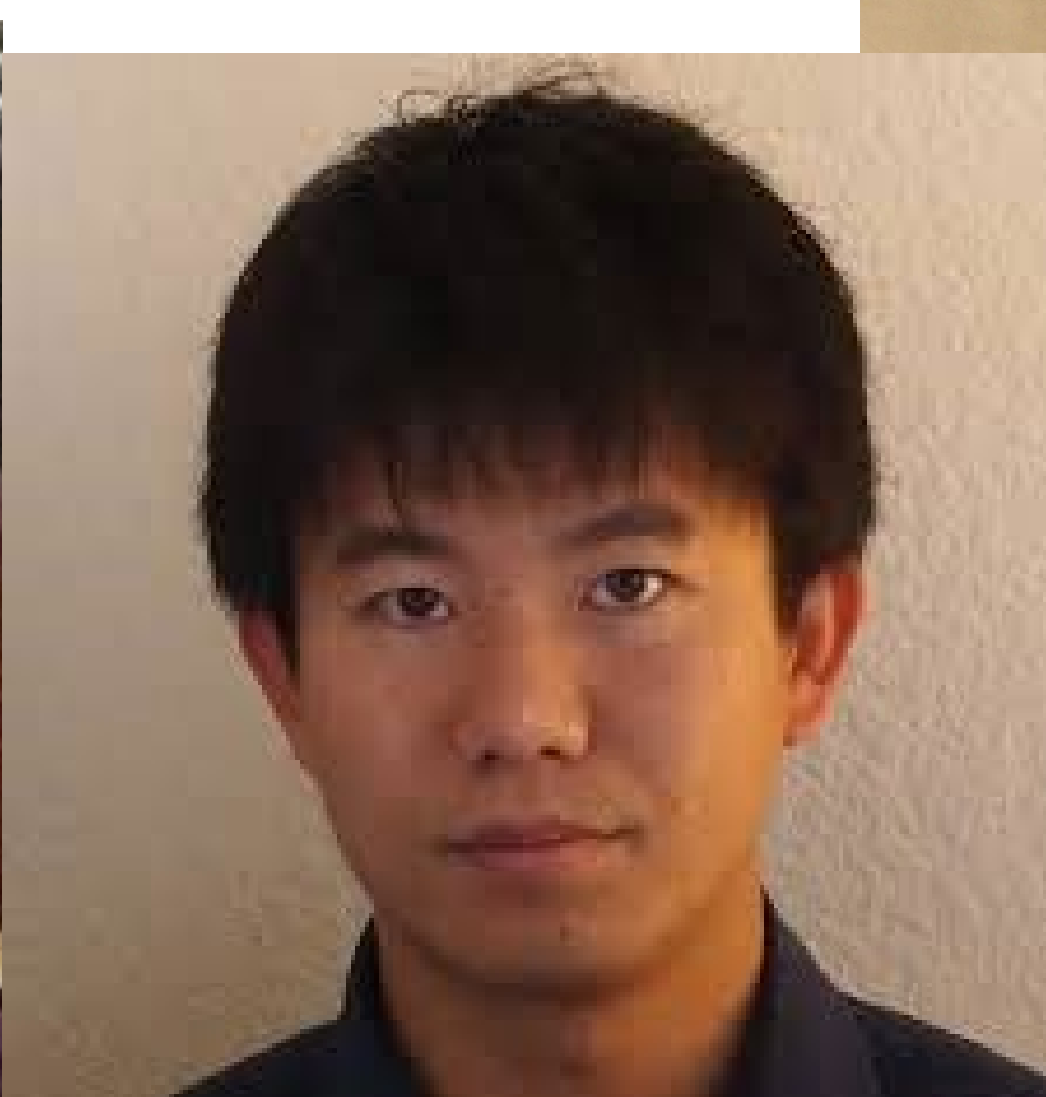
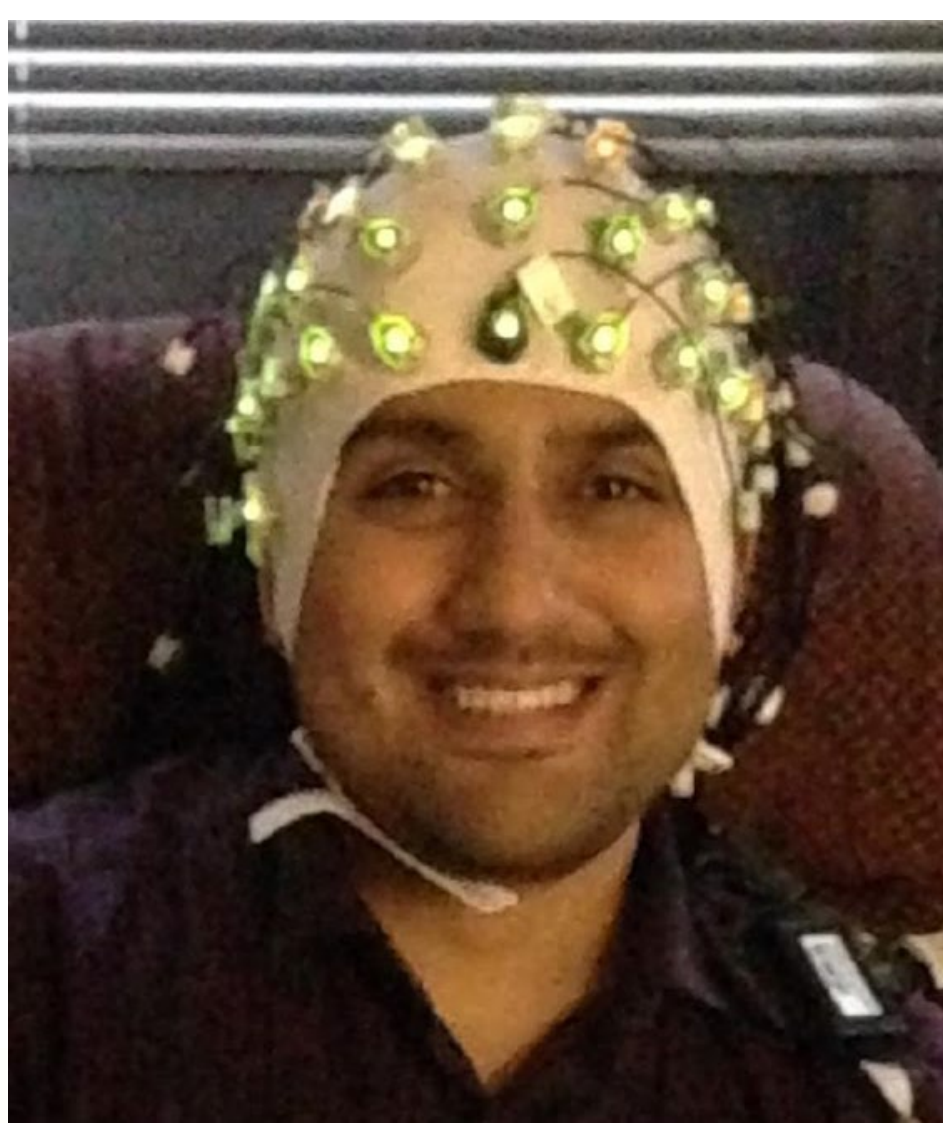
Using Tools of Neuroscience to Make Personalized Care a Reality in Schizophrenia

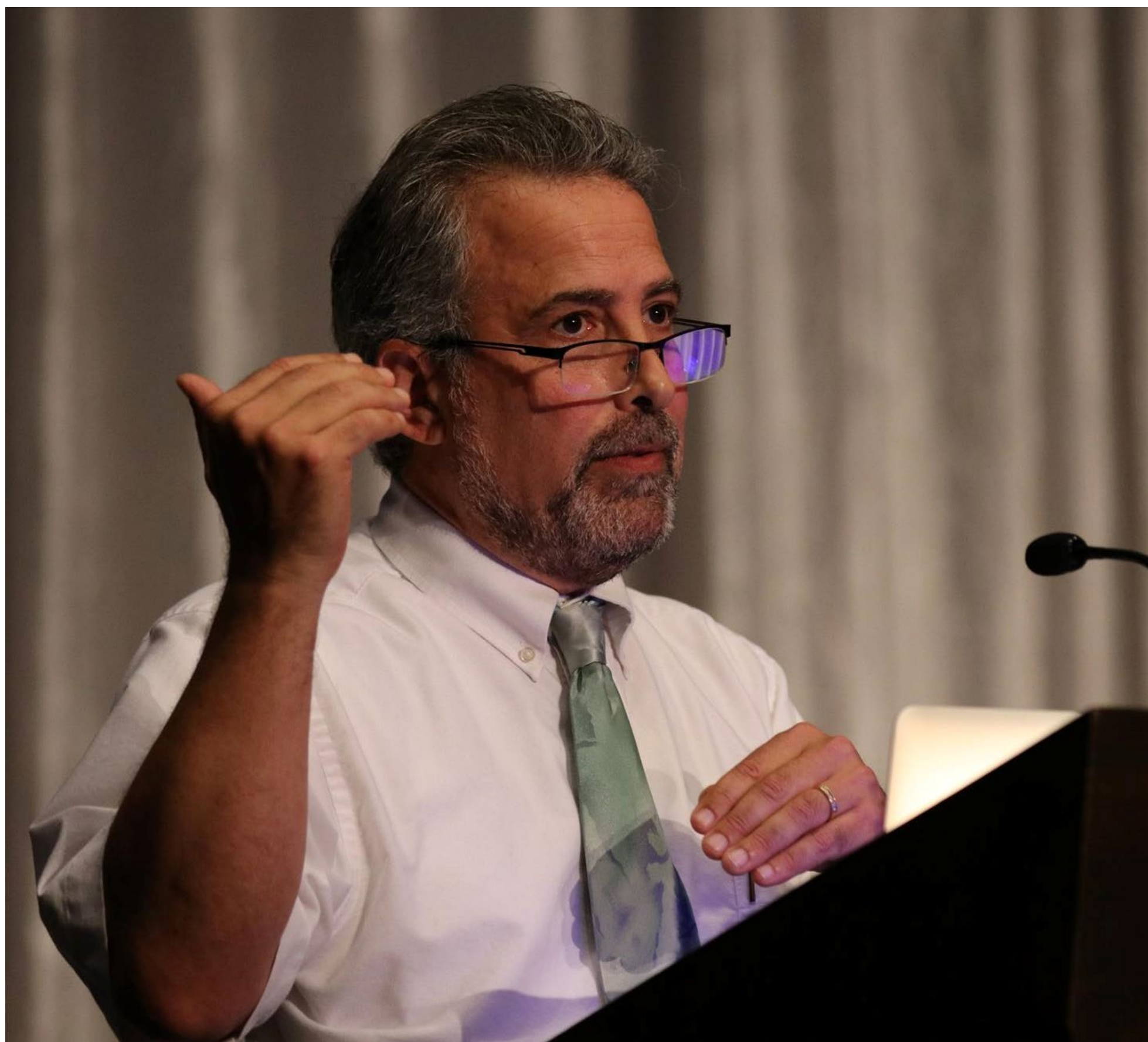
Gregory Light, Ph.D.
UNIVERSITY OF CALIFORNIA, SAN DIEGO
Professor & Assoc. Vice Chair, Dept of Psychiatry

VA SAN DIEGO HEALTHCARE SYSTEM
Co-Director, Mental Health Research
Associate Director: Mental Illness, Research, Education and Clinical Center (MIRECC)
Email: glight@ucsd.edu

 **BRAIN &
BEHAVIOR**
RESEARCH FOUNDATION
.....
Awarding **NARSAD** Grants

 **SIDNEY R. BAER, JR.**
FOUNDATION







Are we studying and treating schizophrenia correctly?

Neal R. Swerdlow*

School of Medicine, University of California, San Diego, 9500 Gilman Dr., La Jolla, CA 92093-0804, United States

ARTICLE INFO

Article history:

Received 1 February 2011

Received in revised form 27 April 2011

Accepted 4 May 2011

Available online 8 June 2011

Keywords:

Antipsychotic

Cognitive therapy

Dopamine

Hippocampus

Prefrontal cortex

Schizophrenia

ABSTRACT

New findings are rapidly revealing an increasingly detailed image of neural- and molecular-level dysfunction in schizophrenia, distributed throughout interconnected cortico–striato–pallido–thalamic circuitry. Some disturbances appear to reflect failures of early brain maturation, that become codified into dysfunctional circuit properties, resulting in a substantial loss of, or failure to develop, both cells and/or appropriate connectivity across widely dispersed brain regions. These circuit disturbances are variable across individuals with schizophrenia, perhaps reflecting the interaction of multiple different risk genes and epigenetic events. Given these complex and variable hard-wired circuit disturbances, it is worth considering how new and emerging findings can be integrated into actionable treatment models. This paper suggests that future efforts towards developing more effective therapeutic approaches for the schizophrenias should diverge from prevailing models in genetics and molecular neuroscience, and focus instead on a more practical three-part treatment strategy: 1) systematic rehabilitative psychotherapies designed to engage healthy neural systems to compensate for and replace dysfunctional higher circuit elements, used in concert with 2) medications that specifically target cognitive mechanisms engaged by these rehabilitative psychotherapies, and 3) antipsychotic medications that target nodal or convergent circuit points within the limbic–motor interface, to constrain the scope and severity of psychotic exacerbations and thereby facilitate engagement in cognitive rehabilitation. The use of targeted cognitive rehabilitative psychotherapy plus synergistic medication has both common sense and time-tested efficacy with numerous other neuropsychiatric disorders.

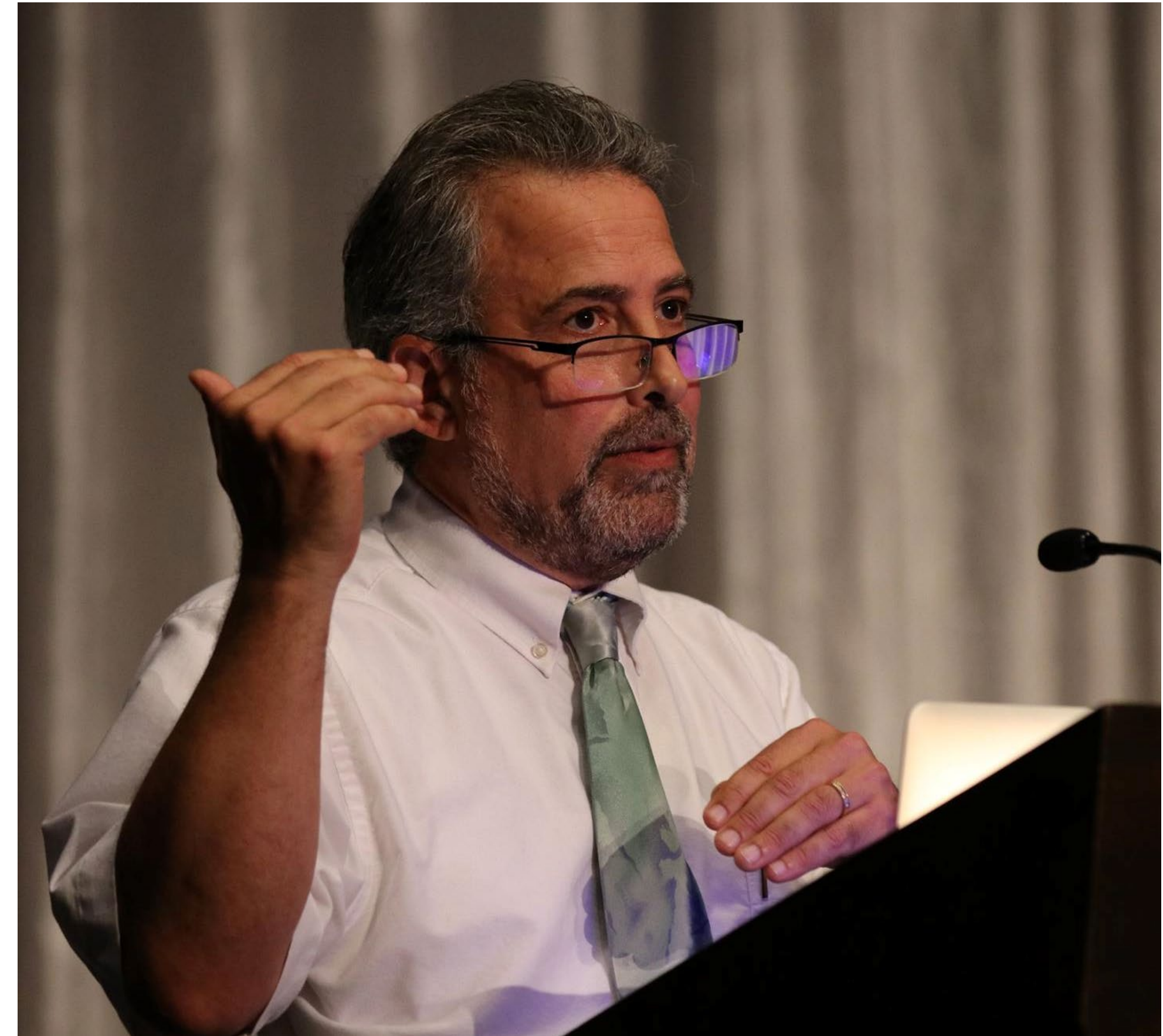
© 2011 Elsevier B.V. All rights reserved.

1. Introduction

With increasing pace, findings are revealing the structural and functional properties of limbic cortical and subcortical circuits that are conveyed through programmed cell migration, pre- and post-natal synaptic reorganization and apoptosis across normal development (cf. [Tau and Peterson, 2010](#)). Current models for the etiology of the schizophrenias (e.g. [Bigos et al., 2010](#); [Kleinman et al., 2011](#)) suggest that this intricate weaving is turned to chaos by predisposing genes and epigenetic events; the resultant or compensatory changes are then hard-wired by tightly choreographed, inter-dependent developmental pro-

causes but instead their final common pathways. It is not like Parkinson's Disease (PD), where motoric symptoms largely reflect the loss of one neuron, whose role is to supply one chemical to cells in a way that can be mimicked by administering one precursor for that chemical; this is possible in PD *because the organization of the post-synaptic circuitry develops normally, and for much of adulthood, retains the detailed interconnections in the "intended" design.*

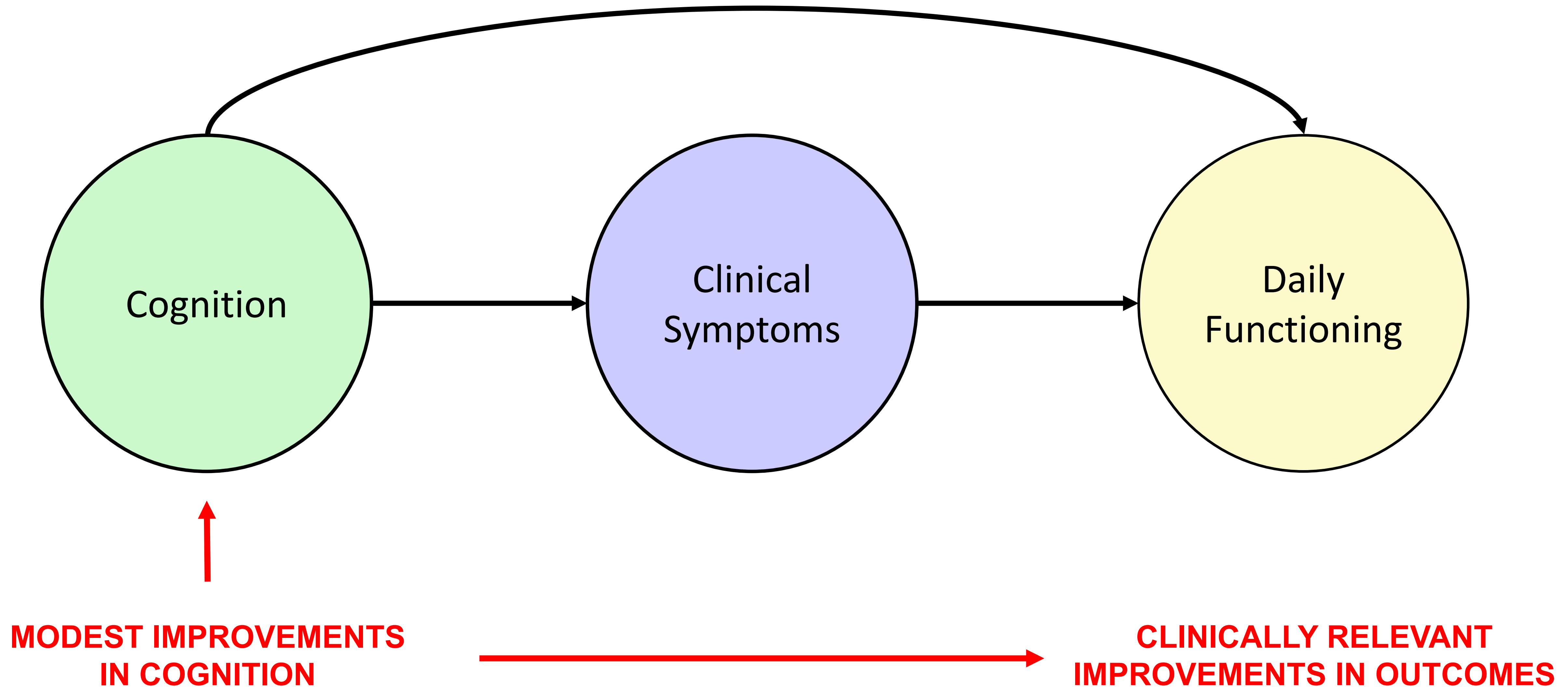
In schizophrenia, the root cause appears to be a developmental interruption and tangling of neural connections ([Weinberger, 1987](#); [Murray et al., 1991](#); [Lewis and Levitt, 2002](#)) that are orders of magnitude too complex to restore or replace, and which in their complexity

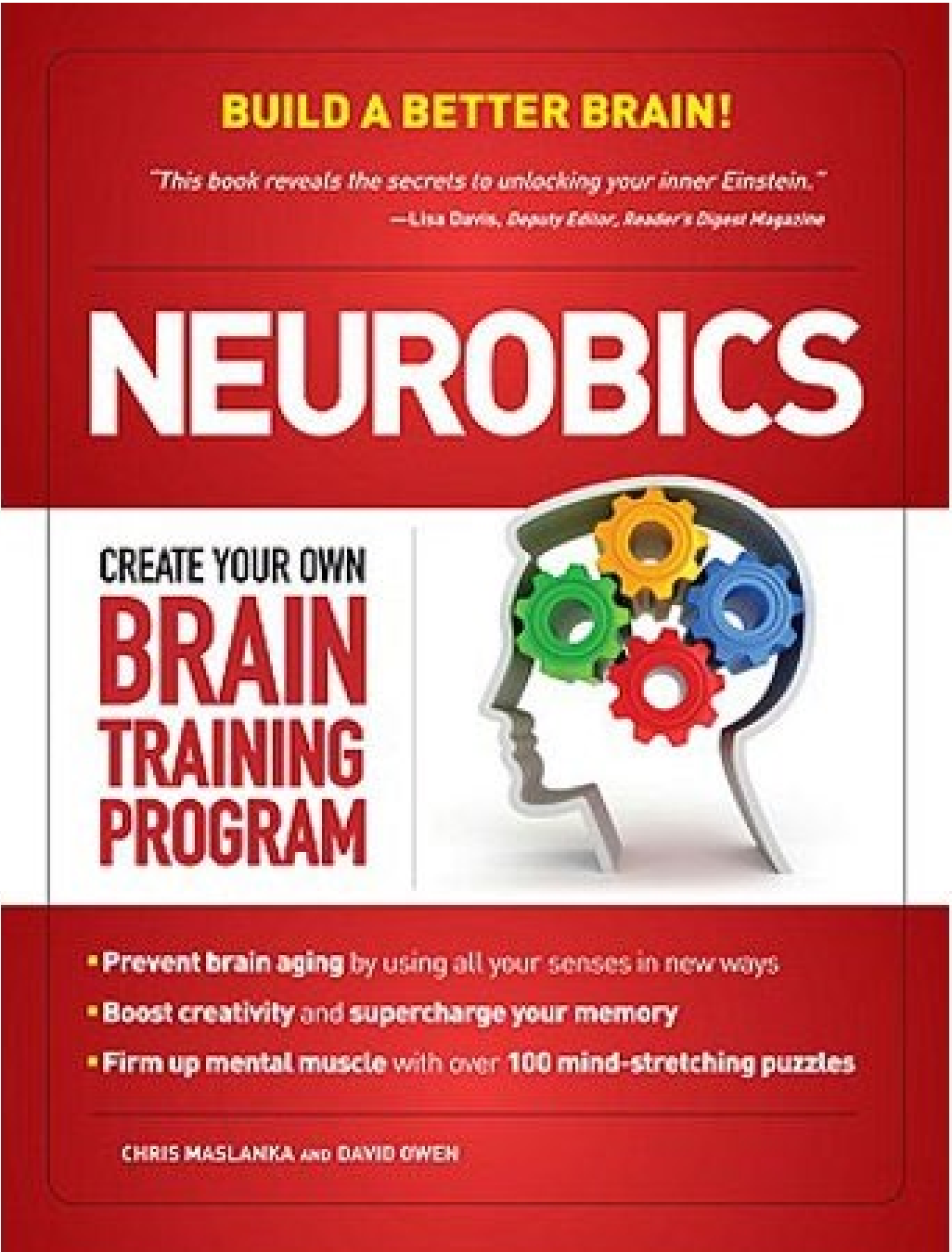
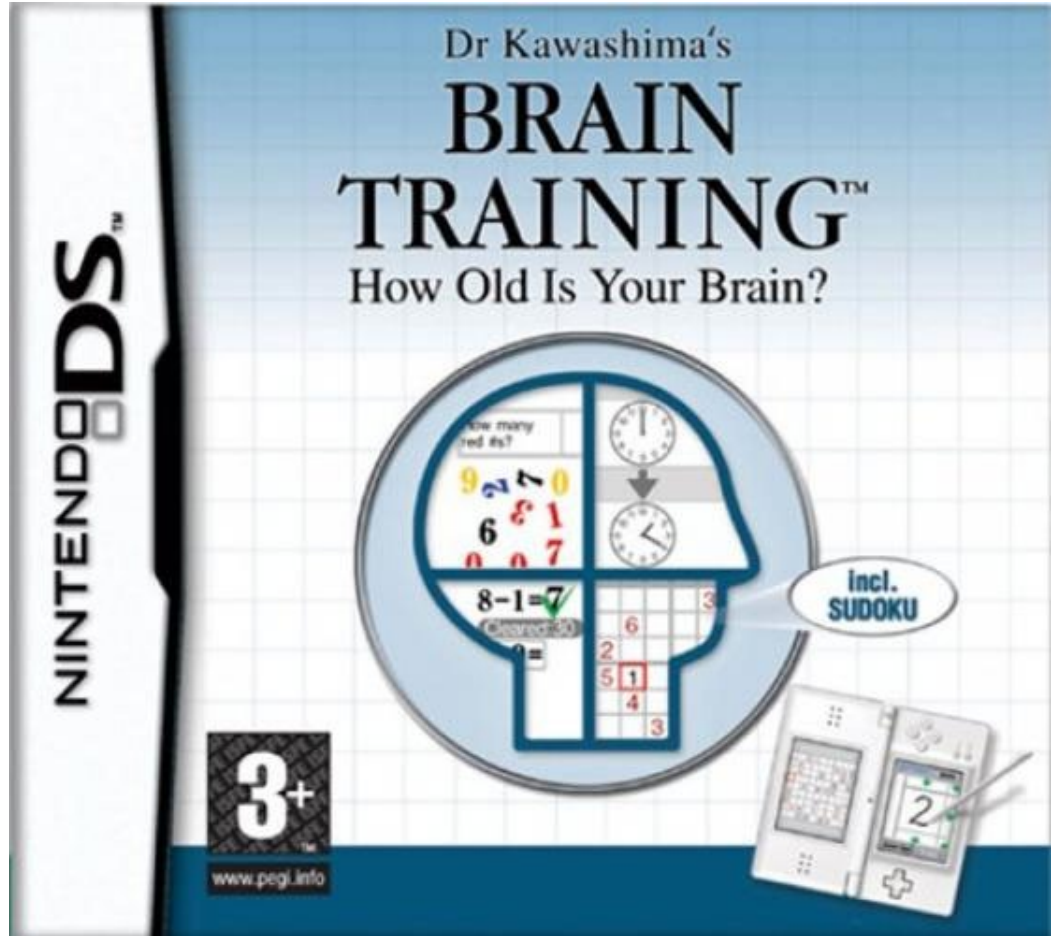






Cognitive impairment underlies functional outcome in SZ





[Submit a Manuscript](#)

[HOME](#)

[CONTENT](#)

[ALERTS](#)

[FOR AUTHORS](#)

[EDITORIAL BOARD](#)

[ABOUT](#)

[Previous](#)

[Next](#)

Research Articles, Behavioral/Cognitive

No Effect of Commercial Cognitive Training on Brain Activity, Choice Behavior, or Cognitive Performance

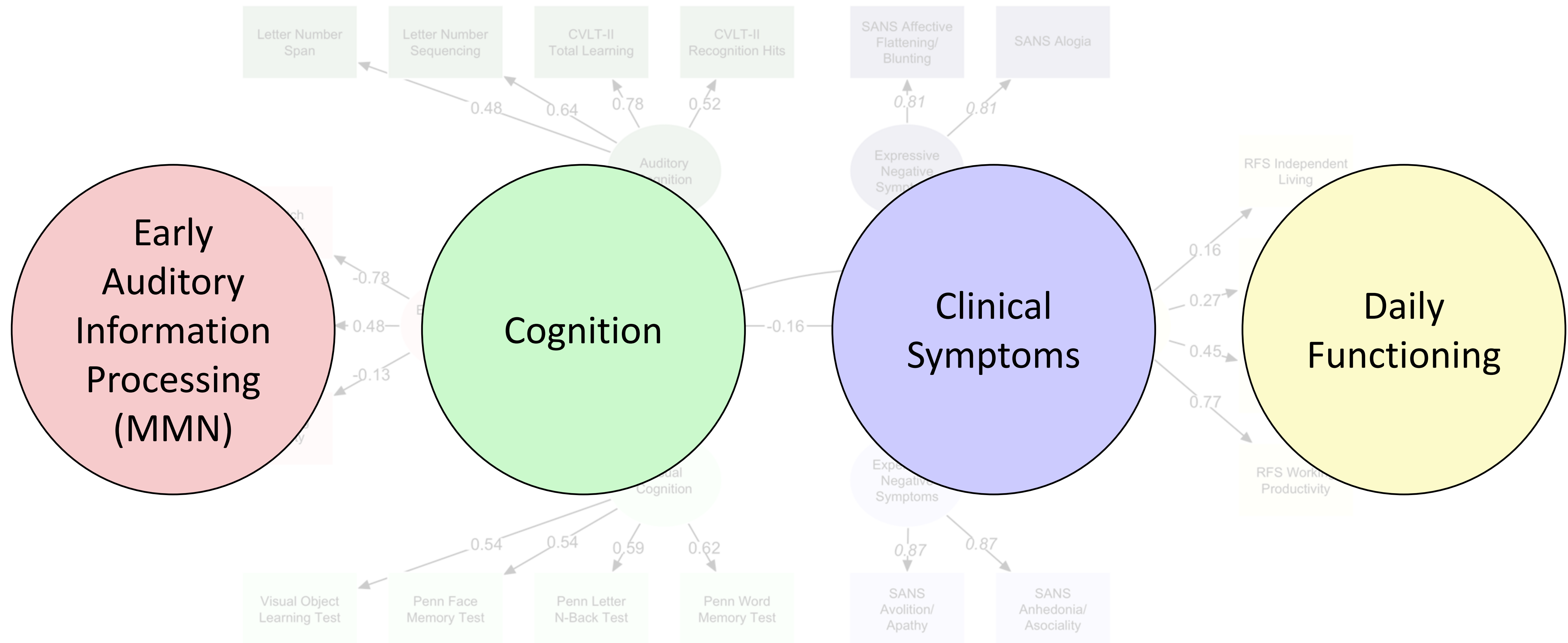
Joseph W. Kable, M. Kathleen Caulfield, Mary Falcone, Mairead McConnell, Leah Bernardo, Trishala Parthasarathi, Nicole Cooper, Rebecca Ashare, Janet Audrain-McGovern, Robert Hornik, Paul Diefenbach, Frank J. Lee, and Caryn Lerman

Journal of Neuroscience 2 August 2017, 37 (31) 7390-7402; DOI: <https://doi.org/10.1523/JNEUROSCI.2832-16.2017>

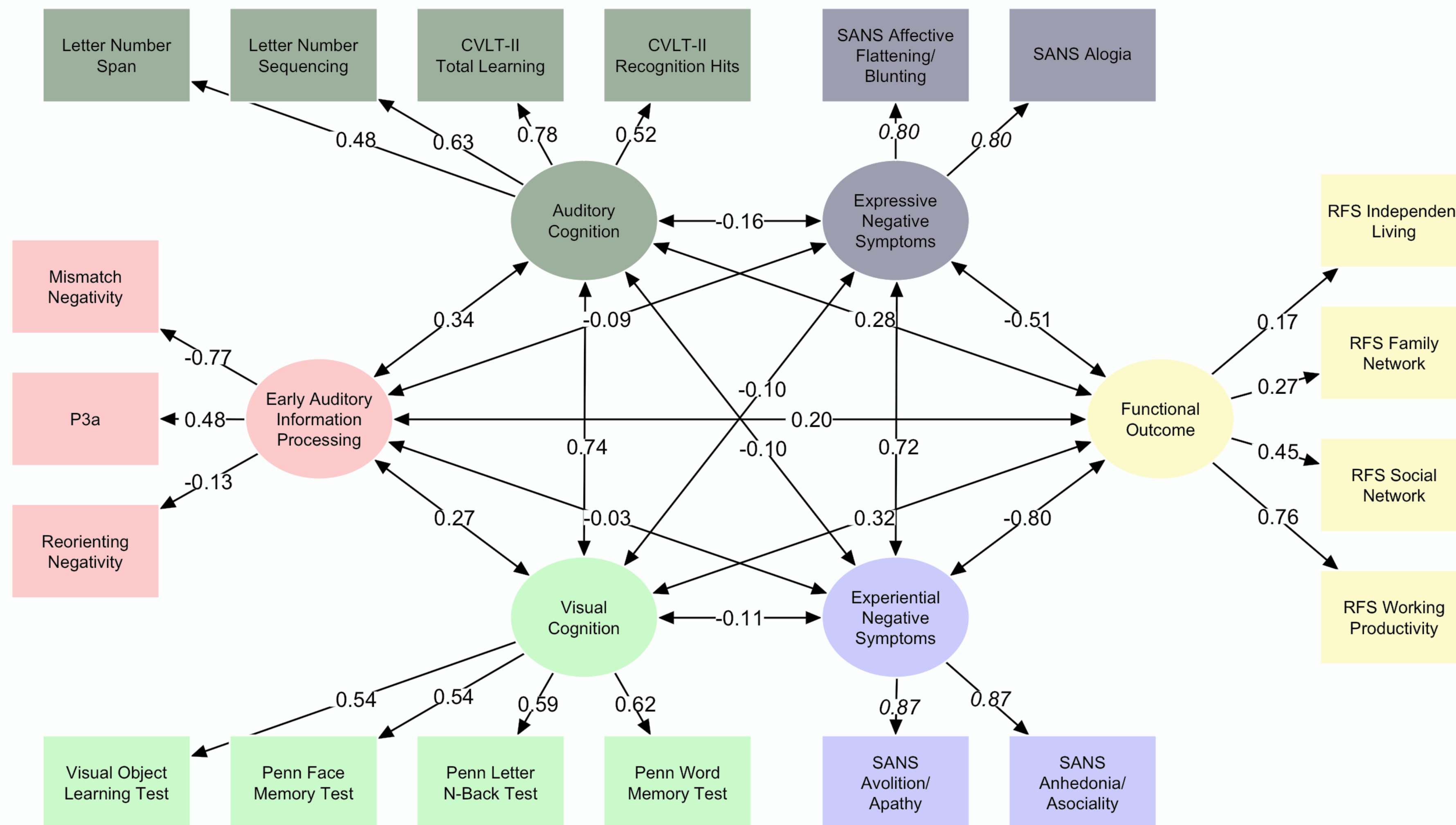
Lumosity to Pay \$2 Million to Settle FTC Deceptive Advertising Charges for Its “Brain Training” Program

Company Claimed Program Would Sharpen Performance in Everyday Life and Protect Against Cognitive Decline

Testing the Information Processing Cascade Model

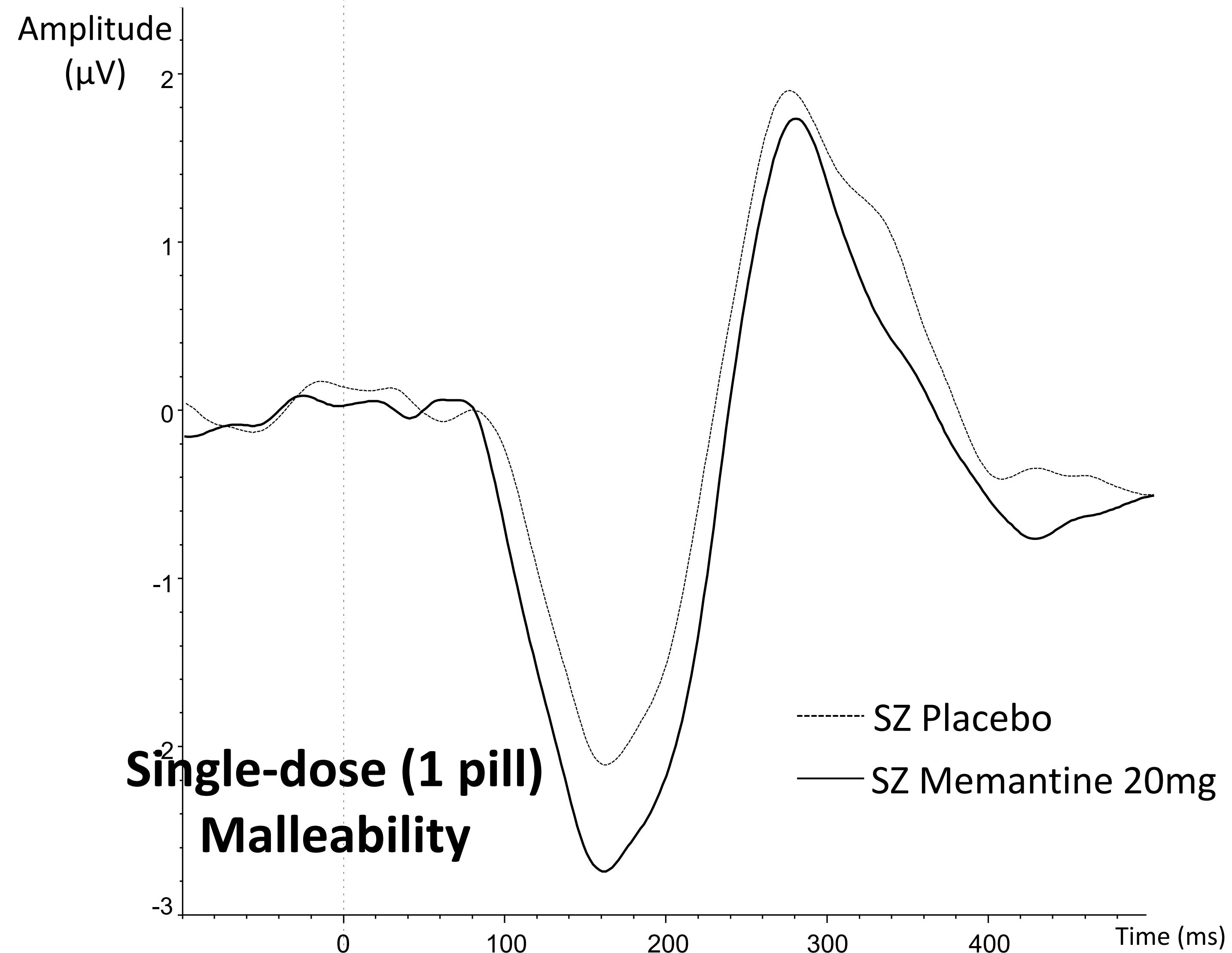


Disentangling Multivariate Relationships: Testing the Information Processing Cascade Model



Thomas ML, Green MF, Helleman G, Sugar CA, Tarasenko M, Calkins ME, Greenwood TA, Gur RE, Gur RC, Lazzeroni LC, Nuechterlein KH, Radant AD, Seidman LJ, Siever LJ, Silverman JM, Sprock J, Stone WS, Swerdlow NR, Tsuang DW, Tsuang MT, Turetsky BI, Braff DL, Light GA. JAMA Psychiatry. 2017 Jan 1;74(1):37-46. doi: 10.1001/jamapsychiatry.2016.2980.

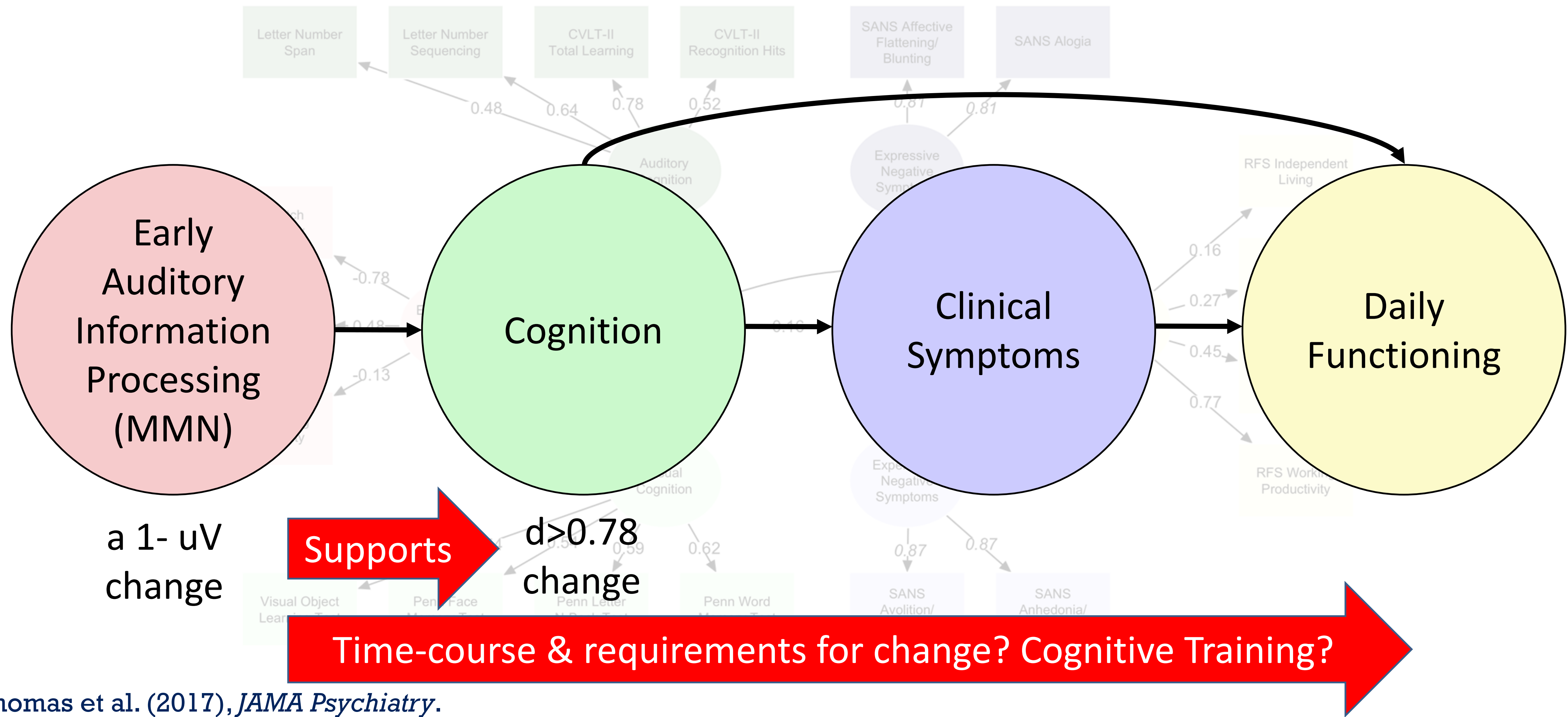
MMN is Sensitive to Initial Exposure to Memantine: 1 pill



Single-dose (1 pill)
Malleability



Testing the Information Processing Cascade Model



“Experimental Medicine” Trial with a Nonpharmacologic Intervention: An Example using Auditory Targeted Cognitive Training (TCT)

- Computerized approach to cognitive remediation
- Aims to improve the accuracy and fidelity of auditory sensory information processing
- Capitalizes on “neuroplasticity based” learning mechanisms via exercises that are: intensive, adaptive, rewarding
- Place progressive demands on higher-order cognitive domains
- Efficacious for improving cognition in psychosis patients at the group level



Previous Studies have Demonstrated Efficacy of TCT in Sz

- **TCT improves verbal learning and memory in adult SZ outpatients.**
Fisher M, et al. Am J Psychiatry. 2009
- **TCT improves verbal learning/memory in recent onset SZ outpatients.**
Fisher M, et al. Schizophrenia Bulletin. 2015
- **TCT improves verbal learning/memory in adolescents and young adults at clinical high risk for psychosis.**
Loewy R, et al. Schizophrenia Bulletin. 2016

-
- **TCT improves verbal learning/memory and auditory hallucinations in treatment refractory schizophrenia inpatients.**
**Thomas ML, Bismark AW, Joshi YB, Tarasenko M, Treichler EBH, Hochberger WC, Zhang W, Nungaray J, Sprock J, Cardoso L, Tiernan K, Attarha M, Braff DL, Vinogradov S, Swerdlow N, Light GA. Schizophrenia Research. 2018*

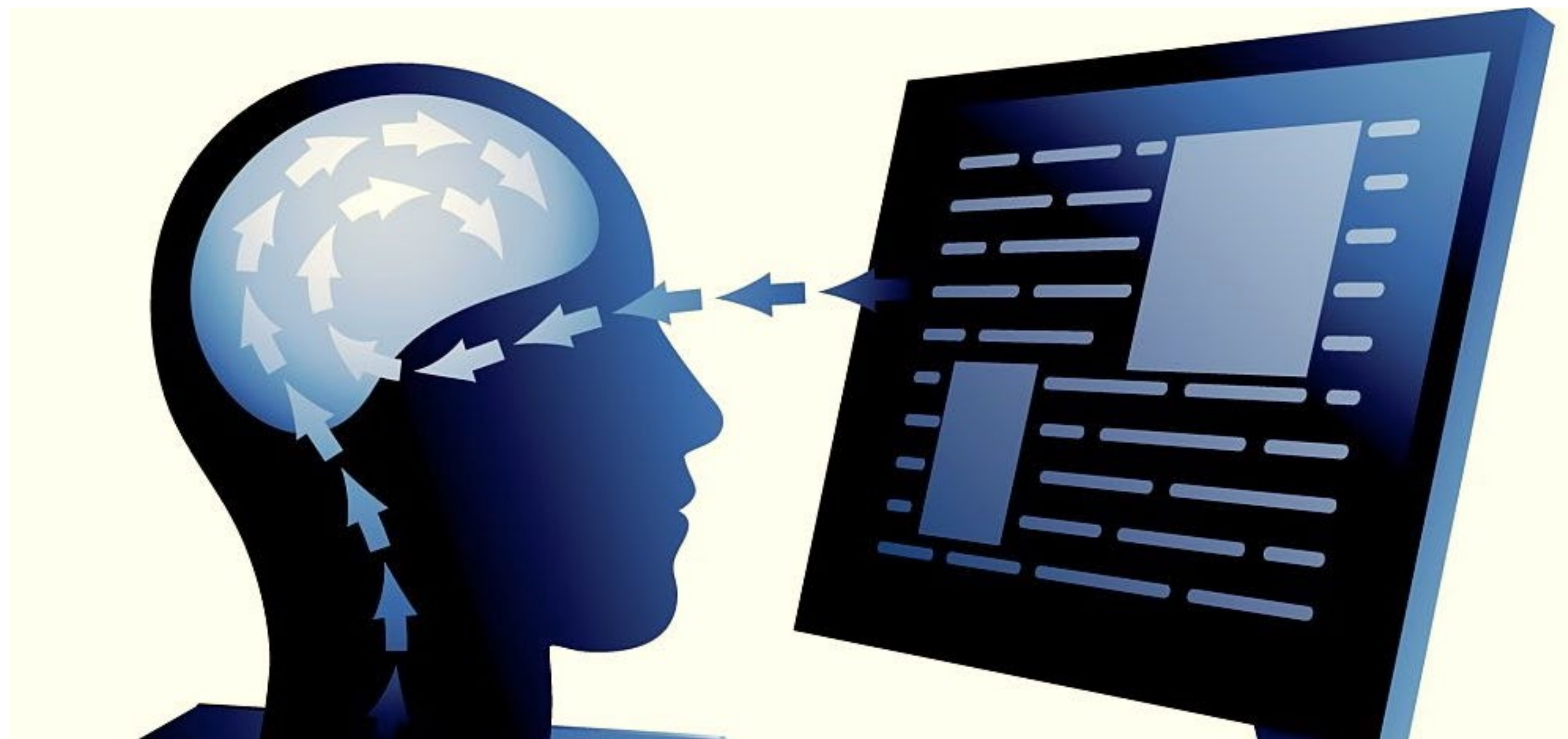
** Top Research Finding of 2018, Brain & Behavior Research Foundation*

Challenges to overcome

TCT has largely been tested in academic labs

TCT is time-intensive and requires resources

TCT does not help all patients



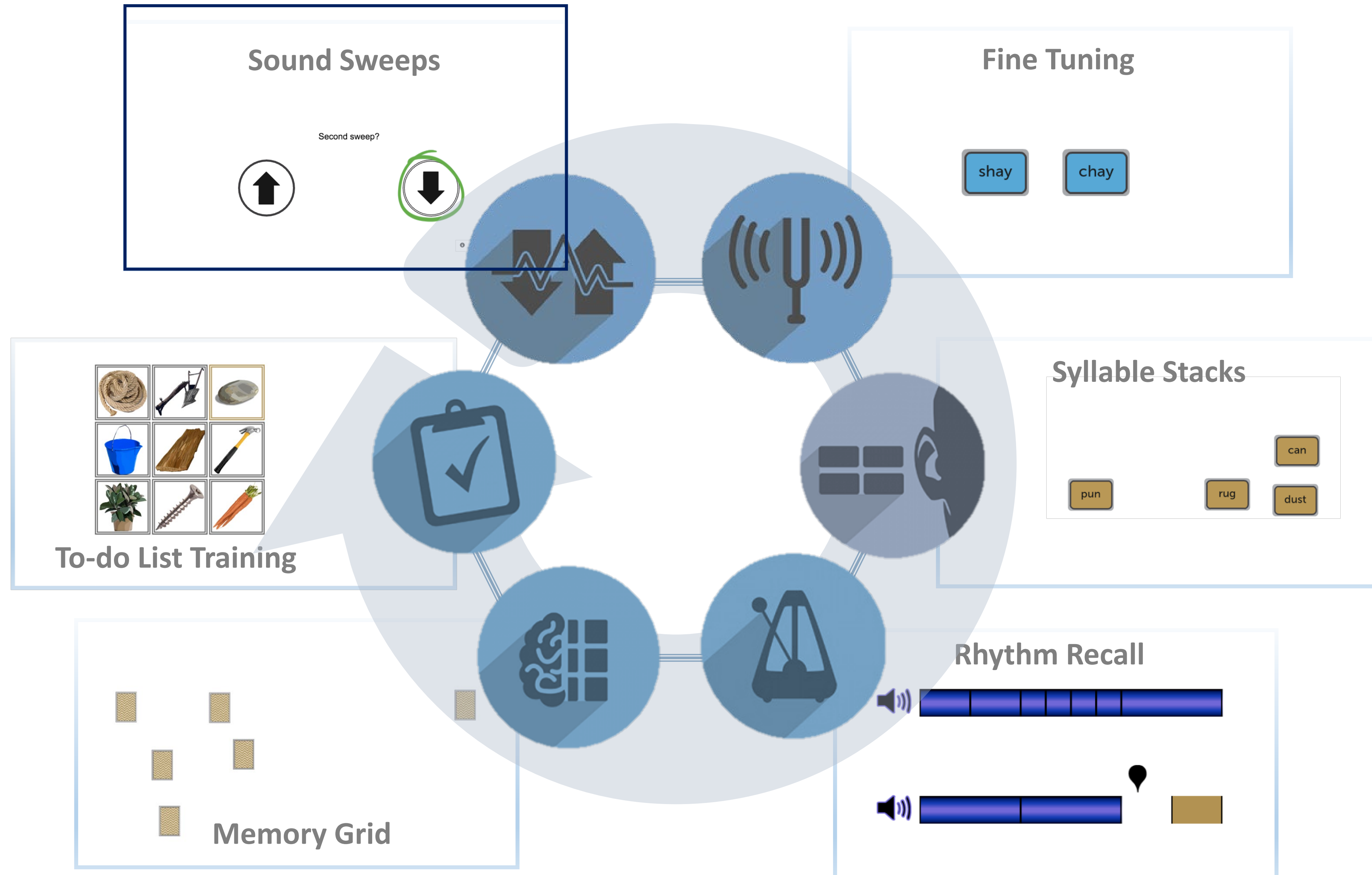
Testing the Effectiveness of TCT & Predictive Utility of EEG Biomarkers

Are EEG measures acutely sensitive to the neural systems engaged by 1h of TCT exercises?

Does 30h of cognitive training “work” in treatment refractory schizophrenia Inpatients?

Do EEG changes following initial exposure to TCT predict future therapeutic benefit?

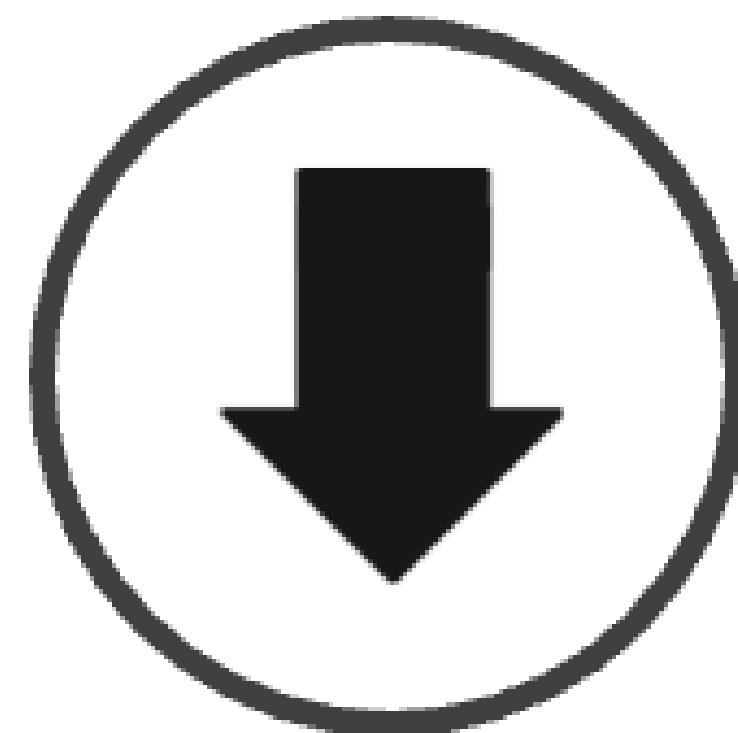
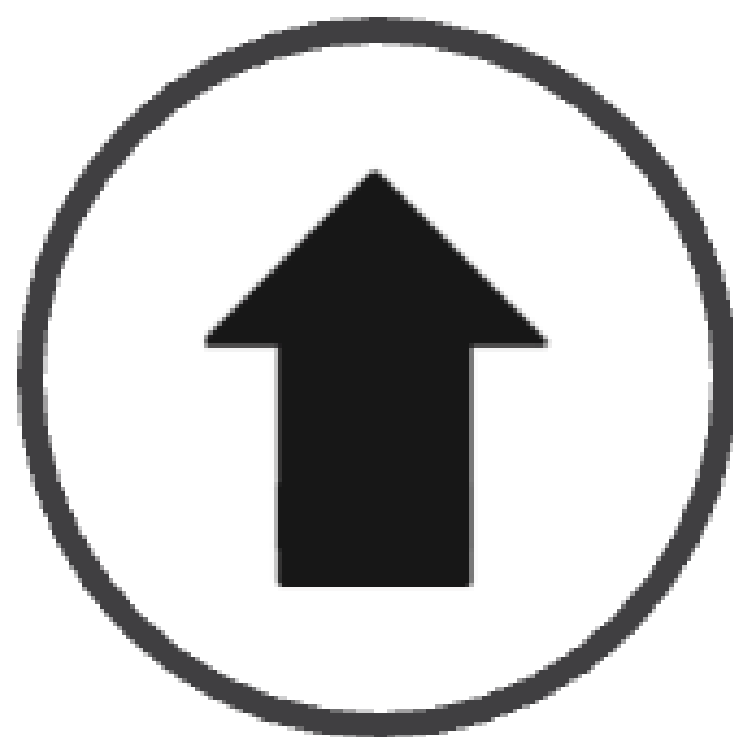
Auditory Targeted Cognitive Training: Brain Fitness Auditory Exercises



Auditory Targeted Cognitive Training



Click the arrow pointing in the direction of the second sweep sound you heard. The correct arrow is highlighted.



Auditory Targeted Cognitive Training



7

Identify faster sweeps >>

19 ms





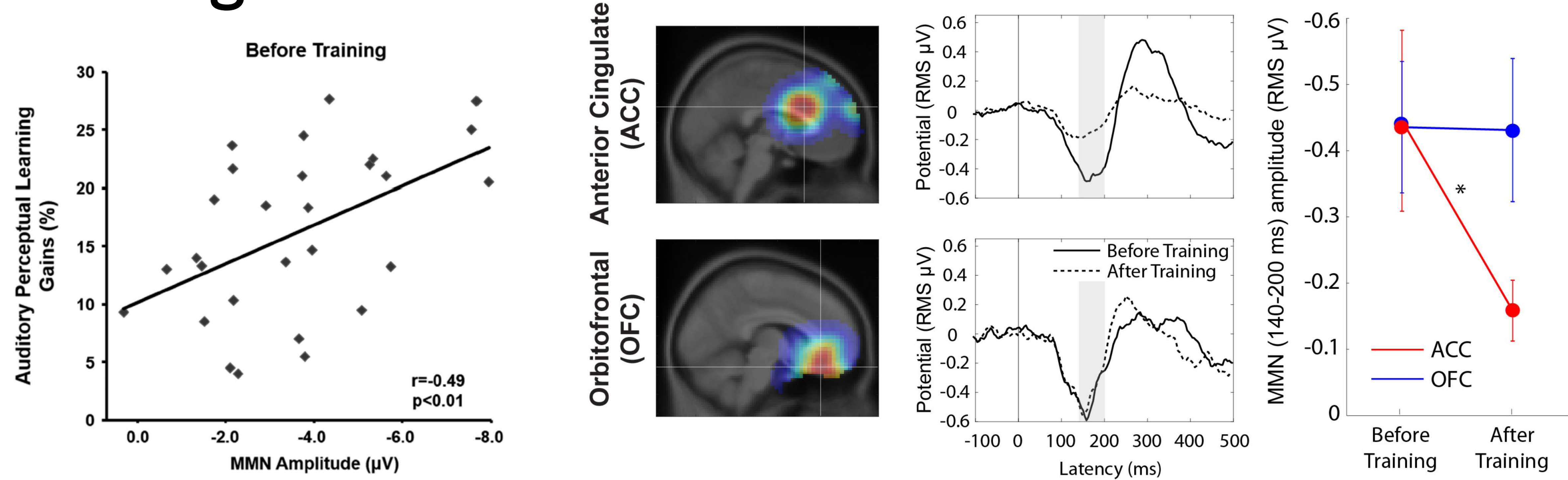
Testing the Effectiveness of TCT & Predictive Utility of EEG Biomarkers

Are EEG measures acutely sensitive to the neural systems engaged by 1h of TCT exercises?

Does 30h of cognitive training “work” in treatment refractory schizophrenia Inpatients?

Do EEG changes following initial exposure to TCT predict future therapeutic benefit?

Changes in Source Contributions after 1h of Cognitive Training



Perez VB et al (2017),
Neuropsychopharmacology

Perez VB et al (2019), *Int J Psychophysiology*



Testing the Effectiveness of TCT & Predictive Utility of EEG Biomarkers

Are EEG measures acutely sensitive to the neural systems engaged by 1h of TCT exercises?

Does 30h of cognitive training “work” in treatment refractory schizophrenia Inpatients?

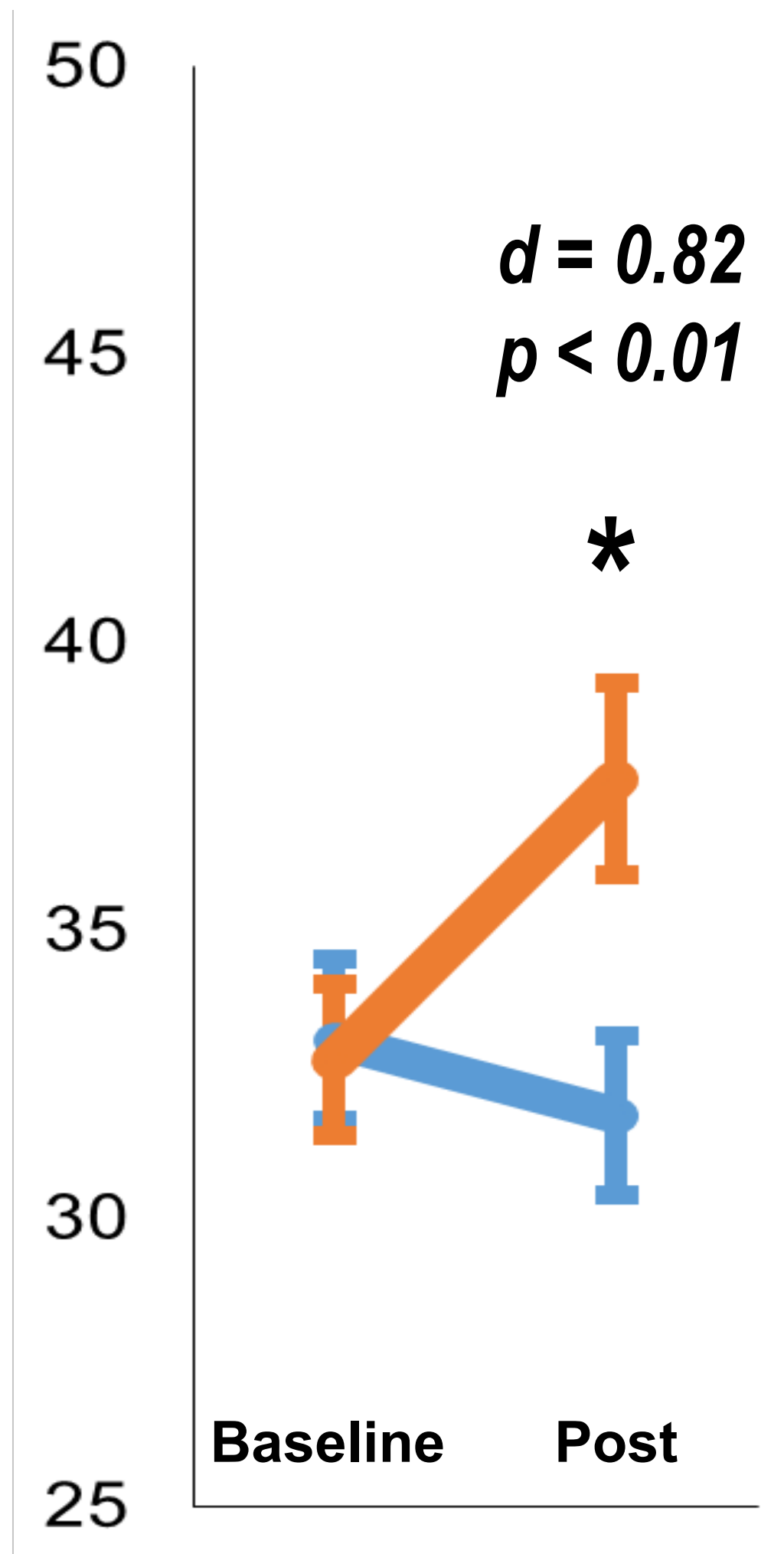
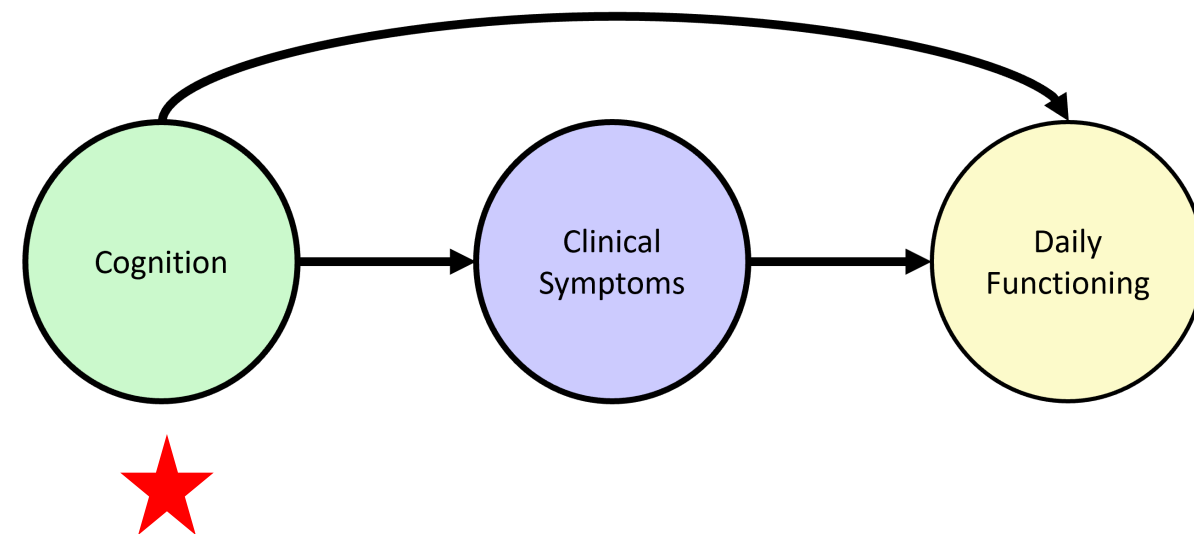
Do EEG changes following initial exposure to TCT predict future therapeutic benefit?

SZ Inpatients Matched on at Randomization to TAU vs. TCT

	Treatment as Usual	Targeted Cognitive Training	<i>p</i>
Sample Size	22	24	
Age	35.73 (13.00)	34.54 (12.13)	0.75
Gender: Male	9 (41%)	13 (54%)	0.55
Hispanic	6 (27%)	4 (17%)	0.61
Race			
African American	3 (14%)	5 (21%)	0.51
Asian	2 (9%)	1 (4%)	
Caucasian	12 (55%)	13 (54%)	
More than one race	5 (23%)	3 (12%)	
Native American	0 (0%)	2 (8%)	
Education	11.95 (2.17)	11.71 (1.99)	0.69
➡ Chlorpromazine Equivalents	982.54 (758.10)	1329.42 (972.78)	0.82
➡ Illness Duration	15.23 (12.78)	16.12 (13.67)	0.82
SAPS	4.45 (5.14)	5.12 (4.00)	0.62
PSYRATS-AH	7.32 (11.10)	8.79 (11.64)	0.66
SANS	6.18 (3.97)	7.75 (4.50)	0.22
➡ MCCB-NC Composite	23.95 (13.71)	23.12 (12.14)	0.83



TCT Enhances Verbal Learning in Severely Disabled SZ inpatients



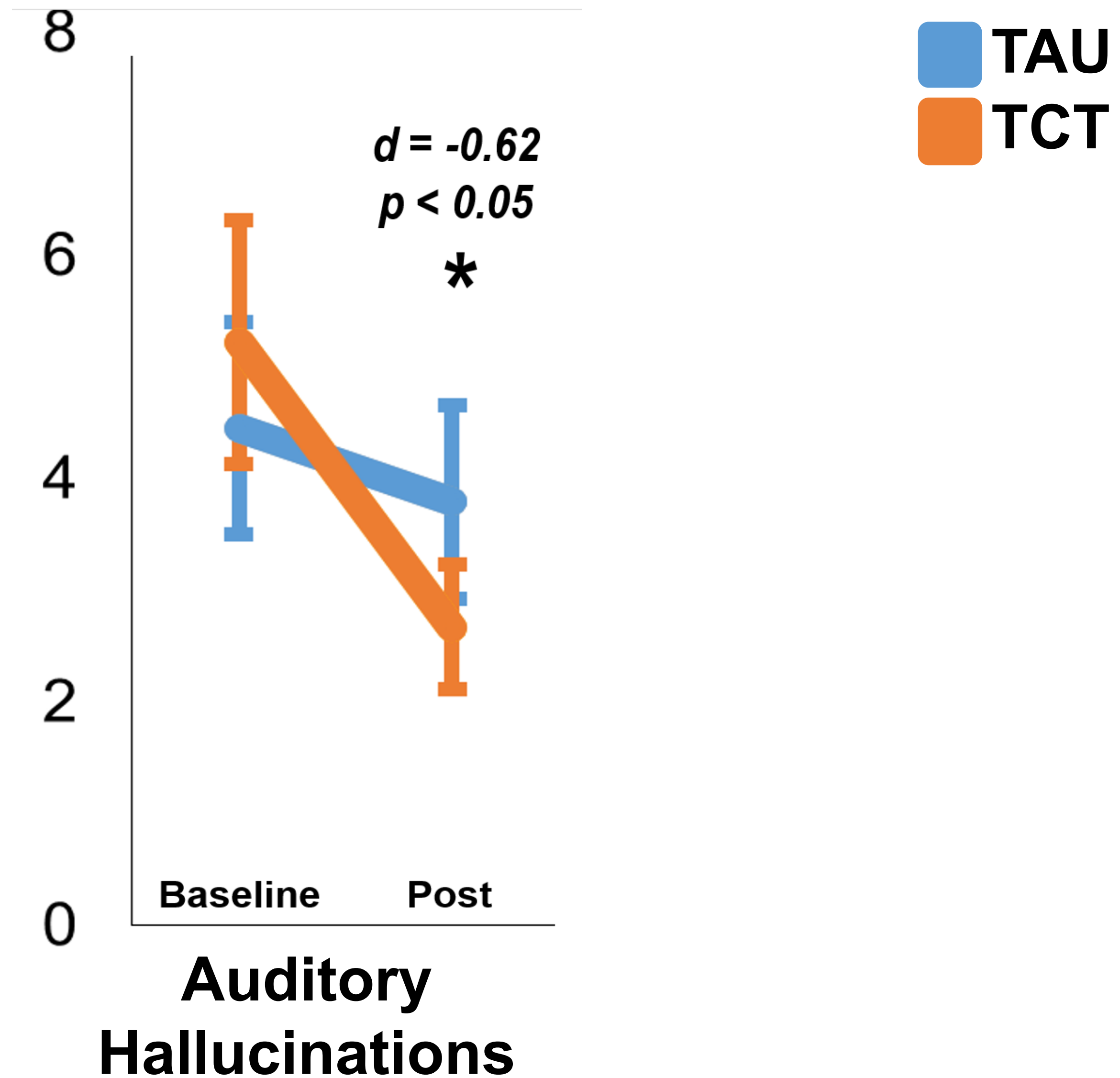
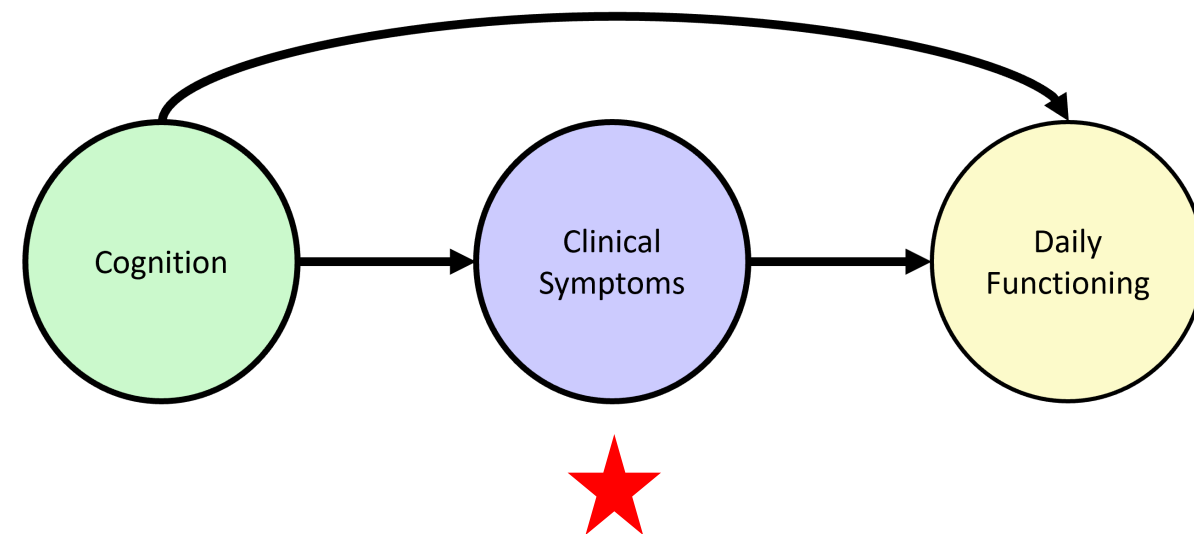
TAU
TCT

Verbal Learning



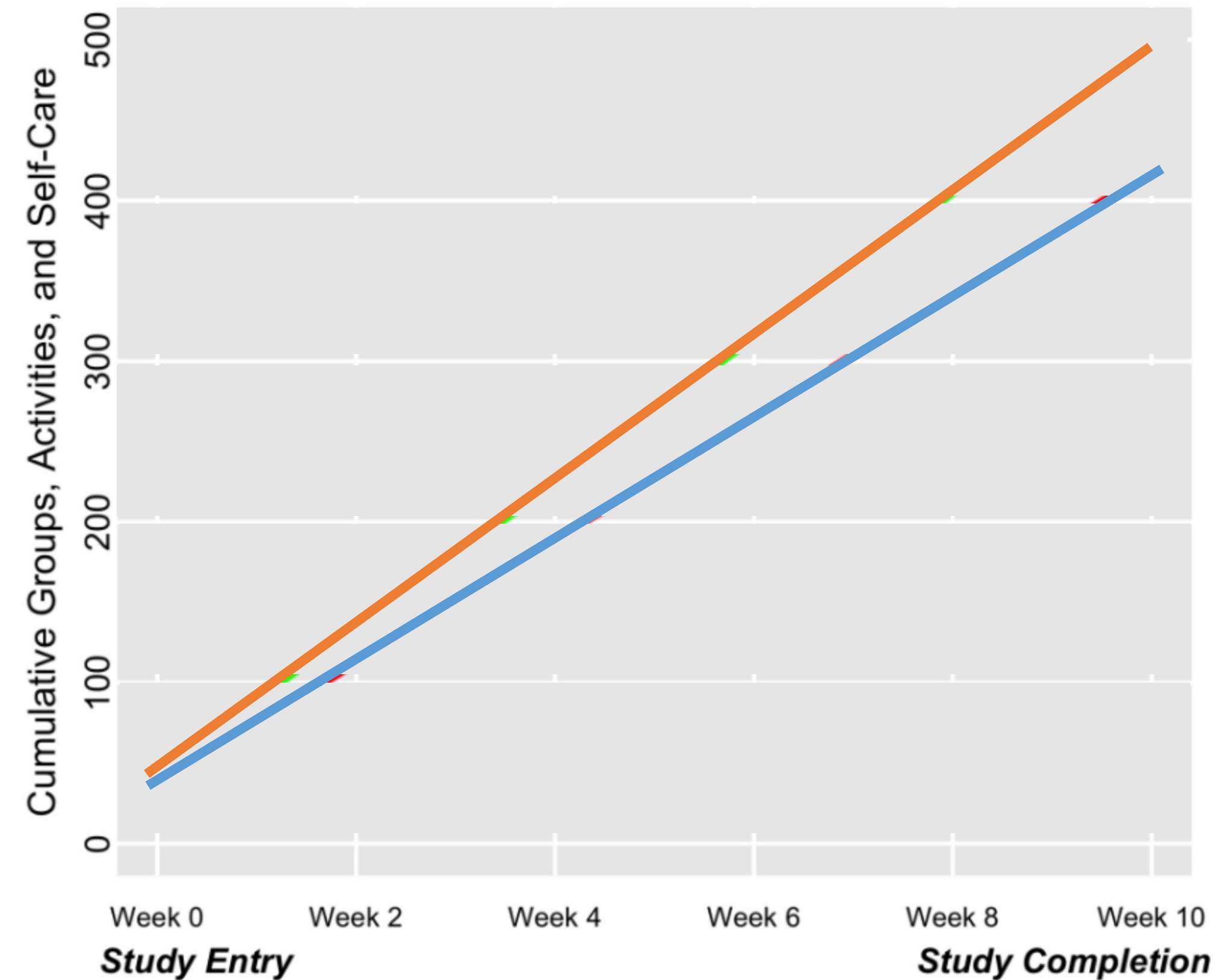
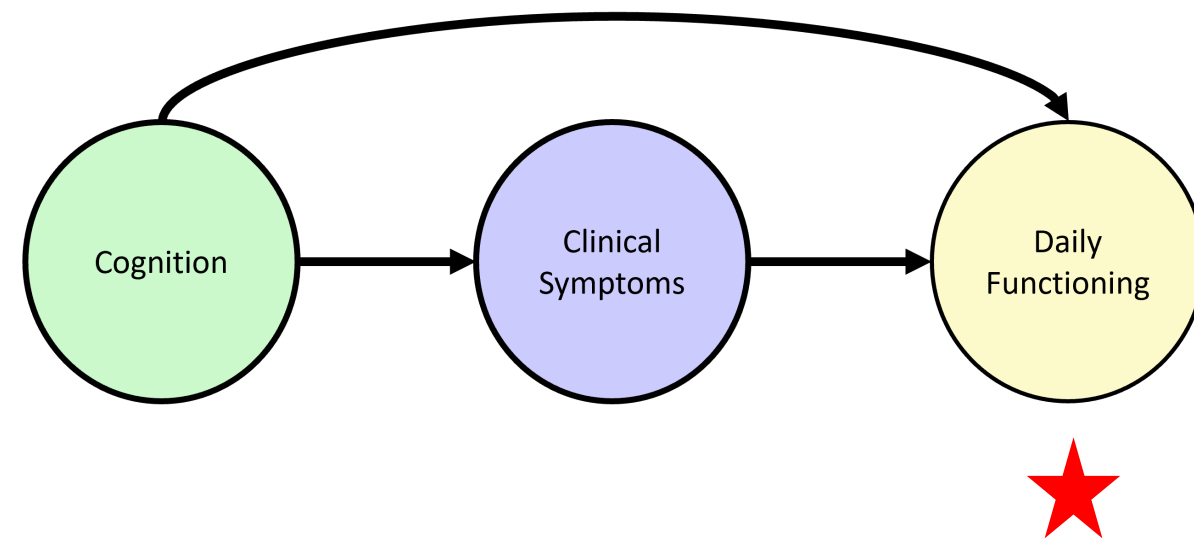
Thomas et al, (2018)

TCT Reduces Hallucinations in Severely Disabled SZ inpatients



Thomas et al, (2018)

TCT Improves Engagement in SZ inpatients



TAU
TCT

+ 1.34 groups activities/wk
+ 0.58 ADLs/wk
+ 0.84 rehabilitation activities/wk



**~1 extra total
week of
rehabilitation**

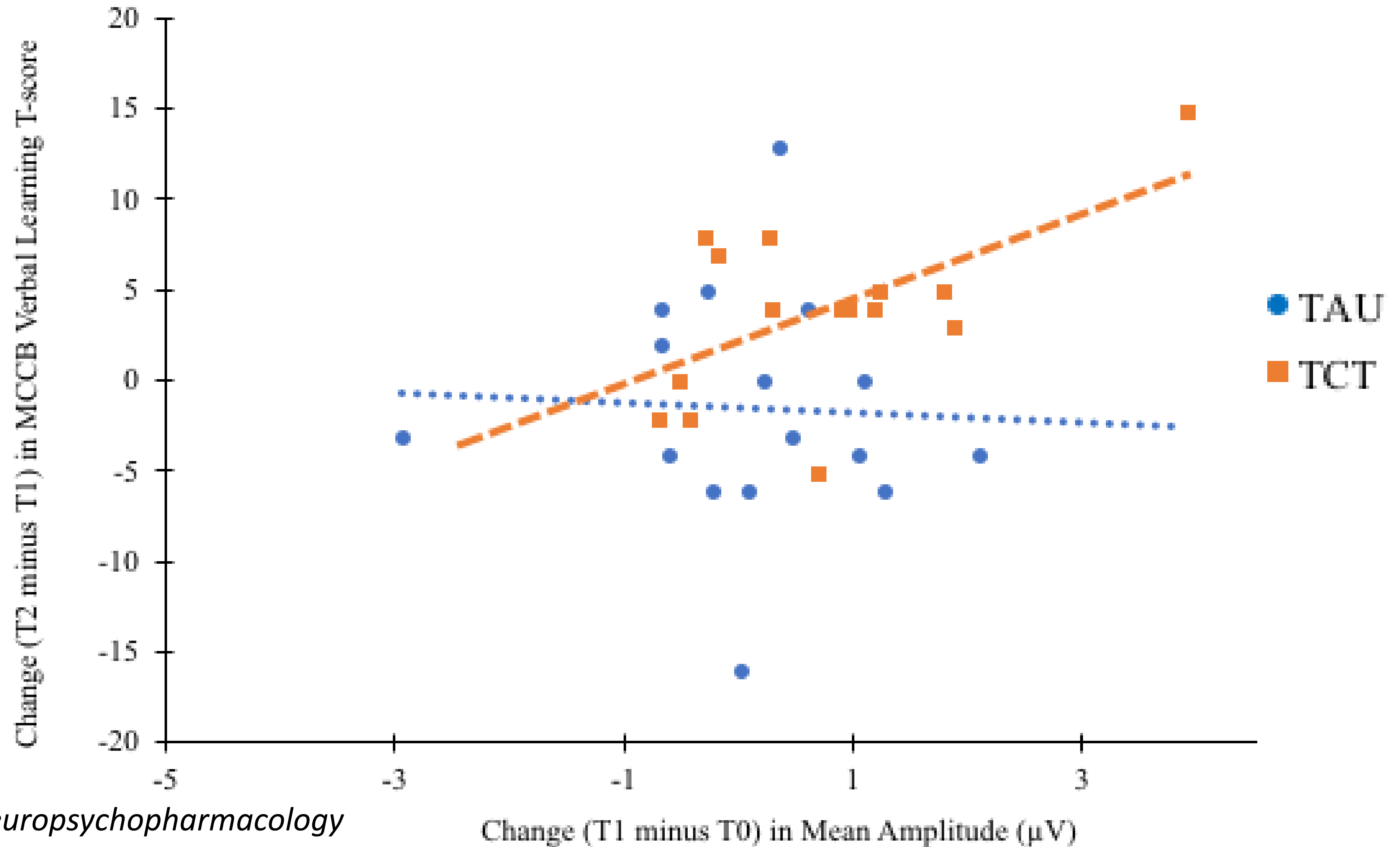
Testing the Effectiveness of TCT & Predictive Utility of EEG Biomarkers

Are EEG measures acutely sensitive to the neural systems engaged by 1h of TCT exercises?

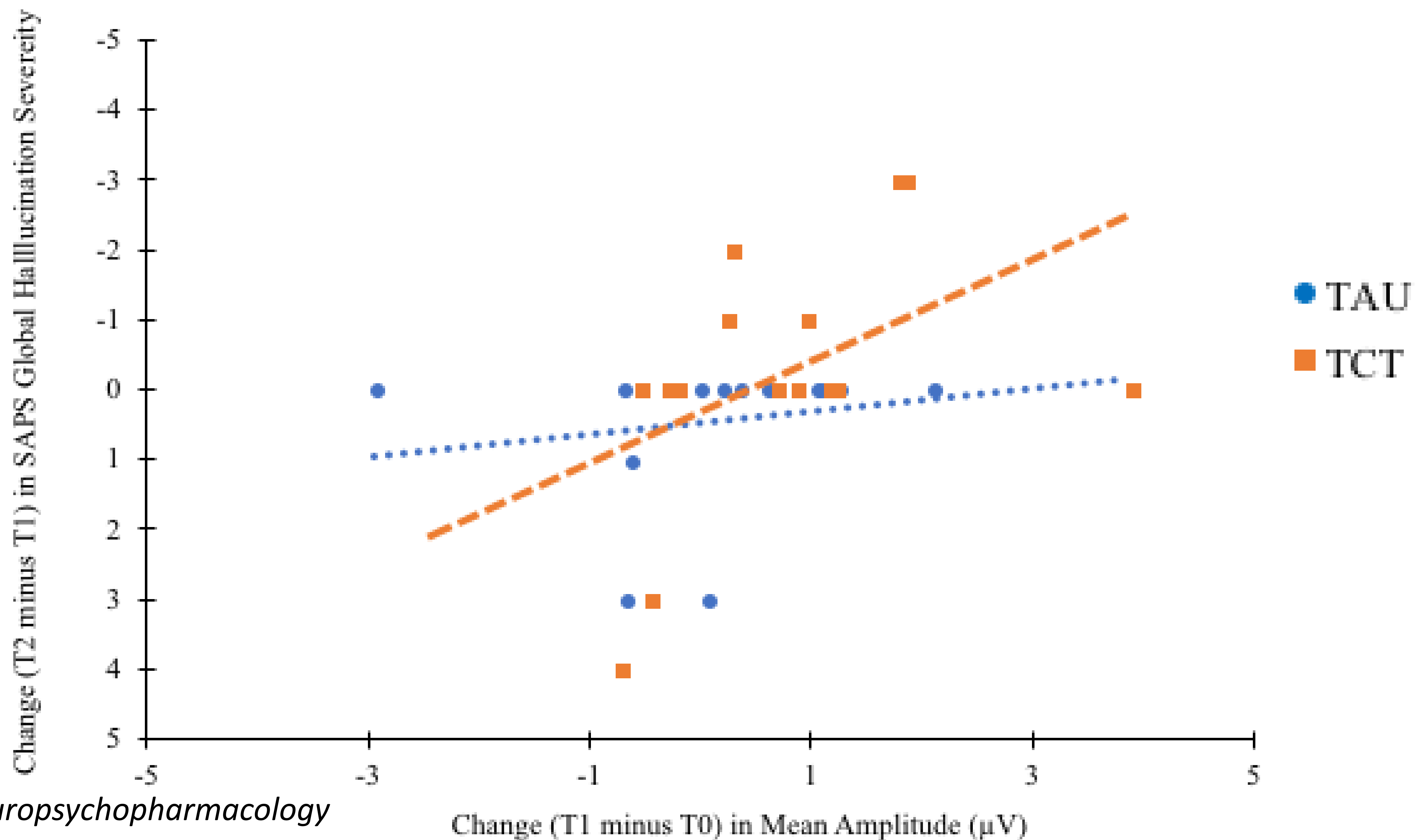
Does 30h of cognitive training “work” in treatment refractory schizophrenia Inpatients?

Do EEG changes following initial exposure to TCT predict future therapeutic benefit?

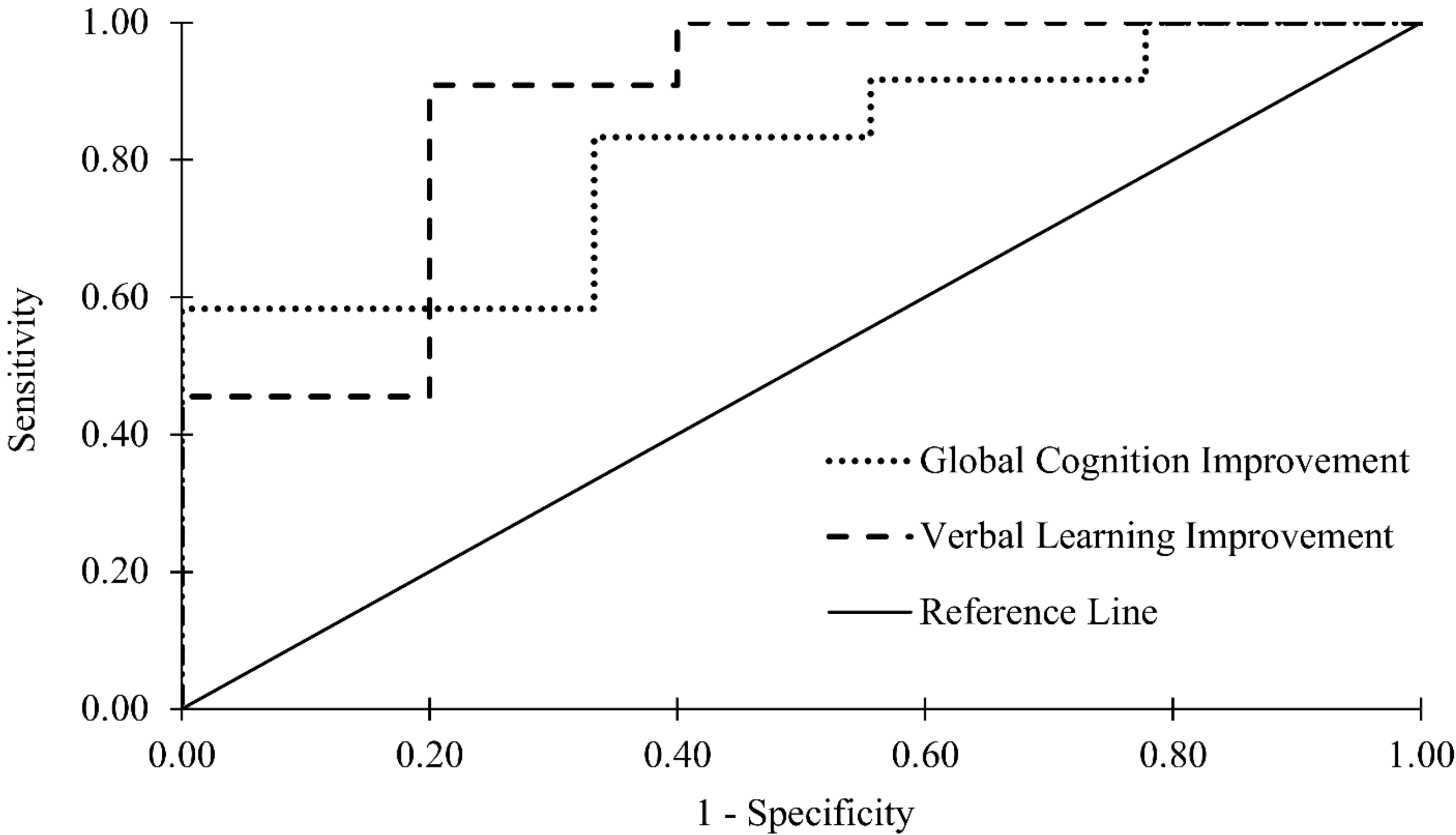
Amplitude Changes After 1h Predicts Improvements in Verbal Learning After 30h



Amplitude Changes After 1h Predicts Reductions in Auditory Hallucinations After 30h



EEG Biomarkers Predict Individual Benefits

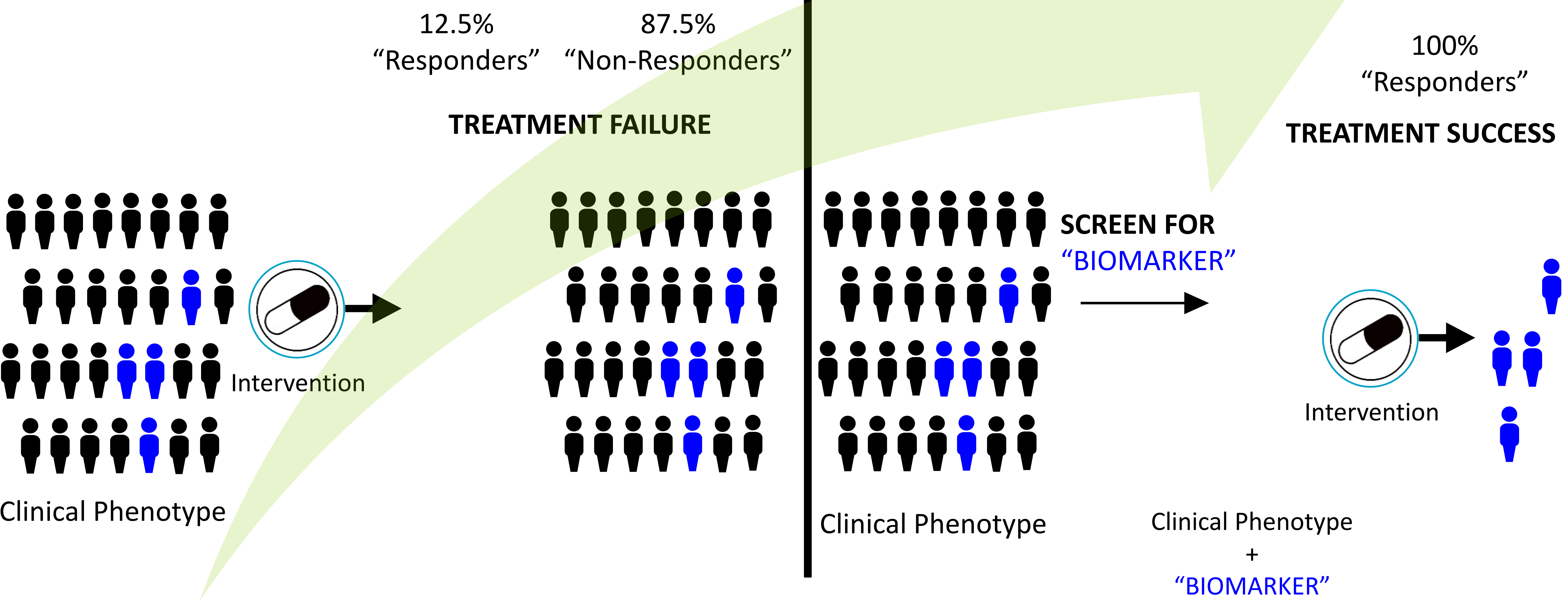


Z-Score Cutoff	≥ -1.35	≥ -0.96	≥ -0.74	≥ -0.55	≥ 0.18	≥ 0.49
Sensitivity	100%	100%	100%	91%	46%	27%
Specificity	20%	40%	60%	80%	100%	100%

Revised Neuroscience-Informed Experimental Medicine Approach

“IMPRECISE MEDICINE”

“PRECISION MEDICINE”



Lessons Learned and Caveats

- This particular form of cognitive training is effective for improving cognitive, clinical, and psychosocial functioning of patients, even those with long-standing illness.
- Patients with greater severity of deficits benefited the most
- Biomarkers measured

- The exercises are not that much fun
- Our sample size was small, others demonstrating similar effectiveness larger
- Not all patients benefited
- *Complaints* of daily cognitive problems were not improved, even among those with larger gains
- Specific cognitive exercises and dose probably matters
- Context of delivery and who administers it probably matters
- Clinical stabilization first
- Get the context right first – embedded within enriched psychosocial experiences.

Ongoing Studies and Future Directions

- Accelerating drug development via translational neuroscience
 - Predicting development of illness in at risk individuals
 - Tracking progression of deficits across course of illness
 - Novel Analytics: Neural mechanisms, temporal dynamics, multivariate composite indices
-
- Biomarker-guided assignment to treatments?
 - Biomarker in early and later phase clinical trials
 - Assessing early response to pharmacologic interventions: PACT

Using Tools of Neuroscience to Make Personalized Care a Reality in Schizophrenia



Gregory Light, Ph.D.
UNIVERSITY OF CALIFORNIA, SAN DIEGO
Professor & Assoc. Vice Chair, Dept of Psychiatry

VA SAN DIEGO HEALTHCARE SYSTEM
Co-Director, Mental Health Research
Associate Director: Mental Illness, Research, Education and Clinical Center (MIRECC)
Email: glight@ucsd.edu

 **BRAIN &
BEHAVIOR**
RESEARCH FOUNDATION
Awarding **NARSAD** Grants

 **SIDNEY R. BAER, JR.**
FOUNDATION